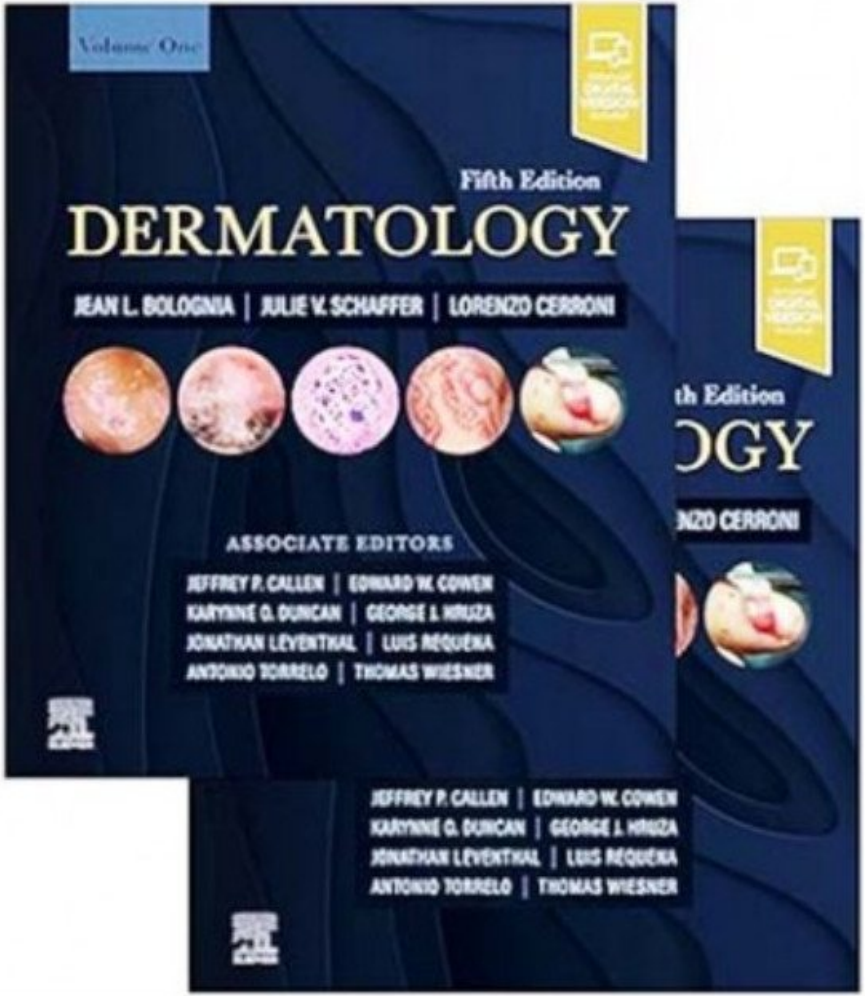
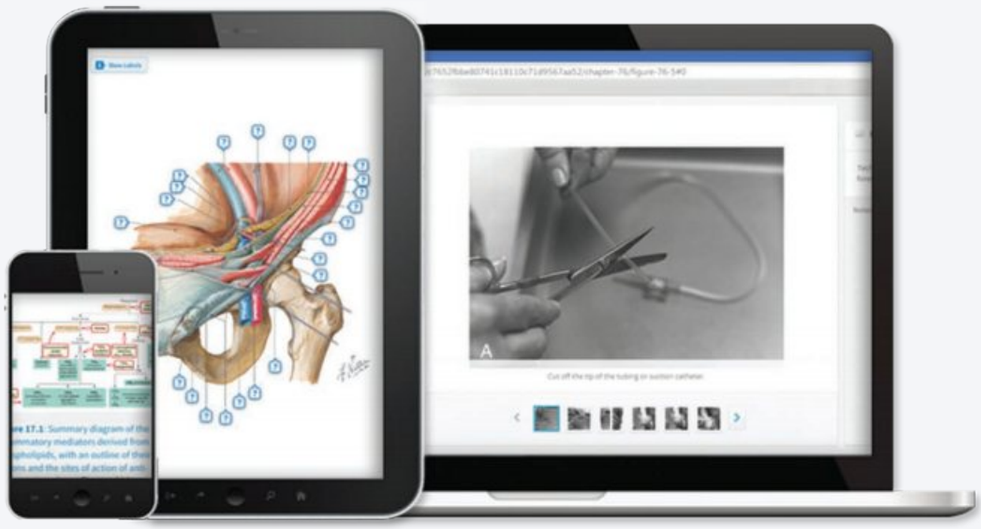

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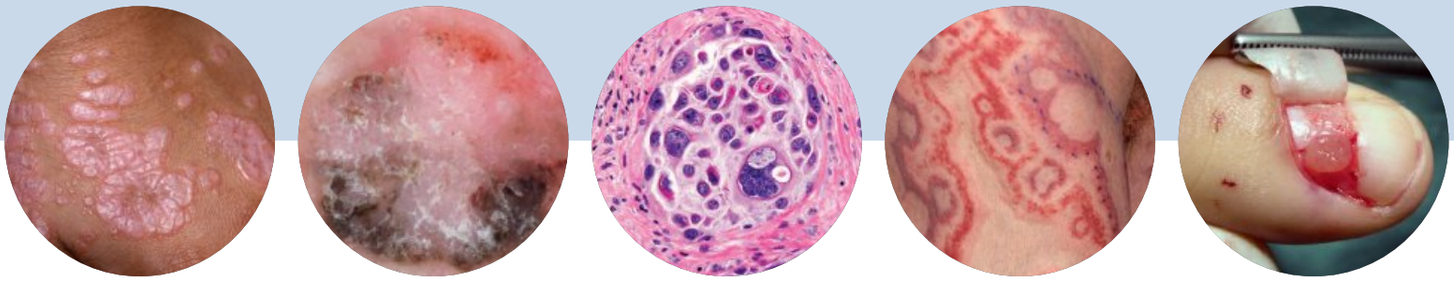
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Fifth Edition

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Alastair Carruthers, Jean Carruthers and Ada Trindade de Almeida

Video 159.6 Neuromodulator Treatment of Chin
Alastair Carruthers, Jean Carruthers and Ada Trindade de Almeida

Video 159.7 Neuromodulator Treatment of Axillary Hyperhidrosis
Elizabeth Tanzi

Preface

The practice of dermatology is based upon a visual approach to clinical disease, with the development of an appreciation of recurrent patterns and images. The entire spectrum of our discipline, from the generation of differential diagnoses to the orientation of rotational flaps, relies upon imagery. As a result, visualization also plays a critical role in how we integrate new information into pre-existing frameworks that serve as the hard drives of our medical memory.

In the textbook *Dermatology* there is a strong emphasis on visual learning. This commitment is reflected in the use of schematic diagrams to convey the principles of skin biology as well as cutaneous surgery, in addition to the inclusion of algorithms, which provide a logical as well as practical approach to commonly encountered clinical problems. The majority of the basic science is integrated throughout the book and appears as introductory chapters to the various sections. There is also an emphasis on clinicopathologic correlations, with photomicrographs demonstrating key histologic findings adjacent to clinical images of the same disorder. Differential diagnosis tables are weighted and there is a "ladder" approach to therapeutic interventions. Lastly, color-coding of sections allows an easy and rapid access to required information.

One goal of the *Dermatology* textbook is for it to never make its way to the bookshelf because it is being used on a weekly, or perhaps even daily, basis. Nowadays, another goal is for the app to be on the home screen of smartphones and tablets. Hopefully, this book will function as a colleague, albeit a non-verbal one, who is easily approachable and possesses the necessary expertise to provide succinct, up-to-date information that is both precise and practical. It is also our hope that the organization is intuitive and information can therefore be quickly retrieved. Realizing this goal required the time and energy of our contributors and associate editors, who have unselfishly shared their knowledge and experience with literally thousands of patients from around the world, and we thank them.

JB, JVS, and LC
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VOLUMES, SECTIONS, AND COLOR CODING

Dermatology is divided into two volumes. The book is divided into 22 sections, which are color-coded as follows for reference:

VOLUME ONE

- **Section 1** Overview of basic science
- **Section 2** Pruritus
- **Section 3** Papulosquamous and eczematous dermatoses
- **Section 4** Urticarias, erythemas, and purpuras
- **Section 5** Vesiculobullous diseases
- **Section 6** Adnexal diseases
- **Section 7** Rheumatologic dermatology
- **Section 8** Metabolic and systemic diseases
- **Section 9** Genodermatoses
- **Section 10** Pigmentary disorders
- **Section 11** Hair, nails, and mucous membranes

VOLUME TWO

- **Section 12** Infections, infestations, and bites
- **Section 13** Disorders due to physical agents
- **Section 14** Disorders of Langerhans cells and macrophages
- **Section 15** Atrophies and disorders of dermal connective tissues
- **Section 16** Disorders of subcutaneous fat
- **Section 17** Vascular disorders
- **Section 18** Neoplasms of the skin
- **Section 19** Medical therapy
- **Section 20** Physical treatment modalities
- **Section 21** Surgery
- **Section 22** Cosmetic surgery

Basic Science Chapters

Basic science chapters in the book are highlighted on the upper corner of each page with the following skin biology symbol:



Therapeutic Ladders



Therapeutic ladders have been standardized for measuring levels of evidence.

Key to evidence-based support:

(1) prospective controlled trial
(2) retrospective study or large case series
(3) small case series or individual case reports.

Dermatology Website

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This book is dedicated to our families, in particular Dennis Cooper, MD, Andrew Schaffer and Ricarda Cerroni, who endured our work on this project and who unwittingly were part of the team, and to all the rest of the team at Elsevier who made it all happen.

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Basic Principles of Dermatology 0

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INTRODUCTION TO CLINICAL DERMATOLOGY

The skin represents the largest organ of the human body. The average adult has 1.75 m^2 (18.5 ft^2) of skin that contains a variety of complex adnexal structures, including hair follicles, nails, glands, and specialized sensory structures, all of which function in protection, homeostasis, and the transmission of sensation. Dermatology is the field of medicine that deals with the macroscopic study of skin, adjacent mucosa (oral and genital), and cutaneous adnexa, while dermatopathology deals with the microscopic study of these same structures. The two fields are closely allied, as they are complementary and requisite to one another.

Multiple studies have shown that dermatologists are the most effective diagnosticians of skin disease[1,2]. This enhanced acumen reflects experience in recognizing distribution patterns and configurations, as well as subtle variations in morphology and colors, in addition to appreciating associated histopathologic findings. This chapter serves as an introduction to classification schemas and to descriptive terminologies and diagnostic tools utilized in dermatology. It also highlights additional means for studying skin, including dermoscopy (dermatoscopy), artificial intelligence, and dermatopathology, with clinicopathologic correlation between macroscopic and microscopic findings.

Etiologic Premises

All students of dermatology, whether beginners or advanced scholars, require a conceptual framework upon which to organize thousands of skin diseases. A useful analogy is that of a tree, with a trunk, major branches, minor branches, twigs, and ultimately, leaves (Fig. 0.1). Instead of memorizing thousands of leaves, a logical, progressive movement along the limbs allows for a complete and sophisticated differential diagnosis.

Inflammatory versus neoplastic

An early and major "branch point" in classifying skin diseases is deciding if a skin condition is "neoplastic" (either benign or malignant) or "inflammatory" (either infectious or non-infectious) (see Fig. 0.1). However, an experienced clinician knows that one must consider possible diagnoses along multiple limbs before narrowing the differential diagnosis, because overlap and mimicry can occur. For example, mycosis fungoides, the most common form of cutaneous T cell lymphoma, is a clonal lymphoproliferative disorder (a "neoplasm"), yet its clinical presentation resembles an inflammatory disorder (Fig. 0.2), particularly in its early stages. Conversely, sarcoidosis is an inflammatory condition, yet it may present as an isolated infiltrated plaque or nodule that may mimic a neoplasm (Fig. 0.3).

Morphology

To an engineer or material scientist, the word "*morphology*" refers to the structure and appearance of a material without regard to function. In dermatology, the term refers to the general appearance of a skin lesion, irrespective of the etiology or underlying pathophysiology. For example, a small cutaneous blister is referred to as a "vesicle," regardless of whether it is due to an infectious process, such as herpes

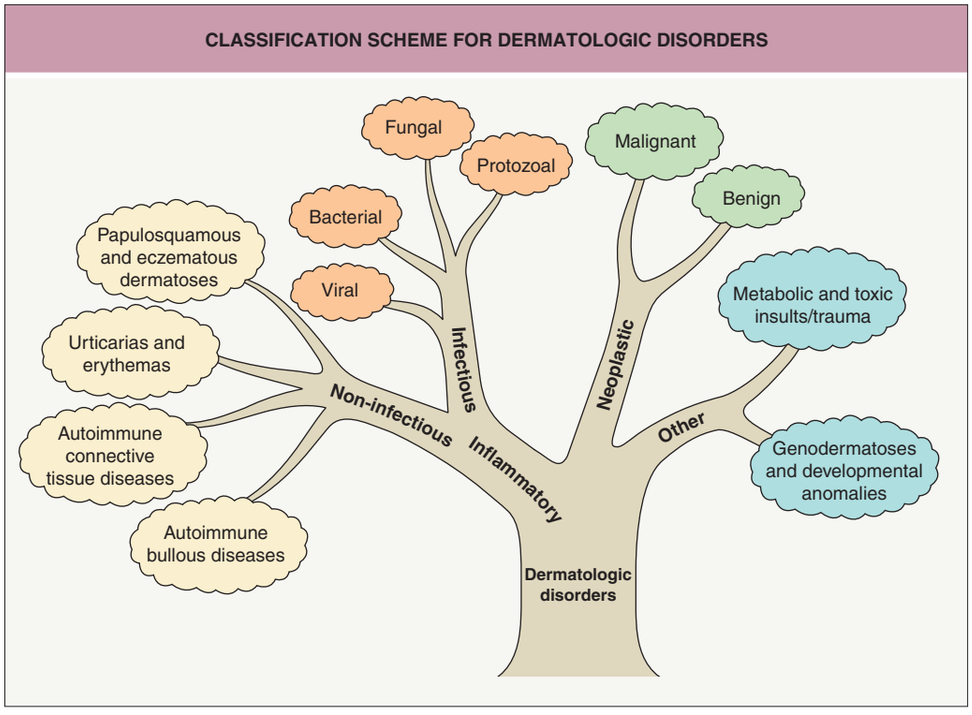


Fig. 0.1 Classification scheme for dermatologic disorders. The "trunk" of dermatology divides into the major etiologic "branches" of inflammatory, neoplastic, and other. Branches narrow and further subdivide, e.g. inflammatory into infectious and non-infectious. Branches ultimately terminate as clustered leaves, representing specific disorders.



Fig. 0.2 Mycosis fungoides, the most common form of cutaneous T cell lymphoma. Mycosis fungoides represents a neoplastic proliferation of monoclonal lymphocytes, but it presents clinically in a manner akin to that of inflammatory disorders. *Courtesy Lorenzo Cerroni, MD.*



Fig. 0.3 Sarcoidosis. It is an inflammatory disorder of uncertain etiology, most prevalent in African-Americans from the southern United States, but sarcoidosis can present as a papulonodule or infiltrated plaque, mimicking a neoplastic disorder.



Fig. 0.4 Herpes zoster, an infectious disease, versus dermatitis herpetiformis, an autoimmune bullous disease. While disparate in etiology, herpes zoster (**A**) and dermatitis herpetiformis (**B**) result in a similar morphology – cutaneous vesicles and bullae – but with different distribution patterns. *Courtesy Lorenzo Cerroni, MD.*

zoster, or an autoimmune process, such as dermatitis herpetiformis (Fig. 0.4). Proper use of morphologic terms establishes a structural framework for grouping skin diseases based upon their macroscopic appearances[3].

In essence, morphologic terms form a "native language" by which dermatologists, and other health professionals, communicate with each other to *describe* skin lesions. As such, they are key elements of our shared lexicon. Without a working knowledge of morphology, it is impossible to describe cutaneous observations in a consistent manner. Ergo, one of the initial steps in studying dermatology is to learn the basic morphologic definitions inherent to the specialty.

There exist both *primary* morphologic terms (Table 0.1), which refer to the most characteristic, representative, or native appearance of skin lesions (e.g. a "papule"), as well as *secondary* morphologic terms (Table 0.2), which augment or supplant primary morphologic terms. Secondary morphologic terms often reflect the effects of exogenous factors or temporal changes (e.g. "scales", "crusts") that evolve during the course of a skin disease.

Secondary features must be considered when performing, or examining histologically, a biopsy of a skin lesion. An astute clinician will biopsy a lesion that is both "fresh" and well-developed as it most aptly demonstrates the primary pathologic process. Lesions with confounding secondary changes such as erosions, excoriations, and lichenification are avoided, if possible, as this allows the dermatopathologist the opportunity to evaluate the histologic features in their native state.

Lastly, the skin is a three-dimensional structure, and like cartographers who construct maps, there are accepted descriptors used by dermatologists to describe the topography of individual skin lesions. Examples include flat-topped (lichenoid), dome-shaped, verrucous, umbilicated, filiform, and pedunculated[3].

Palpation and appreciation of textural changes

Any discussion of morphology must include textural change, and palpating a lesion often provides diagnostic clues. In dermatology, palpation can prove useful in several ways. Firstly, it helps in making a distinction amongst various morphologies (see Table 0.1). For example, the key difference between macules and papules, or patches versus plaques, is that macules and patches are flush with the surrounding skin and cannot be appreciated by palpation. On the other hand, papules and plaques, by definition, must be palpable (Table 0.3). Secondly, palpation may augment understanding of a disease process that is otherwise unimpressive or nonspecific.

For example, in morphea, an autoimmune connective tissue disease that leads to sclerotic collagen in the dermis, the skin feels indurated (firm), yet only mild hyperpigmentation may be evident by visual inspection. The same is true for other fibrotic diseases such as systemic sclerosis. Likewise, atrophy, be it epidermal, dermal or subcutaneous,

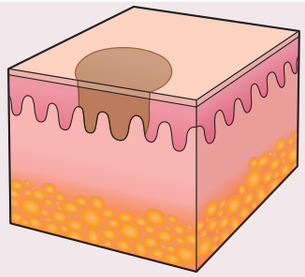
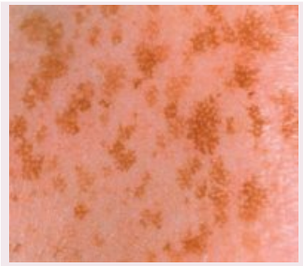
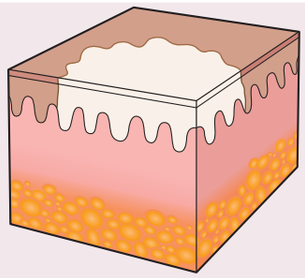
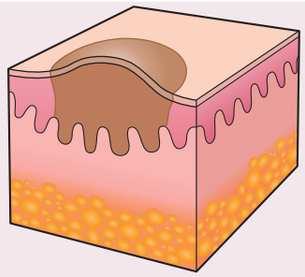
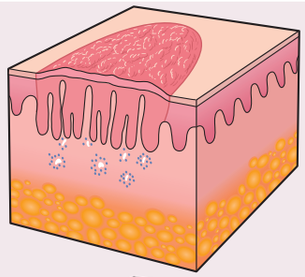
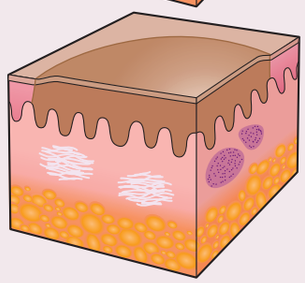
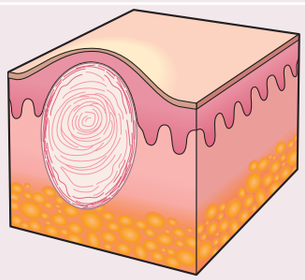
PRIMARY LESIONS – MORPHOLOGICAL TERMS				
Term	**Clinical features**		**Clinical example**	**Clinical disorders**
Macule	• Flat (non-palpable), circumscribed, differs in color from surrounding skin • <1 cm in diameter • Often hypo- or hyperpigmented, but also other colors (e.g. pink, red, violet) • It can be round, oval, or irregular in outline		 Solar lentigines	• Ephelid (freckle) • Lentigo • Idiopathic guttate hypomelanosis • Petechiae • Flat component of viral exanthems
Patch	• Flat (non-palpable), circumscribed, differs in color from surrounding skin • >1 cm in diameter • Often hypo- or hyperpigmented, but also other colors (e.g. blue, violet)		 Vitiligo	• Vitiligo • Melasma • Dermal melanocytosis (Mongolian spot) • Café-au-lait macule • Nevus depigmentosus • Solar purpura • Port-wine birthmark (early)
Papule	• Elevated (palpable), circumscribed • <1 cm in diameter • Elevation due to increased thickness of the epidermis and/or cells or deposits within the dermis • May have secondary changes (e.g. scale, crust) • The profile can be flat-topped (lichenoid), dome-shaped, umbilicated, smooth, or verrucous		 Seborrheic keratosis	• Seborrheic keratosis • Cherry angioma • Compound or intradermal melanocytic nevus • Verruca • Molluscum contagiosum • Fibrous papule (angiofibroma) • Lichen nitidus • Elevated component of viral exanthems • Small vessel vasculitis
Plaque	• Elevated (palpable), circumscribed • >1 cm in diameter • Elevation due to increased thickness of the epidermis and/or cells or deposits within the dermis • May have secondary changes (e.g. scale, crust) • Occasionally, a plaque is palpable but not elevated, as in morphea	 	 Psoriasis  Sarcoidosis	*Primarily epidermal* • Psoriasis • Lichen simplex chronicus • Nummular dermatitis *Dermal* • Granuloma annulare • Sarcoidosis • Hypertrophic scar, keloid • Morphea • Lichen sclerosus *Both epidermal and dermal* • Discoid lupus erythematosus
Nodule	• Palpable, circumscribed • Larger volume than papule, usually >1 cm in diameter • Can be compressible, soft, rubbery, or firm to palpation • Involves the dermis and/or the subcutis • Greatest portion may be beneath the skin surface or exophytic		 Epidermoid (infundibular) cyst	• Epidermoid or tricholemmal cyst • Lipoma • Rheumatoid nodule • Metastasis • Neurofibroma • Panniculitis, e.g. erythema nodosum • Lymphoma cutis

Table 0.1 Primary lesions – morphological terms.

Continued

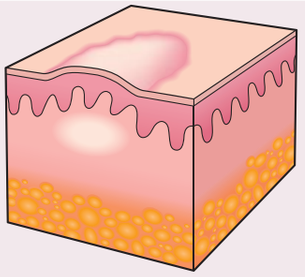
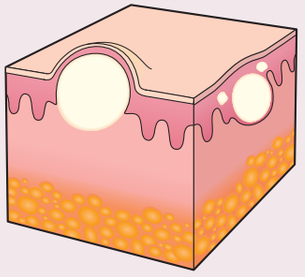
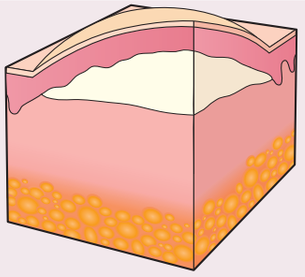
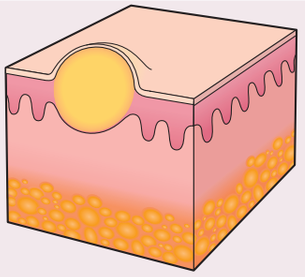
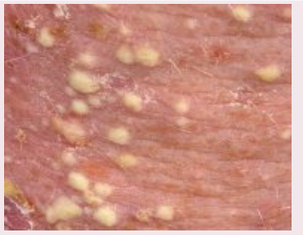
PRIMARY LESIONS – MORPHOLOGICAL TERMS				
Term	**Clinical features**		**Clinical example**	**Clinical disorders**
Wheal	• Transient elevation of the skin due to dermal edema • Often pale centrally with an erythematous rim		 Acute annular urticaria	• Urticaria
Vesicle	• Elevated, circumscribed • <1 cm in diameter • Filled with fluid – clear, serous, or hemorrhagic • May become pustular, umbilicated, or an erosion		 Herpes simplex	• Herpes simplex • Varicella or zoster • Acute allergic contact dermatitis • Dyshidrotic eczema • Dermatitis herpetiformis
Bulla	• Elevated, circumscribed • >1 cm in diameter • Filled with fluid – clear, serous, or hemorrhagic • May become an erosion		 Bullous pemphigoid	• Friction blister • Thermal burn (second-degree) • Bullous insect bite reactions • Bullous pemphigoid • Linear IgA bullous dermatosis • Bullous fixed drug eruption • Coma bulla • Edema bulla
Pustule	• Elevated, circumscribed • Usually <1 cm in diameter • From its onset, filled with purulent fluid • May be infectious or sterile		 Folliculitis	*Follicularly centered* • Folliculitis • Acne vulgaris *Non-follicularly centered* • Pustular psoriasis • Acute generalized exanthematous pustulosis • Subcorneal pustular dermatosis

Table 0.1 Primary lesions – morphological terms. *Some photographs courtesy Jean L. Bolognia, MD; Lorenzo Cerroni, MD; Louis A. Fragola, Jr, MD; Julie V. Schaffer, MD; Kalman Watsky, MD.*

SECONDARY FEATURES – MORPHOLOGICAL TERMS			
Feature	**Description**	**Clinical example**	**Disorders**
Crust	• Dried serum (serous), blood (hemorrhagic), or pus on the surface of the skin • May include bacteria (usually *Staphylococcus*)	 Secondarily infected hand dermatitis	• Eczema/dermatitis (multiple types) • Impetigo • Later phase of herpes simplex, varicella, or zoster • Erythema multiforme
Scale	• Hyperkeratosis • Accumulation of stratum corneum due to increased proliferation and/or delayed desquamation • Represents a primary rather than a secondary feature in ichthyoses	 Psoriasis	• Psoriasis (silvery [micaceous] scale) • Tinea (leading scale) • Erythema annulare centrifugum (trailing scale) • Pityriasis (tinea) versicolor (powdery [furfuraceous] scale) • Actinic keratoses (gritty scale) • Pityriasis rosea (peripheral collarette and central scale)

Table 0.2 Secondary features – morphological terms.

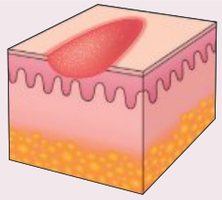
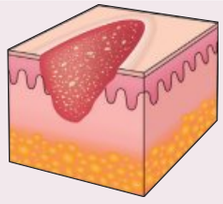
SECONDARY FEATURES – MORPHOLOGICAL TERMS			
Feature	**Description**	**Clinical example**	**Disorders**
Fissure	• Linear cleft in skin • Often painful • Results from marked drying, skin thickening, and loss of elasticity	 Hand dermatitis	• Angular cheilitis • Hand dermatitis • Sebopsoriasis (intergluteal fold) • Irritant cheilitis • Lichen sclerosus (perineum)
Excoriation	• Exogenous injury to all or part of the epidermis (epithelium) • May be linear or punctate	 Neurotic excoriations	• A secondary feature of pruritic conditions, including arthropod bites and atopic dermatitis • Neurotic excoriations • Acne excoriée
Erosion	• Partial loss of the epidermis (epithelium) • A superficial moist, oozing, and/or crusted lesion	  Pemphigus foliaceus	• Impetigo • Friction • Trauma • Pemphigus, vulgaris, and foliaceus
Ulceration	• Full-thickness loss of the epidermis (epithelium) • May have loss of the dermis or even subcutis • The size, shape, and depth should be described as well as the characteristics of the border, base, and surrounding skin • Usually heals with a scar	  Pyoderma gangrenosum	• Venous (stasis) ulcer • Neuropathic ulcer • Arterial ulcer • Decubitus ulcer • Aphthous ulcer • Pyoderma gangrenosum • Ecthyma • Ecthyma gangrenosum
Infarct	• Ischemia of tissue • Color can vary from gray–white to purple to black	 Antiphospholipid syndrome	• Can be due to vascular compromise (e.g. atherosclerosis, calciphylaxis), thrombosis, vasculitis, emboli (infectious or non-infectious), or vasospasm (see Table 0.5)
Atrophy	• Epidermal atrophy – thinning of the epidermis, leading to wrinkling and a shiny appearance • Dermal atrophy – loss of dermal collagen and/or elastin, leading to a depression (see Table 0.3)	 Striae	• Lichen sclerosus • Poikiloderma • Striae • Anetoderma • Focal dermal hypoplasia (Goltz syndrome)

Table 0.2 Secondary features – morphological terms.

Continued

SECONDARY FEATURES – MORPHOLOGICAL TERMS			
Feature	**Description**	**Clinical example**	**Disorders**
Lichenification	• Accentuation of natural skin lines, reflecting thickening (acanthosis) of the epidermis • Often due to rubbing	 Lichen simplex chronicus	• Lichen simplex chronicus, isolated or superimposed on a pruritic condition, e.g. atopic dermatitis

Table 0.2 Secondary features – morphological terms. *Some photographs courtesy Lorenzo Cerroni, MD; Louis A. Fragola, Jr, MD; Jeffrey P. Callen, MD; Luis Requena, MD.*

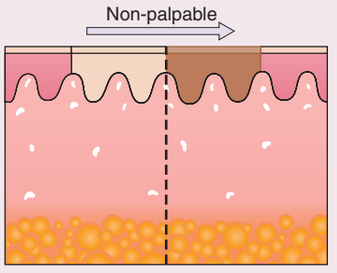
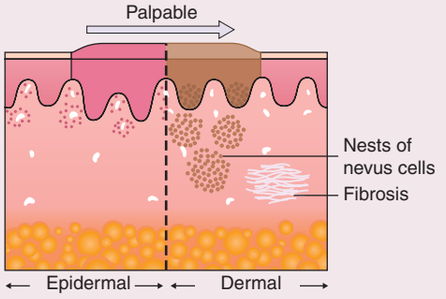
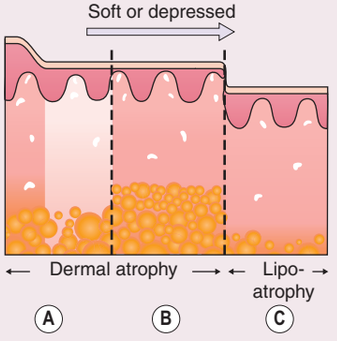
USE OF PALPATION IN DEFINING CUTANEOUS LESIONS		
Types of lesion		**Examples**
Macules & patches (non-palpable)		• Solar lentigines • Idiopathic guttate hypomelanosis • Melasma • Vitiligo • Petechiae • Dermal melanocytosis
Papules & plaques (palpable)		• Psoriasis • Lichen planus • Dermatitis • Intradermal or compound melanocytic nevus • Hypertrophic scar, keloid • Morphea
Atrophy – dermal & subcutaneous		Ⓐ Anetoderma Ⓑ Focal dermal hypoplasia (Goltz syndrome) Ⓒ Lipoatrophy due to corticosteroid injections Lipoatrophy due to panniculitis

Table 0.3 Use of palpation in defining cutaneous lesions.

serves as a diagnostic clue (Fig. 0.5). Lastly, purpura is often classified as palpable or non-palpable, and this division can imply different underlying etiologies (e.g. small vessel vasculitis is aligned more with palpable purpura). Examples of useful distinctions that can be gleaned via palpation are outlined in Table 0.4.

Color

The color of skin lesions provides clues as to the nature of the disease process. Sometimes the perception of color may be modified by palpation (see Table 0.4). For example, while many dermatologic processes appear erythematous (red to purple) in color, it is important to ascertain whether this color is "blanchable" (i.e. disappears with pressure), which suggests it is due to vasodilation, or "non-blanchable," which suggests it is due to extravasation of erythrocytes into the skin. Exogenous sources of pigment, such as topical medicaments, oral drugs, and other ingestants, can also lead to skin discoloration. Table 0.5 lists frequently observed colors of skin lesions and associated disorders.

Variation in skin color within the human population

Many racial and ethnic descriptors are used in common parlance, including African, African-American, Asian, Middle Eastern, Northern European, Southern European, Native American, Pacific Islander, and Hispanic, to describe individuals with similar cutaneous characteristics and heritage. Yet even within racial/ethnic groups, gradations of skin pigmentation exist. Sometimes the term "skin of color" is used to describe all skin tones darker than those of white skin[4]. However, this term encompasses more than skin color and its response to ultraviolet

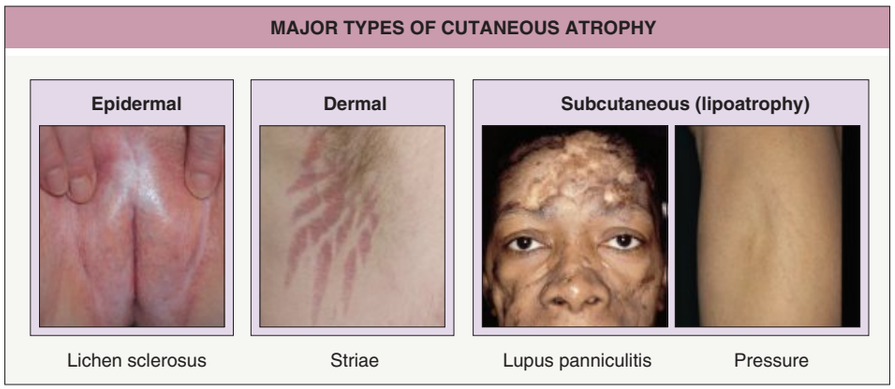


Fig. 0.5 Major types of cutaneous atrophy. *Photographs courtesy Jean L. Bolognia, MD, and Fenella Wojnarowska, MD.*

PALPATION OF CUTANEOUS LESIONS
• Soft (e.g. intradermal nevus) versus firm (e.g. dermatofibroma) versus hard (e.g. calcinosis cutis, osteoma cutis)
• Compressible (e.g. venous lake) versus non-compressible (e.g. fibrous papule)
• Tender (e.g. inflamed epidermoid inclusion cyst, angiolipoma, leiomyoma) versus non-tender (e.g. intradermal melanocytic nevus)
• Blanchable (e.g. erythema due to vasodilation) versus non-blanchable (e.g. purpura)
• Rough (e.g. actinic keratosis) versus smooth (e.g. fibrous papule)
• Mobile (e.g. epidermoid cyst) versus fixed to underlying structures (e.g. soft tissue sarcoma)
• Dermal (e.g. dermatofibroma) versus subcutaneous (e.g. erythema nodosum)
• Temperature – normal versus warmer (e.g. cellulitis) versus cooler (e.g. Raynaud phenomenon)
• Other, e.g. thrill, pulsatile

Table 0.4 Palpation of cutaneous lesions.

irradiation, as is assessed by the Fitzpatrick Scale (skin phototypes I–VI; Table 0.6). It also refers to other shared characteristics, such as hair color, hair texture, and even cutaneous reaction patterns to inflammation (e.g. follicular accentuation) or injury. The practice of dermatology requires a solid understanding and appreciation of the differences in clinical features (e.g. hues of red) amongst individuals with different skin pigmentation – the importance of this cannot be overstated[5].

Variations in skin color are a result of differences in the amount and distribution of melanin within epidermal melanocytes and keratinocytes[6], rather than the number of melanocytes (see Ch. 65). The ratio of eumelanin (brown–black) to pheomelanin (yellow–red) also influences skin color, with pheomelanin the predominant pigment in those with freckles and red hair. Exposure to ultraviolet radiation also impacts melanin production (tanning).

Mucocutaneous pigmentation influences the prevalence of certain cutaneous findings and disorders. For example, individuals with darker skin phototypes are more likely to develop longitudinal melanonychia (see Ch. 71)[7,8], pigmentation of the oral mucosa[9], persistent postinflammatory hyperpigmentation (see Ch. 67), and pigmentary demarcation lines[10] (Futcher lines or Voigt lines; see Fig. 67.12). Whether postinflammatory hypopigmentation[11] is more common or simply more apparent is a matter of debate. In addition, discoid lupus erythematosus, sarcoidosis, and keloids are seen more often in patients with darkly pigmented skin and African ancestry, but there is no known relationship of these disorders to melanocyte function.

There can also be differences in the physiologic properties of the skin. For example, the stratum corneum of black skin often retains more layers and is more compact and cohesive than that of white skin. In addition, darker skin produces less vitamin D_3 in response to equivalent amounts of sunlight, and this is postulated to have been a driving force in the evolution of more lightly pigmented skin as early humans migrated away from the equator[12].

Perhaps the most important point to remember is that erythema (redness) can be difficult to appreciate in darkly pigmented skin. Erythema is caused by vasodilation and/or increased blood flow within the dermis, and if the epidermis is deeply pigmented, the red hues of oxyhemoglobin may be less apparent. For this reason, diseases often described as decidedly erythematous (e.g. cellulitis) or violaceous (e.g. lichen planus) may have a different hue in darker skin types (Fig. 0.6)[13]. When performing diagnostic procedures that depend upon the development of overt erythema, such as patch testing for the evaluation of allergic contact dermatitis, appreciation of the influence of epidermal pigment is important. Lastly, cyanosis (blue hues indicative of poor oxygenation and a critical clinical sign) may be more difficult to appreciate when the skin is darkly pigmented.

Configuration and Distribution

After carefully considering the morphology and color of skin lesions, the dermatologist must analyze two closely related properties – configuration and distribution – in order to generate a differential diagnosis. For example, pruritic and fragile vesicles on the elbows and knees prompt consideration of dermatitis herpetiformis, whereas grouped vesicles on an erythematous base, confined to a single dermatome, mandate consideration of herpes zoster (see Fig. 0.4A) or zosteriform herpes simplex.

Configuration

The configuration or arrangement of skin lesions can provide important diagnostic clues. Examples include *annular* (e.g. tinea corporis, granuloma annulare; see Ch. 19), *serpiginous* (e.g. cutaneous larva migrans), *clustered/grouped* (e.g. piloleiomyomas, herpetiform vesicles), *reticulated* (e.g. erythema ab igne), and *retiform* (e.g. purpura fulminans, purpura due to calciphylaxis [Fig. 0.7]; see Ch. 23). The latter pattern reflects occlusion of cutaneous vasculature[14].

It is important to determine if the lesions have a *linear* configuration (Fig. 0.8). They may follow the lines of Blaschko, which reflect patterns of embryonic development (see Fig. 62.1)[15], or lesions may be confined to a dermatome, which represents an area of skin innervated by a single spinal nerve (see Fig. 80.13). Irrespective of whether lesions are along the lines of Blaschko (e.g. epidermal nevi) or are in a dermatomal pattern (e.g. herpes zoster [see Fig. 0.4A]), there is often characteristic midline demarcation. A linear arrangement can also result from trauma-induced Koebner phenomenon (an isomorphic response [Table 0.7]), as in vitiligo, lichen planus (Fig. 0.9), and psoriasis[16,17], or trauma-induced autoinoculation, as in verrucae vulgares or verrucae planae. Linear lesions are often seen in acute allergic contact dermatitis due to plants (e.g. poison ivy), reflecting a brushing of branches and leaves against skin. Lastly, papulonodules due to a range of infectious agents can align along lymphatic vessels in a sporotrichoid pattern (see Ch. 77).

On occasion, cutaneous lesions have an unusual, even "unnatural", shape that corresponds to an external (exogenous) insult, such as allergic or irritant contact dermatitis (Fig. 0.10), an accidental or purposeful injury (see Ch. 90)[18], or even ritualistic medicinal practices (e.g. "cupping" or "coining"; see Ch. 133).

Distribution

Stepping back and observing the anatomic distribution of skin lesions can also prove useful. For example, plaques of psoriasis often favor *extensor* surfaces (e.g. elbows and knees) while lichenified plaques of atopic dermatitis favor *flexural* surfaces in older children and adults

COLOR AS A CLUE TO THE CLINICAL DIAGNOSIS

Color	Examples of diseases with this color
Pink/red Erythema (pink to red–brown, depending upon the skin phototype)  Morbilliform (exanthematous) drug eruption	• Dermatitis • Psoriasis • Morbilliform drug eruption • Viral exanthem • Any condition that causes vasodilation

Black
 
Necrosis secondary to vasculopathy from levamisole-contaminated cocaine
	• Necrosis of the skin due to:
	  • Vasculitis (e.g. granulomatosis with polyangiitis)
	  • Thrombosis (e.g. DIC, monoclonal cryoglobulinemia)
	  • Emboli (e.g. ecthyma gangrenosum)
	  • Vasospasm (e.g. severe Raynaud phenomenon)
	  • Vascular compromise (e.g. atherosclerosis, calciphylaxis)
	• Eschar (e.g. anthrax)
	• Cutaneous melanoma
	• Traumatic tattoo (e.g. asphalt)

Blue (ceruloderma)  Dermal melanocytosis	• Dermal melanocytosis (e.g. Mongolian spot, nevus of Ota) • Dermal melanocytoma (e.g. blue nevus) • Cyanosis • Ecchymosis • Venous congestion (e.g. venous malformation) • Drugs/deposits (e.g. minocycline, traumatic tattoo)

Brown
 
Melasma
	• Pigmented lesions
	  • Lentigo
	  • Seborrheic keratosis
	  • Junctional, compound, or congenital melanocytic nevus
	  • Café-au-lait macule
	  • Dermatofibroma
	  • Melanoma
	  • Pigmented AK, Bowen disease
	• Postinflammatory hyperpigmentation – epidermal (see Ch. 67)
	• Melasma
	• Phytophotodermatitis
	• Drug-induced hyperpigmentation (e.g. cyclophosphamide)
	• Metabolic (e.g. Addison disease, hemochromatosis)

Gray  Argyria	• Postinflammatory hyperpigmentation – dermal (e.g. erythema dyschromicum perstans; see Ch. 67) • Drugs/deposits (e.g. argyria, chrysiasis) • Combined melanocytic nevus • Traumatic tattoo • See Blue (above)

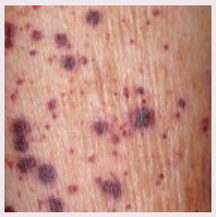
Color	Examples of diseases with this color
Purple (violaceous)  Palpable purpura of cutaneous small vessel vasculitis	• Purpura, non-palpable (e.g. solar purpura) • Purpura, palpable (e.g. small vessel vasculitis) • Vascular neoplasm (e.g. angiokeratoma, angiosarcoma) • Lichen planus • Lymphoma cutis • Pyoderma gangrenosum – border • Morphea – border (lilac)
White  Calcinosis cutis (systemic sclerosis)	• Absence of melanocytes or melanin production (e.g. vitiligo, piebaldism, OCA1A) • Scarring (e.g. scarring in discoid lupus erythematosus) • Vasospasm (e.g. Raynaud phenomenon, nevus anemicus) • Deposits (e.g. calcinosis cutis, gouty tophi) • Macerated stratum corneum – mucosal surfaces (e.g. leukoplakia)
Green  Onycholysis with secondary *Pseudomonas* infection	• *Pseudomonas* infection • Tattoo • Chloroma • Green hair due to copper deposits
Orange–red (salmon)  Pityriasis rubra pilaris with islands of sparing	• Pityriasis rubra pilaris • Mycosis fungoides (sometimes)
Yellow  Xanthelasma	• Solar elastosis • Carotenoderma • Xanthomas (e.g. eruptive, xanthelasma) • Xanthogranulomas • Adnexal tumors and hyperplasias with sebaceous differentiation • Necrobiosis lipoidica • Capillaritis (yellow–brown background) • Deposits/drugs (e.g. tophi, quinacrine)

Table 0.5 Color as a clue to the clinical diagnosis. AKs, actinic keratoses; DIC, disseminated intravascular coagulation; OCA1A, oculocutaneous albinism type 1A.
Some photographs courtesy Jean L. Bolognia, MD; Ronald Rapini, MD; Julie V. Schaffer, MD; Kalman Watsky, MD.

FITZPATRICK SCALE OF SKIN PHOTOTYPES		
Skin phototype	**Skin color**	**Response to UV irradiation**
I	White	Always burns, does not tan
II	White	Burns easily, tans with difficulty
III	Beige	Mild burns, tans gradually
IV	Brown	Rarely burns, tans easily
V	Dark brown	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Table 0.6 Fitzpatrick scale of skin phototypes.

(e.g. the antecubital and popliteal fossae; Table 0.8). However, to complicate matters, there is an "inverse" pattern of psoriasis in which lesions are present in major body folds, i.e. in flexural areas (see Ch. 8). Langer cleavage lines refer to natural skin tension lines used to guide the orientation of surgical excisions. The long axis of oval lesions of pityriasis rosea[19] and erythema dyschromicum perstans may follow these cleavage lines, and this pattern is often most apparent on the posterior trunk.

A *seborrheic* distribution pattern includes the head and neck as well as the upper trunk; it reflects areas rich in sebaceous glands. Seborrheic dermatitis, acne vulgaris, and pityriasis versicolor often have a seborrheic distribution pattern. The term "*photodistribution*"

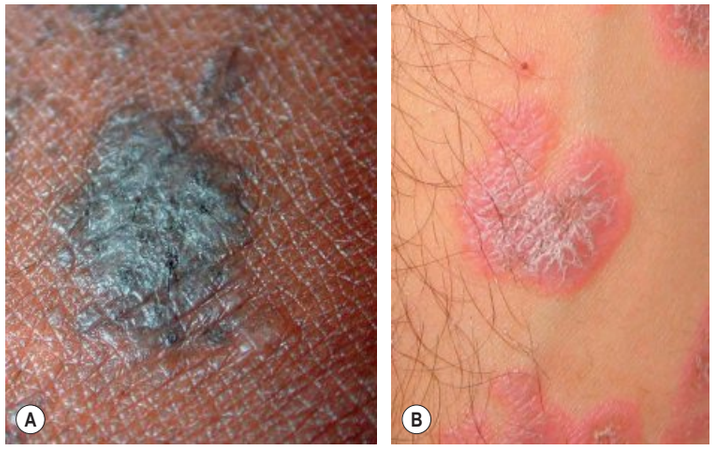


Fig. 0.6 Lichen planus presents differently in darkly pigmented versus lightly pigmented skin. A, B The erythematous to violaceous hue seen in lightly pigmented skin is more muted in darkly pigmented skin and the lesions appear brown–black in color. Wickham striae (lacy white pattern) are more easily seen in **B**.



Fig. 0.7 Retiform purpura and cutaneous necrosis secondary to calciphylaxis. Note the irregular shape of the purpura. *Courtesy Amanda Tauscher, MD.*

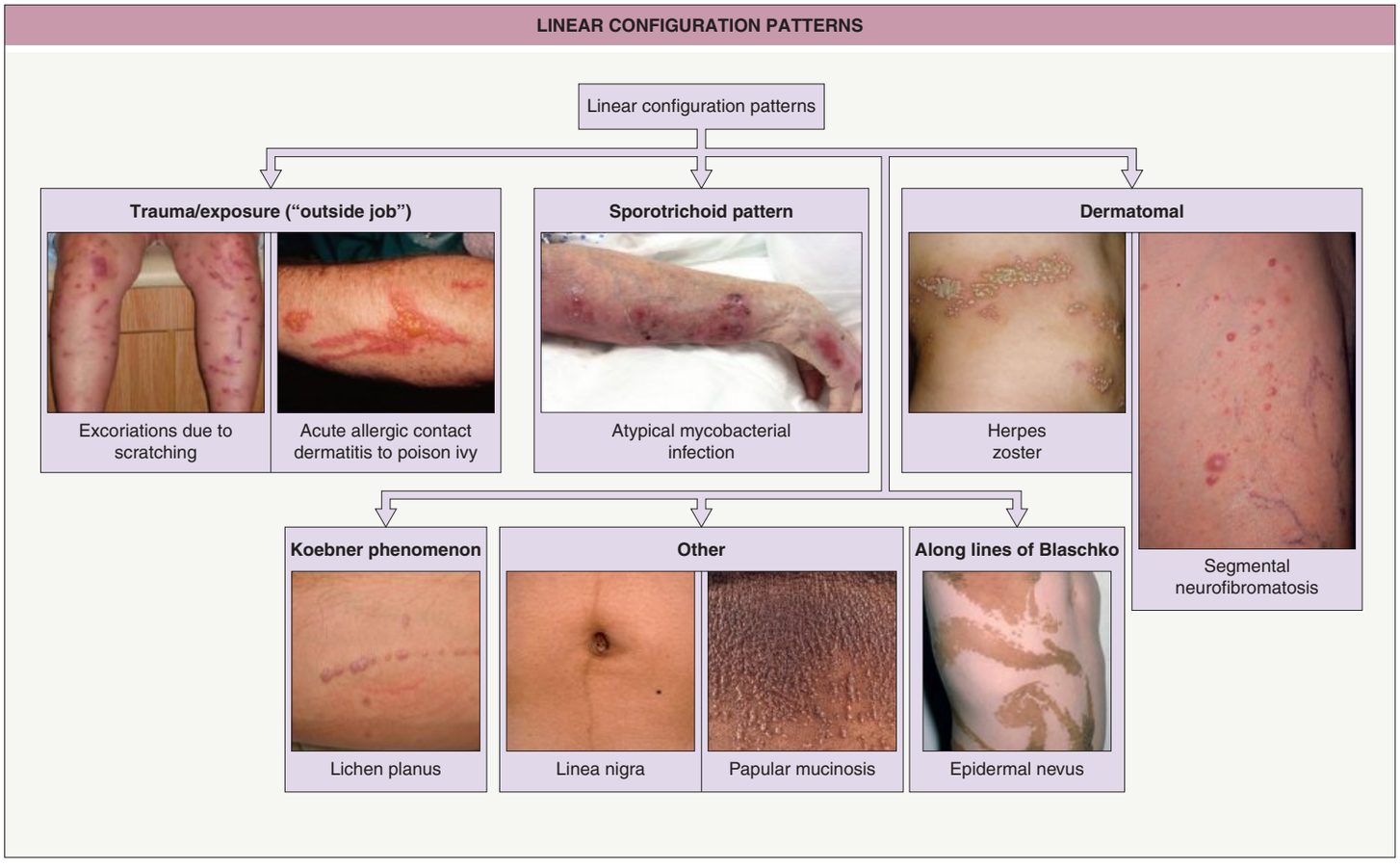


Fig. 0.8 Linear configuration patterns. *Some photographs courtesy Jean L. Bolognia, MD; Edward Cowen, MD; Louis A. Fragola, Jr, MD; Joyce Rico, MD; Kathryn Schwarzenberger, MD.*

CLINICAL ENTITIES THAT COMMONLY DISPLAY THE KOEBNER PHENOMENON (ISOMORPHIC RESPONSE)
• Psoriasis
• Vitiligo
• Lichen planus
• Lichen nitidus
• Cutaneous small vessel vasculitis
• Still disease

Table 0.7 Clinical entities that commonly display the Koebner phenomenon (isomorphic response). This is to be distinguished from *autoinoculation* or pseudo-Koebner phenomenon that is seen with verrucae or mollusca as well as *Wolf isotopic response* where a second skin disease appears at the site of an initial unrelated and often healed skin disease (e.g. granuloma annulare at the site of healed herpes zoster) or *pathergy*.

MAJOR DISTRIBUTION PATTERNS
Disseminated vs localized vs solitary
Unilateral vs bilateral
Symmetric vs asymmetric
Sun-exposed sites vs sun-protected sites
Flexural vs extensor surfaces
Intertriginous/large body folds
Acral (hands, feet, ears, nose)
Palmoplantar
Seborrheic region (head and neck, upper trunk)
Periorificial
Mucosal (mouth, anogenital)
"Linear" – also considered a configuration – see Fig. 0.9

Table 0.8 Major distribution patterns. Occasionally, the pattern represents a *locus minoris resistentiae* (see text).



Fig. 0.9 Koebernization (isomorphic response) of lichen planus secondary to trauma. As a result, the lesions have a linear configuration.



Fig. 0.10 Allergic contact dermatitis to a para-phenylenediamine-based ("black henna") temporary tattoo. The shape of the lesion clearly suggests an exogenous insult/etiology. *Courtesy Colby Evans, MD.*

describes an accentuation of lesions in areas exposed to ultraviolet irradiation. Photodermatoses include polymorphic light eruption, phototoxic drug reactions (e.g. to doxycycline), and subacute cutaneous lupus erythematosus. Of note, sometimes a disorder will display a combination of distribution patterns; for example, in dermatomyositis, lesions can be photodistributed and involve extensor surfaces (e.g. elbows, knees).

In addition to differences in the color of inflammatory lesions, individuals with darkly pigmented skin also have an increased frequency of several cutaneous disorders (see section on Color) and certain types of reaction and distribution patterns[20]. Examples of these reaction patterns include papular eczema and a follicular accentuation of atopic dermatitis and pityriasis versicolor, as well as an annular configuration of seborrheic dermatitis and facial secondary syphilis. With regard to distribution, pityriasis rosea often assumes an "inverse" pattern, in which lesions occur primarily in the axillae and groin rather than on the trunk. Although underlying pathomechanisms are not known, it is important to be aware of their occurrence[20].

Sometimes a distribution pattern is better explained by the phenomenon of *locus minoris resistentiae*, in which certain anatomic sites are more vulnerable than others to a particular disease process[21]. Examples would be cutaneous infections in a lymphedematous limb or asteatotic eczema within a skin graft site. There is also the poorly understood phenomenon of *Wolf isotopic response*, in which a second condition, such as granulomatous dermatitis or leukemia cutis, occurs preferentially in the site of a prior healed process (often herpes zoster; see Table 80.7)[22].

Augmented Examination – Wood's Lamp and Dermoscopy

A Wood's lamp emits primarily ultraviolet A radiation with a peak wavelength of 365 nm. It is often used to assist in the diagnosis of pigmentary disorders and infectious diseases (Table 0.9)[23,24]. A Wood's lamp examination is performed in a dark room, with the lamp held 4–5 inches from the area that is to be illuminated. After the target absorbs the UVA radiation, there is energy loss and as a result, the secondary emission is within the visible range due to its longer wavelength (with less energy). Dermoscopy is discussed in detail later in this chapter.

Temporal Course

Central to any medical history, including that of cutaneous disorders, is the temporal course. The patient should be queried as to duration and relative change in intensity and/or distribution over time. For example, there are some dermatoses that have a cephalocaudal progression over time, such as measles and pityriasis rubra pilaris. Of course, the time course is more prolonged in the latter as compared to the former.

The dermatologist is at an advantage because the skin is so accessible. Information provided by the patient can be readily compared to the physical examination. With experience, a dermatologist can usually determine by observation if cutaneous lesions are acute, subacute, or chronic. As an example, scale (not to be confused with crust) reflects parakeratosis, and due to epidermal transit time, it requires 2 weeks to develop. Intact tense bullae are rarely more than a week old. Lichenification, i.e. thickening of the skin with accentuation of normal skin markings, takes weeks to months to develop. If lichenification is present, the lesion has not appeared acutely, despite what the patient may believe.

In otherwise healthy individuals, there are several diseases whose cutaneous manifestations are often acute in nature, in particular urticaria, morbilliform drug eruption, viral exanthem, acute allergic or irritant contact dermatitis, and pityriasis rosea. This does not mean these skin diseases require emergent management, but rather that the rashes appear abruptly and are distinguished, particularly from neoplasms or chronic dermatoses, by temporal acuity. Of note, sometimes a more serious and potentially life-threatening cutaneous disease may present with skin findings that mimic a more common and less serious disorder, especially early on.

WOOD'S LAMP EXAMINATION OF THE SKIN	
Disorder/infection/colonization	**Fluorescent color/clinical findings**
Pigmentary disorders	
Vitiligo	Chalk-white to dull bluish-white (fluorescence of dermal collagen observed due to a marked decrease or absence of melanin within the epidermis)
Ash leaf spot	Enhancement of hypopigmentation
Hyperpigmentation due to an increase in:	
• epidermal melanin	Enhancement of brown color
• dermal melanin	Difference in color of lesional vs non-lesional skin becomes less obvious
Bacterial infections/colonizations	
Pseudomonas aeruginosa	Green
Corynebacterium minutissimum	Coral red
Cutibacterium (formerly *Propionibacterium*) *acnes*	Orange–red (in comedones)
Fungal infections	
Pityriasis (tinea) versicolor due to *Malassezia* spp.	Yellowish-white, yellow–green, golden, copper–orange
Tinea capitis due to *Microsporum* spp.	Blue–green to yellow–green
Favus due to *Trichophyton schoenleinii*	Blue–white

Table 0.9 Wood's lamp examination of the skin.

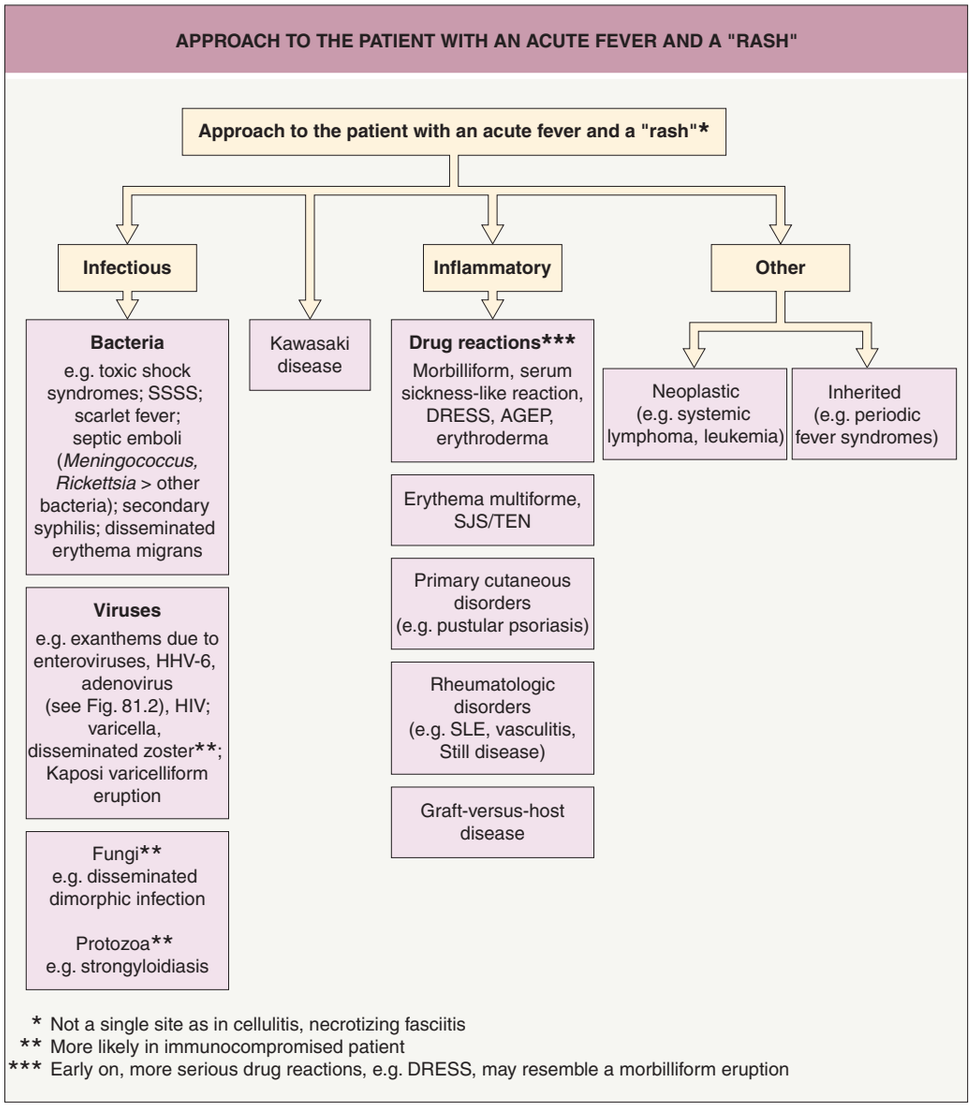


Fig. 0.11 Approach to the patient with an acute fever and a "rash." AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms (also referred to as drug-induced hypersensitivity syndrome [DIHS]); HHV, human herpes virus; HIV, human immunodeficiency virus; SJS, Stevens–Johnson syndrome; SLE, systemic lupus erythematosus; SSSS, staphylococcal scalded skin syndrome; TEN, toxic epidermal necrolysis.

Finally, while emergencies in dermatology are uncommon, there are a few illnesses, particularly those that present with a rash and fever, which are true emergencies and must be recognized promptly and treated accordingly. Examples include Stevens–Johnson syndrome, toxic epidermal necrolysis, Kawasaki disease, meningococcemia (including purpura fulminans), Rocky Mountain spotted fever, necrotizing fasciitis, and endocarditis with cutaneous manifestations. An approach to critical dermatologic emergencies that present with a fever and rash is outlined in Fig. 0.11.

The next two sections of this introductory chapter focus upon basic principles of dermatopathology and dermoscopy, respectively. It is important to remember all diagnostic techniques (unaided clinical examination, histologic examination, dermatoscopy, confocal microscopy, and imaging, including ultrasound [Fig. 0.12]) are complementary. In other words, synergistic strength and clinicopathologic correlation are achieved when the techniques are used in combination. As a corollary, using any one technique, to the exclusion of the others, may be misleading and result in misdiagnosis.

THE ROLE OF DERMATOPATHOLOGY IN CLINICOPATHOLOGIC CORRELATION

Dermatopathology, the study of skin under the microscope, is uniquely related to the study of clinical dermatology, for few other medical specialties place so much emphasis on *both* the clinical and the histologic features of diseases within their realm[25]. However, this union exists not only because of overlapping subject matter, but because dermatology and dermatopathology both rely heavily upon careful observation and pattern recognition. In addition, clinical dermatology represents the "gross macroscopy" of dermatopathology, as clinical examination can be regarded akin to gross examination of biopsy specimens in other organs.

Experienced clinicians may anticipate associated histologic findings as they examine a cutaneous lesion or eruption (e.g. hyperkeratosis and/or parakeratosis when scale is present clinically, or dermal hemorrhage when there is purpura clinically). As a result, a sophisticated differential diagnosis often accompanies a skin biopsy performed by a dermatologist. Moreover, when the microscopic features are clearly delineated in a histopathology report, an experienced dermatologist can utilize clinicopathologic correlation to arrive at a final diagnosis. In a similar fashion, an experienced dermatopathologist can utilize clinical pictures to arrive at a final pathological diagnosis.

The Skin Biopsy

In no other field of medicine is the tissue of interest so readily accessible for histologic analysis. As a result, performing a skin biopsy is an integral component of medical decision-making in dermatology. A skin biopsy may be performed for a multitude of reasons, including:

- uncertainty about the clinical diagnosis
- to investigate a poor response to therapy
- to exclude or investigate the evolution of one condition into another, or
- to investigate symptoms in the absence of clinically recognizable disease.

Regardless of the rationale for performing a skin biopsy, the securing of appropriate tissue involves more than the mere mechanical procurement. Instead, a multistep process is executed, with forethought, precision and care, in order to maximize diagnostic utility[26]. Also, because a skin biopsy is often just a small sampling of a larger process, it may not always be representative of the entire disease state. Inappropriate technique or poor tissue handling may seriously limit the diagnostic yield of a skin biopsy; accordingly, clinicians must have an appreciation of the principles of histologic examination.

Site selection

Often, the first step in performing a biopsy is to identify an unadulterated *primary lesion*. Lesions with obfuscating secondary features, such as those resulting from rubbing or traumatic injury (e.g. lichenification, excoriations) or other superimposed processes (e.g. crusting and impetiginization), should be avoided, unless the purpose of the biopsy is to prove existence of such confounders.

A well-developed, "fresh" lesion is typically chosen for biopsy. Such sampling is premised on an assumption that it will demonstrate the most diagnostic histopathology. Immature lesions may not yet manifest characteristic histopathologic changes, and older lesions may be compromised by secondary features. Of course, there are exceptions to this general principle, such as the sampling of early lesions of cutaneous small vessel vasculitis (<24 hours old) or immunobullous diseases, especially when performing direct immunofluorescence.

While specimens are often taken from the center of a primary lesion, exceptions to this guideline exist, particularly in the case of bullae (see Fig. 29.12) and ulcers or when the histopathologic changes are subtle relative to uninvolved skin. For example, in atrophoderma an incisional biopsy should include both affected and unaffected skin and be sectioned longitudinally, so that subtle differences can be detected (see Ch. 99). In ulcers, nonspecific inflammation of vessels underneath the wound may be misinterpreted as a primary vasculitis, but in a biopsy specimen that includes the surrounding skin, the "vasculitis" disappears a few millimeters away from the ulcer. Biopsying the border of suspected porokeratosis is also recommended in order to best detect the diagnostic cornoid lamella. In sum, selection of a proper biopsy site will always be influenced by knowledge of the suspected underlying pathology.

Biopsy techniques

By employing the appropriate biopsy technique as well as providing adequate clinical data, the quality and amount of information a clinician obtains from a skin biopsy is maximized. A wide range of biopsy techniques exist (see Ch. 146), but those most often performed include: superficial/tangential shave, deep shave ("saucerization"), curettage, punch, and incisional/excisional biopsy (Fig. 0.13). For optimal results, the technique employed must include tissue from the level of the skin or subcutis where the pathologic changes are anticipated, while simultaneously balancing concerns of cosmesis and morbidity. For example, if panniculitis is suspected, a shave would not provide the appropriate tissue to establish or refute such a diagnosis (Table 0.10).

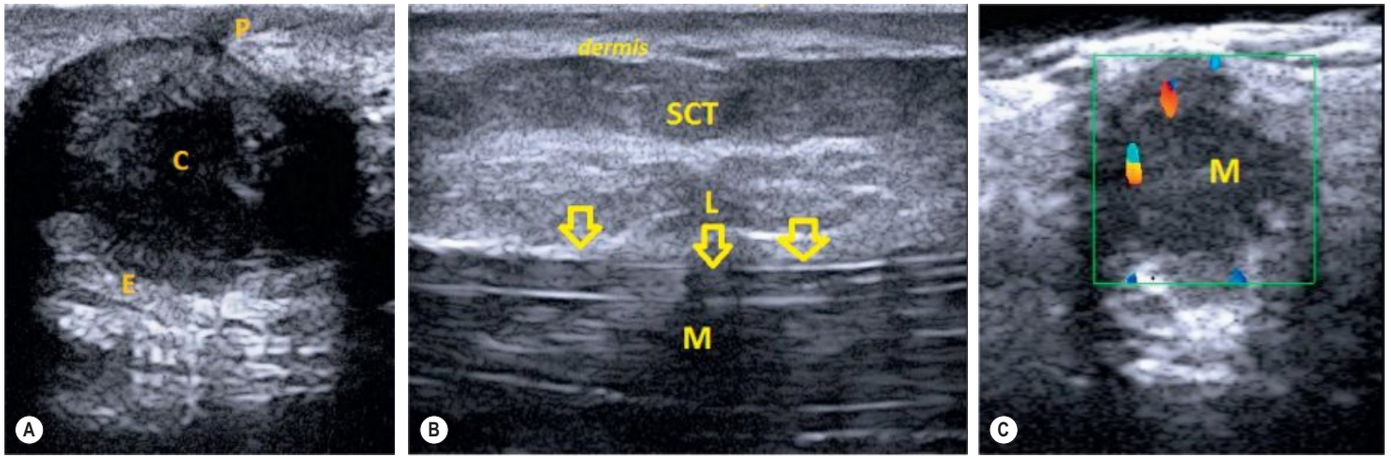


Fig. 0.12 Ultrasound of a cyst, a lipoma, and a cutaneous melanoma metastasis. A A cyst is a well-defined dermal/subcutaneous *hypo*echoic lesion (C) with heterogeneous content; posterior enhancement (E) is a common artefact and an infundibular duct or punctum (P) is usually visible. **B** A subcutaneous lipoma (L) is an ill-defined *hyper*echoic subcutaneous lesion embedded in normal subcutaneous tissue (SCT). Compression of subjacent muscle (M) is evident (arrows). **C** A well-defined, often lobulated, subcutaneous *hypo*echoic lesion (M; green box) with increased intralesional blood flow (multicolored) is characteristic of a metastasis. *Courtesy Fernando Alfageme, MD, PhD.*

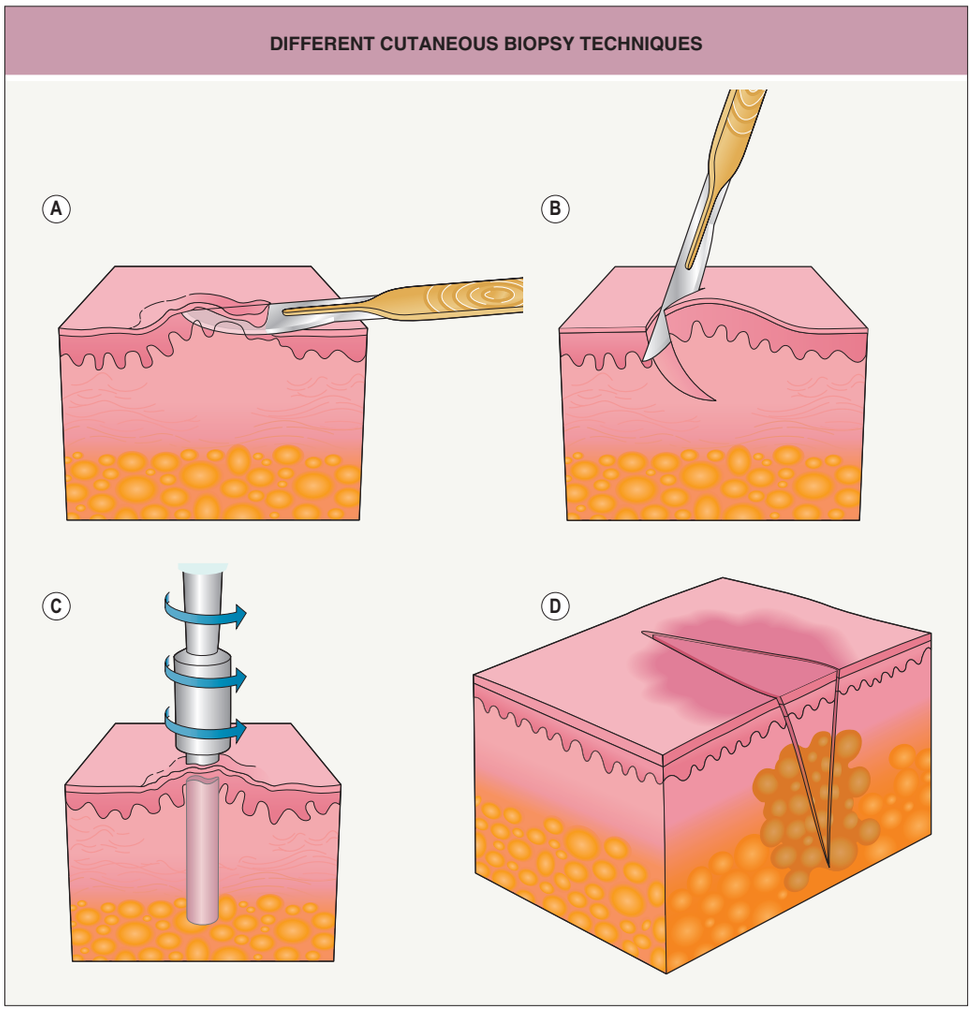


Fig. 0.13 Different cutaneous biopsy techniques. The size, topography, depth and site of the lesion, as well as the clinical differential diagnosis, influence the type of biopsy technique that is performed. **A** Superficial shave biopsy. **B** Deep shave biopsy (saucerization). **C** Punch biopsy. **D** Incisional biopsy. For more details, see text (also see Ch. 146). *Courtesy Suzanne Olbricht, MD.*

OPTIMIZING INFORMATION OBTAINED FROM A SKIN BIOPSY SPECIMEN (BASED UPON PRESUMED DIAGNOSIS)				
Inflammatory diseases				
Disorders (presumed)	***Where and when to biopsy***	***Preferred technique***	***Pitfalls***	***Ancillary techniques to consider***
Vasculitides	• Center of an early lesion • Prefer sites above the knee to avoid poor wound healing or background features due to venous hypertension	Punch or incisional biopsy (depending on the size of affected vessels)	Necrotic or ulcerated lesions may be non-diagnostic	Direct immunofluorescence of lesional skin (early lesions, not older than 24 h)
Livedo reticularis	• Center of the pale areas defined by the surrounding venous plexus network • Corresponds to the site of the ascending arteriole (see Fig. 106.1)	Punch or incisional biopsy	Biopsy of the venous plexus or a biopsy that is too superficial can lead to false-negative results	
Autoimmune connective tissue diseases	• Fully developed lesion • In DLE, biopsy areas of inflammation, not scarred areas	Primarily punch biopsy, unless panniculitis is suspected	• In DLE, biopsies of non-inflammatory scarred areas are often non-diagnostic • Changes of acute LE may be subtle	Direct immunofluorescence of lesional skin
Panniculitides	Early evolving lesion in lobular panniculitides (e.g. lupus panniculitis); fully developed lesion in septal panniculitides (e.g. erythema nodosum)	Large and deep incisional biopsy (must include subcutaneous fat)	• Failure to include enough fat • Late-stage lesions often have nonspecific findings	• Fresh tissue culture and/or PCR (if infectious etiology suspected) • Direct immunofluorescence (if vasculitis suspected)
Autoimmune blistering disorder	• An edematous papule/plaque or an early vesicle is preferred • If only large bullae are present, biopsy the edge of the bulla plus surrounding inflamed skin	Punch biopsy (e.g. 4 mm) or saucerization of: edematous papule/plaque, entire small vesicle, or edge of fresh, intact vesicle/bulla plus surrounding inflamed skin	• Biopsy of late-stage bullae undergoing re-epithelialization may lead to erroneous diagnosis • Late-stage, purulent, crusted, or ulcerated lesions may be non-diagnostic	Direct immunofluorescence of perilesional skin (see Fig. 29.12) or nearby skin (if dermatitis herpetiformis)

Table 0.10 Optimizing information obtained from a skin biopsy specimen (based upon presumed diagnosis).

Continued

OPTIMIZING INFORMATION OBTAINED FROM A SKIN BIOPSY SPECIMEN (BASED UPON PRESUMED DIAGNOSIS)				
Inflammatory diseases (cont'd)				
Disorders (presumed)	***Where and when to biopsy***	***Preferred technique***	***Pitfalls***	***Ancillary techniques to consider***
Alopecias	• Active advancing edge • Areas of perifollicular inflammation	• 4–6 mm punch biopsy oriented parallel to the direction of hair • Include subcutaneous fat	Scarred areas show only end-stage fibrosis	• Horizontal and vertical sectioning of biopsy • Direct immunofluorescence of lesional skin
Infectious diseases	• Prefer mature lesions • If ulcerated, include inflammatory border	Punch biopsy or incisional biopsy (for deep-seated infections)	• Organisms may not be appreciated in histologic sections • Fresh tissue culture and/or PCR often needed	Immunohistochemistry, fresh tissue culture, and/or PCR
Ulcerative dermatoses	Active edge of the ulcer or early lesion if the spectrum of lesions includes a pre-ulcerative stage (e.g. pyoderma gangrenosum)	Punch or incisional biopsy	Avoid center of ulcer where nonspecific changes or possible misleading secondary changes such as underlying vasculitis	Immunohistochemistry, fresh tissue culture, and/or PCR (if infectious etiology suspected)
Pigmentary disorders	Include the edge of the lesion as well as normal skin for comparison	Punch biopsy, rarely incisional biopsy	Subtle findings require clinicopathologic correlation	Special stains and/or immunohistochemistry may be necessary
Urticaria	Include the edge of the lesion as well as normal skin for comparison	Punch biopsy	Small-diameter punch biopsies may lead to false-positive results as retraction of collagen bundles may simulate interstitial edema	Direct immunofluorescence (if urticarial vasculitis is suspected)

Neoplastic processes		
Disease	***Preferred technique****	***Pitfalls***
Melanocytic neoplasms	• Excisional biopsy (preferred when melanoma is strongly suspected) • Saucerization that includes the entire lesion • When major differential diagnosis is macular seborrheic keratosis vs lentigo maligna, broad shave technique as long as no underlying induration • Other techniques may be appropriate depending upon the circumstances and the degree of suspicion	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process
Keratinocytic neoplasms	Punch, saucerization, or excisional biopsy	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process or allow assessment for possible dermal invasion
Dermal neoplasms	Punch, incisional, or excisional biopsy	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process
Deep dermal and/or subcutaneous neoplasms	Excisional or incisional biopsy, depending upon size	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process
Lymphoma cutis and leukemia cutis	• Punch or excisional biopsy • When major differential diagnosis is patch-stage mycosis fungoides vs parapsoriasis, broad saucerization may be performed	• Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process • Artifactual changes, in particular crush artifact and/or desiccation, are common when lymphocytic infiltrates are sampled via a small-diameter punch biopsy and then tweezers are used to remove the specimen and/or the specimen is placed on a gauze†

*On occasion, surgical/clinical/cosmetic constraints may, in the patient's best interest, require consideration and performance of an alternative technique, or even a subtotal biopsy, with acceptance of limitations regarding the diagnostic result.
†Tweezers should not be used to remove the biopsy specimen and the latter should be placed directly into a formalin solution.

Table 0.10 Optimizing information obtained from a skin biopsy specimen (based upon presumed diagnosis). DLE, discoid lupus erythematosus; h, hour; LE, lupus erythematosus; PCR, polymerase chain reaction. *Table created with the assistance of Dr. Stefano Titli.*

Similarly, in the case of a benign exophytic lesion, such as a verruca or skin tag, it would not be expedient, economical, or cosmetically savvy to remove the lesion via an excision with sutured closure. Artifactual changes due to the use of tweezers (crush) or placement of the biopsy specimen on gauze (desiccation) may hinder the dermatopathologist's ability to render an accurate assessment; the cells that are most susceptible to these artifactual changes are those of cutaneous lymphoma and Merkel cell carcinoma.

- **Superficial shave biopsy** – this technique is employed most often when the suspected pathology is chiefly epidermal in nature (e.g. an actinic keratosis, squamous cell carcinoma *in situ*, inflamed seborrheic keratosis), or when there is a desire to remove an exophytic benign lesion (e.g. an intradermal melanocyte nevus) (see Fig. 0.13A). If the findings of interest are suspected to lie in the mid to deep dermis (e.g. discoid lupus erythematosus) then a superficial shave biopsy will not provide diagnostically useful information.
- **Deep shave/saucerization biopsy** – this technique is simply a deeper variant of the superficial shave, where greater angling of the blade removes more of the upper to mid dermis (see Fig. 0.13B). Suspected non-melanoma skin cancer (e.g. basal cell carcinoma, squamous cell carcinoma) is often sampled by deep shave. Evidence suggests that when properly performed, the diagnostic value of a deep shave may rival that of an incisional/excisional procedure[27].
- **Curettage** – this technique is employed to remove superficial lesions that are confined to the epidermis, but it does so in a fragmented and unorientable fashion. In this regard, curettage is

less desirable for diagnostic purposes, and it is not appropriate for pigmented lesions that are suspicious for melanoma or for neoplasms of uncertain etiology.

- **Punch biopsy** – this technique is preferred when the suspected pathology lies within the dermis and when a small sampling is likely to dutifully represent the overall disease process (see Fig. 0.13C). Common punches range from 1.5 to 8.0 mm in diameter, with 4 mm being the most commonly used size for inflammatory diseases. If the sampled lesion can be contained in the punch, then the concern regarding sampling error is rendered moot. It is controversial as to whether punch biopsies, even if performed in a "stacked" fashion, can provide adequate tissue for assessment of deeply infiltrating tumors or panniculitis. Studies suggest that *partial* punch samplings of melanocytic lesions can lead to misdiagnosis or to erroneous staging and therefore should not be performed[28].
- **Incisional/excisional biopsy** – this technique involves the removal of either a portion of a lesion (incisional) or the entire visible lesion (excisional) via a scalpel, using standard surgical techniques (see Ch. 146; see Fig. 0.13D). An incision is often used for examination of the subcutaneous fat (e.g. panniculitis), while an excision is often employed to inspect the entirety of a neoplasm (e.g. a pigmented lesion that is reasonably suspicious for melanoma).

Optimal biopsy techniques based upon the suspected cutaneous disease are outlined in Table 0.10.

Handling of the specimen after biopsy

Skin specimens must be handled carefully upon extirpation. For example, excessive lateral pressure by forceps on small punch biopsy specimens can distort cellular infiltrates, particularly lymphomas and Merkel cell carcinoma, creating so-called "crush" artifact. This type of artifact may compromise the diagnostic utility of a biopsy. These two cell types are also subject to desiccation artifact when the biopsy specimen is placed onto gauze rather than into formalin solution.

For routine histologic analysis, tissue specimens are usually fixed in 10% neutral buffered formalin (NBF) solution, with a volume 10- to 20-fold that of the tissue itself. When culturing for microorganisms, the tissue specimen cannot be placed in 10% NBF; instead it must be placed in a sterile container with a small amount of non-bacteriostatic saline. For direct immunofluorescence (DIF) studies, specimens must be flash-frozen, placed in normal saline (for no more than 24–48 hours), or placed in specialized transport medium (Michel's solution). Recently, honey was shown to be an excellent transport medium for DIF studies[29]. Fixation in paraformaldehyde and glutaraldehyde in a cacodylate buffer is required for electron microscopy.

To obtain the most accurate histopathologic assessment, all biopsy specimens sent to a dermatopathologist should be accompanied by relevant clinical data such as: age and sex of the patient, anatomic site(s) involved, pertinent physical findings, and suspected clinical differential diagnosis. Prior treatments that might impact upon the histologic findings should be disclosed. Any special instructions or requests should be detailed (e.g. inking of an area of special concern in a melanocytic neoplasm, longitudinal sectioning to detect subtle changes in atrophoderma). Inclusion of drawings or clinical photographs (favored) may prove very useful, especially in difficult or complex cases.

Classification of Inflammatory Skin Diseases by Pattern Analysis

First conceived by Dr Hermann Pinkus, but more firmly established by Dr A. Bernard Ackerman[30,31], histopathologic assessment by pattern analysis has emerged as the principal means of classifying inflammatory skin diseases (Fig. 0.14). The number of patterns and the precise descriptors assigned may vary among examiners, but the core principle remains the same – a major pattern is first identified, then additional histologic features are used to further subcategorize the disease process until a final diagnosis is rendered.

The algorithmic approach of pattern analysis is reproducible, and it minimizes subjectivity. However, the method has two important limitations, namely, it is based on artificial disease categories and it cannot include every possible pattern. Furthermore, while pattern analysis clearly narrows the differential diagnosis, a final assessment may require clinical correlation and/or ancillary laboratory testing, imaging, or genetic testing[32].

The histopathologic appearance of skin disease may also vary based upon the age of the lesion, reflecting the "life of a lesion". As noted previously, histologic findings may be altered by previous treatment(s) or by secondary changes such as rubbing, scratching, or infection. Lastly, pattern analysis is not only applicable to inflammatory skin diseases, but is also used for neoplasms, primarily to distinguish benign from malignant.

Ten major patterns defined

Over the past several decades, different classification schema based upon pattern analysis have emerged. The number of patterns in any schema has varied from 9 to 28 or more, but in this introductory chapter, 10 major patterns will be discussed.

Perivascular dermatitis

Perivascular dermatitis is defined and recognized by the presence of an inflammatory infiltrate that is arranged chiefly around dermal blood vessels (Fig. 0.15). Traditionally, perivascular dermatitis has been subdivided into "superficial" and "superficial and deep" variants, and while this division has some diagnostic value, considerable overlap exists. In addition, inflammatory skin diseases can exhibit a spectrum of findings, depending in part upon severity, as well as the duration of an individual lesion (acute vs chronic). Because this pattern is shared by the majority of inflammatory skin diseases, there is a wide range of potential diagnoses.

Once a perivascular pattern is identified (see Fig. 0.14A), the next step is to: (1) determine if there are associated epidermal changes; and (2) characterize the types of inflammatory cell(s) that are present in the infiltrate (e.g. lymphocytes, neutrophils, eosinophils, plasma cells). There are disorders without detectable changes within the epidermis, such as deep gyrate erythemas (see Ch. 19), and when an inflammatory process is beginning or resolving, epidermal changes may be subtle. To further refine the diagnosis, a search is performed to detect subtle *spongiosis* (intercellular edema of the epidermis), subtle *parakeratosis* (aberrant retention of nuclei in the stratum corneum), subtle *interface* and *vacuolar changes* at the dermal–epidermal junction, or extravasated erythrocytes.

Interface dermatitis

This pattern is characterized by inflammation and/or degenerative change(s) at the dermal–epidermal junction (see Fig. 0.14B). Morphologically, this pattern may be further subdivided into primarily *vacuolar* (vacuoles between two adjacent basal cells or between basal cells and the underlying basement membrane with mild or no inflammation; Fig. 0.16) or primarily *lichenoid* (lymphocytes fill the papillary dermis in a band-like fashion and often obscure the dermal–epidermal junction; Fig. 0.17), but there is overlap between these two groups.

It is important to remember that even though an entity has lichenoid features under the microscope (e.g. fixed drug eruption), clinically, it does not have to resemble lichen planus. Also, some degree of lichenoid inflammation may be associated with a variety of benign and malignant neoplasms, such as lichenoid keratoses and melanoma. In these instances, the lichenoid inflammation represents an immunological response to the tumor.

Spongiotic dermatitis

Spongiosis (intercellular edema) is a nonspecific morphologic alteration that is observed in a variety of skin conditions. It manifests as widened spaces between keratinocytes, with elongation of intercellular bridges (see Fig. 0.14C). The degree of spongiosis may vary from microscopic foci to grossly visible vesicles or intraepidermal bullae. There is often associated *exocytosis* of inflammatory cells, with migration from the vasculature into the epidermis. It is important to note that even those spongiotic dermatitides that characteristically develop vesicles, for example acute allergic contact dermatitis, may not do so, i.e. patients have only macules and papules throughout the entire course of their disease.

Spongiotic dermatoses may be further subdivided into acute, subacute, and chronic forms. In acute spongiotic dermatitis, the spongiosis is often severe, sometimes resulting in microvesicles within the epidermis (Fig. 0.18). Parakeratosis, a histologic equivalent of scale, often overlies subacute spongiotic dermatitis. In chronic spongiotic dermatitis, the spongiosis may be more difficult to appreciate, being instead

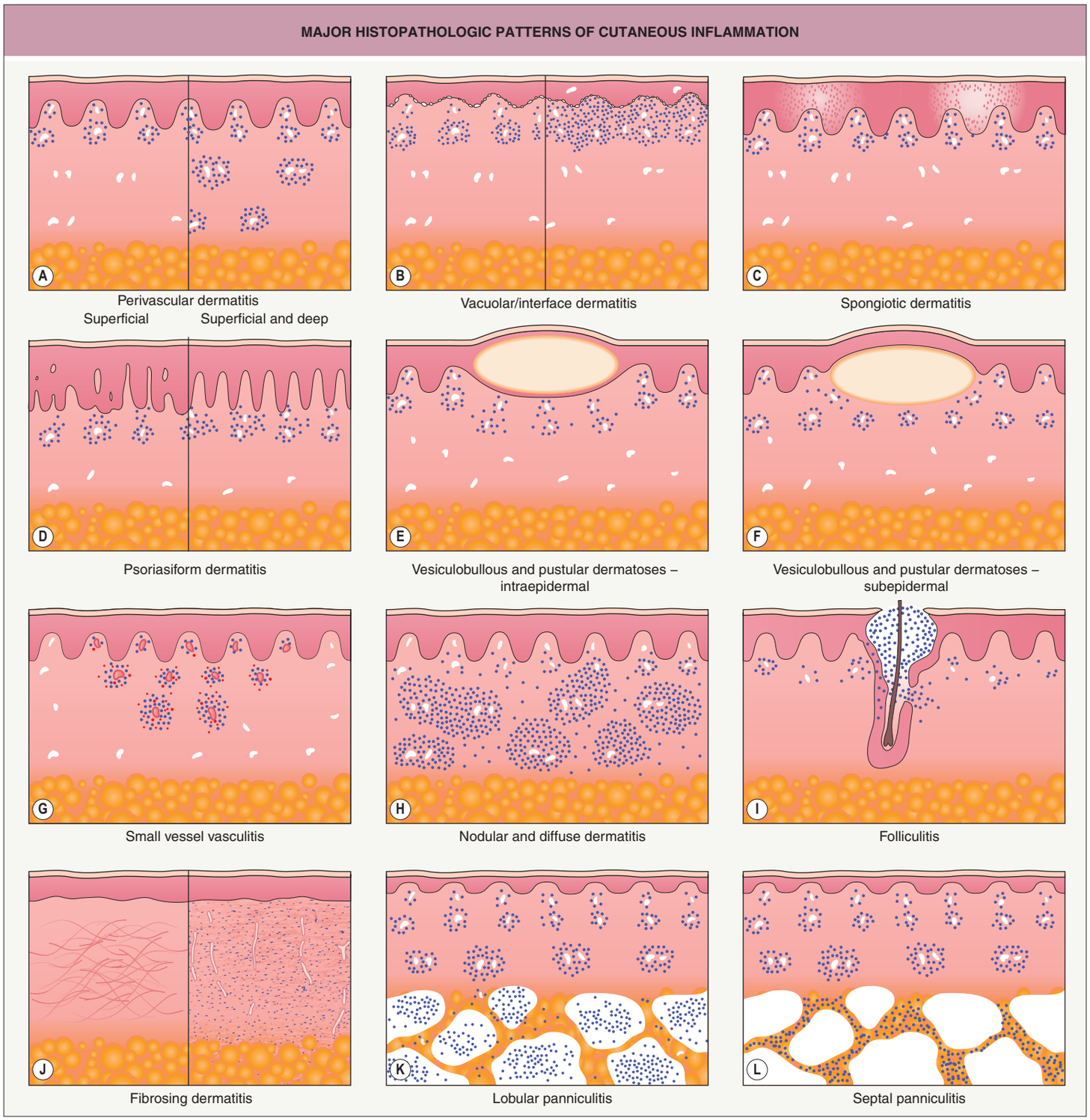


Fig. 0.14 Major histopathologic patterns of cutaneous inflammation (based upon Ackerman's classification). Basic patterns of inflammation result primarily from the distribution of the inflammatory cell infiltrate within the dermis and/or the subcutaneous fat (e.g. nodular, perivascular). It also reflects the character of the inflammatory process itself (e.g. pustular), the presence of injury to blood vessels (e.g. vasculitis), involvement of hair follicles (e.g. folliculitis), abnormal fibrous dermal and/or subcutaneous tissue, and formation of vesicles and bullae. *Adapted from Ackerman AB. Histologic Diagnosis of Inflammatory Skin Diseases: A Method by Pattern Analysis. Philadelphia: Lea & Febiger; 1978.*

overshadowed by epidermal *acanthosis* (thickening of the epidermis). Also, a predominance of certain inflammatory cells in association with spongiosis, such as eosinophils or neutrophils, may serve as a clue to a hypersensitivity component or infectious process, respectively.

Lastly, it is important to recognize that multiple cutaneous disorders with eczematous features, such as allergic contact dermatitis, atopic dermatitis, nummular dermatitis and seborrheic dermatitis, may have histologic evidence of spongiosis, but this pattern is not exclusive to those diseases. In other words, spongiosis may also be seen as a reactive epidermal component of other disorders better classified under another pattern.

Psoriasiform dermatitis

The term "psoriasiform" refers to a regular pattern of *epidermal hyperplasia* (elongation of the rete ridges; see Fig. 0.14D) that is observed not just in psoriasis, but also in a number of other, generally longstanding,

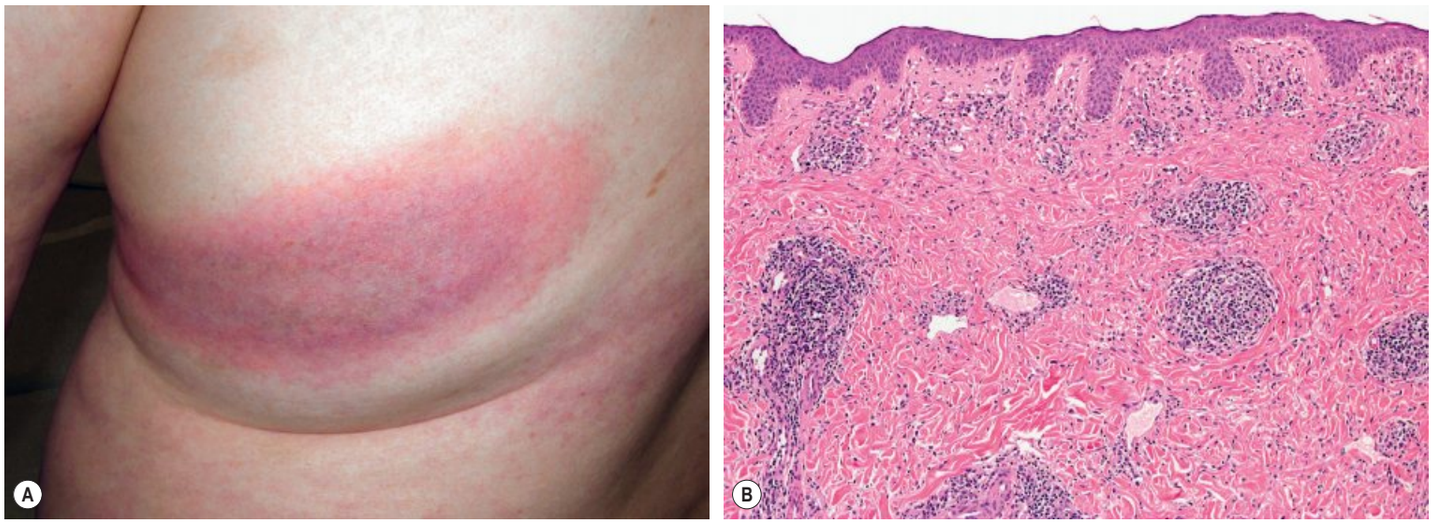


Fig. 0.15 Perivascular dermatitis. A Erythema migrans. **B** Perivascular inflammatory infiltrate composed primarily of lymphocytes. *B, Courtesy Lorenzo Cerroni, MD.*

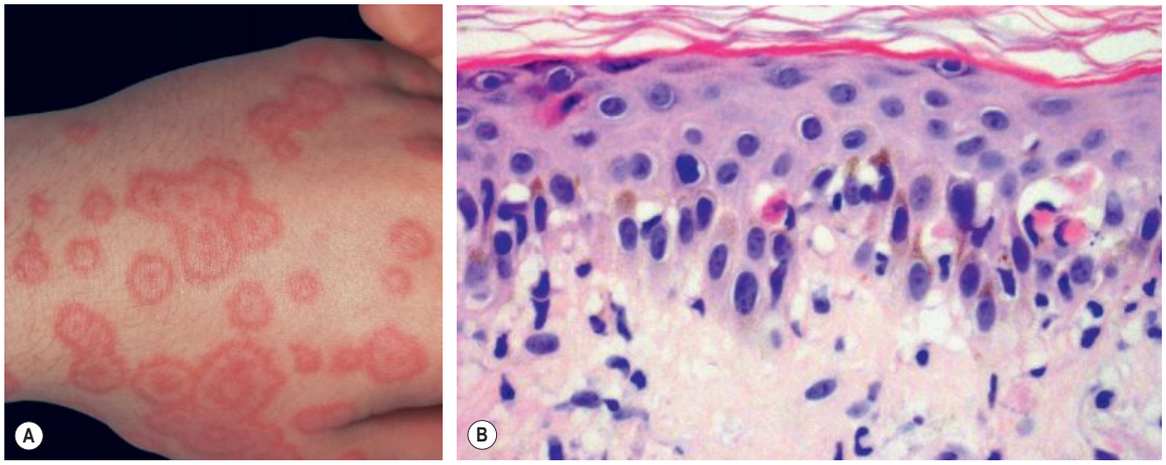


Fig. 0.16 Interface dermatitis, vacuolar type. A Erythema multiforme with target lesions. **B** Vacuolar alteration along the dermal–epidermal junction in association with exocytosis of lymphocytes and several necrotic keratinocytes.

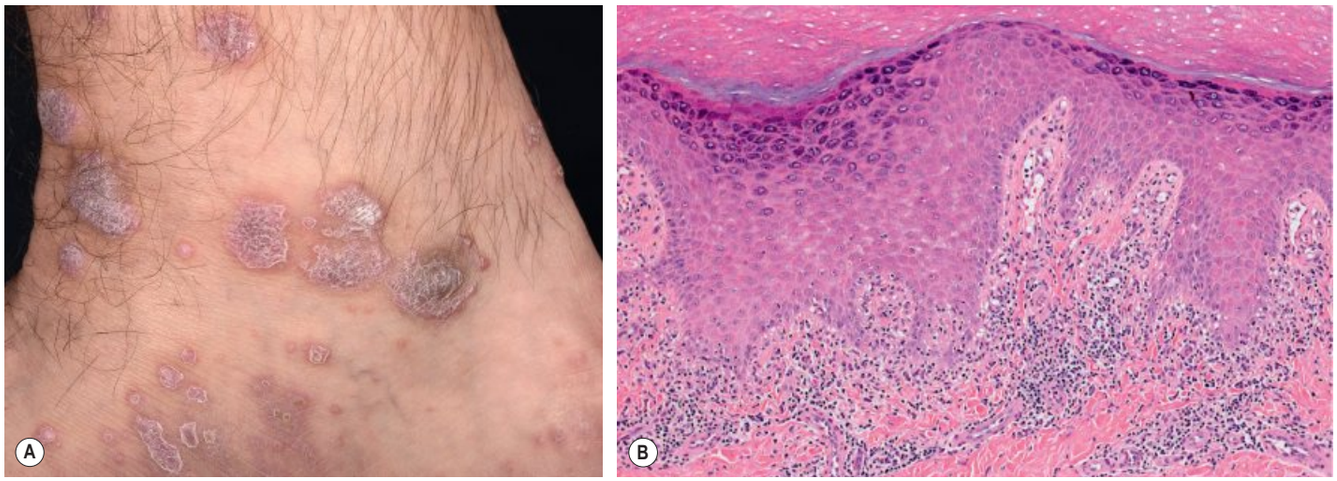


Fig. 0.17 Interface dermatitis, lichenoid type. A Lichen planus. **B** Band-like infiltrate of lymphocytes that obscures the dermal–epidermal junction in addition to jagged epidermal hyperplasia and hypergranulosis. *Courtesy Lorenzo Cerroni, MD.*

conditions. Clinically, this group of psoriasiform disorders is characterized by thickened, scaly papules and plaques (Fig. 0.19). Psoriasiform dermatoses can be further subdivided into those diseases that are exclusively psoriasiform and those that are associated with another pattern (e.g. psoriasiform *and* lichenoid; psoriasiform *and* spongiotic).

Pseudoepitheliomatous hyperplasia represents a related benign condition due primarily to hyperplasia of adnexal epithelium. It may occur in response to a range of insults to the skin, such as chronic rubbing or scratching (e.g. lichen simplex chronicus, prurigo nodularis), or it may appear in inflammatory, neoplastic, and infectious skin diseases (e.g. hypertrophic lupus erythematosus, halogenodermas, chromoblastomycosis).

As with spongiotic dermatitis, psoriasiform dermatitis is a histologic concept, not a specific clinical diagnosis, and its presence mandates consideration of a variety of skin diseases that share this particular pattern.

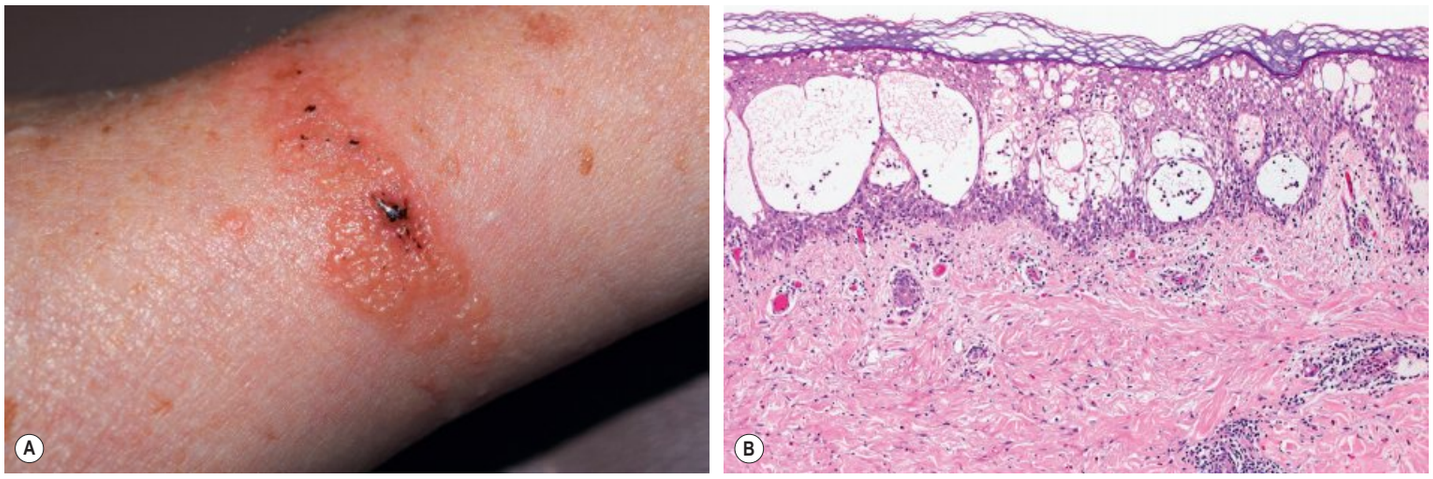


Fig. 0.18 Spongiotic dermatitis. A Acute allergic contact dermatitis from exposure to poison ivy; note the areas of oxidized resin that are black in color. **B** Intercellular edema (spongiosis) and vesicle formation within the epidermis. Lymphocytes are also seen in both the epidermis and dermis. *B, Courtesy Lorenzo Cerroni, MD.*

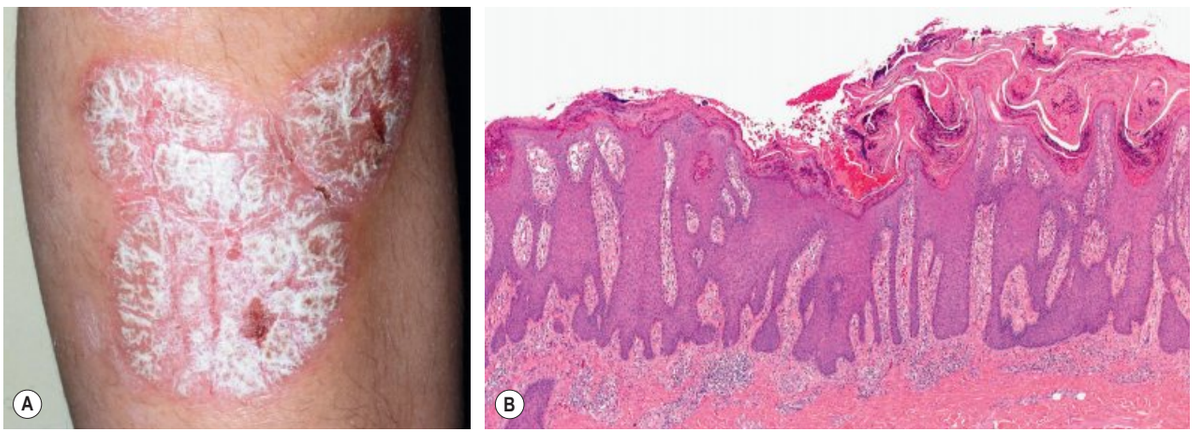


Fig. 0.19 Psoriasiform pattern. A Plaque of psoriasis vulgaris with silvery scale. **B** Regular epidermal hyperplasia and elongated dermal papillae with thin suprapapillary plates and marked confluent parakeratosis. The parakeratosis represents the histologic correlate of the visible scale. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Lorenzo Cerroni, MD.*

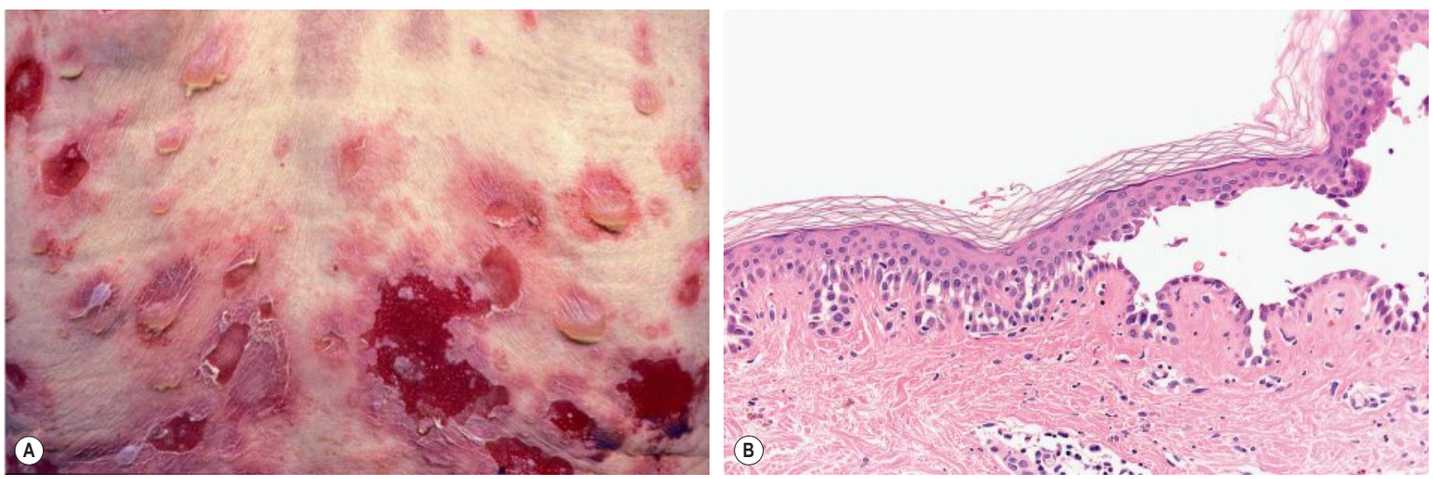


Fig. 0.20 Intraepidermal vesiculobullous dermatosis, acantholytic type. A Pemphigus vulgaris with flaccid bullae and erosions. Note the dependent location of the pustular contents of bullae. **B** The keratinocytes within the lower epidermis have lost their intercellular attachments and have separated from one another, resulting in an intraepidermal blister. *B, Courtesy Lorenzo Cerroni, MD.*

Vesiculobullous and pustular dermatoses

Intraepidermal vesiculation (see Fig. 0.14E)

The concept of intraepidermal vesiculation due to spongiosis has been addressed above, but other disease mechanisms may lead to formation of intraepidermal vesicles or bullae (e.g. acantholysis, ballooning degeneration, prominent basal layer vacuolization, subepidermal edema). *Acantholysis* refers to the discohesion of keratinocytes due to disruption of *desmosomes* (intercellular connections), and this can lead to intraepidermal vesicles or bullae (Fig. 0.20).

Although acantholysis may occur at any level of the epidermis, the location of a blister cavity is often used as a clue to the underlying disorder. For example, superficial (subcorneal) acantholysis may favor pemphigus foliaceus, while acantholysis within the deeper portion of the epidermis is more characteristic of pemphigus vulgaris. *Ballooning degeneration* refers to intracellular edema in response to cytotoxic events (e.g. herpes virus infection, drug reaction), and it is identified by the presence of abundant pale cytoplasm of keratinocytes in the spinous zone. When ballooning is severe, keratinocytes rupture, resulting in reticular degeneration and epidermal necrosis.

Pustule formation (the intraepidermal accumulation of neutrophils) may be seen in a variety of infectious and non-infectious skin diseases. In early pustule formation, neutrophils are scattered within the lower portion of the epidermis, whereas later, accumulation is noted in the upper epidermis and/or beneath the stratum corneum (Fig. 0.21). In a resolving pustule, the neutrophils or their remnants may even appear within a scale-crust in the cornified layer.

In both vesiculobullous and pustular dermatoses, autoimmune and non-autoimmune mechanisms (e.g. subcorneal pustular dermatosis versus IgA pemphigus) may be histopathologically indistinguishable. As a result, direct and indirect immunofluorescence studies are of utility in determining the precise etiology.

Subepidermal vesiculation (see Fig. 0.14F)

In this subcategory of disease, vesicles or bullae form at the junction between the epidermis and dermis (Fig. 0.22), or between the mucosa and submucosa of mucous membranes. While such clefting can be the result of autoantibodies that target specific components of the dermal–epidermal junction (e.g. collagen XVII in bullous pemphigoid, linear IgA bullous dermatosis), it may be the result of an inflammatory or toxic/metabolic insult (e.g. bullous erysipelas or porphyria cutanea tarda, respectively).

The number of inflammatory cells varies within subepidermal blisters, and this variance influences the differential diagnosis. For example, some diseases such as porphyria cutanea tarda are classically pauci-inflammatory, while the majority of cases of bullous pemphigoid contain a significant number of inflammatory cells, particularly eosinophils.

However, because there is histologic overlap among blistering disorders, the final diagnosis must depend upon cumulative information, including direct and indirect immunofluorescence microscopy, ELISA, and, of course, clinicopathologic correlation.

Vasculitis/pseudovasculitis

Vasculitis refers to inflammatory damage to and destruction of blood vessels, which leads ultimately to the deposition of fibrin and/or thrombus formation (see Fig. 0.14G). The histopathologic classification of vasculitis is based upon the size of the vessel involved (small, medium-sized, or large vessel vasculitis; see Ch. 24) as well as the predominant inflammatory cell type that is mediating the damage (neutrophils, lymphocytes, eosinophils, or histiocytes).

The most common form of cutaneous vasculitis is *leukocytoclastic vasculitis* (Fig. 0.23), a process that is mediated by neutrophils and affects chiefly the postcapillary venule. Leukocytoclastic vasculitis begins with deposition of circulating immune complexes in and around blood vessel walls, with neutrophils recruited to these sites of deposition; this ultimately leads to *leukocytoclasia* (nuclear fragmentation) and vessel destruction, with resultant fibrin deposition. In the few longstanding disorders that are mediated by leukocytoclastic vasculitis, such as erythema elevatum diutinum, concentric fibrosis may develop over time.

The concept of *lymphocytic vasculitis* is less well defined and is even a controversial pattern for some authors. However, it is a term used to denote an inflammatory process in which there may be some fibrinoid necrosis of the vessel wall, but the mediating cells

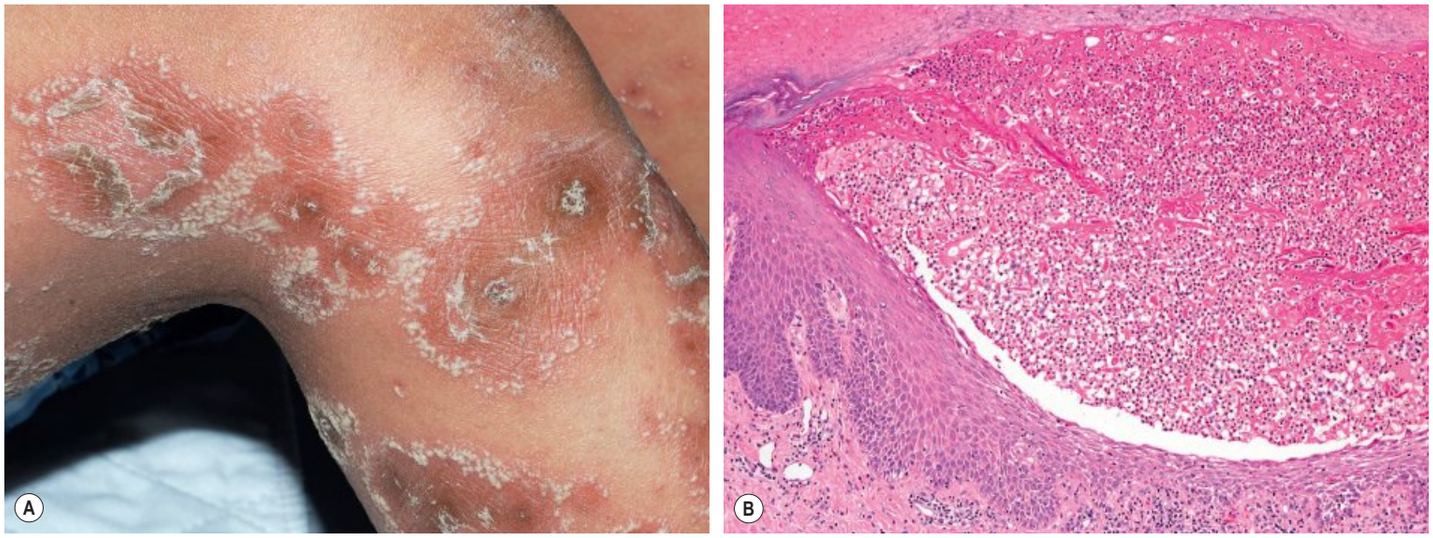


Fig. 0.21 Intraepidermal pustular dermatosis. A Annular variant of pustular psoriasis. **B** Large collection of neutrophils beneath the stratum corneum (subcorneal pustule). *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Lorenzo Cerroni, MD.*

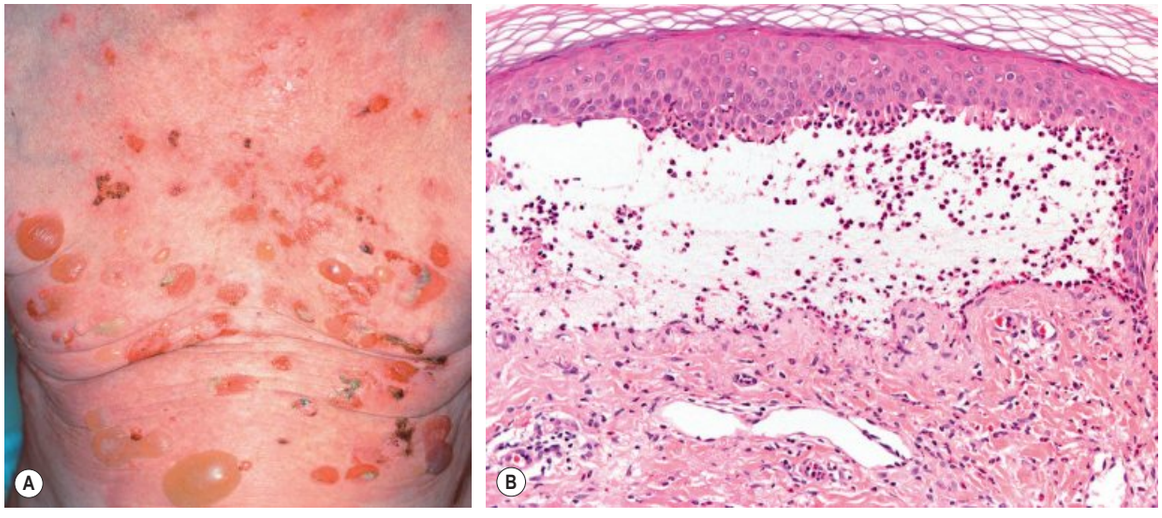


Fig. 0.22 Subepidermal vesiculobullous dermatosis. A Bullous pemphigoid with tense bullae. **B** Subepidermal blister with numerous eosinophils within the blister cavity. *B, Courtesy Lorenzo Cerroni, MD.*

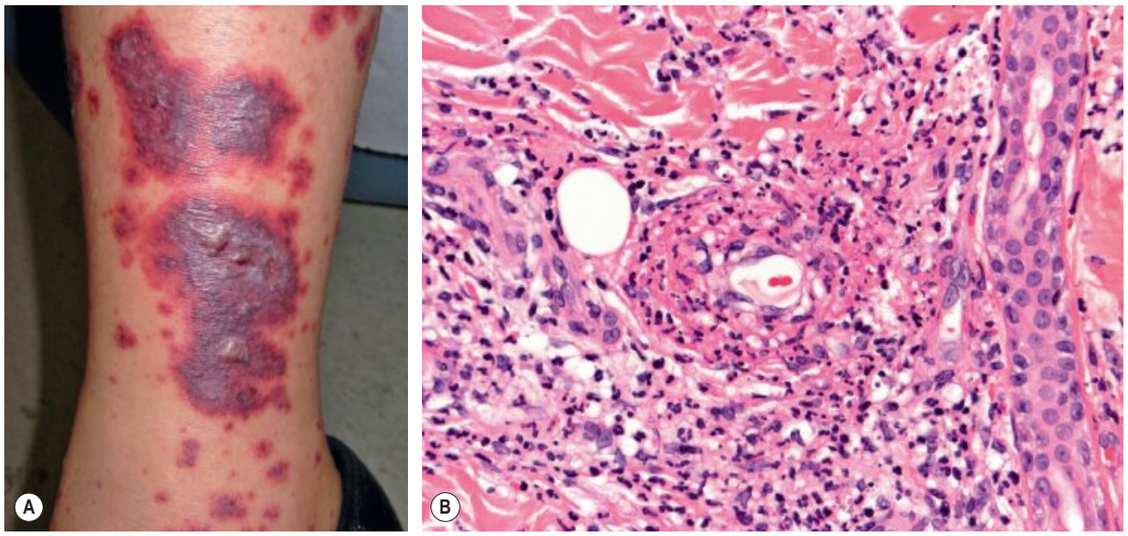


Fig. 0.23 Cutaneous small vessel vasculitis. A Inflammatory palpable purpura of the leg. **B** Perivascular and interstitial infiltrate of neutrophils with nuclear dust (leukocytoclasia). Fibrin within and around the vessel wall and extravasation of erythrocytes is also seen. *B, Courtesy Lorenzo Cerroni, MD.*

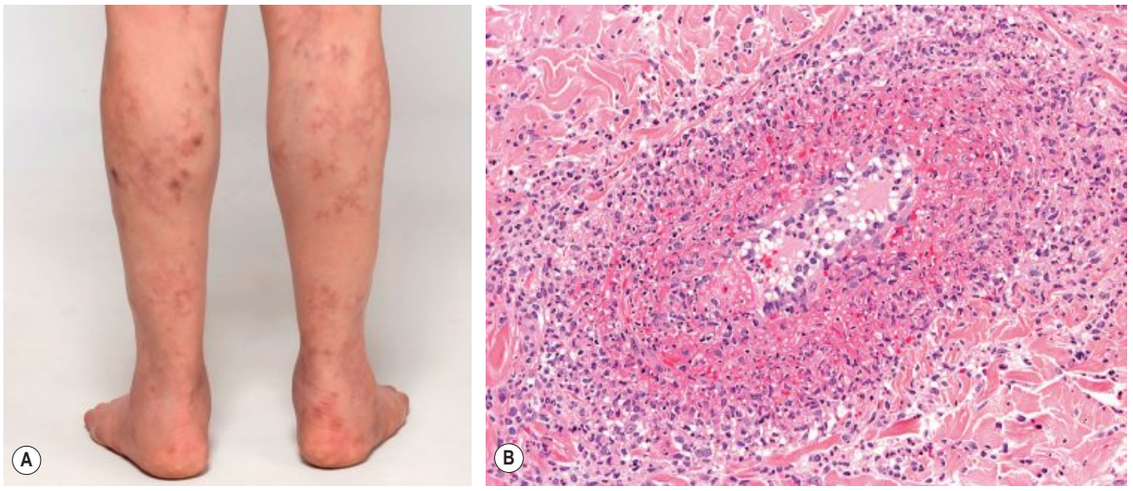


Fig. 0.24 Medium-sized vessel vasculitis. A Nodules of cutaneous arteritis (cutaneous polyarteritis nodosa) admixed with livedo reticularis. **B** Inflammation and destruction of a subcutaneous arteriole with a dense inflammatory infiltrate composed of lymphocytes, histiocytes, and neutrophils admixed with hemorrhage. *A, Courtesy David Wetter, MD; B, Courtesy Lorenzo Cerroni, MD.*

are predominantly lymphocytes. It is postulated as a mechanism in disorders such as pernio, Sneddon syndrome, and pityriasis lichenoides et varioliformis acuta (PLEVA), although the latter lacks fibrinoid necrosis (see Table 24.2).

Granulomatous vasculitis is defined by the presence of histiocytes within and around blood vessel walls, in association with fibrin and/or degenerative and necrotic changes. Like lymphocytic vasculitis, granulomatous vasculitis is a pattern that is observed in a restricted group of diseases which includes granulomatosis with polyangiitis (formerly Wegener granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), and giant cell arteritis (formerly temporal arteritis). Occasionally, it may also represent a later evolutionary stage of another form of vasculitis, either leukocytoclastic or lymphocytic in nature.

In *medium-sized vessel cutaneous vasculitis*, there is involvement of the blood vessels at the dermal–subcutaneous junction and/or within the septa of the subcutaneous fat (Fig. 0.24). For dermatopathologists, cutaneous arteritis (formerly cutaneous polyarteritis nodosa) is the most commonly encountered entity in this disease category. Giant cell arteritis represents a form of large vessel vasculitis, but biopsies of this disorder are rarely performed by dermatologists.

Pseudovasculitis refers to a group of heterogeneous, non-inflammatory conditions that are broadly classified into *non-inflammatory purpura* (disorders that primarily cause hemorrhage) and *occlusive vasculopathies* (conditions that primarily occlude vessels) (see Chs. 22 & 23). Many of these latter disorders involve occlusion of vessels due to emboli, thrombi, vasospasm, intimal–medial hyperplasia secondary to vessel trauma, or non-inflammatory vessel wall pathology. The latter includes calcification, cholesterol emboli, and amyloid deposition.

Nodular and diffuse dermatitis

Nodular dermatitis is somewhat similar to perivascular dermatitis, but the inflammatory infiltrate has enlarged and has coalesced to form one or multiple nodules within the dermis (see Fig. 0.14H). Further expansion of these nodules can fill nearly the entirety of the dermis, yielding a diffuse pattern (Fig. 0.25).

The nodular and diffuse pattern of dermatitis may be further subdivided based upon the predominant inflammatory cell present. When *histiocytes* predominate in one or more foci, the pattern is designated *granulomatous*. This can be observed in a large family of chronic inflammatory diseases due to a wide variety of immunogenic stimuli, including infectious and non-infectious agents. If the granulomatous response is sustained, histiocytes become "epithelioid", i.e. the cells have abundant pink cytoplasm with indistinct borders and plump ovoid nuclei and they appear to touch one another reminiscent of the cells in an epithelium. Granulomas may contain other cells, including neutrophils, eosinophils, plasma cells, lymphocytes, and giant cells. Giant cells form via the fusion of histiocytes and are typically large and multinucleated. There are three major types of multinucleated giant cells whose morphologies differ: Langhans giant cells, foreign body giant cells, and Touton giant cells. None of these giant cells are exclusive to a singular disease, but some disorders are characterized by the conspicuous presence of one or more type(s) (e.g. Touton giant cells in juvenile xanthogranuloma).

Based on the constituent cells and other distinctive features, seven major histopathologic types of granulomas can be defined (Fig. 0.26):

- ***Tuberculoid granuloma*** (see Fig. 0.26A) – comprised of epithelioid histiocytes, including multinucleate forms, surrounded by a dense infiltrate of lymphocytes and plasma cells. Central caseation may be present. The *Langhans type* of multinucleated

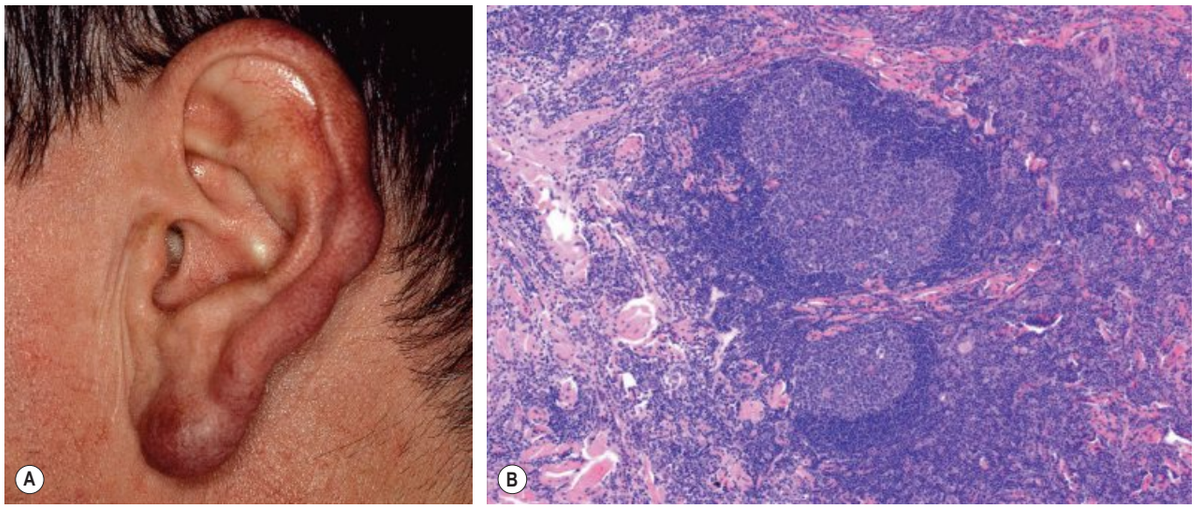


Fig. 0.25 Nodular and diffuse dermatitis, lymphocytic. A Cutaneous lymphoid hyperplasia. The earlobe is a common location. **B** Dense dermal infiltrate containing lymphoid follicles with formation of germinal centers. *B, Courtesy James Patterson, MD.*

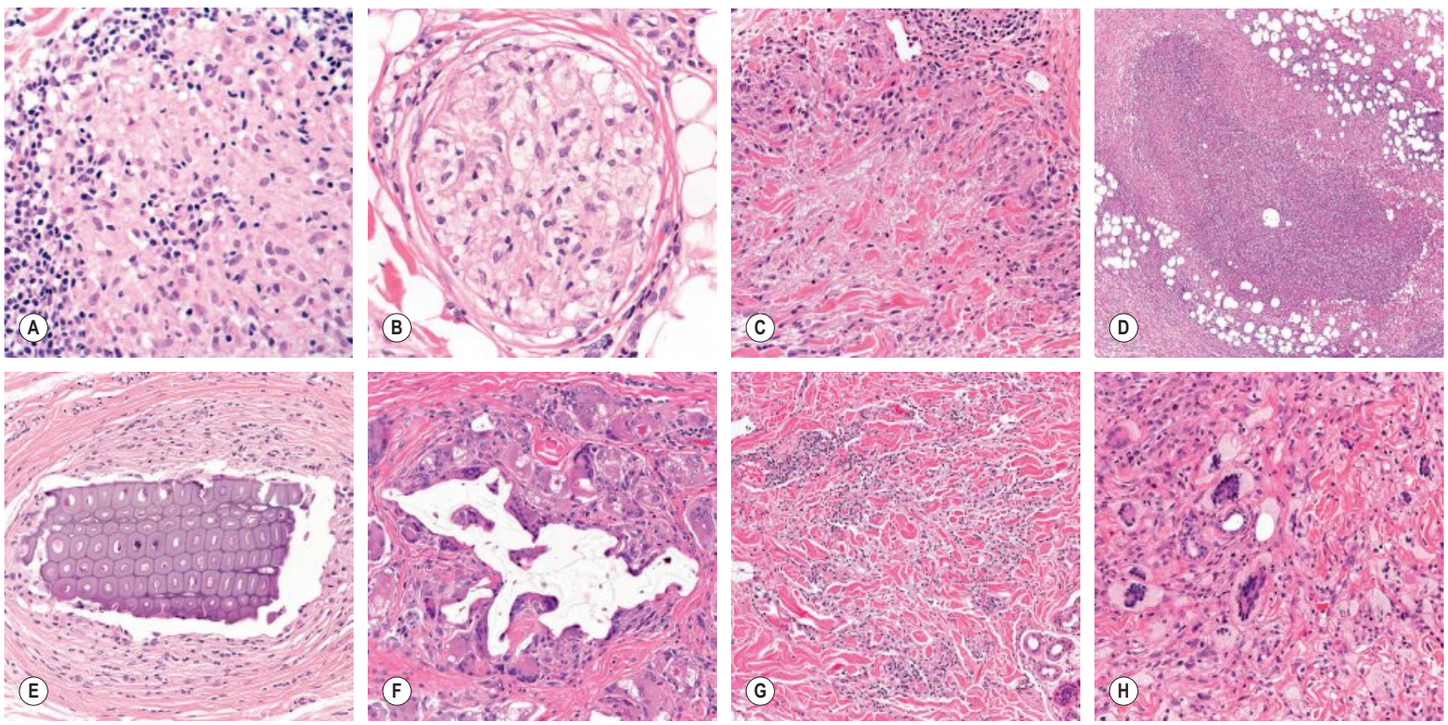


Fig. 0.26 Seven major types of cutaneous granulomas. A Tuberculoid – epithelioid granuloma rimmed by lymphocytes. **B** Sarcoidal – epithelioid granulomas with minimal peripheral lymphocytic infiltrate. **C** Palisaded – granuloma surrounding a focus of degenerated collagen. **D** Suppurative – granulomas with central dense neutrophilic infiltrates. **E** Foreign body – large foreign body representing a portion of a plant with geometric shapes surrounded by histiocytes. **F** Foreign body – irregularly shaped, apparently empty structures (corresponding to implanted aesthetic filler) surrounded by foreign body type giant cells with randomly scattered nuclei in their cytoplasm. **G** Interstitial – epithelioid histiocytes distributed interstitially among the collagen bundles, focally forming small palisades around sclerotic collagen bundles. **H** Xanthogranuloma – numerous foamy histiocytes, lymphocytes, and characteristic Touton giant cells. The latter have a central ring of nuclei and peripheral clear or foamy cytoplasm due to accumulated lipid. *Courtesy Lorenzo Cerroni, MD.*

giant cell, with a horseshoe-like arrangement of nuclei, may be observed in tuberculoid granulomas. This type of granuloma is often, but not invariably, associated with cutaneous infections (e.g. *Mycobacterium tuberculosis*).

- ***Sarcoidal granuloma*** (see Fig. 0.26B) – comprised of aggregates of epithelioid histiocytes, with sparse peripheral lymphocytes or plasma cells (i.e. "naked tubercles"). While multinucleated cells may be identified, no specific type is associated exclusively with sarcoidal granulomas.
- ***Palisaded ("necrobiotic") granuloma*** (see Fig. 0.26C) – comprised of epithelioid histiocytes aligned as a rim around a central area of degenerated collagen with different tinctorial qualities.
- ***Suppurative granuloma*** (see Fig. 0.26D) – comprised of neutrophils within, and sometimes among or surrounding, aggregates of epithelioid histiocytes. Suppurative granulomas may be induced by infectious agents or foreign body material.
- ***Foreign body granuloma*** (see Fig. 0.26E,F) – comprised of epithelioid histiocytes, variable numbers of other inflammatory cells, and large foreign body giant cells. The latter result from the fusion of multiple histiocytes and have nuclei randomly scattered throughout their cytoplasm. Foreign material, either exogenous or endogenous, may be observed within these giant cells and/or in the interstitium.
- ***Interstitial granuloma*** (see Fig. 0.26G) – typified by the predominant distribution of histiocytes between dermal collagen bundles, sometimes forming small palisades around altered collagen bundles, admixed with variable numbers of other inflammatory cells.
- ***Xanthogranuloma*** (see Fig. 0.26H) – comprised of clusters of foamy histiocytes filled with lipids, along with a variable admixture of other inflammatory cells, especially lymphocytes, and Touton giant cells. The latter have a central homogeneous cytoplasm surrounded by a ring of nuclei then a peripheral rim of foamy cytoplasm.

All granulomatous infiltrates, but particularly tuberculoid, sarcoidal and suppurative granulomas, require exclusion of infectious agents and/or foreign material by means of special stains, immunohistochemical stains, tissue culture, PCR, and/or polarization microscopy.

Nodular and diffuse infiltrates comprised chiefly of histiocytes may also be further subcategorized into *Langerhans cell* and *non-Langerhans cell histiocytoses* (see Ch. 91). In Langerhans cell histiocytosis, the cells of interest have reniform (kidney bean-shaped) nuclei and a characteristic immunohistochemical staining pattern (i.e. S100 protein$^+$, CD207$^+$, and CD1a$^+$). Non-Langerhans histiocytes, on the other hand, have a range of cytologic features (vacuolated, spindle-shaped, foamy, scalloped, oncocytic) as well as multiple admixed multinucleated giant cells (Touton type, Langhans type, foreign body type). Sometimes, the histiocytes and giant cells display a homogeneous "ground glass" cytoplasm; these cells are generally S100 protein$^-$, CD1a$^-$, CD68$^+$, and CD163$^+$. The varying histopathologic features of the non-Langerhans histiocytoses may possibly be related to the actual physiologic function of histiocytes within the granuloma[33].

Lastly, *xanthomas* are characterized by the accumulation of *lipophages* (foamy histiocytes filled with lipid) within the dermis (see Ch. 92). The lipid content may impart a yellowish hue to the lesions (Fig. 0.27). Cutaneous xanthomas can take various forms, including widespread papules (*eruptive*), nodules (*tuberous* or *tendinous*), and plaques (*xanthelasma*, *palmar*). Nowadays, intracytoplasmic lipids can be demonstrated in formalin-fixed, paraffin-embedded tissue via immunohistochemical staining with anti-adipophilin antibody. Adipophilin (perilipin-2) is associated with lipid droplets and, unlike the lipid itself, is preserved during tissue processing.

Folliculitis/perifolliculitis

Folliculitis (inflammation of a hair follicle) is defined by the presence of inflammatory cells in the wall and lumen of a hair follicle (see Fig. 0.14I); perifolliculitis refers to the presence of similar cells in the adjacent dermis. Folliculitis may be due to infections (bacterial, fungal, viral, *Demodex* mites), drugs, occlusion, or unknown etiologies (e.g. eosinophilic folliculitis).

The classification of folliculitis (and perifolliculitis) can be made on the basis of the primary inflammatory cell (lymphocytes, neutrophils, or eosinophils), the nature of the underlying pathologic process (e.g. dermatophyte infection), the temporal course (acute versus chronic), and the site of involvement along the length of the hair follicle. If the inflammatory process is severe and/or if it irreversibly damages epithelial stem cells, located in the bulge region of the follicle, permanent "scarring alopecia" may result (Fig. 0.28).

Fibrosing/sclerosing conditions

Fibrosing conditions include a wide spectrum of disorders that result from altered production of collagen, typically related to injury or an autoimmune connective tissue disease (see Fig. 0.14J). Histopathologically, the pattern is characterized by either: (1) abnormal fibrous dermal (and sometimes subcutaneous) tissue with an increased number of fibroblasts and increased, but rather unremarkable, collagen

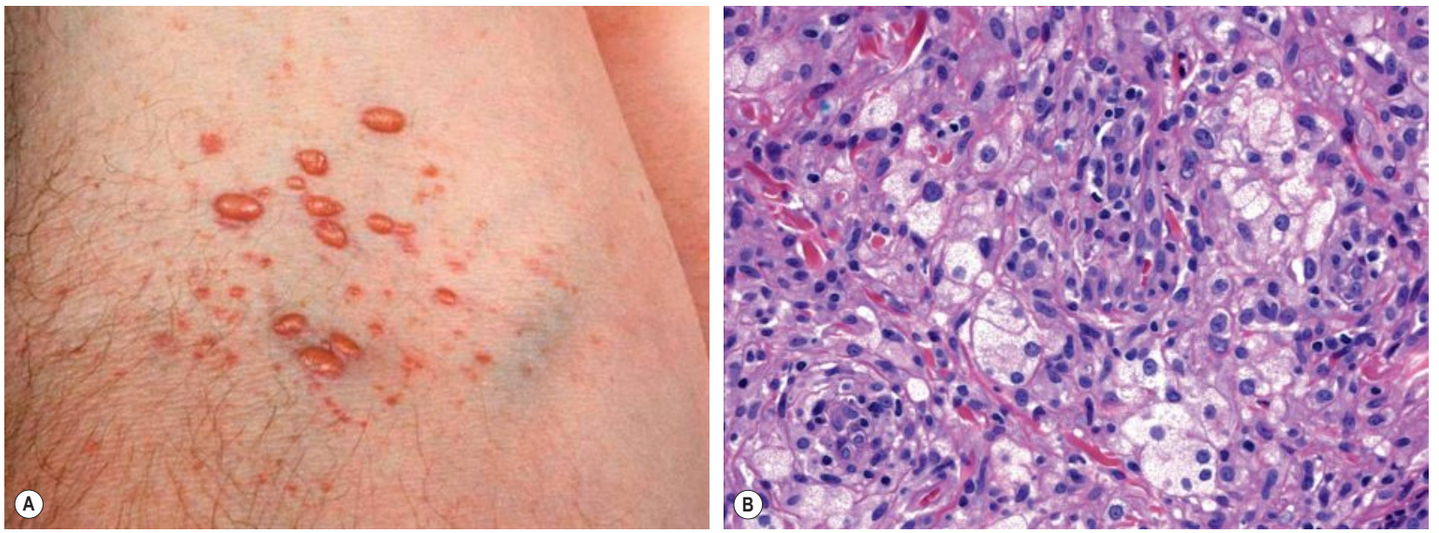


Fig. 0.27 Xanthomas. A Yellow–pink eruptive xanthomas. **B** Lipid-laden macrophages with foamy or vacuolated cytoplasm are present within the dermis. *B, Courtesy James Patterson, MD.*

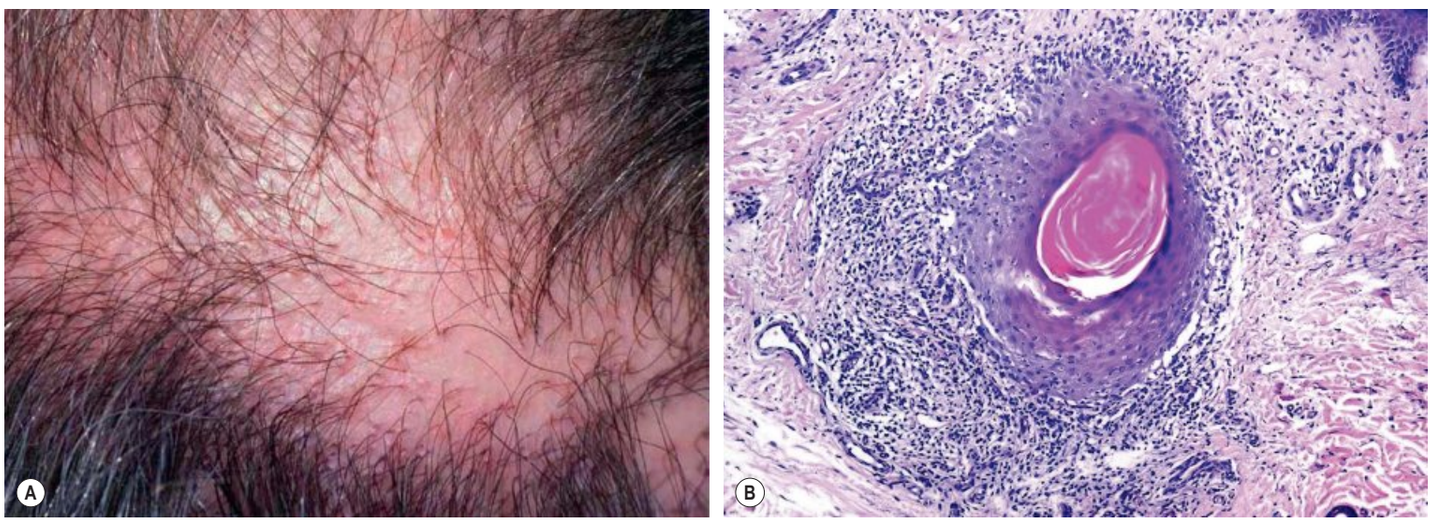


Fig. 0.28 Scarring alopecia. A Lichen planopilaris with areas of scarring alopecia and red–violet rims of inflammation around hair follicles. **B** Band-like lymphocytic infiltrate surrounding a hair follicle, with vacuolar alteration of basilar outer root sheath epithelium.

(*fibrosis*); or (2) homogenized, abnormally enlarged and eosinophilic collagen with a paucity of admixed fibroblasts (*sclerosis*). An example of the former is nephrogenic systemic fibrosis, while an example of the latter is morphea (Fig. 0.29) or systemic sclerosis. These two patterns represent the ends of the spectrum and overlap can occur.

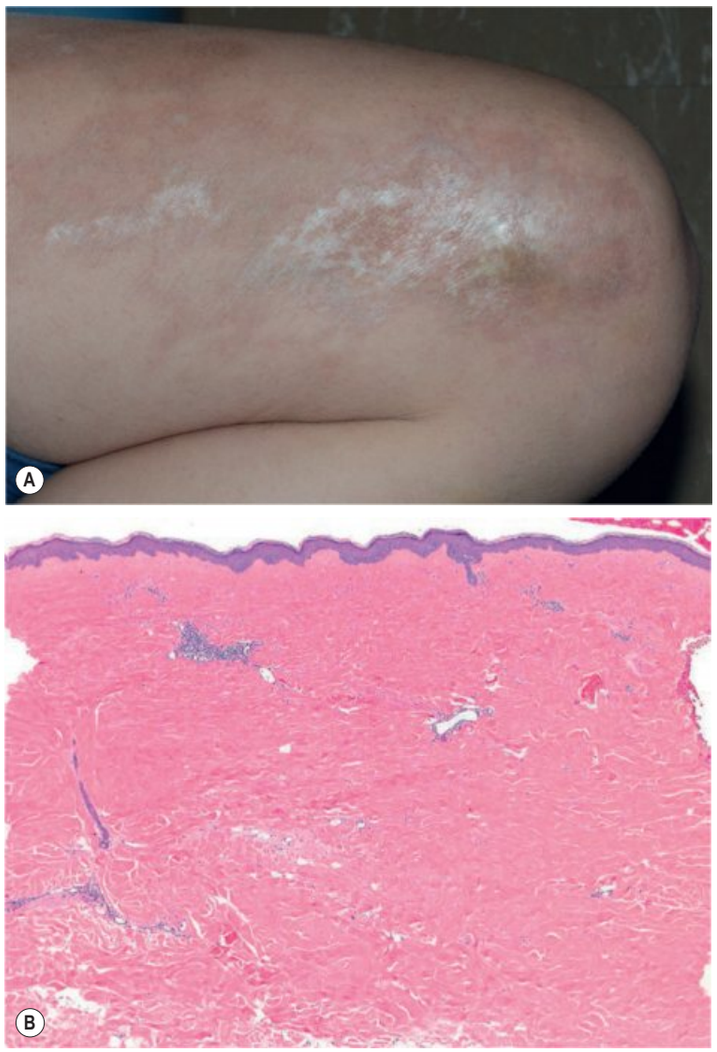


Fig. 0.29 Sclerosing disorder. A Linear distribution of coalescing sclerotic dyschromic plaques on the thigh; note the lilac-colored border. **B** Thickened and hyalinized collagen bundles, loss of adnexal structures and minimal inflammatory cell infiltrate. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Lorenzo Cerroni, MD.*

Panniculitis

Panniculitis represents inflammation of the subcutis (see Fig. 0.14K,L) and it encompasses a wide range of disease processes (see Ch. 100). The diagnosis of panniculitides is difficult for clinicians and for dermatopathologists because the clinical presentation is often nonspecific and the histopathologic changes may vary over time and/or the changes may be nonspecific. Adding to the challenge, biopsy specimens are often inadequate, due to their being too superficial in nature, too narrow in breadth or too badly crushed by forceps, to render a definitive diagnosis.

An important first step in the subdivision of panniculitides is determination of the predominant location of the cellular infiltrate (Figs. 0.30 & 0.31). That is, does it chiefly affect the fat lobules or the septa between the fat lobules? Second, there should be an assessment as to whether a coexisting vasculitis is present or absent. If a coexisting vasculitis is detected, the size and type of the vessels affected must be determined.

With panniculitides, it is important to note the type and quality of the inflammatory infiltrate, as well as peculiarities in the pattern of fat necrosis. Early in the course of erythema nodosum, the most common panniculitis, the infiltrate may include acute inflammatory cells (neutrophils in particular), but in later stages, the infiltrate is composed primarily of chronic inflammatory cells (lymphocytes, histiocytes; see Fig. 0.30). If mononuclear cells are present, the presence or absence of cytologic atypia should be assessed, as subcutaneous panniculitis-like T cell lymphoma may mimic an inflammatory panniculitis. Lastly, peculiarities of fat necrosis, such as the hyaline changes in lupus panniculitis, the basophilic saponification in pancreatic panniculitis (see Fig. 0.31), or the pseudomembranous degeneration in lipodermatosclerosis, should be appreciated.

As is the case for granulomatous infiltrates, panniculitis requires a low threshold for performing special stains to exclude an infectious etiology and polarized light examination to identify foreign material.

Invisible dermatoses

Occasionally, one encounters a dermatosis that lacks an immediately recognizable pattern, and these types of cases are collectively referred to as "invisible dermatoses" (Table 0.11). From the perspective of the dermatopathologist, these invisible dermatoses represent cases where disease appears to exist clinically, but the histologic examination is rather unremarkable with conventional hematoxylin–eosin staining (i.e. the microscopic findings differ minimally from those of normal skin)[34].

Among the "invisible dermatoses" are: (1) diseases with subtle pathologic changes and diseases that require special stains to visualize the diagnostic pathology (e.g. disorders of elastic and collagen tissue without significant fibrosis or sclerosis) (Fig. 0.32); (2) diseases with focal pathologic processes requiring serial tissue levels to identify diagnostic features (e.g. cutaneous arteritis); and (3) diseases that require precise clinical information and/or strict clinical correlation to make the diagnosis (e.g. vitiligo, melasma, telangiectasia macularis eruptiva perstans).

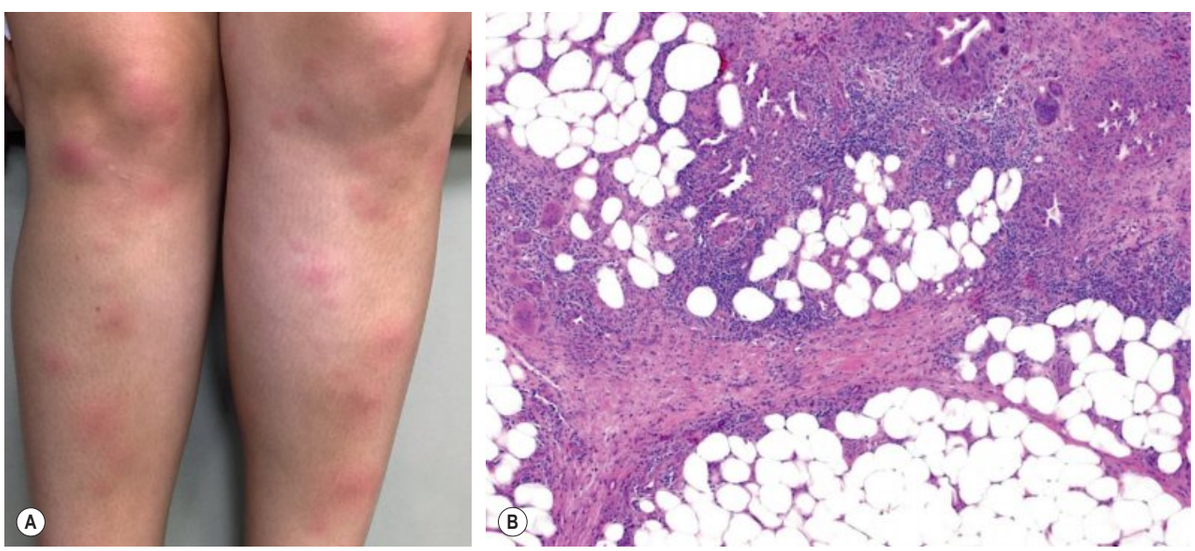


Fig. 0.30 Septal panniculitis. A Multiple pink to pink–violet nodules of erythema nodosum on the shins, admixed with healing bruise-like areas. **B** Predominantly septal granulomatous infiltrate with formation of characteristic Miescher granulomas. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy James Patterson, MD.*

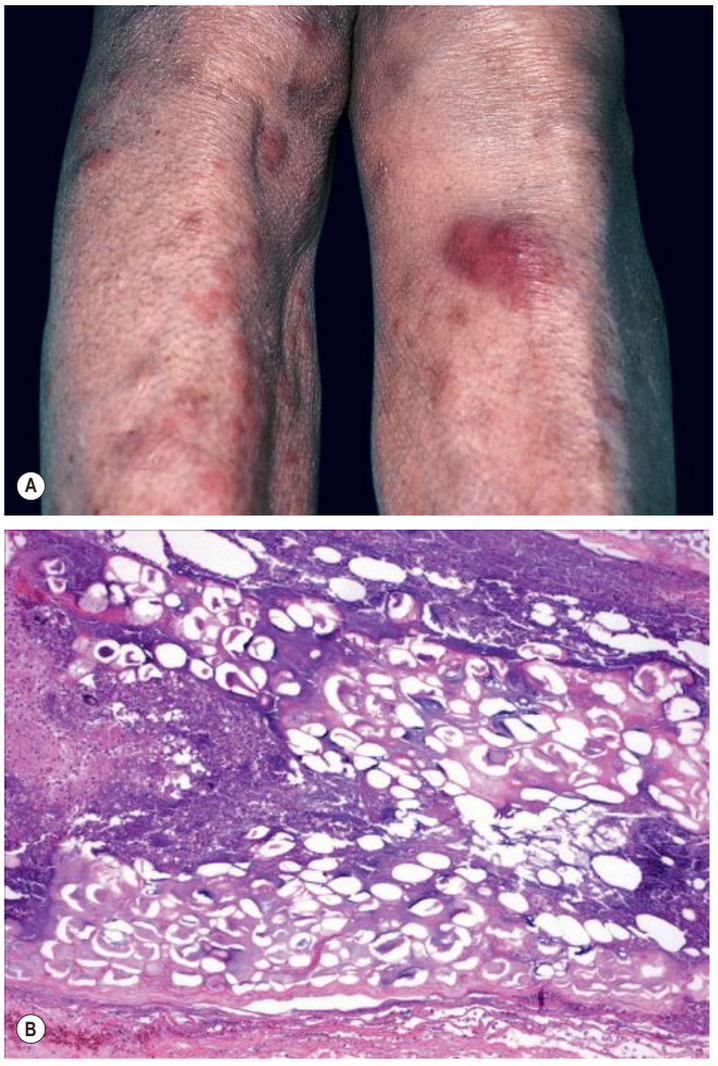


Fig. 0.31 Lobular panniculitis. A Pancreatic panniculitis. **B** Suppurative lobular panniculitis with characteristic enzyme-induced fat necrosis. *A, Courtesy Kenneth Greer, MD; B, Courtesy James Patterson, MD.*

INVISIBLE DERMATOSES		
Microanatomic site	**Abnormality**	**Example dermatoses**
Stratum corneum, granular cell layer	Superficial infections	• Pityriasis (tinea) versicolor • Dermatophytosis • Erythrasma • Pitted keratolysis
	Keratinization disorders	• Ichthyosis • Disseminated superficial actinic porokeratosis
Basilar layer of epidermis	Pigmentation disorders	• Vitiligo • Café-au-lait macule • Melasma
Superficial dermis	Infestations	Onchocerciasis
	Mast cell infiltration	Telangiectasia macularis eruptiva perstans
	Deposition of endogenous substances	Macular amyloidosis
Superficial and deep dermis	Deposition of exogenous substances	Argyria (basement membrane of epithelial structures)
	Deposition of endogenous substances	Systemic amyloidosis (when subtle)
	Collagen abnormalities	• Collagenoma • Atrophoderma
	Elastic tissue abnormalities	• Nevus elasticus • Anetoderma (non-inflammatory) • Mid-dermal elastolysis
Absence of normal epithelial structure	Deficiency of eccrine sweat glands	Hypohidrotic ectodermal dysplasia

Table 0.11 Invisible dermatoses.

Because the histopathologic changes in "invisible dermatoses" are subtle and vexing, careful analysis is recommended. This includes careful searching for diagnostic pathology at all levels of the skin (cornified layer, epidermis, papillary dermis, reticular dermis, hypodermis, adnexa) and the use of special stains or immunohistochemical stains. Lastly, it should be remembered that causes of a seemingly invisible dermatosis may include poor selection of the biopsy site.

Deposition of Materials within the Skin

Occasionally, materials not normally present in the skin are deposited, either by exogenous or metabolic insult, and this can be appreciated histologically. In some patients, there is aberrant deposition of endogenously produced materials, such as uric acid in gouty tophi or light chain-derived amyloid due to an underlying plasma cell dyscrasia, whereas in others, exogenous material has been purposefully or accidentally inoculated into the skin (e.g. cosmetic filler material, tattoo pigment). These materials may accumulate within the dermis, the subcutaneous fat, or both. Deposits of some materials, such as the silver in patients with argyria, may be limited to cutaneous adnexa. Use of polarized light or darkfield microscopy (where light enters tissue at an angle that is not perpendicular to the slide) may be of use in identifying foreign material.

Some deposits engender a granulomatous inflammatory reaction (see Ch. 94), while others evoke no appreciable reaction at all. Deposited material is usually visualized during microscopic examination, but it may be removed during processing (e.g. siliconosis), leaving only characteristic "empty spaces" to suggest its clinical presence. Special stains may be helpful for precise identification, depending upon the suspected nature of the material. Sometimes mass spectrometry is required.

Histologic Stains

The various stains are characterized by their affinity to different pH values within tissues or to different chemical structures. The standard stain in dermatopathology is *hematoxylin and eosin*, referred to as "H&E". This stain yields a predictable pattern, with hematoxylin marking basophilic structures a blue–purple color (cellular nuclei and the granular layer of the epidermis) and eosin marking eosinophilic structures a pink–red (cytoplasm, collagen, muscle, nerve, and fibrin).

H&E staining alone enables the histopathologic diagnosis of many skin diseases, but some disorders require additional special stains to facilitate a diagnosis[35]. For example, elastic tissue, unless significantly altered by ultraviolet radiation or calcium deposits, does not stain with H&E, and special stains such as orcein or Verhoeff–van Gieson are required to identify alterations in these fibers (e.g. in anetoderma; see Fig. 0.32C,I). Similarly, special stains exist to screen for the presence of infectious agents, such as the Brown–Brenn stain (a modified tissue Gram stain) for bacteria, the periodic acid Schiff (PAS) or Grocott methenamine silver stain for fungus, and the Ziehl–Neelsen or Fite-Faraco stain for mycobacteria (see Fig. 0.32F,G). Additional special stains may be utilized to determine the type of infiltrating cell, such as the Giemsa or chloroacetate esterase stain for mast cells. Table 0.12 lists the more commonly employed histochemical ("special") stains used in dermatopathology.

Immunohistochemical Testing

Immunohistochemistry (IHC) is the use of immunologic techniques to identify cellular antigens (proteins) that are not visible in sections stained with H&E. It exploits the principle of antibodies binding specifically to

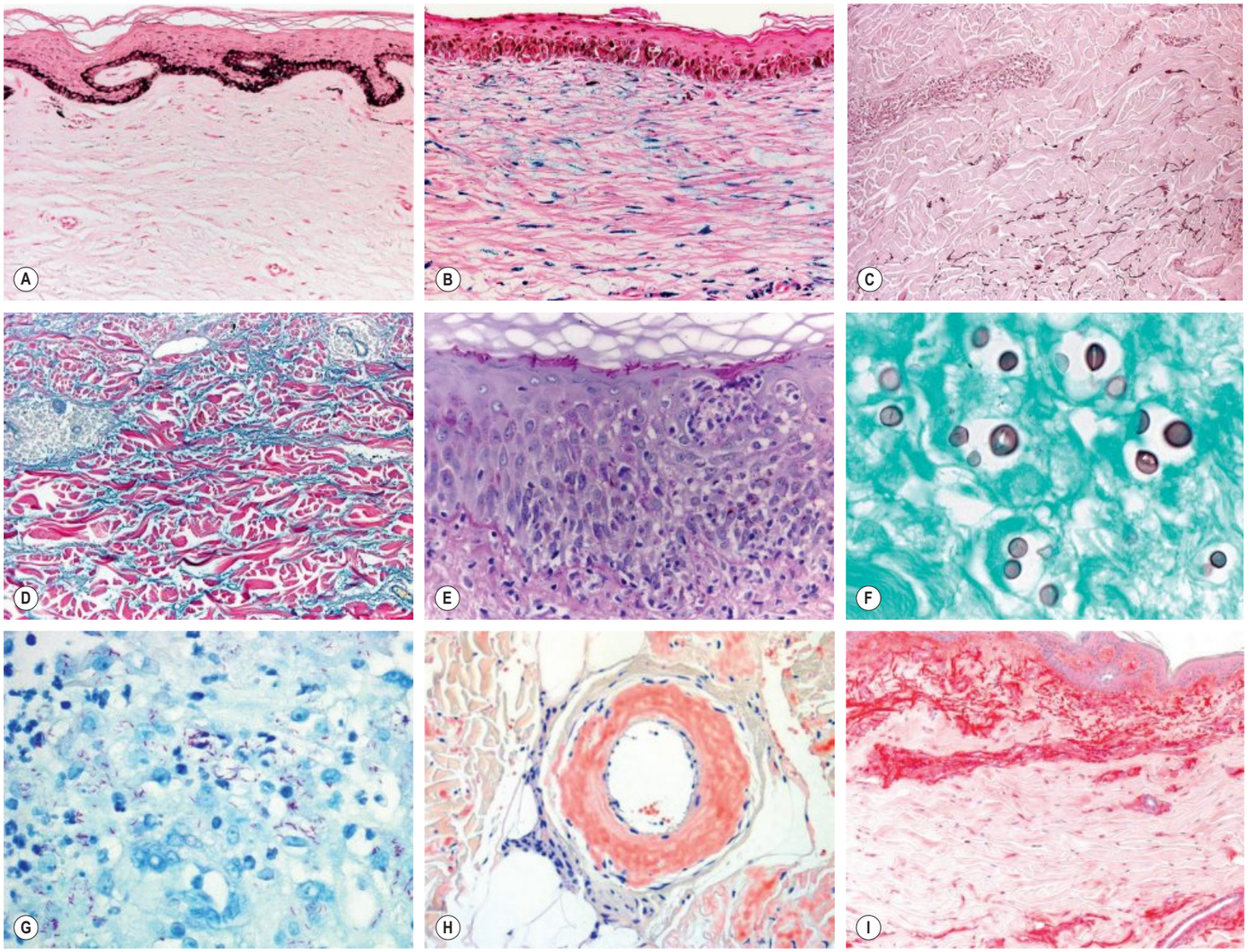


Fig. 0.32 Examples of histochemical stains. Often, histochemical stains reveal structures or substances (e.g. pigments, connective tissue elements, microorganisms) that cannot be clearly seen on H&E-stained sections. **A** Enhancement of increased *melanin* within the basal layer of the epidermis in genital melanosis (black color) – Fontana–Masson stain. **B** Demonstration of *iron* (hemosiderin) within dermal macrophages in purpura (blue color) – Prussian blue (Perls' iron) stain. **C** A near absence of dermal *elastic fibers* (upper left), compared to normal elastic fibers in the lower right, in anetoderma (black color) – orcein elastic tissue stain. **D** Increased *mucin* in the dermis in reticular erythematous mucinosis (blue color) – colloidal iron stain. **E** *Fungal hyphae* within the stratum corneum in dermatophytosis (purple–red color) – PAS stain (also note the staining of the basement membrane zone). **F** Yeast forms of *Cryptococcus neoformans* within the dermis (black color) – Grocott methenamine silver stain. **G** *Mycobacteria* within a granulomatous infiltrate in cutaneous tuberculosis (red–violet color) – Fite stain (modified acid-fast stain). **H** Amyloid deposits around dermal blood vessels in primary systemic AL amyloidosis (orange–red color) – Congo red stain. **I** Complete loss of elastic tissue in the mid dermis in mid-dermal elastolysis (red color) – immunostaining for amyloid P component. *A–F, Courtesy Lorenzo Cerroni, MD; G, Courtesy Karen Warschaw, MD.*

COMMONLY EMPLOYED SPECIAL STAINS IN DERMATOPATHOLOGY			
Stain	**Structures identified**	**Color**	**Application(s)**
Alcian blue (pH 2.5)	Acid mucopolysaccharides (glycosaminoglycans)	Light blue	Mucinoses (see Table 46.1) Lupus erythematosus Extramammary Paget disease Mucopolysaccharidoses
Alcian blue (pH 0.5)	Sulfated mucopolysaccharides (heparan sulfate, chondroitin sulfate)	Blue	
Chloroacetate esterase (Leder)	Myeloid cells and mast cells	Red	Neutrophilic dermatoses Malignant myeloid infiltrates Mastocytosis
Colloidal iron	Acid mucopolysaccharides	Blue	Mucinoses Lupus erythematosus Extramammary Paget disease
Congo red	Amyloid	Red; green in polarized light	Amyloidoses, cutaneous and systemic
Crystal violet	Acid mucopolysaccharides (glycosaminoglycans) and amyloid	Metachromatically purple with blue background	Mucinoses Amyloidoses

Table 0.12 Commonly employed special stains in dermatopathology.

Continued

COMMONLY EMPLOYED SPECIAL STAINS IN DERMATOPATHOLOGY			
Stain	**Structures identified**	**Color**	**Application(s)**
Fite–Faraco	*Mycobacterium leprae* *M. tuberculosis* MOTT (mycobacteria other than tuberculosis)	Red	Hansen disease (leprosy) Cutaneous tuberculosis Atypical mycobacterioses
Fontana–Masson (argentaffin)	Melanin	Black	Distinction between iron and melanin Discoloration due to drugs (e.g. minocycline) Evaluation of vitiligo
Giemsa	Nuclei of cells, microorganisms	Blue	Leishmaniasis Histoplasmosis Granuloma inguinale
	Mast cell granules	Metachromatically purple	Urticaria Mastocytosis
Gram (Brown–Brenn)	Gram-positive bacteria	Blue	Bacterial infections
	Gram-negative bacteria	Red	Bacterial infections
Grocott methenamine silver	Fungal cell walls	Black	Mycotic infections
Masson's trichrome	Smooth muscle	Pink	Distinguishing leiomyomas from dermatofibromas and neural tumors
	Collagen	Blue/green	Evaluating the characteristics of dermal collagen, e.g. perforating disorders
Mucicarmine	Epithelial mucin (acid mucopolysaccharides)	Red	Usually used for sialomucin (e.g. adenocarcinoma, Paget disease) and the capsule of *Cryptococcus neoformans*
Myeloperoxidase	Immature myeloid cells	Orange	Leukemic infiltrates (myelogenous leukemia)
Orcein (acid orcein–Giemsa)	Collagen	Pink	Elastic tissue disorders (e.g. PXE, anetoderma)
	Elastic tissue	Dark brown	
	Muscle and nerves	Yellow	
Pagoda	Amyloid	Orange	Amyloidoses
Periodic acid Schiff (PAS)	Glycogen, fungal walls, neutral mucopolysaccharides, fibrin, basement membranes, many clear cell neoplasms	Red	Mycotic infections Discoid lupus erythematosus (thickened epidermal basement membrane) Porphyria cutanea tarda (thickened vascular walls)
Perls' iron (Prussian blue)	Hemosiderin Ferric ions	Blue	Identification of iron as the source of pigment
Sudan black	Lipids (in frozen sections or formalin-fixed, unprocessed tissue*)	Black	Xanthomatoses Storage diseases (e.g. Fabry disease)
Sudan orange	Lipids (in frozen sections or formalin-fixed, unprocessed tissue*)	Orange	Xanthomatoses Storage diseases
Thioflavin T	Amyloid	Yellow–green by fluorescence microscopy	Amyloidoses
Toluidine blue	Acid mucopolysaccharides and mast cell granules	Metachromatically purple	Mastocytosis
Truant (auramine–rhodamine)	Acid-fast organisms	Reddish-yellow by fluorescence microscopy	Mycobacterial infections More sensitive than Fite stain
Verhoeff–van Gieson or Weigert	Collagen	Pink to red	Elastic tissue disorders (e.g. PXE, anetoderma, mid-dermal elastolysis, acquired cutis laxa)
	Elastic tissue	Black	
	Muscle and nerves	Yellow	
Von Kossa	Calcium salts	Black	Calcium deposits PXE (oxalate salts may not stain with this method) Calciphylaxis
Warthin–Starry (modified Steiner)	Bacteria	Black	Syphilis (and other diseases caused by spirochetes) Bacillary angiomatosis Granuloma inguinale, rhinoscleroma
Ziehl–Neelsen	Acid-fast bacteria	Red	Mycobacterial infections

*If processed, use anti-adipophilin stain.

Table 0.12 Commonly employed special stains in dermatopathology. In parentheses are alternative names or variations of the stain. Some of these special stains are being replaced by immunohistochemical (IHC) stains, e.g. IHC for adipophilin instead of Sudan black or Sudan orange stain. PXE, pseudoxanthoma elasticum.

antigens in biological tissues. Visualizing this antibody–antigen interaction may be accomplished in a number of ways. Most commonly, the tissue to be examined is incubated with antibodies conjugated with an enzyme that catalyzes a color-producing reaction when the antibody–enzyme conjugate is bound to the appropriate antigen within tissue; the enzyme is often peroxidase, hence the older terminology, immunoperoxidase technique.

While IHC is most often used to characterize the cellular lineage of neoplasms, it is also helpful in assessing the biological behavior of tumors and in identifying specific infectious agents that are not discernible or are difficult to detect in routine H&E-stained sections (Fig. 0.33)[36,37]. IHC is also used as a research tool to determine the distribution and localization of specific biomarkers and proteins within biological tissue. Finally, more recently, IHC has been used to verify the presence of antigens targeted by specific drugs (e.g. PD-L1).

When used rationally and appropriately, IHC is a formidable tool in diagnostic dermatopathology, but if used without insight or used excessively, it can be misleading and economically wasteful. Important factors to consider when utilizing IHC include the following: (1) almost no antibody is specific for a certain cell type, therefore a panel of antibodies should be employed to avoid premature, incomplete, or erroneous conclusions; (2) a differential diagnosis must be constructed prior to ordering an antibody panel so that the antibodies requested are appropriate; and (3) no antibody can differentiate irrefutably between a benign and malignant neoplasm (although, on occasion, evidence of an increased proliferative index or the aberrant expression of certain proteins may *support* such a conclusion).

A list of antibodies used most often in dermatopathology, the corresponding antigens, and the disease processes suggested by positive reactions is provided in Table 0.13.

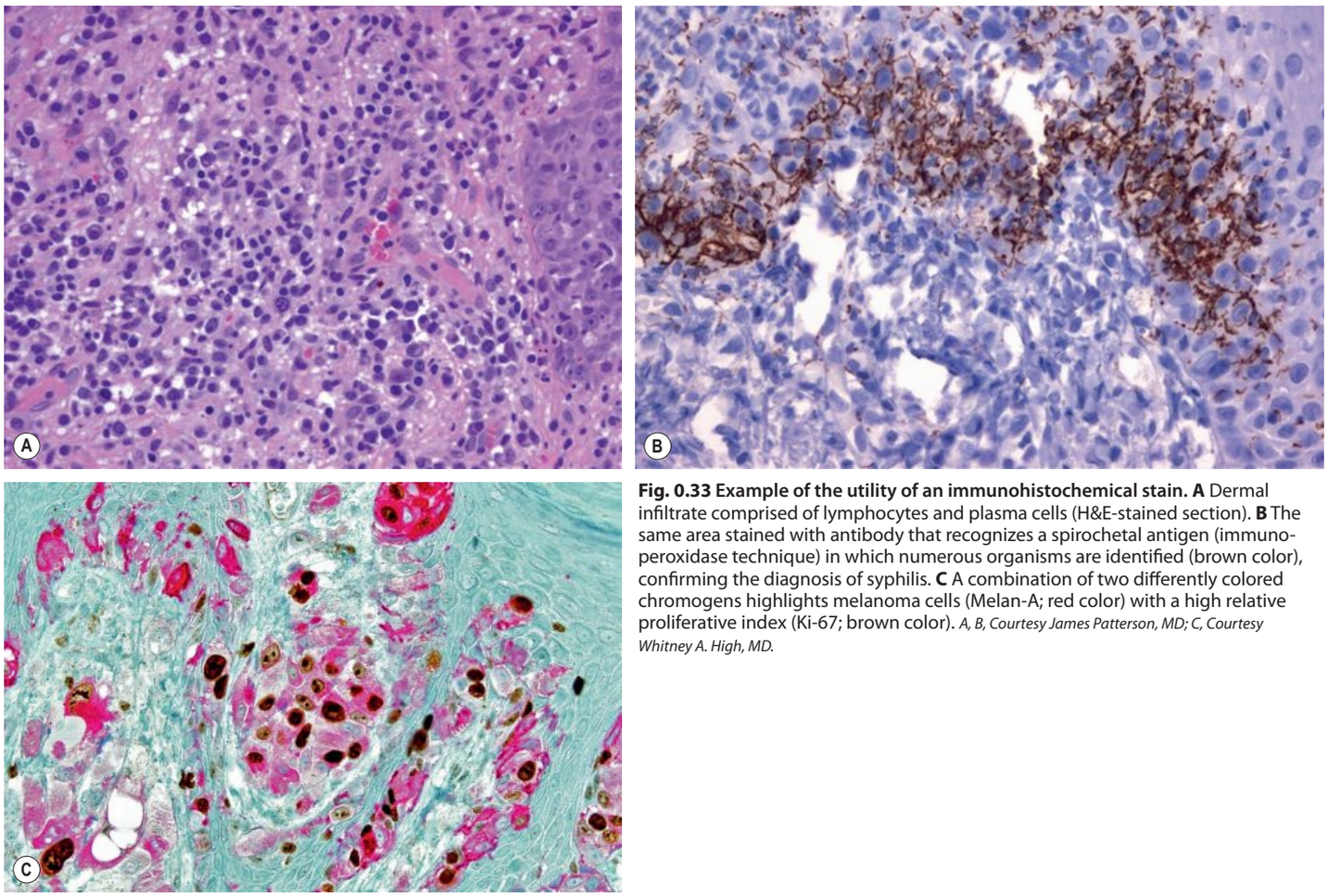


Fig. 0.33 Example of the utility of an immunohistochemical stain. A Dermal infiltrate comprised of lymphocytes and plasma cells (H&E-stained section). **B** The same area stained with antibody that recognizes a spirochetal antigen (immunoperoxidase technique) in which numerous organisms are identified (brown color), confirming the diagnosis of syphilis. **C** A combination of two differently colored chromogens highlights melanoma cells (Melan-A; red color) with a high relative proliferative index (Ki-67; brown color). *A, B, Courtesy James Patterson, MD; C, Courtesy Whitney A. High, MD.*

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
Markers for diagnosis of epithelial tumors		
Adipophilin (perilipin-2)	Marker of intracellular multilocular lipid accumulation	Diagnosis of tumors with sebaceous differentiation
Bcl2	Protein product of an oncogene which inhibits programmed cell death (apoptosis) Expressed in the basal layer of the epidermis (and lymphoid cells; see below)	Distinguishing basal cell carcinoma (diffuse staining) from trichoepithelioma (stains outermost layer)
Ber-EP4	Transmembrane glycoprotein involved in cellular adhesion Broadly distributed in epithelial cells	Distinction of basal cell carcinoma (+) from other cutaneous basaloid tumors (–)
CEA (carcinoembryonic antigen)	Expressed in a variety of epithelia, from gastrointestinal to cutaneous adnexa	Highlights tubular differentiation in epithelial tumors Diagnosis of benign and malignant adnexal neoplasms

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology.

Continued

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
CK5/6	Intermediate-sized basic keratins Expressed in the basal layer of stratified squamous epithelia and myoepithelial cells of eccrine and apocrine secretory tubules	Spindle cell squamous cell carcinomas Myoepithelial neoplasms
CK20	Low-molecular-weight cytokeratin Expressed in simple epithelia and Merkel cells	Most specific marker for Merkel cell carcinoma (especially when combined with negative TTF-1 staining) Cutaneous metastases from different types of adenocarcinomas
EMA (epithelial membrane antigen)	High-molecular-weight transmembrane glycoprotein expressed in many epithelial cells	Highlights ductal differentiation in eccrine and apocrine tumors (benign and malignant) Positive staining in most sebaceous glands Perineurial cells
GCDFP-15 (gross cystic disease fluid protein-15)	Glycoprotein expressed by apocrine glands, eccrine glands (variable), minor salivary glands, bronchial glands, metaplastic epithelium of the breast, benign sweat gland tumors of the skin, and serous cells of the submandibular gland	Breast carcinoma metastases Sweat gland carcinoma with apocrine differentiation
MNF116	Epitope common to several cytokeratins (CK5, 6, 8, 17, and probably 19)	Spindle cell squamous cell carcinomas Adnexal and undifferentiated carcinomas
p63	p53 homolog that acts as a transcription factor Expressed in the basal layer of the epidermis and cutaneous adnexa as well as myoepithelial cells	Myoepithelial neoplasms Distinction of primary cutaneous adenocarcinomas (+) versus cutaneous metastasis from visceral adenocarcinomas (–)
Pancytokeratin AE1/AE3	Mixture of low- and high-molecular-weight cytokeratins	Screening tumors for an epithelial origin Useful for squamous cell carcinomas
MSH2, MLH1, MSH6, PMS2	Mismatch repair proteins	Loss of expression in sebaceous neoplasms; initial screening for Muir–Torre syndrome Not as sensitive or specific as germline mutational analysis and/or microsatellite instability testing
Markers for diagnosis of melanocytic and neural tumors		
S100	Family of low-molecular-weight calcium-binding proteins Neural crest-derived cells (melanocytes, Schwann cells, glial cells), chondrocytes, fat cells, macrophages, Langerhans cells, dendritic cells Some breast epithelial cells	Melanocytic nevi and melanoma Most sensitive marker for spindle cell/desmoplastic melanoma Also stains malignant peripheral nerve sheath tumors and clear cell sarcoma (melanoma of soft parts)
Melan-A (MART-1)	Protein involved in the function of the melanosomal matrix protein pmel17/gp100 Antigen present on melanocytes (and melanoma cells) recognized by cytotoxic T cells	Melanocytic nevi and melanomas Also may stain melanosome-containing keratinocytes in sun-damaged skin Cutaneous PEComas
SOX10	Transcription factor that is expressed in melanocytes Required for survival and proliferation of neural crest cells Controls MITF expression	High sensitivity for primary and metastatic melanomas (97%–100%) Expressed in all melanoma subtypes, including desmoplastic melanoma (~80%–100%) Positive staining in clear cell sarcomas and peripheral nerve sheath tumors Useful for the detection of micrometastases in sentinel lymph nodes
HMB45	Glycoprotein present in premelanosomes and melanosomes (pmel17/gp100) Expressed in melanocytes that are synthesizing melanin	Melanocytic nevi and melanomas (highly specific) Diminished staining with dermal descent more frequent in benign tumors Also may stain melanosome-containing keratinocytes Cutaneous PEComas
MITF (microphthalmia transcription factor)	Transcription factor that regulates several melanogenic enzymes, including tyrosinase, in melanocytes Plays key role in regulating melanocyte development during embryogenesis	Stains the nucleus of melanocytic nevus and melanoma cells Positive staining in most (~80%–100%) of all melanoma subtypes, including desmoplastic (~50%) Lack of staining of melanin-containing keratinocytes helpful in distinguishing solar lentigo from lentigo maligna Less specificity as can also stain non-melanocytic spindle cell tumors
Tyrosinase	Enzyme involved in the initial steps of melanin biosynthesis Expressed in melanocytes	High sensitivity and specificity (97%–100%) Sensitivity decreases with increased clinical stage and in metastases Positive staining in only a small percentage (~6%) of desmoplastic melanomas
PRAME (preferentially expressed antigen of melanoma)	A member of the family of cancer testis antigens (CTA), positive in many examples of different subtypes of melanoma and usually negative in melanocytic nevi Inhibits signaling of retinoic acid via retinoic acid receptors	In positive cases, helpful in distinguishing melanoma cells from associated nevus cells Can assist in assessment of margins in melanoma excisions
BRAF V600E	BRAF = serine/threonine-protein kinase in the MAPK pathway V600E = an amino acid substitution of glutamic acid (E) for valine (V) in the BRAF protein at position 600 due to a mutation in *BRAF* BRAF V600E (less often V600K or V600D) detected in ~50% of cutaneous melanomas This missense mutation leads to activation of the kinase	Compared to PCR, IHC staining is less sensitive Detection of BRAF V600E leads to treatment with targeted inhibitors of BRAF V600E and the MAPK pathway (see Ch. 113) BRAF V600E also present in Langerhans cell histiocytosis, Erdheim-Chester disease

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology.

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
P75	Common receptor for members of the neurotrophins (NT) family Involved in programmed cell death Marker of Schwannian differentiation	Helpful for establishing the diagnosis of desmoplastic and neurotropic melanoma when S100 staining is weak or absent
PNL2	Detects fixative-resistant, uncharacterized melanocyte antigen	Highly sensitive and specific for melanocytic nevi and melanomas Positive staining of intraepidermal nevus cells (up to 100%) and primary and metastatic melanomas (~75%–100%), with the exception of desmoplastic melanomas which are almost invariably negative Clear cell sarcomas, PEComas, and melanocytic schwannomas may stain positively
pHH3 (phospho-histone H3)	Core histone protein Detects mitoses and distinguishes mitoses from apoptotic cells	Precise identification of mitoses within tumors
Markers for diagnosis of neuroendocrine tumors		
Chromogranin	Granules of neuroendocrine cells and sympathetic nerves	Merkel cell carcinoma Mucin-secreting sweat gland carcinoma with neuroendocrine differentiation
CK20 (see above)	Low-molecular-weight cytokeratin Expressed in simple epithelia and Merkel cells	Most sensitive stain for Merkel cell carcinoma (especially when combined with negative TTF-1 staining) Cutaneous metastases from different types of adenocarcinomas Epidermotropic metastases, e.g. secondary extramammary Paget disease
Neurofilament	Intermediate filaments in neurons and neuronal processes of central and peripheral nervous tissue	Merkel cell carcinoma Neuromas and neurofibromas
Synaptophysin	Glycoprotein of presynaptic vesicles found in neurons and neuroendocrine cells	Merkel cell carcinoma Neural tumors Mucin-secreting sweat gland carcinoma with neuroendocrine differentiation
TTF-1 (thyroid transcription factor-1)	Expressed in the epithelia of the thyroid and lung	Thyroid carcinoma Small cell lung carcinoma, visceral neuroendocrine tumors Negative in most cases of Merkel cell carcinoma
Markers for diagnosis of mesenchymal tumors		
Caldesmon	Actin and protomyosin binding protein involved in regulation of muscle and non-muscle contraction	Smooth muscle neoplasms
Calponin	Calcium-binding protein that regulates smooth muscle myosin ATPase activity Expressed in smooth muscle	Neoplasms with smooth muscle differentiation (benign and malignant)
CD99	Cell surface glycoprotein involved in leukocyte migration and T cell adhesion Expressed on most hematopoietic cells	Ewing sarcoma, peripheral neuroectodermal tumor Atypical fibroxanthoma, dermatofibroma (strong), DFSP (weaker) Some hematopoietic neoplasms
Desmin	Intermediate filament expressed predominantly by striated and smooth muscle cells	Smooth and striated muscle cell neoplasms (benign and malignant)
Factor XIIIa	Human coagulation factor XIII Expressed in subsets of dermal dendrocytes and monocytes/macrophages	Dermatofibromas (DFs) Non-Langerhans cell histiocytoses Negative in DFSP
Smooth muscle actin	Expressed in smooth muscle around blood vessels and in arrector pili muscles Expressed in myofibroblasts	Benign and malignant smooth muscle tumors Myofibroblastic tumors and pseudotumors Myoepithelial neoplasms
Vimentin	Intermediate filaments in mesenchymal cells	All mesenchymal cells/tumors Sarcomatoid (spindle cell) carcinoma
Markers for diagnosis of vascular tumors		
CD31	Platelet-endothelial cell adhesion molecule-1 (PECAM-1) Highly sensitive for endothelial cells, but poor specificity	Benign and malignant vascular neoplasms Histiocytes also stain positively
CD34	Surface glycoprotein involved in cell–cell adhesion Highly sensitive for endothelial cells, but poor specificity	Benign and malignant vascular neoplasms DFSP (negative in DFs) Many cutaneous spindle cell neoplasms so poor specificity
Podoplanin (D2-40)	Mucin-type transmembrane glycoprotein Specifically expressed by lymphatic, but not blood vessel, endothelial cells	Kaposi sarcoma, lymphangiomas, angiosarcomas with lymphatic differentiation, schwannomas Distinction of primary cutaneous carcinomas (+) from cutaneous metastases from visceral carcinomas (–)
c-MYC	Proto-oncogene Detection of MYC protein expression correlates with *MYC* translocation	Angiosarcoma (particularly post-radiation) Subset of cutaneous diffuse large cell B cell lymphomas

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology.

Continued

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
ERG	Proto-oncogene Transcription factor expressed in vascular endothelial cells	Benign and malignant tumors derived from endothelial cells Epithelioid sarcoma (~50% of cases)
HHV-8 (human herpesvirus 8)	HHV-8 latent nuclear antigen	Kaposi sarcoma
Markers for diagnosis of histiocytic tumors		
CD1a	Transmembrane glycoprotein structurally related to MHC proteins that plays a role in antigen presentation Expressed in Langerhans cells and precursor T cells	Langerhans cell histiocytoses Some T cell lymphoblastic lymphomas
CD68	Glycoprotein that binds to low-density lipoprotein (LDL) Expressed in monocytes and macrophages, as well as myeloid cells and mast cells	Blastic NK cell lymphoma (some cases), myeloid leukemias Non-Langerhans cell histiocytoses Soft tissue tumors, e.g. some atypical fibroxanthomas, dermatofibromas, giant cell tumors of the tendon sheath
CD163	Member of the scavenger receptor cysteine-rich (SRCR) superfamily that is involved in clearance and endocytosis of hemoglobin/haptoglobin complexes Exclusively expressed by monocytes and macrophages	More specific than CD68 for identifying cells of monocyte/macrophage lineage in reactive and neoplastic conditions Non-Langerhans cell histiocytoses, e.g. juvenile xanthogranuloma, Rosai–Dorfman disease, reticulohistiocytoma Fibrohistiocytic tumors, e.g. dermatofibromas Chronic myelomonocytic leukemia, histiocytic sarcoma
CD207 (Langerin)	Transmembrane cell surface receptor expressed by Langerhans cells and localized within Birbeck granules Involved in internalization of antigens into Birbeck granules	Langerhans cell histiocytoses
S100 (see above)	Family of low-molecular-weight calcium-binding proteins Expressed in Langerhans cells and activated macrophages	Langerhans cell histiocytoses and Rosai–Dorfman disease Some lipomas and liposarcomas
Markers for diagnosis of mast cell tumors		
CD117 (c-KIT)	Receptor for stem cell factor Expressed on hematopoietic stem cells, mast cells, melanocytes Proto-oncogene	Mastocytosis Myeloid leukemia, some melanomas (especially acral or mucosal), melanocytic nevi The efficacy of KIT receptor inhibitors is determined by the location of amino acid substitutions
Mast cell tryptase	Serine protease within mast cell granules	Mastocytosis
Markers for diagnosis of cutaneous metastases (e.g. CK7, CK20, PSA) – see Table 122.4		
Markers for diagnosis of cutaneous lymphoproliferative disorders		
ALK (anaplastic lymphoma kinase)	Membrane-associated tyrosine kinase receptor Expressed in the nervous system, especially during development	Subgroup of anaplastic large cell lymphomas (nodal and very rarely primary cutaneous) Otherwise negative in primary cutaneous T cell lymphomas and other specific types of anaplastic lymphoma with CD30 positivity Also positive in some spitzoid melanocytic tumors, a subset of xanthogranulomas, and in epithelioid fibrous histiocytoma
Bcl-2	Anti-apoptosis factor for T and B cells Expressed in non-germinal center B cells and most T cells	Primary cutaneous diffuse large B cell lymphoma, leg type Distinguishes systemic/nodal follicular lymphomas with secondary skin involvement (+) from primary cutaneous follicle center lymphomas (–)
Bcl-6	Nuclear protein expressed in mature B cells within normal germinal centers Also expressed in T follicular helper cells	Primary cutaneous follicle center lymphoma Reactive lymphoid follicles T follicular helper cells
Immunoglobulin light chains (kappa and lambda)	Small polypeptide subunits of immunoglobulin Expressed in B lymphocytes and plasma cells	Plasma cell and plasmacytoid neoplasms Monotypic expression in clonal neoplasms
CD3	Surface glycoprotein involved in signal transduction to the T cell interior following antigen recognition Pan T cell marker Also expressed in NK cells (cytoplasmic staining for CD3ε)	T cell lymphomas, including HTLV-I associated adult T cell leukemia/lymphoma Reactive infiltrates with T lymphocytes
CD4	Transmembranous glycoprotein involved in T cell activation (MHC class II-restricted) Expressed in T helper cells, monocytes, granulocytes, macrophages, Langerhans cells, nTreg and iTreg cells	Most T cell lymphomas, including mycosis fungoides Blastic plasmacytoid dendritic cell neoplasm
CD5	Transmembrane glycoprotein Expressed in mature T cells, thymocytes, and a subset of mature B cells	T cell lymphomas, B cell chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma Reactive infiltrates with T lymphocytes
CD8	Transmembranous glycoprotein involved in T cell activation (MHC class I-restricted) Expressed in cytotoxic T cells, NK cells, thymocytes	Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T cell lymphoma Subcutaneous panniculitis-like T cell lymphoma Phenotypic variants of several CTCLs (e.g. mycosis fungoides)

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology.

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
CD10/CALLA (common acute lymphoblastic leukemia antigen)	Membrane-associated metallo-endopeptidase Expressed in precursor B cells and germinal center cells Also expressed in follicular T helper cells	Follicle center lymphoma (both systemic and primary cutaneous) B lymphoblastic leukemia/lymphoma [Positive in most atypical fibroxanthomas but not specific]
CD15 (Lewis X)	Membrane protein that is a component of adhesion molecules that bind selectins Expressed on monocytes, granulocytes Absent on normal lymphocytes	Classic Hodgkin lymphoma (expressed on Reed–Sternberg cells) Acute myelogenous leukemia
CD20	Unglycosylated phosphoproteins expressed only on B cells Play a role in B cell activation and proliferation	Different types of cutaneous B cell lymphoma (both systemic and primary cutaneous) Reactive infiltrates with B lymphocytes
CD21	Receptor for the C3d fragment of complement and EBV in B cells and epithelial cells Expressed in follicular dendritic cells and mantle and marginal zone B cells	Follicular dendritic cell neoplasms Follicular dendritic cells within both reactive and neoplastic lymphoid follicles
CD30	Member of the tumor necrosis factor (TNF) receptor family Expressed by activated T and B cells	Anaplastic large T cell lymphoma, lymphomatoid papulosis, Hodgkin lymphoma, large cell transformation of mycosis fungoides May be expressed by a proportion of neoplastic cells in several other types of CTCL (e.g. mycosis fungoides) Expressed in activated T cells in non-neoplastic skin diseases (e.g. herpes virus infections, poxvirus infections)
CD45 (common leukocyte antigen)	Family of high-molecular-weight glycoproteins present on the surface of leukocytes (tyrosine phosphatase) Expressed by both T cells and B cells	Expressed on lymphocytes (benign and malignant, both T and B cell types)
CD56	Neural cell adhesion molecule Expressed on neural cells, NK cells, a subset of $CD3^+$ cytotoxic T cells, a subset of $CD4^+$ T cells, and monocytes	Extranodal NK/T cell lymphoma, nasal type Blastic plasmacytoid dendritic cell neoplasm Myeloma, some myelogenous leukemias, neural neoplasms
CD79a	Surface glycoprotein physically associated with immunoglobulin within the B cell membrane; involved in signal transduction after antigen binding Appears before the pre-B cell stage Expressed on immature and mature B cells, plasma cells	B cell lymphomas (can be positive in cases where CD20 is negative) Plasma cell neoplasms Reactive infiltrates with B lymphocytes
CD123	Marker of dendritic cells, including plasmacytoid	Blastic plasmacytoid dendritic cell neoplasm Positive staining of plasmacytoid dendritic cells in lupus erythematosus and other conditions
CD138	Surface glycoprotein involved in cell–cell and cell–matrix adhesion Expressed in plasma cells, plasmocytoid cells, activated T and B cells	Marginal zone B cell lymphoma, plasmacytoma, myeloma, plasmablastic lymphoma Positive staining of reactive plasma cells
Cyclin D1 (PRAD1; bcl-1)	Increased expression of cyclin D1 due to translocation of the cyclin D1/bcl-1 gene locus to the IgH promoter	Mantle cell lymphoma
EBER-1 (Epstein–Barr virus early ribonucleoprotein 1) [*in situ* hybridization]	EBV-infected cells	EBV-associated cutaneous lymphoproliferative disorders, e.g. hydroa vacciniforme, post-transplant lymphomas, extranodal NK/T cell lymphoma (nasal type), Hodgkin lymphoma
Granzyme B	Serine protease expressed specifically by activated cytotoxic T lymphocytes	Cytotoxic lymphocytes in benign and malignant lymphoid infiltrates
MUM1 (multiple myeloma oncogene-1)	Member of the interferon regulatory factor family of transcription factors Plasma cells, late B cells, and activated T cells	$CD30^+$ lymphoproliferative disorders, anaplastic $CD30^+$ lymphoma Strong expression in cutaneous diffuse large B cell lymphoma, leg type
Myeloperoxidase	Lysosomal protein most abundant in neutrophils and monocytes	Myeloid leukemias
PD-1 (programmed cell death protein 1)	Member of the CD28 family This receptor, along with its two ligands, comprises a checkpoint that downregulates immune responses Expressed primarily in activated T cells	Positive staining of T follicular helper lymphocytes Angioimmunoblastic T cell lymphoma Primary cutaneous CD4-positive small/medium T cell lymphoproliferative disorder Mycosis fungoides, Sézary syndrome Adult T cell leukemia/lymphoma
Perforin	Cytolytic protein stored in cytoplasmic granules and then released from cytotoxic T cells	Cytotoxic lymphocytes in benign and malignant lymphoid infiltrates
TCR-beta (βF1)	Beta chain of the T cell receptor	CTCLs with alpha/beta phenotype Positive staining of most reactive T lymphocytes

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology.

Continued

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
TCR-gamma	Gamma chain of the T cell receptor	CTCLs with gamma/delta phenotype Positive staining of only a few reactive T lymphocytes
TdT (terminal deoxyribonucleotidyl transferase)	Expressed in immature, pre-B and pre-T cells	Lymphoblastic lymphoma/leukemia Variably positive in blastic plasmacytoid dendritic cell neoplasm
TIA-1	Granule-associated RNA-binding protein that defines a subset of $CD8^+$ lymphocytes with cytotoxic potential	Cytotoxic lymphocytes in benign and malignant lymphoid infiltrates
Microorganisms		
Herpes simplex virus (HSV)	Glycoproteins present within the viral envelope and core	HSV-1 or -2 infection
Varicella–zoster virus (VZV)	Glycoprotein I of VZV	Varicella or herpes zoster
Epstein–Barr virus (EBV)	EBV membrane protein encoded by *BNLF*	See EBER-1 under lymphoproliferative disorders
Cytomegalovirus (CMV)	Glycoproteins expressed during the immediate–early and early stages of CMV replication within infected cells	CMV infection
Human herpesvirus 8 (HHV-8)	HHV-8 latency-associated nuclear antigen	Kaposi sarcoma, primary effusion lymphoma, Castleman disease
Merkel cell polyomavirus (MCPyV)	MCPyV large T antigen	Expression may be associated with more favorable prognosis in Merkel cell carcinoma Anti-MCPyV-oncoprotein antibody titers used for monitoring
BCG	Anti-Bacillus Calmette–Guérin	Mycobacterial infections
Treponema pallidum	Specific for all *Treponema pallidum* antigens	Syphilis
Bartonella spp.	*Bartonella henselae, Bartonella quintana*	Bacillary angiomatosis, cat scratch disease, verruga peruana
Proliferation markers and markers for mitoses		
Ki-67	Prototypic antigen for cell cycle-related nuclear proteins, expressed by proliferating cells during the active phases of the cell cycle, but not during the resting phase (G0)	Assessment of proliferative activity
MIB-1	Peptides from recombinant fragments of the gene for Ki-67 antigen	

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology. CD, cluster of differentiation; CK, cytokeratin; CTCLs, cutaneous T cell lymphomas; DFSP, dermatofibrosarcoma protuberans; EBV, Epstein–Barr virus; GIST, gastrointestinal stromal tumor; HTLV-1, human T cell leukemia virus 1 (human T cell lymphotropic virus 1); MAPK, mitogen-activated protein kinase; MART-1, melanoma antigen recognized by T cells; Melan-A, melanocyte antigen; MHC, major histocompatibility complex; NK, natural killer; PEC, perivascular epithelioid cell; PCR, polymerase chain reaction.

INTRODUCTION TO THE USE OF DERMOSCOPY (DERMATOSCOPY)

In the prior two sections, we reviewed the basic principles of clinical dermatology and then dermatopathology, with particular emphasis on clinicopathologic correlations. We now turn to an increasingly utilized ancillary examination technique known as dermoscopy (dermatoscopy). It is a non-invasive diagnostic technique that allows one to observe the morphologic features that are not visible to the naked eye, thus forming a link between macroscopic clinical dermatology and microscopic dermatopathology. This "sub-macroscopic" observation of colors and structures (Figs. 0.34–0.39) enhances clinical assessment by providing new diagnostic criteria for the differentiation of melanoma from other benign and malignant neoplasms, both melanocytic and non-melanocytic[38–40].

The technique of dermoscopy classically involves applying a liquid or gel to the skin surface and then inspecting the lesion using a hand-held, illuminated microscope (also called a dermatoscope), a stereomicroscope, a camera, or a digital imaging system. The magnification of these instruments ranges from 6× to 40× and even up to 100×.

The widely used dermatoscope has a 10-fold magnification, sufficient for routine assessment of skin tumors. When fluid is placed on the lesion this eliminates surface reflection and renders the cornified layer translucent, thus allowing a better visualization of pigmented structures within the epidermis, the dermal–epidermal junction, and the superficial dermis. Moreover, the size and shape of vessels within the superficial vascular plexus are better visualized with this procedure (Fig. 0.40; see Figs. 0.38 & 0.39)[41]. Subsequently, hand-held devices were introduced that utilize polarized light, which renders the epidermis translucent. With these latter devices, the use of a liquid medium is no longer required in order to visualize subsurface structures. The introduction of polarized light dermatoscopes definitively improved the dermoscopic examination of skin lesions by speeding up the process. In addition, this light mode allows the visualization of new features, such as shiny white structures, which were proved to be an additional important clue for the diagnosis of melanoma.

Nowadays, the dermatoscope is increasingly being used by dermatologists as a stethoscope equivalent. This is because it not only facilitates the diagnosis of pigmented and non-pigmented skin tumors, but it also improves recognition of a growing number of non-pigmented skin conditions. For example, dermoscopy can facilitate the diagnosis of scabies due to the presence of the pathognomonic "jet with contrail" sign[42] (see Fig. 0.40D). Additional skin infections and infestations that may be differentiated with increased confidence include pediculosis, phthiriasis, tungiasis, tinea nigra, and molluscum contagiosum (see Fig. 0.40A). For two of the more common inflammatory skin disorders – psoriasis and lichen planus – the use of dermoscopy allows the visualization of specific sub-macroscopic features, including "red dots" pattern in psoriasis and "whitish striae" pattern in lichen planus (see Fig. 0.40E,F). Scalp psoriasis and seborrheic dermatitis may also be differentiated via dermoscopy. The most notable scalp psoriasis features are red dots and globules, twisted red loops, and glomerular vessels, whereas seborrheic dermatitis is characterized by the presence of arborizing vessels and atypical red vessels, as well as featureless areas with no particular vascular pattern and no red dots or globules. In a review of the indications for dermoscopy, more than 35 different inflammatory and infectious skin diseases were listed[43], but nowadays more than 300 dermatologic conditions have been reported in which dermoscopy can be usefully applied. One of the more recent applications

Orange	keratin	epidermis
Yellow	keratin – cholesterol	epidermis – dermis
Black	melanin	stratum corneum
Brown	melanin	basal layer
Gray	melanin	papillary dermis
White	fibrosis	dermis
Blue	melanin	papillary and reticular dermis
Red	hemoglobin	papillary dermis
Purple	hemoglobin	reticular dermis

Fig. 0.34 Dermoscopy colors of keratinizing, melanocytic, and vascular tumors.

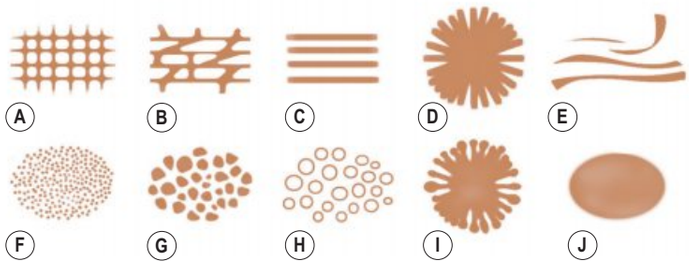


Fig. 0.35 Patterns of dermoscopy. Patterns formed by lines (upper row): **A** Reticular. **B** Branched. **C** Parallel. **D** Radial. **E** Curved lines. Patterns formed by other basic elements (lower row): **F** Pattern of dots. **G** Pattern of clods. **H** Pattern of circles. **I** Pattern of pseudopods. **J** Structureless (absence of discernible basic elements). Combinations of patterns may occur. If multiple patterns are present, they may be arranged symmetrically or asymmetrically.

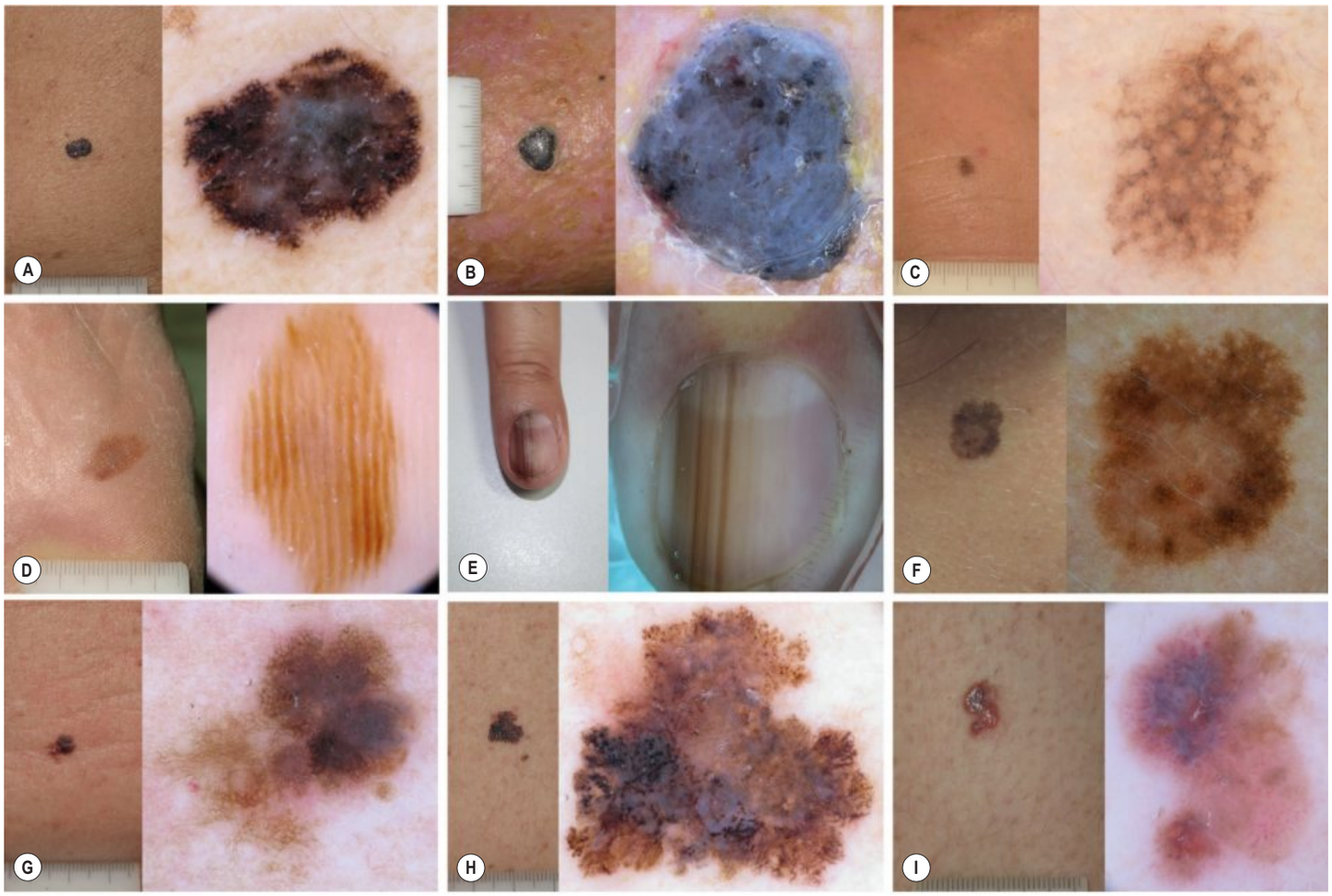


Fig. 0.36 The most common types of melanoma and examples of superficial melanomas of increasing tumor thickness. A Small superficial melanoma typified dermoscopically by asymmetry of color and structure, atypical network, and blue–white structures. **B** Larger thick melanoma with predominant blue–white veil and a few irregular black globules/areas. The combination of blue and black colors (as seen here) is highly specific for the diagnosis of nodular melanoma. **C** Small facial melanoma *in situ* (lentigo maligna) typified by gray granules around the hair follicles. **D** Acral melanoma *in situ* typified by the characteristic parallel-ridge pattern. **E** Nail apparatus melanoma characterized by a pigmented band composed of parallel lines with variable degrees of pigmentation and thickness. **F** Melanoma *in situ* typified dermoscopically by asymmetry of color and structure and atypical network. **G** Melanoma 0.5 mm in depth typified predominantly by an atypical pigment network and blue–white structures. **H** Melanoma 0.8 mm in depth typified by multiple melanoma-specific criteria including asymmetry of color and structure, irregular dots and globules, blue–white structures, and peripheral irregular streaks. **I** Melanoma 1.3 mm in depth typified predominantly by blue–white veil and atypical vascular pattern, both signs of increased tumor thickness. Remnants of an atypical pigment network and irregular brown globules are also observed.

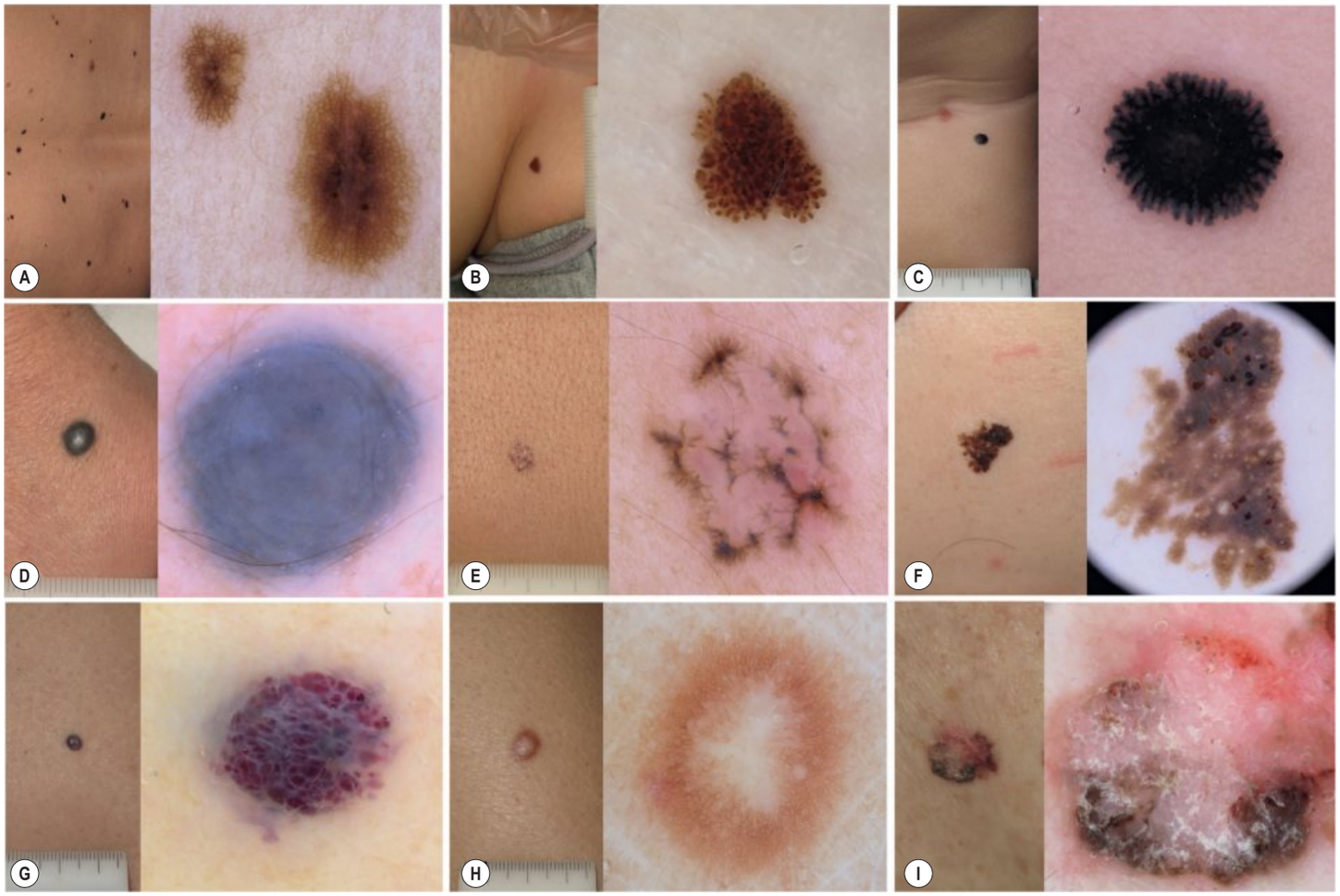


Fig. 0.37 The most common types of melanocytic nevi and non-melanocytic pigmented tumors – clinical and dermoscopic findings. A Two typical acquired nevi with a reticular pattern by dermoscopy. **B** Small congenital nevus with a globular pattern. **C** Reed nevus (pigmented spindle cell nevus) typified dermoscopically by the classic starburst pattern (regular streaks at the periphery of a heavily pigmented and symmetric small macule). **D** Classic homogeneous blue color typically found in blue nevi. **E** Pigmented basal cell carcinoma with typical leaf-like areas (islands of brown–gray color) and blue–gray globules. **F** Seborrheic keratosis with typical milia-like cysts (white shining dots/globules) and comedo-like openings (black targetoid globules). **G** Angiokeratoma with red–blue lacunae clearly visible as well-demarcated roundish structures. **H** Dermatofibroma with characteristic central white patch and peripheral delicate pigment network. **I** Squamous cell carcinoma characterized by a keratotic plaque with white structures, peripheral irregular pigmentation and atypical vessels.

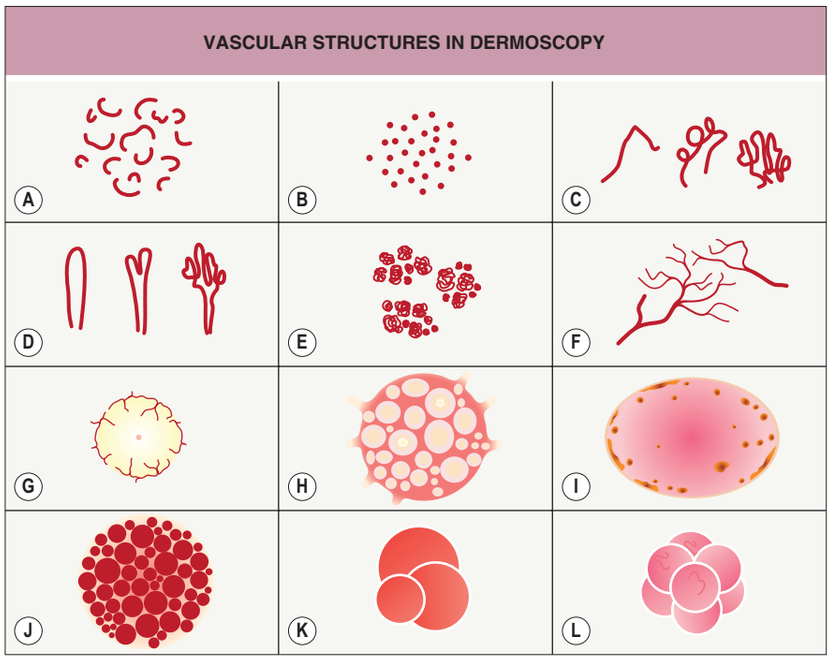


Fig. 0.38 Vascular structures in dermoscopy. (See also Table 0.16 for definitions and diagnostic significance). **A** Comma vessels – typical of dermal and congenital nevi. **B** Dotted vessels – often found in melanoma and Spitz nevi. **C** Linear-irregular vessels – typical of melanoma. **D** Hairpin vessels – most common in keratinizing tumors, such as seborrheic keratosis and squamous cell carcinoma. **E** Glomerular vessels – found in Bowen disease. **F** Arborizing vessels – typical of basal cell carcinoma. **G** Crown vessels – common finding in sebaceous hyperplasia. **H** Strawberry pattern – typical of facial actinic keratosis. **I** Multiple blood crusts over a red background – typical finding in superficial basal cell carcinoma. **J** Red lacunae – typical finding in hemangiomas. **K** Red homogeneous areas intersected by whitish lines – most common in pyogenic granuloma. **L** Milky-red areas – typical of melanoma.

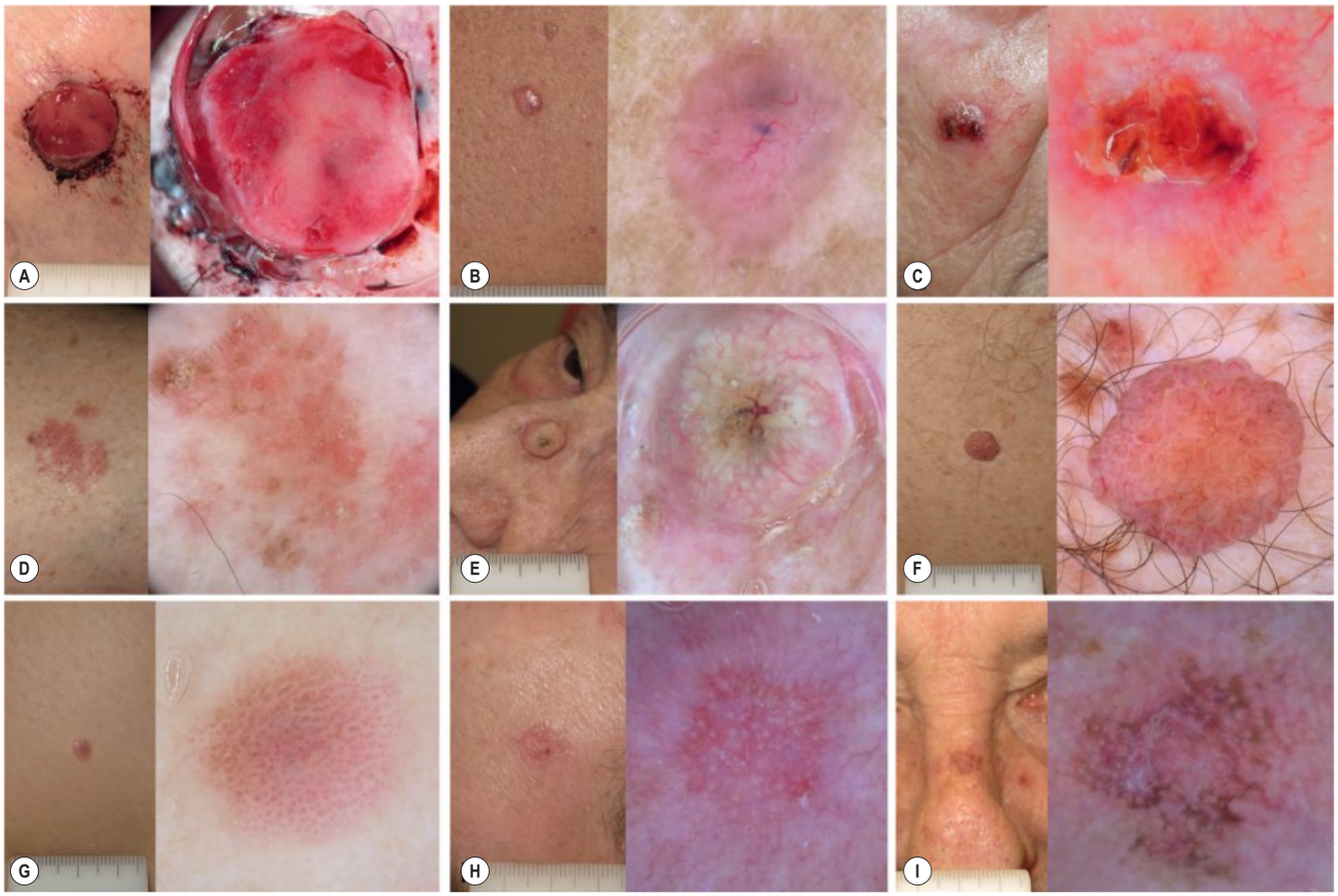


Fig. 0.39 Non-pigmented skin tumors – clinical and dermoscopic findings. A An amelanotic melanoma typified by polymorphic vascular structures and a milky-red color in the background. **B** Nodular basal cell carcinoma with obvious arborizing vessels and blue–gray globules. **C** Merkel cell carcinoma characterized by an atypical vascular pattern. **D** An example of Bowen disease with clusters of dotted/glomerular vessels; these findings in combination with superficial scales are highly specific for the diagnosis. **E** Well-differentiated squamous cell carcinoma with white keratin masses, white circles, white clods, and polymorphic vessels. **F** An intradermal melanocytic nevus with typical comma-shaped vessels. **G** Spitz nevus with dotted vessels and reticular depigmentation. **H** Strawberry pattern and scales of an actinic keratosis. **I** Pigmented variant of actinic keratosis characterized by pigmented scales and rosettes on an erythematous background.

of this technique is trichoscopy, namely the dermoscopic observation of the scalp, which can prove helpful in the differential diagnosis of hair and scalp diseases[44] (see Fig. 0.40G; see Fig. 69.7).

With regard to melanoma screening, the aim of dermoscopy is to maximize early detection while minimizing the unnecessary excision of benign skin tumors. Over the past several years, three meta-analyses and two randomized studies have proven definitively that dermoscopy improves the sensitivity for melanoma detection as compared to just the naked eye[45–49]. In a meta-analysis of dermoscopic studies performed in a clinical setting, the relative odds ratio for dermoscopic diagnosis of cutaneous melanoma (compared to naked eye examination) was 15.6 ($p=0.016$). The average sensitivities for melanoma detection by naked eye versus dermoscopic examinations were 74% and 90%, respectively. Furthermore, this improved sensitivity came about without a decrease in specificity, suggesting that better melanoma detection (16% improvement) occurred without increasing the number of unnecessary excisions of benign lesions[49]. A randomized study found that combining eye and dermoscopic examinations led to a significant reduction in the percentage of patients referred for biopsy (9% vs 15.6%; $p=0.013$)[47]. In summary, the use of dermoscopy is associated with a significant increase in the number of excised melanomas, as well as a significant reduction in the number of excised benign pigmented skin lesions[50,51].

Pattern analysis is the most well-known and reliable method for differentiating pigmented skin tumors. This is based on a two-step algorithm, where first there is recognition of basic criteria for melanocytic and non-melanocytic tumors (first step; Table 0.14) and then benign and malignant features of melanocytic nevi and melanoma, respectively (second step; Tables 0.15 & 0.16)[38]. Attempts to simplify the dermoscopic approach to diagnosing melanocytic nevi and melanoma include the ABCD rule, the Menzies method, and the 7-point checklist[38] (Tables 0.17–0.19).

In a virtual "Consensus Net Meeting on Dermoscopy"[38], 40 experts were able to correctly classify more than 95% of melanocytic lesions and more than 90% of non-melanocytic lesions, with pattern analysis producing the best diagnostic performance. The alternative algorithms (ABCD rule, Menzies method, and 7-point checklist) revealed similar sensitivities as compared to pattern analysis but ~10% less specificity. The favorable results of pattern analysis were not unexpected, as this method probably reflects the human brain's approach to categorizing morphologic images and is similar to the pattern analysis utilized in general clinical dermatology and dermatopathology (see above). That is, there is a subjective perception of the "gestalt" of a given lesion and its integration into an internalized knowledge base, which is the result of expertise on the subject; in contrast, "simplified" algorithms were designed to keep non-experts from failing to detect melanomas, even at the cost of decreased specificity.

Results of the virtual consensus study showed that three criteria (asymmetry, atypical network, and blue–white structures) were especially important in distinguishing malignant from benign pigmented skin tumors (Table 0.20). Using this 3-point dermoscopy rule as a screening test, general physicians with no prior experience in the use of dermoscopy were able to better classify skin lesions suggestive of skin cancer as compared to examination with the naked eye (referral sensitivity of 79% and 54%, respectively), without increasing the number of unnecessary expert consultations[48].

While the continued, skilled use of dermoscopy will undoubtedly aid in the early recognition of melanoma as well as the diagnosis of inflammatory disorders and other cutaneous neoplasms, there are additional technologies that may also have a significant impact on our specialty over the next decade, including confocal microscopy[52] and artificial intelligence. These topics are covered in the next two sections.



Fig. 0.40 Non-pigmented skin lesions – clinical and dermoscopic findings. A Molluscum contagiosum with peripheral arborizing vessels superimposed on a white background. Amorphous white–yellow clods are typically seen in the center. **B** Sebaceous hyperplasia characterized by aggregated yellow blotches and crown vessels. **C** Clear cell acanthoma with dotted vessels linearly arranged as strings of pearls. **D** A 6-month-old boy with scabies. By dermoscopy, a characteristic "jet with contrail" structure can be identified corresponding to the anterior part of the mite (arrow) and the burrow behind it. **E** By dermoscopy, classic psoriasis plaques exhibit regular dotted vessels. **F** The dermoscopic pattern of lichen planus is definitely different from that of psoriasis. In the former, dotted vessels are seen at the border of typical whitish lines and clods, which closely resemble the Wickham striae found in lichen planus of the oral mucosa. **G** Typical follicular yellow dots seen dermoscopically in patches of alopecia on the scalp in alopecia areata. **H** A palmar wart showing hemorrhagic dots corresponding to small intracorneal hemorrhages. **I** An early plaque of discoid lupus erythematosus showing erythema, white scales, and perifollicular whitish halo.

PATTERN ANALYSIS: FIRST-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC AND NON-MELANOCYTIC LESIONS		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
Pigment network – pseudo-network*	Network of brownish interconnected lines over a background of tan diffuse pigmentation. In facial skin, a peculiar pigment network, also called a pseudo-network, is typified by round, equally sized network holes corresponding to the pre-existing follicular ostia	Melanocytic lesion
Aggregated globules	Numerous, variously sized, more or less clustered, round to oval structures with various shades of brown and gray–black. They should be differentiated from multiple blue–gray globules	Melanocytic lesion
Streaks	These have been previously described separately as pseudopods and radial streaming, but are now combined into the one term. They are bulbous and often kinked or finger-like projections seen at the edge of a lesion. They may arise from network structures but more commonly do not. They range in color from tan to black	Melanocytic lesion
Homogeneous blue pigmentation†	Structureless blue pigmentation in the absence of pigment network or other distinctive local features	Melanocytic lesion
Parallel pattern	Seen in melanocytic lesions of palms/soles and mucosal areas. On palms/soles, the pigmentation may follow the sulci or the cristae (i.e. furrows or ridges) of the dermatoglyphics. Rarely arranged at right angles to these structures	Melanocytic lesion
Multiple milia-like cysts	Numerous, variously sized, white or yellowish, roundish structures	Seborrheic keratosis
Comedo-like openings	Brown–yellowish to brown–black, round to oval, sharply circumscribed keratotic plugs in the ostia of hair follicles. When irregularly shaped, comedo-like openings are also called irregular crypts	Seborrheic keratosis
Light-brown fingerprint-like structures	Light-brown, delicate, network-like structures with the pattern of a fingerprint	Seborrheic keratosis

Table 0.14 Pattern analysis: first-step algorithm for differentiation between melanocytic and non-melanocytic lesions.

PATTERN ANALYSIS: FIRST-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC AND NON-MELANOCYTIC LESIONS		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
Cerebriform pattern	Dark-brown furrows between ridges typifying a brain-like appearance	Seborrheic keratosis
Arborizing vessels	Tree-like branching telangiectasias	Basal cell carcinoma[¶]
Leaf-like structures	Brown to gray/blue discrete bulbous structures forming leaf-like patterns. They are discrete pigmented nests (islands) never arising from a pigment network and usually not arising from adjacent confluent pigmented areas	Basal cell carcinoma[¶]
Large blue–gray ovoid nests	Well-circumscribed, confluent or near confluent, pigmented, ovoid, or elongated areas that are larger than globules and not intimately connected to a pigmented tumor body	Basal cell carcinoma[¶]
Multiple blue–gray globules	Multiple globules (not dots) that should be differentiated from multiple blue–gray dots (melanophages)	Basal cell carcinoma[¶]
Spoke-wheel areas	Well-circumscribed radial projections, usually tan in color but sometimes blue or gray, meeting at an often darker (dark brown, black, or blue) central axis	Basal cell carcinoma[¶]
Ulceration[‡]	Absence of the epidermis, often associated with congealed blood, not due to a well-described recent history of trauma	Basal cell carcinoma[¶]
Red–blue lacunae	More or less sharply demarcated, roundish or oval areas with a reddish, red–bluish, or dark-red to black coloration	Vascular lesion
Red–bluish to reddish-black homogeneous areas	Structureless homogeneous areas of red–bluish to red–black coloration	Vascular lesion
None of the listed criteria	Absence of the above-mentioned criteria	Melanocytic lesion

*Exception 1: Pigment network or pseudo-network is also present in solar lentigo and rarely in seborrheic keratosis and pigmented actinic keratosis. A delicate, annular pigment network is also commonly seen in dermatofibroma and accessory nipple (clue for diagnosis of dermatofibroma and accessory nipple: central white patch).
†Exception 2: Homogeneous blue pigmentation (dermoscopic hallmark of blue nevus) is also seen (uncommonly) in some hemangiomas and basal cell carcinomas and (commonly) in intradermal melanoma metastases.
‡Exception 3: Ulceration is also seen less commonly in invasive melanoma.
¶To diagnose a basal cell carcinoma, the negative feature of pigment network must be absent and one or more of the positive features listed here must be present.

Table 0.14 Pattern analysis: first-step algorithm for differentiation between melanocytic and non-melanocytic lesions. *Adapted from Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol 2003;48:679–93.*

PATTERN ANALYSIS: SECOND-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC NEVI AND MELANOMA		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
Global features		
Reticular pattern	Pigment network covering most parts of the lesion	Melanocytic nevus
Globular pattern	Numerous, variously sized, round to oval structures with various shades of brown and gray–black	Melanocytic nevus
Cobblestone pattern	Large, closely aggregated, somehow angulated globule-like structures resembling a cobblestone	Intradermal melanocytic nevus
Homogeneous pattern	Diffuse, brown, gray–blue to gray–black pigmentation in the absence of other distinctive local features	Melanocytic (blue) nevus
Starburst pattern	Pigmented streaks in a radial arrangement at the edge of the lesion	Spitz/Reed nevus
Parallel pattern	Pigmentation on palms/soles that follows the sulci or the cristae (furrows or ridges), rarely arranged at right angles to these structures	Acral nevus/melanoma (see below)
Multicomponent pattern	Combination of three or more of the above patterns	Melanoma
Nonspecific pattern	Pigmented lesion lacking above patterns	Possible melanoma
Local features		
Pigment network	Typical pigment network: light- to dark-brown network with small, uniformly spaced network holes and thin network lines distributed more or less regularly throughout the lesion and usually thinning out at the periphery	Benign melanocytic lesion
	Atypical pigment network: black, brown or gray network with irregular holes and thick lines	Melanoma
Dots/globules	Black, brown, round to oval, variously sized structures regularly or irregularly distributed within the lesion	If regular, benign melanocytic lesion If irregular, melanoma
Streaks	These have been previously described separately as pseudopods and radial streaming. Streaks are bulbous and often kinked or finger-like projections seen at the edge of a lesion. They may arise from network structures but more commonly do not. They range in color from tan to black	If regular, benign melanocytic lesion (Spitz/Reed nevus) If irregular, melanoma
Blue–whitish veil	Irregular, structureless area of confluent blue pigmentation with an overlying white "ground-glass" film. The pigmentation cannot occupy the entire lesion and usually corresponds to a clinically elevated part of the lesion	Melanoma
Regression structures	White scar-like depigmentation and/or blue pepper-like granules usually corresponding to a clinically flat part of the lesion	Melanoma

Table 0.15 Pattern analysis: second-step algorithm for differentiation between melanocytic nevi and melanoma.

Continued

PATTERN ANALYSIS: SECOND-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC NEVI AND MELANOMA		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
Hypopigmentation	Areas with less pigmentation than the overall pigmentation of the lesion	Nonspecific
Blotches	Black, brown, and/or gray structureless areas with symmetrical or asymmetrical distribution within the lesion	If symmetrical, benign melanocytic lesion If asymmetrical, melanoma
Site-related features		
Face	Typical pseudo-network (round, equally sized network holes corresponding to the pre-existing follicular ostia)	Benign melanocytic lesion
	Annular-granular structures (multiple blue–gray dots surrounding the follicular ostia with an annular–granular appearance)	Melanoma
	Gray pseudo-network (gray pigmentation surrounding the follicular ostia, formed by the confluence of annular–granular structures)	Melanoma
	Rhomboidal structures (gray–brown pigmentation surrounding the follicular ostia with a rhomboidal appearance)	Melanoma
	Asymmetric pigmented follicles (eccentric annular pigmentation around follicular ostia)	Melanoma
Palms/soles	Parallel-furrow pattern (pigmentation following the sulci superficiales)	Acral nevus
	Lattice-like pattern (pigmentation following and crossing the furrows)	Acral nevus
	Fibrillar pattern (numerous, finely pigmented filaments perpendicular to the furrows and ridges)	Acral nevus
	Parallel-ridge pattern (pigmentation aligned along the cristae superficiales)	Melanoma

Table 0.15 Pattern analysis: second-step algorithm for differentiation between melanocytic nevi and melanoma. *Adapted from Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol 2003;48:679–93*.

VASCULAR STRUCTURES SEEN IN VARIOUS SKIN TUMORS		
Pattern	**Definition**	**Diagnostic significance**
Comma	Coarse vessels that are slightly curved and barely branching	Congenital and intradermal melanocytic nevi
Dotted	Tiny red dots densely aligned next to each other	Melanocytic lesion (often Spitz nevus and melanoma)
Linear-irregular	Linear, irregularly shaped, sized and distributed red structures	Melanoma
Hairpin	Vascular loops sometimes twisted and bending. They can be surrounded by a whitish halo	With white halo: keratinizing proliferation (seborrheic keratosis, squamous cell carcinoma, keratoacanthoma, verruca) Without white halo: melanoma
Glomerular	Variation on the theme of dotted vessels. They are tortuous capillaries often distributed in clusters mimicking the glomerular apparatus of the kidney	Bowen disease
Arborizing	Stem vessels of large diameter branching irregularly into fine terminal capillaries. The color is bright red, being sharply focused in dermoscopic images due to their location immediately beneath the surface of the tumor	Basal cell carcinoma
Crown	Groups of orderly bending, scarcely branching vessels located along the border of the lesion	Sebaceous hyperplasia
Strawberry	Pink-to-red "pseudo-network" around hair follicles of the face, frequently intermingled with fine, linear-wavy vessels. Often hair follicles are filled with yellowish keratotic plugs	Actinic keratosis
Corkscrew	Linear vessels twisted along a central axis	Thick melanoma or melanoma metastasis
Milky-red color	Globules and/or larger areas of fuzzy or unfocused milky-red color often corresponding to an elevated part of the lesion	Melanoma
Polymorphous	Any combination of two or more different types of vascular structures. The most frequent is linear-irregular and dotted vessels	Malignant tumor, including melanoma, basal cell carcinoma, squamous cell carcinoma

Table 0.16 Vascular structures seen in various skin tumors. See also Figs. 0.38–0.40.

ABCD RULE FOR THE DERMOSCOPIC DIFFERENTIATION BETWEEN BENIGN MELANOCYTIC LESIONS AND MELANOMA			
Dermoscopic criterion	**Definition**	**Score**	**Weight factor**
Asymmetry	In 0, 1, or 2 perpendicular axes; assess not only contour, but also colors and structures	0–2	×1.3
Border	Abrupt ending of pigment pattern at the periphery in 0–8 segments	0–8	×0.1
Color	Presence of up to six colors (white, red, light brown, dark brown, blue–gray, black)	1–6	×0.5
Dermoscopic structures	Presence of network, structureless (homogeneous) areas, branched streaks, dots, and globules	1–5	×0.5

Table 0.17 ABCD rule for the dermoscopic differentiation between benign melanocytic lesions and melanoma. Formula for calculating total score: (A score × 1.3) + (B score × 0.1) + (C score × 0.5) + (D score × 0.5). Interpretation of total score: <4.75, benign melanocytic lesion; 4.75–5.45, suspicious lesion (close follow-up or excision recommended); >5.45, lesion highly suspicious for melanoma. *Adapted from Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol 2003;48:679–93*.

MENZIES SCORING METHOD FOR THE DERMOSCOPIC DIFFERENTIATION BETWEEN BENIGN MELANOCYTIC LESIONS AND MELANOMA	
Dermoscopic criterion	**Definition**
Negative features	
Symmetry of pattern	Symmetry of pattern is required across all axes through the lesion's center of gravity (center of the lesion). Symmetry of pattern does not require shape symmetry
Presence of a single color	The colors scored are black, gray, blue, dark brown, tan, and red. White is not scored as a color
Positive features	
Blue–white veil	An area of irregular, structureless confluent blue pigmentation with an overlying white "ground-glass" haze. It cannot occupy the entire lesion and cannot be associated with red–blue lacunae
Multiple brown dots	Focal areas of multiple brown (usually dark brown) dots (not globules)
Pseudopods	Bulbous and often kinked projections that are found at the edge of a lesion, connected either directly to the tumor body or to the pigmented network. They can never be seen distributed regularly or symmetrically around the lesion. When connected directly to the tumor body, they must have an acute angle to the tumor edge or arise from linear or curvilinear extensions. When connected to the network, the width of the bulbous ending must be greater than the width of any part of the surrounding network and at least double that of its directly connected network projection
Radial streaming	Finger-like extensions at the edge of a lesion which are never distributed regularly or symmetrically around the lesion
Scar-like depigmentation	Areas of white distinct irregular extensions (true scarring), which should not be confused with hypo- or depigmentation due to simple loss of melanin
Peripheral black dots/globules	Black dots/globules found at or near the edge of the lesion
Multiple (5–6) colors	The colors scored are black, gray, blue, dark brown, tan, and red. White is not scored as a color
Multiple blue/gray dots	Foci of multiple blue or gray dots (not globules) often described as "pepper-like" granules in pattern
Broadened network	A network made up of irregular thicker "cords" of the net, often seen focally thicker

Table 0.18 Menzies scoring method for the dermoscopic differentiation between benign melanocytic lesions and melanoma. For melanoma to be diagnosed, a lesion must have neither of both negative features and one or more of the nine positive features. *Adapted from Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol 2003;48:679–93.*

7-POINT CHECKLIST FOR THE DERMOSCOPIC DIFFERENTIATION BETWEEN BENIGN MELANOCYTIC LESIONS AND MELANOMA		
Dermoscopic criterion	**Definition**	**Score**
1. Atypical pigment network	More than one type of network (in terms of color and thickness of the meshes) irregularly distributed within the lesion	2
2. Blue–whitish veil	Irregular, structureless area of confluent blue pigmentation with an overlying white "ground-glass" film. The pigmentation cannot occupy the entire lesion and usually corresponds to a clinically elevated part of the lesion	2
3. Atypical vascular pattern	Linear-irregular or dotted vessels not clearly seen within regression structures	2
4. Irregular streaks	Brown to black, bulbous or finger-like projections irregularly distributed at the edge of a lesion. They may arise from network structures but more commonly do not	1
5. Irregular dots/globules	Black, brown, round to oval, variously sized structures irregularly distributed within the lesion	1
6. Irregular blotches	Black, brown, and/or gray structureless areas asymmetrically distributed within the lesion	1
7. Regression structures	White scar-like depigmentation and/or blue pepper-like granules usually corresponding to a clinically flat part of the lesion	1

Table 0.19 7-point checklist for the dermoscopic differentiation between benign melanocytic lesions and melanoma. By simple addition of the individual scores, a minimum total score of 3 is required for the diagnosis of melanoma, whereas a total score of less than 3 is indicative of non-melanoma. *Adapted from Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol 2003;48:679–93.*

DEFINITIONS OF DERMOSCOPIC CRITERIA FOR THE 3-POINT CHECKLIST	
Criterion	**Definition**
Asymmetry	Asymmetrical distribution of colors and dermoscopic structures
Atypical network*	More than one type of network (in terms of color and thickness of the meshes) irregularly distributed within the lesion
Blue–white structures†	Presence of any type of blue and/or white color
*Usually found in early melanoma. †Usually found in both melanoma and pigmented basal cell carcinoma.	

Table 0.20 Definitions of dermoscopic criteria for the 3-point checklist. The presence of more than one criterion suggests a suspicious lesion. *Adapted from Argenziano G, Puig S, Zalaudek I, et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. J Clin Oncol 2006;24:1877–82.*

INTRODUCTION TO CONFOCAL MICROSCOPY

Reflectance confocal microscopy (RCM) is a non-invasive imaging technique that enables a microscopic, horizontal view of the epidermis and papillary dermis. RCM provides a "virtual" skin biopsy that allows assessment of different layers of the skin at a cellular level[53]. In clinical settings, RCM can be used for the pre-histologic diagnosis of skin tumors as a way of improving patient management. Most commonly, RCM is employed as a second-level analysis to support clinical and dermoscopic evaluation, especially when biopsies are a concern because of anatomic location (e.g. face, genitalia) or the clinical condition of the patient[54]. By increasing specificity and sensitivity, RCM improves the diagnostic accuracy of skin cancers, especially melanocytic tumors. It also reduces the number of unnecessary biopsies and excisions, guides biopsy selection in a suspicious lesion so as to provide a more accurate diagnostic specimen, and helps to define the margins of large tumors to ensure an adequate surgical excision. In addition, RCM is used to monitor and longitudinally evaluate the clinical and therapeutic evolution of neoplastic and inflammatory skin diseases[55].

LIMITATIONS OF REFLECTANCE CONFOCAL MICROSCOPY (RCM) AND POSSIBLE INTERVENTIONS			
	Influence on RCM analysis	**Possible intervention(s)**	**Effectiveness of the intervention(s)**
Body site/features			
Palmoplantar	Thick stratum corneum and acanthosis of the epidermis limits assessment	None	–
Multiple terminal hairs	Poor adherence of the lens and presence of air bubbles in the follicle ostia	Clip hairs and use handheld RCM device	+
Lesion characteristics			
Hyperkeratotic	High backscattering of laser light due to keratin	Pre-treatment with keratolytic ointment	+
Nodular	Penetration of laser is limited to the upper dermis	Evaluation of the surface of the lesion	+/–
Ulcerated or crusted	Presence of fibrin, coagulated blood, and keratin limit examination	Evaluation of the portion of the lesion that surrounds the crust or ulceration	+/–
Deep inflammation	Penetration of laser is limited to the upper dermis	None	–

Table 0.21 Limitations of reflectance confocal microscopy (RCM) and possible interventions.

RCM Principals, Technology, and Limitations

In RCM, the basic principle is to have a point source of light focused on a specific point within tissue. Due to the different refractive indices in the skin, the light is scattered back by various tissue structures. Only light reflected from the tissue focus point can pass through a pinhole-sized spatial filter into the RCM detector; it is then processed by dedicated software. The contrast in confocal images is due to differences in the reflectance index between cellular structures, subcellular structures, and their surroundings. Melanin and keratin have a high reflectance index, as do white blood cells, chromatin, and dermal fibers, but to a lesser extent. Therefore, they appear brighter than surrounding structures in RCM images[54–57]. RCM provides cellular details similar to those seen by histopathology at low magnification.

Commercially available RCM devices often use a near-infrared (830 nm) laser with low power (up to 35 mW) at the tissue level. Immersion oil or water must be applied to the skin lesion to obtain a refractive index close to that of the stratum corneum. The immersion lens is used with water/gels placed between the window and the objective lens and has a refractive index close to that of the epidermis. The laser scans a two-dimensional grid over the skin to obtain a thin horizontal optical section, and back-scattered photons from the illuminated living tissue are detected. Processed data are usually displayed as a grayscale image ("single RCM image": 500 × 500 microns field-of-view) with a lateral resolution of ~0.5 microns and an axial resolution of ~3.5 microns. For most lesions and anatomical sites, RCM examination is feasible, but there are limitations, e.g. hyperkeratotic, acral, or ulcerated lesions (Table 0.21)[54].

Currently, two different RCM instruments are commercially available. They are designed for different indications, based primarily on the clinical lesion and its anatomical site. The static-head RCM device (Vivascope® 1500, Caliber I.D. Inc.) usually employs an automated stepper in order to obtain up to 64 sequential images for a mosaic grid of 16 × 16 contiguous images in the *horizontal* plane (8 × 8 mm field-of-view[54,57]; termed "Vivablock"). By adjusting the focal length of the laser beam, a series of consecutive RCM single images can be stacked *vertically* (termed "Vivastack"), from the skin surface to the superficial dermis. A dermoscopic picture usually serves as a gross map to guide RCM imaging so as to examine the site of interest within the lesion.

The handheld RCM device (Vivascope® 3000, Caliber I.D. Inc.) allows one to investigate anatomic sites that are curved or difficult to reach, such as the nose, ears, eyelids, or mucosa. The technical characteristics are similar, but the field-of-view is smaller and limited to 0.5 × 0.5 mm[54]. The most common application of this device is examination of pigmented macules and patches in photodamaged facial skin. In addition, this handheld device can be moved easily on the skin and allows for analysis of multiple lesions in different body sites, which is particularly useful when studying inflammatory skin diseases.

CUTANEOUS TUMORS – MAJOR REFLECTANCE CONFOCAL MICROSCOPY (RCM) FEATURES		
Cutaneous tumors	**RCM feature**	**Associated diagnosis**
Melanocytic	Pagetoid round cells	Atypical melanocytic lesion, melanoma
	Pagetoid dendritic cells	Atypical melanocytic lesion, melanoma
	Dense nests	Melanocytic nevus
	Sparse nests	Atypical melanocytic lesion, melanoma
	Cerebriform nests	Nodular melanoma
	Dendritic cells around adnexal structures	Lentigo maligna
	Ringed pattern	Melanocytic nevus
	Meshwork pattern	Melanocytic nevus
	Disarray of the dermal–epidermal junction	Atypical melanocytic lesion, melanoma
Keratinocytic	Absent or irregular honeycombed pattern of epidermis	Actinic keratosis, SCC
	Parakeratosis	Actinic keratosis, SCC
	Atypical keratinocytes (different degree)	Actinic keratosis, SCC
	Polycyclic papillae and epidermal bulges	Solar lentigo, seborrheic keratosis
	Epidermal invaginations with keratin pearls	Seborrheic keratosis
	Basaloid nests – dark silhouette	BCC
	Basaloid nests – palisading	BCC
	Peritumoral clefts	BCC
	Dilated vessels	SCC, BCC

Table 0.22 Cutaneous tumors – major reflectance confocal microscopy (RCM) features. BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

RCM Applications

Cutaneous tumors

The RCM criteria for melanocytic and keratinocytic skin tumors have been extensively described in the literature (Table 0.22). RCM is particularly useful for flat pigmented lesions, especially when the differential diagnosis is atypical nevus versus melanoma. It has been shown to significantly reduce the number of unnecessary skin biopsies and excisions. In the case of nodular lesions, RCM does not allow assessment of the deep cellular component, but assessment of the superficial confocal features that reflect the melanocytic proliferation is often sufficient to define the nature of the lesion.

The differential diagnosis of flat pigmented lesions in sun-exposed sites includes melanocytic skin neoplasms, in particular lentigo maligna (Fig. 0.41) and lentigo maligna melanoma, as well as non-melanocytic

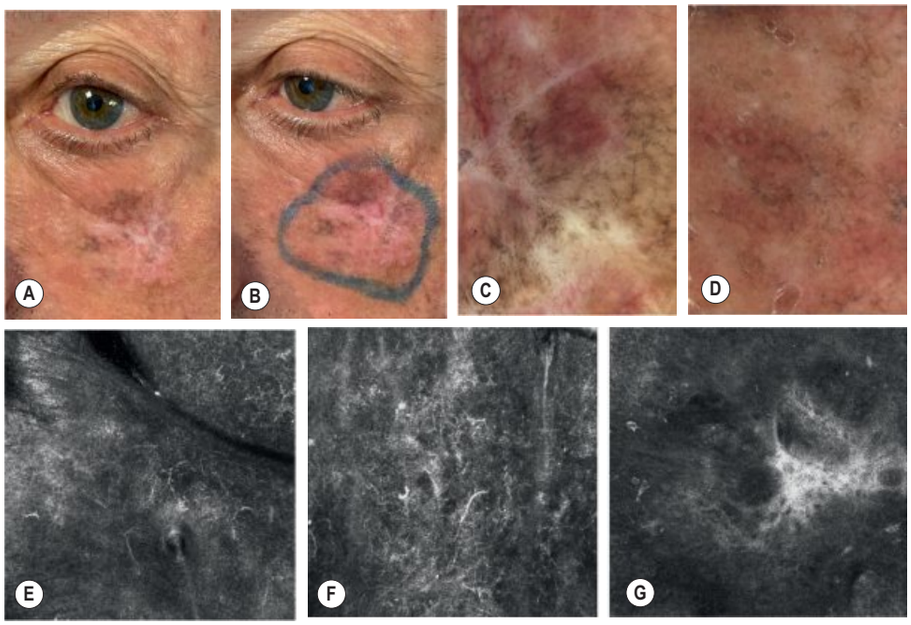


Fig. 0.41 Reflectance confocal microscopy (RCM) of relapsed lentigo maligna. A An X-shaped scar surrounded by a fragmented brown patch with an irregular border. **B** Outline of lesional margins based upon mapping with a handheld RCM device. **C, D** By dermoscopy, there is scar tissue due to the previous excision and an atypical reticular pattern as well as focal gray areas containing fine gray granules. **E, F** RCM illustrates the presence of atypical dendritic melanocytes in the epidermis and pagetoid cells. **G** Scar tissue visible as bright white dermal fibers.

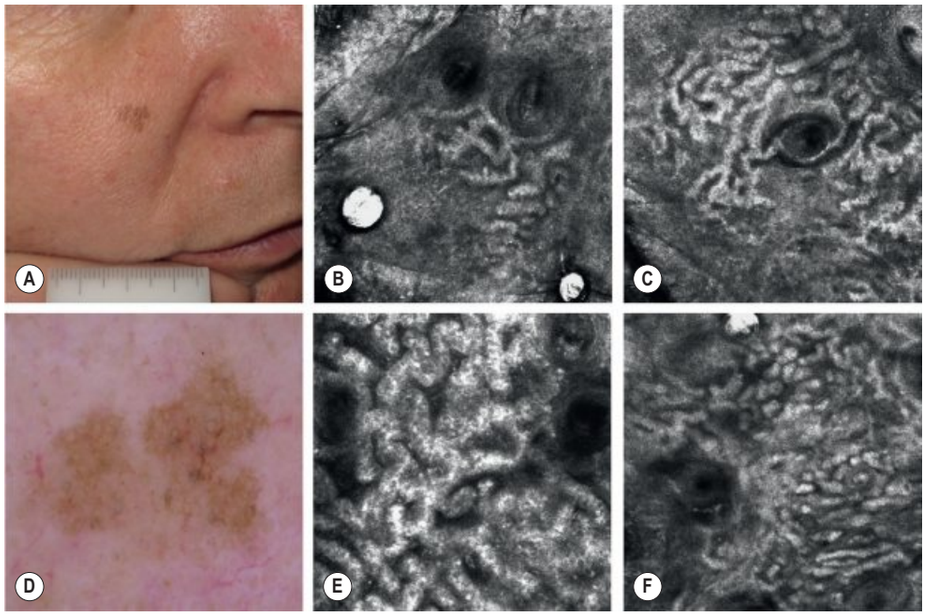


Fig. 0.42 Reflectance confocal microscopy (RCM) of a solar lentigo/macular seborrheic keratosis. A Brown macule on the cheek with a slightly irregular border. **D** By dermoscopy, sharp borders and a pseudo-network are seen. RCM demonstrates epidermal invaginations with keratin pearls (**B, C**) and polycyclic papillae and epidermal bulges (**E, F**).

neoplasms, especially solar lentigines (Fig. 0.42), pigmented actinic keratoses, and lichen planus-like keratoses[58]. When the dermoscopic diagnosis of pigmented macules proves challenging, e.g. when facial lesions have shared dermoscopic features such as a brown pseudo-network and annular granular structures, RCM is often helpful in providing a more definitive diagnosis. For lentigo maligna, RCM can support the diagnosis in addition to identifying its margins[58].

RCM is increasingly being utilized for keratinocytic skin tumors. Characteristic RCM findings of basal cell carcinoma include: dark silhouettes, bright tumor islands with peripheral palisading, cleft-like dark spaces, dendritic cells, plump-bright cells, and dilated canalicular vessels[59,60]. For scaly erythematous lesions in sun-exposed sites or on genitalia (e.g. actinic keratoses, Bowen disease), the detection of atypical keratinocytes is characteristic of a squamous cell proliferation (see Table 0.22). The histologic spectrum, from actinic keratosis (Fig. 0.43) to squamous cell carcinoma, can be assessed by RCM, with the limitation that the dermal portion of the tumor cannot be evaluated[59].

Inflammatory skin diseases

In inflammatory diseases, RCM can assist with clinicopathologic correlations and it provides additional information for confirming the diagnosis and improving therapeutic management[54,56,61]. Psoriasiform dermatitis is characterized by a thickened stratum corneum and epidermis (hyperkeratosis and acanthosis), the presence of highly refractive round-to-polygonal structures within the stratum corneum (parakeratosis), dense and enlarged dermal papillae with thin interpapillary epidermal spaces (papillomatosis), and prominent dark canalicular structures (dilated vessels). Spongiotic dermatitis is characterized by dark intercellular spaces in the epidermis (spongiosis) and oval bright cellular structures between keratinocytes (exocytosis). In acute phases of eczema, intraepidermal vesicles can be detected as well-demarcated dark spaces between keratinocytes, often filled by "floating" inflammatory cells (vesicles with inflammatory cells)[58]. Interface dermatitis is characterized by inflammatory cells within the epidermis and around adnexal structures. Inflammatory cells can be seen at the dermal–epidermal junction, with obscuring of papillary rims, as well as around blood vessels in the upper dermis[62]. Deeper inflammatory processes cannot be assessed by RCM due to the limited penetration of the laser into the skin.

RCM is also helpful in the clinical management of alopecia, thereby avoiding scalp biopsies and allowing for prompt diagnosis. Non-scarring alopecia, in particular androgenic alopecia, is characterized by miniaturization of hair shafts and follicular ostia. RCM findings in lichen planopilaris and lupus erythematosus include involvement of the dermal–epidermal junction, with obscuring of the dermal papillae,

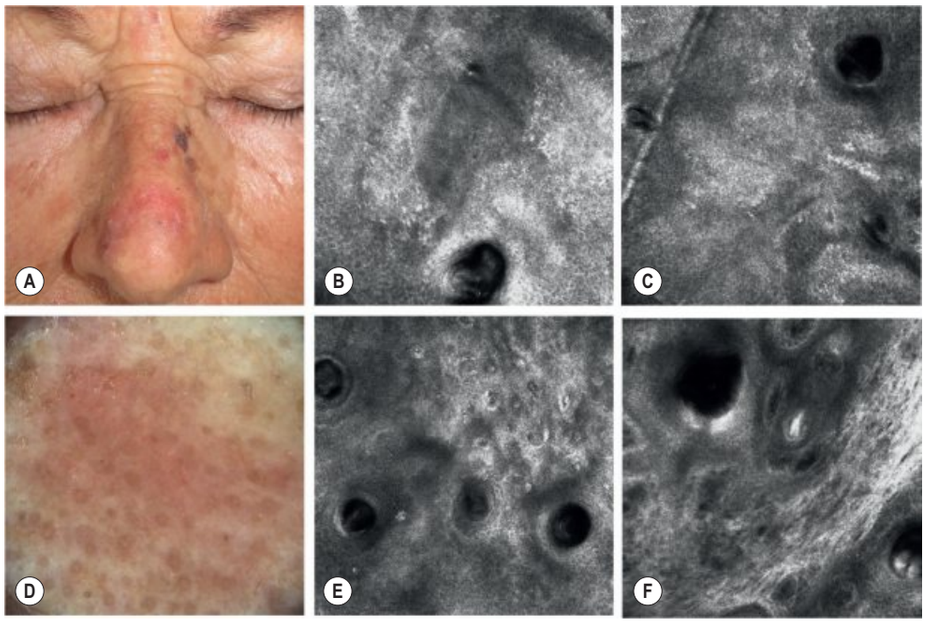


Fig. 0.43 Reflectance confocal microscopy (RCM) of an actinic keratosis on the nose. A Thin erythematous plaque with rough scale. **D** By dermoscopy, there is an erythematous background with the typical strawberry pattern and mild scaling. RCM, progressing from the stratum corneum to the papillary dermis, illustrates parakeratosis (**B**), a mildly atypical honeycombed pattern (**C**), preserved integrity of the dermal–epidermal junction (**E**), and thickening of collagen bundles due to solar damage (**F**).

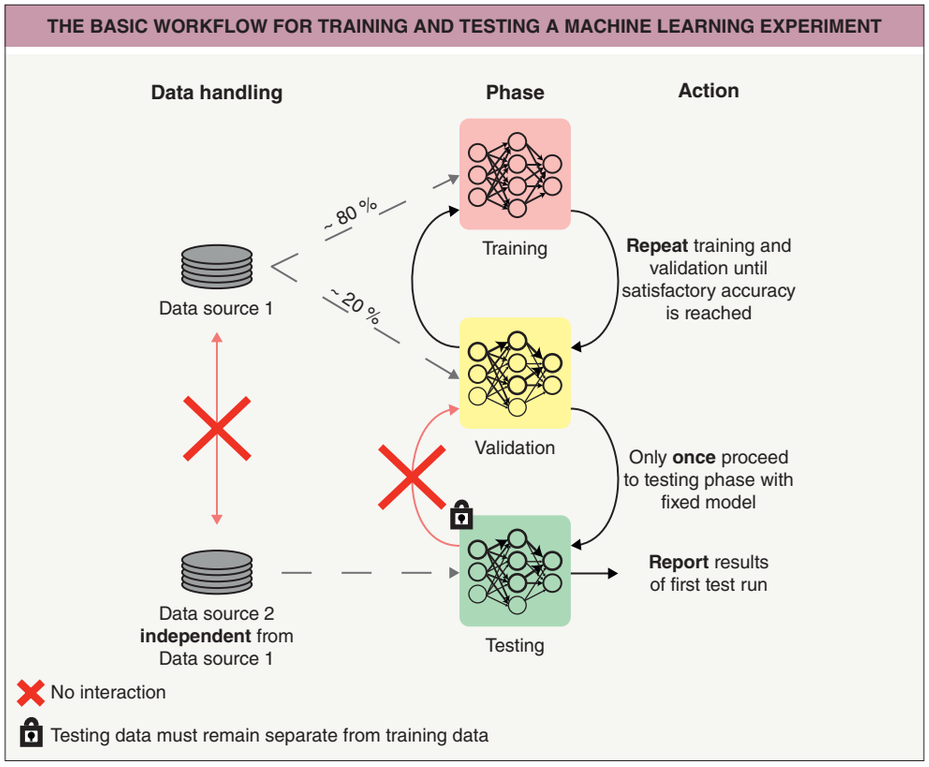


Fig. 0.44 The basic workflow for training and testing a machine learning experiment. The data for the training (pink) and validation (yellow) phases come from a single data collection (Data source 1), while the data for the testing phase (green) should be completely independent (Data source 2). After testing a model, one should not return to the training-validation circle, as this implicitly adds knowledge from the test phase into the training phase and reduces the ability to generalize reported results.

and the presence of inflammatory cells in the epidermis and around adnexal structures. Infiltration of adnexal structures represents a major criterion for lichen planopilaris[54]. Because RCM allows for assessment of the number and distribution of inflammatory cells, disease activity, including response to therapy, can be determined longitudinally[54,58,61].

INTRODUCTION TO ARTIFICIAL INTELLIGENCE

Reports of the potential benefits of artificial intelligence (AI) in healthcare, including dermatology, are rapidly increasing. This section is intended as a guide to basic AI concepts, available technologies, and current and potential future application of computer-aided dermatology. Technical concepts, which are described on an abstract level, are accompanied by instructive schematic illustrations. Clinicians should become familiar with these basic concepts, as they are similar across most models and when understood allow for critical evaluation of current and emerging clinical studies. Although "machine learning" and "AI" are not identical, these terms are used interchangeably below for simplicity. Technical implementations and mathematical concepts are reviewed in referenced publications[63].

Training and Testing AI Models

Machine learning can be viewed as training a virtual machine to solve a task without giving specific instructions but rather by providing training examples along with the known solution. The workflow should consistently follow the same step-by-step pattern (Fig. 0.44), regardless of which specific machine learning model (e.g. support vector machines,

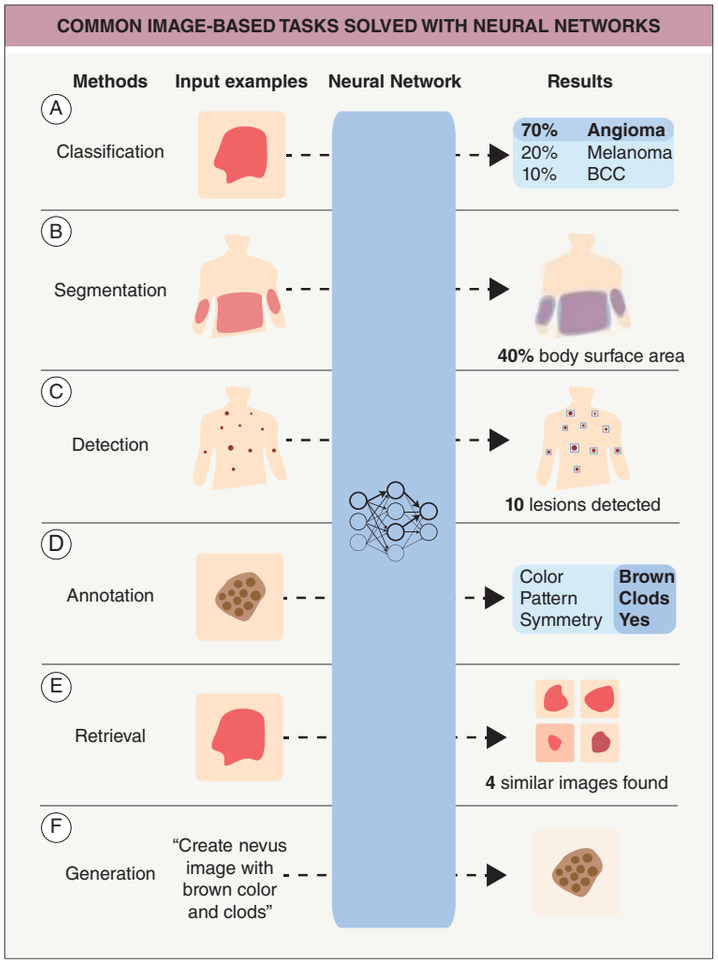


Fig. 0.45 Common image-based tasks solved with neural networks. While basically all tasks can be solved with convolutional neural networks (CNNs) of some type, the specific architecture differs between them. Standard CNNs such as ResNet- or Inception-type networks can solve classification (**A**), annotation (**D**), and retrieval (**E**) just by differing training modalities. However, other architectures are required for image generation (**F**; generative adversarial networks [GANs]) and for segmentation (**B**; e.g. U-Net), object detection (**C**; e.g. RetinaNet, SSD) or both (Mask R-CNN). BCC, basal cell carcinoma.

random forests, convolutional neural networks) is chosen. The steps are as follows:

1. Gather and prepare both **training data** and **test data** for a specified problem that are completely **independent**, e.g. from different study centers. If obtaining independent test data is not possible, ~20% of the original data are initially split off in a random, but usually stratified, fashion as this ensures that cases or patients do not overlap. Test data obtained in this manner must not be touched or examined until the very end; otherwise, the data will have lost their quality as true *test* data. Only the remaining 80% of the data are used as *training* data in steps 2 to 4.
2. **Train** the model with training data for the target task (e.g. probability of melanoma, correct specific diagnosis, affected body surface area); this step utilizes ~80% of the *training* dataset.
3. **Validation:** Measure performance of the model based on the remaining ~20% of the *training* data.
4. **Repeat** steps 2 and 3 while changing training approaches and parameters until a satisfactory performance in the "validation" step is attained.
5. **Lock** the model parameters and proceed to the test phase.
6. **Test**: Measure the model performance on the *test* data **once** and report these results.

This sequence is somewhat simplified, as there are more advanced methodologies such as using *k-fold cross-validation* instead of a fixed, single 20% validation split. However, the steps should reflect the essential concept of strict data handling and experimental workflow in order to avoid negligence or errors that can lead to misinterpretation of results. Unfortunately, the lack of a truly *independent test set* is not uncommon in machine learning and has measurable consequences when generalized, i.e., inferior performance in the real world. A meta-analysis found that studies without an independent test set had systematically different performance results[64].

Image-Based Tasks Solved with Neural Networks

What kind of tasks can a machine learning model potentially solve? Conceptually, anything where there are enough data and the performance can be parameterized as a numeric value, e.g. accuracies of diagnoses in percentages.

Classification (Fig. 0.45A) is the most well-known technique for a visual specialty such as dermatology. The concept is to predict a diagnosis or a list of differential diagnoses from a single image or a sequence of images. This technique can be performed on clinical[65], dermatoscopic[66], or histopathologic images. Utilizing modern neural networks together with large public image datasets[67], experimental, large-scale international studies[68] have shown that the models are equal or superior to dermatologists in classification tasks. Although skin cancer recognition is the most common topic in the literature, one can also automatically grade inflammatory skin diseases or predict diagnoses in general dermatology[65,69]. In addition, tedious tasks such as organizing image databases can be enhanced via classification[67]. Measurements for classification performance are usually chosen for the task at hand and are usually classic diagnostic values such as sensitivity or specificity, crude accuracy, Youden's J, area under the ROC (receiver operating characteristic) curve, or mean sensitivity across multiple diagnoses.

Segmentation (Fig. 0.45B) allows the automatic highlighting and measurement of areas of interest, e.g. affected body area with psoriasis or visual dermatoscopic patterns. In histopathology, semi-automatic and interactive segmentation could enhance the annotation speed of researchers. Well-known measurements for segmentation performance are Intersection-over-Union (IoU, "Jaccard" index) or the Dice coefficient.

Detection (Fig. 0.45C) provides one or multiple marks on an image where an object-of-interest was recognized, as well as the predicted area ("bounding box"). Relevant applications of this technique are detecting skin lesions in full-body images or detecting nuclei in histopathologic images. The detection of skin lesions in full-body images can be combined with a change-detection algorithm to automatically assess whether a lesion has changed over time. The standard measurements for performance is Intersection-over-Union and average precision at prespecified cutoffs of IoU percentages.

Annotation (Fig. 0.45D) is similar to classification, but there is the potential for multiple elements, rather than a single prediction, to be returned. A non-medical analogy would be providing multiple descriptive terms ("hashtags") for an image on social media, e.g. providing all these terms – "scenic", "mountains", "dawn", "alps" – instead of just "mountains". Metrics can be the ones employed in the field of information retrieval such as precision@k, mean reciprocal rank, or average precision.

Retrieval (Fig. 0.45E) of similar cases can be achieved by a technique called *content-based image retrieval* (CBIR), in which a neural network recognizes patterns, structures, and colors from an image, encodes them, and compares them to images in a database. Retrieved similar images can be used for education or for explaining a machine learning model. Although metrics of information retrieval can theoretically be applied to CBIR, the highly subjective nature of visual similarity makes it difficult to evaluate this technique objectively.

Generation (Fig. 0.45F) of artificial images is a more experimental technique. Special types of neural networks, such as GANs (generative adversarial networks)[70], can learn the ability to create artificial images. This application can generate high quality artificial facial and dermatoscopic images, and in the future, it may create genuinely anonymous images for clinical training and reference.

Inputs and results of the techniques mentioned above are basically straightforward, but there are, of course, more advanced applications that use other image material or combinations of data. An example would be automated analysis of histopathologic images to predict genetic changes, prognosis, or treatment efficacy. Since 2012, when Kriszevsky et al.[71] demonstrated the superior performance

of convolutional neural networks (CNNs), image-based machine learning has largely moved from manually crafted "computer vision" techniques to "deep learning", i.e. the application of multilayered neural networks. While there is extensive literature on improvements of CNN models, a detailed discussion is beyond the scope of this section; therefore, they are simply referred to as "neural networks". At the time of this writing, the most well-known modern CNN-based architectures are EfficientNet-, ResNet-, ResNeXt-, SqueezeNet-, MobileNet-, and Inception-type networks for classification and Mask R-CNN, DeepLab, YOLO, SSD, U-Net, and RetinaNet for object detection and/or segmentation.

Although dermatology is a visual domain, it is important to mention other subfields of machine learning that are not image-based but may be helpful to dermatologists. One example is *natural language processing* (NLP), a field in which texts can be analyzed, predicted, or even created. In the future, NLP could automate initial patient interviews through chat-bots, automatically extract ICD-coding from free text, provide diagnosis or management suggestions from patient summaries, automate report generation from a few keywords, or retrieve study patients from electronic health records.

AI does not need to be based on neural networks entirely. For example, another approach that uses classic logic and rule-based systems, in conjunction with a knowledge database, can generate meaningful sets of differential diagnoses from listing clinical descriptions[72].

Shortcomings and Limitations of AI

Convolutional neural networks may learn image-based pattern recognition at a similar pace compared to humans[73], but are inherently limited to the knowledge they can extract from training data. Thus, to achieve a clinically useful and robust performance, CNNs require large, diverse, comprehensive, well-curated training datasets. While such large datasets are available for images of general objects, they are mostly unavailable in dermatology. The nearly exhaustive list of usable public datasets at the time of this writing are dermatoscopic images from PH2, the ISIC archive (including HAM10000 and ISIC challenge datasets), and derm7pt, as well as clinical images from the SD-198 dataset. Except for melanoma in the TCGA, there is basically no relevant public, reusable dataset for dermatopathology at the time of this writing. This limited list highlights that clinicians and clinical researchers are in need of more published useful datasets.

What are the specific impacts of too little data? When only a few datasets are available, the rule of strict test set splitting (see above) may become impossible. Test sets will then originate from the same source as training images, skewing estimates of diagnostic performance[64]. Fewer examples of diagnoses in datasets introduce dataset **bias**. If image examples of one of the diagnoses are mostly from one single center and photographed there with one specific camera or lighting conditions, a CNN will learn to recognize this camera and lighting conditions rather than the diagnosis itself. Another example is that melanomas are often photographed with skin markings or rulers to document their size, resulting in CNNs predicting "melanoma" at a higher rate when skin markings or rulers are included in an image[74]. With techniques to control biases, such as illumination color, de-biasing images is theoretically possible but difficult to implement in practice. Lastly, academic skin cancer centers usually have more expensive equipment to document diseases and well-trained staff to provide high-quality images, both of which may not be available in future point-of-care settings where CNNs will later be deployed.

When predicting diagnoses from clinical images, there is a wide range of **possible diagnoses** in dermatology. CNNs will perform well on common, well-documented diagnoses such as psoriasis or melanoma, but may fail on the "long tail" diagnoses, which are numerous but rare, because there are fewer or even missing training examples.

Another problem is not machine learning itself, but the way it is being studied, measured, and compared to physicians. Often, ensembles of several large CNNs require large computational resources and a lot of time to make predictions. Compared to single human participants (physicians) who make decisions almost instantly, these large ensembles are rarely used in real-life situations. This is because the computing is too expensive, not feasible on smaller devices such as smartphones, or simply too time-consuming.

Target metrics to evaluate performance were briefly mentioned above but are sometimes inadequately chosen in the clinical context. For example, experimental studies measuring the area under the ROC curve for differentiating malignant from benign skin tumors may allow for comparison of differences in performance in general. However, the resulting models may not be useful for clinical applications because no specific cut-off is chosen and measured in a clinically meaningful way.

The quality of clinical endpoints is also difficult to measure. In studies of CNNs that diagnose melanocytic tumors, "ground truth" for comparisons is problematic. Even for experts, interrater reliability in histologic discrimination of melanoma from nevi is far from perfect, and this issue may only be solved by integrating clinical information and dermatoscopic evaluation. The fact that the targeted "ground truth" may not even be true is often not considered in technically focused CNN studies.

Possible Clinical Implementations of AI

The application of automated predictions carries tremendous opportunities, but also significant risks and liability as malignant diseases may be misdiagnosed. As a result, standalone applications in which patients receive an automated diagnosis directly from an AI model have not gained traction in dermatology. Instead, collaborative models involving the interaction of physicians and CNNs seem much more promising. The successful use of AI depends not only on its experimental accuracy, but even more importantly on where, how, and by whom it is used. The different implementation scenarios of AI will depend on the task at hand.

Autonomous predictions (Fig. 0.46A) aimed directly at the patients are currently best suited for low-risk tasks and monitoring, such as calculating the PASI (Psoriasis Area and Severity Index) or monitoring the severity of acne. In the field of skin cancer, direct patient education has been successfully tested, but applications for skin cancer diagnosis have been found to lack accuracy[75]. Although modern CNNs will probably be more accurate in the future, appropriately controlled prospective clinical trials demonstrating utility and safety are lacking at the time of writing.

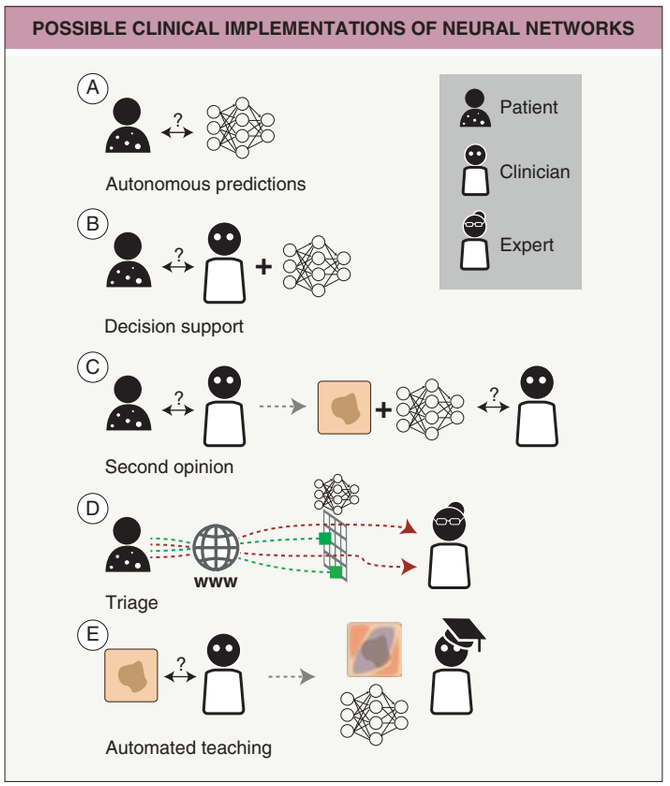


Fig. 0.46 Possible clinical implementations of neural networks. Image-based machine learning models can be implemented at multiple sites of the patient workflow, guided towards and used by different groups such as patients, clinicians, or experts. ? represents a clinical problem such as determining the correct clinical diagnosis or therapy.

Decision support (Fig. 0.46B) for when physicians are examining patients is a more nuanced implementation of automated prediction that keeps the clinicians "in the loop", avoids catastrophic events, and allows for integration of patient context, concerns, and treatment preferences. Experimental data have shown that interaction with automated multi-class predictions can increase physicians' accuracy of clinical and dermatoscopic[76] diagnoses.

Second opinion (Fig. 0.46C) will allow physicians to re-assess a case after a patient visit, similar to consulting an expert, and enable *post hoc* changes in treatment decisions. It has been shown that physicians perform fewer unnecessary biopsies after AI-guided reassessment of their own patient evaluations[76].

Triaging (Fig. 0.46D) patients, referrals, or cases for review is an important task when human and healthcare resources are limited. It has been shown that triage using teledermatology can reduce wait times for skin cancer patients. Patients at high risk for skin cancer can perform self-monitoring to automatically detect skin cancer with reasonable specificity; however, such applications should not be used to avoid in-person screening altogether but rather to increase screening intervals.

Automated teaching (Fig. 0.46E) represents a slower implementation of AI into healthcare and is aimed more at improving physician education. Cai et al.[77] have shown that histologic case retrieval can be improved by interactive use of a machine learning model. Other groups have successfully generated diagnosis lists with a logic-based algorithm as an education tool for building clinical differential diagnoses[72].

Future of AI

In summary, machine learning and AI will almost certainly guide and help physicians in clinical practice in the future. Maybe it will not be necessary to calculate scores like PASI by hand anymore or it will be easier to narrow down diagnostic gray areas in melanocytic lesions, conduct population-wide skin cancer screenings, and perform semi-automated telemedicine/triage. Automated predictive staging systems may replace TNM staging systems. However, what will become a reality depends on physicians and researchers, technical advances, patients, politics, companies, ethical considerations, and regulatory agencies. There are also many other applications and techniques that are not or only briefly covered here, given limitations on content. Finally, the field of machine learning is fast-paced, and critical review of relevant literature is paramount in understanding new concepts and possibilities of AI.

CONCLUSION

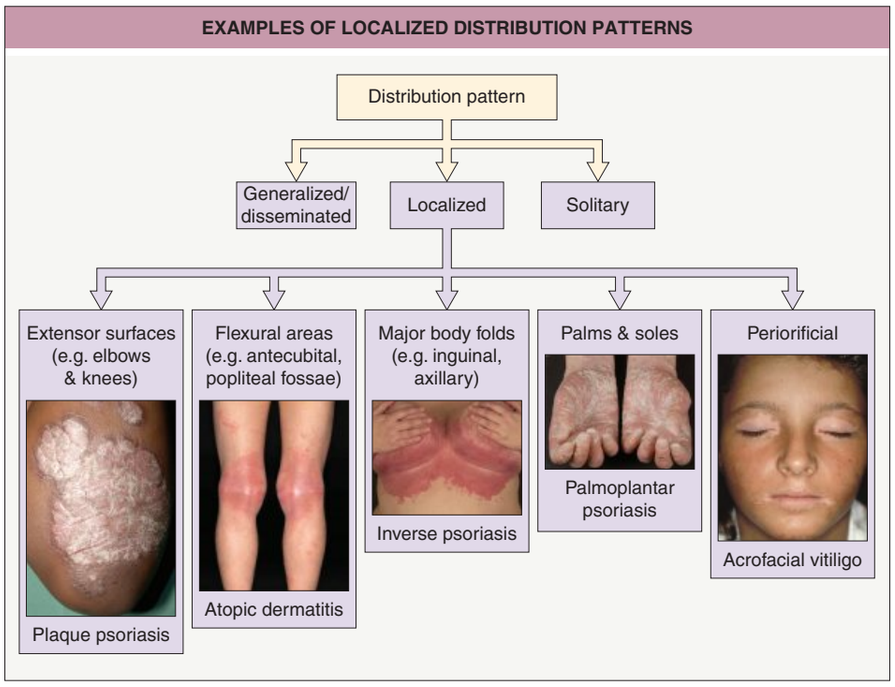
This chapter has sought to provide an introduction and basic structural framework to the study of dermatology by addressing terminology, morphology, pattern recognition, and a number of techniques that will all serve to enhance the practice of clinicopathologic correlation. The desired end results are more accurate diagnoses and better care of patients.

Additional figures and table, Acute cutaneous eruptions in otherwise healthy individuals, available in our eBook (see inside front cover for access code).

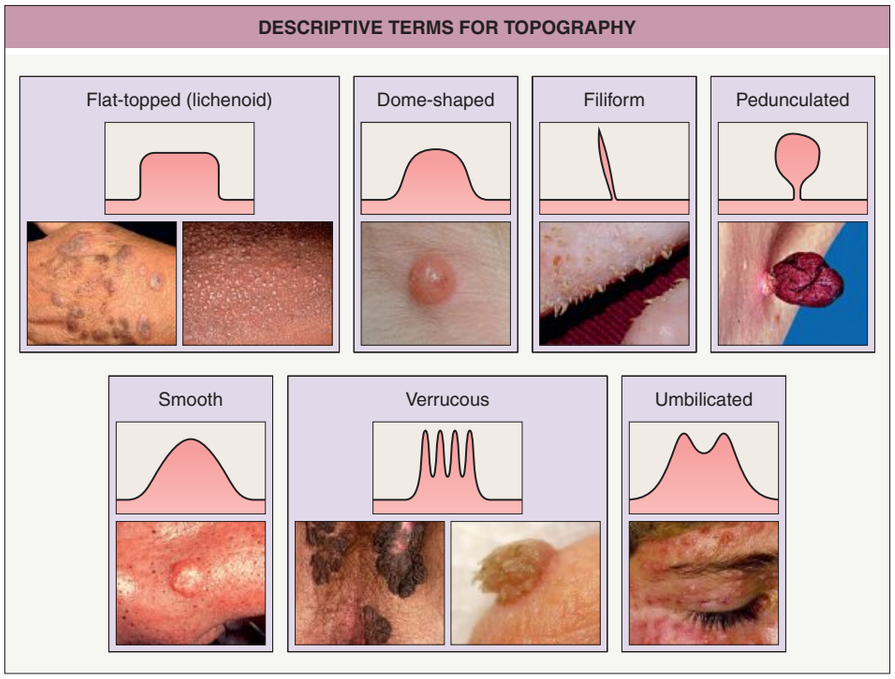
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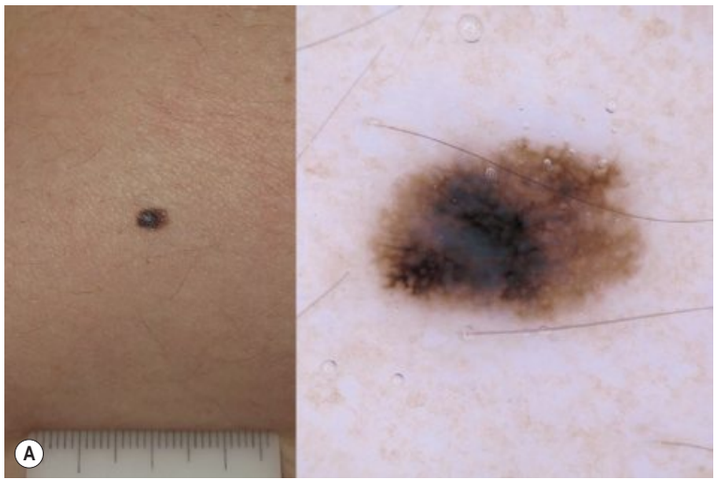
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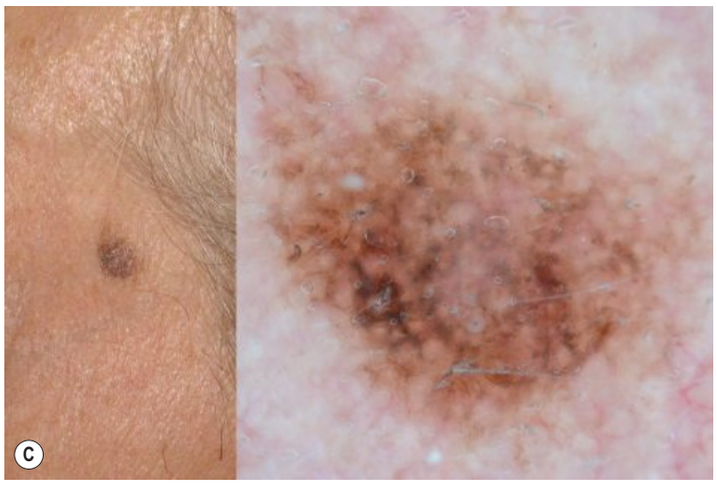
eFig. 0.1 Examples of localized distribution patterns. Additional patterns are outlined in Table 0.8. Generalized lesions are seen in morbilliform drug eruptions and viral exanthems. *Photographs courtesy Peter C.M. van de Kerkhof, MD; Thomas Bieber, MD; and Julie V. Schaffer, MD.*



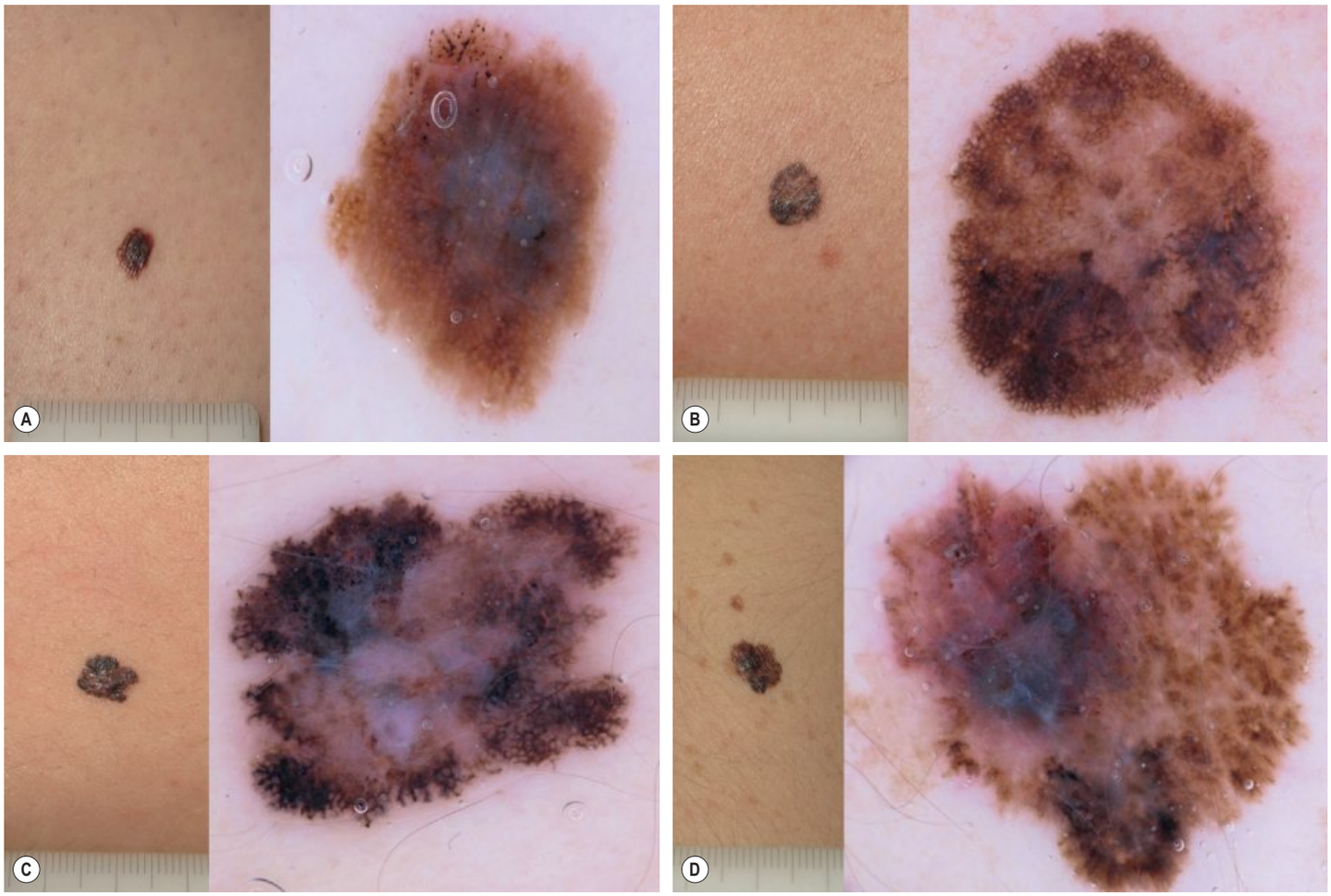
eFig. 0.2 Descriptive terms for topography. *Photographs courtesy Jennifer Choi, MD; Hideko Kamino, MD; Reinhard Kimbauer, MD; Petra Lenz, MD; Frank Samarin, MD; Julie V. Schaffer, MD; and Judit Stenn, MD.*





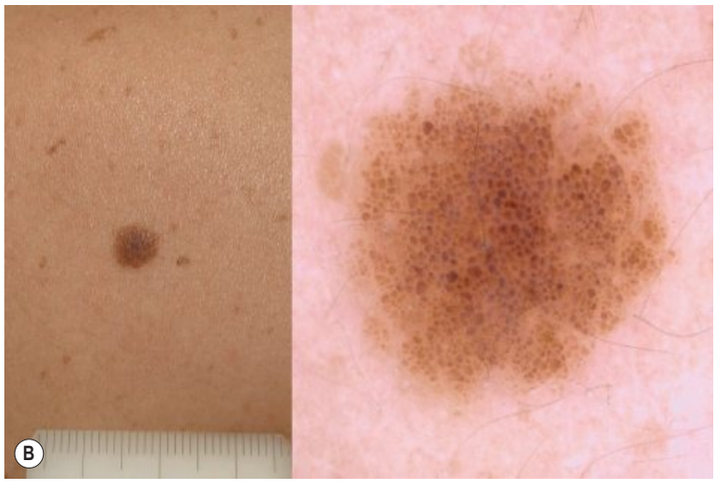


eFig. 0.3 The three most common types of melanoma. A Small superficial melanoma typified dermoscopically by asymmetry of color and structure, atypical network, blue–white structures, and irregular streaks at the periphery. **B** Large thick melanoma with predominant blue–white veil. The combination of blue color with irregular black to brown dots, globules, and blotches (as seen here) is highly specific for the diagnosis of thick melanoma. **C** Small facial melanoma *in situ* (lentigo maligna) typified by gray color and rhomboidal structures in dermoscopy.



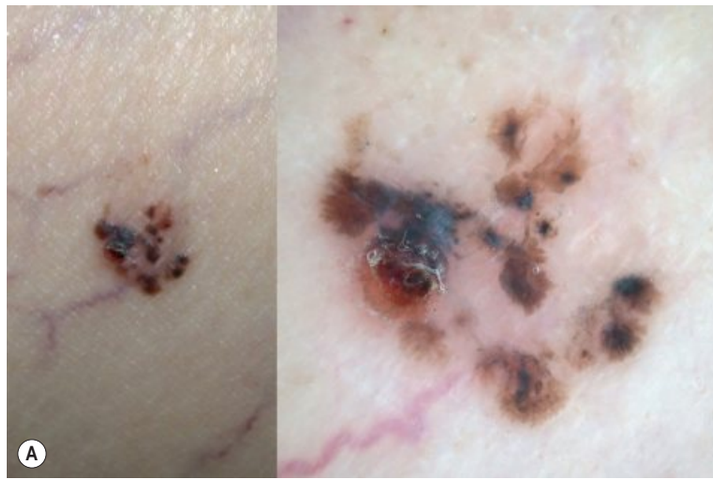
eFig. 0.4 Four examples of superficial melanomas of increasing tumor thickness. A Melanoma *in situ* typified dermoscopically by asymmetry of color and structure, atypical network, blue–white structures, and irregular black dots and globules (at the upper side of the lesion). **B** Melanoma 0.5 mm thick typified predominantly by atypical pigment network and regression structures. The latter are composed by areas of pigment loss (in the center of the lesion) and bluish pepper-like granules corresponding to melanophages. **C** Melanoma 0.75 mm thick typified by multiple melanoma-specific criteria including asymmetry of color and structure, atypical network, irregular streaks at the periphery, irregular dots and globules (upper side of the lesion), and blue–white structures especially in the center. **D** Melanoma 0.9 mm thick. Clinically, a palpable area is visible, corresponding dermoscopically to the presence of blue–white veil, a sign of increased tumor thickness. Irregular dots and globules (at the upper side), irregular streaks at the periphery, and uneven brown to black pigmented areas (blotches) are also observed.



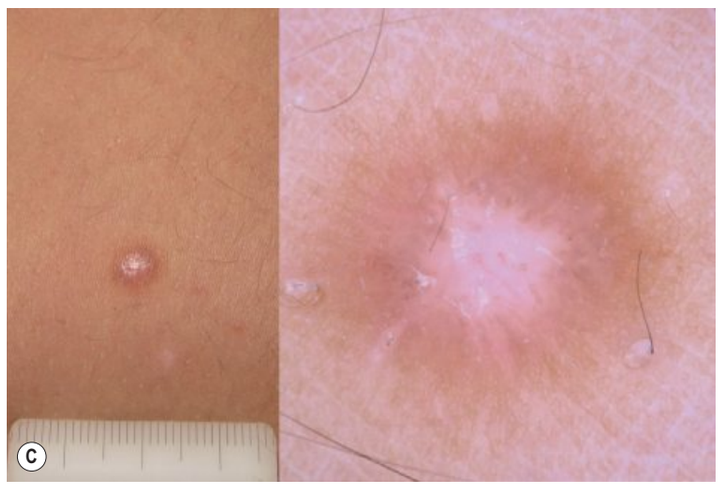




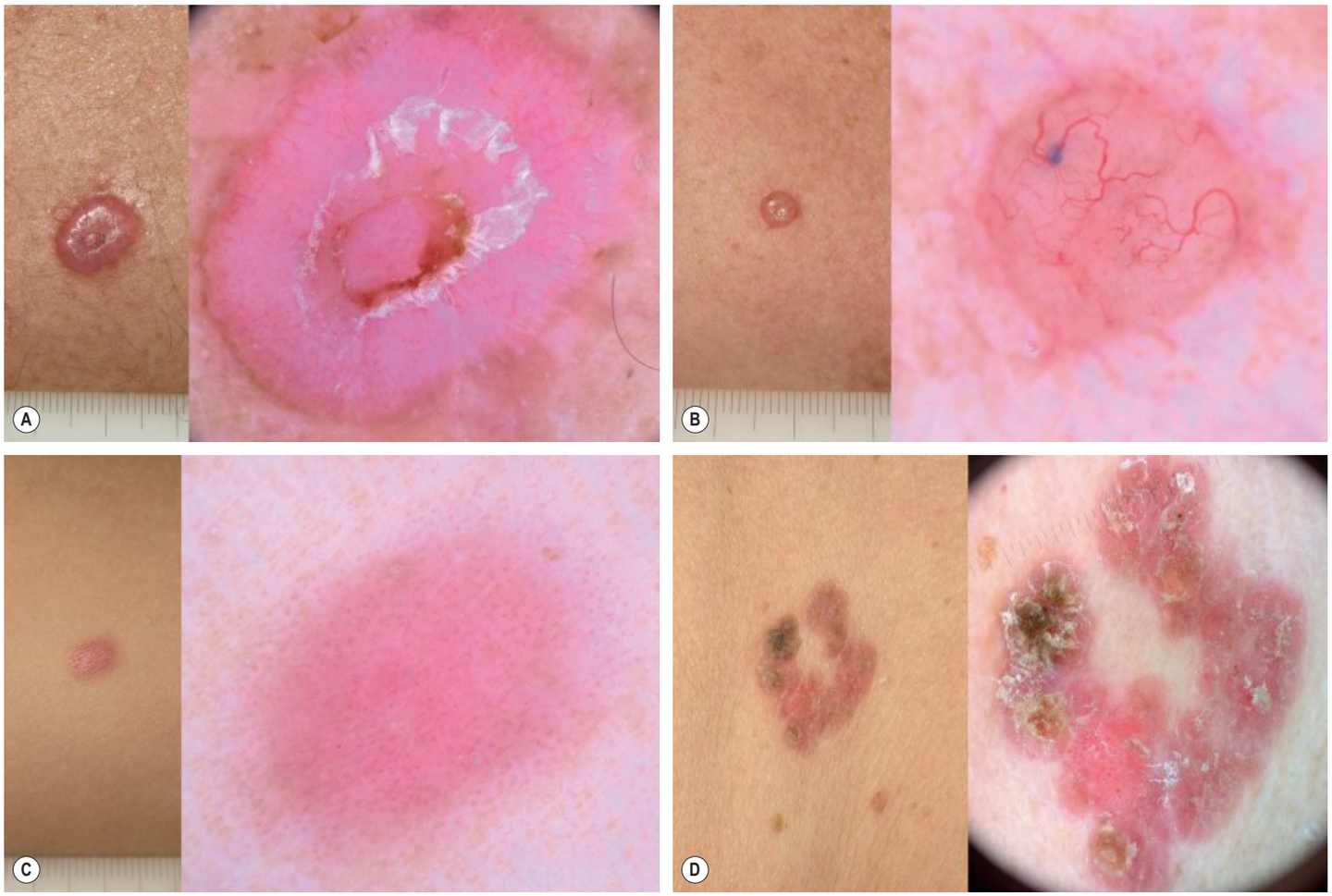
eFig. 0.5 The three most common types of melanocytic nevi – clinical and dermoscopic findings. A Typical acquired nevus with reticular pattern in dermoscopy. **B** Small congenital nevus with globular pattern. **C** Reed nevus typified dermoscopically by the classic starburst pattern (regular streaks at the periphery of a heavily pigmented and symmetric small macule).



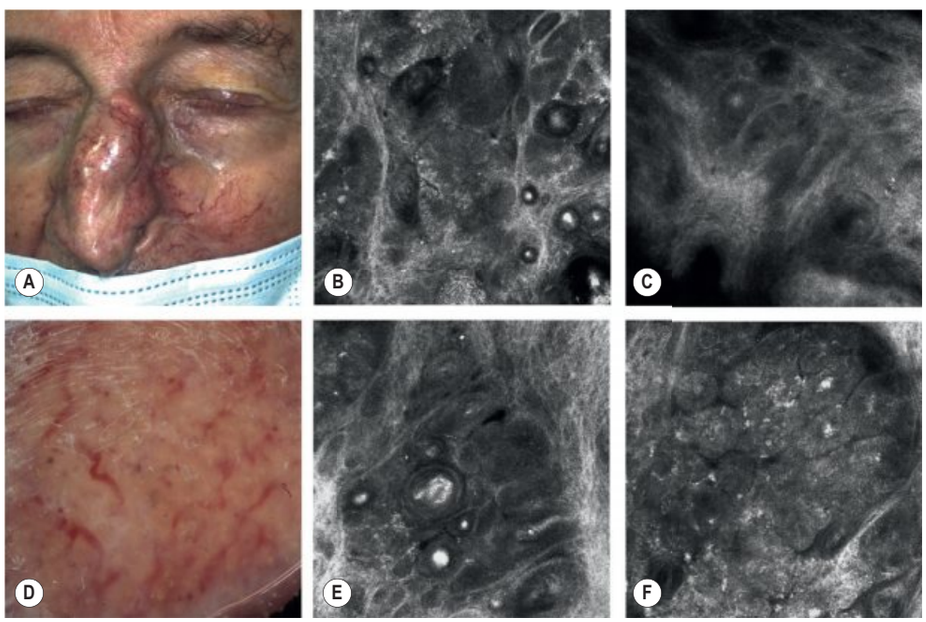




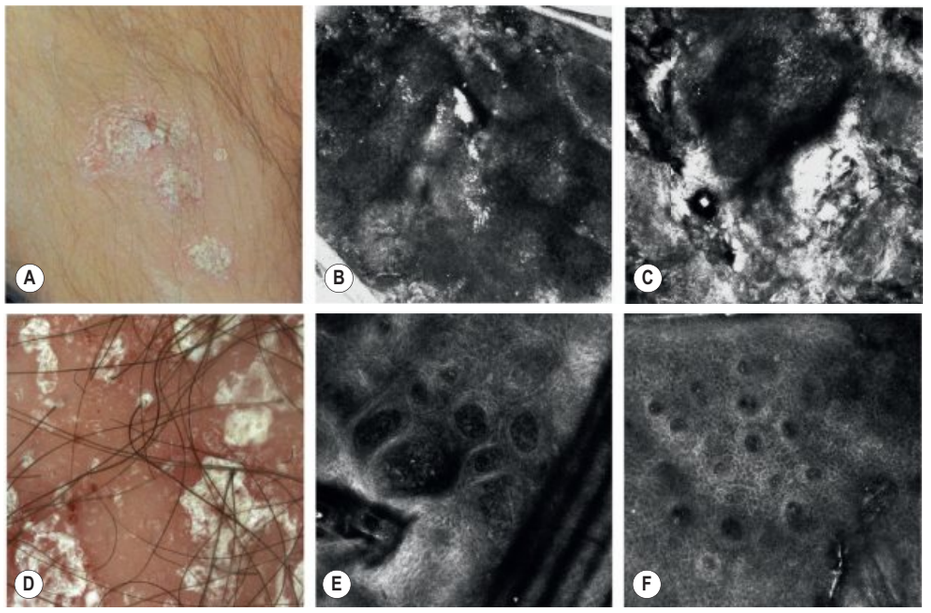
eFig. 0.6 Three non-melanocytic pigmented tumors – clinical and dermoscopic findings. A Pigmented basal cell carcinoma with leaf-like areas (islands of blue–gray color) at the periphery and a small erosion of reddish color at the left side of the lesion. **B** Angiokeratoma with red–black lacunae clearly visible as well-demarcated roundish structures. **C** A dermatofibroma with characteristic central white patch and peripheral delicate pseudo-network.



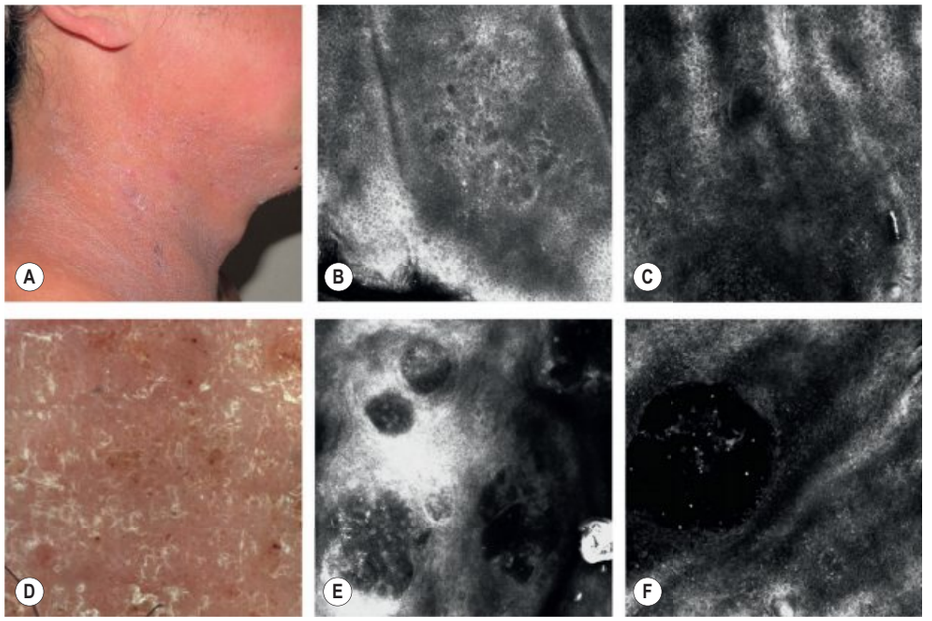
eFig. 0.7 Four non-pigmented skin tumors – clinical and dermoscopic findings. A This amelanotic melanoma is typified by a central ulceration, polymorphic vascular structures (combination of dotted and linear-irregular vessels), and milky-red color in the background. **B** Nodular basal cell carcinoma with striking arborizing vessels. **C** A Spitz nevus with dotted vessels and typical negative pigment network (reticular depigmentation) at the periphery. **D** An example of Bowen disease with clusters of glomerular vessels that in combination with superficial scales are highly specific for the diagnosis.



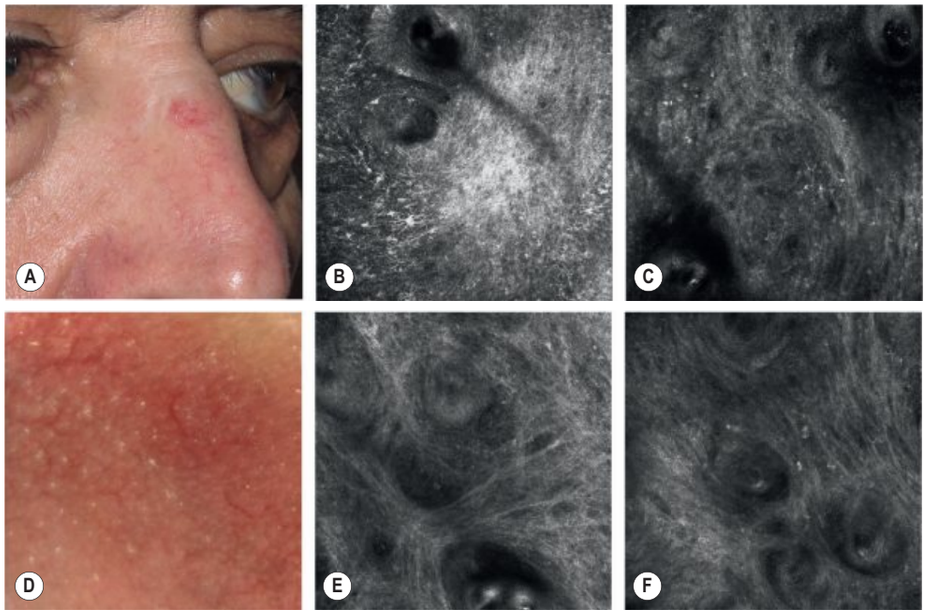
eFig. 0.8 Reflectance confocal microscopy (RCM) of recurrent basal cell carcinoma (BCC). A Recurrence of a BCC on the nose. **D** Telangiectasias seen by dermoscopy. RCM shows tumoral nests with palisading (**B**), dark silhouettes of tumor nests in the dermis (**C**), hyper-reflective stroma surrounding tumor nests (**E**), and peri-tumoral clefts (**F**).



eFig. 0.9 Reflectance confocal microscopy (RCM) of plaque psoriasis. A Discrete pink plaques with thick scale. **D** Diffuse dotted vessels by dermoscopy. RCM of the stratum corneum showing hyperkeratosis (**B**) with parakeratosis (**C**), then in deeper sections, dilated papillae with dilated looping vessels (**E**), and dense dermal papillae (**F**).



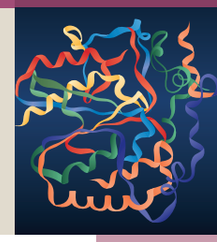
eFig. 0.10 Reflectance confocal microscopy (RCM) of allergic contact dermatitis of the neck. A Diffuse erythema of the neck with scaling and scattered crusts. **D** Yellow scale-crusts and pinpoint hemorrhagic crusts by dermoscopy. RCM of the epidermis with inflammatory cells and dark areas corresponding to spongiosis (**B, C**) and vesicles (**E, F**).



eFig. 0.11 Reflectance confocal microscopy (RCM) of discoid lupus erythematosus. A Single erythematous plaque on the dorsum of the nose that could be misdiagnosed as a non-melanoma skin cancer. **D** By dermoscopy, erythematous telangiectatic background with follicular hyperkeratosis. RCM shows bright white inflammatory cells around adnexal structures (**B**) and within the epidermis (**C**); follicular hyperkeratosis (**E**) and thick collagen bundles plus melanophages (large polygonal cellular structures between collagen bundles; **F**) are also seen.

ACUTE CUTANEOUS ERUPTIONS IN OTHERWISE HEALTHY INDIVIDUALS	
Disorder	**Characteristic findings**
Urticaria (see Ch. 18)	• Pathogenesis involves degranulation of mast cells with release of histamine • Primary lesion: edematous wheal with erythematous flare • Widespread distribution • Very pruritic* • Individual lesions are transient (<24 h in duration) • May become chronic (>6 weeks)
Acute allergic contact dermatitis (see Ch. 14)	• Immune-mediated and requires prior sensitization • Primary lesion: dermatitis, with vesicles, bullae, and weeping when severe • Primarily in sites of exposure; occasionally more widespread due to autosensitization • Pruritus, often marked • Spontaneously resolves over 2–3 weeks if no further exposure to allergen (e.g. poison ivy, nickel)
Acute irritant contact dermatitis (see Ch. 15)	• Direct toxic effect • Primary lesion: ranges from erythema to bullae (e.g. chemical burn) • At sites of exposure • Burning sensation • Spontaneously resolves over 2–3 weeks if no further exposure to irritant (e.g. strong acid, strong alkali)
Exanthematous (morbilliform) drug eruptions (see Ch. 21)	• Immune-mediated and requires prior sensitization • Pink to red–brown, blanching macules and papules; may become purpuric on distal lower extremities • Widespread distribution • May be pruritic • Spontaneously resolves over 7–10 days if no further exposure to inciting drug
Pityriasis rosea (see Ch. 9)	• May follow a viral illness • Primary lesion: oval-shaped, pink to salmon-colored papule or plaque with fine white scale centrally and peripheral collarette; occasionally vesicular • Initial lesion is often largest (herald patch) • Favors trunk and proximal extremities; may have inverse pattern (axillae & groin); long axis of lesions parallel to skin cleavage lines • Spontaneously resolves over 6–10 weeks; exclude secondary syphilis
Viral exanthems (see Ch. 81)	• Due to a broad range of viruses, including rubeola, rubella, enteroviruses, parvovirus, adenovirus (see Fig. 81.2) • Often associated with fever, malaise, arthralgias, myalgias, nausea, upper respiratory symptoms • Primary lesions vary from blanching pink macules and papules to vesicles or petechiae • Distribution varies from acral to widespread; may have an enanthem • Spontaneously resolves over 3–10 days
*May have burning rather than pruritus with urticarial vasculitis, and lesions can last longer than 24 hours.	

eTable 0.1 Acute cutaneous eruptions in otherwise healthy individuals.



1 Anatomy and Pathophysiology

Travis W. Vandergriff

Key features

- The relationship between structure and function of the skin is best demonstrated by presenting diseases that illustrate how skin can fail. Thus, disease reveals function, and function highlights structure
- The most obvious function of the skin is to maintain an internal environment that allows an organism to protect DNA and to reproduce it relatively faithfully
- Cutaneous structures include an *epidermis* that serves as a barrier (preventing loss from within and damage from external insults) and a *dermis* that provides mechanical support, circulation, and nutrition. Other functions provided by the cells in the skin include immune recognition and memory, the ability to repair damage, thermoregulation, and communication
- Evidence that the skin has failed includes barrier disruption, infection, autoimmunity, cancer, and an appearance undesirable to the individual

INTRODUCTION

Most reviews of the anatomy and physiology of skin begin with detailed descriptions of cellular composition, structural proteins, and extracellular matrix. Since each of these topics is covered in subsequent sections of the textbook, this chapter will briefly introduce the cells and structures, with references to the appropriate chapters for further details. We will reverse the conventional approach by examining diseases that illustrate the function of the skin in the context of the cells and structures that sustain it. This method is derived from the assertion that the structure and function of the skin are best illustrated by disease. The strength of this alternative approach may be seen in clinical vignettes easily recognized by those who care for patients with skin disease:

- a 70-year-old man with skin phototype I who works outdoors develops a lentigo maligna melanoma of the face
- a 16-year-old boy with hypohidrotic ectodermal dysplasia suffers a heatstroke while competing in outdoor athletics in Texas
- toxic epidermal necrolysis due to trimethoprim–sulfamethoxazole develops in a 40-year-old woman, leading to dehydration and sepsis
- numerous squamous cell carcinomas arise on the face and extensor forearms of a renal transplant recipient with significant cumulative sun exposure
- linear eruption of grouped vesicles due to varicella–zoster virus develops on the left flank of a young man with HIV infection

These patients and their diseases illustrate at least four of the functions of the skin: photoprotection, thermoregulation, barrier formation, and immunologic protection.

THE BASIC STRUCTURE OF SKIN

The skin is divided into three major layers: the epidermis, dermis, and subcutaneous fat (Fig. 1.1). The anatomic structures observed by light microscopy are fairly similar in most body regions (Fig. 1.2). However, specialized skin regions such as the palms, soles, genitalia, and scalp have modified forms that address regional functional requirements (Fig. 1.3).

Epidermis

In humans, the epidermis contains four major resident populations: keratinocytes (Ch. 56), melanocytes (Ch. 65), Langerhans cells (Ch. 4), and Merkel cells (Chs. 2 & 115). The most obvious function of the epidermis resides in the stratum corneum (Fig. 1.4), a semipermeable, laminated surface aggregate of differentiated (keratinized) squamous epithelial cells. The stratum corneum serves as a physiologic barrier to chemical penetration and microbiologic invasion from the environment, as well as a barrier that prevents fluid and solute loss from within[1] (Ch. 124).

Keratinocytes, the major population, are epithelial cells that originate from a stem cell pool situated in the basal layer; cells that leave this pool then differentiate as they migrate upward, ultimately forming the laminated stratum corneum. The human epidermis has an average thickness of 50 microns and a surface density of ~50 000 nucleated cells/mm^2. Under normal conditions, differentiated keratinocytes require about two weeks to exit the nucleated compartment and another two weeks to move through the stratum corneum[2]. When stimulated by injury, inflammation or disease, keratinocytes can significantly increase their proliferation and maturation rates (Ch. 8).

Melanocytes, as noted in a DOPA-stained whole mount of the epidermis, manufacture the light-absorbing pigment melanin, which plays a major role in protecting the skin from the harmful effects of ultraviolet (UV) radiation (Ch. 86). Melanosomes, with their complement of melanin, are produced by melanocytes and then transferred to nearby keratinocytes, where their preferred location is above the nucleus, providing protection for genetic material (see Fig. 65.5)[3].

Langerhans cells metabolize complex antigens into peptides, some of which are immunogenic. After activation, these cells migrate from the epidermis to regional lymph nodes, where they play a critical role in antigen presentation during the induction and regulation of immunity (see Fig. 4.13).

Merkel cells contain neuroendocrine peptides and are found in the basal layer of the epidermis, although they may not be apparent in routine histologic sections. Although these cells are thought to play a role in mechanoreceptor responses, their precise physiologic role remains an area of inquiry.

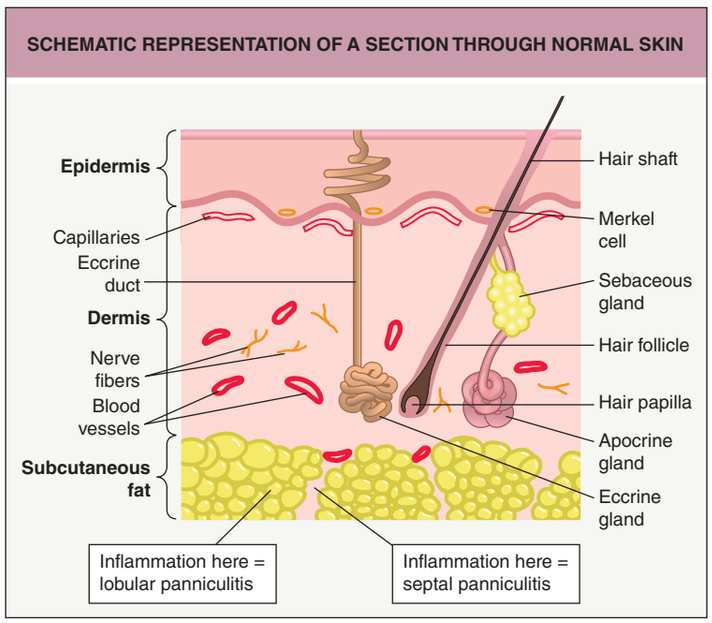


Fig. 1.1 Schematic representation of a section through normal skin. The skin is divided into 3 major layers: (1) the epidermis, which serves as a barrier to prevent loss of fluid and electrolytes and to protect against external insults such as chemicals and microbes (see Fig. 1.4); (2) the dermis, which provides structural and nutritional support (see Fig. 1.5); and (3) the subcutaneous fat. Adnexal structures, including hair follicles, sebaceous glands, eccrine glands and apocrine glands, are found within the dermis.

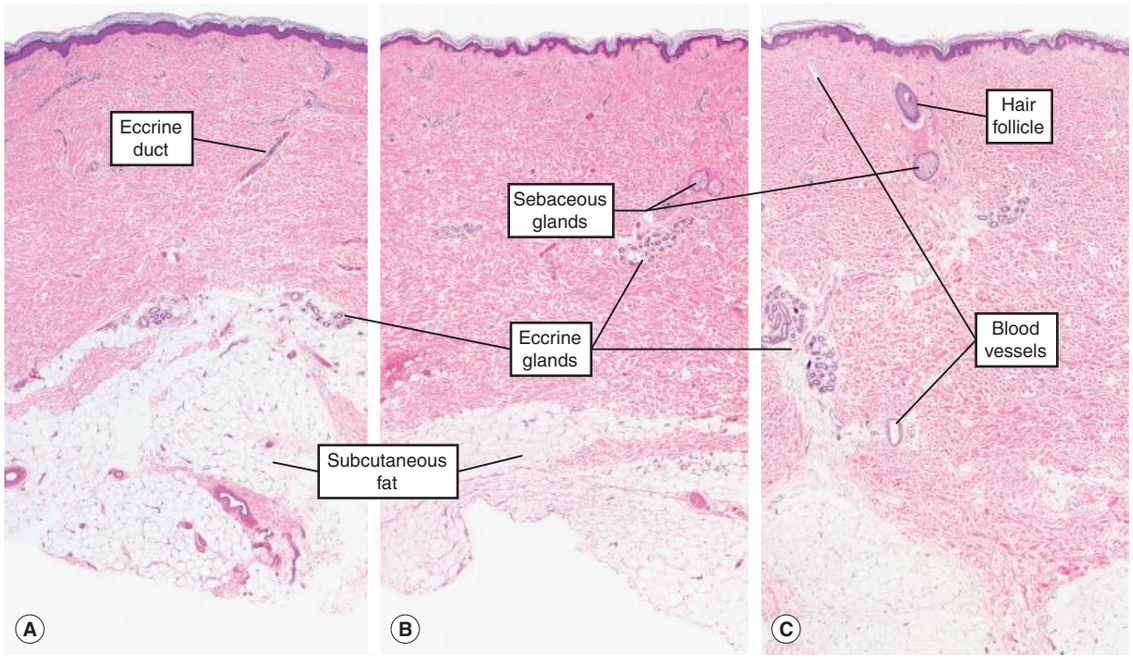


Fig. 1.2 Histopathologic features of normal skin from three different anatomic sites. Comparison of biopsy specimens from the arm (**A**), flank (**B**), and back (**C**) illustrates the increasing thickness of the dermis, but also similarity with regard to the presence of blood vessels and adnexal structures including eccrine glands. *Courtesy Lorenzo Cerroni, MD.*

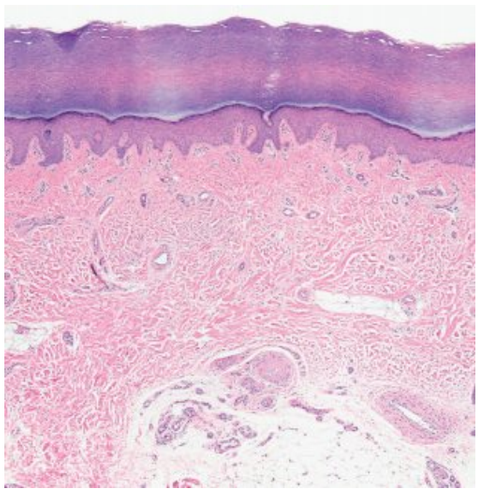


Fig. 1.3 Histopathologic features of normal plantar skin. Note the markedly thickened stratum corneum, compared to the photomicrographs in Fig. 1.2. The thickened stratum corneum protects against mechanical stress. *Courtesy Lorenzo Cerroni, MD.*

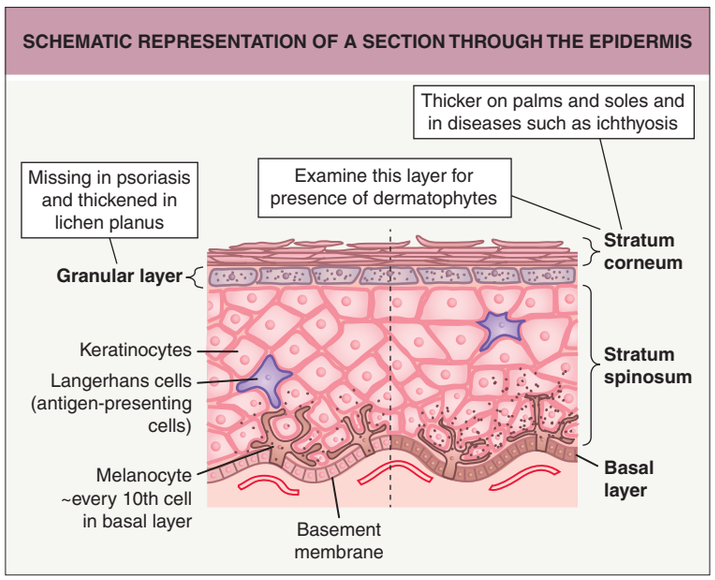


Fig. 1.4 Schematic representation of a section through the epidermis. The epidermal layers from the surface are: (1) the cornified layer (stratum corneum); (2) the granular layer (stratum granulosum); (3) the spinous layer (stratum spinosum); and (4) the basal layer (stratum basale). Under normal conditions, keratinocytes require about two weeks to exit the nucleated compartment and an additional two weeks to move through the stratum corneum. The basement membrane represents the junction between the epidermis and the dermis. Cell populations that reside within the epidermis include melanocytes along the basal layer, which transfer melanin to the surrounding keratinocytes via melanosomes, and Langerhans cells, which serve as antigen-presenting cells. On the left is lightly pigmented skin and on the right is more darkly pigmented skin.

Dermis

Beneath the epidermis, the vascularized dermis provides structural and nutritional support. The dermis is composed of a glycosaminoglycan gel held together by a fibrous connective tissue matrix containing collagen and elastin (Fig. 1.5) (Ch. 95). Vascular structures, accompanied by nerves and mast cells (Ch. 118), course through the dermis to provide nutrition, recirculating cells, and cutaneous sensation. Three additional cells, fibroblasts, macrophages, and dermal dendritic cells, complete the list of dermal residents.

In pathologic conditions such as acute inflammation, the functions and types of dermal cells change substantially, with various infiltrating leukocytes entering via the blood vessels. The composition of cutaneous infiltrates differs depending on the disease entity, providing useful diagnostic clues (Fig. 1.6).

Dermal–Epidermal Interface

The boundary between the epidermis and dermis consists of a specialized aggregation of attachment molecules and associated matrix, collectively known as the basement membrane[4] (Ch. 28). This structure is of considerable interest because various diseases originate from genetic defects in the composition of the basement membrane or from autoantibodies, which render individual components dysfunctional.

STRUCTURE AND FUNCTION OF THE SKIN AS IT RELATES TO DISEASE

We have chosen to present in this chapter a conceptual framework into which the other chapters of this textbook can be placed. This framework is derived from the assertion that knowledge of cutaneous function begins with disease. One corollary of this assertion is that there may be unrecognized skin functions, either because there is no corresponding disease yet recognized or because the disease is fatal. For example, no one would have guessed that incontinentia pigmenti

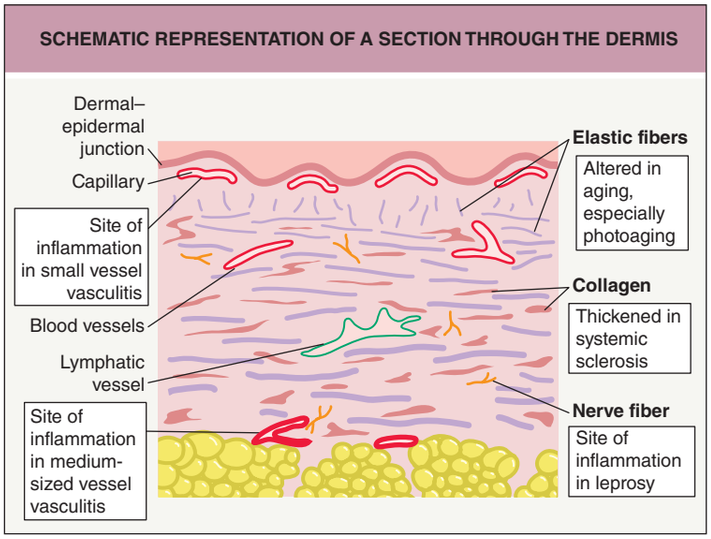


Fig. 1.5 Schematic representation of a section through the dermis. The extracellular matrix of the dermis is composed of structural proteins (collagen, elastin) and a gel-like ground substance (glycosaminoglycans). Blood vessels that supply nutrition and recirculating cells, lymphatic vessels, nerve fibers, and adnexal structures (see Fig. 1.1) are also present, with variations depending upon body site. Other cell types present in the dermis include mast cells, fibroblasts, macrophages, and dermal dendritic cells.



Fig. 1.6 Severe pustular psoriasis in an infant. The pustules represent sterile collections of neutrophils. Sterile infiltrates of neutrophils within the skin are seen most commonly in pustular psoriasis, pustular drug reactions (acute generalized exanthematous pustulosis), and neutrophilic dermatoses (see Ch. 26). *Courtesy Antonio Torrelo, MD.*

was lethal in males (likely due to widespread apoptosis of male fetuses *in utero*) had it not been for the survival of heterozygous females with this X chromosome-linked disease[5].

We deviate from the concept that physicians should always attempt to develop a single diagnosis for an illness. Rather, we believe that it is possible and even likely that two or more disease processes and/or predispositions may underlie an illness and that such simultaneous occurrences may alter the clinical presentation. Dermatologists are well aware of the unusual morphologic features of pityriasis rosea when it occurs in a patient with underlying psoriasis or when a patient with atopic dermatitis improves substantially with antibiotic therapy, even in the absence of obvious infection. Genetic factors and infectious agents also modulate the course of otherwise conventional skin diseases, e.g. a large number of viral warts or mollusca contagiosa may point to an immunodeficiency from an occult HIV infection. Thus, dermatologists have an extra assignment: to find otherwise hidden genetic, infectious, inflammatory, and environmental factors that modify the appearance and severity of cutaneous diseases.

All plants and animals have limiting membranes that define an internal space while also protecting against insults. In mammals, these membranes, which may be described functionally as "barriers", occur primarily in three organs: the respiratory tract, gastrointestinal tract, and skin (Ch. 124). Although similar in concept, the barrier properties of these organs are fundamentally different. Pulmonary and gastrointestinal barriers promote rather than retard the transfer of gases, fluids, nutrients and wastes, and because of their internal location, they are protected from many environmental influences. By contrast, and with the possible exception of UV radiation-facilitated vitamin D_3 production[6], there is no obvious benefit to skin penetration, or, at least, there are as yet no recognized diseases attributed to the failure of any material or form of energy to penetrate the skin. However, biomedical scientists continue to try to subvert the cutaneous barrier, as the skin has become a target of novel therapies based upon percutaneous penetration (Ch. 124)[7]. In addition to serving as a useful portal of entry for pharmaceutical agents, the skin can also serve as a site for immunization with gene-based materials and as a gene-driven cutaneous factory[8].

Protecting the DNA

Although we begin with the common rhetorical question: "What are the functions of skin?", it is followed by a more complicated question: "What are the requirements of skin that allow it to serve those functions?". The skin's primary function is to maintain an internal environment that allows an organism to protect its DNA and reproduce it relatively faithfully. In short, the preservation and reproduction of DNA sustains the species.

A second and highly related process is the generation of beneficial changes in DNA that adapt to new environmental circumstances. For example, skin pigmentation improves reproductive success in tropical climes by protecting folate from UV-mediated degradation, while lightly pigmented skin is advantageous for vitamin D biosynthesis in areas where UV radiation is scarce[9].

So, what are the requirements of skin to protect and replicate DNA? In fact, these requirements have not been identified merely through deductive logic; rather, as noted above, they have been identified by observing various failures that eventuate in skin disease. For this reason, we begin our survey with a listing of failures of skin (Table 1.1).

Immunologic Protection

An intricate system of immunologic recognition, both innate and adaptive, protects the skin from infection (Ch. 4)[10]. The innate immune response is the initial, rapidly deployed arm of the immune system that combats invading microbes and mediates defense against infection. It also plays a role in inflammatory conditions such as acne vulgaris and atopic dermatitis[11]. The cornerstone of adaptive immunity lies in recirculating lymphocytes and antibodies that are specifically recruited and "tuned" to recognize "foreign" materials, primarily peptides derived from infectious agents. Initial recognition occurs when sentinel dendritic cells in the epidermis (Langerhans cells) and dermis (dermal dendritic cells) are activated. Prior to activation, dendritic cells engulf particles and metabolize complex proteins into small immunogenic fragments. Once activated, motility is induced, allowing these cells to travel out of their cutaneous residence and migrate, via draining lymphatics, to regional lymph nodes (see Fig. 4.13). Thus, these residents of normal skin can travel to a distant location where reactive lymphocytes are selected and then expanded. Within a lymph node, activated T helper lymphocytes assist B lymphocytes in generating antibodies, while T helper lymphocytes and cytotoxic T lymphocytes begin to recirculate preferentially to and from the skin. A population of effector memory T lymphocytes that reside within the skin has also been identified, and these cells play a critical role in immune responses[12].

Infection

Cutaneous infections illustrate important aspects of skin function (Chs. 74–85), ranging from a structural barrier provided by the stratum corneum to immunologic recognition and protective immunity. Examining examples of defective resistance to infection, e.g. verrucae, Hansen disease, can provide insights into these functions.

Chronic and recurrent *verrucae* are often a vexing problem, especially when patients are immunocompromised or have epidermodysplasia verruciformis (Chs. 60 & 79)[13]. Trauma to the stratum corneum disrupts a physical barrier that is normally not susceptible to viral infection.

SELECTED REQUIREMENTS AND FAILINGS OF SKIN	
Requirement	**Selected failings**
Immunologic protection	Fungal, bacterial and viral infections; autoimmunity, cancer
Maintain a barrier	Infection, dehydration
Repair injury	Cancer, leg ulcers
Provide circulation	Infarction due to embolization, vasculitis, or other forms of occlusion
Communicate	Sensory neuropathy, pruritus
Provide nutrition	Vitamin D deficiency
Regulate temperature	Hypothermia, hyperthermia

Table 1.1 Selected requirements and failings of skin.



Fig. 1.7 Verrucae vulgares. A Multiple periungual warts. **B** Papillomatosis, hyperkeratosis, mounds of parakeratosis at the tips of the verrucous epidermal projections, and vacuolated keratinocytes (koilocytes) within the upper layers of the epidermis. The latter are due to a halo surrounding a shrunken nucleus. *A, Courtesy Louis A. Fragola, Jr, MD; B, Courtesy Lorenzo Cerroni, MD.*

Following a structural failure, human papillomavirus can infect the basal keratinocytes, which are viable and less resistant (see Fig. 79.3). Immunologic recognition of infected keratinocytes is usually followed by a cytotoxic cellular response, leading to destruction and resolution. When this response fails, chronic infection may ensue (Fig. 1.7). Protective immunity against warts often appears to be balanced precariously such that minor shifts in responsiveness may lead to their elimination in multiple sites simultaneously. In addition to physical destruction, therapeutic options frequently rely on modulating the immune response, including topical application of imiquimod, elicitation of contact sensitivity reactions, and intralesional injection of immunologic recall antigens such as *Candida* or mumps (see Fig. 79.26)[14].

Another example that highlights the importance of the structural integrity of the stratum corneum is *HIV infection* (Ch. 78). HIV penetrates through small tears in genital and rectal mucosae, and once the infection has occurred, the virus cannot be completely eradicated, despite a panoply of very effective therapies. With the loss of immunologic integrity, patients develop AIDS, demonstrating the role cellular immunity plays in protecting against infections by a wide variety of pathogens, including *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, and varicella–zoster (Fig. 1.8).

Hansen disease (leprosy) is also instructive in that most people exposed to its causative organism, *Mycobacterium leprae*, develop an effective immune response that seemingly clears the bacillus (Ch. 75). On the other hand, a small percentage of exposed individuals develop a chronic infection that may take any one of several forms, based on immunologic resistance. Observations in patients with Hansen disease have been important in formulating the Th1/Th2 paradigm, with each person's clinical response falling along a spectrum from tuberculoid to lepromatous (see Fig. 75.2)[15]. Associated neuropathy also illustrates the relevance of cutaneous sensation to protection against traumatic injury.

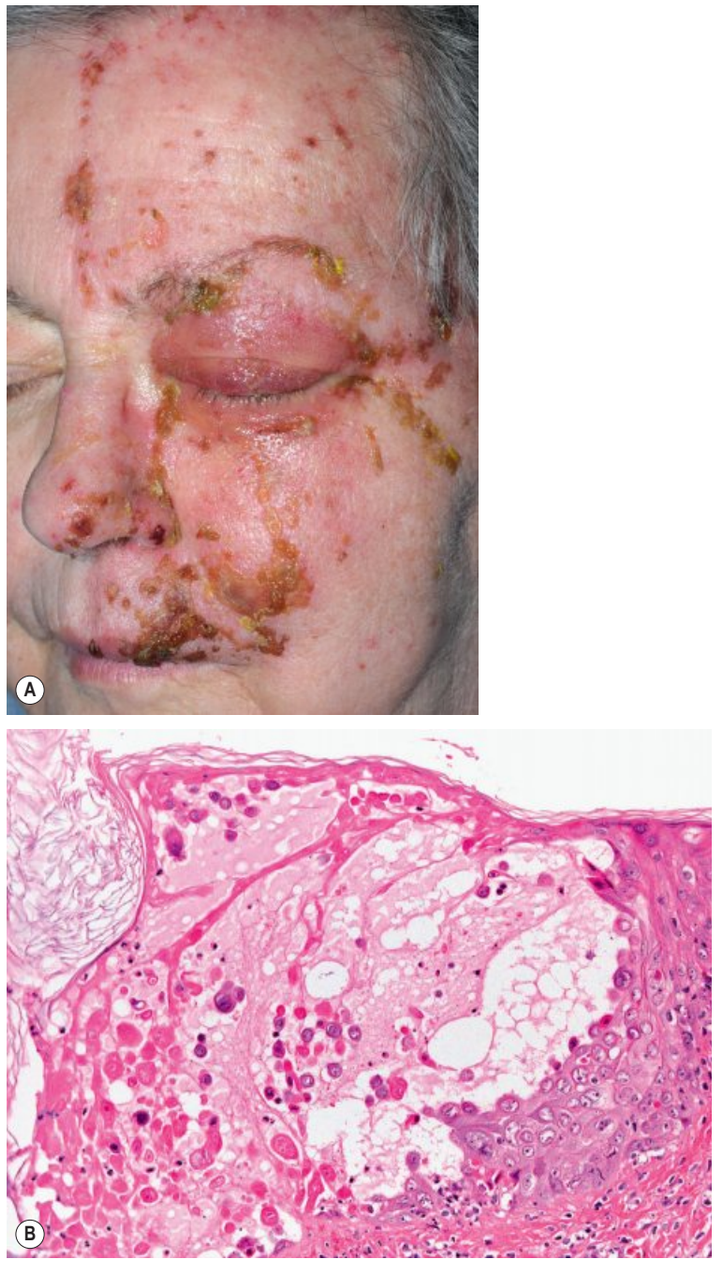


Fig. 1.8 Herpes zoster involving the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve. A Erythema, especially of the eyelids, as well as serous and hemorrhagic crusts on the left side of the forehead, nose, cheek, and upper lip. Note the sharp midline demarcation on the forehead. **B** An intraepidermal vesicle forms as a consequence of ballooning degeneration, acantholysis, and necrosis of infected keratinocytes. Note the keratinocytes with enlarged, partly dyskeratotic nuclei or multiple nuclei in the side wall of the blister cavity, in addition to acantholytic, necrotic keratinocytes and fibrin within the blister. *A, Courtesy Kalman Watsky, MD; B, Courtesy Lorenzo Cerroni, MD.*

Autoimmunity

Whereas the principal task of the immune system is to recognize and destroy infectious organisms, autoimmunity represents a failure to distinguish "self" from "foreign", i.e. a misidentification and destruction of components of the host as if they were dangerous. Autoimmune diseases have different genetic and environmental factors promoting their development, and they may target components of the epidermis, the basement membrane, or the dermis (Table 1.2). In pemphigus vulgaris, for example, autoantibodies directed against desmogleins compromise cell–cell adhesion, resulting in intraepithelial acantholysis and widespread erosions (Fig. 1.9). It has also become apparent that autoimmunity directed against cutaneous antigens may impact other organ systems. For example, patients with paraneoplastic pemphigus have autoantibodies against both desmogleins and plakins (see Table 29.2),

COMMON AUTOIMMUNE SKIN DISEASES		
	Target antigen	**Chapter**
Diseases with identified autoantigens		
Pemphigus foliaceus	Desmoglein 1	29
Pemphigus vulgaris (Fig. 1.9A)	Desmoglein 3 and 1	29
Bullous pemphigoid (Fig. 1.9D)	Collagen XVII (BPAG2), BPAG1*	30
Epidermolysis bullosa acquisita	Collagen VII	30
Dermatitis herpetiformis	Transglutaminase-3	31
Diseases with unknown or multiple autoantigens		
Subacute cutaneous lupus erythematosus	Unknown, possibly SSA/Ro	41
Chronic cutaneous lupus erythematosus	Unknown	41
Psoriasis	Unknown	8
*Neural isoforms are referred to as dystonin.		

Table 1.2 Common autoimmune skin diseases.

which bind to adhesion molecules in keratinocytes but are also pathogenic in the lungs, leading to bronchiolitis obliterans[16,17].

Immune surveillance and cancer

Data supporting the concept that immune responses protect against malignancy are strongest for those malignancies arising in the skin and lymphatic tissues[18], especially cutaneous squamous cell carcinoma (SCC), Merkel cell carcinoma (MCC), and melanoma. Cutaneous SCC is a common complication of immunosuppression in solid organ transplant recipients[19].

Immune suppressive signals on cancer cells can prevent the immune system from attacking them. For example, the interaction of PD-L1 on cancer cells with PD-1 on T cells decreases T cell function. Immune checkpoint inhibitors such as nivolumab and cemiplimab, which block the binding of PD-L1 to PD-1, can activate the immune system and prevent immune evasion of cancer cells (see Fig. 128.9)[20]. These immune checkpoint-blocking antibodies have been used successfully to treat melanoma, MCC, and metastatic and locally advanced basal cell carcinoma and cutaneous SCC.

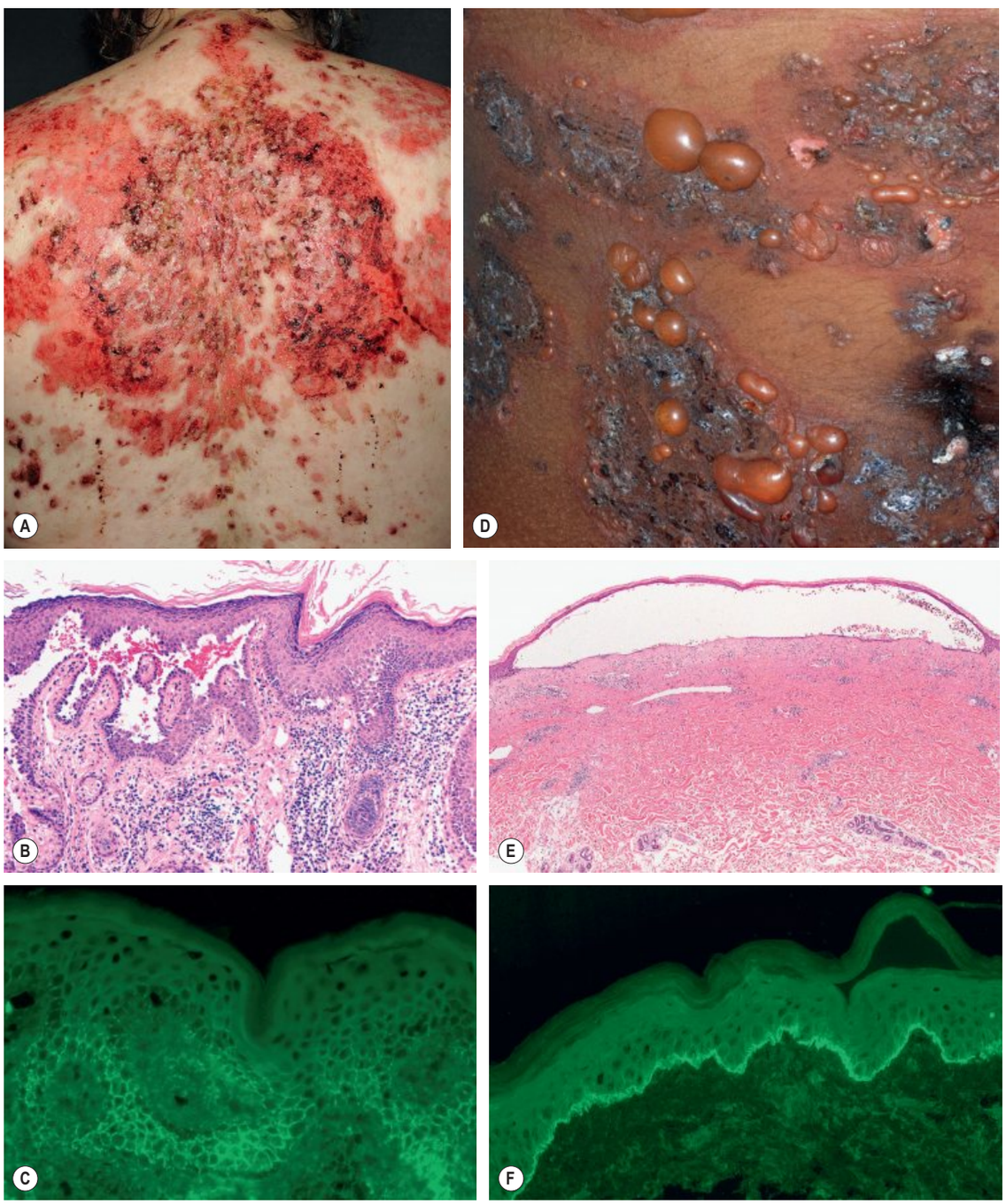


Fig. 1.9 Pemphigus vulgaris versus bullous pemphigoid. **A** In pemphigus vulgaris, fragile blisters are short-lived and rupture easily, leading to crusting and erosions that can become extensive. **B** Acantholysis and an intraepidermal split due to loss of desmosomal function from anti-desmoglein autoantibodies. Note that keratinocytes remain attached to the basement membrane via hemidesmosomes, resembling a row of tombstones. **C** Direct immunofluorescence (DIF) microscopy shows *in vivo* intercellular deposits of IgG within the lower epidermis in a "chicken wire" pattern. **D** In bullous pemphigoid, multiple tense bullae are seen; the contents of the bullae are usually serous. The bullae are longer-lasting than in pemphigus, but do eventually rupture, leading to erosions and crusts. **E** Subepidermal separation is seen. **F** DIF microscopy demonstrates linear deposits of C3 at the basement membrane. *A, B, E, Courtesy Lorenzo Cerroni, MD; C, F, Courtesy Christine Ko, MD; D, Courtesy Julie V. Schaffer, MD.*

Maintaining a Barrier

The most obvious function of the skin is to maintain a barrier that prevents the loss of fluids, electrolytes, and other molecules from within the body, while also preventing penetration by microorganisms, toxic materials, and UV radiation (Ch. 86)[21]. The stratum corneum is the key structure for barrier function. Protection against UV radiation occurs through several phenomena, including photon scattering in the stratum corneum and photon absorption by underlying melanin.

Protection against dehydration and infection

The most dramatic form of epidermal failure occurs in patients with toxic epidermal necrolysis (TEN; Ch. 20). In this drug-induced disease, rapid death of keratinocytes leads to detachment of the epidermis over large areas of the body (Fig. 1.10). TEN is most often associated with sulfonamides, aromatic anticonvulsants, and nonsteroidal anti-inflammatory drugs. The mortality rate depends on the area of skin affected, and death is not uncommon.

There is no specific treatment for TEN, but there is evidence that drug-induced triggering of massive keratinocyte apoptosis may underlie the disease[22]. Inhibition of apoptosis signaling pathways represents a potential therapeutic approach, e.g. by administration of immunomodulators such as cyclosporine and IVIg. Complications associated with significant loss of the epidermis highlight the importance of its barrier function: despite intensive treatment protocols similar to those used for burns, complications are common and include overwhelming infections with sepsis as well as fluid and electrolyte losses, leading to hypovolemia, electrolyte imbalances, and renal insufficiency.

Protection against toxic chemicals

Analysis of barrier failure includes the observation that the stratum corneum is defective in disorders of keratinization as it is less resistant to chemical penetration. In healthy adults with normal barrier function, topical application of the keratolytic salicylic acid in recommended amounts poses minimal, if any, risk of systemic toxicity. However, salicylism, which occasionally has been fatal, can occur in patients with ichthyosis (Fig. 1.11) or other cutaneous disorders with impaired barrier function[23].

Protection against UV radiation

UV radiation induces various changes in the skin, ranging from acute toxicity and immunosuppression to carcinogenesis and premature aging (Chs. 86, 87, 107 & 108). Sun protection is generally recommended to prevent adverse effects from UV radiation (Ch. 132), but at the same time, effective therapies for a number of skin diseases are based on UV radiation (Ch. 134). In addition to wearing clothing and applying topical preparations containing UV-absorbing or UV-blocking molecules, several characteristics of the skin itself limit UV radiation-induced damage. Due to its optical characteristics, the stratum corneum tends to reflect and scatter photons, and those that do penetrate the stratum corneum are usually absorbed by molecules such as melanin.



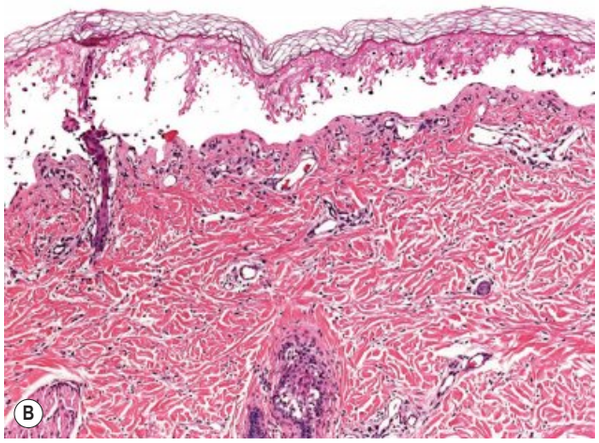


Fig. 1.10 Toxic epidermal necrolysis. A Detachment of necrolytic epidermis, leading to large areas of denuded skin. In the glistening areas, one is looking at dermis. **B** Full-thickness epidermal necrosis with a subepidermal cleft and sparse superficial inflammatory infiltrate. The normal basket-weave stratum corneum points to the acute nature of the disease process. *B, Courtesy Lorenzo Cerroni, MD.*



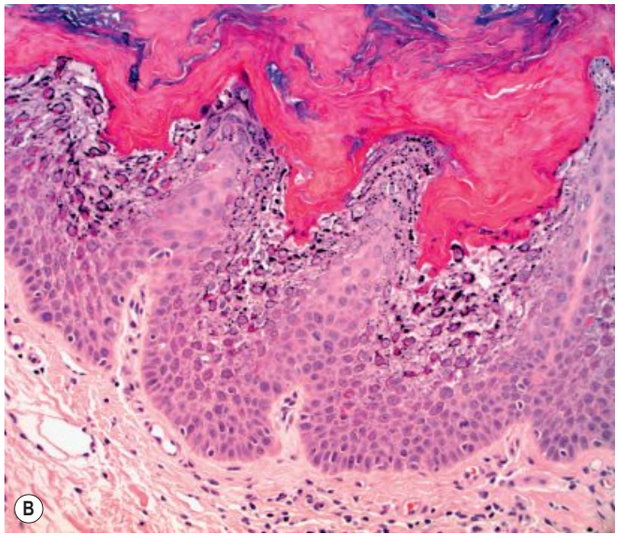


Fig. 1.11 Epidermolytic ichthyosis. A Mild background erythema with markedly thickened scale, especially near the axilla. Note the corrugated pattern of the scale. The fragility of the upper epidermis leads to peeling and erosions. **B** Marked compact orthokeratosis overlies a hyperplastic epidermis with epidermolytic change and dyskeratotic cells in its upper layers. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Lorenzo Cerroni, MD.*

Additional mechanisms include scavenging of reactive oxygen species by antioxidants and repair of damage via DNA repair enzymes.

The importance of melanin in limiting UV penetration is best illustrated by patients with oculocutaneous albinism (OCA, Fig. 1.12). Patients with OCA have decreased melanin production and depending upon the degree of pigmentary dilution and cumulative sun exposure, they can develop multiple SCCs[24] and premature photoaging (Chs. 66 & 87). As an example, in sub-Saharan Africa, metastatic cutaneous SCC is a well-recognized cause of death in individuals with OCA.

Repairing Injury

Physical injuries to the skin are common, and repair of small breaks caused by blunt or sharp objects often goes unnoticed. A special type of injury is caused by UV radiation; this includes a variety of effects ranging from sunburn and immune suppression to accelerated aging and carcinogenesis. Thermal injuries occur when the skin is exposed to a hot object or radiant energy that heats the skin excessively, e.g. from a fire. Injury also occurs when the underlying vascular supply is interrupted. The biology of wound healing is complex and discussed in detail in Chapter 141.

Delayed wound healing

Both delayed and incomplete wound healing are disabling as well as costly. Diabetes mellitus, peripheral artery disease, and aging are risk factors for disturbed wound healing. The management of chronic leg ulcers is an important part of dermatology and rehabilitation medicine (Ch. 105). The need to address issues of chronic cutaneous ulceration led to the formation of the Wound Healing Society (www.woundheal.org), a consortium composed of clinical and basic science investigators along with representatives from industry and government.

Keloids

The formation of hypertrophic scars and keloids can be viewed as an exuberant response to injury. They reflect a unique mix of genetic and environmental factors with anatomic site. While studies have shown that transforming growth factor-β (TGF-β) activity is excessively high in fibroblasts derived from keloids[25], the pathogenesis is clearly more complex.



Fig. 1.12 An infant with oculocutaneous albinism (OCA). The scalp hairs are strikingly white. Patients with OCA are at higher risk for UV radiation-induced carcinogenesis, in particular cutaneous squamous cell carcinoma, as well as ocular abnormalities.

Xeroderma pigmentosum

An important failure occurs when UV radiation (UVR)-induced DNA damage is not effectively repaired. The archetype for this deficiency is the disease xeroderma pigmentosum. The high incidence of several types of skin cancer in these patients supports the assertion that UVR-induced DNA damage is an important cause of skin cancer in humans. This illustrates two points: (1) UVR is dangerous and the skin must protect itself from UVR's harmful effects; and (2) cancers develop more quickly when DNA repair mechanisms are disrupted.

Circulation: Providing Thermoregulation, Nutrition, Immunoregulation

Two circulatory systems mediate the movement of cells and soluble substances to and from the skin. There is a two-way *hematologic* system that conducts blood flow and a one-way *lymphatic* system; the latter returns leukocytes and interstitial fluids, first to draining lymph nodes and then, via the thoracic duct, into the central venous system. Hematologic circulation serves three major functions: nutritional support, the delivery of leukocytes, and thermoregulation. Although the movement of oxygen and solutes from the blood into interstitial tissues occurs largely by passive diffusion, the migration of cells from the vascular space occurs via an orchestrated sequence of signaling, attachment, and migratory processes (Ch. 102).

The hematologic system includes two types of vessels: (1) nutritive vessels (arteries, capillaries, and veins); and (2) anastomosing arteries and veins that participate in heat regulation. The anastomosing system includes an extensive subcutaneous venous plexus, which can hold large quantities of blood (to dissipate heat from the skin's surface), and arteriovenous anastomoses, which provide direct connections between arterial and venous plexuses. These anastomoses are prominent in areas exposed to maximal cooling, such as the volar surfaces of the hands and feet, lips, nose, and ears.

Cutaneous lymphatic drainage begins in microscopic, blind-ended, dermal vessels called lymphatic capillaries. These collect both cells and interstitial substances, which are then directed to the regional lymph nodes. As a result, lymphocytes, macrophages, and dendritic cells can travel from the epidermis through draining lymphatic vessels to the lymph nodes[26].

Embolic occlusion of arteries

The most dramatic form of blood vessel occlusion is emboli-mediated blockage, which can produce changes within hours. This is followed rapidly by ischemic necrosis of all cutaneous structures distal to that blockage. The extent of necrosis depends on the size of the vessel occluded and degree of collateral circulation. Occlusion followed by cutaneous necrosis vividly demonstrates the dependence of skin on arterial circulation.

Vasculitis

Cutaneous inflammation centered in the blood vessel wall is responsible for a spectrum of cutaneous findings that vary depending upon the size of the affected vessel (Fig. 1.13; see Fig. 24.24). Vasculitis is commonly associated with autoimmune connective tissue diseases, particularly Sjögren syndrome, rheumatoid arthritis, and lupus erythematosus (Chs. 24, 41, & 45). The critical element in terms of cutaneous structure is that the skin's survival is highly dependent upon an intact circulation.

Occlusive vasculopathy

Other disorders characterized by vascular occlusion result from thrombosis due to aberrant coagulation or cold-related "gelling" (Ch. 23). Examples of hypercoagulable disorders include antiphospholipid antibody syndrome and factor V Leiden mutation leading to activated protein C resistance (Ch. 105).

Venous insufficiency

Although listed last, venous insufficiency through partial occlusion and valvular incompetence contributes to the most common vascular problem, the development of venous stasis ulcers of the legs (Ch. 105).

Lymphatic blockage

Blockage of lymphatic drainage may also occur in certain inflammatory skin conditions. The inflammation associated with recurrent streptococcal and staphylococcal infections can lead to scarring and loss of



Fig. 1.13 Palpable purpura of the lower extremity due to cutaneous small vessel vasculitis. Immune complex deposition within postcapillary venules leads to circular purpuric macules and papules. *Courtesy Lorenzo Cerrroni, MD.*

lymphatic drainage, resulting in distal edema. With chronic infection, permanent edema may develop, associated with widespread verrucous change at the skin surface, a condition described as elephantiasis nostras verrucosa (Ch. 105). Likewise, blockage of lymphatic drainage in parasitic infections is known to cause deforming patterns of lymphedema (Ch. 83).

Communicating with External and Internal Environments

Communication within the skin occurs by three mechanisms: conventional nerve conduction via cutaneous fibers; intercellular signaling mediated by cytokines and hormones (endocrine, paracrine, and autocrine effects); and the physical movement of "message-carrying" cells from one site to another.

Communication via nerves

The skin is "wired" with afferent and efferent nerve fibers that accompany vascular structures, forming an intricate network in the dermis. They envelop the pilosebaceous apparatus, blood vessels, and sweat glands. Although the head and distal extremities are innervated most densely, the entire skin contains nerves. In the dermis, larger fibers are surrounded by a myelin sheath, but as diameters diminish, many fibers run free. Although most nerve fibers appear to end in the dermis, some small endings penetrate the basement membrane and travel into the epidermis, where they can modulate immune responsiveness[27]. Diminished or functionally impaired intraepidermal nerve fibers lead to neuropathic symptoms, including burning and pruritus[28].

Nerves also control vascular tone, as evidenced in blushing responses, and they mediate the sensations of heat, cold, itch, touch, and pain (Chs. 5 & 6). Defects in sensation and neurologic function are common and can be seen in patients with postherpetic neuralgia, uncontrolled itching, neurologic syndromes (e.g. trigeminal trophic syndrome), and excessive sweating. Intradermal injections of botulinum toxin to uncouple cholinergic nerve fibers have at least two dermatologic applications: (1) to decrease muscle tone, leading to a loss of facial lines for cosmetic purposes; and (2) to inhibit the excessive sweating that characterizes disabling axillary and palmar hyperhidrosis[29] (Ch. 159).

The sensory function of the skin plays an important role in neurologic development and social interactions. Touch reduces physiologic reactions to stress in infants[30] and plays an important role in developing cohesive social units[31]. Tactile stimulation of neonates activates the brain in areas linked to sensory perception and social-affective processing[32].

Itch and pain

Itch is a major problem for patients with skin disease (Chs. 5 & 6). We presume that acute and modest levels of itching confer some beneficial effect, but, most certainly, chronic and excessive itching can be devastating for both personal and social activities. On the other hand, there is little evidence for structural abnormalities that predispose to excessive itching. Postherpetic neuralgia is similarly important (Ch. 80), although, once again, there is no obvious structural defect in this exquisitely painful disorder.

Excessive sweating

Hyperhidrosis is a potentially debilitating disorder of sweating, which usually involves the axillae as well as the palms and soles. Accumulated evidence favors a neurologic abnormality rather than a structural abnormality[29]. Moreover, interruption of sweat gland innervation by injection of botulinum toxin provides considerable relief (Ch. 159).

Loss of sensation

The most obvious and devastating effects of altered touch and pain sensation are seen in patients with peripheral neuropathies associated with diabetes mellitus and Hansen disease[33]. The loss of sensory function results in the patient's inability to recognize, and therefore avoid, cutaneous trauma. In patients with longstanding diabetes mellitus, this can result in neuropathic ulcers in weight-bearing areas of the feet (see Fig. 105.15). Similar ulcers develop in patients with Hansen disease, along with a gradual loss of tissue. In both conditions, the loss of sensation leads to vulnerability of the skin to traumatic injury.

Communication via hormones and cytokines

Hormones

The skin plays a unique hormonal role in calcium metabolism. Vitamin D_3 (cholecalciferol) is produced in the epidermis by the action of UVR on 7-dehydrocholesterol[6]. It then leaves the skin and is hydroxylated in the liver and kidneys to the active form of vitamin D (1,25-dihydroxycholecalciferol; see Fig. 51.11).

An example of indirect hormonal influences on the skin is adrenocorticotropic hormone (ACTH), which was recognized as having systemic effects via its influence on the secretion of adrenal corticosteroids. While corticosteroids have beneficial effects on inflammatory skin disorders such as psoriasis and atopic dermatitis, other diseases like acne can worsen. Several of the clinical signs of Cushing disease (altered fat distribution, vascular dilation, and striae) result from excessive secretion of corticosteroids (Ch. 53). In contrast, diminished production of adrenocortical hormones causes excessive secretion of ACTH, which indirectly gives rise to the hyperpigmentation seen in patients with Addison disease (Ch. 67).

Cytokines

It has been increasingly recognized that cells within the skin produce an array of cytokines[34]. Keratinocytes produce IL-1, IL-8 and TGF-β, with an important physiologic function thought to be the beneficial effect of TGF-β on wound healing[35]. Langerhans cells produce a unique spectrum of cytokines and chemotactic factors related to their immunologic properties[36], and vascular endothelial cells produce IL-1β, IL-6, and IL-8[37]. Cytokine-mediated communication between cells has proven to be enormously complex[38–42], and the interplay between cytokines and cells is often reciprocal[43,44]. For example, mast cells produce tumor necrosis factor (TNF), which affects cutaneous immunity[44], but, at the same time, mast cell function is regulated by other cytokines[45].

As a result of an improved understanding of the role of cytokines in keratinocyte biology, important advances have been made in managing inflammatory skin diseases, most notably psoriasis. Aberrant levels of TNF, IL-17, and IL-23 have emerged as critical targets of immunomodulators used to treat psoriasis (Ch. 128). Similarly, targeting the dysregulated Th2 axis by blocking the IL-4 receptor now represents a treatment option for atopic dermatitis[46].

Communication via cells

In the course of their normal function, certain resident cutaneous cells depart from the skin while in possession of information that directly impacts the function of the skin. These cells include dendritic cells in particular, which, once activated, leave the skin and migrate to regional lymph nodes where they select and prime naive and resting

T lymphocytes (Ch. 4). The activation, migration, and repopulation processes have been intensely studied with the prospect of developing methods to modulate immunity.

Regulating Temperature

Regulation of core temperature is a characteristic of all mammals, which, by definition, are euthermic. For humans, core temperature is maintained at ~37°C (98–99°F). Because environmental influences can alter temperature, there is an intricate regulation system in which the skin plays a decisive role as both radiator and insulator. Temperature regulation occurs primarily through evaporative cooling following eccrine sweating (Ch. 39) and through vasodilation and vasoconstriction.

Human skin includes several million eccrine sweat glands distributed over most of its surface, with a total mass approximately equivalent to one kidney. The secretory activity of eccrine sweat glands consists of two major activities: (1) secretion of an ultrafiltrate of a plasma-like fluid; and (2) reabsorption of sodium by the duct to produce hypotonic sweat.

Effects of excessive heat

Excessive heating may be local or systemic, and when this occurs, the skin plays a cooling role to prevent injury. Cooling may be required under two circumstances: (1) in response to central heating, when heat enters the skin from the environment or when muscle activity generates sufficient energy to raise the core temperature; and (2) in response to sustained local heating, when a portion of the skin is heated to a temperature at which proteins begin to denature (45–50°C; 113–122°F; Ch. 88). The subsequent physiologic responses that lower temperature in order to prevent injury require innervation, circulation, and successful sweating. Elimination of central heat occurs via radiation from the skin surface and the evaporative cooling that follows sweating. Dispersion of local heat takes place through direct radiation to the environment and by heat transfer to other body locations via circulating blood.

The importance of sweating for inducing cooling and ultimately for survival is illustrated in the vignette of hyperthermia at the beginning of this chapter. In patients with hypohidrotic ectodermal dysplasia, the defining defect is an almost complete absence of sweat glands, in association with other features such as hypotrichosis and abnormal teeth (Ch. 63). This disease demonstrates the importance of sweating, as death from overheating during exercise may occur, especially when the environmental temperature is high.

Of note, local heat is also used therapeutically: electrocautery is a time-honored method of therapy in dermatology (Ch. 140). Heat therapy has also been used to treat skin infections, including sporotrichosis, verrucae, and leishmaniasis.

Effects of excessive cold

Cold injuries occur under two related circumstances: (1) in response to heat loss to the environment in amounts that cool the body centrally (hypothermia); and (2) in response to local exposure to sustained below-freezing temperatures that could result in direct freezing injury ("frostbite"). Apart from vascular constriction to reduce radiation of heat from the skin surface and shivering (or exercise) to increase central heating, there are no cutaneous mechanisms to protect against excessive cooling. However, humans have become quite adept at creating artificial methods to prevent cold injury through clothing and shelter. These have enabled humans to survive successfully in geographic areas of extreme temperature.

For over a century, dermatologists have successfully used local cold injury, i.e. cryosurgery, as a therapeutic tool (Ch. 138).

Interpersonal Communication: Beauty, Attention, and Self-Identity

An important function of the skin begins with the human need to communicate with each other so that personal and societal goals can be met. The skin plays an important role in interpersonal communication by conveying beauty to others, attracting attention, and contributing to the development and expression of self-identity. In virtually every society, the appearance and condition of the skin has fundamental importance. There is not sufficient space to list the physical features that are considered beautiful within each cultural context, but let us assert that the perceived loss of these features has much to do with the distress that often affects patients with acne, vitiligo, alopecia, aging, and virtually all other skin diseases.

Over the past two decades, there has been increasing attention paid to the impact of skin disease on quality of life. Myriad reports have been published describing the extent to which chronic skin diseases, including psoriasis, eczema, and pigmentary disorders, affect patients' self-perception. As dermatologists become increasingly aware of the psychosocial impact of chronic skin disease, we will better understand and treat patients with these conditions.

Finally, the skin represents a "canvas" onto which individuals can make modifications to communicate and display aspects of self-identity. Tattoos, ritual scarification, and piercings have long been seen as expressions of self-identity. Dermatologists participate in skin modification by performing procedures designed to alter a patient's appearance and to address a variety of patient concerns (Chs. 152–159).

Failures to present an attractive appearance

Concern about appearance is an intrinsic human behavior. Appropriately proportioned, symmetric, flawless skin seems to be preferred in most societies. The changes that are most undesirable vary from culture to culture, so that one cannot assume that what is considered unattractive in one culture is necessarily considered unattractive elsewhere. Although variations in norms across cultures can be remarkable, the discipline of cosmetic dermatology has arisen to address such concerns, with the goal of improving self-image.

Pigmentation disorders

Pigmentary disorders tend to be more perceptible, and thus more important, in populations with darker constitutive pigmentation. Although dermatologists care for patients with a wide range of disorders of pigmentation, two diseases predominate: vitiligo (Ch. 66) and melasma (Ch. 67). Vitiligo is characterized by the absence of epidermal melanin due to the autoimmune destruction of melanocytes (Fig. 1.14)[47]. It can be accompanied by autoimmune endocrinopathies and this association is recapitulated in patients receiving immune checkpoint-blocking antibodies for melanoma (Ch. 113). Melasma also has a higher prevalence in patients with darker skin phototypes and it can be quite distressing[48].

The preference for unblemished skin is exceedingly important in cultures in which altered pigmentation may be confused with infectious diseases such as Hansen disease (Ch. 75) or conflated with superstitions or folklore. Not only do persons with albinism face the physical consequences of reduced melanin production such as poor vision and increased risk of developing skin cancer, but they also face a variety of social injustices. In sub-Saharan Africa, where OCA is relatively prevalent, these individuals live under the threat of violence from those within their society who believe albinism is a curse[49] or the opposite, that body parts can bring luck or success.

Inappropriate hair distribution

For many individuals, the psychological contributions of hair cannot be underestimated. Scalp hair is a major social and sexual display feature for humans. Two phenomena predominate in concerns about hair: (1) too much hair in the wrong place; and (2) not enough hair in the right place. Too much hair in the wrong place occurs in congenital and acquired forms of hypertrichosis, in response to therapy with minoxidil and cyclosporine, and as a manifestation of androgen excess (Ch. 70). However, most patients who seek help for excessive hair do so primarily for cultural reasons. In terms of insufficient hair (Ch. 69), three diseases predominate: (1) androgenetic alopecia in men; (2) female pattern alopecia in women; and (3) alopecia areata (Fig. 1.15). Inflammatory scarring alopecia, while less common, also creates a significant impact on quality-of-life.

Undesirable fat distribution

With the possible exception of hemifacial atrophy and lipodystrophy syndromes, indications for the absolute removal and the movement of fat are based on psychologic needs rather than on abnormalities in the structure of the skin and subcutaneous tissues. Nevertheless, the movement or reduction of fat is becoming a fairly common procedure, and dermatologists are playing increasingly important roles in this arena (Ch. 156).



Fig. 1.14 Vitiligo in an African-American man. The digits are a common site of involvement and repigmentation of the distal fingers can be difficult due to the lack of hair follicles. Vitiligo and other pigmentary disorders are more noticeable in patients with darker skin.



Fig. 1.15 Circumscribed area of hair loss due to alopecia areata. The detrimental social impact of hair loss in patients with diseases such as alopecia areata cannot be underestimated.

An Important Corollary, with an Eye to the Future

In this chapter, we have asserted that the structure and function of the skin are revealed through careful study of skin diseases. Structure and function are also discovered by observing the outcomes of therapeutic interventions. For example, the mechanism of action of anti-tumor immune checkpoint inhibitors is immune stimulation. A wide range of cutaneous side effects, from lichenoid dermatoses to bullous pemphigoid to sarcoidosis, is providing valuable insights into the pathogenesis of these diseases. Many more such observations are bound to follow as we develop new methods of treating skin disease. Furthermore, the acuity of our power to observe changes in the skin will be aided by advances in technology, including artificial intelligence. If we remain curious about the diseases we treat, the potential for additional discoveries regarding the structure and function of the skin is endless.

Acknowledgment

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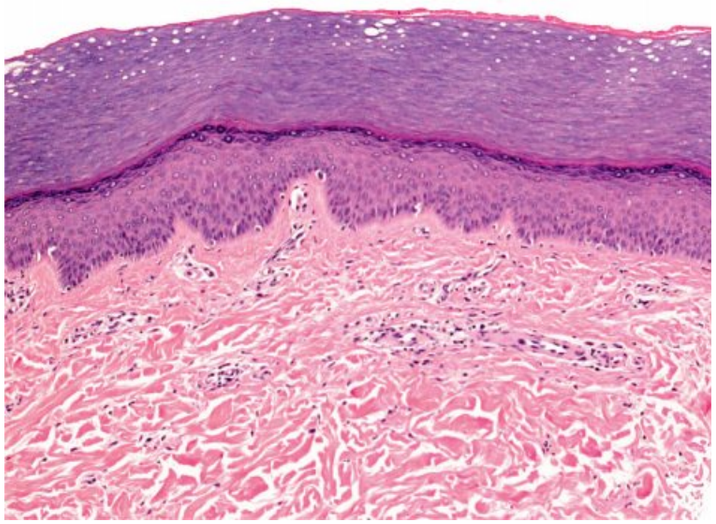
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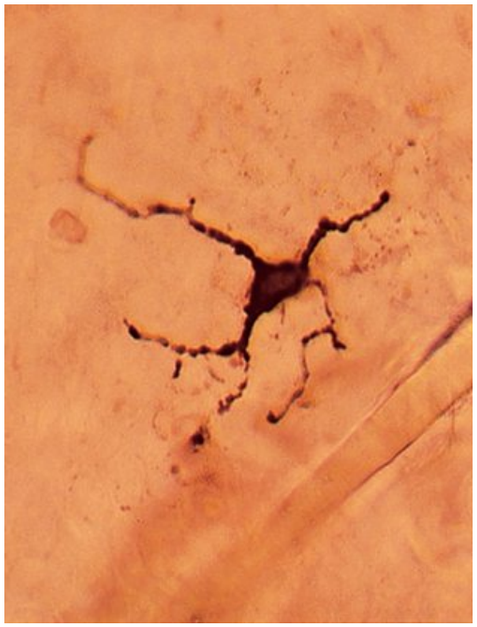
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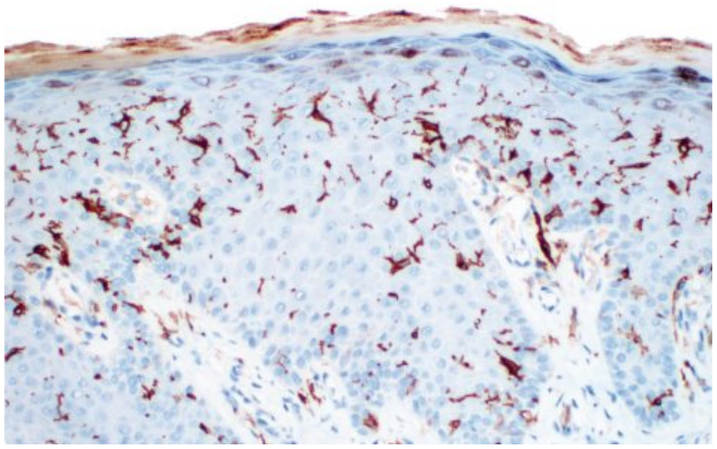




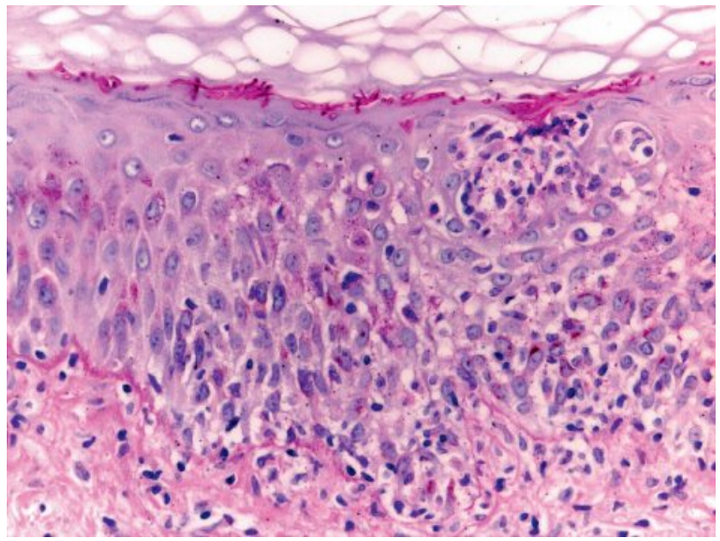
eFig. 1.1 Normal skin: palm. The compact and thick stratum corneum is typical of skin on the palms and soles. *Courtesy Lorenzo Cerroni, MD.*



eFig. 1.2 Normal melanocyte. A whole mount of epidermis has been stained for the presence of the enzyme tyrosinase, which typifies melanocytes. Note that the surrounding keratinocytes are virtually invisible. An adjacent hair shaft passes through the specimen. Melanocytes contain long dendritic processes that deliver protective melanosomes to nearby keratinocytes.



eFig. 1.3 Langerhans cells within the epidermis. An immunohistochemical stain for CD1a highlights Langerhans cells within the epidermis. Note their dendritic morphology.



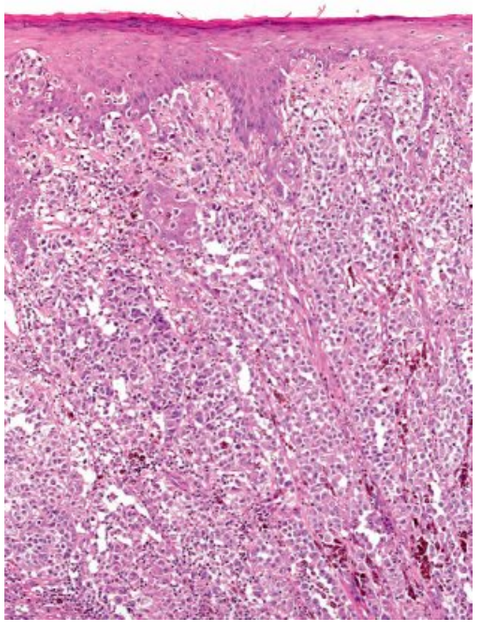
eFig. 1.4 Dermatophytosis. PAS staining for neutral mucopolysaccharides reveals branching red–purple fungal hyphae within the stratum corneum in a patient with tinea corporis. If diastase enzyme is not added, glycogen within keratinocytes also stains with PAS. *Courtesy Lorenzo Cerroni, MD.*



eFig. 1.5 Herpes zoster. Unilateral grouped vesicles and serous crusts on an erythematous background. Note the associated edema of the lip. *Courtesy Louis A. Fragola, Jr, MD.*



eFig. 1.6 Cutaneous melanoma. This black T4 tumor is associated with a significant risk of metastases. In addition to ulceration, there is variation in color and an irregular outline at its base.



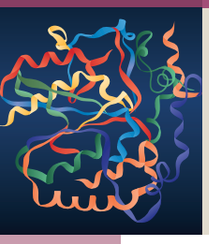
eFig. 1.7 Cutaneous melanoma – histopathologic features. This thick melanoma has virtually no associated inflammatory cells histologically. The thickness and lack of a host response indicate a poor prognosis for the patient. *Courtesy Lorenzo Cerroni MD.*



eFig. 1.8 Toxic epidermal necrolysis. Full-thickness epidermal cell death leads to stripping off of the epidermis. In this patient with skin phototype VI, it becomes apparent that melanin is located predominantly in the epidermis.



eFig. 1.9 Ulcers secondary to Henoch–Schönlein purpura. The ulceration was preceded by coalescent purpuric papules with bulla formation and necrosis. *Courtesy Julie V. Schaffer, MD.*



2 Skin Development and Maintenance

Isaac Brownell, Cynthia A. Loomis and Tamara Koss

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INTRODUCTION

Development of the human embryo is a complex process involving highly orchestrated cell movements, proliferation, death, and differentiation. This chapter focuses on key events and regulatory mechanisms that result in skin morphogenesis, maintenance, and regeneration. The spectrum of cutaneous abnormalities that can result from mutations in genes with critical roles in skin development is discussed. Ultimately, improved understanding of the pathways and signaling cascades essential to skin development will provide the basis for therapeutic approaches for patients with acquired as well as inherited skin disorders.

EMBRYONIC ORIGIN OF THE SKIN

The skin is composed of diverse cell types of both ectodermal (e.g. keratinocytes, melanocytes, Merkel cells, neurons) and mesodermal (e.g. fibroblasts, hematopoietic cells such as Langerhans cells, endothelial cells) lineages. To understand the origins of these cells, it is important to review the early stages of embryogenesis. Immediately after fertilization, cells divide rapidly, and by the end of the first week, the embryo begins to implant into the uterine wall. During the third week, the embryo undergoes gastrulation, a complex process resulting in the formation of the three embryonic germ layers: endoderm, mesoderm, and ectoderm.

During the next stage of embryogenesis, ectodermal cells commit to either a surface ectodermal or neuroectodermal fate. The surface ectodermal cells eventually differentiate into the keratinocytes of the embryonic epidermis, whereas the neuroectodermal cells invaginate to create the neural tube in a process called neurulation. As the neural tube forms, cells in its dorsal portion separate to form the neural crest. An important neural crest-derived cell in the skin is the melanocyte. Although Merkel cells were once believed to be neural crest derivatives, it has now been established that they descend from the epidermal lineage. The lineage of the dermis depends on the body site. The dermis (and other mesenchymal structures) of the face and frontal scalp are derived from the neural crest, whereas the dermis elsewhere is derived from the mesoderm. Knowing from which germ layer and lineage different cell types in the skin derive helps one to understand the pathophysiology of cutaneous disorders such as Waardenburg syndrome in which craniofacial dysmorphism and hearing impairment as well as pigmentary abnormalities reflect disrupted migration and survival of neural crest-derived cells (see Ch. 65).

An overview of key events in the development of skin and its specialized structures is shown in Fig. 2.1.

EPIDERMAL DEVELOPMENT

The ectoderm that covers the developing embryo after gastrulation is a single-layered epithelium (Fig. 2.2A). The first step in epidermal development occurs when cells of the surface ectoderm adopt an epidermal fate[1]. Although this process does not result in major morphologic changes, it is marked by dramatic alterations in gene expression that result in the formation of the embryonic epidermis, which initially consists of a simple epithelium (Fig. 2.2B). Primitive keratinocytes subsequently generate cells of the periderm, a single cell layer that covers the developing epidermis until the cornified cell layer is formed (Figs. 2.2C–F & 2.3A,B). The periderm is believed to exchange substances across fetal skin and to protect the developing epidermis from forming interepithelial adhesions.

The embryonic epidermis begins to stratify at approximately 8 weeks' estimated gestational age (EGA)[2]. At this time, basic organogenesis is complete and bone marrow hematopoiesis commences, marking the transition from embryo to fetus. Of note, expression of *TP63* is required for epidermal stratification. During the first stage of stratification, an intermediate cell layer is formed between the basal layer and periderm (see Figs. 2.2D & 2.3B). Unlike suprabasal keratinocytes in the postnatal epidermis, the intermediate layer consists of actively proliferating cells. As a consequence, it is able to expand to accommodate the rapid growth of the embryo as well as create additional layers of intermediate cells over the next several weeks (see Fig. 2.2E). However, the intermediate cell layer is ultimately replaced by post-mitotic keratinocytes undergoing terminal differentiation.

Terminal differentiation, the process resulting in the formation of mature keratinizing epidermal cells, begins during the second trimester. Early cornification can be observed within the hair canal at approximately 15 weeks' EGA[3], but it does not commence in the interfollicular epidermis until 22–24 weeks' EGA, occurring first in the skin on the head, palms, and soles. The process begins when cells in the intermediate layer permanently withdraw from the cell cycle and differentiate into spinous and granular cells (see Fig. 2.2F). The cornified cell layer, which is composed of "dead" keratinocytes (corneocytes) held together by a matrix of proteins and lipids (see Chs. 56 & 124), subsequently starts to form and is several cells thick by 24–26 weeks' EGA. The corneocytes are a reflection of the closely regulated process of terminal differentiation that is required for normal functioning of the skin. At the time of keratinization, the periderm detaches from the underlying epidermis and is sloughed off into the amniotic fluid, with remnants contributing to the vernix caseosa that coats newborns. During the third trimester, the number of keratohyalin and lamellar granules as well as stratum corneum layers increases. By the mid third trimester, the epidermis is morphologically similar to adult skin (Figs. 2.2G & 2.3C), although it does not acquire full barrier function until a few weeks after birth.

Clinical Relevance

Genetic abnormalities affecting various stages of epidermal morphogenesis have been found to underlie inherited skin disorders in humans. However, generalized abnormalities in epidermal specification, the process through which the surface ectoderm adopts an epidermal fate, have not been identified. It is likely that generalized epidermal defects would be incompatible with survival past the first trimester. Mosaic skin conditions that result in abnormalities of the epidermis and/or its appendages often have a distribution pattern that follows the lines of Blaschko, which are thought to represent the migration pathways of epidermal cells during embryonic development. Classic examples include epidermal nevi (due to postzygotic mutations in genes encoding

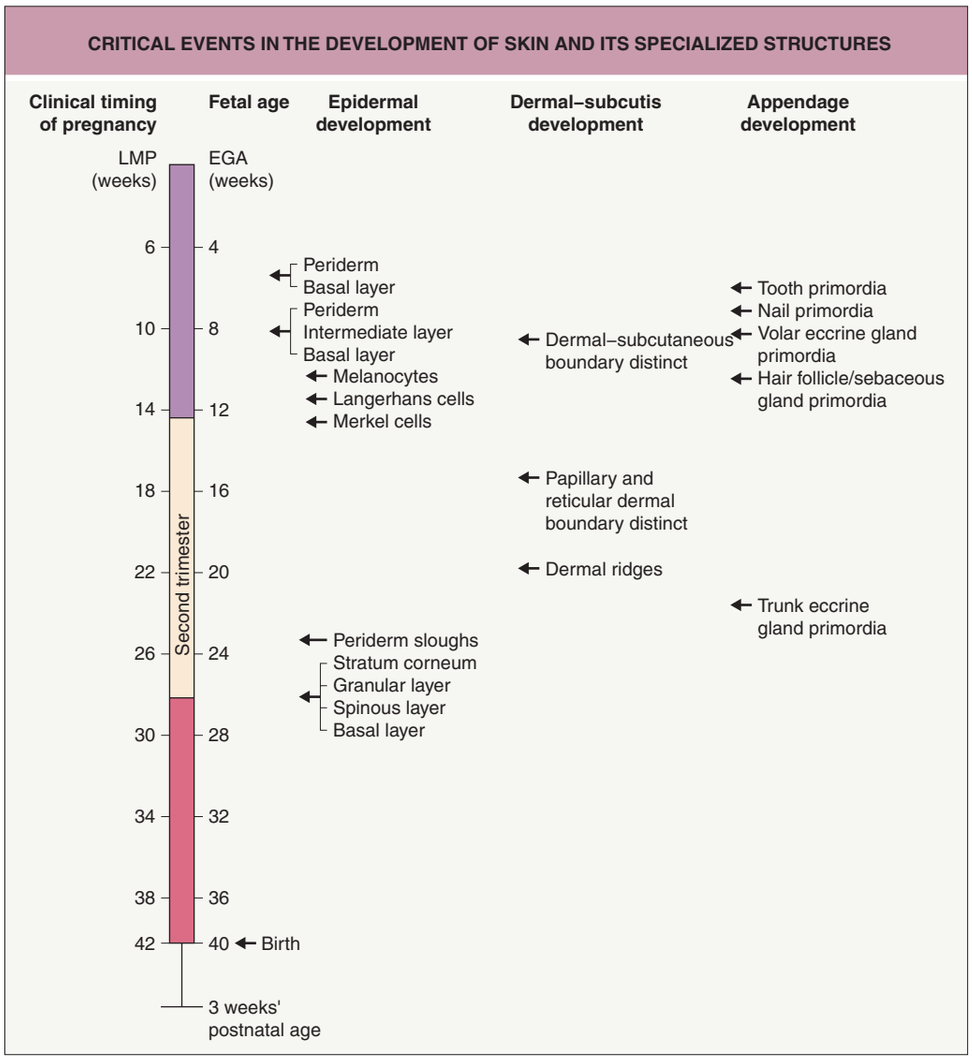


Fig. 2.1 Critical events in the development of the skin and its specialized structures. The timeline indicates the time of initiation defined by estimated gestational age (EGA) and duration of pregnancy (by last menstrual period [LMP]). Refers to skin on the back unless otherwise noted.

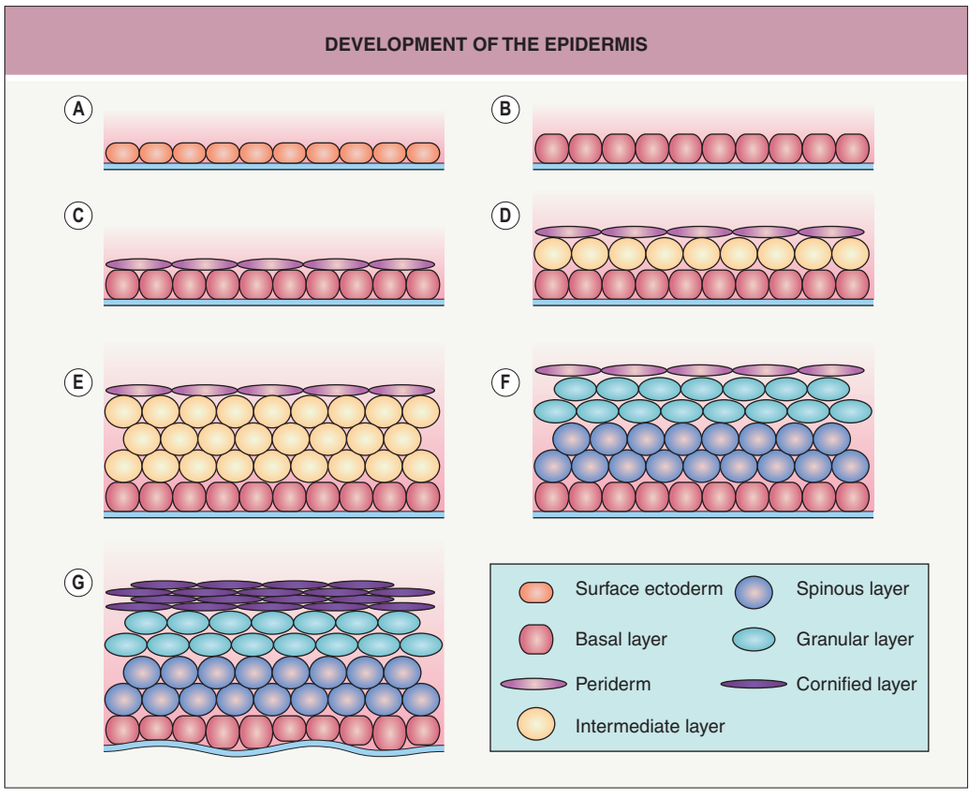


Fig. 2.2 Development of the epidermis. A The epidermis develops from the surface ectoderm, a single-layered epithelium that initially covers the developing embryo. **B** Through changes in gene expression, cells of the surface ectoderm adopt an epidermal fate. **C** Epidermal cells subsequently give rise to the periderm, a cell layer that covers the developing epidermis until cornification occurs. **D** Epidermal stratification begins with the formation of a highly proliferative intermediate layer between the basal layer and the periderm. **E** The intermediate layer becomes several cells thick over the next few weeks. **F** Intermediate cells ultimately withdraw from the cell cycle and differentiate into spinous and granular keratinocytes. **G** The periderm is replaced by the cornified cell layer.

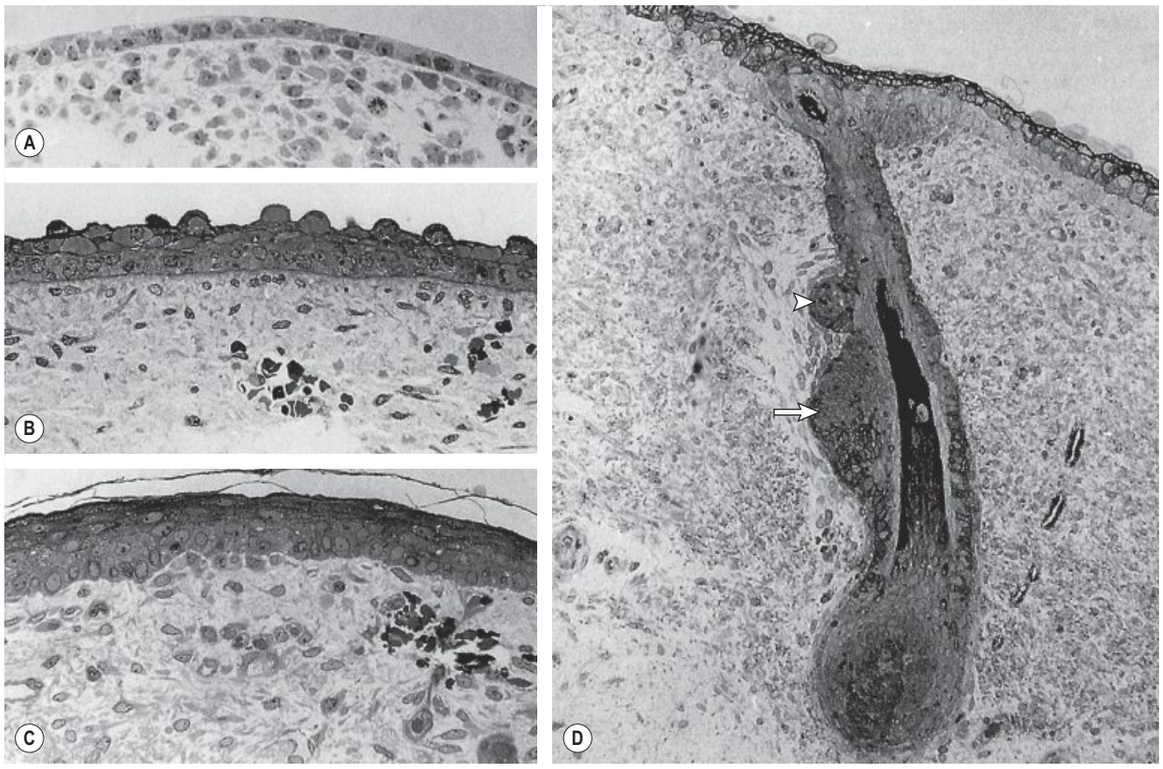


Fig. 2.3 Development of the skin. A At 36 days' estimated gestational age, the embryonic epidermis consists of two layers – a superficial periderm layer overlying a basal layer. **B** By 72 days, the basal layer has given rise to the highly proliferative intermediate cell layer. **C** A distinct granular cell layer and stratum corneum are seen in neonatal skin. **D** An early peg-stage follicle from a mid second trimester fetus. The more superficial bulge consists of the developing sebaceous gland (arrowhead), whereas the deeper bulge represents the insertion point of the future arrector pili muscle and the location of the presumptive follicular stem cells (arrow). *Photomicrographs, courtesy Dr Karen Holbrook, from Loomis CA, Koss T, Chu D. Fetal skin development. In: Eichenfield LF, Frieden IJ (eds). Textbook of Neonatal Dermatology, 3rd edn. Elsevier, 2014:2–5.*

fibroblast growth factor receptors, the phosphoinositide-3-kinase alpha subunit, Ras family members, and keratins) and sebaceous nevi (due to postzygotic mutations in *HRAS* > *KRAS*) (see Ch. 62).

There are a number of genetic disorders that result in abnormal epidermal differentiation and barrier formation. One clinical presentation of such conditions is a "collodion baby" born encased in a taut, shiny, transparent membrane that is formed by aberrant stratum corneum. After shedding the membrane, most of these infants manifest with lamellar ichthyosis or congenital ichthyosiform erythroderma, two forms of autosomal recessive congenital ichthyosis that exist on a spectrum[4]. However, following a collodion membrane, some patients develop normal or almost normal appearing skin. The "self-improving" collodion baby is an example of a dynamic epidermal phenotype that depends on environmental conditions. All of these outcomes can result from mutations in the same set of genes that encode proteins essential for formation of the epidermal barrier, including transglutaminase-1 (an enzyme that cross-links lipids to the cornified cell envelope; *TGM1*), lipid processing enzymes (*ALOXE3*, *ALOX12B*), and lipid transporters (*ABCA12*) (see Ch. 57).

More deleterious mutations in *ABCA12* cause harlequin ichthyosis (HI), an especially severe disorder of cornification characterized by aberrant epidermal maturation. Patients with HI are born with a tremendously thick, armor-like shell of hyperkeratosis, severe ectropion and eclabium, and underdevelopment of the nose and ears. The extreme phenotype of HI highlights the importance of lipid transport into lamellar bodies for epidermal formation and function.

Abnormalities in the stratum corneum are present not only in infants with ichthyosis, but also in premature infants, especially those born before 28 weeks' EGA. The immaturity of the stratum corneum results in impaired barrier function, which leads to an increased risk of infection, dehydration, and excessive absorption of topical medications or chemicals[5]. Even healthy full-term infants do not attain full skin barrier function until 3 weeks of age. The structural features of premature skin and adult skin are summarized in Table 2.1.

DEVELOPMENT OF SPECIALIZED CELLS WITHIN THE EPIDERMIS

Two populations of non-keratinocyte cells – melanocytes and Langerhans cells – migrate to the epidermis during early embryonic development. *Melanocytes* are derived from the neural crest that forms along the dorsal neural tube. Melanocyte precursors migrate away from the neural tube within the mesenchyme beneath the primitive epidermis. They follow a characteristic trajectory, moving dorsolaterally and then ventrally around the trunk to the ventral midline, anteriorly over the scalp and face, and distally along the extremities. Cutaneous melanocytes also arise from Schwann cell/melanocyte precursor cells that migrate along nerves to the skin via a distinct ventral pathway[6].

Melanocytes can be identified within the epidermis at approximately 50 days' EGA based on HMB45 immunostaining and their dendritic morphology. Epidermal melanocyte density is high early in embryonic development (~1000 cells/mm^2), and it increases further (~3000 cells/mm^2) as the epidermis stratifies (80–90 days' EGA) and the appendages begin to develop; later in gestation, the density decreases and becomes similar to that of young adults (800–1500 cells/mm^2). However, epidermal melanin production does not begin until 3–4 months' EGA, and melanosome transfer to keratinocytes is not seen until 5 months' EGA. Even though all melanocytes are functional and in place at birth, the pigmentation of the skin increases over the first few months of life; this process is most pronounced in infants with darker skin phototypes.

Active melanocytes are also present throughout the dermis during embryonic development. Eventually, most of these dermal melanocytes migrate to the epidermis or undergo apoptosis. By the time of birth, dermal melanocytes have generally disappeared, with the exception of certain anatomic sites (head and neck, dorsal aspects of the distal extremities, and sacrococcygeal area), which correspond to the most common locations for dermal melanocytoses and blue nevi (see Ch. 112).

Langerhans cell precursors appear within the epidermis during the first trimester and are detectable as early as 40 days' EGA. These cells can be distinguished by their characteristic dendritic morphology; expression of CD45, HLA-DR, and CD1c; and high levels of ATPase activity. CD1a, Langerin, and Birbeck granules are expressed by 13 weeks' EGA. The density of Langerhans cells in fetal skin remains low early in gestation and increases to typical adult levels during the third trimester.

Merkel cells, highly innervated neuroendocrine cells involved in mechanoreception, are initially identified within the epidermis during the first trimester. These cells are detected as early as 8–12 weeks' EGA in palmoplantar epidermis, and slightly later in interfollicular skin.

COMPARATIVE FEATURES OF PREMATURE, NEWBORN, AND ADULT SKIN			
	Premature	**Newborn**	**Adult**
Skin thickness	0.9 mm	1.2 mm	2.1 mm
Epidermal surface	Vernix (gelatinous)	Vernix	Dry
Epidermal thickness	~20–25 microns	~40–50 microns	~50 microns
Stratum corneum thickness	4–5 microns	9–10 microns	9–15 microns
	5–6 cell layers	>15 cell layers	>15 cell layers
Spinous cell glycogen content	Abundant	Little or none	Little or none
Melanocytes	High number of cells; few mature melanosomes	Similar number of cells to young adult; low melanin production	Numbers decrease with age; melanin production dependent on skin type, body area
Dermal–epidermal junction	All known adult antigens expressed; fewer and smaller desmosomes	Structural features and antigens similar to those of the adult	Well-developed adhesive structures; large number of antigens expressed
Papillary dermis			
• Boundary with reticular dermis	Present but not marked	Present but not marked	Marked
• Size of collagen fiber bundles	Small	Small	Small
• Cellular density	Abundant	Abundant	Moderately abundant
Reticular dermis			
• Boundary with the subcutis	Marked	Marked	Marked
• Size of collagen fiber bundles	Small	Small to intermediate	Large
• Cellular density	Abundant	Moderately abundant	Sparse
Elastic fibers	Sparse; tiny with immature structure	Small size and immature structure; distribution similar to adult	Large in reticular dermis, small and immature in papillary dermis; form network
Hypodermis	Well-developed fatty layer	Well-developed fatty layer	Well-developed fatty layer

Table 2.1 Comparative features of premature, newborn, and adult skin. *Reproduced with permission from Schachner LA, Hansen RC (eds). Pediatric Dermatology, 4th edn. London: Mosby, 2011.*

Merkel cells are identified by the presence of cytoplasmic dense core granules and the expression of cytokeratin 20 and neuropeptides. These cells are found in the basal layer of the epidermis, are often associated with appendages and nerve fibers, and are particularly dense on volar skin. The developmental origin of Merkel cells has been the subject of longstanding controversy, but genetic fate mapping studies have demonstrated that mammalian Merkel cells are derived from an epidermal rather than neural crest lineage[7].

Clinical Relevance

Several inherited pigmentary disorders result from genetic defects that lead to abnormal migration and proliferation of neural crest-derived melanocyte precursors (melanoblasts). Piebaldism and Waardenburg syndrome are characterized by achromic patches of skin on the central forehead, central abdomen, and extremities. This distribution pattern reflects the failure of melanocyte precursors to survive, proliferate, or travel to the distal points of their embryonic migration pathway. A number of different causative genes leading to this phenotype have been identified, including those encoding transcription factors (e.g. microphthalmia-associated transcription factor [*MITF*], *PAX3*, *SOX10*, *SNAI2*) as well as membrane receptors and their ligands (e.g. endothelin-3, endothelin B receptor, KIT receptor)[8] (see Ch. 66). The endothelin B receptor is found on common melanoblast/ganglion cell precursors in the developing neural crest, explaining both the Hirschsprung disease and the pigmentary abnormalities that are associated with defects in this receptor or its ligand.

DEVELOPMENT OF THE DERMIS AND SUBCUTIS

The specification of dermal mesenchymal cells is a complex process that is incompletely understood. Unlike the epidermis, which is derived exclusively from the ectoderm, the origin of the dermis varies depending on the body site. As noted above, the dermal mesenchyme of the face and anterior scalp (as well as the underlying muscle and bone) is derived from neural crest ectoderm, thereby explaining the facial dysmorphia in the neurocristopathy Waardenburg syndrome. On the other hand, the dermal mesenchyme of the back originates from the dermomyotome of the embryonic somite, and the dermal mesenchyme of the extremities and ventral trunk is thought to arise from the lateral plate mesoderm.

Dermal fibroblasts are heterogeneous, and different populations have distinct molecular signatures and functions. The rostral–caudal and proximal–distal positions of dermal fibroblasts correlate with differential embryonic expression of *HOX* genes that is maintained into adulthood. Moreover, at each site in the dermis, mesenchymal precursors differentiate into distinct dermal lineages to produce papillary dermal fibroblasts, reticular dermal fibroblasts, and adipocytes[9]. The different molecular populations influence how the skin regenerates and heals wounds[10].

By 6–8 weeks' EGA, presumptive dermal fibroblasts are situated under the developing epidermis[11]. However, at this developmental stage, there is no distinct demarcation between the cells that will give rise to the dermis and those that will give rise to musculoskeletal components. Although embryonic dermal cells are capable of synthesizing collagens (e.g. types I, III, and IV) and some microfibrillar components, these proteins are not yet assembled into complex fibers. Of note, the ratio of collagen III to collagen I is 3 : 1, the reverse of what is seen in the adult dermis.

The demarcation between the dermis and underlying skeletal condensations becomes distinct at approximately 9 weeks' EGA. By 12–15 weeks' EGA, progressive changes in matrix organization and cell morphology distinguish the fine weave of the papillary dermis located directly beneath the epidermis from the thicker, deeper reticular dermis. At this stage, the collagen proteins produced by fibroblasts start to assemble into collagen fibers, which continue to accumulate in the reticular dermis during the second and third trimesters. Electron microscopy can first detect definitive elastic fibers at approximately 22–24 weeks' EGA. As development progresses, the gelatinous, proteoglycan-rich, cellular dermis of the embryo is modified to the more rigid, fibrous, paucicellular dermis characteristic of adult skin. By the end of the second trimester, the dermis shifts from a non-scarring to a scarring form of wound repair. At birth, the dermis is still thinner and more cellular than is adult dermis.

The basic pattern of the dermal vasculature is discernible by the end of the first trimester. This pattern, however, undergoes extensive remodeling *in utero* and is not fully mature until after birth. Numerous molecular controls are involved in the regulation of angiogenesis, including the vascular endothelial growth factor (VEGF) family as well as the tyrosine kinase receptors Tie-1 and Tie-2 and their stimulatory (Ang-1) and inhibitory (Ang-2) angiopoietin ligands (see Ch. 102).

Nerve networks are formed by the mid to late first trimester but also undergo significant remodeling during later development and early postnatal life. Cutaneous nerves and vessels follow a similar pattern, with nerves dictating arterial differentiation and branching[12]. Accumulation of subcutaneous fat begins during the second trimester and continues through the third trimester, when distinct lobules separated by fibrous septae are formed.

Clinical Relevance

Mutations in genes that encode dermal structural proteins (e.g. collagens, elastic fibers) and the enzymes that process them underlie multiple forms of Ehlers–Danlos syndrome (characterized by skin hyperextensibility and fragility with poor wound healing) and cutis laxa (featuring lax, redundant skin). Genetic defects in regulatory proteins important for extracellular matrix development can lead to abnormalities in the skin and other organs. For example, mutations in the latent transforming growth factor-β (TGF-β) binding protein-4 gene (*LTBP4*) underlie a form of cutis laxa associated with severe pulmonary, gastrointestinal, and genitourinary malformations. The absence of LTBP4, an extracellular matrix protein that controls the bioavailability of TGF-β, leads to defective elastic fiber assembly in many types of tissues.

Another disorder characterized by abnormal dermal development is Goltz syndrome (focal dermal hypoplasia), an X-linked dominant disorder characterized by areas of dermal hypoplasia with fat herniation/hamartomas in a distribution following the lines of Blaschko (thought to reflect pathways of *epidermal* development) as well as skeletal defects and mucosal papillomas. Goltz syndrome is caused by mutations in *PORCN*, an effector of the Wnt signaling pathway[13]. It is likely that epidermal PORCN regulates Wnt signaling to the developing dermis, explaining the distribution of dermal hypoplasia along the lines of Blaschko.

DEVELOPMENT OF THE DERMAL–EPIDERMAL JUNCTION

The dermal–epidermal junction (DEJ) mediates adhesion between the basal keratinocytes and the dermis and provides resistance against shearing forces on the skin (see Ch. 28). The DEJ develops from a simple, generic basement membrane in the embryo to a highly complex, multilayered structure in the second-trimester fetus.

The embryonic DEJ consists of a lamina densa and a lamina lucida, and it is composed of molecules that are common to all basement membranes (e.g. type IV collagen, laminin, heparan sulfate, proteoglycans)[14]. The DEJ becomes progressively more complex, and skin-specific components of the DEJ start to appear after the embryonic–fetal transition at 8 weeks' EGA, coincident with the onset of epidermal stratification. By 12 weeks' EGA, almost all of the structures characteristic of the mature DEJ are in place (see Ch. 28). Hemidesmosomes, anchoring filaments, and anchoring fibrils are synthesized by basal keratinocytes, with type VII collagen-containing anchoring fibrils localizing to the sublamina densa; laminin 332 and the bullous pemphigoid antigens are also expressed. As development progresses, the flat embryonic DEJ acquires the rete ridges and dermal papillae that characterize the adult DEJ.

Clinical Relevance

Epidermolysis bullosa (EB) is a heterogeneous group of genetic disorders characterized by blister formation due to mechanical fragility of the skin. EB can result from mutations in genes that encode several different components of the DEJ[15]. The specific protein affected, as well as the degree to which it is altered, determine disease severity, depth of bulla formation, and involvement of extracutaneous tissues (see Ch. 32). Analogously, the pathogenesis of a number of autoimmune blistering diseases involves autoantibodies targeting components of the DEJ (see Chs. 29–31).

DEVELOPMENT OF SKIN APPENDAGES (ADNEXAE)

Skin appendages include eccrine, apocrine, and sebaceous glands as well as the hair and nails. Normal development of these structures depends on tightly regulated interactions and signaling between the early dermis and epidermis; disruption of either component or their communications leads to aberrant development. Despite the differences in the structure and function of the various types of cutaneous appendages, the developmental processes that regulate their formation are remarkably similar[16] (see Fig. 68.1).

Hair Follicle Development

The genetics and complex dermal–epidermal signaling that occur in appendageal development are best understood in hair follicle induction. Follicle formation is initiated by signals from the dermis that direct the embryonic epidermis to form focal thickenings, called placodes (see Fig. 68.2)[17]. Placodes are first seen on the scalp and face between 10 and 11 weeks' EGA; they subsequently develop in a caudal and then in a ventral direction. The epidermal placodes instruct the underlying dermal cells to condense and form the presumptive dermal papilla. The dermal papilla then directs the keratinocytes of the placode to proliferate and extend deeper into the dermis, thereby forming the hair germ (Fig. 2.4; see Fig. 68.2). By 12–14 weeks' EGA, the base of the developing hair follicle surrounds the presumptive dermal papilla, forming the hair peg (see Figs. 2.4 & 68.2). The superficial portion of the developing hair follicle has two distinct bulges. The more superficial bulge consists of the developing sebaceous gland, whereas the deeper bulge represents the insertion point of the future arrector pili muscle and the location of the presumptive follicular stem cells (Fig. 2.3D).

Hair follicles undergo further maturation during the second trimester, forming seven concentric cell layers (from outer to inner): outer root sheath; inner root sheath, composed of Henle's and Huxley's layers and a cuticle; and then the hair shaft cuticle, cortex, and medulla (see Fig. 68.5). The hair canal is fully formed by 18–21 weeks' EGA, and hair shafts begin growing shortly thereafter. The hairs continue to grow until 24–28 weeks' EGA, when they leave the active growing phase (anagen) and enter the short-lasting degenerative phase (catagen) and subsequently the resting phase (telogen). The follicles then start the second hair cycle by re-entering anagen; new hairs grow and push out the first group of telogen hairs (exogen), which are shed into the amniotic fluid (see Fig. 68.4).

Hair cycling through anagen, catagen, and telogen continues throughout life, but the hair cycles for individual follicles become asynchronous after birth. The third hair cycle is initiated perinatally, leading to the shedding of the second wave of fine lanugo hair follicles. Most hairs become thicker and coarser with subsequent growth cycles, leading to vellus and then adult-like terminal hairs on the scalp and in the eyebrows.

Many genes important for hair follicle development and cycling have been identified (see Ch. 68). Sonic hedgehog (SHH), a signaling molecule secreted by cells of the developing hair follicle, is required for the maturation of the dermal papilla and for the progression of the follicle placode to the peg hair stage. SHH also appears to be critical in mediating the transition from telogen to anagen during postnatal hair cycling. Members of the Wnt, bone morphogenetic protein (BMP), and fibroblast growth factor (FGF) families of signaling molecules are also important in hair follicle development and cycling. Transcription factors with roles in follicular differentiation have also been identified, including HOXC13 and FOXN1.

Sebaceous gland development parallels follicular development. The presumptive sebaceous gland is first seen at around 13–16 weeks' EGA as the most superficial bulge on the developing hair follicle. The outer proliferative layer of the sebaceous gland generates lipogenic cells that progressively accumulate lipid/sebum until they are terminally differentiated, at which time they disintegrate and release their products into

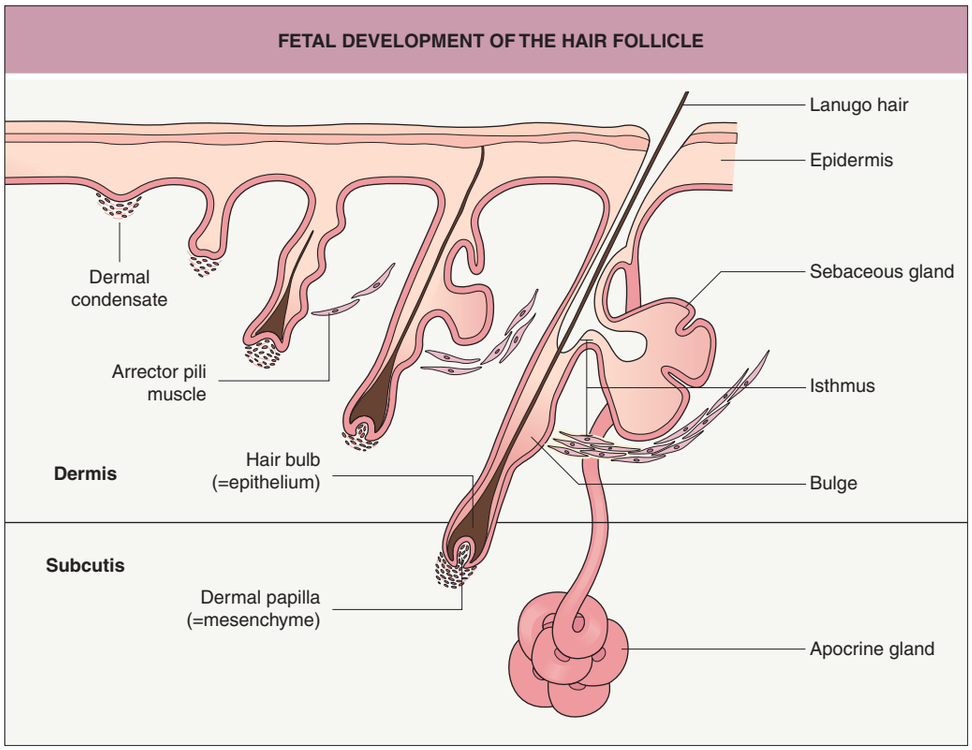


Fig. 2.4 Fetal development of the hair follicle. The hair follicle begins as a small epithelial thickening (placode) that induces a dermal condensate. Reciprocal signaling between these two structures subsequently directs the patterning and growth of a complex, multi-cylindrical, hair-forming structure with an associated dermal papilla, sebaceous gland, and apocrine gland.

the upper portion of the hair canal, contributing to the vernix caseosa. Both maternal hormones and androgen production from the "fetal zone" of the developing adrenal gland (which involutes postnatally) result in sebaceous gland hypertrophy and increased sebum production during the second and third trimesters.

Nail Development

Fingernail development begins at 8–10 weeks' EGA and is completed by the fifth month of intrauterine development (see Fig. 68.8). The flat, rectangular surface of the future nail bed on the dorsal digital tips is first demarcated by folds visible at 8–10 weeks' EGA. The nail bed on the dorsal digit is the first skin structure to keratinize, at around 11 weeks' EGA; keratinization begins distally and then continues toward the proximal nail fold. A wedge of ectoderm invaginates obliquely into the mesenchyme along the proximal end of the early nail field, forming the proximal nail fold by 13 weeks' EGA. The presumptive nail matrix cells, which will later produce the differentiated nail plate, are found ventral to the proximal nail fold. A differentiated nail plate emerges from under the proximal nail fold during the fourth month of gestation and grows distally to completely cover the nail bed by the fifth month. Toenails develop by a similar process that occurs ~4 weeks later than the fingernails.

Eccrine and Apocrine Sweat Gland Development

Like hair and nails, palmoplantar eccrine sweat glands begin to develop during the first trimester and are fully developed by the second trimester. Sweat gland development starts with the formation of large mesenchymal bulges or pads (analogous to the paw pads of other mammals) on the palms and soles between 55 and 65 days' EGA. Parallel ectodermal ridges are induced in the epidermis overlying these pads between 12 and 14 weeks' EGA. The curves and whorls formed by these ridges result in characteristic dermatoglyphics (fingerprints), which can be seen on the digit tips by the fifth month of gestation. Unlike most other mammals, the mesenchymal pads in the human fetus regress by the third trimester.

Beginning between 14 and 16 weeks' EGA, individual eccrine gland primordia bud along the ectodermal ridges at regularly spaced intervals. The buds elongate as cords of cells that enter the pad mesenchyme. By 16 weeks' EGA, glandular structures form at the terminal portion of the buds and secretory and myoepithelial cells appear. Canalization of the dermal component of the eccrine duct is also complete by 16 weeks' EGA; this occurs via a loss of the desmosomal adhesions along the innermost ectodermal surfaces, with concomitant maintenance of the adhesion between duct cells and the gland walls. Canalization of the epidermal component of the duct is not complete until 22 weeks' EGA.

Interfollicular eccrine glands and apocrine glands begin to form during the fifth month of gestation. Like sebaceous glands, apocrine glands typically arise from the upper portion of a hair follicle, whereas interfollicular eccrine glands originate independently. Glandular cords of cells elongate during the ensuing weeks, and by 7 months' EGA the clear cells and mucin-secreting dark cells characteristic of apocrine glands can be visualized. Apocrine glands function transiently during the third trimester and subsequently become quiescent in the neonate. In contrast, eccrine glands mature and begin functioning postnatally.

Clinical Relevance

Ectodermal dysplasias are a large, heterogeneous group of genetic disorders characterized by developmental abnormalities in two or more major ectodermal appendages – hair, teeth, nails, and sweat glands; other ectodermal structures (e.g. sebaceous glands) can also be affected[18] (see Ch. 63). Hypohidrotic ectodermal dysplasia (HED) is a relatively common type of ectodermal dysplasia that affects the sweat glands (hypohidrosis), hair (hypotrichosis), and teeth (hypodontia). HED is caused by mutations in genes encoding components of the ectodysplasin A (EDA) signaling pathway, which is critical for the initiation of sweat gland, hair follicle, and tooth morphogenesis. Underlying mutations can occur in the genes encoding the EDA ligand, EDA receptor (EDAR), or EDAR-associated death domain (an intracellular adaptor protein that functions in EDAR signaling). Mutations in EDA are responsible for the X-linked form of HED (XLHED), which leads to "full-blown" disease in affected males and areas of involved skin following the lines of Blaschko in heterozygous females. Because the underlying defect is in a soluble ligand that is only required for a brief period during the initiation of appendage formation, XLHED is a prime target for protein therapy. Encouragingly, studies in mice and dogs have demonstrated an almost complete correction of the XLHED phenotype upon prenatal or neonatal treatment with recombinant EDA protein[19,20]. Intra-amniotic

administration of recombinant EDA-Fc fusion protein to human fetuses with X-linked HED during the late second and early third trimesters has had positive effects on tooth development and sweating ability, and additional clinical trials are ongoing.

In addition to mutations in genes that are required for appendage development, ectodermal dysplasias can also be caused by mutations in genes that are required for epidermal development[21]. In these instances, abnormal appendages result from disruption of cross-talk between the developing epidermis and dermis. Mutations in *TP63*, a gene that is required for epidermal morphogenesis, can cause several types of ectodermal dysplasia, including the ankyloblepharon–ectodermal dysplasia–cleft lip/palate (AEC) and ectrodactyly–ectodermal dysplasia–cleft lip/palate (EEC) syndromes (see Ch. 63). The phenotypic differences between AEC and EEC are explained by underlying mutations in separate regions of *TP63*, which affect different functions and isotypes of the p63 protein.

Genetic defects in the Wnt signaling pathway, which is critical for appendageal development, underlie conditions ranging from hereditary hypotrichosis simplex to onycho-odonto-dermal dysplasia and Schöpf–Schulz–Passarge syndrome (see Fig. 55.6)[22]. The basal cell nevus (Gorlin) syndrome is caused by mutations in the *PTCH* tumor suppressor gene that result in overactivation of the sonic hedgehog (SHH) signaling pathway (see Fig. 107.6), which has important roles in neurologic and anterior–posterior axis development as well as hair follicle formation[23]. This explains the broad range of developmental anomalies, including craniofacial and skeletal defects, and the propensity for medulloblastomas, odontogenic keratocysts, and multiple basal cell carcinomas (BCCs) to arise (see Ch. 108).

SKIN STEM CELLS

Stem cells are present in each self-renewing tissue and are responsible for maintaining and repairing the tissue in which they reside. These somatic stem cells have two defining properties: (1) the ability to produce daughter cells that can differentiate to renew or repair the tissue; and (2) the ability to produce a new stem cell (self-renewal). The epidermis, dermis, appendages, and melanocytes are each maintained by different lineage-specific stem cells[24]. Stem cells often reside in a protective niche microenvironment that provides necessary signaling factors. During periods of homeostasis, stem cells generally divide very infrequently, a feature believed to protect them from acquiring mutations during cell cycle progression. After an injury, however, stem cells can divide more rapidly as part of wound healing.

One distinguishing characteristic of stem cells is that they can be maintained in culture virtually indefinitely. For example, a subset of epidermal basal cells forms highly proliferative colonies that can be passaged long-term *in vitro*; referred to as holoclones, they presumably represent stem cells[25]. Holoclones can reconstitute epidermis *in vitro*, and they have been utilized as skin grafts for the treatment of burns and inherited skin disorders (see below). Within the skin, stem cells that maintain the epidermis and hair follicles have been most extensively studied. The properties of different cutaneous stem cells, including their molecular markers, are summarized in Table 2.2.

Epidermal Stem Cells

The human epidermis renews itself every 40–56 days[26]. This constant turnover is mediated by epidermal stem cells, which reside in the basal layer[27]. Stem cells comprise a small percentage of the basal epidermis, although their precise location and number is unclear. There is conflicting evidence regarding whether palmoplantar epidermal stem cells are found at the bottom or top of rete ridges, with more protection from environmental stress in the former location. Similarly, there are two competing models – hierarchical and stochastic – to account for proliferative, undifferentiated cells in the basal epidermis (Fig. 2.5)[25].

Hair Follicle Stem Cells

The hair follicle bulge, which is located in the outer root sheath just deep to the sebaceous gland and adjacent to the arrector pili muscle attachment site, is thought to harbor hair follicle stem cells (Fig. 2.6).

CUTANEOUS STEM CELLS				
Stem cell	**Location (niche)**	**Tissue regeneration in homeostasis**	**Tissue regeneration in injury repair**	**Markers**
Keratinocyte				
Interfollicular epidermis	Basal layer	Interfollicular epidermis	Hair follicle Sebaceous gland Interfollicular epidermis	Delta 1, MCSP, α_6* and β_1 integrins, LRIG1; *low* levels of CD71
Hair follicle†	Bulge‡	Hair follicle	Hair follicle Sebaceous gland Interfollicular epidermis	Keratin 15, α_6 and β_1 integrins, CD200, PHLDA1, follistatin, frizzled homolog 1, LGR5; *low* levels of CD24, CD34¶, CD71, CD146, SOX9
Sebaceous gland§	At or near the bud of the sebaceous gland	Sebaceous gland	Sebaceous gland	Blimp1
Merkel cell§	Touch domes of hairy skin	Interfollicular epidermis	Interfollicular epidermis	α_6 integrin*, keratin 17, CD200, GLI1, SOX2, ATOH1
Melanocyte§	Lower bulge and sub-bulge region‖	Hair matrix and epidermal melanocytes	Hair matrix and epidermal melanocytes	Pax3, TYRP2; *negative* for KIT, tyrosinase, TYRP1
Eccrine gland lumen§	Suprabasilar eccrine duct	Eccrine luminal cells	Acral epidermis	Keratins 15, 18, & 19

*Also expressed by basal keratinocytes.
†Additional stem cell populations identified within the hair follicle in mice include LGR6-positive cells in the central isthmus and LRIG1-positive cells in the upper isthmus, both of which contribute to the interfollicular epidermis and sebaceous glands during homeostasis.
‡Within the outer root sheath just below the sebaceous gland, at or near the site of insertion of the arrector pili muscle.
¶Upregulated in mouse bulge cells.
§Studied primarily in mice.
‖Lowest permanent portion of the hair follicle.

Table 2.2 Cutaneous stem cells. ATOH1, atonal homolog 1; CD24, glycoprotein involved in cell adhesion and signaling; CD34, marker of hematopoietic progenitor cells and endothelial cells; CD71, transferrin receptor; CD146, melanoma cell adhesion molecule/MUC18/S-Endo-1 antigen; CD200, transmembrane glycoprotein that delivers a negative immunoregulatory signal (may be involved in maintaining immune tolerance); GLI1, GLI family zinc finger 1; LGR5/6, leucine-rich repeat-containing G protein-coupled receptor 5/6; LRIG1, leucine-rich repeats and immunoglobulin-like domains 1 (epidermal growth factor receptor antagonist and regulator of stem cell quiescence); MCSP, melanoma-associated chondroitin sulfate proteoglycan; PHLDA1, pleckstrin homology-like domain, family A, member 1; SCA1, stem cell antigen 1; SOX2/9, SRY (sex determining region Y)-box 2/9; TYRP, tyrosinase-related protein.

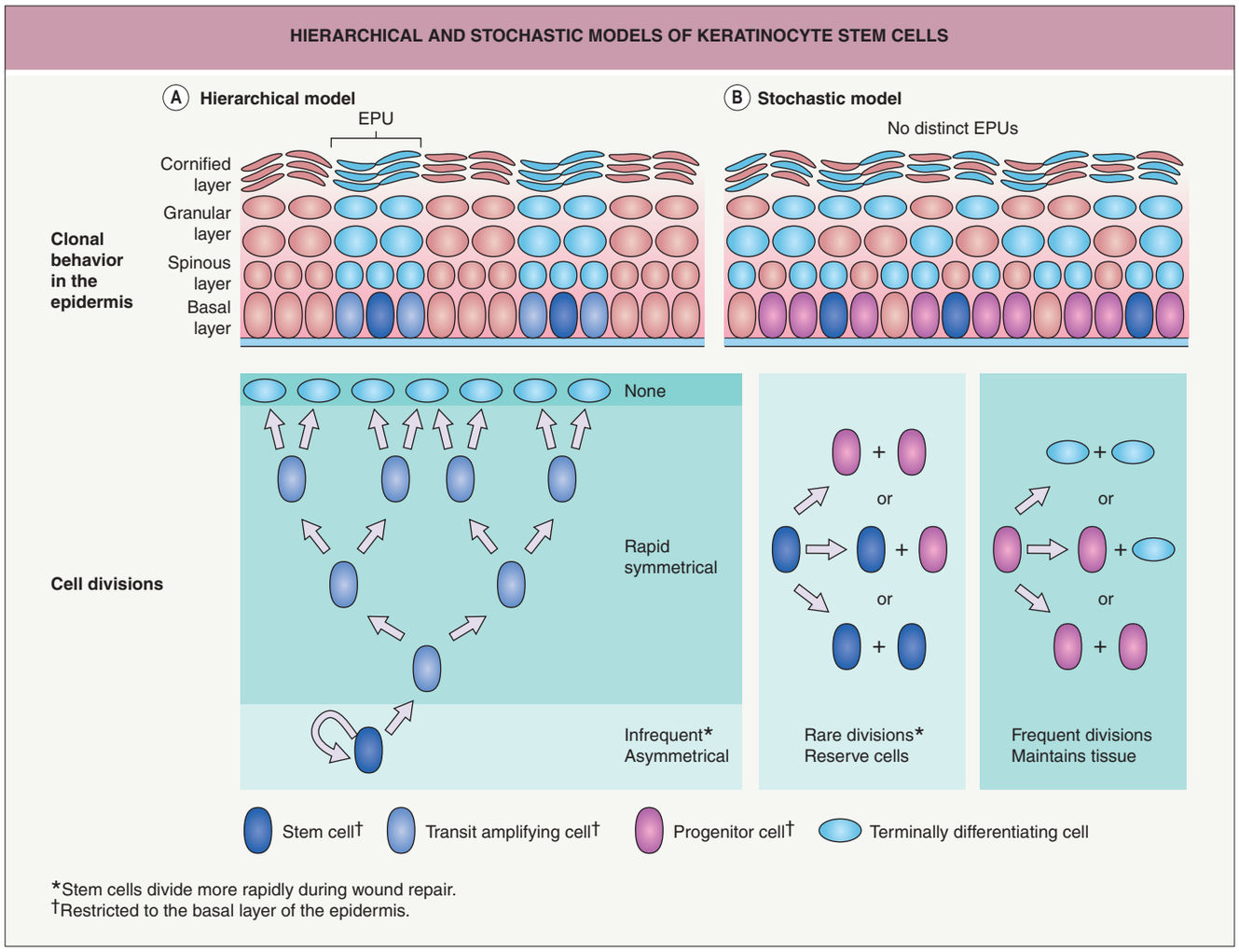


Fig. 2.5 Hierarchical and stochastic models of keratinocyte stem cells. These two models have been utilized to explain the behavior of stem cells and other proliferative cells in the basal epidermis. **A** In the *hierarchical model*, stem cells undergo infrequent asymmetric division, generating one new stem cell and one daughter transit amplifying (TA) cell. Unlike stem cells, TA cells divide frequently and symmetrically, producing two TA cells; in this model, they constitute the majority of basal keratinocytes. After a few rounds of division, TA cells withdraw from the cell cycle and move suprabasally, initiating the keratinocyte terminal differentiation program. Each epidermal stem cell and its progeny form a vertical column of progressively differentiating cells, which is known as an epidermal proliferation unit (EPU). **B** In the *stochastic model*, epidermal stem cell divisions are rare and usually asymmetrical, generating a new stem cell and a committed progenitor cell; however, random symmetric divisions resulting in either two stem cells or two progenitor cells also occasionally occur. In this model, committed progenitor cells make up the bulk of the basal layer, where they divide frequently to maintain the epidermis by producing either a new progenitor and a cell that leaves the basal layer to undergo terminal differentiation or two cells of either fate. It is possible that aspects of both stem cell models occur in the skin, depending on location or external stimuli, explaining why experimental evidence exists to support both models. Retention of a DNA label (e.g. 5-bromo-2-deoxyuridine or tritiated thymidine) is utilized as an *in vivo* marker of stem cells based on their slowly cycling nature.

The bulge represents the lowest portion of the hair follicle that does not regress during the catagen phase, and it contains morphologically undifferentiated cells[28]. Hair follicle bulge cells are slow-cycling and have a high clonogenic potential in culture, as well as being self-renewing and multipotent. *In vivo*, they typically proliferate only when the hair follicle re-enters the anagen phase, in order to regenerate the bottom two-thirds of the follicle. In addition, appendageal stem cells of the bulge and eccrine duct provide an important ectodermal reserve, allowing reconstitution of the surface epidermis after wounding.

The bulb region at the base of the anagen follicle contains self-renewing, rapidly dividing, clonogenic matrix cells that produce the hair shaft and inner root sheath. These cells have the properties of stem cells, except they regress along with the rest of the lower follicle during catagen. Whether bulb cells are best described as transit amplifying cells or committed progenitor cells is a matter of debate.

Stem Cell Plasticity

Under homeostatic conditions, epidermal and hair follicle stem cells only contribute to their respective tissues of origin. However, bulge-derived keratinocytes can also contribute to the repair of the interfollicular epidermis in response to injury[28]. Although most bulge-derived cells survive only transiently within the healing epidermis, a subpopulation of bulge cells can transdifferentiate into long-living epidermal stem cells[29]. Similarly, epidermal stem cells can contribute to new hair follicle formation in the center of large wounds[30].

Like many organs, the skin and subcutaneous fat contain rare cells that can produce sphere-like colonies when provided with multiple growth factors in three-dimensional culture. These sphere cells represent *pluripotent* stem cells that can be directed to produce many tissue types, and their use for autologous stem cell therapies is being explored. However, the *in situ* location and function of these cells in the skin remains unknown.

Along the same lines, cells in adult mammals are far more "flexible" in their potential to form other cell types than previously thought. Some cell types, particularly bone marrow cells, have the potential to incorporate themselves into diverse tissues (e.g. epidermis, heart) and adopt the fates of resident cells, contributing progeny to the tissue. Induced pluripotent stem (iPS) cells are somatic cells

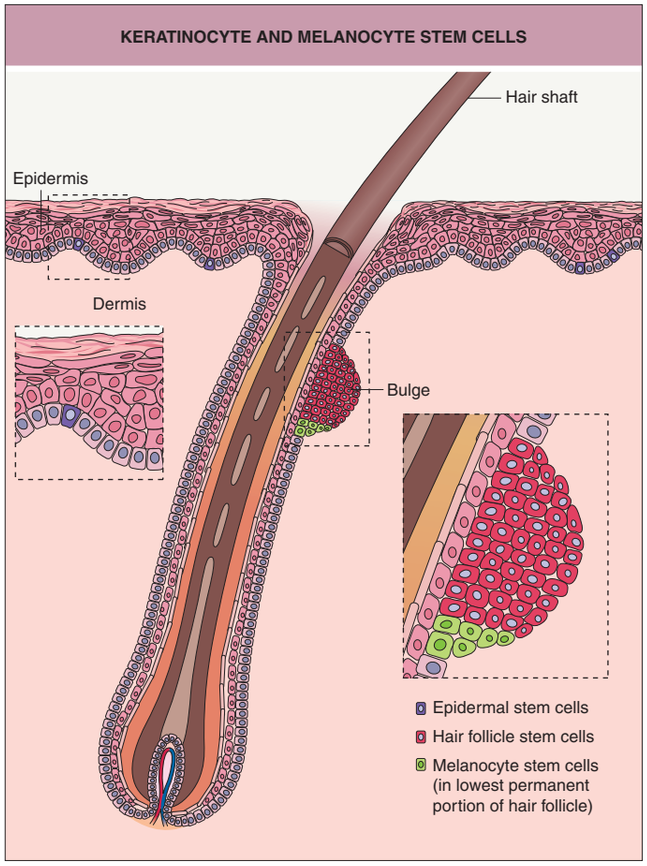


Fig. 2.6 Keratinocyte and melanocyte stem cells. Note that the bulge is continuous with the outer root sheath.

(e.g. fibroblasts) that have been reprogrammed into an embryonic stem cell-like state[31]; these cells can be stimulated to differentiate into a variety of cell types, including keratinocytes. Thus, adult cells, including different skin cell types, may be capable of dedifferentiating into pluripotent stem cells.

Stem Cell-Based Therapy for Genetic Skin Disease

Stem cells have been utilized in several strategies for gene therapy of heritable skin diseases (Fig. 2.7). Treatment via delivery of gene-corrected stem cells has the advantage of continuous protein synthesis in the skin, but it may carry a risk of oncogenesis, especially with retroviral vectors. Laminin-β3-deficient skin from patients with junctional EB has been corrected by transplantation of stem cell-enriched epidermal grafts transduced *ex vivo* with a retroviral vector encoding normal *LAMB3* cDNA. The treatment resulted in expression of functional laminin 332 and an absence of blistering in the corrected epidermis, both sustained over years of follow-up[32]. In patients with severe recessive dystrophic EB (RDEB), similar gene-corrected autologous keratinocyte grafts as well as intradermal and intravenous injections of allogeneic mesenchymal stromal/stem cells have also led to improved wound healing. In clinical trials investigating the use of allogeneic bone marrow-derived stem cell transplantation in children with severe RDEB, collagen VII deposition at the dermal–epidermal junction and variably decreased blistering were observed, with associated morbidity and mortality partially ameliorated by using reduced-intensity conditioning regimens[33]. Other investigators are studying alternative sources of stem cells for the treatment of EB, including autologous iPS cells derived from revertant keratinocytes[34].

PRENATAL DIAGNOSIS OF GENODERMATOSES

Many genodermatoses are incompatible with survival to term or are associated with significant morbidity or even mortality after birth, making prenatal diagnosis desirable. In the early 1980s, fetal skin biopsy obtained at 19–22 weeks' EGA via ultrasound guidance became the first technique available for prenatal diagnosis of inherited skin diseases. Epidermolytic ichthyosis and severe junctional EB were the first diseases diagnosed prenatally by light and/or electron microscopy of fetal skin biopsies.

As the causative genes for many genodermatoses have been discovered, DNA-based testing using material obtained from chorionic villus sampling (10–12 weeks after the last menstrual period/8–10 weeks' EGA) or amniocentesis (14–16 weeks after the last menstrual period/12–14 weeks' EGA) has largely replaced fetal skin biopsy, as these techniques can be performed earlier and pose less risk to the mother and fetus. More recently, non-invasive prenatal testing techniques utilizing circulating fetal cells or cell-free DNA have been developed[35]. With these approaches, the pathogenic mutation(s) must be identified in family members prior to prenatal testing.

Preimplantation genetic diagnosis allows for prenatal diagnosis before the embryo is implanted and pregnancy begins. This technique requires the use of *in vitro* fertilization. One or two cells are taken from the embryo at the blastocyst (6- to 10-cell) stage. The cellular DNA is amplified using PCR and analyzed for the known family mutation(s); unaffected embryos are then selected for uterine implantation. For X-linked disorders, sex determination has been utilized both in conjunction with specific genetic analysis and to identify embryos of a particular sex for selective transfer. Preimplantation genetic diagnosis obviates the need to terminate a pregnancy with an affected fetus. However, it has several disadvantages compared to chorionic villus sampling or amniocentesis, including higher cost, technical difficulties (e.g. contamination by extraneous DNA), and a low rate of completed pregnancies.

SIGNIFICANCE OF SKIN DEVELOPMENT IN POSTNATAL LIFE

Understanding skin development is essential for the appropriate diagnosis and management of congenital skin disorders. This knowledge is useful far beyond the neonatal period, however, as many of the regulatory pathways central to development are recapitulated in postnatal life. For example, hedgehog signaling through PTCH and SMO is critical for postnatal hair cycling as well as hair follicle development. In addition to the germline *PTCH* mutations that result in basal cell nevus syndrome, somatic *PTCH* mutations represent a pathogenic factor in sporadic BCCs. Knowledge of this pathway enabled the development of SMO inhibitors (e.g. vismodegib) to treat locally advanced and metastatic BCC and explains the hair loss caused by these drugs. Similarly, identifying the mechanisms controlling angiogenesis and wound healing during intrauterine development holds promise for developing new cancer treatments and wound care interventions. Furthermore, elucidating the mechanisms of cutaneous stem cell formation and maintenance will help to design potential stem cell-based therapies. Thus, advancing the understanding of skin embryology and stem cell biology may lead to life-saving or life-enhancing medical advancements.

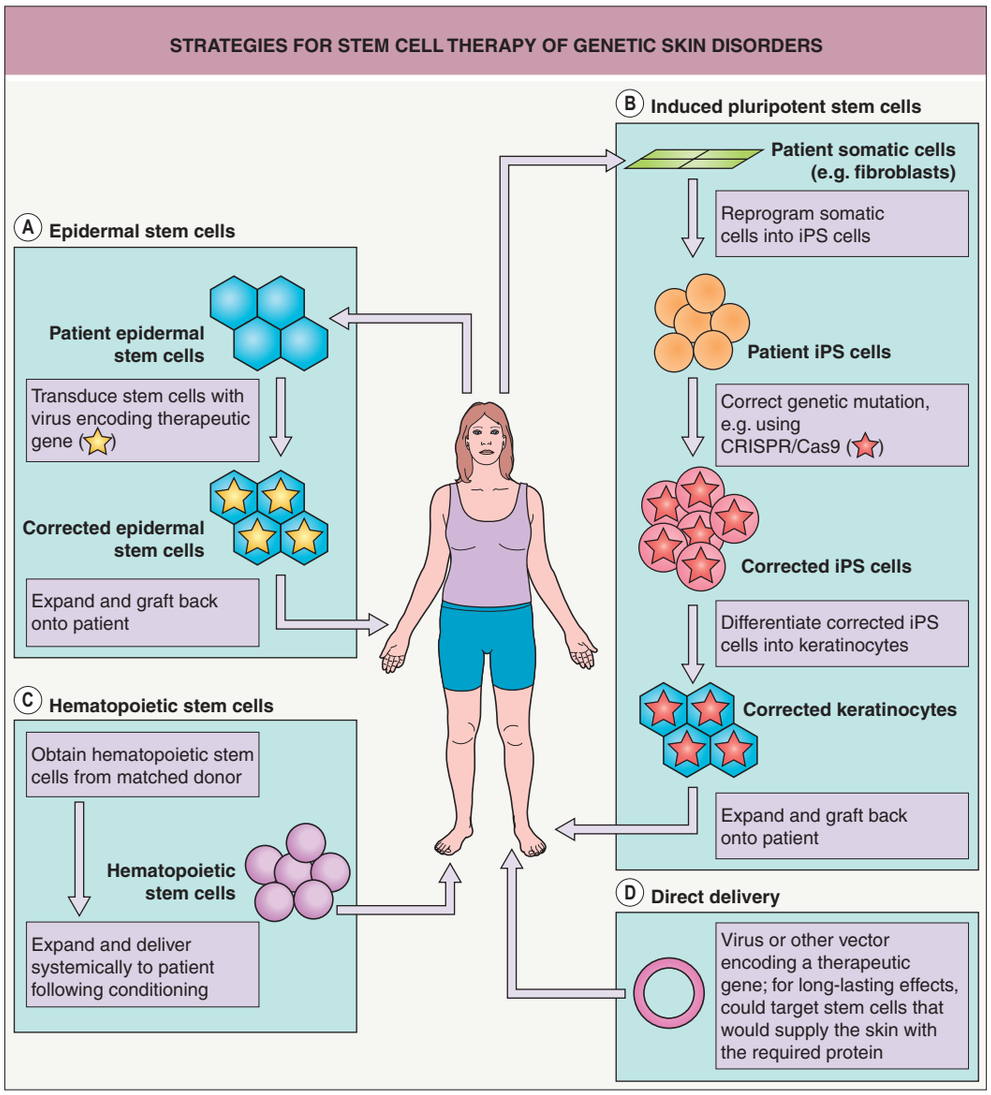
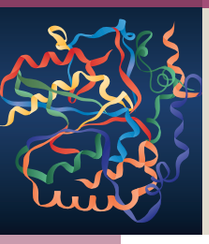


Fig. 2.7 Strategies for stem cell therapy of genetic skin disorders. A One strategy is to isolate epidermal stem cells from a patient, correct the genetic defect *in vitro* (e.g. using a viral vector), and graft epithelial sheets containing the corrected stem cells back onto the patient. **B** Gene therapy could also potentially utilize induced pluripotent stem (iPS) cells, which are generated from somatic cells (e.g. fibroblasts). The genetic defect could be corrected via techniques such as CRISPR/Cas9-based targeted genome editing in these cells (see Fig. 3.13), which would then be differentiated into keratinocytes and grafted onto the patient. **C** A third strategy involves the use of hematopoietic stem cells (HSC). Upon systemic administration (following conditioning), allogeneic HSC cells have the capacity to home to the skin (e.g. to sites of injury in patients with epidermolysis bullosa) and produce differentiated progeny cells that provide the needed skin protein (e.g. collagen VII). **D** Finally, therapeutic genes could be directly administered to patients via a virus or another vector. To achieve permanent correction, the vector must target stem cells that could supply the protein to the skin.
Courtesy Maranke I. Koster, PhD.

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3 Molecular Biology

Amaya Virós and Thomas N. Darling

INTRODUCTION

Advances in molecular biology are rapidly changing our understanding of skin biology and disease. Increased knowledge is being translated into new molecular diagnostic tests that are transforming clinical practice. Molecular analyses are currently being employed to diagnose genodermatoses[1], cutaneous infections[2], melanomas[3,4], lymphomas[5], and inherited[6] or autoimmune blistering disorders[7]. This enhanced knowledge has also led to new targeted therapies, many of which require determination of the molecular basis of a disease in order to appropriately implement treatment[8]. Molecular analyses are also used to screen for drug efficacy and susceptibility to adverse reactions to certain medications[9].

To utilize these tests appropriately, dermatologists nowadays have an even greater need to understand basic concepts of molecular biology. The goal of this chapter is to explain key concepts and methods of molecular biology in order to provide practicing dermatologists with a basic understanding of the tools their colleagues are employing and developing in the laboratory to transform clinical diagnosis, patient stratification, and therapy.

EXPERIMENTAL TECHNIQUES

Tissue Processing

Dermatologists are accustomed to placing a biopsy specimen in formalin followed by paraffin embedding and then staining tissue sections with hematoxylin and eosin. However, this is just one of several possible starting points for tissue processing (Fig. 3.1). By placing the sample in formalin (for light microscopy), glutaraldehyde (for electron microscopy), or freezing a fresh sample before processing and sectioning, the sample can be analyzed histologically in various ways, including by routine staining, immunohistochemistry, or *in situ* hybridization.

Cryosections from frozen samples have lower quality tissue architecture than sections from formalin-fixed, paraffin-embedded tissues, but the former preserve DNA, RNA, and protein better than other fixation methods. Fresh or frozen tissue can also be processed directly with buffers and reagents to extract DNA, RNA, and protein from the *whole tissue*. In addition, fresh tissue can be used to prepare a suspension of *single cells* for single-cell analysis of DNA, RNA, or protein. The desired lineage of cells (e.g., keratinocytes, fibroblasts, immunocytes, endothelial cells) can be propagated *in vitro* by using selective culture media and isolation techniques.

One method for isolating a particular cell population from a tissue section is laser microdissection, which allows selection of microanatomic regions for analysis (Fig. 3.2)[10]. Alternatively, once tissue is dissociated and living cells are in a single cell suspension, flow cytometry can be used to identify populations of cells (Fig. 3.3)[11]. Individual cells pass through in a stream and through a set of lasers and electronic detectors that can measure multiple parameters for each cell. Fluorescence-activated cell sorting (FACS) utilizes an electrostatic deflection system and it can be used to obtain pure cell populations with specific desired characteristics, e.g. cells tagged by lineage-specific antibodies. The field of single-cell molecular biology is rapidly evolving, and it has become possible to analyze 40 or more parameters for each cell by combining the principles of flow cytometry and elemental mass spectrometry in a technique called mass cytometry[12].

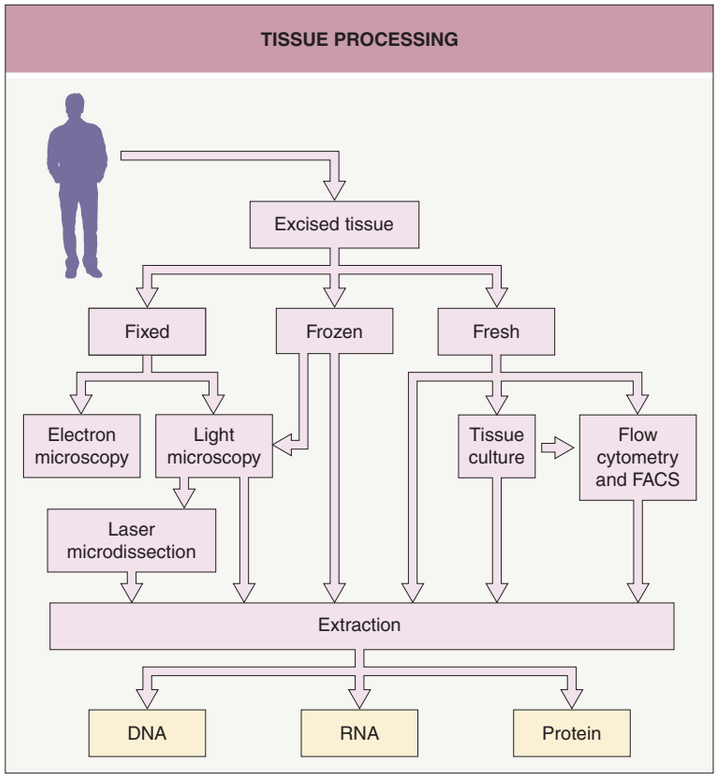


Fig. 3.1 Tissue processing. A tissue sample can be processed in various ways for the analysis of DNA, RNA, or protein. FACS, fluorescence-activated cell sorting.

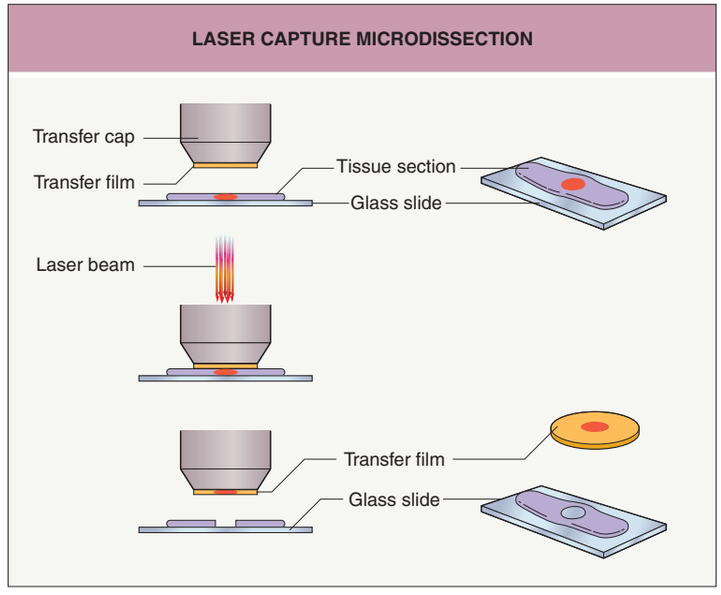


Fig. 3.2 Laser capture microdissection. Laser capture microdissection is one method of microdissection used to selectively procure individual cells or clusters of cells from tissue sections. A cap coated with a thermoplastic transfer membrane is placed directly over the tissue section. The operator visually identifies the cells of interest and triggers a low-energy infrared laser to melt the transfer film onto cells of interest. The cap is then lifted from the section to separate the selected cells from the remainder of the tissue section.

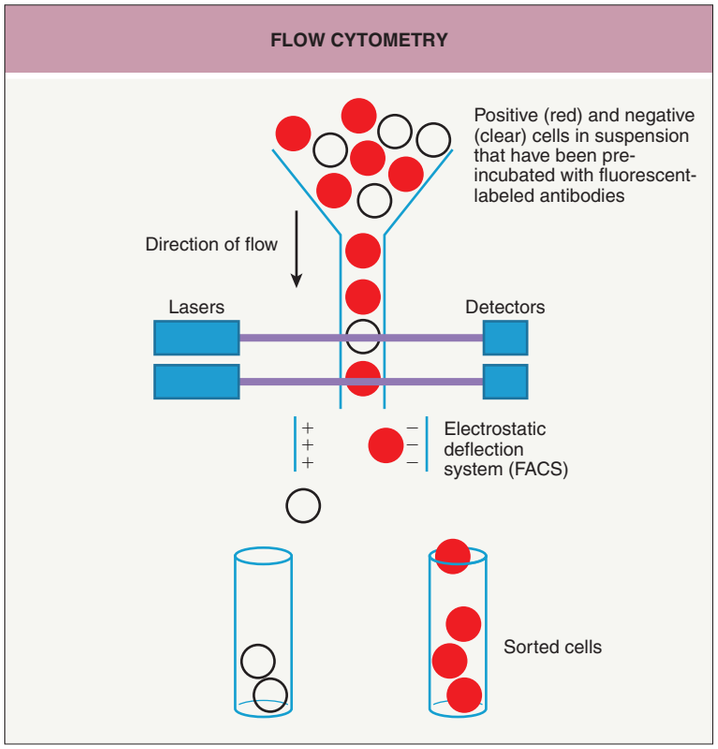


Fig. 3.3 Flow cytometry. Cells in suspension, pre-incubated with fluorescent-labeled antibodies, flow single file in a liquid stream through lasers. Detectors measure the fluorescence intensities of each cell. In fluorescence-activated cell sorting (FACS), the single cells are divided into charged droplets that are separated into different tubes based on the marker(s) of interest as they pass through an electrostatic deflection system.

The Foundations of Molecular Techniques for Analyzing DNA, RNA, and Protein

The concepts behind molecular biology are simple and unifying. In general, they consist of extracting the molecules of interest, amplifying them to measurable amounts, and then detecting them. Polymerase chain reaction (PCR) is a standard technique for amplifying *DNA* (Table 3.1; Fig. 3.4)[13]. To perform PCR, short sequences of synthetic DNA (primers) are used to hybridize to a DNA region of interest, which is then replicated through multiple cycles. The PCR-amplified DNA, typically 50 to 2000 base pairs in size depending on the primers designed, can be detected in a gel using an intercalating dye that fluoresces with ultraviolet light. The nucleotide sequence can then be determined via fluorescence sequencing techniques. This simple and relatively inexpensive approach, also called Sanger sequencing, is still widely used.

Nowadays, however, massively parallel sequencing, also known as next-generation sequencing, offers the opportunity for reading millions of DNA fragments in a single run at a marginally higher cost (Table 3.2; Fig. 3.5)[14]. The advent of massively parallel sequencing not only allows access to DNA sequences, but it also allows one to infer DNA copy number changes. This is because the final amplified DNA is proportional to the number of DNA copies in the original reaction, allowing inference of copy number variation of specific genes and genomic regions. One limitation of massively parallel sequencing is that its increased power and reading depth requires bioinformatics and sophisticated data analyses, which are challenging to standardize in clinical practice.

RNA is also easy to purify, but is more unstable and degrades much faster than DNA. Therefore, a typical first step in the analysis of RNA is to convert it into DNA using reverse transcription (RT; Table 3.3; Fig. 3.6). Following RT, the generated complementary DNA (cDNA) can be amplified by PCR, as described above. The technique of RT-PCR has also been modified to allow accurate quantitation of

POLYMERASE CHAIN REACTION
Purpose
• Amplify a specific piece of DNA from a complex mixture
Requirements
• Need to know the sequence of the DNA of interest (at least of its ends)
Underlying concepts
• Double-stranded DNA can be unwound (denatured) with a higher temperature to single strands; when cooled, the single strands come back together to form double strands (hybridize) if the nucleotide sequences are complementary • During the hybridization process, two complementary strands bind to each other. The A nucleotides bind to T nucleotides on the complementary strand, whereas C nucleotides bind to G nucleotides on the complementary strand • In PCR, short DNA strands called oligonucleotide primers are designed to hybridize to target sequences in the template DNA
Outline of method (Fig. 3.4)
• Oligonucleotide primers are designed to hybridize to specific sequences at each end of the DNA of interest. These primers are added to a reaction vessel mixture containing the template DNA along with a thermostable DNA polymerase, the nucleotides dATP (A), dTTP (T), dGTP (G) and dCTP (C), and a reaction buffer • The reaction vessel is placed in a thermal cycler, which controls the temperature of the reaction through many cycles • Each cycle contains the following steps: (1) denaturation; (2) primer annealing or primer hybridization; (3) primer extension; and (4) repeat of the complete cycle of PCR 30–40 times leading to amplification of the target sequence
Benefits
• PCR is simple, rapid, and sensitive • Each cycle increases the number of PCR products twofold. The total number of PCR products after n cycles will be 2^n
Limitations/errors
• Because of its high sensitivity, contamination can cause misleading results • Primers used for PCR can anneal to sequences that are similar, but not identical, to the sequence of interest, causing misleading results • DNA polymerase occasionally incorporates incorrect nucleotides
Experimental applications
• DNA can be amplified either for detection of a specific sequence or for cloning • PCR can be used to label DNA with fluorescent or radioactive nucleotides
Modifications/alternatives
• Quantitative PCR – the amount (number of copies) of a specific piece of DNA can be quantified by a variety of methods utilizing PCR. A relatively simple and high-throughput method, called real-time quantitative PCR, measures the amount of PCR product formed after each cycle. The higher the amount of DNA, the earlier the product can be detected.

Table 3.1 Polymerase chain reaction.

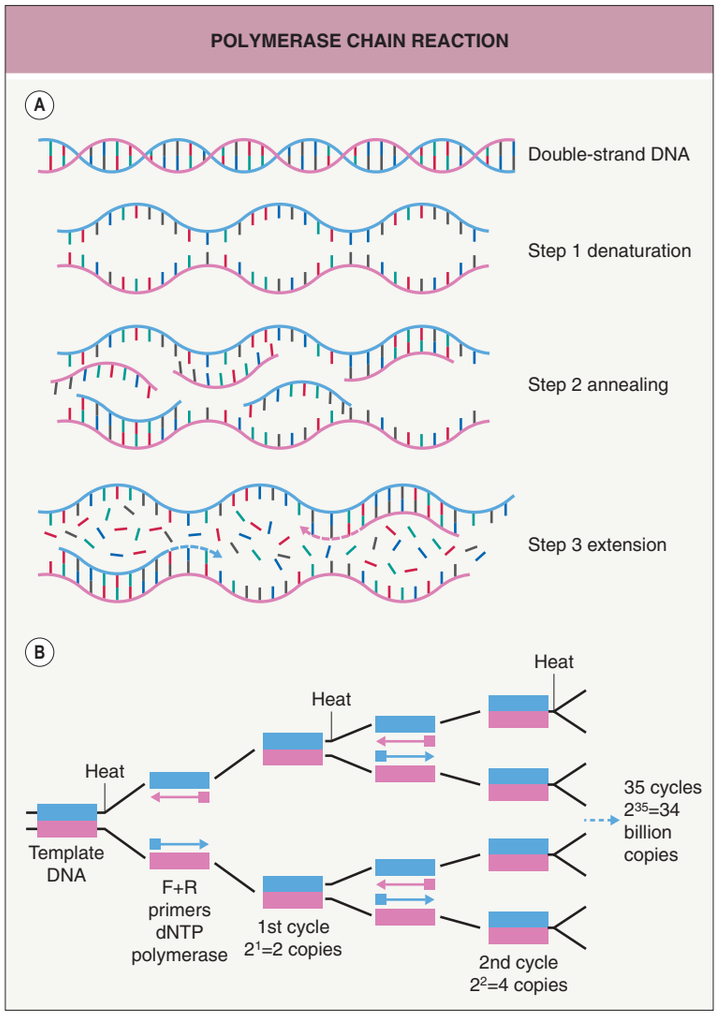


Fig. 3.4 Polymerase chain reaction. A Each cycle contains the following steps: (1) denaturation – separate the two strands of DNA by heating to >90°C; (2) primer annealing or primer hybridization – allow the oligonucleotide primers to bind to the template DNA by cooling to 50–65°C; (3) primer extension – DNA polymerase catalyzes the addition of nucleotides (A, G, C, T) that are complementary to the DNA template, beginning with the primer and extending 3′ at the optimal temperature of 72°C; and (4) repeat the complete cycle 30–40 times. **B** Each cycle increases the number of PCR products twofold. The total number of PCR products after *n* cycles will be 2^n times the original amount. F+R, forward and reverse.

MASSIVELY PARALLEL SEQUENCING
Purpose
• Determine the sequence or order of nucleotides (A, G, C, T) in a genome or parts of the genome
Requirements
• DNA to be sequenced should be high quality
Underlying concepts
• Millions of DNA fragments are sequenced simultaneously on the same solid surface with spatial separation of templates • Reversible chain termination is used to incorporate fluorescent nucleotides sequentially for optical detection of the nucleotide sequence
Outline of method (Fig. 3.5)
• Library preparation: sequencing libraries can be created using adapter ligation or multiplex PCR (amplicon sequencing). In adapter ligation, DNA is randomly fragmented followed by ligating sequencing adapters to both ends of the DNA fragments. The adapter-ligated DNA fragments may be used directly for whole-genome sequencing or enriched for specific regions of interest (target enrichment) by hybridizing to biotinylated probes that are isolated by magnetic pull-down • Sequencing: oligonucleotides complementary to the sequencing adaptors are bound on the surface of a glass slide (the flow cell). Each DNA fragment of the sequencing library that is bound to its complementary oligonucleotide on the surface of the flow cell is amplified into a clonal cluster of DNA fragments using a PCR-based method (cluster generation). Millions of clusters are simultaneously sequenced using DNA polymerase and four different fluorescently labeled reversible dNTP terminators. The nucleotide incorporated at each cycle on unique clusters is detected optically, after which the fluorescent label is enzymatically cleaved and a nucleotide is incorporated before moving to the next nucleotide for detection • Data analysis: the sequencing reads are computationally aligned to a reference genome, and various types of computational analyses are then performed to detect single nucleotide variants, insertions, deletions, translocations, and DNA copy number variations
Benefits
• Rapid sequencing of the entire genome at low cost • Targeted sequencing of all protein-coding DNA regions (exome sequencing; ~2% of the genome) or only a few selected genes (e.g. cancer-related gene panels)
Limitations/errors
• Read lengths of about 150 to 300 bp • 99.9% accuracy of reads
Experimental applications
• Identifying genomic aberrations, including mutations, copy number changes, and translocations • Sequencing of microbiomes
Modifications/alternatives
• Nanopore technology and Sanger sequencing • ChIP-seq combines massively parallel sequencing with chromatin immunoprecipitation to analyze protein interactions with DNA • ATAC-seq assesses genome-wide chromatin accessibility

Table 3.2 Massively parallel sequencing.

very low levels of mRNA[15]. Because the amount of PCR product is monitored during each amplification cycle, this technique is called "real-time" quantitative PCR.

The amount of *protein* in a cell is a complex balance of synthesis and degradation controlled at multiple steps, including efficiency of protein translation and post-translational modifications that affect protein stability. One method for measuring protein levels is the Western blot, which is also called an immunoblot because an antibody is used to detect the protein of interest (Table 3.4; Fig. 3.7). In addition to measuring protein levels, Western blot analysis can determine protein size and whether there are different forms of the protein[16]. Another common method for measuring protein levels is an enzyme-linked immunosorbent assay (ELISA; see Table 3.4), which can provide accurate quantifications of proteins[17]. In multiplex bead-based immunoassays, up to 100 analytes can be detected simultaneously (see Fig. 40.2). For this, distinct fluorophore-colored microbeads, coupled to specific antibodies, are incubated with a sample; this mixture is then exposed to secondary detection antibodies and reporters, followed by exposure to laser excitation. The technique allows for a quantitative interpretation of the amount of analyte bound to the bead.

Measuring Cells Within Tissues

For populations of cells, PCR, RT-PCR, and Western blots are useful for measuring DNA, RNA, and protein, respectively. However, to identify features at a cellular level, tissue sections can be analyzed via various assays. For example, fluorescence *in situ* hybridization (FISH) is employed to assess the presence or expression of *DNA or RNA*. This technique relies on the use of fluorescently labeled nucleic acid probes that are complementary to the DNA or RNA sequences of interest in the tissue sections (Table 3.5; Fig. 3.8). The probes are hybridized to the target sequences in the tissue, and the slide is then examined using

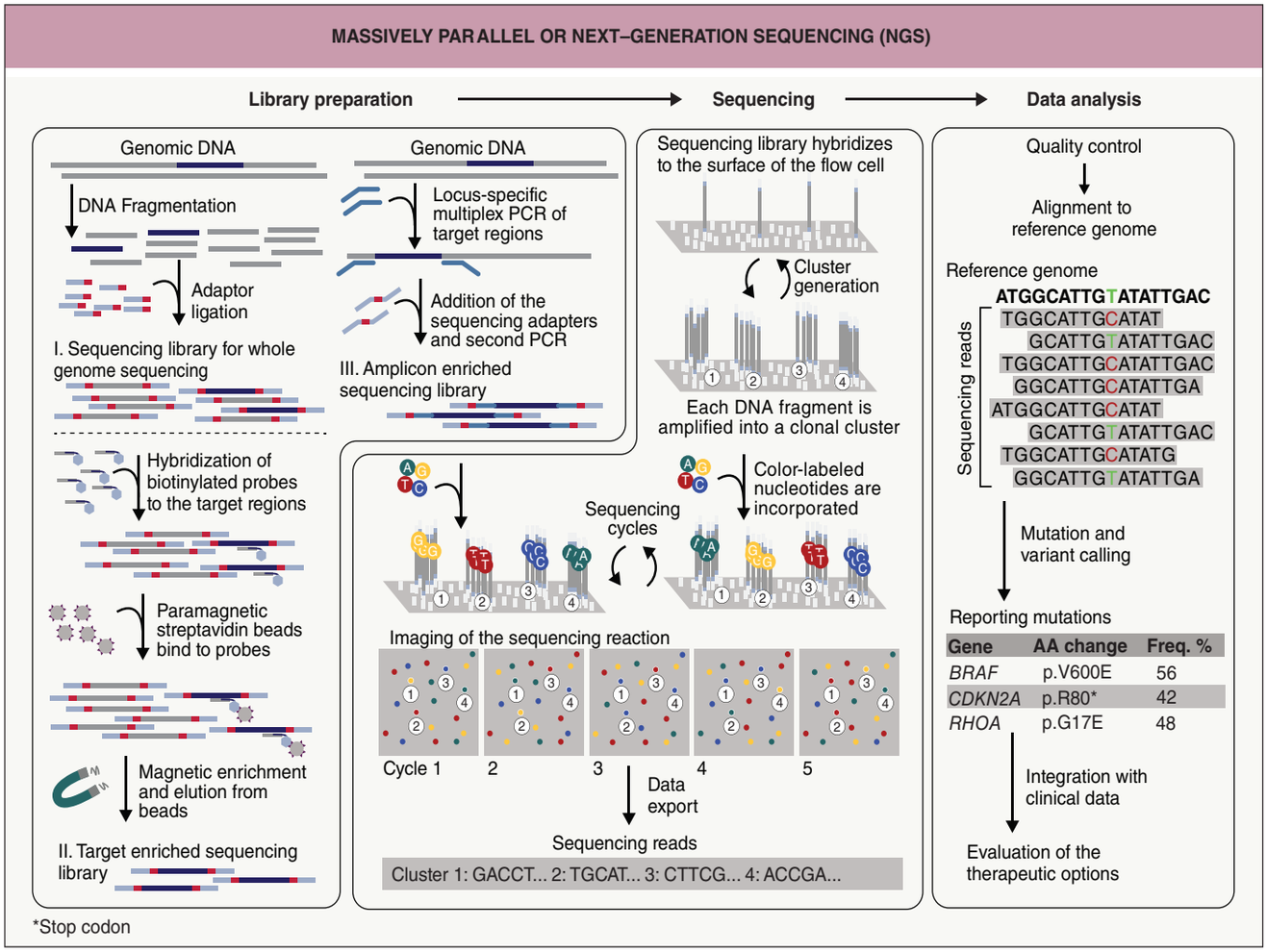


Fig. 3.5 Massively parallel or next generation sequencing (NGS). The technology used for massively parallel sequencing varies among different platforms. The workflow on Illumina platforms can be divided into three steps: (1) *library preparation* – the test DNA is flanked with sequencing adaptors either by ligation (adaptor ligation) or PCR (amplicon sequencing); (2) *sequencing* – the adaptor-flanked test DNA binds to oligonucleotides on the surface of the flow cell and DNA polymerases catalyze the incorporation of fluorescently labeled nucleotides, which are identified by imaging; after enzymatic removal of the fluorophores, a new fluorescently labeled nucleotide is incorporated and read out by imaging; (3) *data analysis* – after quality controls and alignment of the sequencing reads to reference genomes, the genetic aberrations are called and annotated using computational algorithms. Freq, frequency

fluorescence microscopy[18]. As a diagnostic tool, FISH can be used to detect genomic aberrations in single cancer cells (see Fig. 117.19).

Immunohistochemistry is employed to assess the expression of *proteins* in tissue sections. An antibody is added to a tissue section where it specifically binds to the protein of interest. The bound antibody is usually detected based on an enzymatic reaction that generates a colored product at the binding site. Immunohistochemistry can be used to determine the locations and expression level of a protein within a tissue, including proteins that mark specific cell lineages or cell states such as differentiation, activation, proliferation, or apoptosis. Of note, immunohistochemistry has evolved beyond quantitative visualization of a single protein – it can also detect specific sequences of *messenger RNA* (mRNA) in a tissue. In addition, revolutionary visualization assays allow assessment with multiple antibodies, utilizing the same principles of antibody-bound color reagents (multiplex IHC and FISH).

Measuring the Transcriptome and Proteome

There are several approaches to quantitatively analyze the expression levels of nearly all cellular genes, i.e. the *transcriptome*. RNA-seq utilizes massively parallel sequencing to evaluate gene expression levels, gene splicing, non-coding RNA, microRNA, gene fusions, and mutations[19]. Nowadays it is also possible to perform RNA-seq on single cells, an approach that is providing new insights into the complexity of human skin[20]. Additional methods are based on the hybridization of labeled sample mRNA to known oligonucleotide or cDNA sequences (representing thousands of genes) placed on chips, beads, or glass slides (arrays)[21]. The level of hybridization to the nucleotide sequence of a given gene indicates how much mRNA of that gene is present.

The *proteome* represents all cellular proteins expressed under specific conditions. Mass spectrometry provides extremely accurate measurements of protein mass by ionizing the protein and measuring the "time-of-flight" through a tube to a detector on the opposite end (Table 3.6; Fig. 3.9)[22]. In most instances, the proteins are separated by two-dimensional gel electrophoresis or capillary electrophoresis before mass spectrometry. Quantification is accomplished by labeling proteins with stable isotopes to provide internal standards or by label-free shotgun proteomic approaches that allow a faster analysis at lower costs[22]. Another technique is the use of reverse-phase protein arrays, in which whole protein lysates are spotted onto slides and probed using antibodies to specific proteins[23]. The field of proteomics promises to provide a tremendous amount of information regarding cell biology and disease states.

Mouse Models of Skin Disease

Transgenic mice are commonly used as experimental models for elucidating the *in vivo* functions of genes[24,25]. The traditional approach is to microinject the gene of interest into a fertilized mouse egg, where it randomly integrates into the mouse genome (Table 3.7; Fig. 3.10). Although the gene is present in every cell as the egg develops into a mouse, expression of the gene can be limited or targeted to specific tissues or cell types by using a promoter that is only expressed in a

REVERSE TRANSCRIPTION PCR
Purpose
• To amplify mRNA by PCR • mRNA is first converted to DNA (called complementary DNA or cDNA), followed by PCR amplification of a specific region of the cDNA to detectable levels
Requirements
• Starting material can be total cellular RNA or purified mRNA
Underlying concept
• Many methods that study RNA first convert RNA to cDNA with an enzyme called reverse transcriptase, because cDNA is more stable than RNA
Outline of method (Fig. 3.6)
• Reverse transcriptase can convert mRNA to cDNA by three different methods, depending on the primer used for the initial RT step: (1) random hexamer primers contain six nucleotides (6-mer) that have all possible sequence combinations of the dA, dG, dC, and dT nucleotides (4^6 possible combinations) and hybridize to complementary sequences in the RNA; (2) oligo dT primers contain only dT nucleotides and hybridize to the complementary string of dA nucleotides that are present at the end of mRNA molecules (poly-A tail); or (3) primer that will only hybridize to a specific mRNA sequence • After the mRNA has been converted to cDNA, primers that hybridize to specific sequences are added and PCR amplification is performed
Benefits
• RT-PCR is simple, rapid, and sensitive
Limitations/errors
• If the RNA sample is contaminated with DNA, a PCR product may be amplified from the DNA even though the corresponding mRNA for the gene is not present • RNA is fragile, and the absence of a specific mRNA transcript may result from RNA degradation during and following extraction
Experimental applications
• The mRNA gene transcripts can be amplified for subsequent cloning or sequencing
Modifications/alternatives
• Quantitative RT-PCR – by adding a reverse transcription step to quantitative PCR, the levels of mRNA transcripts can be quantified. Samples that contain fewer mRNA transcripts will require more PCR cycles, and different RNA samples can be precisely compared by measuring the number of PCR cycles needed to produce a defined amount of PCR product • Alternative methods to measure RNA levels include digital PCR, in which the sample is partitioned into individual nucleic acids

Table 3.3 Reverse transcription PCR (RT-PCR).

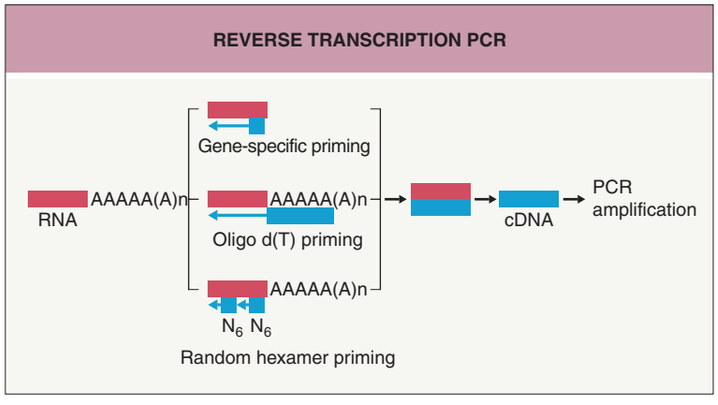


Fig. 3.6 Reverse transcription PCR (RT-PCR). Reverse transcriptase can convert mRNA to cDNA in three different ways, depending on the primer used: (1) random hexamer primers; (2) oligo dT primers; and (3) gene-specific primers. After the mRNA has been converted to cDNA, primers that can hybridize to specific nucleotide sequences are added and PCR is performed.

WESTERN BLOT
Purpose
• Determines the size and the amount of protein present in a sample
Requirements
• An antibody that is specific for the protein of interest
Underlying concepts
• Polyclonal antibodies react to several epitopes on a protein and they are obtained by injecting a protein into an animal and later isolating the antibodies from the serum • Monoclonal antibodies react to only one epitope of a protein and they are obtained by injecting a protein into an animal followed by fusing of the animal's reactive lymphocytes with an immortal myeloma cell line to create cells that are able to provide antibodies indefinitely • The primary polyclonal or monoclonal antibodies bind to the protein. The primary antibodies are detected by a secondary antibody, which is labeled with a fluorescent probe that can produce light or with an enzyme that can produce a detectable substrate by an enzymatic reaction
Outline of method (Fig. 3.7)
• A solubilized protein mix is separated on a polyacrylamide gel and transferred electrophoretically to a membrane. The membrane is then soaked in a buffer containing the antibody. Bound antibody is detected by a chromogenic or chemiluminescent assay
Benefits
• A simple and sensitive method to detect and quantify proteins • Can determine the molecular weight of a specific protein relative to standard controls
Limitations/errors
• Specific antibodies are required that recognize the protein • May contain a high background of nonspecific staining • Proteins may degrade during extraction
Experimental applications
• Detection, quantification, and characterization of a specific protein • Identification of antibody activity to a known antigen
Modifications/alternatives
• Immunoprecipitation (IP): the specific antibody is added to the protein mixture, and the resulting antibody–protein complexes are then isolated; because proteins are not denatured by IP, they can be detected in a more native configuration • IP–Western: protein–protein interactions can be studied by first immunoprecipitating the protein with one antibody, bringing down a protein complex. The protein complex is then separated on a polyacrylamide gel, followed by Western blotting to detect the members of the protein complex • Enzyme-linked immunosorbent assay (ELISA): a sensitive and specific method for quantifying the amount of a protein. The protein of interest is captured on a plate coated with a monoclonal antibody and other proteins are washed away. The protein is then detected using a second antibody that has been modified for detection using a colorimetric or luminescent assay • Immunohistochemistry: allows visualization of the cellular localization of a protein. A primary antibody that recognizes the protein of interest is applied to a tissue section. The protein is then detected using a secondary antibody coupled to an enzyme that reacts with a substrate to produce a colored precipitate

Table 3.4 Western blot.

particular cell linage. Promoters initiate mRNA expression and are located upstream of the gene's coding region. For example, a promoter that ensures that a gene is expressed only in melanocytes would be a promoter of a gene involved in melanin biosynthesis, such as tyrosinase. Although every mouse cell will contain a randomly integrated copy of this new gene, it is expressed only in melanocytes, because of the melanocyte-specific promoter. This principle can be applied to other cell lineages[24].

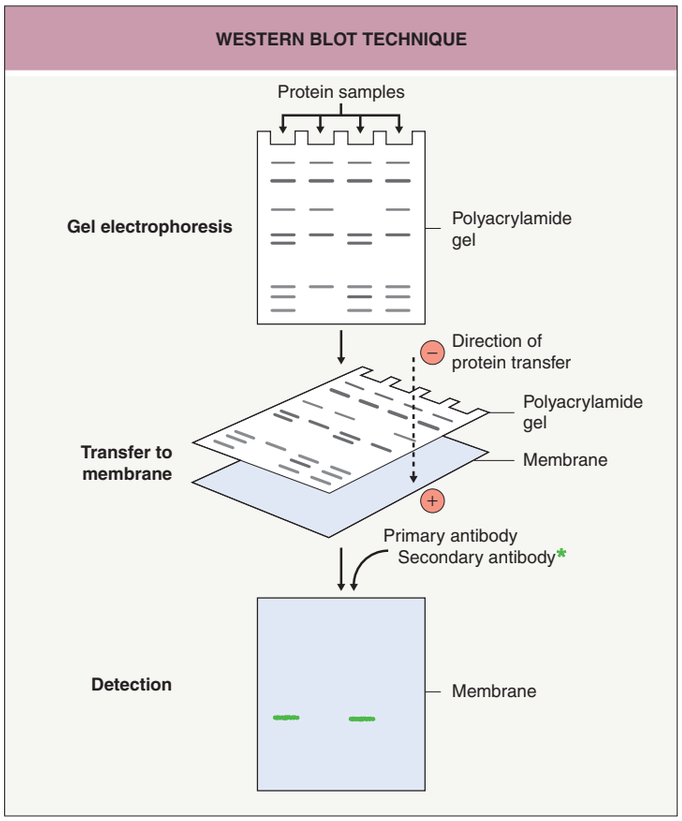


Fig. 3.7 Western blot technique. A solubilized protein mix is separated on a polyacrylamide gel and electrophoretically transferred to a membrane. The membrane is soaked in an antibody-containing buffer, and the bound antibody is detected by a chromogenic or chemiluminescent assay utilizing a labeled secondary antibody (green asterisk).

FLUORESCENCE *IN SITU* HYBRIDIZATION (FISH)
Purpose
• To visualize locations and levels of specific sequences of DNA or RNA in tissue sections
Requirements
• Tissue section of formalin-fixed paraffin-embedded tissue or fresh-frozen tissue • The target sequence must be known
Underlying concepts
• A fluorescently labeled nucleic acid probe hybridizes to complementary sequences in tissue sections
Outline of method (Fig. 3.8)
• A probe is designed that is complementary to the target sequence and is directly or indirectly labeled with a fluorochrome • Nucleic acids in the tissue section are denatured, and then the FISH probe is applied to the tissue section to hybridize to the target sequence • The unbound probe is washed away • The signal is detected using fluorescence microscopy
Benefits
• Identifies specific abnormalities in DNA, such as gene deletion, amplification, or translocation • Determines which cells are expressing a particular gene
Limitations/errors
• Subject to interlaboratory and interobserver variability • Technical issues may complicate results, such as incomplete hybridization or nonspecific binding
Experimental applications
• Identification of DNA copy number aberrations and translocations in cancer cells • Determining the spatial pattern of gene expression in a tissue
Modifications/alternatives
• Single molecule RNA FISH • FISH of metaphase preparations to diagnose chromosomal abnormalities

Table 3.5 Fluorescence *in situ* hybridization (FISH).

The functional loss of a gene can also be studied by creating a "knockout" transgenic mouse (Table 3.8; Fig. 3.11)[26]. It is also possible to *selectively* delete a gene (e.g. a tumor suppressor gene) in a specific cell type or tissue rather than deleting the gene from all cells in the mouse (Fig. 3.12)[26]. A further refinement is to trigger deletion of the gene at a particular point in time, including during development[27]. One advantage of these inducible systems over gene deletion in all mouse cells is that they may more faithfully mimic how gene deletion occurs in a specific tissue of a patient, faithfully recapitulating the hallmarks of diseases such as cancer. Inducible models can also circumvent problems that arise from gene deletion in all mouse cells, which often impact normal mouse development. In addition to using tamoxifen to control Cre expression (see Fig. 3.12), the "Tet-On/Off" system can be used to address the problem of embryonic death due to gene deletion.

The discovery of CRISPR-Cas9 genome editing tools has revolutionized and accelerated mouse model engineering, allowing for the precise introduction of mutations at targeted DNA sites (Fig. 3.13). The CRISPR-Cas9 system facilitates RNA-guided, site-specific cleavage of DNA, which results in the deletion of a DNA region following DNA repair (*knockout*); alternatively, exogenous DNA is used as a template during the repair process and this leads to a new genetic code (*knock-in*). These new techniques simplify the engineering of models for skin diseases and hold the potential to accelerate therapy development.

Gene-Based Therapy for Skin Diseases

Gene-based therapy is a therapeutic approach that holds promise as a treatment for skin diseases[28]. In gene-based therapy, DNA or RNA is manipulated to add or correct a gene in the cells of a target tissue in order to achieve a therapeutic effect (Table 3.9). Although this therapy could be administered directly to the patient's skin *in vivo*, there are concerns regarding safety and the potential for genetic alteration of the germline. Therefore, *ex vivo* techniques have been developed in which cells are grown from a skin sample, treated *in vitro*, and grafted back onto the patient (see Fig. 2.7).

Because genetic manipulation of stem cells may result in long-term engraftment and stable benefits[29], they are often preferred. However, the number of stem cells that can be obtained from adult tissues is limited, so there is considerable interest in gene therapy utilizing induced pluripotent stem (iPS) cells (see Ch. 2). Fibroblasts grown from human skin can be reprogrammed into iPS cells via exposure to transcription factors; these iPS cells are pluripotent and can be propagated *in vitro* indefinitely[30]. iPS cells from a patient may be genetically corrected and then differentiated into the desired cell type, such as keratinocytes, for grafting back to the patient (see Fig. 2.7).

In gene therapy, there are several ways to manipulate DNA. To compensate for the loss-of-function of a gene, a new copy of the gene may be introduced into cells utilizing either non-viral or viral vectors. *Sleeping Beauty* is a non-viral, cut-and-paste DNA transposon that improves long-term gene expression compared to that obtained when only DNA from the gene of interest is used. However, the DNA transposon poses risks for insertional mutagenesis because it may randomly insert near a proto-oncogene that then becomes activated[31]. Viral vectors can also be used to introduce DNA, including self-inactivating lentiviral and gamma retroviral vectors. These vectors integrate into the genome and have less risk of insertional mutagenesis compared to earlier retroviral vectors. However, viral vectors also have disadvantages such as immunogenicity, broad tropism, and limited DNA packaging capacity[32].

It may be possible to avoid the complication of insertional mutagenesis by *correcting the endogenous gene* rather than inserting a gene. Methods for targeted gene correction include the use of zinc

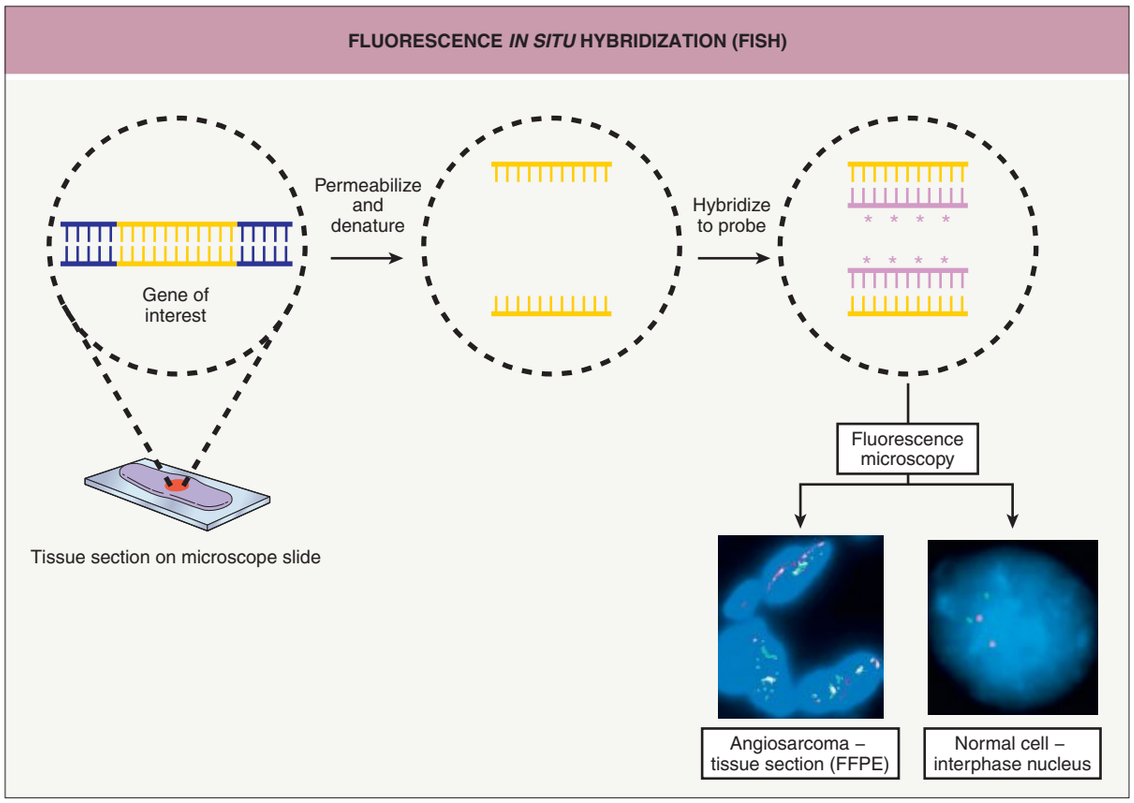


Fig. 3.8 Fluorescence *in situ* hybridization (FISH). A tissue section on a microscope slide is fixed and permeabilized. The nucleotides on the section (yellow) and the fluorescently labeled (asterisks) probes (dark pink) are denatured; then the probes are added to the section to hybridize with complementary sequences. The unbound probe is washed away, and the tissue is examined by fluorescence microscopy. Normally, two fluorescent signals appear in each nucleus for an autosomal gene, but in cancer cells, there may be only one signal, indicating a deletion, or three or more signals, indicating an amplification. Here, a normal nucleus contains two green signals and two dark pink signals for two separate autosomal genes, whereas a tissue section from an angiosarcoma shows multiple separate signals using a *MYC* break-apart probe (the probe consists of two flanking sequences in which variable breakpoints have been observed) instead of only two copies of the two signals attached to one another. FFPE, formalin-fixed, paraffin-embedded.

PROTEOMICS WITH MASS SPECTROMETRY
Purpose
• High-throughput analysis to rapidly and quantitatively assess complex mixtures of proteins present in a cell
Requirements
• A mixture of cellular proteins, or peptides derived from these proteins, is purified from a defined population of cells and then separated into proteins and/or peptides prior to mass spectrometry
Underlying concepts
• Mass spectrometry measures the size or mass of proteins and peptides by giving these peptides a positive charge (ionization) and then measuring the time required for the positively charged peptide ions to move through a tube to a detector (time-of-flight)
Outline of method (Fig. 3.9)
• The first step is to reduce the complexity of the mixture of cellular proteins or peptides to be analyzed, usually by liquid chromatography columns • The separated proteins/peptides are positively charged using lasers, electrospray ionization, or nanospray ionization. Based upon the time-of-flight of the charged peptides, the peptide mass/charge ratio can be measured and this allows identification of the peptide sequence and the protein that contained the peptide • Tandem mass spectrometry (MS/MS) can "ion trap" a given peptide ion and then sequence the peptide by fragmenting it into its component amino acids. Bioinformatics software can use this sequence information to search protein databases for rapid protein identification
Benefits
• Mass spectrometry is extremely sensitive and able to detect very small amounts of proteins/peptides
Limitations/errors
• Better technology to reduce the complexity of protein/peptide mixtures and differentially separate the proteins/peptides in a high-throughput manner is being developed • Although mass spectrometry can measure the mass of proteins/peptides very precisely, it is more difficult to measure the amount of protein/peptide quantitatively
Experimental applications
• Mass spectrometry can be used to determine the complete set of proteins present in a defined population of cells
Modifications/alternatives
• Isotope labeling approaches for quantitative mass spectrometry, including isotope-coded affinity tag (ICAT), stable isotope labeling by amino acids in cell culture (SILAC), tandem mass tags (TT), and isobaric tags for relative and absolute quantification (iTRAQ) • Label-free quantitative proteomics • Antibody protein arrays and reverse-phase protein arrays

Table 3.6 Proteomics with mass spectrometry.

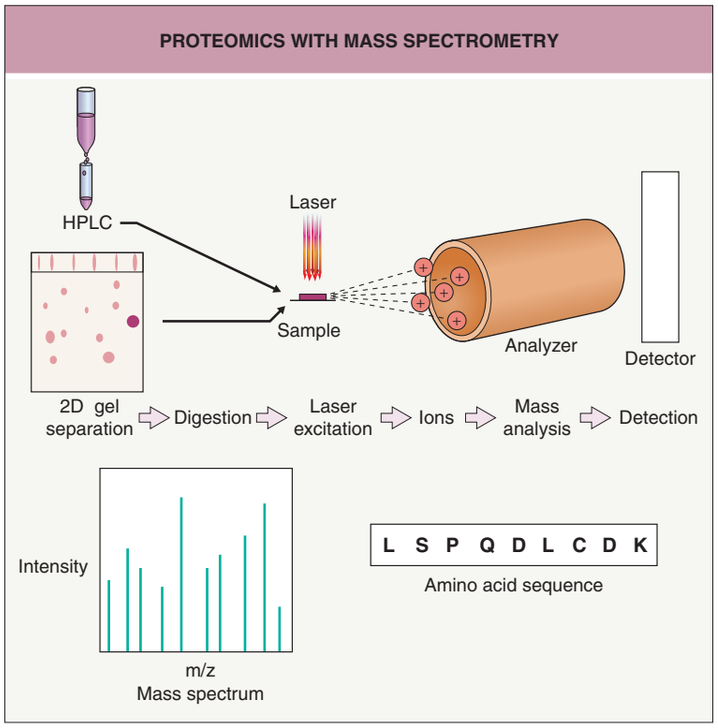


Fig. 3.9 Proteomics with mass spectrometry. The first step is to reduce the complexity of the mixture of cellular proteins or peptides to be analyzed. The two main methods to separate proteins/peptides from each other are high-performance liquid chromatography (HPLC) columns or two-dimensional (2D) gel electrophoresis. Mass spectrometry analysis is then performed by first ionizing the separated proteins/peptides into positively charged ions using lasers. Based on the time-of-flight of the charged ion, mass spectrometry can measure, record, and print out the mass/charge ratio of every peptide along with signal intensity.

finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and, most importantly, CRISPR-Cas9 (see Fig. 3.13)[33]. These nucleases have sequence-specific DNA-binding modules that are linked to a DNA cleavage domain and this allows them to induce a DNA double-strand break at a specified site. The double-strand break increases the frequency of homology-directed repair so that a co-delivered plasmid with extended homology arms can correct the existing gene. Correction of endogenous genes holds promise for treating genetically based diseases.

Another therapeutic approach is to target specific mRNAs for degradation. Double-stranded RNAs with a length of 21–23 nucleotides and complementary to the mRNA of interest are designed. These synthesized antisense oligodeoxynucleotides (AS-ODNs) are delivered to the cell, where they mediate sequence-specific mRNA degradation using an endogenous complex of proteins called the RNA-induced silencing complex (RISC). However, AS-ODN techniques are being replaced by synthetic vectors that deliver short interfering RNA (siRNA) and microRNA (miRNA) (Fig. 3.14). These synthetic delivery vectors include lipid-based or polymer-based nanoparticles, as well as covalent delivery systems such as dynamic polyconjugates and GalNAc conjugates[32]. These approaches have been used successfully in the laboratory and are being tested in clinical trials.

CONCLUSIONS

In this chapter, we have presented a variety of techniques used in dermatology research and clinical practice. Some of these are new, whereas others are long-established and still widely used. New technologies continue to appear and change the way research is done. These technologic advances allow experiments to be done faster and with less and less starting material. They allow the measurement of thousands of different genes or proteins in single experiments. To handle all the information

TRANSGENIC MICE
Purpose
• Investigating the effects of a transgene (the gene of interest) on a cellular, tissue, and whole animal level. The transgene can be selectively expressed in a particular cell type by using a promoter/enhancer regulatory region that is specific for that cell type
Requirements
• A gene of interest, whose biologic function is to be characterized • A regulatory region (promoter/enhancer) that will selectively express the gene of interest in a specific tissue
Underlying concepts
• After injection of a transgene into a fertilized mouse egg, the transgene randomly integrates into the genome. As the embryo develops into a mouse, the integrated transgene will be present in every cell type, tissue, and organ in the mouse. The transgene will only be expressed in cells where the promoter/enhancer regulatory region is active • Phenotypes that develop in mice can help us understand the biologic effects of the transgene
Outline of method (Fig. 3.10)
• A transgene construct, defined as the transgene (gene of interest) and a regulatory region (promoter/enhancer), is microinjected into fertilized eggs. The transgene then integrates into the genome, usually at a single site • The injected eggs are then implanted into a recipient mother, who gives birth to a heterozygous "founder" mouse. The founder mouse contains the transgene on one of the two paired chromosomes (e.g. only one copy of chromosome 7 contains the transgene, whereas the other chromosome 7 does not) • The founder mice are bred with normal non-transgenic mice of the same strain. The progeny mice will be both heterozygous transgenic and non-transgenic, according to Mendelian genetics • To derive homozygous transgenic mice that contain the transgene on both of the paired chromosomes (e.g. both copies of chromosome 7 contain the transgene), two heterozygous transgenic mice are mated. Homozygous transgenic mice will have a double dose of the transgene, which may lead to different phenotypes and biologic effects compared to heterozygous transgenic mice
Benefits
• Transgenic mouse models help us to understand the biologic effects of genes
Limitations/errors
• The regulation of the expression level as well as the timing of gene expression during development (turning the transgene on or off during development) have been relatively difficult. Advancements in transgenic design, including inducible promoters, have improved the regulation of transgene expression • When expressed in mouse tissues, a human transgene may have different biologic effects compared to its effects in human tissues • Because classic transgenic mouse models only add a new transgene to cells, they do not allow investigation of the biologic effects of gene mutations or deletions that result in loss of gene expression
Experimental applications
• Transgenic mouse models of disease can be used to test the effectiveness of new therapeutic agents
Modifications/alternatives
• More precise control of transgene expression can be achieved with promoters/enhancers that are inducible and can be regulated (i.e. turned off and on at different time points) • Programmable nuclease systems for RNA-guided genome editing such as clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated protein (Cas) (CRISPR-Cas9; Fig. 3.13) • "Knockout" transgenic mouse models (Table 3.8) allow investigation of the biologic effects of gene mutations and deletions that cause a loss of specific proteins

Table 3.7 Transgenic mice.

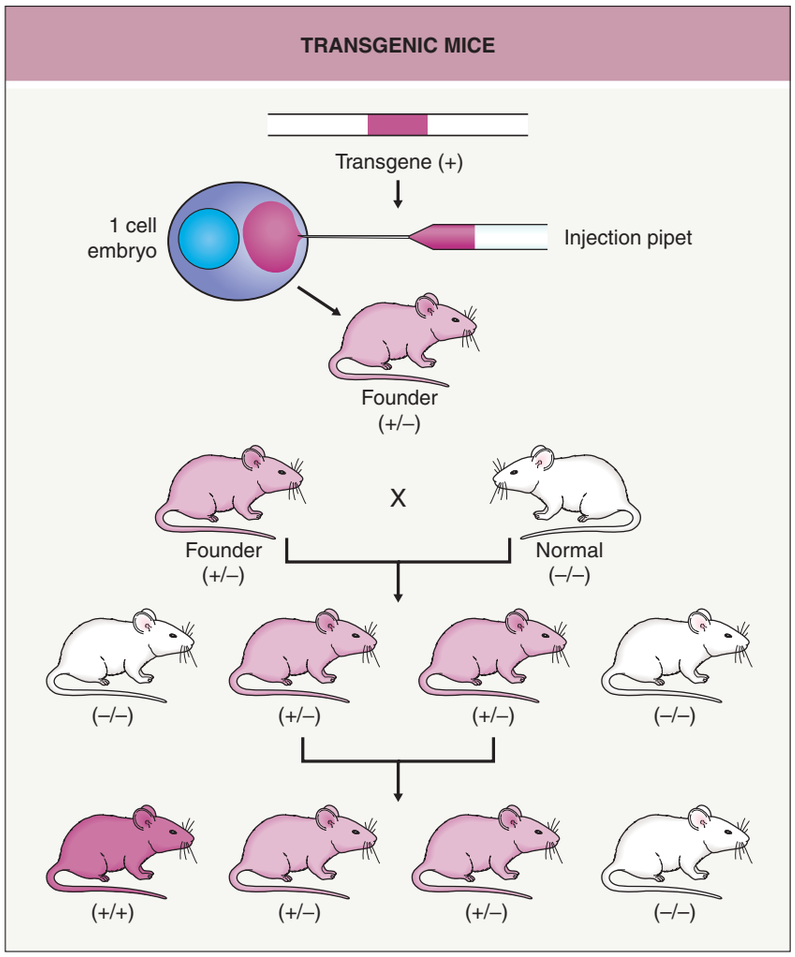


Fig. 3.10 Transgenic mice. A transgene construct, defined as the transgene and regulatory region (promoter/enhancer), is prepared for injection. The transgene is microinjected into fertilized eggs (single-cell stage) and the transgene integrates into the genome, usually at a single site. These injected eggs are then implanted into a recipient mother, who then gives birth to a heterozygous "founder" mouse. The founder mice are bred with normal non-transgenic mice of the same strain, and then two heterozygous transgenic mice are mated.

KNOCKOUT TRANSGENIC MICE
Purpose
• In knockout transgenic mice, both alleles of a normal endogenous gene are modified, mutated, or deleted so that protein can no longer be produced by that gene. Knockout transgenic can be used to study what happens to a cell or tissue when a particular gene can no longer be expressed
Requirements
• Embryonic stem cells (ES cells) capable of forming and reconstituting all tissues and organs of a mouse • A targeting construct that modifies the normal endogenous gene so that it is no longer able to express a functional protein
Underlying concepts
• In knockout transgenic mice, all cells (whole animal or targeted tissue) lack the gene that has been "knocked out" and do not express any functional protein from that gene • Technology is available to selectively target and delete an endogenous gene in its normal chromosomal location in ES cells
Outline of method (Fig. 3.11)
• A targeting construct that contains some sequences of the gene to be knocked out is created and introduced into ES cells. The targeting construct specifically hybridizes to one of the endogenous alleles, and through homologous recombination, the targeting vector modifies or deletes the endogenous gene so that no normal protein is produced • ES cells containing the "knocked out" gene are introduced into early mouse embryos, known as blastocysts, which are then implanted into recipient mothers. The progeny will be chimeric mice; all tissues and organs, including testes and ovaries, will contain a mixture of normal cells and cells that lack the "knockout" gene allele • The chimeric mice are next mated to normal mice. Depending on the degree of chimerism, a certain percentage of the offspring will be heterozygous, containing one normal allele and one allele that has been knocked out • To obtain completely "knocked out" mice, two heterozygous mice are mated
Benefits
• This approach yields mice that completely lack the gene product in all cells of the whole animal or targeted tissues
Limitations/errors
• Investigators have to ascertain that no normal gene product is being produced. It is possible that the homologous recombination process used to knock out a gene may result in a gene that encodes a mutant protein that still has biologic effects
Experimental applications
• Knockout transgenic mice make it possible to study the biologic effects from loss of gene expression, which is particularly important for examining the role of tumor suppressor genes in cancer development
Modifications/alternatives
• To more accurately mimic *in vivo* situations, the gene of interest can be selectively deleted in only one organ or tissue. These *conditional* knockout mice allow investigators to study the effects of gene loss in a particular tissue without the complications of losing gene expression in all the other tissues (Fig. 3.12) • Targeted genome editing using CRISPR-Cas9 (Fig. 3.13)

Table 3.8 Knockout transgenic mice.

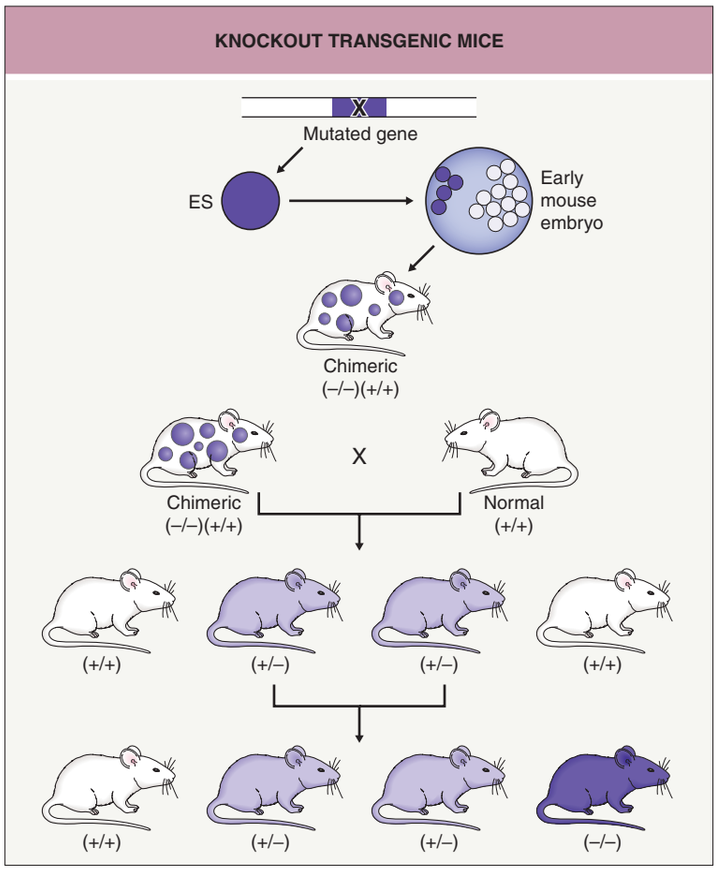


Fig. 3.11 Knockout transgenic mice. A targeting vector that contains some sequences of the gene to be targeted is created and introduced into cells. This targeting vector hybridizes to one of the endogenous alleles of a gene and modifies or deletes the endogenous gene so that no normal protein is produced. The embryonic stem (ES) cells containing the "knocked out" gene are introduced into early mouse embryos, which are then implanted into recipient mothers. The progeny will be chimeric mice, which are then mated to normal mice. To obtain completely knocked out mice, two heterozygous mice are mated.

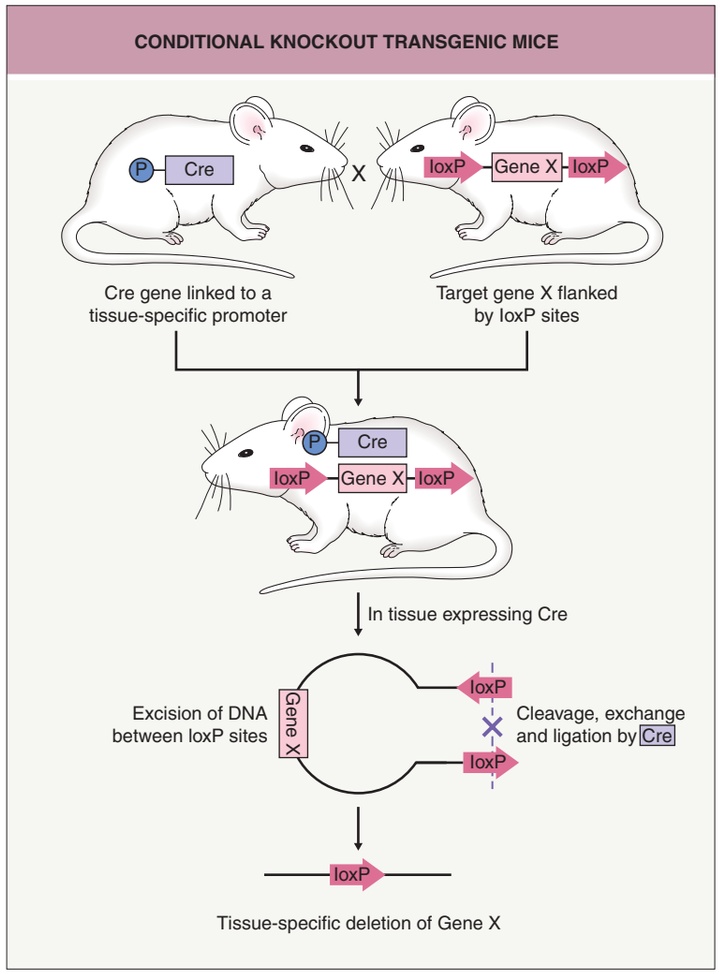


Fig. 3.12 Conditional knockout transgenic mice. In the conditional knockout model using the Cre-lox system, a target gene can be selectively deleted in a particular organ or tissue. Cre is a site-specific DNA recombinase that catalyzes recombination between two loxP sites, resulting in cleavage, exchange, and ligation; this leads to excision (and subsequent degradation) of the DNA between the loxP sites. A transgenic mouse with the Cre gene linked to a tissue-specific promoter is mated to a transgenic mouse with two loxP sites flanking the target gene. Progeny inherit both of these constructs, and the target gene is knocked out only in cells that activate the tissue-specific promoter. By adding a ligand-binding domain to the Cre recombinase, such as one that binds tamoxifen, investigators can achieve temporal control of Cre expression in these cells. The target gene can be temporally deleted, inverted, or translocated, depending on the orientation of the loxP sites.

currently being generated by life sciences, advances in computer science and bioinformatics are progressing along with the technologic advances, accelerating the pace of scientific research.

Advances in our scientific understanding also translate into new developments in disease diagnosis and management. For dermatology, this provides hope that diseases can be diagnosed more rapidly and reliably, and that individualized prognoses can be provided. Therapies have been and will continue to be developed that specifically target the genetic abnormality causing the disease. In the future, therapies may be tailored to the individual, taking into consideration the individual's genetic make-up and the individual's disease course. These future possibilities are exciting.

For discussions of types of polymorphisms and genome-wide association studies, see Chapter 54.

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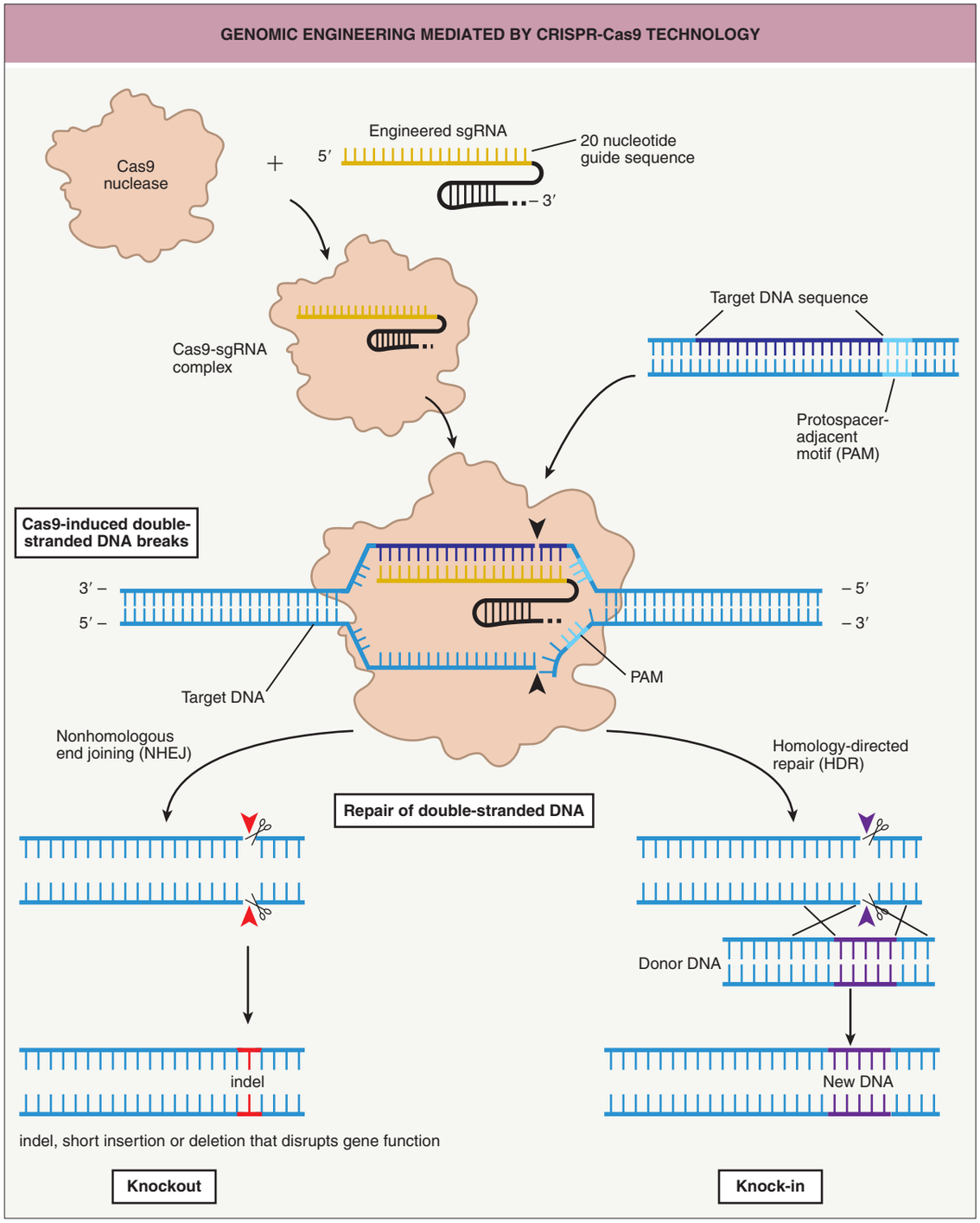


Fig. 3.13 Genomic engineering mediated by CRISPR-Cas9 technology. A single-guide RNA (sgRNA) is engineered to target genomic DNA adjacent to a protospacer adjacent motif (PAM) utilizing a 20-nucleotide guide sequence. The hairpin structure recruits Cas9 to form a complex that binds to the target sequence. Cas9 catalyzes the cleavage of both strands of DNA three nucleotides upstream of the PAM. A double-strand break may be repaired by non-homologous end-joining (NHEJ) that leads to the formation of short insertions or deletions that disrupts gene function. In the presence of a DNA-repair template, homology-directed repair (HDR) may occur to introduce exogenous DNA at the site of the break.

SKIN GENE-BASED THERAPY
Purpose
• Genes are introduced and expressed, corrected, or knocked down in the skin for therapeutic purposes • Skin gene therapy is a promising field that has the potential to provide new treatments for both skin and systemic diseases, in which the skin is used as a vehicle for the systemic delivery of a needed factor or substance
Requirements
• A gene that is able to achieve the desired therapeutic effect when expressed in skin cells • A delivery vector that can efficiently introduce the desired gene into cells. Both viral vectors and non-viral vectors can be used to deliver a desired gene to a target cell type

Table 3.9 Skin gene-based therapy. *Continued*

SKIN GENE-BASED THERAPY
Underlying concepts
• There are two general approaches for introducing genes into the skin: a direct *in vivo* approach and an *ex vivo* approach • Many issues need to be considered when choosing a vector and determining the best approach to deliver the desired gene to the skin. In some situations, short-term or transient expression is sufficient; in other cases, long-term expression is preferable
Outline of method
• In the direct *in vivo* approach, the desired gene is introduced directly into the skin by injection or physical methods such as gene gun or electroporation. *In vivo* approaches are simple and straightforward, but expression is usually only transient and the percentage of cells containing the desired transgene may be low • In the *ex vivo* approach, keratinocytes are removed from the donor, the desired gene is introduced into cultured keratinocytes which form a skin equivalent, and then the genetically modified keratinocytes are grafted back onto the donor. *Ex vivo* approaches are more complicated and technically demanding than *in vivo* approaches, but are superior at achieving long-term expression in a higher percentage of cells
Benefits
• As our understanding of the molecular basis of disease increases, genetic therapies will become more important • The effectiveness of skin gene therapy can be assessed in animal models
Limitations/errors
• Skin gene therapy with long-term expression of a desired gene in a high percentage of cells has been difficult to achieve in animal models • Skin gene therapy for recessive genetic skin diseases is problematic because of the development of an unwanted immune response against the normal protein • Risk of oncogenesis, especially with retroviral vectors
Experimental applications
• Treatment of genetic skin diseases and non-genetic skin diseases if a sufficient understanding of the molecular basis of the disease exists • Systemic delivery of cytokines, hormones, and growth factors • Genetic immunization
Modifications/alternatives
• Use of short (small) interfering RNA (siRNA) that targets and silences expression of dominant-negative mutant genes (Fig. 3.14) • Gene-based therapy utilizing induced pluripotent stem (iPS) cells (see Fig. 2.7)

Table 3.9 Skin gene-based therapy.

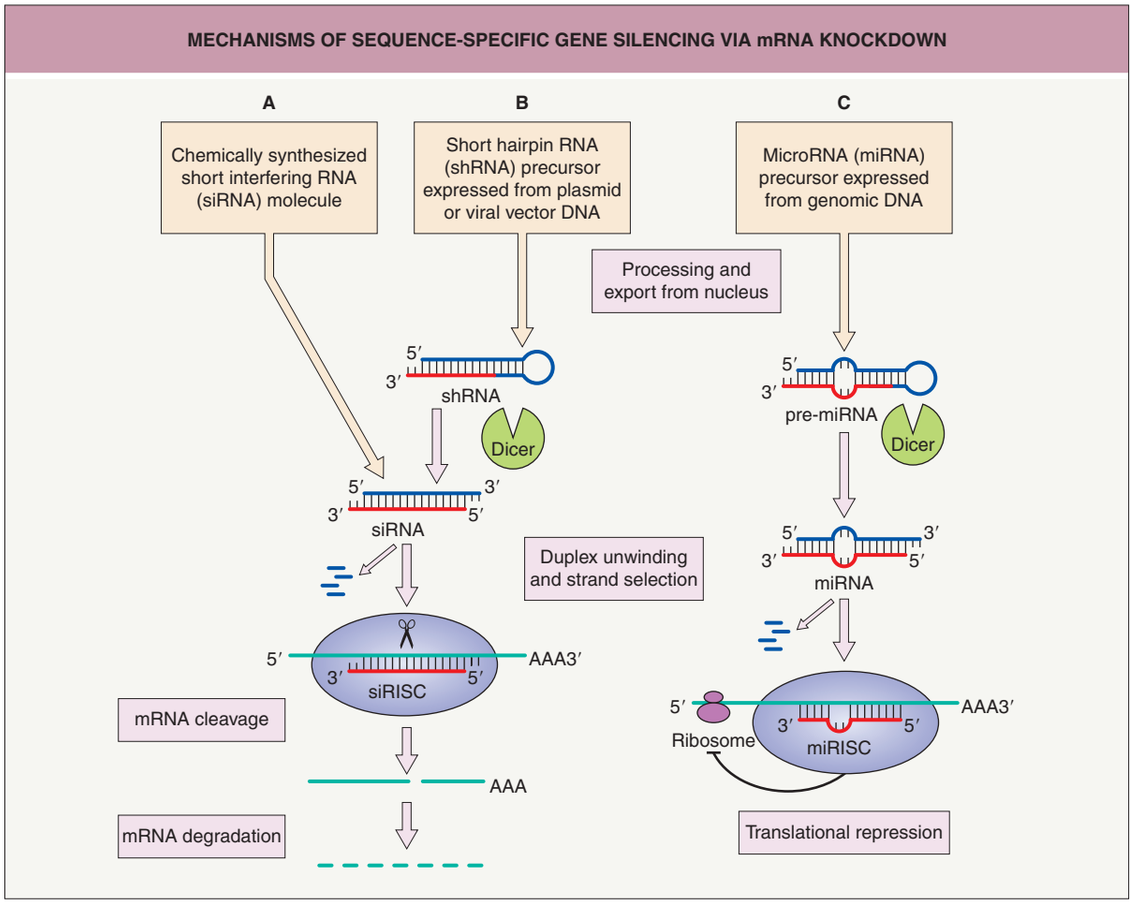
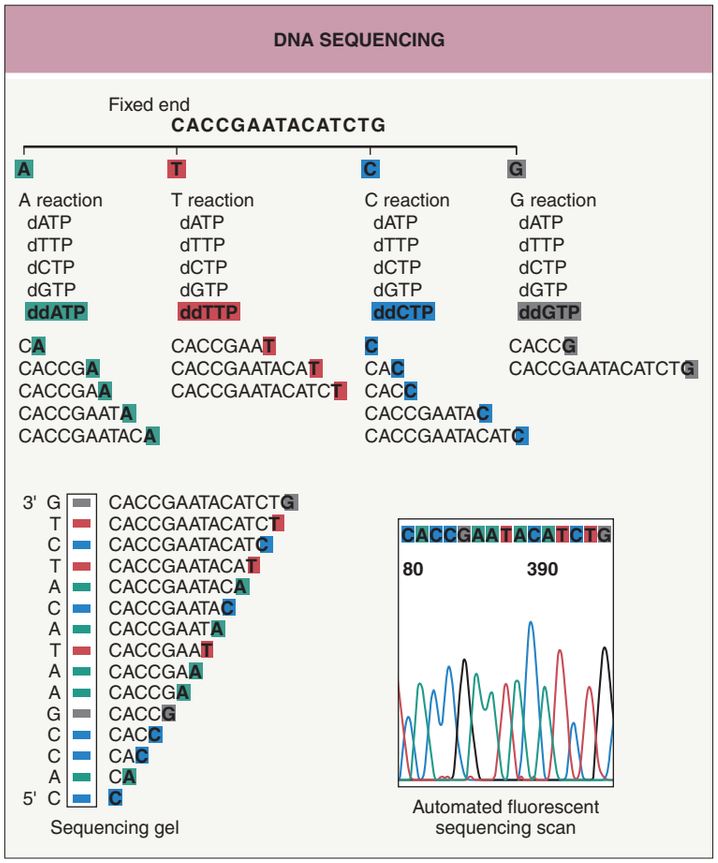


Fig. 3.14 Mechanisms of sequence-specific gene silencing via mRNA knockdown. A Short (small) interfering RNA (siRNA) is unwound, and the "guide" antisense strand is incorporated into an RNA-induced silencing complex (RISC) that degrades a specific target mRNA sequence. Processing of short hairpin RNA (shRNA; **B**) and pre-microRNA (miRNA; **C**) by the Dicer enzyme can generate siRNA and miRNA, respectively. **C** Endogenously produced miRNA regulates up to a third of human genes and tends to have less complementarity with target mRNA; it recruits RISC proteins and typically inhibits mRNA translation (rather than decreasing mRNA levels).

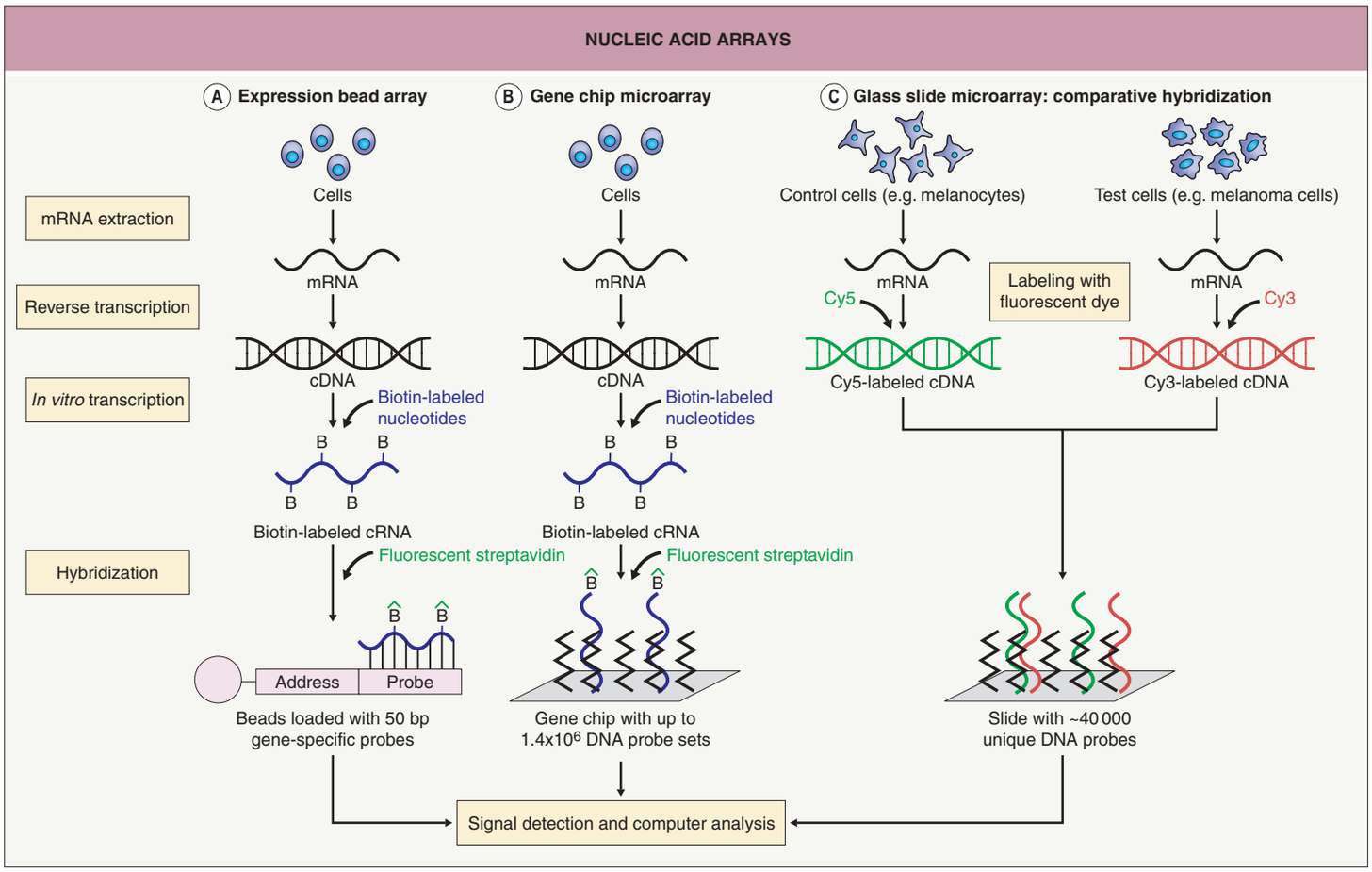


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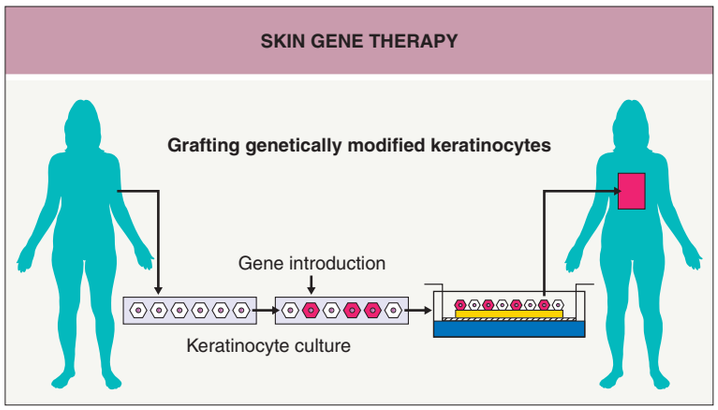
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eFig. 3.1 DNA sequencing. An oligonucleotide primer hybridizes to the DNA to be sequenced, and DNA polymerase synthesizes a second complementary strand. The synthesis of the second strand is interrupted randomly by the incorporation of fluorescent nucleotide analogues (ddATP, ddGTP, ddCTP, ddTTP). The DNA fragments containing this final nucleotide analogue can be identified because each of the four ddNTPs is labeled with a different color fluorochrome. Gel electrophoresis is used to separate the different sizes of DNA fragments. The different-length DNA strands terminating with different fluorochrome-labeled nucleotide analogues pass a fluorescence detector and indicate the order of the DNA sequence.

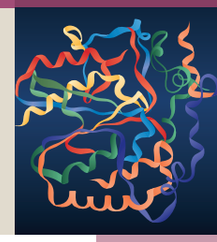


eFig. 3.2 Nucleic acid arrays. A In the expression bead array, RNA is extracted from cells and reverse transcribed to generate cDNA. *In vitro* transcription of the cDNA in the presence of biotinylated nucleotides yields biotin-labeled cRNA. Labeled cRNAs bind to their respective 50-base probes that are linked to separate beads using additional nucleotides as an address to decode the gene. Fluorescent streptavidin is added, which strongly binds to biotin. The fluorescent intensities on different beads are related to the amount of cRNA, and the latter is a reflection of the level of expression of mRNA by specific genes. Usually, the patterns of gene expression of two samples are compared, such as normal versus tumor or treated versus untreated. **B** In the gene chip microarray, labeled cRNA molecules are hybridized to small DNA fragments chemically synthesized on a surface, with the surface containing thousands of specific sequences at different locations. **C** In a third approach using glass slides, two samples can be labeled with differently colored fluorescent probes (e.g. Cy5, Cy3) that are hybridized to an oligonucleotide array simultaneously. Arrays can also be used to analyze DNA rather than RNA; examples include single nucleotide polymorphism (SNP) arrays and array comparative genomic hybridization (CGH) (see Chs. 54 & 113).



eFig. 3.3 Skin gene therapy. In the *ex vivo* approach, keratinocytes are removed from the donor and, during *ex vivo* culture, the desired gene is efficiently introduced, usually with viral vectors. Skin equivalents or raft cultures containing these genetically modified keratinocytes (along with a dermal portion containing fibroblasts) are constructed and then grafted back onto the donor.

Immunology 4



Karin Pfisterer, Wolfgang Weninger and Thomas Schwarz

Abbreviations

AMP	antimicrobial peptides
APC	antigen presenting cell
CCL	C-C motif chemokine ligand
CCR	C-C motif chemokine receptor
CLA	cutaneous lymphocyte antigen
CTL	cytotoxic T lymphocyte
DAMP	danger-associated molecular pattern
DC	dendritic cell
ILC	innate lymphoid cell
iTreg	induced Treg
LC	Langerhans cell
nTreg	natural Treg
PAMP	pathogen-associated molecular pattern
pDC	plasmacytoid dendritic cell
Tc cell	cytotoxic T cell
Tcm	central memory T cell
Tem	effector memory T cell
Tfh cell	T follicular helper cell
Th cell	helper T cell
Tmm	migratory memory T cell
Treg	regulatory T cell
Trm	resident memory T cell

Key features

- The major purpose of the immune system is protection against harmful agents such as pathogens and tumor cells. This is achieved by a rapid "primitive" reaction, called the *innate immune response*, and a more highly developed specific reaction, called the *adaptive immune response*
- The characteristics of an adaptive immune response are specificity and the accumulation of memory, thus enabling improvement with each successive encounter with a particular antigen
- The key event in an adaptive immune response is antigen presentation, yielding either a cell-mediated or a humoral response. The cellular response involves primarily T cells, whereas the humoral response involves B cells that ultimately mature into antibody-secreting plasma cells
- Immune responses are not always protective and can even be pathogenic if the response induces severe tissue destruction or is directed against an autoantigen
- As a barrier organ to the external environment, the skin is endowed with the capacity and the necessary cellular components to mount an immune response

INTRODUCTION

As a major barrier against the external environment, one of the skin's major functions is defense against potential insults by microbial, chemical, and physical agents. Over the past several decades, it has become clear that the skin is not a mere passive mechanical barrier to the outside world but rather represents an active member of the body's immune system. As such, the skin is inhabited by a myriad of resident immune cells, which, together with recruited inflammatory and adaptive immune cells, protect the individual from external and internal danger signals. Accordingly, the term "skin-associated lymphoid tissues" (SALT) has been coined to reflect the importance of the cutaneous immune response in tissue homeostasis and repair[1].

The classical immune response, also referred to as the adaptive immune response, is characterized by specificity that is due to immunologic memory (specific immunity). Innate immunity is a more primitive defense system that acts in a rapid but less specific manner. Both types of responses can be generated in the skin. Adaptive immune responses in the skin, however, are not always protective but can also be harmful in nature, e.g. allergic or autoimmune reactions. Numerous skin diseases are caused by T lymphocytes and/or autoantibodies and are therefore immunologically mediated. Consequently, many dermatoses respond favorably to immunosuppressive therapy administered either systemically or topically.

INNATE IMMUNE RESPONSE

Essential components of the cutaneous innate immune system include tissue-resident cells such as mast cells, macrophages, dendritic cells (DCs), non-classical T cells, natural killer (NK) cells, and innate lymphoid cells. In addition, circulating cells, including neutrophils and eosinophils, can be rapidly recruited from the bloodstream into the skin. Innate immune cells are characterized by their capacity to immediately respond to harmful signals by virtue of expression of danger sensing receptors such as Toll-like receptors (TLRs). Soluble mediators, including cytokines and complement factors, represent effector molecules of the innate immune response. In addition, microbiota as well as antimicrobial peptides produced by the epithelium and other cells support these responses against invading pathogens. Innate immune reactions are less complicated than adaptive responses and developed earlier in evolution. Nevertheless, failures in these "primitive" immune responses may be associated with severe, even fatal, health problems.

Complement

The complement system plays an important role in innate immunity. It consists of at least 20 serum glycoproteins that are activated by an enzymatic amplifying cascade (see Ch. 60). Complement proteins sense and transmit internal danger signals originating from tissue disruption (damage-associated molecular patterns, DAMPs) or products released from microbes (microorganism-associated molecular patterns, MAMPs). Three pathways can trigger the proteolytic cascade which results in protein fragments that activate complement receptors. The classical pathway is stimulated by antigen–antibody complexes, the alternative pathway by polysaccharides derived from microbial cell walls, and the later identified lectin pathway by the interaction of microbial carbohydrates with mannose-binding proteins. All three pathways lead to activation of the central C3 component and, finally, the generation of a number of immunologically active substances. For example, C3b, the cleavage product of C3, binds to the surface of microbes. Since phagocytic cells express receptors for C3b, phagocytosis of the microorganisms is enhanced. In addition, complement components bind to antigen–antibody immune complexes, which help complement receptor-bearing antigen-presenting cells target these immune complexes.

C5a is a powerful attractant for neutrophils. C3a, C4a, and C5a, also called anaphylatoxins, induce the release of inflammatory mediators from mast cells. This increases vascular permeability, thereby enabling proteins (e.g. antibodies) to enter the tissue. Assembly of the complement components C5b, C6, C7, C8, and C9 forms the membrane-attack complex (MAC), which generates pores in cell membranes and leads to death by osmotic lysis. Human cells are much less susceptible to killing by complement than microbes, since the former express certain complement receptors that can inhibit cell lysis. For example,

human cells express complement receptor type 1 (CR1, CD35), decay-accelerating factor (DAF, CD55), and membrane cofactor protein (MCP, CD46), which inhibit C3 convertase and thereby block progression of the complement cascade. In addition, CD59 is a protein that binds to C8 and inhibits insertion of C9 into the cell membrane.

Complement fragments can also bind to complement receptors expressed on immune cells, such as NK cells, neutrophils, monocytes, macrophages, DCs, and, although still controversial, B and T cells. Complement receptor engagement induces and modifies several effector functions including phagocytosis of apoptotic cells and immune complexes, cell migration and adhesion, surface receptor and cytokine expression, tissue repair, and modification of cell signaling responses to pattern recognition receptors[2]. Furthermore, components of the complement system can crosstalk and modulate TLR signaling cascades. These synergistic interactions potentially boost immune system responses directed against invading pathogens[2].

Toll-Like Receptors

Several families of pattern recognition receptors (PRRs) mediate responses to pathogen-associated molecular patterns (PAMPs) that are conserved among microorganisms. TLRs, the mammalian homologs of the Toll receptors identified in *Drosophila*, are one such family of PRRs. To date, ten TLRs have been identified in humans (Fig. 4.1)[3], and those localized to the cell surface have the following specificities: TLR2 (in association with either TLR1 or TLR6) – recognition of lipoproteins and peptidoglycans; TLR4 – lipopolysaccharide; and TLR5 – flagellin (a component of bacterial flagella). TLR3, TLR7, TLR8, and TLR9 reside within endosomal vesicles and recognize nucleic acids[4], with TLR9 recognizing bacterial CpG DNA sequences and the other intracellular TLRs involved in the recognition of viral RNA[5].

The signaling pathway of TLRs is highly homologous to that of the receptor for interleukin (IL)-1. Upon interaction with myeloid differentiation factor 88 (MyD88), IL-1 receptor-associated kinase (IRAK) is recruited, ultimately leading to activation of the transcription factor NF-κB (see Fig. 4.1). Activation of TLRs can also result in the release of interferons (IFNs) via activation of interferon regulatory factor 3 (IRF3).

DCs express several types of TLRs. Upon activation of these receptors by microbial components, DCs mature and migrate to the lymph nodes, where they present pathogen-derived antigens to naive T cells and induce an adaptive immune response. TLRs thereby bridge the gap between the innate and adaptive immune systems. These two systems constantly interact within the skin, and therefore the innate immune system represents a potential target for modulating adaptive immune responses[6]. Different PAMPs and danger signals polarize DCs, giving them the ability to produce certain cytokines and to induce T cells to differentiate into particular subtypes.

Inflammasomes

Closely connected with the rapid recognition of danger signals are inflammasomes – innate multi-protein complexes that sense intracellular DAMPs or PAMPs. Four types of inflammasomes have been identified: Aim2 (*a*bsent *i*n *m*elanoma *2*), the *p*yrin domain-containing NLRP1 (*n*ucleotide-binding domain *l*eucine-rich *r*epeat-containing receptor *1*, also called NALP), NLRP3, and NLRC4 (*N*od-*l*ike *r*eceptor *C*ARD domain-containing 4)[7]. Aim2 is activated by double-stranded DNA resulting from either viral or bacterial intracellular pathogens, NLRP1 by muramyl dipeptide, and NLRC4 by flagellin. NLRP3 is triggered by numerous PAMPs and DAMPs and is thus the most important inflammasome (Fig. 4.2). The ultimate result of activation of inflammasomes is the cleavage of pro-IL-1β into active IL-1β, a highly potent inflammatory mediator. NLRPs are large backbone proteins of the complex which, upon assembly of the inflammasome complex, bind to ASC (*a*poptosis-associated *s*peck-like protein containing a *ca*spase *r*ecruitment *d*omain [CARD]). The latter interacts with caspase-1, resulting in its activation. Active caspase-1 cleaves and activates pro-IL-1β, as well as the proinflammatory cytokine pro-IL-18. Dysregulation of inflammasomes is the cause of a group of inherited autoinflammatory diseases called cryopyrin-associated periodic syndromes (CAPS) which are associated with recurrent episodes of fever, urticarial skin lesions, arthritis, and systemic inflammation (see Ch. 45). These disorders respond very well to IL-1 blocking drugs (see Fig. 4.2).

The Skin Microbiota and Antimicrobial Peptides

The skin microbiota is comprised of billions of bacteria, archaea, viruses, and fungi that are in symbiosis with the host. Extensive research over the past decade has shown that the commensal microorganisms on the skin are essential for training cells of the cutaneous

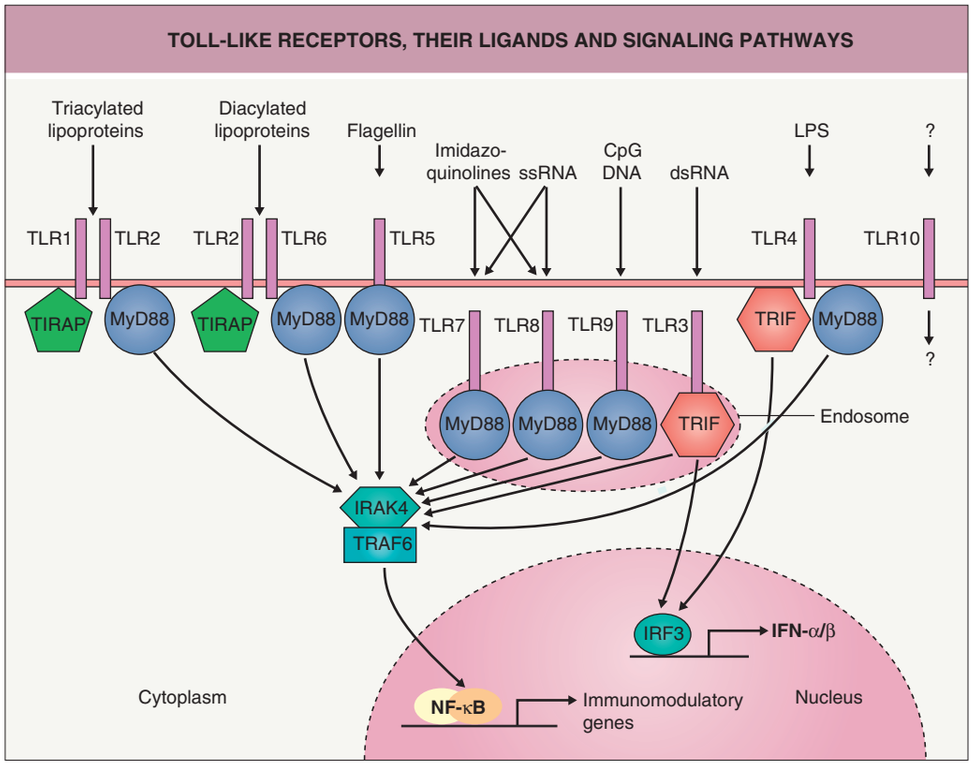


Fig. 4.1 Toll-like receptors, their ligands, and signaling pathways. Toll-like receptors (TLRs) recognize pathogen-associated molecular patterns and/or synthetic compounds in a specific fashion. A TLR2/TLR1 dimer recognizes triacylated lipoproteins, and a TLR2/TRL6 dimer interacts with diacylated lipoproteins. TLR5 recognizes flagellin and TLR4 recognizes lipopolysaccharide (LPS). These TLRs are located on the cell membrane and are internalized upon ligand interaction. TLR3, TLR7, TLR8, and TLR9 are located on intracellular membranes of endosomes and lysosomes. TLR3 recognizes viral double-stranded RNA (dsRNA); TLR7 and TLR8 viral single-stranded RNA (ssRNA); and TLR9 bacterial and viral hypomethylated DNA (CpG [5′-C-phosphate-G-3′] motifs). TLR7 and TLR8 also bind to synthetic compounds (imidazoquinolones). All TLRs except TLR3 utilize myeloid differentiation factor 88 (MyD88) for signaling, while TLR2 and TLR6 also require Toll-interleukin-1 receptor domain-containing adaptor protein (TIRAP). MyD88 signaling via IL-1 receptor-associated kinase-4 (IRAK-4) and tumor necrosis factor receptor-activated factor-6 (TRAF-6) mostly results in activation of nuclear factor κB (NF-κB), ultimately inducing transcription of genes encoding immunomodulatory and proinflammatory molecules. TLR3 and TLR4 signal via TIR-domain-containing adapter-inducing interferon-β (TRIF). The TRIF pathway induces the production of interferons (IFNs) via interferon regulatory factor-3 (IRF3). Both the ligand and signaling pathway of TLR10 are still unknown. *Adapted from Miller LS. Toll-like receptors in skin. Adv Dermatol 2008;24:71–87 and from McInturff JE, Modlin RL, Kim J. The role of toll-like receptors in the pathogenesis and treatment of dermatological disease. J Invest Dermatol 2005;125:1–8.*

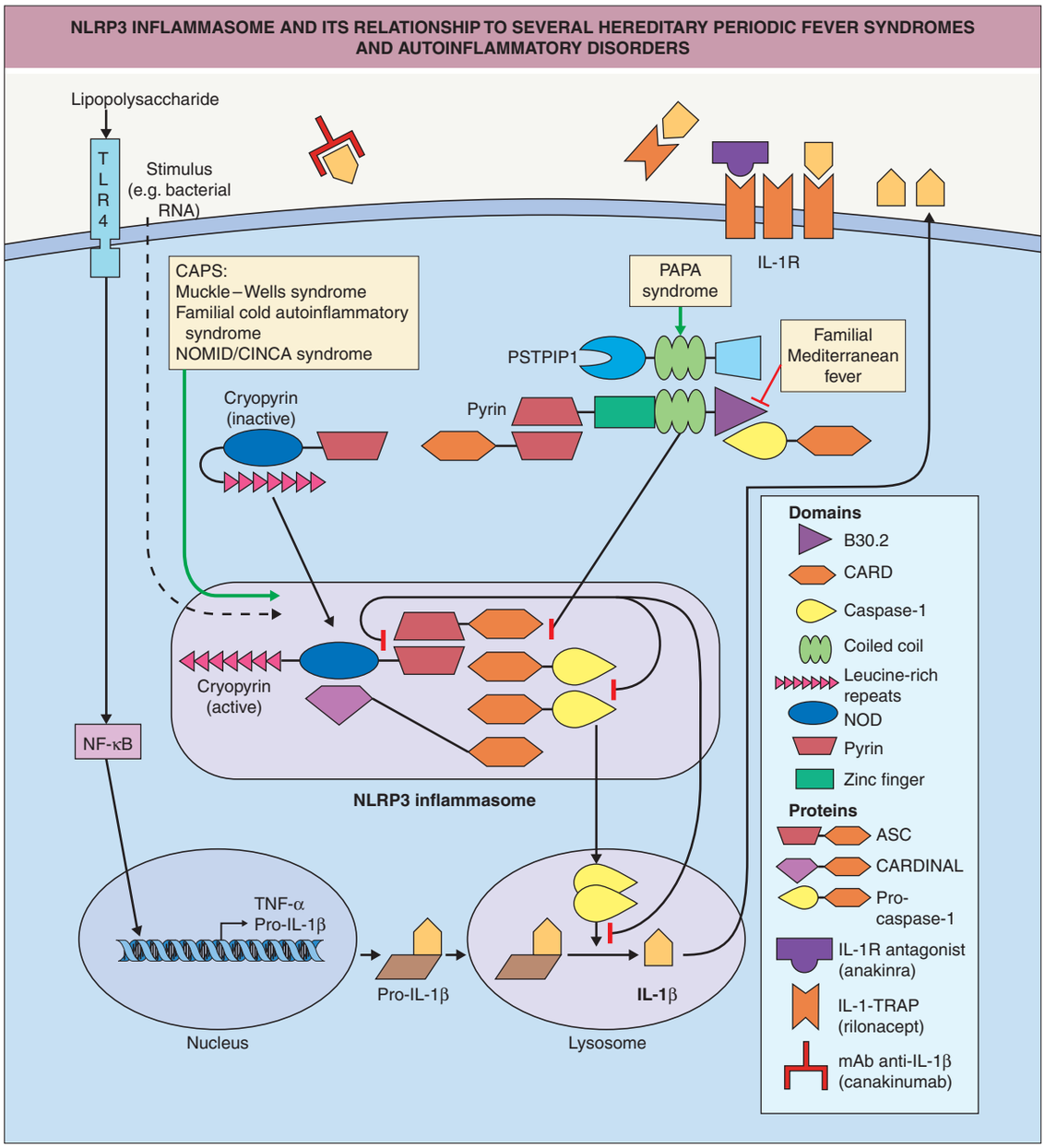


Fig. 4.2 NLRP3 inflammasome and its relationship to several hereditary periodic fever syndromes and autoinflammatory disorders. Upon release of autoinhibition, cryopyrin interacts with *a*poptosis-associated *s*peck-like protein with a *C*ARD domain (ASC) and *CARD-i*nhibitor of *N*F-κB-*a*ctivating *l*igand (CARDINAL) within an inflammasome, leading to activation of caspase-1 and generation of mature interleukin (IL)-1β. Pyrin can competitively bind ASC and (pro)-caspase-1, thereby preventing them from being incorporated into the NLRP3 inflammasome. *P*roline–*s*erine–*t*hreonine *p*hosphatase-*i*nteracting *p*rotein 1 (PSTPIP1) binds (and perhaps inhibits) pyrin, and this interaction is strengthened by the *PSTPIP1* mutations that underlie PAPA syndrome. CAPS, cryopyrin-associated periodic syndromes; CARD, *ca*spase-*r*ecruitment *d*omain; CINCA, *c*hronic *i*nfantile *n*eurologic, *c*utaneous and *a*rticular syndrome; IL-1R, interleukin-1 receptor; NF-κB, nuclear factor-κB; NLRP3, *N*OD-*l*ike *r*eceptor *p*yrin domain-containing protein 3; NOD, *n*ucleotide-binding *o*ligomerization *d*omain; NOMID, *n*eonatal-*o*nset *m*ultisystem *i*nflammatory *d*isease; PAPA, *p*yogenic *a*rthritis, *p*yoderma gangrenosum and *a*cne; TLR, Toll-like receptor; TNF, tumor necrosis factor. *Courtesy Julie V. Schaffer, MD.*

immune system as well as for protecting against invasion of pathogenic microbes[8]. Re-evaluation of the composition of the skin microbiota via next generation sequencing (see Fig. 3.5) has expanded the microbiome kingdom landscape beyond bacteria. The diversity of bacterial species and strains (see Fig. 74.1), viruses, and fungi is strongly dependent on host genetics, body site, skin pH, sebum content, moisture, and UV radiation exposure[9,10].

On healthy skin, microbiota outcompete pathogenic microorganisms by building a physical and biological barrier which contributes to the first line of defense against pathogen invasion. Some commensal bacteria can produce antimicrobial substances (e.g. antibiotics, serine proteases) while others interact with and train immune and skin cells to secrete interleukins, complement components, and antimicrobial peptides (AMPs)[8,9]. A change in the equilibrium of commensal microbiota and pathogens is an important factor in the pathogenesis of several skin disorders, most notably atopic dermatitis in which there is an overgrowth of *Staphylococcus aureus*[11].

To cope with pathogenic invaders, plants and invertebrates produce a variety of highly effective AMPs. Human epithelia, including the epidermis, also secrete AMPs as a mechanism of innate defense. The first AMP to be isolated from human skin was human β-defensin-2 (hBD-2)[12]. A number of other AMPs have subsequently been described (Table 4.1). In addition to antibacterial properties, some of these peptides possess antimycotic and, likely, antiviral activity. As demonstrated for psoriasin, which prevents *Escherichia coli* infection[13], these peptides may protect the skin from pathogenic bacterial infections.

Expression of AMPs can be induced by bacteria, bacterial products, or proinflammatory cytokines via TLRs and other mechanisms. Enhanced and reduced production of these peptides in psoriasis and atopic dermatitis, respectively, may explain why superinfections are so rare in the former disease and common in the latter[12,14]. However, enhanced expression of AMPs in atopic skin has also been reported, which may reflect disruption of the epidermal barrier[15]. Ultraviolet (UV) B radiation has been shown to induce expression of AMPs, potentially explaining the paucity of UVB-related bacterial infections despite its immunosuppressive effects (see Ch. 86)[16]. The role of microbiota in the response of the epidermis and the immune system to UV radiation has been shown experimentally in a mouse model under germ-free conditions[17].

Beta-defensins can also attract immature DCs and memory T cells via the chemokine receptor (CCR)-6, illustrating another link between innate epithelial defense and adaptive immunity[18]. The antimicrobial peptide LL-37, also known as cathelicidin antimicrobial peptide (CAMP), mediates DC activation in psoriasis by binding self-DNA and forming structures that stimulate TLR9 and thereby induce IFN production (see Fig. 4.1)[19].

SKIN-DERIVED ANTIMICROBIAL PEPTIDES						
			Antimicrobial activity			Inducibility (e.g. by bacteria, cytokines)
			Bacteria		Fungi	
Name	Size (kD)	Cellular source	Gram+	Gram–		
Antileukoprotease (ALP)	11.7	Keratinocytes Airway epithelia	++	++	++	–
Dermcidin (DCD)-1	4.7	Sweat glands	+++	+++	++	–
Human β-defensin (HBD)-2	4.3	Keratinocytes Airway epithelia Intestinal tract	(+)*	+++	++	+
HBD-3	5.2	Keratinocytes Airway epithelia	+++	+++	+++	+
HBD-4	6.0	Keratinocytes Airway epithelia (mRNA)	++	++	+	+
LL-37/cathelicidin antimicrobial peptide (CAMP)/human cationic antimicrobial peptide 18 (hCAP18)	4.5	Keratinocytes Airway epithelia Urogenital tract Granulocytes	++	++	++	+
Lysozyme	14.7	Keratinocytes Airway epithelia	++	++	–	–
Psoriasin	11.4	Keratinocytes Sebocytes	(+)*	++†	(+)*	+
RNase 7	14.5	Keratinocytes Airway epithelia	+++	+++	+++	+

*In high concentrations.
†*Escherichia coli*, others in high concentrations.

Table 4.1 Skin-derived antimicrobial peptides. In the skin, antileukoprotease (ALP) is also referred to as SKALP, skin-derived ALP.

Cytokines

Cytokines represent a large, heterogeneous family of low-molecular-weight messenger substances that play a crucial role in intercellular communication. Cytokines can be secreted by almost any cell type, and they may act in an autocrine, paracrine, or endocrine manner. Cytokines exert their biologic activities by binding to specific cell surface receptors. Although the vast majority of cytokines occur in a soluble form, some can be membrane-bound. In addition, soluble cytokines can be sequestered by extracellular matrix molecules thereby becoming immobilized. The latter limits diffusion, aids in the build-up of cytokine concentration gradients within tissues, and results in increased force loads being transferred onto the cellular cytoskeleton. These intracellular forces can enhance stimulatory signals following cytokine binding resulting in increased cellular responses.

Cytokines influence the proliferation, differentiation, and activation of cells. Each cytokine exhibits multiple activities, a fact that can complicate strict categorization. Cytokines that are produced by leukocytes and exert effects preferentially on other white blood cells are called interleukins (ILs). Colony-stimulating factors (CSFs) are mediators that induce differentiation and proliferation of hematopoietic progenitor cells while IFNs interfere with viral replication. Cytokines that have chemoattractant activity are termed chemokines, and they play a crucial role in leukocyte migration. The main subgroups of chemokines are differentiated according to the position of two cysteine (C) residues compared with the other amino acid residues (X), CXC (α-chemokines) and CC (β-chemokines). Chemokines that recruit leukocytes are termed inflammatory chemokines, whereas those that regulate trafficking within lymphoid tissues are called lymphoid chemokines.

Early *innate* immune responses are dominated by cytokines with inflammatory (e.g. IL-1, IL-6, IL-10, IL-12, IL-18, tumor necrosis factor [TNF], inflammatory chemokines) and antiviral (e.g. IFN-α, IFN-β) capacities. Induction of *adaptive* immune responses is critically dependent on cytokines with immunomodulatory capacities (e.g. IL-2, IL-4, IL-5, IL-12, IL-13, IL-17, IL-22, IL-23, IFN-γ and TGF-β). However, since most of these mediators exhibit multiple and sometimes overlapping activities, a strict separation into inflammatory and immunomodulatory cytokines is not possible. Due to structural similarities, some cytokines are grouped into families, e.g. the IL-6 family (IL-6, IL-11, oncostatin M, leukemia inhibitory factor [LIF]), the IL-10 family (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26), or the IL-12 family (IL-12, IL-23, IL-27).

Monocytes and Macrophages

Monocytes are short-lived mononuclear cells with proinflammatory and regulatory activities. Two main subtypes of monocytes and one intermediate stage with distinct functions have been described in human blood: classical $CD14^{++}CD16^{-}$; intermediate/transitional $CD14^{+}CD16^{+}$; and non-classical $CD14^{dim}CD16^{++}$[20]. Monocytes are derived from a common myeloid progenitor in the bone marrow, circulate in the bloodstream, and migrate into tissues to respond to inflammation and infection. Within tissue, they can give rise to inflammatory DCs and macrophages whose functions are defined by the tissue environment and tissue type[21]. Although residing in different niches, these cell types have similar functions: phagocytosis, antigen presentation to T cells, and production of cytokines.

Monocyte-derived macrophages express receptors for carbohydrates that are usually *not* expressed on vertebrate cells (e.g. mannose). Through this mechanism, macrophages can discriminate between "foreign" and "self" molecules. Furthermore, macrophages possess receptors for antibodies and complement. Hence, microorganisms that are coated with antibodies and/or complement are more readily phagocytosed[22]. After phagocytosis, the microorganisms are exposed to a variety of toxic intracellular molecules, including superoxide anions, hydroxyl radicals, hypochlorous acid, nitric oxide, lysozyme, and antimicrobial cationic proteins. Macrophages can also present processed antigens to T and B cells. However, their T cell stimulatory capacity is less effective than that of DCs.

Activated macrophages release granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF). These two cytokines induce the division of myeloid precursors in the bone marrow, releasing millions of neutrophils into the circulation.

Neutrophils

Under normal conditions, neutrophils circulate in the bloodstream, some rolling along the vascular endothelium[23]. To enter the site of an infection, neutrophils utilize a complex process that involves adhesion molecules (e.g. integrins), chemoattractants, and other surface receptors (see Chs. 25 & 102). The recruited neutrophils phagocytose organisms and kill them within phagolysosomes by using oxygen-dependent and oxygen-independent mechanisms. The former, called the respiratory burst, involves the production of hydrogen peroxide, hydroxyl radicals, and singlet oxygen. The oxygen-independent mechanism utilizes highly toxic cationic proteins and enzymes, such as myeloperoxidase (MPO) and lysozyme. Organisms that are coated with antibodies or complement components bind to Fc and complement receptors, respectively, on neutrophils (as well as macrophages) and are more effectively phagocytosed and killed.

Ectosomes are vesicles released from the plasma membrane of neutrophils upon their stimulation (e.g. by bacteria)[24]. They carry membrane surface receptors (e.g. CD15, L-selectin), phosphatidylserine, and granule proteins (e.g. CD66b, CD87, MPO, elastase, proteinase 3, defensins, lactoferrin, collagenase I). Depending on the composition, ectosomes can induce a variety of responses in their target cells which include endothelial cells, platelets, natural killer cells, and DCs.

In addition, neutrophils can release neutrophilic extracellular traps (NETs) and thereby develop into anuclear cytoplasts[24]. NETs are composed of extracellular strands of DNA bound to neutrophil-derived AMPs and proteins. Because NETs can entrap bacteria, fungi, and viruses, they may offer some antimicrobial protection. On the other hand, NETs can induce autoimmunity by stimulating immune responses against the NET-associated nuclear antigens (see Fig. 41.1). Whether formation of NETs contributes to the exacerbation of autoimmune diseases by infections remains to be determined.

Eosinophils

The major function of eosinophils is most likely to protect the host from infections by parasites, particularly nematodes. Infections with these organisms are associated with the production of antigen-specific IgE antibodies that coat the parasite. Via their low-affinity receptors (FcεRII, CD23), eosinophils bind to IgE antibodies and become activated. In contrast to macrophages and neutrophils, eosinophils are only weakly phagocytic. They harbor large granules that contain major basic protein, eosinophilic cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin (see Fig. 26.1). Upon activation, eosinophils release these toxic products, which can kill parasites, together with prostaglandins, leukotrienes, and various cytokines[25]. Eosinophils also play an important role in the pathogenesis of allergic reactions.

Basophils and Mast Cells

Basophils (found in the blood) and mast cells (located within tissues) exhibit similar functional and morphologic characteristics. At least two populations of mast cells exist, which can be differentiated by the enzymes they contain and by their tissue location. Mucosal mast cells contain only trypsin, while connective tissue mast cells contain both trypsin and chymotrypsin (see Ch. 118). In contrast to pulmonary, uterine, and tonsillar mast cells, cutaneous mast cells express the receptor for C5a (CD88), which implies that triggering of mast cells through the anaphylatoxin C5a results in cutaneous, but not systemic, reactions[26]. Further, skin mast cells have been shown to express CD117 (c-Kit), CD26 (dipeptidyl peptidase IV), and the neural cell adhesion molecule L1[27]. Both basophils and mast cells express high-affinity receptors for IgE (FcεRI) that avidly bind IgE (see Ch. 18).

When a specific antigen binds to mast cell-bound IgE, the FcεRI becomes activated, which leads to degranulation and release of preformed mediators, including histamine and serotonin. Other mediators such as prostaglandins, leukotrienes (B_4, C_4, D_4 and E_4), and platelet-activating factor are also released, and they enhance vascular permeability, bronchoconstriction, and induction of an inflammatory response (see Ch. 18). Hence, basophils and mast cells play an important role in immediate-type allergic reactions such as urticaria and angioedema. There is also evidence that mast cells are involved in contact hypersensitivity reactions.

Innate Lymphoid Cells

Innate lymphoid cells (ILCs) are lymphoid progenitor-derived leukocytes which lack T and B cell receptors and do not express conventional hematopoietic lineage markers[28]. ILCs require the transcription factor Id2 and the cytokine IL-7 for their development. Three subgroups have been defined based upon their cytokine and transcription factor expression profiles. *ILC1s* rely on the T-bet transcription factor and secrete type 1 cytokines such as IFN-γ and TNF in response to intracellular pathogens. *ILC2s* are under the control of GATA3 and ROR-α transcription factors and produce type 2 cytokines (e.g. IL-4, IL-5, IL-9, IL-13) in response to extracellular parasite infections. *ILC3s* are under the control of the ROR-γt transcription factor and produce IL-17, IL-22, and GM-CSF. There may be some plasticity between different ILC subgroups, but this is still under investigation.

The exact role of ILC1s in physiologic and pathologic processes within the skin still remains to be determined. In contrast, there is mounting evidence to support the role of ILC2s in allergic skin diseases such as atopic dermatitis. ILC2s activate B cells to secrete IgE via class switching, increase mast cell degranulation, and induce eosinophilia. ILC3s may play a role in triggering psoriatic flares since an increase in $NKp44^+$ILC3s that release IL-17 and IL-22 have been found in the circulation and skin of psoriatic patients. Their potential pathogenic role is also supported by a significant reduction in $NKp44^+$ILC3s after successful treatment with adalimumab. These ILC subsets have distinct gene expression profiles and localize to different skin compartments[29]. For example, when they reside in compartments close to hair follicles and sebaceous glands, they negatively regulate sebaceous gland function in a TNF- and lymphotoxin-dependent manner; absence of ILCs results in overgrowth of sebaceous glands and increased fatty acid production. By controlling the production of antimicrobial lipids these cells positively influence microbiota diversity[29].

Natural Killer Cells

The major task of natural killer (NK) cells is to eliminate virally infected or malignant cells[30]. NK cells can recognize their targets in two ways. Since they express Fc receptors that bind IgG (FcγRIII, CD16), NK cells can adhere to and kill target cells that are coated with IgG. This killing process is referred to as *antibody-dependent cellular cytotoxicity* (ADCC).

The second recognition system involves killer-activating and killer-inhibitory receptors. *Killer-activating receptors* recognize molecules that are expressed by nucleated cells. This provides a signal for the NK cell to kill the target cell by secretion of perforins, which make holes in the cell membrane through which granzymes are injected. Granzymes lyse target cells by activating the apoptotic caspase cascade. *Killer-inhibitory receptors* (KIR) on NK cells recognize major histocompatibility complex (MHC) class I molecules. KIRs shut off the killer signal and thus prevent autolysis of the host. Tumor cells and viruses often downregulate MHC class I molecules to escape recognition by cytotoxic T cells, but this renders "MHC class I-low" cells susceptible to recognition by NK cells.

ADAPTIVE IMMUNE RESPONSE

The characteristic features of an adaptive immune response are its specificity and enhancement with each successive antigen encounter owing to the accumulation of cellular "memory". A crucial event during the generation of an adaptive immune response is antigen presentation.

Antigen-Presenting Cells

Various cells can present antigens, depending on how and where the antigen first encounters cells of the immune system. Professional antigen-presenting cells (APCs), such as DCs and B cells, are specialized in capturing and displaying antigens to lymphocytes. Within the epidermis, Langerhans cells (LCs) are key APCs.

Langerhans cells

In 1868, Paul Langerhans first described dendritic cells that localized within the epidermis. Because of their shape, Langerhans thought that these cells might be of neural origin. More than 100 years later, it was shown that LCs are derived from bone marrow. LCs share ontogeny

with tissue-resident macrophages, but functionally resemble DCs[31]. Formation of LCs depends on transforming growth factor-β1 (TGF-β1) and macrophage colony-stimulating factor receptor (M-CSFR) ligands (M-CSF, IL-34), which are provided in an autocrine fashion.

LCs are intimately associated with nerve fibers that extend from the dermis into the epidermis and they can modulate LC function via the release of neuropeptides such as calcitonin gene-related peptide (CGRP)[32]. Psychological stress has been shown to result in a reduction of LCs and to influence local neuropeptide expression in human skin[33], suggesting a connection between environmental influences, mental health, and skin immune homeostasis. In humans, the number of LCs is reduced on the palms and soles, genitalia, and buccal mucosa. Of note, their density decreases with age and is reduced in chronically UV-exposed skin[34].

Ultrastructurally, LCs have rod-shaped organelles termed Birbeck granules (see Fig. 91.5). A Ca^{2+}-dependent lectin with mannose-binding specificity called langerin (CD207) is associated with and responsible for the formation of Birbeck granules[35]. Birbeck granules result from the antigen-capture function of langerin, which routes antigens into these organelles and provides access to a non-classical antigen-processing pathway. Activated LCs elongate their dendrites which can then penetrate keratinocyte tight junctions and survey the area just beneath the stratum corneum for antigens[36]. These penetrating dendrites take up antigens which co-localize with langerin/Birbeck granules. By forming new tight junctions, keratinocytes rapidly close the defects produced by the penetrating dendrites, thereby maintaining skin integrity during antigen uptake.

Histochemically, human LCs can be visualized by staining for adenosine triphosphatase (ATPase), a membrane-bound, formalin-resistant, sulfhydryl-dependent enzyme. In addition to langerin, antigenic moieties present on human LCs include the pan-hematopoietic marker CD45, MHC class II antigens (HLA-DR), CD1a, S100 protein, and vimentin. CD1a is a useful marker for LCs, since within the epidermis (normal or inflamed) it is exclusively expressed on LCs, whereas HLA-DR antigens are expressed on keratinocytes in inflamed skin (Table 4.2). Since CD1a does not exist in the murine system, staining for MHC class II antigens is often used for detection of murine LCs in non-perturbed skin (Fig. 4.3)[34]. In addition, human LCs express the high-affinity IgE receptor (FcεRI)[37]. Subtle differences in the surface marker expression of resident LCs, migrating LCs, and langerin$^-$ dermal DCs have been described (Table 4.2).

Other dendritic cells

DCs are professional APCs that display an extraordinary capacity to stimulate naive T cells and initiate a primary immune response[38]. They also control skin immune homeostasis via interactions with a variety of other immune cells, such as mast cells, macrophages, and ILCs, either via direct cell–cell contact or by secreted cytokine messengers. DCs can develop from different types of progenitor cells, while the same progenitor cell can give rise to a variety of functional phenotypes of DCs[39]. The DC system is very complex, and to further complicate matters, there are a number of differences between the experimental systems used to study human and murine DCs.

In general, dermal DCs can be divided into conventional DCs (cDCs) comprising cDC1 and cDC2 cells, and plasmacytoid DCs (pDCs)[40]. cDCs are the major dermal DC type under non-inflammatory conditions and they reside mainly in the upper dermis, compared to dermal macrophages which are found primarily in the deeper, vascular-rich dermis. Human cDC1s are defined by the expression of CD141 and BDCA3 and cDC2s by CD1c[41]. The two subgroups have overlapping, but distinct, immune functions – cDC1 cells can cross-present viral antigens and self-antigens and elicit Th1 immune responses, whereas hapten- or protein-primed cDC2 cells induce Th2-specific immune responses, while reducing Th17 cytokines[41,42].

Plasmacytoid DCs (pDCs; $CD123^+$) are specialized DCs that secrete large amounts of type I IFN in response to TLR7 or TLR9 activation. As such, they are powerful defenders against viral infections, but are normally absent in healthy human skin. Although pDC numbers are quite low in healthy individuals, circulating pDCs are significantly increased in patients with systemic lupus erythematosus (SLE)[43]. In addition, pDCs have been shown to infiltrate lesions of cutaneous lupus and psoriasis and further promote inflammation[44].

In the dermis of mice, two other subsets of DCs have been described, double-negative (DN) DCs and monocyte-derived DCs. The human counterpart of the latter are $CD14^+$ dermal cells, whereas the counterpart of the former is still elusive[42]. In the skin, monocyte-derived DCs have the potential to locally present antigens by forming immune clusters and thereby activating skin-resident T cells and regulatory T cells (Tregs)[42].

In humans, lymphoid and plasmacytoid DCs induce Th2 responses while myeloid DCs generate Th1 reactions[45]. Activation of TLR7 via the immunomodulator imiquimod, an imidazoquinoline (see Fig. 4.1), drives myeloid DCs to express perforin and granzyme B and drives plasmacytoid DCs to express TNF-related apoptosis-inducing ligand (TRAIL). This enables killing of tumor cells, indicating that both myeloid and plasmacytoid DCs may be directly involved in imiquimod-induced destruction of skin cancer[46].

The type of immune response that is generated is also critically dependent on the state of maturation of the stimulating DC at the time of antigen presentation. For the induction of Th1 responses, the presence of IL-12 is crucial. DCs tend to produce IL-12 directly after an activating step in their maturation, driving T cells into a Th1 phenotype if they meet the DCs at this stage[47]. At later time points,

PHENOTYPIC MARKERS OF RESIDENT VERSUS MIGRATING HUMAN LANGERHANS CELLS VERSUS HUMAN LANGERIN$^-$ DERMAL DENDRITIC CELLS

	Resident LC	Migrating LC	Langerin$^-$ dermal DC
Birbeck granules	++	++	–
Langerin (CD207)	+++	++	–
MHC class II	++	+++	++
CD45	+	+	+
CD1a	+++	+++	++
CD11c	+	+	+
CD11b	+/–	+/–	++
E-cadherin	++	+	–
Epithelial cell adhesion molecule (EpCAM)	+	+	–
CCR6	+	–	–
CCR7	–	+	+

Table 4.2 Phenotypic markers of resident versus migrating human Langerhans cells (LCs) versus human langerin$^-$ dermal dendritic cells (DCs). CCR, CC-chemokine receptor. Adapted from ref. 131.

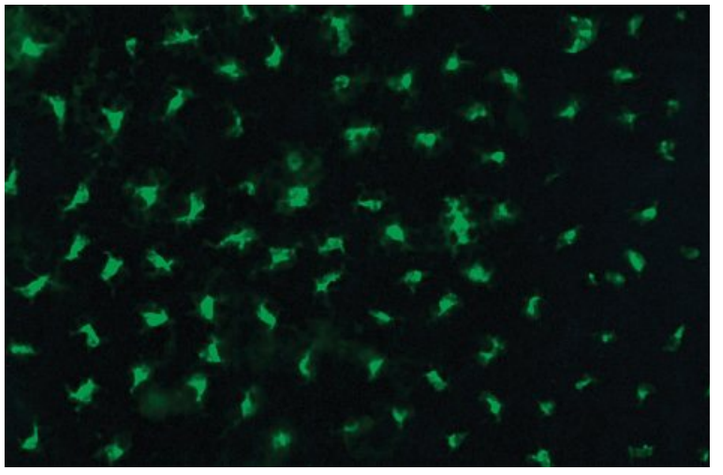


Fig. 4.3 Langerhans cells express MHC class II molecules. In a sheet preparation of murine epidermis, numerous Langerhans cells can be visualized by staining with an antibody against MHC class II molecules (Ia antigen). Note the dendritic shape of Langerhans cells. *Courtesy N. Romani, Department of Dermatology, University of Innsbruck.*

the production of IL-12 decreases, thereby favoring the development of a Th2 response. This process is also influenced by the innate immune system (e.g. stimulation by TLRs) and mast cells which can further skew T cells to produce Th1 and Th17 cytokines[42]. Taken together, the parameters responsible for the type of Th cell differentiation induced by DCs remain to be fully defined. Of note, immature DCs induce tolerance due to incomplete T cell activation, resulting in regulatory T cells that suppress immune responses[48].

Antigen presentation

Antigen-presenting cells: activation and migration

To initiate sensitization, antigens must be presented to T cells by APCs. For many years, LCs were thought to be the most important APC in the skin since contact sensitization could not be induced in sites that were naturally devoid of LCs (e.g. murine tail skin) or in which LCs had been depleted (e.g. by UV radiation)[49]. However, transgenic mice in which LCs are completely depleted demonstrated variably diminished but not completely abrogated sensitization responses[50]; in one such model, the sensitization response was completely normal[51]. In a different knockout mouse model characterized by constitutive and durable absence of epidermal LCs[52], an enhanced sensitization response was actually observed, suggesting that LCs may have regulatory functions. This "LC paradigm" proposes that LCs may be tolerogenic when they present antigens under steady-state non-inflammatory conditions, but sensitizing upon stimulation by inflammatory mediators. Which of these activities is the main function of LCs remains to be determined, and there is accumulating evidence that dermal DCs are equally, if not even more, important than LCs for presenting antigens to mount productive immune responses.

Cutaneous APCs actively take up antigens in the skin, but antigen presentation to lymphocytes takes place in the regional lymph nodes. In the presence of inflammation, the APCs become activated, leave the skin, and then migrate to the draining lymph nodes via afferent lymphatics. During migration, they change their phenotypic and functional behavior and develop into mature DCs. For example, molecules involved in antigen uptake and processing (Birbeck granules, Fc receptors) are downregulated on activated DCs[53]. When compared, gene expression profiles of LCs and migratory dermal DCs (e.g. cDC1s) are very similar and both have the capacity to prime naive helper T cells in lymph nodes.

In activated LCs, CD44, a hyaluronic acid receptor involved in the tissue homing of leukocytes, is upregulated. The splice variant CD44v6 supports binding of LCs to T cell-rich areas of lymph nodes[54]. Furthermore, the integrins $\alpha_6\beta_1$ and $\alpha_6\beta_4$, which exhibit affinity to the basement membrane zone, are induced on the surface of emigrating LCs[55]. The release of proteolytic enzymes like matrix metalloproteinase-9 (type IV collagenase) may enable their penetration through the basement membrane. Their dendricity becomes less pronounced, and surface molecules necessary for antigen presentation and T cell priming are upregulated (e.g. MHC class I, MHC class II, CD40, CD54, CD58, CD80, CD86). At this stage, LCs emigrating from the epidermis are almost indistinguishable from DCs obtained from lymphoid organs[53].

Antigen presentation to T cells

In contrast to B cells, T cells cannot recognize soluble protein antigens *per se*; instead, the T cell receptor (TCR) recognizes antigen-derived peptides bound to MHC locus-encoded molecules expressed on APCs. $CD4^+$ T cells recognize antigens in association with MHC class II molecules, while $CD8^+$ T cells recognize antigens in association with MHC class I molecules (Fig. 4.4).

Two pathways exist by which antigens can be "loaded" onto MHC molecules. If the antigen has been produced *endogenously* within the cell (e.g. viral or tumor proteins), it is complexed with *MHC class I* molecules through intracellular processing pathways (Fig. 4.5)[56]. The proteasome degrades cytosolic antigens produced by the cell. Resulting peptides (which consist of 8 to 12 amino acid residues) are then imported into the endoplasmic reticulum (ER) in a TAP (transporter associated with antigen processing)-dependent manner and loaded onto MHC class I molecules[57]. After binding to the MHC class I–β_2 microglobulin complex, these peptides are transported to the cell surface via the Golgi apparatus. Alternative pathways by which exogenous proteins are phagocytosed with the phagosome fusing to the ER may also exist. The proteins would subsequently be re-transported out of the ER into the cytoplasm and then degraded by the proteasome. The degraded peptides could then enter the pathway that is normally employed for endogenous proteins via the TAP protein. As the vast majority of nucleated cells express MHC class I molecules, many cell types can serve as nonprofessional APCs for MHC class I-restricted antigen presentation in a secondary immune response. This can also result in activation of effector cytotoxic T lymphocytes.

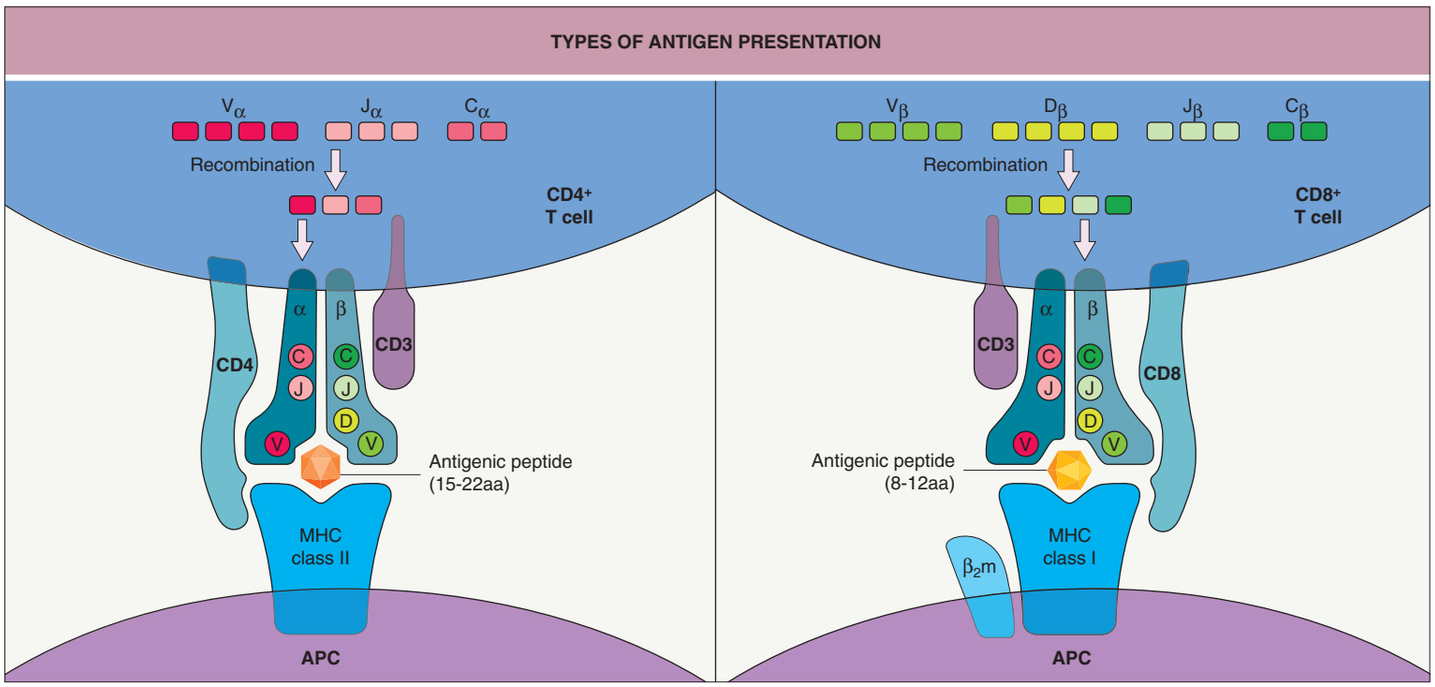


Fig. 4.4 Types of antigen presentation. Antigens are presented by antigen-presenting cells to the T cell receptor of $CD4^+$ or $CD8^+$ T cells in association with either MHC class II or MHC class I molecules. The diversity of the T cell receptors is generated by gene rearrangement. For reasons of clarity, the simplified gene rearrangement of the α-chain is shown only in the $CD4^+$ T cell and that of the β-chain in the $CD8^+$ T cell. aa, amino acids; APC, antigen-presenting cell; β_2m, β_2-microglobulin; V, variable; D, diversity; J, joining; C, constant. *Adapted from Modlin RL. Lymphocytes. In: Freedberg IM, Eisen AZ, Wolf K, et al. (eds). Fitzpatrick's Dermatology in General Medicine, vol. 1. New York: McGraw-Hill, 1999;32:400–5.*

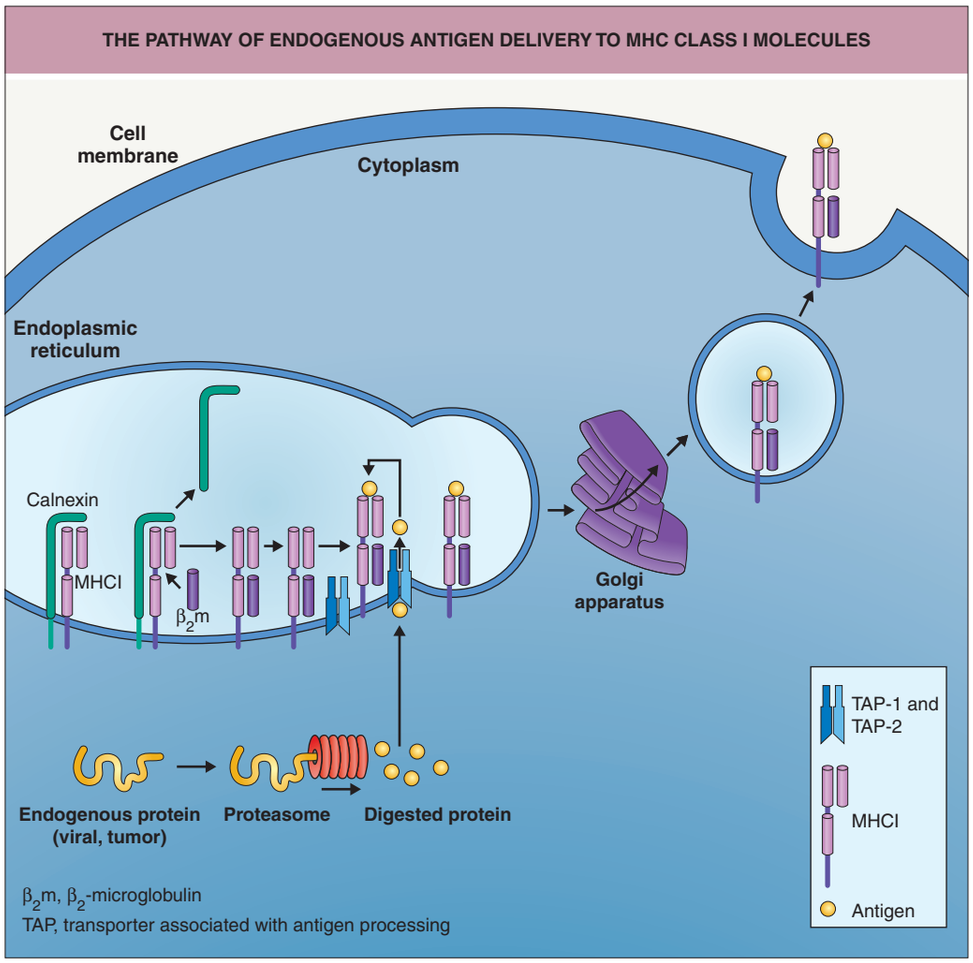


Fig. 4.5 The pathway of endogenous antigen delivery to MHC class I molecules. Newly synthesized MHC class I molecules are stabilized by calnexin. When β_2-microglobulin (β_2m) binds to the complex, calnexin dissociates. This complex associates with the TAP (transporter associated with antigen processing) protein waiting for a suitable peptide. Endogenous antigens are degraded by the proteasome and transported via TAP into the endoplasmic reticulum (ER), where they bind to the MHC class I/β_2m complex. Finally, the peptide/MHC complex is transported through the Golgi apparatus to the cell surface. Not pictured is a possible alternate pathway in which exogenous proteins are phagocytosed and the phagosome fuses to the ER. The proteins are then retransported out of the ER into the cytoplasm and degraded by proteasomes. The degraded peptides can now enter this pathway via the TAP protein.
Adapted from Parkin J, Cohen B. An overview of the immune system. Lancet 2001;357:1777–89. With permission from Elsevier.

MHC class II-dependent antigen presentation is critically dependent on DCs, B cells, and monocytes/macrophages. *MHC class II*-associated antigen presentation targets primarily *exogenous* and less frequently endogenous antigens[58]. Exogenous antigens are taken up via macro- or micropinocytosis or by receptor-mediated endocytosis (Fig. 4.6). One example of the latter is the DEC-205 receptor (CD205), which guides antigens into endocytic vesicles that reside deeper inside the cell and contain MHC class II molecules. As a consequence of this unique intracellular targeting, antigens endocytosed by the DEC-205 receptor stimulate respective T cells up to 500-fold greater than antigens taken up by pinocytosis or other receptors. Protein degradation eventually takes place in the endo-/lysosomes, yielding peptides with a typical length of 15 to 22 amino acid residues. These peptide fragments enter specialized endosomal compartments containing MHC class II molecules that are generated in the ER[59].

Newly synthesized MHC class II molecules are associated with an invariant chain, which inhibits dissociation of empty MHC class II molecules and transports the MHC class II complex from the ER to the specialized endosomal compartments where the molecules can interact with antigen peptide fragments (see Fig. 4.6). In this compartment, the invariant chain is cleaved by proteases, leaving a small fragment called CLIP (class II-associated invariant peptide) that binds to the class II molecule. Upon interaction with the antigenic peptides, the CLIP fragment is released from the complex. The MHC class II molecule with the bound antigen peptide is subsequently expressed on the cell surface, allowing antigen recognition by T cells carrying the appropriate TCR.

Classically, MHC class I molecules present self- or pathogen-derived antigens that are synthesized within the cell to $CD8^+$ T cells (see Fig. 4.5), whereas exogenous antigens derived via endocytic uptake are loaded onto MHC class II molecules for presentation to $CD4^+$ T cells (see Fig. 4.6). However, it has become evident that some DCs are also able to process exogenous antigens into the MHC class I pathway for presentation to $CD8^+$ T cells. This mechanism, referred to as cross-presentation[60], allows DCs to induce either tolerance (to self-antigens) or immunity (to exogenous pathogens).

T Cells

T cell precursors continuously migrate from the bone marrow to the thymus, where T cells develop[61]. In the thymus, T cells bearing the α/β TCR are subjected to a complex selection process. In contrast to antibodies, which represent the antigen receptor on B cells and recognize antigens in their naive form, the α/β TCR recognizes only short peptide fragments that are generated during antigen processing (see above). These processed antigens are presented to the TCR by MHC molecules on the cell surface. The amino acid sequences recognized by the TCR include those from both the MHC molecule and the antigenic peptide. Consequently, the TCR recognizes a combination of "self" MHC molecules (which are highly polymorphic) and "foreign" peptides. T cells that recognize "self" MHC molecules but *not* "self" peptides are useful for immune defense and do not lead to undesirable autoimmunity. This requirement is achieved by a complex process involving both positive and negative selection within the thymus.

T cell development

Developing T cells within the cortex of the thymus engage MHC complexes on thymic DCs. When the T cells are able to recognize these MHC molecules via their TCR, they receive a survival signal (*positive selection*). Otherwise, the T cells undergo apoptotic cell death. At this stage, more than 95% of the developing T cells die in the thymus because they are not selected due to their uselessness (i.e. inability to recognize "self" MHC molecules)[62]. In addition, T cells that express a TCR with a high affinity for the complex of a "self" peptide plus a "self" MHC molecule are eliminated by apoptosis, since they are potentially harmful. This process, called *negative selection*, takes place in the thymic medulla and involves DCs and macrophages that process and present a spectrum of "self" antigens. Positive and negative selection

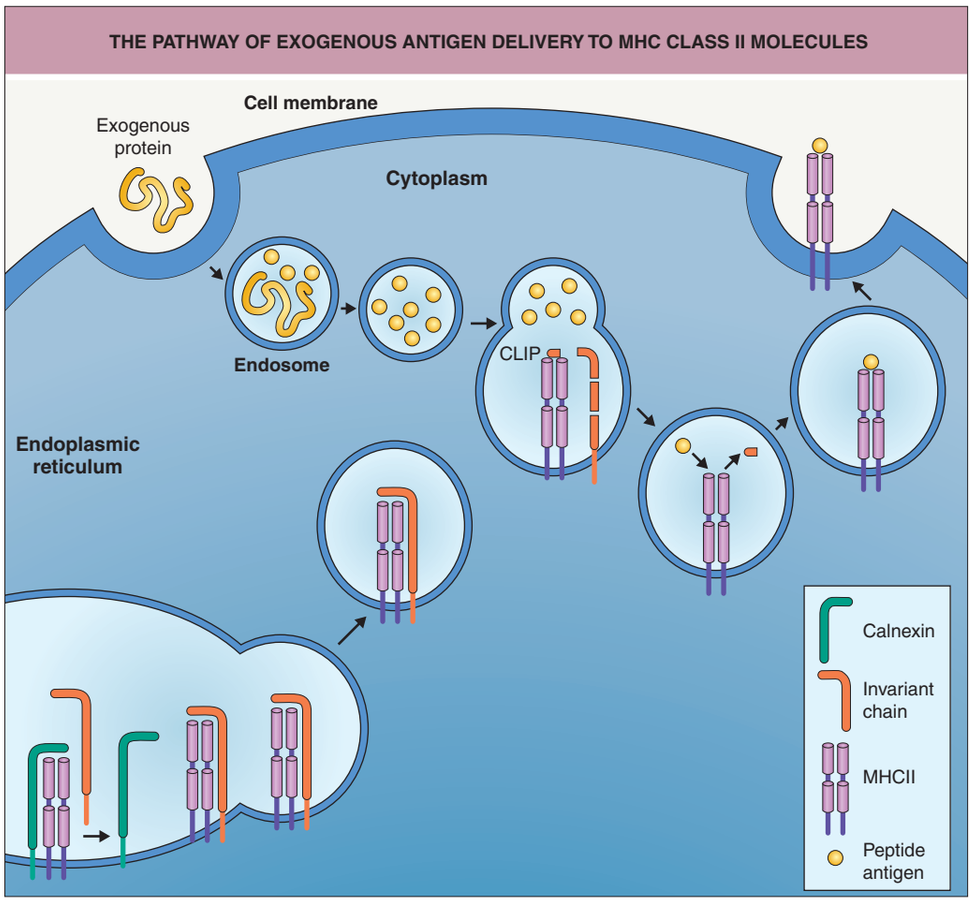


Fig. 4.6 The pathway of exogenous antigen delivery to MHC class II molecules. Exogenous antigens are taken up into the cell by endosomes. The protein is cleaved into peptides within the endosomes, which become increasingly acidic. In the endoplasmic reticulum (ER), newly synthesized MHC class II molecules bind to an invariant chain, which inhibits their disassociation while empty. During this assembly, the complex is stabilized by calnexin. The invariant chain transports the MHC class II molecule from the ER (via the Golgi apparatus) into the endosomal compartment, where the MHC class II complex meets the peptides. The invariant chain is cleaved, leaving a small fragment (CLIP) in the groove of the MHC class II molecule. Finally, CLIP is replaced by the antigenic peptide. The complex is transported to the cell membrane and expressed on the cell surface. CLIP, class II-associated invariant peptide.
Adapted from Parkin J, Cohen B. An overview of the immune system. Lancet 2001;357:1777–89. With permission from Elsevier.

allow the survival of just those T cells that recognize foreign (but not "self") peptides in the context of "self" MHC molecules and thus are useful for immune defense without causing auto-attack[63].

During thymic education, a variety of surface molecules are switched on and off. Components of the CD3/TCR complex, together with CD4 or CD8 molecules, have roles in this process. In general, $CD4^+$ T cells function as helper T cells and recognize antigens presented by MHC class II molecules, whereas $CD8^+$ T cells are usually cytotoxic and recognize antigens in association with MHC class I molecules (see Fig. 4.4). During their early stage of development within the thymus, T cells express both CD4 and CD8[64]. Upon expression of an appropriate TCR, these immature T cells exhibit the capacity to recognize antigenic peptides associated with either MHC class I or class II, since they still express both CD4 and CD8 (double-positive stage). In the subsequent process, one of these surface markers is lost, resulting in single-positive T cells expressing either CD4 or CD8.

T cell receptor

One major feature of an adaptive immune response is the recognition of specific antigens. This is achieved either by the TCR during a T cell-mediated response or by antibodies during a B cell response. TCRs are transmembrane molecules consisting of α/β (vast majority of T cells) or γ/δ (<10% of T cells) heterodimers[65]. Antigen recognition by γ/δ T cells appears to be independent of classic MHC molecules, instead utilizing other MHC-like molecules (e.g. CD1) that preferentially present certain lipid and glycolipid antigens[66].

T cell receptor diversity

An amazing feature of the immune system is that it provides specific receptors for every possible peptide antigen. B cells are capable of producing approximately 10^{16} different antibody variable regions, and T cells generate a comparable number of TCR variable regions. Remarkably, these numerous proteins are encoded by fewer than 400 genes. This tremendous diversity is created via a unique recombination process that cuts, splices, and modifies genes in the variable region[67].

Four segments of genes are involved in TCR formation: the variable (V), diversity (D), joining (J), and constant (C) regions (see Fig. 4.4). In contrast to the TCRβ and TCRδ loci (both on chromosome 7), the TCRα and TCRγ loci (both on chromosome 14) do not contain D segments. The segments are cut out by nucleases and spliced together by ligases, ultimately forming the final gene sequence that encodes the receptor molecule. The tremendous diversity is explained by the multiplicity of all these regions within the genome (e.g. ~70–80 V genes and ~60 J genes for the TCRα alone), but only one of each type is used for a particular TCR.

Each lymphocyte utilizes a different combination of V, D, and J gene segments to form the genetic code of its antigen receptor. Any one of the genes can join with any other one to form the final VDJ region, thereby creating tremendous diversity. In addition, the recombination process is subject to inaccuracies during splicing, which cause slight variations at the VDJ junctions, and additional nucleotides can be inserted by the enzyme deoxyribonucleotidyl transferase at the spliced regions. These two events increase the diversity even further. Of note, only a tiny minority of these cells will become functional over a lifetime, with the vast majority dying without ever having met their antigen.

Defects in the *r*ecombination-*a*ctivating *g*enes *RAG1* and *RAG2*[68], which encode two of the enzymes that mediate the recombination of variable-region genes in both B cells and T cells, cause a form of severe combined immunodeficiency (see Ch. 60). Affected individuals are unable to produce lymphocytes bearing functional antigen receptors[69].

T cell receptor signaling

TCRs are associated with the CD3 complex, which transmits signals upon antigen binding. CD3 consists of CD3γ, CD3δ, two molecules of CD3ε, and a disulfide-linked CD3ζ homodimer[70]. Upon binding to the peptide–MHC complexes, TCRs become cross-linked (Fig. 4.7). Aggregation of the TCRs causes phosphorylation of tyrosines in the cytoplasmic tails of the CD3 complex, which contain *i*mmunoreceptor *t*yrosine-based *a*ctivation *m*otifs (ITAMs). Phosphorylation involves kinases such as Lck (which also binds to the cytoplasmic tails of CD4 and CD8), Fyn, and ZAP70 (see Fig. 4.7)[71]. These events ultimately lead to the transcriptional activation of genes that encode cytokines and induce cellular proliferation and differentiation.

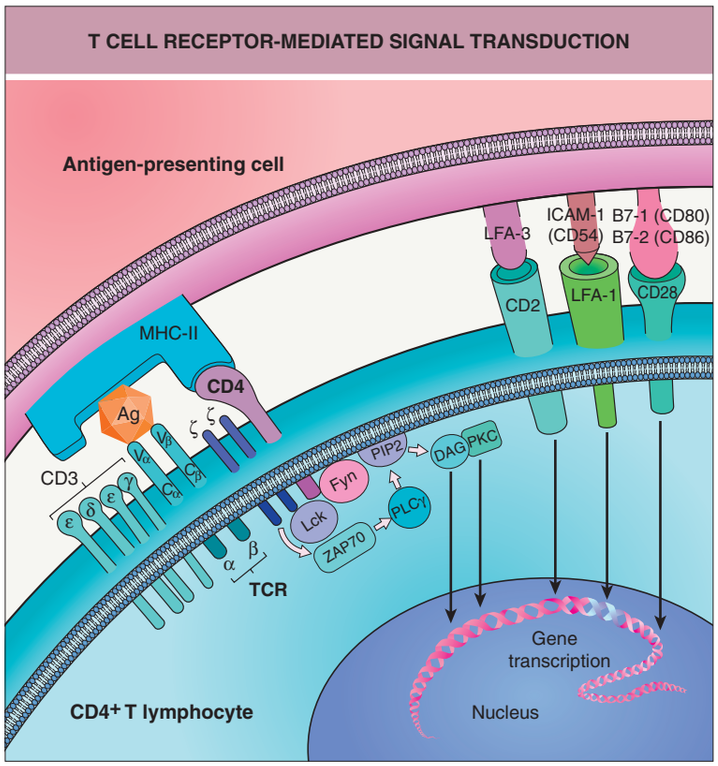


Fig. 4.7 T cell receptor-mediated signal transduction. Activation of the T cell receptor (TCR) by presentation of the appropriate antigen by antigen-presenting cells in association with MHC molecules induces a complex signal transduction cascade. The T cell receptor-associated signal transduction is primarily mediated by the CD3 complex and the ζ chain. Upon activation, the cytoplasmic tails of these molecules become phosphorylated by protein kinases (Lck, Fyn, ZAP70). This causes downstream signaling which ultimately leads to transcriptional activation of particular genes. Additional stimuli are provided by the signaling of costimulatory molecules (CD2, LFA-1, CD28). DAG, diacylglycerol; PIP2, phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; PLC, phospholipase C.

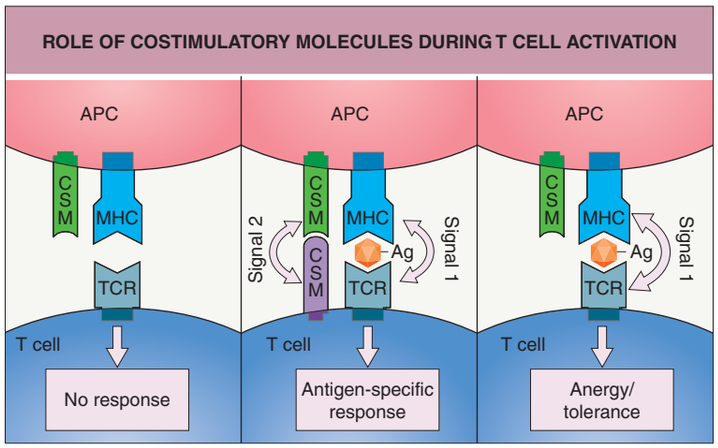


Fig. 4.8 Role of costimulatory molecules during T cell activation. Presentation of the antigen by antigen-presenting cells to the T cell receptor in association with MHC molecules delivers the first signal necessary for T cell activation. The second signal is provided by the interaction of costimulatory molecules present on antigen-presenting cells and T cells. An antigen-specific response is only induced when signal 1 and signal 2 are provided. Presentation of the antigen in the absence of signal 2 does not lead to an antigen-specific response but induces anergy and tolerance. APC, antigen-presenting cell; CSM, costimulatory molecule; MHC, major histocompatibility complex; TCR, T cell receptor.

COSTIMULATORY MOLECULES AND THEIR LIGANDS*

Receptor molecule	Expression†	Co-receptor molecule	Expression†
CD80 (B7-1)	APC	CD28, CD152 (CTLA-4)	T
CD86 (B7-2)	APC	CD28, CD152 (CTLA-4)	T
CD275 (ICOS-L, B7H2, B7h, B7RP1)	APC	CD278 (ICOS)	T
CD274 (PD-L1, B7H1)	APC	CD279 (PD-1)	T, B
CD273 (PD-L2, B7DC)	APC	CD279 (PD-1)	T, B
CD40	APC, B	CD154 (CD40L)	T
CD134 (OX40)	T	CD252 (OX40L)	APC, B
CD27	APC, T	CD70 (CD27L)	T, B
CDw137 (4-1BB)	T, B	4-1BBL	APC, B
CD265 (RANK)	APC	CD254 (RANKL, TRANCE)	APC, T
CD30	T, B	CD153 (CD30L)	T, B, APC
CD58 (LFA-3)	APC	CD2	T

*Only important costimulatory molecules and those with known ligands are included.
†Expression refers only to T cells (T), B cells (B), and antigen-presenting cells (APC) including dendritic cells and Langerhans cells.

B7 family | TNF receptor family | adhesion molecules

Table 4.3 Costimulatory molecules and their ligands. CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; ICOS, inducible costimulator; LFA-3, lymphocyte function antigen-3; PD-L1, programmed death ligand 1; TNF, tumor necrosis factor.

Costimulatory signals

Signaling through the TCR complex alone is not sufficient for naive T cell activation. The presence of costimulatory signals is needed for T cells to undergo antigen-specific clonal expansion[72]. Hence, development of a productive T cell immune response requires at least two types of stimuli. The *first signal* is the interaction of the TCR with peptide–MHC complexes presented by APCs, which determines the specificity of the immune response. The *second signal* involves surface molecules and cytokines, which determine the clonal expansion of specific T cells and their differentiation into effector and memory cells (Fig. 4.8). Without these costimuli, signaling by the antigen receptors alone will either cause anergy (non-reactivity) or apoptotic cell death. The major receptors and ligands expressed on APCs and T cells that play a role in activation are listed in Table 4.3.

The most relevant accessory molecules belong to the B7-CD28 superfamily which includes the following receptor:ligand pairs – CD28/CTLA-4:CD80/CD86, ICOS:ICOS-L, and PD-1:PD-L1/PD-L2[73]. The best-investigated costimulators for T cells are B7-1 (CD80) and B7-2 (CD86)[74]. Both are induced on immature, resting APCs by various TLR ligands or by cytokines (e.g. TNF, IL-1). The CD28 receptor on T cells recognizes the B7 molecules and delivers activating signals, including the expression of antiapoptotic genes and the production of cytokines such as IL-2 (see Fig. 4.7). Interaction of ICOS (*i*nducible T cell *co*-stimulator; CD278) with ICOS-L (CD275) induces less IL-2 but promotes T helper cell differentiation and effector function through the production of IL-10, -4, -17, -21, and IFN-γ[73]. The ICOS:ICOS-L signaling pathway is also crucial for T cell-dependent B cell responses.

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4 [CD152]) also binds to the B7 molecules, with even higher avidity than CD28. However, unlike CD28 binding, cross-linking of CTLA-4 to B7 downregulates IL-2 production and cell cycle progression, whereas blockade of CTLA-4 signaling prolongs T cell activation. Hence, CTLA-4 is regarded as a T cell-associated co-receptor with negative regulatory effects[75]. PD-L1 (CD274) and PD-L2 (CD273) also deliver a co-inhibitory signal to T cells via PD-1 (*p*rogrammed *d*eath-*1*; CD279) and thus inhibit T cell proliferation and cytokine production. Through the expression of CTLA-4, PD-Ll, and PD-L2, tumor cells may escape an immune response. Neutralization of these inhibitory molecules by antibodies (e.g. anti-CTLA-4 [ipilimumab], anti-PD-1 [nivolumab, pembrolizumab, cemiplimab], anti-PD-L1 [avelumab]), referred to as immune checkpoint inhibitors, has proven to be a highly effective therapy for a variety of malignancies including metastatic melanoma (see Ch. 128). Many of the associated side effects of these therapies such as colitis, hepatitis, and hypophysitis are due to autoimmune phenomena.

If a T cell recognizes its specific antigen peptide in association with the appropriate MHC molecules and becomes activated by costimulatory signals, then cell division and clonal expansion occur. Cytokines, especially inflammatory mediators like IL-1, IL-6 and TNF, also provide costimulatory signals by themselves and, in addition, upregulate other costimulatory molecules. Hence, a T cell is much more likely to be activated if it meets its specific antigen via an APC that has been exposed to an inflammatory environment. Polarizing cytokines such as IL-4, IL-12, and IL-23 also critically influence the differentiation of naive T cells.

Memory cells

Memory T cells have a longer lifespan than effector cells and react more rapidly upon re-exposure to their specific antigen. While naive T cells express CD45RA, memory T cells are characterized by the expression of the surface molecule CD45RO. Two distinct subsets of human memory T cells have been described. Stationary, tissue-resident memory T cells that comprise resident memory T cells (Trms) and effector memory T cells (Tems). They express receptors for migration into inflamed tissues to fulfill their effector functions[76]. Both subsets express low or no levels of the lymph node homing receptor CCR7, preventing tissue egress. In contrast, $CCR7^+$ memory T cells comprise central memory T cells (Tcms) and migratory memory T cells (Tmms) and they have the potential to recirculate to lymph nodes. Tcms lack immediate effector function, but efficiently stimulate DCs to produce IL-12 and can differentiate into Tems upon secondary stimulation.

Organ-specific adhesion molecules guide memory T cells to various locations, including the skin[23,76]. It is estimated that human skin contains twice as many T cells as the blood (~20 billion T cells). In normal human skin, 2% to 3% of T cells reside within the epidermis while the bulk of T cells are in the dermis. The majority of T cells express the α/β TCR and either CD8 or CD4. Trms express the skin-homing receptor CLA (see below) as well as CD2, CD5, and CD45RO; they are CCR7-negative and can be CD4- or CD8-positive[77].

Trms play a major role in host defense against previously encountered antigens[78] and with infections can populate the entire skin surface[79]. Upon antigen encounter, Trms proliferate and clear the pathogen. Associated inflammation causes nonspecific recruitment of T cells from the bloodstream via endothelial cell activation; the few antigen-specific T cells recruited into the skin in this manner also contribute to the clearance of the pathogen. In addition, DCs carry the antigen to the skin-draining lymph nodes and present it to Tcms. This gives rise to new populations of skin-homing Tems which migrate to the skin and also participate in the clearance of the antigenic attack.

Trms differ from other memory T cells as they do not circulate back to lymph nodes once they are recruited to the skin due to encounters with pathogens. More recently, these long-lived cells have been shown to reside within human skin for a decade and are at least partially resistant to radiochemotherapy[80]. Despite their beneficial effect in rapid on-site clearing of infections, Trms have also been reported to enhance allergic and autoimmune skin diseases and play a role in skin cancer biology.

Conventional T cells

Two major types of effector T cells have been identified: $CD4^+$ T helper (Th) cells and $CD8^+$ cytotoxic T (Tc) cells. The former activate B cells and modulate important components of cell-mediated immune responses, mainly via cytokine production. $CD8^+$ Tc cells are crucial to antiviral and antitumor responses.

T helper cells

$CD4^+$ Th cells recognize "their" antigenic peptides in association with MHC class II molecules (see Fig. 4.4). Based primarily on differences in their cytokine secretion patterns, several types of Th cells have been described[81]. Naive precursor Th cells only produce IL-2 whereas preactivated precursor cells, called Th0, can release a wide variety of cytokines (e.g. IL-2, IFN-γ, lymphotoxin, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, GM-CSF, TNF). As they develop into Th1, Th2 or Th17 cells, the cytokine secretion pattern becomes more restricted and specific (see below). More recently described Th9 and Th22 cells may represent separate types.

Morphologically, the cells in the various Th subsets are almost indistinguishable, although surface differences (especially in chemokine receptors) have been described[82]. Differentiation of naive Th cells into effector Th subsets is driven by well-defined transcription factors. However, Th cell differentiation into effector cells is not irreversible. Effector Th cells sustain plasticity and can differentiate into other subsets thereby flexibly adjusting to environmental changes[83].

Th1 cells: Typical Th1 cytokines are IFN-γ, lymphotoxin, and IL-2. IL-2 induces proliferation of $CD4^+$ cells in an autocrine manner and affects the cytokine differentiation pattern; however, it also stimulates $CD8^+$ T cell division and cytotoxicity, thereby providing "help" for $CD8^+$ Tc cells. IFN-γ activates macrophages to kill intracellular pathogens (e.g. mycobacteria, fungi, protozoa) and stimulates NK cell cytotoxicity. Therefore, Th1 cells are involved in the clearance of intracellular pathogens, and their cytokines preferentially induce a cell-mediated inflammatory response, such as the granulomatous lesions of tuberculosis or leprosy. Macrophages stimulated by IFN-γ release IL-12, the major cytokine that drives Th0 cells towards a Th1 phenotype (Fig. 4.9)[84]. In addition, the transcription factor T-bet drives differentiation towards the Th1 phenotype.

Th1 cells also promote the isotype switch of B cells to produce complement-binding antibodies and they contribute to the pathogenesis of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, allergic contact dermatitis, and psoriasis.

Th2 cells: Th2 cells are under the control of the transcription factor GATA3 and produce primarily IL-4, IL-5, and IL-13. These cytokines favor production of non-complement-binding antibodies. IL-4 switches B cells to produce IgE, and IL-5 promotes an expansion of eosinophils. Therefore, Th2 responses are often associated with allergic diseases. Comparable to the role of IL-12 in inducing Th1 responses, IL-4 is the key cytokine in driving Th2 responses (see Fig. 4.9). In addition, IL-4 suppresses Th1 and Th17 differentiation. However, IL-4 seems to exert opposing effects on $CD4^+$ T cells and DCs, since it can stimulate DCs to produce IL-12 and thus paradoxically promote Th1 development[85].

Many TLR signals and infections are strong inducers of IL-12 and therefore favor a Th1 response. However, other TLR signals to DCs and early production of IL-4 favor the generation of Th2 cells. Additional factors that influence the Th1/Th2 decision include the dose of the antigen, the APCs involved[39], the cytokines secreted (by APCs and bystander cells), the genetic background of the host, and the presence of costimulatory molecules. Of note, many immune responses are not strongly polarized in the Th1 or Th2 direction.

Th9 cells: In response to TGF-β and IL-4, $CD4^+$ T cells secrete IL-9. The development of Th9 cells depends on the IL-4-activated transcription factor PU.1. Th9 cells predominantly reside in human skin and are involved in protecting against pathogens, but also play a role in allergic and non-allergic inflammatory skin diseases[86]. In addition, they contribute to extracutaneous allergic diseases in that IL-9 is highly expressed in the lungs of asthmatic patients, especially children.

Th17 cells: $CD4^+$ T cells that produce IL-17, but not IFN-γ or IL-4, are referred to as Th17 cells[87]. Besides IL-17A, these cells also secrete IL-17F, IL-21, IL-22, IL-25 and IL-26. Whereas the heterodimeric cytokine IL-12 (consisting of a p35 chain and a p40 chain) is crucially involved in the development of Th1 cells, the IL-12-related cytokine IL-23 (consisting of a p19 chain and the same p40 chain; see Fig. 128.9) is essential for the generation of Th17 cells. Naive T cells do not express the IL-23 receptor. In mice, a combination of TGF-β and IL-6 induces expression of the transcription factor *r*etinoid acid receptor-related *o*rphan *r*eceptor-γt (ROR-γt), which stimulates transcription of the IL-17 gene and expression of the IL-23 receptor (see Fig. 4.9). IL-6 and IL-23 enhance the expression of IL-17 and IL-22 and suppress production of IL-10 and IFN-γ, thereby stabilizing the Th17 phenotype. IL-21 is also produced in large amounts by mature Th17 cells and amplifies Th17-cell differentiation[87]. In human T cells, combinations of TGF-β plus IL-21, TGF-β plus IL-6 and IL-23, or IL-6 plus IL-21 appear to be involved in the differentiation of Th17 cells by inducing the expression of ROR-c, the human analogue of murine ROR-γt.

Th17 cells are rapidly induced in response to infectious agents – in particular, bacteria and fungi. Patients with a defective Th17 response due to mutations in the gene encoding *s*ignal *t*ransducer and *a*ctivator of *t*ranscription 3 (STAT3), another transcription factor involved in Th17 cell development (see Fig. 4.9), have hyperimmunoglobulin E (hyper-IgE) syndrome and suffer from recurrent *Candida albicans* and *Staphylococcus aureus* infections of the skin and lungs (see Ch. 60)[88]. Th17 responses have important roles in chronic inflammation and in mediating autoimmune reactions. There is evidence that Th17 cells are involved in rheumatoid arthritis, psoriasis, multiple sclerosis, and inflammatory bowel diseases[87]. Genetic studies have linked variants of

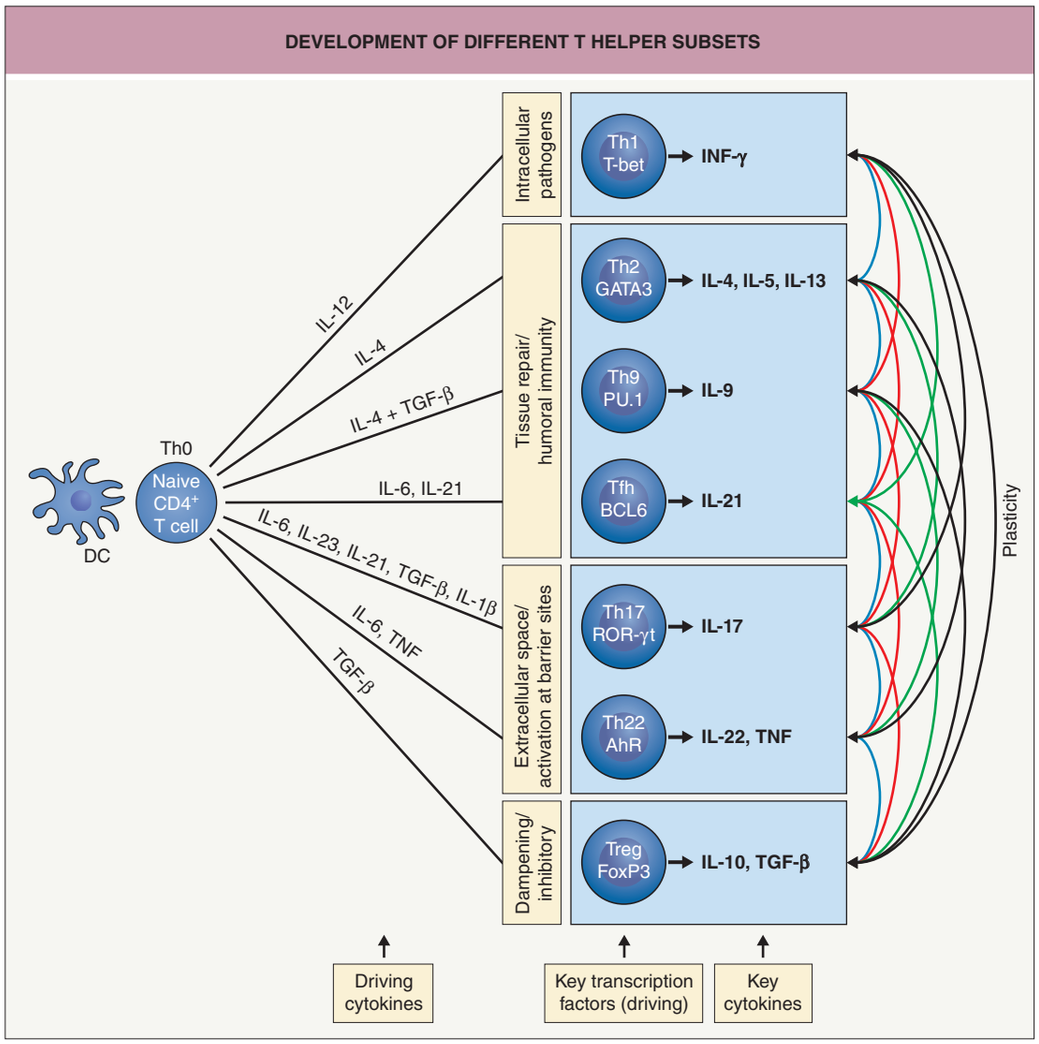


Fig. 4.9 Development of different T helper subsets. Key cytokines drive the differentiation of naive T helper (Th) cells into various Th cell subtypes. Th cell differentiation is non-linear and highly plastic, thus allowing trans-differentiation of already committed cells into other subtypes (plasticity model). Each $CD4^+$ T cell subtype is depicted with its major driving cytokines (e.g. IL-12, IL-4, TGF-β) and fate-determining transcription factors (e.g. T-bet, GATA3, PU.1, BCL6, ROR-γt, AhR), which direct differentiation. There are additional transcription factors (e.g. STAT3) that play an important role. Differentiated Th cells secrete unique cytokines that influence other immune cells. Th1 cells are crucial for T cell-mediated immunity against intracellular pathogens whereas Th2, Th9, and Tfh cells support the development of humoral immunity and provide assistance in tissue repair. Th17 and Th22 cells are activated at barrier sites, such as the skin and gut mucosa, to protect the extracellular space and are involved in chronic inflammatory and autoimmune reactions. Tregs are crucial for maintaining immune homeostasis by dampening immune reactions. AhR, aryl hydrocarbon receptor; BCL6, B cell lymphoma 6; FoxP3, forkhead box P3; GATA3, transcription factor that binds to the DNA sequence "G-A-T-A"; IL, interleukin; IFN-γ, interferon-γ; PU.1, transcription factor that binds to purine-rich DNA sequence (PU-box); ROR-γt, retinoid acid receptor-related orphan receptor-γt; T-bet, T-box expressed in T cells; Tfh, T follicular helper cell; TGF-β, transforming growth factor-β; Th, T helper, Treg, T regulatory. *Adapted from Tuzlak S, Dejean AS, Iannacone M, et al. Repositioning TH cell polarization from single cytokines to complex help. Nat Immunol 2021;22:1210–7 and O'Shea JJ, Paul WE. Mechanisms underlying lineage commitment and plasticity of helper CD4+ T cells. Science 2010;327:1098–102.*

the IL-23 and IL-23 receptor genes to susceptibility for psoriasis and psoriatic arthritis[89]. Since IL-23 enhances IL-17 production, inhibition of IL-23 is a target for therapeutic intervention. Indeed, the monoclonal antibody ustekinumab, which is directed against the common p40 chain and therefore blocks signaling by both IL-12 and IL-23, represents an effective treatment for psoriasis[90] as do guselkumab, tildrakizumab and risankizumab which target the p19 chain of IL-23; the same applies for agents blocking either IL-17A (ixekizumab, secukinumab) or the IL-17 receptor (brodalumab) (see Fig. 128.9).

Th22 cells: A subset of human $CD4^+$ Th cells characterized by secretion of IL-22 and TNF (in the absence of IFN-γ, IL-4, or IL-17) are termed Th22 cells and are potentially under the control of AhR, the aryl hydrocarbon receptor transcription factor which links extracellular signals to cellular responses via ligand-induced translocation from the plasma membrane to the nucleus[91]. IL-22, a member of the IL-10 cytokine family, binds to a heterodimeric receptor, which is expressed by non-hematopoietic cells including keratinocytes. IL-22 induces the expression of antimicrobial peptides (e.g. S100 proteins, defensins) as well as inflammatory chemokines and cytokines including IL-6. IL-22 is also involved in tissue repair by inducing epithelial cell proliferation and enhancing cell survival. IL-22 and Th22 cells appear to play an important role in psoriasis since IL-22 is highly expressed in psoriatic plaques and neutralization of IL-22 prevented the development of lesions in a murine model of psoriasis[92]. Tapinarof, an AhR agonist, was recently introduced as a topical treatment for psoriasis.

T follicular helper cells (Tfh): Tfh cells mainly produce IL-21 and this cytokine in turn drives their differentiation via the master transcription factor Bcl-6. Although Tfh cells reside primarily within secondary lymphoid organs where they aid B cell functions, skin DCs can also drive their expansion[93]. Little is known about their role in skin pathologies beyond a suggested involvement in skin fibrosis[94].

Cytotoxic T cells

Cytotoxic T (Tc) cells are $CD8^+$, recognize "their" antigenic peptides in association with MHC class I molecules, and can directly lyse their targets (e.g. virally infected or tumor cells). For example, virally infected cells present peptides derived from intracellular viral proteins on MHC class I molecules, and Tc cells that recognize this viral peptide–MHC complex are stimulated to kill the infected cell. Tc cells have at least three different pathways of killing[95], two of which involve direct contact with the target cell. In one method, Tc cells insert perforins into the membrane of the target cell; this creates pores in the membrane, through which granzymes are released from the Tc cell into the target cell. Granzymes then activate caspases which are proteolytic enzymes that induce apoptosis in the target cell. In a second mechanism, Tc cells activate the death receptor Fas (CD95) on the target cell by expressing the cognate death ligand FasL (CD95L). Activated Fas also triggers apoptosis in the target cell. The third pathway is mediated by cytokines, including TNF and IFN-γ, which are released as long as TCR stimulation continues. These mediators can affect distant cells as well as the target cell[95].

Naive $CD8^+$ T cells (Tc0 cells) can develop into Tc1, Tc2, Tc9, Tc17, and Tc22 cells[96]. Comparable to Th1 and Th2 cells, Tc1 and Tc2 cells are differentiated based on their different cytokine secretion patterns. However, their exact functional roles in skin still remain to be determined. Even though there is evidence that some $CD8^+$ T cells exhibit suppressor functions[97], most $CD8^+$ Tc1 and Tc2 cells develop a cytotoxic phenotype.

Regulatory T cells

Regulatory T cells (Tregs) were discovered by the observation that chronic activation of $CD4^+$ T cells in the presence of IL-10 induced $CD4^+$ T cell clones with a low proliferative capacity that produced high

levels of IL-10, low levels of IL-2, and no IL-4[98]. These antigen-specific T cell clones suppressed the proliferation of $CD4^+$ T cells in response to antigen and prevented T cell-mediated colitis in SCID mice. This $CD4^+$ T cell subset was designated T regulatory cells 1 (Tr1).

Another subset of $CD4^+$ Treg is characterized by the constitutive expression of the α-chain of the IL-2 receptor (CD25). Some $CD4^+CD25^+$ Tregs are generated in the thymus and become activated upon re-encountering their antigen in the periphery. Thymectomized mice that do not develop $CD4^+CD25^+$ T cells develop autoimmune diseases[99]. In turn, reinjection of such cells prevents the development of the autoimmune phenomena, indicating that the $CD4^+CD25^+$ cells prevent autoimmunity and thus can act in a suppressive fashion. FoxP3, a transcription factor whose inherited dysfunction leads to an autoimmune and inflammatory syndrome in humans (IPEX: *i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked) and mice (*Scurfy* strain), is specifically expressed in naturally arising $CD4^+CD25^+$ Tregs[100]. Retroviral gene transfer of *Foxp3* converts naive T cells toward a Treg phenotype. Thus, *Foxp3* is a key regulatory gene in the development of Tregs.

Natural Tregs (*nTregs*) are produced in the thymus as a functionally mature subpopulation of T cells and constitute ~10% of all murine peripheral $CD4^+$ T cells[101]. *Induced Tregs* (*iTregs*) can also develop from naive T cells in the periphery through several mechanisms (Fig. 4.10). Immature DCs appear to be involved in the generation of human iTregs. Upon repeated stimulation by immature DCs, allogeneic $CD4^+$ T cells have been shown to: express the negative regulatory molecule CTLA-4; lose their capacity to produce IFN-γ, IL-2, or IL-4; and differentiate into non-proliferating, IL-10-producing T cells[48]. In co-culture experiments, these T cells inhibited the antigen-driven proliferation of Th1 cells in a cell contact-dependent manner. The same may apply for damaged APCs, since the migration of UV-damaged LCs is required for the generation of Tregs by UV radiation[102].

Together, these findings show that immature and mature DCs induce different types of T cell responses: (1) mature, IL-12-producing DCs result in inflammatory Th1 cells; (2) less well-defined "DC2s" result in Th2 cells; and (3) immature or damaged DCs result in IL-10-producing iTregs. These observations provide evidence for constant control of peripheral tolerance to self-antigens[103]. In this scenario, immature DCs constantly take up proteins from normal cells as they undergo regular cell turnover. In the absence of inflammatory signals, DCs do not mature and therefore enter the regional lymph nodes in an immature stage. Self-antigens expressed on immature DCs lead to the development of Tregs, which then migrate to the respective organ where they exhibit suppressive effects. During an infection, immature DCs take up self-antigens and mature in the presence of TLR and inflammatory signals. In the regional lymph nodes, the mature DCs prime naive $CD4^+$ or $CD8^+$ T cells, which become effector T cells. These cells re-migrate to the initial site of inflammation, where they encounter the inhibitory effects of Tregs that are already present. This process normally prevents the development of autoimmunity under both normal and inflammatory conditions.

Tregs exert their suppressive functions in several ways[101] (see Fig. 4.10). They release inhibitory cytokines (e.g. IL-10, IL-35, TGF-β) and can induce apoptosis of target effector T cells via perforin and granzymes. Tregs also interfere with metabolic functions in their target T cells by depriving them of IL-2 (which results in apoptosis), increasing their intracellular levels of cAMP (which inhibits T cell proliferation and IL-2 production), and increasing pericellular levels of adenosine (which is cytotoxic). Furthermore, negative regulation of the maturation and function of APCs occurs through the interaction of CTLA-4 and lymphocyte-activation gene-3 (LAG-3) on Tregs with CD80/CD86 and MHC class II ligands, respectively, on APCs. Induction of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO) in DCs has been suggested as another mechanism by which Tregs exert suppression.

Tregs colonize the skin soon after birth, and in a mouse model, hair follicle morphogenesis and the presence of commensal microbiota within the follicles are essential for this process[104]. This hand-in-hand accumulation of bacteria and Tregs in and around skin appendages allows for induction of tolerance to commensals and is essential in maintaining skin homeostasis. Later in life, $FoxP3^+$ Tregs predominantly localize around hair follicles in both human and mouse skin. They promote hair follicle cycling via modifying stem cell activation and differentiation as well as regulating wound healing by controlling inflammatory responses at the hair follicle-stem cell niche[105,106].

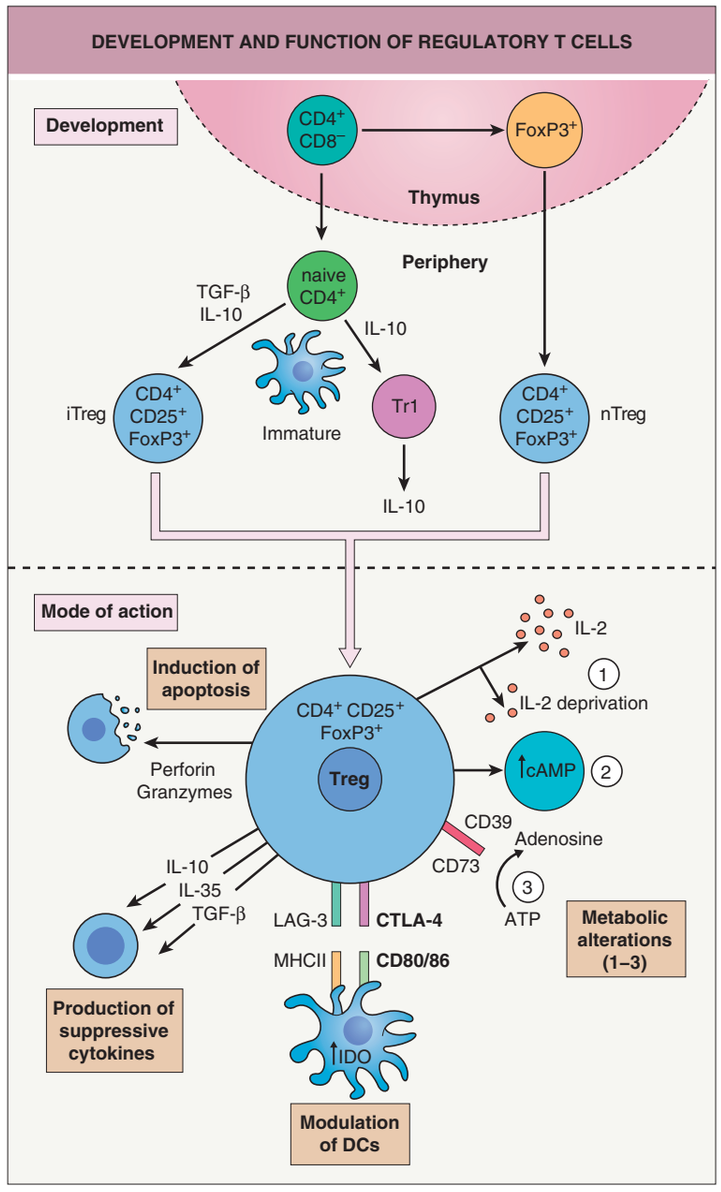


Fig. 4.10 Development and function of regulatory T cells. Natural regulatory T cells (nTregs), which express CD4, CD25 and FoxP3, develop from $CD4^+CD8^-$ T cells in the thymus. In the periphery, naive conventional $CD4^+$ T cells (in the presence of interleukin [IL]-10 and/or transforming growth factor-β [TGF-β]) can develop into $FoxP3^-$ regulatory type 1 cells (Tr1) or induced regulatory T cells (iTregs) that express CD24, CD25, and FoxP3. Tregs exert their inhibitory functions in several ways. They release inhibitory cytokines (e.g. IL-10, IL-35, TGF-β), induce apoptosis of their target effector T cells via release of granzymes and perforin, and interfere with metabolic functions of their target T cells. The latter can be accomplished by: (1) IL-2 deprivation, which triggers apoptosis; (2) transferring cAMP, which inhibits proliferation and IL-2 production, into target cells; and (3) increasing pericellular levels of cytotoxic adenosine via conversion of ATP to adenosine by CD39 and CD73, two ectonucleotidases expressed on the surface of Tregs. Tregs also modulate dendritic cell (DC) maturation and function via interaction of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and lymphocyte-activation gene-3 (LAG-3) on Tregs with their ligands CD80/CD86 and MHC class II, respectively, on DCs and induction of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase [IDO] in DCs. *Adapted from Workman CJ, Szymczak-Workman AL, Collison LW, et al. The development and function of regulatory T cells. Cell Mol Life Sci 2009;66:2603–22 and from Sakaguchi S, et al. Regulatory T cells and immune tolerance. Cell 2008;133:775–87.*

Unconventional T cells

Natural killer T cells

NK T cells are a distinct subset of peripheral T cells that have characteristics of both T cells and NK cells[107]. They express the NK cell marker

NK1.1 and an invariant TCR restricted to CD1d. NK T cells produce various cytokines, including IFN-γ, IL-4, and IL-10. They are present in the thymus during early stages of ontogeny and are probably involved in the differentiation of various T cell subsets, especially Th2 cells. Since NK T cells are numerically and functionally deficient in mice with autoimmune diseases, they may also play a role in the control of autoimmunity.

Invariant NK T (iNKT) cells express an invariant TCR α chain and recognize endogenous and foreign antigens, such as bacterial lipid antigens presented by CD1d. They secrete Th1-, Th2-, or Th17-specific cytokines and modulate effector functions of NK cells, DCs, macrophages, B cells, and T cells.

γ/δ T cells

Under normal conditions, the vast majority of T cells found in the skin belong to the α/β type, but a subset of T cells carries a TCR composed of γ and δ (rather than α and β) protein chains. Although in normal skin γ/δ T cells were long thought to be found exclusively within the epidermis, more recent evidence has shown that a subset resides in the dermis, where they are involved in responses against bacterial infections[108]. In certain infectious diseases such as leprosy and leishmaniasis, γ/δ T cells can account for almost one-third of the T cells infiltrating the skin. The precise functional role of γ/δ T cells remains to be determined, but they may be involved in the recognition of non-peptide moieties expressed by microbial pathogens[109]. γ/δ T cells depend on IL-7 signaling for their maintenance and predominantly recognize lipid antigens. Skin inflammation quickly results in γ/δ T cell activation and IL-17 production followed by neutrophil recruitment and bacterial clearance[110].

Dendritic epidermal γ/δ T cells

$CD3^+$ lymphocytes found in the epidermis of mice have a dendritic shape and are therefore termed dendritic epidermal T cells (DETCs)[111]. These murine DETCs express a γ/δ type of TCR with limited diversity. The same TCR configuration is detected in early thymocytes, giving rise to speculation that fetal thymocytes are the progenitors of DETCs; alternatively, maturation could take place in the skin. DETCs are thought to protect stressed keratinocytes and they exhibit NK cell function, but also downregulate T cell responses. However, despite extensive studies, to date the functional role of DETCs has not been fully elucidated, and a human equivalent of DETCs has not yet been identified.

Mucosal associated invariant T cells

Mucosal associated invariant T (MAIT) cells share features of innate and adaptive cells. MAIT cells recognize riboflavin-derived antigens that are presented by MR1, a MHC-like protein. Classical MAIT cells are present in human blood and also colonize tissues that are in cross-talk with commensal microbiota. They secrete a plethora of cytokines, including IFN-γ, TNF, IL-2, and IL-17A, and they play a role in infections, autoimmune diseases, and allergic and inflammatory disorders[112]. In human skin, MAIT cells are also important for tissue repair and require the presence of riboflavin-synthesizing bacteria in the microbiota to colonize the skin early in life[113].

Lymphocyte recruitment

A major challenge for T lymphocytes is to be at the right place at the right time in order to find and recognize cognate antigen. Naive lymphocytes encounter their antigens for the first time in secondary lymphoid organs, while memory cells can also do this in the periphery. Naive T cells continuously recirculate between the blood and lymphoid organs[114]. Expression of the surface molecule L-selectin (CD62L) allows naive T cells to attach to and roll on the inner surface of the high endothelial venules, specialized postcapillary venules within the lymph nodes and Peyer's patches. The venules express the secondary lymphoid-tissue chemokine (SLC/CCL21)[115] which interacts with the chemokine receptor CCR7. Subsequently, T cells adhere tightly to these high endothelial venules via interaction of endothelial intercellular adhesion molecule-1 (ICAM-1, CD54) with lymphocyte function antigen-1 (LFA-1, CD11a). This is followed by transmigration into the T cell areas of the lymph node. The T cells can then return to the bloodstream by leaving the lymph node via efferent lymphatics.

Upon activation by APCs presenting cognate antigenic peptides, T cells start to proliferate and begin to express activation molecules, thereby developing into effector/memory T cells. During this process, they express new surface molecules that allow them to exit the blood vessels and enter extranodal tissues[116]. A hallmark of activated T cells is their ability to "remember" the anatomic location that the lymph node was draining. Due to the expression of specific adhesion molecules, they exhibit the capacity to migrate primarily into the sites where the antigen was first encountered by the host. Hence, lymph nodes draining different organs generate distinct, "tissue-specific" memory T cells.

Memory T cells entering the skin express *cutaneous lymphocyte antigen* (CLA), whereas memory T cells found in other tissues are primarily CLA-negative. CLA is generated by modification of the pre-existing P-selectin glycoprotein ligand-1 (PSGL-1, CD162) by glycosylation enzymes[117]. The function of CLA is to allow the early tethering of T cells to the endothelium of cutaneous postcapillary venules, leading to the slowing, arrest, and then extravasation of the T cells. The endothelial ligand for CLA is E-selectin (CD62E), which is constitutively expressed at low levels on cutaneous microvessels and highly upregulated during inflammation. Although interaction between CLA and E-selectin is an important initial step, it does not suffice for transmigration. Interactions of LFA-1 and the β-integrin very late antigen-4 (VLA-4) on T cells with ICAM-1 (CD54) and VCAM-1 (CD106), respectively, on endothelial cells produce the firm adhesion required for extravasation of T cells from the blood into the skin (see Ch. 102).

CLA^+ T cells often co-express CCR4[118]. CCR4 binds the ligand CCL17, which is present in a steady state on cutaneous vasculature and upregulated on keratinocytes and dermal fibroblasts in inflammatory skin diseases, such as atopic dermatitis or psoriasis[119]. CCR4-CCL17 binding arrests rolling T cells and enhances T cell adhesion to the endothelium for efficient extravasation into tissue. Approximately 50% of skin-resident memory T cells also express the chemokine receptor CCR8. Upon exposure to dermal DCs in combination with IL-7 and IL-15, $CCR8^+$ T cells markedly proliferate, a hallmark of homeostatic proliferation of Trms[120]. CCL1, the ligand of CCR8, is expressed on epidermal LCs and vascular endothelial cells and may also be involved in homeostatic immune cell migration in healthy skin[119].

B Cells

The major task of B cells is the production of immunoglobulins (antibodies) that bind to specific antigens. Antibodies also interact with components of the innate immune system by preventing foreign organisms from adhering to mucosal surfaces, by activating complement, and by opsonizing bacteria for phagocytosis. Immunoglobulins are secreted products of mature B cells. However, during early B cell development, immunoglobulins function as antigen-specific B cell receptors on the cell membrane, equivalent to the TCR on T cells. CD19, CD20, and CD22 are the major markers currently used to identify B cells. Activation of B cells results in cell division and maturation into plasma cells, which secrete specific antibodies during humoral immune responses. Although B cells are infrequently found in healthy skin, they may play an incompletely understood role in pro- and anti-inflammatory processes associated with skin cancer, atopic dermatitis, psoriasis, and delayed-type hypersensitivity reactions[121].

Immunoglobulins

Immunoglobulins consist of two identical heavy chains and two identical light chains, linked together by disulfide bonds[122] (Fig. 4.11). The N-terminus of each chain contains a variable domain that binds the antigen through three hypervariable complementarity-determining regions (CDRs). The C-terminal domains of the heavy and light chains form the constant regions. Five classes of immunoglobulin (IgG, IgA, IgM, IgD, and IgE) are defined by the amino acid sequences of the constant regions of the heavy chains. The designation of κ or λ depends on the constant region of the light chain. The class/subclass and titer of the antibody that is formed depend on: the physical and chemical properties of the antigen; the site, duration, repetition, and amount of antigen exposure; and the individual's propensity to recognize the antigen as foreign.

Digestion of immunoglobulins with the enzyme papain yields an antigen-binding fragment termed Fab and a fragment that spontaneously crystallizes with time and thus is called the Fc portion. Immunoglobulins are divalent, since twice as many Fab fragments than Fc portions are obtained upon cleavage with papain. Digestion of

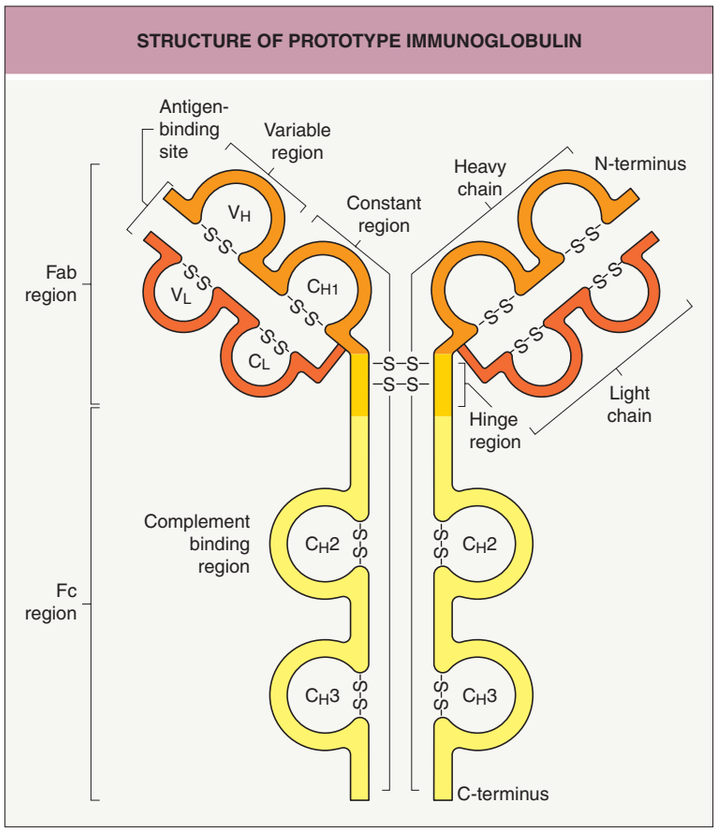


Fig. 4.11 Structure of a prototype immunoglobulin. The basic immunoglobulin structure consists of two identical light polypeptide chains and two identical heavy polypeptide chains, which are linked together by disulfide bonds. The antigen-binding site is at the N-terminal end.

immunoglobulins with pepsin provides Fab fragments that are disulfide bond-linked and thus called F(ab) fragments.

Through their CDRs, antibodies recognize the conformational structure of their epitopes. No antigen processing is required. As for the TCR, extensive gene rearrangement involving V, D, and J regions allows the generation of a nearly infinite variety of immunoglobulins specific for any putative antigen[67] (see T cell receptor diversity above). An even greater repertoire of B cell receptors than TCRs is produced, since further gene rearrangement of immunoglobulins occurs during B cell division after antigen stimulation, a process called somatic hypermutation.

The ability to induce effector functions resides in the Fc portion of the heavy chain. The Fc portion of IgG contains domains called C_H1, C_H2 and C_H3 for IgG. Complement activation is mediated via the C_H2 domain, while binding to macrophages or monocytes is mediated via the C_H3 domain. Binding of the Fc portion of IgG to phagocytic cells via their Fcγ receptors promotes phagocytosis of antibody–antigen complexes. Three receptors for human IgG exist. FcγRI (CD64) binds monomeric IgG with a high degree of affinity. FcγRII (CD32) is broadly distributed on cells and binds only complexed IgG with a low degree of affinity. FcγRIII (CD16) is expressed on macrophages, NK cells, and some T cells, and it interacts with both monomeric and complexed IgG. IgA binds only to the FcαR (CD89), while IgE can bind to three surface molecules: FcεRI, FcεRII (CD23), and the IgE-binding protein.

Immunoglobulin M

IgM is the major immunoglobulin produced in primary immune responses. With a size of ~900 Da, IgM is the largest immunoglobulin. IgM molecules are pentamers that contain one J chain in addition to light and heavy chains. Upon binding to its antigen, IgM induces agglutination and activates the classical complement pathway.

Immunoglobulin G

IgG is the most abundant immunoglobulin, accounting for ~75% of the total amount of serum immunoglobulin, and it is the major immunoglobulin of the secondary immune response. Four subclasses (IgG1, IgG2, IgG3, IgG4) are defined by the amino acid sequences of their constant region. They differ in their ability to activate complement. While IgG1 and IgG3 are potent activators of the classical complement pathway, IgG2 is less effective and IgG4 lacks such ability. In addition, IgG1 and IgG3 bind more avidly to mononuclear cells, i.e. they are more cytophilic. Most of the autoimmune dermatoses caused by autoantibodies are mediated by IgG, most often IgG4.

Immunoglobulin A

IgA is the predominant immunoglobulin present in mucosal surfaces, where it protects the host from invasion of microorganisms. IgA can activate the complement system via the alternative (but not the classical) pathway. Two subclasses of IgA exist, IgA1 and IgA2. IgA molecules can be joined by a J chain; this dimer form is mostly found in secretions, while in the serum, IgA circulates primarily as a monomer. IgA molecules can be involved in the pathogenesis of bullous autoimmune diseases.

Immunoglobulin E

IgE is the classic anaphylactic antibody that mediates most immediate allergic and anaphylactic reactions. Although in normal serum IgE is present in only small amounts (10–70 mcg/100 ml), just a few molecules appear to be required for sensitization. Mast cells and basophils express high-affinity receptors for the Fc portion of IgE (FcεRI). Antigens, anti-IgE antibodies, or other substances that cross-link at least two IgE molecules bound on mast cells induce the release of mediators such as histamine, serotonin, leukotrienes, and prostaglandins (see Ch. 18).

In addition to mast cells and basophils, several other cell types such as LCs[37], dermal DCs, and peripheral blood DCs can bind monomeric IgE via the high-affinity FcεRI[123]. Both quantitatively and qualitatively, FcεRI is the crucial serum IgE-binding structure on APCs of atopic individuals and functions as an allergen-focusing molecule. Allergens are more efficiently taken up, processed, and presented to T cells following targeting to APCs via the FcεRI. Thus, FcεRI-IgE-dependent allergen presentation may lower the threshold to elicit allergen-specific T cell responses in atopic individuals[115]. This may perpetuate allergen-specific IgE production and even modulate T cell-mediated delayed-type hypersensitivity reactions in allergen-exposed tissues.

The second IgE receptor, FcεRII (CD23), exhibits weaker binding affinity and is expressed on macrophages, eosinophils, platelets, and particular subtypes of T and B cells. Macrophages stimulated via activation of FcεRII exhibit increased phagocytic and cytotoxic activity; secrete prostaglandins, leukotrienes, and lysosomal enzymes; and generate superoxides.

Immunoglobulin D

The function of IgD is mysterious. Secreted IgD has a short half-life of 2–3 days and does not activate the complement system, but may recruit lectins[124]. More recent evidence suggests that IgD participates in respiratory immune defense[125]. It binds to basophils and mast cells, stimulating their production of antimicrobial factors. IgD may also exert proinflammatory functions, as illustrated by the hyperimmunoglobulinemia D with periodic fever syndrome (HIDS; see Table 45.2).

B cell activation

B cells can respond to some antigens in a T cell-*independent* manner[126]. Such antigens have numerous repeating epitopes (mainly polysaccharides), which bind and cross-link multiple B cell receptors and activate the B cells directly to secrete IgM. However, this response is limited to IgM and is of short duration and poor specificity due to the lack of germinal center formation, affinity maturation, Ig class switching, and memory.

Most B cell responses are activated in a T cell-*dependent* manner. Upon recognition by the specific IgM on the B cell surface, the antigen is internalized, processed, and re-expressed within the MHC class II molecule on the surface. As a result, the B cell can present the antigen to a specific T cell. Primed Th cells, in turn, secrete cytokines (IL-2, IL-4, IL-5, IL-6, IFN-γ) that function as B cell growth factors, inducing proliferation, isotype switch, and maturation to plasma cells. Activation of CD40 (expressed on B cells) by CD40 ligand (CD154; expressed on T cells) is needed for isotype switching from the initial IgM to an IgG response (Fig. 4.12). Once the switch from IgM to another isotype has occurred, some of the activated cells become long-lived memory cells

that can rapidly produce antibodies upon re-challenge with the same antigen. Mutations in the genes encoding CD40 ligand and CD40 are associated with forms of primary immunodeficiency known as hyper-IgM syndromes, which are characterized by low or undetectable levels of IgG, IgA, and IgE but elevated levels of IgM (see Ch. 60).

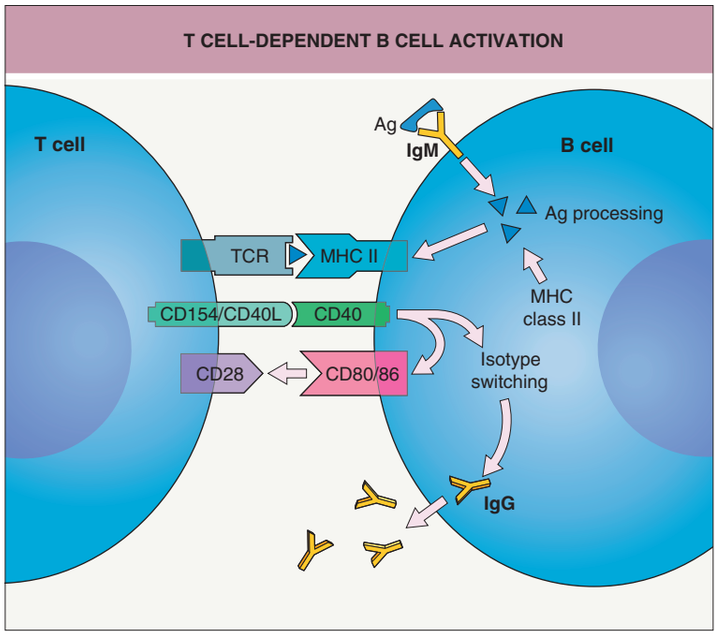


Fig. 4.12 T cell-dependent B cell activation. B cells present the antigen in association with MHC II molecules to $CD4^+$ T cells. This results in the upregulation of CD154/CD40 ligand which interacts with CD40 expressed on B cells. CD40–CD40 ligand interaction causes isotype switching of immunoglobulins and upregulation of CD80/86 which interacts with CD28 expressed on T cells. This results in further activation of T cells. Ag, antigen; CD40L, CD40 ligand; Ig, immunoglobulin; MHC II, major histocompatibility complex II.

Upon subsequent antigen exposure, B cells become activated by follicular DCs, which are located in the germinal centers of the lymph nodes. Follicular DCs bear Fc and complement receptors and bind immune complexes. In contrast to "conventional" DCs, follicular DCs do not endocytose and process antigens. Instead, they trap antigen–antibody complexes and provide intact antigen for interaction with the B cell receptor. This interaction stimulates B cell activation and differentiation. In addition, follicular DCs form immune complex-coated bodies (iccosomes) that are taken up by B cells. Upon processing, B cells present this follicular DC-derived antigen to T cells and thus may obtain T cell assistance[127].

Allergic Contact Hypersensitivity

Allergic contact hypersensitivity (CHS) is highly relevant for dermatologists, since it is the pathogenic basis for allergic contact dermatitis, a frequent inflammatory dermatosis. In addition, important basic immunologic discoveries have been made utilizing the model of CHS[128].

Induction of CHS

Most contact allergens are low-molecular-weight chemicals that, after penetrating the skin, have to couple with host proteins to be able to act as full antigens. This process is called haptenization, and the low-molecular-weight allergens are referred to as haptens. Upon epicutaneous application of a hapten in a naive host, APCs in the skin take up the hapten, migrate to the regional lymph nodes and present it to naive T cells (Fig. 4.13). Although this was previously thought to be done only by LCs, it has been established that other cutaneous APCs (e.g. dermal DCs) can present antigens, and the role of LCs as the primary APC in the skin is currently under debate (see Antigen presentation above).

During the emigration from the skin, APCs convert from a "resting" into an "activated" functional state. This process is initiated by keratinocytes, which secrete inflammatory cytokines as a result of hapten application; triggering of TLRs and direct effects of haptens on the APCs may also be involved. Furthermore, the inflammasomes within keratinocytes become activated by contact sensitizers resulting in the release of biologically active IL-1β and IL-18. It follows that

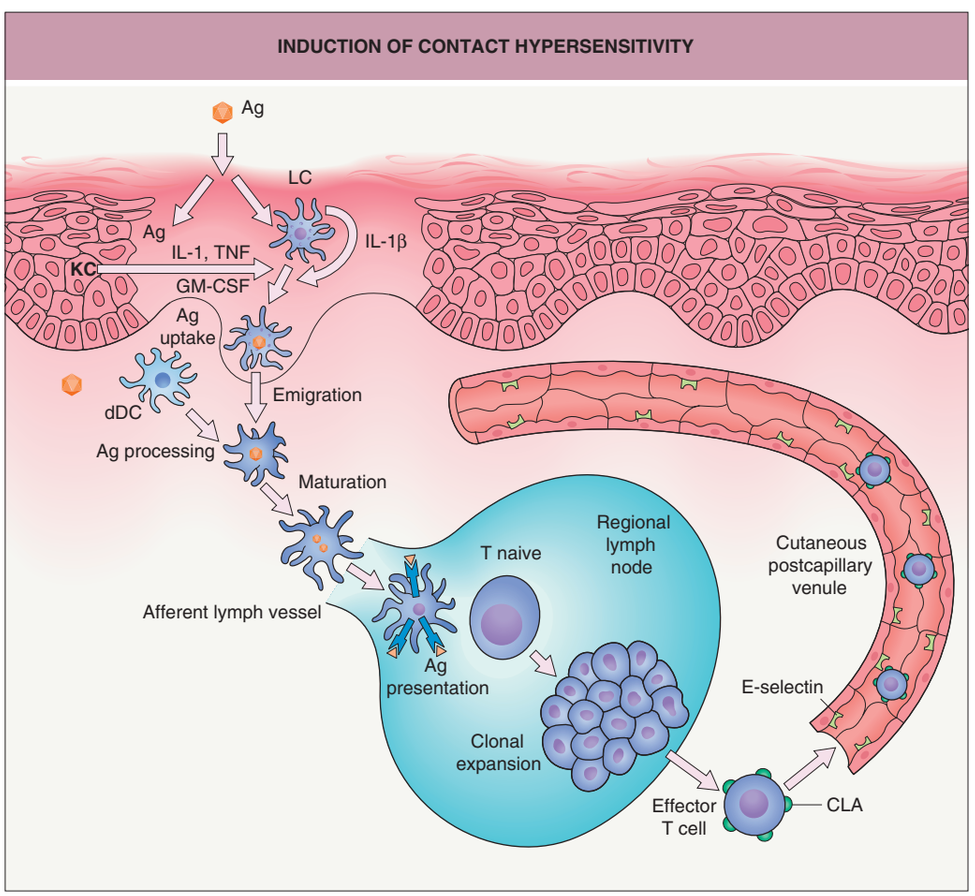


Fig. 4.13 Induction of contact hypersensitivity. Application of contact allergens (Ag) induces the release of cytokines by keratinocytes (KCs), Langerhans cells (LCs), and other cells within the skin. These cytokines in turn activate LCs and/or dermal dendritic cells (dDCs), which uptake the antigen and emigrate into the regional lymph nodes. During this process, they develop into mature antigen-presenting cells. In addition, the antigen is processed, re-expressed on the surface, and, finally, presented to naive T cells in the regional lymph node. Upon antigen presentation, T cells bearing the appropriate T cell receptor clonally expand and become effector T cells. These alter their migratory behavior due to the expression of specific surface molecules like cutaneous lymphocyte antigen (CLA). Effector T cells recirculate into the periphery, where they may later meet the antigen again.

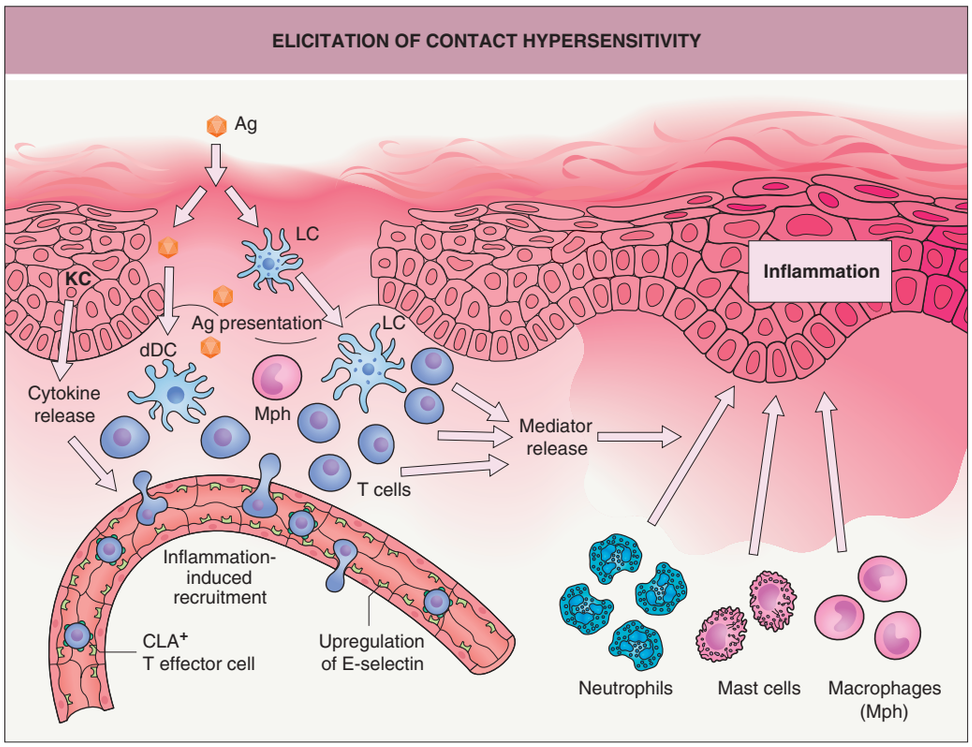


Fig. 4.14 Elicitation of contact hypersensitivity. Application of contact allergens (Ag) onto a sensitized individual causes the release of cytokines by keratinocytes (KCs) and Langerhans cells (LCs). These cytokines induce the expression of adhesion molecules and activation of endothelial cells, which ultimately attracts leukocytes to the site of antigen application. Among these cells, T effector cells are present, which are now activated upon antigen presentation either by LCs, dermal dendritic cells (dDCs), or infiltrating macrophages (Mphs). Antigen-specific T cell activation again induces the release of cytokines by T cells. This causes the attraction of other inflammatory cells, including granulocytes and macrophages, which ultimately cause the clinical manifestation of contact dermatitis. CLA, cutaneous lymphocyte antigen.

inflammasome-deficient mice (ASC- and NALP3-knockout mice) display an impaired response to contact allergens[129]. Induction of IL-1β appears to be specific for haptens, since it is not observed with irritants or tolerogens. In addition, other cytokines, including chemokines, TNF-α, and GM-CSF, may also contribute to APC activation and migration. Hence, the hapten itself, through its capacity to provoke a specific cytokine pattern, seems to be the initial trigger that activates APCs and induces sensitization (see Fig. 4.13).

Presentation of the hapten by APCs in the regional lymph nodes causes activation of naive T cells carrying the appropriate TCR and results in the generation of effector cells. In contrast to other types of delayed-type hypersensitivity responses, which are mediated by $CD4^+$ T cells, most haptens induce a T cell response of predominantly $CD8^+$ effector T cells[128]. In addition, Treg populations that inhibit the CHS response are induced. The balance between effector T cells and Tregs seems to depend on the dose of the antigen applied, since application of extremely low doses of the hapten does not result in sensitization, but rather in tolerance[97].

Elicitation of CHS

T cells that have been primed in the draining cutaneous lymph nodes express the skin-homing marker CLA and thereby exhibit the capacity to enter the skin[77]. These T cells become activated when they encounter their relevant hapten presented by APCs within the skin. However, in contrast to the sensitization phase, antigen presentation can now be effectively performed by other cells (including keratinocytes, dermal mast cells, and macrophages) that are capable of presenting antigen at least in a MHC class I-restricted fashion[128]. Alternatively, inflammatory cells that infiltrate the site of hapten application very early during the response may function as APCs.

The earliest histopathologic findings during a CHS response are mast cell degranulation, vasodilation, and an influx of neutrophils, which is followed by infiltration of monocytes and T cells (Fig. 4.14). However, the pathophysiologic events that result in allergic contact dermatitis are clearly T cell-dependent, since T cell-deficient mice are unable to mount a CHS response. Furthermore, low doses of hapten that are sufficient to stimulate hapten-specific T cells are insufficient to elicit a CHS response. This indicates that the elicitation of a CHS response requires, in addition to hapten-specific recognition, a proinflammatory stimulus that can be provided in a dose-dependent manner by the hapten itself[130].

Additional figure available in our eBook (see inside front cover for access code).

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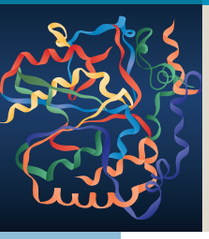
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eFig. 4.1 Electron microscopic picture of a Langerhans cell. Arrows indicate the Birbeck granules, rod-shaped organelles specific for Langerhans cells. They are said to resemble tennis rackets. *Courtesy N. Romani, Department of Dermatology, University of Innsbruck.*



5 Cutaneous Neurophysiology

Gil Yosipovitch and Brian Kim

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Key features

- At least three subsets of pruriceptive C neurons exist that respond to histamine or other pruritogens and then activate distinct spinothalamic and spinoparabrachial tract neurons
- Peripheral itch mediators include histamine, proteases, and multiple interleukins
- Central itch mediators include opioids, gastrin-releasing peptide, and B-type natriuretic peptide
- There is an overlap between chronic itch and chronic pain, including activation of multiple brain areas and associated neuromediators and receptors, e.g. nerve growth factor, neurotrophin 4, transient receptor potential (TRP) channels
- Cross-talk between cutaneous nerve fibers and the stratum corneum is a possible mechanism for the pruritus associated with impaired barrier function (e.g. xerosis, atopic dermatitis)
- Therapies with topical and systemic drugs that reduce itch sensitization by counteracting the responsible mediators represent promising treatment strategies

INTRODUCTION

The skin contains a network of highly specialized *afferent* sensory nerves that convey sensations such as pain, itch, temperature, and touch (Table 5.1). In addition, peptidergic nerve fibers release neuropeptides such as substance P, calcitonin gene related peptide (CGRP), nerve growth factor (NGF), and other neurotrophins whose effects include immune modulation. Because pruritus is largely restricted to the skin, the latter represents the major target organ of somatosensation.

Pruritus (itch) is the dominant symptom of many cutaneous diseases and is mediated by sensory nerves traditionally classified as non-peptidergic (NP). Although itch elicits scratching via a reflex arc, it is actually multidimensional with cognitive, evaluative, and motivational components. Pruritus can also occur in association with systemic diseases (e.g. chronic kidney disease, cholestasis; see Ch. 6), psychiatric conditions (see Ch. 7), and damage to nerve fibers.

The link between itch and scratching is so close that in some languages the same word refers to both itch and scratch. Although similarities to pain exist, itch is distinct – pain elicits a reflex withdrawal, whereas itch leads to a scratching response[1]. Despite being an extremely common complaint that is highly conserved across species, medical science is still struggling to understand the mechanisms of itch and how it can be inhibited.

PRURITUS PATHWAYS

The neurophysiology of itch involves specific itch mediators and nerve fibers that transmit itch both peripherally and centrally[2]. While the concept of pruritus as a sensory modality separate from pain was not generally appreciated until the mid-twentieth century, studies have clearly identified individual histaminergic and non-histaminergic C fibers that uniquely transmit itch[3]. C fibers that transmit itch have exceptionally slow conduction velocities (0.3–1.0 m/second) and innervate unusually wide territories.

Histamine-sensitive C fibers are sensitive to heat as well as pruritogenic stimuli but generally not to mechanical stimuli; in contrast, the vast majority of other C fibers, while sensitive to heat stimuli, have little or no response to histamine[3]. The co-responsiveness of itch-transmitting C fibers to temperature explains aggravation of pruritus in a warm environment. However, the ineffectiveness of oral antihistamines for most types of pruritus suggests that other fibers play important roles in itch sensation[4].

Indeed, distinct parallel pathways of *non-histaminergic C fibers* that transmit itch have been identified in the peripheral nervous system of humans and the spinothalamic tract of other primates[4,5]. Itch transmission can be elicited by spicules of the tropical legume cowhage (*Mucuna pruriens*), which produce an intense itch when rubbed, inserted, or injected into the skin, without producing a histaminergic axon reflex[5]. Cowhage spicules induce itch via release of the protease mucunain, which activates proteinase-activated receptor (PAR)-2 and PAR-4[6]. Cowhage-sensitive fibers transmit a burning sensation together with itch and are also sensitive to mechanical and other stimuli. PAR-2 receptors have been implicated in itch associated with atopic dermatitis[7] (see Ch. 12). The non-histaminergic, polymodal C fibers stimulated by mucunain may also have clinical relevance in chronic itch. In addition to C fibers, A-delta fibers contribute to cowhage-evoked itch with a more rapid onset[8].

MAS-related G protein-coupled receptor D (MRGPRD) is a β-alanine receptor that is exclusively expressed by a subset of pruriceptive C fibers classified as type 1 non-peptidergic (NP1) neurons. Similarly, the pharmacologic pruritogen chloroquine directly activates NP2 (type 2) neurons, whereas the Th2 cytokine IL-31 elicits itch via NP3 (type 3) neurons[9]. Collectively, recent studies suggest that a variety of sensory neurons respond to different itch stimuli via distinct pathways, explaining why there are so many types of itch.

Within the spinal cord, there is another layer of itch circuitry where signals from the skin are integrated and the perception of itch is then relayed to the brain. The first itch-specific receptor to be identified, gastrin-releasing peptide receptor (GRPR), is found in the spinal cord and represents a key downstream mediator of non-histaminergic itch responses. Overexpression of gastrin-releasing peptide (GRP) in cutaneous nerve fibers and GRPR in the spinal cord has been observed in mice and primates with chronic itch. B-type natriuretic peptide, an itch-selective neuropeptide found in dorsal root ganglia neurons, is believed to act upstream of the GRPR itch spinal circuit. Substance P is also expressed by a distinct population of murine dorsal horn neurons that respond to pruritic and noxious stimuli[9,10].

The perceived sensation of pruritus can vary greatly in quality. Patients may describe burning, pricking, "insects crawling" on the skin, or even a tickle, but the neurophysiologic and psychologic correlates of these qualitative differences have not yet been elucidated. However, information obtained from itch questionnaires has enabled a better understanding of the different characteristics of itch and its features in various skin diseases[11].

Central Pathways to Higher Nervous System Centers

In the spinal cord, pruriceptive C fibers synapse with secondary sensory neurons in the gray matter of the dorsal horn (Fig. 5.1). These neurons then cross over and ascend in the lateral spinothalamic tract to the

PRIMARY AFFERENT NEURONS THAT INNERVATE THE SKIN				
Fiber	**Diameter**	**Myelination**	**Conduction velocity**	**Responds to**
A-beta (Aβ)	Large	+	>30 m/s	Light touch Moving stimuli
A-delta (Aδ)	Small	+	2–30 m/s	Pain (nociceptors) Itch, cowhage-sensitive* Thermal Mechanical
C	Small	–	<2 m/s	Pain (nociceptors) Itch†, histamine-sensitive‡ Itch†, cowhage-sensitive* Itch†, NP2 neurons: chloroquine, BAM8-22 Itch†, NP3 neurons: interleukin-31, leukotriene C_4 Thermal‡ Mechanical

*Transmit pruritus accompanied by a burning sensation; also sensitive to mechanical stimuli.
†~5% of total C fibers transmit itch.
‡Separate C fibers carry both pruritogenic and thermal stimuli, but not mechanical stimuli.

Table 5.1 Primary afferent neurons that innervate the skin. BAM8-22, bovine adrenal medulla 8-22 protein; NP2/3, non-peptidergic 2/3.

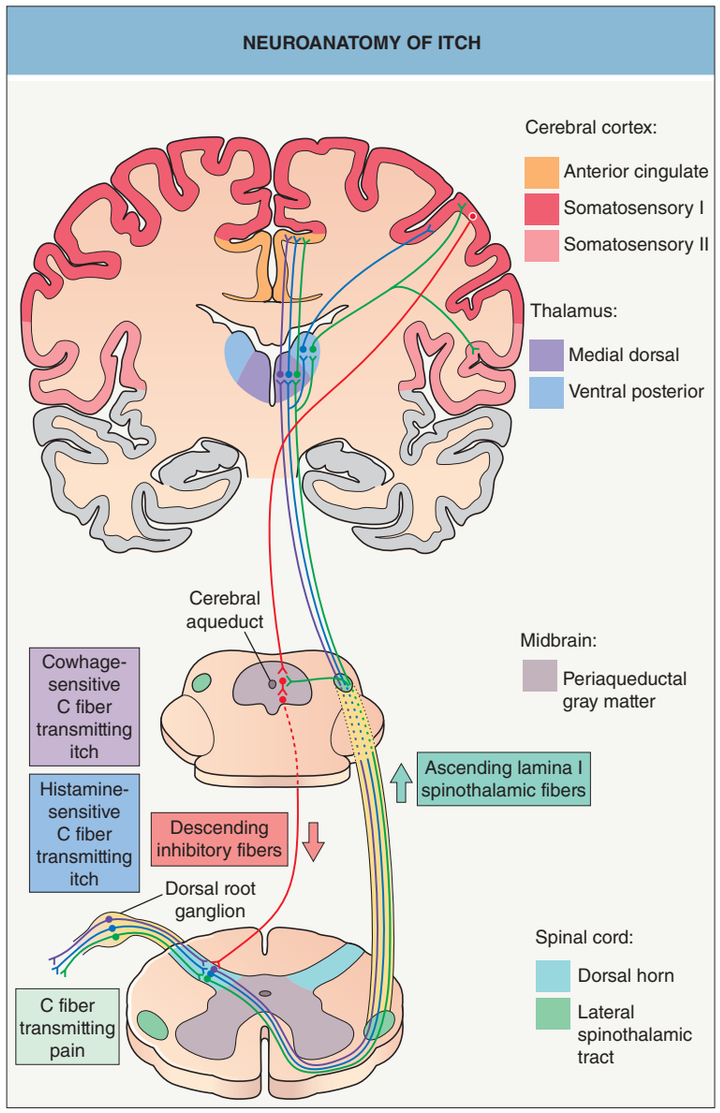


Fig. 5.1 Neuroanatomy of itch. Itch and pain transmission occur via unmyelinated C nerve fibers that excite lamina I neurons in the dorsal horn of the spinal cord. Two subsets of pruritoceptive C-fiber neurons (which respond to histamine and cowhage, respectively) are conducted through distinct lateral spinothalamic pathways, with projections to the thalamus. Processing of itch through either pathway activates several regions of the brain, which are similar to those involved in pain (see Table 5.4). Concomitant painful stimuli can reduce the sensation of itch, possibly by a descending inhibitory mechanism resulting from activation of the periaqueductal gray matter. In mice, gastrin-releasing peptide receptor-positive neurons transmit itch (but not pain) within the spinal cord; the role of such neurons in humans remains to be determined. *Adapted from Yosipovitch G. Pruritus: an update. Curr Probl Dermatol 2003;15:137–64.*

thalamus. *In vivo* studies using extracellular recordings from cats identified a subclass of lamina I spinothalamic tract neurons that are excited by iontophoretically administered histamine[12]. Neurophysiologic experiments in primates found that cowhage-induced itch stimulates a distinct population of spinothalamic tract neurons that are not involved in the transmission of histamine-mediated itch (see above)[13]. Studies in humans utilizing functional MRI or positron emission tomography (PET) have shown that histamine and cowhage activate different brain areas, providing insight into the supraspinal processing of itch[14].

In healthy individuals, induction of itch by either histamine or cowhage can elicit activation of various regions, including the anterior and posterior cingulate cortex, precuneus, somatosensory areas I and II, supramarginal gyrus, inferior parietal lobe, and insula–claustrum complex. The activation of multiple brain areas argues against a single "itch center" and underscores the multidimensionality of the itch sensation. Of note, pain shows a similar pattern of brain activation across cortical regions[15] (see Fig. 5.1). In mice, optogenetic studies, in which expression of light-induced proteins within neuronal cell membranes is measured, detected a spinoparabrachial pathway that sends itch signals to the parabrachial nucleus of the brain stem[16].

Seeing other people scratching can trigger itch and atopic dermatitis patients experience increased itch when exposed to visual stimuli[17]. Studies utilizing functional MRI showed that "contagious itch" activates many of the neural regions linked to the physical perception of itch[18]. In mice, the suprachiasmatic nucleus is a key visual organ that mediates contagious scratching behavior[19].

In addition to inhibiting activation of the cingulate cortex, scratching has been found to activate the prefrontal cortex and cerebellum. It is possible that the cerebellum plays a role in coordinating the itch–scratch cycle[20,21]. Scratching inhibits histamine-evoked activity of spinothalamic neurons in primates, but not spontaneous or pain-triggered activity[22]. Scratching also activates areas of the brain involved in reward processing, including the striatum and substantia nigra. While these responses correlate with the pleasure of scratching, activation of other areas is associated with itch relief[23].

Pruritus Receptor Units

Removal of the epidermis largely abolishes the perception of itch. Light microscopic and ultrastructural studies of human skin have shown the existence of intraepidermal nerve fibers with "free" non-specialized nerve endings extending to the stratum granulosum. A subclass of C fibers in the epidermis that express MRGPRs, in particular MRGPRX1, are involved in chloroquine-induced pruritus (see Fig. 5.2F)[24]. Cathepsin S, an endogenous protease, can cleave and thereby activate MRGPRX2 (murine MrgprC11), which leads to scratching behavior, as well as PAR-2/4 receptors[25].

Keratinocytes express a variety of neural mediators and receptors involved in the sensation of itch (Table 5.2). These include opioids, proteases, substance P, NGF, and neurotrophin 4 in addition to their respective receptors, including μ- and κ-opioid receptors, PAR-2, neurotrophic tyrosine kinase receptor type 1 (NTRK1), and transient receptor potential vanilloid ion channels (particularly TRPV1 and TRPV3). Keratinocytes also have ATP-gated ion channels and adenosine receptor ligands similar to those observed in C fibers involved in pain transmission. These structural similarities to nerve fibers suggest that keratinocytes may be involved in the transduction and generation of itch.

MAJOR MEDIATORS OF PRURITUS: RELATIVE POTENCIES WITH REGARD TO PRURITUS AND PAIN		
Mediator	**Pruritus**	**Pain**
Primary mediators		
Histamine	+++*	+*
Tryptase (protease)	+++	+
Cathepsin S (protease)	+++	?
Gastrin-releasing peptide (GRP)	+++	–
Brain natriuretic peptide (BNP)	+++	–
Leukotriene C_4	+++	?
Interleukin-31	+++	?
Interleukin-33	++	?
Interleukin-4 and -13	+	?
Periostin (binds αVβ3 integrin)	++	?
Secondary mediators		
Prostaglandin $E_{1,2}$	+†	+
Substance P‡	++	+
μ-Opioid receptor agonists	++	–
Nerve growth factor (NGF)	+	++
Kallikrein 7	+++	?
Interleukin-2	+++	+/–
Interleukin-4 and -13	++	?

*Superficial (intraepidermal) injection of histamine causes pruritus; deep dermal injection causes pain.
†Lowers threshold to pruritus induced by other mediators.
‡Actions partly due to histamine release from mast cells.

Table 5.2 Major mediators of pruritus: relative potencies with regard to pruritus and pain. +/–, little or no activity; +, weak activity; ++, moderately active; +++, highly active; –, no activity.

MEDIATORS OF PRURITUS

Various mediators that act centrally and/or peripherally are involved in pruritus, including histamine, proteases, substance P, opiates, NGF, and prostaglandins (Fig. 5.2A). In inflammatory skin diseases, proinflammatory mediators produce pruritus and other signs of inflammation, in particular erythema due to vasodilation and edema from increased vascular permeability. However, cytokines and other inflammatory mediators can also act directly on sensory neurons to influence itch sensation[9]. The relative potencies of the major mediators are listed in Table 5.2.

Histamine

Histamine is the archetypal mediator of inflammation, including pruritus. In the skin, histamine is contained primarily within the granules of dermal mast cells. Histamine can be released from mast cells upon activation of a range of receptors, including the high-affinity IgE receptor (FcεRI), the KIT receptor, MRGPRX2, and receptors for various neuropeptides (e.g. NGF) and complement C5a[9]. In IgE-mediated acute urticaria, histamine is released when a specific antigen/allergen cross-links adjacent receptor-bound specific IgE antibodies on mast cells. In autoimmune chronic urticaria, similar cross-linking occurs via functional circulating IgG that react with epitopes expressed on the α-chain of adjacent FcεRIs or less commonly anti-IgE autoantibodies (see Fig. 18.3). Histologically, dermal mast cells and unmyelinated neurons are juxtaposed (Fig. 5.2B,C,E), indicating a close ("synapse-like") functional relationship between the immune and nervous systems. However, evidence for histamine as the main mediator of pruritus is limited to a few skin diseases, including acute and chronic urticaria and mastocytosis.

Recognition of the histamine H4 receptor has expanded our understanding of the physiologic actions of histamine beyond the traditional H1 receptor. The H4 receptor is expressed by neurons and immune cells such as eosinophils, mast cells, dendritic cells, monocytes, and $CD8^+$ T cells. It mediates chemotaxis and plays a role in the inflammation and pruritus of atopic dermatitis. H4 antagonists are under development and have been shown to alleviate experimental pruritus. In animal models of itch, the effects of H4 antagonists are synergistic with those of centrally acting H1 antihistamines (e.g. diphenhydramine)[26,27].

Gastrin-Releasing Peptide

As noted above, itch-specific GRPR-positive neurons have been identified in the dorsal horn of the spinal cord in mice[28]. Although named for its role in regulating gastrointestinal functions, gastrin-releasing peptide (GRP) is expressed in many tissues. Whether peripheral sensory neurons express GRP is still debated[9].

B-Type Natriuretic Peptide

B-type natriuretic peptide (BNP; natriuretic polypeptide B) is a 32-amino acid peptide that is secreted by the cardiac ventricles to regulate blood pressure and fluid balance. BNP is also expressed by a subset of C fibers and may function in itch transmission in the spinal cord[9].

Proteases

Mast cells produce two proteases, tryptase and chymase. Tryptase, released by activated mast cells, cleaves PAR-2, a G protein-coupled receptor present on C-fiber terminals (Fig. 5.2B,D); this exposes a tethered ligand domain and thereby "self-activates" PAR-2, leading to itch transmission. Tryptase levels are increased four-fold in non-lesional forearm skin of atopic dermatitis patients, while expression of PAR-2 is significantly increased in the epidermis and cutaneous nerve fibers of eczematous lesions and to a lesser degree in non-lesional skin.

Kallikreins and cathepsins can also activate PAR-2 via their protease activity. In addition, kallikrein 7, which does not activate PAR-2, triggers itch in the setting of atopic dermatitis-like disease in mice and is enriched in lesional human atopic dermatitis skin[29]. Cathepsin S can evoke itch by cleaving and thereby activating MRGPRX2 as well as PAR-2 (see above). Furthermore, proteases such as cathepsin B can be found in common allergens (e.g. grass pollen, house dust mites), and *Staphylococcus aureus* can induce secretion of proteases; both of these exogenous factors are known to aggravate atopic dermatitis and itch[30].

Transgenic mice overexpressing various serine proteases exhibit severe itch and scratching (Table 5.3). In Netherton syndrome, serine protease inhibitor deficiency leads to excess epidermal protease activity, resulting in pruritus and atopic manifestations (see Ch. 57). These observations demonstrate that interactions between proteases and receptors on C fibers play key roles in itch.

Opioid Peptides

Central pruritus, which involves pruritic mediators within the CNS, can occur in both cutaneous and systemic diseases. Endogenous opioids modify the perception of pruritus via central and peripheral opioid receptors. Generalized pruritus may be induced by an imbalance between the μ- and κ-opioid systems, activation of which stimulates and inhibits itch perception, respectively[31]. κ-Opioid receptor agonists can act within the skin, spinal cord, and brain to reduce itch and are utilized as therapies for chronic pruritus[32,33].

Morphine as well as other exogenous and endogenous μ-opioid receptor agonists may cause generalized pruritus. Morphine also produces local pruritus and erythema when injected intradermally; this response is only partially inhibited by the μ-opioid receptor antagonist naloxone but is substantially inhibited by topical pretreatment with the H1 antihistamine doxepin, indicating the ability of morphine to activate mast cells[34]. Therefore, two possible mechanisms for opioid-induced itch are: (1) degranulation of cutaneous mast cells[35]; and (2) activation of μ-opioid receptors with direct central and peripheral pruritogenic effects[32,33].

Substance P

Substance P, a neuropeptide with a widespread distribution in peripheral nerves and the CNS, is involved in itch perception. Substance P is

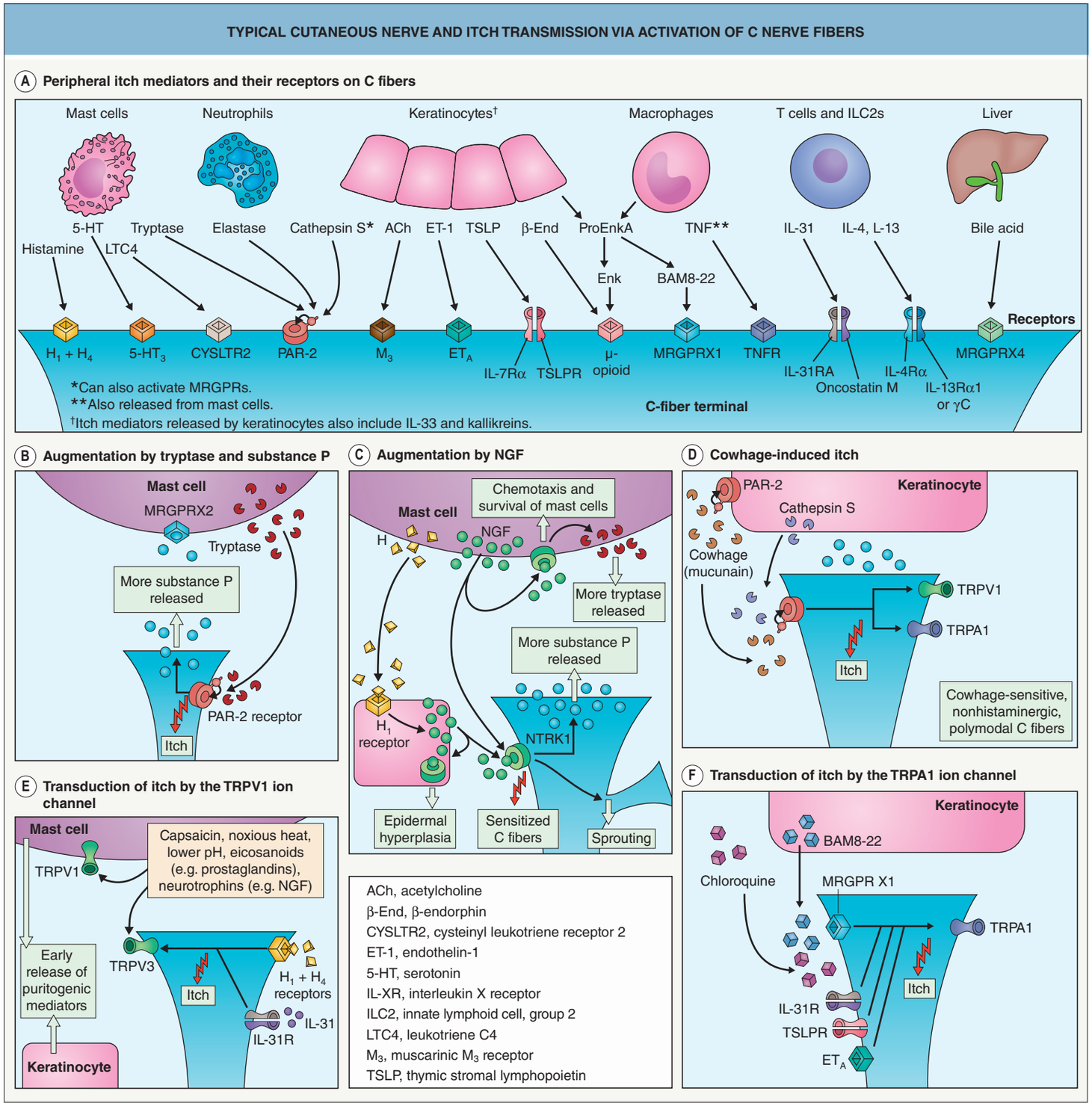


Fig. 5.2 Typical cutaneous nerve and itch transmission via activation of C nerve fibers. There are two categories of axons in a typical cutaneous nerve: (1) primary afferent Aβ, Aδ, and C fibers with cell bodies in dorsal root ganglia; and (2) sympathetic postganglionic fibers with cell bodies in sympathetic ganglia. Separate C fibers (~5% of the total) carry pruritogenic stimuli via two pathways: (1) *histamine-induced itch* that is transmitted by mechanically insensitive, capsaicin-sensitive fibers via the *t*ransient *r*eceptor *p*otential *v*anilloid receptor 1 (TRPV1); and (2) *cowhage (mucunain)-induced itch* accompanied by a burning sensation that is transmitted by polymodal fibers sensitive to both capsaicin and mechanical stimuli. **A** Peripheral itch mediators released by immune cells, keratinocytes, and the liver activate pruriceptors on C-fiber terminals in the skin. For example, activated mast cells release histamine, which triggers itch via histamine H1 and H4 receptors on histamine-sensitive C fibers. Proteases such as tryptase, elastase, and cathepsin S can cleave proteinase-activated receptor-2 (PAR-2), exposing a tethered ligand and thereby resulting in "self-activation". Proenkephalin A (ProEnkA) may be cleaved to form enkephalin (ENK) or bovine adrenal medulla 8-22 peptide (BAM8-22). **B** Self-activation of PAR-2 following tryptase cleavage results in transmission of itch by the C fibers as well as release of additional substance P, which primes mast cells via neurokinin-1 receptors (NK1Rs). **C** Nerve growth factor (NGF) released by mast cells and keratinocytes (with NGF production stimulated by histamine [H]) activates neurotrophic tyrosine kinase receptor type 1 (NTRK1 [TRKA]) on C fibers, mast cells, and keratinocytes. This induces C fiber sprouting, sensitization to cowhage-induced itch, and increased substance P release; mast cell chemotaxis, survival, and increased tryptase release; and epidermal hyperplasia. **D** Cowhage-induced itch occurs through the release of mucunain, a protease that activates PAR-2 and PAR-4 receptors (the latter not yet identified in the skin); these receptors can also be activated by endogenous proteases such as cathepsin S as well as tryptase. Activation of PAR-2/4 sensitizes TRPV1 and TRP ankyrin 1 (TRPA1) channels, resulting in cross-talk and itch transmission. **E** Activation of H1/H4 receptors and the IL-31 receptor (IL-31R) heterodimer leads to membrane depolarization of C fibers via TRPV1, which is required for transduction of histamine-induced itch. The TRPV1 ion channel on C fibers, keratinocytes, and mast cells can also be activated by capsaicin, heat, low pH, eicosanoids, and neurotrophins; although this initially stimulates transmission of itch and release of pruritogenic mediators, it may eventually lead to desensitization, neuropeptide depletion, and attenuation of itch. **F** C fibers (including those responsive to histamine) in the epidermis express MAS-related G protein-coupled receptors (MRGPRs), which can be activated by chloroquine, BAM8-22, and cathepsin S. TRPA1 is involved in transduction of itch by MRGPRs as well as other pruriceptors, including the IL-31R, thymic stromal lymphopoietin receptor (TSLPR) heterodimer, and endothelin type A receptor (ET_A).

MURINE MODELS OF ITCH		
Model	**Clinical and laboratory features**	**Pathogenesis/comments**
Transgenic mice overexpressing PAR-2	Epidermal hyperplasia and scaling as well as pruritus and scratching	
Transgenic mice overexpressing a serine protease	Pruritus and scratching	
TRPV1-deficient mice and Pirt-deficient mice	Lack of response to pruritogens	Pirt normally plays an important role in sensing itch (histaminergic and non-histaminergic) as well as pain via TRPV1 channels (and also TRPV1-independent itch)
Mrgpr-deficient mice and TRPA1-deficient mice	Lack of scratching response to chloroquine and BAM8-22, but preserved response to histamine	Mrgprs are normally activated by chloroquine and BAM8-22, so the lack of response in TRPA1-deficient mice implicates this receptor in downstream signaling
GRPR-deficient mice	Lack scratching response to pruritogens, but preserved response to painful stimuli	GRPR is expressed in the dorsal spinal cord
Bhlhb5-deficient mice	Enhanced scratching response to pruritogens	Selective loss of inhibitory interneurons in the dorsal horn that regulate pruritus
μ-Opioid receptor-deficient mice	Thinner epidermis, higher density of epidermal nerve endings, and less scratching after induction of dry skin	
Transgenic mice overexpressing interleukin-31	Pruritus, scratching, excoriations and alopecia	

Table 5.3 Murine models of itch. Bhlhb5, basic helix-loop-helix family member B5; GRPR, gastrin-releasing peptide receptor; Mrgpr, Mas-related G protein-coupled receptors; PAR-2, protease-activated receptor 2; Pirt, phosphoinositide-interacting regulator of transient receptor potential channels; TRPV1, transient receptor potential vanilloid 1.

synthesized in the cell bodies of C neurons, transported towards the peripheral nerve terminals, and released by antidromic depolarization to cause vasodilation and increased vascular permeability. High concentrations of substance P can cause immediate mast cell degranulation via MRGPRX2 receptors, whereas low concentrations specifically activate neurokinin-1 (NK-1) receptors on mast cells, leading to sensitization of these cells and increased production of tumor necrosis factor (TNF; Fig. 5.2B)[36].

Direct activation of mast cells by substance P triggers itch transmission[37,38]. When injected intradermally, it provokes neurogenic inflammation, including erythema and the wheal-and-flare reaction, in addition to itch. Levels of substance P in the serum of patients with atopic dermatitis are elevated and correlate with disease severity[39].

Neurotrophins

Neurotrophins are factors that regulate the growth and function of neurons. Members of this family include the prototypic nerve growth factor (NGF) as well as brain-derived neurotrophic factor (BDNF) and neurotrophins 3, 4, and 5[40]. Increased levels of epidermal NGF correlate with proliferation of terminal cutaneous nerves and upregulated expression of neuropeptides such as substance P[41]. NGF can also induce sprouting of nerve fibers, sensitization of nerve endings, and axonal transport in dorsal root ganglia cells (Fig. 5.2C)[42].

Keratinocytes express high levels of NGF, which is not only required for survival and regeneration of sensory neurons but also controls the responsiveness of neurons to external stimuli[43,44]. NGF is thought to act as a signaling molecule between mast cells and keratinocytes in allergic skin diseases. Mast cell-derived histamine induces keratinocytes to increase NGF production, and the latter may promote infiltration of mast cells into inflamed skin. Patients with atopic dermatitis and psoriasis have increased expression of NGF in cutaneous mast cells, keratinocytes, and fibroblasts[45,46]. Upregulation of other neurotrophins, such as neurotrophin 4, has also been observed in keratinocytes from atopic dermatitis patients[47].

Prostanoids and Leukotrienes

Prostaglandins are the products of the conversion of arachidonic acid by cyclooxygenase-1 (COX-1) or 2 (COX-2), and they enhance histamine-induced itch[48,49]. When injected into the dermis, prostaglandin E_1 (PGE_1) is not itself pruritogenic but enhances pruritus due to histamine subsequently injected into the same site[50]. It appears that only itch-mediating neurons that display lasting activation following exposure to histamine are excited by PGE_2, and mechanosensitive fibers are unresponsive to both histamine and PGE_2. PGE_2 has also been shown to have a direct, low-level pruritogenic effect in both atopic dermatitis patients and unaffected individuals without inducing protein extravasation. This suggests that prostanoids' peripheral action is not solely via histamine and that prostanoids may potentiate pruritus via other effects on nerve fibers. Although oral administration of aspirin, a cyclooxygenase inhibitor, does not generally ameliorate pruritus, topical application of aspirin may reduce chronic localized itch[50].

The role of other eicosanoids, including leukotrienes and 12-hydroxyeicosatetraenoic acid (12-HETE), in the pathogenesis of pruritus is unclear. In mice, leukotriene B_4 can provoke scratching and may be involved in skin disease-related itch[51]. More recent studies have shown that basophil- and mast cell-derived leukotriene C_4 directly activates NP3 neurons and acts as a pruritogen in acute itch flares of atopic dermatitis[52,53,53a].

Mediators That Activate Transient Receptor Potential Receptors

Neuromediators that activate ion channels in the *t*ransient *r*eceptor *p*otential (TRP) family are also involved in the sensation of itch. TRP vanilloid 1 (TRPV1) is located on C fibers (see Fig. 5.2E) and is activated by capsaicin, endogenous substances such as cannabinoids (e.g. anandamide), prostaglandins, neurotrophins, a lower pH, and temperatures >43°C (109°F). TRPV1-expressing C nerve fibers can mediate heat pain and they house many pruriceptors. In addition, experimental induction of histamine-mediated itch requires cooperation of TRPV1 ion channels[54]. Stimulation of TRPV1-positive nerve fibers also leads to the release of pruritoceptive mediators such as neuropeptides.

TRPV3 is a thermosensor of warmth (>33°C, 91°F) that is expressed in keratinocytes and dorsal root ganglion neurons. Gain-of-function missense mutations in *TRPV3* result in chronic itch, scratching, and an atopic-like dermatitis in mice and Olmsted syndrome in humans. The latter features pruritus as well as palmoplantar keratoderma and periorificial hyperkeratosis (see Ch. 58)[55]. PAR2 can induce itch via TRPV3 signaling in keratinocytes, and enhanced thermal sensitivity of TRPV3 in keratinocytes plays a role in heat-induced release of pruritogens such as thymic stromal lymphopoietin (TSLP), NGF, and PGE_2 in patients

with atopic dermatitis[56,57]. Intradermal injection of citrusinine-II, a plant-based TRPV3 inhibitor, was recently shown to attenuate itch in mouse models[58]. In contrast, TRP melastatin 8 (TRPM8) on C nerve fibers functions as a thermosensor of cool temperatures (<28°C, 82°F) and is activated by menthol and icilin, which provide a "cooling" sensation that may relieve itch.

TRP ankyrin 1 (TRPA1), a polymodal ion channel, functions as a downstream mediator of histamine-independent itch stimulated by MRGPRs in a subset of epidermal C fibers[59]. TRPA1 can be activated directly by menthol as well as via pruriceptors such as the TSLP receptor subunit[60] (see Fig. 5.2F).

Other Peripheral Mediators of Itch

Other neurotransmitters

Intradermal injection of acetylcholine, an important neurotransmitter in the autonomic nervous system, typically induces pain; however, in patients with chronic pruritus, it can induce itch. Activation of the muscarinic receptor 3 triggers itch in mice[61]. Norepinephrine, a catecholamine neurotransmitter, exerts tonic inhibition of itch signaling in the spinal cord[62]. Although serotonin can induce itch in mice, in humans it is a very mild pruritogen. Currently there are no data regarding the role of epinephrine or dopamine in itch transmission.

Other mediators with potential roles in itch

Nitric oxide may induce itch via neurogenic inflammation[63]. The bovine adrenal medulla 8-22 (BAM8-22) peptide, a proteolytically cleaved product of proenkephalin A, is a potent activator of MRGPRs and can stimulate itch, usually accompanied by a stinging or burning sensation (see Fig. 5.2F)[64]. Chloroquine can also induce itch by activating MRGPRs, which are expressed by a subset of C fibers in the epidermis.

Immune Cells as Itch Mediators and Modulators

Interactions between the nervous and immune systems in the skin play important roles in itch induction. Neuropeptides such as substance P, CGRP, and vasoactive intestinal peptide, which are released from cutaneous sensory nerves, regulate the expression of adhesion molecules and proinflammatory cytokines, thereby modulating immune and inflammatory responses[9]. These neuropeptides also influence cell proliferation and differentiation, tissue repair, and antigen presentation involving keratinocytes, mast cells, dermal microvascular endothelial cells, and Langerhans cells. These interactions are bidirectional, as cytokines and chemokines also regulate primary nerve afferents via receptor activation.

IL-31 is produced by Th2 cells and belongs to the IL-6 family. It induces pruritus by modulating the function of sensory neurons[65]. The IL-31 receptor (IL-31R) is a heterodimer composed of the oncostatin M receptor (OSMR) β protein plus the IL-31 receptor A (IL-31RA). The IL-31R is found on TRPV1$^+$/ TRPA1$^+$ cutaneous C fibers and in dorsal root ganglia.

Signaling via either the IL-31R or OSMR, a heterodimer composed of the OSMR β protein and a gp130 subunit, can result in cutaneous inflammation as well as keratinocyte proliferation, differentiation, and apoptosis. Mutations in the gene encoding the OSMR β protein underlie *familial primary localized cutaneous amyloidosis*, an autosomal dominant disorder characterized by chronic localized itching and scratching that results in deposition of keratin-derived amyloid in the dermis[66]. Of note, increased levels of IL-31 are found in the skin of patients with atopic dermatitis, prurigo nodularis, and cutaneous T cell lymphoma. In randomized controlled trials, nemolizumab, an anti-IL-31RA monoclonal antibody, reduced itch and skin lesions in patients with atopic dermatitis and prurigo nodularis. Vixarelimab, an anti-OSMRβ monoclonal antibody, is currently under investigation as a therapy for prurigo nodularis and other chronic pruritic skin conditions.

Thymic stromal lymphopoietin (TSLP) is produced by keratinocytes and promotes Th2 cell-associated responses. TSLP acts directly on TRPA1-expressing neurons to elicit itch in mice[60], and TSLP expression is increased within lesions of atopic dermatitis.

IL-4 and ***IL-13*** produced by Th2 cells contribute to the itch of atopic dermatitis via activation of JAK (Janus kinase)/STAT (signal transducer and activator of transcription) signaling cascades in sensory neurons[67]. In addition to reducing itch in patients with atopic dermatitis, both JAK inhibitors and monoclonal antibodies that target IL-4/-13 signaling (e.g. dupilumab, tralokinumab, lebrikizumab) lead to improvement of other chronic pruritic disorders such as prurigo nodularis.

IL-33 has been associated with chronic pruritus of unknown origin and mediates itch in the context of allergic contact dermatitis and xerotic skin[68].

CHRONIC ITCH

Chronic itch may occur in the setting of inflammatory itch secondary to skin diseases, neuropathic itch due to pathology in the nervous system, and systemic or psychiatric disorders (see Ch. 6). It often has a significant effect on patients' quality of life. Chronic itch and chronic pain share several features, with both potentially involving peripheral and central sensitization (Table 5.4; Fig. 5.3).

Peripheral Sensitization in Chronic Itch

Patients with chronic itch in the setting of atopic dermatitis have increased neurotrophin levels in involved skin, including NGF and neurotrophin 4. Chronic localized pain is also associated with elevated levels of the same neurotrophins, which are known to sensitize nociceptive neurons.

Central Sensitization in Chronic Itch

Chronic itch leads to sensitization of second-order neurons within the dorsal horn of the spinal cord (see Fig. 5.1). There are two forms of increased sensitivity to itch, alloknesis and hyperknesis. In *alloknesis*, stimuli that normally do not induce itch such as touch or gentle warming do so in the skin that surrounds a pruritic area. This phenomenon is analogous to allodynia, in which gentle mechanical stimuli give rise to a perception of pain. Like allodynia, alloknesis requires ongoing activity in primary afferent C fibers and is probably mediated by low-threshold myelinated mechanoreceptor Aβ fibers (see Fig. 5.2). Alloknesis is common and represents a prominent feature of atopic dermatitis, explaining pruritus associated with dressing and undressing. Expression of the channel protein Piezo2 on Merkel cells has been shown to limit alloknesis in mice[69].

Hyperknesis is characterized by more intense itch induced by a stimulus that usually produces slight itch and occurs within the skin surrounding an area of inflammation. It is similar to the phenomenon in chronic pain termed hyperalgesia. In mice, neurokinin-1

COMPARISON OF CHARACTERISTICS OF CHRONIC ITCH AND CHRONIC PAIN

	Chronic itch	Chronic pain
Peripheral sensitization	• Sensitized C nerve fibers	• Sensitized C nerve fibers
Central sensitization	• Alloknesis • Hyperknesis	• Allodynia • Hyperalgesia
Selected neuromediators	• Nerve growth factor • Neurotrophin 4	• Nerve growth factor • Neurotrophin 4
Selected chemical mediators	• Histamine • Cowhage (mucunain) • Most opioids induce itch	• Bradykinin • Most opioids reduce pain
CNS areas activated	• Anterior and posterior cingulate cortex • Premotor area • Precuneus • Supramarginal gyrus • Dorsolateral prefrontal cortex • Insula–claustrum complex • Somatosensory cortex I, II • Parabrachial nuclei	• Anterior cingulate cortex • Premotor area • Somatosensory cortex I, II • Dorsolateral prefrontal cortex • Insula–claustrum complex

Table 5.4 Comparison of characteristics of chronic itch and chronic pain.

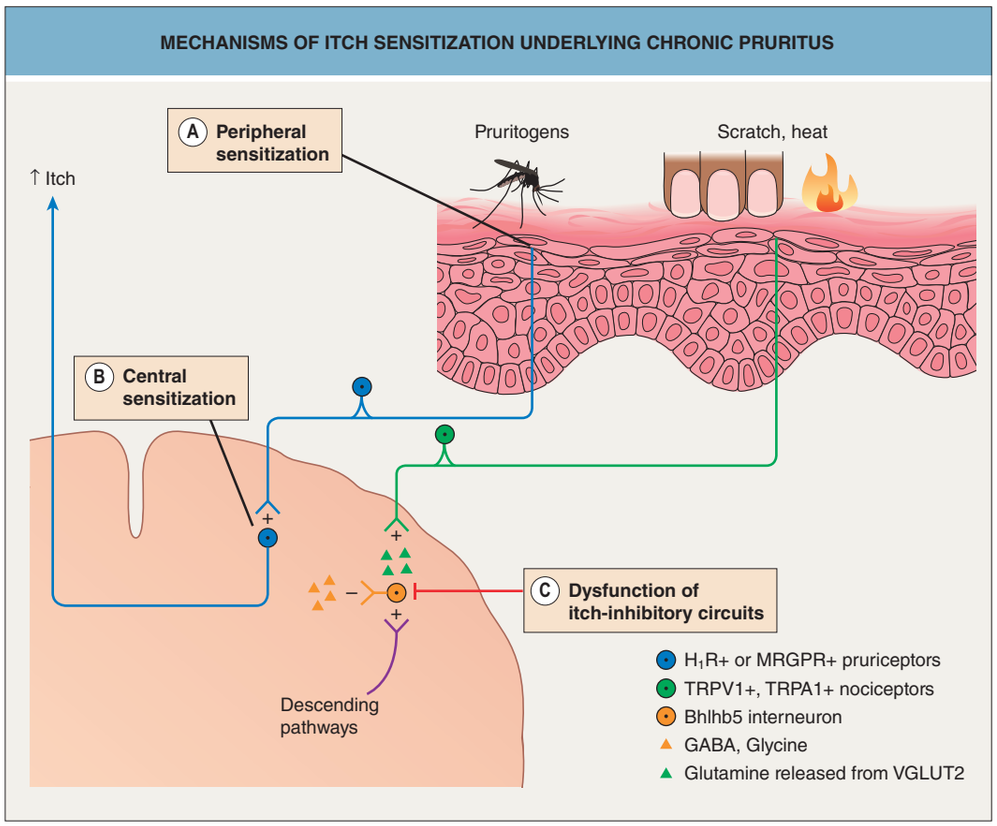


Fig. 5.3 Mechanisms of itch sensitization underlying chronic pruritus. Three main mechanisms of itch sensitization have important roles in chronic pruritus. **A** Peripheral sensitization of C-fiber pruriceptors occurs in the setting of chronic pruritus, which may be associated with increased levels of neurotrophins such as nerve growth factor (NGF; see Fig. 5.2C). PAR-2 activation in C fibers can also play a role in itch sensitization by enhancing responses to MAS-related G protein-coupled receptor (MRGPR) agonists. **B** Spinal itch-transmitting neurons are sensitized in the setting of chronic pruritus. There may be increased synaptic efficacy and signaling via additional synapses. **C** Itch-inhibitory circuits are normally driven by vesicular glutamate transporter 2 (VGLUT2)-dependent glutamate release from nociceptors as well as by descending pathways; this results in activation of itch-inhibitory Bhlhb5 interneurons, which release GABA, glycine, and/or dynorphins. Decreased function of these interneurons can result in disinhibition of itch. H_1R, histamine H1 receptor; TRPA1, transient receptor potential ankyrin receptor 1; TRPV1, transient receptor potential vanilloid receptor 1.

receptor-expressing spinal neurons play a major role in chronic itch, whereas gastrin-releasing peptide receptor-expressing spinal neurons contribute to hyperknesis, but not alloknesis or ongoing itch.

In patients with chronic itch, painful electrical and heat stimuli may be perceived as itch. An analogous phenomenon can occur in patients with chronic pain, in whom histamine iontophoresis may be perceived as painful. These findings indicate that pain-induced inhibition of pruritus may be compromised in patients with chronic itch. This may also explain why scratching aggravates itch in patients with chronic itch, thereby inducing a vicious itch–scratch cycle.

Itch Related to Impaired Skin Barrier Function

Itch is a common symptom of xerotic skin and is aggravated during the winter in cold climates when the relative humidity falls indoors. Damage to the stratum corneum and the impaired barrier function that results can induce itch even in the absence of inflammation. Environmental changes in pH, temperature, and humidity may activate C fibers to transmit the sensation of itch. Cross-talk between the stratum corneum and nerve fibers may explain the pruritus associated with impaired barrier function. Keratinocytes release neuromediators upon damage to the stratum corneum barrier, and nerve fibers sprout in the epidermis in response to this damage. Indeed, factors such as IL-33 have been shown to directly stimulate sensory neurons and evoke itch in the setting of xerotic skin[68].

Itch in Older Adults

Itch is particularly frequent in individuals over 65 years of age[68]. Although dry skin is probably the most common trigger, elderly patients can have idiopathic itch without xerosis. Other possible explanations include age-related changes in nerve fibers and central disinhibition of itch due to loss of input from pain fibers. Additional changes that may contribute to pruritus as well as xerosis in elderly patients include decreased skin surface lipids, diminished skin barrier repair, and immunosenescence (e.g. enhanced Th2 activity).

Cholestatic Pruritus

The enzyme autotaxin and its product lysophosphatidic acid (LPA), a neuronal activator, have a pathogenic role in cholestatic pruritus (see Ch. 6). Serum autotaxin levels correlate with itch intensity in patients with cholestasis. In addition, the G protein-coupled bile acid receptor-1 (Gpbar1; TGR5) has been found to have a role in cholestatic pruritus in mouse models. Murine MrgprA1 and human MRGPRX4 have been identified as itch receptors for bilirubin, suggesting another mechanism by which cholestatic itch is elicited[70,71].

TREATMENTS FOR PRURITUS

Unlike pain, for which a host of effective medications are available, there are no general-purpose, consistently beneficial antipruritic drugs. The mechanisms, uses, and adverse effects of currently available antipruritic drug treatments are outlined in Table 5.5. A number of new and emerging therapies for atopic dermatitis provide ways to treat itch by targeting the neuro-immune interface. These include agents that block IL-4/-13 and IL-31 signaling as well as JAK inhibitors. Additional pruritus treatments are likely to result from further advances in our understanding of itch biology.

FUTURE DIRECTIONS

Continued progress in itch research will help to determine how itch transmission pathways contribute to neuropathic, inflammatory, and even idiopathic forms of pruritus, providing the basis for novel therapies.

DRUG TREATMENT OF PRURITUS			
Medication	**Mechanism(s) of action**	**Uses and efficacy**	**Major adverse effects**
Topical agents			
"Barrier repair" creams, other emollients and humectants	• Diminish transepidermal water loss and decrease flux between a distended and desiccated state • Minimize microfissures that expose C nerve fibers • Agents that acidify the stratum corneum may reduce itch, as alkaline agents (e.g. bar soaps) can activate proteases and increase lipid rigidity	• Decrease itch in patients with atopic dermatitis	None

Capsaicin (active component in hot chili peppers)	• Activates and subsequently desensitizes TRPV1, a vanilloid TRP receptor
	• Causes release from C neurons and (eventually) depleted stores of neuropeptides (e.g. substance P, CGRP, somatostatin)
	• Prolonged use leads to neuronal degeneration at sites of application, which can result in a reversible decrease in epidermal nerve fiber density
		• Used primarily for localized, chronic pruritic disorders, especially those of neuropathic origin
		• Controlled studies support use for:
		  • Notalgia paresthetica
		  • Brachioradial pruritus
		  • Hemodialysis-associated pruritus
		  • Postherpetic neuralgia, with a transdermal patch FDA-approved for this indication
			• Transient burning sensation, which usually resolves after several days of consistent use; application of topical lidocaine or EMLA may be helpful

Doxepin	• Tricyclic compound with potent antihistamine effects (H1 and H2) • Also anticholinergic properties	• Shown to relieve pruritus in patients with atopic dermatitis	• Drowsiness in ~25% of patients due to percutaneous absorption • Allergic contact dermatitis, followed by risk of systemic contact dermatitis with oral doxepin
Ketamine–amitriptyline–lidocaine (10%–5%–5% compounded cream)	• Anesthetic effect; targets ion channels in peripheral nerves and NMDA receptors	• May decrease neuropathic itch and other forms of pruritus, including the itch of prurigo nodularis	• Mild burning sensation • Potential systemic absorption • Not FDA approved
Menthol	• Activates TRPM8 and TRPA1, producing a cool sensation	• Inconsistent results in controlled studies • May be especially beneficial for patients whose itch is relieved by cold showers	• Skin irritation
Pramoxine	• Anesthetic (blocks transmission of nerve impulses)	• Beneficial for histamine-induced itch and uremic pruritus in end-stage renal disease	• Allergic contact dermatitis (uncommon)
Ruxolitinib	• Inhibit JAK 1 and 2, thus decreasing signaling by IL-4, IL-31, and TSLP	• Decreases itch in patients with atopic dermatitis	• Acne at application site • Possibly nasopharyngitis
Strontium	• Calcimimetic thought to inhibit ion channels in nerve fibers	• Strontium 4% hydrogel was shown to relieve localized cowhage-induced itch	• None identified • Not FDA approved
Tacrolimus, pimecrolimus	• Calcineurin inhibitors that block production of multiple proinflammatory cytokines (see Ch. 128) • May initially activate and subsequently desensitize TRPV1	• Can decrease itch related to the inflammation of atopic dermatitis	• Transient burning sensation
Systemic agents			
Antihistamines (especially doxepin)	• Doxepin is a tricyclic compound with potent antihistamine effects (H1 and H2) and anticholinergic properties; first-generation, sedating antihistamine	• Decrease wheal formation as well as pruritus in patients with urticaria	• Sedation • Anticholinergic effects • Interaction with MAO inhibitors (for doxepin)
Aprepitant	• Antagonist of the neurokinin-1 receptor, which is activated by substance P	• Primarily used as an antiemetic in oncology patients; reports of reduced pruritus in patients with atopic dermatitis, Sézary syndrome, and other forms of CTCL as well as decreases in pruritus induced by anti-EGFR antibodies or tyrosine kinase inhibitors	• Fatigue • Hiccups
Butorphanol	• κ-Opioid receptor agonist and μ-opioid receptor antagonist*	• Relieves pruritus associated with morphine with epidural administration of both agents • May reduce severe pruritus associated with systemic disease or inflammatory skin conditions‡	• Nausea/vomiting • Sedation • Dependence (rare)
Difelikefalin, nalfurafine†	• κ-Opioid receptor agonists*	• Controlled trials show efficacy for renal pruritus; difelikefalin is FDA-approved for this indication	• Insomnia

Table 5.5 Drug treatment of pruritus.

Continued

DRUG TREATMENT OF PRURITUS			
Medication	**Mechanism(s) of action**	**Uses and efficacy**	**Major adverse effects**
Naloxone, naltrexone	• μ-Opioid receptor antagonists*	• Controlled trials show efficacy for cholestatic and renal pruritus • May be of benefit for severe pruritus of other etiologies	• Hepatotoxicity • Nausea/vomiting • Insomnia • Reversal of analgesia
Thalidomide	• Blocks neuropathic afferent pathways (peripherally and centrally) • Inhibits TNF synthesis	• May be helpful for prurigo nodularis, actinic prurigo, and pruritus of advanced age	• Teratogenicity • Peripheral neuropathy
Dupilumab, tralokinumab lebrikizumab	• Block IL-4Rα (dupilumab) on immune cells and neurons • Block IL-13 (tralokinumab, lebrikizumab)	• Decrease pruritus in patients with atopic dermatitis and prurigo nodularis	• Conjunctivitis, keratitis • Facial dermatitis • Injection site reaction
Nemolizumab	• Blocks IL-31RA	• Reduces pruritus in patients with atopic dermatitis and prurigo nodularis	• Injection site reaction • Peripheral edema
Gabapentin, pregabalin	• Structural analogues of the neurotransmitter GABA • Thought to inhibit central itch pathways	• Beneficial for neuropathic itch (e.g. brachioradial pruritus), post-burn pruritus and postherpetic neuralgia	• Peripheral edema • Sedation • Abdominal pain
Mirtazapine	• Serotonin and norepinephrine inverse agonist that reduces central itch perception	• May reduce nocturnal pruritus (at low doses, e.g. 15 mg nightly)	• Sedation • Weight gain
Omalizumab, ligelizumab	• Block IgE	• Decrease pruritus in patients with chronic spontaneous urticaria and associated with immune checkpoint inhibitor and anti-HER2 therapies	• Rare anaphylactoid reactions (epinephrine [adrenaline] autoinjector should be prescribed for all patients) • Injection site reaction
Paroxetine	• Selective serotonin reuptake inhibitor (SSRI)	• A controlled study showed benefit for pruritus related to systemic disease	• Sexual dysfunction • Sedation • Insomnia • Weight gain
Upadacitinib, abrocitinib, baricitinib	• Inhibition of JAK1 (+ JAK2 for baricitinib) in immune cells and neurons	• Decrease pruritus within 1–2 weeks in patients with atopic dermatitis	• Risk of acne, serious infections, cytopenias, thrombosis, hyperlipidemia, major cardiovascular events, cancer, and (for upadacitinib & baricitinib) gastrointestinal perforation

*Inhibit itch transmission within the central nervous system.
†Currently not commercially available in the US.
‡An intranasal spray is currently available.

Table 5.5 Drug treatment of pruritus. Topical naltrexone, aspirin, and cannabinoids may also have antipruritic effects, and injections of botulinum toxin type A have been used to treat neuropathic itch. Of note, although capable of relieving pruritus by treating inflammatory skin disease, corticosteroids are not intrinsically antipruritic. The ileal bile acid transporter inhibitors odevixibat and maralixibat are FDA-approved to treat cholestatic pruritus in patients with progressive familial intrahepatic cholestasis and Alagille syndrome, respectively. In the future, topical anti-itch medications may target serine proteases (e.g. cathepsin S), nerve growth factor, or neurotrophin 4. CGRP, calcitonin gene-related polypeptide; CTCL, cutaneous T cell lymphoma; EGFR, epidermal growth factor receptor; EMLA, eutectic mixture of local anesthetics (lidocaine + prilocaine); FDA, US Food and Drug Administration; GABA, γ-aminobutyric acid; IL, interleukin; MAO, monoamine oxidase; NMDA, N-methyl-D-aspartate; TNF, tumor necrosis factor; TRP, transient receptor potential ion channel family; TSLP, thymic stromal lymphopoietin.

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6 Pruritus and Dysesthesia

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INTRODUCTION

Pruritus can be defined as an unpleasant sensation that elicits a desire to scratch. The presumed biologic purpose of pruritus is to provoke scratching to remove a parasite or other harmful pruritogen. Pruritus is the most common skin-related symptom. It often arises from a primary cutaneous disorder but can be a manifestation of an underlying systemic disease in 15%–50% of affected individuals, especially when generalized[1,2]. Non-dermatologic conditions that can lead to generalized pruritus include hepatic, renal, or thyroid dysfunction; lymphoma, myeloproliferative neoplasms (e.g. polycythemia vera), and chronic lymphocytic leukemia; HIV or parasitic infections; and neuropsychiatric disorders (see Ch. 7).

A clinical classification scheme for chronic pruritus was proposed in 2007 by the International Forum for the Study of Itch[3]. In this system, there are three major groups of pruritus: (1) chronic pruritus of lesional (inflamed) skin; (2) chronic pruritus of non-lesional (non-inflamed) skin; and (3) chronic pruritus presenting with secondary scratch-induced lesions (e.g. prurigo nodularis, lichen simplex chronicus). Following initial evaluation, the etiology of the pruritus is categorized as dermatologic, systemic, neurologic, psychogenic, mixed, or other/unknown[3]. Such classification assists in planning further evaluation and treatment of the underlying disease (if possible) as well as the pruritus itself. Recent advances in our understanding of the mechanisms underlying chronic pruritus have led to the development of targeted therapies, and additional promising drugs are expected in the near future.

EPIDEMIOLOGY

It is assumed that all humans experience the sensation of pruritus at some point in their life, e.g. from insect bites (Fig. 6.1). However, relatively few studies have investigated the overall incidence and prevalence of pruritus. In a Norwegian population-based, cross-sectional study of self-reported skin morbidities, pruritus was the dominant symptom among adults, experienced within the past week by 9% of women and 7.5% of men[4]. A German population-based, cross-sectional study found that the self-reported point, 12-month, and lifetime prevalences of chronic pruritus (lasting ≥6 weeks) were 13.5%, 16%, and 22%, respectively[5]; in a follow-up cohort study, a 7% 12-month cumulative incidence of chronic pruritus was observed[6]. Women have a higher lifetime prevalence of chronic pruritus than men, and older adults are more frequently affected. Table 6.1 summarizes the prevalence of pruritus in various medical conditions[7].

EVALUATION OF THE PATIENT

A structured approach to the evaluation of patients with a chief complaint of pruritus is presented in Fig. 6.2. Pruritus is a subjective sensation, and currently its presence or severity cannot be assessed objectively. Thus, a thorough history that includes the patient's itch sensation plus a complete cutaneous examination for any evidence of skin lesions are important for correct diagnosis and allow assignment of the patient to one of the three clinical groups of pruritus (see above).



Fig. 6.1 Insect bites. Linear pruritic papules with central crusts demonstrating the "breakfast, lunch, and dinner" sign. *Courtesy Antonio Torrelo, MD.*

PREVALENCE OF PRURITUS IN SELECTED CONDITIONS	
Disorder	**Reported prevalence of pruritus**
Atopic dermatitis	100% (diagnostic criterion)
Lichen planus	~95%
Psoriasis	60%–95%
End-stage kidney disease on hemodialysis	25%–30%
Primary biliary cholangitis	80% (often the presenting symptom)
Hepatitis C viral infection	~15%
Cutaneous T cell lymphoma	60%–80% overall; >90% in Sézary syndrome
Polycythemia vera	30%–50%
Hodgkin lymphoma	≤30%
Non-Hodgkin lymphoma	≤10%
Leukemias	<5%
Herpes zoster	≤60%
Postherpetic neuralgia	≤30%
Pregnancy	~20%

Table 6.1 Prevalence of pruritus in selected conditions (see text).

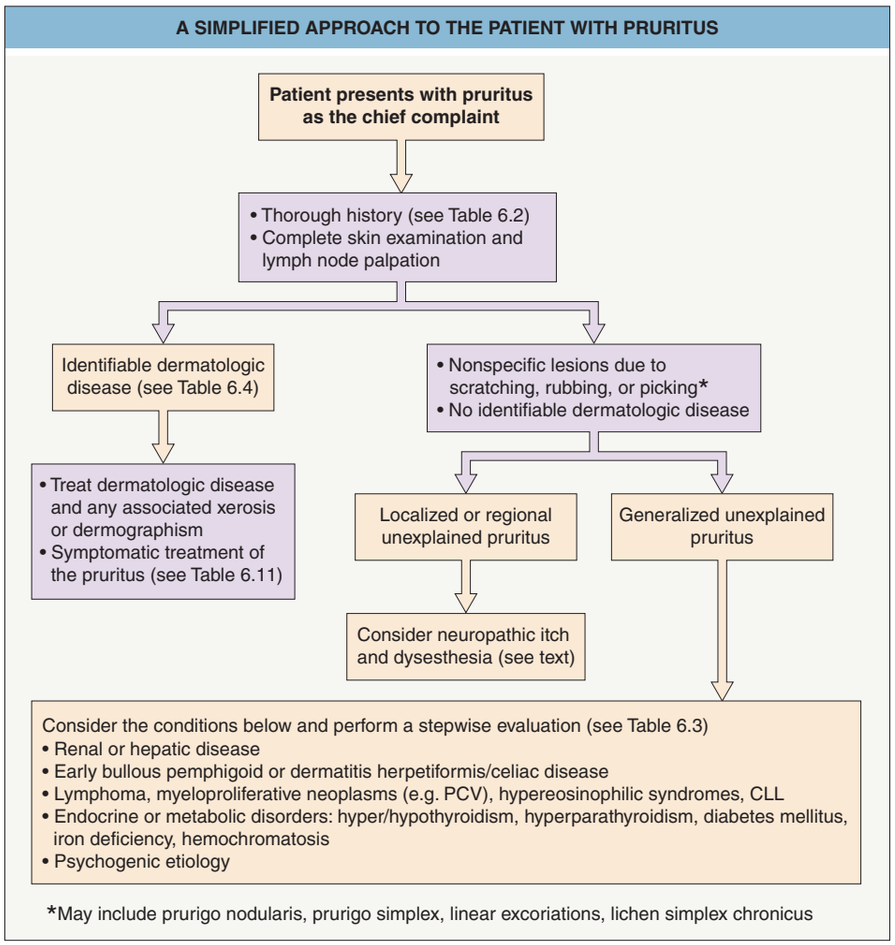


Fig. 6.2 A simplified approach to the patient with pruritus. CLL, chronic lymphocytic leukemia; PCV, polycythemia vera.

Patients with evidence of a particular skin condition should be treated accordingly, while those with no identifiable primary skin disease (i.e. an absence of or only secondary skin lesions) require further investigation to determine the etiology of their pruritus. Also, chronic pruritus can have multiple underlying factors, and a pruritic skin condition that has nonspecific clinical findings initially may over time develop diagnostic features. Therefore, longitudinal evaluation is essential.

History

A precise history may provide insight into the patient's disease processes. In addition to the patient's spontaneous description, specific questions regarding the onset, location, duration, and nature of the pruritus can help to determine its cause (Table 6.2)[8]. The use of standardized instruments to assess itch intensity (e.g. a numerical rating scale) and impairment of quality of life (e.g. ItchyQol) is recommended[9]. A medical and medication history should also be obtained. Although chronic, progressive, generalized pruritus without primary skin lesions raises suspicion of an underlying systemic disease, no particular clinical characteristics reliably predict the likelihood of a systemic etiology[8].

Examination

Careful and complete examination of the skin, nails, scalp, hair, mucous membranes (e.g. oral, conjunctival), and anogenital area at the initial visit is recommended. The morphology and distribution of primary lesions and secondary changes (e.g. excoriations, crusts, lichenification) should be assessed, with particular attention to xerosis, the presence of dermographism (Fig. 6.3), and skin signs of systemic diseases (see Ch. 53). Lesions on the mid upper back suggest a primary skin disease, since this difficult-to-reach area is typically spared (the "butterfly sign") in patients with skin lesions secondary to scratching (see Fig. 6.5A). However, this region can be accessed with "back-scratching" devices.

The examination should include palpation of major peripheral lymph node groups (e.g. cervical, supraclavicular, axillary, inguinal), especially in those with no obvious primary inflammatory skin disease. Together with a general physical examination performed by the patient's primary care physician, this may disclose an undiagnosed extracutaneous disease (e.g. lymphoma) in individuals with pruritus of unknown etiology[8].

Laboratory Investigation and Radiographic Imaging

In the setting of pruritus of unknown etiology, a stepwise approach to laboratory tests and other investigations (e.g. radiographic imaging) is recommended (Table 6.3). Microscopic examination of skin scrapings for signs of scabies or a fungal infection as well as examination of stool samples for parasites can also be considered. Biopsies of representative skin lesions, even if nonspecific clinically, are occasionally informative, and direct immunofluorescence studies of perilesional skin or normal-appearing skin (in the vicinity of lesions if present) may point to a specific dermatologic disease such as bullous pemphigoid or dermatitis herpetiformis, respectively. Radiographic examinations may be performed to exclude an underlying malignancy or other systemic condition as well as peripheral nerve impingement when neuropathic itch is suspected[8].

PRURITUS IN DERMATOLOGIC DISEASE

This section focuses on the sensation of pruritus in selected skin diseases where this symptom is a prominent feature. A more comprehensive discussion of the diseases mentioned and the many additional dermatoses in which pruritus is a characteristic feature (Table 6.4) may be found in other chapters.

Inflammatory Dermatoses

Urticaria

Urticaria is often intensely pruritic and can also produce stinging or prickling sensations. Early lesions and small superficial wheals are

DESCRIPTIVE FEATURES OF THE PRURITUS AND ADDITIONAL PATIENT HISTORY
Questions to ask regarding the pruritus
• WHEN did it start? *Duration:* days, weeks, months, years • WHERE did it start? WHERE is it now? *Location*: localized or generalized; unilateral or bilateral; within lesional (inflamed) skin or non-lesional (non-inflamed) skin • HOW did it develop? *Onset*: abrupt, gradual, progressive, prior history of pruritic episodes • HOW does it feel? *Nature:* prickling, crawling, burning, stinging • HOW intense is it? *Severity:* on numerical ranking scale (1–10); mild, moderate, severe; interference with normal activities or sleep • HOW often do you feel it? *Time course:* intermittent, continuous, cyclical, nocturnal • WHAT makes it worse? *Provoking/aggravating factors:* heat, cold, water, air, exercise, occupation, hobbies • WHAT makes it better? *Itch relief:* cold, heat, scratching/rubbing/hurting, cool/hot showering • WHAT do you think is the cause? *Patient's theory of pruritus etiology*
Additional patient history
• Skin care, bathing habits, exposure to irritants • Medications (including topical agents): prescribed, over-the-counter; duration of use and relationship to onset of pruritus • Use of nicotine, alcohol, and recreational/illicit drugs • Allergies (known and suspected): drugs, airborne, food, contact • Atopic history: atopic dermatitis, allergic rhinoconjunctivitis, asthma • Past and present medical history: thyroid, liver, or renal dysfunction; other systemic diseases; psychological disease; surgeries or accidents • Family history: atopy, skin disease, similar pruritic conditions • Occupation, hobbies, personal stress • Household and personal contacts; pets and their care • Dietary habits • Sexual history • Travel history • Prior diagnoses made by physician or patient

Table 6.2 Descriptive features of the pruritus and additional patient history.



Fig. 6.3 Dermographism. Linear streaks of urticaria induced by scratching the skin. Assessment for dermographism should be performed in all patients with pruritus.

LABORATORY AND RADIOGRAPHIC EVALUATION IN PATIENTS WITH PRURITUS OF UNKNOWN ETIOLOGY
Basic initial evaluation
• Complete blood count (CBC) with differential and platelet count • Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) • Creatinine, blood urea nitrogen (BUN) • Liver transaminases, alkaline phosphatase, bilirubin • Lactate dehydrogenase (LDH) • Thyroid stimulating hormone (TSH) • Fasting plasma glucose • Serum ferritin, serum iron, and total iron binding capacity
Possible additional evaluation
Skin biopsy • Routine histology (if skin lesions are present) • Direct immunofluorescence studies* *Other laboratory tests* • Serum total and/or allergen-specific IgE • Serum protein electrophoresis, serum immunofixation electrophoresis • Viral hepatitis panel (including hepatitis B and C viruses); HIV testing • Parathyroid function (calcium, phosphate, parathyroid hormone levels) • Serum tryptase • Anti-BP180 and anti-BP230 bullous pemphigoid IgG antibodies; anti-tissue transglutaminase IgA antibody • Anti-mitochondrial and anti-smooth muscle antibodies • Stool for ova/parasites *Radiographic studies* • Chest X-ray or CT scan • Abdominal and pelvic ultrasonography or CT scan • Lymph node ultrasonography • Spinal X-ray or MRI (for regional pruritus) *Other investigations* • Patch testing • Prick testing for major atopy and relevant occupational allergens • Age-appropriate cancer screening (in conjunction with primary care physician) • If hydroxyethyl starch (HES)-induced pruritus is suspected, electron microscopy of a biopsy sample from normal-appearing skin
*Biopsy perilesional skin or normal-appearing skin (in vicinity of lesions if present) to assess for bullous pemphigoid and dermatitis herpetiformis, respectively.

Table 6.3 Laboratory and radiographic evaluation in patients with pruritus of unknown etiology. A general physical examination should also be performed by the patient's primary care physician. Selection of particular tests beyond the basic initial evaluation is based upon the patient's history, physical examination findings, and pruritus severity. The results of initial testing can also help to direct further evaluation[8].

particularly symptomatic[1]. Histamine plays a primary role in the pruritus of urticaria, and H1-receptor antagonists usually decrease or eliminate this sensation as well as the wheals themselves[10]. Several other mediators are involved in the pathophysiology of urticaria, and interleukin (IL)-31 levels correlate with itch intensity[11]. When refractory to higher doses of antihistamines, omalizumab, and cyclosporine represent alternative treatments for urticaria (see Ch. 18).

Atopic dermatitis

Pruritus is such an important aspect of atopic dermatitis that "the diagnosis of active atopic dermatitis cannot be made if there is no history of pruritus"[12] (see Ch. 12). The itch sensation typically comes in "attacks", which may be severe and significantly impact quality of life[13]. Often, pruritus is the first indication of a disease flare. Moreover, scratching as a response to itch leads to excoriations and lichenification, which represent additional clinical features of atopic dermatitis[14]. Pruritus can be provoked by exposure to aeroallergens or ingestion of foods to which the patient is sensitized as well as non-immunologic triggers, including emotional stress, overheating, perspiration, and contact with rough fabrics or even air (atmokinesis)[15] (Fig. 6.4). Although most affected children experience worsening of symptoms during the winter, others have exacerbations primarily during the summer[16]. Of note, pruritus may persist after resolution of inflammatory skin lesions.

The minimal effectiveness of antihistamines in alleviating the itch of atopic dermatitis indicates that histamine is probably not the predominant mediator of the pruritic sensation[17–19]. Rather, the benefit of antihistamines in atopic dermatitis is most likely due to their sedative effects. Type 2 cytokines such as IL-4, IL-13, IL-31, and thymic stromal lymphopoietin play a key role in the inflammation of atopic dermatitis. As a result, therapies that target Th2 signaling via IL-4/-13 (e.g. dupilumab, tralokinumab, lebrikizumab), IL-31 (nemolizumab), or Janus kinase (JAK) 1/2 have anti-pruritic effects[14].

Other mediators and receptors with possible roles in the pruritus of atopic dermatitis include neuropeptides (e.g. substance P, calcitonin gene-related peptide [CGRP]), neurotrophic factors (e.g. nerve growth factor [NGF], artemin [causes warmth-provoked itching]), epidermal opioid receptors (downregulated), and endothelin-1[14,18,19]. In addition, itch transmission results from kallikrein-related peptidase and mast

PRIMARY DERMATOLOGIC CONDITIONS ASSOCIATED WITH PRURITUS	
Cause	**Dermatologic disease**
Inflammation	• Atopic dermatitis • Allergic or irritant contact dermatitis • Seborrheic dermatitis, especially of the scalp • Stasis dermatitis • Psoriasis • Parapsoriasis • Pityriasis rubra pilaris • Lichen planus and its variants • Urticaria, dermographism • Mastocytosis • Papular urticaria, urticarial dermatitis • Drug eruptions, e.g. morbilliform • Polymorphous light eruption, actinic prurigo, chronic actinic dermatitis • Bullous diseases, e.g. DH, BP • Polymorphic eruption of pregnancy (PEP) • Eosinophilic folliculitis • Dermatomyositis • Prurigo pigmentosa • Lichen sclerosus • Graft-versus-host disease
Infestation/ bites & stings	• Scabies • Pediculosis • Arthropod bites
Infections	• Bacterial infections, e.g. folliculitis • Viral infections, e.g. varicella • Fungal infections, e.g. inflammatory tinea • Parasitic infections, e.g. schistosomal cercarial dermatitis
Neoplastic	• Cutaneous T cell lymphoma, e.g. mycosis fungoides, Sézary syndrome
Genetic/ nevoid	• Darier disease and Hailey–Hailey disease • Ichthyoses, e.g. Netherton, Sjögren–Larsson, and peeling skin syndromes • Pruriginosa subtype of dominant dystrophic EB • Porphyrias, e.g. porphyria cutanea tarda and erythropoietic protoporphyria • Inflammatory linear verrucous epidermal nevus (ILVEN) • Large/giant congenital melanocytic nevi, occasionally, especially in bulky lesions with neural differentiation • Multiple intestinal atresia, early-onset IBD, and combined immunodeficiency (*TTC7A* mutations)
Other	• Xerosis, eczema craquelé • Primary cutaneous amyloidosis (macular, lichenoid) • Postburn pruritus • Scar-associated pruritus • Radiation-associated pruritus • Fiberglass dermatitis (see Ch. 16)

Table 6.4 Primary dermatologic conditions associated with pruritus. BP, bullous pemphigoid; DH, dermatitis herpetiformis; EB, epidermolysis bullosa; IBD, inflammatory bowel disease.



Fig. 6.4 Atopic dermatitis. A Excoriated eczematous plaques in the popliteal fossae, a classic flexural location for atopic dermatitis. **B** Prurigo simplex, prurigo nodularis-like lesions, and angulated ulcerations; the latter two are primarily on the knees. *Courtesy Antonio Torrelo, MD.*

cell tryptase binding to protease-activated receptors (PAR-2; see Ch. 5). In atopic patients, morphologic alterations of cutaneous nerves and neuronal sensitization may also contribute to an increased itch sensation and even the perception of painful stimuli as itch[20].

Psoriasis

Although not traditionally regarded as a pruritic disease, studies have shown that up to 60%–95% of psoriasis patients suffer from pruritus, with xerosis, heat, sweating, and emotional stress serving as exacerbating factors[21]. While lesions on the scalp, back, and legs are most often pruritic, generalized pruritus can occur in plaque-type as well as erythrodermic and pustular psoriasis[21]. Patients frequently describe the pruritus as having tickling, crawling, and burning components, and antihistamines rarely provide relief. Although the pathophysiology of psoriatic itch is still largely unknown, it is thought to be multifactorial and a variety of itch mediators (e.g. substance P, NGF, protein gene product 9.5, CGRP, neuropeptide Y, IL-2, opioid receptors) have been implicated[21]. Coadministration of β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or antacids may be associated with the development of psoriatic itch[22]. Successful treatment of psoriasis can reduce associated pruritus (see Ch. 8)[21,23].

Infestations

Scabies

In patients with scabies, pruritus can be localized or generalized, and it may have a burning component. It is usually more intense at night and typically spares the head. The pruritus usually begins 3–6 weeks after a first-time infestation, and within a few days in subsequent infestations; multiple family members are often affected (see Ch. 84). The itch reflects various components of the immune response against mites, eggs, and scybala[1]. Bacterial superinfection and eczematization of skin lesions may also contribute to itch in patients with scabies[24].

Pediculosis (lice)

Pruritus at the primary sites of infestation (e.g. scalp, groin) is a clue to the diagnosis of head and pubic lice (see Ch. 84). Generalized pruritus is characteristic of body lice but can also occur with other forms of lice infestation[1].

Cutaneous T Cell Lymphoma (CTCL)

Pruritus affects >60% of patients with CTCL, with an increased frequency and intensity in those with later-stage disease, especially Sézary syndrome (>90% of patients) and folliculotropic mycosis fungoides (MF)[25,26]. A variant of Sézary syndrome presenting with

generalized pruritus and minimal or no clinically evident skin disease has also been described[27]. Pruritus significantly reduces the quality of life in CTCL patients[28], and it has been associated with an increased risk of disease progression and death.

IL-31 is a putative mediator of itch in CTCL, especially in late-stage disease, and lower serum IL-31 levels have been observed in association with reduced pruritus following treatment with histone deacetylase inhibitors and mogamulizumab (anti-CC-chemokine receptor type-4 antibody)[29–31]. Other possible mediators of CTCL-related itch include IL-4, IL-5, IL-10, IL-13, substance P, NGF, endogenous opioids, and visfatin[31].

Treatment strategies for severe pruritus not responsive to disease-directed therapy in CTCL patients include gabapentin (900–2400 mg daily in divided doses) and/or mirtazapine (7.5–15 mg nightly) as well as opioid antagonists (e.g. naltrexone 50–150 mg daily)[8]. Aprepitant has also been reported to relieve intractable pruritus in patients with Sézary syndrome and other forms of CTCL, suggesting a role for neurokinin-1 (NK1) receptors and substance P in CTCL-related itch[32]. However, in a recent randomized controlled trial (RCT), aprepitant failed to demonstrate an antipruritic effect compared to placebo in patients with Sézary syndrome[33].

DERMATOSES INDUCED BY PRURITUS-ASSOCIATED SCRATCHING OR RUBBING

Prurigo Nodularis

Prurigo nodularis is associated with chronic itch (i.e. lasting ≥6 weeks), where skin lesions are produced by repetitive, focused scratching or picking of the skin[34]. Neuronal sensitization and the development of an itch–scratch cycle contribute to disease chronicity[35]. Prurigo nodularis most often occurs in adults, especially women, but can affect any age group, including children and adolescents with an atopic diathesis[36].

Multiple pruritic papulonodules are most commonly observed on the extensor aspects of the extremities, and their distribution is usually symmetric. The upper back, lumbosacral region, and buttocks may also be involved, but the difficult-to-reach mid upper back is classically spared ("butterfly sign") (Fig. 6.5A). Flexural areas as well as the face and groin are often spared.

The firm, dome-shaped papulonodules have varying degrees of central scale, crust, erosion, or ulceration (Fig. 6.5A–C). The color ranges from skin-toned to erythematous to brown, with hyperpigmentation often seen in individuals with more darkly pigmented skin (see Fig. 6.5C). Lesions can develop a verrucous or fissured surface and lichenification of adjacent skin may be observed. When crusted smaller papules are the predominant finding, the term prurigo simplex is sometimes utilized.

The etiology of the underlying pruritus varies and may include atopic dermatitis (up to 50% of patients), xerosis, another skin disorder, or a systemic disease (e.g. hepatic or renal dysfunction)[35]. Psychological afflictions (e.g. emotional distress) and neuropsychiatric conditions (e.g. obsessive–compulsive disorder, autism spectrum disorders) can also lead to repetitive scratching. Occasionally, prurigo nodularis is associated with an underlying lymphoma and less often solid tumor malignancies[37]. The clinical differential diagnosis of prurigo nodularis may include pemphigoid nodularis (Fig. 6.6), hypertrophic lichen planus, hypertrophic lupus erythematosus, scabietic nodules, persistent insect bite reactions, the pruriginous type of dominant dystrophic epidermolysis bullosa, and neoplasms such as multiple keratoacanthomas or granular cell tumors.

Histologically, there is marked epidermal hyperplasia and thick, compact hyperkeratosis[38]. Keratinocyte atypia is absent, and small areas of erosion or ulceration may be seen. Fibrosis of the papillary dermis with vertically arranged collagen fibers, increased numbers of fibroblasts and capillaries, and a perivascular or interstitial mixed inflammatory infiltrate represent additional findings.

Possibly as a result of intense scratching, pruriginous lesions demonstrate hypertrophy and an increased density of dermal nerve fibers. In contrast, the number of nerve fibers within the epidermis is reduced. There is increased expression of substance P, CGRP, and NGF receptors by the dermal nerve fibers and prominent NGF immunoreactivity in lesional dermis. The dermal neuronal hyperplasia and epidermal "small fiber neuropathy" may play a pathogenic role in perpetuating the pruritus of prurigo nodularis[20,39]. Additionally, proinflammatory



Fig. 6.5 Prurigo nodularis. A Numerous excoriated nodules on the back, buttocks, and arms as well as linear excoriations. Note the sparing of the mid upper back ("butterfly sign"). **B** Nodules and plaques in various stages on the knees of a patient with atopic dermatitis. **C** Firm, hyperpigmented papulonodules on the extensor forearm. *A, Courtesy Luis Requena; B, Courtesy Antonio Torrelo, MD; C, Courtesy Ronald P. Rapini, MD.*



Fig. 6.6 Bullous pemphigoid presenting as pruritus with lesions of prurigo simplex. Bullous pemphigoid is often intensely pruritic and may not present with intact vesiculobullae. *Courtesy Department of Dermatology, Medical University of Graz.*

mediators such as IL-31 are upregulated in pruriginous lesions and contribute to neurogenic inflammation.

Treatment of prurigo nodularis is usually difficult and typically requires a multifaceted approach, which should be individualized depending on etiologic factors and the extent of disease[40]. Any underlying conditions (e.g. atopic dermatitis, chronic kidney disease, cholestasis) should be identified and treated if possible. Ideally, significantly reducing the pruritus would break the itch–scratch cycle, eventually leading to healing of the lesions; however, this is often not possible, especially when there is a psychological underpinning. Topical antipruritic agents (e.g. menthol, pramoxine, polidocanol) and oral antihistamines may help to decrease itch intensity. The former can be applied repeatedly as a "substitute" for scratching, and a sedating antihistamine at bedtime may be beneficial for sleep disturbances.

The skin lesions may respond to superpotent topical corticosteroids under occlusion, corticosteroid-impregnated tape, intralesional corticosteroids, phototherapy (e.g. narrowband or broadband UVB, psoralen plus UVA [PUVA]), or excimer laser treatment. Other topical treatments with potential benefit include capsaicin (0.025%–0.1% 4–6 times daily, applied locally), calcipotriene (calcipotriol), and calcineurin inhibitors. Based upon RCTs in which ~45%–50% of patients with prurigo nodularis achieved clear or almost clear skin after 24 weeks of therapy, dupilumab was FDA approved for this indication[40a]. The IL-31 receptor inhibitor nemolizumab was also found in RCTs to significantly reduce pruritus and cutaneous lesions in adults with prurigo nodularis[41].

Improvement of prurigo nodularis with gabapentinoids (e.g. gabapentin, pregabalin), μ-opioid receptor antagonists (e.g. naloxone, naltrexone), or combined μ-opioid receptor antagonist/κ-opioid receptor agonists (e.g. nalbuphine) has been described. Systemic immunosuppressive drugs such as cyclosporine or methotrexate may be of benefit, especially in patients in which the inflammatory component of the disease predominates. Treatment directed toward any underlying compulsive behavior is important. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants have both been employed successfully, especially when a component of depression is present. Thalidomide (50–200 mg daily) has been reported to be highly effective for patients with recalcitrant prurigo nodularis, although its use is limited by teratogenicity and the potentially irreversible side effect of peripheral neuropathy.

Lichen Simplex Chronicus

In lichen simplex chronicus (LSC), there is epidermal hypertrophy secondary to chronic, habitual rubbing or scratching of localized areas of skin. Lesions of LSC are broader and thinner than those of prurigo nodularis. LSC is most frequently observed in adults and is relatively uncommon in children, with the exception of lichenified lesions in atopic dermatitis.



Fig. 6.7 Lichen simplex chronicus. A Lichenified pink plaque on the ankle of a young man. **B** Note the increased skin markings in this hyperpigmented plaque on the posterior neck. *B, Courtesy Ronald P. Rapini, MD.*

LSC is characterized by well-defined plaques exhibiting exaggerated skin lines (lichenification) with a "leathery" appearance, coalescing papules, hyperpigmentation, and varying degrees of erythema. Lesions may be solitary or multiple, with a predilection for the posterolateral neck, occipital scalp, anogenital region (e.g. scrotum, vulva), shins, ankles, and dorsal aspects of the hands, feet, and forearms (Fig. 6.7). Predisposing factors include xerosis, atopy, psoriasis, stasis dermatitis, anxiety, obsessive–compulsive disorder, localized neuropathic itch, and pruritus related to systemic disease.

The clinical differential diagnosis may include lichen amyloidosis and hypertrophic lichen planus, both of which present with chronic pruritic plaques favoring the shins. *Lichen ruber moniliformis* is a historic condition that presents with rows of papules and cord-like fibrotic bands, which may be both pruritic and painful. Histologic features of LSC are similar to those of prurigo nodularis (see above), with compact hyperkeratosis, acanthosis with irregular elongation of rete ridges, hypergranulosis, and vertically oriented collagen bundles in the papillary dermis.

Like prurigo nodularis, lesions of LSC itch spontaneously, which leads to an "itch–rub/scratch–itch" cycle that often makes it resistant to treatment. Underlying pruritic disorders should be identified and treated if possible. Management strategies are similar to those described for prurigo nodularis (see above), with topical corticosteroids (± occlusion) and intralesional corticosteroids as the mainstays of therapy. Repeated application of a hydrocolloid dressing can lead to improvement. Informal insight-oriented psychotherapy and application

of topical antipruritic agents as "substitutes" for rubbing/scratching may be of benefit. Use of topical lidocaine 5% or capsaicin 8% patches, licensed for the treatment of postherpetic neuralgia, may be helpful in recalcitrant cases. Additional treatments may include antihistamines, gabapentinoids, antidepressants, phototherapy, transcutaneous electrical stimulation, and focused ultrasound[42].

PRURITUS IN SPECIFIC LOCATIONS

Scalp Pruritus

Skin disorders involving the scalp (e.g. seborrheic dermatitis, psoriasis, folliculitis, lichen planopilaris, dermatomyositis) may present with pruritus localized to this area. However, scalp pruritus also occurs in the absence of any objective changes including in the setting of neuropathic disorders (e.g. small-fiber neuropathy, postherpetic neuralgia) or psychogenic itch[43]. Trigger factors should be avoided and any underlying cause treated if possible. Topical corticosteroids and antipruritic agents have been employed with inconsistent efficacy[44].

Anogenital Pruritus

Pruritus ani

Pruritus localized to the anus and perianal skin occurs in 1%–5% of the general population, with a male : female ratio of ~4 : 1[45]. The onset is typically insidious, and symptoms may be present for weeks or years before patients seek medical attention.

Pruritus ani can be primary (idiopathic) or secondary in nature. Primary pruritus ani is defined as pruritus in the absence of any apparent cutaneous, anorectal, or colonic disorder; it accounts for 25%–95% of reported cases, depending upon the series. Possible causes include dietary factors such as poor personal hygiene and psychiatric disorders. Secondary pruritus ani has an identifiable etiology such as chronic diarrhea, fecal incontinence/anal seepage, hemorrhoids, anal fissures or fistulas, rectal prolapse, primary cutaneous disorders (e.g. psoriasis, lichen sclerosus, seborrheic dermatitis, allergic contact dermatitis), sexually transmitted diseases, other infections, infestations (e.g. pinworms), previous radiation therapy or trauma, and neoplasms (e.g. anal cancer)[45]. Pruritus ani (as well as pruritus vulvae or scroti) can also be neuropathic in origin and be due to compression or irritation of lumbosacral nerves from prolapsed intervertebral discs, vertebral body fractures, or osteophytic processes.

Findings on physical examination range from normal-appearing skin or mild perianal erythema to severe irritation with crusting, lichenification, and erosion or ulceration. Histologically, a nonspecific, chronic dermatitis is usually seen, but specific dermatoses (e.g. lichen sclerosus) and neoplastic disorders (e.g. extramammary Paget disease) can be excluded.

Evaluation includes a thorough history, complete cutaneous and general physical examination, and psychiatric screening. The latter is of importance considering that anxiety and depression may be aggravating factors for pruritus ani. Patch testing should be considered to exclude allergic contact dermatitis. Rectosigmoidoscopy and/or colonoscopy may be necessary, especially in patients with recalcitrant pruritus ani, in order to detect underlying conditions ranging from hemorrhoids to cancer. The possibility of pinworm infection should be considered, particularly in affected children[46]. In patients receiving chronic antibiotic therapy who have liquid stools with a pH of 8–10, *Lactobacillus* replacement therapy is recommended.

While secondary pruritus ani usually improves with treatment of the underlying disorder, management of primary disease can be very challenging. Mild cases often respond to elimination of irritants and triggers, sitz baths (e.g. with astringents such as black tea), cool compresses, and meticulous hygiene using water-moistened, fragrance-free toilet paper or a bidet. The area is then dried with blotting or a fan, with avoidance of rubbing and alkaline soaps[46] (see Ch. 153). Application of zinc oxide paste can help to protect the skin from further irritation and friction.

A mild corticosteroid cream (class 6 or 7) is often effective in controlling symptoms. However, with greater disease severity or the presence of lichenification, more potent topical corticosteroids and prolonged treatment may be required, raising the risk of cutaneous atrophy. Topical calcineurin inhibitors, including use on a rotational basis with topical corticosteroids, may be helpful when longer courses of therapy are necessary[47].

Pruritus vulvae and scroti

These common disorders, which may be incapacitating and emotionally disturbing, are solely psychogenic in only 1%–10% of patients[1]. Like pruritus ani, patients with pruritus of the vulva or scrotum typically complain of symptoms that are worse at night, and repeated rubbing or scratching leads to lichenification. The evaluation, differential diagnosis, and treatment options are similar to those for pruritus ani.

Acute pruritus of the vulva or scrotum is often related to infections such as candidiasis or scabies, but allergic or irritant contact dermatitis should also be considered. *Chronic* pruritus in these sites may be caused by dermatoses (e.g. psoriasis, atopic dermatitis, lichen sclerosus, lichen planus, LSC), malignancy (e.g. extramammary Paget disease, squamous cell carcinoma), or atrophic vulvovaginitis[46]. Scrotal pruritus secondary to lumbosacral radiculopathy has also been described[48]. In general, irritation of sensitive genital skin from cleansing and toilet habits needs to be addressed, as well as treatment of any identifiable underlying cause.

PRURITUS VARIANTS

Aquagenic Pruritus

Aquagenic pruritus is usually secondary to a systemic disease (e.g. polycythemia vera) or another skin disorder (e.g. urticaria, dermographism; Table 6.5), whereas primary (idiopathic) aquagenic pruritus is relatively uncommon. Aquagenic pruritus presents with prickling, tingling, burning, or stinging sensations within 30 minutes of water contact, irrespective of its temperature or salinity, and lasts for up to 2 hours[1]. Typically, symptoms begin on the lower extremities and then generalize, with sparing of the head, palms, soles, and mucosae[49]; on examination, specific skin lesions are not seen. The pathologic mechanism is unknown, although elevated dermal and epidermal levels of acetylcholine, histamine, serotonin, and prostaglandin E_2 have been described[1].

Treatment of aquagenic pruritus is difficult. Aspirin (300–500 mg daily) was of benefit in one RCT. Treatment with narrowband or broadband UVB or PUVA may also be effective. Based upon case reports and case series, alkalization of bath water with baking soda, capsaicin cream (0.025%–0.1% applied 3–6 times daily for ≥4 weeks), and systemic agents including β-blockers (e.g. propranolol, atenolol), clonidine, ibuprofen prior to bathing, pregabalin, H2-blockers, opioid receptor antagonists, antidepressants, and interferon-α may be helpful[8]. In secondary forms of aquagenic pruritus, treatments should target any underlying condition, e.g. antihistamines for dermographism.

DIFFERENTIAL DIAGNOSIS OF PRURITUS OR PRICKLING SENSATIONS PROVOKED BY WATER CONTACT
Disease-associated skin findings typically evident at time of visit
• Polycythemia vera (ruddy complexion; see text) • Mastocytosis (cutaneous lesions, positive Darier's sign) • Hypereosinophilic syndrome (cutaneous lesions in >50% of patients) • Hemochromatosis (diffuse hyperpigmentation)
Urticaria by history and/or challenge
• Dermographism • Cold urticaria • Cholinergic urticaria (with hot water exposure) • Aquagenic urticaria
Skin findings (other than those due to scratching) typically absent
• Hodgkin lymphoma • Myelodysplastic syndromes • Essential thrombocythemia • Testosterone-induced erythrocytosis • Drug-related (e.g. antimalarials, bupropion, clomipramine) • Aquagenic pruritus of the elderly (xerosis may be subtle) • Primary (idiopathic) aquagenic pruritus

Table 6.5 Differential diagnosis of pruritus or prickling sensations provoked by water contact. A possible relationship with lactose intolerance in a subset of patients has also been reported.

Pruritus in Scars

Scar remodeling can last from 6 months to 2 years. Pruritus associated with wound healing is common and usually resolves over time, but it is occasionally prolonged, especially in hypertrophic or keloidal scarring. The pruritus in immature or abnormal scars is most likely a consequence of physical and chemical stimuli as well as nerve regeneration. Physical stimuli include direct mechanical stimulation of nerve endings during scar remodeling. Histamine, vasoactive peptides (e.g. kinins), and prostaglandins E1/E2 may account for a "chemogenic" pruritus. Nerve regeneration occurs in all healing wounds, and a disproportionate number of thinly myelinated and unmyelinated C-fibers in immature or abnormal scars may contribute to increased itch perception. The observation of abnormalities in small nerve fiber morphology and function within keloids has raised the possibility of a small nerve fiber neuropathy[50].

Therapy includes emollients, topical and intralesional corticosteroids, cryotherapy, brachytherapy, and silicone gel sheets. Oral antihistamines do not have a significant benefit. Relief of pain and pruritus associated with giant keloids was observed with oral pentoxifylline (400 mg 2–3 times daily)[51].

Post-Thermal Burn Pruritus

Approximately 85% of patients with burns experience pruritus during the healing phase, particularly when the burns involve the limbs[52]. A gradual decrease in pruritus usually occurs, but it may persist for years. Both neuropathic and pruritogenic mechanisms are thought to contribute to the development of itch after a burn[53]. Reported predictors of pruritus include a deep dermal burn injury, female sex, and psychological distress[54]. Morphine therapy may also contribute to postburn pruritus. Emollients, topical anesthetics (e.g. lidocaine/prilocaine) or doxepin, massage therapy, bathing in oiled water or with colloidal oatmeal, extracorporeal shockwave therapy, and botulinum toxin may be of benefit[55,56]. In an RCT, oral gabapentin was found to be more effective than cetirizine for postburn pruritus[57]. Other systemic therapy options include ondansetron, opioid modulators, and antidepressants[53,58].

Fiberglass Dermatitis

Fiberglass exposure is common in individuals who work in manufacturing or construction. Deposition of fiberglass particles on the skin may provoke severe pruritus, sometimes in the absence of visible skin lesions (see Ch. 16). Involvement of the hands and other non-covered sites such as the arms, face, and upper trunk is typical. Cutaneous findings vary and include erythema, papules, vesicles, excoriations, and lichenification. The clinical presentation may resemble scabies, eczematous dermatitis, folliculitis, or urticaria. Tolerance often develops with prolonged fiberglass exposure[59].

PRURITUS IN SYSTEMIC DISEASE

Chronic Kidney Disease-Associated Pruritus (Renal Pruritus)

Pruritus is a frequent symptom in patients with advanced chronic (not acute) kidney disease, especially those requiring dialysis[7,60]. Although the term "uremic pruritus" is used synonymously, it incorrectly implies that the symptom is secondary to elevated serum urea levels. Nowadays, chronic kidney disease-associated pruritus (CKD-aP), rather than renal pruritus, is the preferred term.

CKD-aP may be localized or generalized, and the intensity and distribution often vary over time. Prurigo nodularis and other secondary skin lesions can develop due to scratching, rubbing, or picking the skin. CKD-aP represents an independent predictor of mortality in dialysis patients and is associated with sleep disturbances, depression, and impaired quality of life[61].

In general, the occurrence of CKD-aP is not associated with sex, race, duration of dialysis, or etiology of the kidney disease[7]; it is rare in children but otherwise does not correlate with age. From 25% to 45% of hemodialysis patients suffer from pruritus[7,62]; a decrease in pruritus frequency over the past few decades likely reflects improvements in dialysis procedures, such as utilization of high-permeability rather than conventional hemodialysis[63]. Patients receiving continuous ambulatory peritoneal dialysis (CAPD) appear to be slightly less or equally affected by pruritus compared to those on hemodialysis[1]. In patients receiving standard thrice weekly hemodialysis, pruritus usually peaks in the evening after 2 days without dialysis, is relatively high during dialysis, and is lowest the following day[64,65].

The etiology of CKD-aP is poorly understood. The role of mast cells and histamine is controversial, with no relationship between plasma histamine levels and the severity of pruritus[66]. This finding is supported by the failure of antihistamine therapy in most affected individuals. Another possible explanation for CKD-aP is an accumulation of compounds that cross the dialysis membranes slowly[1].

Parathyroid gland activity is commonly increased in chronic kidney disease, and dramatic relief of pruritus after subtotal parathyroidectomy has been reported in some patients[1]. However, although higher serum levels of calcium, phosphate, and parathyroid hormone (PTH) have been detected in dialysis patients with pruritus than in those without pruritus, no correlation between degree of pruritus and PTH levels has been observed[67]. Furthermore, studies have failed to demonstrate PTH immunoreactivity within the skin, PTH does not produce pruritus when injected intradermally, and pruritus is not always present in uremic patients with hyperparathyroidism.

Although dry, scaly skin is common in patients with chronic kidney disease (Fig. 6.8), the presence of pruritus does not correlate with xerosis, stratum corneum hydration, or sweat secretion[68,69]. Peripheral neuropathy affects up to 65% of patients who receive dialysis, raising the possibility that pruritus may be a manifestation of a neuropathy. Loss of itch-*inhibiting* CGRP-expressing neurons in the papillary dermis has been observed in CKD-aP patients[70]. Opioids could potentially play a role, as they accumulate with renal failure. However, this accumulation is unrelated to the duration of disease and levels are unaltered by hemodialysis[1]. A recent study found a decrease of κ-opioid receptors in the skin of hemodialysis patients with pruritus, suggesting a role of the peripheral opioid system in renal itch[68]. It has also been suggested that an immunologic alteration characterized by a proinflammatory pattern is involved in the pathogenesis of CKD-aP, and elevated serum IL-31 levels have been reported[69]. Lastly, higher serum aluminum levels have also been associated with pruritus in hemodialysis patients[71].

The management of CKD-aP is often very challenging, and currently available therapeutic options are outlined in Table 6.6. Xerosis should be addressed with gentle skin care and emollients (see Table 6.11). Treatment with topical γ-linolenic acid, pramoxine, corticosteroids, tacrolimus, or capsaicin may be helpful. Antihistamines typically have only marginal efficacy, with improvement related primarily to their sedative effects[1].



Fig. 6.8 Xerosis and scratching in a patient with end-stage kidney disease undergoing hemodialysis. There are a few papules of acquired perforating dermatosis admixed with the scratch marks. *Courtesy Jean L. Bolognia, MD.*

THERAPEUTIC LADDER FOR RENAL PRURITUS	
First-line	Gabapentin (100–300 mg po*) (1) Pregabalin (25–75 mg po*) (1) Difelikefalin† (0.5 mcg/kg iv*) (1)
Second-line	UVB narrowband or broadband phototherapy (alone or in combination with other treatments) (1)
Third-line	Naltrexone‡ (25–50 mg po daily) (2) Naloxone‡ (0.002–0.2 mcg/kg body weight/min iv × 8 hours for 3–5 days, repeated monthly) (3) Nalfurafine† (2.5–5 mcg po or iv*) (1)
Localized itch	Capsaicin cream (0.025% 3–5 times daily) (2)
Additional options	*Topical* γ-linolenic acid (2.2% cream 4 times daily) (1) Pramoxine (1% lotion 2–4 times daily) (1) Cromolyn sodium (4% cream twice daily) (1) *Systemic* Activated charcoal (6 g po daily) (1) Montelukast (10 mg po daily) (1) Cromolyn sodium (100–135 mg po 3–4 times daily) (1) Doxepin (10–20 mg po daily) (1) Ketotifen (1–2 mg po daily) (2) Sertraline (25–100 mg po daily) (2) Pentoxifylline (600 mg iv*) (3) Lidocaine (200 mg iv daily) (3) Erythropoietin (36 U/kg sc 3 times weekly) (3) Cholestyramine (4–16 g po daily in divided doses) (2)

*Typically administered post-hemodialysis; in non-dialysis-dependent patients, dose adjustments for gabapentinoids are made based upon degree of renal impairment.
†κ-opioid receptor agonist; nalfurafine is available in Japan.
‡μ-opioid receptor antagonist.

Table 6.6 Therapeutic ladder for renal pruritus[136]. Additional interventions include addressing underlying xerosis, evaluating the quality of dialysis (see text), and assessing serum parathyroid hormone (PTH) level, with treatment of hyperparathyroidism if present. The combined μ-opioid receptor antagonist/κ-opioid receptor agonist nalbuphine was found to have benefit in an RCT, but the extended release oral formulation used in the study is not currently available. General measures for pruritus management are summarized in Table 6.11. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. iv, intravenously; po, per os; sc, subcutaneously.

In patients with CKD-aP, serum PTH levels should be assessed and hyperparathyroidism treated if present. The quality of dialysis should also be evaluated to ensure that the Kt/V (urea clearance [K] multiplied by dialysis time [t] divided by volume of urea distribution [V]) is ≥1.2. If itch persists, gabapentin (100–300 mg orally) after each dialysis session can be tried; low-dose pregabalin may be equally effective[72]. Phototherapy, especially broadband or narrowband UVB, represents an alternative or adjunctive modality. Difelikefalin, a peripherally acting κ-opioid receptor agonist, was shown in an RCT to significantly reduce itch intensity in hemodialysis patients and is now an FDA/EMA-approved treatment for CKD-aP[73]. Nalfurafine (available in Japan) is another κ-opioid receptor agonist that was found to be effective in multicenter controlled studies[74]. The μ-opioid receptor antagonist naltrexone (25–100 mg orally daily) represents an additional option. Even in patients with intractable CKD-aP, renal transplantation generally leads to resolution of itch.

Cholestatic Pruritus

Nearly any liver disease can present with pruritus, but the most commonly associated entities are primary biliary cholangitis (primary biliary cirrhosis), primary sclerosing cholangitis, obstructive choledocholithiasis, carcinoma of the bile duct, cholestasis (may also be drug-induced), chronic hepatitis C viral infection, and other forms of viral hepatitis[1]. Pruritus in these settings tends to be generalized, migratory, and not relieved by scratching. It tends to be more pronounced at night and is typically worse on the hands and feet (especially the palms and soles) as well as body regions constricted by clothing. In patients with chronic cholestasis, pruritus can be an early symptom that develops years before any other manifestation of the liver disease[1].

The exact etiology of cholestatic pruritus is unknown. MRGPRX4 (Mas-related G-protein coupled receptor member X4), a bile acid receptor expressed in sensory neurons, is involved in itch transmission and may represent a therapeutic target.[75,76] However, elevated serum levels of bile acids are not always associated with pruritus, and in patients with severe cholestasis the development of hepatocellular failure tends to result in spontaneous cessation of pruritus[77]. Increased opioidergic neurotransmission or neuromodulation in the CNS is also hypothesized to contribute to cholestatic pruritus[78].

Other studies have provided evidence that lysophosphatidic acid (LPA), a neuronal activator, and autotaxin (ATX, lysophospholipase D), the enzyme responsible for production of LPA from lysophosphatidylcholine, play significant roles in cholestatic pruritus[79]. Unlike other putative mediators, ATX levels correlate with the intensity of itch in patients with cholestasis[77]. However, the factors presumably present in the enterohepatic circulation that are responsible for induction of ATX expression remain to be determined[80,81].

The disease underlying cholestatic pruritus should be treated if possible, such as gallstone removal, drug withdrawal, and therapy for chronic hepatitis C infection with direct-acting antiviral agents. A stepwise approach to the treatment of cholestatic pruritus is provided in Table 6.7[77,81]. In intrahepatic cholestasis of pregnancy (see Ch. 27), ursodeoxycholic acid (UDCA) significantly reduces itch and serum bile acid levels, probably due to improvement of hepatobiliary secretion, and it represents first-line therapy[82]. Although UCDA is also used in other cholestatic conditions, itch has not been studied as the primary endpoint. The ileal bile acid transporter inhibitors odevixibat and maralixibat are FDA-approved to treat cholestatic pruritus in patients with progressive familial intrahepatic cholestasis and Alagille syndrome, respectively[83,84]. The recommended first-line treatment for other forms of cholestatic pruritus is the anion exchange resin cholestyramine, which binds bile acids in the small intestine and results in their fecal excretion[85]. Rifampin represents a second-line option and may work by reducing ATX expression on a transcriptional level[86]. Opioid antagonists (e.g. naltrexone, naloxone) and the SSRI sertraline can also have antipruritic effects in cholestatic itch[87–89]. Fibrates, phototherapy, albumin dialysis, and plasmapheresis are additional treatment options[85]. Ultimately, liver transplantation for end-stage liver failure can improve symptoms.

Hematologic Pruritus

Significant pruritus can occur in association with a number of hematologic diseases, especially hypereosinophilic syndromes (see Ch. 25) and myeloproliferative neoplasms such as polycythemia vera and Hodgkin lymphoma, and less often essential thrombocythemia. Occasionally, patients with myelodysplastic syndrome have significant pruritus.

Iron deficiency

In patients with iron deficiency plus generalized or localized pruritus, especially of the perianal or vulvar region, improvement with iron supplementation has been described[1,90]. Of note, iron deficiency can be a sign of polycythemia vera and other malignancies or systemic diseases that themselves may cause pruritus. In addition to laboratory confirmation, the etiology of the iron deficiency should be determined, including exclusion of a gastrointestinal source of blood loss.

Polycythemia vera

Aquagenic pruritus may precede the development of polycythemia vera by several years and eventually affects ~30%–50% of polycythemia vera patients. Thus, this diagnosis should be considered in all patients with aquagenic pruritus (see above). Additional cutaneous findings include a ruddy facial complexion, erythema of the hands and feet, and conjunctival injection. Approximately 97% of patients with polycythemia vera have a somatic mutation (V617F) in the Janus kinase 2 gene (*JAK2*) that results in constitutive activation and agonist hypersensitivity in basophils, which may have a pathogenic role in their aquagenic pruritus. Platelet aggregation has also been suggested as a possible underlying mechanism, with release of serotonin and other pruritogenic factors such as histamine. In RCTs, the JAK 1/2 inhibitor ruxolitinib led to rapid improvement of polycythemia vera and its associated pruritus[91,92]. Other treatment options include hydroxyurea, aspirin (300 mg daily), UVB or PUVA phototherapy (reports of success), SSRIs (effective in small series), interferon-α-2b (approved therapy with good efficacy), and oral H1- or H2-receptor antagonists (variable results)[1,93].

TREATMENT OPTIONS FOR HEPATIC OR CHOLESTATIC PRURITUS		
	Treatment and dosing	**Specific indications**
First-line	Cholestyramine (4–16 g po daily, with 4-hour interval if taking other medications) (1)	Cholestatic pruritus
	Odevixibat* (40–120 mcg po daily, maximum 6 mg daily) (1)	Progressive familial intrahepatic cholestasis
	Maralixibat* (190–380 mcg/kg po daily) (1)	Alagille syndrome
	Ursodeoxycholic acid (13–15 mg/kg or 1 g po daily) (1)	Intrahepatic cholestasis of pregnancy
Second-line	Rifampin (150–600 mg po daily) (1)	
Third-line	Bezafibrate (400 mg po daily) (1)	Primary biliary cholangitis, primary sclerosing cholangitis
Fourth-line	Naltrexone† (25–50 mg po daily) (1) Naloxone† (0.002–0.2 mcg/kg body weight/min iv × 8 hours for 3–5 days, repeated monthly) (1) Gabapentin (300–3600 mg daily) (3) Pregabalin (75–600 mg po daily) (3)	
Fifth-line	Sertraline (75–100 mg po daily) (1)	
Additional options	Phototherapy with narrowband or broadband UVB (3) Nalmefene† (escalating twice daily po dose: 2 mg [day 1], 5 mg [day 2], 10 mg [day 3], then 20 mg; further increases as needed, maximum of 120 mg) (1) Nalfurafine‡ (2.5–5 mcg po daily) (1) Butorphanol nasal spray¶ (1–2 mg [1–2 puffs] daily) (3) Paroxetine (10–20 mg po daily) (3) Dronabinol (5 mg po nightly) (3) Phenobarbital (2–5 mg/kg po daily) (3) Lidocaine 100 mg iv daily (1) Thalidomide 100 mg po daily (3)	
Procedural interventions	Nasobiliary drainage (3) Plasmapheresis, plasma separation and anion adsorption (3) Extracorporeal albumin dialysis (e.g. MARS – molecular adsorbents recirculating system) (3)	

*Ileal bile acid transporter inhibitor.
†μ-opioid receptor antagonist.
‡κ-opioid receptor agonist; nalfurafine is available in Japan.
¶Combined κ-opioid receptor agonist and μ-opioid receptor antagonist.

Table 6.7 Treatment options for hepatic or cholestatic pruritus[136]. Antihistamines have limited benefit other than their sedating properties. Gabapentin did not have a therapeutic advantage over placebo in a controlled study. Ileal bile transporter inhibition with linerixibat was shown to be of benefit for primary biliary cholangitis in an RCT. General measures for pruritus management are summarized in Table 6.11. Potential adverse effects of rifampin include hepatitis, hemolytic anemia, and renal failure, necessitating periodic laboratory monitoring in patients with cholestasis. Potential adverse effects of bezafibrate include hepatic toxicity, rhabdomyolysis, and osteoporosis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. iv, intravenously; po, per os.

Pruritus and Malignancy

Virtually any malignancy can induce pruritus, but the precise relationship between cancer and this symptom is unclear. In 2014, a special interest group of the International Forum on the Study of Itch[94] defined "paraneoplastic itch" as "a systemic reaction to the presence of a tumor or a hematological malignancy, neither induced by the local presence of cancer cells nor by tumor therapy". They noted that the itch usually disappears with remission of the neoplasm and returns with a disease relapse.

Paraneoplastic itch is most frequent with myeloproliferative neoplasms (e.g. polycythemia vera > essential thrombocythemia), lymphoma (Hodgkin > non-Hodgkin), and cancers of the liver or biliary system[91]. A population-based cohort study found that patients with chronic pruritus without concomitant skin findings (n = 8744; mean age, 61 years) had 2- and 3.7-fold increased risks of an incident hematologic or bile duct malignancy, respectively[92]. Another study found a 1-year absolute risk of cancer of 1.6% in patients with pruritus[95]. In pediatric patients, itch is most often associated with hematologic malignancies[96]. Thus, persistent unexplained pruritus or failure of generalized pruritus to respond to conventional therapy should warrant evaluation for an underlying malignancy, including a complete blood count and hepatic panel as well as a thorough review of systems and physical examination[10,94].

Paraneoplastic pruritus can occur in advanced disease or represent an early sign, which is sometimes present for several years prior to diagnosis. However, the intensity and extent of pruritus do not generally correlate with the extent of tumor involvement[1]. Proposed mechanisms of tumor-associated pruritus include toxic products from necrotic tumor cells entering the systemic circulation, production of chemical mediators of pruritus by the tumor, allergic reactions to tumor-specific antigens, increased proteolytic activity, and histamine release[8]. Pruritus can also be a symptom of malignancies that obstruct the biliary tree (e.g. carcinoma of the head of the pancreas or bile duct) or involve the brain ("central" pruritus)[8]. In addition, pruritus may develop due to treatment with surgery, radiotherapy, cytotoxic chemotherapy, targeted tumor therapy[94], or immunotherapy[97].

Treatment of the underlying malignancy is the most effective measure. In refractory cases, or when the tumor is not treatable, therapeutic options include antidepressants (e.g. paroxetine, mirtazapine), gabapentinoids, opioid modulators, NK1 receptor antagonists, and histone deacetylase inhibitors[8,98].

Hodgkin lymphoma

Up to 30% of patients with Hodgkin lymphoma experience pruritus. It is usually generalized and classically manifests at night in association with chills and sweating[1,8]. Severe, persistent pruritus is predictive of a poor prognosis, and return of this symptom may portend tumor recurrence. It has been proposed that pruritus should be added to the list of the "B symptoms" in this disease[1].

Factors contributing to pruritus in Hodgkin lymphoma may include eosinophilia and release of histamine (from basophils), leukopeptidases, or bradykinin. Hepatic involvement by the lymphoma may occasionally play a role. Production of IL-5 by Reed–Sternberg cells can lead to eosinophilia, but whether the eosinophil count correlates with the degree of pruritus is unclear. While the pruritus usually resolves following successful treatment of the lymphoma, based upon case reports and series, phototherapy, cimetidine, carbamazepine, mirtazapine, oral corticosteroids, and NK1 receptor antagonists may lead to some improvement[8,93].

Non-Hodgkin lymphoma

Pruritus is generally less prevalent in non-Hodgkin lymphoma than in Hodgkin lymphoma. Up to 10% of patients with non-Hodgkin lymphoma suffer from pruritus at some time during their disease course, often with improvement after successful therapy.

Leukemia

Pruritus is not a common symptom in patients with leukemia, but when it occurs, it is usually generalized. Chronic lymphocytic leukemia (CLL) and hypereosinophilic syndromes, which include patients with eosinophilic leukemia and other hematologic malignancies (see Ch. 25), are most often associated with pruritus. In addition, patients with CLL can develop exaggerated reactions to insect bites (see Ch. 33). Leukemia cutis may produce localized symptoms that include pruritus[10].

Endocrine Pruritus

Thyroid disease

Severe generalized pruritus may be a presenting symptom of hyperthyroidism. The cause is not known, but it is postulated to result from a direct effect of thyroid hormone on the skin[1]. Localized or generalized pruritus may also be seen in patients with hypothyroidism, but not as frequently. The skin in individuals with hypothyroidism is often dry, which can lead to asteatotic eczema accompanied by pruritus.

Diabetes mellitus

Generalized pruritus is a fairly common symptom of diabetes mellitus, with itch often first developing on the back[99]. Diabetic polyneuropathy is characteristically associated with pain as well as burning or prickling sensations, but it can also present with pruritus that starts on the feet and lower legs[99].

Pruritus in HIV Infection

Severe, treatment-resistant pruritus can be seen in HIV-infected individuals, and a possible correlation between intractable pruritus and increased HIV viral load has been observed[100]. Immunologic parameters associated with pruritus in HIV patients include markedly elevated IgE levels, peripheral hypereosinophilia, and a Th2-type cytokine profile.

HIV-infected individuals may develop a number of pruritic dermatoses such as pruritic papular eruption, eosinophilic folliculitis, severe seborrheic dermatitis, psoriasis, scabies, insect bite reactions, drug eruptions, xerosis, and acquired ichthyosis (see Ch. 78). Kaposi sarcoma lesions are occasionally pruritic. Patients with HIV infection may also have other causes of pruritus, such as chronic kidney disease, liver disease, and non-Hodgkin lymphoma and they can develop prurigo nodularis[101].

Treatment should be directed at any underlying dermatoses that can be identified (see above). Topical corticosteroids and antihistamines can be used symptomatically; antihistamines with anti-eosinophilic potential (e.g. cetirizine) may be more effective. UVB is an additional therapeutic option and is considered to be safe in HIV-infected individuals[102]. Although antiretroviral therapy (ART) can lead to improvement in several pruritic dermatologic diseases, a variety of infectious, inflammatory, and neoplastic skin conditions may flare when ART is started (immune reconstitution inflammatory syndrome; see Ch. 78)[101]. Thalidomide (100–300 mg daily) is used to treat pruritus and prurigo nodularis in patients with HIV infection and AIDS, as it is not an immunosuppressant[10,103].

PRURITUS IN PREGNANCY

Approximately 20% of pregnant women experience pruritus. This symptom can have multiple etiologies in a pregnant patient[104] and is discussed in Chapter 27.

PHARMACOLOGIC PRURITUS

Virtually any drug can cause a skin reaction that is associated with pruritus[1]. Pruritic drug reactions most often present as morbilliform or urticarial eruptions (see Ch. 21). Occasionally, however, pruritus is the predominant manifestation with an absence of skin findings (Table 6.8)[105,106]. Some medication effects (e.g. hepatotoxicity) that can lead to pruritus have a relatively long latency period. The primary goal is to identify and discontinue the offending drug, with supportive antipruritic therapy as needed (see Table 6.11).

COMMON PHARMACOLOGIC ETIOLOGIES OF PRURITUS

Pathomechanism	Medication(s)
Cholestasis	Erythromycin estolate, estrogens (including oral contraceptives), captopril, sulfonamides, chlorpromazine
Hepatotoxicity	Acetaminophen, anabolic steroids (including testosterone), isoniazid, minocycline, amoxicillin–clavulanic acid, halothane, phenytoin, sulfonamides
Xerosis	Retinoids, β-blockers, calcium channel blockers, hydrochlorothiazide, tamoxifen, busulfan, clofibrate
Phototoxicity	8-Methoxypsoralen
Neurologic	Methamphetamine, tramadol, codeine, cocaine, morphine*,†, butorphanol*, fentanyl*
Increased serotonin signaling	Selective serotonin reuptake inhibitors (e.g. sertraline, fluoxetine)
Increased bradykinin levels‡	Angiotensin-converting enzyme (ACE) inhibitors
Increased leukotriene levels	Nonsteroidal anti-inflammatory drugs (NSAIDs)
Histamine analogue	Betahistine
MRGPR¶ stimulation	Chloroquine (pruritus may be generalized, localized to the hands/feet, or aquagenic; most common in individuals of African descent)
T cell activation due to CTLA-4, PD-1, or PD-L1 inhibition	Ipilimumab, nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab, durvalumab
EGFR inhibition	Cetuximab, panitumumab, erlotinib, gefitinib, afatinib, osimertinib
Selective BRAF or MEK inhibition	Dabrafenib, encorafenib, vemurafenib; binimetinib, cobimetinib, trametinib
Other tyrosine kinase inhibition	Sorafenib (especially scalp pruritus), imatinib, dasatinib, nilotinib (see Table 21.16)
Deposition	Hydroxyethyl starch
Idiopathic	Clonidine, lithium, bleomycin, gold salts

*Pruritus is more likely with intrathecal/epidural than systemic administration.
†Also causes non-immunologic release of histamine from mast cells.
‡Pruritus may precede development of angioedema.
¶MAS-related G protein-coupled receptor expressed by epidermal C-nerve fibers.

Table 6.8 Common pharmacologic etiologies of pruritus[137–141]. Itch may also occur as a direct effect of interleukin 2 therapy. CTLA-4, cytotoxic T lymphocyte-associated antigen 4; EGFR, epidermal growth factor receptor; PD-1, programmed cell death protein 1.

PSYCHOGENIC PRURITUS

Generalized pruritus can be associated with anxiety disorders, depression, anorexia, and even psychoses (e.g. delusional infestation; see Ch. 7). In true psychogenic pruritus, patients present with a purely sensory complaint (pruritus) without evidence of a delusional component, primary skin disease, or underlying medical condition. It is rare and must be separated from excoriation (skin-picking) disorder, in which a patient creates cutaneous lesions without pre-existing pruritus. The intensity of psychogenic pruritus tends to parallel the emotional state and is often exaggerated[10]. No primary lesions are seen, and secondary lesions range from lichenification to excoriations. Although the patient's sleep pattern is usually uninterrupted, sedative antipruritics (e.g. doxepin) may be utilized as therapy because topical agents alone are rarely effective. Consultation with a psychiatrist is recommended.

NEUROPATHIC ETIOLOGIES OF PRURITUS AND DYSESTHESIA

A dysesthesia is defined as an unpleasant abnormal skin sensation, such as tingling, burning, numbness, or pruritus; it can be spontaneous or evoked and may result from abnormalities in the central or peripheral nervous system. Dysesthesias, including pruritus, are usually localized or regional in distribution and can affect almost any site. For dysesthesias related to disorders of the CNS, the location of the abnormality is more important than its cause. In other words, a stroke, tumor, or multiple sclerosis plaque in the same region of the brain will generate similar neurologic signs and symptoms[107].

Neuropathic pruritus most often results from damage, compression, or irritation affecting a nerve or group of nerves[3]. These neuropathies typically present with localized pruritus and secondary skin lesions due to repeated rubbing or scratching in a circumscribed area supplied by the afflicted nerve(s) (Fig. 6.9A). Pruritus may occasionally spread beyond the initial site, likely due to sensitization mechanisms. Pruritus of neurogenic origin occurs without neuronal damage, such as increased endogenous μ-opioids leading to disinhibition of itch.

Sensory (Mono)Neuropathies with Pruritus and Dysesthesia

Sensory (mono)neuropathies that are most often brought to the attention of dermatologists are notalgia paresthetica and brachioradial pruritus. Less often, symptoms of meralgia, cheiralgia, or digitalgia paresthetica require dermatologic assessment (see Fig. 6.9). Secondary skin lesions, if present, include excoriations, crusted papules, hyperpigmentation, and lichenification; these findings are localized to the area of dysesthesias that corresponds to the receptive field of one or a few sensory nerves[108].

Treatment with topical capsaicin (0.025%–0.1%) 3–6 times daily for ≥4–6 weeks or a capsaicin 8% patch (applied for one hour under physician supervision; may be repeated every 3 months, if needed) may be helpful. Other treatment options include topical anesthetics (e.g. lidocaine, pramoxine), topical corticosteroids, oral gabapentin/pregabalin, and acupuncture.

Notalgia paresthetica

Notalgia paresthetica is a common condition in adults that is characterized by focal, intense pruritus of the upper back, especially over the medial scapular borders. Most evidence suggests that notalgia paresthetica represents a sensory neuropathy. The posterior rami of T2–T6 pursue a right-angle course through the multifidus spinae muscle that extends along the vertebral column, potentially predisposing these nerves to entrapment and injury (Fig. 6.9C). Degenerative changes of the spine corresponding to the affected dermatome(s) are present in a subset of patients[109]. Notalgia paresthetica can also represent a sign of multiple endocrine neoplasia type 2A (Sipple syndrome; see Ch. 63), especially if the onset is during childhood or adolescence.

In addition to itch, patients may occasionally report pain, dysesthesias, paresthesias, or hyperesthesias[109]. A characteristic finding on physical examination is a hyperpigmented patch due to chronic rubbing of the affected area. Dermal melanophages are evident histologically, and there is considerable overlap with macular amyloidosis (see Ch. 47).

Treatment of notalgia paresthetica is often difficult. Topical antipruritics (e.g. pramoxine) and corticosteroids are typically ineffective. Topical capsaicin may provide temporary benefit, and oxcarbazepine and gabapentin have demonstrated variable improvement in case series. Oral difelikefalin is under investigation, but currently it requires intravenous administration. Additional case reports have shown benefits from botulinum toxin A, but in an RCT, intradermal botulinum toxin A injection showed no benefit over placebo. If spinal pathology is suspected, management considerations include spinal imaging, referral for orthopedic or neurologic consultation; and treatment of the underlying cause with modalities such as physical therapy (e.g. rolling on a massage ball), nerve blocks, and surgical decompression.

Brachioradial pruritus

This chronic sensory neuropathy of the radial dorsal antebrachial cutaneous nerve is characterized by intermittent pruritus or burning

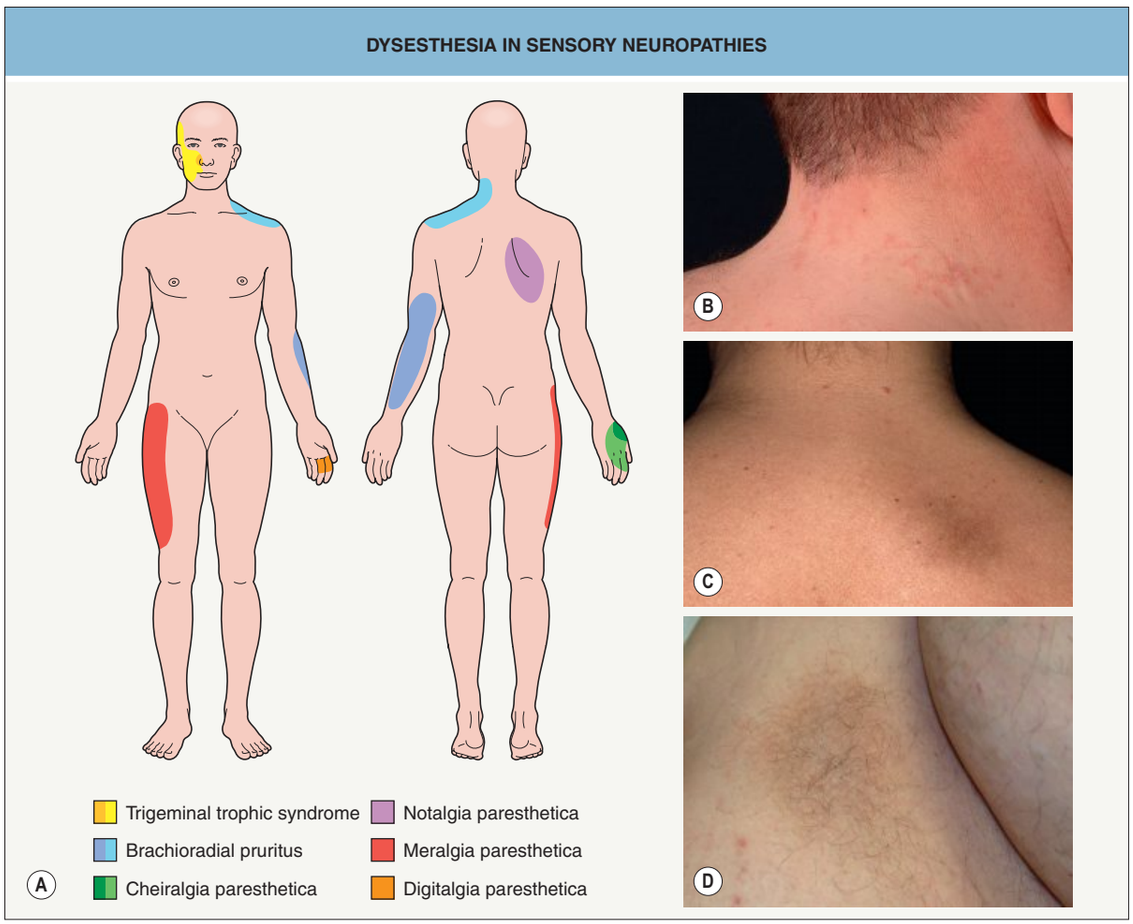


Fig. 6.9 Dysesthesia in sensory neuropathies. A Distribution of dysesthesia in selected neuropathic conditions. The names for these entities come from Greek terms, e.g. *notos* = back, *meros* = thigh, *cheiron* = hand, *algos* = pain. Darker shades indicate more common areas of involvement. **B** Secondary skin lesions on the right neck in a patient with cervical osteoarthropathy. **C** Classic notalgia paresthetica with hyperpigmentation on the right upper back at the medial scapular border. **D** Meralgia paresthetica presenting as hyperpigmentation and lichenification in a discrete area of dysesthesia on the anterior thigh. *A, Courtesy Karynne O. Duncan, MD; C, Courtesy Lorenzo Cerroni, MD.*

pain on the dorsolateral aspects of the forearms and elbows; there is sometimes more extensive involvement (e.g. of the shoulder and neck; Fig. 6.9B)[110]. More than half of patients have radiographic evidence of degenerative osteoarthritis of the spine compressing their cervical nerve roots[111], and there are rare reports of an associated spinal cord tumor. Cumulative sun exposure represents another predisposing factor. Due to hypersensitivity of cutaneous nerves, acute UV light exposure can also exacerbate the condition[1,110], and patients living in temperate climates often experience remissions during the fall and winter. Patients may relate that application of ice provides some relief.

Skin examination often reveals a variable number of excoriations, prurigo simplex or nodularis lesions, and even scars localized to the vicinity of the brachioradialis muscle. Evaluation should include a neurologic examination and, based on the results, consideration of cervical spine imaging to exclude myelopathy or tumors. In addition to the treatments noted above, diligent sun protection may be of benefit.

Meralgia paresthetica

Meralgia paresthetica presents with numbness, burning pain, tingling, and/or itching of the anterolateral thigh (Fig. 6.9D)[108]. Allodynia (increased sensitivity to light touch) is another manifestation, but cutaneous findings such as hyperpigmentation are less common than in notalgia paresthetica. Meralgia paresthetica occurs in the territory of the lateral femoral cutaneous nerve, and it results from pressure on this nerve as it passes under the inguinal ligament. Predisposing factors include obesity, pregnancy, prolonged sitting, tight clothing, and carrying heavy wallets in trouser pockets. Much less often, it results from a lumbar radiculopathy.

Cheiralgia paresthetica

Cheiralgia paresthetica is a sensory mononeuropathy of the superficial branch of the radial nerve[108]. Patients report numbness, tingling, or burning involving the dorsoradial aspect of the hand and proximal thumb (see Fig. 6.9A). The cause is usually trauma or pressure, e.g. from a tight wristwatch or handcuffs.

Digitalgia paresthetica

Digitalgia paraesthetica is a sensory neuropathy affecting digital nerves of the fingers and less often the toes[108]. It results from trauma or pressure, e.g. on the fingers from carrying heavy plastic grocery bags or on the toes from long marches or hikes.

Regional Dysesthesias with Burning or Pain

Burning mouth syndrome

Burning mouth syndrome (orodynia) is characterized by burning mucosal pain without clinically detectable oral lesions. The pain is typically bilateral, often involving the anterior two-thirds of the tongue, palate, and lower lip[112]. The buccal mucosa and floor of the mouth are rarely involved. The histology of the affected areas in primary burning mouth syndrome is unremarkable; however, secondary causes may be identified.

The condition typically affects middle-aged or older adults, with a female : male ratio of ~7 : 1[113]. Symptoms can last from a few months to several years. A classification system based on the pattern of disease over time has been described: *type 1* (35%) – absence of symptoms upon awakening, with a gradual increase in severity over the course of the day; *type 2* (55%) – constant burning, both day and night; and *type 3* (10%) – days of remission that follow no identifiable pattern[113].

The evaluation of burning mouth syndrome should include a thorough physical examination to help exclude secondary causes, although the disorder is frequently idiopathic. Localized burning or itch may be the first indication of a malignant lesion (e.g. an oral squamous cell carcinoma). Ill-fitting dentures, oral candidiasis, xerostomia, and contact dermatitis to dental work have been reported as other secondary causes. All prescription and over-the-counter medications should be reviewed to identify any that have xerostomia as a side effect. Additional precipitating factors include iron, zinc, folate, and vitamin B_{12} deficiencies as well as type 2 diabetes mellitus, hypothyroidism, and menopause[114]. Lastly, depression and anxiety are more common in patients with burning mouth syndrome than in pain-free controls[113].

Any underlying disorders should be treated, which may require referral for dental or psychiatric evaluation. In primary burning mouth syndrome, reportedly efficacious treatments include oral tricyclic antidepressants (e.g. amitriptyline, doxepin), topical or low-dose oral clonazepam (start at 0.25 mg and slowly titrate to 1–1.5 mg per day, in 3 divided doses), and gabapentinoids[115]. Antidepressant doses should be low initially and then increased slowly to minimize problematic side effects such as xerostomia and sedation. In case reports and series, successful treatments have included topical antifungal agents (even when cultures were negative), capsaicin, and anesthetics such as lidocaine or dyclonine; in addition, mouthwashes containing various combinations of anesthetics, nystatin, tetracycline, hydrocortisone, and diphenhydramine have been utilized. Cognitive behavioral therapy and α-lipoic acid (600 mg daily) may also improve symptoms[116,117].

Burning scalp syndrome

Burning scalp syndrome (scalp dysesthesia)[118,119] presents with diffuse burning pain, pruritus, numbness, or tingling of the scalp without objective findings. Secondary causes such as seborrheic dermatitis, folliculitis, lichen planopilaris, allergic or irritant contact dermatitis, and dermatomyositis should be excluded and treated if present. Burning scalp syndrome is often associated with underlying depression and anxiety. Like other dysesthesias, it can be treated with gabapentinoids, tricyclic antidepressants, and topical capsaicin[118].

Red ear syndrome

Patients have intermittent episodes of erythema involving one external ear and less often both ears. The redness can persist for minutes to hours and is associated with burning and/or pain. Triggers include heat, cold, and touch. Clinically, this disorder has been likened to erythromelalgia and associated with migraine headaches, but the precise etiology remains unclear. One hypothesis is dysregulation of sympathetic outflow, while some patients have evidence of cervical spine disease. Reported treatments include indomethacin and β-blockers as well as therapies used for other regional dysesthesias.

Dysesthetic anogenital pain syndromes

The most common causes of anal pain are hemorrhoids and fissures. Likewise, genital pain is often related to etiologies such as trauma, infection (e.g. *Chlamydia*, herpes simplex, candidiasis, mpox), and (in men) testicular torsion. Since chronic pain may be a harbinger of malignancy, a thorough evaluation is indicated. However, patients with chronic or recurrent anogenital pain but no detectable abnormalities on physical examination may have a dysesthetic anogenital pain syndrome (Table 6.9). Vulvodynia is discussed in Chapter 73. Of note, anogenital pruritus (see above) can also represent a dysesthetic state.

Trigeminal neuralgia and trigeminal trophic syndrome

Trigeminal neuralgia (tic douloureux) is characterized by recurrent paroxysms of sharp pain lasting seconds to minutes and radiating into the territory of one or more of the trigeminal sensory divisions. The pain is usually unilateral (most often right-sided) and described as a stabbing, burning, or shocking sensation. Attacks occur as often as several times per day or as infrequently as a few times per month. Potential triggers include touching or washing the face, brushing of teeth, eating, and talking. Cutaneous and neurologic examinations are

DYSESTHETIC ANOGENITAL PAIN SYNDROMES	
Syndrome	**Clinical history**
Levator ani syndrome	Brief intermittent burning pain or tenesmus of the rectal or perineal area. Aggravated by sitting or elimination
Proctalgia fugax	Sudden stabbing pain in the perirectal area. Awakens patient from sleep
Coccydynia	Intermittent or persistent pain, usually burning type, localized to the coccyx
Male genital pain syndrome	Intermittent, continuous, or episodic pain during penetration, ejaculation, micturition, or exercise
Koro syndrome	Psychogenic disorder characterized by acute anxiety, fear of death, and sensations that the genitalia are inwardly retracted and (variably) burning pain

Table 6.9 Dysesthetic anogenital pain syndromes. Vulvodynia is discussed in Chapter 73.

typically normal; if neurologic findings are present, the possibility of an underlying tumor or multiple sclerosis should be considered.

MRI should be performed to exclude secondary causes of trigeminal neuralgia ("painful trigeminal neuropathy"), such as multiple sclerosis, trauma, or a tumor. In ~80%–90% of patients with trigeminal neuralgia, high-resolution MRI with MRA demonstrates compression of the trigeminal nerve root by a vascular loop (referred to as the "classic" form)[120]. Rare familial forms have been linked to variants in genes encoding voltage-gated ion channels and transient receptor potential channels[121,122].

Regardless of etiology, carbamazepine (200–1200 mg daily) and oxcarbazepine (300–1800 mg daily) are considered first-line therapies for trigeminal neuralgia, providing relief in ~90% of patients[122]. Additional treatment options include gabapentinoids, lamotrigine, and baclofen. Botulinum toxin A injections may also be of benefit[123]. In refractory disease, surgical interventions such as microvascular decompression and ablative procedures (e.g. gamma knife radiosurgery) can be employed.

Trigeminal trophic syndrome is a self-induced ulcerative condition of the central face that classically involves the nasal ala[124,125]. Patients characteristically present with a small crust that develops into a crescentic ulcer, which may gradually extend to involve the cheek and upper lip (Fig. 6.10). The self-mutilation is triggered by dysesthesia together with hypesthesia, both resulting from damage to the sensory portion of the trigeminal nerve. The nasal tip, which is supplied by the external nasal branch of the anterior ethmoidal nerve (see Ch. 142), is typically spared. The underlying nerve damage is most often iatrogenic due to therapeutic ablation for trigeminal neuralgia; other causes include stroke, herpes zoster, trauma, and craniofacial surgery[125]. *Cervical trophic syndrome* represents a similar condition in which dysesthesia and self-mutilation occur in a cervical distribution[126].

The differential diagnosis of a non-healing facial ulcer includes malignancies (e.g. basal cell or squamous cell carcinoma, nasal NK/T cell lymphoma), infections (e.g. chronic herpes simplex, *Leishmania* spp., dimorphic fungi), inflammatory disorders (e.g. granulomatosis with polyangiitis, pyoderma gangrenosum), and factitial disease (see Table 45.3). Treatment of trigeminal trophic syndrome is challenging. Medications such as carbamazepine, gabapentinoids, amitriptyline, and pimozide have limited effectiveness. Protective barriers worn at night and patient education are important measures. Surgical repair of the defect(s) with innervated skin flaps provides the greatest chance for resolution[124,125].



Fig. 6.10 Trigeminal trophic syndrome. A Ulceration with serohemorrhagic crusting on the nasal ala, as well as excoriations, superficial ulcers, and scars on the upper lip, chin, and cheek. **B** Ulceration localized to the nasal ala and adjacent cheek. *A, Courtesy Lorenzo Cerroni, MD; B, Courtesy Edward Cowen, MD.*

Complex regional pain syndrome (reflex sympathetic dystrophy)

Complex regional pain syndrome (CRPS; reflex sympathetic dystrophy) is characterized by continuing regional pain that is seemingly disproportionate to the usual course following trauma or other insults; evidence of damage to peripheral nerves is present in a subset of patients. The upper extremities, especially the hands (Fig. 6.11), are most commonly affected, but the distal lower extremities may also be involved. Regional insult to nociceptive terminals results in a signal cascade that ultimately amplifies the pain response in the CNS. The disease was traditionally described as progressing through several stages, which were thought to be due to autonomic nervous system dysfunction[119].

Signs and symptoms within the affected region include burning pain, hyperalgesia, allodynia, vasomotor dysfunction (e.g. edema, erythema, livedo reticularis, cyanosis), hypertrichosis, hyperhidrosis, nail dystrophy, motor dysfunction, and eventually atrophy. Patients suspected to have CRPS should be referred to a neurologist for further evaluation and treatment. Physical and occupational therapy represent first-line treatment options. Therapies may be directed toward interruption of the autonomic nervous system, but they often have limited efficacy[127].

Congenital Insensitivity to Pain and Related Conditions

Congenital insensitivity to pain belongs to a group of hereditary sensory and autonomic neuropathies (HSAN) in which neurons fail to develop or degenerate[128] (Table 6.10).



Fig. 6.11 Complex regional pain syndrome with scaling and erosions of the fingertips. *Courtesy Kalman Watsky, MD.*

CONGENITAL INSENSITIVITY TO PAIN (CIP) AND RELATED HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES (HSANs)			
Features of CIP: • Oral self-mutilation due to biting of lips, tongue, and buccal mucosa • Biting of fingertips resulting in ulceration and eventual autoamputation • Bruises, cuts/wounds, burns, skin infections, joint dislocations, and fractures with resulting scars and deformities • Immunohistochemical staining for neuronal markers (e.g. PGP-9.5) shows almost complete absence of innervation to sweat glands, blood vessels, and arrector pili muscles within the skin			
HSAN type, disorder name	**Gene(s) (inheritance)**	**Protein**	**Additional clinical features**
II, Morvan disease	*WNK1, FAM134B, KIF1A* (AR)	WNK lysine deficient protein kinase 1, FAM134B, kinesin family member 1A	• Hyporeflexia, hypotonia • GI dysmotility • Acral anhidrosis, episodic hyperhidrosis
IID, CIP	*SCN9A** (AR)	Sodium voltage-gated channel α subunit 9	• Variable hearing impairment, anosmia • Variable hypohidrosis
III, familial dysautonomia (Riley–Day syndrome)	*IKBKAP* (AR)	Inhibitor of κ light polypeptide gene enhancer in B cells, kinase complex-associated protein	• Ashkenazi Jewish patients • Hyporeflexia, hypotonia • Less impaired pain/temp perception, acral sparing • No emotional tears • Postural hypotension, episodic hypertension • Vomiting crises with blotchy erythema of skin • Absent lingual fungiform papillae
IV, CIP with anhidrosis	*NTRK1* (AR)	Neurotrophic receptor tyrosine kinase 1 (high-affinity NGF receptor)	• Complete lack of pain (including visceral) and temp sensation, but normal touch and reflexes • Anhidrosis with febrile episodes • Intellectual disability • Increased susceptibility to staphylococcal infections
V, CIP	*NGF* (AR)	Nerve growth factor	• As in IV but variable anhidrosis and intellectual disability
VI	*DST* (AR)	Dystonin	• Similar to III
VII, CIP with GI dysfunction and hyperhidrosis	*SCN11A** (AD)	Sodium voltage-gated channel α subunit 11	• Diarrhea, constipation • Hyperhidrosis, pruritus • Muscular weakness
VIII, CIP	*PRDM12* (AR)	PR/SET domain 12	• Variable hypohidrosis and reduced tearing
*Gain-of-function mutations can result in hereditary neuropathies presenting with burning/episodic pain or (for *SCN9A*) erythromelalgia.			

Table 6.10 Congenital insensitivity to pain (CIP) and related hereditary sensory and autonomic neuropathies (HSANs)[128]. HSAN type I includes several autosomal dominant disorders with onset typically in later childhood or adulthood; features include motor as well as sensory neuropathy, dysesthesia with "lightning" pains, and variable hearing loss and hyperhidrosis. AD, autosomal dominant; AR, autosomal recessive; FAM134B, family with sequence similarity 134, member B; PGP-9.5, protein gene product 9.5; temp, temperature.

TREATMENT

Thus far, no antipruritic drug is indicated for relief of itch irrespective of its origin. Thus, individualized management of each patient and pruritic disease process is necessary[8,10]. General measures and specific treatments that can be selected according to the patient's complaints are discussed below and summarized in Table 6.11.

General Measures

Patient education and elimination of provocative factors are important, including wearing soft breathable clothing (i.e. no wool or rough fabrics), avoiding excessive bathing (lukewarm baths or showers with mild synthetic detergents [syndets]), using emollients on a daily basis with application immediately after bathing, and managing dermographism if present. Patients can be taught methods of interrupting the itch–scratch cycle, such as application of a cold washcloth or gentle pressure. Controlled physical exercise, relaxation therapy, and minimization of exposure to heat as well as reduction of stress and anxiety are beneficial. Avoid telling patients "don't scratch" given how difficult it is to follow this advice.

Topical Treatment

A large variety of topical compounds that have antipruritic properties are available, including corticosteroids, anesthetics (e.g. pramoxine, polidocanol), and counterirritants (e.g. menthol, camphor).

Topical anesthetic agents (e.g. lidocaine/prilocaine) decrease pain and pruritic sensations and they may relieve tingling and dysesthesias[129]. Topical doxepin has demonstrated antipruritic effects in atopic dermatitis and other eczematous dermatoses, including lichen simplex chronicus, nummular eczema, and contact dermatitis[130]. However, side effects such as drowsiness can occur when it is applied to large portions of the body or in young children. In addition, the possibility of allergic contact dermatitis to topical doxepin and potentially systemic contact dermatitis with subsequent oral administration should be considered. Compounded topical cromolyn sodium has been found to relieve allergen- and histamine-induced pruritus without blocking wheal formation, suggesting a mechanism other than prevention of mast cell degranulation.

Capsaicin is a naturally occurring alkaloid found in many species of the nightshade family (Solanaceae), especially chili peppers. Capsaicin enhances the release and secondarily inhibits the re-accumulation of neuropeptides such as substance P. It also transiently destroys intraepidermal nerve fibers. Topical capsaicin has successfully been used in several dermatologic disorders, although it is not beneficial in atopic dermatitis[131]. Concentrations usually range from 0.025%–0.1%, and it needs to be applied three to six times daily for maximal effect. While capsaicin can be safely applied to large areas of skin[132], and its side effects of stinging, burning, pain, erythema, and irritation decrease with continued use, it is typically utilized to treat localized pruritus.

Topical tacrolimus and pimecrolimus have both anti-inflammatory and antipruritic effects[133] and are successfully used in pruritic conditions including atopic dermatitis (see Ch. 128). Burning and erythema at the application site are the most commonly reported adverse events. Rapid improvement of pruritus has also been reported in patients with atopic dermatitis treated with topical ruxolitinib[134].

GENERAL MEASURES FOR THE TREATMENT OF PRURITUS AND DYSESTHESIA
Skin care
• Twice daily application of a moisturizing cream or ointment • Warm (not hot) baths/showers ≤ once daily, with minimal use of a mild soap/non-soap cleanser, and followed immediately by moisturizer application; especially in winter, consider limiting use of soap to odorous regions such as the axillae and anogenital area • Avoid wool and other rough fabrics • Keep nails cut short
Topicals
• *Cooling agents/counterirritants*: e.g. menthol, camphor • *Capsaicin* • *Anesthetics*: e.g. pramoxine, lidocaine, prilocaine, polidocanol, palmitoylethanolamine • *Anti-inflammatory agents*: corticosteroids, calcineurin inhibitors, Janus kinase (JAK) inhibitors
Systemic medications
• *Antihistamines*: especially if there is a component of dermographism or urticaria; otherwise limited efficacy beyond sedative effects • *Gabapentinoids*: gabapentin, pregabalin • *Antidepressants:* SSRIs (e.g. fluoxetine, paroxetine, sertraline, venlafaxine), tricyclics (e.g. amitriptyline, doxepin), mirtazapine • *Opioid antagonists/agonists:* e.g. naltrexone, butorphanol nasal spray, nalfurafine, nalbuphine, naloxone • *Targeted immune modulators* (especially for atopic dermatitis and prurigo nodularis): e.g. dupilumab, tralokinumab (anti-IL-4/-13); nemolizumab (anti-IL-31); JAK inhibitors • *Other:* thalidomide (especially for prurigo nodularis), aprepitant (NK1 receptor antagonist)
Physical modalities
• *Phototherapy*: UVB (broadband or narrowband), PUVA, UVA, UVA-1 • Acupuncture
Psychological approaches
• Behavior modification therapy, biofeedback • Support groups

Table 6.11 General measures for the treatment of pruritus and dysesthesia. NK1, neurokinin 1; PUVA, psoralen plus UVA; SSRI, selective serotonin reuptake inhibitor.

Systemic Treatment

Systemic drugs with antipruritic properties often act centrally and have sedating effects. With progress in understanding the pathophysiology of pruritus, treatments targeting specific mediators and pathways have become possible, such as κ-opioid receptor agonists (e.g. difelikefalin, nalfurafine) and/or μ-opioid receptor antagonists (e.g. naloxone, naltrexone); NK1 receptor antagonists (e.g. aprepitant); and antibodies targeting IL-31 signaling (e.g. nemolizumab)[135]. However, placebo responses in pruritus patients are often substantial (e.g. 66% in one study)[10], demonstrating the powerful central modulation of pruritus. Placebo-controlled studies are therefore essential to evaluate drugs with potential antipruritic effects.

Physical Treatment Modalities

UV light therapies (broadband and narrowband UVB, UVA, UVA-1, UVA/UVB, PUVA) have beneficial effects in pruritic inflammatory dermatoses, maculopapular cutaneous mastocytosis, renal and cholestatic pruritus, pruritus associated with HIV infection, aquagenic pruritus, and prurigo nodularis[102].

Transcutaneous electronic nerve stimulation has been reported as beneficial in different types of pruritus, such as that found in aged skin. This may be partially a placebo effect as it tends to decline with continued therapy[10]. Acupuncture has also been described as a successful treatment for pruritus vulvae, allergic contact dermatitis, and renal pruritus. Acupuncture was reported to decrease experimental histamine-induced pruritus but had no effect on maximal pruritus intensity or onset time[10].

Psychological Approaches

Pruritus may be precipitated, prolonged, or enhanced by a number of stress-related mediators such as histamine and neuropeptides. There are also multiple secondary psychosomatic mechanisms through which pruritus may be generated or exacerbated, e.g. sweating, alterations in cutaneous blood flow, and scratching[1]. Of note, psychological factors are thought to be able to diminish as well as augment pruritus.

Studies have shown that group psychotherapy, behavioral therapy, controlled physical exercise, support groups, and biofeedback can help to stop scratching and improve quality of life[1,10].

Additional figures available in our eBook (see inside front cover for access code).

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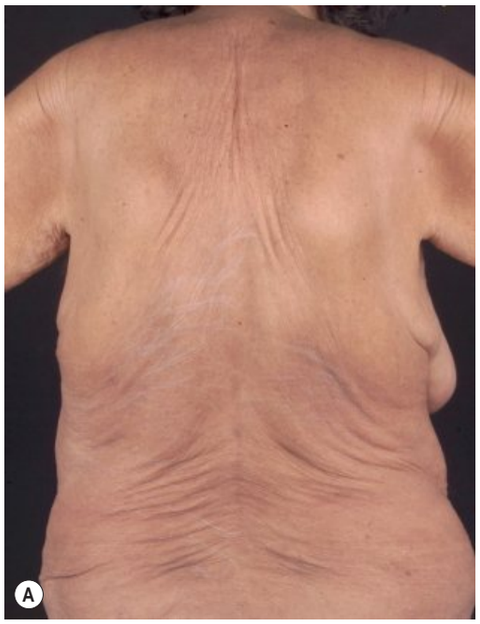
eFig. 6.1 Atopic dermatitis. A Multiple lesions of prurigo nodularis. **B** Multiple linear excoriations are seen on the leg.



eFig. 6.2 Prurigo nodularis. A, B Numerous excoriated papules and nodules on the back, with sparing of the mid upper back ("butterfly sign"). **C** Crusted papules on the upper arm. **D** Papulonodules with central ulcerations due to picking admixed with scars. *D, Courtesy Kalman Watsky, MD.*



eFig. 6.3 Lichen simplex chronicus (LSC). A LSC of the scrotum; secondary pigmentary changes are more common in patients with darkly pigmented skin. **B** LSC on the neck of a man; note the increased skin markings. *A, Courtesy Louis Fragola, MD.*





eFig. 6.4 Xerosis. A Xerosis and scratching in a patient with renal insufficiency undergoing hemodialysis. **B** Extreme xerosis associated with pruritus in an HIV-infected patient.



eFig. 6.5 Pemphigoid nodularis. Multiple crusted lesions and scars are evident. Bullous pemphigoid is often intensely pruritic and may not present with intact vesiculobullae. *Courtesy Jeffrey P. Callen, MD.*





eFig. 6.6 Pruritus from sensory neuropathies. A Notalgia paresthetica presenting with hyperpigmented patches with lichenification on the infrascapular and suprascapular right back. **B** Brachioradial pruritus. The affected area is outlined by ink.





eFig. 6.7 Trigeminal trophic syndrome. Erosions and ulcerations with hemorrhagic crusts favor the ala nasi (**A, B**). Obvious linear excoriations are seen in the second patient **(B)**. *Courtesy Kalman Watsky MD.*

7 Psychocutaneous Diseases

Karynne O. Duncan, Josie Howard and John Y.M. Koo

INTRODUCTION

"Psychodermatology" refers to any aspect of dermatology in which psychological factors play a significant role in the genesis, exacerbation, or sequelae of a skin condition. At least a third of patients seen in dermatology practices require consideration of associated emotional and psychosocial factors for effective management of their cutaneous disease[1].

Many patients with psychodermatologic problems decline referral to a mental health professional, and some become upset if such a referral is suggested. Ironically, the individuals who are the most psychologically "ill" often have the least insight into the psychogenic nature of their condition and frequently refuse a psychiatric referral. The dermatologist is then faced with two choices. The first is to try to address the psychologic condition. If a dermatologist decides to take this route, it is necessary to be familiar with the approach to diagnosis, therapeutic options (both pharmacologic and non-pharmacologic, including potential side effects of medications), and limitations of what can be accomplished in a dermatology practice. The other option is to disregard the psychologic problem and allow this component of the patient's disorder to remain untreated. However, this option represents a disservice to the patient and may lead to unnecessary utilization of healthcare services and persistent psychopathology. Dermatologists can learn to effectively handle psychodermatologic issues within the limits of their training and practice setting. Although less comprehensive than treatment delivered in collaboration with a psychiatrist, in the authors' opinion, management of these issues by a dermatologist is important.

Clinically useful methods of conceptualizing and classifying psychodermatologic disorders are presented in Fig. 7.1. This incorporates updates from the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5™)[2]. Selected primary and secondary psychologic conditions that are commonly encountered in a dermatologic practice are discussed in this chapter. Strategies for the evaluation and management of patients with these disorders are reviewed, including pharmacologic and non-pharmacologic treatments. Disorders characterized by pruritus and dysesthesia are covered in Chapter 6.

OVERVIEW

Psychodermatologic disorders can be conceptualized in two ways: (1) by the specific psychodermatologic condition; or (2) by the symptom complex and diagnostic pattern of the underlying psychopathology, including anxiety, depression, psychosis, and obsession–compulsion. The latter approach is useful because knowledge of the psychopathologic manifestations enables the clinician to choose the most appropriate psychopharmacologic agent (Table 7.1). For example, if the underlying psychopathology involves obsessions and/or compulsions, a selective serotonin reuptake inhibitor (SSRI; e.g. fluoxetine) would be a logical choice of therapy[3,4].

In the classification method based on psychodermatologic conditions, most patients can be grouped into one of four categories[3] (see Fig. 7.1):

- *primary psychodermatologic disorders*, in which the patient typically has no primary skin disease and cutaneous lesions are self-induced (e.g. delusional infestation, body-focused repetitive behaviors)
- *secondary psychodermatologic disorders*, in which the patient develops psychologic distress or a psychologic disorder as a result of a skin disease
- *psychogenic pruritus and dysesthesia*, in which the patient presents with a purely sensory complaint (e.g. pruritus, burning, stinging) without evidence of a delusional component, primary skin disease, or underlying medical condition (see Ch. 6)
- *psychophysiologic disorders*, in which a primary skin disorder (e.g. atopic dermatitis, psoriasis) is exacerbated by psychologic or behavioral factors (e.g. stress, anxiety)

PRIMARY PSYCHODERMATOLOGIC DISORDERS

Delusional Infestation

Synonyms: ■ Delusional parasitosis ■ Delusions of parasitosis ■ Primary delusional disorder somatic type ■ Morgellons disease

Key features

- Fixed, false belief that the skin is infested with animate organisms (e.g. insects, parasites) or inanimate materials (e.g. fibers) despite evidence to the contrary
- Occurs spontaneously and is not secondary to another medical or psychiatric condition or medication/substance use
- Requires establishment of a good patient–physician relationship and treatment with an antipsychotic medication

Introduction

The term "delusions of parasitosis" was introduced in 1946 to describe patients whose fixed false belief was that their skin was infested with what they believed to be parasites such as fleas, ticks, and various other organisms[5]. More recently, the term "Morgellons disease" has been used by patients to describe what they falsely perceive as fibers extruding from their skin[6]. To better encompass both of these conditions, which are felt to be along the same spectrum of delusional disorders, the term "delusional infestation" has been proposed and is currently more widely used.

Delusional infestation (DI) is classified as a *somatic type of delusional disorder* (previously referred to as monosymptomatic hypochondriacal psychosis) within the broad group of *schizophrenia spectrum and other psychotic disorders*[2]. *Delusions* are defined as fixed false beliefs that are not amenable to change despite conflicting evidence, and *somatic* delusions are focused on bodily functions or sensations. Individuals with DI have the isolated and fixed belief that their skin is infested by animate organisms (e.g. insects, parasites) or inanimate materials (e.g. fibers) in the absence of any objective evidence[4,7].

Epidemiology

The average age of onset is 55–60 years[8]. Among individuals over 50 years of age, women experience the disorder at least twice as often as men; however, prior to age 50, men and women are equally affected. Younger patients with this disorder are usually of a lower socioeconomic status and may have a history of substance abuse, while older patients are frequently of a higher socio-economic status.

Clinical features

Patients with DI do not meet criteria for a diagnosis of schizophrenia. However, they should fulfill the DSM-5™ diagnostic criteria for a delusional disorder, which are: (1) the delusion must be present for ≥1 month; (2) the patient does not exhibit impaired functioning or bizarre behavior apart from the impact of the delusion; and (3) the delusion cannot be attributable to the effects of a substance, medication, medical condition, or other psychiatric disorder[2]. The delusional belief

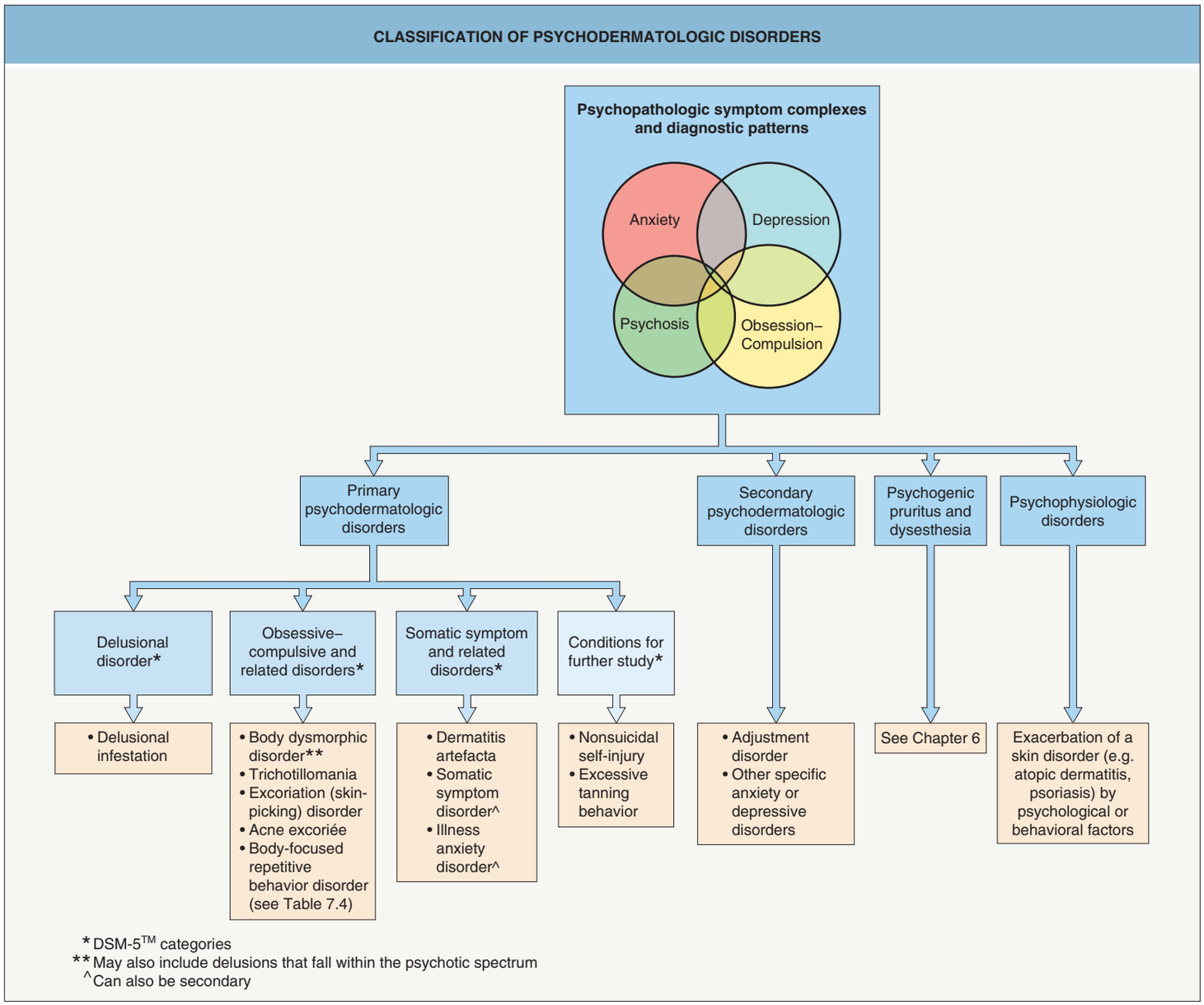


Fig. 7.1 Classification of psychodermatologic disorders. Psychocutaneous disorders can be conceptualized by: (1) the specific psychodermatologic condition and its classification; and (2) the presenting symptom complex of the underlying psychopathology. *Primary psychodermatologic disorders* are those in which the patient typically has no primary skin disease and cutaneous lesions are self-induced. *Secondary psychodermatologic disorders* are those in which the patient develops psychological distress or a psychologic disorder as a result of a skin disease. *Psychophysiologic disorders* are those in which a primary skin condition, such as psoriasis, is exacerbated by psychological or behavioral factors (e.g. stress, anxiety). A particular patient with a psychodermatologic disorder can have a presenting symptom complex with features from one or more of the four major psychopathologic patterns of anxiety, depression, psychosis, and obsessions/compulsions.

is "encapsulated", i.e. there is a narrow and specific focus on skin infestation. Patients may be able to state that others view their beliefs as irrational ("factual insight"), but they lack the true insight necessary to personally accept the valid explanation.

Individuals with DI typically present with a history of symptoms for months or even years. They have often already been evaluated by many physicians and have tried to eradicate alleged "parasites" by methods such as using pesticides, hiring exterminators, or changing their residence. Patients frequently bring in bits of skin, lint, and other samples that they believe represent "parasites"/fibers, which is referred to as the "matchbox sign" (Fig. 7.2). In addition to or in place of these samples, they may also bring in photographic documentation.

Skin findings in DI range from none to excoriations, lichenification, prurigo nodularis, and ulcerations (see Fig. 7.2). All of these are self-induced, usually resulting from the patient's efforts to dig out "parasites"/inanimate materials. Patients often report accompanying pruritus and stinging as well as biting and crawling sensations (formication).

One intriguing aspect of this disorder is the potential for a shared delusional system whereby the patient's close contacts come to believe in the delusion as well. *Folie à deux* ("craziness for two") is the term used to describe two people who share the same delusion. Occasionally, larger numbers of people harbor the same delusion, which may include the patient's parent(s) and children[9].

Differential diagnosis

By definition, DI occurs spontaneously and is not caused by another psychiatric or medical disorder; however, the term "secondary DI" is sometimes used for the latter situation. It is essential to exclude an underlying condition before making the diagnosis of "primary" DI. Conditions to consider in the differential diagnosis include: an actual skin infestation (e.g. scabies); formication due to neurologic disease; an underlying psychiatric disorder (e.g. schizophrenia) or medical condition (e.g. dementia, B_{12} deficiency, pruritus related to systemic disease); and medication/substance use (e.g. dopamine agonists, amphetamines, cocaine [see Ch. 89]). A thorough history and physical examination should be accompanied by microscopic evaluation of samples brought by the patient. When indicated, skin scrapings, skin biopsies, and laboratory evaluation are also performed.

PSYCHOPATHOLOGIC PATTERNS AND PSYCHOTROPIC MEDICATIONS USED IN DERMATOLOGY		
Underlying psychopathology and symptom complex	**Possible pharmacologic treatment**	**Comments and precautions**
Anxiety		
• Excessive anxiety and worry • Restlessness; feeling "keyed up" or "on edge" • Irritability • Fatigability • Difficulty concentrating or mind going blank • Muscle tension or feeling "shaky" • Sleep disturbance • Somatic symptoms, e.g. dizziness, sweating, palpitations, abdominal complaints	**Acute anxiety:** *Benzodiazepines* • Alprazolam (0.125–0.25 mg every 6–8 hours, as needed) • Lorazepam (0.5–2 mg every 6–8 hours, as needed) • Clonazepam (0.5–2 mg once or twice daily, as needed)	• Treatment not to exceed 4 weeks because of dependency/addiction risk • May cause sedation • Taper dosage to avoid withdrawal symptoms

	Chronic anxiety:
	• *SSRIs* (see Depression below)
	• *SNRIs*
	  • Venlafaxine, extended release (37.5–75 mg/day, up to 225 mg/day)
	• *Other*
	  • Buspirone (initial dose 7.5 mg twice a day; increase daily dose by 5 mg every 2–3 days, up to a maximum of 60 mg/day if needed)
	  • Doxepin (10–25 mg, at bedtime)
	  • Hydroxyzine (10–25 mg every 6–8 hours)
		• Onset of action often delayed 2–4 weeks
		• Do not cause dependency/addiction
		• SSRIs and SNRIs are considered as first-line treatment; therapeutic doses are similar to those used for depression
		• Buspirone often used as augmentation when partial response to antidepressant
		• Hydroxyzine and doxepin are sedating and may be helpful for pruritus

Depression		

• Depressed mood
• Anhedonia
• Unexplained weight loss/gain or appetite change
• Insomnia or hypersomnia
• Psychomotor agitation or retardation
• Fatigue, lack of energy
• Feelings of hopelessness, worthlessness
• Excessive guilt
• Difficulty with concentration, indecisiveness
• Suicidal ideation/plan
• Crying spells
• Preoccupation with physical concerns
	• *SSRIs* – start at minimal effective dose and increase every week or every other week as tolerated; if no response at 6–8 weeks, then change to a different class of antidepressants
	  • Fluoxetine (10–20 mg/day, up to 40–60 mg/day)
	  • Paroxetine (10–20 mg/day, up to 50 mg/day)
	  • Sertraline (25–50 mg/day, up to 200 mg/day)
	  • Escitalopram (5–10 mg/day, up to 20 mg/day)
	  • Citalopram (10–20 mg/day, up to 40 mg/day)
	• Bupropion XL (150–300 mg/day) can be used if sexual dysfunction is an issue/concern and if anxiety is not a prominent symptom
	• Mirtazapine (7.5–30 mg/day) may be useful in patients with insomnia or marked weight loss
		• SSRIs are typically the first-line treatment; slow onset of action, with full therapeutic response after ~6–8 weeks
		• SSRIs may cause gastrointestinal disturbances, sexual dysfunction
		• May unmask mania in patients with an undiagnosed bipolar disorder
		• Avoid abrupt discontinuation of SSRIs, as may cause dysphoria, dizziness, gastrointestinal distress
		• Citalopram and escitalopram can cause dose-dependent QT prolongation

	• *Tricyclic antidepressants (TCAs)* • Doxepin (dosage for pruritus is typically 10–25 mg at bedtime; for depression, typically start at 10–25 mg at bedtime and increase every 1–2 weeks to a therapeutic dose of 25–150 mg at bedtime or up to 300 mg in divided doses, depending on tolerance and disease severity)	• TCAs can lead to weight gain, cardiac conduction abnormalities, orthostatic hypotension, and anticholinergic side effects • Doxepin often causes sedation, especially in the elderly and smaller individuals; should be started at low doses (e.g. 10 mg/day); long-term use associated with increased risk of dementia; as dose approaches 100 mg daily, check trough serum level to guide future dose adjustments
Psychosis		
• Delusions are the most common feature that presents to dermatologists • Fixed false belief that the patient is convinced is true • Delusion is usually encapsulated (narrow focus)	• *First-generation antipsychotics* • Pimozide (start at 0.5–1.0 mg/day and increase by 0.5–1.0 mg every 2–4 weeks, as tolerated, to the lowest clinically effective dose – typically 2–6 mg/day). Once adequate clinical response, maintain dose for at least three months, followed by a gradual taper. Most patients require a 5- to 6-month treatment course	• Gradual taper to avoid withdrawal symptoms such as dyskinetic movements • Associated with QT prolongation, arrhythmias (doses ≥10 mg/day), EPS, TD (with long-term use), and drug interactions (avoid if taking opiates, citalopram, escitalopram, sertraline, macrolides, protease inhibitors, azole antifungals, grapefruit juice) • Baseline ECG often recommended when starting pimozide

	• *Second-generation antipsychotics*
	  • Risperidone (0.5 mg/day, up to 4 mg/day [Table 7.2])
	  • Olanzapine (2.5 mg/day, up to 10–15 mg/day)
	  • Aripiprazole (2 mg/day, up to 10–15 mg/day)
		• Weight gain, metabolic effects, and other side effects listed in Table 7.3
		• Risperidone is increasingly being used first-line for delusional infestation because of a lower risk of EPS and TD compared to pimozide, but has greater metabolic side effects (see Tables 7.2 and 7.3).

Obsessive–compulsive disorder (OCD)		

• Presence of intrusive obsessions and/or compulsions (see text)
• Varying degrees of insight
	• *SSRIs* (start at low dose and increase every week or every other week until reach therapeutic range)
	  • Fluoxetine (10 mg/day, up to 40–80 mg/day)
	  • Paroxetine (20 mg/day, up to 40–60 mg/day)
	  • Sertraline (25 mg/day, up to 200 mg/day)
	  • Fluvoxamine (50 mg/day, up to 200–300 mg/day)
	  • Escitalopram (5 mg/day, up to 20 mg/day)
	  • Citalopram (10 mg/day, up to 40 mg/day)
		• SSRIs are first-line pharmacologic treatment, but often need higher doses and longer time to respond (e.g. 10–12 weeks)
		• OCD is a chronic condition with rare complete remission; once a therapeutic response is achieved on a stable, tolerable regimen, most experts recommend continuation of treatment
		• If necessary or desired, a very slow taper can be attempted, with close monitoring for symptom recurrence

	• *Tricyclic antidepressants* • Clomipramine (25 mg/day, up to 100–250 mg/day)	• Clomipramine has a less tolerable side-effect profile than SSRIs, including cardiac toxicity and arrhythmias; baseline ECG; check blood levels when the dose is ≥150 mg/day
	• *SNRIs* • Venlafaxine (75 mg/day, up to 225–350 mg/day)	• Venlafaxine may cause hypertension and an increased risk of gastrointestinal bleeding

Table 7.1 Psychopathologic patterns and psychotropic medications used in dermatology. The pharmacologic treatment of psychodermatologic disorders can be chosen based on the underlying pathophysiology. This list is not exhaustive and focuses on psychotropic medications that are more frequently used in a dermatologic practice. SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; EPS, extrapyramidal side effects; TD, tardive dyskinesia.



Fig. 7.2 Delusional infestation. A Multiple excoriations and hypopigmented scars resulting from the patient's attempts to "dig out" parasites. **B** Samples of alleged "parasites" brought in by a patient ("matchbox sign" or "specimen sign"). *Courtesy Kalman Watsky, MD.*

Treatment

After assessing the differential diagnosis, the first step in management is to establish rapport and address the patients' concerns seriously without challenging their beliefs. Short follow-up visits and serial skin examinations can be helpful in building a strong therapeutic relationship. When discussing the diagnosis, communicate it in a matter-of-fact manner and refrain from making any statements that may be misinterpreted by patients as supporting their delusional ideation. It is important to validate the person's experience, without validating the delusion itself, and to ensure that the patient does not feel dismissed in the process of treatment.

The most challenging aspect of treatment is getting patients to agree to a trial of an antipsychotic agent, which is the mainstay of therapy for DI. Systematic reviews have not demonstrated superior efficacy of any particular antipsychotic agent for treatment of DI, and to date there have been no randomized controlled trials. The choice of antipsychotic therapy should take into account patient characteristics and medication side effect profiles (Tables 7.1–7.3). First-line treatment has traditionally been pimozide, which is usually effective at a very low dose and may be better accepted by patients because it has no psychiatric FDA indication (see Table 7.1). However, second-generation antipsychotics (e.g. risperidone; see Table 7.2) have more recently gained favor because of their decreased risk for EPS[7,10], but they do have potential metabolic side effects (see Table 7.3). Compared to individuals with other psychotic disorders, patients with DI typically respond to lower doses of antipsychotic agents and can often be successfully tapered off medication after 2–6 months.

General Features of Obsessive–Compulsive and Related Disorders

Several conditions included in the *obsessive–compulsive and related disorders* group have dermatologic manifestations (see Fig. 7.1). *Obsessions* are recurrent and persistent thoughts, images, or urges that are intrusive and unwanted. *Compulsions* are repetitive behaviors or mental acts that an individual feels driven to perform in order to reduce anxiety or distress, especially that arising from obsessions. In all of these disorders, the preoccupations and/or behaviors lead to significant distress or impairment in social, occupational, or other areas of functioning. Some of these conditions feature *body-focused repetitive behaviors* (e.g. hair pulling, skin picking) that continue despite repeated attempts to stop or decrease the behavior (Table 7.4; Fig. 7.3).

Body Dysmorphic Disorder

Synonym: ▪ Dysmorphophobia

Key features

- May affect as many as 10%–15% of dermatology patients
- Often begins in late adolescence or early adulthood
- Preoccupation with a non-existent or slight defect in appearance
- Frequent body sites of concern include the skin, hair, nose, breasts, and genitalia
- Typically associated with compulsive or ritualistic behaviors

Introduction

Dermatologists, particularly those performing cosmetic procedures, and plastic surgeons are often consulted by patients with body dysmorphic disorder, a distressing and socially impairing preoccupation with a non-existent or slight defect in appearance[11].

Epidemiology

The prevalence of body dysmorphic disorder in the general US population is estimated to be ~2.5% in women and 2% in men, but it is as high as 10%–15% in dermatology and cosmetic surgery patients. The mean age at onset is late teens, and the course tends to be chronic[2,4,11].

Clinical features

Patients with body dysmorphic disorder have a fundamental disturbance in their body image. They focus on perceived faults in their skin (e.g. acne, wrinkles, scars), hair (e.g. thinning, excessive), or body structures such as the nose, mouth, breasts, and genitalia. These preoccupations are time-consuming and cause significant distress, frequently leading to social isolation or functional impairment. In addition, affected individuals often adopt compulsive or ritualistic behaviors such as spending an excessive amount of time in front of a mirror or repeatedly checking for perceived imperfections. Personal insight regarding this condition is usually poor.

Treatment

The spectrum of body dysmorphic disorder includes: (1) *obsessions* with perceived inadequacies, which fall within the *obsessive–compulsive disorder (OCD) spectrum*; and (2) *delusions* (fixed false beliefs) about their appearance, which fall within the *psychotic spectrum*. For the purpose of treatment, it is useful to classify patients into one of these two categories, although the distinction is not always clear and individual patients may fluctuate between delusional and non-delusional thinking. Patients with the delusional variant have no insight into their disease and often go to extraordinary lengths, such as multiple surgeries, to correct their perceived deformity. It is important for cosmetic surgeons to recognize this disorder and avoid performing unnecessary procedures. In addition, patients with body dysmorphic disorder are often dissatisfied with the results of any procedure that is performed.

The first-line therapy for patients with the OCD variant of this disease includes cognitive behavioral therapy (CBT), typically in conjunction

USE OF RISPERIDONE IN DERMATOLOGY						
Drug properties: Second-generation antipsychotic; dopamine type 2 (D_2) and serotonin receptor ($5HT_2$) antagonist **Dermatologic indications:** Delusional disorders (e.g. delusional infestation) **Dosage:** Start at 0.5 mg/day at bedtime and increase weekly, as tolerated, to the lowest clinically effective dose (typically 2–4 mg/day dosed once or twice daily). Once an adequate clinical response has been reached, maintain therapeutic dose for at least three months, followed by a gradual taper; most patients require a 5- to 6-month course **Side effects:** See Table 7.3 **Monitoring guidelines**:						
Measure	**Baseline**	**4 weeks**	**8 weeks**	**12 weeks**	**Quarterly**	**Annually**
Personal/family history of metabolic syndrome, heart disease	X					X
Weight	X	X	X	X	X	
Waist circumference	X			X		X
Blood pressure (orthostatic measurements)	X			X		X
Fasting blood glucose/ hemoglobin A1C	X			X		X
Fasting lipid profile	X			X		X
Abnormal Involuntary Movement Scale (AIMS)*	X			X	X†	
Contraindications: Known hypersensitivity to risperidone or paliperidone; history of QT interval prolongation, arrythmias, cardiac conduction abnormalities; elderly patients, especially those with dementia-related psychosis (increased risk of death). **Pregnancy and lactation:** Use during third trimester of pregnancy can increase risk of EPS and/or withdrawal symptoms in newborns. Caution advised with breast-feeding, as it does pass into breast milk. **Drug interactions:** AVOID concomitant use of the following: medications which prolong the QT interval (e.g. macrolide antibiotics, citalopram, escitalopram); strong CYP2D6 inhibitors (*increase* the levels and effects of risperidone; e.g. fluoxetine, paroxetine, divalproex sodium, verapamil); strong CYP2D6 inducers (*decrease* the levels and effects of risperidone; e.g. carbamazepine, phenytoin, phenobarbital, rifampin).						
*For details, see qxmd.com/calculate/calculator_601/abnormal-involuntary-movement-scale-aims#; in the treatment of delusional infestation, tardive dyskinesia and EPS are rare given the use of lower dosages and relatively short duration of therapy. †If ≥50 years of age monitor the AIMS every 3 months; if <50 years of age, every 6 months.						

Table 7.2 Use of risperidone in dermatology. Compared to first-generation antipsychotics (e.g. pimozide), second-generation antipsychotics (SGAs) such as risperidone have reduced neurologic sequelae and a decreased incidence of extrapyramidal side effects (EPS) and tardive dyskinesia, but a greater risk of metabolic side effects for which monitoring is required. *Monitoring guidelines adapted from American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596–601.*

SIDE EFFECTS OF PIMOZIDE AND SELECTED SECOND-GENERATION ANTIPSYCHOTIC DRUGS								
	Anticholinergic effects	**Sedation/ somnolence**	**QT prolongation**	**Increased prolactin**	**Weight gain**	**Metabolic effects***	**Extrapyramidal effects†**	**Tardive dyskinesia‡**
Pimozide (Orap®)	+	+	++	+++	+	+	+++	+++
Second-generation antipsychotic drugs								
Aripiprazole (Abilify®)	+	+	–	+	+	+	+	+
Asenapine (Saphris®)	+	++	+	++	++	++	++	++
Brexpiprazole (Rexulti®)	+	++	–	+	+	+	+	+
Cariprazine (Vraylar®)	++	++	–	+	++	+	+	+
Clozapine (Clozaril®)¶	+++	+++	++	+	+++	+++	+	+
Iloperidone (Fanapt®)	+	++	+	++	++	++	+	+
Lumateperone (Caplyta®)	+	+	–	+	+	+	+	+
Lurasidone (Latuda®)	+	++	–	+	+	++	++	++
Olanzapine (Zyprexa®)	++	+++	++	++	+++	+++	++	+
Quetiapine (Seroquel®)	++	+++	++	+	++	++	+	+
Risperidone (Risperdal®)§	+	++	++	+++	++	++	++	++
Ziprasidone (Geodon®)	+	++	+++	++	+	+	+	+
*E.g. insulin resistance/type 2 diabetes mellitus, hyperlipidemia (especially hypertriglyceridemia). †Parkinsonian symptoms, restlessness, stiffness, tremor; can be managed with benztropine 1–2 mg, 2–3×/day or diphenhydramine 25–50 mg every 6–8 hours (sedating). ‡Uncontrolled slow or jerky movements, often starting with tongue rolling and chewing; valbenazine is an FDA-approved treatment, but may be irreversible. ¶Use is limited by a 1% incidence of potentially life-threatening agranulocytosis as well as increased risks of seizures (dose-dependent), venous thromboembolism, and myocarditis. §Another second-generation antipsychotic drug, paliperidone (Invega®), represents the primary active metabolite of risperidone.								

Table 7.3 Side effects of pimozide and selected second-generation antipsychotic drugs. The use of antipsychotic drugs in elderly patients with dementia has been associated with an increased risk of mortality. A dose-dependent increased risk of sudden cardiac death has also been documented in patients receiving antipsychotic drugs. Olanzapine- and ziprasidone-induced drug reaction with eosinophilia and systemic symptoms (DRESS) has been described. With the lower doses and typically shorter duration of therapy for treating delusional infestation, tardive dyskinesia and extrapyramidal side effects are rarely seen.

BODY-FOCUSED REPETITIVE BEHAVIORS (BFRBs) AND ASSOCIATED MUCOCUTANEOUS FINDINGS	
Body-focused repetitive behavior	**Associated mucocutaneous findings**
Lip licking	Irritant contact dermatitis, secondary bacterial or yeast infections
Lip picking or biting	Multiple erosions or ulcerations, recurrent HSV
Cheek chewing or biting	Bite fibroma, morsicatio buccarum (see Fig. 72.12)
Cuticle pulling, picking, or biting (see Figs. 7.3 & 7.6)	Paronychia, nail surface irregularities
Nail biting (onychophagia) (see Fig. 7.3)	Paronychia, nail dystrophy, subungual hemorrhages
Nail picking or pulling (onychotillomania)	
Habit-tic deformity of the thumbnail (see Ch. 71)	Multiple midline Beau's lines with prominent longitudinal central depression
Thumb or finger sucking	Skin maceration, dermatitis, secondary bacterial or yeast infections
Skin biting (dermatophagia) (see Fig 7.6)	Pseudo-knuckle pads ("chewing pads")
Nose picking (rhinotillexomania)	Erosions, secondary bacterial infections
Hair pulling (trichotillomania; see Fig. 7.4)	See text
Skin picking (excoriation; see Fig. 7.6)	See text

Table 7.4 Body-focused repetitive behaviors (BFRBs) and associated mucocutaneous findings. BFRBs occur on a chronic basis and present with characteristic mucocutaneous findings, depending on the body site and behavior type. These behaviors exist along a spectrum, with habits at one end and body-focused repetitive behavioral disorders at the other end. The latter disorders continue despite repeated attempts to stop and lead to impaired functioning (e.g. social, occupational) or to distress manifesting as feelings of loss of control, embarrassment, or shame. HSV, herpes simplex virus.

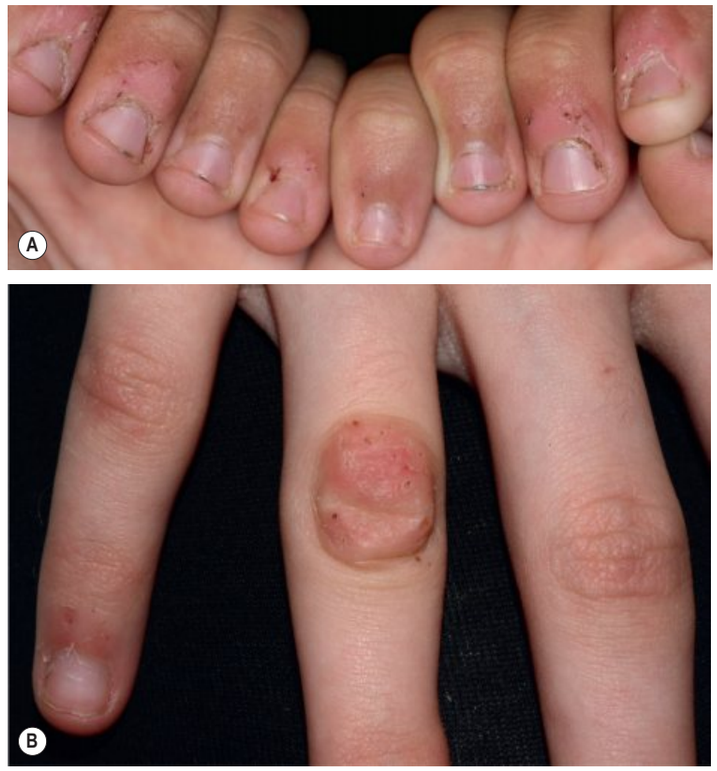


Fig. 7.3 Body-focused repetitive behaviors. A Sequelae of nail biting (onychophagia) and cuticle picking. **B** Pseudo-knuckle pad due to habitual repetitive hand movements. *B, Courtesy Julie V. Schaffer, MD.*

with an SSRI (often requiring a relatively high dose). Antipsychotics are the treatment of choice for patients who are truly delusional (see Tables 7.1–7.3)[12,13]. It is also important to treat any psychiatric comorbidities that may be contributing to the body dysmorphia, such as depression, anxiety, and panic disorder.

Trichotillomania

Synonyms: ■ Habitual hair pulling ■ Hair-pulling disorder

Key features

- Recurrent pulling out of one's hair, most often from the scalp, eyebrows, and eyelashes
- Varying lengths of hair are typically seen within areas of alopecia
- Behavior modification therapy is the mainstay of treatment

Introduction

Trichotillomania represents a body-focused repetitive behavior disorder characterized by hair pulling.

Epidemiology

The prevalence of trichotillomania in adolescents and adults in the general population is roughly 1%–2%[2]. The female:male ratio is as high as 10:1 in adults but more equal in children. The peak onset of hair pulling is around the time of puberty[14]. The majority of patients also have other body-focused repetitive behaviors such as nail biting or skin picking (see Table 7.4). In dermatologic practice, trichotillomania is usually seen in relatively psychologically intact individuals. Of note, hair pulling in toddlers and preschool-aged children is more common in boys than girls and, unlike trichotillomania in older children, tends to resolve spontaneously.

Clinical features

The DSM-5™ diagnostic criteria for trichotillomania include: (1) recurrent pulling out of one's hair, resulting in hair loss; (2) repeated attempts to decrease or stop the hair pulling; (3) significant distress or impaired functioning related to the hair pulling; and (4) no underlying medical condition or other mental disorder that explains the hair loss/pulling[2]. In dermatologic practice, the spectrum ranges from inattentive, habitual hair pulling to obvious obsessive–compulsive psychopathology involving well-planned rituals.

The most common sites of hair pulling are the scalp, eyebrows, eyelashes, and pubic region. Hair pulling typically occurs while alone or in the presence of close family members. It may be preceded or accompanied by anxiety or boredom, and some patients describe a prior tingling sensation. Pulling of the hair results in gratification, pleasure, or a sense of relief in some patients, while others display a more automatic behavior with less conscious awareness[2]. Pulling may be confined to a specific time of the day and place, with ritualized manipulation of the pulled hairs prior to discarding them. Some patients practice *trichophagy*, the chewing and swallowing of the hair that has been pulled out, which can lead to intestinal obstruction from trichobezoars. Occasionally, affected individuals pull hair from family members, pets, dolls, sweaters, or carpets.

The classic physical finding is hairs of varying lengths distributed within the area of alopecia, with uninvolved areas appearing completely normal (Fig. 7.4); the hairs are sometimes referred to as "irregularly irregular". This pattern likely reflects a hair-pulling technique of twisting multiple strands around the fingers and pulling them simultaneously. Lesions are often single and can be large; the vertex and parietal scalp are the most common sites[2]. While broken hairs and black dots are seen



Fig. 7.4 Trichotillomania. Note the hairs of varying lengths and small areas of sparing.

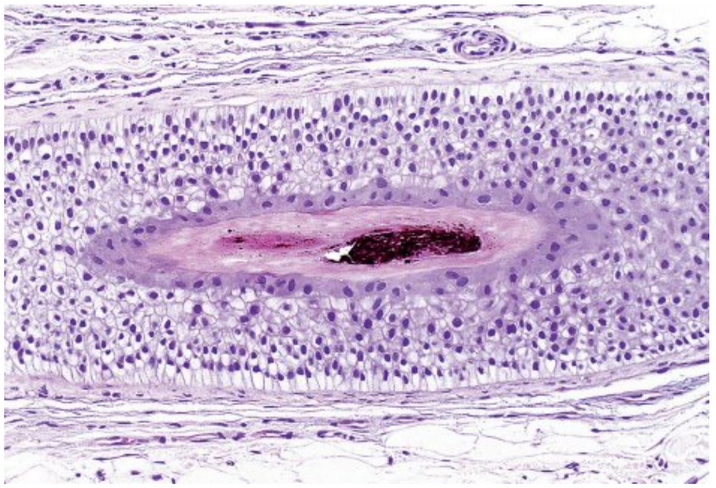


Fig. 7.5 Histopathology of trichotillomania. Pigmented follicular cast. *Courtesy Ronald P. Rapini, MD.*

by trichoscopy, more specific findings include hook, coiled, tulip and flame hairs, the V-sign, and trichoptilosis (see Ch. 69)[15]. Patients may try to conceal the hair loss with make-up, scarves, hats, or wigs.

Diagnosis and pathology

Many patients admit to hair pulling, but trichoscopy and biopsy may be helpful when the diagnosis is in doubt. Another useful test is the "clipped hair square", in which a small section of affected hair is clipped close to the scalp with scissors or shaving; too short to pull out, the hairs display uniform regrowth.

Histopathologic findings can include deformed hair shafts (trichomalacia), empty follicles, and pigmented hair casts (Fig. 7.5), which may also be seen with traction alopecia and other forms of follicular trauma. Inflammatory cells are usually sparse or absent. Perifollicular hemorrhage is sometimes found in early lesions, and perifollicular fibrosis represents a late change. If the follicle is destroyed, a vertical fibrous tract often remains at the site.

Differential diagnosis

The differential diagnosis includes other causes of circumscribed non-scarring alopecia such as alopecia areata (see Ch. 69), which occasionally coexists with trichotillomania, and tinea capitis. However, in trichotillomania there are no exclamation point hairs, scaling and pustules are absent, and fungal cultures are negative.

Treatment

The prognosis and approach to treatment of trichotillomania depend upon the age of onset and degree of underlying psychopathology. As noted above, preschool children typically outgrow the habit, and management usually involves bringing awareness to the parents and patient. Onset in the pre-adolescent to young adult years often portends a chronic, relapsing course requiring more intervention. Later adult onset is frequently associated with psychopathology that requires psychiatric referral.

Behavior modification therapy (e.g. habit reversal training, CBT) is the mainstay of treatment[16,17]. This includes awareness training, teaching the patients to do something else whenever they feel the urge to pull their hair, relaxation techniques, and positive reinforcement. In addition, a family and peer support network may be helpful. Antidepressants (especially SSRIs and clomipramine) have been reported to be effective in some studies[14]. However, two randomized controlled trials failed to show benefit of antidepressants compared to placebo, and several others found that behavioral therapy was more effective than antidepressants. In other randomized controlled studies, treatment with olanzapine or *N*-acetylcysteine (a glutamatergic agent; 1200–2400 mg/day) led to more improvement in adults with trichotillomania than did placebo[18,19].

Excoriation Disorder

Synonyms: ■ Skin-picking disorder ■ Neurotic excoriations ■ Dermatillomania ■ Psychogenic excoriations

Key features

- Recurrent picking, scratching, or rubbing that results in skin lesions
- Most often on the face, scalp, dorsal hands/forearms, and upper back but can occur on any reachable body surface
- Most commonly seen in middle-aged women

Introduction

Excoriation disorder is categorized in DSM-5™ as a body-focused repetitive behavior disorder characterized by skin picking. Some people have a tendency to inattentively but habitually pick incidental skin lesions, such as an arthropod bite, keratin plug, or lesion of acne or folliculitis. This action may be episodic or occur on a regular basis, and it can be regarded as an innocuous habit when controllable and not causing distress or psychosocial impairment. In contrast, patients with excoriation disorder have a conscious, repetitive, and uncontrollable desire to pick, scratch, or rub their skin, which results in characteristic lesions. Picking activity may begin inadvertently as the hand comes across an irregularity on the skin, or it may take place in a ritualistic fashion.

Epidemiology

The lifetime prevalence of excoriation disorder in the general population is estimated to be 1.5%, with a female : male ratio of 3 : 1[2]. Onset is most often around the time of puberty, and it frequently begins with a dermatologic condition such as acne (see Acne Excoriée below)[2]. The usual course is chronic, with waxing and waning of symptoms over a period of years. Excoriation disorder is more common in individuals with OCD and their first-degree family members, and many patients exhibit other body-focused repetitive behaviors (e.g. hair pulling, nail biting; see Table 7.4)[20]. Underlying depression may also be present.

Clinical features

The DSM-5™ diagnostic criteria for excoriation disorder, analogous to those for trichotillomania, include: (1) recurrent skin picking, resulting in skin lesions; (2) repeated attempts to decrease or stop the picking; (3) significant distress or impaired functioning related to the picking; and (4) no underlying medical condition or other mental disorder that explains the picking[2]. The psychological aspects of the skin picking are similar to those for the hair pulling of trichotillomania (see above).

Skin lesions may be created *de novo* or evolve from a pre-existing urticarial papule, acneiform lesion, or crust. Repeated picking, scratching, or rubbing of the skin can result in erosions or ulcerations with linear/angular or circular/oval shapes (Fig. 7.6). The distribution characteristically favors the dorsal hands and forearms as well as the scalp, face, upper outer arms, upper back, and buttocks. Some patients favor only "hidden" areas such as the buttocks.



Fig. 7.6 Excoriation (skin-picking) disorder. This patient continued to pick at a mosquito bite, creating a deep ulceration with raised borders. Note the sequelae of concomitant body-focused repetitive behaviors – short nails with surrounding erythema, thickening, peeling, and hemorrhagic crusts from nail biting (onychophagia) and cuticle picking.



Fig. 7.7 Acne excoriée. This patient compulsively picked at his acne lesions. *Courtesy Richard Odom, MD.*

Lesions range in size from a few millimeters to several centimeters. Several stages of evolution are often evident, from small superficial erosions to deep ulcerations with hypertrophic borders to hypo- or hyperpigmented scars. On the scalp, there may be broken hairs as well as areas of scarring alopecia. The presence of mature scars points to chronicity.

Differential diagnosis

Underlying causes of pruritus and dysesthesia should be considered (see Ch. 6). Body-focused repetitive behaviors, including skin picking and hair pulling, should not be confused with stereotypic movement disorders, which are characterized by repetitive, seemingly driven, apparently purposeless motor behaviors that typically begin during early childhood. Stereotypic movement disorders can occur in the setting of autism spectrum disorder and other neurodevelopmental conditions.

Treatment

Once causes of pruritus or dysesthesia are excluded and treatment of underlying cutaneous disorders (e.g. folliculitis) has been instituted, therapy can focus on associated pruritus (if present) and the psychological aspects of the condition. When pruritus is present, topical lotions containing pramoxine or menthol may be helpful. Cool compresses are soothing, hydrate the skin, and facilitate debridement of crusts. Antihistamines such as hydroxyzine can have beneficial sedative and antipruritic effects in some patients. Intralesional corticosteroids and flurandrenolide tape address the inflammatory component of existing lesions but not the formation of new lesions.

Doxepin, a tricyclic antidepressant with potent antihistamine properties, may be particularly useful in patients with excoriation disorder associated with pruritus, anxiety, and/or difficulty sleeping. Starting at a low dose (e.g. 10 mg) at bedtime is recommended, with a gradual titration to a beneficial effect (often 25–50 mg nightly [lower in elderly patients]). This allows one to build tolerance to associated daytime somnolence. If significant depression or anxiety is present and not controlled by low-dose doxepin, addition of an SSRI is preferred so as to avoid the potential side effects of higher doxepin doses (see Table 7.1).

Since obsessive–compulsive symptoms are associated with serotonin-mediated neural pathways, SSRIs can be helpful in patients with excoriation disorder as well as OCD itself (see Table 7.1). CBT and habit reversal training have been reported to reduce skin picking in systematic reviews[21,22]. In addition, *N*-acetylcysteine (1200–3000 mg/day) led to more improvement than placebo in a randomized controlled study of adults with excoriation disorder, with similar findings in a systematic review[23–25]. Potential side effects include occasional gastrointestinal symptoms such as flatulence.

Acne Excoriée

Synonym: ■ Acne excoriée des jeunes filles

Key features

- Subset of excoriation disorder
- Frequently seen in young women
- Ritualistic picking of acne lesions

Clinical features

Acne excoriée is a subset of excoriation disorder (see above) in which the picking is directed at acne lesions. The underlying acne is often mild but accompanied by extensive excoriations that may lead to scarring (Fig. 7.7).

Treatment

Treatment includes comprehensive therapy for the underlying acne (see Ch. 36) together with management of the obsessive–compulsive component and other psychological aspects as described above for excoriation disorder. Recurrence of even mild acne may be accompanied by resumption of picking unless the associated psychologic disorder is addressed.

Dermatitis Artefacta

Synonyms: ■ Factitial dermatitis ■ Factitious disorder

Key features

- More common in women than men
- Motive is usually subconscious and patients deny their role in causation
- Self-inflicted cutaneous lesions that are often induced by foreign objects
- Typically located in areas that are easily reached by the hands

Introduction

Dermatitis artefacta represents a type of *factitious disorder* within the broad DSM-5™ category of *somatic symptom and related disorders*[2]. Patients inflict cutaneous lesions upon themselves to satisfy a psychologic need of which they are usually not consciously aware. If asked, the patients deny having any role in creating the skin lesions. While some of these individuals create skin lesions as a maladaptive response to an acute psychosocial stress, many suffer from borderline personality disorder[4]. Because patients may dissociate in the process of creating these lesions, they are often unable to give an accurate history, making this disorder challenging to diagnose and treat. "*Factitious disorder imposed on another*" (previously known as *Munchausen syndrome by proxy*) is a related condition in which an individual surreptitiously inflicts lesions on another person in order to satisfy a subconscious psychologic need.

Epidemiology

Dermatitis artefacta is uncommon and is reported to have a female : male ratio of up to 20 : 1[4]. Although the onset is most frequently during adolescence and young adulthood, it can occur at any age. Many patients either work in or have a close family member who works in the healthcare field.

Clinical features

Dermatitis artefacta can mimic a wide variety of dermatoses. The lesions may be single or multiple and unilateral or bilateral. Although usually within easy reach of the hands, the lesions can be caused by methods such as carving with sharp instruments, applying chemicals, injecting foreign substances, thermal burns, and the "salt and ice challenge" publicized on the Internet[26,27]. The morphology ranges from vesicles and bullae to purpura to subcutaneous emphysema to erosions and ulcerations. A clue to the diagnosis is unusual shapes, particularly with angulated edges, that suggest an external method of induction (Fig. 7.8).

Pathology

Histopathologic changes seen with dermatitis artefacta vary considerably, depending upon the manner in which the lesions were produced. The findings are generally not diagnostic and can include erosion, ulceration, epidermal necrosis with multinucleated keratinocytes, hyperkeratosis, irregular acanthosis, vascular proliferation, hypertrophied nerves (as observed in prurigo nodularis), and fibroplasia[28]. Polarizing exogenous material with a variable foreign body response is occasionally evident[29].

Differential diagnosis

In addition to excluding a primary skin disorder (e.g. ecthyma), dermatitis artefacta must be distinguished from delusional infestation, excoriation disorder, and malingering; the latter is characterized by skin lesions that are self-inflicted for a *conscious* gain. In *nonsuicidal self-injury* (see below), patients acknowledge that they inflicted the lesions on themselves.

Treatment

Initially, wound care to help with healing is often indicated and the possibility of a primary dermatologic disorder needs to be excluded. There is controversy as to whether or not to confront the patient upon recognition of dermatitis artefacta, as this might acutely exacerbate their self-harm behaviors. Therefore, it is often more fruitful to provide a supportive environment early in the doctor–patient relationship and then advance to the psychological aspects of the disease at subsequent visits. Antidepressant, antianxiety, or antipsychotic medications may be indicated when affected individuals have an underlying psychiatric disorder (see Table 7.1). Children or adults in whom the lesions represent a response to a transient stress have the most favorable prognosis. Dermatitis artefacta usually has a chronic course, with waxing and waning depending upon circumstances in the affected individual's life.

Other Somatic Symptom and Related Disorders

Other conditions within the *somatic symptom and related disorders* category in DSM-5™ are characterized by somatic symptoms (either medically validated or unexplained) that are more severe than expected and associated with significant distress or functional impairment. Disorders in this category that may be seen in dermatologic practice include somatic symptom disorder and illness anxiety disorder.

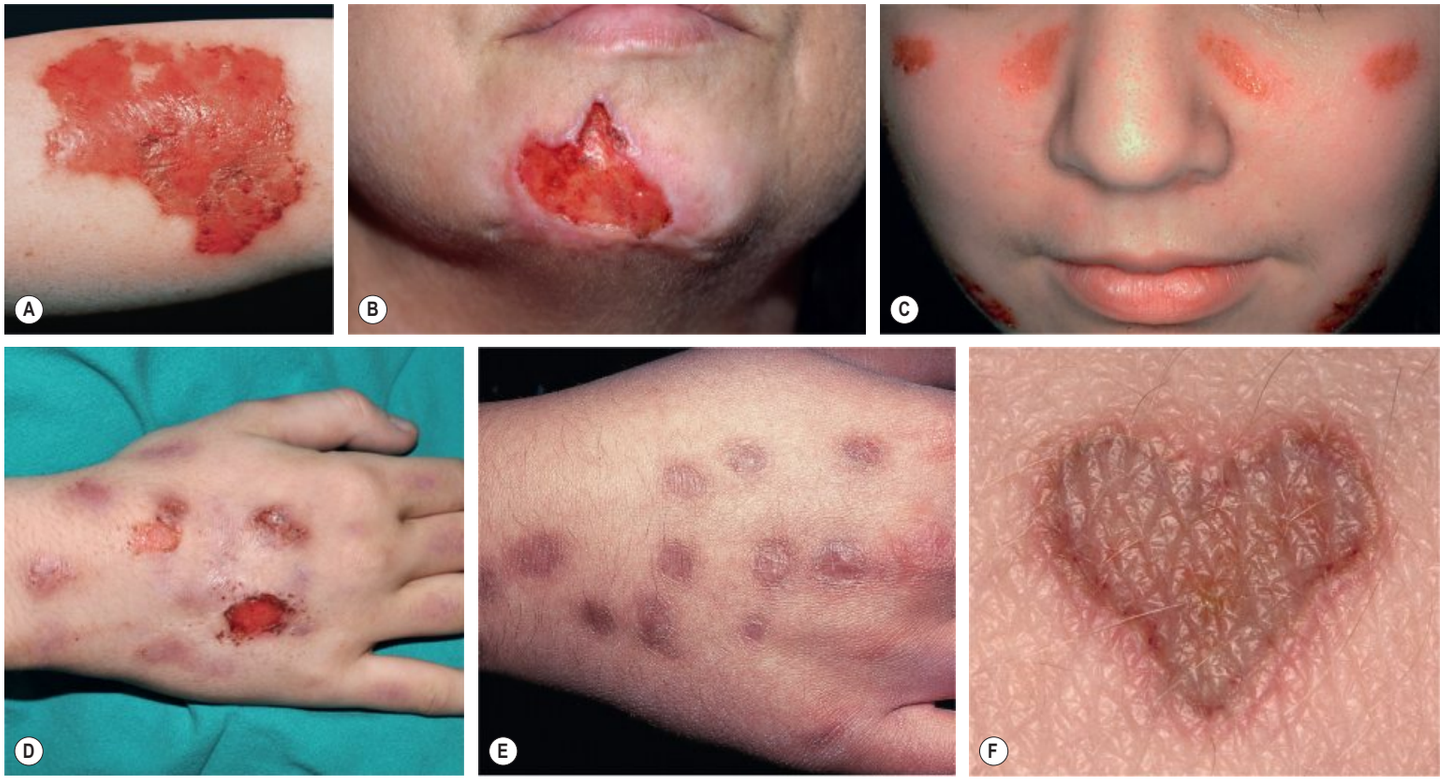


Fig. 7.8 Dermatitis artefacta. Erosion (**A**) and ulcer (**B**) with "bizarre" shapes and angulated borders, possibly created with sharp instruments. **C** Symmetric erosions on the cheeks of an adolescent girl. **D** Erosions in different stages of healing. **E** Scars from cigarette burns. **F** The patient carved this heart-shaped lesion into her skin. These patients all denied knowing how the lesions had developed or having any role in the process. *B, Courtesy Kalman Watsky, MD; D, Courtesy Antonio Torrelo, MD; E Courtesy Ronald P. Rapini, MD; F, Courtesy Department of Dermatology, Medical University of Graz.*

In *somatic symptom disorder*, affected individuals overestimate the seriousness of their symptoms, which lead to persistent thoughts, high levels of anxiety, and/or excessive expenditure of time and energy. Such patients are rarely reassured and may feel that their medical care has been inadequate. For example, a patient may interpret normal daily hair shedding as evidence of having alopecia areata, resulting in severe anxiety and substantial time spent collecting hairs.

Illness anxiety disorder is characterized by an excessive preoccupation with the idea of having or acquiring a serious illness[30]. Somatic symptoms are absent or mild, and there is an inappropriately high level of health-related anxiety. The individual may either be: (1) *care-seeking* with increased health-related behaviors, e.g. daily skin self-examinations looking for skin cancers; or (2) *care-avoidant* in a maladaptive manner, e.g. failing to go to the dermatologist for skin examinations despite a family history of melanoma.

Somatic symptom and illness anxiety disorders respond best to a combination of pharmacologic (e.g. SSRIs) and non-pharmacologic (e.g. CBT, psychotherapy) measures[30,31]. Coordination of care between providers is helpful to avoid unnecessary evaluation and treatment.



Fig. 7.9 Nonsuicidal self-injury. Repeated episodes of self-cutting with a razor blade caused these hypopigmented scars on the dorsal hand and forearm of this young woman.

Nonsuicidal Self-Injury

Synonym: ■ "Cutting"

Key features

- Repeated infliction of cutaneous injuries, e.g. via cutting, stabbing, or burning
- Represents a response to psychological distress without suicidal intent

Epidemiology and clinical features

Nonsuicidal self-injury features repeated infliction of shallow injuries to the surface of the body, typically via cutting, stabbing, or burning. There is no suicidal intent, and the purpose is usually to reduce negative emotions or resolve an interpersonal difficulty. The injury may be inflicted with a sharp object (e.g. knife, razor, needle), cigarette, or eraser that is rubbed vigorously. The most common sites are the dorsal forearms and anterior thighs. Most patients do not seek medical help and will admit that they inflicted the lesions on themselves[32]; scars are often the only visible sign of the behavior (Fig. 7.9). Onset is usually in early adolescence and can continue for many years. The overall female : male ratio is approximately 1.5 : 1[33]. Although nonsuicidal self-injury is classically associated with borderline personality disorder, depression and anxiety are more common in affected individuals.

Treatment

Initial management should focus on the patient's safety and treatment of associated psychiatric conditions. Basic tenets of treatment include determining the patient's psychologic needs and developing alternative methods to fulfill them. Dialectical behavioral therapy addressing impulse control, affect regulation, distress tolerance, and interpersonal effectiveness can be of benefit for patients with an underlying borderline personality disorder.

Excessive Tanning Behavior

There is increasing evidence that excessive tanning can represent an addictive behavior[34–36]. It involves an impulse towards and repetition of tanning that leads to impaired psychosocial functioning and continues despite potentially serious or fatal consequences, e.g. following the diagnosis of cutaneous melanoma.

SECONDARY PSYCHODERMATOLOGIC DISORDERS

Patients often experience concern and suffering due to skin conditions that are life-threatening (e.g. melanoma), disfiguring (e.g. alopecia areata, vitiligo), intensely pruritic or painful (e.g. atopic dermatitis, hidradenitis suppurativa), or even relatively minor but troublesome. When the magnitude of the distress exceeds that which would be expected and/or there is impairment in life functioning, then a secondary psychodermatologic condition such as anxiety, depression, and/or adjustment disorder should be considered.

Adjustment Disorder

Adjustment disorders are common in medical practice and may occur in response to a dermatologic condition. DSM-5™ defines an adjustment disorder as the development of emotional or behavioral symptoms in response to an identifiable stressor that results in either marked distress out of proportion to the severity of the stressor or significant impairment in life functioning. The stress-related reaction does not meet criteria for another psychiatric disorder (e.g. depression), arises within 3 months of the onset of the stressor, and does not persist for more than 6 months after the stressor has ended. If the stressor or its consequences persist, the adjustment disorder may continue and become chronic[2]. Adjustment disorders have been associated with an increased risk of suicidal behavior and substance abuse as well as with interference in medical treatment and worsening of the medical condition.

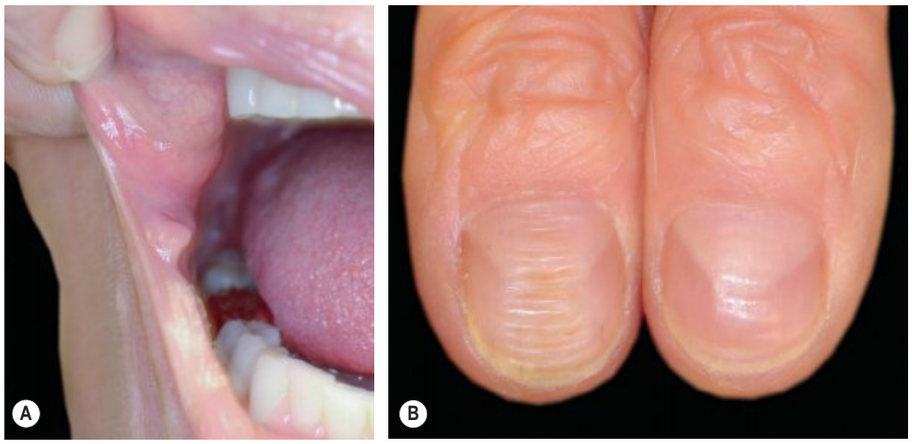
By asking open-ended questions about patients' experiences with their skin conditions, dermatologists can recognize and address their concerns, identify pathologic psychological responses, and make appropriate referrals to mental health providers. Adjustment disorder is best managed with psychotherapy, which can often be brief and solution-oriented, focusing on coping skills and managing problems associated with the dermatologic condition. Pharmacotherapy to address anxiety and/or depression, if present, may also be helpful (see Table 7.1).

Additional figures and tables, Abnormal involuntary movement scale (AIMS), The effect of psychotropics on QTc, available in our eBook (see inside front cover for access code).

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eFig. 7.1 Body-focused repetitive behaviors. A Bite fibroma from years of cheek chewing. **B** Habit-tic deformity of the thumbnail.



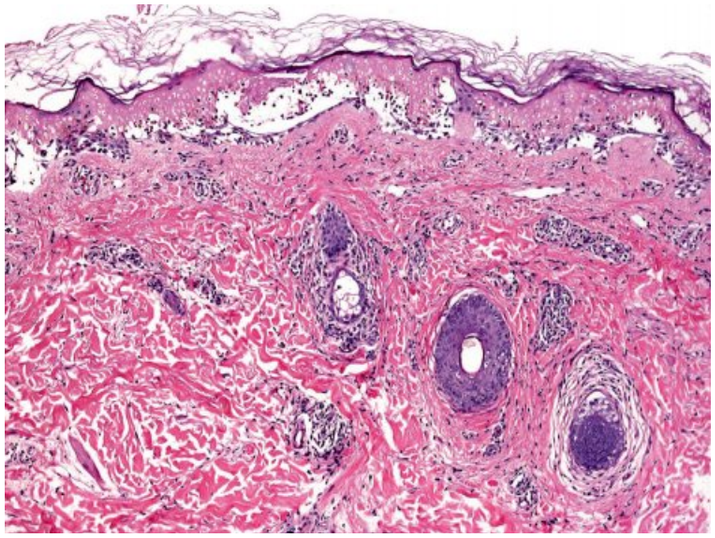
eFig. 7.2 Excoriation (skin-picking) disorder. This patient picked vigorously at any blemish that he found on his face.



eFig. 7.3 Excoriation (skin-picking) disorder. This 69-year-old woman routinely scratched and picked at her skin for several hours at the same time each day when she found herself alone at home. She had associated anxiety and depression and responded to doxepin. Note the admixture of crusted erosions, linear hyper- and hypopigmented scars on the back (**A**) and the numerous hypopigmented scars on the chest (**B**). She also picked at her daughter's skin.



eFig. 7.4 Dermatitis artefacta. Erosions and ulcers with angulated borders in various stages of healing on the leg of a teenage girl. The patient denied knowing how the lesions had developed or having any role in the process.



eFig. 7.5 Histopathology of dermatitis artefacta. Acute, full-thickness necrosis of the epidermis with sparse inflammatory infiltrates in the superficial dermis. *Courtesy Lorenzo Cerroni, MD.*

AIMS EXAMINATION PROCEDURE

SHOULD BE COMPLETED BEFORE ENTERING THE RATINGS ON THE ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS) FORM.

Either before or after completing the Examination Procedure, observe the patient unobtrusively at rest (e.g. in waiting room).

The chair to be used in this examination should be a hard, firm one without arms.

1: Ask patient whether there is anything in his/her mouth (i.e. gum, candy, etc) and if there is, to remove it.

2: Ask patient about the current condition of his/her teeth. Ask patient if he/she wears dentures. Do teeth or dentures bother patient now?

3: Ask patient whether he/she notices any movements in mouth, face, hands, or feet. If yes, ask to describe and to what extent they currently bother patient or interfere with his/her activities.

4: Have patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at entire body for movements while in this position.)

5: Ask patient to sit with hands hanging unsupported. If male, between legs, if female, and wearing a dress, hanging over knees. (Observe hands and other body areas.)

6: Ask patient to open mouth. (Observe tongue at rest within mouth.) Do this twice.

7: Ask patient to protrude tongue. (Observe abnormalities of tongue movement.)

*8: Ask patient to tap thumb, with each finger, as rapidly as possible for 10–15 seconds: separately with right hand, then with left hand. (Observe facial and leg movements.)

9: Flex and extend patient's left and right arms, one at a time. (Note any rigidity and rate it.)

10: Ask patient to stand up. (Observe in profile. Observe all body areas again, hips included.)

*11: Ask patient to extend both arms outstretched in front with palms down. (Observe trunk, legs, and mouth.)

*12: Have patient walk a few paces, turn, and walk back to chair. (Observe hands and gait.) Do this twice.

*Activated movements.

eTable 7.1 Abnormal involuntary movement scale (AIMS).

Patient's name _____ Patient's ID information _____

Examiner's name _____

CURRENT MEDICATIONS AND TOTAL MG/DAY

Medication #1 _____ Total mg/day _____ Medication #2 _____ Total mg/day _____

INSTRUCTIONS: COMPLETE THE EXAMINATION PROCEDURE BEFORE ENTERING THESE RATINGS.

	None, Normal	Minimal (may be extreme normal)	Mild	Moderate	Severe
Facial and Oral Movements					
1. Muscles of facial expression e.g. movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing	☐0	☐1	☐2	☐3	☐4
2. Lips and perioral area e.g. puckering, pouting, smacking	☐0	☐1	☐2	☐3	☐4
3. Jaw e.g. biting, clenching, chewing, mouth opening, lateral movement	☐0	☐1	☐2	☐3	☐4
4. Tongue Rate only increases in movement both in and out of mouth, NOT inability to sustain movement	☐0	☐1	☐2	☐3	☐4
Extremity Movements					
5. Upper (arms, wrists, hands, fingers) Include choreic movements (i.e. rapid, objectively purposeless, irregular, spontaneous); athetoid movements (i.e. slow, irregular, complex, serpentine) DO NOT include tremor (i.e. repetitive, regular, rhythmic).	☐0	☐1	☐2	☐3	☐4
6. Lower (legs, knees, ankles, toes) e.g. lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	☐0	☐1	☐2	☐3	☐4
Trunk Movements					
7. Neck, shoulders, hips e.g. rocking, twisting, squirming, pelvic gyrations	☐0	☐1	☐2	☐3	☐4

SCORING:
- Score the highest amplitude or frequency in a movement on the 0–4 scale, not the average;
- Score Activated Movements the same way; do not lower those numbers as was proposed at one time;
- A POSITIVE AIMS EXAMINATION IS A SCORE OF 2 IN TWO OR MORE MOVEMENTS or a SCORE OF 3 OR 4 IN A SINGLE MOVEMENT
- Do not sum the scores: e.g. a patient who has scores 1 in four movements DOES NOT have a positive AIMS score of 4.

Overall Severity					
8. Severity of abnormal movements	☐0	☐1	☐2	☐3	☐4
9. Incapacitation due to abnormal movements	☐0	☐1	☐2	☐3	☐4
	No Awareness	Aware, No Distress	Aware, Mild Distress	Aware, Moderate Distress	Aware, Severe Distress
10. Patient's awareness of abnormal movements (rate only patient's report)	☐0	☐1	☐2	☐3	☐4
Dental Status					
11. Current problems with teeth and/or dentures?	☐Yes	☐No			
12. Does patient usually wear dentures?	☐Yes	☐No			

Comments: _____

Examiner's Signature _____ Next Exam Date _____

Guy W: ECDEU Assessment Manual for Psychopharmacology - Revised (DHEW Publ No ADM 76-338), US Department of Health, Education, and Welfare; 1976

eTable 7.1 Abnormal involuntary movement scale (AIMS). The AIMS is a 12-item clinician-rated scale to assess the presence and severity of abnormal involuntary movements in patients taking antipsychotic medications. Development of such abnormal involuntary movements is unusual with the use of such medications in dermatology (e.g. for delusional infestation), as the doses are typically much lower and the durations significantly shorter than those used for other psychiatric conditions (e.g. schizophrenia). Items are scored on a 0 (none) to 4 (severe) basis. The scale provides a total score (items 1–7) or item 8 can be used alone to indicate the level of symptom severity. A positive AIMS examination is a score of 2 in two or more movements or a score of 3 or 4 in a single movement. *From Guy W. ECDEU Assessment Manual for Psychopharmacology – Revised (DHEW Publ No ADM 76-338), US Department of Health, Education, and Welfare; 1976.*

THE EFFECT OF PSYCHOTROPICS ON QTc
No effect
Brexpiprazole Cariprazine Lurasidone
Low effect (only in overdose or <10 ms increases in QTc)
*Aripiprazole**, asenapine, clozapine, haloperidol, perphenazine, prochlorperazine, *olanzapine*†, *risperidone*, loxapine, paliperidone*
Moderate effect (>10 ms QTc prolongation at clinical doses)
Chlorpromazine, iloperidone, *quetiapine*, ziprasidone
High effect (>20 ms QTc prolongation at average clinical doses)
Pimozide Any drug or combination of drugs used in doses exceeding recommended maximum
*Data on paliperidone are confusing (some suggest no effect) and recent data suggest aripiprazole prolongs QTc to a small extent and is probably torsadogenic. †Isolated cases of QTc prolongation demonstrated effect on inwardly rectifying potassium channels (IKr); other data suggest no effect on QT.

eTable 7.2 The effect of psychotropics on QTc. Drugs in *italics* are currently the most commonly prescribed antipsychotic medications in the US. ms, milliseconds; QTc, QT interval corrected for heart rate. *Modified from Taylor DM, Barnes TRE, Young AH. Maudsley Prescribing Guidelines in Psychiatry. 13th edition. Chichester: Wiley Blackwell; 2018. Reproduced with permission.*

8 Psoriasis

Peter C.M. van de Kerkhof and Lars Iversen

Key features

- Psoriasis is a chronic, immune-mediated disorder that results from a polygenic predisposition combined with environmental triggers, e.g. trauma, infections, medications, psychological stress
- The underlying pathophysiology involves various classes of T cells and their interactions with dendritic cells and cells involved in innate immunity, including neutrophils and keratinocytes
- Identification of susceptibility genes has pointed to a major role for the innate and adaptive immune systems as well as altered epidermal differentiation
- Sharply demarcated, scaly, erythematous plaques characterize the most common form of psoriasis; occasionally, sterile pustules are seen
- The most common sites of involvement are the scalp, elbows, and knees, followed by the nails, hands, feet, and trunk (including the intergluteal fold)
- Typical histologic findings include acanthosis with elongated rete ridges, hypogranulosis, hyper- and parakeratosis, dilated blood vessels, and a perivascular infiltrate of lymphocytes with neutrophils singly or within aggregates in the epidermis
- Psoriatic arthritis is the major associated systemic manifestation and the most common presentation is asymmetric oligoarthritis of the small joints of the hands and feet; other comorbidities include depression, metabolic syndrome, and cardiovascular disease in patients with moderate to severe disease
- Topical therapy is used to treat limited disease, whereas phototherapy, methotrexate, cyclosporine, and targeted immunomodulators ("biologic" therapies) that modify key immune effector cells and cytokines lead to significant clinical improvement of moderate to severe psoriasis

INTRODUCTION

Psoriasis is an immune-mediated polygenic skin disorder[1]. Various environmental triggering factors, e.g. trauma, infections, medications, may elicit disease in predisposed individuals[1]. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution. Histologically, hyperkeratosis, parakeratosis, acanthosis of the epidermis, tortuous and dilated vessels, and an inflammatory infiltrate composed predominantly of lymphocytes are observed.

Psoriasis is a systemic disease process in which up to 20%–30% of patients have or will develop psoriatic arthritis. In addition, in patients with moderate to severe psoriasis, there is an increased relative risk for metabolic syndrome, atherosclerotic cardiovascular disease, and depression. Psoriasis also has a significant impact on patients' quality of life[2], and in surveys, patients feel that the current treatments, although often effective, do not provide a satisfactory long-term solution.

HISTORY

Hippocrates and his school (460–377 BCE) provided meticulous descriptions of many skin disorders. In their classification, dry scaly eruptions were grouped together under the heading "lopoi". This group probably included psoriasis and leprosy.

Between 129 and 99 BCE, the word "psora" (meaning a desquamative condition) was first used by Galen to describe a skin disorder characterized by a scaliness of the eyelids, corners of the eyes, and scrotum. The condition was pruritic and excoriations were present. Although called psoriasis, this affliction was probably a type of eczema.

It was not until the nineteenth century that psoriasis was recognized as an entity distinct from leprosy. Although Robert Willan (1809) was the first to give an accurate description of psoriasis, it would be another 30 years before Hebra (in 1841) definitively separated the clinical features of psoriasis from those of leprosy. In 1879, Heinrich Koebner described the development of psoriatic plaques at sites of skin injury. The World Health Organization (WHO) passed a resolution in 2014 recognizing psoriasis as a "chronic, noncommunicable, painful, disfiguring and disabling disease for which there is no cure".

EPIDEMIOLOGY AND GENETICS

In most reviews, the prevalence of psoriasis is said to be 2% of the world's population. However, in the US and Canada, prevalences as high as 4.6% and 4.7% have been reported, respectively. This contrasts with frequencies in Africans, African-Americans, Norwegian Lapps, or Asians of between 0.4% and 0.7%. A worldwide systematic literature review was performed by the Global Psoriasis Atlas (www.globalpsoriasisatlas.org) focusing on the epidemiology of psoriasis[3]. The incidence varied from 30 per 100 000 person-years in Taiwan to 321 per 100 000 person-years in Italy. Psoriasis proved to be more frequent in high-income countries and in regions with older populations.

One population-based study noted that 73% of affected individuals had mild to moderate psoriasis, while 27% suffered from more severe involvement[2]. In one large group of patients with psoriasis (n = 1728), 79% had nail changes[4]. Psoriatic arthritis has been found to affect 5%–30% of patients with cutaneous psoriasis, depending upon the series[1].

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 20–30 years of age and a second peak at 50–60 years. In ~75% of patients, the onset is before the age of 40 years[5–7], and in 35%–50%, it is before the age of 20 years. Although the age of onset is earlier in women than in men, the natural history is similar – chronic with intermittent remissions. In one epidemiologic study, 39% of the patients stated they had experienced remissions of 1–54 years[6].

In Europe, the overall prevalence rate for juvenile psoriasis was found to be ~0.7%, with an increase from 0.37%–0.55% in those 0 to 9 years of age to 1.01%–1.37% in those 10–19 years of age[5–8]. Plaque psoriasis is the most frequent form of the disease in children, followed by guttate psoriasis.

Genetic Factors

Depending upon the series, a positive family history has been reported by 35% to 90% of patients with psoriasis. Based on a large survey-based study in Germany, if both parents had psoriasis, the risk of their child developing psoriasis was 41%, whereas if only one parent were affected, the risk was 14%; the risk was 6% if just one sibling had psoriasis[9].

Analysis of concordance rates among monozygotic and dizygotic twins is another method for examining the influence of genetic factors on a disease. One literature review found that of 141 monozygotic twin pairs, 82 were concordant for psoriasis and 59 were discordant; of 155 dizygotic twin pairs, only 31 were concordant and 124 were discordant for psoriasis[10]. Thus, there is a two- to threefold increased risk of psoriasis in monozygotic twins as compared to dizygotic twins, implying that genetic factors are important. The distribution of the lesions, the severity, and the age of onset were similar in the monozygotic twin pairs, whereas these features differed in the dizygotic twin pairs. This observation suggested that genetic factors also play a role in the clinical course of psoriasis.

HLA studies

Histocompatibility antigens (HLA) are surface antigens on human cells, and the corresponding chromosomal region is called the major histocompatibility complex (MHC). It is situated on the short arm (p) of chromosome 6. Psoriasis is associated with HLA-Cw6, with the presence of HLA-Cw6 conferring a relative risk of 13 for developing psoriasis in the White population and 25 in the Japanese.

HLA-Cw6 is strongly linked to the age of onset of psoriasis. In one series, HLA-Cw6 was expressed in 90% of the patients with early-onset psoriasis, in 50% of those with late-onset psoriasis, and only in 7% of a control population. A specific MHC class II antigen (DRB1*0701/2) also appeared to be associated with early-onset psoriasis, and the psoriasis-associated HLA alleles were often in an extended haplotype: Cw6-B57-DRB1*0701-DQA1*0201-DQB1*0303. Individuals carrying this haplotype were found to have a 26-fold increased risk of developing early-onset psoriasis[11].

As a result, some clinicians have designated patients with early-onset psoriasis, a positive family history of psoriasis, and expression of HLA-Cw6 as having *type I psoriasis* and those with late-onset disease, no family history, and a lack of expression of HLA-Cw6 as having *type II psoriasis*[12]. While HLA-Cw6 may serve as a biomarker for clinical and therapeutic stratification[13], to date there are no treatments that specifically target HLA-Cw6. Other HLA alleles can be associated with different psoriasis variants and related conditions, e.g. the HLA-B27 allele is a marker for sacroiliitis-associated psoriasis and reactive arthritis (see below).

Genome-wide association studies

Classic genome-wide linkage analysis identified at least nine psoriasis susceptibility regions *(PSORS1–9)* in different chromosomal locations[14]. By far the most important genetic region was *PSORS1* (on chromosome 6p), which is estimated to account for up to 50% of psoriasis risk. *PSORS1* contains genes such as *HLA-C* (with the *HLA-Cw6* risk allele; see above) and corneodesmosin (*CDSN*). Due to high linkage disequilibrium in *PSORS1* (i.e. genes within this region are inherited as a block), it has been challenging to determine which gene(s) within *PSORS1* contribute to psoriasis pathogenesis.

In genome-wide association studies (GWASs), in which hundreds of thousands of *s*ingle *n*ucleotide *p*olymorphisms (SNPs) across the entire human genome are examined in thousands of patients (see Ch. 54), at least 80 risk loci have been identified[15]. It has been estimated that these loci explain ~28% of genetic heritability[15]. GWASs have led to several conclusions regarding the genetic factors in psoriasis (Table 8.1)[16,17]. First, most of the genes that have been implicated have immune-related functions, underscoring the importance of the innate and adaptive immune systems in the pathogenesis of psoriasis; in contrast, relatively few genes that encode skin-specific proteins have been associated with psoriasis. Second, thus far surprisingly few interactions among the genetic variants have been identified (with the exception of HLA-Cw6 and ERAP-1; see below). Third, associated genes encode proteins with roles in particular immunologic and signaling pathways, especially those involving tumor necrosis factor (TNF), NF-κB, interferons (IFNs), and interleukin (IL)-23/Th17 cells (see Table 8.1)[17,18]. Lastly, *ERAP1*, which encodes an aminopeptidase involved in MHC class I antigen processing, interacts synergistically with the *HLA-Cw6* risk allele, providing another argument for the role of an MHC-restricted antigen and its presentation through HLA-C in the pathogenesis of psoriasis[17].

More recently, greater insights into the genetics of pustular psoriasis have been made. In patients with generalized pustular psoriasis, several groups identified homozygous or compound heterozygous loss-of-function mutations in *IL36RN*, which encodes the IL-36 receptor antagonist[19]. Patients with the autoinflammatory disorder DITRA (deficiency of IL-36 receptor antagonist) present with widespread psoriasiform plaques whose edges contain sterile pustules (see Figs. 45.11B & 45.12). Based upon susceptibility loci and transcriptomics, a significant IL-36 signature was also observed in patients with plaque psoriasis[20].

Functional genomic studies

Microarray technology has been utilized to obtain a comprehensive picture of the genes expressed in psoriatic skin[21]. More than 1300 genes were found to be differentially expressed when compared to normal human skin. This group of genes included known markers of psoriasis in the skin, but it also contained numerous genes not known to be expressed in the skin. These analyses confirmed (on a genomic scale) the involvement of T cells and dendritic cells (DCs) and also implicated a role for comorbidity-associated genes involved in atherosclerosis signaling and fatty acid metabolism.

Another important gene family differentially expressed in psoriatic epidermis encodes antimicrobial peptides. These peptides are expressed at high levels in psoriatic skin but at low levels in skin affected by atopic dermatitis[22]. Additionally, complete functional impairment of the IL-36 receptor antagonist secondary to null mutations in *IL36RN* has highlighted the importance of repressing IL-36-dependent activation of the NF-κB pathway[23]. Such insights led to the recent introduction of an interleukin-36 receptor inhibitor for the treatment of generalized pustular psoriasis.

PATHOGENESIS

Because it primarily affects the interfollicular epidermis, psoriasis was long regarded as an epidermal disease in which the fundamental biochemical or cellular defect resided within the keratinocyte. Accordingly, prior to the early 1980s[24], a number of biochemical mediators, enzymes, and pathways involved in epidermal function were incriminated as being abnormal in psoriasis, including cyclic AMP, eicosanoids, protein kinase C, phospholipase C, polyamines, and transforming growth factor (TGF)-α. Although associated immunologic abnormalities were reported in the late 1970s[25], a major paradigm shift occurred when T cell suppressive agents such as cyclosporine were found to result in dramatic improvement of psoriasis[26]. Over the past three decades, psoriasis has been regarded as a T cell-driven disease[1]. The role of lymphocyte subsets as well as cytokines involved in chemotaxis, homing, and activation of inflammatory cells has been extensively investigated, culminating in the development of novel therapeutic approaches[1]. In sum, psoriasis is a chronic, inflammatory, autoimmune skin disease elicited by environmental factors or autoantigens in genetically predisposed individuals and it involves complex interactions amongst the innate and adaptive immune systems as well as keratinocytes and other cells residing within the skin.

Immunopathogenesis

Role of T cells and dendritic cells

A pathogenic role for antigen-presenting cells and T cells is strongly suggested by the association of psoriasis with particular MHC alleles, e.g. *HLA-Cw6*, as well as (in individuals who carry such alleles) variants in *ERAP1*, which encodes an aminopeptidase involved in antigen processing. The presence of specific T cell subsets within the epidermis and dermis of lesional skin is well documented (Fig. 8.1A). Also, a number of compounds that affect T cell function (e.g. by targeting the IL-2 receptor, CD2, CD11a, or CD4) were found to result in clinical improvement of psoriasis[27]. Another argument supporting involvement of the adaptive immune system is the disappearance or development of psoriasis following hematopoietic stem cell transplantation[28]. In addition, analysis of lesional T cells has shown oligoclonality, indicating potential antigen-specific expansion of T cell subpopulations, possibly triggered by exogenous microbial or viral antigens or cross-reacting autoantigens, e.g. keratins. Other implicated autoantigens include the antimicrobial peptide LL37 (cathelicidin)[29] and the melanocyte antigen ADAMTSL5[30].

Animal models for psoriasis have also demonstrated the importance of T cells. In xenograft models in which uninvolved psoriatic skin was transplanted onto immunodeficient mice, donor immune cells (in particular resident T cells) were capable of expanding and inducing the complete lesional phenotype[31]. Induction of psoriatic lesions in these models was also shown to be dependent on TNF and on IFN-α derived from plasmacytoid DCs (pDCs)[32]. These experiments demonstrated that T cells can trigger psoriasis in a suitable patient-derived environment.

In humans, several cell types have been implicated in the initiation and maintenance of psoriatic lesions (see Fig. 8.1A). Most of the epidermal T cells are $CD8^+$, whereas the dermal infiltrate is a mixture of $CD4^+$ and $CD8^+$ cells. The majority of the cells in both locations are memory T cells that express cutaneous lymphocyte antigen (CLA; the skin homing receptor) and chemokine receptors such as CCR4. Expression of $\alpha_1\beta_1$ integrin (VLA-1) on psoriatic T cells, which allows

EXAMPLES OF PSORIASIS SUSCEPTIBILITY GENES					
Class	**Gene(s)**	**Pathway**	**Protein function**	**OR**	**Disease overlap**
Skin specific	*LCE3B/3C/3D*	Skin barrier formation	KC structural protein	1.26	
	KLF4	Skin barrier formation IL-17 signaling	Transcription factor	1.12	
	ETSI	Unknown	Transcription factor	1.12	
Innate immunity	*IL-28RA*	IFN signaling	IL-29 receptor subunit	1.21	
	IFIHI	IFN signaling	Innate antiviral receptor	1.27	
	RNF114	IFN signaling	E3 ubiquitin ligase	1.16	
	ELMOI	IFN signaling	Involved in TLR-mediated IFN-α signaling	1.11	
	DDX58	IFN signaling	Innate antiviral receptor	1.11	
	NOS2	Inflammation	Induced nitric oxide synthase	1.22	
	REL	NF-κB signaling	NF-κB subunit	1.17	RA
	TNIP1	NF-κB signaling	Inhibitor of TNF-induced NF-κB activation	1.59	
	TNFAIP3	NF-κB signaling	Inhibitor of TNF-induced NF-κB activation	1.23	
	NFKBIA	NF-κB signaling	Inhibitor of NF-κB activation	1.16	
	FBXL19	NF-κB signaling	Putative inhibitor of NF-κB activation	1.16	
	CARDI4	NF-κB signaling	Activator of NF-κB pathway	1.11	
	*CARMI**	NF-κB signaling	Transcriptional coactivator of NF-κB	1.17	
	*UBE2L3**	NF-κB signaling	Ubiquitin-conjugating enzyme	1.13	Cel, RA, Cro
At the interface between innate and adaptive immunity	*TRAF31P3*	IL-23/IL-17 axis NF-κB signaling	Adaptor molecule mediating IL-17-induced NF-κB activation	1.52	
	IL-12B	IL-23/IL-17 axis	Shared subunit of IL-12/IL-23	1.58	
	IL-23A	IL-23/IL-17 axis	Unique subunit of IL-23	1.39	
	TYK2	IL-23/IL-17 axis IFN signaling	Tyrosine kinase associated with cytokines receptors	1.88	
	HLA-C	Antigen presentation	MHC class 1 antigen	4.32	
	ERAPI	Antigen presentation	Enzyme processing MHC class 1 ligands	1.2	AS
Adaptive immunity	*IL-23R*	IL-23/IL-17 axis	Unique subunit of IL-23 receptor complex	1.52	AS, UC, Cro
	*STAT3**	IL-23/IL-17 axis	Transcription factor	1.15	
	*IRF4**	IL-17 signaling	Transcription factor	1.12	
	RUNX3	T-bet pathway	Transcription factor	1.13	AS, Cel
	IL-4/IL-13	IL-4/IL-13 signaling	IL-4 and IL-13 cytokines	1.18	
	*TNFRSF9**	T cell differentiation	Adaptor molecule	1.13	
	TAGAP	T cell activation	Rho GTPase-activating protein	1.12	RA
	ZMIZI	TGF-β signaling	Protein inhibitor of activated STAT (PIAS) family of proteins	1.1	MS
	SOCSI	Type II IFN signaling	Suppressor of cytokine signaling	1.13	
Other	*PRDX5*	Intracellular redox signaling	Antioxidant enzyme	1.09	
	B3GNT2	Carbohydrate metabolism	Enzyme	1.12	AS
	*MBD2**	Unknown	Transcriptional repressor	1.12	
	ZC3H12C	Unknown	Zinc finger protein with putative RNase function	1.14	

*Most notable gene mapped by the identified SNP.

Table 8.1 Examples of psoriasis susceptibility genes. PSORS1 = *HLA-C* and *CDSN*, PSORS2 = *CARD14*, PSORS14 = *IL36RN*, and PSOR15 = *AP1S3*; PSORS3–12 are at the following loci: 4q, 1q21, 3q21, 19p13, 1p, 16q, 4q31, 18p11, 5q31–q33, and 20q13. PSORS13 is conferred by variation in *TRAF3IP2*. AS, ankylosing spondylitis; Cro, Crohn disease; Cel, celiac disease; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; KC, keratinocyte; LCE, late cornified envelope; MHC, major histocompatibility complex; MS, multiple sclerosis; OR, odds ratio; RA, rheumatoid arthritis; TLR, toll-like receptor; TNF, tumor necrosis factor; UC, ulcerative colitis.
Modified from Di Meglio P, Villanova F, Nestle FO. Psoriasis. Cold Spring Harb Perspect Med. 2014;4:a015354. Additional references are online (e1–e19).

their interaction with basement membrane collagen IV, is key for the entrance of these cells into psoriatic epidermis and establishment of the psoriatic epithelial phenotype[33]. Unconventional T cells also contribute to the pathogenesis of psoriasis via secretion of proinflammatory cytokines and chemokines. These include natural killer (NK) T cells, gamma delta (γδ) T cells, and innate lymphoid cells (ILCs).

DCs are present in both uninvolved and lesional psoriatic skin, and because of their potent immunostimulatory capacity, they are likely to be involved in its pathogenesis. There is an increased number of dermal DCs in psoriatic skin, and they have an enhanced ability to activate T cells when compared to DCs from normal skin. The role of DCs in psoriasis has been validated by the presence of a prominent genomic DC signature and the decrease of DCs during effective targeted therapy.

Based upon studies in humans and a xenograft model, a subtype of DC, the pDC, was shown to initiate psoriasis via the production of IFN-α[32]. Complexes of self DNA or RNA (from keratinocytes) plus antimicrobial peptide LL37 trigger IFN-α release by pDCs via a Toll-like receptor 9 (TLR9)-dependent mechanism (see Fig. 8.1A). This leads to

a breaking of tolerance to self nucleic acids and potentially explains the start of the inflammatory cascade in psoriasis[34,35].

The presence of neutrophils in the epidermis, either in spongiform pustules of Kogoj or in microabscesses of Munro, is a typical histopathologic feature of psoriasis, especially acute or pustular forms. Neutrophils are typically prominent in active lesions and in the marginal zone of expanding plaques, but, in contrast to T cells, they are not a consistent feature of lesional skin. Although activated neutrophils could contribute to its pathogenesis, they are not considered to be the primary cause of psoriasis.

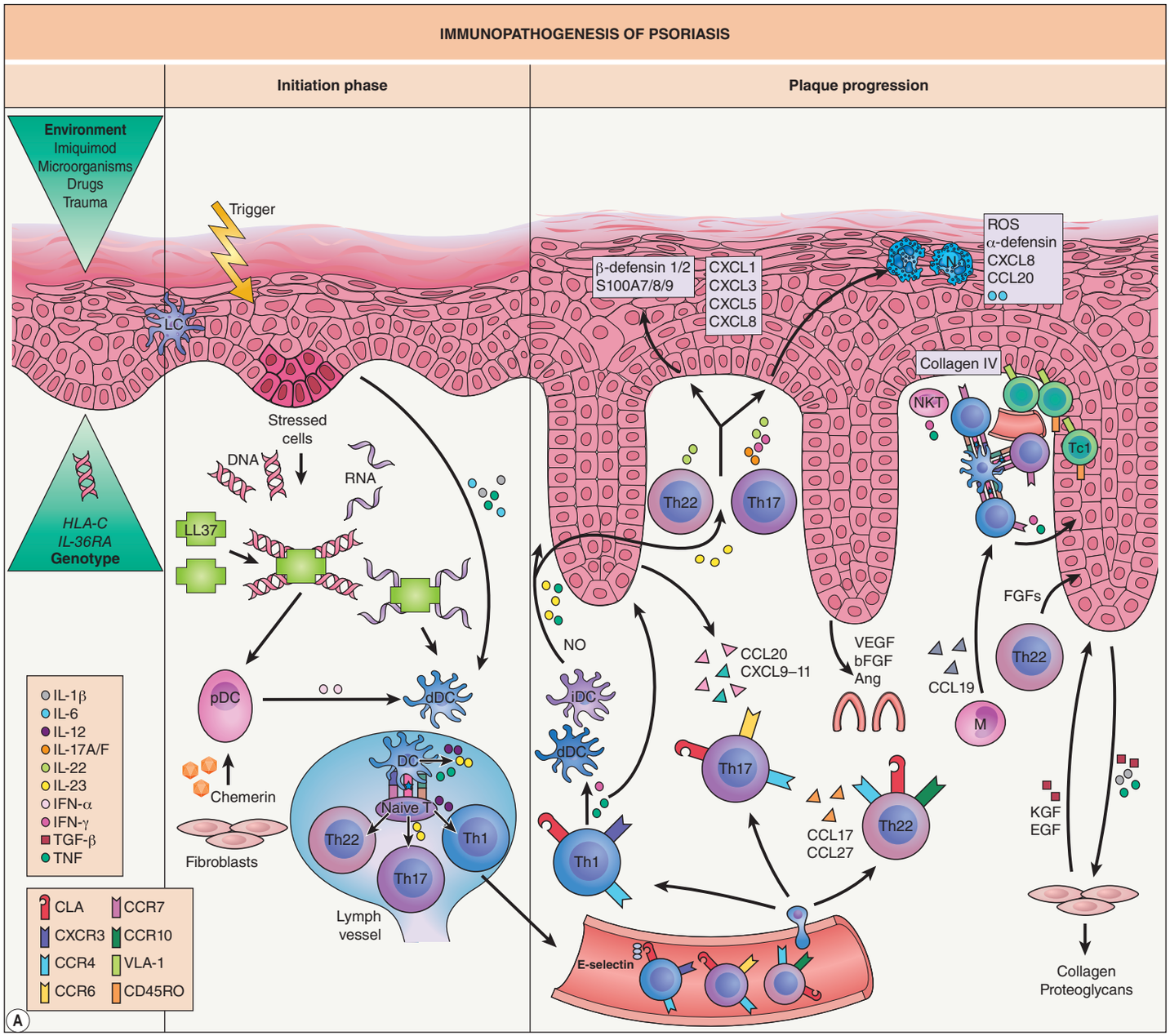


Fig. 8.1A Immunopathogenesis of psoriasis. The occurrence of triggering environmental factors in genetically predisposed individuals, carrying susceptibility alleles of psoriasis-associated genes, results in disease development. During the initiation phase, stressed keratinocytes can release self DNA and RNA, which form complexes with the cathelicidin LL37 that then induce interferon-α (IFN-α) production by plasmacytoid dendritic cells (pDCs; recruited into the skin via fibroblast-released chemerin), thereby activating dermal DCs (dDCs). Keratinocyte-derived interleukin-1β (IL-1β), IL-6, and tumor necrosis factor (TNF) also contribute to the activation of dDCs. Activated dDCs then migrate to the skin-draining lymph nodes to present an as-yet-unknown antigen (either of self or of microbial origin) to naive T cells and (via secretion of different types of cytokines such as IL-12 and IL-23 by DCs) promote their differentiation into T helper 1 (Th1), Th17, and Th22 cells. Th1 cells (expressing cutaneous lymphocyte antigen [CLA], CXC-chemokine receptor 3 [CXCR3], and CC-chemokine receptor 4 [CCR4]), Th17 cells (expressing CLA, CCR4, and CCR6), and Th22 cells (expressing CLA, CCR4, and CCR10) migrate via lymphatic and blood vessels into psoriatic dermis, attracted by the keratinocyte-derived chemokines CCL20, CXCL9–11, CCL17, and CCL27; this ultimately leads to the formation of a psoriatic plaque. Th1 cells release IFN-γ and TNF, which amplify the inflammatory cascade, acting on keratinocytes and dDCs. Th17 cells secrete IL-17A and IL-17F (and also IFN-γ and IL-22), which stimulate keratinocyte proliferation and the release of β-defensin 1/2, S100A7/8/9, and the neutrophil-recruiting chemokines CXCL1, CXCL3, CXCL5, and CXCL8. Neutrophils (N) infiltrate the stratum corneum and produce reactive oxygen species (ROS) and α-defensin with antimicrobial activity, as well as CXCL8, IL-6, and CCL20. Th22 cells secrete IL-22, which induces further release of keratinocyte-derived T cell-recruiting chemokines. Moreover, inflammatory DCs (iDCs) produce IL-23, nitric oxide (NO) radicals, and TNF, while natural killer T (NKT) cells release TNF and IFN-γ. Keratinocytes also release vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and angiopoietin (Ang), thereby promoting neoangiogenesis. Macrophage (M)-derived chemokine CCL19 promotes clustering of Th cells expressing chemokine receptor CCR7 with DCs in the proximity of blood vessels, with further T cell activation. At the dermal–epidermal junction, memory $CD8^+$ cytotoxic T cells (Tc1) expressing very-late antigen-1 (VLA-1) bind to collagen IV, allowing entry into the epidermis and contributing to disease pathogenesis by releasing both Th1 and Th17 cytokines. Cross-talk between keratinocytes, producing TNF, IL-1β and transforming growth factor-β (TGF-β), and fibroblasts, which in turn release keratinocyte growth factor (KGF), epidermal growth factor (EGF) and TGF-β, and possibly Th22 cells releasing FGFs, contribute to tissue reorganization and deposition of extracellular matrix (e.g. collagen, proteoglycans).

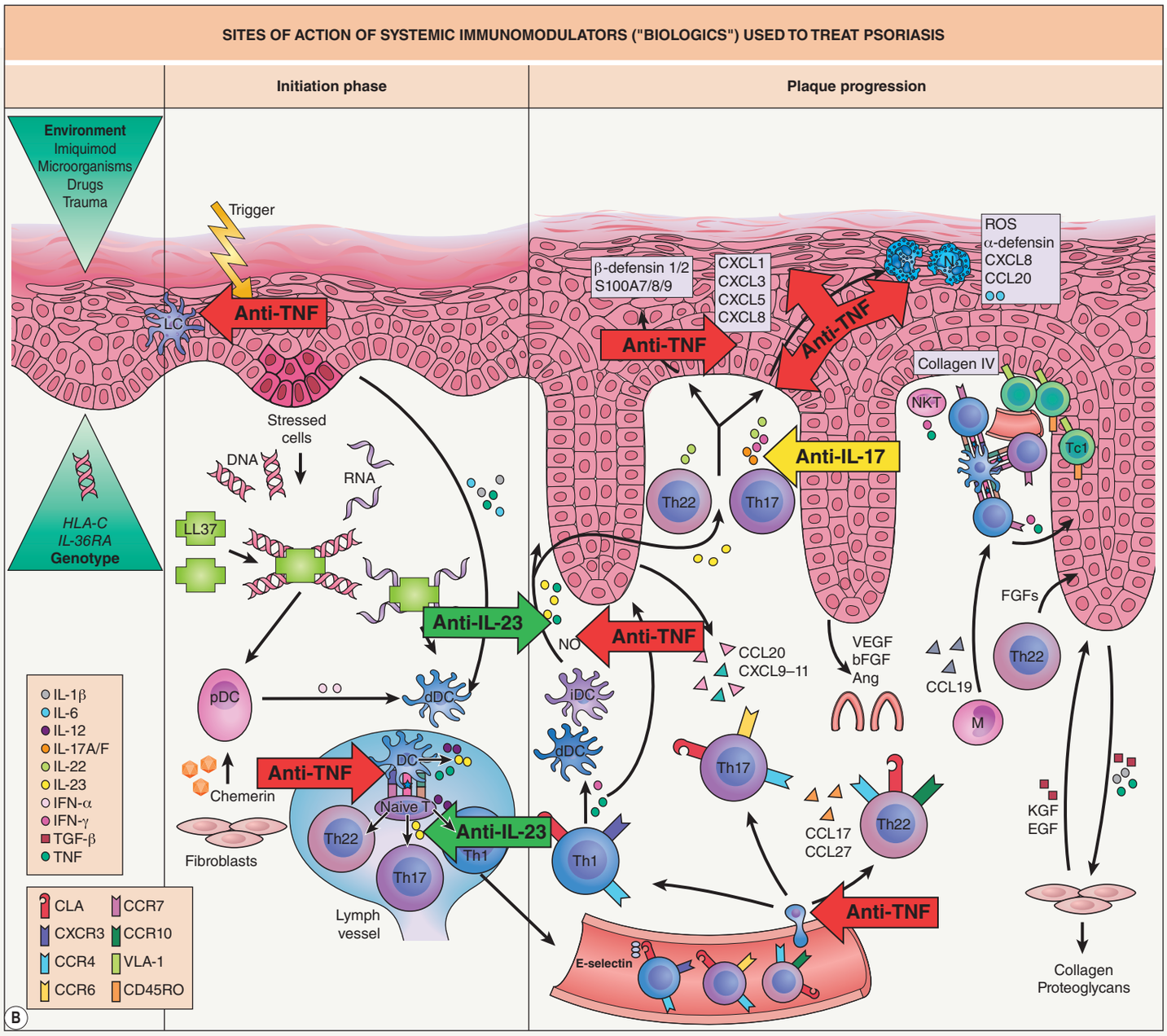


Fig. 8.1B Sites of action of systemic immunomodulators ("biologics") used to treat psoriasis. Note the multiple sites for TNF inhibitors while anti-IL-17 and -IL-23 antibodies are more selective. In the epidermis of psoriatic lesions, IL-17A, IL-17F, and IL-22 induce host defense proteins and several proinflammatory cytokines, including IL-36; there is greater expression of IL-36 in patients with generalized pustular psoriasis and in those with a loss-of-function mutation in the gene that encodes the IL-36 receptor antagonist. Recently, the first anti-IL-36 receptor antibody was approved by the FDA to treat patients with flares of generalized pustular psoriasis. LC, Langerhans cell. *Courtesy Dr Paola DiMeglio.*

Prominent angiogenesis is observed within plaques of psoriasis. There is increased expression of vascular endothelial growth factor (VEGF)[36], and anti-VEGF therapy leads to improvement in mouse models of psoriatic inflammation.

Cytokines, chemokines, and transcription factors

Psoriasis is considered to be a disease with prominent involvement of T helper cell subsets and their secreted *cytokines*[37]. This is supported by the significant clinical responses observed following administration of monoclonal antibodies that target specific cytokines (Fig. 8.1B). Increased amounts of Th1 (IFN-γ and IL-2), Th17 (IL-17A and -17F), and Th22 cytokines (IL-22) are observed, whereas levels of the anti-inflammatory cytokine IL-10 are reduced. The concerted action of these cytokines leads to proliferation of keratinocytes and dermal inflammation (see Fig. 8.1A)[38].

Following activation of pDCs, large amounts of type I IFN are produced, leading to maturation and activation of dDCs. The latter cells then secrete IL-23, which together with other cytokines (e.g. IL-6, TGF-β), drives naive T cells in a Th17 direction. Within the skin-draining lymph nodes, a naive T cell can differentiate into a Th1, Th17, or Th22 cell. After migrating into the skin, these cells release their signature cytokines; release of IL-17A and IL-17F leads, often in synergy with TNF, to an activation of the MAPK and NF-κB signaling pathways in keratinocytes[39] and other skin resident cells. This creates a "feed-forward" inflammatory response that can be self-amplifying and result in activation and recruitment of Th1 and Th22 cells into the psoriatic lesion[40,41].

Any model of pathogenesis has to also account for the dramatically increased proliferation rate of keratinocytes. Within psoriatic plaques, keratinocytes express the transcription factor STAT3, and in a transgenic animal model, epidermal expression of STAT3 (in cooperation with T cells) was found to induce psoriasis-like lesions. STAT3 induces upregulation of a number of psoriasis-relevant genes (e.g. *ICAM1*, *TGFA*), with TGF-α having been shown to stimulate proliferation of keratinocytes in psoriasis via an autocrine loop. Furthermore, STAT3 activation occurs downstream of several cytokines involved in the pathogenesis of psoriasis such as IL-6, IL-22, and IL-23[42]. In addition,

STAT3 activation induces differentiations of Th17 cells[43] and it directly activates the promoters of *IL17A* and *IL17F*[44].

IFN-γ is released by activated T cells and NKT cells within the epidermis, and it activates members of the STAT transcription factor family, which drive the expression of a large number of immune-related genes that have roles in psoriasis pathogenesis (see above). The IFN-γ-activated pathway is a key feature of psoriasis and explains several phenotypic alterations such as vasodilation (by the induction of nitric oxide synthase [iNOS]) and accumulation of T cells (via the expression of various chemokines). The innate immune cytokines IL-1, IL-6, and TNF are also upregulated in psoriatic skin. TNF is a particularly relevant cytokine and its importance is underscored by the therapeutic efficacy of TNF inhibitors (see Fig. 8.1B).

Chemokines are important mediators in the trafficking of leukocytes, and the increase in several chemokines and their cognate receptors within psoriatic lesions has been extensively documented. CXCL8 is thought to mediate the often-prominent infiltration by neutrophils. CCL17, CCL20, CCL27, and CXCL9–11 are implicated in attracting T cells to the psoriatic plaque. A pDC-attracting chemokine, chemerin, is increased in psoriatic skin and might contribute to the early recruitment of pDCs into psoriatic lesions[45].

Lastly, there is significant overlap between the cytokines, transcription factors, and subsequent signaling pathways discussed in this section and the psoriasis susceptibility genes outlined in Table 8.1.

Innate immunity and role of keratinocytes

In the skin, various cell types are involved in innate (non-adaptive) immune response pathways. These include DCs (myeloid DCs and pDCs), NKT cells, γδT cells, ILCs, and neutrophils, as well as epidermal keratinocytes. For example, keratinocytes constitutively express antimicrobial proteins such as β-defensin-1 (hBD1) and secretory leukocyte protease inhibitor (SLPI), which have direct antimicrobial activity against a broad spectrum of pathogens. In addition, keratinocytes can be stimulated to express a wide variety of other inducible antimicrobials such as hBD2, the cathelicidin LL37, and SKALP/elafin[46]. In addition to these effector molecules, keratinocytes express TLRs and secrete signaling molecules such as IL-1, IL-6, IL-8, and TNF (see Fig. 8.1A). Interestingly, the antimicrobial effector protein hBD2 was also shown to have chemotactic activity via CCR6 and to bind to TLR4. Since most of these proteins are highly expressed in lesional psoriatic skin, it is likely that they are involved in the initiation or control of the inflammatory process; however, their precise roles remain to be determined.

Disease memory

It is well known that psoriasis often relapses at previously affected body sites after treatment cessation[47]. The origin of this disease memory is unknown, but both tissue-resident memory T cells[48] and epithelial stem cells[49] have been proposed as candidate cells responsible for this phenomenon. The hypothesis that disease memory develops when lesions become chronic has led to the speculation that early and intensive interventions could avoid this phenomenon[50].

Triggering Factors

Triggering factors, both external (directly interacting with the skin) and systemic, can elicit psoriasis in genetically predisposed individuals.

External triggering factors

The Koebner or isomorphic phenomenon, i.e. the elicitation of psoriatic lesions by injury to the skin, is observed in ~25% of patients with psoriasis. A particular patient may be "Koebner-negative" at one point in time and later become "Koebner-positive". The Koebner phenomenon suggests that psoriasis is a generalized skin disease that can be triggered locally. Psoriatic lesions can also be induced by other forms of cutaneous injury, e.g. sunburn, morbilliform drug eruption, viral exanthem. The lag time between the trauma and the appearance of skin lesions is usually 2–6 weeks.

Systemic triggering factors

Infections

Infections, particularly bacterial infections, may induce or aggravate psoriasis. Provoking infections have been observed in up to 45% of psoriatic patients. Streptococcal infections, especially pharyngitis, are the most common offenders. In the palatine tonsils of psoriasis patients, immune responses have been shown to be dysregulated, with elevated expression of CLA and the IL-23 receptor[51]. Streptococci can also be isolated from other sites of infection, e.g. dental abscesses, perianal cellulitis, impetigo. Recently, group A streptococcal infections were shown to induce clonal expansion of CD1a-restricted T cells that can drive autoreactivity in psoriasis[51a].

HIV

HIV infection has also been shown to aggravate psoriasis (see Ch. 78).

Endocrine factors

Hypocalcemia has been reported to be a triggering factor for generalized pustular psoriasis. Although active vitamin D_3 analogues improve psoriasis, abnormal vitamin D_3 levels have not been shown to induce psoriasis. Pregnancy may alter disease activity, e.g. 50% of the patients in one series reported improvement during pregnancy. However, pregnant women may develop pustular psoriasis, also referred to as impetigo herpetiformis, and sometimes in association with hypocalcemia. As in pustular psoriasis in non-pregnant individuals, the pustules in impetigo herpetiformis are sterile.

Psychogenic stress

Psychogenic stress is a well-established systemic triggering factor in psoriasis, with a heightened cortisol response to stress having been demonstrated in affected patients[52]. Stress is associated with initial presentations of the disease as well as flares of pre-existing psoriasis. In a prospective study, cognitive and behavioral patterns of worrying and scratching were both independently related to an increase in disease severity and pruritus 4 weeks later[53].

Drugs

Several drugs have been incriminated as inducers of psoriasis, in particular lithium, IFNs, anti-PD-1 antibodies, β-blockers, and antimalarials. The association with immune checkpoint inhibitors may be related to increased levels of IL-6[54]. A rapid taper of systemic corticosteroids can induce pustular psoriasis as well as flares of plaque psoriasis. Patients receiving TNF inhibitors, e.g. for Crohn disease or rheumatoid arthritis, may experience new-onset or worsening of psoriasis, including pustulosis of the palms and soles (see Fig. 21.24). In addition, patients with atopic dermatitis who receive dupilumab can develop psoriasiform lesions, presumably due to a phenotypic shift from predominantly Th2-mediated inflammation to a Th1 immune response.

Alcohol consumption, smoking, and obesity

Obesity, increased alcohol consumption, and smoking have all been associated with psoriasis. In one analysis, smoking appeared to have a role in the onset of psoriasis, while obesity appeared to be a consequence of psoriasis. However, other studies have suggested that weight gain often precedes the development of psoriasis. Some studies have found that the prevalence of psoriasis in a population of individuals who stop smoking or who lose weight eventually reverts to background levels.

CLINICAL FEATURES

The extent to which psoriasis represents a spectrum of different manifestations of a single disease versus several separate disease entities remains a matter of debate. As knowledge regarding genotypes expands, will entities be defined by the associated genetic findings (e.g. in *CARD14* or *IL36RN*) or will there continue to be classifications based upon different phenotypes? Either way, recognition of characteristic skin findings remains essential.

Chronic plaque psoriasis, the most common variant of psoriasis vulgaris, presents as sharply demarcated and erythematous papulosquamous lesions. Less often, nearly all of the body surface is involved (*erythrodermic psoriasis*) or numerous, small, widely disseminated papules and plaques are seen (*guttate psoriasis*).

Given the spectrum of cutaneous manifestations, at any one point in time, different variants may coexist in a single individual. However, the skin lesions all share the same important hallmarks: erythema, thickening, and scale. As previously noted, there is also significant interindividual variability. For example, in patients with chronic plaque psoriasis, those with type I disease (HLA-Cw6$^+$) have an earlier onset,



Fig. 8.2 Annular plaques of psoriasis due to central clearing. *Courtesy Julie V. Schaffer, MD.*

more widespread disease and frequent recurrences, compared to those with type II psoriasis.

Although the size of a lesion may vary from a pinpoint papule to over 20 cm in diameter, the outline of the lesion is usually circular, oval, or polycyclic (the latter indicating that the lesion is derived from several smaller units). The configuration of psoriatic lesions due to the Koebner phenomenon reflects the etiology of the trauma. In addition to their highly characteristic sharp demarcation, psoriatic lesions are sometimes surrounded by a pale blanching ring, which is referred to as *Woronoff's ring*.

The classic findings of erythema, thickening, and scale are reflections of the histologic findings of elongated dilated capillaries that are close to the skin surface, epidermal acanthosis plus cellular infiltrates, and abnormal keratinization, respectively. If the superficial silvery white (micaceous) scales are removed, then a wet surface is seen with characteristic pinpoint bleeding. This finding, called Auspitz sign, is the clinical reflection of elongated vessels in the dermal papillae together with thinning of the suprapapillary epidermis.

During exacerbations, psoriatic lesions often itch. Pinpoint papules surrounding existing psoriatic plaques indicate that the patient is in an unstable phase of the disease. In addition, expanding psoriatic lesions are characterized by an active edge with a more intense erythema. Inflamed lesions may even be slightly tender. The involution of a lesion usually starts in its center, resulting in annular psoriatic lesions (Fig. 8.2).

Chronic Plaque Psoriasis

In chronic plaque psoriasis, there is a relatively symmetric distribution of sharply defined, erythematous, scaly plaques (Figs. 8.3 & 8.4). The degree of body surface area involvement can vary, from limited to extensive. The scalp, elbows, knees and lumbosacral area are sites of predilection, as are the hands and feet (Figs. 8.5 & 8.6). The genitalia are involved in up to 45% of patients (Fig. 8.7; see Ch. 73).

Plaques can persist for months to years at the same locations. In contrast, periods of complete remission do occur and remissions lasting for at least 5 years have been reported in ~15% of patients. When the disease is flaring, including in response to a triggering factor, pinpoint papules and deep erythematous rims may develop. The latter serve as clues the psoriasis has entered an unstable phase and occasionally sterile pustules may be observed. Differentiation of unstable psoriasis with pustule formation from generalized pustular psoriasis can be difficult.

Because the percentage of body surface area involved does not reflect the severity of the individual lesions with respect to erythema, induration, and scaling, the Psoriasis Area and Severity Index (PASI) was formulated (Table 8.2). This is a single calculated score that is based on the body surface area involved (in each of four anatomic areas – head, upper extremities, trunk, and lower extremities) and clinical grading of lesional erythema, induration, and scaling. The PASI is a cumbersome calculation and is more commonly utilized for clinical trials than for the routine management of patients with psoriasis. Other outcome measures of disease severity include the Palmoplantar Psoriasis Physician Global Assessment[55], Psoriasis Scalp Severity Index[56], Nail Psoriasis Severity Index[57], and Static Physician Global Assessment of Genitalia[58].





Fig. 8.3 Psoriatic plaques. A, B Note the sharp demarcation and silvery scale. The plaques can vary in thickness and amount of scale. *B, Courtesy Lorenzo Cerroni, MD.*



Fig. 8.4 Multiple large plaques of psoriasis. There is obvious symmetry of the plaques on the upper extremities. Some patients have associated pruritus and hemorrhagic crusts due to scratching. *Courtesy Luis Requena, MD.*

Guttate Psoriasis

Guttate psoriasis is more commonly seen in children and adolescents and is frequently preceded by an upper respiratory tract infection (Fig. 8.8). In over half of the patients, an elevated antistreptolysin O,



Fig. 8.5 Palmar psoriasis. Well demarcated scaly plaques of the volar wrist and palms. Comparison of the color of the plaques in a lightly pigmented (**A**) versus darkly pigmented (**B**) patient. *Courtesy Kalman Watsky, MD.*

anti-DNase B, or streptozyme titer is found, indicating a recent streptococcal infection (see previous section).

Erythrodermic Psoriasis

This variant of psoriasis is characterized by generalized erythema and scaling, and its onset can be gradual or acute. Although there are many causes of erythroderma (see Ch. 10), clues to the diagnosis of psoriatic erythroderma include previous plaques in classic locations, characteristic nail changes, and central facial sparing.

CARD14-associated papulosquamous eruption

In patients with CARD14-associated papulosquamous eruption that is due to *CARD14* mutations, there are features of both psoriasis and pityriasis rubra pilaris (PRP)[59]. Features include an early age of onset, prominent involvement of the cheeks, chin, and ears, a family history of psoriasis or PRP, minimal response to conventional topical and systemic psoriasis therapies, and improvement with ustekinumab (Fig. 8.9). NF-κB is upregulated in the skin of those with this disorder and *CARD14* mutations, resulting in an increase in IL-8 and CCL20 which recruit and activate inflammatory cells. The latter leads to production of IL-23 by dendritic cells and IL-17 and IL-22 by T cells. This provides an explanation for the therapeutic response to ustekinumab.

Pustular Disease

Generalized pustular psoriasis

In generalized pustular psoriasis, infiltration of neutrophils dominates the histologic picture, explaining the bright erythema and sterile pustules (Fig. 8.10). It is an unusual manifestation of psoriasis, and triggering factors include pregnancy, rapid tapering of corticosteroids (or other systemic therapies), hypocalcemia, infections, and, in the case of the localized pattern, topical irritants. Generalized pustular psoriasis during pregnancy is also referred to as *impetigo herpetiformis*.



Fig. 8.6 Palmoplantar psoriasis. Diffuse involvement with erythema and scaling of the palmar (**A**) and plantar surfaces (**B**).

Of note, some patients with the phenotype of pustular psoriasis have an autoinflammatory disorder with a distinct genotype (see Tables 45.6 & 45.7). This group includes DIRA (deficiency of IL-1 receptor antagonist; see Figs. 45.11A & 45.12A) and DITRA (deficiency of IL-36 receptor antagonist; see Figs. 45.11B & 45.12B). Future pathogenetic discoveries may lead to additional discrete entities.

Pustular psoriasis has four distinct phenotypic patterns:

- **von Zumbusch pattern**. This is a generalized eruption starting abruptly with erythema and pustulation (see Fig. 8.10). The skin is painful during this phase, and the patient has a fever and feels ill. After several days, the pustules usually resolve and extensive scaling is observed. Sometimes, chronic plaques of psoriasis, if present, can resolve. In the original case report by von Zumbusch (1910), nine episodes of pustulation occurred over a period of 10 years.
- **Annular pattern**. The eruption is characterized by annular lesions, consisting of erythema and scaling with pustulation at the advancing edge (Fig. 8.11). The lesions enlarge by centrifugal expansion over a period of hours to days, while healing occurs centrally.

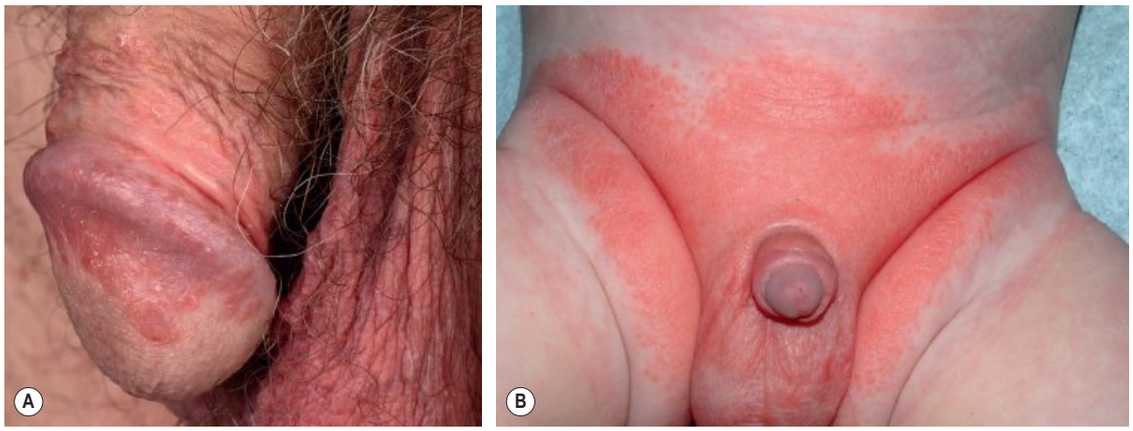


Fig. 8.7 Psoriasis of the genitalia. **A** Well-demarcated erythematous plaques with scale on the glans and shaft of the penis in an adult. **B** Infantile psoriasis with a well-demarcated erythematous plaque of the diaper area, along with involvement of the penis and scrotum. This is in contrast to atopic dermatitis where there is often sparing of the diaper area. *A, Courtesy Lorenzo Cerroni, MD; B, Courtesy Julie V. Schaffer, MD.*

CALCULATION OF THE PSORIASIS AREA AND SEVERITY INDEX (PASI)				
Severity of psoriatic lesions				
[0, none; 1, slight; 2, moderate; 3, severe; 4, very severe]				
	Head	***Trunk***	***Upper limbs***	***Lower limbs***
Erythema	0 to 4	0 to 4	0 to 4	0 to 4
Induration	0 to 4	0 to 4	0 to 4	0 to 4
Scaling	0 to 4	0 to 4	0 to 4	0 to 4
Total score = ❶	Sum of the above	Sum of the above	Sum of the above	Sum of the above
Area of psoriatic involvement				
[0, none; 1, <10%; 2, 10 to <30%; 3, 30 to <50%; 4, 50 to <70%; 5, 70 to <90%; 6, 90%–100%]				
Degree of involvement = ❷	0 to 6	0 to 6	0 to 6	0 to 6
Multiply ❶ × ❷	❶ × ❷	❶ × ❷	❶ × ❷	❶ × ❷
Correction factor for area of involvement = ❸	0.10	0.30	0.20	0.40
❶ × ❷ × ❸	**A**	**B**	**C**	**D**
A + **B** + **C** + **D** = total PASI				

Table 8.2 Calculation of the Psoriasis Area and Severity Index (PASI). The PASI ranges from 0 to 72.

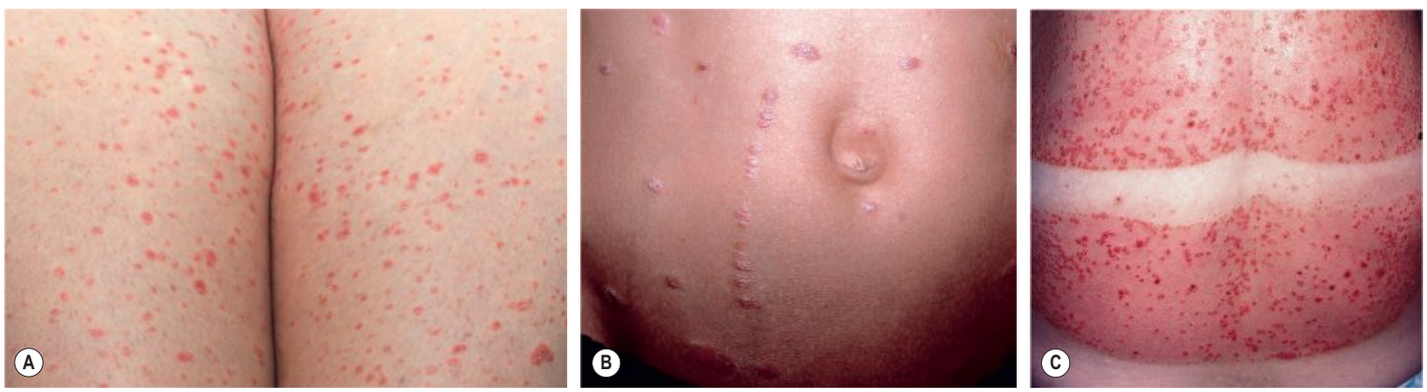


Fig. 8.8 Guttate psoriasis. A Numerous, small, discrete papules with scale on the thighs. **B** This adolescent has evidence of a linear Koebner phenomenon in addition to more widely scattered guttate lesions. **C** Numerous papules due to a sunburn-related Koebner phenomenon. *A, Courtesy Kalman Watsky, MD; C, Courtesy Ronald P. Rapini, MD.*

- **Exanthematic type**. This is an acute eruption of small pustules, abruptly appearing and disappearing over a few days. It usually follows an infection or may occur as a result of administration of specific medications, e.g. lithium. Systemic symptoms usually do not occur. There is overlap between this form of pustular psoriasis and pustular drug eruptions, also referred to as acute generalized exanthematous pustulosis (AGEP; see Ch. 21).
- **"Localized" pattern**. Sometimes pustules appear within or at the edge of existing psoriatic plaques. This can be seen during the unstable phase of chronic plaque psoriasis and following the application of irritants, e.g. tars, anthralin.

Pustulosis of the palms and soles

Pustulosis of the palms and soles is characterized by "sterile" pustules of the palmoplantar surfaces admixed with yellow–brown macules (Fig. 8.12); scaly erythematous plaques may also be seen. A minority of patients have chronic plaque psoriasis elsewhere. In contrast to the natural history of generalized pustular psoriasis, the pustules remain localized to the palmoplantar surfaces and the course of this disease is chronic. Focal infections and stress have been reported as triggering factors and smoking may aggravate the condition. Pustulosis of the palms and soles is one of the entities most commonly associated with sterile inflammatory bone lesions within the context of SAPHO



Fig. 8.9 CARD14-associated erythroderma. Extensive erythema and scale resembling erythrodermic psoriasis. *Courtesy Edward Cowen, MD.*



Fig. 8.12 Pustulosis of the palms and soles. Multiple sterile papules are admixed with yellow–brown macules on the palm.



Fig. 8.10 Generalized pustular psoriasis. Broad areas of erythema with numerous pustules and the formation of lakes of pus. *Courtesy Julie V. Schaffer, MD.*



Fig. 8.13 Acrodermatitis continua of Hallopeau. Erythema and slight scale of the distal digit, pustules within the nail bed, and partial shedding of the nail plate.

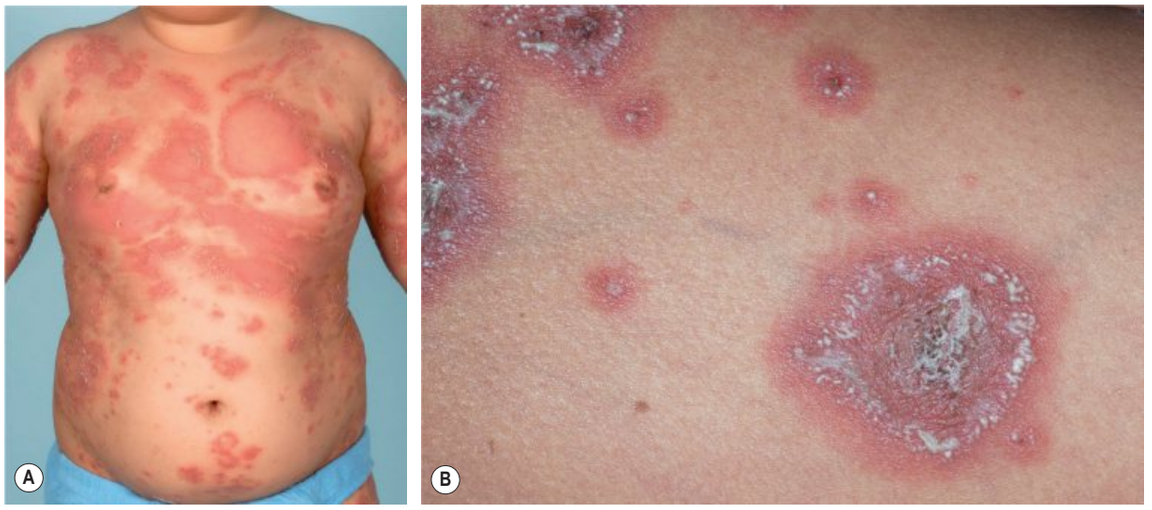


Fig. 8.11 Annular pustular psoriasis. A, B Multiple annular inflammatory plaques whose active borders are studded with pustules followed by desquamation. As these lesions enlarge, there is central clearing. The intensity of erythema can vary and the color is influenced by the skin phototype. *A, Courtesy Marieke M. B. Seyger, MD, PhD; B, Courtesy Julie V. Schaffer, MD.*

syndrome, which consists of *s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis and *o*steitis. Several neutrophilic dermatoses are associated with SAPHO (see Table 25.18). As noted previously, pustulosis of the palms and soles can occur as a paradoxical reaction in patients receiving TNF inhibitors for disorders such rheumatoid arthritis or inflammatory bowel disease (see Fig. 21.24).

Acrodermatitis continua of Hallopeau

This is a rare manifestation of psoriasis. Clinically, pustules are seen on the distal portions of the fingers (Fig. 8.13) and occasionally the toes. Pustulation is often followed by scaling and crust formation. Pustules may also form in the nail bed (beneath the nail plate), and there may be shedding of nail plates. Transition into other forms of psoriasis can



Fig. 8.14 Scalp psoriasis with extension onto the neck. Note the involvement of the external auditory canal.

occur and acrodermatitis continua may be accompanied by annulus migrans of the tongue (see below).

Special Locations

Scalp psoriasis

The scalp is one of the most common sites for psoriasis. Unless there is complete confluence, the individual lesions are discrete, in contrast to the less well-defined areas of involvement in seborrheic dermatitis. At times, however, it is not possible to distinguish seborrheic dermatitis from psoriasis, and the two disorders may coexist. The lesions of psoriasis often advance onto the periphery of the face, the retroauricular areas and the posterior upper neck (Fig. 8.14). The scales sometimes have an asbestos-like appearance and can adhere to hair shafts in clumps (pityriasis amiantacea). Although pityriasis amiantacea can also be seen in patients with seborrheic dermatitis, secondarily infected atopic dermatitis, and tinea capitis, psoriasis is the most common cause. Alopecia occasionally develops within involved areas, including in the setting of TNF inhibitor-induced psoriasis (see Ch. 69). In addition, patients with dermatomyositis involving the scalp may have lesions that resemble psoriasis.

Flexural psoriasis

Flexural lesions are characterized by shiny, pink to red, sharply demarcated thin plaques (Fig. 8.15). There is much less scale than in untreated chronic plaque psoriasis. Often a central fissure is seen. The most common sites of involvement are the retroauricular fold, intergluteal cleft, inguinal crease, axilla, and inframammary region. When flexural areas are the only sites of involvement, the term "inverse" psoriasis is sometimes used. Localized dermatophyte, candidal, or bacterial infections can be a trigger for flexural psoriasis.

Oral mucosa

Migratory annular erythematous lesions with hydrated white scale (annulus migrans) have been observed in patients with acrodermatitis continua of Hallopeau and generalized pustular psoriasis. The most common location is the tongue, and the clinical (and histologic) appearance is similar to geographic tongue (see Fig. 72.3). Occasionally, lesions are observed on the buccal mucosa.

Nail psoriasis

Nail involvement has been reported in 10%–80% of psoriatic patients, depending upon the series. The fingernails are more often affected than the toenails (Fig. 8.16). In a survey from the Netherlands, 79% of patients reported involvement of their nails, with 52% experiencing associated pain and 14% major restrictions in daily life due to the nail changes. Patients with nail involvement appear to have an increased incidence of psoriatic arthritis.



Fig. 8.15 Inverse psoriasis. Shiny erythematous plaques of the inframammary folds that lack scale. *Courtesy Luis Requena, MD.*



Fig. 8.16 Nail psoriasis. Nail plate pitting, distal onycholysis, oil drop changes, and subungual and proximal hyperkeratosis are seen. There is also proximal nail-fold inflammation with loss of the cuticle, especially of the forefingers. *Courtesy Marcel C. Pasch, MD.*

Psoriasis affects the nail matrix, nail bed, and hyponychium. Small parakeratotic foci in the proximal portion of the nail matrix lead to pits in the nails (see Fig. 71.2). Leukonychia and loss of transparency (less common findings) are due to involvement of the midportion of the matrix. If the entire nail matrix is involved, a whitish, crumbly, poorly adherent "nail" is seen. Psoriatic changes of the nail bed result in the "oil drop" or "salmon patch" phenomenon, which reflects exocytosis of leukocytes beneath the nail plate (see Fig. 71.13). Splinter hemorrhages are the result of increased capillary fragility, and subungual hyperkeratosis and distal onycholysis are due to parakeratosis of the distal nail bed. Vigorous removal of distal subungual debris may be an exacerbating factor.

Psoriatic Arthritis

Psoriatic arthritis occurs in 5%–30% of patients with cutaneous psoriasis[1], with some clinical investigators suggesting that classic studies of psoriatic arthritis may have underestimated its prevalence. In a minority of patients (10%–15%), the symptoms of psoriatic arthritis appear before involvement of the skin. Currently, there are no specific serologic tests for establishing the diagnosis of psoriatic arthritis, but an important hallmark is erosive change radiographically, which may occur years after the presenting peri-articular inflammation. Psoriatic arthritis is more prevalent among patients with relatively severe psoriasis. Risk factors for a more severe course of the arthritis include: initial presentation at an early age, female sex, polyarticular involvement, genetic predisposition, and radiographic signs of the disease early on. The five major forms of psoriatic arthritis are outlined in Table 8.3[60].

In one study involving 1511 patients with chronic plaque psoriasis, ~20% of the affected individuals had psoriatic arthritis[61]. DIP

FIVE MAJOR TYPES OF PSORIATIC ARTHRITIS	
Type	**Clinical findings**
Mono- and asymmetric oligoarthritis (most common type)	• Inflammation of the DIP and PIP joints of the hands and feet (Fig. 8.17) • Involvement of the PIP or both the DIP and PIP joints of a single digit can result in the classic "sausage" digit (Fig. 8.18) • MCP joint involvement unusual (unlike RA) • May be accompanied by inflammation of larger joints
Arthritis of the distal interphalangeal joints	• Exclusive involvement of the DIP joints • Classic but uncommon presentation • The joints may become fixed in a flexed position
Rheumatoid arthritis-like presentation (difficult to distinguish from RA clinically*)	• *Symmetric* polyarthritis that involves small and medium-sized joints, in particular the PIP, MCP, wrist, ankle, and elbow • Most patients are seronegative for RF
Arthritis mutilans† (least common type)	• Severe, rapidly progressive joint inflammation that results in destruction of the joints and permanent deformity • Digits become shorter, wider, and softer to palpation because of osteolysis and a telescoping phenomenon
Spondylitis and sacroiliitis (also have peripheral joint involvement)	• Spondylitis resembles that seen in ankylosing spondylitis, with axial arthritis as well as involvement of the knees and sacroiliac joints • Patients are often HLA-B27-positive and may have associated inflammatory bowel disease and/or uveitis

*Whether some seropositive patients have an overlap of the two disorders is possible.
†Also occurs in multicentric reticulohistiocytosis (see Fig. 91.17D).

Table 8.3 Five major types of psoriatic arthritis. Patients with psoriatic arthritis can have tendonitis, enthesitis, and dactylitis. DIP, distal interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal; RA, rheumatoid arthritis; RF, rheumatoid factor.

involvement was observed in ~40% of the patients with arthritis, and 5% suffered from arthritis mutilans[61]. Patients with psoriatic arthritis can have involvement of juxta-articular tendons (tendonitis) and the sites where they insert into bone (enthesitis) as well as swelling of the fingers (dactylitis). Enthesitis and dactylitis have been reported in ~20% and 15%–30%, respectively, of patients with "probable" or definite psoriatic arthritis. In patients with psoriasis, nail involvement is a strong predictor of concomitant psoriatic arthritis[62].

Early diagnosis of psoriatic arthritis is important, as disease progression often results in loss of function and irreversible joint destruction.

Disorders Related to Psoriasis

A few disorders share important clinical and histologic features with psoriasis, but are distinct disease entities based upon genetic, epidemiologic, or clinical features.



Fig. 8.18 Psoriatic arthritis. Asymmetric involvement of the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints. A "sausage" digit (third digit bilaterally) results from involvement of both the DIP and PIP joints. Note the yellowing, thickening, and crumbling of several fingernails.

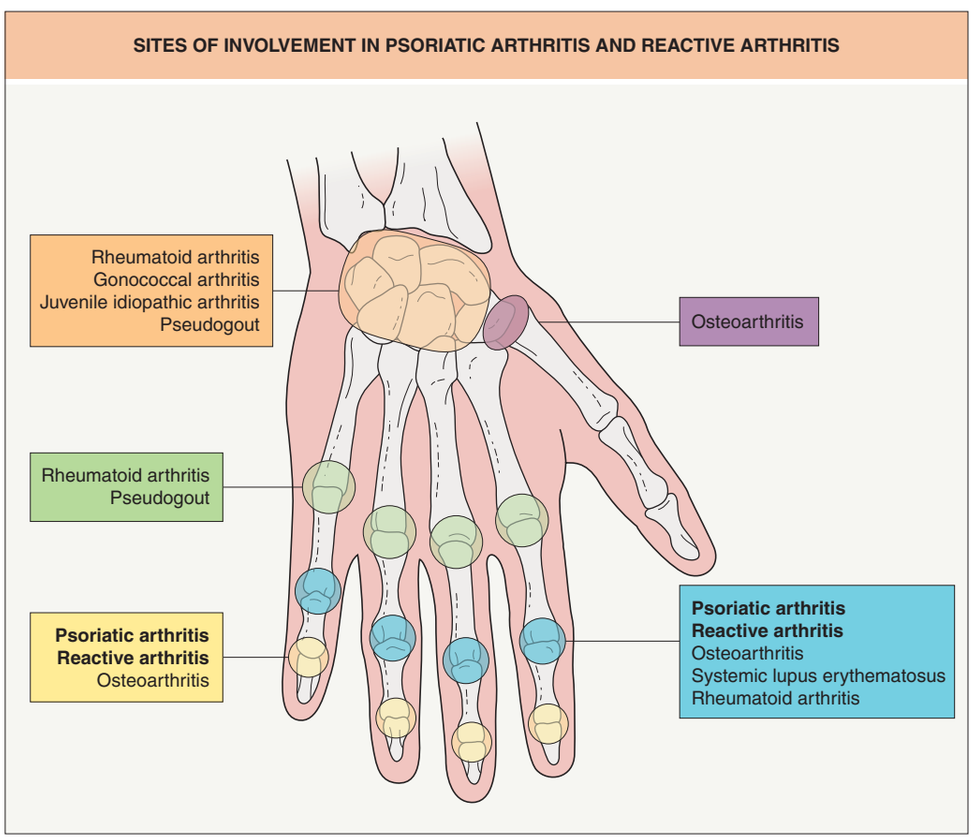


Fig. 8.17 Sites of psoriatic arthritis and reactive arthritis (formerly Reiter disease). *Adapted from Cush JJ. Evaluation of musculoskeletal complaints. In: Rheumatology: Diagnosis and Therapeutics, 2nd ed. Lippincott, 2003.*



Fig. 8.19 Reactive arthritis (formerly Reiter disease). A, B Plantar lesions of keratoderma blennorrhagicum. The amount of scale can vary and when sterile pustules form, they are often admixed with yellow–brown macules. **C** Papulosquamous lesions on the glans and shaft of the penis. *B, Courtesy Eugene Mirrer, MD.*

Inflammatory linear verrucous epidermal nevus (ILVEN)

ILVEN is characterized by linear psoriasiform lesions (i.e. scaling and erythematous plaques) that follow the lines of Blaschko (see Ch. 62). Based upon its chronicity and resistance to therapy, ILVEN is thought to be an entity separate from linear psoriasis. However, a subset of patients were found to have mosaicism for heterozygous missense variants in *CARD14*.

Reactive arthritis

This syndrome features urethritis, arthritis, ocular findings, and oral ulcers, in addition to psoriasiform skin lesions. The disorder is uncommon in children and occurs more frequently in men than in women. The urethritis may be mild or severe and accompanied by complications such as cystitis, cervicitis, and salpingitis. *Chlamydia trachomatis* is a major cause of urethritis and may trigger the entire syndrome, as may other infections such as shigellosis. Conjunctivitis is a common eye finding in affected patients, although iritis, uveitis with glaucoma, and keratitis may also occur. Polyarthritis and sacroiliitis are the most frequent joint manifestations. Cutaneous lesions occur in ~5% of reactive arthritis patients, with a predilection for the soles, extensor surfaces of the legs, penis, dorsal aspects of the hands, fingers, nails, and scalp (Fig. 8.19). The lesions on the plantar surface usually have thick yellow scale and are often pustular (keratoderma blennorrhagicum). Psoriatic plaques on the penis are referred to as balanitis circinata.

Reactive arthritis has a strong association with HLA-B27. Although the course is often self-limited, lasting weeks to months, some patients have disease that is chronic and disabling. Of note, HIV-infected patients can also develop this disorder and it may be severe.

Sneddon–Wilkinson disease (subcorneal pustular dermatosis)

This disorder is characterized by annular or polycyclic lesions, usually commencing in the flexures (Fig. 8.20A). Very superficial (subcorneal) sterile pustules are the hallmark of Sneddon–Wilkinson disease, hence its second name (Fig. 8.20B). There may be a gravity-induced demarcation in some vesiculopustules, with clear fluid superiorly and pus inferiorly. This disease has a cyclic course, i.e. as the pustules resolve they are replaced by superficial scaling and then new pustules form again. Some patients with Sneddon–Wilkinson disease have an associated IgA paraproteinemia. Its response to dapsone, combined with subcorneal pustules (in the absence of spongiform pustules), provide support for this condition being a disease entity distinct from pustular psoriasis, although some authors have questioned the existence of Sneddon–Wilkinson disease as a distinct entity. Of note, immunofluorescence studies are required to distinguish the subcorneal pustular dermatosis type of IgA pemphigus from Sneddon–Wilkinson disease.



Fig. 8.20 Sneddon–Wilkinson disease. A Annular and polycyclic plaques in the axilla with small pustules, erosions, and scale in the border. **B** Numerous, fragile, subcorneal pustules arising within a background of erythema. There is dependent pooling of the pustular contents in some of the larger lesions. There is significant overlap with pustular psoriasis. *B, Courtesy Department of Dermatology, Medical University of Graz.*

Associations Between Psoriasis and Other Diseases

Associations with skin diseases

There is a pronounced under-representation of allergic skin diseases in psoriatic patients as compared to age-matched controls without psoriasis. The frequencies of atopic dermatitis, asthma, urticaria, and allergic contact dermatitis have been found to be lower in psoriatic patients. For example, in one study atopic dermatitis was seen ~50 times less often in psoriatic compared with non-psoriatic patients[1]. An obvious explanation is the immunologic difference between these two conditions, with a predominantly Th1 and Th17 response in psoriasis and a predominantly Th2 response in atopic dermatitis. However, in patients with psoriasis in atypical locations and/or treatment-resistant lesions, the possibility of allergic or irritant contact dermatitis as a triggering factor needs to be considered.

A bi-directional relationship exists between lichen simplex chronicus (LSC) and psoriasis. If a psoriatic lesion is pruritic, superimposed

LSC may develop and the surface becomes shiny with increased skin markings. Because the LSC itself is pruritic, the resultant rubbing may worsen the psoriasis (Koebner phenomenon). The patient then enters a vicious cycle. Therapeutic regimens must address both disorders.

Seborrheic dermatitis is characterized by pink to red patches with yellowish, sometimes greasy, scales (see Ch. 13). The sites of predilection are the scalp, central face, ears, presternal area, and intertriginous zones. As the clinical features of psoriasis and seborrheic dermatitis can be seen in the same patient, some authors use the term "sebopsoriasis", especially when diagnostic lesions of psoriasis are not present elsewhere.

Infections

In contrast to atopic dermatitis, psoriatic lesions are seldomly impetiginized, i.e. secondarily infected by bacteria. One explanation for this resistance to secondary bacterial infections is increased production of skin-derived antimicrobial peptides, e.g. defensins, SKALP/elafin (see Pathogenesis).

The prevalence of onychomycosis, due to *Candida* species or dermatophytes, is increased in psoriatic patients (average, ~18%), compared to control groups[63]. In flexural psoriasis, concomitant *Candida* infections are frequently observed and have been incriminated as a local triggering factor.

Cancer

Patients with psoriasis may have a slightly higher incidence rate of all malignancies compared to the general population[64]. With the exception of a significantly higher rate of non-melanoma skin cancer in those who had received phototherapy (type not specified), differences in rates were minimal when various systemic therapies were compared[64]. It has been shown that psoriatic patients who have had >200 PUVA treatments are at increased risk for the development of skin cancers, especially squamous cell carcinomas (SCCs). Of note, the use of cyclosporine in patients previously treated with PUVA significantly increases the number and rate of appearance of SCCs. Lastly, there is controversy as to whether PUVA-treated patients have an increased risk of cutaneous melanoma.

Association with internal diseases (including comorbidities)

Cardiovascular diseases, e.g. myocardial infarctions, peripheral arterial disease, cerebrovascular accidents, are more common in patients with severe psoriasis. The latter is associated with a threefold increased risk for myocardial infarction and a 3.5- to 4.5-year reduction in life expectancy. This is largely due to an increased risk for having metabolic syndrome (see Table 53.5)[65–67]. In Mendelian randomization studies, it has been shown that the presence of cardiovascular disease can have a significant causal effect on psoriasis, but not vice versa, in that systemic inflammation (which causes cardiovascular disease) can increase the risk of psoriasis[67a]. In patients with psoriatic arthritis, serum levels of C-reactive protein (CRP) have been reported to be elevated (as compared to healthy controls), and elevated CRP levels represent a risk factor for the development of cardiovascular disease. It has also been shown that TNF and IL-6 can target adipocytes and induce dyslipidemia. Several studies have found that treatment with methotrexate and/or targeted immunomodulators ("biologics") may reduce the risk of atherosclerotic cardiovascular disease. Patients with psoriasis may also be at increased risk for the development of venous thromboembolism.

Non-alcoholic steatohepatitis, characterized by fatty infiltration, periportal inflammation, and focal necrosis, is more commonly observed in patients with psoriasis. In a study of 142 adults with psoriasis, non-alcoholic fatty liver disease was detected in 59%, and it correlated with the presence of obesity, hyperlipidemia, the metabolic syndrome, an AST:ALT ratio >1, and psoriatic arthritis[68]. Chronic administration of methotrexate is associated with a significant risk for hepatic damage in patients with psoriasis, whereas similar methotrexate dosages in patients with rheumatoid arthritis do not pose such hepatotoxic potential. Although the reason for this difference is not known, several possible explanations have been put forward, including a genetic predisposition, increased alcohol consumption by psoriasis patients, and a higher incidence of non-alcoholic fatty liver disease.

Crohn disease, ulcerative colitis, and psoriasis share an association with sacroiliitis and HLA-B27 positivity. In genome-wide association studies of Crohn disease and psoriasis, shared susceptibility loci were identified[69]. Additional disorders that share susceptibility genes with psoriasis are listed in Table 8.1. Of note, patients with psoriasis have also been shown to be at increased risk of depression, anxiety, and suicidal ideation[70]. Lastly, in a population-based cohort study, an association between psoriasis and kidney disease was suggested[71].

Patients with both psoriasis and lupus erythematosus, Sjögren syndrome, or dermatomyositis have been reported in the literature. It is not clear whether this is true-true related or true-true unrelated. However, the presence of a coexisting autoimmune connective tissue disease does have therapeutic implications in an individual patient[72].

DIFFERENTIAL DIAGNOSIS

Although both seborrheic dermatitis (see above) and LSC are in the differential diagnosis of psoriasis, it is important to remember that either can coexist with psoriasis. Due to the Koebner phenomenon, psoriasis can also develop within areas of contact dermatitis. When there is a single or limited number of erythematous plaques, especially if they are treatment-resistant, the possibility of SCC *in situ* (e.g. Bowen disease, erythroplasia of Queyrat) needs to be excluded via histologic examination. Occasionally, a biopsy is necessary to distinguish chronic plaque psoriasis from mycosis fungoides. Clinical features suggestive of the latter include wrinkling due to epidermal atrophy and progression to infiltrated plaques. Dermatomyositis can involve the scalp, elbows and knees, as well as the hands, and initially may be diagnosed as psoriasis.

When plaques of psoriasis involve the shins, they may be misdiagnosed as hypertrophic lichen planus, but characteristic violaceous lesions elsewhere and mucosal involvement usually point to the correct diagnosis. There is clinical overlap between palmoplantar plaque psoriasis and keratotic eczema of the palms and soles, and both may have fissures and be exacerbated by repeated trauma. Sharp margination of the lesions favors psoriasis and examination of the remainder of the skin surface can provide clues to the diagnosis, e.g. involvement of the scalp or intergluteal fold with psoriasis. Elsewhere, chronic lesions of dermatitis may develop an appearance that is similar (clinically and histologically) to partially treated psoriasis and vice versa. However, over time, characteristic lesions often become apparent. When plaques of psoriasis develop pronounced hyperkeratosis (rupioid psoriasis), the possibility of concomitant hypothyroidism should be considered.

In addition to psoriasis, there are other causes of erythroderma, including Sézary syndrome, pityriasis rubra pilaris, and drug reactions (see Ch. 10). For guttate psoriasis, the differential diagnosis may include small plaque parapsoriasis, pityriasis lichenoides chronica, secondary syphilis, and pityriasis rosea. The lesions of guttate psoriasis rarely involve the palms or soles and are often more erythematous than those of parapsoriasis. When lesions are limited in number or have an annular configuration, the possibility of tinea corporis is raised, and when the upper trunk is the predominant site of involvement, pemphigus foliaceus may be considered.

Psoriasis of the flexures is one cause of intertrigo (see Figs. 13.4 & 13.12). Other etiologies include seborrheic dermatitis, contact dermatitis, cutaneous candidiasis, tinea incognito, erythrasma, and extramammary Paget disease. Although KOH examination of associated scale allows a narrowing of the differential diagnosis, psoriasis and candidiasis can coexist (see above). In infants (more so than adults), the possibility of Langerhans cell histiocytosis needs to be considered. In these patients, there may also be scalp involvement with scaling and crusts. Occasionally, tinea capitis is in the differential diagnosis of scalp psoriasis.

When there are widespread pustules on a background of erythema, the possibility of a pustular drug eruption, also referred to as AGEP, needs to be considered (in addition to generalized pustular psoriasis). The histologic findings of these conditions can be similar, including spongiform pustules of Kogoj and microabscesses in the stratum corneum. If eosinophils are also present, a pustular drug eruption is favored. Autoinflammatory disorders, in particular DIRA and DITRA (deficiency of IL-1 or -36 receptor antagonist), can also present with a phenotype similar to pustular psoriasis (see Tables 45.6 & 45.7). In patients with pustulosis of the palms and soles and acrodermatitis continua, the initial evaluation includes the exclusion of a dermatophyte infection or secondarily infected dermatitis. The differential diagnosis of the annular form of pustular psoriasis includes Sneddon–Wilkinson disease and other causes of subcorneal pustules (Table 8.4). Reactive arthritis needs to be considered in any patient with the diagnosis of arthritis in the setting of psoriasiform skin lesions.

DIFFERENTIAL DIAGNOSIS OF SUBCORNEAL/INTRAEPIDERMAL NEUTROPHILIC PUSTULES	
Disorder	**Histologic clues**
Impetigo	Gram-positive cocci in bulla cavity
Superficial candidiasis	Yeast and pseudohyphae in stratum corneum
Dermatophyte infection	Branching hyphae in stratum corneum
Superficial folliculitis	Pustule at follicular orifice and in infundibulum
Pemphigus foliaceus, pemphigus erythematosus	Acantholytic cells; DIF, IIF: intercellular IgG deposits; anti-desmoglein 1 antibodies
IgA pemphigus, subcorneal pustular dermatosis type	DIF > IIF: intercellular IgA deposits; anti-desmocollin 1 antibodies
Sneddon–Wilkinson disease (subcorneal pustular dermatosis)	May be indistinguishable from IgA pemphigus, but negative DIF
Pustular psoriasis	Spongiform pustules*
Acute generalized exanthematous pustulosis	Mild spongiform pustulation (less prominent than in pustular psoriasis), eosinophils*
Amicrobial pustulosis of the folds	Spongiform pustules*
Transient neonatal pustular melanosis	Subcorneal and intracorneal pustules, few eosinophils*
Acropustulosis of infancy	Intraepidermal or subcorneal pustules, few eosinophils*
Pustular miliaria	Pustules centered upon an intraepidermal sweat duct
Erosive pustular dermatosis	Erosion and dense, mixed dermal inflammatory infiltrate in addition to subcorneal pustules
Eosinophilic pustular folliculitis (Ofuji disease)	Large numbers of eosinophils within the pustules, epithelium, and dermal inflammatory infiltrate
*Not all cases.	

Table 8.4 Differential diagnosis of subcorneal/intraepidermal neutrophilic pustules. DIF, direct immunofluorescence; IIF, indirect immunofluorescence.

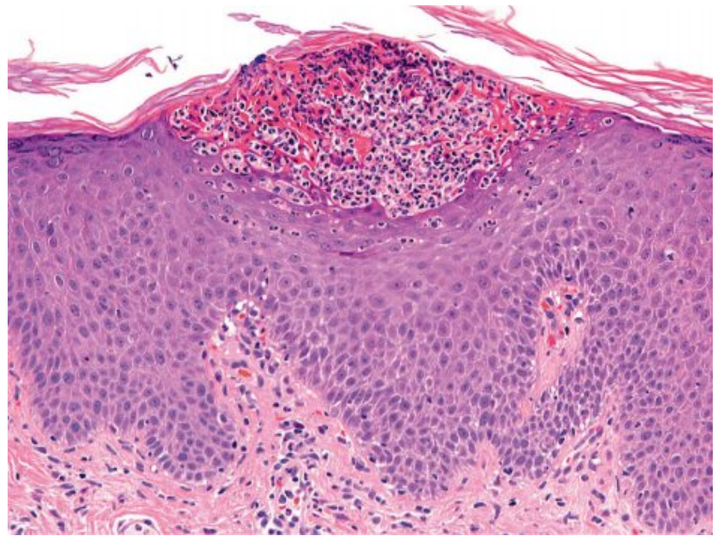


Fig. 8.21 Spongiform pustule of Kogoj. A collection of neutrophils is seen within the upper stratum spinosum. *Courtesy Lorenzo Cerroni, MD.*

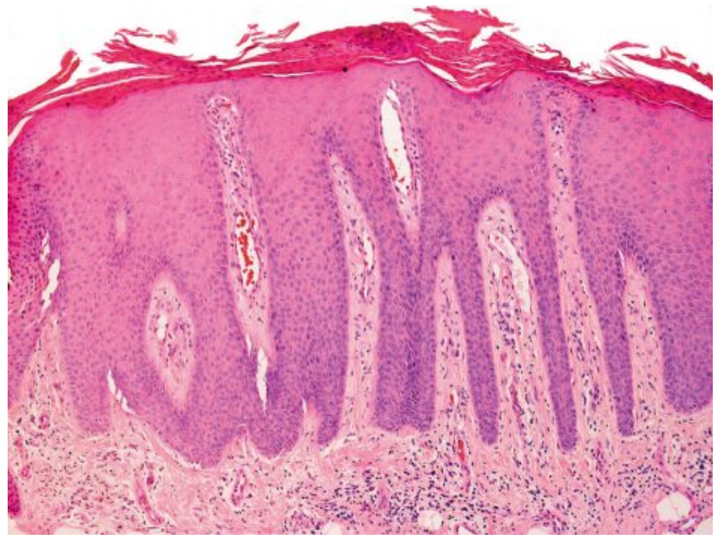


Fig. 8.22 Stable plaque psoriasis. Hyperplasia of the epidermis with "squared-off" rete ridges, elongation of the dermal papillae, dilated superficial blood vessels, hypogranulosis, and parakeratosis plus remnants of neutrophils (microabscess of Munro). *Courtesy Lorenzo Cerroni, MD.*

PATHOLOGY

Papulosquamous Lesions

Initial lesion

In the initial lesion, i.e. a pinhead-sized papule, the histopathologic features are not yet diagnostic. A superficial perivascular infiltrate of lymphocytes and histiocytes is seen in the dermis along with papillary edema and a dilation of capillaries. In acute eruptive guttate lesions, mast cell degranulation is a constant feature.

There is mild epidermal acanthosis without parakeratosis and the keratinocytes have a swollen appearance. Histiocytes (detected by CD68 staining) and lymphocytes appear within the epidermis, accompanied by mild focal spongiosis. In this early phase, neutrophils are not yet detectable.

Active lesion

A fully developed guttate lesion or the marginal zone of an enlarging psoriatic plaque is designated as an "active lesion". The histopathologic findings in an active lesion are diagnostic for psoriasis.

In the papillary dermis, the capillaries are increased in number and length and they have a tortuous appearance. Edema is seen, especially at the tops of the papillae. There is a mixed perivascular infiltrate of lymphocytes, histiocytes, and neutrophils.

The epidermis is acanthotic with focal accumulations of neutrophils and lymphocytes. At these sites, the epidermis is variably spongiotic. Above these foci, the granular layer is absent and the stratum corneum still contains flattened nuclei (parakeratosis). The accumulation of neutrophils within a spongiotic pustule is referred to as a "spongiform pustule of Kogoj" (Fig. 8.21) and the accumulation of neutrophils and/or neutrophil remnants in the stratum corneum, surrounded by parakeratosis, as a "microabscess of Munro". These two findings are pathognomonic for psoriasis and AGEP.

Stable lesion

In the papillary dermis, the capillaries are elongated and tortuous, extending upward into elongated club-shaped dermal papillae; only a small suprapapillary plate of epidermal cells covers the tip of these dermal papillae. This micromorphology explains the "Auspitz" phenomenon (see earlier). A modest perivascular infiltrate is seen that consists primarily of lymphocytes and histiocytes. The psoriatic lesion is heterogeneous, consisting of active areas (hot spots) and chronic nonspecific areas (cold spots).

The hyperproliferation of the epidermis now has reached its characteristic pattern (Fig. 8.22). The rete ridges are elongated and have a squared-off appearance. The bases of some of the rete ridges also coalesce. The horny layer has parakeratotic foci with an absence of the stratum granulosum. In some lesions, micropustules of Kogoj and microabscesses of Munro may be seen.

Pustular Psoriasis

In pustular psoriasis, accumulation of neutrophils is the predominant feature. The epidermis is usually acanthotic. Numerous neutrophils accumulate between eosinophilic strands of keratinocytes. In the stratum corneum, large accumulations of neutrophils are observed, surrounded by parakeratosis (see Fig. 0.21B). As a result, exaggerated spongiform pustules of Kogoj and microabscesses of Munro, the histologic hallmarks of "active" psoriasis, are seen in pustular psoriasis.

TREATMENT

Care of the psoriatic patient needs to focus not only on the skin, but also on the comorbidities that exist or might develop. An appropriate treatment regimen for a particular patient is selected from available topical and systemic medications as well as phototherapies. In clinical trials, single agents are usually evaluated, but in practice most patients receive combination therapy. To date, no treatment has been shown to cure this disease, so counseling of the patient and family members regarding its natural history and management strategies is essential.

The management of psoriasis requires individualization of therapy, with consideration of the extent of the disease and its effects on the patient's quality of life as well as the likely benefits and potential side effects of specific treatments. The chronic nature of psoriasis necessitates adoption of a long-term approach with avoidance of dramatic short-term "fixes" that may actually produce a more reactive disease state (see below).

Topical Treatments

Guidelines of care for the treatment of psoriasis with topical therapies have been developed by the American Academy of Dermatology[73].

Corticosteroids

Since their introduction in the early 1950s, topical corticosteroids have become a mainstay in the treatment of psoriasis. They are first-line therapy in mild to moderate psoriasis and in sites such as the flexures and genitalia, where other topical agents can induce irritation. Chapter 125 provides detailed information on mechanisms of action, pharmacologic aspects, and side effects of corticosteroid therapy.

Corticosteroids are available in various vehicles, from ointments, creams, and lotions to gels, foams, sprays, and shampoos[74]; ointment formulations, in general, have the highest efficacy (see Ch. 125). By increasing lipophilicity via masking of hydrophilic 16- or 17-hydroxy groups or by introducing acetonides, valerates or propionates, their anti-inflammatory properties have been significantly improved. Application under plastic or hydrocolloid occlusion also enhances the penetration. Once-daily application has been shown to be as effective as twice-daily application, and long-term remissions may be maintained by applications on alternate days[75]. The indications and contraindications of topical corticosteroids for the treatment of psoriasis are summarized in Table 8.5.

At least 80% of patients treated with high-potency topical corticosteroids experience clearance. In fact, the maximum improvement is usually achieved within 2 weeks. With maintenance therapy consisting of 12 weeks of intermittent applications of betamethasone dipropionate ointment (restricted to weekends), 74% of patients remained in remission, compared with 21% of the patients receiving a placebo ointment[75]. Unfortunately, no efficacy data are available on prolonged treatment for more than 3 months. As tachyphylaxis and/or rebound can occur fairly rapidly, i.e. within a few days to weeks, intermittent treatment schedules (e.g. once every 2 or 3 days or on weekends) are advised for more prolonged treatment courses. Combination topical therapy can take advantage of both the rapid effect of topical corticosteroids plus the prolonged benefits of long-term treatment with topical agents such as vitamin D_3 analogues.

Vitamin D_3 analogues

In the early 1990s, vitamin D_3 analogues became available as a topical treatment for psoriasis. When the epidermis is hyperproliferative, vitamin D_3 inhibits epidermal proliferation, and it induces normal differentiation by enhancing cornified envelope formation and activating transglutaminase; it also inhibits several neutrophil functions. Due to their therapeutic efficacy and limited toxicity, calcipotriene (calcipotriol) and other vitamin D_3 analogues have become a first-line therapy for psoriasis[76].

For a detailed description of topical vitamin D_3 analogues, the reader is referred to Chapter 129. Table 8.6 summarizes the major characteristics of commercially available vitamin D_3 analogues. Calcipotriene monotherapy has been shown to result in an ~60% reduction of PASI after 8 weeks of treatment, but in practice combination therapy with topical corticosteroids is commonly employed, both during the clearing phase as well as intermittently during long-term treatment. When calcipotriene and betamethasone dipropionate are combined, an ~70% reduction in PASI has been observed (ointment or foam formulation)[77,78], as has clearing/minimal disease in ~70% of patients with scalp psoriasis (gel formulation)[79].

Anthralin

Anthralin (dithranol) has been available since 1916; it is still used as a treatment for psoriasis, although it was more commonly utilized in the past (see Ch. 129). It has marked epidermal effects, including an anti-hyperproliferative effect. Anthralin also inhibits mitogen-induced T lymphocyte proliferation and neutrophil chemotaxis. In Europe and other regions outside the US, it is used most often in day-care centers and the inpatient setting[80].

The indications and contraindications for the use of anthralin in the treatment of psoriasis are summarized in Table 8.7. In the authors' experience, total clearing of psoriasis in at least 80% of patients occurs with 3–5 weeks of treatment in an inpatient setting or day-care center. If the anthralin treatment is performed at home, the efficacy is substantially less.

Topical retinoids

All-*trans*-retinoic acid and 13-*cis*-retinoic acid, although effective in the treatment of acne, are not effective for psoriasis. However, topical tazarotene, an acetylene retinoid that selectively binds retinoic acid receptor (RAR)-β and RAR-γ, can be used to treat psoriasis. Tazarotene has been shown to decrease epidermal proliferation and it inhibits psoriasis-associated differentiation (e.g. transglutaminase expression, K16 expression). It is manufactured in cream and gel formulations and is usually applied once daily.

Indications and contraindications of tazarotene for the treatment of psoriasis are summarized in Table 8.8. In view of its modest efficacy as monotherapy, it is usually prescribed as a second-line therapy. Irritation of the skin with burning, pruritus, and erythema can limit the use of tazarotene. For this reason, combination therapy with topical corticosteroids (e.g. halbetasol) is useful. The maximal area that can be treated with tazarotene is 10%–20% of the body surface, and safety data are available for up to 1 year of treatment.

INDICATIONS AND CONTRAINDICATIONS FOR TOPICAL CORTICOSTEROIDS

Indications

- Mild to moderate psoriasis: first-line treatment as monotherapy or in combination
- Severe psoriasis: often in combination with a vitamin D_3 analogue, a topical retinoid, anthralin, or tar; also as an adjunct to systemic therapy or photo(chemo)therapy
- Monotherapy for flexural and facial psoriasis (usually mild strength)
- Recalcitrant plaques often require occlusion (plastic, hydrocolloid)

Contraindications

- Bacterial, viral, and mycotic infections
- Atrophy of the skin
- Allergic contact dermatitis due to corticosteroids or constituents of the formulation

Table 8.5 Indications and contraindications for topical corticosteroids. Maximal quantities: 50 g/week of a superpotent corticosteroid; 100 g/week of a potent corticosteroid.

VITAMIN D_3 ANALOGUES			
	Calcipotriene/calcipotriol	**Calcitriol**	**Tacalcitol**
Concentration	50 mcg/g	3 mcg/g	2 mcg/g; 4 mcg/g
Formulations	Ointment, cream, lotion, solution, foam	Ointment	Ointment, lotion
Frequency	BID	BID	BID; daily
Maximum weekly amount*	100 g	200 g	70 g; 70 g†
Chemical structure	26,27-cyclo-vitamin D_3 22,23 double bond Transposition of the 25-OH to the 24 position	1α,25-dihydroxy vitamin D (active natural vitamin D_3)	1α,24-dihydroxy vitamin D_3
Inactivating enzymes	22,23-reductase; 24-oxido-reductase	24-hydroxylase	25-hydroxylase

*To avoid hypercalcemia.
†Maximum weekly amount for 8 weeks of treatment.

Table 8.6 Vitamin D_3 analogues. Calcipotriene is the US Adopted Name (USAN) and calcipotriol is the International Nonproprietary Name (INN). These medications should be avoided or limited in patients with abnormalities in bone or calcium metabolism (e.g. sarcoidosis) or renal insufficiency. If used in recommended weekly amounts, they are considered safe in pregnancy (pregnancy category C in previous classification). If used in conjunction with phototherapy, need to apply after UV irradiation or at least several hours prior, because they may reduce UV penetration into the skin. BID, twice daily.

INDICATIONS AND CONTRAINDICATIONS FOR ANTHRALIN
Indications
• Mild to moderate or severe* psoriasis: second-line treatment as monotherapy or in combination
Contraindications
• Unstable plaque psoriasis in a phase of progression • Pustular psoriasis • Erythrodermic psoriasis
*Severe psoriasis usually treated in day-care center or inpatient setting.

Table 8.7 Indications and contraindications for anthralin. To minimize irritation, concentration and application time are gradually escalated; neither should be increased more often than once every 3 days, given that peak erythema is seen 3–4 days following application.

INDICATIONS AND CONTRAINDICATIONS FOR TOPICAL TAZAROTENE
Indications
• Mild to moderate psoriasis: second-line treatment as monotherapy or in combination with a topical corticosteroid (e.g. halbetasol)
Contraindications
• Unstable plaque psoriasis in a phase of progression • Erythrodermic psoriasis • Allergic contact dermatitis to tazarotene or constituents of the formulation • Pregnancy or lactation

Table 8.8 Indications and contraindications for topical tazarotene.

Additional topical treatments

If the psoriatic plaques have thick scale, this needs to be reduced in order to enhance penetration of topical medications and ultraviolet (UV) light. Options include salt-water baths, topical salicylic acid, and oral retinoids. *Salicylic acid* 5%–10% has a substantial keratolytic effect and, in the case of scalp psoriasis, salicylic acid can be formulated in an oil or ointment base. Application of salicylic acid to localized areas can be done daily, but, for more widespread areas, two to three times per week is preferred. This is to prevent systemic intoxication (see Ch. 129), especially in infants or those with reduced renal function.

Coal tar has a range of anti-inflammatory actions and is effective as an antipruritic. Although crude coal tar may be the most effective tar available for the treatment of psoriasis (see Ch. 129), a distilled and alcohol-derived tar product, liquor carbonis detergens (LCD), is also used. In view of its mutagenic potential, tar is contraindicated in pregnant or lactating women. However, guidelines on the use of tar products may differ between countries.

Calcineurin inhibitors are used to treat facial and flexural psoriasis. Randomized, placebo-controlled studies have demonstrated efficacy and safety for this indication[81,82].

Recently approved topical treatments

Tapinarof cream is a first-in-class aryl hydrocarbon receptor (AhR) modulating agent. It reduces proinflammatory Th17 and Th22 cytokines, upregulates antioxidant activity, and promotes epidermal barrier restoration by filaggrin. In phase 3 studies, 35%–40% of patients reached Physician Global Assessment (PGA) 0 after 12 weeks and 35%–47% of patients reached PASI 75[83]. Up to 6% of patients have discontinued topical tapinarof due to dermatitis, folliculitis, or nasopharyngitis.

Roflumilast cream is a PDE-4 inhibitor with the same mechanism of action as apremilast (see Fig. 130.4). In a phase 2b, double-blind, randomized trial, 28% of the patients were clear or almost clear after 6 weeks of daily application of roflumilast 0.3% cream[84]. Improvement of intertriginous psoriasis in ~70% of patients has also been reported. In two phase 3 trials, there was a 65%–70% improvement in the Dermatology Life Quality Index (DLQI). Potential side effects include diarrhea (3%), headache (2%), and application site pain (1%)[84a].

Photo(chemo)therapy and Systemic Medications

Evidence-based guidelines for the treatment of psoriasis with photo(chemo)therapy and classic systemic medications have been developed by various dermatologic organizations[84–87], and the tables in this chapter are adapted from these recommendations.

Photo(chemo)therapy

Photo(chemo)therapy represents a mainstay in the treatment of moderate to severe psoriasis. Phototherapy with broadband or narrowband ultraviolet B (UVB) and photochemotherapy with ultraviolet A (UVA) following ingestion of or topical application of a psoralen are classic treatment options. In the late 1970s, monotherapy with erythemogenic doses of broadband UVB was proven to be an effective approach; later on, narrowband UVB (311 nm) was developed and is the optimal irradiation currently available. Monochromatic 308 nm light from an excimer laser or equivalent source can be used to target individual psoriatic plaques.

Photo(chemo)therapy is discussed in detail in Chapter 134, and its indications and contraindications for psoriasis are summarized in Table 8.9.

Methotrexate

In 1971, amethopterin (methotrexate; MTX) was approved by the FDA as a treatment for psoriasis. The effect of MTX on lymphocytes, circulating and cutaneous, is a likely explanation for its antipsoriatic activity.

MTX is a first-line systemic therapy for psoriasis as it is highly efficacious for severe disease and all clinical variants of psoriasis. In chronic plaque psoriasis, initial improvement is observed between 1 and 7 weeks and maximum improvement can be expected after 8–12 weeks of treatment. Based upon an international consensus, MTX should be administered weekly as a single dose, usually orally but switched to subcutaneously if there are gastrointestinal adverse effects or insufficient efficacy[88]. Occasionally, it is administered intramuscularly. The recommended

INDICATIONS AND CONTRAINDICATIONS FOR PHOTO(CHEMO)THERAPY FOR PSORIASIS
Indications
• Moderate to severe psoriasis: first-line treatment as monotherapy or in combination
Contraindications (absolute or relative)
• Genetic disorders characterized by increased photosensitivity or an increased risk of skin cancer (UVB and PUVA)*
• High cumulative number of PUVA treatments, i.e. >150–200 individual treatments (PUVA)*
• Concurrent treatment with cyclosporine (UVB and PUVA)*
• Previous history of skin cancer (UVB and PUVA; * if current skin cancer, especially SCC or melanoma)
• Pregnancy or lactation (PUVA)*
• Skin type I (UVB and PUVA)†
• Photosensitive dermatoses (UVB and PUVA)†
• Unavoidable phototoxic systemic or topical medications (UVB and PUVA)†
• Vitiligo (UVB and PUVA)†
• Previous history of arsenic exposure, ionizing irradiation, or excessive photo(chemo)therapy (UVB and PUVA)
• Immunosuppressive medication (UVB and PUVA)
• Atypical melanocytic nevi (UVB and PUVA)
• Seizure disorder (risk of fall/injury; UVB and PUVA)
• Poor compliance (UVB and PUVA)
• Men and women in reproductive years without contraception (PUVA)
• Impaired liver function or hepatotoxic medication (PUVA)
• Cataracts (PUVA)
*Absolute contraindication. †Need to adjust the dose and monitor closely.

Table 8.9 Indications and contraindications for photo(chemo)therapy for psoriasis. Some clinicians use UVA alone. PUVA, psoralen + ultraviolet A; SCC, squamous cell carcinoma; UVB, ultraviolet B.

INDICATIONS AND CONTRAINDICATIONS FOR METHOTREXATE
Indications

• Severe psoriasis
  • Chronic plaque psoriasis (>10%–15% BSA or interference with employment or social functioning)
  • Pustular psoriasis (generalized or localized)
  • Erythrodermic psoriasis
  • Psoriatic arthritis (moderate to severe)
  • Severe nail psoriasis

• Psoriasis not responding to topical treatments, photo(chemo)therapy and/or systemic retinoids
Contraindications (absolute or relative)
• Severe anemia, leukopenia, and/or thrombocytopenia*
• Significant liver function abnormalities, hepatitis (active and/or recent), severe fibrosis, cirrhosis, excessive alcohol intake*
• Impaired kidney function (creatinine clearance <60 ml/min)†
• Concomitant medications that increase MTX levels, e.g. daily trimethoprim–sulfamethoxazole*
• Significantly reduced pulmonary function*
• Pregnancy or lactation*
• Currently planning to have children (male and female patients)‡
• Severe infections* or active infections
• Peptic ulcer (active)* or gastritis
• Hypersensitivity to MTX*
• Unreliable patient*
• Pleural effusion or ascites†
• Concomitant hepatotoxic medications
• Immunodeficiency syndromes
• Concomitant radiation therapy
*Absolute contraindication. †Requires significant reduction in dosage. ‡Because of possible mutagenic risk and teratogenicity, discontinue MTX 3 months prior to attempts to conceive; continue contraception during these 3 months.

Table 8.10 Indications and contraindications for methotrexate (MTX). BSA, body surface area.

maximum weekly dosage is 15 mg (children) or 25 mg (adults), with supplemental folic acid administered 24 hours after the MTX[88]. Depending on the dosage regimen, the percentage of patients reaching PASI 75, i.e. a 75% reduction in the PASI score, ranges from 25% (low starting dose) to 60% (high starting dose) after 12–16 weeks of treatment[89,90].

Potential side effects restrict its use to moderate to severe disease resistant to topical treatments and phototherapy and/or situations in which these are contraindicated. However, provided that the guidelines are carefully followed, MTX can be employed as an effective long-term therapy. Hepatotoxicity is one of the well-known side effects, but a correlation between the cumulative dose of MTX and liver fibrosis could not be established[91]. The use of folic acid supplementation during MTX administration is recommended as it reduces side effects, including gastrointestinal. Guidelines for MTX usage vary depending on the country and disease state.

Chapter 130 describes the mechanism of action, pharmacology, and safety issues of MTX, with Fig. 130.7 outlining the monitoring guidelines for MTX-related hepatotoxicity. Tables 8.10 and 8.11 summarize indications and contraindications as well as side effects of MTX.

Cyclosporine

Cyclosporine is a cyclic undecapeptide that was isolated from the fungus *Tolypocladium inflatum*. Based on large controlled studies, cyclosporine is a highly effective treatment for the severe manifestations of psoriasis. As a calcineurin inhibitor, it prevents T lymphocyte activation from being translated into the release of effector cytokines such as IL-2. Cyclosporine can be used safely, provided that the guidelines are strictly followed. In view of its nephrotoxic effects (e.g. reduced glomerular filtration rate, tubular atrophy), cyclosporine should be given for several-month courses (i.e. maximally 1 year, although this duration is still debated) and alternated with other therapies. An alternative is an intermittent schedule using multiple short courses of a few weeks' duration.

The indications and contraindications of cyclosporine are summarized in Table 8.12. Cyclosporine can produce dramatic rapid improvement of psoriasis, but this must be balanced by the requirement for an appropriate replacement therapy, given the need to ultimately stop cyclosporine therapy.

Guidelines for pre-cyclosporine screening and long-term evaluation during cyclosporine administration are outlined in Chapter 130. An important aspect is assessment of renal function, and creatinine clearance should be estimated using the Cockcroft–Gault formula:

$$\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{\text{serum creatinine}\,(\text{mg}/100\,\text{ml}) \times 72}$$

In elderly patients and patients with a history of hypertension, the risks of renal impairment and hypertension are increased.

Cyclosporine treatment in psoriatic patients has been reported to increase the frequency of SCCs, especially in those previously treated with PUVA. The underlying mechanism is not mutagenesis but a decrease in immunosurveillance of the skin. In particular, psoriatic patients who have been exposed to high cumulative doses of UV radiation are at risk for development of cutaneous malignancies. Although cyclosporine is an immunosuppressive agent, no increase in serious infections has been reported in patients treated with cyclosporine alone. Other side effects include gastrointestinal discomfort, hypertrichosis, paresthesias, gingival hyperplasia, headache, vertigo, muscle cramps, and tremor[94]. Metabolic side effects include hyperkalemia, hypomagnesemia, hyperuricemia (due to decreased clearance of uric acid), and elevated cholesterol and triglycerides.

The efficacy of cyclosporine for psoriasis has been clearly shown in multiple controlled and uncontrolled studies. For example, the European multicenter dose-finding studies found that doses of 1.25, 2.5–3, and 5 mg/kg/day of cyclosporine resulted in reductions of the PASI of 35%, 57%, and 86%, respectively[95]. An improvement in the PASI of 75% was achieved in 24%, 52%, and 88% of the patients[95]. Of note, because the criteria for these studies were different from those used for FDA approval of targeted immunomodulators ("biologic" therapies), the PASI numbers are not directly comparable. Efficacy of cyclosporine has been demonstrated in all variants of psoriasis (including nail psoriasis), but less so for psoriatic arthropathy. In general, a reduction of the

SIDE EFFECTS OF METHOTREXATE		
Subjective symptoms	**Hematopoietic†**	**Mucocutaneous**
*Most frequent**,† Nausea Vomiting Abdominal pain Fatigue Headache *Occasional* Loss of libido Impaired memory	Leukopenia‡ Thrombocytopenia Anemia	Oral erosions† Alopecia Delayed phototoxicity Tenderness and/or necrosis of plaques due to overdose Rarely, urticaria, angioedema, vasculitis
Hepatic	**Pulmonary**	**Fetal development**
Hepatitis† Cirrhosis¶	Interstitial pneumonitis (acute-onset cough, dyspnea)	Birth defects: cranial and absence of digits
Carcinogenesis§	**Idiosyncratic reaction**	
In rheumatoid arthritis patients, increased risk of lymphoma Risk factor for cutaneous SCC in PUVA-treated patients	Early in course with full dosage Severe pneumonia Gastrointestinal hemorrhage Pancytopenia	
Opportunistic infections	**Additional/unusual**	
Pneumocystis jirovecii pneumonia Cryptococcosis Disseminated histoplasmosis Disseminated herpes zoster	Osteopathy (pain, osteoporosis, compression fractures) Ventricular cardiac arrhythmias Lowered seizure threshold	

*Same day or 2–3 days following MTX administration; may respond to folic acid, dose reduction, or antiemetic drug.
†May be reduced by folic acid (5 mg, 24 hours after MTX dose).
‡Up to 10% of patients on oral regimens.
¶Up to 25% of patients receiving long-term therapy.
§No increased risk of malignancy was observed in large series of psoriasis patients[92,93].

Table 8.11 Side effects of methotrexate (MTX). PUVA, psoralen + ultraviolet A; SCC, squamous cell carcinoma.

PASI of 60%–70% can be reached within 4 weeks of treatment. During long-term treatment, there are no signs of tachyphylaxis.

Systemic retinoids

By the 1930s, vitamin A deficiency was known to cause hyperkeratosis of the skin (phrynoderma). Thirty years later, modifications of the vitamin A molecule resulted in the discovery of the so-called first generation of retinoids, including all-*trans*-retinoic acid (tretinoin) and 13-*cis*-retinoic acid (isotretinoin). Further research resulted in the development of the second generation of retinoids, the mono-aromatic retinoids, etretinate and its free metabolite acitretin.

Acitretin is an effective treatment for psoriasis, but a major problem with systemic retinoids is their teratogenicity, making contraception mandatory in women of childbearing age during treatment and (depending on the drug half-life) for a period of 1 month (isotretinoin) to 3 years (acitretin) after discontinuing therapy. Chapter 126 provides a description of the modes of action, pharmacologic aspects, and side effects of systemic retinoids.

The indications and contraindications for the use of acitretin in the treatment of psoriasis are summarized in Table 8.13, and the recommended initial and ongoing evaluations are outlined in Table 8.14.

In patients with chronic plaque psoriasis, 0.5 mg/kg/day is the initial dosage, which can be increased depending upon the clinical response and side effects. For erythrodermic psoriasis, the initial dosage is 0.25 mg/kg/day, and in pustular psoriasis, the dose should be maximized, i.e. up to 1 mg/kg/day. In patients with chronic plaque psoriasis, mild cheilitis (just perceivable by the patient) is the goal, whereas in patients with pustular psoriasis, a dose that causes a clinically apparent but tolerable cheilitis is an endpoint.

INDICATIONS AND CONTRAINDICATIONS FOR CYCLOSPORINE
Indications
• Severe psoriasis • Conventional therapies (topical treatments, photo(chemo)therapy, acitretin, methotrexate) ineffective or inappropriate
Contraindications
• Impaired renal function* • Uncontrolled hypertension* • Past or present* malignancy • History of excessive photo(chemo)therapy (>200 PUVA treatments) or concurrent photo(chemo)therapy* • Concomitant drugs affecting cyclosporine pharmacokinetics† • Radiotherapy* • Severe infections* or active infections • Hypersensitivity to cyclosporine* • Unreliable patient* • Primary or secondary immunodeficiency • Concomitant immunosuppressive therapy • History of arsenic exposure • Pregnancy or lactation • Concurrent methotrexate administration • Significant hepatic disease • Hyperuricemia, hyperkalemia • Vaccination with live vaccines • Seizure disorder • Poorly controlled diabetes mellitus • Severe chronic organ dysfunction • Alcohol and drug abuse • Malabsorption
*Absolute contraindications. †Requires dose adjustment and careful monitoring; cyclosporine is inactivated by the cytochrome P450 3A isoform.

Table 8.12 Indications and contraindications for cyclosporine. The recommended starting dose is 3 mg/kg/day in two divided doses; at 2-week intervals, dosage can be increased to a maximum of 5 mg/kg/day. PUVA, psoralen + ultraviolet A.

INDICATIONS AND CONTRAINDICATIONS FOR ACITRETIN
Indications
• Severe psoriasis that cannot be managed by topical treatments or photo(chemo)therapy • Monotherapy is indicated for erythrodermic or pustular psoriasis • Combination therapy is indicated for chronic plaque psoriasis
Contraindications
• Severe liver dysfunction* • Severe kidney dysfunction (elimination reduced)* • Pregnancy or lactation* • Women of childbearing potential who cannot guarantee adequate contraception during and up to 3 years following discontinuation of acitretin* • Hyperlipidemia, especially hypertriglyceridemia, that cannot be controlled* • Excessive alcohol intake* • Unreliable patient* • Concomitant medications that interfere with retinoid bioavailability or whose metabolism is altered† • Concomitant hepatotoxic drugs, e.g. methotrexate‡ • Poorly controlled diabetes mellitus • History of pancreatitis • Atherosclerosis
*Absolute contraindications. †Requires dose adjustment and careful monitoring, e.g. phenytoin competes for plasma protein binding. ‡Reserved for treatment-resistant patients.

Table 8.13 Indications and contraindications for acitretin. Blood donation is contraindicated in patients receiving acitretin. Patients who wear contact lenses need to use lubricants or may need to switch to glasses.

The efficacy of acitretin monotherapy in chronic plaque psoriasis is limited, with ~70% of patients achieving a moderate or better response. In one study, 23% of patients treated with 50 mg of acitretin daily for 8 weeks achieved ≥75% improvement in their PASI[96]. Combination

treatment with photo(chemo)therapy and/or vitamin D_3 analogues results in a substantial improvement in clinical response. Maximal therapeutic efficacy is reached after 2–3 months. Acitretin has been shown to be an effective maintenance therapy. As monotherapy, acitretin is highly effective in erythrodermic and pustular psoriasis. Its efficacy in nail psoriasis and psoriatic arthritis is only modest.

JAK and TYK2 inhibitors

Oral JAK inhibitors (e.g. tofacitinib, upadacitinib) have been approved for psoriatic arthritis and several are currently in phase 3 trials for plaque psoriasis. There are four JAK enzymes – JAK1, JAK2, JAK3, and TYK2 – and depending upon the drug, one or more enzymes are inhibited. Oral deucravacitinib, a selective TYK2 inhibitor, was recently approved for plaque psoriasis based upon two phase 3 trials in which it was compared to apremilast or placebo. A PASI 75 improvement was observed in 55%–60% of patients who received deucravacitinib, compared to 35% and 13% for apremilast and placebo, respectively[97].

Inhibition of the JAK/STAT pathway eventually leads to a reduction in IL-17- and IL-23-mediated inflammation and type I IFN-driven responses. The mechanisms of action and side effects of this group of medications are reviewed in Chapter 128.

Apremilast and other systemic therapies

Apremilast is an oral phosphodiesterase 4 inhibitor that prevents cyclic AMP degradation within keratinocytes, dendritic cells, monocytes, and neutrophils. Increased intracellular cAMP levels then lead to a reduction in proinflammatory mediators (see Fig. 130.4). Chapter 130 reviews the dosages and side effects of apremilast. In a third of patients with plaque psoriasis, apremilast leads to a PASI 75 improvement and it significantly decreases pruritus. Scalp psoriasis may have a relatively better response.

Additional systemic therapies that have been reported as beneficial in the management of psoriasis are outlined in Table 8.15. In general, they are used less often than the other medications described in this chapter, and there are regional differences in their use.

Targeted immunomodulators ("biologic" therapies)

Beginning in 2000, targeted immunomodulators were introduced for the treatment of psoriatic arthritis and moderate to severe psoriasis. Their targets are cytokines, including TNF, IL-12, IL-17, and IL-23 (see Fig. 8.1B). Table 8.16 lists the biologic agents that are currently commercially available and Chapter 128 provides a description of their modes of action, dosages, side effects, and monitoring recommendations. Guidelines, including European S3-Guidelines and those developed by the American Academy of Dermatology and National Psoriasis Foundation, have been proposed for the treatment of psoriasis patients with TNF inhibitors (adalimumab, etanercept, certolizumab, infliximab)

ACITRETIN – EVALUATION PRIOR TO AND DURING TREATMENT
Pre-acitretin screening
• History to exclude contraindications • Complete blood count • Liver function tests (AST, ALT, γGT, alkaline phosphatase, bilirubin) • Serum triglycerides, cholesterol, HDL • Glucose • Serum creatinine • Pregnancy test • Consider spinal X-ray (often initially performed during the first 3 months of therapy if long-term treatment is anticipated)
Evaluation during acitretin treatment
• Monitor mucocutaneous side effects • Serum triglycerides, cholesterol/HDL, and liver function tests (every month for the first 2 months then every 2–3 months) • Serum creatinine (elderly patients or patients with mild to moderate renal dysfunction) • Monitor for development of hyperostosis by history (twice yearly) and by X-ray of spine (e.g. once yearly or every other year in patients receiving long-term treatment)* • Pregnancy test (twice yearly throughout treatment)*
*Frequency varies amongst clinicians.

Table 8.14 Acitretin – evaluation prior to and during treatment. ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, gamma glutamyl transpeptidase; HDL, high-density lipoproteins.

ADDITIONAL SYSTEMIC THERAPIES FOR PSORIASIS	
Medication	**Side effects**
Fumarates[98]	Renal impairment, flushing, gastrointestinal disturbances, headache, fatigue, Fanconi syndrome, progressive multifocal leukoencephalopathy (rare)
Mycophenolate mofetil[99]	See Ch. 130
Oral calcitriol (0.5–3 mcg/day)[100]	Hypercalcemia, hypercalciuria
6-thioguanine (40–160 mg/day)	Myelosuppression, hepatotoxicity, gastrointestinal disturbances
Hydroxyurea	See Table 130.10

Table 8.15 Additional systemic therapies for psoriasis. BID, twice daily.

COMMERCIALLY AVAILABLE BIOLOGIC AGENTS FOR THE TREATMENT OF PSORIASIS INCLUDING GENERALIZED PUSTULAR PSORIASIS			
Biologic agent	**Target**	**Molecule**	**Approved***
Etanercept	TNF†	Human fusion protein	FDA + EMA
Infliximab	TNF‡	Chimeric antibody	FDA + EMA
Adalimumab	TNF‡	Human antibody	FDA + EMA
Certolizumab	TNF‡	Humanized antibody	FDA + EMA
Ustekinumab	p40 subunit of IL-12/23	Human antibody	FDA + EMA
Secukinumab	IL-17A	Human antibody	FDA + EMA
Ixekizumab	IL-17A	Humanized antibody	FDA + EMA
Bimekizumab	IL-17A, IL-17F	Humanized antibody	EMA
Brodalumab	IL-17 receptor	Human antibody	FDA + EMA
Guselkumab	IL-23	Human antibody	FDA + EMA
Risankizumab	IL-23	Humanized antibody	FDA + EMA
Tildrakizumab	IL-23	Humanized antibody	FDA + EMA
Spesolimab	IL-36 receptor	Humanized antibody	FDA + EMA

*By registration authorities for the treatment of psoriasis as of June 2023. Biosimilar products, e.g. adalimumab-atto, etanercept-szzs, infliximab-dyyb, are also commercially available.
†Soluble form.
‡Soluble form and transmembrane TNF receptor.

Table 8.16 Commercially available biologic agents for the treatment of psoriasis including generalized pustular psoriasis. See Ch. 128 for details. EMA, European Medicines Agency; FDA, Food and Drug Administration; IL, interleukin; TNF, tumor necrosis factor.

as well as anti-IL-12/23 (ustekinumab), -IL-17 (secukinumab, ixekizumab, brodalumab), and -IL-23 (guselkumab, tildrakizumab, risankizumab) antibodies[86,101–103]. The evidence in these guidelines is based upon both short-term clinical trials (12- to 16-week efficacy and safety data) and long-term clinical trials (up to 5-year efficacy and safety data).

Based upon a network meta-analysis, the relative efficacies of multiple biologic agents are outlined in Table 8.17[104]. With regard to *short-term* efficacy, there is significant overlap amongst first-generation (TNF inhibitors) and second-generation (ustekinumab) biologic agents, photo(chemo)therapy, and classic systemic medications such as MTX and cyclosporine. However, third-generation (anti-IL-17 antibodies) and fourth-generation (anti-IL-23 antibodies) biologic agents are associated with a significant enhancement in short-term efficacy. The latter has led to assessments of PASI 90, not just PASI 75, with 60%–70% of patients achieving at least PASI 90.

In the treatment of psoriasis, *long-term* efficacy also matters. With the introduction of TNF inhibitors and ustekinumab came a dramatic reduction in both inpatient and day-care units dedicated to treating psoriasis. Data from clinical trials that included 5-year follow-up periods for first- to fourth-generation target immunomodulators demonstrated that clinical improvements were maintained long-term[105–107]. In addition, long-term safety data were reassuring.

Because clinical trials often enroll selective populations, it is important to assess real-world efficacy and safety. Real-world data have confirmed effective and safe long-term control by TNF inhibitors and ustekinumab, with a 50% drug survival over 2–6 years[108]. The improved efficacy profile of anti-IL-17 and -IL-23 antibodies has also proved to be sustainable[109]. In a recent analysis of five of the more commonly used antibodies (adalimumab, guselkumab, ixekizumab, secukinumab, ustekinumab), guselkumab had the highest drug survival[110].

At the time of writing, bimekizumab, a dual-inhibitor of IL-17A and IL-17F, has been EMA, but not yet FDA, approved for the treatment of plaque psoriasis[111]. Of note, spesolimab-sbzo, an interleukin-36 receptor inhibitor, was recently approved for the treatment of generalized pustular psoriasis[112].

More so in the past, biologic agents were prescribed primarily for "high-need" patients in whom some or all classic systemic treatments were either contraindicated or had led to insufficient improvement. This stepwise approach has gradually been replaced by the use of targeted immunomodulators early on in order to control disease activity. Of course, the latter recommendation has to be balanced against the high cost of these medications. Both indications and contraindications for currently commercially available therapies are outlined in Table 8.18.

Therapeutic Management

General considerations

Before considering a specific treatment in an individual psoriatic patient, it is important to exclude triggering factors. Aggravating factors such as focal infections, medications, and psychological stress have been described above. As psoriasis is a systemic disease, comorbidities and disease-modifying factors need to be addressed. These include arthritis, nail disease (a prognostic marker for the development of arthritis), metabolic syndrome with its associated cardiovascular disease and obesity, depression, and smoking. Furthermore, it is also crucial to assess the various aspects of disease severity, in particular[113]:

- The areas of involvement and the degree of erythema, induration, and desquamation of the cutaneous lesions (see Table 8.2).
- The impairment of quality of life. The visibility of the lesions and symptoms such as pruritus are relevant factors, and psycho-emotional stress and the response of family and friends to the psoriasis should also be considered. Impact of psoriasis on quality of life can be measured by questionnaires (e.g. Dermatology Life Quality Index [DLQI], Skindex-29).
- The responsiveness to previous treatments. Individual patients report a wide variation with respect to their clinical response to various treatments. For example, some patients, even those with widespread disease, may experience excellent improvement with a mild topical therapy, whereas patients with localized disease may prove recalcitrant to even high-dose systemic treatments.

Relative and absolute contraindications to the various treatment options have to be recognized, especially in the case of photo(chemo) therapy and systemic medications. Because psoriasis is a chronic condition, patients have to cope not only with their disease, but also with the various treatments and their costs for prolonged periods of time. For example, individual circumstances may restrict the time available for intensive daily treatments. Also, some patients cannot accept a few coin-sized lesions in visible sites, while for others this is less of a problem. Therefore, treatment selection is a multivariable decision-making process and not a simple stepwise therapeutic ladder.

In addition, classically assessing disease severity as mild, moderate, or severe can sometimes prove challenging as no consensus has been reached on their definitions based upon PASI, PGA, or DLQI. The International Psoriasis Council has redefined disease severity in practice-driven rather than data-driven terms: psoriasis patients should be classified as candidates for either topical therapy (mild disease) or systemic therapy (severe disease). The latter group should meet at

SENSITIVITY ANALYSIS: GLOBAL TRIALS ONLY						
Treatment	**PASI 75 Posterior median, 95% CrI**		**PASI 90 Posterior median, 95% CrI**		**PASI 100 Posterior median, 95% CrI**	
Risankizumab 150 mg	89.4%	(87.2%, 91.3%)	71.7%	(67.8%, 75.4%)	41.1%	(36.9%, 45.6%)
Ixekizumab 80 mg	88.5%	(86.2%, 90.5%)	70.0%	(66.1%, 73.7%)	39.3%	(35.2%, 43.5%)
Brodalumab 210 mg	88.0%	(85.8%, 90.1%)	69.2%	(65.4%, 73.0%)	38.3%	(34.4%, 42.6%)
Gusalkumab 100 mg	87.3%	(84.4%, 90.0%)	68.0%	(63.2%, 72.9%)	37.1%	(32.2%, 42.6%)
Secukinumab 300 mg	82.6%	(79.9%, 85.2%)	60.4%	(56.5%, 64.5%)	29.7%	(26.3%, 33.5%)
Infliximab 5 mg/kg	79.9%	(75.6%, 83.7%)	56.5%	(50.8%, 62.2%)	26.3%	(21.8%, 31.3%)
Cetrilizumab pegol 400 mg	71.0%	(65.7%, 75.9%)	45.2%	(39.4%, 51.2%)	18.0%	(14.3%, 22.2%)
Ustekinumab 45 mg ≤100 kg, 90 mg >100 kg	69.4%	(66.1%, 72.7%)	43.4%	(39.8%, 47.2%)	16.8%	(14.5%, 19.3%)
Adalimumab 40 mg	70.2%	(66.7%, 73.5%)	44.3%	(40.4%, 48.l%)	17.3%	(14.9%, 20.0%)
Certolizumab pegol 200 mg	66.1%	(59.9%, 71.9%)	39.8%	(33.6%, 46.3%)	14.6%	(11.1%, 18.7%)
Tildrakizumab 100 mg	63.0%	(57.8%, 68.1%)	36.6%	(31.7%, 41.9%)	12.7%	(10.1%, 15.8%)
Tildrakizumab 200 mg	64.9%	(59.8%, 70.0%)	38.6%	(33.5%, 44.0%)	13.8%	(11.1%, 17.2%)
Etanercept 25 mg twice weekly/50 mg once weekly	39.8%	(35.3%, 44.6%)	17.6%	(14.7%, 20.9%)	4.2%	(3.2%, 5.4%)
Apremilast 30 mg	31.8%	(27.7%, 36.2%)	12.6%	(10.2%, 15.3%)	2.6%	(1.9%, 3.4%)
Dimethyl fumarate	30.9%	(23.4%, 39.7%)	12.1%	(8.1%, 17.5%)	2.5%	(l.4%, 4.2%)

Table 8.17 Estimated short-term (12–16 weeks) response rates based upon a network meta-analysis of PASI scores. This sensitivity analysis included only global trials and phase III trials that were conducted in an expanded treatment space. CrI, credible interval. *From Armstrong AW, Puig L, Joshi A, et al. Comparison of biologics and oral treatments for plaque psoriasis: A meta-analysis. JAMA Dermatol 2020;156:258–69.*

INDICATIONS AND CONTRAINDICATIONS FOR COMMERCIALLY AVAILABLE TARGETED IMMUNOMODULATORS ("BIOLOGIC" AGENTS)
Indications
General indications
• Patients with moderate to severe psoriasis, eligible for a systemic treatment • Patients with psoriatic arthritis, particularly those who have failed other disease-modifying antirheumatic drugs (DMARDs)
Restricted indication
• Patients with moderate to severe psoriasis who are not candidates for topical treatments, photo(chemo)therapy, or classic systemic treatments because of insufficient efficacy or contraindications†
Contraindications
(The exact contraindications vary by agent [see Ch. 128]; some listed below are relative, while others are absolute [*])
• Significant viral, bacterial, or fungal infection, including active *Salmonella* or dimorphic fungal infection* • Increased risk for developing sepsis* • Active tuberculosis* • Allergic reaction to the biologic agent* • *Selective for TNF inhibitors:* ANA+ (especially if high titer) or autoimmune connective tissue disease, blood dyscrasias, congestive heart failure (NYHA grade III or IV), or demyelinization disorders (the latter also if in first-degree relative)* • *Selective for ustekinumab:* BCG vaccination within the past 12 months (mode of action expected to increase susceptibility to mycobacterial infections) • *Selective for secukinumab, ixekizumab, and brodalumab:* active Crohn disease (may cause exacerbation of bowel disease) • History of hepatitis B viral (HBV) infection‡ • History of hepatitis C viral infection (risk of activation)¶ • Immunosuppressed patient • Pregnancy (TNF inhibitors appear to be safe) • Breastfeeding • Malignancy within the past 5 years (does not include adequately treated cutaneous squamous or basal cell carcinoma) • Excessive chronic sun exposure or photo(chemo)therapy
*Absolute contraindications. †Guttate, pustular, or erythrodermic psoriasis are not established indications, but there is anecdotal evidence for efficacy and safety. ‡If HBsAg-positive, measure HBV DNA and treat with antiviral agent (e.g. tenofovir, entecavir, telbivudine) prior to immunosuppressive therapy. Monitor for reactivation in those with anti-HBs or -HBc antibodies who are HBsAg-negative). ¶Need to monitor liver function tests and viral load.

Table 8.18 Indications and contraindications for commercially available targeted immunomodulators ("biologic" agents). Administration of live vaccines (see Table 128.8) is contraindicated in patients receiving biologic agents for psoriasis. BCG, bacillus Calmette–Guérin; NYHA, New York Heart Association.

least one of the following criteria: (1) body surface area (BSA) >10%; (2) disease involving special sites; and (3) failure of topical therapy[114].

Management with topical agents

It is important before instituting topical therapy that the patient understands that due to the Koebner phenomenon, trauma (e.g. from scratching or debriding lesions) can negate therapeutic interventions. Although it may seem obvious, patients should also be told that topical agents do not prevent new lesions from appearing at additional sites. For patients with mild disease, topical treatments are the first choice. Patients with more widespread involvement may also be treated with a topical agent; however, a high degree of compliance is required and this can be difficult to achieve.

Evidence for the efficacy of various topical treatments was reassessed in a meta-analysis[115]. From this analysis, it was concluded that only very potent topical corticosteroids tended to be more effective than monotherapy with the vitamin D_3 analogue calcipotriene. In ambulatory patients, calcipotriene was more effective than anthralin, coal tar, the other vitamin D_3 analogues (tacalcitol and calcitriol), and the retinoid tazarotene. The efficacy of coal tar and anthralin are difficult to assess, as the success of these topicals is highly dependent on the treatment setting. A day-care or inpatient setting is optimal, as it allows the patient to more easily cope with the side effects of staining, stinging, and irritation.

Combination treatment is advised for the vast majority of patients, thereby increasing efficacy and reducing side effects[116]. For example, a fixed combination of calcipotriene and betamethasone dipropionate applied once daily proved to be superior to twice-daily calcipotriene or twice-daily betamethasone dipropionate monotherapy. Nonetheless, one common initial approach is to apply either calcipotriene twice daily or a potent corticosteroid once daily for a period of 4 to 8 weeks (except for sensitive skin areas and the scalp). If this regimen is not successful or if rapid clearing is required, then both calcipotriene and a potent topical corticosteroid can be applied for 4 to 8 weeks. In the case of an insufficient response, another vitamin D_3 analogue or tazarotene may be tried as monotherapy or in combination with a topical corticosteroid. In addition, a topical corticosteroid under hydrocolloid occlusion can be used for a few recalcitrant plaques, especially when there is superimposed LSC.

A trial of tar or anthralin may be tried, especially in patients with longstanding disease and incomplete responses or fast relapses. These treatments often require a day-care or inpatient facility as their use in the ambulatory setting is inconvenient and disappointing. With regard to maintenance therapy, some patients prefer only intermittent clearing courses with no intervening therapy, while other patients want continuous treatment. Daily use of a topical vitamin D_3 analogue (below the maximum allowed weekly dosage) provides a safe long-term form of maintenance therapy. If the therapeutic response is insufficient, additional intermittent application of a topical corticosteroid (once or twice weekly) is helpful.

Certain body areas may require a more site-specific approach, e.g. roflumilast cream or a topical calcineurin inhibitor, rather than a potent topical corticosteroid, for psoriasis involving major body folds. If topical therapies do not provide adequate improvement, then treatment with photo(chemo)therapy or a systemic agent is indicated.

Management with photo(chemo)therapy and classic systemic medications

For patients with more severe involvement, topical therapies may be ineffective or impractical. On a chronic basis, patients with widespread disease often cannot manage their psoriasis with topical treatments and become frustrated and non-compliant. Evidence for the efficacy of photo(chemo)therapy and classic systemic treatments has been reassessed in a meta-analysis[117]. PUVA had the highest percentage of patients with clearance (70%), followed by UVB (68%) and cyclosporine (64%). However, PUVA has become a seldomly used therapy for psoriasis due to its potential for cumulative carcinogenicity.

In the selection of a systemic treatment for an individual patient, the existence of relative and absolute contraindications has to be considered. For example, photo(chemo)therapy would not be chosen for patients with a history of excessive exposure to UV radiation, but these same patients could be excellent candidates for retinoid therapy (considering its anticancer effects). Methotrexate is contraindicated in patients with excessive alcohol intake or active hepatitis, while cyclosporine is contraindicated in those with renal insufficiency or hypertension.

As noted previously, some guidelines recommend a stepwise approach utilizing less expensive treatments first, i.e. UVB phototherapy initially, followed by one of the classic systemic medications. Because of psoriasis' chronicity, maintenance therapy also needs to be addressed. While cyclosporine should not be used long-term, methotrexate, acitretin, and fumarates (available in some European countries) can be, as long as the potential for cumulative toxicity is monitored. However, increasingly, targeted immunomodulators have become first-line therapy for moderate to severe disease, with the goal of complete or nearly complete clearance as well as a reduction in systemic inflammation[118].

Management with targeted immunomodulators ("biologic" therapies)

Several biologic therapies are currently available worldwide for the treatment of psoriasis and/or psoriatic arthritis (see Table 8.16). Relative response rates are reviewed in Table 8.17 with indications and contraindications outlined in Table 8.18. In addition to moderate to severe disease, there may be other situations in which targeted immunomodulators become first-line therapy, e.g. acute arthritis, severe depression, suicidal ideation.

The side effect profiles are very different from those of photo(chemo) therapy and classic systemic medications, as there is no indication of cumulative toxicity. Because a 1-year course of biologic therapy costs up to $60 000 in the US and up to €35 000 in Europe (with costs varying depending upon the country), national health authorities and managed care insurance companies have adopted a restrictive approach. Therefore, in many countries, biologic agents are available exclusively for those patients with severe psoriasis who cannot be treated adequately with the classic treatments. However, an improvement in quality of life and the possible impact on comorbidities also need to be considered.

Combining treatments

Enhanced clinical response and a possible reduction in side effects are the goals of combination therapy. However, for safety reasons, some combinations are contraindicated.

Beneficial combinations

For topical treatments, systematic literature reviews have been published[115,116]. As noted previously, the combination of calcipotriene with potent topical corticosteroids has been shown to be more effective than either treatment as monotherapy. The irritation caused by vitamin D_3 analogues and tazarotene can be reduced by the addition of a medium- or high-strength corticosteroid. While not comprehensively investigated in controlled studies, topical therapies are often used for persistent lesions in patients receiving systemic agents. Those biologic agents that can induce autoantibodies (e.g. adalimumab, infliximab) may be combined with MTX.

Contraindicated combinations and combinations with restricted use

The combination of acitretin and cyclosporine carries the risk of accumulation of cyclosporine, because cyclosporine is inactivated by the cytochrome P450 system, which is inhibited by acitretin. The combination of cyclosporine and methotrexate has been viewed as high risk because both are immunosuppressants. However, this combination has been used with success by rheumatologists, and, in recalcitrant psoriasis, the combination has proved to be very effective without major side effects. The combination of methotrexate and acitretin has been used in those patients in whom all treatments have failed[119]. Although this combination can be very effective, severe hepatotoxicity has been reported; therefore, careful monitoring is mandatory. If a patient has received PUVA therapy in the past, the use of cyclosporine should be avoided.

Management of childhood psoriasis

The efficacy and safety of treatment modalities in children have been reviewed[120]. Only two randomized controlled trials were identified; one examined topical calcipotriene and the other etanercept. Of note, since then, ustekinumab and ixekizumab have been studied in controlled trials. The authors recommended topical calcipotriene as first-line therapy for mild to moderate juvenile psoriasis, combined with mild- to moderate-strength topical corticosteroids (if necessary). For treatment-resistant flexural and/or facial psoriasis, tacrolimus 0.1% ointment can be added to the treatment regimen. In some countries, anthralin is then considered if this treatment regimen is not effective or if the psoriasis is moderate to severe. The next step is to recommend treatment with narrowband UVB, especially in adolescents, with attention to the number of treatments. Although controversial, the use of antibiotics can be considered in patients with guttate psoriasis where there is suspicion of a streptococcal infection.

Of the systemic medications, methotrexate is regarded as the treatment of choice, with retinoids considered in pustular and erythrodermic psoriasis. Cyclosporine is occasionally utilized for exceptional cases[120]. Four systemic immunomodulators – etanercept, ustekinumab, secukinumab, and ixekizumab – have been approved by the FDA for use in children from the ages of 4, 6, 6, and 6 years, respectively. The EMA has also approved these four medications as well as adalimumab (in children ≥4 years of age), but its age for etanercept is ≥6 years. The EMA has also approved adalimumab for children 4 years of age or older. National recommendations for the treatment of psoriasis in children have also been published by Italian and German expert groups[121,122].

Management of psoriasis in patients with comorbidities

Comorbidities, in particular metabolic syndrome, are often observed in patients with more moderate to severe forms of psoriasis. Recommended therapies for patients with various comorbidities are summarized in Table 8.19.

SYSTEMIC TREATMENT OF PSORIASIS IN THE SETTING OF COMORBIDITIES

Comorbidity	MTX	CSA	Acitretin	Apremilast	JAK, TYK2 inhibitor	Anti-TNF	Anti-IL -12/23, -23	Anti-IL -17, -17R
Psoriatic arthritis	+	+/–	+/–	+	+	+	+	+
Crohn disease	+	+	+/–	+	+	+	+	–
Congestive heart failure (higher grades)	+	+	+	+	+/–(cardiac events)	–	+	+
Multiple sclerosis	+	+	+	+	+	–	+	+
SLE	+	+	+	+	+	+/–	+	+
Depression	+	+	+	+/–¶	+	+	+	+ IL-17 / – IL-17R
Clotting disorder (e.g. DVT, PE)	+	+	+	+	–	+	+	+
Significant infection, active tuberculosis	–	–	+	+	–	–	–	–
Latent tuberculosis*	+/–	+/–	+	+	+/–	+/–	+	+
Hepatitis B† or C viral infection	–	+/–	–	+	+/–	– Hep B / + Hep C	+/–	+/–
History of internal malignancy (e.g. lymphoma, lung cancer)‡	+/–	–	+	+	–	+/–	+/–	+/–

*Begin treatment for latent tuberculosis prior to initiating systemic therapy.
†If HBsAg-positive, measure HBV DNA and treat with antiviral agent (e.g. tenofovir, entecavir, telbivudine) prior to immunosuppressive therapy. Monitor for reactivation in those with anti-HBs or -HBc antibodies who are HBsAg-negative.
‡Especially within last five years; consider consultation with hematologist/oncologist prior to biologic therapy.
¶Consider consultation with psychiatrist or mental health care professional.

Table 8.19 Systemic treatment of psoriasis in the setting of comorbidities. Note (+) indicates preferred agents; (–) indicates agents that should be avoided; (+/–) indicates agents that can be used with caution or agents that are not preferred (e.g. there are not enough data, benefits of use outweigh the risks for an individual case). When there is a history of an internal malignancy and anti-IL-12/23, -23, -17, or -17R antibodies are available, they are preferred over anti-TNF agents. CSA, cyclosporine; DVT, deep venous thrombosis; IL, interleukin; JAK, Janus-associated kinase; MTX, methotrexate; PE, pulmonary embolus; R, receptor; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor; TYK2, tyrosine kinase 2.

Treatment of elderly patients

To address the efficacy and safety of systemic medications in older patients (≥65 years of age), a systematic literature review was conducted[123]. The effectiveness of acitretin, etanercept, adalimumab, and secukinumab did not correlate with age. For other systemic therapies, studies with age group comparisons were not available. Elderly patients often have a greater number of comorbidities, in addition to those associated with psoriasis. As a result, they may require altered dosing as well as more frequent laboratory and clinical monitoring. More real-world evidence and age-based (sub)analyses in prospective cohort studies are needed given the rise in this patient population.

Additional figures, tables, Therapeutic options for psoriasis and relevant safety information for use during pregnancy, Management of psoriasis at specific sites, and Topical treatment and ultraviolet B phototherapy in the setting of comorbidities, and references available in our eBook (see inside front cover for access code).

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eFig. 8.1 Plaque psoriasis. Note the sharp demarcation and silvery scale.



eFig. 8.2 Plaque psoriasis. Well-demarcated pink plaque with scale. *Courtesy Julie V. Schaffer, MD.*







eFig. 8.3 Chronic plaque psoriasis. The elbow (**A**), extensor surfaces (**B**), and umbilicus (**C**) are common sites of involvement. *A, Courtesy Jean L. Bolognia, MD; B, Courtesy Julie V. Schaffer, MD; C, Courtesy Jeffrey P. Callen, MD.*



eFig. 8.4 Plaque psoriasis in an adolescent. Note the sharp demarcation and silvery scale. *Courtesy Julie V. Schaffer, MD.*



eFig. 8.6 Symmetric distribution of psoriatic plaques. Both small and large plaques have a symmetric distribution pattern. Note the active border at the proximal edge of the plaques on the calves.



eFig. 8.5 Chronic plaque psoriasis. Large pink plaques with scale on the legs. *Courtesy Edward Cowen, MD.*





eFig. 8.7 Psoriasis of the fingers. A Diffuse erythema with scale and digital swelling as well as severe nail involvement with yellow discoloration, thickening and crumbling. **B** Less pronounced erythema with scale and fissure formation; the possibility of repeated trauma (Koebner phenomenon) should be investigated. B, *Courtesy Kalman Watsky, MD.*



eFig. 8.8 Plantar psoriasis. Hyperkeratosis with minimal erythema.



eFig. 8.10 Plantar psoriasis. There can be diffuse involvement with erythema and scale as well as scattered scaly erythematous papules. The possibility of reactive arthritis should be considered.

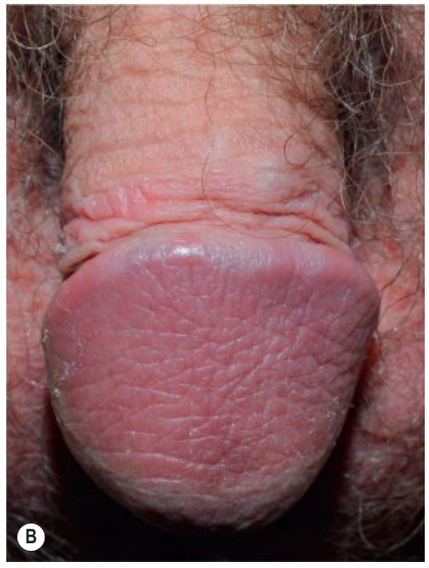


eFig. 8.9 Plantar psoriasis in a patient with skin phototype V. *Courtesy Kalman Watsky, MD.*



eFig. 8.11 Psoriasis of the genitalia. Erythematous plaques with scale on the penis and scrotum.





eFig. 8.12 Penile psoriasis. A, B Discrete papules and plaques of the glans and distal shaft. There is diffuse involvement of the glans in **B**. *Courtesy Kalman Watsky, MD.*





eFig. 8.13 Guttate lesions of psoriasis. Multiple dark pink papules with varying degrees of scale in addition to areas of confluence (**A**) and a large midline plaque (**B**). *A, Courtesy Kalman Watsky, MD.*



eFig. 8.14 Symmetric distribution of psoriatic plaques. Plaques of varying sizes have a symmetric distribution pattern.



eFig. 8.16 Linear psoriasis. Linear streak along the lines of Blaschko composed of several pink plaques with scale. *Courtesy Julie V. Schaffer, MD.*



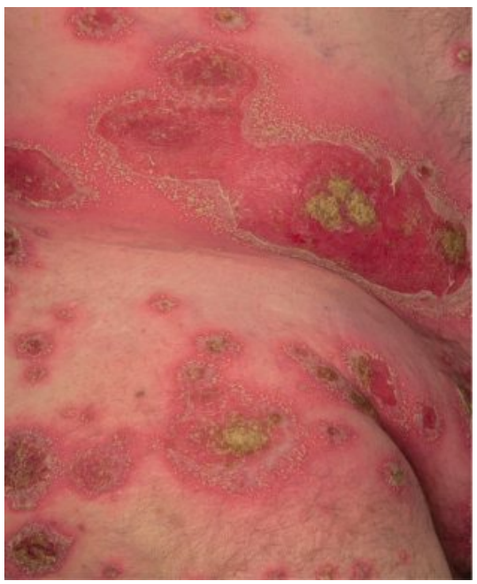
eFig. 8.15 Childhood psoriasis. The scalp is a common site of involvement and psoriasis is distinguished by its sharp demarcation. *Courtesy Julie V. Schaffer, MD.*



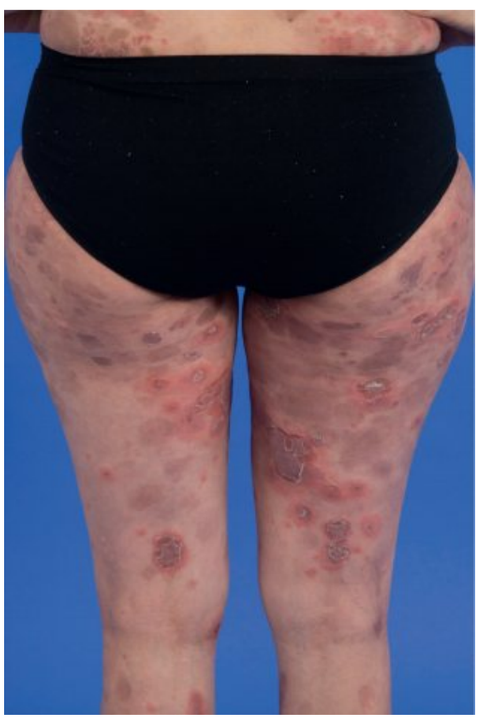
eFig. 8.17 Generalized pustular psoriasis. Advancing red border studded with pustules, some of which have formed "lakes of pus".



eFig. 8.18 Annular pustular psoriasis. Multiple annular inflammatory plaques studded with pustules. As the lesions enlarge, there can be central clearing and dry desquamation.



eFig. 8.19 Annular pustular psoriasis. Multiple annular inflammatory plaques studded with pustules. As the lesions enlarge, there can be central clearing, dry desquamation, and/or moist desquamation that resembles wet cigarette paper.



eFig. 8.20 Annular pustular psoriasis. Erythematous plaques with scale and an annular rim of pustules. *Courtesy Edward Cowen, MD.*



eFig. 8.21 "Localized" pattern of pustular psoriasis. The pustules are limited to pre-existing plaques of psoriasis.



eFig. 8.22 Acrodermatitis continua of Hallopeau. Erythema and scale of the distal digit, pustules within the nail bed, and partial shedding of the nail plate.



eFig. 8.23 Inverse psoriasis. A, B When psoriasis involves major body folds, scale is minimal to absent. However, the erythematous plaques are still well demarcated. **C** Discrete plaque involving the pubic region, inguinal folds, penis, and scrotum in addition to guttate lesions and an umbilical plaque. *A, Courtesy Jean L. Bolognia, MD; B, C, Courtesy Julie V. Schaffer, MD.*



eFig. 8.24 Inverse psoriasis. Shiny erythematous plaques of the inframammary folds that lack scale.



eFig. 8.25 Nail psoriasis. A Pitting and oil drop change (salmon patch). **B** Onycholysis with a rim of erythema proximally. *B, Courtesy Luis Requena, MD.*



eFig. 8.26 Sneddon–Wilkinson disease. Annular plaques with a peripheral rim of pustules. *Courtesy Edward Cowen, MD.*



eFig. 8.29 Bazex syndrome. Psoriasiform lesions on the thigh that may be misdiagnosed as psoriasis. Involvement of the helices and nasal tip point to this diagnosis. *Courtesy Kathleen C. Suozzi, MD.*



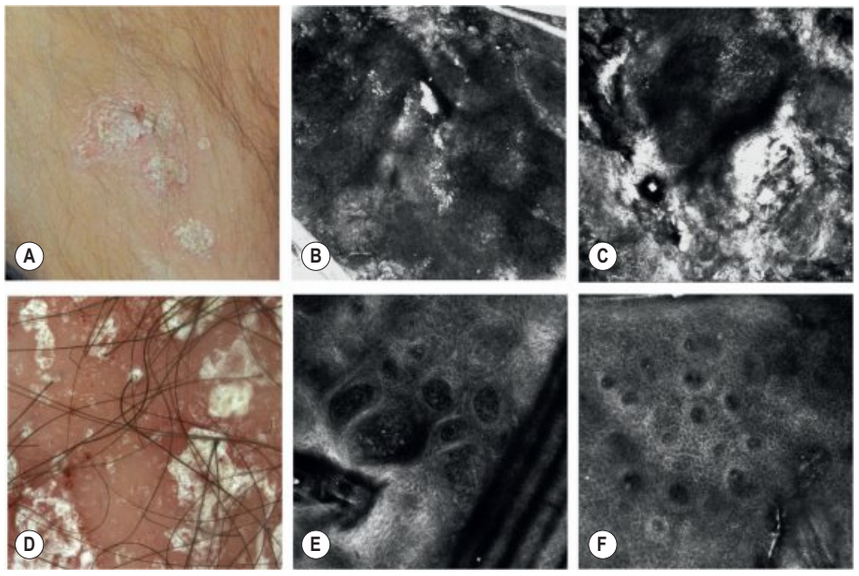
eFig. 8.27 Sneddon–Wilkinson disease. Discrete subcorneal pustule with an erythematous rim. *Courtesy Joyce Rico, MD.*



eFig. 8.30 Keratotic eczema of the central palm. The differential diagnosis includes psoriasis with the possibility of a Koebner phenomenon. *Courtesy Kalman Watsky, MD.*



eFig. 8.28 Pityriasis amiantacea. The thick scales that are adherent to the scalp hairs have been likened to asbestos. Psoriasis is a leading cause of pityriasis amiantacea. *Courtesy Jeffrey M. Cohen, MD*



eFig. 8.31 Reflectance confocal microscopy (RCM) of plaque psoriasis. A Discrete pink plaques with thick scale. **D** Diffuse dotted vessels by dermoscopy. RCM of the stratum corneum showing hyperkeratosis (**B**) with parakeratosis (**C**), then in deeper sections, dilated papillae with dilated looping vessels (**E**), and dense, dermal papillae (**F**). *Courtesy Marco Ardigo, MD, PhD and Chiara Franceschini, MD.*

THERAPEUTIC OPTIONS FOR PSORIASIS AND RELEVANT SAFETY INFORMATION FOR USE DURING PREGNANCY

(M)RHD: (Maximum) Recommended Human Dose
Green: Use or limited use of drug is safe in pregnancy.
Orange: Limited use is likely safe if medically necessary or is recommended for specific indications.
Yellow: Use with caution in pregnancy due to limited safety data.
Blue: Use with caution in pregnancy due to potential adverse fetal effects.
Red: Use is contraindicated in pregnancy.

Dermatologic medication	Implications for use during pregnancy	Former FDA category
Topical agents		
Vitamin D analogues (calcipotriene)	No well-controlled studies in pregnant women. Calcium imbalance, skeletal and bone ossification abnormalities seen in animal studies. **Safe** in pregnancy with topical application of doses <100 g/week.	C
Corticosteroids (hydrocortisone, triamcinolone, fluocinonide, clobetasol)	No well-controlled studies in pregnant women. No associations with malformations in large studies. Fetal growth restriction reported only with extensive use of potent topical corticosteroids in the third trimester and with extensive use (particularly >300 g). **Limited use is safe** in pregnancy. Mild-to-moderate potency corticosteroids are preferred over potent corticosteroids, but potent corticosteroids may be used for a limited period of time.	C
Calcineurin inhibitors (tacrolimus, pimecrolimus)	No well-controlled studies in pregnant women. Low systemic absorption with topical application. Teratogenic and embryotoxic (decreased weight and viability) effects with oral use and high maternal doses in animal studies. **Limited use is safe** with topical application in pregnancy.	C
Salicylic acid	No well-controlled studies in pregnant women. Teratogenic in animal studies. Low systemic absorption with topical application. **Limited use is safe** in pregnancy. Avoid occlusive dressings.	C
Coal tar	Limited data in pregnant women. No increased risk of teratogenicity in a series of pregnant women. Associated with spontaneous abortions and congenital disorders in animal studies. **Limited use is safe** in 2nd and 3rd trimester of pregnancy.	N/A
Anthralin/dithranol	Limited data in pregnant women. Lack of animal studies. **Not recommended** in pregnancy.	C
Roflumilast	Limited data in pregnant women. Lack of animal studies. Oral administration at doses higher than MRHD resulted in teratogenicity in animal studies. **Not recommended** in pregnancy until further studies are available.	N/A
Tapinarof	Limited data in pregnant women. No teratogenicity in animal studies. **Not recommended** in pregnancy until further studies are available.	N/A
Tazarotene	Teratogenic (retinoid malformations, spina bifida, hydrocephaly, heart defects) and embryo-toxic (reduced fetal body weight and skeletal ossification) in animal studies. Healthy deliveries have been reported with topical tazarotene use. **Contraindicated** in pregnancy; embryo-fetal toxicity warning.	X

eTable 8.1 Therapeutic options for psoriasis and relevant safety information for use during pregnancy.

Dermatologic medication	Implications for use during pregnancy	Former FDA category
Phototherapy		
Narrowband UVB/ broadband UVB	No associated fetal abnormalities or premature deliveries. Avoid overheating/burns. **Safe** in pregnancy.	N/A
Psoralen plus UVA (PUVA)	Psoralen has a theoretical risk of teratogenic and mutagenic effects on a fetus due to the inhibition of DNA synthesis and cell division. Animal studies are lacking. Few case reports have demonstrated premature labor and fetal abnormalities. **Avoid** in pregnancy.	C
Oral agents		
Cyclosporine	No well-controlled studies in pregnant women. Low risk for teratogenicity, but premature labor and infants who are small for gestational age have been reported. Embryo-fetal toxicity (reduced fetal weight, skeletal growth delay) seen at maternally toxic doses, but no teratogenic effects found in animal studies. **Use recommended** only for severe maternal disease.	C
Apremilast	No associated congenital defects or adverse fetal outcomes in human studies. Embryo-fetal toxicity (fetal loss and incomplete skeletal ossification) at higher than MRHD, but no teratogenicity in animal studies. **Use with caution** due to potential adverse fetal effects and limited safety data.	C
Deucravacitinib	No well-controlled studies (pregnant women were excluded from initial studies). No teratogenic effects in animal studies. Other JAK inhibitors have demonstrated adverse fetal effects at higher than MRHD in animal studies. **Use with caution** due to limited safety data.	N/A
Methotrexate	Associated with spontaneous abortions, congenital malformations (skull anomalies, facial dysmorphisms, central nervous system abnormalities, limb abnormalities, cardiac anomalies), and intellectual impairment with first trimester exposure. Associated with intrauterine growth restriction and functional abnormalities with second and third trimester exposure. Potential risk in fetus with preconception exposure. **Contraindicated** in pregnancy. Use effective contraception during and 6 months after final dose. If administered intramuscularly, use preservative-free formulations, when possible, to avoid benzyl alcohol toxicity.	X
Acitretin	Fetal exposure may lead to "retinoic acid embryopathy", which is characterized by malformations of the central nervous system (e.g. meningomyelocele, meningoencephalocele) and thymic structures as well as craniofacial and cardiac alterations. **Contraindicated** in pregnancy. Recommended to discontinue at least 3 years before conceiving a child.	X
Biologic agents		
TNF inhibitor (certolizumab)	Negligible placental transfer. No teratogenic effects or embryo-fetal toxicity in animal studies. **Likely safe** in pregnancy. Preferred choice biologic because pegylation of antibody prevents placental transfer.	N/A
Other TNF inhibitors (etanercept, infliximab, adalimumab)	No teratogenic effects or embryo-fetal toxicity in animal studies. **Use recommended** for severe, recalcitrant disease during pregnancy. Consider discontinuation after 30 weeks of gestation as monoclonal antibodies are actively transferred across placenta in third trimester. Avoid live vaccines in exposed infants for the first 6 months of life.	B
IL-17 & IL-17R inhibitors (secukinumab, ixekizumab, brodalumab)	Limited studies in pregnancy. No clear patterns of congenital abnormalities or spontaneous abortions were identified in pregnant women in post-marketing surveillance data for this class. In animal studies, no teratogenicity or embryo-fetal toxicity seen with secukinumab, but embryo-fetal toxicity seen at higher than MRHD with ixekizumab. **Use with caution** due to limited safety data. Consider discontinuation after 30 weeks of gestation as monoclonal antibodies are actively transferred across placenta in third trimester. Avoid live vaccines in exposed infants for the first 6 months of life.	B (secukinumab) N/A (ixekizumab, brodalumab)
IL-12/23 & IL-23 inhibitors (ustekinumab, guselkumab, risankizumab, tildrakizumab)	No adverse effects reported in infants exposed to ustekinumab during pregnancy. No teratogenicity, embryo-fetal toxicity or adverse developmental effects in animal studies seen with ustekinumab, but neonatal deaths at higher than MRHD found with guselkumab. **Use with caution** due to limited safety data. Consider discontinuation after 30 weeks of gestation as monoclonal antibodies are actively transferred across placenta in third trimester. Avoid live vaccines in exposed infants for the first 6 months of life.	B (ustekinumab) N/A (all others)

eTable 8.1 Therapeutic options for psoriasis and relevant safety information for use during pregnancy. Please see eTable 27.1 for additional information. IL, interleukin; R, receptor; TNF, tumor necrosis factor; UVB, ultraviolet B. *Adapted from Ferreira C, Azevedo A, Nogueira M, Torres T. Management of psoriasis in pregnancy – a review of the evidence to date. Drugs Context 2020;9:2019-11-6.*

MANAGEMENT OF PSORIASIS AT SPECIFIC SITES	
Specific sites	**Special considerations and practical treatments**
Scalp	• Remove scale with topical 10%–15% salicylic acid • Apply potent or ultrapotent corticosteroids in a lotion, gel, foam or shampoo formulation, either alone or in combination with calcipotriene
Face; groin, axilla, and other body folds	• First-line: mild topical corticosteroids • Second-line: topical calcineurin inhibitors, roflumilast cream, tapinarof cream, or tacalcitol/calcitriol in combination with a mild topical corticosteroid
Nail (see Ch. 71)	• Differentiate proximal versus distal nail unit pathology due to nail matrix versus nail bed pathology, respectively; consider coexisting onychomycosis • For distal nail unit pathology: vitamin D_3 analogues topically (limited evidence) • For proximal pathology: intralesional corticosteroids and/or systemic antipsoriatic therapies

eTable 8.2 Management of psoriasis at specific sites. These sites do improve with systemic therapies, but involvement of these sites alone is usually not a sufficient indication for a systemic therapy.

TOPICAL TREATMENT AND ULTRAVIOLET B PHOTOTHERAPY IN THE SETTING OF COMORBIDITIES			
	Topical therapies		**Phototherapy**
Comorbidity or special situation	**Corticosteroids**	**Other topical agents**	
Liver disease	√	√	√
Hepatitis B or C viral infection	√	√	√
Metabolic syndrome	√	√	√
Immunosuppression (e.g. HIV/AIDS)	√	√	√
Pregnancy	√ (mild–moderate strength)		√
History of internal malignancy (e.g. lymphoma, lung cancer)	√	√	√
History of frequent skin cancers	√	√ (vitamin D_3 analogues, retinoids)	
Latent tuberculosis	√	√	√

eTable 8.3 Topical treatment and ultraviolet B phototherapy in the setting of comorbidities. Indicated = √.

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9 Other Papulosquamous Disorders

Bernard Cribier, Gary S. Wood and George T. Reizner

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SMALL PLAQUE PARAPSORIASIS

Synonyms: ■ Chronic superficial [scaly] dermatitis ■ Digitate dermatosis

Key features

- Chronic, asymptomatic, erythematous scaly patches
- Lesions are generally <5 cm in diameter or digitate
- Histologically, mild, nonspecific spongiotic dermatitis with parakeratosis is seen
- There is a predominance of $CD4^+$ T cells in the lymphocytic infiltrate
- A dominant T cell clonality is demonstrable in some cases

Introduction and History

Since the introduction of the term "parapsoriasis" by Brocq in 1902[1], there has been much confusion and debate regarding this controversial topic[2]. For example, the term "parapsoriasis en gouttes" is no longer used as it specifically refers to the entity pityriasis lichenoides. In addition, it can be difficult to clearly define the term "parapsoriasis en plaques", as the lesions vary in size from small to large and are often patches rather than plaques. Since the 1990s, many authors have proposed that *large plaque parapsoriasis* represents either the early patch stage of mycosis fungoides (MF), which has an indolent course and excellent prognosis, or is a precursor of MF[2]. Because the vast majority of patients have a benign clinical presentation and course, *small plaque parapsoriasis* is considered a separate entity[3]. Reports of patients with small plaque parapsoriasis progressing to MF are quite rare[4].

Epidemiology

Small plaque parapsoriasis is more common in middle-aged and elderly individuals, but it may also occur in children. Parapsoriasis peaks during the fifth decade of life and occurs in all racial groups and geographic regions. There is a male predominance (male : female ratio ~3 : 1).

Pathogenesis

The etiology of small plaque parapsoriasis is unknown. It is characterized by sparse lymphoid infiltrates within the superficial dermis (with variable exocytosis into the epidermis) that are composed primarily of $CD4^+$ T cells[5]. In some cases of small plaque parapsoriasis, T cell clonality has been demonstrated within the cutaneous infiltrate[5,6], and a clonal population may also be detected in the blood[7]. However, determining the significance of these findings can prove difficult. In most patients, molecular genetic studies demonstrate an oligoclonal or pseudo-monoclonal pattern[5].

Clinical Features

Despite inclusion of the word "plaque" in the terminology, small plaque parapsoriasis is a disease composed of patches with fine scales. The lesions are chronic and generally asymptomatic or mildly pruritic. They may wax and wane early on during their clinical course, but they typically become persistent and can slowly progress to become more extensive. Some cases regress fully, either spontaneously or after therapy, but this may require several months or years. Lesions can be widespread on the trunk and extremities or more limited in their distribution. In the latter instance, they often favor more sun-protected sites.

Small plaque parapsoriasis typically presents as round to oval patches that are generally <5 cm in diameter (Fig. 9.1A). They are variably erythematous (but often less intense than psoriasis) and covered with a fine scale. Some have a yellow hue, hence the historic term "xanthoerythrodermia perstans"[1]. A distinct and perhaps the most typical presentation is "digitate dermatosis", which presents as elongated, finger-like patches symmetrically distributed on the flanks[3] (Fig. 9.1B). These lesions are an exception to the 5-cm rule in that they may measure 10 cm or more along their long axis. Progression to MF is very rare, with <20 cases reported to date in the literature[4,5].

Pathology

Patches of small plaque parapsoriasis exhibit a mild, nonspecific spongiotic dermatitis with focal parakeratosis. Exocytosis of lymphocytes is variable but usually present. There are neither Pautrier microabscesses nor atypical lymphocytes, but haloed lymphocytes within the basal layer can be seen[5].

Differential Diagnosis

The diagnosis of small plaque parapsoriasis is based on clinicopathologic correlation, with other tests of minimal value. It is distinguished from large plaque parapsoriasis primarily on the basis of clinical features. The principal entities in the differential diagnosis are listed in Table 9.1.

Pityriasis rosea is distinguished from small plaque parapsoriasis by the presence of a herald patch and spontaneous resolution within a few months. Psoriasis and secondary syphilis are excluded on the basis of clinicopathologic and serologic features. Patients with pityriasis

PRINCIPAL DIFFERENTIAL DIAGNOSIS OF SMALL PLAQUE PARAPSORIASIS AND LARGE PLAQUE PARAPSORIASIS/ EARLY STAGE MYCOSIS FUNGOIDES

Small plaque parapsoriasis	Large plaque parapsoriasis/ early stage mycosis fungoides*
Pityriasis rosea	Drug eruption, in particular mycosis fungoides-like
Drug eruption, in particular pityriasis rosea-like	Psoriasis
Pityriasis lichenoides chronica	Poikilodermatous autoimmune connective tissue disease (e.g. dermatomyositis)
Psoriasis, including guttate	Poikilodermatous genodermatoses (see Table 63.9)
Mycosis fungoides	Chronic radiodermatitis
Secondary syphilis	
Nummular dermatitis	

*While some authors believe that large plaque parapsoriasis represents an entity distinct from mycosis fungoides (MF) or a potential precursor of MF, many authorities in the field of cutaneous lymphomas consider it to be an early manifestation of MF.

Table 9.1 Principal differential diagnosis of small plaque parapsoriasis and large plaque parapsoriasis/early stage mycosis fungoides.



Fig. 9.1 Small plaque parapsoriasis. A Small (<5 cm), dull pink, slightly scaly patches on the trunk. **B** Digitate dermatosis with elongated finger-like lesions on the flank that are pink–brown to yellow–brown in color. *A, Courtesy Lorenzo Cerroni, MD.*

THERAPEUTIC LADDER FOR SMALL PLAQUE PARAPSORIASIS AND LARGE PLAQUE PARAPSORIASIS/ EARLY STAGE MYCOSIS FUNGOIDES	
Small plaque parapsoriasis	**Large plaque parapsoriasis/ early stage mycosis fungoides* (see Ch. 120)**
• Topical corticosteroids, mid- to high-potency (2) • Sunlight (2) • Ultraviolet B (UVB) phototherapy – broadband or narrowband (2) • PUVA (psoralen plus UVA) phototherapy (2) • UVA1 phototherapy (2) • Antihistamines†	• Topical corticosteroids, high-potency (2) • Ultraviolet B (UVB) phototherapy – broadband or narrowband (2) • PUVA (psoralen plus UVA) phototherapy (2) • UVA1 phototherapy (2) • Topical bexarotene (2) • Topical imiquimod (3) • Topical nitrogen mustard (3) • Antihistamines†
*While some authors believe that large plaque parapsoriasis represents an entity distinct from mycosis fungoides (MF) or a potential precursor of MF, many authorities in the field of cutaneous lymphomas consider it to be an early manifestation of MF. †If pruritus is present.	

Table 9.2 Therapeutic ladder for small plaque parapsoriasis and large plaque parapsoriasis/early stage mycosis fungoides. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

lichenoides, acute and chronic, have lesions that are smaller and more widely distributed than do patients with small plaque parapsoriasis. Drug eruptions resembling pityriasis rosea or MF need to be considered and excluded.

Treatment

All therapeutic approaches are based primarily on uncontrolled case series, case reports, or anecdotal evidence (Table 9.2). Patients with small plaque parapsoriasis should be reassured that the risk of developing MF is extremely low. Patients may be followed without treatment if they prefer. Standard therapy includes topical corticosteroids and narrowband ultraviolet B (NB-UVB) therapy[8,9]. Clinical improvement is usually observed, but recurrences are common[9]. The role of phototherapy in terms of preventing progression to MF is uncertain[10].

LARGE PLAQUE PARAPSORIASIS

The exact nosology of large plaque parapsoriasis is still debated. While some authors believe that it represents an entity distinct from MF or a potential precursor of MF (see Ch. 120), many authorities in the field of cutaneous lymphomas consider it to be an early stage of MF. The clinical morphology (erythematous patches) and location (sun-protected sites) are similar to those of early MF, and the histopathologic features of untreated lesions can be indistinguishable from those of MF. The treatment options are the same as in early lesions of MF, and as in stage 1 A MF, a minority of patients progress to life-threatening disease and as a group they have the same survival as the general population. It should be emphasized that a diagnosis of early MF should be based on convincing clinicopathologic findings, eventually corroborated by molecular analysis of T cell receptor gene rearrangements.

PITYRIASIS LICHENOIDES

Synonyms: ■ Pityriasis lichenoides et varioliformis acuta (PLEVA) ■ Mucha–Habermann disease (PLEVA) ■ Pityriasis lichenoides chronica (PLC) ■ Guttate parapsoriasis (PLC)

Key features

- Pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC) are two ends of a disease spectrum
- Both entities are characterized by recurrent crops of spontaneously regressing erythematous papules
- Lesions of PLEVA are crusted and occasionally vesiculopustular, whereas in PLC they are scaly
- Individual patients may show intermediate or mixed lesions
- Histologically, an interface dermatitis with necrotic keratinocytes is seen
- The infiltrate is predominantly T cells that are often monoclonal

Introduction

Pityriasis lichenoides is an uncommon disorder that encompasses pityriasis lichenoides et varioliformis acuta (PLEVA), the febrile ulceronecrotic Mucha–Habermann disease (FUMHD) variant of PLEVA, and pityriasis lichenoides chronica (PLC). These acute and chronic forms of pityriasis lichenoides exist on a disease spectrum with variable presentations that can pose diagnostic and therapeutic challenges[11,12]. They are papular, often clonal T cell disorders that may rarely be associated with MF[13].

History

The two major variants of pityriasis lichenoides – PLEVA and PLC – were described as the 19th century ended and the 20th century began[11]. Pityriasis lichenoides was included in Brocq's 1902 treatise[1] on a group of chronic, idiopathic dermatoses that he termed "parapsoriasis". Nowadays, however, it is considered a separate entity.

Epidemiology

Pityriasis lichenoides is more prevalent in the pediatric population[12], but it affects patients in all age groups, races, and geographic regions. There is a male predominance.

Pathogenesis

The etiology of pityriasis lichenoides is unknown. It has been postulated to be a response to foreign antigens such as infectious agents and drugs. There is some evidence to support PLEVA being associated with viral infections, especially varicella–zoster virus[14], and in a few reports, HIV[15], parvovirus B19[16], and Epstein–Barr virus. Additional reports have described its association with medications (e.g. estrogen–progesterone, infliximab, adalimumab, statins), radiocontrast dye, and vaccines[17,18].

Both PLEVA and PLC contain lesional T cell infiltrates, sometimes with dominant T cell clonality. The concept of pityriasis lichenoides as a T cell lymphoproliferative disorder may help to explain its occasional association with other lymphoproliferative disorders such as MF[13]. In addition, this would account for the variants of pityriasis lichenoides that have numerous $CD30^+$ cells[19] or γδ T cells[20] as well as the subgroups that have been referred to as atypical pityriasis lichenoides[21] and lymphomatoid pityriasis lichenoides[22]. Because differentiation from T cell lymphomas is sometimes difficult, patients with pityriasis lichenoides and an aberrant T cell phenotype should undergo longitudinal evaluation, with the final diagnosis based upon repeated clinicopathologic correlation, including phenotypic and molecular studies of T cell clonality[21].

Clinical Features

Pityriasis lichenoides presents as recurrent crops of spontaneously regressing erythematous to purpuric papules (Fig. 9.2). The acute form (PLEVA) and the chronic form (PLC) exist on a disease continuum. Many patients have intermediate or mixed manifestations, either serially or concurrently. In patients with PLEVA, individual lesions develop crusts, ulcers, and occasionally vesicles or pustules, which



Fig. 9.2 Clinical spectrum of pityriasis lichenoides. A–C In the acute form (PLEVA), widespread erythematous papules and papulovesicles are admixed with crusted lesions; sometimes, there can be an ulcerative component (**C**). **D** Individuals with the chronic form (PLC) develop multiple dull red–brown papules, some of which have scale and may be hypopigmented. **E** In some patients the majority of lesions are characteristic of one end of the spectrum, e.g. PLEVA, but with scattered lesions suggestive of PLC. **F** Rarely, a more severe potentially life-threatening form of PLEVA, termed febrile ulceronecrotic Mucha–Habermann disease (FUMHD), may occur *de novo* or in the setting of pre-existing PLEVA. *A, D, Courtesy Julie V. Schaffer, MD; B, Courtesy Thomas Schwarz, MD; C, F, Courtesy Lorenzo Cerroni, MD.*

may heal with varioliform scars if dermal damage is extensive. Lesions are usually asymptomatic and typically resolve within weeks. Disease manifestations are confined to the skin, except rarely, when acute lesions are associated with malaise, fever, lymphadenopathy, arthritis, and/or bacteremia. The term *febrile ulceronecrotic Mucha–Habermann disease (FUMHD)* has been used to refer to such severe variants in which large, confluent necrotic skin lesions (see Fig. 9.2F) as well as mucosal, gastrointestinal, and pulmonary involvement can be observed[23,24]. In the latter group, an associated mortality rate of up to 15% has been reported[23].

In PLC, the papules are erythematous to red–brown and scaly (see Fig. 9.2D). They pursue a more indolent course, regressing over weeks to months. When these lesions subside, there may be residual hypopigmented macules; the latter are more obvious in individuals with darker skin phototypes and may be the presenting complaint (Fig. 9.3). Pityriasis lichenoides can resolve spontaneously after weeks to months or it may pursue a chronic relapsing course, sometimes interspersed with long periods of remission. Some studies have suggested that the distribution of skin lesions is more important than their acute or chronic nature in predicting outcome[25]. The average course of disease was shorter in patients with a diffuse distribution, while those with a peripheral distribution had the longest clinical course. Compared to adults, children tend to have a more persistent course and widespread distribution of lesions[26].



Fig. 9.3 Chronic form of pityriasis lichenoides (PLC) presenting as macules of hypopigmentation. This is more common in individuals with darker skin phototypes. *Courtesy Antonio Torrelo, MD.*

Pathology

Pityriasis lichenoides exhibits a superficial perivascular interface dermatitis in all cases (Fig. 9.4). Those lesions at the acute end of the spectrum contain a denser infiltrate that may be top-heavy and wedge-shaped. There is commonly an infiltration of lymphocytes into the adnexal epithelia, both follicular and eccrine[27]. Lymphocytes predominate in the infiltrate, although neutrophils may be admixed. The epidermis shows parakeratosis and evidence of damage ranging from edema to extensive epidermal necrosis in well-developed lesions. Extravasation of erythrocytes is a frequent finding. While a perivascular lymphocytic infiltrate is a constant feature, a true lymphocytic vasculitis with fibrinoid necrosis of blood vessels is uncommon, occasionally occurring in PLEVA. All of these changes are blunted in the more chronic skin lesions, where the principal microscopic features include parakeratosis and a milder interface lymphocytic infiltrate that is accompanied by focal keratinocyte necrosis and mild erythrocyte extravasation.

Lymphoid atypia is not a standard feature of pityriasis lichenoides. What has been referred to as atypical pityriasis lichenoides was defined by conventional clinical and histologic features but with an aberrant T cell phenotype[21]. Some pathologists allow occasional atypical lymphocytes or $CD30^+$ lymphocytes[19], whereas others regard this as a sign of lymphomatoid papulosis[22]. Patients with small papules that resemble pityriasis lichenoides clinically but have Pautrier microabscesses histologically were described as having "pityriasis lichenoides-like mycosis fungoides"[28], but no patients in that series evolved into typical MF. Controversies regarding T cell lymphoproliferative disorders, however, still remain.

Differential Diagnosis

The diagnosis of pityriasis lichenoides is made by the correlation of clinical features with lesional histopathology. The principal differential diagnostic considerations for pityriasis lichenoides are listed in Table 9.3. For the more acute form (PLEVA), the primary entities in the clinical and histopathologic differential diagnosis include lymphomatoid papulosis, arthropod reactions, cutaneous small vessel vasculitis, varicella, and drug eruptions[29]. For the chronic form (PLC), the principal differential diagnosis includes guttate psoriasis, lichen planus (exanthematous), pityriasis rosea, secondary syphilis, lymphomatoid papulosis, drug eruptions, and papular dermatitis. All of these alternative diagnoses can usually be excluded on the basis of key historical, clinical, pathologic, and laboratory findings. More than one biopsy specimen, T cell immunophenotyping, and molecular studies of T cell clonality may be required to achieve clinicopathologic correlation. PCR, direct fluorescent antibody (DFA), and serologic testing as well as immunohistochemical staining are helpful in excluding varicella and syphilis.

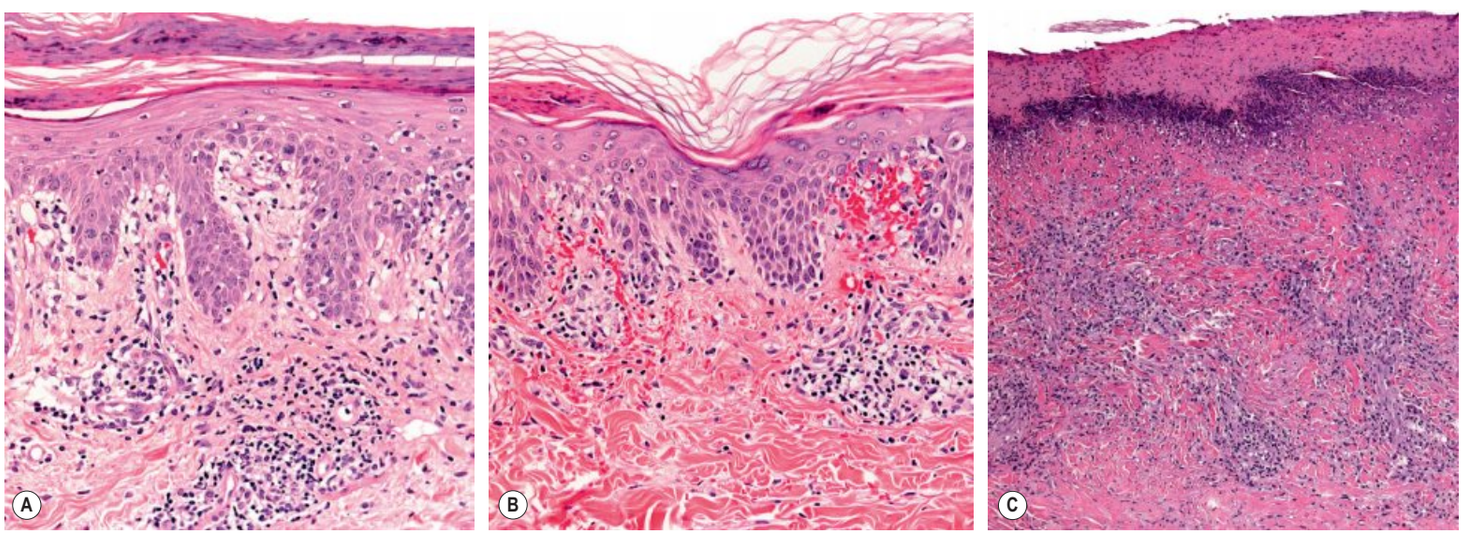


Fig. 9.4 Pityriasis lichenoides – histopathologic features. A In the chronic form (PLC), parakeratosis may be more prominent than in the acute form, but the epidermal destruction is less intense. **B** In the acute form (PLEVA), scattered necrotic keratinocytes are seen in addition to parakeratosis. The perivascular lymphoid infiltrates in the dermis are accompanied by extravasated erythrocytes, which are even present within the epidermis. As with the clinical presentations, there is a continuous histologic spectrum. **C** In the ulceronecrotic form, there is complete ulceration covered by crust. An intense lymphocytic infiltrate is seen within the dermis. *Courtesy Lorenzo Cerroni, MD.*

DIFFERENTIAL DIAGNOSIS OF PITYRIASIS LICHENOIDES	
Acute form (PLEVA)	**Chronic form (PLC)**
Lymphomatoid papulosis	Small plaque parapsoriasis
Cutaneous small vessel vasculitis	Guttate psoriasis
Varicella, enteroviral exanthems	Lichen planus (exanthematous)
Arthropod reactions	Pityriasis rosea
Erythema multiforme	Secondary syphilis
Lichenoid drug eruption	Lymphomatoid papulosis
PLEVA-like drug eruption (e.g. immune checkpoint inhibitors)	Papular dermatitis
Folliculitis	Lichenoid drug eruption
Dermatitis herpetiformis	PLC-like drug eruption (e.g. immune checkpoint inhibitors)
	When hypopigmented, extrafacial pityriasis alba

Table 9.3 Differential diagnosis of pityriasis lichenoides.

THERAPEUTIC LADDER FOR PITYRIASIS LICHENOIDES
Topical corticosteroids (2)
Topical calcineurin inhibitors (2)
Oral erythromycin (2)
Oral tetracyclines (2)
Oral azithromycin (3)
Ultraviolet B (UVB) phototherapy – broadband or narrowband (1)
PUVA (psoralen plus UVA) phototherapy (1)
Methotrexate (2)
Oral retinoids (3)
Dapsone (3)
Special treatments (3):
Antihistamines*
Systemic antibiotics†
Systemic corticosteroids‡, IVIg‡, cyclosporine‡ or TNF inhibitors‡
For recalcitrant FUMHD, JAK inhibitors or IL-6 inhibitors
*If there is pruritus.
†If there is secondary infection.
‡If there is fever, arthritis, or other systemic findings.

Table 9.4 Therapeutic ladder for pityriasis lichenoides. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

Treatment

All treatments for pityriasis lichenoides are based primarily on uncontrolled case series, case reports, or anecdotes (Table 9.4)[30]. If a drug association is suspected, trial discontinuance of the suspected agent is warranted. First-line therapy includes topical corticosteroids (limited efficacy), tetracyclines, macrolide antibiotics (e.g. erythromycin, azithromycin) and various types of phototherapy (most effective; e.g. narrowband UVB)[31]. Oral antibiotics are used for their anti-inflammatory effects, with macrolides favored in younger children. A several-month course is often required, followed by a gradual taper.

More fulminant cases may require low-dose weekly methotrexate. Those rare cases associated with fever and arthritis may benefit from systemic corticosteroids, IVIg or cyclosporine, once infection has been excluded. There are also reports of the efficacy of TNF inhibitors.

PITYRIASIS RUBRA PILARIS

Synonyms: ■ Lichen ruber pilaris ■ Devergie disease ■ Lichen ruber acuminatus

Key features

- Follicular papules with an erythematous base are a characteristic finding, including on the proximal dorsal fingers
- There is a coalescence of orange–red plaques, but with obvious islands of sparing
- An orange–red waxy keratoderma of the palms and soles is often seen
- Of the six types described, the classic adult form is the most common
- The classic types (adult and juvenile) typically resolve within 3–5 years
- Type V, the atypical juvenile form, is frequently due to *CARD14* mutations
- Histologically, there is alternating ortho- and parakeratosis, both vertically and horizontally

History

Pityriasis rubra pilaris (PRP) was first described in 1835 by Claudius Tarral as a variant of psoriasis and it was given several names during the 19th century. Devergie called it "pityriasis pilaris", and later Besnier recommended the name "pityriasis rubra pilaris" in the first comprehensive illustrated article on the disease.

Epidemiology

Although PRP shows no sex bias, affecting both men and women equally, ethnic variations may exist. The incidence of this uncommon disease has two major peaks, one during the first and second decades and the second during the sixth decade[32].

Most cases are acquired, but there are familial forms, primarily autosomal dominant and less frequently autosomal recessive. The dominantly inherited form of PRP is associated with heterozygous gain-of-function mutations in *CARD14*, which encodes the caspase recruitment domain family member 14[33]. Except for the latter group of patients and those with the non-classic forms, PRP appears to be a self-limited disease process, resolving within 3 to 5 years in almost all cases.

Pathogenesis

Excluding inherited PRP due to *CARD14* mutations, infections, UV exposure, and various minor traumas to the skin have been reported to precede the onset of PRP. Autoimmunity (e.g. associated thyroid disease) or an abnormal immunologic response to particular antigens may play a role, as in patients with HIV-associated PRP (type VI). Paraneoplastic PRP has also been described in individuals with solid-organ malignancies such as renal cell, bronchogenic, and hepatocellular[34]. Rarely, drugs or vaccines have been implicated in triggering PRP, including infliximab, tyrosine kinase inhibitors (e.g. ponatinib, imatinib), and antivirals (e.g. sofosbuvir)[35].

Clinical Features

The clinical features of classic PRP are helpful in making the diagnosis. Follicular hyperkeratosis on an erythematous base is a key finding (Fig. 9.5). This results in rough papules, especially on the dorsal aspect of the proximal fingers, reminiscent of a nutmeg grater. These papules are also seen on the trunk and extremities, and they can coalesce to form large salmon-colored to orange–red plaques with distinctive "islands of sparing". The plaques can then progress to an erythrodermic appearance with varying degrees of exfoliation (see Figs. 10.7 & 10.8). The palms and soles are commonly involved with a distinctive orange–red waxy keratoderma (Fig. 9.6). Erythema with a fine diffuse scale is often seen on the scalp. Of note, scalp disease that mimics seborrheic dermatitis is a common initial clinical manifestation of adult PRP, and rapid progression to erythroderma can occur over several weeks.



Fig. 9.5 Pityriasis rubra pilaris. A Orange–red follicular papules with coalescence into large scaly plaques, in addition to islands of sparing; follicular hyperkeratosis is often easier to appreciate within the relatively spared islands. **B** On the dorsal aspects of the digits, clustered keratotic follicular papules can resemble a "nutmeg grater". **C** The islands of sparing may be sharply demarcated; note the salmon color of the plaques. Both photoaggravated and phototriggered forms of PRP exist. Patients can eventually become diffusely erythrodermic, but follicular accentuation of the scale (**D**) and small islands of sparing (**E**) can provide clues. *B, Courtesy Antonio Torrelo, MD; C, Used with permission of the Mayo Foundation for Medical Education and Research.*

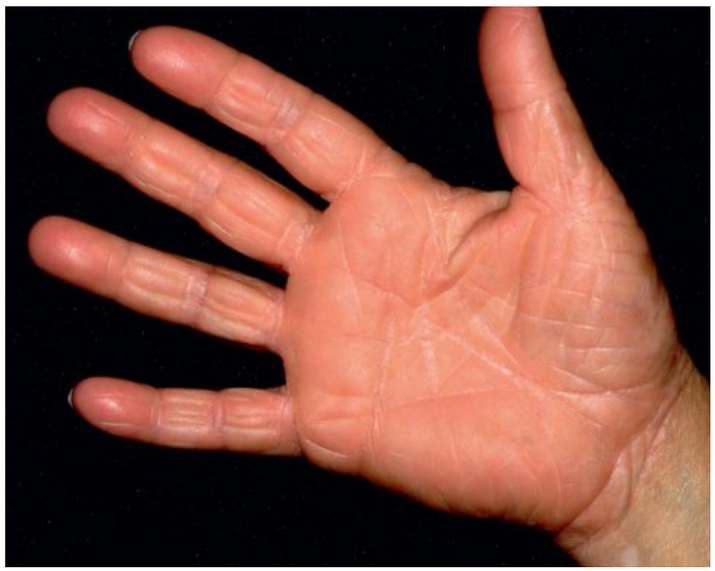


Fig. 9.6 Pityriasis rubra pilaris. The orange–red color of the skin, including that of the palmar keratoderma, aids in the clinical diagnosis. *Courtesy Luis Requena, MD.*

Nail involvement is characterized by a thickened plate with a yellow–brown discoloration and subungual debris. The mucous membranes are rarely involved, but they may show features similar to oral lichen planus.

The most common form of PRP (type I) usually begins in the head and neck region and then progressively advances caudally. Pruritus and burning have been reported in 20% of patients with PRP. Although less common than in atopic dermatitis or Darier disease, Kaposi varicelliform eruption can occur in patients with PRP. As with other forms of erythroderma (see Ch. 10), eruptive seborrheic keratoses may appear. Both photoaggravated and phototriggered forms of PRP can also occur (see Fig. 9.5C). Resolving PRP may have a clinical appearance that resembles erythema gyratum repens (see Fig. 19.9).

The classification of the different forms of PRP is based upon age, duration, and type of cutaneous involvement (Fig. 9.7)[36]. Type I (classic adult) PRP is the most common form and is typically self-limited, clearing within 3 years in 80% of patients. Type II differs from type I by a palmoplantar keratoderma with a coarse and lamellated scale, a more ichthyosiform scaling on the lower extremities, occasional alopecia, and a protracted clinical course.

PRP types III–V are seen in children and adolescents. Type III, the classic juvenile form, closely resembles the classic adult form and

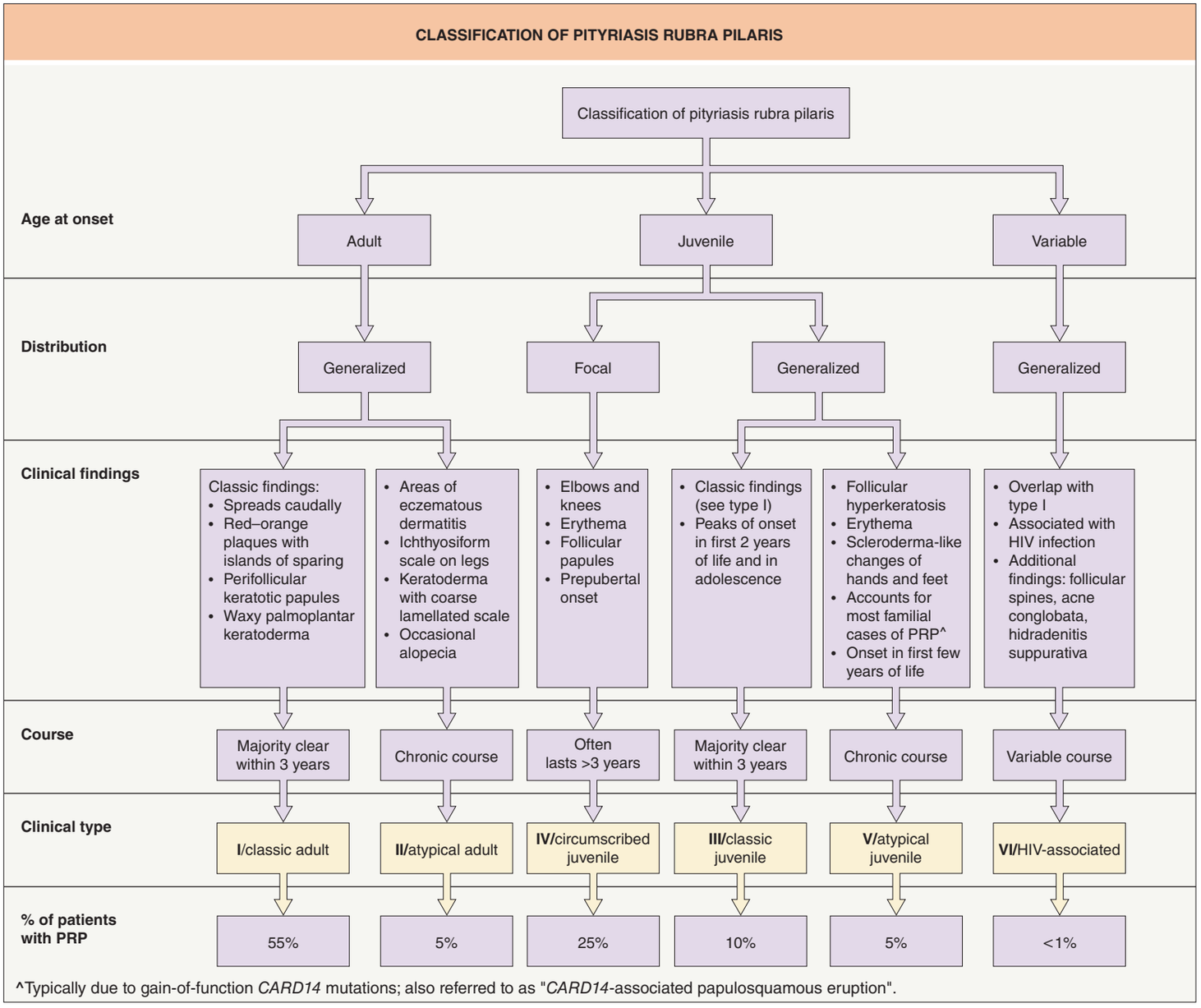


Fig. 9.7 Classification of pityriasis rubra pilaris (PRP). Type VI PRP is also referred to as HIV-associated follicular syndrome.

also typically clears within 3 years. Type IV (circumscribed) is the most common of the juvenile forms, and its focal nature sets it apart from the other clinical presentations (Fig. 9.8). Type V, the atypical juvenile form, is frequently due to *CARD14* mutations; it has features similar to type II but with more ichthyosiform scaling and a chronic course (see Fig. 8.9). Patients with *CARD14* mutations tend to present with clinical features observed in both PRP (often resembling type V PRP but sometimes with classic "islands of sparing") and psoriasis. These patients have been referred to as having "*CARD14*-associated papulosquamous eruption (CAPE)". In addition to a family history of PRP or psoriasis, characteristic features of CAPE include an early age of onset; prominent involvement of the cheeks, chin, and ears; involvement of the palms and soles; and a chronic course with a variable response to conventional treatments[33]. Gain-of-function *CARD14* mutations have rarely been detected in other types of PRP[37].

PRP type VI is associated with HIV infection, and while it often fails to respond to conventional therapy for PRP, it may improve with antiretroviral therapy. These patients can have erythematous follicular papules and keratotic spines as well as nodulocystic lesions of acne conglobata and hidradenitis suppurativa. In addition, coalescence of inflammatory plaques into an erythroderma may occur, as in PRP type I.

Pathology

Psoriasiform dermatitis with irregular hyperkeratosis and alternating vertical and horizontal ortho- and parakeratosis ("checkerboard pattern") is distinctive (Fig. 9.9A). The hair follicles are dilated and filled with a keratinous plug, while the "shoulder" of stratum corneum surrounding the follicular opening frequently shows parakeratosis (Fig. 9.9B). The interfollicular epidermis often exhibits hypergranulosis as well as thick, shortened rete pegs. A sparse lymphohistiocytic perivascular infiltrate is seen in the underlying dermis. Acantholysis and focal acantholytic dyskeratosis within the epidermis have also been described and can be helpful in distinguishing PRP from psoriasis. In CAPE, histopathologic features are more similar to PRP than to psoriasis, including alternating checkerboard parakeratosis and orthokeratosis and follicular plugging[38].

Differential Diagnosis

The major entity in the differential diagnosis is psoriasis. The distinctive orange–red palmoplantar keratoderma plus the keratotic follicular papules with a nutmeg grater appearance, the classic islands of sparing of the trunk, and a finer scale (see Fig. 10.7), help differentiate PRP from psoriasis. The presence of oil-drop changes, small pits, and marginal

onycholysis of the nails favor psoriasis. Microscopically, acantholysis and focal acantholytic dyskeratosis, if present, are especially useful in diagnosing PRP rather than psoriasis. A thickened granular cell layer, short thicker rete pegs, limited vascular dilation in the dermal papillae, and the absence of both neutrophilic migration towards the epidermis and Munro microabscesses further help distinguish PRP from psoriasis. Histopathologic features of PRP may be seen in patients with what has been described as facial discoid dermatosis.

Early PRP of the scalp can mimic seborrheic dermatitis. The relative recalcitrant nature of scalp PRP may serve as a clue to the diagnosis. A PRP-like eruption can be seen in patients with dermatomyositis (Wong type) and cutaneous T cell lymphoma, as can erythema and scaling of the scalp. Children with acute-onset PRP may be misdiagnosed as having Kawasaki disease, and, occasionally, PRP is confused with erythrokeratodermia variabilis et progressiva or ichthyosis with confetti.

Keratotic follicular papules are also seen in keratosis pilaris and lichen spinulosus, but the lesions are more limited in scope and the other manifestations of PRP are absent. The various disorders that can present as an erythroderma are discussed in Chapter 10.



Fig. 9.8 Circumscribed juvenile pityriasis rubra pilaris (type IV). Symmetric pink plaques with scale are present on the dorsal aspect of the fingers, metacarpophalangeal joints, and knees. There are follicular keratotic papules on the knees. *Courtesy Antonio Torrelo, MD.*

Treatment

Therapy for PRP is primarily empiric, based upon case series and case reports, and often involves a combination of topical and systemic therapies. *Topical therapies* alone are typically insufficient for most patients with PRP, unless there is limited disease. Topical high-potency corticosteroids, tar, calcipotriene (calcipotriol), keratolytics (e.g. urea, salicyclic acid), and retinoids (e.g. tazarotene, tretinoin) can be used as adjuncts to systemic therapy.

Systemic retinoids represent a first-line treatment for PRP in both adults and children; an excellent response is seen in >40% of patients[39]. Isotretinoin (0.5 to 1 mg/kg/day) and acitretin (0.5 mg/kg/day) are the two most commonly prescribed retinoids, with scattered reports of some efficacy with alitretinoin. There are reports of the occasional use of higher doses of isotretinoin, but in the opinion of the authors, this is not recommended. Significant clearing is usually seen within 3–6 months of instituting therapy.

Methotrexate (5–25 mg/week) is considered second-line therapy for PRP, in particular for patients who have failed or cannot tolerate systemic retinoids. A response rate of >90% and complete clearance in ~40% of patients has been observed[40]. As with retinoids, clinical responses are usually seen within 3–6 months. Hepatotoxicity and myelosuppression are well-known potential side effects (see Ch. 130).

In severe cases of PRP, a combination of methotrexate (5–25 mg/week) plus a systemic retinoid (acitretin) has been utilized. Both agents can be given at the onset of therapy, or the second medication can be added if the response to the first is inadequate. In this situation, an increased risk for hepatotoxicity must be kept in mind.

Based upon case reports and small case series, TNF inhibitors (e.g. etanercept, infliximab, adalimumab), secukinumab, and ustekinumab have led to improvement of PRP[41]. A marked to complete response was noted in 50%–80% of patients. In a small series of patients, ixekizumab was reported to be moderately successful[42]. Ustekinumab, often at higher doses, has been reported as beneficial in patients with CAPE. Due to limited data as well as the natural history of PRP, precise efficacy is difficult to assess.

Other anecdotal potential therapies include systemic immunosuppressives (e.g. azathioprine, prednisone, cyclosporine), apremilast, and IVIg, with variable results observed. Although UV light therapy runs the risk of exacerbating the disease, there are some reports of success with narrowband UVB, UVA1, or PUVA in combination with an oral retinoid[36,43].

Less toxic regimens are recommended for the classic juvenile form of PRP, given the high likelihood of spontaneous remission and the potential long-term effects of aggressive systemic therapies.

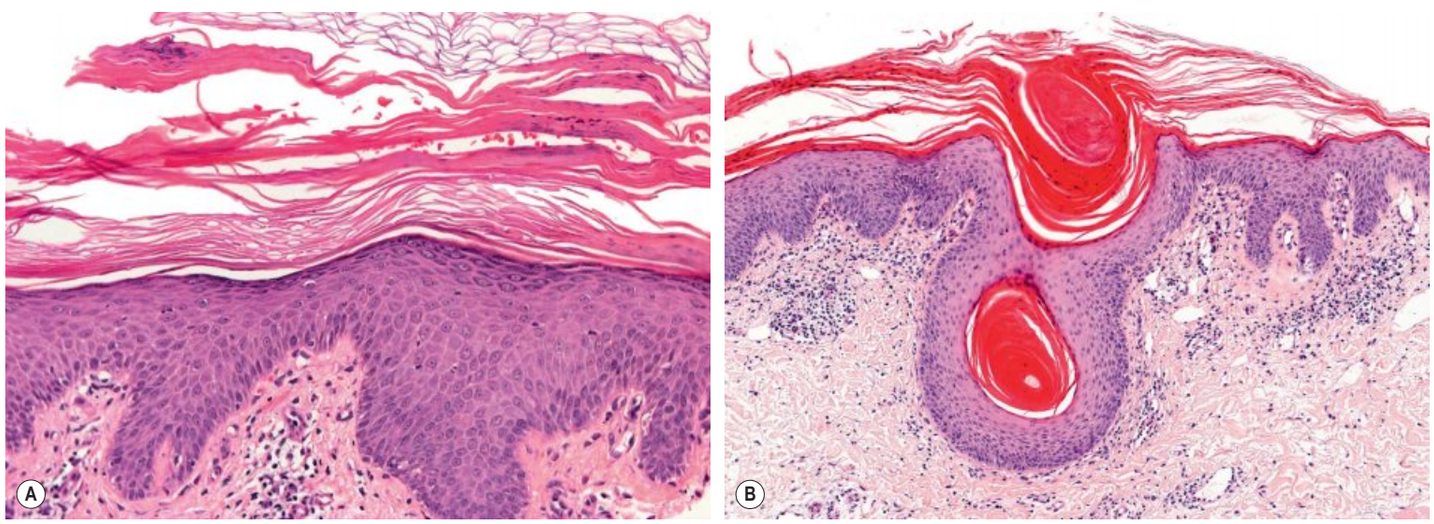


Fig. 9.9 Pityriasis rubra pilaris – histopathologic features. Psoriasiform dermatitis with alternating vertical and horizontal ortho- and parakeratosis ("checkerboard pattern") (**A**), as well as follicular hyperkeratosis with parakeratosis in the shoulders of the follicular plug (**B**). *Courtesy Lorenzo Cerroni, MD.*

PITYRIASIS ROSEA

Synonym: ■ Pityriasis rosea Gibert

Key features

- A self-limited papulosquamous eruption that is occasionally pruritic
- Seen primarily in adolescents and young adults, favoring the trunk and proximal extremities
- Herald patch followed by lesions that are usually oval in shape and oriented with their long axes along Langer cleavage lines
- Less common variants include inverse, vesicular, purpuric, and pustular

Introduction

Pityriasis rosea is a common, "acute", self-limited papulosquamous eruption that favors otherwise healthy adolescents and young adults. Its striking appearance often prompts a request for medical evaluation. There is an absence of significant systemic manifestations, and its spontaneous resolution provides great consolation to the patient. Although the classic presentation is readily recognized, atypical forms may present a greater challenge. A viral etiology has been postulated, but this remains unproven.

History

Robert Willan described "roseola annulata" in 1798 as a self-limited eruption in otherwise healthy children. In 1860, the French physician Camille Melchior Gibert first named the condition pityriasis (scaly) rosea (pink). This aptly conveyed the clinical features and remains the name that is still used today.

Epidemiology

Most cases of pityriasis rosea occur in young healthy persons, the majority of whom are between the ages of 10 and 35 years[44]. Its peak incidence is during adolescence, and it is rarely diagnosed before the age of 2 years. There is no racial predilection and it is found worldwide. There may be a slight female predominance. The typical eruption lasts 6 to 8 weeks, though exceptionally it can persist for 5 months or longer. Some authors report a modest seasonal variation with peaks in the spring and fall or in some countries during the rainy season.

Pathogenesis

The precise cause of pityriasis rosea remains elusive, and although a viral etiology is frequently proposed, this remains controversial[45]. While attention has focused on human herpesvirus-7 (HHV-7) and, less so, on HHV-6, some studies have shown no difference in the prevalence of DNA from HHV-6 or HHV-7 in peripheral blood mononuclear cells of patients with pityriasis rosea. An association with HHV-8, H1N1 influenza virus, and SARS-CoV-2 has also been reported[46]. Proponents of a viral etiology point to the prodromal symptoms experienced by some patients, the clustering of cases, and the rarity of recurrent episodes, suggesting an immunologic defense against an infectious agent. Pityriasis rosea is considered a prototypic paraviral exanthem, i.e. a characteristic skin disease associated with a possible viral infection or reactivation, but without virus identified in the cutaneous lesions[47,48].

Clinical Features

Although classic pityriasis rosea is usually easily recognized, the more unusual variants can be more challenging to diagnose[49]. In the classic presentation, a solitary lesion appears on the trunk and enlarges over several days (Fig. 9.10)[49,50]. Less often, this initial lesion is seen on the neck or proximal extremities. It predates the remainder of the eruption by hours to days and is referred to as the "herald patch" because it heralds the onset of the disease. Its incidence varies, but in most series it has been seen in over 50% of cases. Multiple herald patches have also been reported.

The herald patch is a pink- to salmon- to pink–brown-colored patch or plaque with a slightly raised advancing margin (Fig. 9.11). The size commonly varies from 2 to 4 cm, but it can be as small as 1 cm or as large as 10 cm. The center shows the characteristic small fine scales



Fig. 9.10 Pityriasis rosea with a herald patch on the left breast. Numerous symmetrically distributed pink papules on the trunk that are round or oval in shape; associated scale is most obvious on the neck and breasts. Fewer lesions are noted on the flexor surfaces of the arms.

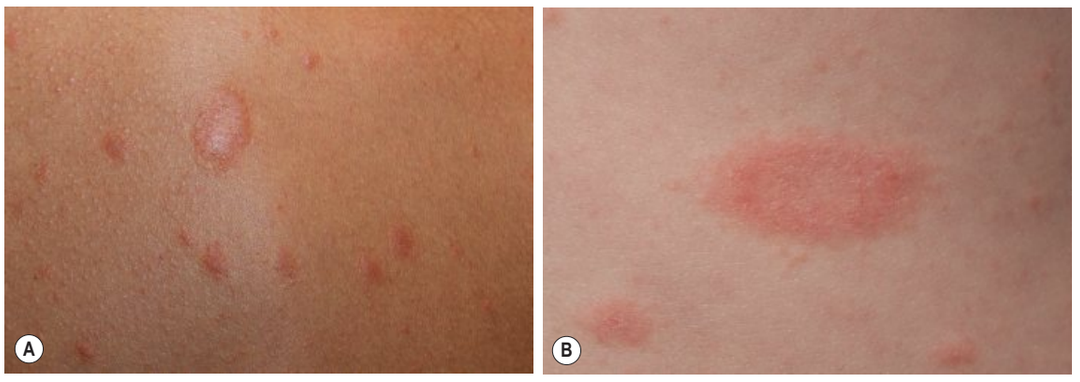


Fig. 9.11 Pityriasis rosea. A, B Herald patches in two patients with different skin phototypes. Either central or peripheral white scale can be seen. *A, Courtesy Kalman Watsky, MD; B, Used with permission of the Mayo Foundation for Medical Education and Research.*

of pityriasis rosea, and the margin has a larger, more obvious trailing collarette of scale with the free edge pointing inwards. There may be a mild prodrome with headache, fever, arthralgias, or general malaise. On occasion, the herald patch appears simultaneously with the more widespread eruption.

Typically, within the next few days, there is a blossoming of lesions on the trunk and proximal extremities. These numerous smaller thin papules and plaques are reminiscent of the larger herald patch that predated them; in more darkly pigmented skin, the lesions tend to be more papular, folliculocentric, and hyperpigmented (Fig. 9.12). Again, there is a subtle advancing border, central fine scaling, and the characteristic collarette of scale (Fig. 9.13A,B). The lesions are usually round to oval in shape, with their long axis following Langer cleavage lines (Fig. 9.13C). On the posterior trunk, such an orientation leads to what is often referred to as a "fir tree" or "Christmas tree" pattern. Minute pustules can also be seen during this initial phase of pityriasis rosea. The face, palms, and soles are usually (but not always) spared. When all these features are present, the diagnosis is easiest to establish.

The eruption of pityriasis rosea usually persists for 6–8 weeks and then spontaneously resolves; however, occasional patients have lesions that may last 5 months or longer[49]. In the latter situation, the possibility of pityriasis lichenoides chronica arises. Most patients with pityriasis rosea experience few symptoms, but in some individuals, pruritus is noted that is mild to severe.

Atypical forms of pityriasis rosea require a more astute observer. Inverse pityriasis rosea involves the axillae and inguinal areas (see Fig. 9.13B) and sometimes the face. It is more common in younger children and in those with darker skin phototypes. Oral lesions are also uncommon, but they may be underreported and palmoplantar involvement is unusual. Urticarial, erythema multiforme-like, vesicular, pustular, and purpuric variants have also been described.



Fig. 9.12 Follicular accentuation of pityriasis rosea in darkly pigmented skin. Note the central hyperpigmentation and the small follicular papules. *Courtesy Aisha Sethi, MD.*

Pathology

The microscopic features of pityriasis rosea include spongiotic dermatitis, along with elongation of the rete ridges and enlargement of the dermal papillae. Small mounds of parakeratosis and a predominantly papillary dermal infiltrate comprised of lymphocytes and histiocytes are also common features (Fig. 9.13D). There may be mild erythrocyte extravasation with scattered intraepidermal erythrocytes. In severe cases, these features are more pronounced, including the rare formation of intraepidermal pustules.

Most patients with pityriasis rosea do not have biopsies performed, because the clinical picture is quite characteristic.

Differential Diagnosis

Pityriasis rosea can sometimes be difficult to distinguish from secondary syphilis. The presence of cutaneous signs such as split papules and condyloma lata points to syphilis, as does the history or presence of a primary chancre. Patients with secondary syphilis usually have more systemic complaints, and they often have peripheral lymphadenopathy. Histologically, the absence of plasma cells favors pityriasis rosea and immunohistochemical staining for spirochetal antigens can also be done (see Ch. 0). Serologic testing allows the diagnosis of secondary syphilis to be confirmed.

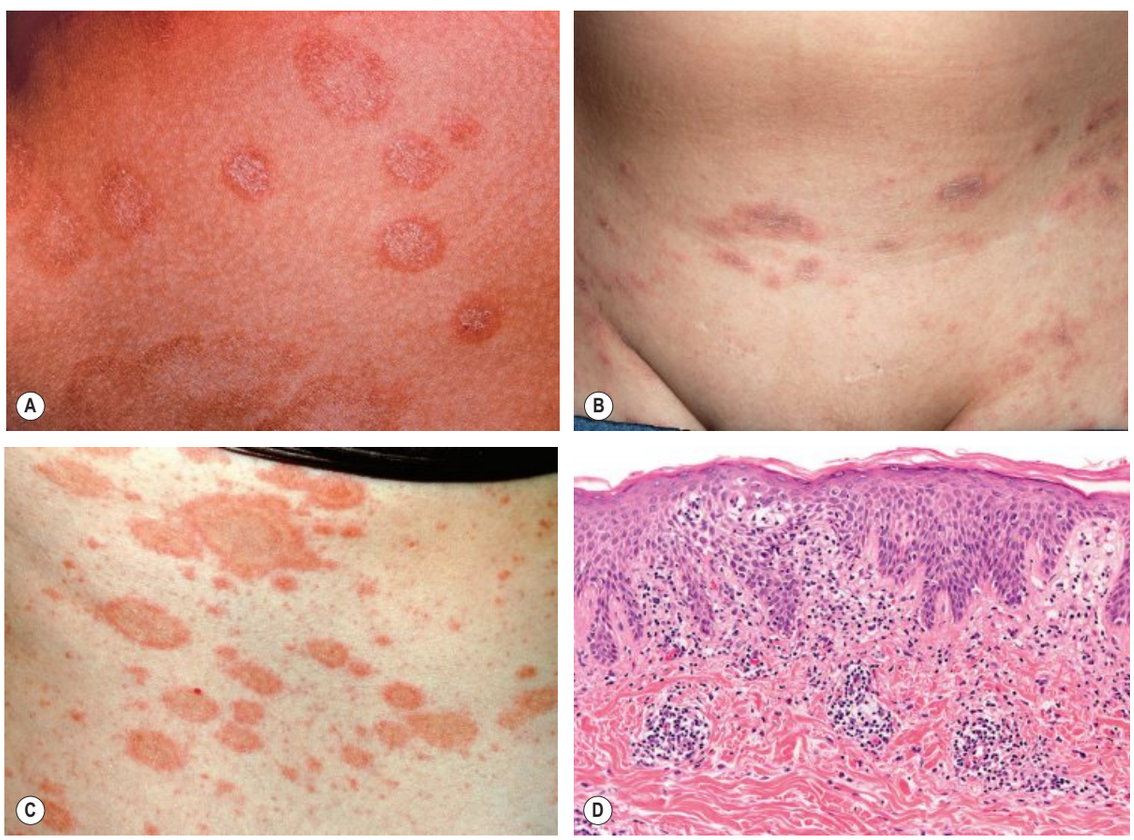


Fig. 9.13 Pityriasis rosea. A Both oval and round plaques can be seen as well as central fine scale. **B** A collarette of scale can also be seen and when lesions are limited to the pelvic region and/or axillae, the pattern of involvement is termed *inverse*. **C** A more inflammatory border may be seen and the long axes of the oval plaques follow skin cleavage lines. **D** Histopathologically, parakeratosis, mild spongiosis associated with exocytosis of lymphocytes into the epidermis, perivascular dermal lymphocytic infiltrates, and extravasated red blood cells are seen. *B, Courtesy Luis Requena, MD; C, Courtesy Julie V. Schaffer, MD; D, Courtesy Lorenzo Cerroni, MD.*

There are drug eruptions that can mimic pityriasis rosea; they have been reported in patients receiving angiotensin-converting enzyme (ACE) inhibitors, β-blockers, metronidazole, and isotretinoin, as well as arsenic, bismuth, gold, barbiturates, clonidine, hydrochlorothiazide, imatinib, omeprazole, terbinafine, TNF inhibitors, NSAIDs, and multiple vaccines[51]. A drug-induced pityriasis rosea-like eruption is often slower to resolve than the idiopathic form.

The herald patch or generalized eruption can resemble tinea corporis, tinea versicolor, or nummular dermatitis. The presence of the collarette of scale, the orientation of the lesions, and the history can help distinguish pityriasis rosea from nummular dermatitis. Guttate psoriasis usually has a thicker scale, smaller size, and lacks the fir-tree distribution. Other papulosquamous disorders such as pityriasis lichenoides should also be considered, especially when lesions last longer than 4 months.

Treatment

Because pityriasis rosea is often asymptomatic and self-limited, patient education and reassurance represent a satisfactory treatment plan. In patients with pruritus, counterirritant antipruritic lotions or low- to medium-strength topical corticosteroids may be needed for symptomatic relief. In more severe cases, UVB phototherapy (broadband or narrowband) or natural sunlight exposure and oral antihistamines can be used[52]. Rarely, a brief course of systemic corticosteroids may be required. In a 2019 Cochrane review, oral acyclovir was found to lead to "good or excellent" improvement of lesions with inconclusive effect on pruritus and oral erythromycin was shown to decrease pruritus[53]. However, a pathogenetic explanation for these findings is not clear.

Lastly, in pregnant women, there is a possible association between the development of pityriasis rosea and spontaneous abortion when there is active HHV-6 infection, in particular during the first 15 weeks of gestation[54].

PITYRIASIS ROTUNDA

Synonyms: ■ Tinea circinata ■ Pityriasis circinata

Key features

- Asymptomatic dermatosis seen primarily in the Far East and Mediterranean basin and in individuals of African descent
- There are large circular and polycyclic scaly patches with sharp margins that are typically hyperpigmented > hypopigmented and localized to the trunk and proximal extremities
- Histologic features are similar to those of ichthyosis vulgaris

Introduction

Pityriasis rotunda is an unusual dermatosis that can occur alone or in association with a number of unrelated conditions. There are familial cases that may represent a minor acquired ichthyosis.

History

Pityriasis rotunda was first described by Toyama in 1906 as "tinea circinata" and was later named pityriasis rotunda by Matsura.

Epidemiology

Pityriasis rotunda is most commonly observed in adults in their 30s and in children and has a slight female predominance[55,56]. It has been described in the Far East (Japan and China), the Mediterranean basin (Morocco, Italy, and Israel), and in Africans, African-Americans, and Afro-Caribbeans.

Pathogenesis

No clear unifying cause has been identified. In adults, possible associations include malnutrition, mycobacterial diseases (tuberculosis and leprosy), malignancies (e.g. hepatocellular carcinoma, gastric carcinoma, multiple myeloma), and hepatic cirrhosis[57]. However, the majority of patients, especially children, are in good health[58]. An absence of profilaggrin N-terminal domain and decreased expression of filaggrin-2 have been observed in some patients[59].



Fig. 9.14 Pityriasis rotunda. Circular, well demarcated, thin plaque with scale. *Courtesy Richard M. Haber, MD.*

Clinical Features

Pityriasis rotunda is typically asymptomatic and is characterized by large circular and polycyclic lesions that are often 10 cm (but may be up to 30 cm) in diameter (Fig. 9.14). They have associated fine scale and are moderately hyperpigmented with a sharp margin and no inflammation. The trunk and extremities are favored. A hypopigmented halo has been described in some patients, and sometimes the entire lesion can be hypopigmented.

Grimalt proposed categorizing pityriasis rotunda into two groups[60]. Type I is seen primarily in Black and Asian individuals as hyperpigmented lesions, possibly in association with malnutrition or internal malignancy but with no family history. Type II occurs in younger White individuals with numerous (>30) lesions who sometimes have a family history, but no associated diseases.

Pathology

Pityriasis rotunda has microscopic features of ichthyosis vulgaris, i.e. an absent or diminished granular cell layer and moderate hyperkeratosis without parakeratosis[59]. Increased pigmentation of the basal cell layer, pigment incontinence, a perivascular lymphohistiocytic infiltrate, and follicular plugging may also be observed. Special stains for fungi are negative.

Differential Diagnosis

The differential diagnosis includes tinea corporis, tinea versicolor, leprosy, and MF. The combination of fungal culture and routine histology excludes major entities in the differential diagnosis. The hypopigmented variant of pityriasis rotunda can resemble one variant of progressive macular hypomelanosis, which has no associated scale and lacks the histologic features of ichthyosis vulgaris.

Treatment

Pityriasis rotunda is relatively difficult to treat. Trials with topical lactic acid, urea, tars, emollients, and corticosteroids have provided little benefit. Topical tretinoin cream can result in modest improvement and systemic retinoids warrant consideration for patients with more extensive disease. Spontaneous remission is possible[55].

GRANULAR PARAKERATOSIS

Synonyms: ■ Axillary granular parakeratosis ■ Intertriginous granular parakeratosis

Key features

- Brownish-red keratotic papules that can coalesce into plaques
- Adult form occurs more often in women and favors the axillae over other intertriginous areas
- Infantile form is associated with diaper wearing or chemical irritation (e.g. use of benzalkonium chloride) and presents as bilateral inguinal plaques or erythematous geometric plaques underneath diaper pressure points
- Histopathology is distinct, with retention of basophilic keratohyaline granules within areas of parakeratosis in the stratum corneum
- A defect in processing profilaggrin to filaggrin is a proposed mechanism

Introduction

Granular parakeratosis is an acquired, typically pruritic disorder of the axillae and other intertriginous sites, e.g. the groin and inframammary and abdominal folds. It has distinct histopathologic findings, suggesting a disorder in keratinization[61].

History

Northcutt and colleagues[61] first described granular parakeratosis in 1991. Multiple cases have been described since then in various clinical settings, suggesting a multifactorial reactive condition[62].

Epidemiology

Granular parakeratosis is observed most commonly in middle-aged women[62]. Although it is less common in young adults, there are reports in infants and children linked to diaper-wearing and exposure to benzalkonium chloride in laundry rinse aids[63]. Granular parakeratosis has been observed in all skin phototypes.

Pathogenesis

Granular parakeratosis is an acquired keratotic dermatosis originally linked to maceration and the use of various personal hygiene products, such as deodorants and antiperspirants. More recently, occlusion from diapers or chemical irritation from benzalkonium chloride (see above) has been implicated[63].

A disorder of keratinization characterized by a basic defect in the processing of profilaggrin to filaggrin has also been proposed, based upon ultrastructural and immunohistochemical studies, i.e. retention of keratohyalin granules within the stratum corneum due to a defect in filaggrin metabolism[64]. This suggests a distinctive reactive pattern rather than a specific entity[65].

Clinical Features

The primary lesions are keratotic, brownish-red papules that can have a conical shape. They may coalesce into larger, well-demarcated plaques with various degrees of maceration secondary to local occlusion (Fig. 9.15). Lesions can persist for months or longer and recur. Pruritus is the most common complaint, but irritation is also a problem if there are erosions or fissures. Some patients experience a flare with an increase in ambient temperature and sweating. The axilla is the most common site of involvement, followed in frequency by other major body folds (e.g. inguinal, inframammary). Occasionally granular parakeratosis develops in the genital area[66].

In infants, bilateral plaques within the inguinal folds or erythematous geometric plaques underlying pressure points from the diaper can be seen. Larger lesions in other intertriginous sites have been observed in older children[63].

Pathology

The characteristic feature is an unusual form of parakeratosis. The stratum corneum is thickened and compacted with increased eosinophilic staining (Fig. 9.16). Retained nuclei are present throughout this keratin layer, creating parakeratosis. The most unusual feature is the visible retention of basophilic keratohyalin granules within these areas of parakeratosis[61,64]. Because clinically similar lesions may not have these characteristic histologic features, the encompassing term "hyperkeratotic flexural erythema" has been proposed[65].



Fig. 9.15 Granular parakeratosis involving the axilla. Coalescing brown papules with hyperkeratosis and slight maceration. *Courtesy Kalman Watsky, MD.*

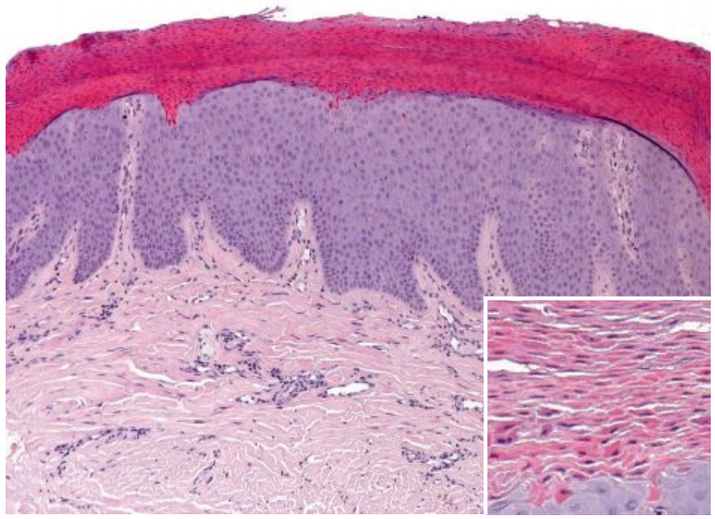


Fig. 9.16 Axillary granular parakeratosis – histopathologic findings. Marked, compact parakeratosis with small bluish granules within the stratum corneum representing keratohyaline granules (inset). *Courtesy Lorenzo Cerroni, MD.*

Differential Diagnosis

The differential diagnosis includes the most common causes of intertrigo (e.g. seborrheic dermatitis, candidiasis, inverse psoriasis, erythrasma) as well as Hailey–Hailey disease, Darier disease, and pemphigus vegetans. Irritant or allergic contact dermatitis also needs to be considered in some patients. A biopsy will confirm the diagnosis of granular parakeratosis.

Treatment

Based upon case reports and small series, therapeutic success has been reported with topical corticosteroids, vitamin D analogues, retinoids, ammonium lactate, and antifungals. In addition, cryotherapy, laser therapy[67], and oral isotretinoin or antibiotics have been used[65]. Spontaneous resolution has also been observed (including in infants), as have relapses.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 9.1 Small plaque parapsoriasis – digitate dermatosis. A, B Elongated finger-like lesions on the flank, admixed with smaller papules in **B.** *B, Courtesy Jeffrey P. Callen, MD.*



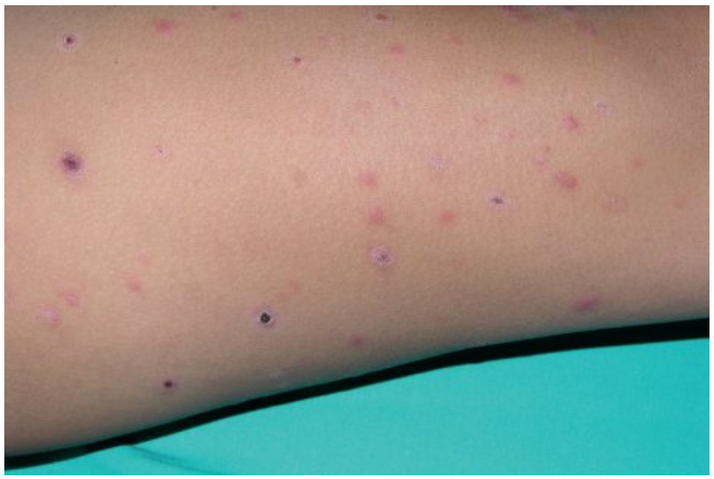
eFig. 9.2 Large plaque parapsoriasis. A Large, variably erythematous patches in the bathing trunk region is a classic presentation. **B** Retiform parapsoriasis with atrophic, red–brown papules in a net-like pattern. While some authors view large plaque parapsoriasis as an entity distinct from mycosis fungoides (MF) or as a potential precursor of MF, many within the field of cutaneous lymphoma consider it to be an early stage of MF.



eFig. 9.3 Chronic form of pityriasis lichenoides (PLC). Multiple, dull red–brown papules, some of which have scale.



eFig. 9.4 Pityriasis lichenoides. Some patients have lesions characteristic of both PLEVA and PLC. *Courtesy Kalman Watsky, MD.*



eFig. 9.5 Pityriasis lichenoides. An admixture of crusted and scaly papules characteristic of PLEVA and PLC, respectively, are seen. *Courtesy Antonio Torrelo, MD.*



eFig. 9.6 Acute form of pityriasis lichenoides (PLEVA). Widespread erythematous papules, some of which have crusts while others have an ulcerative component.



eFig. 9.7 Ulceronecrotic pityriasis lichenoides et varioliformis acuta (PLEVA). Widespread rather monomorphous ulcerations. *Courtesy Lorenzo Cerroni, MD.*



eFig. 9.8 Chronic form of pityriasis lichenoides (PLC). Numerous red–brown papules and hypopigmented macules with variable scaling. *Courtesy Julie V. Schaffer, MD.*



eFig. 9.9 Chronic form of pityriasis lichenoides (PLC) presenting with hypopigmentation. This is more common in darker skin phototypes.



eFig. 9.10 Pityriasis rubra pilaris. Orange–red keratotic follicular papules. *Courtesy Luis Requena, MD.*



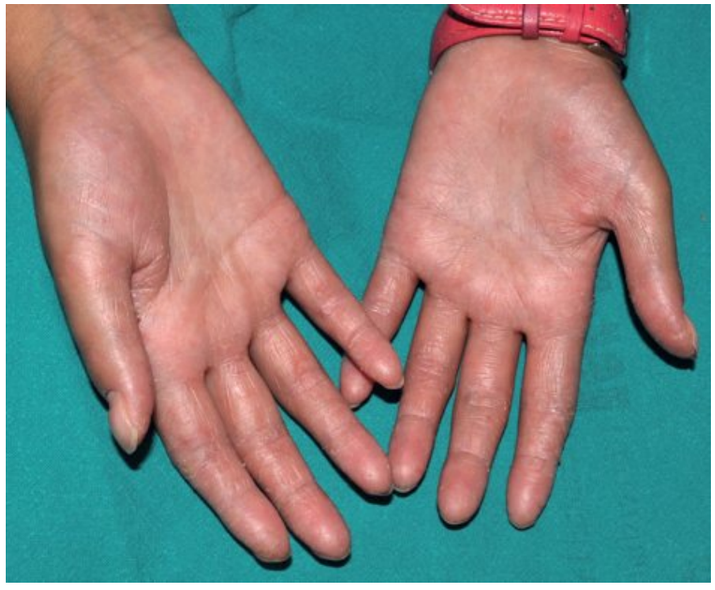
eFig. 9.12 Pityriasis rubra pilaris. Well-demarcated, confluent orange–red plaques with scattered follicular papules within areas of sparing.



eFig. 9.11 Pityriasis rubra pilaris. Striking symmetric islands of sparing on the flanks. Follicular papules are present at the periphery of the diffuse erythema. *Used with permission of the Mayo Foundation for Medical Education and Research.*



eFig. 9.13 Pityriasis rubra pilaris. The orange–red color of the skin, including that of the palms, aids in the clinical diagnosis; note the waxy appearance of the keratoderma. *Courtesy Irwin Braverman, MD.*



eFig. 9.14 Pityriasis rubra pilaris-like presentation in Wong variant of juvenile dermatomyositis. *Courtesy Antonio Torrelo, MD.*



eFig. 9.15 Pityriasis rubra pilaris. A, B Erythroderma with hyperkeratosis of the knees. **C** Palmar erythema and scaling with fissures. *Courtesy Jeffrey P. Callen, MD.*



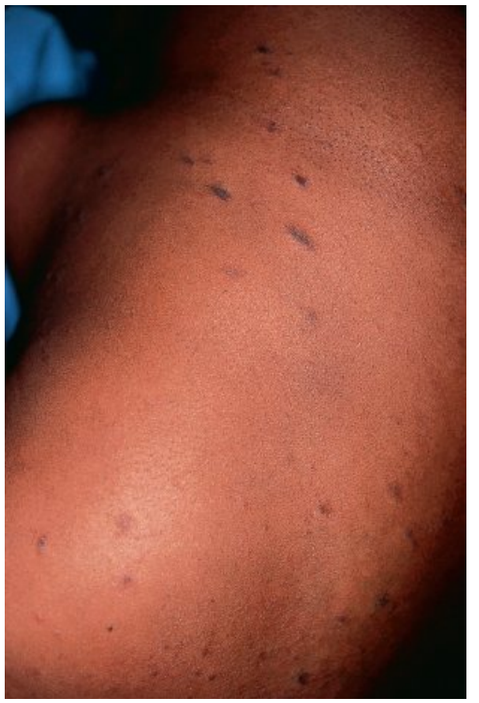
eFig. 9.16 Pityriasis rosea. There is confluence of the lesions on the mid anterior trunk; note the scale in several lesions. *Courtesy Antonio Torrelo, MD.*



eFig. 9.17 Pityriasis rosea. Papules of varying size and small plaques, some of which are oval in shape. The patient was 59 years old. *Courtesy Jeffrey P. Callen, MD.*



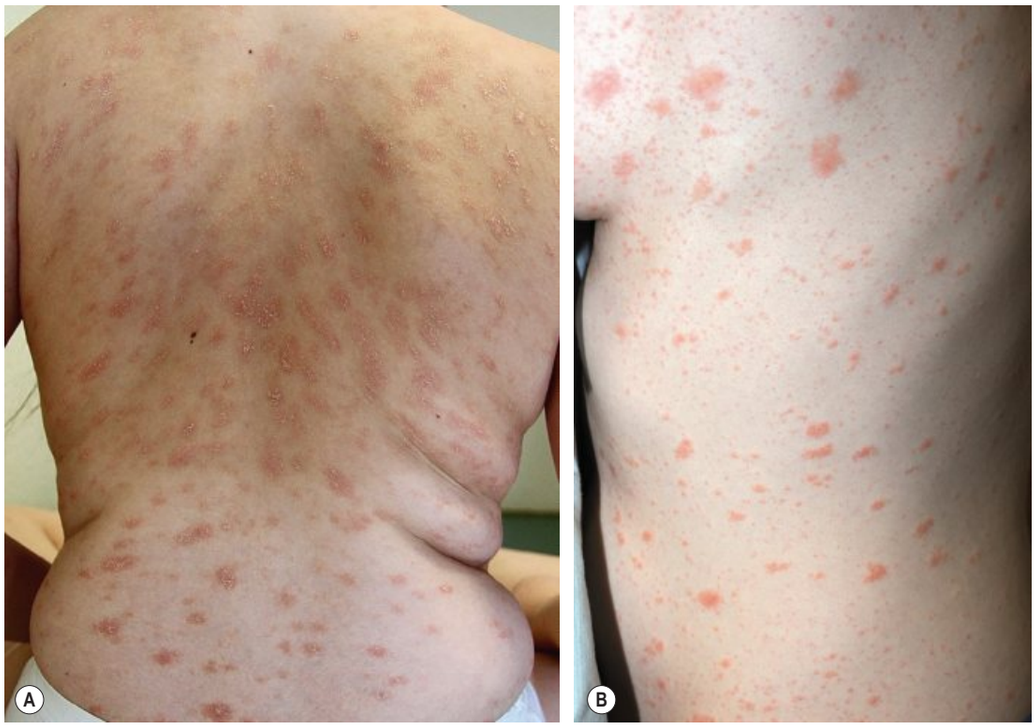
eFig. 9.18 Pityriasis rosea. Both oval and round plaques can be seen as well as central fine scale or a collarette of scale. *Courtesy Julie V. Schaffer, MD.*



eFig. 9.19 Pityriasis rosea in more darkly pigmented skin. Note the associated hyperpigmentation.



eFig. 9.20 Pityriasis rosea. Two herald patches are seen. *Courtesy Kalman Watsky, MD.*



eFig. 9.21 Pityriasis rosea. A Multiple papulosquamous lesions on the back whose long axes follow the skin tension lines, leading to a "fir tree" or "Christmas tree" pattern. **B** On the flank, mixture of classic lesions with tiny pink papules. *B, Courtesy Kalman Watsky, MD.*



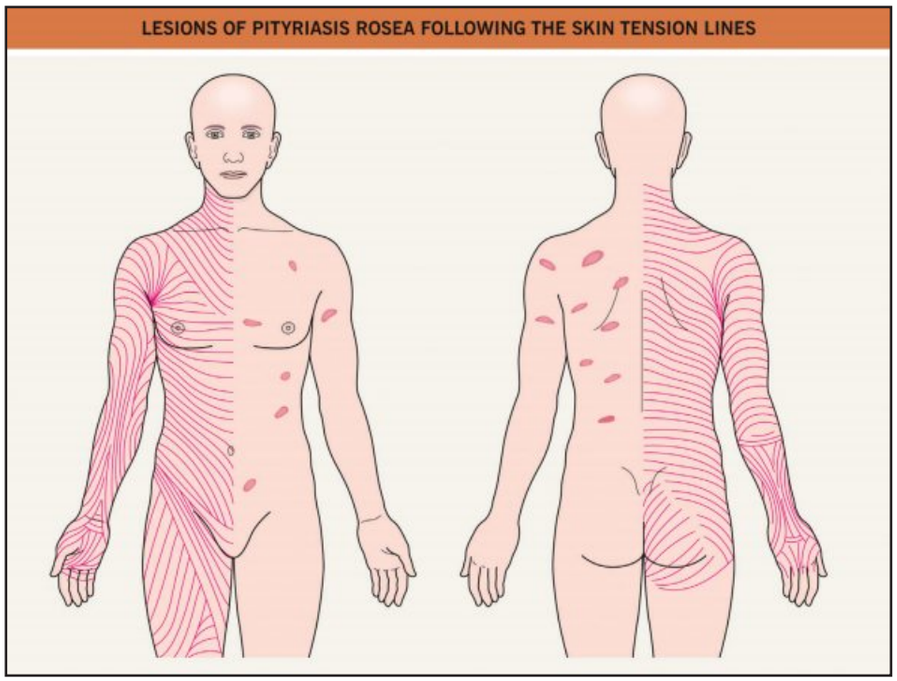
eFig. 9.22 Inverse pityriasis rosea. Circular and oval-shaped plaques; some have central white scale while others have a more peripheral collarette of scale. *Courtesy Kalman Watsky, MD*



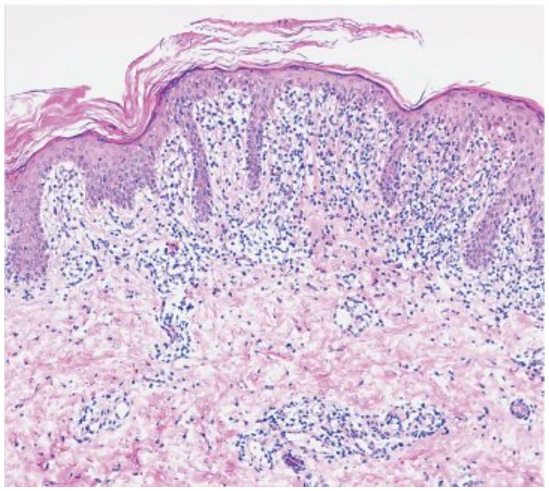
eFig. 9.23 Pityriasis rosea. Several of the dull pink plaques have a collarette of white scale. *Courtesy Jean L. Bolognia, MD.*



eFig. 9.24 Inverse pityriasis rosea. Oval plaques with peripheral scale on the central buttocks. *Used with permission of the Mayo Foundation for Medical Education and Research.*



eFig. 9.25 Lesions of pityriasis rosea following the skin tension lines. These lines are often referred to as Langer cleavage lines. The long axis of the individual lesions aligns with these lines.



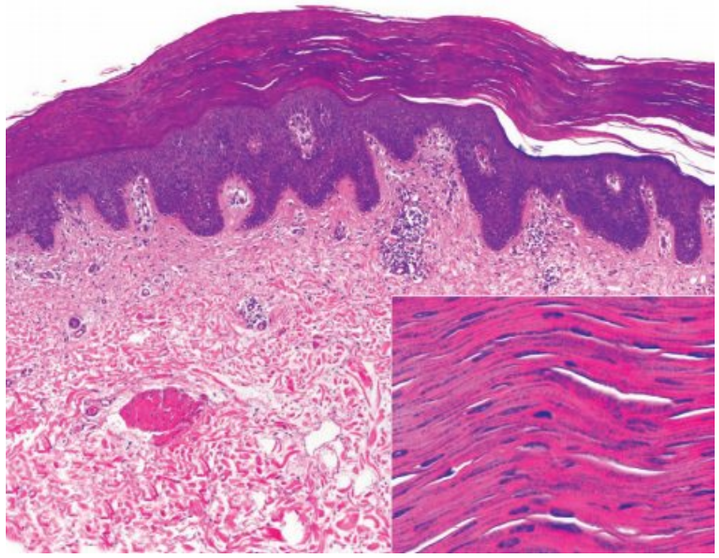
eFig. 9.26 Lichenoid interface dermatitis with exocytosis of lymphocytes and focal parakeratosis.



eFig. 9.27 Pityriasis rotunda. Circular, well demarcated, thin hyperpigmented plaques with scale. *Courtesy John Hughes, MD.*



eFig. 9.28 Granular parakeratosis. Brownish-red papules with coalescence into a keratotic plaque in the axilla. *Courtesy David Mehregan, MD.*



eFig. 9.29 Axillary granular parakeratosis – histopathology. Marked, compact parakeratosis with small bluish granules within the stratum corneum representing keratohyaline granules (inset). *Courtesy Luis Requena, MD.*

Erythroderma 10

Sean Whittaker

Synonyms: ■ Exfoliative dermatitis ■ Exfoliative erythroderma ■ Red man syndrome (becoming historical term)

Key features

- Erythroderma is clinically defined as erythema and scaling involving >80% of the body surface area
- Systemic manifestations include peripheral edema, tachycardia, loss of fluid and proteins, and disturbances in thermoregulation
- Erythroderma has multiple etiologies; in adults, the most common causes are psoriasis, drug reactions, atopic dermatitis, and cutaneous T cell lymphoma (CTCL)
- Establishing the correct diagnosis requires consideration of initial sites of involvement, additional clinical findings, histopathologic and molecular features, and associated systemic abnormalities, as well as a complete medical history
- Despite an intensive evaluation, the cause remains unknown (idiopathic) in ~25% of patients; some of these patients eventually develop CTCL
- Treatment strategies should address the dermatologic disease as well as the underlying etiology and the systemic complications of the erythroderma

INTRODUCTION

Erythroderma is defined as generalized erythema and scaling involving >80% of the body surface area (BSA). However, it does not represent a defined entity, but rather is a striking and severe clinical presentation that can arise from a variety of diseases. Most commonly, erythroderma is due to generalization of pre-existing dermatoses (such as psoriasis or atopic dermatitis), drug reactions, or cutaneous T cell lymphoma (CTCL). Although up to 50% of the patients have a history of more localized skin lesions prior to the onset of the erythroderma, identification of the underlying disease process represents one of the most complex challenges in dermatology. Sustained efforts during longitudinal evaluation may lead to the precise identification of the etiology. In approximately one-quarter of the patients, no specific etiology is found, and these cases are called "idiopathic erythroderma".

Attention should also be focused on the potential systemic complications of acute erythroderma. Hypothermia, peripheral edema, and loss of fluid, electrolytes and albumin with subsequent tachycardia and cardiac failure are serious threats to the erythrodermic patient. In addition, chronic erythrodermas may be accompanied by cachexia, diffuse alopecia, palmoplantar keratoderma, nail dystrophy, and ectropion.

HISTORICAL PERSPECTIVE

The term "erythroderma" was introduced in 1868 by Hebra to describe an exfoliative dermatitis involving more than 90% of the skin surface. Based upon the clinical course, erythroderma was classified into chronically relapsing (Wilson–Brocq), chronically persisting (Hebra), and self-limiting epidemic (Savill) variants. However, these subdivisions are no longer employed. Even though originally more strictly defined as erythema and scaling involving >90% of BSA, nowadays the term erythroderma is often more liberally applied when there is >80% of BSA involvement.

EPIDEMIOLOGY

No precise data exist regarding the prevalence or incidence of erythroderma as most reports are retrospective but an overall incidence of 1 per 100 000 has been proposed. Large series of patients have focused on male-to-female ratios, average age, and underlying diseases[1–7]. Men are more commonly affected, with the male-to-female ratio ranging from approximately 2:1 to 4:1. An even higher ratio can be found in the subset of idiopathic erythroderma, also referred to as "red man syndrome" (not to be confused with the acute cutaneous reaction to rapid infusion of vancomycin). The average age at onset of erythroderma in these series was 52 years, with an average of 48 years in those including children, and 60 years in series excluding them[1,3,4,6].

Based upon several large series of patients, dermatitis (24%), psoriasis (20%), drug reactions (19%), and CTCL (8%; including Sézary syndrome and erythrodermic mycosis fungoides [MF]) represented the most common underlying causes of erythroderma[1–7]. In a more recent prospective study of over 300 patients, CTCL was diagnosed in a higher proportion of patients (18%)[8], but this could represent tertiary care referral bias or greater access to molecular diagnostics[9]. When categories within the dermatitis group were examined, atopic dermatitis (9%) was the most common type, followed by contact dermatitis (6%), seborrheic dermatitis (4%), and chronic actinic dermatitis (3%)[1,3,4,6]. With regard to etiology, no specific geographic differences have been noted[7,10]. In adults with erythroderma, overall relapse rates at one year range from 20% to 30%.

For adults, uncommon causes include pityriasis rubra pilaris, ichthyoses, bullous dermatoses (usually pemphigus foliaceus), graft-versus-host disease (GVHD), infestations (most often scabies), and autoimmune connective tissue diseases (acute lupus erythematosus, juvenile dermatomyositis). Table 10.1 lists additional unusual causes, from paraneoplastic (e.g. lymphoma, solid organ malignancies) to inflammatory (e.g. sarcoidosis) and neoplastic (e.g. hypereosinophilic syndrome). Despite multiple skin biopsies, an in-depth clinical investigation and a detailed medical history, the underlying cause of erythroderma is not found in at least 25% of patients. Unfortunately, cases of idiopathic erythroderma tend to be chronic and are more likely to recur after treatment[7].

Erythroderma in neonates and infants is rare and causes include inherited ichthyoses, dermatitides, psoriasis, immunodeficiencies[12] (e.g. Omenn syndrome), and consequences of infection (e.g. staphylococcal scalded skin syndrome) (Table 10.2)[13]. In addition, the possibility of drug-induced erythroderma should always be considered.

PATHOGENESIS

The pathogenetic mechanisms of the underlying diseases will be discussed in the respective chapters. The pathways involved in the *de novo* genesis of erythroderma or the generalization of pre-existing skin lesions are not well understood. The number of germinative keratinocytes as well as their mitotic rate is increased in erythrodermic skin, and the transit time of cells through the epidermis is shortened. Consequently, scales consist of material normally retained by the skin (nucleic acids, amino acids, soluble protein), and the daily loss of scales increases from 500–1000 mg to 20–30 g[14]. In acute erythroderma, the desquamated material usually has marginal metabolic significance, but in chronic erythroderma protein loss can be significant, leading to hypoalbuminemia and contributing to anemia of chronic disease. Given that the peak age of onset is during the 6th to 7th decade of life, it is possible that age-related immune senescence is a contributory factor in the development of idiopathic erythroderma. Likewise, the striking presentation of erythroderma in children with immunodeficiencies supports a role for immune dysregulation. Erythroderma in neonates often has a genetic basis and molecular diagnostics can play an important role in identifying causative mutations[15].

CAUSES OF ERYTHRODERMA IN ADULTS			
Underlying disease	**Clinical clues**	**Histologic clues**	**Additional hints**
Common			
Psoriasis (Ch. 8)	• Pre-existing psoriatic plaques or lesions of pustular psoriasis • Often spares the central face • Nail changes (oil-drop, pits, onycholysis) • Subcorneal pustules • Inflammatory arthritis	• Confluent or focal parakeratosis • Epidermal hyperplasia with bottleneck-like rete ridges • Tortuous vessels in a slightly edematous papillary dermis • Neutrophils within epidermis; sparse lymphohistiocytic infiltrate within dermis • Often reduced or absent granular layer	• Personal or family history of psoriasis • Withdrawal of corticosteroids, methotrexate, cyclosporine or targeted immunomodulators ("biologics") • Receiving medication that can exacerbate psoriasis (e.g. lithium, hydroxychloroquine, dupilumab)
Atopic dermatitis (Ch. 12)	• Pre-existing lesions (flexures) • Severe pruritus • Lichenification, including eyelids • Prurigo nodularis	• Mild to moderate acanthosis • Variable spongiosis • Dermal eosinophils • Parakeratosis • Variable lymphohistiocytic infiltrate with exocytosis of lymphocytes • Variable dermal edema	• Elevated serum IgE, eosinophilia • Personal or family history of atopy (e.g. asthma, allergic rhinitis, atopic dermatitis) • Cataracts/keratoconus
Drug reactions (Ch. 21)	• Preceded by morbilliform or scarlatiniform exanthem • Facial edema • In dependent areas, may become purpuric	• Variable patterns, including perivascular, lichenoid, spongiotic, and pseudolymphomatous • Eosinophils can be present, irrespective of pattern • Vacuolar degeneration of basal layer • SJS/TEN: apoptotic keratinocytes at all levels of epidermis • DRESS/DIHS: spongiotic and lichenoid patterns	• No history of skin diseases • More acute onset • Usually resolves within 2–6 weeks after withdrawal of responsible drug; possible exception is DRESS/DIHS • More common in HIV-infected patients • Specific HLA alleles increase risk (see Table 21.3)
Idiopathic erythroderma	• Elderly men • Chronic, relapsing • Severe pruritus • Palmoplantar keratoderma • Dermatopathic lymphadenopathy	• Nonspecific • Acute forms – parakeratosis, spongiosis, and a moderate lymphohistiocytic infiltrate • Chronic forms – compact ortho- and/or hyperparakeratosis, psoriasiform acanthosis, and expanded papillary dermis	• Consider less commonly associated drugs (see Table 10.3) • Continue to re-evaluate for cutaneous T cell lymphoma, including serial skin biopsies
Less common			
Cutaneous T cell lymphoma (Sézary syndrome > erythrodermic mycosis fungoides) (Ch. 120)	• Intense pruritus with excoriations; can develop lichenification or prurigo nodularis • Deep purple–red hue; pigmentary changes (melanoerythroderma) • Infiltration and/or edema; leonine facies • Painful, fissured palmoplantar keratoderma • Alopecia • Lymphadenopathy • Nail dystrophy	• Cerebriform pleomorphic lymphocytes • Clustering of atypical cells within epidermis uncommon • Band-like and occasionally lichenoid infiltrate • Cutaneous histology is non-diagnostic in at least 30% of patients with Sézary syndrome	• Sézary syndrome: peripheral blood $CD4^+$ lymphocytosis (≥1000 Sézary cells/mm^3; CD4/CD8 ratio ≥10; ≥40% $CD4^+/CD7^-$; or ≥30% $CD4^+/CD26^-$) • Sézary syndrome: detection of identical clonal T cell population in skin and lymph node/blood • Erythrodermic MF: variable presence of T cell clone in blood • Erythrodermic MF: lower levels or no Sézary cells (see Table 120.4) • Can mimic several other causes of erythroderma
Dermatitis (non-atopic), including contact (Chs. 14 and 15) and stasis with autosensitization (Ch. 13)	• Pre-existing localized disease • Distribution of initial lesions	• Variable spongiosis	• Occupation and hobbies • Patch testing • Review oral medications (systemic contact dermatitis)
Uncommon			
Pityriasis rubra pilaris (Ch. 9)	• Salmon-colored erythema • Islands of sparing (nappes claires) • Waxy keratoderma • Perifollicular keratotic papules	• Psoriasiform epidermal hyperplasia • Granular layer is normal • Alternating parakeratosis and orthokeratosis, both vertically and horizontally • Follicular plugs with "shoulder parakeratosis" • No neutrophils	• Flare after sun exposure • Cephalocaudal progression • Appearance of erythema gyratum-like lesions as erythroderma improves
Paraneoplastic erythroderma	• Fine scaling • Melanoerythroderma • Cachexia	• Nonspecific changes (skin does not contain malignant cellular infiltrates)	• Lymphoproliferative disorders, including lymphomas other than Sézary syndrome, and rarely thymomas • In the case of solid-organ malignancies, usually late-stage

Table 10.1 Causes of erythroderma in adults.

CAUSES OF ERYTHRODERMA IN ADULTS			
Underlying disease	**Clinical clues**	**Histologic clues**	**Additional hints**
Bullous dermatoses (Chs. 29 and 30) and inherited ichthyoses (Ch. 57)			
Pemphigus foliaceus	• Pre-existing lesions, often on upper trunk • Impetigo-like erosions and vesicles • Moist scale-crust; cornflake scale	• Acantholysis within the superficial epidermis • DIF, intercellular IgG	• IIF, intercellular • Anti-DSG1 Ab
Bullous pemphigoid	• Urticarial plaques • Tense bullae • Elderly patients	• Interface dermatitis and spongiosis; subepidermal blisters may be present • Many eosinophils, in part along the DEJ • DIF, BMZ C3 and IgG	• IIF, BMZ • Anti-BP180/BP230 Ab for longitudinal evaluation
Paraneoplastic pemphigus	• Mucosal erosions and hemorrhagic crusts • Erythema multiforme-like lesions • Mucocutaneous lichenoid lesions	• Interface dermatitis with necrotic keratinocytes • Parakeratosis • Focal acantholysis • DIF, intercellular and BMZ IgG	• IIF, intercellular and BMZ (+ IIF rat bladder)
Inherited ichthyoses	• Present from birth or early infancy (see Table 10.2)	• See Table 10.2	• See Table 10.2
Rare			
Papuloerythroderma of Ofuji	• Widespread, pruritic, flat-topped, red–brown papules that can become confluent • Sparing of skin folds ("deck-chair" sign) • Favors elderly men	• Dense perivascular infiltrate of lymphocytes and eosinophils in the upper to mid dermis	• Multiple etiologies, including CTCL > atopy, other lymphomas; drugs (e.g. DDI, aspirin); infections (e.g. HIV, hepatitis C virus); paraneoplastic phenomenon • May have peripheral eosinophilia, lymphopenia
Chronic actinic dermatitis (Ch. 87)	• Initial lesions in photodistribution • Allergic airborne contact dermatitis to *Compositae*	• Lichenoid infiltrate of lymphocytes and epidermal exocytosis • Acanthosis of epidermis and compact hyperkeratosis • Possible lymphocyte nuclear pleomorphism	• Drug history • UVA, UVB and visible light phototesting • Photopatch testing
Other unusual causes			
• Crusted (Norwegian) scabies • Dermatophyte infection • Leprosy • Toxic shock syndrome (usually staphylococcal) • Toxic exfoliative shock syndrome associated with SARS-CoV-2[11] • Primary immunodeficiencies • Lichen planus • Autoimmune connective tissue disease (e.g. acute or subacute cutaneous lupus erythematosus, juvenile dermatomyositis [adolescents])		• GVHD • Sarcoidosis • Hypereosinophilic syndrome • Other T cell hematologic malignancies (e.g. adult T cell leukemia/lymphoma, angioimmunoblastic T cell lymphoma, T cell prolymphocytic leukemia) • Mastocytosis • Langerhans cell histiocytosis	

Table 10.1 Causes of erythroderma in adults. Ab, antibody; BMZ, basement membrane zone; DDI, dideoxyinosine; DEJ, dermal–epidermal junction; DIF, direct immunofluorescence; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; IIF, indirect immunofluorescence; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

CAUSES OF ERYTHRODERMA IN NEONATES AND INFANTS			
Underlying disease	**Clinical clues**	**Histologic clues**	**Additional findings**
Inherited ichthyoses (Ch. 57)			
Non-syndromic			
Congenital ichthyosiform erythroderma	• Collodion baby • Generalized scaling involving flexures • Cicatricial alopecia, nail dystrophy, often palmoplantar hyperkeratosis • Ectropion	• Non-diagnostic	• Autosomal recessive • Mutations in multiple genes, e.g. *TGM1*, *ALOXE3*, *ALOX12B* (encode transglutaminase 1 and arachidonate lipoxygenases); see Table 57.1 for complete list
Epidermolytic ichthyosis	• Formation of superficial blisters and erosions during the first days of life • Later, corrugated hyperkeratosis in flexural areas	• Classic epidermolytic hyperkeratosis	• Autosomal dominant, very rarely autosomal recessive • Mutations in *KRT1* and *KRT10* (encode keratins 1 and 10)

Table 10.2 Causes of erythroderma in neonates and infants.

Continued

CAUSES OF ERYTHRODERMA IN NEONATES AND INFANTS			
Underlying disease	**Clinical clues**	**Histologic clues**	**Additional findings**
Syndromic			
Netherton syndrome	• Atopic-like dermatitis • Food allergies • Immune deficiency • Erythroderma in neonates • Erythroderma may persist or ichthyosis linearis circumflexa develops • Examine eyebrows and eyelashes as well as scalp hairs for trichorrhexis invaginata ("bamboo hair") • Failure to thrive	• Routine histology – non-diagnostic • Loss of tissue LEKTI expression	• Autosomal recessive • Elevated serum IgE levels • Mutations in *SPINK5* (encodes serine peptidase inhibitor, Kazal type 5, also known as lympho-epithelial Kazal-type-related inhibitor [LEKTI])
Conradi–Hünermann–Happle syndrome (X-linked dominant chondrodysplasia punctata)	• Linear and swirled pattern • Skeletal (chondrodysplasia punctata) and ocular anomalies (cataracts)	• Hyperkeratosis, reduced granular layer, follicular plugging with dystrophic calcification	• Mutations in *EBP* (encodes emopamil binding protein [sterol isomerase])
• Other rare ichthyoses and related disorders, e.g. trichothiodystrophy, keratitis–ichthyosis–deafness (KID) syndrome, Sjögren–Larsson syndrome, neutral lipid storage disease with ichthyosis, ichthyosis with confetti, ichthyosis prematurity syndrome, generalized inflammatory peeling skin syndrome, severe dermatitis–multiple allergies–metabolic wasting (SAM) syndrome, other desmosomal disorders, inflammatory skin and bowel disease*			
Immunodeficiencies (Ch. 60)			
Omenn syndrome	• Onset in neonatal period • Exfoliative erythroderma with diffuse alopecia • Lymphadenopathy and hepatosplenomegaly • Recurrent infections • Diarrhea	• Apoptosis of keratinocytes • Vacuolization of basal keratinocytes • Dense dermal infiltrate (predominantly T cells) • Acanthosis, parakeratosis • Degeneration of subcutaneous fat lobules	• Leukocytosis, peripheral eosinophilia • Hypogammaglobulinemia • Elevated serum IgE levels • Lymph nodes: disruption of germinal centers and abundant $S100^+$ interdigitating reticulum cells • Classically, *RAG1* or *RAG2* mutations, but this phenotype can also result from mutations in other genes causing SCID (see Ch. 60)
Other forms of SCID, agammaglobulinemia, complement deficiencies (e.g. C3, C5), IPEX syndrome	• "Leiner phenotype" of exfoliative dermatitis, chronic diarrhea, and recurrent infections	• Non-diagnostic	• See Ch. 60 • Many different genetic etiologies
Wiskott–Aldrich syndrome	• Primarily affects boys • Petechiae, ecchymoses • Atopic-like dermatitis • Recurrent sinopulmonary infections	• Non-diagnostic	• Microthrombocytopenia • Lymphopenia, peripheral eosinophilia • Elevated serum IgE levels • Mutations in *WAS*
• Other primary immunodeficiencies, e.g. DiGeorge syndrome and hyper IgE syndromes • GVHD (e.g. maternal–fetal or transfusion-related) in the setting of SCID (see Fig. 10.11; Ch. 52)			
Primary dermatoses			
Atopic dermatitis (Ch. 12)	• Crusted eczematous lesions on extensor surfaces, face, scalp • Spares diaper area • Pruritus • Onset week 6–16	• See Table 10.1	• See Table 10.1
Seborrheic dermatitis (Ch. 13)	• Greasy, scaling plaques and satellite papules on scalp and in skin folds • Diaper area involvement • Non-pruritic • Early onset (week 2–12)	• Psoriasiform hyperplasia of the epidermis with parakeratosis • Nonspecific inflammatory infiltrate	
Psoriasis (Ch. 8)	• Silvery white scaling and sharply demarcated plaques on face, elbows, and knees • Diaper area involvement • Nail pits • Usually later onset	• See Table 10.1	• Family history of psoriasis • See Table 10.1 • Familial erythrodermic psoriasis (and PRP) can be due to activating mutations in *CARD14* and may respond to ustekinumab • Generalized pustular psoriasis seen in DITRA and (together with sterile osteolysis and neonatal distress) DIRA (see Table 45.7)
• Other primary dermatoses, e.g. pityriasis rubra pilaris and CARD14-associated papulosquamous eruption (Ch. 9)			

Table 10.2 Causes of erythroderma in neonates and infants.

CAUSES OF ERYTHRODERMA IN NEONATES AND INFANTS			
Underlying disease	**Clinical clues**	**Histologic clues**	**Additional findings**
Drug reactions (Tables 10.1 and 10.3)			
Infections			
Staphylococcal scalded skin syndrome	• Temperature instability/low-grade fever • Irritability • Skin-fold accentuation • Large areas of tender erythema • Superficial bulla formation followed by desquamation • Radiating perioral scale-crusts • Extracutaneous staphylococcal infections often responsible	• Blister roof consists of the cornified layer and parts of the granular layer • Subcorneal blisters contain sparse acantholytic keratinocytes and only a few neutrophils and lymphocytes	• Positive culture for *Staphylococcus aureus* (conjunctivae, nares, throat, umbilicus, rectum) • Identification of exfoliative toxins (ET-A & ET-B) via slide latex agglutination, double immunodiffusion, or ELISA (see Ch. 74) • ET-A produced by *S. aureus* specifically cleaves desmoglein 1
Neonatal "toxic shock-like" exanthematous disease	• Generalized diffuse macular erythema or morbilliform eruption with confluence • Minimal scaling • Fever • Occurs during first week of life		• Colonization of umbilical stump, nasopharynx or skin with TSST-1-producing MRSA • Thrombocytopenia • Reported primarily in Japan
Congenital cutaneous candidiasis	• Maternal vaginal *Candida* infection with intrauterine spread • Pustules, collarettes of scale • Oral cavity spared • May have paronychia and nail dystrophy	• Yeast and pseudohyphae in the stratum corneum (PAS) • Subcorneal and spongiform pustules within the epidermis	• KOH examination, fungal culture
• Other infections and infestations, including viral exanthems (e.g. parechovirus), syphilis, and scabies			
Others			
• Ectodermal dysplasias*, e.g. ankyloblepharon–ectodermal dysplasia–clefting (AEC) syndrome, hypohidrotic ectodermal dysplasia with immune deficiency (Ch. 63), neonatal inflammatory skin and bowel syndrome type 1 due to *ADAM17* mutations (psoriatic erythroderma) • Nutritional and enzyme deficiency diseases such as kwashiorkor, organic acidurias, cystic fibrosis, specific deficiencies (e.g. zinc, essential fatty acids, biotin), and Gaucher disease (Chs. 51 and 63)			
*Desmosomal disorders characterized by erythrokeratodermia, ectodermal dysplasia, and/or skin fragility may also present with neonatal erythroderma (Chs. 56 and 57)			

Table 10.2 Causes of erythroderma in neonates and infants. CARD14, caspase recruitment domain family member 14; DIRA, deficiency of interleukin-1 receptor antagonist; DITRA, deficiency of interleukin-36 receptor antagonist; ELISA, enzyme-linked immunosorbent assay; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MRSA, methicillin-resistant *Staphylococcus aureus*; SCID, severe combined immunodeficiency; TSST-1, toxic shock syndrome toxin 1.

CLINICAL FEATURES

Cutaneous Manifestations

Erythroderma is clinically defined by the presence of erythema and scaling involving more than 80% of the skin surface. Based upon its clinical course, erythroderma can be classified into primary or secondary types. In the primary form, the erythema (often initially on the trunk) extends within a few days or weeks to involve the entire skin surface, accompanied by the development of scaling (Fig. 10.1). The secondary form of erythroderma is defined as a generalization of a preceding localized skin disease – for example, psoriasis or atopic dermatitis. An acute onset most commonly occurs when the underlying cause is a drug reaction or dermatitis.

With the exception of very slowly progressing secondary erythroderma, erythema precedes the development of exfoliation by 2–6 days. The associated scaling varies extensively in size and color depending upon the stage of the erythroderma and nature of the underlying disease. During acute phases, scales are usually large and crusted, whereas in chronic states they tend to be smaller and drier. Occasionally, the cause of the erythroderma is suggested by the character of the scale – for example, fine in atopic dermatitis or dermatophytosis, bran-like in seborrheic dermatitis, crusted in pemphigus foliaceus, and exfoliative (i.e. peeling) in drug reactions. The color of the skin can also vary, from pink or red to reddish brown to deep red or purple.

Pruritus, the most frequent complaint, is observed in up to 90% of patients and it varies according to the underlying cause, but is most severe in patients with dermatitis or Sézary syndrome[16]. Given the itch–scratch cycle, the skin may become thickened, and areas of lichenification are seen in one-third of cases. Patients, especially those with a chronic erythroderma, may develop dyspigmentation, with hyperpigmentation (40/90 patients, 45%) observed more frequently than hypo- or depigmentation (18/90 patients, 20%) in one series[4]. Palmoplantar keratoderma appears in ~30% of erythrodermic patients and is often an early sign in pityriasis rubra pilaris[16]. Keratoderma with scale-crust can point to crusted scabies, whereas a painful and fissured keratoderma can occur in Sézary syndrome.



Fig. 10.1 Erythroderma with desquamation. Obvious exfoliation of scale with underlying erythema.

In cases of pre-existing dermatoses, nail changes may precede the erythroderma (e.g. pits in psoriasis or horizontal ridging in atopic dermatitis), whereas others develop subsequently. Nail changes are said to be present in ~40% of patients. Most often "shiny" nails are observed, but discoloration, brittleness, dullness, subungual hyperkeratosis, Beau's lines, paronychia, and splinter hemorrhages can be seen. The nails may even be totally shed. Diffuse non-scarring alopecia of the scalp or other sites appears in 20% of patients with chronic erythroderma, including those with CTCL. Cicatricial alopecia can also develop in the setting of Sézary syndrome or erythrodermic MF.

Patients with erythroderma can develop multiple seborrheic keratoses, which may be pale in color compared with the background erythema. Colonization of the skin with *Staphylococcus aureus* is common and can lead to secondary cutaneous infections as well as bacteremia. Bilateral ectropion and purulent conjunctivitis can also develop as ocular complications (Fig. 10.2). Lastly, an exacerbation of erythroderma may follow UV irradiation or drug ingestion; this is not necessarily restricted to patients with photosensitive eczema or drug-induced erythroderma[4].

Systemic Manifestations

An awareness of potential systemic complications of erythroderma is essential. Pedal or pretibial edema is observed in ~50% of patients (182/380)[1,3–5], and results from hypoalbuminemia and a shift of fluid into extracellular spaces. In patients with CTCL-associated or drug-induced erythroderma, generalized anasarca can develop. Because of the markedly increased blood flow through the skin and increased fluid loss by transpiration, tachycardia affects 40% of patients, and there is a risk of high-output cardiac failure, particularly in the elderly. Furthermore, increased skin perfusion leads to thermoregulatory disturbances. Although hyperthermia is more frequently observed than hypothermia, most patients describe chilly, rigor-like sensations[1,2,4,6,7,10]. The chronic and excessive loss of heat can lead to compensatory hypermetabolism with subsequent development of cachexia. Anemia, reflecting both iron deficiency and chronic disease, may also be observed in patients with chronic erythroderma.

The most common extracutaneous manifestation of erythroderma is peripheral lymphadenopathy, which is found in approximately half of the patients. Even in the absence of an underlying lymphoproliferative disorder, lymphadenopathy may be prominent and, if so, histologic and molecular examination of a lymph node is recommended (in particular, immunophenotypic studies and T cell receptor gene analysis)[17]. A core or excisional lymph node biopsy is preferable to a fine needle aspirate as the former provides sufficient tissue for accurate assessment of nodal architecture and cellular morphology. The major differential diagnosis is between lymphomatous involvement and reactive dermatopathic lymphadenopathy. Prior to histopathologic examination of an enlarged lymph node, a CT or PET-CT scan can identify the most morphologically abnormal and/or fluorodeoxyglucose (FDG)-avid node.

Hepatomegaly occurs in 20% of the cases (113/578), with a slight predominance in erythroderma due to drug-induced hypersensitivity. Splenomegaly is rarely seen and occurs most often in association with systemic lymphoma[1–4,6].



Fig. 10.2 Ectropion in the setting of erythroderma.

Specific Findings of the Underlying Disease

In addition to the general features previously discussed, the clinical presentation may have features suggestive of the underlying etiology (see Tables 10.1 and 10.2).

Psoriasis

Psoriasis is the most common underlying disorder in adults with erythroderma. Invariably, psoriatic erythroderma is preceded by typical psoriatic lesions (see Ch. 8). Its onset is most often due to withdrawal of potent topical or oral corticosteroids, cyclosporine or methotrexate; occasionally, widespread flares follow a systemic infection, phototoxicity, an irritant contact dermatitis to topical medications such as tar, or withdrawal of targeted immunomodulators ("biologics"). After generalization of the erythema, the typical features of psoriasis are often lost (Fig. 10.3), and generalized pustular psoriasis with disseminated sterile subcorneal pustules may develop (see Fig. 1.6). Due to a slower turnover rate, nail changes, such as oil-drop changes, onycholysis or nail pits, may still be visible and provide clues to the diagnosis of psoriatic erythroderma. Treatment of the erythroderma may result in the subsequent reappearance of characteristic psoriatic plaques.

Atopic dermatitis

Although occurring at any age, erythroderma develops most frequently in patients with a history of moderate to severe atopic dermatitis (Fig. 10.4). As a result, well-established pre-existing lesions can be found, especially when the erythroderma is of recent onset. The pruritus is intense, and secondary excoriations or prurigo-like lesions are frequently observed. Lichenification is often prominent and atrophy of the skin due to topical corticosteroids may be seen. Increased serum IgE and eosinophilia may accompany other signs and symptoms of atopy.

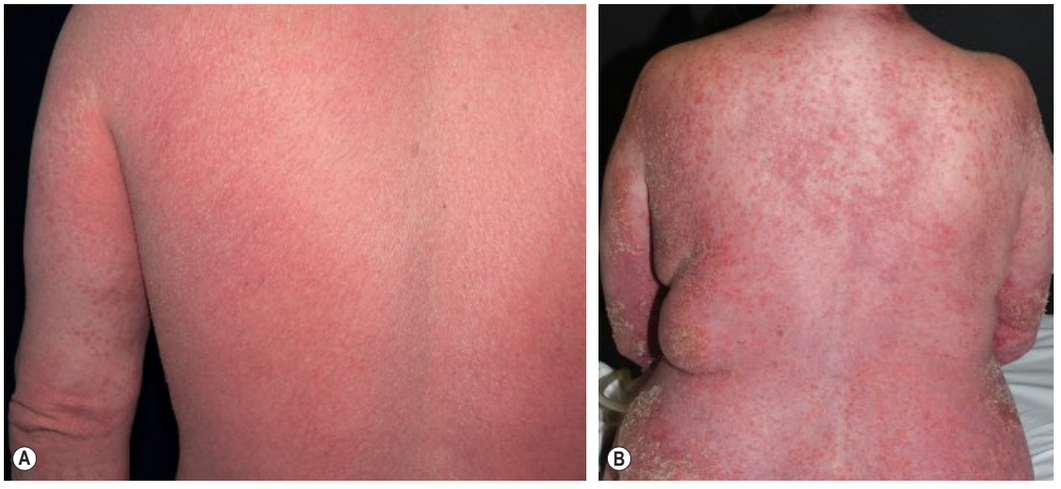


Fig. 10.3 Psoriatic erythroderma. **A** There is diffuse involvement of the trunk but a clue to the diagnosis is the individual lesions on the arm. **B** Significant exfoliation of the lateral trunk and arms. *A, Courtesy Luis Requena, MD; B, Courtesy Lorenzo Cerroni, MD.*



Fig. 10.4 Erythroderma due to atopic dermatitis. **A** Widespread erythema with fine white scaling and excoriations. **B** Fine white scaling and obvious pruritus in addition to circumoral pallor. *A, Courtesy Lorenzo Cerroni, MD; B, Courtesy Antonio Torrelo, MD.*

Drug reactions

The number of drugs implicated as causes of erythroderma is staggering (Table 10.3; see also Ch. 21)[18]. Whereas erythroderma resulting from topical medications usually begins as an irritant or allergic contact dermatitis, erythroderma due to systemic drugs often begins with the acute onset of a morbilliform or scarlatiniform exanthem. There are occasional exceptions such as the chronic eczematous eruptions associated with calcium channel blockers. In areas of greatest hydrostatic pressure (distal lower extremities), the eruption may become secondarily purpuric. While drug-induced erythrodermas have the shortest duration, usually resolving 2–6 weeks after withdrawal of the responsible drug, rarely erythroderma persists despite withdrawal of the putative drug and such cases may then be designated as idiopathic. Occasionally, there is a pseudolymphomatous presentation which can be associated with a transient peripheral blood lymphocytosis[19].

A minority of patients with DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, also referred to as drug-induced hypersensitivity syndrome (DIHS), become erythrodermic[20]. In addition to fever, these patients can develop peripheral blood eosinophilia, hepatitis, and peripheral lymphadenopathy (see Table 21.9).

Idiopathic erythroderma

In ~25% of erythrodermic patients, no underlying disease is detectable. This group consists primarily of elderly men with a chronic pruritic erythroderma in association with dermatopathic lymphadenopathy and extensive palmoplantar keratoderma (Fig. 10.5); this constellation is often referred to as "red man syndrome" or "l'homme rouge" (not to be confused with the infusion reaction ["red man syndrome"] that accompanies rapid intravenous infusions of vancomycin). When this group was compared with the entire group of erythrodermic patients, lymphadenopathy (68% vs 44%) and peripheral edema (54% vs 40%) were found to be more common than in other types of erythroderma, and hypothermia exceeded hyperthermia[21].

In one series of patients with idiopathic erythroderma, atopic dermatitis, drug-induced, and CTCL were the most common etiologies eventually identified[2]. In a second series, in which detection of a clonal T cell population in the skin was a diagnostic criterion for CTCL, the latter was the most common underlying disease[22]. However, it is important to note that in the absence of additional clinicopathologic features, the sole presence of a T cell clone in the skin is insufficient for the diagnosis of CTCL. Furthermore, peripheral blood T cell clones can be detected in elderly individuals and may reflect a diminished T cell receptor repertoire due to immune senescence rather than CTCL. Nonetheless, the detection of identical T cell clones in multiple biopsy specimens can serve as an important diagnostic clue for CTCL. Lastly, chronic actinic dermatitis should be considered in this group of patients.

DRUGS ASSOCIATED WITH ERYTHRODERMA	
Common	
• Allopurinol • β-lactam antibiotics • Carbamazepine/oxcarbazepine • Gold • Phenobarbital	• Phenytoins • Sulfasalazine • Sulfonamides* • Zalcitabine
Less common	
• Captopril/lisinopril • Carboplatin/cisplatin • Cytarabine • Cytokines (IL-2/GM-CSF) • Dapsone • Diflunisal • Dupilumab • Fluindione • Hydroxychloroquine/chloroquine • Immune checkpoint inhibitors† • Isoniazid	• Isotretinoin/acitretin • Lithium • Mercury compounds • Minocycline • Omeprazole/lansoprazole • Ribavirin • Telaprevir • Thalidomide • Tocilizumab • Vancomycin‡
Rare¶	
• Abacavir • Amiodarone • Aspirin (ASA) • Aztreonam • β-blockers • Chlorpromazine • Cimetidine • Ciprofloxacin • Clofazimine • Codeine • Erythropoietin • Fluorouracil • Imatinib • Indinavir • Lamotrigine • Methotrexate	• Mitomycin C • Nifedipine/diltiazem • Other antiretrovirals (e.g. efavirenz) • Other NSAIDs • Penicillamine • Pentostatin • Pseudoephedrine • Rifampin • St John's wort • Sulfonylureas • Tear gas (CS gas) • Terbinafine • Tobramycin • Tramadol • Vinca alkaloids • Zidovudine
*Includes furosemide. †Including ipilimumab, nivolumab, pembrolizumab. ‡Not to be confused with the infusion reaction ("red man syndrome") due to rapid infusion of drug. ¶For additional drugs, see ref. 18.	

Table 10.3 Drugs associated with erythroderma.

Cutaneous T cell lymphoma (Sézary syndrome and erythrodermic mycosis fungoides)

CTCL can mimic other causes of erythroderma and is frequently a significant diagnostic challenge. Erythroderma due to CTCL is subdivided into Sézary syndrome and erythrodermic MF (see Ch. 120). Sézary syndrome is defined by the triad of erythroderma, generalized lymphadenopathy, and peripheral blood lymphocytosis with morphologically abnormal Sézary cells; however, patients may have more limited skin involvement prior to the development of erythroderma[23]. Additional clinical features include a painful and fissured keratoderma, diffuse alopecia, edema, and leonine facies. The skin is often infiltrated or hyperpigmented (melanoerythroderma) and severe pruritus is common (Fig. 10.6).

To distinguish between Sézary syndrome and erythrodermic MF, revised criteria were proposed by the International Society of Cutaneous Lymphomas and the Cutaneous Lymphoma Task Force of the EORTC for the diagnosis of Sézary syndrome, namely erythroderma and evidence of an identical T cell clone in the blood and skin plus one of the following: (1) ≥1000 Sézary cells/mm^3; (2) a CD4:CD8 ratio of ≥10:1; or (3) an increased percentage of CD4$^+$ cells with an abnormal phenotype (≥40% CD4$^+$/CD7$^-$ or ≥30% CD4$^+$/CD26$^-$) by peripheral blood flow cytometry (B_2 in the TNMB classification; see Table 120.4). The latter cellular analysis provides a more objective measure of circulating tumor burden[24]. Erythrodermic MF can also have an identical T cell clone in the skin and blood, but flow cytometry results are normal or demonstrate low-level blood involvement (B_0 or B_1). In addition, diagnosis of erythrodermic MF can be challenging because the histopathologic findings are not diagnostic in at least one-third of patients.

Longitudinal evaluation, including repeated skin biopsies and PET-CT scans as well as lymph node biopsies and peripheral blood flow cytometry, is required to distinguish CTCL from idiopathic erythroderma. Identification of identical dominant T cell clones via more sensitive and specific high-throughput T cell receptor sequencing may prove helpful. Rarely patients with other hematologic malignancies, in particular angioimmunoblastic T cell lymphoma, adult T cell leukemia/lymphoma or T cell prolymphocytic leukemia, can present with erythroderma due to cutaneous infiltration of malignant T cells.

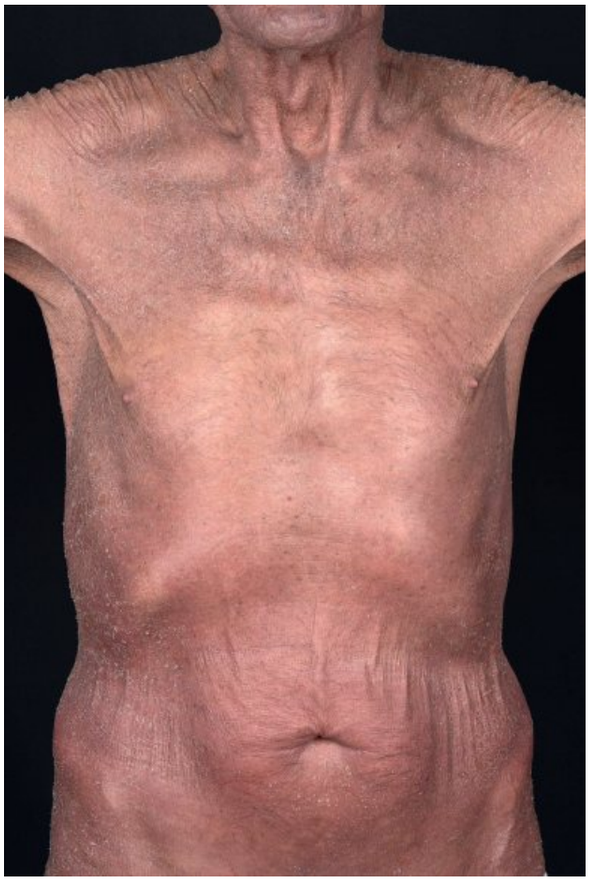


Fig. 10.5 Idiopathic erythroderma. This is the type of patient who requires longitudinal evaluation to exclude the development of cutaneous T cell lymphoma. *Courtesy Lorenzo Cerroni, MD.*

Pityriasis rubra pilaris

Erythrodermic pityriasis rubra pilaris (PRP) can be observed in children and adults (see Ch. 9). Usually, the lesions have a salmon to orange–red color. The degree of scaling varies, but it can be marked with large scales (Fig. 10.7). The combination of follicular keratotic papules on the knees, elbows and dorsal aspects of the fingers plus nappes claires (islands of uninvolved skin within the erythroderma) favors the diagnosis of PRP (Fig. 10.8). When the classic histologic features are present (see below), this is also helpful in distinguishing PRP from psoriasis. Occasionally, CTCL and the Wong type of dermatomyositis can have an appearance similar to PRP.

Papuloerythroderma of Ofuji

This represents a distinctive reaction pattern most often described in older men. Pruritic, monomorphic reddish brown papules often become confluent, with sparing of skin folds ("deck-chair" sign). In one review of

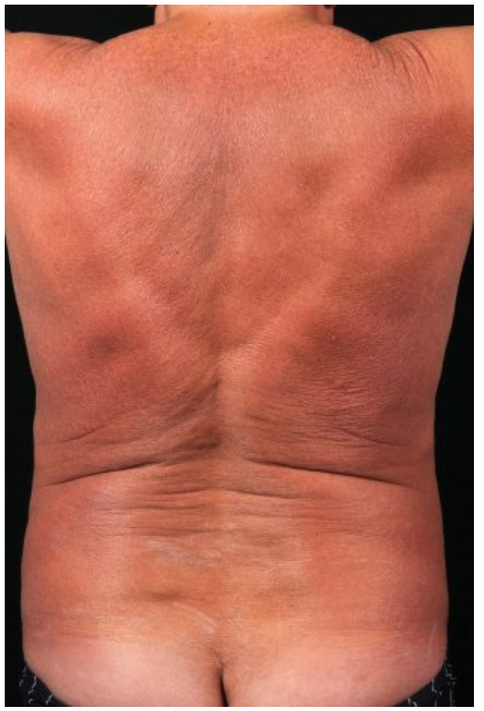


Fig. 10.6 Sézary syndrome. Diffuse erythroderma with a red–brown color. Note the evidence of scratching on the lower back. *Courtesy Lorenzo Cerroni, MD.*



Fig. 10.7 Erythroderma due to pityriasis rubra pilaris. Large thin scales are seen as well as the characteristic orange–red color.



Fig. 10.8 Erythroderma secondary to pityriasis rubra pilaris. Islands of sparing are noted on the flank and breast. Note the salmon color.



Fig. 10.9 Erythroderma due to pemphigus foliaceus. Generalized erythema with widespread scale-crusts and large areas of erosion.

170 reported cases, a causative factor was not identified in the majority of patients. Of the remaining individuals, CTCL represented the most common underlying etiology and thus needs to be excluded (see Table 10.1 for additional etiologies)[25].

Paraneoplastic erythroderma

Paraneoplastic erythroderma is most commonly associated with lymphoproliferative disorders, including systemic lymphomas and rarely thymomas. In patients with solid organ malignancies, erythroderma is rare and usually only appears during the late stages of the disease. Of note, in these patients the skin does not contain malignant cellular infiltrates. Fine scales and erythema can be accompanied by a brownish hue (i.e. melanoerythroderma). Additional signs of malignancy, such as cachexia or fatigue, may be seen.

Bullous dermatoses

Among the bullous dermatoses, pemphigus foliaceus is the one most likely, albeit rarely, to present as erythroderma; erythrodermic forms of paraneoplastic pemphigus and bullous pemphigoid have also been reported (see Table 10.1; see also Chs. 29 and 30). In pemphigus foliaceus, impetigo-like blisters and erosions are followed by collarettes of scale and scale-like crusts (Fig. 10.9). The erythroderma is usually preceded by localized lesions on the face and upper trunk.

Ichthyoses

Erythroderma due to one of the syndromic or non-syndromic inherited ichthyoses is usually present from birth or infancy (see Table 57.1)[26,27]. In neonates, congenital ichthyosiform erythroderma (CIE; previously referred to as non-bullous CIE), epidermolytic ichthyosis (previously referred to as bullous CIE), and Netherton syndrome should be considered (see Table 10.2). As a rule, CIE presents as a collodion baby (90% of the cases)[28], and within a few days after birth, an erythroderma with fine white scaling appears. Epidermolytic ichthyosis initially presents as generalized erythema with superimposed superficial blisters and erosions. This disorder may be mistakenly diagnosed as staphylococcal scalded skin syndrome or as a form of epidermolysis bullosa. Later, children develop spiny, corrugated hyperkeratoses, particularly in flexural areas, and blisters and erosions become less prevalent. Netherton syndrome manifests as an ichthyosiform erythroderma in neonates. It is associated with trichorrhexis invaginata ("bamboo hair"), elevated serum levels of IgE, and an immune defect that can result in life-threatening infections, particularly within the first years of life. Later, either the ichthyosiform erythroderma persists or ichthyosis linearis circumflexa develops, which is characterized by garland-like scaly eruptions. Because there are very rare ichthyoses that can present with an ichthyosiform erythroderma as well as multiple genes associated with a specific ichthyosis (see Table 57.1), molecular diagnostics consisting of next generation sequencing of large gene panels or whole exome sequencing have become an important evaluation tool[15].

Staphylococcal scalded skin syndrome

Staphylococcal scalded skin syndrome (SSSS; see Ch. 74) is seen primarily in children (<5 years of age), and it is due to a circulating exfoliative toxin produced by *S. aureus*. Since desmoglein 1 is cleaved by exfoliative toxin A, pemphigus foliaceus and SSSS exhibit clinical similarities, with the latter often becoming erythrodermic. Common foci for the initial infection include the nares, nasopharynx, conjunctivae, and umbilicus. After a period of 1–2 days of a low-grade fever, large areas of tender erythema develop. The skin appears tense and subcorneal blisters appear, which subsequently desquamate. A very similar syndrome, the toxic shock syndrome, can be caused by staphylococcal or streptococcal exotoxins, but more commonly affects adults and acral exfoliation has a delayed appearance, usually 2 weeks later.

Omenn syndrome

Omenn syndrome represents an autosomal recessive form of severe combined immunodeficiency (SCID; see Table 60.16). It is characterized by failure to thrive, leukocytosis with prominent eosinophilia, hypogammaglobulinemia, and elevated serum IgE levels. Cutaneous findings, which appear in neonates, are generally the first sign of the syndrome and include an erythroderma with diffuse alopecia. Systemic manifestations include prominent lymphadenopathy, hepatosplenomegaly, and recurrent diarrhea. In the absence of hematopoietic stem cell or bone marrow transplantation, severe infections lead to early death. Additional forms of SCID can also cause exfoliative dermatitis in neonates (see Table 60.16).

PATHOLOGY

Although sometimes subtle, histopathologic features of the underlying disease are present in about two-thirds of patients (see Tables 10.1 and 10.2)[29]. As a result, biopsy specimens in one-third of individuals with erythrodermic MF or Sézary syndrome are non-diagnostic[30]. Of note, epidermotropism of neoplastic lymphocytes is less commonly observed in these two disorders than in conventional MF[29]. Diagnostic findings are frequently found in psoriatic erythroderma[31], but less often in PRP.

It is important to remember that concurrent topical or systemic therapies as well as superimposed phenomena, e.g. atopic diathesis, contact dermatitis, impetiginization, can modify the histopathologic findings. In addition, multiple and sequential biopsies are often necessary in the evaluation of erythroderma.

DIFFERENTIAL DIAGNOSIS

Erythroderma is a clinical presentation for a variety of diseases, and identification of the underlying etiology represents one of the most complex challenges in dermatology (Figs. 10.10 and 10.11; see Tables 10.1 and 10.2). The evaluation starts with a complete medical history: up to 45% of the patients will have a prior history of a more localized skin disease, and ~20% of cases represent drug reactions[1–6]. A comprehensive clinical examination may reveal additional clues to the underlying disease. However, it is important to recognize that pre-morbid susceptibilities may modify the clinical morphology of an erythroderma, e.g. a drug reaction in an atopic individual may appear lichenified. Once the number of possible underlying diseases is reduced, further laboratory investigation can aid in establishing the final diagnosis. Hopefully in the future, specific diagnostic biomarkers will emerge that can assist in establishing a precise etiology[32]. For erythroderma in neonates and young children, molecular diagnostics represent a critical laboratory investigation (see above)[15].

TREATMENT

Erythroderma can represent a serious medical threat to the patient and therefore hospitalization may be required. Regardless of the underlying disease, the initial management consists of nutritional assessment, correction of fluid and electrolyte imbalances, prevention of hypothermia, and both prevention and treatment of secondary infections. Sedating oral antihistamines may ease severe pruritus[16]. Systemic corticosteroids may be necessary in idiopathic erythroderma and drug reactions. With an initial prednisone dose of 1–2 mg/kg/day and a maintenance dose of 0.5 mg/kg/day or less, rapid clearing of the erythroderma can be achieved. Caution must be exercised upon tapering, as rebound may occur. Topical therapy includes open wet dressings and bland emollients or low-potency corticosteroid ointments. High-potency topical corticosteroids should be reserved for lichenified areas, and because of enhanced transcutaneous absorption via erythrodermic skin, chronic, extensive application should be avoided. Coal tar ointments and phototherapy may aggravate the condition.

In neonates and children with erythroderma, management of fluid and electrolyte balance is critical in order to prevent hypernatremic dehydration. Emollients, topical antibiotics and, depending upon the extent and severity of the secondary infections, systemic antibiotics are administered. Due to increased transcutaneous absorption, topical salicylic and lactic acid should be avoided[33].

Treatment of specific underlying diseases is outlined in the respective chapters (see Tables 10.1 and 10.2). In the case of psoriatic erythroderma, administration of methotrexate, acitretin, cyclosporine or targeted immunomodulators ("biologics") is preferred over systemic corticosteroids, given the risk of a pustular flare when corticosteroids are tapered[34]. For drug reactions, discontinuation of all non-essential drugs and all suspected drugs will usually lead to

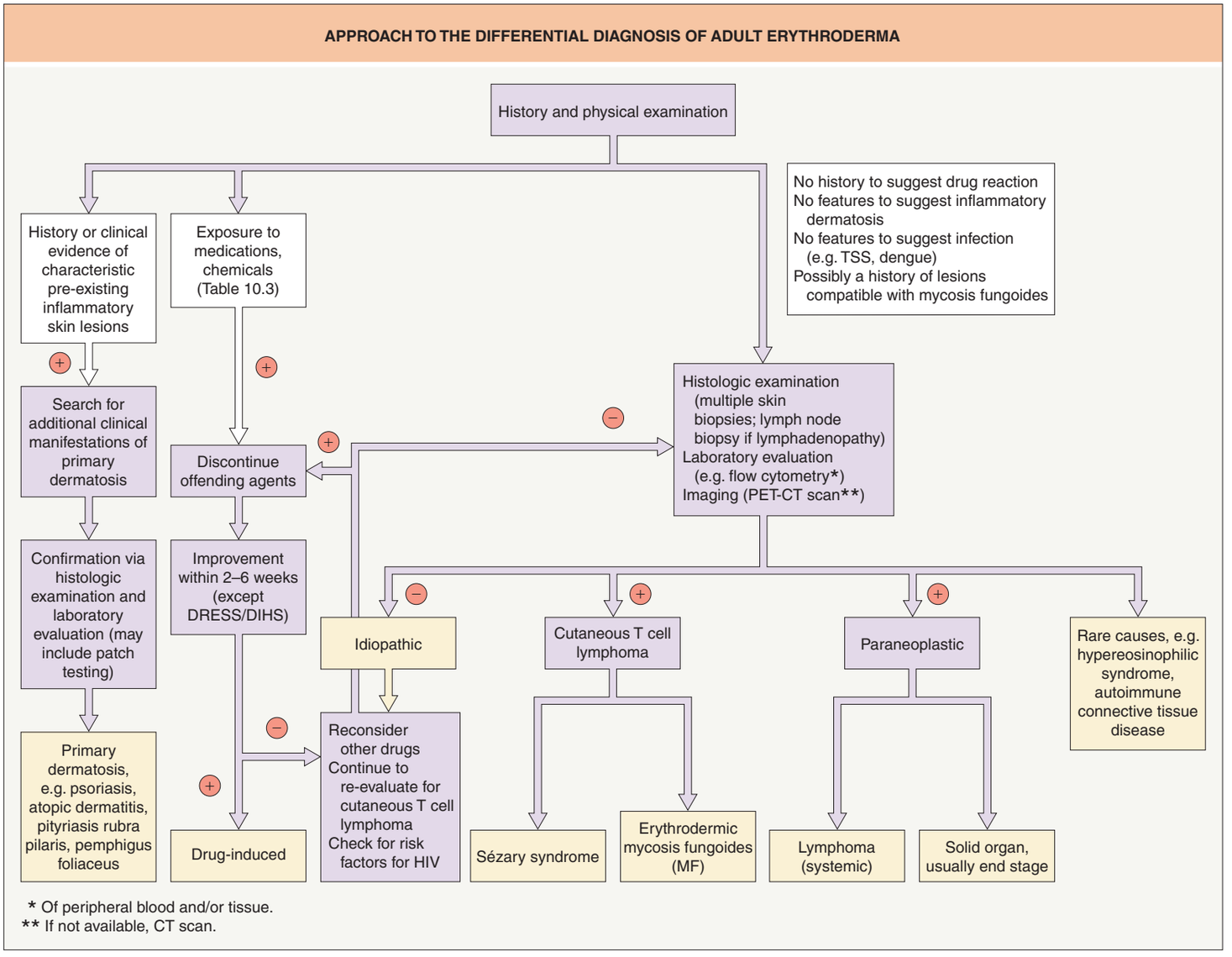
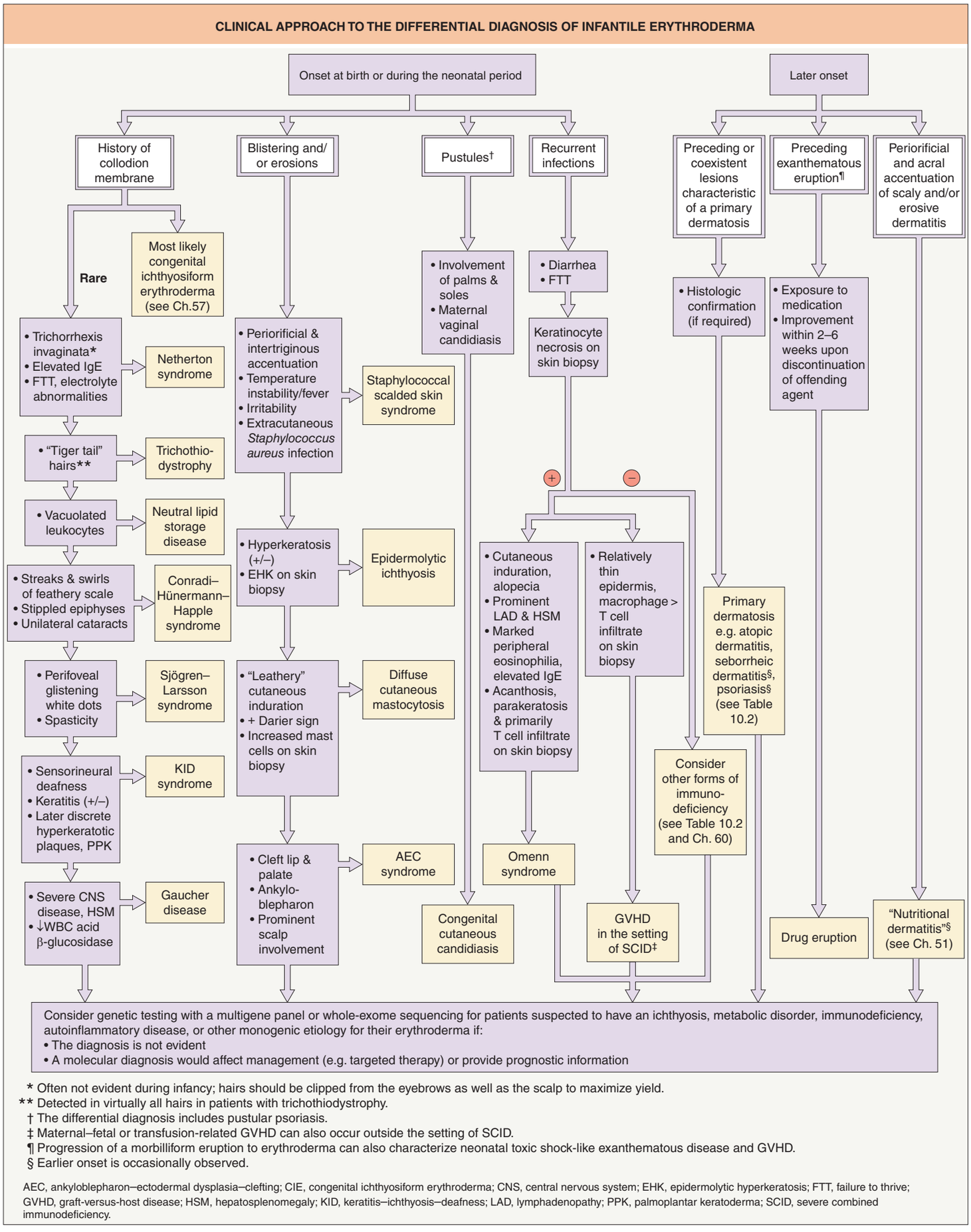


Fig. 10.10 Approach to the differential diagnosis of adult erythroderma. CT, computed tomography; DRESS/DIHS, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome; PET, positron emission tomography; TSS, toxic shock syndrome.



* Often not evident during infancy; hairs should be clipped from the eyebrows as well as the scalp to maximize yield.
** Detected in virtually all hairs in patients with trichothiodystrophy.
† The differential diagnosis includes pustular psoriasis.
‡ Maternal–fetal or transfusion-related GVHD can also occur outside the setting of SCID.
¶ Progression of a morbilliform eruption to erythroderma can also characterize neonatal toxic shock-like exanthematous disease and GVHD.
§ Earlier onset is occasionally observed.

AEC, ankyloblepharon–ectodermal dysplasia–clefting; CIE, congenital ichthyosiform erythroderma; CNS, central nervous system; EHK, epidermolytic hyperkeratosis; FTT, failure to thrive; GVHD, graft-versus-host disease; HSM, hepatosplenomegaly; KID, keratitis–ichthyosis–deafness; LAD, lymphadenopathy; PPK, palmoplantar keratoderma; SCID, severe combined immunodeficiency.

Fig. 10.11 Clinical approach to the differential diagnosis of infantile erythroderma.

improvement within 2–6 weeks (with the exception of some patients with DRESS/DIHS). However, systemic prednisone (1–2 mg/kg/day) or even the co-administration of IVIg may be useful in severe cases. After careful exclusion of any underlying cause, idiopathic erythroderma may be treated with low-potency topical corticosteroids and oral antihistamines. In refractory cases, cyclosporine has been used successfully, with an initial dosage of 5 mg/kg/day, and subsequent reduction to 1–3 mg/kg/day. Additional steroid-sparing agents include methotrexate, azathioprine and mycophenolate mofetil, all of which have been used anecdotally, with dosages similar to those for recalcitrant atopic dermatitis.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 10.1 Erythroderma with desquamation. Obvious exfoliation of scale with underlying erythema.



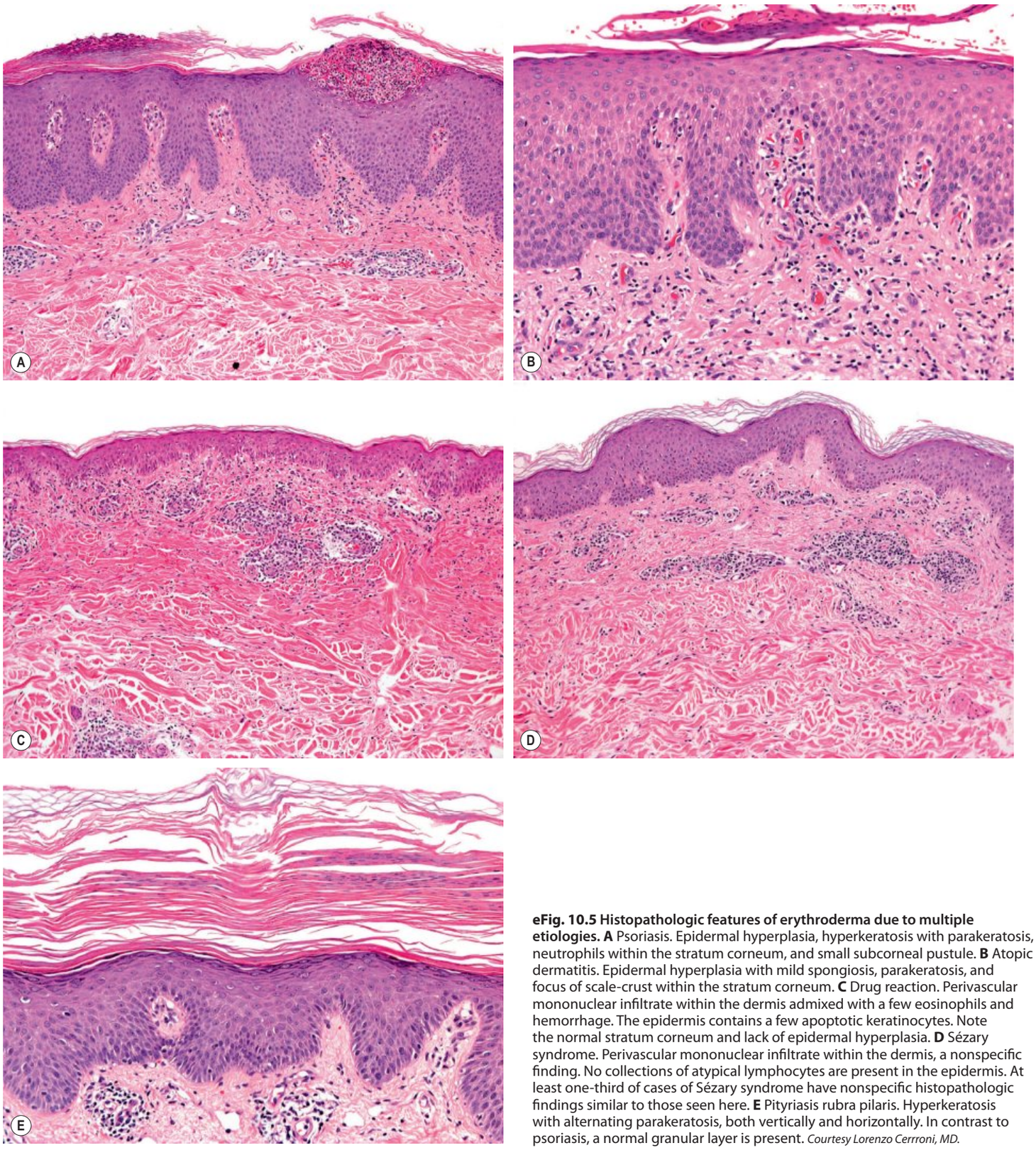
eFig. 10.2 Psoriatic erythroderma. The disease flare correlated with the administration of lithium. *Courtesy Jean L. Bolognia, MD.*



eFig. 10.3 Psoriatic erythroderma. Nail findings (pitting and onycholysis with a proximal rim of inflammation) point to the diagnosis of psoriasis.



eFig. 10.4 Eruptive seborrheic keratoses in a patient with idiopathic erythroderma. *Courtesy Jean L. Bolognia, MD.*



eFig. 10.5 Histopathologic features of erythroderma due to multiple etiologies. A Psoriasis. Epidermal hyperplasia, hyperkeratosis with parakeratosis, neutrophils within the stratum corneum, and small subcorneal pustule. **B** Atopic dermatitis. Epidermal hyperplasia with mild spongiosis, parakeratosis, and focus of scale-crust within the stratum corneum. **C** Drug reaction. Perivascular mononuclear infiltrate within the dermis admixed with a few eosinophils and hemorrhage. The epidermis contains a few apoptotic keratinocytes. Note the normal stratum corneum and lack of epidermal hyperplasia. **D** Sézary syndrome. Perivascular mononuclear infiltrate within the dermis, a nonspecific finding. No collections of atypical lymphocytes are present in the epidermis. At least one-third of cases of Sézary syndrome have nonspecific histopathologic findings similar to those seen here. **E** Pityriasis rubra pilaris. Hyperkeratosis with alternating parakeratosis, both vertically and horizontally. In contrast to psoriasis, a normal granular layer is present. *Courtesy Lorenzo Cerrroni, MD.*

Lichen Planus and Lichenoid Dermatoses 11

Tetsuo Shiohara and Yoshiko Mizukawa

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LICHEN PLANUS

Synonym: ■ Lichen ruber planus

Key features

- Idiopathic inflammatory disease of the skin, hair, nails and mucous membranes, seen most commonly in middle-aged adults
- Flat-topped violaceous papules and plaques favoring the wrists, forearms, genitalia, distal lower extremities, and presacral area
- Clinical variants include actinic, annular, atrophic, bullous, hypertrophic, inverse, linear, ulcerative, vulvovaginal–gingival, lichen planopilaris, lichen planus pigmentosus, and drug-induced
- Some lichenoid drug eruptions have a photodistribution, while others are clinically and histologically indistinguishable from idiopathic lichen planus
- The most commonly incriminated drugs include angiotensin-converting enzyme (ACE) inhibitors, thiazide diuretics, antimalarials, quinidine, and, especially in the past, gold
- In most patients, the therapeutic approach to immune checkpoint inhibitor (ICI)-related lichenoid eruptions consists of topical corticosteroids and continuation of the ICI; systemic corticosteroids and a brief drug holiday may be required when the eruption is severe or recalcitrant
- Histologically, there is a dense, band-like lymphocytic infiltrate and keratinocyte apoptosis with destruction of the epidermal basal cell layer
- In this T cell-mediated autoimmune disorder, basal keratinocytes express altered self-antigens on their surface

Introduction

Lichen planus (LP), the prototype of lichenoid dermatoses, is an idiopathic inflammatory disease of the skin and mucous membranes. Classic LP is characterized by pruritic, violaceous papules that favor the extremities[1]. Histologically, a dense, band-like lymphocytic infiltrate is seen underlying an acanthotic epidermis with hypergranulosis, apoptosis, and destruction of the basal cell layer. The etiology and pathogenesis of LP are not fully understood, but the disorder has been associated with multiple environmental exposures, including viral infections, medications, vaccinations, and dental restorative materials.

LP-like lesions that resemble idiopathic LP may also develop in chronic GVHD, where alloreactive T cells that recognize foreign major histocompatibility complex (MHC) molecules are central effectors (see Ch. 52). This lends support to the hypothesis that an autoimmune reaction against epitopes on lesional keratinocytes that have been modified by viral or drug antigens may be responsible for LP.

A number of clinically distinct inflammatory dermatoses have in common varying elements of a lichenoid tissue reaction, and they are referred to as lichenoid dermatoses (Table 11.1).

History

The term lichen planus was initially introduced by Erasmus Wilson in 1869 to describe the condition that had been previously named leichen ruber by Hebra[1].

Epidemiology

Although its incidence varies depending upon geographic locale, cutaneous LP has been reported to affect from 0.2% to 1% of the adult population[1], whereas oral lesions have been observed in up to 1%–4% of the population. There is no overt racial predisposition. LP most commonly has its onset during the fifth or sixth decade, with two-thirds of patients developing the disease between the ages of 30 and 60 years. It is rare in both infants and the elderly and, typically, only 1%–4% of patients are children. However, more recent studies have suggested that LP may actually be more common in children, especially in Arab populations. Oral LP is also quite uncommon in young people and it usually affects middle-aged to elderly individuals (mean age at diagnosis being 52 years). Although LP is frequently thought to have no gender predilection, some studies have found that women were affected nearly twice as often as men.

Mucosal involvement, particularly oral lesions, is observed in up to 75% of patients with cutaneous LP, but the former can be the only manifestation of the disease. Only 10%–20% of patients whose initial presentation is oral LP will eventually develop cutaneous LP. Although reports of familial LP are rare, it may occur more frequently than previously thought; for example, LP occurs in up to 10% of first-degree relatives of affected patients. Cases of familial LP tend to have an earlier age of onset, a higher relapse rate, and more frequent oral mucosal involvement. Of note, reports of concurrent LP in monozygotic twins who were living together suggest an environmental trigger. Lastly, individuals with Good syndrome, a primary immunodeficiency that is associated with thymomas, there is an increased risk of developing lichen planus.

Pathogenesis

There is a growing body of evidence that LP represents T cell-mediated autoimmune damage to basal keratinocytes that express altered self-antigens on their surface.

Target antigens

Clinical observations and anecdotal evidence have long suggested a relationship between exposure to a number of exogenous agents (e.g. viruses, medications, contact allergens) and the development of LP (see Table 11.1). In theory, T cells that normally do not respond to skin (epidermis)-restricted antigens are primed by exogenous agents when the latter possess cross-reactive antigens that can activate autoreactive T cells via molecular mimicry. In other words, the T cell receptors on the T cells that induce mucocutaneous LP could cross-react with exogenous antigens.

Hepatitis C virus

Of the many potential exogenous antigens, significant attention has been focused on the possible role of viruses, particularly hepatitis C virus (HCV). In several case–control studies, the prevalence of HCV

MAJOR LICHENOID DERMATOSES AND POSSIBLE ASSOCIATED TARGET ANTIGENS	
Lichenoid dermatoses	**Possible target antigens**
Lichen planus	V, D, C, T
Lichenoid drug eruption	D
Erythema dyschromicum perstans	V, D
Graft-versus-host disease (see Ch. 52)	Allo, V
Keratosis lichenoides chronica	
Pityriasis lichenoides* (see Ch. 9)	V
Lichen nitidus	V
Lichen striatus	V
Lichen sclerosus (see Ch. 44)	V, Auto
Fixed drug eruption (see Ch. 21)	D
Erythema multiforme (see Ch. 20)	V, D, C
Lupus erythematosus (see Ch. 41)	V, Auto, D
Dermatomyositis (see Ch. 42)	V, Auto, T, D
Paraneoplastic pemphigus (see Ch. 29)	T
Mycosis fungoides (see Ch. 120)	T, V
Lichenoid pigmented purpura (see Ch. 22)	D, V
Secondary syphilis (see Ch. 82)	
Lichenoid reaction to tattoo	C
*Acute and chronic.	

Table 11.1 Major lichenoid dermatoses and possible associated target antigens. The variation in clinical presentations may reflect the differences in the effector mechanisms by which epidermal cells are damaged and/or target antigens. The shaded entities are discussed in this chapter. Allo, alloantigens; Auto, autoantigens; C, contact allergens; D, drug antigens; T, tumor antigens; V, viral antigens.

(3.5%–38%) was 2- to 13.5-fold higher in patients with LP than in controls. This association seems to be strongest in Japanese and Mediterranean populations, probably due to the high prevalence of HCV infection in these countries. In the US, one case–control study found that 12 (55%) of 22 patients with LP had anti-HCV antibodies, and this was significantly higher than the 25% of 40 psoriatic patients or the 0.17% of blood donors who tested positive[2]. However, a systematic review and meta-analysis of existing epidemiologic studies demonstrated that an association between LP and HCV infection did exist in certain geographic regions (e.g. East and Southeast Asia, South America, the Middle East, Europe), but not in others (e.g. North America, South Asia, and Africa)[3].

An increased frequency of the HLA-DR6 allele has been reported in Italian patients with HCV-associated oral LP[4], raising the possibility that $CD4^+$ T cells activated upon recognition of HCV-encoded peptides bound to HLA-DR6 molecules could be directly involved in the pathogenesis of LP. In support of this possibility, HCV tetramer analysis has shown that HCV-specific $CD4^+$ and/or $CD8^+$ T cells are present with higher frequency in oral LP lesions compared with the circulating compartment, suggesting that they play a role in the pathogenesis of LP[5].

Of the various types of LP, it is the oral form that is most commonly viewed as a manifestation of HCV infection. By PCR, HCV RNA was detected in 93% of oral LP lesions[6], suggesting HCV replication within LP lesions. However, these PCR results were not confirmed by other studies. In patients receiving anti-HCV therapy, originally interferon and ribavirin and more recently direct-acting antiviral agents that target nonstructural proteins, the effects on mucocutaneous LP have varied[7]. Lesions have improved in some patients while others experienced a flare of disease activity.

Other viruses

With regard to the role of other viruses in LP, human herpesvirus *(HHV)-6* and *HHV-7* DNA has been detected in some LP lesions[8]. Remission of LP was associated with decreased HHV-7 protein expression, in particular within infiltrating plasmacytoid dendritic cells[9]. There have been multiple reports that either *SARS-CoV-2* (COVID-19) infection or COVID-19 vaccines can trigger LP[10]. Of note, in two recent systematic reviews, a stronger association was observed between LP and COVID-19 vaccination as compared to COVID-19 infection[10a,10b].

There are also sporadic case reports of LP lesions developing in areas recently affected by herpes simplex virus (*HSV*) or varicella–zoster virus (*VZV*) infections[11,12] (see Table 80.7). Possible explanations include a nonspecific Koebner phenomenon or isotopic response or an immune reaction to the virus. In an immunohistochemical study involving eight patients, VZV-gE antigen was detected within the eccrine epithelia of LP lesions if they were in a dermatomal (zosteriform) pattern but not if they were in a linear array along the lines of Blaschko[12]. Two of the patients with the dermatomal pattern reported no preceding episode of herpes zoster, leading the authors to speculate if LP could be triggered by subclinical VZV reactivation. A link between human papillomavirus (*HPV*) and oral LP has also been suggested based upon the identification of a clonal expansion of HPV-16-specific $CD8^+$ T cells within the lesions[13].

While measurements (via PCR) of viral genomes within lesional skin or blood have been inconclusive, as noted above, virus-specific T cells have been detected within lesions. This suggests that the pathology is a direct consequence of immune responses, perhaps to virally induced alterations in the antigenicity of epidermal cells rather than the viruses themselves. However, it is also possible that virus-specific T cells are nonspecifically trapped within sites of inflammation, having been activated systemically or locally at distant sites, and then they expand and mediate tissue damage "accidently" due to cross-reactivity with other antigens (e.g. drugs)[14].

Vaccines

In addition to COVID-19 vaccines (see above), a number of reports have described the appearance of LP after administration of influenza vaccines, rabies vaccines, and different types of HBV vaccines[15]. The time interval between the initial dose and the development of cutaneous or mucosal lesions has varied from a few days to 5 months. One recommendation is that patients who develop LP before completing their vaccination series should avoid further injections because of an increased risk of developing severe LP lesions, including the bullous variant.

Bacteria

Investigations regarding a relationship between bacteria and cutaneous LP have been limited. In tissue and saliva samples, the diversity and composition of microbial communities differed when patients with oral LP were compared to healthy controls, suggesting a possible role for the local microbiome.

Contact allergens

The role of contact allergy to a variety of metals in the exacerbation or induction of oral LP has been well described, based on exposure to metallic dental restorations or constructions, positive patch test results, and then regression or complete clearing after removal of the sensitizing metal and replacement with other materials. However, improvement has also been observed after removal of metals in patch test-negative patients. The metals reported to aggravate oral LP include amalgam (mercury), copper, and gold.

Of note, the development of contact allergy to metals within dental restorations in patients with LP could be explained by easy penetration of the metal via damaged mucosa.

Drugs

Cutaneous eruptions similar or even identical to LP, both clinically and histologically, have been linked to a variety of drugs. The terms "lichen planus-like" and "lichenoid" are often used to describe this phenomenon[16,17]. A wide variety of drugs have been associated with lichenoid drug eruptions and the list of such drugs steadily increases (Table 11.2). However, recurrence of the lesions subsequent to drug rechallenge has not been documented for the majority of these drugs.

Autoantigens, including tumor antigens

In occasional patients, LP has been reported as a possible autoimmune reaction triggered by an underlying neoplasm. Also, a lichenoid tissue reaction is seen in patients with paraneoplastic pemphigus. The temporal relationship between LP and the underlying neoplasm in the

DRUGS IMPLICATED IN LICHENOID DRUG ERUPTIONS	
Antimicrobials	
• Ethambutol • Griseofulvin • Isoniazid • Ketoconazole	• Pyrimethamine • Streptomycin • Sulfamethoxazole • Tetracyclines
Antihypertensives	
• **Captopril** • **Enalapril** • **Labetalol** • **Methyldopa** • **Propranolol**	• Diazoxide* • Doxazosin • Nifedipine • Prazosin
Antimalarials	
• **Chloroquine** • **Hydroxychloroquine**	• **Quinacrine**
Antidepressants, anti-anxiety drugs, antipsychotics and anticonvulsants	
• Amitriptyline • Carbamazepine • Chlorpromazine • Imipramine	• Levomepromazine • Lorazepam • Methopromazine • Phenytoin
Diuretics	
• **Chlorothiazide** • **Hydrochlorothiazide**	• Furosemide • Spironolactone
Hypoglycemic agents	
• Chlorpropamide • Glyburide	• Tolazamide • Tolbutamide
Immune checkpoint inhibitors	
• Anti-CTLA-4 antibodies (e.g. ipilimumab) • **Anti-PD-1 antibodies** (e.g. nivolumab, pembrolizumab)	• **Anti-PD-L1 antibodies** (e.g. atezolizumab, avelumab, durvalumab)
Metals	
• **Gold salts**† • Arsenic • Bismuth	• Mercury • Palladium
NSAIDs	
• Acetylsalicylic acid • Benoxaprofen • Diflunisal • Fenclofenac • Flurbiprofen	• **Ibuprofen** • Indomethacin • Naproxen • Piroxicam • Sulindac
TNF inhibitors	
• **Etanercept** • **Infliximab**	• **Adalimumab** • Lenercept
Miscellaneous drugs	
• Allopurinol • Amiphenazole • Anakinra • Cinnarizine • Crizotinib • Cyanamide • Dapsone • Denosumab • Dupilumab • Enzalutamide • Gemfibrozil • Hydroxyurea • **Imatinib** • Interferon-α • Iodides • Isotretinoin • Levamisole	• Lithium • Mercapto-propionylglycine • Mesalamine • Methycran • Omeprazole • Orlistat • **Penicillamine** • Procainamide • Propylthiouracil • Pyrithioxin • Simvastatin • **Quinidine** • Quinine • Rituximab • Sildenafil • Sulfasalazine • Trihexyphenidyl
*Also used to treat hypoglycemia. †Including in alcoholic beverages, e.g. Goldschläger, and foods, e.g. gold luster dust.	

Table 11.2 Drugs implicated in lichenoid drug eruptions. More commonly associated drugs are in **bold**. Topical medications, e.g. imiquimod, can exacerbate LP. CTLA-4, cytotoxic T lymphocyte-associated antigen; NSAIDs, nonsteroidal anti-inflammatory drugs; PD, programmed cell death protein; PD-L, programmed cell death ligand.

reported patients suggests that the neoplasms may have stimulated a cell-mediated immune response against tumor antigens that led to the generation of autoreactive T cells that cross-reacted against antigens expressed on epidermal cells.

Although numerous case reports describe patients with both LP and autoimmune diseases, studies with larger numbers of patients with LP have shown no increased incidence of autoimmune diseases. Multiple investigators have described a significant association between specific HLA antigens (e.g. HLA-DR1, -DR6, -DR9) and LP. However, a true association with a particular HLA allele has been difficult to establish because of significant geographic heterogeneity and clinical patient selection.

A murine model of LP has been established by employing autoreactive T cells capable of producing interferon-γ (IFN-γ) and tumor necrosis factor (TNF-α) (Fig. 11.1)[18]. Intradermal inoculation of $CD4^+$ autoreactive T cell clones into the footpads of syngeneic mice can induce local histologic changes similar to LP or lichenoid skin diseases. In this model, the autoreactive T cells can respond to self MHC class II antigens constitutively expressed on macrophages and Langerhans cells, and they migrate into the epidermis, resulting in epidermal injury. These T cells, therefore, can induce LP-like lesions without any alteration in the antigenicity of the epidermis. In subsequent studies, desmoglein-specific T cells were also capable of inducing LP-like changes histologically[19]. Thus, LP could be induced by different types of T cells – those that specifically target antigens constitutively expressed in the epidermis but also T cells that target antigens not expressed within the epidermis.

Additionally, in the natural disease process, exogenous agents (e.g. viral infections, drugs) could induce alterations in the antigenicity of epidermal cells and trigger the activation of T cells. Of note, such autoaggressive reactions could function to eliminate abnormal keratinocytes altered by these exogenous agents. However, in the situation where T cells initially responding to self-antigens modified by exogenous agents subsequently become cross-reactive with some self-epitopes, these T cells would then chronically respond to the previously ignored self-epitopes, leading to perpetuation of an autoimmune attack by such T cells[18] rather than elimination of the abnormal keratinocytes.

Effector cells

There are conflicting data regarding the phenotype of the inflammatory infiltrate in LP lesions. Although initial immunohistochemical studies showed that the cellular infiltrate contained an increased ratio of $CD4^+$:$CD8^+$ T cells[20], other investigators found a predominance of $CD8^+$ T cells, particularly in older lesions. Evidence to support the crucial role of $CD8^+$ T cells in autoimmune damage to basal keratinocytes has been provided by $CD8^+$ T cells isolated from lesional skin; these T cells exhibited specific cytotoxic activity against autologous lesional and normal keratinocytes[21].

Cellular damage, as evidenced by apoptotic DNA fragments, is greatest within the basal layer of the epidermis. A possible mechanism is as follows: IFN-γ produced by $CD8^+$ T cells upregulates Fas expression by keratinocytes, rendering them susceptible to T cell-mediated, Fas ligand-driven apoptosis. This interaction triggers a cascade of intracellular enzymatic reactions resulting in DNA fragmentation (see Ch. 107). In addition to Fas, death receptor-induced apoptosis involves signaling processes via TNF-R1, TRAIL-R1 and 2, and DR3 or DR6. Because type 1 helper T cells (Th1), such as the autoreactive $CD4^+$ T cells in the murine model (see Fig. 11.1), can produce large amounts of IFN-γ and lymphotoxin-α (TNF-β) upon activation and thereby induce or enhance the expression of apoptosis-associated proteins such as Fas and TRAIL, they may also play a role in extensive epidermal damage by promoting apoptotic death of keratinocytes. More recent studies have shown that granule exocytosis with release of perforin and granzyme B, rather than the Fas/Fas-ligand system, is the main pathway of cytotoxicity mediated by $CD4^+$ and $CD8^+$ T cells in humans[22]. However, a combination of the two mechanisms is most likely, with predominance depending upon the particular stage in the disease process.

The innate immune system, regulatory T cells (Tregs), and Th17 cells

Recent studies have provided evidence for the involvement of Toll-like receptor (TLR) signaling in the induction of autoimmunity. As depicted in Figure 4.1, certain TLRs recognize viral RNA as well as imidazoquinolones (e.g. imiquimod). Interestingly, topical application

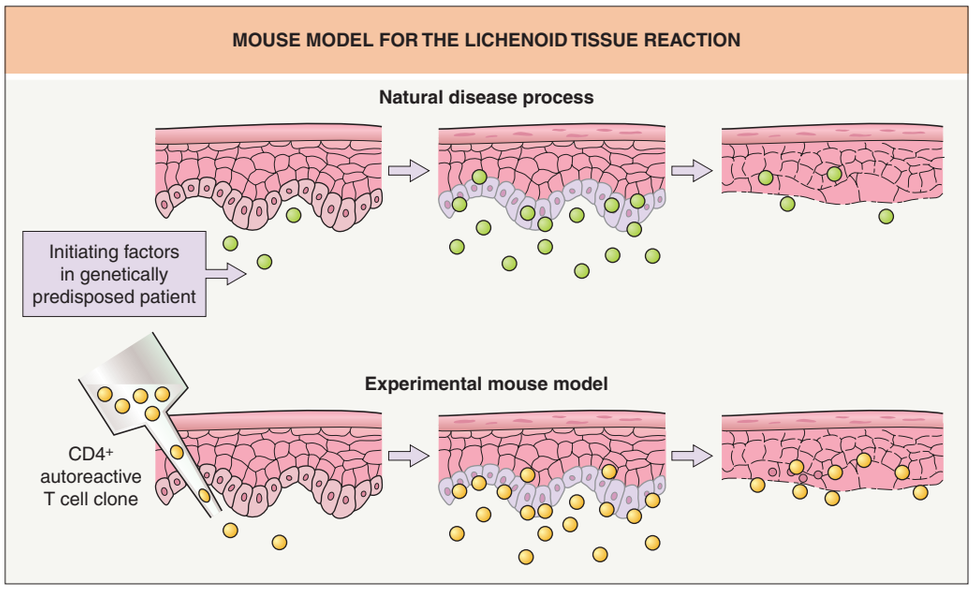


Fig. 11.1 Mouse model for the lichenoid tissue reaction. Because in humans all the analyses are performed on existing skin lesions (after the inflammatory response is underway), it is difficult to provide insight into initiating events and to establish whether the T cells present are indeed relevant to the pathogenesis. This experimentally induced animal model has the advantage that the orchestrated series of events resulting in epidermal injury can be examined from the onset and over time. Of note, injection of suboptimal or supraoptimal doses of T cells can lead to the histologic features of fixed drug eruption or toxic epidermal necrolysis, respectively.

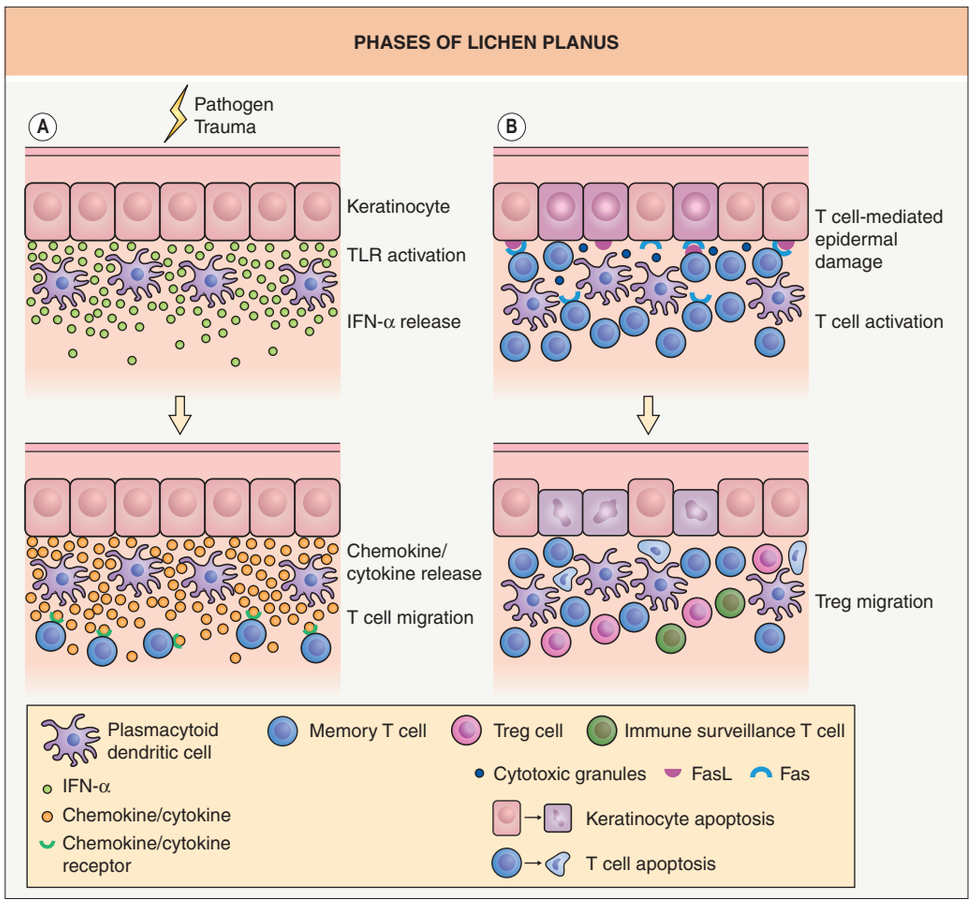


Fig. 11.2 Phases of lichen planus. A In the *induction phase*, keratinocytes and plasmacytoid dendritic cells (pDCs), upon stimulation of their Toll-like receptors (TLRs) by pathogens or endogenous ligands, can release type 1 IFNs (e.g. IFN-α); this represents an early event in the cascade leading to T cell-mediated epidermal damage. Activated keratinocytes, via production of IL-1β and TNF-α, can induce activation and migration of DCs. Chemokines, such as IP-10/CXCL10, released locally by pDCs, serve to attract CXCR3-expressing $CD8^+$ or $CD4^+$ effector memory T cells (which have differentiated from naive T cells within lymph nodes following presentation by DCs of self-peptides modified by exogenous antigens [viruses, medications and contact allergens]). Additional chemokine and chemokine receptor pairs have also been implicated in this process (see Table 11.3), and the precise mix of chemokines and cytokines released into the tissue plays an important role in determining the composition of the inflammatory infiltrates. **B** In the *evolution phase*, effector T cells (Te) that come to express skin-homing receptors (E-selectin ligands) migrate into the inflammatory site and upon recognition of antigens, are activated and release proinflammatory cytokines and cytotoxic granules, which in turn cause epidermal injury. In addition, Fas/FasL interactions can trigger cell death of both lymphocytes and keratinocytes with possible elimination of potentially harmful autoaggressive T cells. "Inflammatory" and "homeostatic" chemokines produced by keratinocytes direct the traffic of not only "pathogenic" T cells (Te) but also "immune surveillance" T cells (Ts) or regulatory T cells (Treg) into the sites; the relative balance of chemokines produced may determine the outcome of the T cell-mediated immune responses. FasL, Fas ligand.

of imiquimod, which can lead to enhanced migration and maturation of dermal dendritic cells, followed by increased production of proinflammatory cytokines and activation of antigen-specific $CD8^+$ T cells, may exacerbate lesions of LP.

In some autoimmune diseases, T cell differentiation may shift from Treg cells (immune suppression) to Th17 cells (see Ch. 4), but an increase in both populations has been found in LP lesions. However, the functionality of the Treg cells within these lesions has been questioned.

Effector T cells' access to the epidermis

A critical event in the initiation of immune responses in LP lesions is for memory T cells to migrate from the circulation into a particular skin site. Release of type 1 IFNs, such as IFN-α, from activated plasmacytoid dendritic cells (pDCs) and keratinocytes may be critical in inducing skin-directed migration of effector memory T cells (Fig. 11.2A). Stimulation of TLRs expressed on pDCs and keratinocytes by pathogens or endogenous ligands (released via skin damage) represents one of the earliest events and it is sufficient to induce type 1 IFN production. Type 1 IFN signaling and type 1 IFN-inducible chemokines (e.g. IP-10/CXCL10) then serve to recruit chemokine receptor CXCR3-expressing effector memory T cells (Th1 cells) into the skin via CXCR3/IP-10 interactions (Table 11.3). A number of other molecular interactions, such as CCR4/TARC, CCR10/CTACK and LFA-1/ICAM-1 expressed on T cells and keratinocytes, respectively, have also been implicated in

CHEMOKINES AND CHEMOKINE RECEPTORS INVOLVED IN T CELL MIGRATION INTO THE SKIN		
Chemokines*	**Chemokine receptors**	**Functional type of chemokines/T cells attracted†**
RANTES (CCL5) MCP-2 (CCL8) Eotaxin-1, -2, -3 (CCL11, 24, 26)	CCR3	Inflammatory/Th2 cells
TARC (CCL17) MDC (CCL22)	CCR4	Inflammatory/Th2 cells
MIP-1α,β (CCL3, 4) RANTES (CCL5) MCP-2 (CCL8)	CCR5	Inflammatory/Th2 cells
CCL1	CCR8	Homeostatic/memory T cells
CTACK (CCL27) MEC (CCL28)	CCR10	Homeostatic/memory T cells
MIG (CXCL9) IP-10 (CXCL10) I-TAC (CXCL11)	CXCR3	Inflammatory/Th1 cells
CXCL16	CXCR6	Inflammatory/Th1 cells

*Cytokines that have chemoattractant activity; two major groups are differentiated based on the position of two cysteine (C) residues compared with the other amino acid residues (X): CXC- or α-chemokines and CC- or β-chemokines.
†"Inflammatory" chemokines are produced at sites of cutaneous inflammation and mediate skin-directed migration of memory T cells (Th1, Th2); "homeostatic" chemokines are constitutively produced within non-inflamed skin and mediate skin-directed migration of memory T cells with an "immune surveillance" function.

Table 11.3 Chemokines and chemokine receptors involved in T cell migration into the skin. Binding of MCP-1 (CCL2) to CCR2 on monocytes plays an important role in their recruitment to sites of cutaneous inflammation. CCR, receptor for CC chemokines; CTACK, cutaneous T cell-attracting chemokine; CXCR, receptor for CXC chemokines; IP-10, interferon-inducible protein 10; I-TAC, interferon-inducible T cell α-chemoattractant; MCP-2, monocyte chemoattractant protein 2; MDC, macrophage-derived chemokine; MEC, mucosal-associated epithelial chemokine; MIG, monokine induced by interferon-γ; MIP-1α, macrophage inflammatory protein 1α; RANTES, regulated on activation normal T cell expressed and secreted; TARC, thymus- and activation-regulated chemokine.

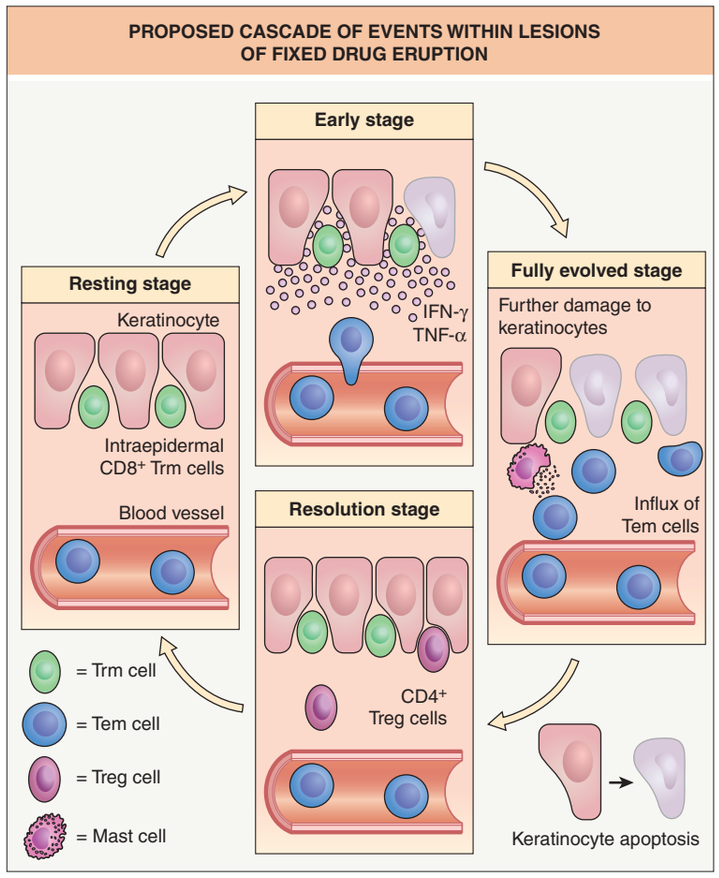


Fig. 11.3 Proposed cascade of events within lesions of fixed drug eruption. Skin tissue-resident memory T cells (Trm cells) and effector memory T cells (Tem cells) both play a role in producing tissue damage. In the resting stage, a stable population of $CD8^+$ Trm cells resides within the epidermis without exerting their cytotoxic potential (the physiologic role of these cells includes local protection against pathogens). When stimulated by cross-reactive antigens such as drugs, Trm cells then display cytolytic activity towards surrounding keratinocytes. The Trm cells also release IFN-γ and TNF-α into the local environment, leading to the recruitment of $CD4^+$ and $CD8^+$ Tem cells from the circulation into the skin. This leads to additional tissue damage. During the resolution stage, Treg cells are recruited into the site of inflammation, in part due to the release of preformed cytokines, including IL-16, by mast cells. Although the majority of activated cell populations are removed by apoptosis (see Fig. 11.2), a proportion of Trm cells are prevented from undergoing apoptosis by IL-15 produced by surrounding keratinocytes.

the recruitment of memory T cells and pDCs to the dermal–epidermal junction[23–25]. Because IFN-α from pDCs induces IFN-γ production by T cells and IFN-γ also sustains IFN-α production, a positive feedback loop may be operational within LP lesions. This ordered sequence of events provides a possible explanation for why LP lesions develop within traumatized sites and virally induced lesions.

Although chemokines produced at inflammatory skin sites are thought to regulate the composition of the Th1- or Th2-driven cellular infiltrates, memory T cells with a "surveillance" function can also migrate to skin sites under non-inflamed conditions (Fig. 11.2B). "Homeostatic" chemokines constitutively produced under non-inflamed conditions can mediate the skin-directed migration of these "immune surveillance" T cells (see Table 11.3), leading to clearance of invading pathogens such as viruses. In addition, Treg cells that have the capacity to suppress activated T cells are also able to enter inflamed skin sites. However, in LP lesions, there is no definitive means of distinguishing "immune surveillance" T cells or protective Treg cells from "pathogenic" T cells. Lastly, identification of the cells responsible for LP is further complicated by the presence of both skin tissue-resident memory T cells (Trm cells) and effector memory T cells (Tem cells) within skin lesions, with the former, whose physiologic role includes local protection against pathogens, becoming a mediator of tissue damage.

Of note, while the epidermotropic migration of effector T cells leading to epidermal damage in lichenoid tissue reactions is clearly a complicated, multistep process, the latter can be bypassed (at least in part) in the case of fixed drug eruptions (FDE). This is because effector $CD8^+$ T cells responsible for the epidermal damage persist as a stable population within previously affected sites, even when the skin becomes normal-appearing[26]. In particular, $CD8^+$ Trm cells (see above) populate the epidermis of "resting" FDE lesions and although these cells are the principal mediators of localized tissue damage, $CD4^+$ and $CD8^+$ Tem cells, recruited from the circulation, also contribute to the epidermal damage (Fig. 11.3).

Sweating disturbance

Sweat contains interleukin (IL)-1, IL-6, IL-8, and TNF-α, proinflammatory cytokines that have been implicated in the induction of T cell recruitment into the skin[27–29]. In theory, extravasated sweat could explain the syringotropic T cell migration occasionally seen in the early lesions of LP. Recent studies have shown that leakage of sweat into the dermal–epidermal junction initiates a complex sequence of events which leads to syringotropic T cell migration[29].

Clinical Features

The characteristic primary lesion of LP is a small, polygonal-shaped, violaceous, flat-topped papule (Fig. 11.4); occasionally papules are umbilicated. The surface is slightly shiny or transparent, and a network of fine white lines called "Wickham striae" or small gray–white puncta are also seen. The latter correspond histologically to focal thickening of the granular layer. Wickham striae are readily apparent by dermoscopy (see Ch. 0). Postinflammatory hyperpigmentation is also a common finding (Fig. 11.5).

The papules of LP may be widely dispersed or they may cluster or coalesce into larger plaques. LP is usually pruritic. Although the Koebner phenomenon (i.e. isomorphic response) is commonly seen in LP (Fig. 11.6), excoriations and impetiginization are unusual. A linear array of lesions can be seen as a consequence of the Koebner phenomenon or an isotopic response at the site of healed herpes zoster, as well as in the linear variant of LP which follows the lines of Blaschko.

The most common sites of involvement are the flexor wrists and forearms, the dorsal hands, the shins, and the presacral area. Mucous membranes, especially the oral mucosa (see below), are affected in more than half of patients, and this is often the only site of disease. Lesions are also commonly seen on the glans penis (Fig. 11.7A), where they can have an annular or figurate configuration and may become erosive.

The duration of the disease can vary depending upon the LP variant. While the lesions of exanthematous LP typically resolve within a year, hypertrophic, oral, and nail LP tend to be more persistent. In particular, ulcerative oral LP may be a lifelong affliction.

Actinic LP

This variant is reported under a variety of names, including LP actinicus, LP subtropicus, LP tropicus and lichenoid melanodermatitis. Although the majority of reported patients have been from Middle Eastern countries, this variant has been observed worldwide. Most patients are young adults or children, but there is no sex predilection. Lesions primarily involve sun-exposed skin of the face, followed by the neck and dorsal surfaces of the hands and arms. They usually consist of red–brown plaques with an annular configuration, but melasma-like hyperpigmented patches have been observed. In temperate climates, spontaneous improvement may occur during the winter months.

Acute (exanthematous) LP

Because lesions are usually widely distributed and disseminate rapidly, this form is also known as exanthematous or eruptive LP. The commonly affected areas include the trunk (Fig. 11.8), the inner aspects of the wrists and the dorsal feet. Reports in the literature of this variant probably include lichenoid drug eruptions. The clinical course is usually self-limited, and in general lesions resolve with hyperpigmentation within 3 to 9 months.

Annular LP

This form is thought to occur when papules spread peripherally and the central area resolves. The annular edge is slightly raised and typically

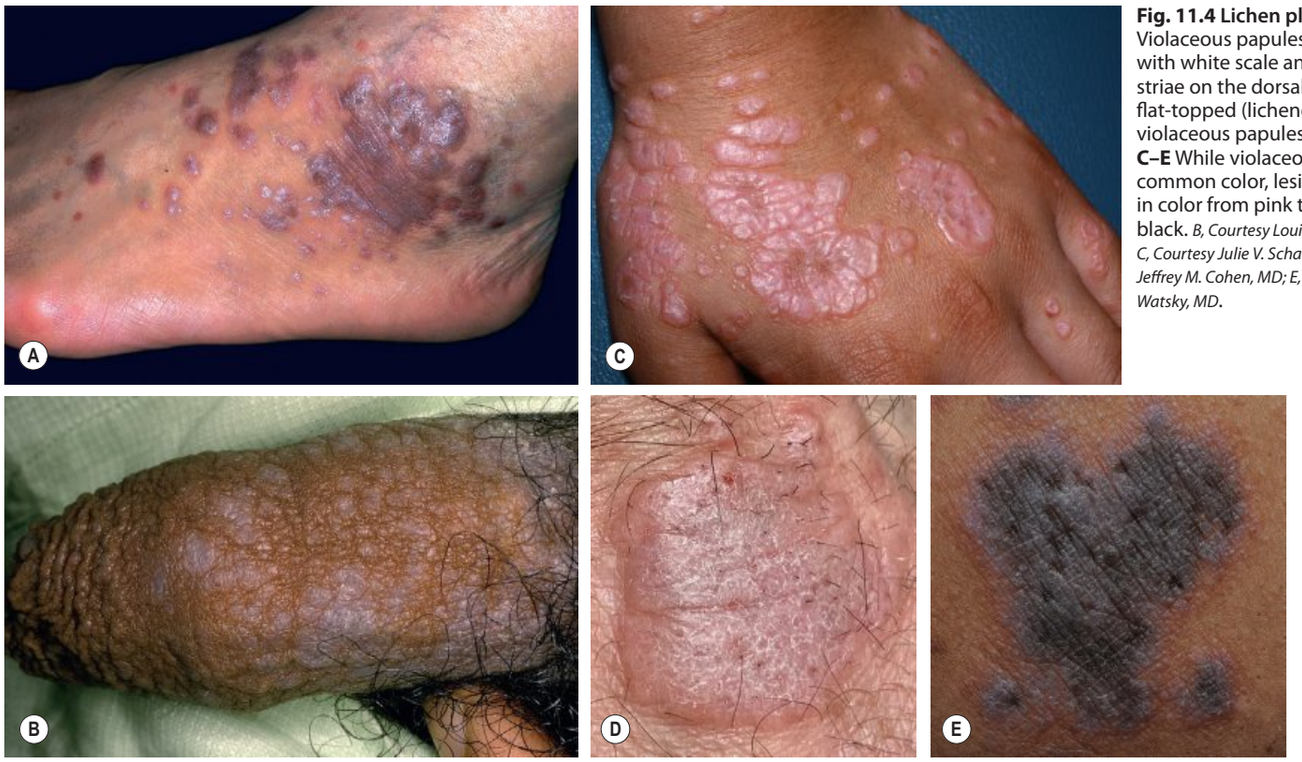


Fig. 11.4 Lichen planus. A Violaceous papules and plaques with white scale and Wickham striae on the dorsal foot. **B** Note the flat-topped (lichenoid) nature of the violaceous papules on the penis. **C–E** While violaceous is the most common color, lesions can vary in color from pink to dark purple–black. *B, Courtesy Louis A. Fragola, Jr, MD; C, Courtesy Julie V. Schaffer, MD; D, Courtesy Jeffrey M. Cohen, MD; E, Courtesy Kalman Watsky, MD.*

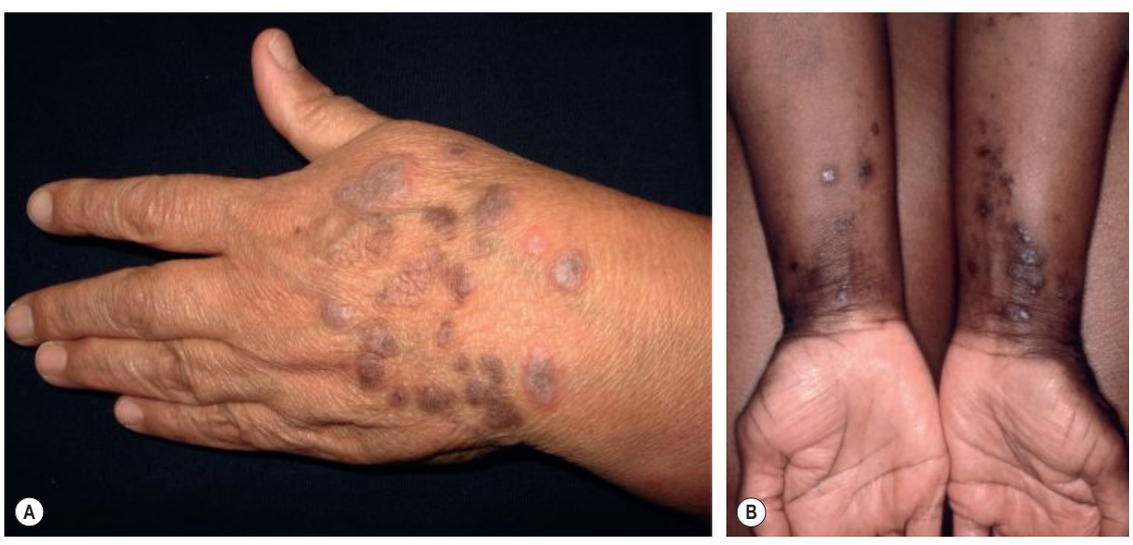


Fig. 11.5 Lichen planus with postinflammatory hyperpigmentation. A The clinical diagnosis is based upon the presence of violaceous plaques with scale, Wickham striae (uppermost lesion), and postinflammatory hyperpigmentation. **B** The most notable finding is postinflammatory hyperpigmentation, but the distribution on the flexor wrists and the presence of Wickham striae in the upper lesion on the right arm point to the diagnosis. *A, Courtesy Frank Samarin, MD.*



Fig. 11.6 Koebnerization of lichen planus into the site of the excision of the saphenous vein. Lesions also appeared where Steri-Strips™ had been applied.





Fig. 11.7 Annular lichen planus. A On the penis, the lesions have a figurate outline with a thin pale violet border and central hyperpigmentation. **B** On the trunk, the lesions have a thin hyperpigmented rim. *A, Courtesy Frank Samarin, MD.*

purple to white in color, while the central portion is hyperpigmented or skin-colored (see Fig. 11.7). Lesions can resemble porokeratosis, tinea or if there is minimal scale, granuloma annulare. Annular lesions occur in ~10% of patients with LP and are usually scattered among more typical lesions (see Fig. 11.4C), but the former may represent the predominant finding. The most common site of involvement is the axilla, followed by the penis, extremities, and groin. While some have pruritus, most patients are asymptomatic.



Fig. 11.8 Exanthematous lichen planus. Papulosquamous lesions on the back.

Atrophic LP

Atrophic LP may represent a resolving phase of LP, given the history of the lesions: papules coalesce to form larger plaques that over time become atrophic centrally, with residual hyperpigmentation. The clinical appearance of atrophic LP is likely a result of thinning of the epidermis rather than degeneration of elastic fibers, and the epidermal atrophy may be accentuated by the use of potent topical corticosteroids. Common sites of involvement include the intertriginous zones and the lower extremities (Fig. 11.9A).

Bullous LP and LP pemphigoides

In *bullous LP*, vesicles and bullae develop within pre-existing lesions of LP as a result of intense lichenoid inflammation and significant epidermal damage (Fig. 11.9B). This leads to epidermal–dermal separation, i.e. exaggerated Max-Joseph spaces. In contrast, patients with *LP pemphigoides* have circulating IgG autoantibodies directed against the 180 kDa BP antigen (BP180; BPAG2), as in idiopathic BP. However, compared to BP, LP pemphigoides has a younger age of onset. In this variant, bullae can arise either within LP lesions or previously uninvolved skin (Fig. 11.9C), but the diagnosis of LP usually precedes the LP pemphigoides.

These findings suggest that damage to the basal layer by a lichenoid infiltrate may expose hidden antigens to the autoreactive T cells, leading to the formation of autoantibodies and subepidermal bullae. Indeed, LP pemphigoides evolving into pemphigoid nodularis has been described. There are conflicting results regarding the autoantigen in LP pemphigoides, but one study suggested a novel epitope within the C-terminal NC16A domain of BP180 (see Fig. 31.9)[30].To date, no reactivity against the 230 kDa BP antigen, type VII collagen, or the laminin-5 subunits has been detected. An additional difference between these two disorders is the finding of abundant VZV antigen-bearing monocytes and mast cells in the upper dermis of bullous LP lesions as opposed to such cells being rare in LP pemphigoides.

Hypertrophic LP

This variant is also referred to as LP verrucosus (Fig. 11.10). Extremely pruritic, thick, hyperkeratotic plaques are seen primarily on the shins or dorsal aspect of the feet and may be covered by a fine adherent scale. The lesions are usually symmetric and tend to be chronic because of repetitive scratching. The average duration of hypertrophic LP in patients whose lesions had cleared was reported to be 6 years. Chronic venous stasis frequently contributes to the development of this condition. As in hypertrophic LE, squamous cell carcinoma (SCC) may arise within longstanding hypertrophic LP, and distinguishing pseudoepitheliomatous hyperplasia from SCC can be difficult. In one retrospective review, the presence of an increased number of eosinophils pointed to the diagnosis of hypertrophic LP[31].

Inverse LP

In this unusual variant, an inverse distribution pattern is observed. Pink to violaceous papules and plaques appear in intertriginous zones (axillae > inguinal and inframammary folds) and less often in the popliteal

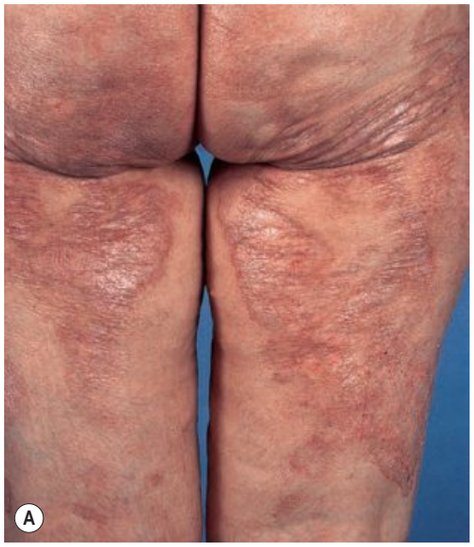






Fig. 11.9 Unusual variants of lichen planus. A Atrophic lichen planus of the lower extremities. **B** Bullous lichen planus on the shin. **C** Lichen planus pemphigoides in a patient with anti-BP180 autoantibodies.

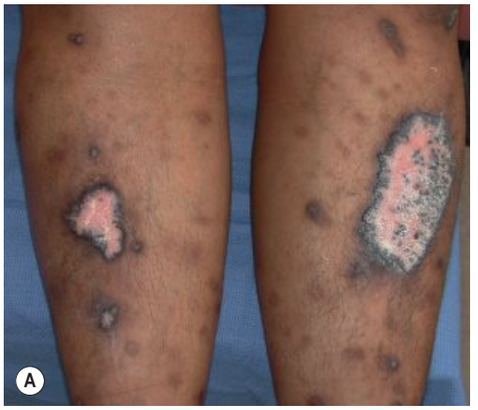




Fig. 11.10 Hypertrophic lichen planus. A On the shins, very thick discrete plaques with dyspigmentation are admixed with smaller linear plaques and areas of postinflammatory hyperpigmentation. **B** On the dorsal digits, thin violaceous plaques in addition to thick keratotic plaques that favor the knuckles. *Courtesy Joyce Rico, MD.*



Fig. 11.11 Inverse lichen planus. Oval thin violaceous plaques in the axilla. Postinflammatory hyperpigmentation is also present. *Courtesy Jeffrey P. Callen, MD.*

and antecubital fossae (Fig. 11.11). Occasionally, there are LP lesions elsewhere on the body. Hyperpigmentation is usually present as well and it may be the sole manifestation, leading to overlap with LP pigmentosus.

LP pigmentosus

LP pigmentosus typically presents as brown to gray–brown macules in sun-exposed areas of the face and neck, usually with no preceding erythema and often evolving into diffuse or reticulated pigmentation (see Ch. 67). This variant favors individuals with skin types III and IV, in particular those from South Asia, Latin America, and the Middle East. Involvement of intertriginous sites is occasionally observed (Fig. 11.12), and a linear distribution following the lines of Blaschko has also been described. In the photodistributed form, topical application of mustard oil, which contains a potential photosensitizer, has been implicated as a possible trigger.

Given the similarity of histologic findings, distinction from erythema dyschromicum perstans (EDP) is based primarily upon clinical features.



Fig. 11.12 Lichen planus pigmentosus – intertriginous variant. The initial clinical presentation was that of multiple hyperpigmented macules and patches within the axillary vaults.

In EDP, there is often truncal involvement, a younger mean age of onset, and lack of either diffuse pigmentation or the occasional coexisting LP lesions. Of note, small nests of keratinocytes can be seen within the basal layer and these may be confused with nests of melanocytes.

Lichen planopilaris

In lichen planopilaris, involvement of the hair follicle is observed, both clinically and histologically. This variant is also called follicular LP and LP acuminatus. Multiple, keratotic plugs surrounded by a narrow violaceous rim are observed primarily on the scalp, although other hair-bearing areas can also be affected (Fig. 11.13). The inflammatory process may result in scarring and loss of follicular structure, i.e. a permanent alopecia. Over time, the areas of involvement often "burn out" centrally and are indistinguishable from other causes of "end-stage" cicatricial alopecia (see Ch. 69). However, examination of the periphery may reveal the primary lesions. Women are more frequently affected than men, and this form may occur alone or with typical LP lesions elsewhere.

A variant of lichen planopilaris known as Graham-Little–Piccardi–Lassueur syndrome is characterized by the triad of: (1) non-cicatricial loss of pubic and axillary hairs and disseminated spinous or acuminated follicular papules (see Fig. 11.13B); (2) typical cutaneous or mucosal LP; and (3) scarring alopecia of the scalp with or without atrophy (see Fig. 11.13C). These features need not be present simultaneously. Another more recently recognized variant of LP of the scalp is frontal fibrosing alopecia which occurs more commonly in older women and can affect the eyebrows as well (see Ch. 69); patients may also have LP pigmentosus and papules on the face.

Linear LP

Although linear lesions frequently occur in sites of scratching or trauma in patients with LP as a result of the Koebner phenomenon, the term linear LP (Fig. 11.14) is usually reserved for lesions that appear spontaneously within the lines of Blaschko (see Fig. 11.13A). This form has also been referred to as zosteriform, but with the exception of LP developing within the site of previous herpes zoster, the distribution pattern of linear LP is generally not dermatomal. The possibility exists that when LP has a strictly dermatomal pattern, it may have been preceded by "zoster sine herpete". As noted previously (see Pathogenesis), in a case series, VZV antigen was detected in the zosteriform variant of LP but not in the linear variant[12]. Attempts to determine genetic differences between involved and uninvolved skin are ongoing[32].

Discoid lupus erythematosus/lichen planus overlap syndrome

Patients whose lesions have overlapping features of both LP and lupus erythematosus (LE) have been reported. These lesions are preferentially located in acral sites, particularly the palms and soles. Histologic and



Fig. 11.13 Lichen planopilaris. A Keratotic spines surrounded by a violaceous rim in the linear variant. **B** Multiple clusters of follicular keratotic plugs on the leg admixed with small violaceous papules, some of which are folliculocentric. **C** Cicatricial alopecia with "end-stage" changes centrally, but perifollicular inflammation at the margins.

direct immunofluorescence (DIF) microscopic findings show features of both LP and LE. Whether systemic immunologic abnormalities such as high titers of ANA are present in these patients is controversial, but case reports suggest that some patients have disease at the chronic cutaneous LE end of the clinical spectrum while others meet the criteria for systemic LE (see Ch. 41).

Nail LP

The nails are affected in ~10% of patients with LP and usually several nails are affected (see Ch. 71). The characteristic nail abnormalities include lateral thinning (Fig. 11.15A), longitudinal ridging, and

fissuring (Fig. 11.15B). These changes are manifestations of matrix damage, which can lead to scarring and dorsal pterygium formation if left untreated (Fig. 11.15C). Nonspecific changes in the nail bed include yellow discoloration, onycholysis, and subungual hyperkeratosis. In some patients, twenty-nail dystrophy may represent a variant of LP. Nail LP presenting as twenty-nail dystrophy is much more common in children than in adults, although other forms of nail involvement are extremely rare in children.



Fig. 11.14 Linear lichen planus. Coalescence of violaceous lesions with Wickham striae along the lines of Blaschko on an extremity. Note the postinflammatory hyperpigmentation proximally. *Courtesy Joyce Rico, MD.*

Oral LP

Oral LP can appear in at least seven forms, which occur separately or simultaneously: atrophic, bullous, erosive, papular, pigmented, plaque-like, and reticular. The most common and characteristic form of oral LP is the reticular pattern (Fig. 11.16A). It is characterized by slightly raised, whitish linear lines in a lace-like pattern or in rings with short radiating spines. This form is usually asymptomatic and the most common site of involvement is the buccal mucosa; lesions are often bilateral and symmetric. Gingival involvement is common, and oral LP affecting the gingivae exclusively is seen in ~10% of cases. It typically presents as chronic desquamative gingivitis (see Fig. 72.7). Gingivitis also occurs as a component of the "vulvovaginal–gingival syndrome" (see below).

Atrophic, erosive, and bullous lesions are associated with symptoms ranging from mild discomfort to severe pain (Fig. 11.16B). There is a higher incidence of plaque-like lesions among tobacco smokers. For unknown reasons, oral LP is very uncommon in young patients, and in some studies, women have been affected about twice as often as men.

Patients with oral LP should be questioned about symptoms related to esophageal involvement[33] and examined for other mucosal lesions, particularly genital lesions, and vice versa, because ~70% of patients with mucosal vulvovaginal LP have clinical signs of oral LP. Esophageal LP has been increasingly recognized. It tends to be chronic and is associated with the development of dysphagia, strictures, stenosis, and even SCC.

Reportedly, the erosive or ulcerative type of oral LP is less frequently associated with cutaneous LP than are all other types of oral LP. Such mucous membrane lesions are more therapy-resistant and less likely to



Fig. 11.15 Nail lichen planus. A Thinning of the nail plate with lateral loss. **B** Longitudinal fissuring of shortened nail plates. **C** Violaceous discoloration of the periungual area with pterygium formation.

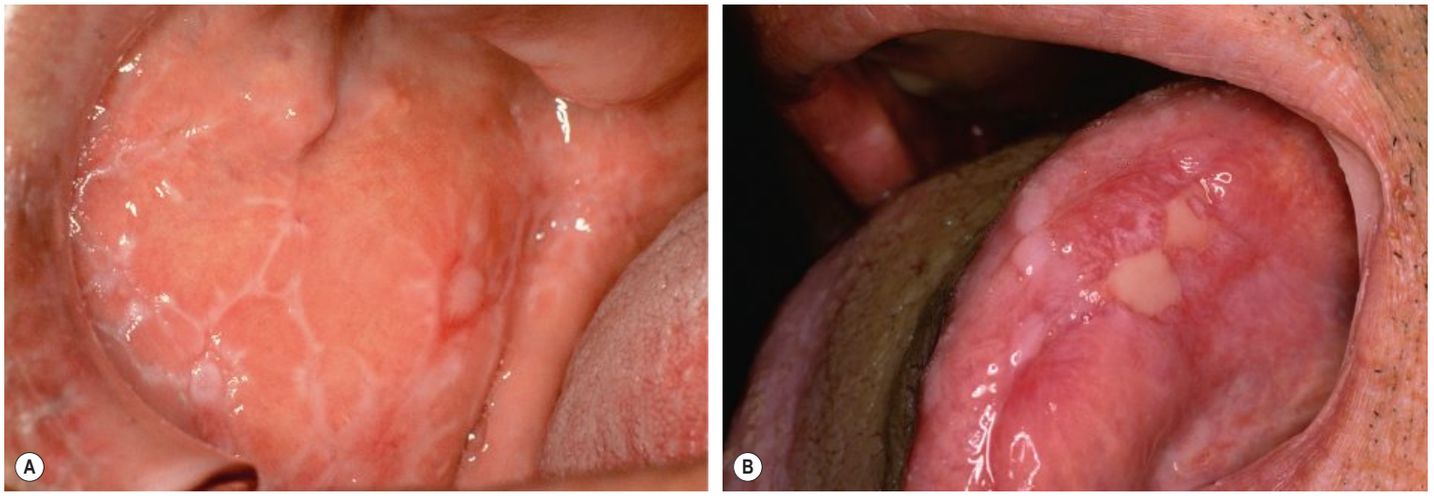


Fig. 11.16 Oral lichen planus. A White lacy pattern and an erosion on the buccal mucosa, the most common location for the reticular form. Note the ring configuration with short radiating spines. **B** Erosions on the lateral aspect of the tongue in addition to lacy white plaques and scarring. *B, Courtesy Louis A. Fragola, Jr, MD.*

spontaneously remit than cutaneous lesions. Malignant transformation of longstanding, non-healing oral LP has been reported, but it must be distinguished from pseudoepitheliomatous hyperplasia. The WHO has defined oral LP as a "premalignant condition" because of this risk.

Several studies have reported a relationship between oral LP and chronic liver disease, particularly that due to HCV infection (see Pathogenesis)[4,6]. In the HCV-positive oral LP group, oral lesions were more frequently located on the tongue, labial mucosa, and gingivae[34].

Ulcerative LP

Ulcerations can occur within palmoplantar lesions of LP, particularly those on the soles. Palmoplantar LP is not as rare as was once thought and usually appears between the third and fifth decade of life. Although palmoplantar LP is more common in men than in women, ulcerative LP prevails in female patients. Typical LP lesions may be present in additional sites of the body. The ulcers are intensely painful and often recalcitrant to conventional therapy. Chronic ulcerative lesions are at risk of developing SCC.

Vulvovaginal LP

LP of the vulva can present with several clinical variants, but the most common appears to be erosive disease[35]. Vaginal involvement occurs in up to 70% of women with erosive vulvar LP, and because there is often oral mucosal involvement as well, the term "vulvovaginal–gingival syndrome" has been introduced. The differential diagnosis of vulvar and vulvovaginal LP includes lichen sclerosus and blistering diseases, respectively (see Ch. 73). Since scarring may be a sequela of vulvovaginal LP, patients should be carefully monitored for the development of SCC, including after the resolution of active disease[36]. Less often an ano-gingival variant is observed.

Lichenoid drug eruption (drug-induced LP)

Despite the significant overlap between LP and lichenoid drug eruption (Fig. 11.17), there are both clinical and histologic clues that favor one diagnosis over the other (Table 11.4)[37].

There is usually a latent period of several months from drug introduction to the appearance of the cutaneous eruption. In a series of 17 patients with lichenoid eruptions induced by a variety of drugs, the mean latent period was 12 months[16]. The latent period varies depending not only on the offending drug, but also on other factors such as the frequency of drug administration, the dosage, and the intensity of the patient's individual reaction to the offending drug. For example, the latent period has been reported to be between 2 months and 3 years for penicillamine, ~1 year for β-blockers, and 4–6 weeks for quinacrine. In contrast to morbilliform eruptions, the time course between drug cessation and lesional resolution can be several weeks to months.

A wide range of cutaneous eruptions have been observed in patients receiving TNF inhibitors; they include new onset or paradoxical worsening of psoriasis (including palmoplantar pustulosis), eczematous eruptions, interstitial granulomatous dermatitis, cutaneous small vessel vasculitis, cutaneous LE, and lichenoid eruptions. The latter are not limited to any particular TNF inhibitor, and while some patients have clinical features similar to idiopathic LP, others have less specific skin lesions clinically, but on histologic examination lichenoid interface changes are seen. The time interval between initiation of TNF blockade and appearance of the lichenoid eruption varies from 3 weeks to 16 months. In some patients, complete resolution or significant improvement followed discontinuation of the TNF inhibitor, whereas in others, clearance occurred despite continued administration of the drug. In that TNF inhibitors are used to treat severe LP, a possible explanation for the paradoxical induction of lichenoid eruptions is a tipping of the balance between Th1 vs Th2 immune responses, Treg vs Th17 cellular responses, or IFN-α vs IFN-γ production. Perhaps inhibition of TNF allows for upregulation of other cytokines such as IFN-α.

Lichenoid granulomatous dermatitis

"Lichenoid granulomatous dermatitis," also referred to as "giant cell lichenoid dermatitis," is usually drug-related and is characterized by a lichenoid dermatitis with a granulomatous infiltrate composed of histiocytes and multinucleated giant cells[38]. In addition to being

FEATURES FOR DISTINGUISHING LICHENOID DRUG ERUPTION FROM LICHEN PLANUS

Feature	Lichenoid drug eruption	Idiopathic lichen planus
Mean age	65 years	50 years
Location	More generalized (including the trunk) and symmetric; often spares the "classic" sites of LP	Wrists, flexor forearms, dorsal hands, presacral area, lower legs, genitalia
Morphology	More eczematous, psoriasiform or pityriasis rosea-like	Shiny, flat-topped, polygonal, violaceous papules
Wickham striae	Uncommon	Present
Hyperpigmentation	Very common, sometimes persistent	Common
Photodistribution	Frequency varies*	Unusual
Mucous membranes	Usually spared	Often involved
Histology	Varying degree of eosinophilic and/or plasma cell infiltrates	Eosinophils and plasma cells uncommon
	Deep perivascular infiltrate may be present (<50% of cases)	Dense band-like infiltrate of lymphocytes in the papillary dermis
	Focal parakeratosis and focal interruption of the granular layer	Parakeratosis uncommon
	Cytoid bodies in cornified, granular and upper spinous layers	Cytoid bodies in lower spinous layer

*Very common with photosensitizing medications such as hydrochlorothiazide.

Table 11.4 Features for distinguishing lichenoid drug eruption from lichen planus. Drugs implicated in lichenoid drug eruptions are listed in Table 11.2.

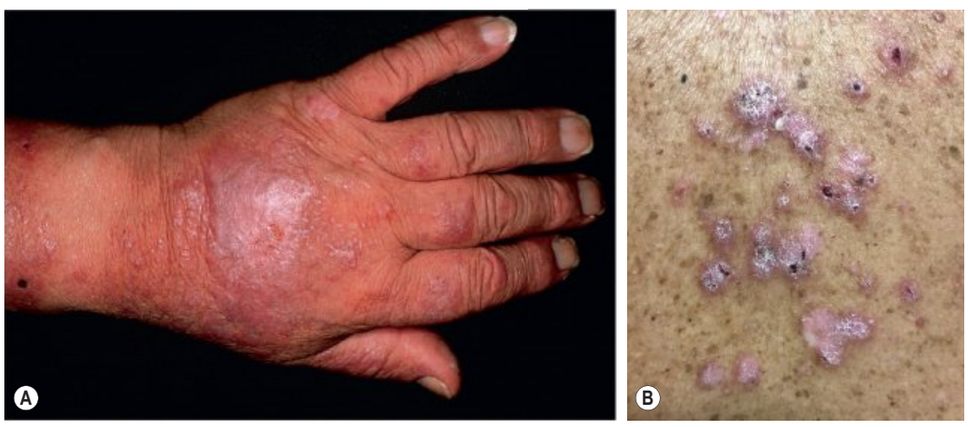


Fig. 11.17 Lichenoid drug eruption. A Photodistributed lichenoid eruption due to hydrochlorothiazide (note sparing under watchband). **B** Lichenoid dermatitis secondary to anti-PD-1 antibody therapy for non-small cell lung cancer that is characterized by pink–violet papules and plaques with white scale and crusts on the back. *B, Courtesy Jonathan S. Leventhal, MD.*

drug-induced, it can be associated with cutaneous T cell lymphoma, rheumatoid arthritis, sarcoidosis, and viral infections. Patients present with red–purple papules and plaques, and the diagnosis is based upon histologic features. The implicated drugs include antibiotics, ACE inhibitors, β-blockers, lipid-lowering agents, phenolphthalein, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Immune checkpoint inhibitor-induced lichenoid eruption

Immune checkpoint inhibitors (ICIs) include monoclonal antibodies that bind cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed cell death ligand 1 (PD-L1). They are increasingly being employed for a wide range of malignancies, with the development of *i*mmune-*r*elated *a*dverse *e*vents (irAEs) correlating with therapeutic response. Cutaneous irAEs occur in at least 50% of patients and they can appear early on, i.e. within 1 to 2 months. In addition to pruritus, maculopapular, psoriasiform, eczematous, and lichenoid eruptions are the most frequently observed cutaneous irAEs. In some patients, lichenoid eruptions arise *de novo* while in others they evolve from a maculopapular rash[39], typically after several months of ICI therapy. Of note, eruptions can have a delayed onset and may even appear after discontinuation of the ICI.

ICI-induced lichenoid eruptions range from classic LP to exanthematous. Histologically, compared to classic LP, there are eosinophils and a variable number of histiocytes. Given the clinical scenario, the goal is to use topical and systemic corticosteroids, phototherapy, or other medications (e.g. acitretin, methotrexate, apremilast) to allow either continuation of the ICI or a brief drug holiday. If a severe cutaneous adverse reaction develops, e.g. Stevens–Johnson syndrome, the ICI is discontinued.

Pathology

Despite its different clinical manifestations, the histopathology of LP is relatively uniform. The primary features are hyperkeratosis without parakeratosis, focal increases in the granular cell layer, irregular acanthosis with a "sawtooth" appearance, vacuolar degeneration of the basal cell layer, and a band-like lymphocytic infiltrate at the dermal–epidermal junction (Fig. 11.18). Colloid bodies representing apoptotic or dyskeratotic keratinocytes (also referred to as Civatte, hyaline, or cytoid bodies) are usually present in the lower levels of the epidermis and the superficial dermis. Vacuolar changes within the basal cell layer may become confluent and result in small separations between the epidermis and the dermis, termed "Max-Joseph spaces". There is often incontinence of pigment with multiple dermal melanophages.

The number of epidermal Langerhans cells is usually increased in active lesions. The majority of cells in the inflammatory infiltrate are lymphocytes, mainly $CD3^+$ T cells (see Pathogenesis). However, exocytosis of lymphocytes into the epidermis is usually not abundant in LP. Plasma cells, macrophages, eosinophils, and mast cells may be seen within the dermis, but not frequently. Occasionally, inflammation and destruction of the distal and proximal ends of the sweat ducts are also seen.

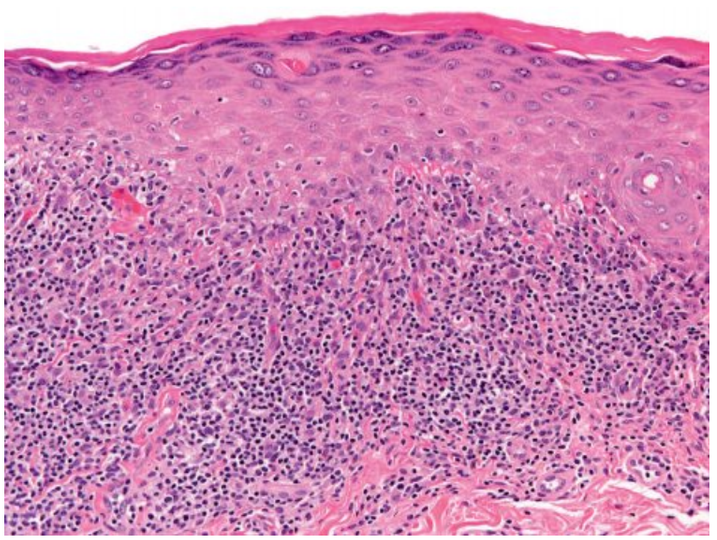


Fig. 11.18 Lichen planus – histopathologic features. Hyperkeratosis, focal increase in the granular layer, sawtoothing of the epidermis with keratinization of the basal layer, and a lichenoid infiltrate. Apoptosis of keratinocytes is also present. *Courtesy Lorenzo Cerroni, MD.*

Oral LP lesions often show parakeratosis rather than hyperkeratosis, and the epithelium may become atrophic in late stages. Lesions of lichen planopilaris are characterized by an inflammatory cell infiltrate around the hair follicles even at an early stage (see Ch. 69). Most of the inflammation involves the upper half of the follicle, with the isthmus affected in one-third of patients. Destruction of the follicles with fibrosis represents a later stage. In LP pemphigoides, a primary histologic feature of the bullous lesions is a subepidermal separation with an abundance of eosinophils (occasionally neutrophil-rich infiltrates), whereas the papular lesions have the usual features of LP.

In a nonspecific "sponge-like" manner, colloid bodies often stain for IgM, IgA, IgG or C3, and this is the characteristic finding by DIF microscopy. In lichen planopilaris lesions, IgM, IgG and IgA are found in varying combinations along the follicle–dermal interface.

The histologic changes in lichenoid drug eruption are very similar to those in idiopathic LP (see Table 11.4). In a retrospective study of 15 patients with idiopathic LP and 15 with a lichenoid drug eruption, no single histologic feature was significantly more likely to occur in the latter than in the former[37]. Although eosinophils were observed exclusively in the lichenoid drug eruptions, they were found in only 2 of the 15 cases. These results indicate that the absence of eosinophils cannot be interpreted as a sign of idiopathic LP. In addition, a few eosinophils may occasionally be seen in conventional LP. Therefore, it would be ill-advised to make the diagnosis of lichenoid drug eruption solely on the basis of histologic criteria.

Differential Diagnosis

LP can be viewed as one of the major reaction patterns in response to various exogenous agents such as drugs, viruses, and contact allergens. Before labeling patients as having "idiopathic LP", an in-depth search should be undertaken to identify any such inducing factors, because there are no definite criteria (either clinical or histologic) for differentiating drug-induced LP from idiopathic LP. Patients with oral LP lesions in apposition to metallic dental restorations should undergo patch testing with relevant metals (see Ch. 14). These metals include amalgam (mercury), copper, and gold. A lichenoid "id" reaction can be seen in children with contact dermatitis to nickel, e.g. in metal snaps in pants.

Other inflammatory conditions that are in the clinical differential diagnosis include LE and erythema dyschromicum perstans, as well as other papulosquamous disorders including pityriasis rosea, psoriasis and secondary syphilis and other lichenoid dermatoses including lichen nitidus, lichen striatus, keratosis lichenoides chronica, lichenoid GVHD, and in the anogenital region, lichen sclerosus. Hypertrophic LP needs be distinguished from lichen simplex chronicus, but in some patients the latter may be superimposed on the former. Patients with paraneoplastic pemphigus can have clinical features of a mucocutaneous lichenoid eruption (see Ch. 29). Multiple lichenoid keratoses arising in sun-damaged skin may be misdiagnosed as a lichenoid drug eruption.

Distinguishing LP from LE can be difficult, especially when there are only oral or scalp lesions, and it may require longitudinal observation, additional biopsies, and DIF studies. Granular or homogeneous bands of immunoglobulin in the basement membrane zone have been demonstrated in lesional mucosa in those with systemic LE (100%) or discoid LE (73%), but only rarely in LP (4%)[40]. The situation becomes even more complicated when there is a flare of disease in a patient with cutaneous LE who is receiving an antimalarial drug, one of the more common causes of a lichenoid drug eruption (see Table 11.2).

When LP affects the mucosal surface of the vulva, the lesions may be difficult to differentiate clinically or histologically from other inflammatory diseases, especially lichen sclerosus. While LP typically involves the inner aspects of the labia minora and consists of a glazed erythema that may easily bleed on touching, lichen sclerosus is typically observed on the outer aspects of the labia minora, and the vagina and oral mucosa are usually not involved (see Ch. 73). This mucosal vulvar variant of LP affects adult women and has not been reported before puberty, while

lichen sclerosus is frequently seen in children. Both lichen sclerosus and LP can involve perianal skin.

Treatment

It is difficult to evaluate the efficacy of different forms of therapy in LP because the majority of therapeutic recommendations are based upon small case series or anecdotes (Table 11.5). In addition, spontaneous remission of cutaneous and oral LP can occur after varying amounts of time. For example, spontaneous remission of cutaneous LP has been observed in up to two-thirds of patients after 1 year, whereas the reported mean duration of oral LP is about 5 years and the erosive form rarely spontaneously resolves[34].

In all instances, the possibility that LP is drug-induced should be considered before embarking on therapy. The diagnosis of lichenoid drug eruption is confirmed by withdrawal of the suspected drug followed by gradual disappearance of the lesions and their recurrence upon re-exposure to the drug. However, rechallenge is often not performed. There are reports of patch testing and *in vitro* tests that involve incubation with the offending drug (e.g. lymphocyte stimulation and macrophage migration inhibition tests) being used to identify the causative drugs[16], but they remain of limited value in confirming the diagnosis.

The next step is to determine which drug – or drugs, if multiple drugs are prescribed – should be withdrawn. The degree of difficulty depends upon the ability to substitute an unrelated but equally effective drug. Lastly, both the patient and the physician who prescribed the medication must be advised that withdrawal of the causative drug may not lead to quick resolution of the skin eruption and that therapies utilized for idiopathic LP may be required.

Well-described therapies for LP include topical, intralesional and systemic corticosteroids, systemic retinoids, narrowband UVB, PUVA, topical calcineurin inhibitors, antimalarials and, for severe or treatment-resistant cases, oral immunosuppressive agents (see Table 11.5). For mild disease, symptomatic treatment includes topical corticosteroids and oral antihistamines for reducing pruritus. Topical corticosteroids are particularly popular for children. Hypertrophic LP lesions may benefit from intralesional corticosteroids or topical corticosteroids under occlusion. Vulvovaginal LP is best treated with topical superpotent (class I) corticosteroids and calcineurin inhibitors[41] plus intravaginal corticosteroids, but if they fail, oral immunosuppressive drugs (e.g. methotrexate, azathioprine, mycophenolate mofetil) and/or low-dose oral prednisone may be required. Inhaled forms of corticosteroids are sometimes used for oral LP. Of note, despite their worldwide use as a mainstay of therapy, the efficacy of topical corticosteroids in cutaneous LP has not been systematically evaluated.

In several studies, tacrolimus 0.1% ointment was found to be effective in reducing the symptoms of oral LP unresponsive to more conventional therapies, including erosive disease. Most patients experienced symptomatic improvement in less than 1 month following twice-daily application. However, in one study, the median relapse time was 5 weeks (range, 2 to 20 weeks), and patients often require intermittent therapy as maintenance to prevent subsequent flares[42]. Symptoms of burning did resolve with continued use of the ointment. To date, serious adverse effects from long-term use (>1 year) have not been reported. However, given the FDA warning regarding topical calcineurin inhibitors and a possible increased risk of cutaneous carcinomas plus the increased risk of developing SCC in the setting of erosive oral and vulvar LP, continued safety monitoring is recommended.

In a more recent small case series, topical rapamycin (sirolimus) resulted in a complete (4/6 patients) or partial (2/6 patients) remission by 3 months in individuals with refractory erosive oral LP. In an open-label, randomized, controlled trial, topical calcipotriene (calcipotriol) and betamethasone valerate had equal efficacy. There are also reports of improvement with an oral suspension of apremilast (two 30 mg tablets crushed; swish and swallow). Maintaining oral hygiene is essential for patients with oral LP (see Ch. 72).

Systemic therapies

In severe, acute LP, systemic *corticosteroids* remain a commonly employed intervention. Although different dosage regimens have been proposed, the minimal effective daily dose of prednisone is usually 15 to 20 mg[1]; treatment is continued for 2–6 weeks and then gradually tapered over several weeks. Rebound and relapses may occur, but long-term maintenance therapy with systemic corticosteroids should be avoided. One study demonstrated that the median time to clearing was 18 weeks in the corticosteroid-treated group and 29 weeks in the placebo group[43].

Acitretin is the only systemic retinoid that has a relatively good level of evidence regarding its efficacy in the treatment of cutaneous LP.

THERAPEUTIC LADDER FOR LICHEN PLANUS			
	Cutaneous	Oral	LPP (scalp)
Topical/intralesional			
Corticosteroids, including superpotent and under occlusion	√ (2)	√ (1)	√ (2)
Calcineurin inhibitors – tacrolimus, cyclosporine, pimecrolimus	√ (3)	√ (1)	√ (3)
Sirolimus		√ (1)	
Calcipotriene	√ (1)		
JAK inhibitors	√ (2)	√ (3)	√ (3)
Moisturizers, including under occlusion	√ (3)		
Retinoids (e.g. isotretinoin 0.05%–0.1%)		√ (3)	
Sulfasalazine		√ (2)	
Minoxidil			√ (2 as adjunctive)
Intralesional corticosteroids	√ (2)	√ (2)	√ (2)
Phototherapy			
Narrowband UVB	√ (2)	√ (2)	
PUVA	√ (2)	√ (2)	
UVA1	√ (2)	√ (2)	
308-nm excimer laser	√ (2)	√ (2)	√ (3)
Photodynamic therapy		√ (3)	
Systemic			
Corticosteroids†	√ (1)	√ (1)	√ (2)‡
Intramuscular triamcinolone acetonide	√ (3)	√ (3)	
Hydroxychloroquine*	√ (2)	√ (2)	√ (1)
Retinoids* – acitretin†; alitretinoin; isotretinoin	√ (1); √ (3); √ (2)	√ (1); √ (1); √ (2)	√ (3); √ (3); √(2)
Metronidazole	√ (2)	√ (2)	
Griseofulvin*	√ (2)	√ (2)	√ (3)
Sulfasalazine*	√ (1)		
Apremilast	√ (2)	√ (2)	√ (3)
Low-dose weekly methotrexate	√ (2)	√ (2)	√ (1)
Mycophenolate mofetil	√ (2)	√ (2)	√ (2)
JAK inhibitors	√ (3)	√ (3)	√ (2)
Thalidomide	√ (2)	√ (2)	√ (3)
Azathioprine	√ (3)	√ (3)	
Cyclosporine†	√ (3)	√ (3)	√ (1)‡
Intravenous immunoglobulin (IVIg)	√ (3)	√ (3)	
TNF inhibitors*	√ (3)	√ (3)	
Dapsone	√ (2)	√ (2)	
Tetracyclines (e.g. doxycycline)			√ (2)
5-α-reductase inhibitors (e.g. dutasteride)			√ (2)
Pioglitazone			√ (2)
Extracorporeal photochemotherapy	√ (2)	√ (2)	

*Implicated in lichenoid drug eruptions.
†Often a first-line therapy for severe, acute cutaneous LP.
‡Short-term for severe disease.

Table 11.5 Therapeutic ladder for lichen planus. Systemic treatments are usually reserved for more severe disease. Recently, oral minoxidil has been used to increase the thickness of remaining scalp hairs in lichen planopilaris (LPP). Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

A therapeutic regimen consisting of acitretin 30 mg/day for 8 weeks resulted in significant improvement or remission in 64% of those in the treatment group, compared with 13% in the placebo group[44]. In case reports, alitretinoin, up to 25 mg/day for 4 weeks, was reported to clear oral, esophageal, and cutaneous LP.

Long-term (3 to 6 months) administration of *griseofulvin* was reported to result in a complete response in 86% of patients with LP[1]. In particular, oral erosive lesions have been reported to respond favorably to this drug. As a result, griseofulvin is often tried in such patients. A complete response or significant improvement (79%) of generalized LP (mean duration of disease, 3.5 months) was observed with *metronidazole*, 500 mg twice daily for 20 to 60 days[45]. More recently, in a retrospective study, *hydroxychloroquine* (200 mg twice daily) was shown to improve both lichen planopilaris and frontal fibrosing alopecia[46]; the latter is also treated with oral 5-α-reductase inhibitors, tetracyclines, and mycophenolate mofetil. Oral *sulfasalazine* administered in increasing doses from 1.5 to 3 g/day for at least 4 weeks was reported to be effective for cutaneous LP but not for mucosal LP. A randomized, double-blind, placebo-controlled trial utilizing a maximum of 2.5 g/day of sulfasalazine observed cutaneous improvement (>50%) in 82.6% vs 9.6% of patients at six weeks[47].

Based upon a case series, weekly low-dose *methotrexate* was noted to improve oral LP[48]. Efficacy of methotrexate for generalized LP has also been described.

Based on a small case series, oral *cyclosporine* was reported as useful in inducing a remission in severe cases of LP resistant to systemic retinoids and corticosteroids[49]. Complete responses were observed with doses of cyclosporine ranging from 1 to 6 mg/kg/day. The majority of patients experienced a relapse during follow-up periods of several months, and a rebound in disease activity can occur upon discontinuation of cyclosporine. Similar results were described in lichen planopilaris; alleviation of symptoms, resolution of clinical activity, and halting the progression of hair loss was achieved within 3 to 5 months[50]. However, long-term use of cyclosporine can be associated with renal toxicity, hypertension, and an increased risk of developing cutaneous SCCs (see Ch. 130).

Mycophenolate mofetil, an immunosuppressive agent which specifically and reversibly inhibits the proliferation of activated T cells, was reported to be effective in the management of disseminated, erosive, hypertrophic and bullous variants of LP as well as lichen planopilaris[51]. It may be preferable to other immunosuppressive drugs such as cyclosporine because of its safer side-effect profile. *Thalidomide* has also been reported to be an effective therapy.

TNF inhibitors have been used in scattered patients with severe recalcitrant LP. Paradoxically, TNF inhibitors can induce LP-like eruptions (see above), usually within two months of initial administration[52]. However, resolution was observed in a few patients despite continued use of the drug.

An open-label pilot study of *apremilast*, an oral phosphodiesterase IV inhibitor, in 10 patients with moderate to severe LP demonstrated statistically significant clinical improvement in all of the patients after 12 weeks[53]. In a patient with steroid-refractory oral LP, improvement was observed after 2 cycles of IVIg (0.4 g/kg/day for 5 days), in combination with oral prednisolone (20 mg/day). *Janus kinase (JAK) inhibitors*, both topical and systemic, are emerging as a new therapeutic tool for cutaneous diseases[53a]. Oral JAK inhibitors, including tofacitinib, upadacitinib and baricitinib, have resulted in marked improvement in erosive LP, as well as nail LP, lichen planopilaris, and hypertrophic LP[54–57,57a].

Phototherapy

In patients with resistant longstanding LP, significant improvement has been observed after bath or systemic PUVA. However, the risk of promoting carcinogenesis, especially in patients with skin types I and II, has to be balanced against the benefits. The usefulness of PUVA prompted evaluation of extracorporeal photopheresis (ECP) for recalcitrant LP. One case series demonstrated that erosive oral LP cleared in all seven patients after an average of 24 sessions of ECP (two consecutive days per month) and follow-up at 24 months revealed no recurrences[58]. The use of narrowband UVB for recalcitrant LP has also been reported. In an open prospective trial in 10 patients with recalcitrant LP, complete clearance occurred after 30 exposures (mean cumulative dose, 17.7 J/cm^2) in five patients, while partial responses were observed in the remainder. The excimer laser (308 nm) was used to treat oral LP unresponsive to conventional therapies and was reported to produce excellent results[59]. Remission times ranged from 2 to 17 months. Of note, the only poor responder in the study had chronic active HCV infection.

LICHEN STRIATUS

Synonyms: ■ Linear lichenoid dermatosis ■ *B*laschko *l*inear *a*cquired *i*nflammatory *s*kin *e*ruption (BLAISE)

Key features

- An asymptomatic, linear dermatosis that primarily affects children
- The primary lesion is a small, flat-topped papule that ranges in color from pink to skin-colored to tan (hypopigmented)
- Multiple lesions appear over the course of days to weeks along the lines of Blaschko and usually on an extremity
- Spontaneously resolves over months to a few years
- Digital involvement may result in nail dystrophy

Introduction

Lichen striatus is an asymptomatic, uncommon, self-limited, linear dermatosis of unknown etiology that generally affects children. The diagnosis is usually made clinically based upon the appearance of the primary lesions and the distinctive developmental pattern. Its distribution along the lines of Blaschko plus the age of the patient usually narrows the differential diagnosis rather quickly. Occasionally, there is overlap with linear LP and "blaschkitis" (see Ch. 62).

History

In 1898, Balzer and Mercier first described a peculiar linear papular eruption that they termed "lichenoid trophoneurosis". Forty years later, Senear and Caro proposed the name "lichen striatus". Ever since the condition was first described, the pathogenesis of its linearity has been the subject of debate.

Epidemiology

Lichen striatus is seen primarily in children between the ages of 4 months and 15 years, although the disorder occasionally occurs in adults. The median age of onset is 2 to 3 years and the vast majority of cases occur in preschool-age children[60]. The reported female : male ratio has varied from 1.6 : 1[61] to 2 : 1[60].

Pathogenesis

Although the distribution of lichen striatus along the lines of Blaschko points to somatic mosaicism (see Ch. 62), neither the gene(s) involved nor the triggering factors are known. Environmental agents, particularly viruses, have been implicated, given the predominance of the disorder in young children and its seasonal variation (it appears more commonly during spring and summer). However, to date, a viral association has not been proven via serologic testing or cultures. Concurrent familial occurrence of lichen striatus in a mother and child has been touted as evidence for a viral trigger.

In theory, during early fetal development, aberrant clone(s) of epidermal cells produced by somatic mutation migrate out along the lines of Blaschko. Exposure to an infectious agent (e.g. virus, BCG vaccine) or other precipitant could then break previous tolerance to the aberrant clone by inducing a novel membrane antigen. The presence of CD8$^+$ T cells scattered or in clusters around necrotic keratinocytes supports a cell-mediated immunologic reaction by which cytotoxic T cells would attack and eliminate the mutated or virally modified keratinocyte clones. A similar mechanism has been proposed for linear LP, and a post-transplant loss of tolerance could explain linear GVHD.

Lichen striatus may represent a manifestation of an atopic diathesis with the abnormal immune responses usually associated with atopy being a predisposing factor. The timing and relative infrequency

of lichen striatus suggests that an infectious agent acts as a trigger in genetically predisposed individuals. Lastly, there are scattered reports of lichen striatus occurring at sites of injury (e.g. the periphery of a burn scar[61]) rather than along the lines of Blaschko, but this could also be explained by a break in tolerance.

Clinical Features

Lichen striatus is typically asymptomatic, but intense pruritus can occasionally occur. The eruption consists of a continuous or interrupted band composed of discrete or clustered pink, skin-colored or tan (hypopigmented) papules that are flat-topped, smooth or scaly, and range in size from 2 to 4 mm. Infrequently, vesicles may be present. Often, there is a single, unilateral streak on an extremity along the lines of Blaschko (Fig. 11.19); occasionally, there is a bilateral distribution pattern and/or multiple parallel bands. It is uncommon for lichen striatus to involve the trunk or head and neck region. There are reports of the eruption spreading distally from the trunk down an extremity, as well as observations of proximal extension along an extremity[62]. Although lichen striatus does not usually recur, relapses may occasionally occur, either in the same site or on the same side of the body[60].

The eruption usually appears suddenly, develops fully over days to weeks, and after several months to a year or more, undergoes spontaneous resolution. Postinflammatory hypopigmentation may be seen, particularly in those with more darkly pigmented skin. In the latter individuals, the eruption is often first noticed as linear hypopigmentation. When lesions involve the nail apparatus, onycholysis, splitting, fraying and total nail loss may result.



Fig. 11.19 Lichen striatus. A Linear streak on the leg that follows the lines of Blaschko. It is composed of numerous small, tan (hypopigmented), flat-topped papules. **B** Three linear streaks on the lower extremity composed of multiple pink papules, some of which are flat-topped with scale. The primary differential diagnosis would be blaschkitis. *A, Courtesy Antonio Torrello, MD.*

Pathology

The histologic features of lichen striatus are variable and depend upon the age of the lesion at the time the biopsy is performed. In addition, different sites within the same streak can have different findings. In general, there is a lichenoid tissue reaction in addition to varying degrees of involvement of the hair follicles and sweat glands and ducts (Fig. 11.20). Even though the lichenoid inflammation that may be present around hair follicles is indistinguishable from that seen in lichen planopilaris, sweat gland and hair follicle involvement can still be a helpful diagnostic feature of lichen striatus[61]. Exocytosis, parakeratosis, dyskeratosis, and focal or diffuse vacuolar degeneration can be seen in the epidermis overlying the lichenoid infiltrate. Occasionally, older lesions may have features similar to LP.

By immunohistochemistry, $CD3^+$ T cell infiltrates were noted in which $CD8^+$ T cells surrounded necrotic keratinocytes and infiltrated vesicles filled with Langerhans cells. Depending upon the age of the lesions, Langerhans cells were either decreased (earlier lesions) or increased (later phase due to an influx of precursor cells).

Differential Diagnosis

Although the differential diagnosis includes other inflammatory diseases that can assume a linear pattern, such as linear porokeratosis, linear psoriasis, inflammatory linear verrucous epidermal nevus, linear lichen sclerosus and linear Darier disease, the primary differential

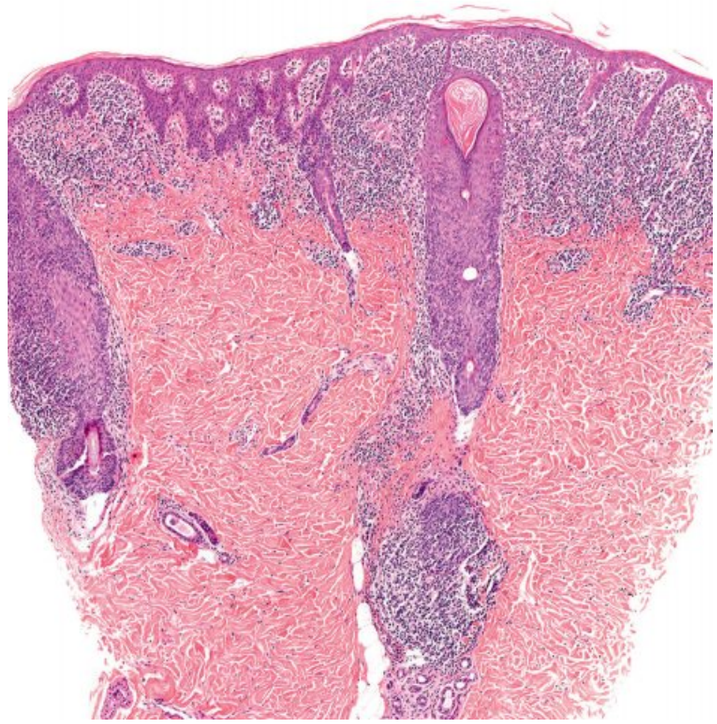


Fig. 11.20 Lichen striatus – histopathologic features. In addition to hyperkeratosis with focal parakeratosis, both a lichenoid and a perivascular and periadnexal lymphocytic infiltrate extending into the deeper dermis is seen. *Courtesy Lorenzo Cerroni, MD.*

diagnosis is linear LP, blaschkitis, and linear GVHD. The latter occurs in a specific clinical setting, while blaschkitis favors the trunk, is usually seen in adults, often consists of multiple streaks, recurs, and can have features of dermatitis. Although linear LP and lichen striatus can occasionally be indistinguishable histologically, the primary lesions usually differ in size and color, and hypopigmentation is a frequent sequela of lichen striatus, while, in general, hyperpigmentation appears in the wake of LP. In lichen nitidus, linear lesions reflect previous traumatic injury to the skin.

Treatment

Treatment of lichen striatus is usually not needed because it is self-limited, usually resolving within 1 to 2 years. Topical corticosteroids under occlusion can be used to hasten spontaneous resolution. In scattered case reports, topical calcineurin inhibitors have also been reported to be effective, including for the nail dystrophy. Obviously, with any purported therapy, the natural history of lichen striatus must be kept in mind.

LICHEN NITIDUS

Key features

- The eruption consists of multiple, tiny, discrete, shiny papules, often in clusters
- Favored sites of involvement include the flexor aspects of the upper extremities, the genitalia, and the anterior trunk
- Linear arrays of papules occur secondary to the Koebner phenomenon
- The histologic correlate of the papule is a well-circumscribed infiltrate composed of lymphocytes and epithelioid cells confined to the width of two to three dermal papillae

Introduction

Lichen nitidus is an uncommon chronic eruption consisting of multiple, tiny, discrete, skin-colored papules that are often arranged in larger clusters. The papules have a distinctive histology with a dense, well-circumscribed, lymphohistiocytic infiltrate closely apposed to the epidermis. There has been considerable debate, however, as to whether lichen nitidus represents a distinct and separate entity or should be regarded as an unusual variant of LP; their coexistence has certainly been reported and progression from lichen nitidus to LP has also been observed. It is generally accepted that lichen nitidus has no relationship to any systemic illness. Only a few authors believe that it may be a cutaneous manifestation of Crohn disease[63].

History

In 1901, Pinkus first described a peculiar papular eruption he termed "lichen nitidus" and suggested that it was a distinct entity histologically.

Epidemiology

Reliable epidemiologic data are difficult to accumulate because of the relative rarity of lichen nitidus. In a US study of 43 patients, primarily Caucasians and African-Americans, the disorder was not found to be restricted to any specific population group based on race, sex, or age[64]. Other authors have observed that lichen nitidus is more prevalent among children or young adults, and a female predominance has been described in the generalized variant. It has also been reported in patients with Down syndrome. Familial lichen nitidus, including in identical twins, is very rare.

Pathogenesis

Although much attention has been focused on the relationship of lichen nitidus to LP, there has been limited recent research regarding its pathogenesis. Lichen nitidus was initially thought to represent a tuberculous lesion or tuberculid because of its histologic features. However, no causative infectious agents have ever been demonstrated, even by repeated inoculations of tissue into animals.

Even though LP and lichen nitidus can coexist in the same patient and they share some similar clinical features (Table 11.6), most authors believe that lichen nitidus is a separate entity because of its distinctive clinical and histologic features. The possibility exists that the two conditions represent different responses to a similar triggering factor, e.g. hepatitis B vaccine. An additional example would be a patient who had Crohn disease in whom LP and lichen nitidus developed over different time frames[63].

Clinical Features

Lichen nitidus is characterized by numerous tiny, discrete, skin-colored, uniform, pinhead-sized papules (Fig. 11.21A). Individual papules are usually flat with a shiny surface (Fig. 11.21B); occasionally they have a central depression. There may be pruritus, but it is an uncommon feature. Although most often skin-colored, the papules can exhibit a variety of hues, from pink or yellow to red–blue or brown. In darkly pigmented individuals, the papules tend to be hypopigmented, but sometimes they are hyperpigmented; marked hyperpigmentation has rarely been reported.

COMPARISON OF CLINICAL AND HISTOLOGIC FEATURES OF LICHEN NITIDUS VERSUS LICHEN PLANUS

	Lichen nitidus	Lichen planus
Clinical		
Size	Pinhead	Pinhead to larger plaques
Color	Skin-colored	Violaceous
Number	Multiple to numerous	Multiple
Distribution	Upper extremities (flexor aspects), genitalia, chest, abdomen	Wrists, flexor forearms, presacral area, dorsal hands, shins, genitalia
Oral involvement	Rare*	Common (>50%)
Nail involvement	<5%–10%	~10%
Wickham striae	Absent	Common
Hyperpigmentation	Uncommon	Common
Hypopigmentation	Common†	Unusual
Koebner phenomenon	Common	Common
Pruritus	Sometimes	Common
Histologic		
Parakeratotic cap	Common	Rare
Granular layer	Thin to absent	Focally increased
Dermal infiltrate	Lymphocytes, epithelioid histiocytic cells, and occasional Langhans giant cells; usually confined to width of 1–3 dermal papillae; "ball and claw" configuration due to hyperplastic rete ridges	Band-like infiltrate of lymphocytes
Deposits of immunoreactants	Absent	Globular deposits of IgG, IgA, IgM, and/or C3 in the papillary dermis

*May be underestimated.
†Especially in individuals with darker skin phototypes.

Table 11.6 Comparison of clinical and histologic features of lichen nitidus versus lichen planus.

The lesions are usually distributed on the flexor aspects of the upper extremities as well as the chest, abdomen, dorsal aspects of the hands, and genitalia (Fig. 11.21A,C). Less commonly, the face, neck, lower extremities, palms, soles, and mucous membranes are involved. Oral lesions are thought to be rare but are probably underestimated; they appear as minute, flat, gray–white papules on the soft mucosa or white plaques on the tongue and hard palate. Nail involvement is observed in up to 10% of patients (primarily adults) and the changes include pitting, rippling, longitudinal ridging, terminal splitting, and increased longitudinal linear striations.

Lichen nitidus is one of several diseases that exhibit the Koebner phenomenon. Vesicular and hemorrhagic lesions are found in some patients, and they are often admixed with the more typical papules. Several other clinical variants have been described, including palmoplantar, linear, and follicular spines. A perforating variant has also been reported, usually in association with LP. In the generalized form, lesions occasionally coalesce. According to one study, the duration in two-thirds of the patients was 1 year or less and the longest duration was 8 years[64].

Pathology

The constellation of histologic features in lichen nitidus is very distinctive. As a result, the clinical diagnosis can be confirmed histologically.

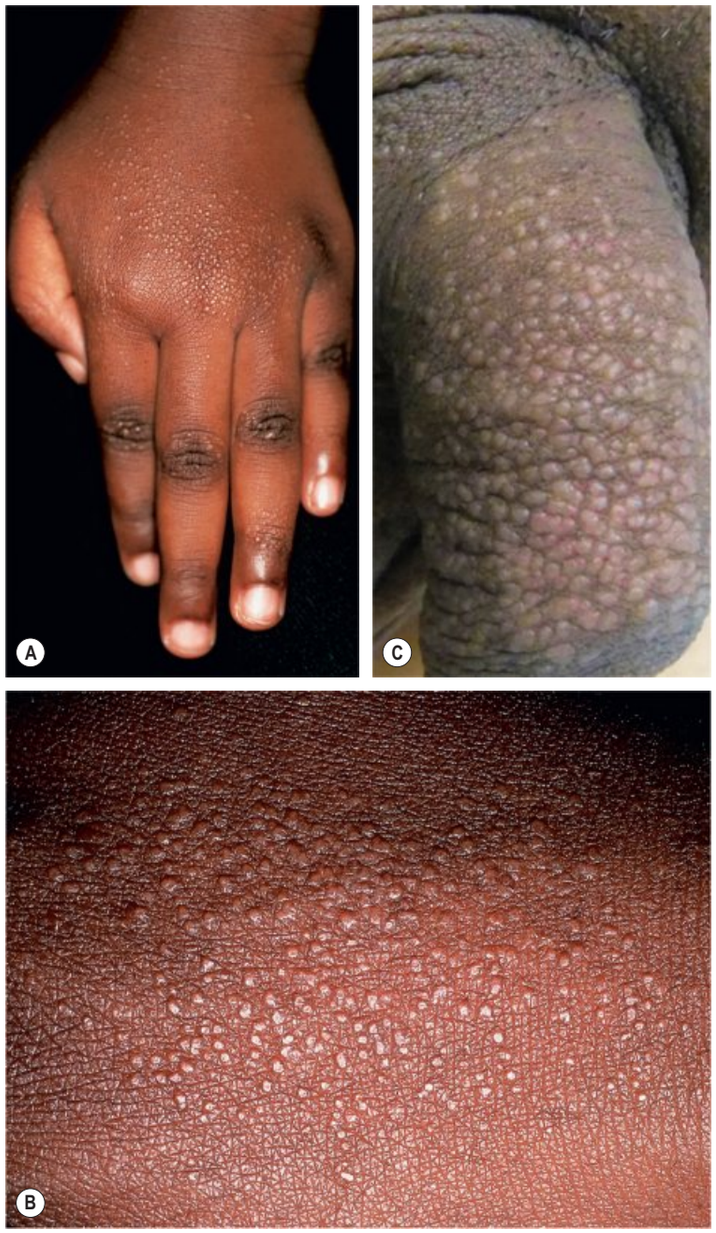


Fig. 11.21 Lichen nitidus. A Numerous tiny flat-topped papules on the hand. **B** A close-up view shows the shiny surface. **C** Numerous pink lesions on penis. *C, Courtesy Kiran Motaparthi, MD.*

A well-circumscribed infiltrate composed of lymphocytes, epithelioid cells, and occasional Langhans giant cells is typically "clutched" by the surrounding hyperplastic rete ridges in a "ball and claw" configuration (Fig. 11.22). In most lesions, the infiltrate is confined to the width of one to three dermal papillae.

The overlying epidermis is usually atrophic and frequently exhibits a parakeratotic "cap" centrally. Absence or thinning of the overlying granular layer is seen and vacuolar degeneration of the basal layer is consistently observed, often accompanied by incontinence of melanin pigment. Civatte bodies are occasionally seen. A Max-Joseph-like space, i.e. focal separation of the epidermis and dermis secondary to vacuolar degeneration, is sometimes observed. The lichenoid infiltrate closely apposes the epidermis and is thought to play a role in inducing reactive epidermal hyperplasia of the surrounding rete ridges. In perforating lichen nitidus, transepidermal elimination is observed (see Ch. 96).

The predominant cell types in the dermal infiltrate are lymphocytes and epithelioid histiocytic cells, and in some cases, epithelioid cells predominate. Immunohistochemical studies have shown a marked predominance of $CD4^+$ T cells over $CD8^+$ T cells[65], as well as the presence of large numbers of $CD1^+$ Langerhans cells in the dermal infiltrates. Of note, the pattern in lichen nitidus lesions of a mixed cellular infiltrate characterized by macrophages and a helper T cell response with few *c*utaneous *l*ymphocyte *a*ntigen-positive (CLA^+) cells is different from that seen in LP[66].

Differential Diagnosis

The differential diagnosis includes LP, guttate lichen sclerosus, lichen spinulosus, frictional lichenoid dermatitis (elbows and knees), and papular eczema (especially in skin phototypes V and VI), as well as verruca plana, lichen scrofulosorum, lichen striatus, papular sarcoidosis, and the lichenoid variant of secondary syphilis. All of these diagnoses, except LP and perhaps lichen scrofulosorum, can usually be excluded relatively easily on the basis of clinical plus histologic findings. It is not always possible to differentiate early tiny papules of LP because they may be clinically and histologically indistinguishable from lichen nitidus (see Table 11.6). Furthermore, lesions identical to lichen nitidus can be found in 25% to 30% of patients with LP. In such cases, the lack of variation in size, the absence of a violaceous color or Wickham striae, and no deposits of immunoglobulin in dermal papillae would suggest the diagnosis of lichen nitidus.

Periadnexal inflammation is more typical of lichen striatus, but patients with the latter have been described where both periadnexal inflammation and superficial features of lichen nitidus were present, suggesting a morphologic spectrum. Lichen spinulosus is characterized by follicular keratotic papules, 1–3 mm in size with a central horny spine, that are grouped into patches on the neck, arms, abdomen and buttocks. The possibility of the spinous follicular variant of lichen

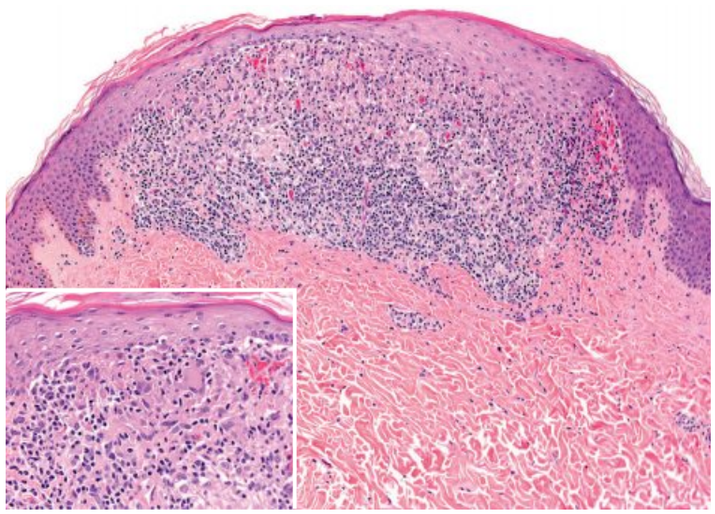


Fig. 11.22 Lichen nitidus – histopathologic features. Note the typical "ball and claw" configuration for the infiltrate and epidermis, respectively. There is thinning of the epidermis that overlies the infiltrate. Several Langhans giant cells are within the infiltrate (inset). *Courtesy Lorenzo Cerroni, MD.*

nitidus should be kept in mind when a patient presents with spiny keratotic papules plus typical histologic features of lichen nitidus. Lastly, lichen nitidus-like lesions can be seen in a photodistribution in summertime actinic lichenoid eruption, also referred to as actinic lichen nitidus (see below).

Treatment

Since the majority of patients experience spontaneous clearing within one or several years, treatment is primarily symptomatic. When significant pruritus is present, topical corticosteroids and oral antihistamines may be helpful. Anecdotally, topical calcineurin inhibitors have been reported as an effective therapy in children with lichen nitidus. Generalized lichen nitidus that had failed to respond to topical corticosteroids has been successfully treated with either narrowband UVB or PUVA[67]. One patient with peripheral $CD4^+$ T cell lymphocytopenia and lichen nitidus who was treated with topical dinitrochlorobenzene (DNCB) developed a pruritic erythematous eruption followed by resolution of the lesions of lichen nitidus[68].

ERYTHEMA DYSCHROMICUM PERSTANS

Synonyms: ■ Ashy dermatosis ■ Ashy dermatitis

Key features

- Slowly progressive appearance of gray, gray–blue or gray–brown, oval-shaped macules and patches
- Occasionally, there is a peripheral rim of erythema
- As in pityriasis rosea, the long axis of oval lesions can follow skin cleavage lines
- Seen most commonly in Latin American patients with skin phototypes III and IV
- Histologic examination demonstrates primarily dermal melanophages

Introduction

This entity was first described in 1957 by Ramírez as an asymptomatic, slowly progressive, ashy-colored, macular hyperpigmentation and was referred to as "dermatitis cenicienta". The disorder was subsequently renamed erythema dyschromicum perstans (EDP) or ashy dermatosis. Some authors consider EDP to be a variant of LP because of the overlapping clinical and histologic features (see LP pigmentosus). However, flat-topped violaceous papules and plaques are not seen in patients with EDP, and in this textbook, they are viewed as separate entities.

History

In 1957, Ramírez referred to these patients as *los cenicientos* (the ash-colored ones) and named the condition "dermatitis cenicienta". Subsequently, five patients from Venezuela were reported who were believed to be similar to those described by Ramírez. These authors suggested calling the disorder "erythema chronicum figuratum melanodermicum" because they considered it to be a new variant of erythema perstans. Sulzberger then proposed a less cumbersome and more descriptive term, "erythema dyschromicum perstans".

Epidemiology

Although it has been observed that EDP occurs most often in more darkly pigmented Latin Americans, there have been occasional reports in Asians and Caucasians. The disorder clearly favors individuals with skin phototypes III and IV. In general, no sex predilection exists, although a few authors reported that women were more commonly affected than men. While the age of onset is variable, EDP frequently appears during the first to third decade of life.

Pathogenesis

In 1973, Pinkus[69] speculated that an as-yet-unidentified set of pollutants in the environment, either contactants or inhaled or ingested substances, may be the cause of EDP in certain predisposed individuals. Indeed, there have been sporadic case reports of temporal associations with: the ingestion of ammonium nitrate, benzodiazepines, or penicillin; exposure to pesticides or toxins; whipworm infestation; and HIV seroconversion. In one patient, characteristic lesions occurred suddenly after a radiographic study using orally administered contrast medium (barium sulfate). However, to date, a rigorous epidemiologic study examining potential triggers has not been performed. Lastly, the possibility has been raised that some patients with multiple lesions of FDE or lichenoid drug eruptions are misdiagnosed as having EDP[70], emphasizing the need to carefully review all medications, including over-the-counter drugs and herbal remedies.

Clinical Features

Most patients present with a slow progression of gray, gray–brown or gray–blue macules and patches (Fig. 11.23). The presence of an erythematous, peripheral margin measuring 1–2 mm in width is actually uncommon. When present, these borders eventually disappear after several months. Most lesions measure between 0.5 and 2.5 cm but can be larger. Although the lesions may vary in shape, many are oval with their long axes following skin cleavage lines, thus assuming a pattern similar to that of pityriasis rosea.

The macules may slowly enlarge or multiply to involve large areas of the body. The most common sites of involvement are the neck, trunk and proximal arms, and the distribution is usually symmetric. Occasionally, asymmetric lesions, usually located on the face or neck, have been observed as have lesions along the lines of Blaschko. Characteristically, there is sparing of the palms, soles, scalp, and mucous membranes. Although spontaneous clearing can occur, especially in prepubertal children (~70% within 2–3 years), the lesions usually slowly progress and then persist for years in adults. The persistence is a reflection of the lack of response to various therapies.

Pathology

The histologic findings vary depending on the phase in the life of the lesion. In the border of active lesions, vacuolization of the basal layer, occasional colloid bodies, and a very mild lichenoid lymphocytic infiltrate are typically seen. These histologic findings may be seen even in the perilesional normal-appearing skin, suggesting that the pathologic processes have already begun in these areas. In inactive ashy-colored lesions, a considerable amount of pigment incontinence with variable epidermal change, including atrophy and effacement of the normal pattern of rete ridges, is seen. These changes are indistinguishable from those observed in other types of postinflammatory hyperpigmentation.



Fig. 11.23 Erythema dyschromicum perstans. Numerous oval to polygonal, gray–brown macules and patches on the lower extremities. *Courtesy Wake Forest University.*

DIF microscopy studies of the active border have demonstrated IgM, IgG, fibrinogen, and C3 staining of colloid bodies, as in LP. However, positive staining for fibrinogen at the dermal–epidermal junction is often the only finding. Immunopathologic studies have shown the dermal infiltrate (when present) to be composed of $CD4^+$ and $CD8^+$ T cells, a common pattern in LP.

Differential Diagnosis

The clinical differential diagnosis includes primarily postinflammatory hyperpigmentation secondary to a lichenoid drug eruption, pityriasis rosea, small plaque parapsoriasis, LP, or generalized FDE. Although the lesions of pityriasis rosea are often oval, the resultant hyperpigmentation is predominantly epidermal, not dermal. In patients with generalized FDE, there is incontinence of pigment histologically, but clinically the shape of the lesions is usually more circular and the color more brown. Less common entities in the differential diagnosis are macular urticaria pigmentosa, pinta, and leprosy.

There is a lack of consensus as to whether idiopathic eruptive macular pigmentation is a variant of EDP seen more commonly in children or a distinct entity. Distinguishing EDP from a lichenoid drug eruption can prove quite difficult and a search for incriminating drugs is essential.

Treatment

In general, proposed treatments for EDP are unsuccessful; they include sun protection, topical corticosteroids, calcineurin inhibitors, retinoids and vitamin C, chemical peels, oral antibiotics, vitamin A, dapsone, antimalarials, griseofulvin, and systemic corticosteroids. On the basis of a case series, clofazimine was reported as a successful treatment. In a systematic review, NB-UVB was also determined to be effective and laser therapy ineffective[71]. Spontaneous remission can occur, but unfortunately many patients have the disease for years.

KERATOSIS LICHENOIDES CHRONICA

This entity was first described in 1895 by Kaposi. He used the term "lichen ruber acuminatus verrucosus et reticularis" to describe a patient with a linear, warty lichenoid eruption. Since his original description, patients with similar lesions have been reported, but with a confusing nomenclature which includes lichen verrucosus et reticularis, porokeratosis striata lichenoides, keratosis lichenoides chronica, lichenoid trikeratosis, and Nékam disease[72]. Over time, keratosis lichenoides chronica has become the most consistently used name for this disorder.

Keratosis lichenoides chronica is characterized by violaceous, keratotic, lichenoid papules that are arranged in a characteristic linear and reticulated pattern (Fig. 11.24A). Lesions are usually symmetrically distributed on the limbs (Fig. 11.24B) and the trunk[72]. Another prominent feature is a greasy and scaly eruption involving the upper portion of the face which has been described as a seborrheic dermatitis-like mediofacial eruption or psoriasiform scaling plaques (Fig. 11.24C). Keratotic papules are sometimes present on the palms and soles, and the nails and scalp may also be affected. Although the clinical course of keratosis lichenoides chronica is usually chronic and progressive, occasionally, regression of individual lesions during the summer or with aging has been reported.

The histologic features of keratosis lichenoides chronica are very similar to those seen in LP. Furthermore, there are no significant differences in immunofluorescence or immunopathologic findings between keratosis lichenoides chronica and idiopathic LP, suggesting that it may be an unusual variant of LP or an unusual isomorphic response. Treatment should be symptomatic and it is usually unsatisfactory. Topical and systemic corticosteroids, methotrexate, cyclosporine, etretinate, oral vitamin A, and PUVA have all been tried but with little success, although a beneficial effect from UVB or etretinate plus PUVA has been reported. Nowadays, acitretin would be prescribed instead of etretinate.

ACTINIC LICHEN NITIDUS (SUMMERTIME ACTINIC LICHENOID ERUPTION)

Summertime actinic lichenoid eruption was first described by Bedi[73] in 1978. Since its initial description, the disorder has been reported under a variety of names, including LP subtropicus, LP tropicus, lichenoid melanodermatitis, LP atrophicus annularis, and LP actinicus. Of note, the last-mentioned is synonymous with actinic LP and the first three terms have also been used to describe actinic LP, so although many authors have regarded summertime actinic lichenoid eruption as synonymous with actinic LP, Bedi considered it to be a separate entity. The former typically occurs in young adults with skin phototypes IV or V following prolonged exposure to the summer sun and presents with pinhead-sized lichenoid papules that are almost exclusively confined to sun-exposed areas.

Isaacson et al.[74] broadened the clinical spectrum of summertime actinic lichenoid eruption to include several types of lichenoid eruptions: annular hyperpigmented plaques, melasma-like patches, grayish-white



Fig. 11.24 Keratosis lichenoides chronica. **A** Linear and stellate keratotic plaques. **B** Symmetrical distribution of linear and reticulated keratotic plaques admixed with small, violaceous lichenoid papules. **C** Crusted psoriasiform scaling plaques on the face. *B, Courtesy Kathryn Schwarzenberger, MD; C, Courtesy Jiro Arata, MD.*

pinhead-sized papules, and typical LP-like papules/plaques. As a result, their description of the histologic findings varied according to the morphology of the different types of clinical lesions. Hussain[75] then proposed that the designation "summertime actinic lichenoid eruption" should be limited to papular eruptions exclusively in sun-exposed areas with lichen nitidus-like histologic features, while the term actinic LP should be used to describe annular lesions with classic histopathologic features of LP. In addition, he suggested abolishing the term summertime actinic lichenoid eruption and replacing it with actinic lichen nitidus or lichen nitidus actinicus. This view has been supported by other authors. In addition to actinic LP, the differential diagnosis includes micropapular polymorphous light eruption and response to hydroxychloroquine has been reported.

ANNULAR LICHENOID DERMATITIS (OF YOUTH)

Annular lichenoid dermatitis of youth was first described in 2003 by Annessi and colleagues[76]. They observed, in a series of young patients, peculiar annular lesions whose clinical features appeared to overlap with those of inflammatory morphea, mycosis fungoides, inflammatory vitiligo, and figurate erythemas. In the initial reports, the annular lichenoid dermatitis occurred primarily in children and young adults (age range, 5–22 years), with no sex predilection. However, in a more recently reported series of six patients, four were adult men, ranging in age from 33 to 45 years[77].

Patients present with erythematous macules that enlarge into annular patches with a reddish-brown, non-scaling border and central hypopigmentation. The lesions are usually 5 to 15 cm in diameter, involve primarily the groin and flanks, and are either solitary or multiple (range, 2–12 lesions; mean, 3).

Histologically, there is a band-like lymphocytic infiltrate within the papillary dermis, along with vacuolar changes of the epidermal basal layer and epidermotropism of lymphocytes. Although variable in number, apoptotic keratinocytes are localized to the tips of the rete ridges (so-called squaring of rete ridges, a finding that distinguishes this entity from mycosis fungoides where squaring of the rete ridges is only rarely observed). Neither spongiosis nor changes in the horny and granular layers are observed. The infiltrate is composed primarily of $CD4^+$ or $CD8^+$ T cells, with few B cells and macrophages. A normal number of melanocytes is present in the hypopigmented areas, a finding that is helpful in differentiating annular lichenoid dermatitis from inflammatory vitiligo. The absence of T cell receptor rearrangements aids in excluding indolent mycosis fungoides[77,78].

The disease follows a chronic course, with some lesions spontaneously resolving while others are quite persistent. Topical or systemic corticosteroids and phototherapy have led to marked improvement or complete regression of the lesions.

Additional figures and table, Variants of lichen planus, available in our eBook (see inside front cover for access code).

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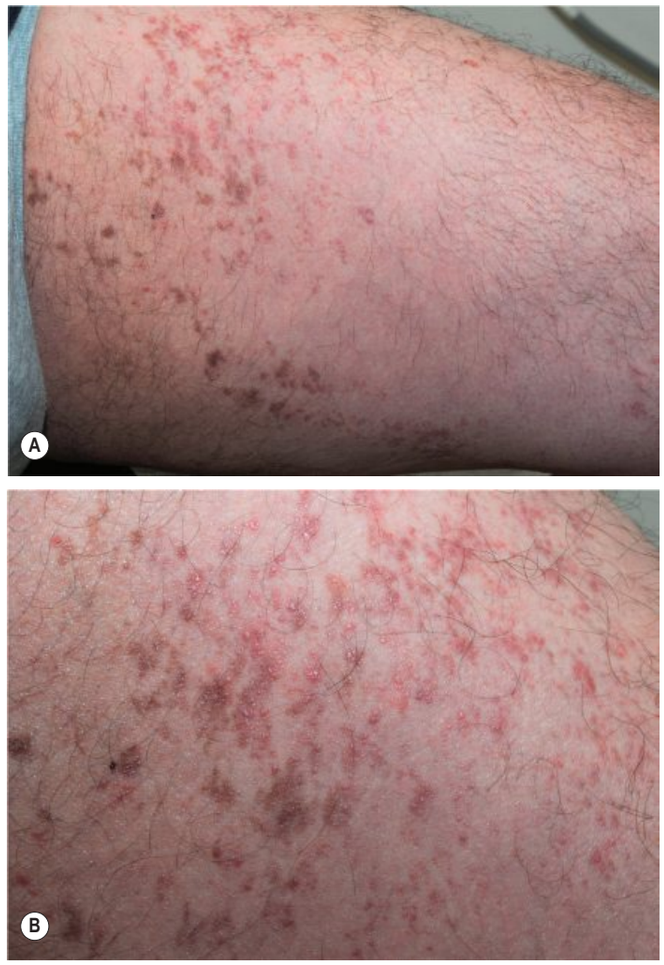
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eFig. 11.1 Lichen planus. Violaceous, flat-topped papules and plaques with Wickham striae on the upper extremity. Scattered lesions are also present on the thigh. *Courtesy Julie V. Schaffer, MD.*



eFig. 11.2 Lichen planus. Pink, flat-topped papules with white scale on the hand and wrist. *Courtesy Jeffrey M. Cohen, MD.*



eFig. 11.3 Lichen planus. A, B Multiple small, pink–violet papules admixed with postinflammatory hyperpigmentation on the thigh. *Courtesy Kalman Watsky, MD.*



eFig. 11.4 Lichen planus of the penis. *Courtesy Kalman Watsky, MD.*



eFig. 11.5 Hypertrophic lichen planus of the shin. The violaceous plaques have obvious Wickham striae. *Courtesy Kalman Watsky, MD.*



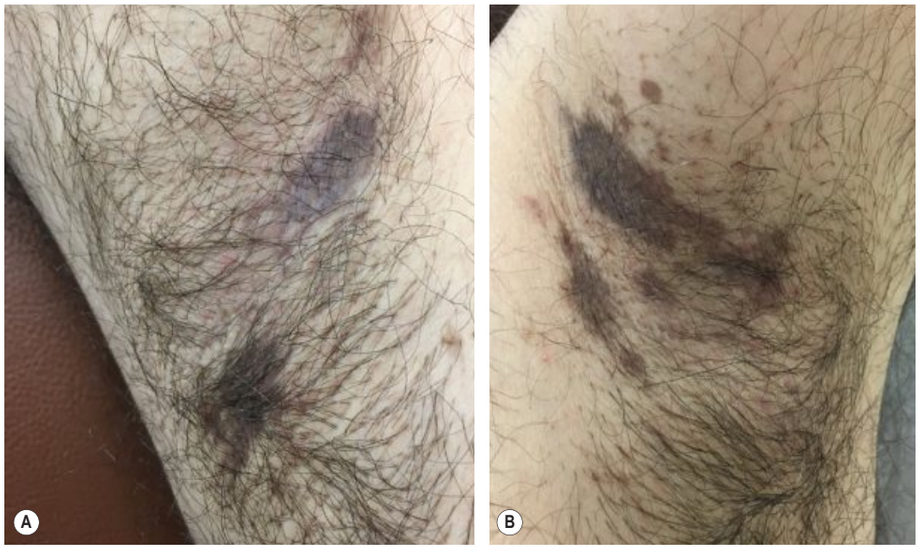
eFig. 11.8 Lichenoid drug eruption. Thick violaceous plaques on the shin of a patient receiving nivolumab. *Courtesy Jeffrey P. Callen, MD.*



eFig. 11.6 Erosive cheilitis of the lower vermilion lip due to lichen planus. Peripherally, a white reticulated lace-like pattern is seen. *Courtesy Kalman Watsky, MD.*



eFig. 11.9 Lichen striatus. Single streak on the lower extremity composed of multiple pink flat-topped papules. The primary differential diagnosis would be blaschkitis and linear LP.



eFig. 11.7 Lichen planus pigmentosus – intertriginous variant. *Courtesy Kalman Watsky, MD.*



eFig. 11.10 Lichen nitidus. Numerous small, flat-topped, skin-colored papules on the hands. *Courtesy Richard Antaya, MD.*



eFig. 11.11 Lichen nitidus. Cluster of small, flat-topped, skin-colored papules with evidence of Koebner phenomenon.

VARIANTS OF LICHEN PLANUS		
Type	**Clinical aspects**	**Comments**
Actinic LP	Sun-exposed sites, especially face, neck, dorsal aspect of arms Red–brown annular plaques or melasma-like appearance	Middle East Young adults, children
Acute (exanthematous; eruptive) LP	Abrupt onset Widespread distribution	Usually self-limited (3–9 months) Exclude lichenoid drug eruption, pityriasis rosea, secondary syphilis
Annular LP	Thin raised border, with hyperpigmented or skin-colored center	Favors axillae, groin/penis, extremities
Atrophic LP	Large plaques with epidermal atrophy Later stage of disease	**DDx:** lichen sclerosus Annular variant with loss of elastic fibers centrally
Bullous LP	Bullae within pre-existing lesions	Separation of epidermis from dermis with underlying lichenoid lymphocytic infiltrate
Hypertrophic LP	Favors shins and dorsal feet Thick pruritic plaques with scale Can develop SCC	Average duration – 6 years **DDx:** lichen amyloidosis and LSC
Inverse LP	Violaceous plaques Axillae > inguinal or other major body folds	Overlap with LP pigmentosus as lesions resolve with hyperpigmentation
LP pemphigoides	Variable distribution of vesicobullae, including previously uninvolved skin	Routine histology and DIF of bullous lesions – similar to BP; IIF: autoAb to BPAG2
LP pigmentosus	Brown to gray–brown macules and patches in sun-exposed areas of the face and neck *or* intertriginous zones Inflammatory phase usually absent	Skin phototypes III and IV Coexisting LP lesions in 20% of patients **DDx:** erythema dyschromicum perstans
Lichen planopilaris	Keratotic plugs within hair follicles with narrow surrounding red to violet-colored rim Hair-bearing sites, especially the scalp	A form of scarring alopecia Variant – frontal fibrosing alopecia **DDx** for scalp: discoid LE
Linear LP	Need to distinguish Koebner phenomenon from lesions following lines of Blaschko	**DDx:** lichen striatus if along lines of Blaschko
LP/LE overlap	Lesions favor acral sites Overlapping features	Spectrum – from only cutaneous LE to systemic LE
Nail LP	Lateral thinning, longitudinal ridging, fissuring Dorsal pterygium	Variant – twenty-nail dystrophy (more common in children)
Oral LP	Reticular form – white lacy lines or circle with short radiating spikes (buccal mucosa) Erosive form* – includes chronic desquamative gingivitis	Patients can have both gingival and vulvovaginal involvement May be associated with HCV infection
Ulcerative LP	Plantar surface > palms	
Vulvovaginal LP	Inner aspects of labia minora Glazed erythema that easily bleeds	**DDx:** lichen sclerosus

*If erosive variant plus lichenoid cutaneous lesions, DDx includes paraneoplastic pemphigus.

eTable 11.1 Variants of lichen planus. AutoAb, autoantibody; BP, bullous pemphigoid; BPAG2, bullous pemphigoid antigen 2 (type XVII collagen); DIF, direct immunofluorescence; HCV, hepatitis C virus; IIF, indirect immunofluorescence; LE, lupus erythematosus; LSC, lichen simplex chronicus; SCC, squamous cell carcinoma.

12 Atopic Dermatitis

Maeve A. McAleer and Alan D. Irvine

Synonym: ■ Atopic eczema

Key features

- Common inflammatory skin condition that typically begins during infancy or early childhood and is often associated with other atopic disorders such as asthma, allergic rhinoconjunctivitis, food allergies, and eosinophilic esophagitis
- Complex genetic disease with environmental influences
- Characterized by intense pruritus and a chronic or chronically relapsing course
- Acute inflammation and involvement of the cheeks, scalp and extensor aspects of the extremities predominates in infants, shifting to chronic inflammation with lichenification and a predilection for flexural sites in children and adults
- Associated with a predisposition to skin infections, especially with *Staphylococcus aureus* and herpes simplex virus
- A proactive approach to management is recommended, including avoidance of trigger factors, regular use of emollients, and anti-inflammatory therapy to control subclinical inflammation as well as overt flares; targeted immunomodulatory therapy is available for more severe disease

INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, and its increasing prevalence presents a major public health problem worldwide[1]. Characteristic features of AD include pruritus and a chronic or chronically relapsing course, usually beginning during infancy (early onset) but occasionally first developing in adulthood (late onset)[2]. AD is a complex genetic disease and is often accompanied by other atopic disorders such as allergic rhinoconjunctivitis, asthma, food allergies, and less often eosinophilic esophagitis. These conditions may appear simultaneously or develop in succession. AD and food allergy have a predilection for infants and young children, while asthma favors older children and rhinoconjunctivitis predominates in adolescents. This age-dependent sequence, referred to as the "atopic march"[3] (Fig. 12.1), represents one of many potential pathways to atopic multimorbidity in children with AD[4]. Given that atopic disease usually starts with AD, management should not be concentrated solely on the treatment of acute flares, but also be directed towards ameliorating the underlying genetically determined epidermal barrier dysfunction and preventing active dermatitis via maintenance therapy.

HISTORY AND DEFINITIONS

The association of AD with allergic rhinitis and asthma was recognized by Besnier in 1892. The term "atopy" originates from the Greek word *atopos* meaning strange or unusual; it was first applied to this triad in the 1920s, including the use of "atopic eczema". A decade later, Hill and Sulzberger proposed the name "atopic dermatitis". The list of characteristic features proposed by Hanifin and Rajka[5] in 1980 helped to unify the clinical concept of AD. In 1994, Williams and co-workers[6] simplified Hanifin and Rajka's criteria to establish the UK Working Party's Diagnostic Criteria for AD, which were validated for the purpose of clinical studies; these criteria were modified slightly by Williams in 2005[2]. In 2003, a consensus conference, spearheaded by the American Academy of Dermatology, suggested revised Hanifin and Rajka criteria that are more streamlined and applicable to the full range of patient ages (Table 12.1).

According to the consensus nomenclature by the World Allergy Organization (WAO)[7], the term "atopy" is tightly linked to the presence of allergen-specific IgE antibodies in the serum, as documented by positive fluorescence enzyme immunoassays (previously radioallergosorbent [RAST] tests) or skin prick tests. Thus, an *IgE-associated* or *allergic* form of dermatitis, formerly known as *extrinsic AD*, corresponds to AD in the strict sense. The remaining 20%–30% of patients with the clinical phenotype of AD who have no evidence of IgE-sensitization are categorized as having a *non-IgE-associated* or *non-allergic* form of dermatitis, formerly known as *intrinsic AD*. However, IgE-associated/allergic "true" AD and non-IgE-associated/non-allergic dermatitis have substantial overlap and cannot be considered as two separate diseases; for example, the latter often represents an early transitional form of IgE-associated AD.

EPIDEMIOLOGY

The current prevalence of AD in most high-income and some low-income countries is ~10%–30% in children and 2%–10% in adults. This represents a two- to threefold increase over the past several decades[1]. In general, the prevalence of AD in rural areas and low-income countries is significantly lower than in their urban and high-income counterparts. More recently, however, the prevalence of AD appears to be plateauing in many high-income countries, where there tends to be an inverse socioeconomic gradient in prevalence. These patterns illustrate the importance of lifestyle and environment in the pathogenesis of atopic disease.

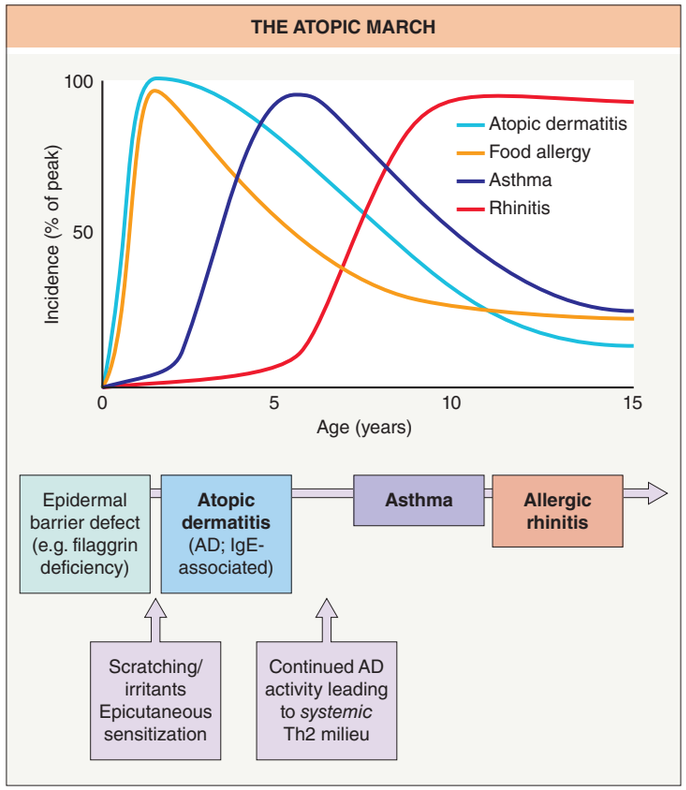


Fig. 12.1 The atopic march. This characteristic sequence represents one of many possible pathways to atopic multimorbidity in children with AD.

DIAGNOSTIC FEATURES AND TRIGGERS OF ATOPIC DERMATITIS (AD)
Essential features: must be present and are sufficient for diagnosis

• Pruritus
  • Rubbing or scratching can initiate or exacerbate flares ("the itch that rashes")
  • Often worse in the evening and triggered by exogenous factors (e.g. sweating, rough clothing)
• Typical eczematous morphology and age-specific distribution patterns (see Fig. 12.3)
  • Face, neck, and extensor extremities in infants and young children
  • Flexural lesions at any age
  • Sparing of groin and axillae
• Chronic or relapsing course

Important features: seen in most cases, supportive of diagnosis
• Onset during infancy or early childhood • Personal and/or family history of atopy (IgE reactivity) • Xerosis   • Dry skin with fine scale in areas *without* clinically apparent inflammation; often leads to pruritus
Associated features: suggestive of the diagnosis, but less specific (see Figs. 12.3 & 12.15)
• Other filaggrin deficiency-associated conditions: keratosis pilaris, hyperlinear palms, ichthyosis vulgaris • Follicular prominence, lichenification, prurigo lesions • Ocular findings: recurrent conjunctivitis, anterior subcapsular cataract; periorbital changes: pleats, darkening • Other regional findings, e.g. perioral or periauricular dermatitis, pityriasis alba • Atypical vascular responses, e.g. midfacial pallor, white dermographism*, delayed blanch
Triggers

• *Climate:* extremes of temperature (winter or summer), low humidity
• *Irritants:* wool/rough fabrics, perspiration, detergents, solvents
• *Infections:* cutaneous (e.g. *Staphylococcus aureus*, molluscum contagiosum, herpes simplex) or systemic (e.g. URI)
• *Environmental allergies:* e.g. to dust mites, pollen, contact allergens
• *Food allergies:*
  • Trigger in small minority of AD patients, e.g. 10%–30% of those with moderate to severe, refractory AD
  • Common allergens: egg > milk, peanuts/tree nuts, (shell)fish, soy, wheat
  • Detection of allergen-specific IgE (via blood and skin prick tests) does *not* necessarily mean that allergy is triggering the patient's AD

*Stroking the skin leads to a white streak that reflects excessive vasoconstriction.

Table 12.1 Diagnostic features and triggers of atopic dermatitis (AD). URI, upper respiratory infection. *Adapted from the American Academy of Dermatology Consensus Conference on Pediatric Atopic Dermatitis (Eichenfield LF, Hanifin JM, Luger TA, et al. J Am Acad Dermatol 2004;49:1088–95).*

Although it is clear that the incidence of AD peaks in infancy and chronic disease is frequently observed, clinical expression over time varies considerably. Recognized AD trajectories include transient, relapsing-remitting, and chronic persistent disease[8,9]. Predictors of persistence into adulthood include a young age at onset, concurrent asthma and/or allergic rhinoconjunctivitis, low socioeconomic status, non-White ethnicity, and filaggrin mutations (see Pathogenesis below). However, it is unclear if these predictors are independent of disease severity[10,11]. Three subsets of AD based on age of onset have been described based on epidemiologic studies:

- *early-onset AD*: defined as AD beginning in the first 2 years of life. This is the most common type of AD, which develops during the first 6 months of life in 45% of affected individuals, during the first year of life in 60%, and before 5 years of age in 85%. Approximately half of children with disease onset during the first 2 years of life develop allergen-specific IgE antibodies by 2 years of age. About 60% of infants and young children with AD go into remission by 12 years of age, including a group with resolution by 4–6 years of age[8,9], while in others disease activity persists into adolescence and adulthood.
- *late-onset AD*: defined as AD that starts after puberty. There are few epidemiological studies on AD with an onset in adulthood. Approximately 30% of AD patients overall are in the non-IgE-associated category, and among adults, the vast majority of such patients are women.
- *AD in the elderly*: a subset of AD that begins after 60 years of age[12].

PATHOGENESIS

The pathogenesis of AD can be divided into three major categories: (1) *epidermal barrier dysfunction*; (2) *immune dysregulation*; and (3) alteration of the *microbiome*. These mechanisms interact with each other and are modulated by both genetic and environmental factors (Fig. 12.2).

Genetic Factors

Genetic factors account for a large proportion of susceptibility to early-onset AD[13], with a significantly higher concordance rate in monozygotic twins (77%) compared to dizygotic twins (15%)[14]. Although the entities in the atopic triad cluster together in families, a parental history of AD is a stronger risk factor for the development of AD than either asthma or allergic rhinitis, supporting the existence of genes specific to AD susceptibility[15]. Genes that encode proteins important to the epidermal barrier and immunologic functions have been implicated in AD pathogenesis (Table 12.2). AD is a complex genetic disease, and both gene–gene and gene–environment interactions have important roles[16].

Epidermal Barrier Dysfunction

A defective epidermal permeability barrier represents a consistent feature of AD and is evident in non-lesional as well as lesional skin of affected individuals[17]. Manifestations of epidermal barrier dysfunction include increases in transepidermal water loss (TEWL), pH and permeability, as well as altered lipid composition[18–23]. The level of TEWL in non-lesional skin of children with AD correlates with disease severity[24,25]. Epidermal barrier dysfunction permits an easier entry for irritants, allergens, and microbes, which trigger immune responses that include the release of proinflammatory cytokines[26]. In infants, greater TEWL is associated with an increased likelihood of epicutaneous sensitization to aeroallergens, which could potentially play a role in the development of asthma and allergic rhinoconjunctivitis[16,27,28]. Factors that contribute to the impaired cutaneous barrier in AD are discussed next.

Filaggrin and other structural proteins

Filaggrin is a keratin *fil*ament-*aggr*egating prote*in* that serves as a major structural component of the stratum corneum. *FLG* loss-of-function (LOF) variants represent the strongest known genetic risk factor for AD and are also responsible for ichthyosis vulgaris[29–32] (see Ch. 57), with carrier frequencies of up to 10% in European and ~3% in East Asian populations[33–35]. Approximately 20%–50% of European and Asian children with moderate-to-severe AD have at least one *FLG* LOF variant; the penetrance of AD is ~40% for one and ~90% for two LOF alleles[30]. This implicates epidermal barrier dysfunction in the initiation of AD, with subsequent development of Th2-biased immune responses[34]. Although *FLG* LOF variants also play a role in the pathogenesis and persistence of AD in children of African descent, they appear to be rare in individuals from sub-Saharan Africa[36–40]; however, technical limitations may have reduced detection of uncommon *FLG* variants in earlier studies[36–38]. Of note, filaggrin expression is also affected by intragenic copy number variation and reduced by increased local pH, protease activity, and Th2 cytokine levels[32,41].

FLG mutations are associated with early-onset AD, greater disease severity, and persistence into adulthood as well as enhanced epicutaneous sensitization and an increased risk of irritant contact dermatitis, hand eczema, herpes simplex virus (HSV) infections, and food allergy[30,35,42]. *FLG* mutations have also been linked to an increased risk for the development of asthma and greater asthma severity; however, these effects are only seen in patients with pre-existing AD[43]. Since filaggrin is not found in the gastrointestinal or bronchial mucosa, the association of *FLG* mutations with food allergy and asthma strongly suggests that epicutaneous sensitization and/or cutaneous inflammation can contribute to the development of systemic atopic disease[44].

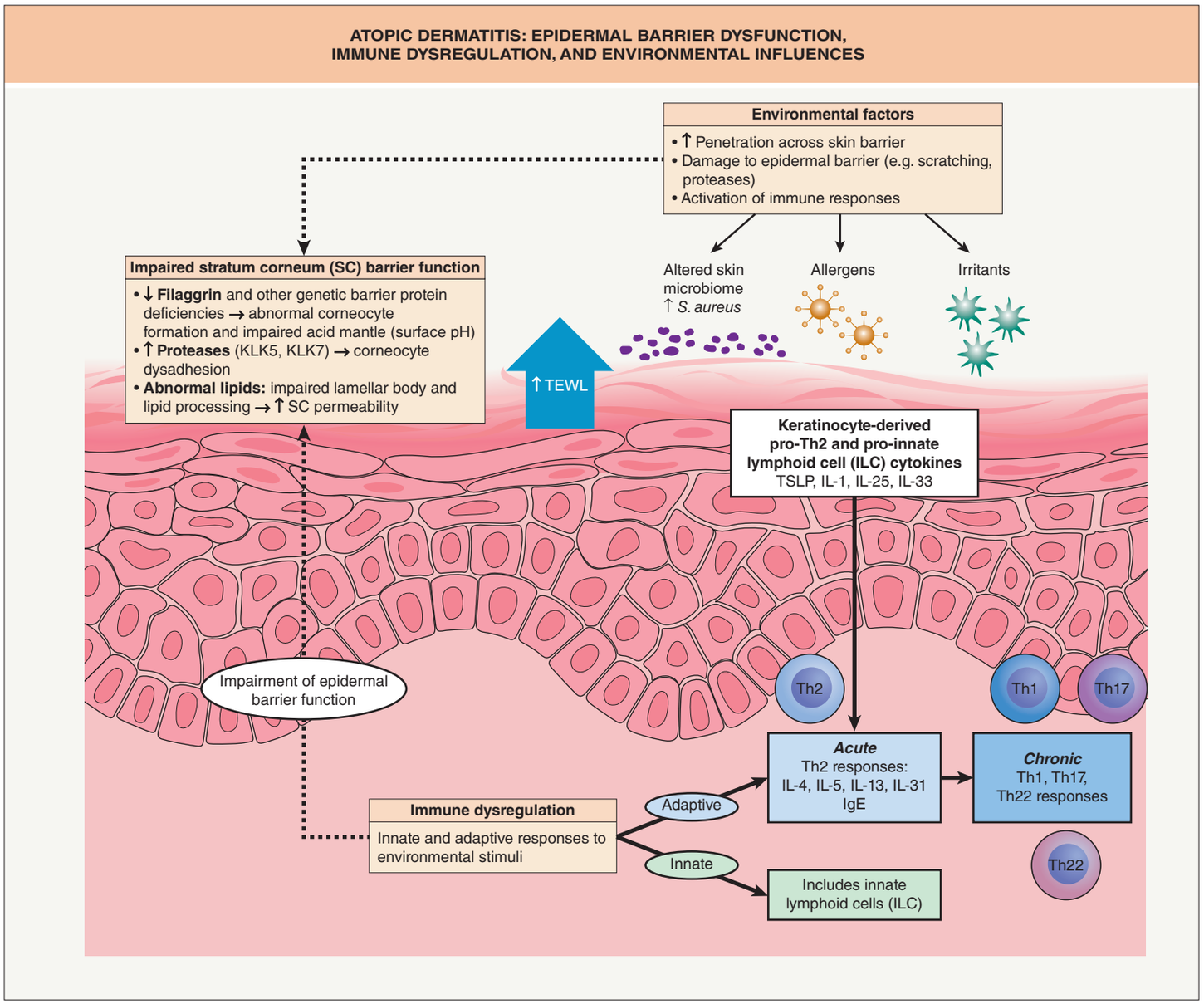


Fig. 12.2 Atopic dermatitis results from defects in epidermal barrier function, immune dysregulation, and environmental influences. SC, stratum corneum; KLK, kallikrein; TEWL, transepidermal water loss; TSLP, thymic stromal lymphopoietin. *Courtesy Harvey Lui, MD.*

Filaggrin breakdown products such as histidine contribute to epidermal hydration, acid mantle formation, lipid processing, and barrier function[30,42]. Gene expression profiling and immunohistochemical analysis of lesional and non-lesional skin from AD patients have shown broad defects in terminal differentiation, with downregulation of other epidermal barrier proteins such as loricrin, corneodesmosin, involucrin, small prolene rich proteins 3/4 (SPRR3/4), claudin-1, and late cornified envelope protein 2B[45–49].

Stratum corneum lipids

The composition, organization, and biochemical processing of stratum corneum lipids are critical determinants of epidermal permeability barrier function (see Ch. 124). In AD, a filaggrin-deficient cytoskeletal scaffold contributes to abnormal loading and secretion of lamellar bodies, with subsequent defects in post-secretory lipid organization and processing[50–52]. Disruption of the skin's acidic mantle leads to reduced activity of lipid-processing enzymes such as β-glucoscerebrosidase and acid sphingomyelinase[53,54]. Th2 cytokines also negatively affect generation of stratum corneum lipid components[52,55,56]. Lastly, *Staphylococcus aureus* colonization of the skin affects lipid composition and contributes to epidermal barrier impairment[21].

Proteases and protease inhibitors

Lesional AD skin demonstrates elevated levels of endogenous serine proteases, e.g. kallikrein 5 and 7 (KLK5/7), due to an imbalance in the activities of these proteolytic enzymes and protease inhibitors, such as the lymphoepithelial Kazal-type trypsin inhibitor (LEKTI) encoded by *SPINK5*. Biallelic loss-of-function *SPINK5* mutations underlie Netherton syndrome, which features profoundly compromised barrier function and atopy (see Ch. 57), while *SPINK5* polymorphisms have been linked to increased risk of AD in some populations[57]. Other factors that enhance proteolysis include increased skin surface pH and exogenous proteases from allergens (e.g. house dust mites, pollens), *S. aureus*, and *Malassezia*[58].

LEKTI deficiency results in excessive degradation of the corneodesmosomal component desmoglein-1 (Dsg1), causing abnormal stratum corneum detachment and thereby disrupting the epidermal barrier[59]. The *S. aureus* extracellular V8 protease, which has a sequence similar to those of *S. aureus* exfoliative toxins, is also thought to degrade Dsg1[60]. In addition, unrestrained protease activity leads to degradation of lipid-processing enzymes and antimicrobial peptides as well as activation of proinflammatory cytokines[58,61].

SELECTED CANDIDATE GENES FOR ATOPIC DERMATITIS	
Candidate gene(s)	**Defective protein(s)**
Genes encoding epidermal proteins	
FLG	Filaggrin (loss-of-function variants; see text)
FLG2	Filaggrin family member 2
SPINK5	Serine protease inhibitor LETKI
KLK5/SCTE, KLK7/SCCE	Kallikrein-related peptidases 5 & 7/stratum corneum tryptic & chymotryptic enzymes
CLDN1	Claudin-1
SPRR3	Small proline-rich protein 3
TMEM79	Transmembrane protein 79 (mattrin)
KIF3A	Kinesin family member 3A
Genes encoding immunologic proteins	
FCER1A	Fc fragment of high-affinity IgE receptor I, α chain
TLR2, 4, 6, 9	Toll-like receptor-2, -4, -6, and -9
IRF2	Interferon regulatory factor 2
IL4, 5, 12B, 13, 18, 31	Interleukin-4, -5, -12B, -13, -18, and -31
IL4RA, IL5RA, IL13RA	Interleukin-4, -5, and -13 receptors, α subunits
GM-CSF	Granulocyte–macrophage colony-stimulating factor
CD14	Monocyte differentiation antigen CD14
DEFB1	β-defensin 1
GSTP1	Glutathione S-transferase P1
CMA1	Mast cell chymase
CCL5/RANTES	Chemokine (C-C motif) ligand 5/RANTES
TSLP	Thymic stromal lymphopoietin
CARD11, CARD14	Caspase recruitment domain family members 11 and 14
RETN	Resistin
MIF	Macrophage migration inhibitory factor
VDR	Vitamin D receptor
CYP27A1, CYP2R1	Cytochrome p450 family members 27A1 and 2R1

Table 12.2 Selected candidate genes for atopic dermatitis. LETKI, lymphoepithelial Kazal-type-related inhibitor; RANTES, regulated on activation, normally T cell expressed and secreted; *SPINK5*, serine peptidase inhibitor Kazal type 5.

Immune Dysregulation

Both innate and adaptive immune systems play dynamic interrelated roles in the pathogenesis of AD. The inflammatory profile is diverse, with activation of skin-resident inflammatory dendritic cells, group 2 innate lymphoid cells, and Langerhans cells[62]. Acute AD lesions have a predominance of Th2 cytokines, but there is subsequent evolution to a chronic phase characterized by Th1 and Th22 cytokine profiles, as well as variable levels of Th17 cytokines in both acute and chronic AD[63]. The acute phase features IL-4, IL-5, and IL-13; activation of eosinophils and mast cells; and production of allergen-specific IgE[64,65]. Keratinocyte-derived cytokines, including IL-1, thymic stromal lymphopoietin (TSLP), IL-25 (IL-17E) and IL-33, promote a Th2 immune response. Th2 cytokines inhibit expression of major terminal differentiation proteins such as loricrin, filaggrin, and involucrin as well as β-defensin-2/3 antimicrobial peptides[23,46,66,67].

Thymic stromal lymphopoietin (TSLP)

TSLP is an IL-7-like cytokine that is known as the "master-switch of allergic inflammation" due to its central role in evoking a Th2 response via dendritic cell activation[61,68–70]. Exposure to allergens, viral infections, trauma, and other cytokines (e.g. IL-1β, TNF) can trigger TSLP production by keratinocytes, fibroblasts, and mast cells[71]. TSLP is highly expressed in acute and chronic lesions of AD, but not in the non-lesional skin of patients with AD or in unaffected individuals[72].

IL-4 and IL-13

IL-4 has a key role in driving Th2 cell differentiation, IgE production, and eosinophil recruitment[73,74]. Transgenic mice overexpressing IL-4 in their epidermis develop atopic dermatitis-like lesions, pruritus, an altered microbiome, and elevated IgE levels[75]. The heterodimeric receptors for IL-4 and IL-13 both contain the IL-4 receptor α subunit (IL-4Rα; see Fig. 128.9C) and activate signal transducer and activator of transcription 6 (STAT6), which promotes the differentiation of naive T cells into Th2 effector cells[76]. Although IL-4 and IL-13 share 25% sequence homology and effector functions, studies in human subjects, and human keratinocyte cell lines, support an independent role for IL-13 in AD pathogenesis. Monoclonal antibodies that target IL-4/-13 represent effective treatments for AD[77] (see Ch. 128 and below).

Other cytokines

Th17 cells are important in the regulation of innate immunity, in particular neutrophil recruitment, and have also been implicated in allergic disorders[78]. Th17 cells are found in acute as well as chronic AD lesions[79], and production of IL-17 and IL-19 is especially characteristic of new-onset pediatric AD[80]. IL-26, which is also produced by Th17 cells, induces production of Th2- and Th17-associated cytokines, thereby potentially acting as a bridge between Th2 and Th17 responses[81].

IL-31 is a Th2 cytokine that is highly expressed in lesional skin and serum of patients with AD as well as in other pruritic skin disorders such as prurigo nodularis[82–84]. Cutaneous exposure to staphylococcal superantigen rapidly induces IL-31 expression in atopic individuals, establishing a link between staphylococcal colonization of the skin and pruritus. The heterodimeric receptor for IL-31 is expressed by keratinocytes, eosinophils, activated macrophages, cutaneous C nerve fibers, and dorsal root ganglia (see Ch. 5)[85,86]. Randomized, placebo-controlled trials (RCTs) have shown that nemolizumab, a humanized monoclonal antibody against the IL-31 receptor A subunit, can significantly reduce pruritus in patients with moderate to severe AD, although improvements in disease severity scores were modest[87].

IL-33, a member of the IL-1 cytokine family, protects against helminth infection by promoting a Th2-type immune response. IL-33 expression is increased in AD lesions compared to the skin of unaffected individuals[88], and AD therapies targeting IL-33 are under development.

Innate lymphoid cells

The innate lymphoid cell (ILC) family includes natural killer cells and three groups of non-cytotoxic ILCs that orchestrate immunity, inflammation, and homeostasis in multiple tissues[89]. The group 2 ILC (ILC2) population is expanded in AD lesions and stimulated by TSLP, IL-25 (IL-17E), and IL-33[90–92]. ILC2s interact with other immune cells (e.g. mast cells, eosinophils) in the skin to promote Th2-type inflammation in a T cell independent manner.

The Cutaneous Microbiome

The cutaneous microbiome represents a complex and highly diverse community of pathogenic and commensal bacteria, fungi, and viruses that play a critical role in epidermal homeostasis, with microbial dysbiosis contributing to the pathogenesis of AD. More than 90% of patients with AD have skin colonized with *S. aureus*, compared to about 5% of unaffected individuals, presumably reflecting the disrupted acid mantle, decreased antimicrobial peptides (e.g. cathelicidins, defensins), and altered cytokine milieu of AD skin[93]. During AD flares, bacterial diversity decreases and the proportion of the microbiome accounted for by *Staphylococcus* spp. increases from ~35% to ~90%[94]. Conversely, normalization of the microbial population correlates with clinical improvement in AD[95].

Superantigens can promote the development of a Th2 immune response, and exotoxins with superantigenic properties are produced by up to 65% of the *S. aureus* strains that colonize AD patients[96]. Compared to unaffected controls, an IgE response to the *S. aureus* superantigens enterotoxin A and enterotoxin B occurs more frequently in patients with AD[97]. The *S. aureus* δ-toxin also stimulates mast cell degranulation and Th2 inflammation[98]. In addition, filaggrin deficiency increases the susceptibility of keratinocytes to *S. aureus* α-toxin-induced cytotoxicity[99]. Lastly, *Malassezia* spp. may also contribute to inflammation in AD, and adults with severe head and neck disease often display IgE reactivity to *Malassezia* antigens[100–102].

Alterations in the skin microbiome of AD patients related to the use of cleansers and topical immunomodulatory or antimicrobial agents may

have potential effects on cutaneous inflammation and barrier function. Topical administration of coagulase-negative *Staphylococcus* strains with antimicrobial activity or the Gram-negative commensal *Roseomonas mucosa* has been shown to markedly reduce *S. aureus* colonization in AD patients[103,104]. *R. mucosa* application was also associated with decreased AD severity and topical corticosteroid requirement[104], providing the basis for bacteriotherapy as a potential AD treatment.

CLINICAL FEATURES

Age-Related Cutaneous Findings

AD has a broad clinical spectrum that varies depending upon the age of the patient. It is divided into infantile, childhood, and adolescent/adult stages (Fig. 12.3). In each stage, patients may develop acute, subacute, and chronic eczematous lesions, all of which are intensely pruritic and often excoriated. Acute lesions predominate in infantile AD and are characterized by edematous, erythematous papules and plaques that may exhibit vesiculation, oozing, and serous crusting. Subacute eczematous lesions display erythema, scaling, and variable crusting. Chronic lesions, which typify adolescent/adult AD, present as thickened plaques with lichenification as well as scale; prurigo nodule-like lesions can also develop (see below). Perifollicular accentuation and small, flat-topped papules (papular eczema) are particularly common in Black or Asian patients (Fig. 12.4). In any stage of AD, a generalized exfoliative erythroderma may develop in the most severely affected patients (see Ch. 10). All types of AD lesions can leave postinflammatory hyper-, hypo-, or occasionally depigmentation upon resolution (Fig. 12.5).

Infantile AD (age <2 years) typically develops after the second month of life, often initially appearing as edematous papules and papulovesicles on the cheeks, with sparing of the central face; the lesions may evolve to form large plaques with oozing and crusting (Fig. 12.6). The scalp, neck, extensor aspects of the extremities, and trunk may also be involved, usually with sparing of the diaper area (Fig. 12.7). In the first

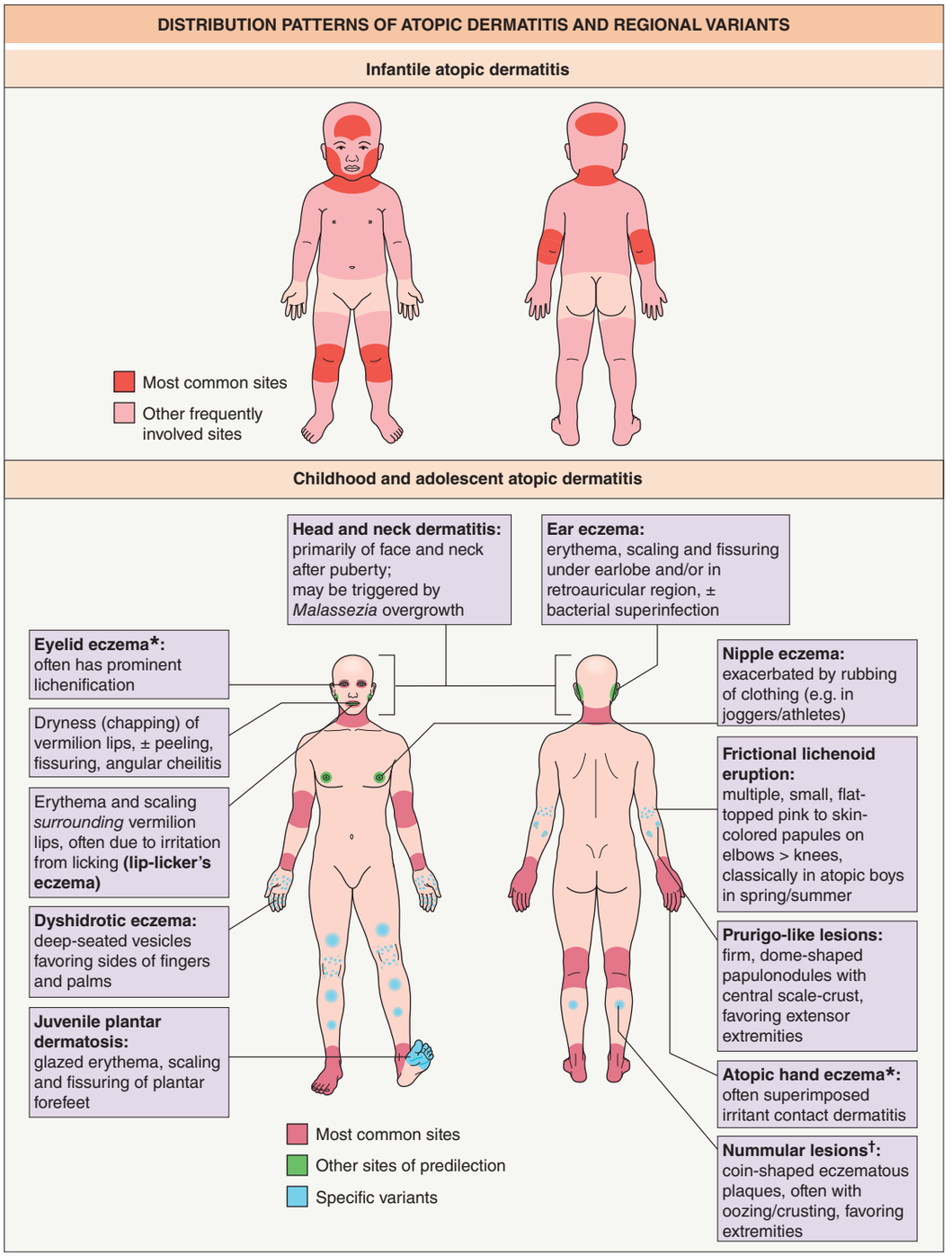


Fig. 12.3 Distribution patterns of atopic dermatitis (AD) and regional variants. *May be the only manifestation of AD in adults. †Not to be confused with nummular eczema occurring outside the setting of AD.



Fig. 12.4 Atopic dermatitis – papular pattern. This clinical variant is more commonly observed in patients with more darkly pigmented skin. There is also lichenification in the antecubital fossae. *Courtesy Gail Todd, MD.*



Fig. 12.5 Postinflammatory hypopigmentation in atopic dermatitis. *Courtesy Thomas Bieber, MD and Caroline Bussmann, MD.*





Fig. 12.6 Infantile atopic dermatitis on the face. A Erythema with scale-crust on the cheeks. Note the sparing of the central face. **B** More severe, widespread facial dermatitis with accentuation of scale-crust around the mouth. *A, Courtesy Julie V. Schaffer, MD.*

6 months of life, the face is affected in >90% of patients with AD[105]. Young infants may attempt to relieve itch through rubbing movements against their bedding, whereas older infants are better able to directly scratch affected areas.

In ***childhood AD (age 2 to 12 years)***, the lesions tend to be less exudative and often become lichenified. The classic sites of predilection are the antecubital and popliteal fossae (flexural eczema) (Fig. 12.8). Other common locations include the wrists, hands, ankles, feet, neck, and eyelids, although any area can be involved (Fig. 12.9). Xerosis typically becomes pronounced and widespread.

Adult/adolescent AD (age >12 years) also features subacute to chronic, lichenified lesions, and involvement of the flexural folds typically continues (Fig. 12.10). However, the clinical picture may also change. Adults with AD frequently present with chronic hand dermatitis that has both endogenous and exogenous components (Fig. 12.11), while others have primarily facial dermatitis (Fig. 12.12), often with severe eyelid involvement (see below). Patients who have suffered from continuous AD since childhood are more likely to have extensive disease that is resistant to treatment. Such individuals may also have severe excoriations and chronic papular skin lesions because of habitual scratching and rubbing (Fig. 12.13A).

AD in the elderly (age >60 years) is characterized by marked xerosis. Most of these patients do not have the lichenified flexural lesions typical of AD in children and younger adults[12].

Regional Variants of Atopic Dermatitis

Several regional variants of AD can occur in isolation or together with the classic age-related patterns of involvement described above (see Fig. 12.3). The face is a frequent location for site-specific manifestations. Eczema of the lips, referred to as ***cheilitis sicca***, is common in AD patients, especially during the winter (Fig. 12.14A). It is characterized by dryness ("chapping") of the vermilion lips, sometimes with peeling and fissuring, and may be associated with angular cheilitis. Patients try to moisten their lips by licking, which in turn may irritate the skin around the mouth, resulting in so-called ***lip-licker's eczema***. Another common feature of childhood AD is ***ear eczema***, presenting as erythema, scaling, and fissures under the earlobe and in the retroauricular area, sometimes in association with bacterial superinfection. ***Eyelid eczema*** can represent the only manifestation of AD, especially in adults. In contrast to eyelid eczema due to other causes, it is characterized by lichenification of the periorbital skin.

"Head and neck dermatitis" represents a variant of AD that typically occurs after puberty and primarily involves the face, scalp, and neck. When older children and teenagers present with this form of AD, it usually persists into adulthood. *Malassezia* yeasts, which are members of the skin microbiome in the head and neck area, may be an aggravating factor for this presentation[106], and systemic antifungal treatment with itraconazole or fluconazole may be of benefit.

Eczema variants also occur in acral sites. ***Juvenile plantar dermatosis*** presents with "glazed" erythema, scale, and fissuring on the balls of the feet and plantar aspect of the toes in children with AD (see Ch. 13). ***Atopic hand eczema*** (see Fig. 12.11) affects ~60% of adults with AD and may be the only manifestation of the condition. *FLG* mutations are associated with increased likelihood of hand eczema in children

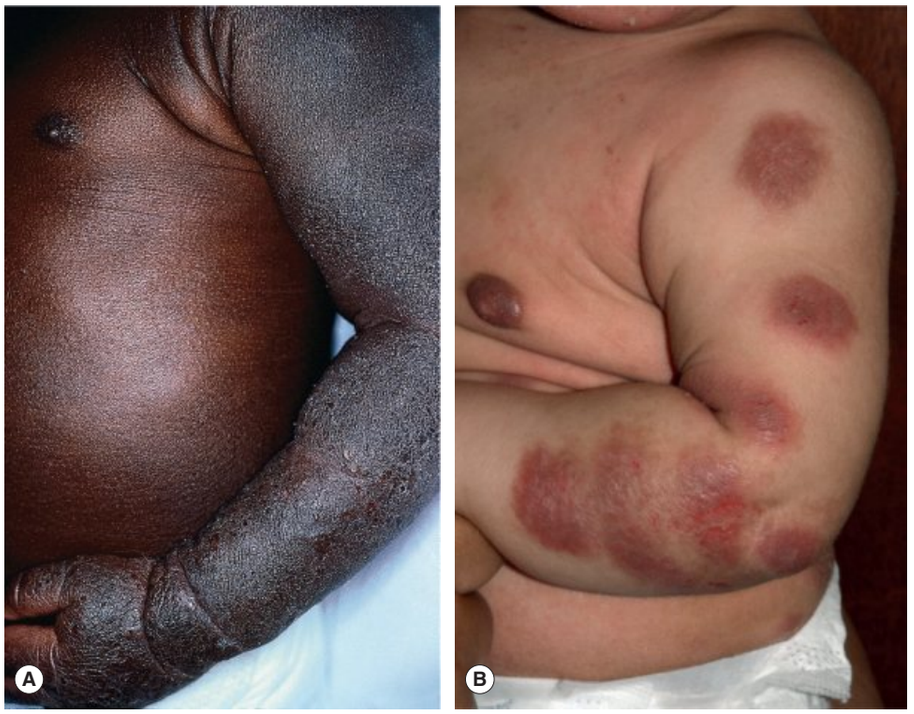


Fig. 12.7 Infantile atopic dermatitis on the extensor arms. **A** Chronic diffuse involvement of the extensor arms with scaling and hyperpigmentation. Note the follicular prominence on the trunk. **B** Nummular lesions on the extensor aspect of the arm and nipple eczema. *B, Courtesy Julie V. Schaffer, MD.*



Fig. 12.8 Flexural atopic dermatitis in a child. The popliteal fossa is a typical location. Note the excoriations. *Courtesy Julie V. Schaffer, MD.*



Fig. 12.9 Extensive atopic dermatitis in a child. Excoriations, crusting, and lichenification are evident.



Fig. 12.10 Chronic atopic dermatitis. **A** Lichenification, scale, and punctate excoriations in the antecubital fossae. **B** Coalescing papules and lichenification on the ankle due to chronic scratching and rubbing. **C** Thick eczematous plaques with lichenification and excoriation on the dorsal hands and wrists. *Courtesy Julie V. Schaffer, MD.*



Fig. 12.11 Atopic dermatitis with severe chronic hand involvement. Note the marked lichenification. *Courtesy Julie V. Schaffer, MD.*



Fig. 12.12 Severe atopic dermatitis with facial involvement in an adult.

and adults[107], and frequent exposure to water and other irritants in household or occupational settings represents another risk factor. Atopic hand eczema typically involves the volar wrists and dorsum of the hands. The palms and sides of the fingers may develop the deep-seated vesicles of ***dyshidrotic eczema*** (see Ch. 13).

The ***prurigo form of AD*** favors the extensor aspects of the extremities and is characterized by firm, dome-shaped papules and nodules with central scale-crust, similar to prurigo nodularis lesions in non-atopic patients (Fig. 12.13B). ***Nummular (discoid) lesions*** also tend to develop on the extremities in children and adults with AD, appearing as coin-shaped eczematous plaques, usually 1 to 3 cm in diameter and often with prominent oozing and crusting (Fig. 12.13C; see Fig. 12.7B). They are similar in appearance to nummular dermatitis occurring outside the setting of atopy (see Ch. 13). ***Frictional lichenoid eruption*** has a predilection for atopic children and presents as multiple small, flat-topped, pink to skin-colored papules on the elbows and (less often) knees and dorsal hands. Lastly, chronic ***nipple eczema*** can develop in children and adults with AD (Fig. 12.14B).

Associated Cutaneous Features

Pruritus

Intense pruritus is a hallmark of AD. The itch is often worse in the evening and may be exacerbated by exogenous factors such as sweating or wool clothing. Rubbing and scratching in response to pruritus can initiate flares or exacerbate existing dermatitis, explaining why AD is known as the "itch that rashes". Excoriations (linear or punctate) are frequently present, providing evidence of scratching (Fig. 12.15; see Figs. 12.8–12.10). With repeated rubbing and scratching, the skin becomes thickened and leathery with exaggerated skin markings, referred to as lichenification (see Fig. 12.10 & 12.11).

Atopic stigmata

Physical findings other than dermatitis that are frequently observed in patients with AD are presented in Table 12.3 and Figs. 12.16–12.18.

Pityriasis alba

Pityriasis alba frequently affects children and adolescents with AD. It is characterized by multiple, ill-defined, hypopigmented macules and patches, usually 0.5 to 2 cm in diameter, with fine scaling. The lesions are typically located on the face, especially the cheeks (see Fig. 12.18), but occasionally appear on the shoulders and arms. Pityriasis alba is most obvious in individuals with darkly pigmented skin and/or following sun exposure. It is thought to result from a low-grade eczematous dermatitis that disrupts the transfer of melanosomes from melanocytes to keratinocytes.

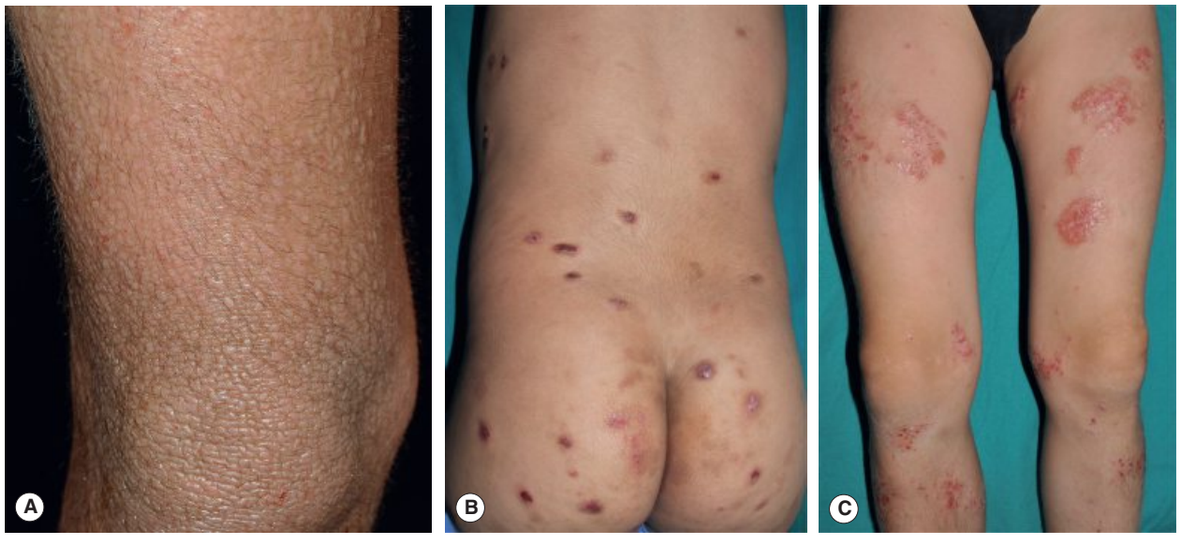


Fig. 12.13 Atopic dermatitis variants. A Chronic papular lesions resulting from habitual rubbing and scratching in the setting of longstanding disease. **B** Prurigo lesions presenting as firm, dome-shaped papules and nodules with central hemorrhagic crust. **C** Nummular plaques with oozing and crusting on the legs. *A, Courtesy Thomas Bieber, MD and Caroline Bussmann, MD; B, C, Courtesy Antonio Torrelo, MD.*

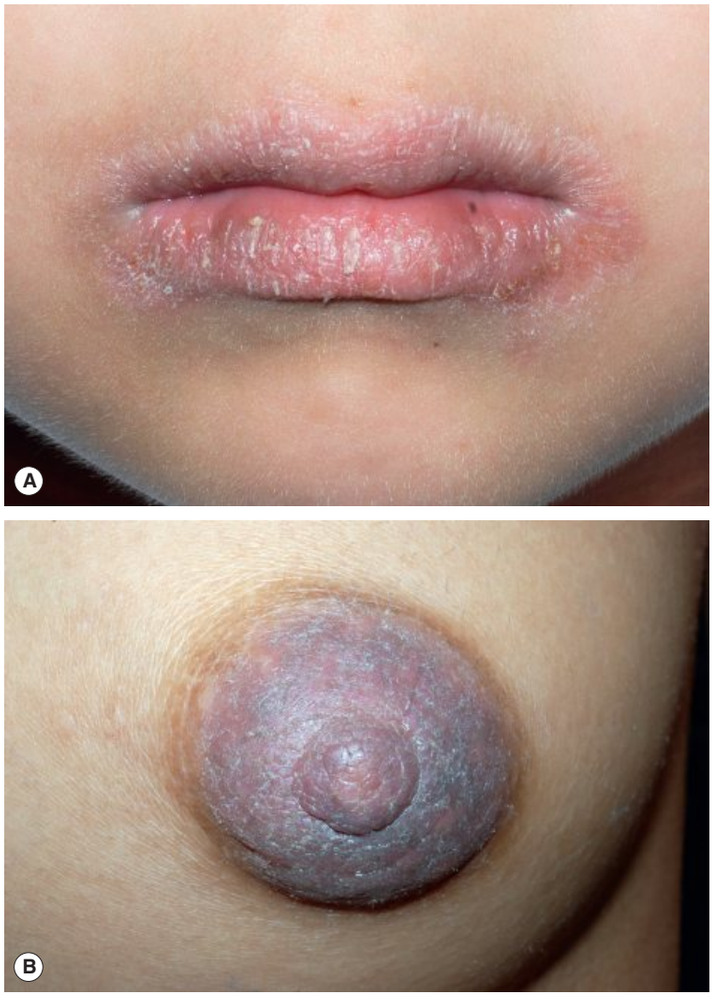


Fig. 12.14 Regional variants of atopic dermatitis. A Atopic cheilitis involving both the vermilion lip and surrounding skin (lip-licker's eczema). **B** Nipple eczema in an adolescent. *Courtesy Julie V. Schaffer, MD.*

Similar hypopigmented lesions can appear upon resolution of more overtly inflamed, erythematous lesions of AD. The differential diagnosis of pityriasis alba also includes postinflammatory hypopigmentation secondary to other dermatoses such as seborrheic dermatitis or pityriasis lichenoides chronica. Tinea versicolor is typically more sharply demarcated, with small lesions that may coalesce centrally in involved areas, and vitiligo is also sharply demarcated and depigmented rather than hypopigmented. Hypopigmented mycosis fungoides may occasionally represent a diagnostic consideration if there is extrafacial involvement. Regular use of sunscreens and other forms of photoprotection may minimize the appearance of pityriasis alba.

Infectious Complications

Bacterial and viral infections represent the most common complications of AD. Considering that *S. aureus* colonizes the skin of the vast majority of patients with AD, it is not surprising that ***impetiginization***, which can also be caused by *Streptococcus pyogenes*, occurs frequently (Fig. 12.19). Bacterial infections may exacerbate AD by stimulating the inflammatory cascade, e.g. via *S. aureus* exotoxins that act as superantigens (see above).

Eczema herpeticum represents rapid dissemination of a herpes simplex viral infection over the eczematous skin of AD patients. It initially develops as an eruption of vesicles, but affected individuals more often present with numerous monomorphic, punched-out erosions with hemorrhagic crusting (Fig. 12.20). Eczema herpeticum is frequently widespread and may occur at any site, with a predilection for the head, neck, and trunk. It is often associated with fever, malaise, and lymphadenopathy, and complications may include superinfection with *S. aureus* or *S. pyogenes* as well as herpetic keratoconjunctivitis and meningoencephalitis[108]. Patients with mutations in the filaggrin gene and those who have both severe AD and asthma have an increased risk for eczema herpeticum, and decreased production of antimicrobial peptides may have a pathogenic role. Patients with AD are also predisposed to the development of widespread ***molluscum contagiosum*** (see Ch. 81).

Impact on Quality of Life

AD has profound and multifaceted adverse impacts on the quality of life of affected children and adults as well as their families and caregivers[109,110]. Intense pruritus and stigmatization often result in sleep disturbances, psychological distress, social isolation, disrupted family dynamics, and impaired functioning at school or work. Children with AD experience greater impairment in their quality of life than those with diabetes mellitus or epilepsy[111], and detrimental effects on productivity have also been documented in adults[112,113].

Associated Extracutaneous Disorders

Ocular manifestations

In addition to allergic rhinoconjunctivitis, the spectrum of atopic eye disease includes chronic manifestations such as atopic keratoconjunctivitis, which typically affects adults, and vernal keratoconjunctivitis that favors children living in warm climates. Symptoms include ocular itching, burning, tearing, and mucus discharge, often in association with conjunctival injection and blepharitis manifesting as swelling and scaling of the eyelids. Vernal keratoconjunctivitis features large, cobblestone-like papillae on the upper palpebral conjunctiva, and atopic keratoconjunctivitis is more prone to scarring. Additional infrequent ocular complications of AD include keratoconus and subcapsular cataracts, with anterior cataracts more specifically related to AD and posterior cataracts occurring more commonly[114]; rarely there is retinal detachment.

Psychiatric disease and psychosocial burden

AD is associated with an increased risk of depression, anxiety, suicidal ideation, sleep disorders, and (in children) attention deficit hyperactivity disorder[115–118]. Sleep deprivation, pruritus, visible disease, stress, and low self-esteem contribute the psychosocial burden of AD.

Cardiovascular complications

A recent meta-analysis of cohort studies found that AD is associated with an increased risk of cardiovascular complications such as angina and myocardial infarction, cerebrovascular accidents, and heart failure during adulthood[119].

DIAGNOSTIC CRITERIA AND SEVERITY SCORES

Several authors and groups have suggested guidelines to assist in establishing the clinical diagnosis of AD. Major features in these sets of criteria include pruritus, eczematous skin lesions in typical age-specific distribution patterns, a chronic or chronically relapsing course, early age at onset, and a personal and/or family history of atopy (see Table 12.1). Atopic stigmata, especially xerosis, are also recognized as supporting features (see Table 12.3 and Fig. 12.15). The Diepgen score represents another validated set of diagnostic criteria that are separated into objective, subjective, and laboratory features[120].

Validated scores to assess the severity of AD include the EASI (Eczema Area Scoring Index), SCORAD (SCORing Atopic Dermatitis), and POEM (Patient-Oriented Eczema Measure) (see Appendix)[121]. The vIGA-AD (Validated Investigator Global Assessment scale for AD) that is required by the FDA as the primary end point for clinical trials is a rapid and simple assessment. However, it does not include body surface area affected by AD and thus omits an important aspect of disease severity[122].

The use of heterogeneous outcome measures makes it difficult to pool and compare AD study data, thereby hampering evidence-based clinical decision-making. This issue has been addressed by the Harmonizing Outcome Measures for Eczema (HOME) initiative, which recommends that POEM be utilized as the core instrument in all future clinical trials, potentially in conjunction with other measures of interest[123]. In addition, the HOME in Clinical Practice Initiative recommends using POEM and/or the Patient Oriented-SCORAD (PO-SCORAD) for

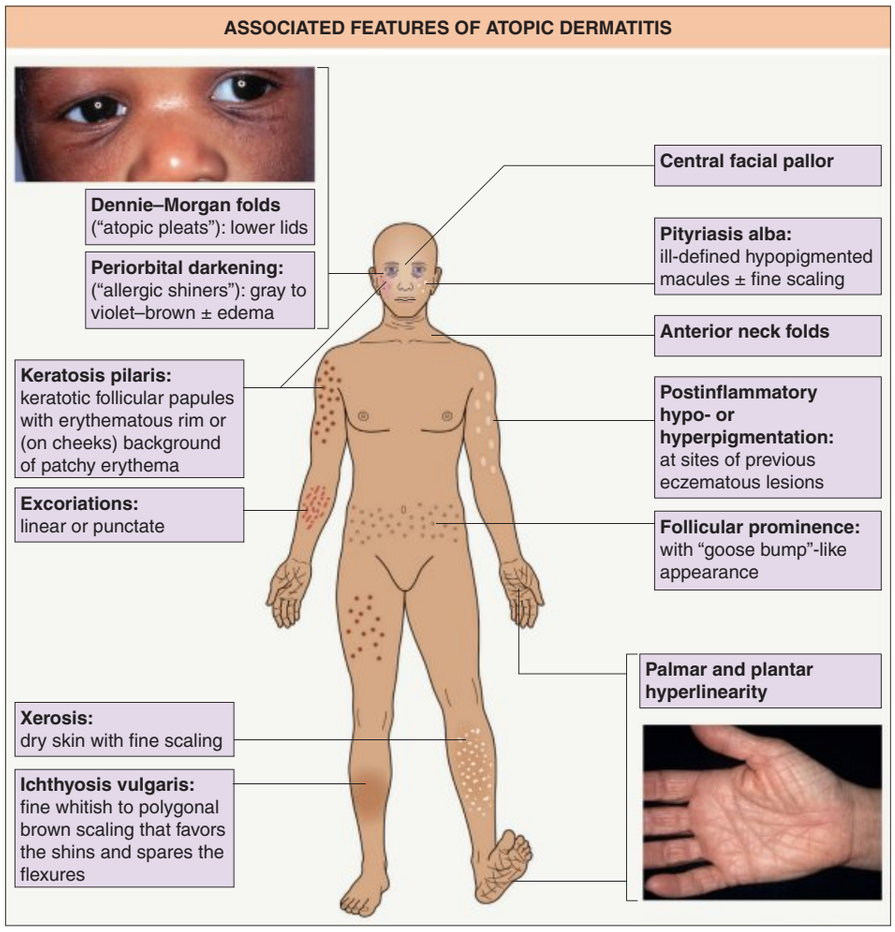


Fig. 12.15 Associated features of atopic dermatitis. See Table 12.3. *Inset of hand: Courtesy Jean L. Bolognia, MD.*

measuring AD symptoms in patient care settings[124], anticipating that they will assist in treatment choices[125].

PATHOLOGY

The histologic features of AD depend upon the clinical stage of the lesion sampled. *Acute*, exudative eczema is characterized by marked spongiosis, with intraepidermal fluid collection leading to the formation of vesicles (micro and macro) or even bullae. Some dermal edema may also be present, together with perivascular lymphocytes that extend into the epidermis and a variable number of eosinophils (Fig. 12.21A). In *subacute* lesions, vesiculation is absent whereas acanthosis, hyperkeratosis, and parakeratosis become evident (Fig. 12.21B). In *chronic*, lichenified AD, epidermal thickening is more pronounced in a pattern that may be either irregular or regular (psoriasiform). Changes in the granular layer vary from thickening secondary to rubbing, as seen in lichen simplex chronicus, to thinning when there is a psoriasiform pattern, seen in some nummular lesions. Spongiosis and inflammation are less conspicuous, but there may be an increased number of mast cells and dermal fibrosis.

These features are not specific, as similar findings are observed in other eczematous dermatoses such as allergic contact dermatitis. There are occasionally histologic clues to the etiology, such as individually necrotic keratinocytes that suggest an irritant contact dermatitis. However, a skin biopsy is usually more helpful in excluding other entities that can mimic AD clinically, such as mycosis fungoides.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of AD is broad and includes other chronic dermatoses, infections, infestations, and malignancies as well as metabolic, genetic (e.g. primary immunodeficiencies), and autoimmune disorders (Table 12.4).

In infants, AD is often preceded and/or accompanied by seborrheic dermatitis, which commonly presents during the first month of life as yellowish-white, adherent scale-crusts on the scalp. In contrast to the typical distribution of infantile AD on the extensor surfaces of the extremities and cheeks as well as the scalp, infantile seborrheic dermatitis has a predilection for the skin folds, where lesions tend to lack scale, and the forehead. Scabies in infants often has generalized involvement and can mimic AD; in addition to the presence of burrows or identification of the mite or eggs via dermoscopy or skin scrapings, scabies can usually be distinguished by the predominance of discrete small crusted papules, involvement of the axillae and diaper area, and the presence of acral vesiculopustules. Other less common conditions that occasionally represent a diagnostic consideration in infants, such as primary immunodeficiencies, are listed in Table 12.4.

Adolescents and adults without a history of atopy who present with an eczematous eruption should have a thorough history and consideration of patch testing to assess for allergic contact dermatitis. This diagnosis should also be considered in children and adults with established AD who fail to respond as expected to treatment or who develop lesions in an atypical distribution pattern. Components of emollients or topical corticosteroid preparations represent potential allergens in these individuals. Protein contact dermatitis has a predilection for atopic individuals and can also present as a chronic eczematous dermatitis. Causes include a variety of foods and animal products (Table 12.5; see Ch. 16), and it is diagnosed by prick testing or observation of an urticarial reaction within 30 minutes of patch testing on previously affected skin.

Mycosis fungoides (MF) should be considered in adolescents and adults with chronic dermatitis poorly responsive to topical corticosteroid treatment. Because the histologic findings of early MF may be difficult to distinguish from those of AD, multiple biopsies are recommended, preferably from untreated areas of skin since corticosteroids

ASSOCIATED FEATURES OF ATOPIC DERMATITIS ("ATOPIC STIGMATA")	
Xerosis	• Important feature that is present in most patients with AD • Often most prominent on the lower legs; may be generalized • Dry skin with fine scale in areas without clinically apparent inflammation • Typically worse during the winter • Impaired epidermal barrier function from decreased water content in the stratum corneum leads to easier entry of irritants, which can promote pruritus and initiate an inflammatory response
Ichthyosis vulgaris	• Autosomal semidominant disorder with incomplete penetrance caused by mutations in the filaggrin gene (*FLG*; see text and Ch. 57) • ~15% of patients with AD have moderate-to-severe ichthyosis vulgaris; conversely, >50% of patients with ichthyosis vulgaris have AD • Excessive fine, whitish to brown scaling that favors the lower legs (especially the shins) and spares the flexures
Keratosis pilaris	• Common condition that affects >40% of patients with AD and ~75% of those with ichthyosis vulgaris • Onset typically in childhood; may improve after puberty (especially facial involvement) • Affects the lateral aspect of the upper arms, thighs, and lateral cheeks (especially in children) > trunk and extensor aspects of the distal extremities • Keratotic follicular papules, often with a rim of erythema (see Fig. 12.17A) or a background of patchy erythema (especially on the cheeks) • The *keratosis pilaris rubra (KPR)* variant features numerous tiny, "grain-like" follicular papules superimposed on prominent confluent erythema (see Fig. 12.17B); often widespread on face & ears > trunk & proximal extremities, and tends to persist after puberty; presence of erythema rather than hyperpigmentation differentiates KPR from erythromelanosis follicularis faciei et colli, and a lack of atrophy in KPR differentiates it from keratosis pilaris atrophicans (see Ch. 38) • Keratolytic agents and topical retinoids are sometimes used to decrease the hyperkeratotic component, but the benefit is limited and these agents can be irritating, especially in AD patients; treatment with vascular lasers (e.g. pulsed dye laser) can sometimes improve associated erythema
Palmar and plantar hyperlinearity	• Increased prominence of the palmar and, less often, plantar creases • Associated with ichthyosis vulgaris and *FLG* mutations
Dennie–Morgan lines	• Symmetric, prominent horizontal fold(s) (single or double) just beneath the margin of the lower lid, originating at or near the inner canthus and extending one-half to two-thirds the width of the lid
Periorbital darkening ("allergic shiners")	• Skin around the eyes appears gray to violet–brown, while the rest of the facial skin is rather pale • Periorbital edema and lichenification may also be seen
Anterior neck folds	• Horizontal folds across the middle of the anterior neck
Hertoghe sign	• Absence or thinning of the lateral eyebrows
White dermographism	• Stroking the skin leads to a white streak that reflects excessive vasoconstriction • Most apparent on the forehead • Midfacial pallor and a delayed blanch response represent additional manifestations of aberrant vascular reactivity in patients with atopic dermatitis
Follicular prominence	• "Goose bump-like" appearance of the skin, most often on the trunk (see Fig. 12.7) • More commonly observed in children with darkly pigmented skin

Table 12.3 Associated features of atopic dermatitis ("atopic stigmata"). AD, atopic dermatitis. See Fig. 12.15.



Fig. 12.16 Excoriations. Numerous punctate and a few linear excoriations in an area of papular eczema on the lower back. *Courtesy Antonio Torrelo, MD.*

can eliminate the epidermotropic T cells that point to the diagnosis of MF. Longitudinal evaluation of such individuals is required, especially when the clinical and/or histologic features are not classic for AD, with additional biopsies as indicated.

TREATMENT

General Approach

Because AD is a chronic, relapsing disease, the traditional approach was reactive management targeting acute flares with short-term treatment regimens. Based on insights into the underlying skin barrier defect and its relationship to inflammatory processes in the skin and other organs, a proactive approach that includes long-term maintenance therapy is now recommended (Fig. 12.22)[126]. This treatment strategy may modify the overall disease course and possibly prevent the development of atopic comorbidities. Management of AD includes education of patients/parents, gentle skin care, moisturizer use, and anti-inflammatory therapy to control subclinical inflammation as well as overt flares. Topical agents represent the mainstay of treatment. Severe disease may require phototherapy or systemic medications, usually in conjunction with continued topical therapy (Table 12.6)[126]. Factors that can potentially exacerbate AD should be identified and, if possible, avoided (see Table 12.1).

Educational interventions

Education of patients and families to promote AD self-management has been shown to improve outcomes[127–129]. Knowledge of disease mechanisms and course, potential triggers, appropriate use of therapies, and the goals of management can increase treatment adherence and reduce fear and misconceptions[130–133]. Parents often seek an eradicable cause for their child's AD and have difficulty accepting "control" rather than a "cure" for the condition. Addressing their specific concerns and acknowledging the stresses associated with this chronic disease, as well



Fig. 12.17 Keratosis pilaris. A Discrete perifollicular papules with central keratotic cores on the extensor surface of the upper arm. Each papule has a rim of erythema. **B** Keratosis pilaris rubra on the lateral face. This variant is characterized by tiny, "grain-like" follicular papules superimposed on confluent erythema. *A, Courtesy Luis Requena, MD; B, Courtesy Angela Hernández-Martín, MD.*

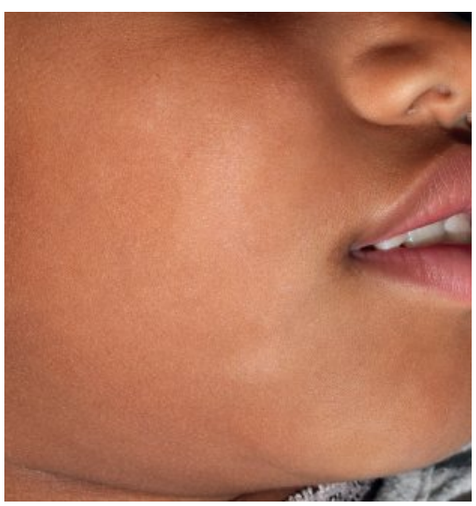


Fig. 12.18 Pityriasis alba. Note the slight scale associated with the hypopigmented macules and patches on the cheeks. *Courtesy Antonio Torrelo, MD.*



Fig. 12.19 Superinfection with group A *Streptococcus* in a patient with atopic dermatitis. Pustules and impetigo-like crusting are evident. *Courtesy Julie V. Schaffer, MD.*



Fig. 12.20 Eczema herpeticum. Grouped punched-out monomorphic erosions with hemorrhagic crusts on the arm **(A)** and posterior neck **(B)**. Vesicles are rarely evident. *B, Courtesy Julie V. Schaffer, MD.*

as noting the improvement in pruritus and sleep disturbances likely to result from treatment, can lead to more effective care. Educational approaches include counseling clinic visits with a team approach/multidisciplinary input, online resources (e.g. nationaleczema.org), and structured teaching programs ("eczema schools"). Written action plans have also been shown to be beneficial in AD management[134–136]. Psychological interventions to aid in coping with AD may prove useful, with reported approaches including biofeedback, cognitive-behavioral therapy, and stress management[137].

Bathing

Bathing can hydrate the skin and remove scale, crust, irritants, and allergens. Although there is a paucity of objective data on optimal bathing practices for AD, it is generally recommended that patients bathe or shower once daily for 5–10 minutes in warm (not hot) water, with use

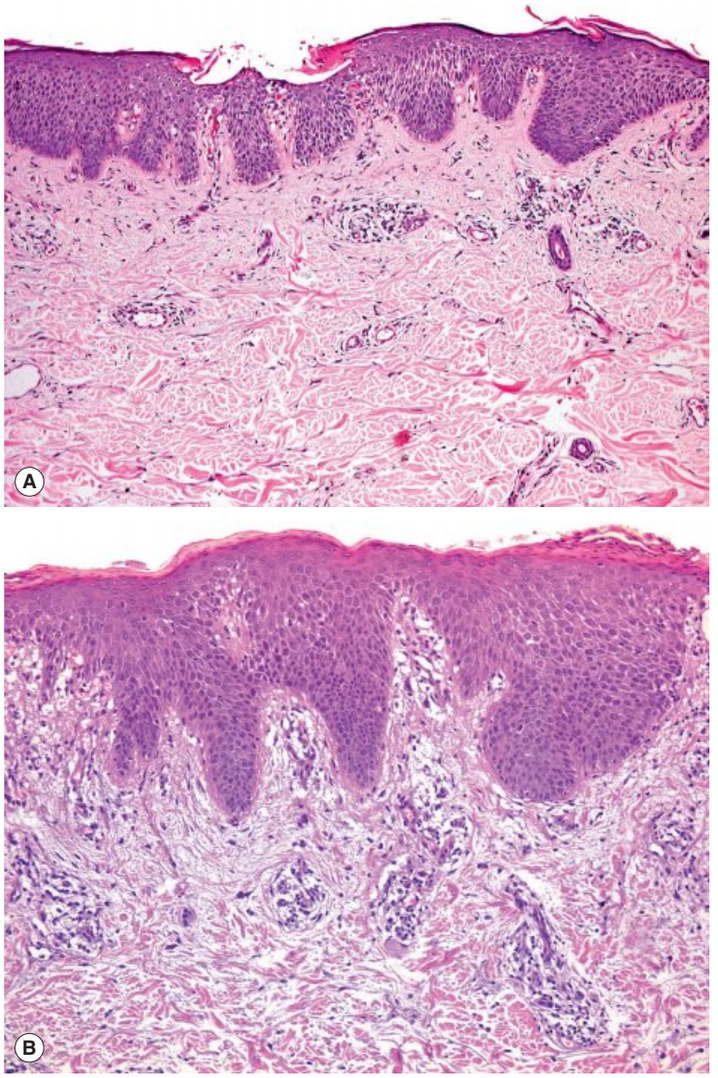


Fig. 12.21 Histologic features of acute and subacute atopic dermatitis. A Acute lesion showing prominent spongiosis, epidermal hyperplasia, and a mild inflammatory infiltrate in the upper dermis. **B** Subacute lesion with parakeratosis and less spongiosis. *A, Courtesy Lorenzo Cerroni, MD.*

of a fragrance-free non-soap cleanser with a neutral to low pH as needed (e.g. syndets; see Ch. 153)[126,138,139]. Application of a moisturizer shortly after bathing is essential to maintain skin hydration[140]. If treatment with a topical corticosteroid or other anti-inflammatory agent is needed, it should be applied immediately after bathing, prior to the moisturizer; this has been referred to as the "soak and smear" technique[138]. With the exception of bleach (see below), there are no RCTs to support the use of bath oils, other bath additives, acidic spring water, or water-softening devices for AD[126,141].

Moisturizers

Daily use of moisturizers to counteract dry skin and reduce transepidermal water loss is a cornerstone of AD management that helps to prevent disease flares[142]. Moisturizer application can reduce xerosis, pruritus, erythema, fissuring, and lichenification[126], thereby decreasing the amount of anti-inflammatory medication required for disease control[143]. Standard moisturizers contain varying amounts of emollient agents that lubricate the skin, occlusive agents that prevent water loss, and humectants that attract water[126]. Preparations should be free of dyes, fragrances, food-derived allergens such as peanut protein, and other potentially sensitizing ingredients[144]. Factors in selecting the formulation of the moisturizer include the degree of xerosis, the sites of application, acceptance by the patient, and the season. Ointments (e.g. petrolatum) contain higher concentrations of lipids, have occlusive properties, and are typically preservative-free; although they tend to cause less stinging when applied to inflamed skin, the greasiness of ointments is bothersome to some patients[126,142]. Creams may be a more acceptable option for such individuals, whereas lotions contain a higher water content and are not ideal for the xerosis of AD. Products with higher concentrations of urea or α-/β-hydroxy acids, which can decrease scaling, may also sting when used in children and on acutely inflamed or excoriated skin.

There are limited data on the optimal amount and frequency of moisturizer application or comparing the effectiveness of different moisturizing products, and no particular preparation has been shown to be superior[142,143,145]. Weekly use of 150–200 g of moisturizer in young children and 250–500 g in older children/adults has been recommended, with liberal and frequent application[139]. Prescription emollient devices (PEDs) that aim to improve the defective skin barrier of AD include preparations that contain specific ratios of lipids (e.g. cholesterol, fatty acids, ceramides), palmitoylethanolamide, glycyrrhetinic acid, and other hydrolipids[126]. There is currently no evidence that these agents are superior to over-the-counter preparations.

Topical Anti-Inflammatory Therapy

Topical corticosteroids

Topical corticosteroids represent first-line pharmacologic therapy for AD. These agents have anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive actions, with effects on cutaneous T cells, macrophages, and dendritic cells (see Ch. 125)[126,142]. The efficacy of topical corticosteroids in AD has been verified in >100 RCTs[146], and they have been shown to decrease the acute and chronic inflammation of AD as well as associated pruritus[126]. Topical corticosteroids are used to treat acute flares of AD and as maintenance therapy to prevent relapse.

Factors in selecting the potency and vehicle of the topical corticosteroid include the location, type (e.g. acute versus chronic), thickness, and extent of the AD lesions; patient age and preference as well as the cost and availability of different preparations represent additional considerations. The corticosteroid should have an appropriate potency to quickly gain control of the flare, and continuation of daily therapy until the active dermatitis is completely clear can minimize the likelihood of a rebound. Long-term daily use of an inadequately potent topical corticosteroid can result in a greater risk of side effects as well as less control of the eczema than relatively brief use of a more potent agent. RCTs in children and adults with AD have demonstrated that the risk of relapse can be significantly reduced by proactive maintenance with twice-weekly application of a mid-potency topical corticosteroid to the usual areas of involvement when clear, with no evidence of cutaneous atrophy after up to 40 weeks of treatment[126,147–149].

For the face and body folds, high potency corticosteroids (especially long-term use) should be avoided if possible due to risk of cutaneous atrophy and (for the face) acneiform eruptions. However, short-term use of a potent agent (e.g. mometasone furoate ointment) may be required to clear thick, exuberant lesions on the cheeks of infants. More potent corticosteroids (e.g. class 1–2) are often needed for lichenified plaques, nummular or prurigo-like lesions, and involvement of the palms and soles. Corticosteroid ointments (which minimize stinging) and creams are generally preferred considering the dryness of the skin in AD patients and the moisturizing effects of these vehicles. Application immediately after bathing improves cutaneous penetration and also decreases stinging. Corticosteroid solutions, foams, and oils represent options for AD on the scalp.

Systematic reviews have concluded that topical corticosteroids have a favorable safety profile with short-term (up to several weeks) daily use and long-term intermittent use (see Ch. 125)[150]. However, aversion or hesitancy regarding use of topical corticosteroids ("steroid phobia") is very common among AD patients and their parents, and it often leads to delayed and inadequate treatment[151–153]. It is essential that these fears and incorrect beliefs about topical corticosteroids are addressed to ensure adherence to the treatment plan.

When AD does not respond as expected to topical corticosteroid therapy, adherence should be assessed, including the amount (grams/tubes) and duration (consecutive days) of use. If possible, in-patient therapy for patients with severe AD can allow direct observation and

DIFFERENTIAL DIAGNOSIS OF ATOPIC DERMATITIS		
Chronic dermatoses		
C > A	Seborrheic dermatitis	Common
B	Contact dermatitis – allergic* or irritant	Common
B	Psoriasis	Common
A > C	Nummular dermatitis	Uncommon (although nummular lesions can be seen in AD, nummular eczema outside this setting is uncommon)
A	Asteatotic eczema	Common
A > C	Lichen simplex chronicus (secondary to pruritus of variable etiology)	Common
Infections and infestations		
B	Scabies	Common
B	Dermatophytosis*	Common
B	HIV-associated dermatoses	Variable
C	HTLV-1-associated "infective dermatitis"	Variable
C	Chronic mucocutaneous candidiasis	Rare
C	Neonatal mucocutaneous candidiasis	Variable
B	Impetigo	Variable (nummular lesions of AD can mimic impetigo)
C	Congenital syphilis	Variable
Primary immunodeficiencies		
C	Wiskott–Aldrich syndrome	Rare
C	Hyperimmunoglobulin E syndromes	Rare
C	IPEX (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked) syndrome and IPEX-like conditions	Rare
C	Omenn syndrome	Rare
C	DiGeorge syndrome (congenital thymic aplasia)	Rare
C	Immunodeficiency 23	Rare
C	Immunoglobulin deficiencies: X-linked hypogammaglobulinemia, common variable immunodeficiency, IgA deficiency	Variable
Malignancies		
A > C	Mycosis fungoides and Sézary syndrome	Uncommon
C	Langerhans cell histiocytosis	Rare
Metabolic and genetic disorders		
C	Netherton syndrome, generalized inflammatory peeling skin syndrome	Rare
C	Ectodermal dysplasias	Rare
C	*S*evere dermatitis–*a*llergies–*me*tabolic wasting (SAM) syndrome	Rare
B	Keratosis pilaris	Common
C	Hartnup disease	Rare
C	Phenylketonuria	Rare
C	Prolidase deficiency	Rare
B	Acrodermatitis enteropathica, glucagonoma syndrome, pellagra, riboflavin deficiency	Rare
C > A	Other causes of "nutritional dermatitis", e.g. biotin deficiency, essential fatty acid deficiency, organic acidurias, cystic fibrosis	Rare
Autoimmune disorders		
A > C	Dermatitis herpetiformis	Uncommon
A > C	Pemphigus foliaceus	Uncommon
B	Dermatomyositis	Uncommon (but often misdiagnosed as AD in children)
A > C	Lupus erythematosus	Uncommon
Other		
B	Drug eruptions	Uncommon (although drug eruptions are common, those resembling atopic dermatitis are uncommon)
A > C	Photoallergic contact dermatitis	Uncommon
A	Chronic actinic dermatitis	Uncommon
B	Graft-versus-host disease	Uncommon

*More common causes of disseminated eczema ("id reaction"), which is especially frequent in the setting of stasis dermatitis + allergic contact dermatitis.

Table 12.4 Differential diagnosis of atopic dermatitis. A, adults; B, both; C, children/infants.

intensive education. Potential complicating factors should be investigated, such as disease exacerbation by superinfection, irritants, or allergens. The latter can include immediate hypersensitivity reactions to foods and aeroallergens as well as delayed hypersensitivity to contact allergens, including components of moisturizers and topical mediations[142].

Topical calcineurin inhibitors

Two topical calcineurin inhibitors (TCIs) have been FDA-approved for the treatment of AD: (1) tacrolimus 0.03% and 0.1% ointment for moderate to severe disease; and (2) pimecrolimus 1% cream for mild to moderate disease (see Ch. 129). These agents suppress T cell activation and modulate the secretion of cytokines and other proinflammatory mediators; they also decrease mast cell and dendritic cell activity[144,154]. The efficacy of TCIs in the treatment of AD has been proven in large clinical trials in adults and children ≥2 years of age and, for pimecrolimus, infants ages 3–23 months, although it is not currently approved for the latter group[155].

TCIs are particularly useful for AD affecting the face and intertriginous areas, sites where corticosteroid-induced skin atrophy is of increased concern and TCI therapy is especially effective[142]. TCIs are also beneficial in patients with frequently flaring or persistent AD that would otherwise require almost continual use of topical corticosteroids. Randomized controlled studies have shown that the proactive application of tacrolimus ointment 2–3 times weekly as maintenance can prevent flares of AD without increasing the overall amount of medication used[156].

The most common adverse effects with TCIs are local stinging and burning. These symptoms lessen after several applications, or if TCI use is preceded by a short topical corticosteroid course. For both topical tacrolimus and pimecrolimus, there has been no short-term or intermediate-term (>15 years) evidence of systemic immunosuppression in either clinical studies or post-marketing surveillance, and long-term data collection is ongoing[157,158]. In 2006 the FDA introduced black box warnings for both drugs concerning a theoretical cancer risk; this was based on the occurrence of lymphomas in mice exposed to systemic levels 30- to 50-fold greater than the highest recorded blood levels in human patients. Pharmacokinetic studies in children and adults with AD have demonstrated minimal systemic absorption of TCIs, with transient detectable but low blood levels occasionally observed in patients with severe AD involving a large portion of the body surface area. Of note, recent meta-analyses found no association between TCI use and overall cancer or skin cancer (keratinocyte carcinoma, melanoma) risk, with a slight increase in lymphoma risk in adults that may potentially be explained by early cutaneous T cell lymphoma being misdiagnosed as AD and treated with TCIs[157,158].

Crisaborole

Crisaborole 2% ointment is a phosphodiesterase-4 (PDE-4) inhibitor that is FDA-approved for the treatment of mild to moderate AD in patients ≥3 months of age. In large RCTs, ~30% of such individuals achieved clear/almost clear skin with a ≥2-grade improvement after 4 weeks of twice daily treatment[159]. PDE-4 degrades cAMP, which leads to increased production of cytokines including IL-10 and IL-4 (see Fig. 130.3). The most common side effect is stinging or burning in the area of application.

Topical JAK inhibitors

Ruxolitinib 1.5% cream is a Janus kinase 1/2 (JAK1/2)-selective inhibitor that was recently FDA-approved for short-term or non-continuous chronic treatment (using ≤60 g/week) of mild to moderate AD in patients ≥12 years of age. In RCTs (total n=1249), 50%–55% of individuals treated with ruxolitinib 1.5% cream twice daily for 8 weeks had clear/almost clear skin with a ≥2-grade improvement, compared to 7%–15% for the vehicle control[160]. Mean plasma concentrations were

CAUSES OF PROTEIN CONTACT DERMATITIS
• Fruits (banana, fig, kiwi, lemon, pineapple)
• Grains (barley, rye and wheat flours)
• Latex
• "Meats" (fish, seafood, beef, pork, poultry)
• Mites and insects (rice flour beetle, dust mite, storage mite)
• Nuts (almond, hazelnut, peanut)
• Spices (caraway, curry, dill, garlic, paprika, parsley)
• Vegetables (carrot, cauliflower, celery, cucumber, lettuce, mushroom, onion, parsnip, potato)
• Animal dander, hair, saliva or urine (cow, deer, goat, dog, cat, rodents, hedgehog, rabbit, giraffe)

Table 12.5 Causes of protein contact dermatitis.

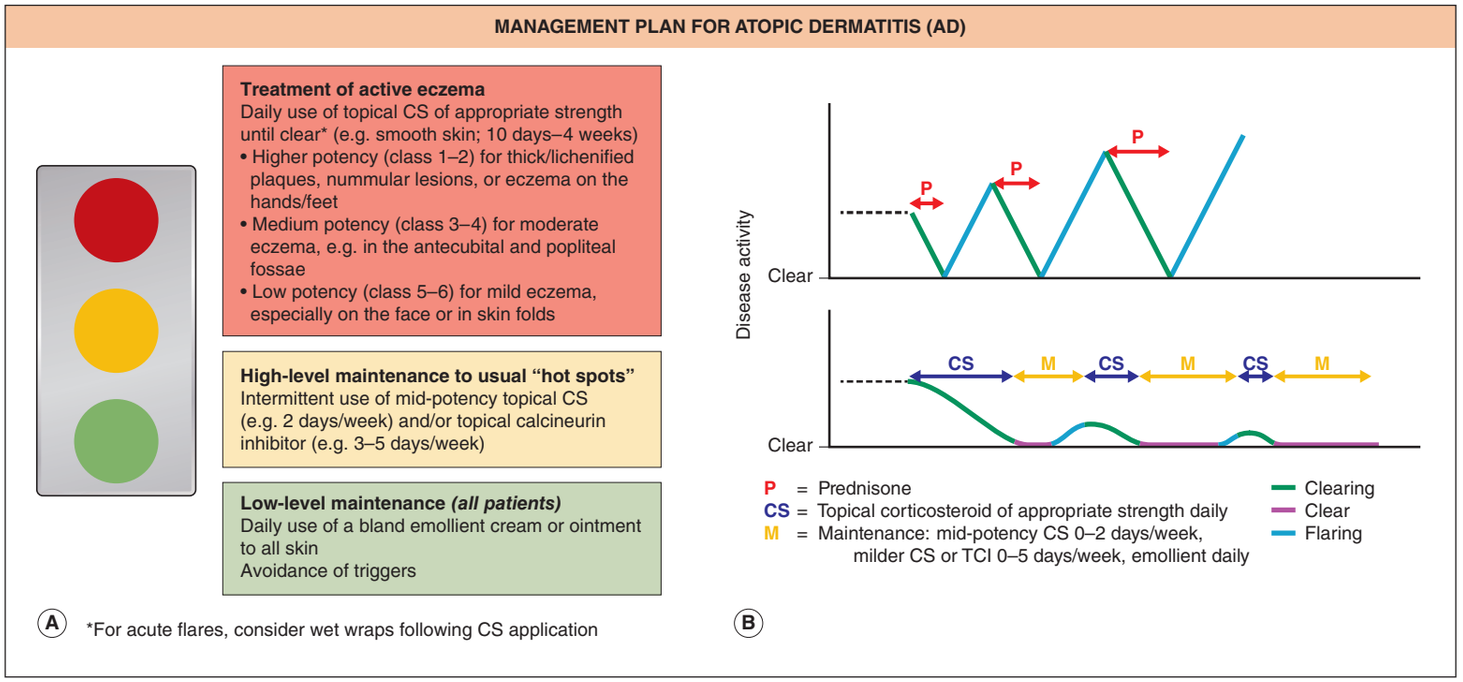


Fig. 12.22 Management plan for atopic dermatitis. A The therapeutic regimen should include both treatment of active eczema and maintenance that includes the low-level in all and the high-level in some patients. **B** Intermittent courses of a systemic corticosteroid result in rebound flares and worsening of disease over time. In contrast, a proactive regimen utilizing topical corticosteroid leads to longer clear periods and milder disease over time.

THERAPEUTIC LADDER FOR ATOPIC DERMATITIS (AD)	
Topical therapies	**Evidence**
Moisturizers	1
Corticosteroids	1
Calcineurin inhibitors	1
Crisaborole	1
JAK inhibitors e.g. ruxolitinib (FDA-approved), delgocitinib (approved in Japan)	1
Phototherapy	
Narrowband UVB, UVA–UVB, UVA1	1
Systemic therapies	**Evidence**
Dupilumab	1
IL-13 inhibitors, e.g. tralokinumab, lebrikizumab	1
JAK inhibitors, e.g. upadacitinib, abrocitinib, baricitinib	1
Cyclosporine (short-/intermediate-term)	1
Azathioprine	1
Mycophenolate mofetil/enteric-coated mycophenolate sodium	1/2
Methotrexate	1/2
Systemic corticosteroids (short-term for severe acute flares; "rebound" exacerbations often occur upon discontinuation)	2
Omalizumab	2*
Nemolizumab† (anti-IL-31 receptor A; not currently FDA-approved)	1†
Rituximab	2
Interferon-γ	‡
IVIg	2*
Adjunctive therapies	
Wet wraps, open wet dressings, or soaks combined with topical corticosteroids for acute flares	
Dilute sodium hypochlorite (bleach) baths	
Treatment of associated bacterial, viral, or fungal infections	
Oral antihistamines for associated conditions (e.g. dermographism, rhinoconjunctivitis) and sedative effects	
Leukotriene antagonists¶	
Sodium cromoglycate (topical or oral)¶	

*No significant benefit was found in a small controlled trial.
†Benefit for pruritus in patients with moderate to severe AD.
‡Although found to be effective in one randomized controlled trial, results of other studies have been inconsistent (see Ch. 128).
¶Inconsistent demonstration of efficacy in controlled trials.

Table 12.6 Therapeutic ladder for atopic dermatitis (AD). Key to evidence-based support: (1) prospective controlled trial; (2) retrospective trial or large case series; (3) small series or individual case reports.

<15% of the whole blood IC_{50} for JAK2 inhibition[160]. However, the JAK inhibitor class-wide black box warning notes potential increased risks of serious infection, death, cancer, cardiovascular events, and thrombosis (see Chs. 128 & 129). Delgocitinib 0.5% ointment (pan-JAK inhibitor; approved in Japan for AD in adults) has shown greater efficacy than vehicle in phase 2 and 3 RCTs in AD patients ≥2 years of age[161,162].

Wet wrap therapy

Wet wrap therapy may be helpful in severe recalcitrant AD or during an acute flare. These moist, occlusive dressings increase skin hydration, act as a barrier to scratching, and enhance the penetration of topical corticosteroids. However, because of the latter effect, care should be exercised when using moderate and potent topical corticosteroids with wet wraps, and a possible increased risk of bacterial skin infections has been noted[163]. The wraps consist of application of a topical corticosteroid (sometimes diluted), followed by an inner wet layer and outer dry layer of cotton gauze or garments; they are left in place 8–24 hours per day, and the treatment duration should not exceed 2 weeks.

Phototherapy

Narrowband UVB, UVA1, and *UVA combined with UVB* have each been shown to improve atopic dermatitis and associated pruritus[164–166]. The immunomodulatory effects of phototherapy occur via induction of T cell apoptosis, reduction of dendritic cells, and decreased expression of Th2 cytokines such as IL-5, IL-13, and IL-31 (see Ch. 134). In addition, treatment with UVB has been shown to reduce *S. aureus* colonization of the skin in AD patients. Narrowband UVB and UVA1 can both be helpful for chronic AD lesions, and UVA1 may also be useful in the treatment of acute flares. Phototherapy can be combined with topical corticosteroids, especially in the initial phase of treatment. The side effect profile of phototherapy is favorable compared to systemic immunosuppressive agents, with potential "sunburn" and, with long-term treatment, photoaging and possibly an increased risk of skin cancer. The time required to travel several times a week to a phototherapy center may disrupt school or work for some patients, and a home UV unit may be an option for those receiving chronic treatment. In young children, phototherapy may be difficult for practical reasons, e.g. lack of cooperation.

Systemic Anti-Inflammatory Therapy

Systemic anti-inflammatory medications may be employed for children and adults with moderate to severe AD that has failed to respond adequately to optimized topical treatment[164]. The risk–benefit profile should be carefully considered before starting an immunosuppressive agent, and patients receiving these medications require close monitoring for side effects (see Chs. 128 & 130). Combination of systemic treatment with topical corticosteroid therapy is frequently required to maximize benefit. In addition to the medications discussed below, a number of promising targeted immunomodulatory therapies are under investigation.

Interleukin-4/-13 receptor inhibitors

Dupilumab is a human monoclonal antibody that targets the IL-4Rα subunit of heterodimeric IL-4 and IL-13 receptors (Fig. 128.9C). It blocks signaling by these cytokines and the resulting Th2-mediated inflammation. Dupilumab is FDA-approved for the treatment of patients ≥6 months of age with moderate to severe atopic dermatitis that is not adequately controlled with topical therapy. Large RCTs have demonstrated a significant benefit in this patient population, with ~40%–50% of adolescents or adults who received dupilumab alone and ~55%–70% of infants, children or adults who received dupilumab plus topical corticosteroids achieving a 75% improvement in their EASI score after 16 weeks of treatment, with sustained efficacy through 52 weeks[77,165–168a].

Dupilumab is administered via subcutaneous injection. Adults receive a 600 mg loading dose followed by 300 mg every 2 weeks. Pediatric patients have weight-tiered dosing: the adult regimen if ≥60 kg; a 400 mg loading dose then 200 mg every 2 weeks if 30–59 kg; a 600 mg loading dose then 300 mg every 4 weeks if 15–29 kg (with no loading dose if <6 years of age); and 200 mg every 4 weeks if 5–14 kg. Dupilumab has a favorable side effect profile, with injection site reactions occurring in ~10% of patients and conjunctivitis in ~10% and ~25% of patients in clinical trials and real-world settings, respectively[169,170]. Ocular surface disease appears to be an AD-specific drug–disease interaction and can often be managed with topical therapies while continuing dupilumab. Some patients develop facial erythema distinct from their usual AD, with possible etiologies including rosacea, allergic contact dermatitis, and *Malassezia*-related dermatitis[171]. Lastly, dupilumab therapy for AD is associated with a decreased risk of skin infections including eczema herpeticum[172,173].

Interleukin-13 inhibitors

Tralokinumab is a human monoclonal antibody that binds to free IL-13, blocking its interaction with IL-13Rα1 and IL-13Rα2 (see Fig. 128.9C)[174]. It was recently FDA-approved for the treatment of adults with moderate to severe atopic dermatitis that is not adequately controlled with topical therapy. In large RCTs, tralokinumab monotherapy and combination therapy with topical corticosteroids were superior to placebo at 16 weeks, with ~30% and 55% of patients achieving a 75% improvement in their EASI score, respectively[175,176]. The majority of responders maintained their response at 52 weeks, and side effects included conjunctivitis[175,176]. *Lebrikizumab* is a human monoclonal antibody that also binds to soluble IL-13 and blocks its interaction with IL-4Rα, preventing heterodimerization with IL-13Rα1 and resultant IL-13 signaling (see Fig. 128.9C). In RCTs, ~55% of adolescents and adults with moderate to severe AD treated with lebrikizumab achieved a 75% improvement in their EASI score at 16 weeks[176a], and ~80% of these individuals maintained this response at 52 weeks.

Oral JAK inhibitors (see Ch. 128)

The oral JAK1-selective inhibitors *upadacitinib* and *abrocitinib* were recently FDA-approved for the treatment of recalcitrant, moderate to severe AD that is not adequately controlled with other systemic medications in patients ≥12 years of age (with weight ≥40 kg) and ≥18 years of age, respectively. In large RCTs involving adolescents and adults with moderate to severe AD, these medications were superior to placebo, with a 75% improvement in the EASI score in 65% (15 mg) and 75% (30 mg) of those who received upadacitinib daily for 16 weeks, and 40% (100 mg) and 60% (200 mg) of those who received abrocitinib daily for 12 weeks[177–180]; efficacy was sustained through 52 weeks of treatment[181]. The 15 mg and 100 mg daily starting doses for upadacitinib and abrocitinib, respectively, can be doubled if the response is not adequate. *Baricitinib* is a JAK1/2-selective inhibitor approved in Europe for treatment of adults with moderate to severe AD, with RCTs demonstrating a 75% improvement in the EASI score in 18% (2 mg) and 23% (4 mg) of such individuals[182].

Oral JAK inhibitor therapy for AD has a rapid onset of action, typically with reduction in pruritus within 1–2 weeks and improvement of clinical signs within 2–4 weeks. Laboratory monitoring is required and possible adverse effects include acne, serious infections (e.g. bacterial pneumonia, herpes zoster, tuberculosis), cytopenias, thrombosis, hyperlipidemia, major cardiovascular events, and for upadacitinib and baricitinib, gastrointestinal perforation (see Ch. 128). Long-term studies are needed to better establish the risk–benefit ratios of oral JAK inhibitors with different selectivity profiles.

Conventional immunosuppressive agents (for details see Ch. 130)

Cyclosporine typically leads to rapid improvement of AD in adults and children, and its efficacy has been established in RCTs[146,183]. However, because of potential side effects such as nephrotoxicity and hypertension, it is mainly used as a short-term treatment for AD, serving as a bridge between other therapies. Doses utilized for AD range from 3 to 6 mg/kg/day; treatment is often initiated at 5 mg/kg/day with subsequent tapering.

Azathioprine can be an effective treatment for moderate to severe AD in children and adults, with modest benefit documented in RCTs[184–186]. When dosages are based upon thiopurine methyltransferase (TPMT) activity and/or genotyping for *TPMT* polymorphisms, the risk of myelotoxicity is reduced (see Table 130.6). It has a slow onset of action, with clinical improvement after 1–2 months and full benefit requiring 2–3 months of treatment[142].

Methotrexate can lead to improvement of refractory AD in adults and children at a weekly dose of 7.5–25 mg or 0.3–0.5 mg/kg, respectively, together with folic acid supplementation[187]. This regimen is well tolerated, with a clinical effect typically seen after 2–3 months of therapy[188]. *Mycophenolate mofetil* (MMF) may also be of benefit for recalcitrant AD in adults and children, with 2–3 months of treatment typically required for maximum effect[189]. Dosing generally ranges from 1 to 3 g/day in adults and 30–50 mg/kg/day in children[164].

Continuous or chronic intermittent use of *systemic corticosteroids* for AD is not recommended due to a propensity for significant rebound flares upon their discontinuation and the unacceptable side effects of long-term administration (see Fig. 12.22 and Ch. 125)[190]. However, a short course of systemic corticosteroids may occasionally be considered for a severe, debilitating acute flare of AD while phototherapy or immunomodulatory treatment is being initiated.

Adjunctive Therapy

Antimicrobials and antiseptics

Although skin colonization and infection with *S. aureus* can play a role in triggering AD flares, there is no evidence to support the use of topical antibiotics or antiseptic agents to treat AD, with the possible exception of "bleach baths". In an initial RCT, bathing in 0.005% sodium hypochlorite (0.5 cup of household bleach [6% sodium hypochlorite] in a full 40-gallon bathtub) twice weekly together with a monthly 5-day course of intranasal topical mupirocin for 3 months led to greater improvement of moderate to severe, superinfected AD than placebo; both groups initially received a 2-week course of oral cephalexin and continued their topical anti-inflammatory regimen[191]. Subsequent controlled studies evaluating "bleach baths" in AD patients without a recent superinfection have had inconsistent results regarding efficacy for eczema; no decreases in *S. aureus* colonization or effects on skin barrier function have been observed[192].

The routine use of systemic antibiotics for AD is not recommended. However, systemic antibiotics can be utilized when AD patients display clinical evidence of bacterial infection, such as pustules, a purulent exudate, or furuncles. Similarly, systemic antiviral agents should be used to treat eczema herpeticum.

Antihistamines

The role of histamine in the itch of AD is unclear[139]. Topical antihistamines are not effective for AD and are associated with risks of allergic contact dermatitis and systemic side effects[126]. Routine use of oral antihistamines to treat AD is not recommended[142,193]. Non-sedating antihistamines are not useful in the absence of additional conditions such as urticaria, dermographism, or allergic rhinoconjunctivitis[164]. Short-term use of sedating antihistamines may be employed during an acute AD flare associated with significant sleep disturbance.

Melatonin

Reduced nocturnal melatonin is associated with sleep disturbance and disease severity in pediatric AD. RCTs have demonstrated that melatonin supplementation can improve sleep and decrease AD activity in children[194,195].

Omalizumab

The anti-IgE monoclonal antibody omalizumab is FDA-approved for chronic idiopathic urticaria in patients ≥12 years of age and for asthma in patients ≥6 years of age (see Ch. 128). It is administered every 2–4 weeks via subcutaneous injection, and potential side effects include a risk of anaphylaxis. Although observational studies have reported positive effects of omalizumab in AD, small RCTs found that omalizumab was no more effective than placebo[196,197].

Systemic immunotherapy

Allergen-specific immunotherapy to abrogate allergic sensitizations has been employed to treat asthma and allergic rhinoconjunctivitis. The benefit of sublingual or subcutaneous immunotherapy for AD with allergens such as dust mites has also been investigated, but heterogeneous studies with poor methodologies make the results difficult to interpret[198,199]. A Cochrane review concluded that there was no evidence of a benefit for specific allergen immunotherapy in AD, and this treatment approach is currently not recommended[200].

Dietary manipulation and supplements

In unselected children with AD, there is no high-quality evidence to support dietary manipulation. However, controlled trials have demonstrated significant improvement in AD following exclusion diets in individuals with confirmed egg and cow's milk allergies[201]. There is also no substantial evidence that oral supplementation with probiotics

(e.g. *Lactobacilli*), prebiotics (oligosaccharides that promote growth of desirable bacteria), or synbiotics (probiotics plus prebiotics) leads to improvement of AD[202]. Meta-analyses have demonstrated significantly lower vitamin D levels in children with AD compared to controls and vitamin D supplementation is recommended for AD patients with vitamin D insufficiency or deficiency[203]. Nonetheless, a systematic review concluded the evidence was weak for vitamin D supplementation decreasing AD severity in children[204].

Complementary Therapies

In systemic and meta-analyses as well as two RCTs, there was no evidence of a benefit for Chinese herbal medicines in AD[205,206]. In one report, analysis of "herbal creams" noted by parents in the UK to improve their children's AD revealed that 80% contained a corticosteroid, more than half of which represented clobetasol propionate[207]. Currently there also is no evidence that homeopathic treatment is of benefit for AD[208].

Management of Coexisting Disease

Food allergies

Food hypersensitivity affects up to 30% of infants and young children with AD, and ~90% of reactions in this population are caused by five allergens: eggs (most often linked to AD exacerbations), milk, peanuts, soy, and wheat. Reactivity to peanuts as well as tree nuts, fish, and shellfish tends to persist, but children usually outgrow sensitivities to other foods. In infants with AD, introduction of age-appropriate peanut-containing food as early as 4–6 months of age is recommended to reduce the risk of peanut allergy, with prior peanut-specific IgE and/or skin prick testing advised in those with severe AD[209]. Exposure to food allergens may exacerbate eczema in ~10%–30% of infants and young children with AD, especially those with severe, recalcitrant disease[210]. However, food allergens more often produce an immediate/IgE-mediated reaction with urticaria, flushing, or itch within 1–2 hours of exposure.

The National Institute of Allergy and Infectious Diseases (NIAID) recommends consideration of limited food allergy testing in children <5 years of age with moderate to severe AD if they also have: (1) persistent AD activity despite optimized management; or (2) a reliable history of an immediate allergic reaction after ingestion of a specific food[211,212]. Allergen-specific IgE assays and skin prick tests have high negative predictive values (>95%) but low specificities and positive predictive values (40%–60%)[213]. The clinical history and (in selected instances) provocation tests should be used to determine the *relevance* of positive laboratory and skin prick tests, since these allergens may not necessarily be exacerbating the patient's AD. When relevant food allergens are identified and avoided, skin-directed AD therapy is still crucial. It is important that parents and/or patients understand that coexistent food allergies are not the "cause" of AD. Even in patients with a clinically relevant allergy, elimination diets can prevent immediate hypersensitivity but are less likely to affect the course of the AD[214]. The potential benefits must be balanced with the possible adverse sequelae from unnecessarily restrictive diets, and modified diets should be supervised by a pediatric dietician to assure that they are nutritionally adequate.

Aeroallergen reactivity

Aeroallergen reactivity increases with age and is more prevalent in those with moderate to severe AD[215]. Common aeroallergens include dust mites, pollens, animal dander, and fungi. Exacerbation by aeroallergens should be considered when AD is more severe in exposed areas, and direct skin contact with aeroallergens may trigger the development of eczematous lesions in some patients. Evaluation includes assessment of specific IgE antibodies and skin prick testing[131].

Allergic contact dermatitis (ACD)

Patch testing to assess for contact sensitivity should be considered in AD patients with findings suggestive of ACD, a distribution pattern atypical of AD, sudden worsening, or recalcitrance to treatment. Common contact allergens in AD patients include components of topical medications and skin care products, such as fragrance, preservatives, lanolin, propylene glycol, cocamidopropyl betaine, bacitracin, neomycin, and sometimes corticosteroids (see Ch. 14)[216–218].

Prevention

Although the therapeutic armamentarium available for AD can successfully control the disease in most patients, primary prevention of AD represents a highly desirable goal. There is no evidence that maternal food allergen avoidance during pregnancy or lactation protects against the development of AD in the child[219]. For infants with a family history of atopy, exclusive breastfeeding during the first 3–4 months of life may potentially decrease the risk of AD[220]. However, exclusive breastfeeding for 6 months versus 3–4 months does not confer additional protection against the development of AD[221]. A Cochrane review concluded that there was no evidence for short- or long-term feeding with hydrolyzed formula compared with cow's milk formula for the prevention of AD in infants[222]. Timing of introduction of allergenic foods during infancy also appears to have no effect on AD risk[223].

While high intake of fish rich in anti-inflammatory long-chain polyunsaturated fatty acids (LC-PUFAs) during infancy may have a protective effect on the development of AD, meta-analyses found no significant association between either fish intake during pregnancy or maternal (during pregnancy or lactation) or infant PUFA supplementation and AD risk[224–227]. Low maternal prenatal vitamin D levels may be associated with an increased risk of early-onset AD during infancy[228]. However, there is no evidence that vitamin D supplementation during pregnancy, breastfeeding, or early infancy prevents allergic diseases[229].

Probiotics and prebiotics

Overall, studies investigating the effects of prebiotics, probiotics, and synbiotics on AD risk lack high-quality evidence due to methodological heterogeneity, differing definitions, and the wide variety of supplementations used. A systematic review and meta-analysis found no significant effect of prebiotic supplementation in pregnant women, breastfeeding mothers, or infants on the incidence of allergic disease[230]. Further investigation is required to determine whether pro-/prebiotic agents are beneficial for AD prevention and, if so, which agents as well as the optimal time of administration[231].

Emollients

Two large RCTs found that daily emollient application ± adding oil to the bath water during the first 8 to 12 months of life did not reduce the incidence of AD; in one of the studies, emollient use was associated with a mildly increased rate of skin infections[232,233]. Further investigations are needed to determine whether skin care interventions during infancy promote or prevent AD and whether they influence the risk of food allergy[234].

APPENDIX
POEM (Patient-Oriented Eczema Measure): www.nottingham.ac.uk/research/groups/cebd/resources/poem.aspx
EASI (Eczema Area Scoring Index): https://dermnetnz.org/topics/easi-score
SCORAD (SCORing Atopic Dermatitis): http://adserver.sante.univ-nantes.fr/Scorad.html

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 12.1 Atopic dermatitis of the popliteal fossa. Both excoriations and exaggerated skin markings are present. *Courtesy Julie V. Schaffer, MD.*



eFig. 12.2 Atopic dermatitis of the antecubital fossa. Note the excoriations. *Courtesy Julie V. Schaffer, MD.*



eFig. 12.3 Postinflammatory pigmentary alteration in atopic dermatitis. Postinflammatory depigmentation in a patient with widespread, severe disease and multiple lesions of prurigo nodularis. *Courtesy Jean L. Bolognia, MD.*



eFig. 12.4 Lichenification in a young child with atopic dermatitis. Exaggerated skin markings are seen on the extensor surfaces of the arm.



eFig. 12.5 Lichenification in an adult with atopic dermatitis. Note the flexural site.



eFig. 12.6 Atopic dermatitis with lichenified plaques. A, B Two skin phototypes. *Courtesy Julie V. Schaffer, MD.*



eFig. 12.7 Lip-licking eczema. *Courtesy Julie V. Schaffer, MD.*



eFig. 12.8 Infantile atopic dermatitis. Acute lesions with oozing and serous crusting are common in this age group and favor the face (**A**, **B**) and extensor extremities (**C**). *Courtesy Julie V. Schaffer, MD.*



eFig. 12.9 Widespread infantile atopic dermatitis. Facial involvement is prominent and there are nummular lesions on the shoulder. *Courtesy Julie V. Schaffer, MD.*



eFig. 12.12 Atopic dermatitis in childhood exacerbated by *Malassezia*. The patient has scaling of the scalp and confluent erythema of the upper face.



eFig. 12.10 Infantile atopic dermatitis. Erythema and scale-crust on the cheeks, with sparing of the central face. *Courtesy Julie V. Schaffer, MD.*



eFig. 12.11 Childhood atopic dermatitis. **A** Extension from the antecubital fossae to the wrists and hands. Note the excoriations and lichenification. **B** Widespread eczematous dermatitis. *A, Courtesy Thomas Bieber, MD and Caroline Bussmann, MD; B, Courtesy Luis Requena, MD.*



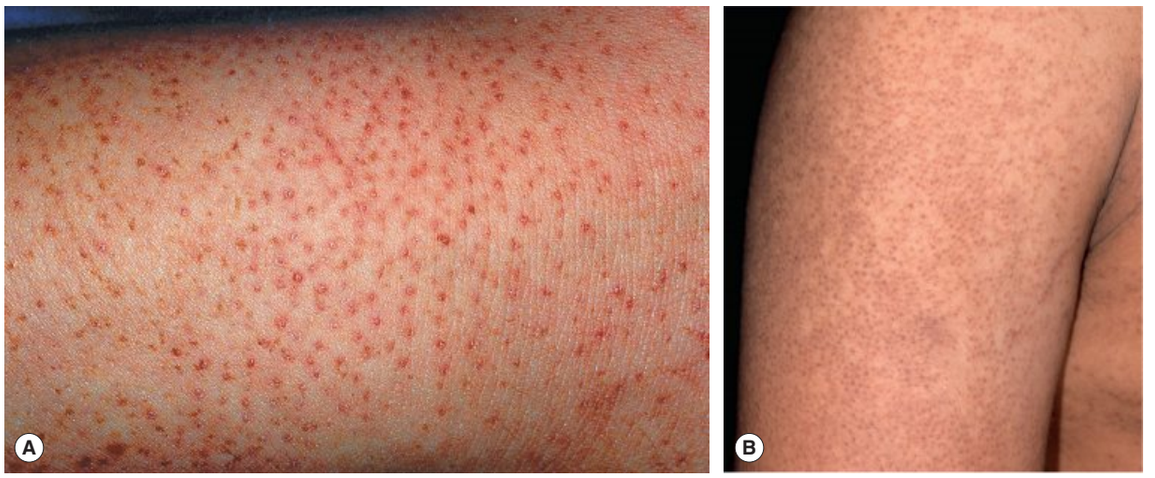
eFig. 12.13 Chronic atopic dermatitis. A Coalescing papules and lichenification on the ankle due to chronic scratching and rubbing. **B** Thick eczematous plaques with lichenification and excoriation on the dorsal hands and wrists. *A, Courtesy Antonio Torrelo, MD. B, Courtesy Julie V. Schaffer, MD.*



eFig. 12.14 Chronic atopic dermatitis. Coalescing papules on the ankle. *Courtesy Julie V. Schaffer, MD.*



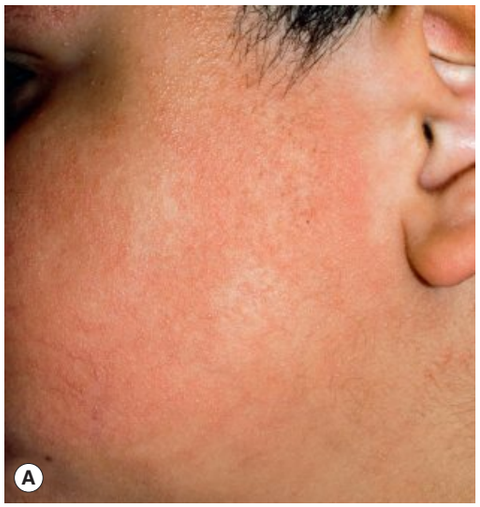
eFig. 12.16 Keratosis pilaris. Keratotic follicular papules with a background of subtle patchy erythema on the extensor surface of the upper arm. *Courtesy Karynne O. Duncan, MD.*



eFig. 12.15 Keratosis pilaris. Perifollicular keratotic papules on the upper outer arm with associated erythema (**A**) or hyperpigmentation (**B**). *B, Courtesy Luis Requena, MD.*



eFig. 12.17 Widespread keratosis pilaris in a patient with atopic dermatitis. *Courtesy Luis Requena, MD.*





eFig. 12.18 Keratosis pilaris rubra . A, B Keratosis pilaris rubra on the lateral face. This variant is characterized by tiny, "grain-like" follicular papules superimposed on confluent erythema. *Courtesy Julie V. Schaffer, MD.*



eFig. 12.19 Severe chronic hand dermatitis in an adult with atopic dermatitis.



eFig. 12.20 Infected hand dermatitis in a patient with atopic dermatitis. There is impetigo-like crusting as well as pustules. *Courtesy Louis A. Fragola, Jr, MD.*



eFig. 12.21 Folliculitis of the back due to methicillin-resistant *Staphylococcus aureus*. The patient had atopic dermatitis. *Courtesy Karynne O. Duncan, MD.*

13 Other Eczematous Eruptions

Norbert Reider and Irina Gasslitter

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In addition to contact and atopic dermatitis, there exists a heterogeneous group of inflammatory skin diseases that obviously share the hallmarks of eczema, but display characteristic additional features. Their pathogenesis is generally less well understood, but most exhibit distinctive etiologic features.

SEBORRHEIC DERMATITIS

Key features

- Infantile and adult forms
- Lesions favor the scalp, ears, face, central chest, and intertriginous areas
- Etiologic links with active sebaceous glands, abnormal sebum composition, and *Malassezia* (*Pityrosporum*) spp.
- Can be a cutaneous sign of HIV infection

Introduction

Seborrheic dermatitis is a common, mild, chronic eczema typically confined to skin regions with high sebum production and the large body folds. Although its pathogenesis is not fully elucidated, there is a link to sebum overproduction (seborrhea), the commensal yeast *Malassezia*, and individual susceptibility.

History

Seborrheic dermatitis was first described by Unna[1], who also suspected *Malassezia furfur* (*Pityrosporum ovale*) as a causative factor. The nosologic position of seborrheic dermatitis was widely discussed for decades, the focus resting on dysfunction of the sebaceous glands and the high amounts of *M. furfur* present in scales of seborrheic dermatitis. In 1984 it was shown that seborrheic dermatitis could be suppressed by systemic ketoconazole[2]. This finding was corroborated by later studies[3], and it became clear that seborrheic dermatitis was strongly linked to these yeasts. Today, it is accepted that several species of *Malassezia*, including *M. furfur*, play a direct role in seborrheic dermatitis (see Table 77.3)[4].

Epidemiology

There are infantile and adult forms, with the former being self-limited and most prevalent the first 3–4 months of life, while the latter is chronic with a peak in the fourth to sixth decades. The prevalence of seborrheic dermatitis is estimated to be 5%, but its lifetime incidence is likely much higher. Men are afflicted more often than women. Extensive and therapy-resistant seborrheic dermatitis is an important cutaneous sign of HIV infection. It is more commonly observed in patients with neurologic diseases (e.g. Parkinson disease, cerebrovascular accidents)[5] or who are immunosuppressed. Additional contributing factors include nutritional deficiencies, impaired epidermal barrier, and occasionally medications (e.g. neuroleptics, atypical antipsychotics). Seborrheic dermatitis-like eruptions have also been reported with dupilumab and antineoplastic agents (e.g. tyrosine kinase inhibitors).

Pathogenesis

Malassezia

The genus *Malassezia* consists of lipophilic yeasts that are part of the normal resident skin flora[6,7]. Studies on the predominance of certain *Malassezia* spp. have revealed conflicting results[8,9]. *M. furfur* may behave as an opportunistic pathogen (e.g. fungemia in neonates receiving intravenous lipid emulsions) or cause or aggravate a spectrum of skin diseases: pityriasis versicolor, *Malassezia (Pityrosporum)* folliculitis, seborrheic dermatitis, and possibly atopic dermatitis.

Malassezia *and seborrheic dermatitis*

M. furfur and related species can be regularly isolated from lesions of seborrheic dermatitis, including infantile seborrheic dermatitis (whereas healthy prepubertal children are not colonized to a significant degree). This coincides with the presence of enlarged sebaceous glands during the neonatal period. There is no simple quantitative relationship between yeast number and severity of seborrheic dermatitis, and unaffected skin may carry a load of organisms similar to seborrheic dermatitis lesions. Even in the scalp, where *M. furfur* predominates amongst the resident flora, only twice as many yeasts may be recovered from areas of seborrheic dermatitis as from normal controls[6]. Amongst patients with AIDS, harboring of *Malassezia* spp. is equivalent, irrespective of the presence or absence of seborrheic dermatitis clinically; however, there is a difference in the amount of yeasts[10].

Active sebaceous glands and seborrheic dermatitis

Seborrheic dermatitis occurs predominantly in areas of the skin with active sebaceous glands and is often associated with sebum overproduction, which in turn can facilitate the growth of *Malassezia*. In infants, sebum is produced for a few weeks after birth, and the adult form of seborrheic dermatitis does not develop before puberty. This argues for a role for sebaceous gland activation by androgens. However, patients with seborrheic dermatitis may have normal sebum production and those with excessive sebum production are often free of seborrheic dermatitis. Thus, the amount of sebum produced alone does not appear to be the decisive risk factor.

It has been proposed that the composition of the skin surface lipids is the relevant factor[11]. In patients with seborrheic dermatitis, triglycerides and cholesterol are elevated but squalene and free fatty acids are significantly decreased. Free fatty acids (which have a known antimicrobial effect) are formed from triglycerides by bacterial lipases produced by the lipolytic *Cutibacterium* (formerly *Propionibacterium*) *acnes*. A major constituent of the resident microbial skin flora, *C. acnes* has been found to be greatly reduced in seborrheic dermatitis[12]. Seborrheic dermatitis may thus be linked to an imbalance of the microbial flora.

Immune responses to Malassezia *in seborrheic dermatitis*

An etiologic role for immune mechanisms against *Malassezia* – particularly in view of the prominence of seborrheic dermatitis in HIV-infected individuals – has been suspected but never convincingly proven. Intrinsic host factors, such as changes in sebum production and a defective epidermal barrier, could favor overgrowth of *Malassezia* spp. which

then incites a host inflammatory response[13]. However, additional studies on cellular immunity have yielded contradictory results[6,7]. The inflammation seen in seborrheic dermatitis might be irritant, caused by toxic metabolites, lipase, and reactive oxygen species[6,13].

Clinical Features

Seborrheic dermatitis is defined by clinical parameters, including:

- sharply demarcated patches or thin plaques that vary from pink–yellow to dull red to red–brown with bran-like to flaky "greasy" scales; vesiculation and crusting may occur but are rare and mostly due to irritation
- a predilection for areas rich in sebaceous glands – scalp, face, ears, presternal region – and, less often, the intertriginous areas
- a mild course with little or moderate discomfort.

Seborrheic dermatitis is most often limited in extent, but generalized and even erythrodermic forms can occur, albeit rarely.

Infantile seborrheic dermatitis

This form usually begins about one week after birth and may persist for several months. Initially, mild greasy scales adherent to the vertex and anterior fontanelle regions arise which may later extend over the entire scalp. Inflammation and oozing may finally result in a coherent scaly and crusty mass covering most of the scalp ("cradle cap"; Fig. 13.1A). Lesions of the axillae, inguinal creases, neck, and retroauricular folds are often acutely inflamed, oozing, sharply demarcated, and surrounded by satellite lesions (Fig. 13.1B). Superinfection with *Candida* spp. or occasionally bacteria (e.g. group A *Streptococcus*) can occur. A disseminated eruption of scaly papules with a psoriasiform appearance ("psoriasiform id reaction") may develop on the trunk, proximal extremities, and face in association with exuberant or superinfected seborrheic dermatitis, especially of the diaper area.



Fig. 13.1 Infantile seborrheic dermatitis. A Involvement of the scalp with thick adherent yellow scale overlying mild inflammation is often referred to as "cradle cap". **B** Glistening red plaques of the neck, axillary and inguinal folds as well as the penis and umbilicus. Note disseminated lesions on the trunk and extremities. *A, Courtesy Antonio Torello, MD; B, Courtesy Robert Hartman, MD.*

Adult seborrheic dermatitis

In adults, seborrheic dermatitis is generally found on the scalp and, usually of milder intensity, on the face; less often, lesions occur on the central upper chest and the intertriginous areas. Erythrodermic seborrheic dermatitis has been described as a rarity.

Pityriasis simplex capillitii (dandruff) is defined as a diffuse, slight to moderate, fine white or greasy scaling of the scalp and terminal hair-bearing areas of the face (beard area), but without significant erythema or irritation. Scales accumulate visibly on dark clothing. This common condition may be considered the mildest form of seborrheic dermatitis of the scalp.

In seborrheic dermatitis of the scalp, there is inflammation and pruritus in addition to dandruff. The vertex and parietal regions are predominantly affected, but in a more diffuse pattern than the discrete plaques of psoriasis. Towards the forehead, the erythema and scaling are usually sharply demarcated from uninvolved skin, with the border either at the hairline or slightly transgressing beyond it. Pruritus is usually moderate but may be intense, particularly in patients with male pattern alopecia; folliculitis, furuncles, and meibomitis are not uncommon complications, elicited by scratching and rubbing.

Seborrheic dermatitis of the facial skin is often strikingly symmetric, affecting the forehead, medial portions of the eyebrows, upper eyelids, nasolabial folds and lateral aspects of the nose, retroauricular areas, and occasionally the occiput and neck (Fig. 13.2). Lesions are yellowish-red, with a typical bran-like scale. Non-purulent otitis externa is often observed. If present, lesions of the trunk are preferentially found in the presternal and intertriginous areas (Fig. 13.3); those on the central chest can have a petaloid appearance. Seborrheic dermatitis, like inverse psoriasis, is a cause of intertrigo (Fig. 13.4).

In patients with seborrheic dermatitis, the skin is sensitive to irritation, and exposure to sun or heat, febrile illnesses, and overly aggressive topical therapy may precipitate flares and dissemination. Rebound flares can also follow tapers of systemic corticosteroids. Seborrheic dermatitis is more common during the winter in patients with skin phototypes I–II, most likely a reflection of increased xerosis and decreased epidermal barrier function[14].

Irritated seborrheic dermatitis lesions can become bright red and erosive. *Malassezia (Pityrosporum)* folliculitis is another complication characterized by pruritic erythematous follicular papules, sometimes pustules, typically in sites rich in sebaceous glands.

Adult seborrheic dermatitis has a chronic relapsing course. Patients feel well and systemic signs are absent. Extensive and severe seborrheic dermatitis, however, should raise the suspicion of underlying HIV infection. Among patients with seborrheic dermatitis tested for HIV infection, 2% were found to be positive, frequently in a late stage of their disease[15]. In patients with Parkinson disease, seborrheic dermatitis is a common finding, along with seborrhea. Its severity, however, is not correlated with that of the Parkinson disease[16]. The facial immobility of patients with Parkinson disease might result in a greater accumulation of sebum on the skin, resulting in a permissive effect on the growth of *Malassezia*[16,17]. Seborrheic dermatitis may also be more common in patients with other causes of immobility such as cerebrovascular accidents.

Pathology

Acute seborrheic dermatitis displays spongiosis with a superficial perivascular and perifollicular lymphocytic infiltrate composed mainly of lymphocytes. Older lesions show irregular acanthosis and focal parakeratosis. The latter may appear similar to psoriasis, but exocytosis of neutrophils, Munro microabscesses, and confluent parakeratotic horny layers are absent.

Differential Diagnosis

Infantile seborrheic dermatitis is distinguished from *atopic dermatitis* by its earlier onset, different distribution pattern, and, most importantly, by the absence of pruritus, irritability, and sleeplessness. In contrast to



Fig. 13.2 Adult seborrheic dermatitis of the face, ear and scalp. A Rather sharply demarcated pink plaque with flaky white and greasy scale. Note the fissure in the retroauricular sulcus. **B** Sharply demarcated pink–orange thin plaques with yellow, greasy scale, especially in the nasolabial fold. When this degree of severity is seen, the possibility of underlying HIV infection needs to be considered. **C** Symmetric red–brown to violet plaques of the central forehead, nasal bridge, and medial cheeks with an associated hypopigmented peripheral and figurate rim. **D** Involvement of the upper eyelids, medial canthal regions, and infraorbital creases; seborrheic dermatitis confined to the major crease in the outer canthal region can also be seen. *C, Courtesy Jeffrey P. Callen, MD; D, Courtesy Kalman Watsky, MD.*



Fig. 13.3 Seborrheic dermatitis of the presternal region in an adult. It sometimes resembles the petals of a flower.

atopic dermatitis, infants with seborrheic dermatitis generally feed well and are content. *Irritant diaper dermatitis* is confined to the diaper area and tends to spare the skin folds (see below). *Candidiasis* of the diaper area can result from colonization with fecal yeast and some infants have seborrheic dermatitis with a superimposed candidal infection. The differential diagnosis also includes *streptococcal intertrigo* (see Fig. 13.12). *Infantile psoriasis* may be difficult to distinguish from psoriasiform seborrheic dermatitis. Although psoriasiform diaper dermatitis can represent the initial manifestation of psoriasis, many affected infants do not subsequently develop psoriasis elsewhere.

Rare conditions to be considered are Langerhans cell histiocytosis, "nutritional dermatitis" (e.g. acrodermatitis enteropathica; see Fig. 51.13), and Leiner disease. The last-mentioned is a questionable entity, once thought to be the maximal variant of infantile seborrheic dermatitis, but nowadays viewed as erythroderma in the setting of underlying immunosuppression (see Chs. 10 & 60).

When scalp scaling is present in prepubertal, especially Black, children, the possibility of *tinea capitis* due to *Trichophyton tonsurans* should be considered. In *pityriasis amiantacea*, thick asbestos-like scales adhere to tufts of scalp hairs; up to a third of the affected children and adolescents eventually develop psoriasis.

A number of entities are included in the differential diagnosis of **adult** seborrheic dermatitis. Distinction of seborrheic dermatitis *of the scalp* from psoriasis can be difficult, and there may be an overlap in some patients ("sebopsoriasis"). However, the plaques of psoriasis tend to be thicker, with silvery white scale, more discrete, less pruritic, and unassociated with seborrhea. In addition, features of psoriasis may be found elsewhere. Dry scaling of the scalp, along with dry brittle hair (as opposed to greasy hair), is a symptom of xerotic skin (e.g. in atopic dermatitis), frequently mistaken for (and mistreated as) seborrheic dermatitis. Mild erythema and scale of the posterior scalp, often with demonstrable hair loss, can be seen in dermatomyositis[18].

Seborrheic dermatitis *of the face* may closely resemble both early rosacea and the butterfly lesions of systemic lupus erythematosus. Lupus erythematosus rarely affects the nasolabial folds and often has a clearly demonstrable photodistribution. Notably, seborrheic dermatitis and rosacea frequently coexist. The facial dermatitis seen in patients receiving dupilumab may resemble seborrheic dermatitis. The differential diagnosis of seborrheic dermatitis *of the trunk* includes pityriasis rosea (but in this latter entity the lesions are ellipsoid in shape, have collarette-like scaling, and there is no predilection for the central chest) as well as superficial eruptive psoriasis and subacute cutaneous lupus erythematosus.

Seborrheic dermatitis *of the intertriginous areas* must be distinguished from inverse psoriasis, erythrasma, intertriginous dermatitis, candidiasis, and, rarely, Langerhans cell histiocytosis (see Fig. 13.4).

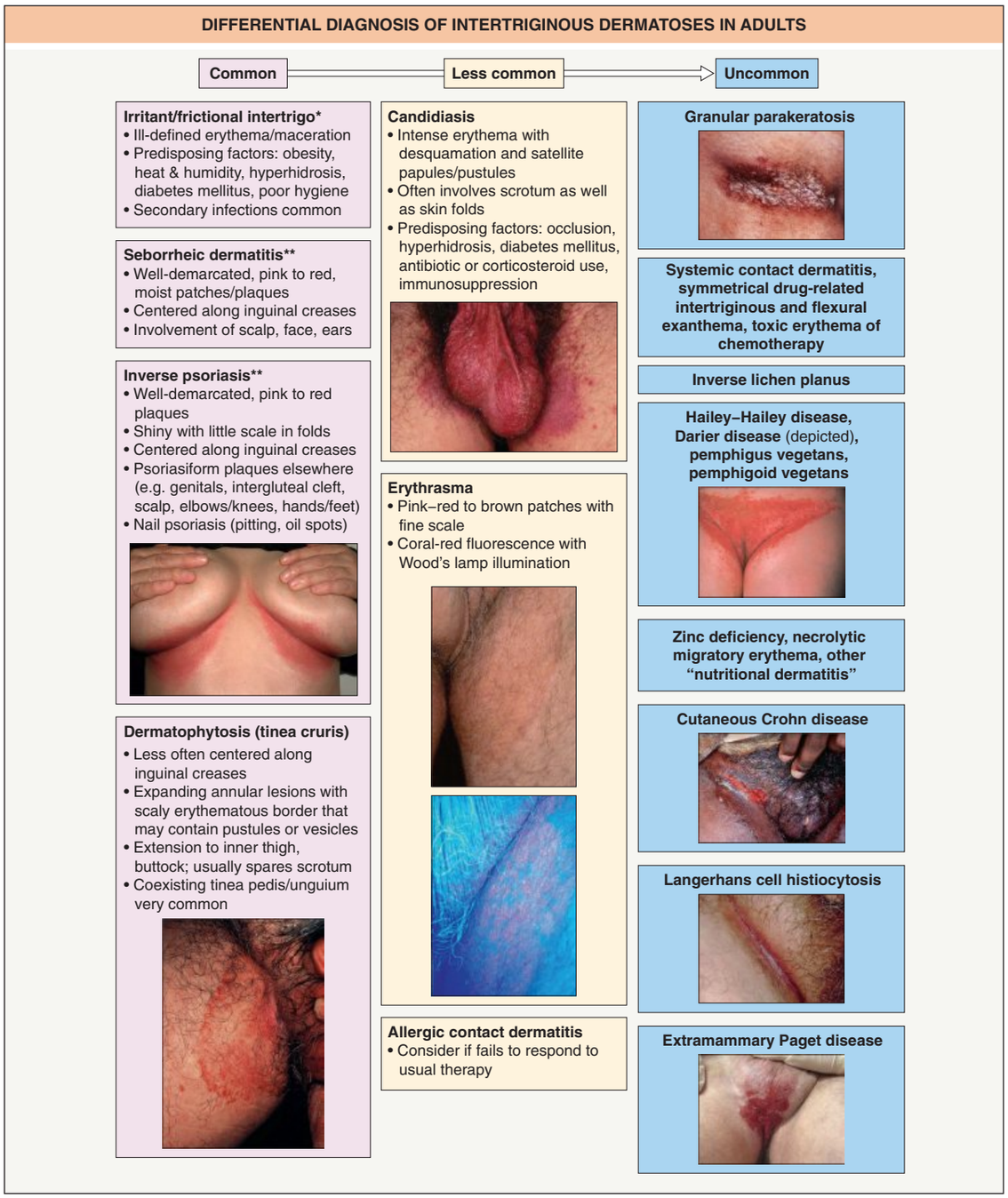


Fig. 13.4 Differential diagnosis of intertriginous dermatoses in adults. Individual patients often have multiple disorders superimposed upon one another. Bullous impetigo and streptococcal intertrigo are considerably more common in children than adults. *Also referred to more nonspecifically as intertriginous dermatitis or intertrigo. **The term "sebopsoriasis" may be used when features of both seborrheic dermatitis and psoriasis are present. *Insets: Courtesy Luis Requena, MD; Eugene Mirrer, MD; Louis A. Fragola, Jr, MD; David Mehregan, MD; Julie V. Schaffer, MD.*

Treatment

Infantile seborrheic dermatitis

Infantile seborrheic dermatitis usually responds satisfactorily to bathing and application of emollients. Ketoconazole cream (2%) is indicated in more extensive or persistent cases[19]. Short courses of low-potency topical corticosteroids may be used initially to suppress inflammation. Mild shampoos are recommended for the removal of scalp scales and crusts. Avoidance of irritation (e.g. the use of strong keratolytic shampoos or mechanical measures to remove the scales from the scalp) is important.

Adult seborrheic dermatitis

The mainstay of therapy is the use of topical azoles (e.g. ketoconazole), either as shampoos (scalp) or as creams (body). The high response rate (75%–90%) of this treatment has been documented in double-blind trials[3]. Ciclopirox olamine has antifungal and anti-inflammatory activities and has also been shown to be effective as a shampoo or cream in double-blind, randomized trials. Seborrheic dermatitis tends to relapse if a maintenance regimen is not instituted. As *M. furfur* has a slow proliferation rate, an interval of two to several weeks will pass until relapses appear. The intervals of topical therapy should follow this rhythm.

Additional measures, particularly in the initial stages of treatment, include emollients and low-potency topical corticosteroids; the latter were found to be equally efficacious as topical azoles in a Cochrane analysis[20]. Second-line treatment options include zinc pyrithione, selenium sulfide, and tar shampoos as well as topical calcineurin inhibitors. Systemic antimycotics (e.g. weekly fluconazole) should only be used in cases of severe findings or frequent recurrences.

ASTEATOTIC ECZEMA

Synonyms: ■ Eczema craquelé ■ Winter eczema ■ Winter itch ■ Desiccation dermatitis

Key features

- Dry, rough, scaly, and inflamed skin with superficial cracking that resembles a "dried riverbed"
- Sites of predilection are the shins, lower flanks, and posterior axillary line
- Associated with aging, xerosis, low relative humidity, and frequent bathing

Introduction

Dry skin (xerosis, asteatosis, exsiccosis) may result from both exogenous and endogenous causes: a dry climate or low indoor humidity; excessive exposure to water, soaps, and surfactants; marasmus and malnutrition; chronic kidney diseases and hemodialysis; hypothyroidism; HIV infection; and heritable conditions such as ichthyosis vulgaris and atopic dermatitis. Asteatotic eczema also arises in patients with reduced sweat gland function (e.g. chronic graft-versus-host disease) or in sites of edema due to hypoalbuminemia from hepatic cirrhosis or nephrotic syndrome. That said, the most common cause of xerosis is aging. Rarely, but especially when widespread and refractory to therapy, asteatotic eczema may be related to an underlying neoplasm, including lymphoma[21].

History and Epidemiology

Asteatosis as the cause of "nummular eczema" was first mentioned by Gross[22] in the late 1940s. Dry skin probably occurs in everyone over the age of 60 years, but its severity is strongly linked to the exogenous and endogenous factors mentioned above.

Pathogenesis

Xerosis of aging skin is not caused by deficient sebum production, but by a complex dysfunction of the stratum corneum (see Ch. 124)[23]. There is a decrease of intercellular lipids with a deficiency of all key stratum corneum lipids[24] and an altered ratio of esterified fatty acids to ceramide 1[25]; this, plus a persistence of corneodesmosomes[26] and premature expression of involucrin and formation of the cornified envelope[27], results in corneocyte retention and marked impairment of barrier recovery[24]. The water-binding capacity of the stratum corneum is reduced owing to decreased synthesis of "natural moisturizing factor" (NMF) as well as decreased intercellular lipids and glycerol content[28]. Consequently, the stratum corneum desiccates, loses its pliability, and forms small cracks, which render the skin surface dull, rough, and scaly.

Mild xerosis is asymptomatic, but if more pronounced, the skin conveys unpleasant sensations such as pruritus and stinging. Inflammation is enhanced by the release of proinflammatory cytokines secondary to barrier perturbation, mechanical factors (scratching, rubbing), and the application of irritating or sensitizing substances in topical preparations and skin care products.

Occasionally, eczema craquelé can appear in the setting of acute edema[29], e.g. from congestive heart failure or the re-feeding of patients with anorexia nervosa. One theory is that this is related to the rate of distention of the skin.

Clinical Features

Xerosis first arises on the shins. Later it may spread to the proximal extremities and trunk, but spares the face and neck as well as the palms and soles. It develops insidiously over many years, whereas asteatotic eczema often has a more subacute to acute onset.

Xerotic skin is dry and dull, with fine bran-like scales that may be released as powdery clouds when patients take off their stockings. If more advanced, the skin exhibits a criss-cross pattern of superficial cracks and fissures of the horny layer ("crazy-paving", eczema craquelé, "dried riverbed") and appears pink to light red in color (Fig. 13.5). The skin becomes rough, and it may develop an appearance similar to ichthyosis vulgaris ("pseudo-ichthyosis"). In more advanced stages of asteatotic eczema, there is a dull erythema as well as oozing, crusting, and abundant excoriations; disseminated nummular lesions are frequently seen. Vesiculation and lichenification are not regular features except when irritant or allergic contact dermatitis is superimposed. Hemorrhage into the fissures is occasionally observed.



Fig. 13.5 Asteatotic eczema (eczema craquelé). A On the shins, a criss-cross pattern of superficial cracks, fissures, and hemorrhagic crusts said to resemble a dried riverbed. **B** Xerosis with adherent white scales (pseudo-ichthyosis) and inflammation as well as the criss-cross pattern of superficial cracks and fissures. *A, Courtesy Kalman Watsky, MD; B, Courtesy Louis A. Fragola, Jr, MD.*

Pathology

Histologically, xerotic skin appears rather normal except for a compact and slightly irregular stratum corneum. Asteatotic eczema in addition exhibits mild focal spongiosis, focal parakeratosis, and a sparse inflammatory infiltrate in the superficial dermis.

Differential Diagnosis

Conditions that need to be distinguished from asteatotic eczema include stasis dermatitis, adult atopic dermatitis (which may overlap with asteatotic eczema), allergic contact dermatitis, nummular dermatitis, and scabies.

Treatment

Asteatotic eczema usually clears within a few days of the application of topical corticosteroid ointment. Proper attention must be given to the care of xerosis in order to avoid relapses: regular use of petrolatum, water-in-oil emollients, urea-, ceramide- or lactic acid-containing preparations, use of bath oils, and the elimination of factors that aggravate dry skin (see above). Topical calcineurin inhibitors have also been used. Coexisting stasis dermatitis should be treated as well (see below).

DISSEMINATED ECZEMA (AUTOSENSITIZATION)

Synonyms: ■ Autosensitization dermatitis ■ Autoeczematization ■ Generalized eczema ■ Id reaction

Key features

- Secondary lesions of eczema distant from the primary site of exposure or involvement
- Symmetric distribution pattern
- Most often associated with allergic contact dermatitis and stasis dermatitis

Introduction

Dermatitis caused by exogenous agents initially arises at the site of contact. Not infrequently, additional patches of eczema develop at distant sites. This phenomenon, termed secondary dissemination, has puzzled dermatologists for decades. It is most often observed in allergic contact dermatitis, particularly if associated with stasis dermatitis (see Fig. 13.8), but may occur with uncomplicated stasis dermatitis, other forms of eczema, and, occasionally, severe tinea pedis.

Disseminated eczema appears later than the primary lesions by a few days to weeks, tends to follow a strikingly symmetric distribution pattern, and shows a predilection for analogous anatomic sites (e.g. extensor aspects of the lower and upper extremities, palms, and soles). It may even arise in the absence of and without a preceding "primary" eczema, e.g. in nummular dermatitis (see below). Disseminated eczema must be distinguished from atopic dermatitis, which arises *a priori* in a disseminated fashion.

History and Pathogenesis

The phenomenon of secondary dissemination of eczemas was first described by Whitfield[30], but its pathogenesis is still not fully elucidated. The orderly and symmetric distribution pattern may reflect systemic (hematogenous) dissemination and argues against simple spread of contact irritants or allergens on the body surface. It is unclear, however, as to exactly what is disseminated via the bloodstream. It could be allergens; for example, the ingestion of allergens such as nickel has been shown to elicit disseminated eczema in sensitized individuals[31,32].

Hematogenous dissemination of microbial products leading to a variety of (non-infectious) manifestations distant from the site of infection, such as "tuberculids" and "bacterids", was an accepted pathogenic model in the first half of the twentieth century and was extrapolated to the phenomenon of disseminated eczema. Dyshidrotic eczema of the soles, for example, was interpreted as an "id" reaction associated with tinea pedis, and nummular eczema as an "id" reaction caused by "focal" infections of the tonsils. Because disseminated eczema could hardly be attributed solely to infections, attention shifted to an "autosensitization" to epidermal antigens mediated by cytotoxic autoantibodies. This hypothesis, however, has never been verified.

Instead, it became clear both from animal experiments[33] and from routine patch testing ("excited skin syndrome", "angry back")[34,35] that inflammatory processes of the skin, both allergic and irritant or caused by infections, lower the irritancy threshold of distant skin and thus facilitate the development of an eczematous reaction. Obviously, circulating activated memory T cells may play an additional role in disseminated eczema associated with allergic contact dermatitis, including that seen with rebound poison ivy dermatitis following a short, rapid taper of systemic corticosteroids. It remains to be determined which factors regulate the symmetric distribution of disseminated eczema.

Epidemiology

An estimated two-thirds or more of patients with contact dermatitis associated with stasis dermatitis develop episodes of disseminated eczema. The incidence is much lower in the other types of eczema or tinea pedis.

Clinical Features

Disseminated eczema associated with allergic contact dermatitis is characterized by moderately to poorly demarcated patches of eczema, most often on the extremities (Fig. 13.6A). Lesions are also found on the face, and less so on the trunk (Fig. 13.6B). The areas of involvement vary greatly in size and number and may consist of discrete papules which are often excoriated. Disseminated eczema in patients with seborrheic and asteatotic eczema differs slightly in predilection sites and morphology (see above).

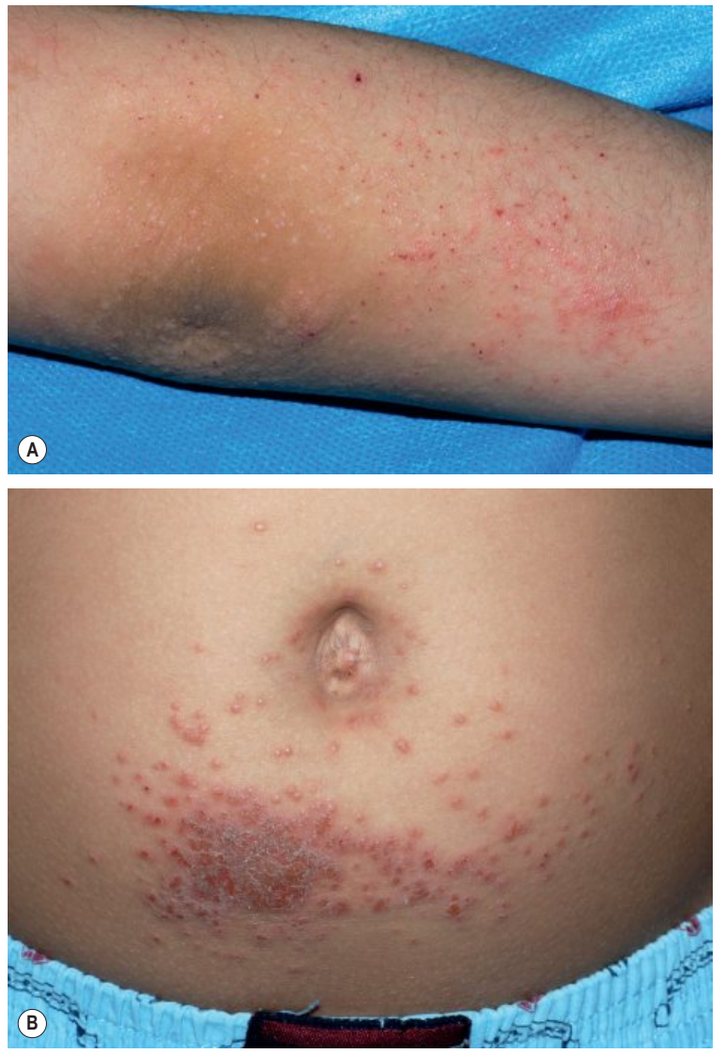


Fig. 13.6 Id reactions in children due to allergic contact dermatitis (ACD) to nickel. **A** Multiple flat-topped papules, several of which have been excoriated, in addition to patches of eczema. **B** Square-shaped area of ACD due to nickel in a buckle with an associated id reaction. The latter consists of edematous crusted papules that are separate from the area of direct nickel contact. *Courtesy Julie V. Schaffer, MD.*

Pathology

In biopsy specimens of disseminated eczema, the histologic findings are those of an acute or subacute eczematous dermatitis (see section "Stasis dermatitis").

Differential Diagnosis

Conditions to be distinguished are those eczemas that can arise in a widespread or disseminated fashion: atopic dermatitis, airborne contact dermatitis, contact dermatitis caused by constituents of textiles, photoallergic dermatitis, and eczematous drug eruptions (e.g. calcium channel blockers). Other conditions to be considered are mycosis fungoides and Sézary syndrome.

Treatment

Topical corticosteroids and systemic antihistamines are the mainstay of therapy. Short courses of systemic corticosteroids may be required, but identification and aggressive topical treatment of the inciting dermatosis is necessary to help prevent recurrences or a rebound flare.

NUMMULAR DERMATITIS

Synonyms: ■ Nummular eczema ■ Discoid eczema ■ Microbial eczema

Key features

- Coin-shaped, disseminated, eczematous lesions
- Usually very pruritic
- Chronic course

Introduction

Nummular dermatitis is an uncommon, disseminated eczema characterized by its coin-shaped lesions. Because such lesions can occur as a feature of atopic dermatitis, asteatotic eczema, and stasis dermatitis, the nosologic position of nummular dermatitis as an independent clinical entity has been questioned.

Epidemiology

Nummular lesions of eczema are not uncommon. However, in the literature there are widely discrepant data on the prevalence of nummular dermatitis, ranging from 0.1% to 9.1%[36]. Some of this variability may reflect the degree to which a distinction is made between nummular dermatitis and coin-shaped lesions observed in patients with other forms of eczema. Men are affected slightly more often and at a later age than women (>50 vs <30 years, respectively).

Pathogenesis

Nummular lesions of dermatitis are not infrequently associated with contact sensitization as well as with xerosis and venous hypertension. In a study of ~30 000 consecutive patients with different types of eczema who underwent patch testing, 3.5% were diagnosed as having nummular dermatitis; 32.5% of these individuals had at least one positive patch test reaction, most often to nickel sulfate, potassium dichromate, and cobalt chloride[36]. Clinical and laboratory signs of atopy are absent in "true" nummular dermatitis.

Clinical Features

Nummular dermatitis is defined as an eruption of round (discoid) eczematous patches almost exclusively of the extremities, often the lower legs in men and the forearms and dorsal aspects of the hands in women (Fig. 13.7A)[36]. The lesions are well demarcated and measure 1–3 cm, only occasionally being larger (Fig. 13.7B,C). They may be acutely inflamed with vesicles and weeping, but are often lichenified and hyperkeratotic. Pruritus may be intense and excoriations are often prominent. Nummular dermatitis usually takes a very chronic course. A particularly therapy-resistant variety has been termed "oid-oid" disease, also referred to as exudative discoid and lichenoid chronic dermatitis or Sulzberger–Garbe syndrome.

Pathology

Histologically, the changes of subacute to chronic eczematous dermatitis are seen (Fig. 13.7D; see section "Stasis dermatitis").

Differential Diagnosis

Nummular dermatitis must be distinguished from nummular lesions of atopic dermatitis and dissemination secondary to contact dermatitis or stasis dermatitis. Other conditions to be considered are psoriasis, inflammatory tinea corporis, mycosis fungoides, and Bowen disease.

Treatment

Options include medium- to high-potency topical corticosteroid ointments, topical tacrolimus or pimecrolimus, and emollients. Tar preparations have also been used successfully. However, a number of patients will require phototherapy to clear the lesions. Methotrexate has led to long-term improvement in children, and dupilumab is a therapeutic option for recalcitrant disease[37].

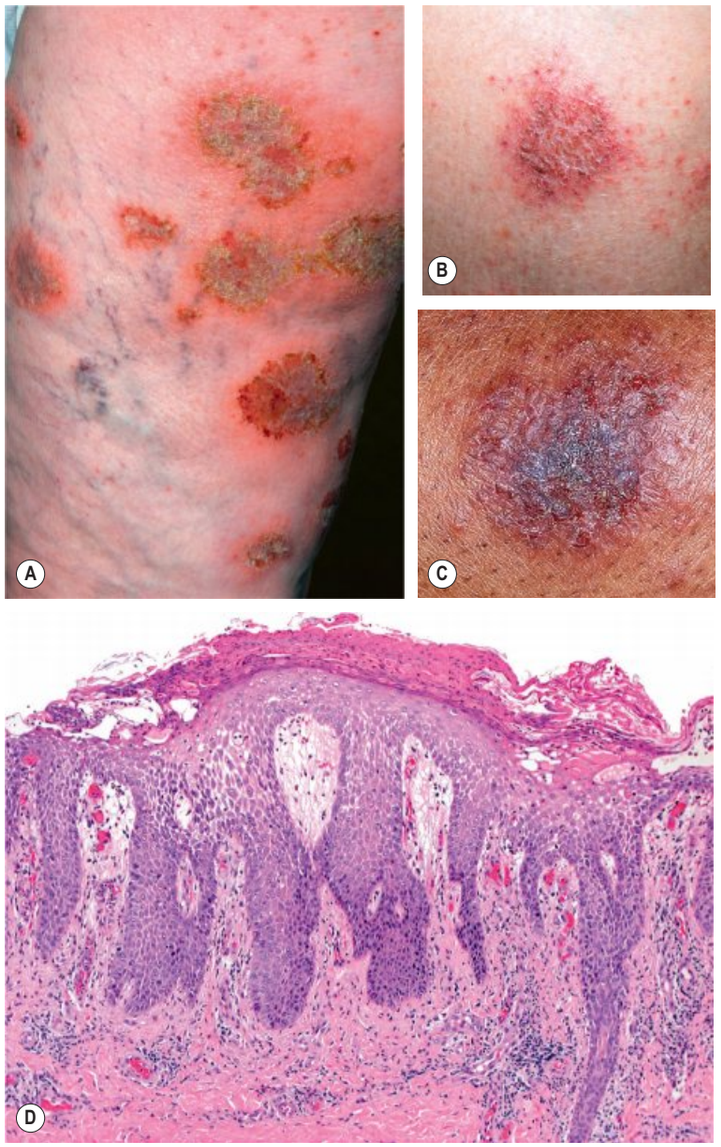


Fig. 13.7 Nummular dermatitis – clinical and histopathologic features. A Multiple coin-shaped lesions of acute and subacute dermatitis on the leg that are fairly well demarcated. There is often marked pruritus. **B, C** Coin-shaped eczematous plaques with scale-crust in two patients with different skin phototypes. Patients may report oozing of lesions. **D** Irregular acanthosis of the epidermis is accompanied by marked spongiosis as well as parakeratotic scale and crust. A lymphohistiocytic infiltrate is present in the dermis with a few lymphocytes within the epidermis. Edema is present in the papillary dermis. *B, C, Courtesy Kalman Watsky, MD; D, Courtesy Lorenzo Cerroni, MD.*

PITYRIASIS ALBA

See Chapter 12.

HTLV-ASSOCIATED INFECTIVE DERMATITIS

Key features

- Rare dermatologic disorder of childhood and adolescence
- Association with human T-cell lymphotropic virus type I (HTLV-1)
- Eczema of the scalp, axillae, and groin; watery discharge of the nose
- Prompt response to antibiotics

Introduction and Pathogenesis

Human T cell lymphotropic virus type I (HTLV-1), also referred to as human T cell leukemia virus type I and adult T cell lymphoma virus type 1, was first detected in 1980[38], and it can infect T cells, B cells, and monocytes. HTLV-1 is transmitted primarily via breastfeeding, but also by sexual intercourse, blood transfusion, and needle sharing in intravenous drug users. It has been associated with adult T cell leukemia/lymphoma (ATLL), myelopathy/tropical spastic paraparesis, and infective dermatitis. Presumably, HTLV-1-induced dysregulation of the immune system leads to immunosuppression and subsequent infections with *Staphylococcus aureus* or β-hemolytic streptococci[39]. There is also a potential role for genetic factors, low socioeconomic status, and malnutrition.

The activity of HTLV-1 in infected subjects appears to be low – more than 90% of carriers remain asymptomatic[40] and the majority of disease symptoms (other than infective dermatitis) emerge during adulthood. HTLV-1 induces spontaneous T cell proliferation independent of exogenous stimuli, followed by interleukin (IL)-2 receptor expression (CD25), increased IL-2 secretion, and induction of interferon-γ, IL-5, and IL-10. In symptomatic patients, levels of tumor necrosis factor and IL-6 are elevated[41]. In addition to bacterial infections, affected individuals are more susceptible to parasitoses such as scabies and strongyloidiasis[42].

History and Epidemiology

Major endemic areas of HTLV-1 infection include sub-Saharan Africa, northern South America, the Caribbean basin, southern Japan, and Iran, affecting 10–20 million people worldwide. Infective dermatitis was first described in 1966 by Sweet[43], and a year later Walshe[44] suggested an underlying immune defect was present because relapses of the dermatitis frequently occurred, even after a prompt initial response to antibiotic treatment. In 1990, the association with HTLV-1 was first reported[39]. The probability of developing infective dermatitis was estimated to be 2% amongst HTLV-1-infected children[45], with cutaneous manifestations typically appearing only after protective maternal antibodies had disappeared.

Clinical Features

Infective dermatitis presents as an exudative and crusty eczematous dermatosis, affecting primarily the head and neck region, including the scalp, ears, eyelid margins, and paranasal skin, as well as the axillae and groin[40]. A generalized fine papular rash is occasionally observed and there is usually secondary infection with *Staphylococcus aureus* or β-hemolytic streptococci. Complications include parasitic infestations, corneal opacities, and progression to more severe HTLV-1-associated disorders (e.g. ATLL). Infective dermatitis rarely persists into adulthood. However, in a series of adult patients in Bahia with HTLV-1-associated ATLL, 44% had a history of infective dermatitis[46]. Diagnosis is established by major and minor criteria (Table 13.1)

Differential Diagnosis

The major entity in the differential diagnosis is atopic dermatitis. Apart from serologic evidence of HTLV-1 infection, lesions of infective dermatitis are more exuberant and obviously infected, but pruritus is less intense. Crusting of the nasal vestibule and blepharoconjunctivitis are more prominent than in atopic dermatitis. Furthermore, it is not associated with atopy. Other disorders to consider include seborrheic dermatitis and impetigo.

Treatment

Antibiotics (e.g. sulfamethoxazole–trimethoprim, cephalexin, erythromycin) result in improvement of the skin lesions but do not prevent relapses. Topical treatments include antibiotics (including intranasal), corticosteroids, and bleach baths.

CRITERIA FOR THE DIAGNOSIS OF HTLV-ASSOCIATED INFECTIVE DERMATITIS
Major
• Eczema of the head and neck region, including the scalp, ears, eyelid margins, and paranasal skin, as well as the axillae and groin
• Chronic watery nasal discharge and/or crusting of the anterior nares
• Chronic relapsing dermatitis which responds quickly to antibiotics but relapses promptly after withdrawal
• Onset during early childhood
• **Seropositivity for HTLV-1**
Minor
• Positive cultures for *Staphylococcus aureus* and/or β-hemolytic streptococci from the skin or anterior nares
• Generalized fine papular rash
• Anemia, elevated erythrocyte sedimentation rate
• Hyperimmunoglobulinemia
• Elevated $CD4^+$ and $CD8^+$ T cell counts; elevated CD4/CD8 ratio

Table 13.1 Criteria for the diagnosis of HTLV-associated infective dermatitis. To establish the diagnosis, four major criteria are required, with mandatory inclusion of human T-cell lymphotropic/leukemia virus type I (HTLV-1) seropositivity. For the first major criterion, the involvement of at least two body regions is required. *Adapted from La Grenade L, Manns A, Fletcher V, et al. Clinical, pathologic, and immunologic features of human T-lymphotrophic virus type I-associated infective dermatitis in children. Arch Dermatol 1998;134:439–44.*

REGIONAL ECZEMATOUS DISORDERS

Stasis Dermatitis

Synonyms: ■ Gravitational dermatitis ■ Varicose eczema ■ Congestion eczema

Key features

- Often associated with other signs of venous hypertension
- Can be complicated by allergic contact dermatitis
- One of the most common causes of disseminated eczema (autosensitization dermatitis)

Introduction

Stasis dermatitis is a common component of the clinical spectrum of chronic venous insufficiency of the lower extremities (see Ch. 105). It may arise as an early sign of chronic venous insufficiency, but can persist or recur throughout all stages and is often most prominent when ulcers are present. There is little doubt that chronic venous hypertension *per se* is the initial trigger for stasis dermatitis[47]. Over time, additional etiological factors may act in concert, most importantly contact sensitization to ingredients of topical therapies. Stasis dermatitis is one of the most common causes of secondary dissemination of dermatitis, and is therefore a complex and multifactorial condition.

History

The term "stasis dermatitis" was introduced by Pillsbury[48], and the term "gravitation dermatitis" by Belisario[49].

Epidemiology

The prevalence of chronic venous insufficiency is variable among different ethnic groups and societies. In Central Europe, ~15% of the adult population has symptoms of chronic venous insufficiency and about 1% suffers from venous ulcers. Prevalence rates clearly rise with age.

Pathogenesis

Venous hypertension of the lower limbs is linked to the upright position and is caused by multiple factors, most importantly valvular incompetence of the deep leg veins (see Fig. 105.2). With venous hypertension, there is a slowing of blood flow within the microvasculature, distension of capillaries, and damage to the capillary permeability barrier, allowing the passage of fluid and plasma proteins into the tissue (edema) and extravasation of erythrocytes (stasis "purpura" and hemosiderin deposition). These processes lead to microangiopathy, with serious consequences (Table 13.2)[58].

Both microangiopathy and chronic inflammation are likely to be responsible for stasis dermatitis. Stasis dermatitis typically occurs in the same (i.e. the medial supramalleolar) regions where microangiopathy is most intense, and the patches of dermatitis arise preferentially

PATHOGENETIC FACTORS IN STASIS DERMATITIS	
Factor	**Consequence**
Chronic venous insufficiency and the microvasculature	
Deposition of proteins, particularly fibrin, around vessels as hyaline cuffs	• Deposits inhibit oxygen diffusion and metabolic exchange in combination with interstitial edema
Slow blood flow	• Upregulation of ICAM-1 and VCAM-1 on endothelia[50] • Activation of neutrophils and macrophages[51] • Expression of L-selectin on neutrophils[52] • Neutrophils attracted into and trapped within affected areas, notably the medial supramalleolar region[53]
Release of inflammatory mediators, free radicals, and proteases by neutrophils	• Pericapillary inflammation
Free iron ions released from hemosiderin deposits	• Increase in free radical production and lipid peroxidation • Activation of matrix metalloproteinases[54]
Platelet accumulation within the microvasculature	• May trigger focal thrombosis
Fibrosis and tissue remodeling due to imbalances within the capillary network	• Lipodermatosclerosis – dermal sclerosis and septal sclerosis that present as sclerosing panniculitis • Lymphatic dysfunction • "Atrophie blanche" – stellate sclerotic areas depleted of capillaries with the formation of peripheral giant capillaries • May lead to the formation of venous ulcers
Elevated plasma levels of homocysteine[55]	• Hyperhomocysteinemia is associated with an increased risk of thromboses
Complicating factors	

Allergic contact dermatitis	• Sensitizers are often in topical agents used to combat pruritus, xerosis, and presumed infection[56,57]
	  • Antibiotics, e.g. bacitracin, neomycin
	  • Lanolin derivatives
	  • Corticosteroids
	  • Fragrances, e.g. Balsam of Peru
	  • Preservatives
	  • Emulsifiers
	  • Antiseptics, e.g. iodine*
	  • Chemicals of plant origin, rubber in pressure stockings
	  • Wound dressing components
	• Patients with chronic venous insufficiency often exhibit multiple contact allergies

Irritant contact dermatitis	• The exudate from draining ulcers leads to maceration, increased inflammation, and bacterial colonization of surrounding skin • Infectious eczematous dermatitis may occur
*More commonly, irritant contact dermatitis.	

Table 13.2 Pathogenetic factors in stasis dermatitis. See Fig. 105.3.

CUTANEOUS SIGNS OF CHRONIC VENOUS HYPERTENSION
• Edema, often tender • Varicosities, including venulectasias of the instep • Petechiae superimposed on a yellow–brown discoloration due to hemosiderin deposits (stasis purpura) • Stasis dermatitis • Lipodermatosclerosis, acute and chronic • Stasis ulcerations, in particular above the medial malleolus • Acroangiodermatitis (pseudo-Kaposi sarcoma) • Livedoid vasculopathy ("atrophie blanche"): porcelain-white scars surrounded by punctate telangiectasias and painful ulcerations*
*Need to exclude causes of hypercoagulability/thrombophilia (see Table 105.9).

Table 13.3 Cutaneous signs of chronic venous hypertension. See Figs. 105.4, 105.5 and 105.7.



Fig. 13.8 Autosensitization dermatitis in a patient with venous ulceration. Note the involvement of the extensor surfaces of the upper extremities in this patient with an allergic contact dermatitis to neomycin, as well as stasis dermatitis and venous ulceration. *Courtesy Jean L. Bolognia, MD.*

over dilated varicose veins. Also, dermal inflammation is known to induce epidermal dysfunction, including barrier impairment.

Sometimes, patients report intense pruritus that even develops before the eczema. Pruritus may be caused by repeated congestion and decongestion, as well as by the release of inflammatory mediators within the dermis. Scratching or rubbing worsens and perpetuates the dermatitis. In addition, patients often apply topical agents to combat the pruritus and xerosis, increasing the risk of contact dermatitis (see Table 13.2).

Clinical features

The first sign of chronic venous insufficiency is usually a cushion-like pitting edema of the medial aspects of the shin and calf around and proximal to the ankle, corresponding to the location of the major communicating veins (Table 13.3). Edema is more pronounced in the evening and resolves overnight. Bouts of stasis purpura lead to areas of hemosiderin deposition. At this stage, stasis dermatitis is mild or absent; the skin may be dry and pruritic. Later, the edema extends to the distal third of the calf and subfascial edema arises, often accompanied by inflammation which may mimic cellulitis (acute lipodermatosclerosis; "pseudoerysipelas"). Over a period of years, the skin, subcutaneous adipose tissue, and deep fascia become progressively indurated and mutually adherent (chronic lipodermatosclerosis). A firm circular cuff is formed which appears to strangle the distal calf, creating an inverted wine bottle appearance. The skin may show intense hemosiderin pigmentation and changes of atrophie blanche. In this setting, venous ulcers develop spontaneously or are triggered by scratching or other trauma. They arise most often in the supramalleolar region, but may later expand (see Ch. 105).

Often stasis dermatitis appears when lipodermatosclerosis develops (see Fig. 105.5). Erythema and scaling are most pronounced around the inner malleoli, but may extend to involve the entire distal lower extremity. Stasis dermatitis is markedly pruritic, as evidenced by multiple excoriations which lead to oozing and crusting. Episodes of vesiculation occur infrequently, always raising the suspicion of superimposed contact sensitization. Chronic lesions of stasis dermatitis invariably exhibit considerable lichenification. Once ulcers form, stasis dermatitis frequently becomes highly irritated, oozing, and erosive (see Fig. 105.4).

Contact sensitization often leads to secondary dissemination. Patches of eczema arise in a strikingly symmetric distribution pattern, particularly on the anterior aspect of the contralateral leg, the anterior thighs, and the extensor surface of the upper extremities (Fig. 13.8); lesions may generalize to involve the trunk and face.

Pathology

The histologic features of eczema, including stasis dermatitis, vary according to the stage of the lesion. In *acute* eczematous eruptions, intraepithelial edema (spongiosis) predominates, with focal fluid accumulation as micro- or macrovesicles, accompanied by lymphocytes in a perivascular array in the superficial dermis and exocytosis of lymphocytes into the epidermis. There is usually focal parakeratosis. In the *subacute* phase, spongiosis is still evident, but may be more subtle and intraepidermal vesicles are less prominent. The epidermis thickens variably and parakeratosis is present focally (see Fig. 13.7D). Lymphocytes persist in the dermis and epidermis. In both acute and subacute stages, edema may be present in the papillary dermis.

In the *chronic* phase, thickening of the epidermis (acanthosis) is more pronounced and it occurs in a regular, psoriasiform pattern or, more often, has a more irregular profile. Inflammation and spongiosis are mild and may be absent. Changes in the granular layer are variable, from thickening, simulating lichen simplex chronicus, to thinning, where the pattern more closely approaches psoriasis; the latter is seen more often in nummular eczema. Ascribing a specific cause of the dermatitis based upon this constellation of histologic findings is impossible.

In stasis dermatitis, biopsy specimens display the histologic features just outlined, as well as signs of venous hypertension: an increased number of capillaries which are dilated and surrounded by cuffs of fibrin, hemosiderin deposits, and hyperplastic (and at times thrombotic) venules (Fig. 13.9). The increase in vessel number can be marked so as to mimic a vascular proliferation. In later stages, there is fibrosis of the dermal connective tissue and sclerosis of the adipose tissue (see Ch. 100).

Differential diagnosis

Stasis dermatitis is a straightforward diagnosis if the cutaneous signs of venous hypertension are present (see Table 13.2). Difficulties may arise in differentiating the individual etiologic components, such as asteatotic eczema and irritant or allergic contact dermatitis. Patch testing is required to exclude the latter. Plaques of stasis dermatitis may be mistaken for nummular eczema, psoriasis, or even mycosis fungoides.

Treatment

The major aim of therapy is the management of venous hypertension – a complex goal which is reviewed in Chapter 105. Basic measures include the regular use of adequate compression bandages or stockings to improve venous return, lifestyle changes, and exercise of the calf muscles. If indicated, surgical strategies are undertaken (see Ch. 155).

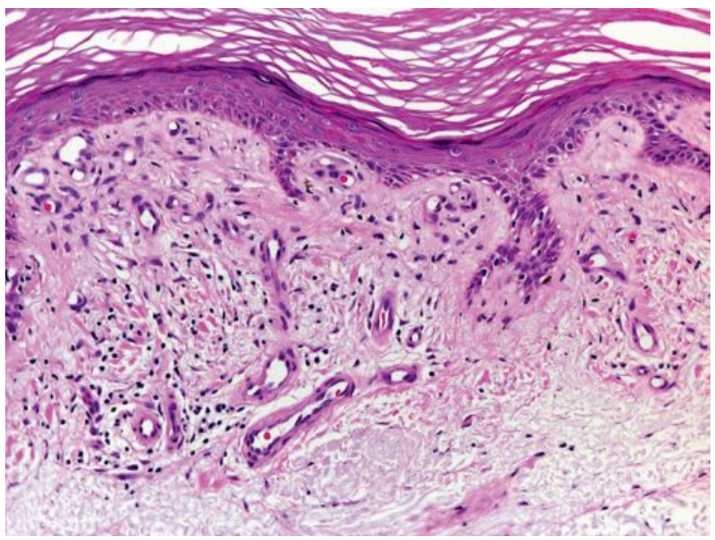


Fig. 13.9 Stasis dermatitis – histologic features. Orthohyperkeratosis and minimal spongiosis in the epidermis. There is an increased number of blood vessels surrounded by a fibrin cuff in a slightly fibrotic papillary dermis. Note also extravasation of erythrocytes and a mild lymphocytic infiltrate. *Courtesy Lorenzo Cerroni, MD.*

However, these surgical approaches do not replace the need for ongoing compression therapy. Topical treatment is the same as for other types of eczemas: judicious use of topical corticosteroids and emollients.

Dyshidrotic Eczema

Synonyms: ■ Pompholyx (larger vesicles and bullae) ■ Acute and recurrent vesicular hand dermatitis

Key features

- Firm, pruritic vesicles of the palms, soles, and lateral and medial aspects of the fingers and toes
- Association with atopic dermatitis and contact dermatitis (allergic and irritant)
- No disturbance of sweat gland function

Introduction

Dyshidrotic eczema is a not-infrequent, chronic, relapsing palmoplantar eczematous dermatosis characterized by firm, pruritic vesicles and bullae. While the vesicles are due to spongiosis within the epidermis, their intact nature is explained by the thick tear-proof horny layer in these sites. Dyshidrotic eczema is not an independent disease entity because it is often a manifestation of other types of eczema, especially atopic dermatitis and irritant or allergic contact dermatitis.

Pathogenesis

Although the formation of vesicles is not linked to sweat gland dysfunction or trapping of sweat within the epidermis (as the term may suggest), hyperhidrosis can be an aggravating factor in some patients. Notably, treatment of hyperhidrosis with onabotulinumtoxin A may ameliorate dyshidrotic eczema[59].

Dyshidrotic eczema is frequently an expression of atopic dermatitis, particularly as a late-stage manifestation. In these patients, its intensity is usually low to moderate with a protracted and relapsing course, and it is accompanied by only a few other signs of atopic dermatitis. Less often, dyshidrotic eczema is a manifestation of acute or subacute allergic contact dermatitis. Flares can also result from exposure to known irritants (see Ch. 15).

Occasionally, administration of IVIg is followed by acute episodes of dyshidrotic eczema. The role of ingestants, in particular nickel and cobalt, has been debated, but improvement with a low-nickel diet (in nickel-sensitive patients with a positive oral provocation test) has been observed. Lastly, flares can also follow periods of emotional stress as well as exposure to hot climates and rarely sunlight.

Clinical features

Dyshidrotic eczema is characterized by symmetric, firm, deep-seated vesicles of the palms, the lateral and medial aspects of the fingers, and less often the soles and toes (Fig. 13.10A). The size of the vesicles may vary from pinhead-sized to several centimeters ("pompholyx"). When smaller lesions are clustered, they have been likened to tapioca pudding (Fig. 13.10B). While the markedly pruritic vesicles initially contain clear fluid, they have a tendency for purulent superinfection. Dyshidrotic eczema resolves via desquamation of characteristically thick scales.

Dyshidrosis lamellosa sicca (also referred to as keratolysis exfoliativa) is a minimal variant which displays no blisters but only small annular collarettes of white scale (see Fig. 39.13).

Pathology

Histologically, a spongiotic dermatitis is seen with the formation of micro- and macrovesicles within the epidermis (Fig. 13.10C). There is no association with sweat glands.

Differential diagnosis

Inflammatory tinea manuum and pedis, scabies, and palmoplantar pustular psoriasis need to be considered as well as dyshidrosiform pemphigoid, dyshidrotic cutaneous T cell lymphoma, erythema

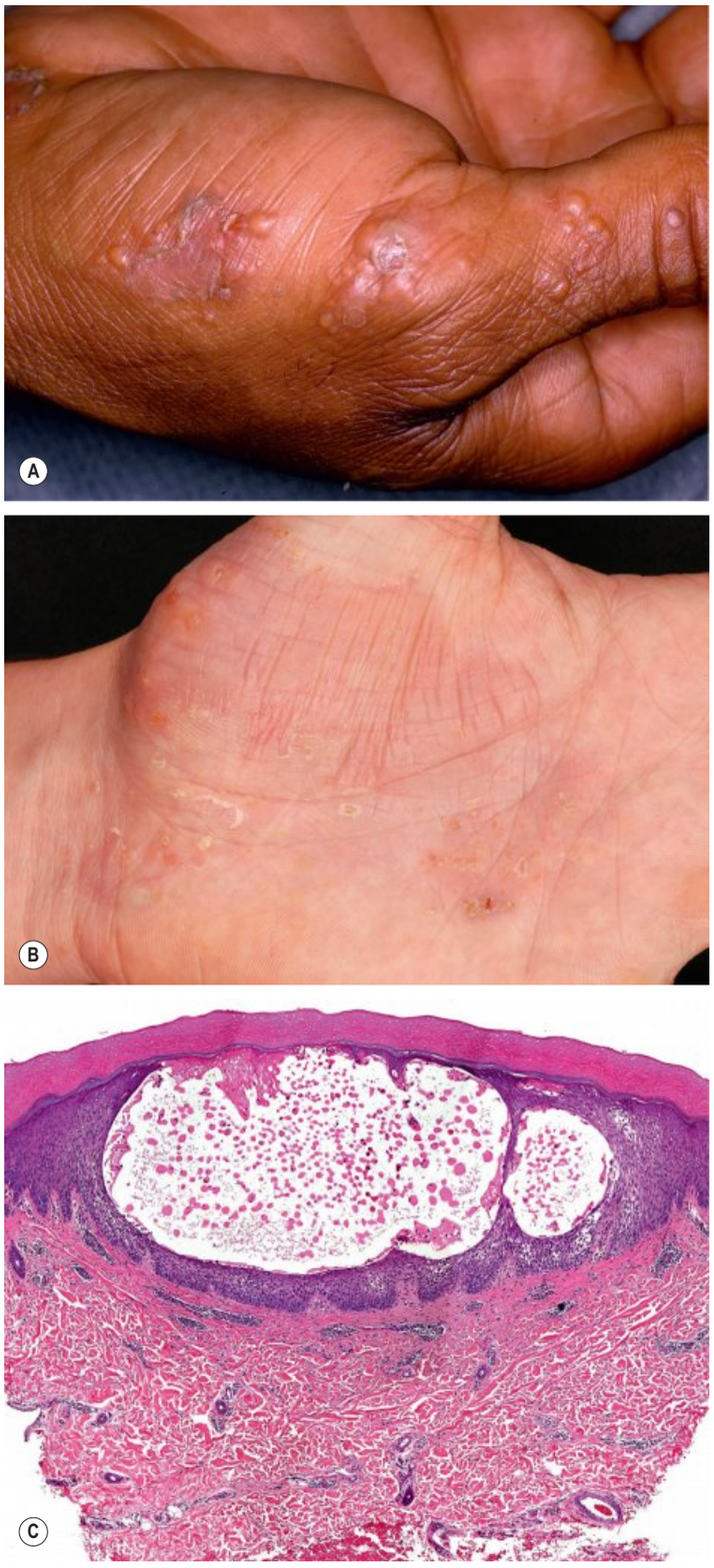


Fig. 13.10 Dyshidrotic eczema – clinical and histopathologic features. A Firm vesicles are seen along the side of the thumb and thenar eminence. Some of them are deep-seated. **B** Clusters of tiny vesicles and annular collarettes of scale where the vesicles have ruptured superimposed on plaques of dermatitis. **C** Histologically, spongiosis within the epidermis is accompanied by macrovesicles; the thick stratum corneum points to an acral location. *A, Courtesy Louis A. Fragola, Jr, MD; B, C, Courtesy Lorenzo Cerroni, MD.*

multiforme, fixed drug eruption, and, in children, infantile acropustulosis. Distinguishing between an id reaction involving the palms or soles and dyshidrotic eczema can sometimes be difficult and some clinicians view them as overlapping entities.

Treatment

Topical emollients and corticosteroids are the mainstay of treatment. Other topical treatments such as calcineurin inhibitors, retinoids, and PUVA (bath > systemic) may also be helpful. An underlying allergic or irritant contact dermatitis needs to be considered and addressed. In chronic relapsing or recalcitrant cases, systemic therapy (e.g. retinoids, oral corticosteroids, or other immunosuppressants such as cyclosporine) may be considered[60].

Infectious Eczematous Dermatitis

This entity is regarded as an eczematous reaction to a localized infection with purulent drainage, most often due to *Staphylococcus* or *Streptococcus* spp. It is thought to result from a sensitization to bacterial antigens. Clinically, pustules and vesicles spread from an infectious nidus. More advanced stages are characterized by crusting, scaling, and oozing[61]. In children, the nares, ears, and face are the most common sites of involvement, whereas in adults, the distal lower extremities are most often affected. Milder forms can be treated with open wet dressings, topical antibiotics, topical corticosteroids, and emollients whereas more severe disease usually requires the addition of oral antibiotics and sometimes oral corticosteroids.

Infectious eczematous dermatitis should be distinguished from eczema due to autosensitization, in which lesions develop at a distance from the primary site. Lastly, this disease should not be confused with HTLV-associated infective dermatitis (see above).

Juvenile Plantar Dermatosis

Synonyms: ■ Atopic winter feet ■ Forefoot dermatitis ■ Dermatitis plantaris sicca ■ Moon-boot foot syndrome ■ Sweaty sock dermatitis

Key features

- Dry, scaly, glazed and fissured plantar surface of the forefoot
- Prepubertal children are affected
- Association with atopy and exogenous factors

Introduction

The feet are a fairly common site for various eczematous dermatoses (Table 13.4). Juvenile plantar dermatosis is a characteristic condition that occurs primarily (but not exclusively) in children with an atopic diathesis.

History

Juvenile plantar dermatosis was first reported by Mackie and Husain[62].

Epidemiology

Juvenile plantar dermatosis occurs in prepubertal children, from the age of 3 years and upwards, when shoes are worn for longer periods of time. It is only occasionally seen in adults. There is seasonal variation, with worsening during the winter, and boys are affected slightly more often than girls.

Pathogenesis

An atopic disposition is clearly a risk factor, but exogenous factors play an equally important role, including plastic- and rubber-constructed sports shoes that youngsters often wear all day long. The humid environment leads to hydration of the horny layer, making it much less resistant to wear and tear. When the stratum corneum is rubbed off by friction, this leads to a characteristic glazed and thinned appearance of the skin. As involved areas become xerotic, cracks are formed. The inherently dry skin of atopic individuals may be a predisposing factor. Adults have a much thicker horny layer of their plantar skin and are thus less at risk of developing the condition.

Clinical features

The balls of the feet and the toe pads exhibit strikingly symmetrical changes: fairly well demarcated shiny, reddish, tender, dry lesions with

DIFFERENTIAL DIAGNOSIS OF DERMATITIS OF THE FOOT
Allergic contact dermatitis (footwear dermatitis)
• Dermatitis of the dorsal aspects of the feet and toes (allergen contained in the "top" of the shoes) • Dermatitis of the weightbearing areas of the soles (allergens contained in the sole of the shoes) • Most common allergens: dichromate, rubber accelerators, colophony, dyes, formaldehyde resins; also consider topical antibiotics, e.g. bacitracin • Association with atopy and hyperhidrosis • Distinguish from sock and stocking dermatitis where lesions extend more proximally (popliteal area, thighs) – most common allergen is azo dyes
Tylosis
• Mechanically induced hyperkeratosis, dryness, and fissuring • Predilection sites: heels and weightbearing areas of the soles • In middle-aged to elderly individuals • Associated with obesity and hyperhidrosis
Acquired plantar keratoderma (keratoderma climactericum)
• Same as tylosis but more intense • Typically occurs in women over the age of 45 years, but may also be seen in men • Similar lesions may appear on palms
Juvenile plantar dermatosis
See section in this chapter
Tinea pedis (athlete's foot)
• Dermatophyte infections of the plantar skin are usually accompanied by involvement of the interdigital spaces as well as lateral aspects of the foot • Often symmetric, accompanied by onychomycosis • Lesions on the lateral and dorsal aspects of the feet have well-demarcated circinate borders • Occasionally vesicular variant
Psoriasis (see Ch. 8)
• Well-circumscribed plaques or diffuse erythema with thick adherent scales, dryness, and fissuring • Psoriatic plaques found elsewhere on the body • Nail involvement, e.g. pitting and oil-drop changes
Dyshidrotic eczema
See section in this chapter
Recurrent focal palmar and plantar peeling (keratolysis exfoliativa)
• Probably represents a mild form of dyshidrosis • Dry, circinate, thin scales of palms and soles • Vesicles are absent
Pustulosis of the palms and soles (see Ch. 8)
• A neutrophilic dermatosis, possibly related to pustular psoriasis • Chronic course with crops of non-pruritic, short-lived, superficial pustules, particularly of the instep • Yellow–brown macules admixed with pustules
Sézary syndrome (see Ch. 120)
• Palms and soles are tender and exhibit scaling, which can be quite thick • Associated with hypertrophic onychodystrophy and erythroderma
Other
• Atopic dermatitis • Irritant contact dermatitis (e.g. due to occlusive footwear) • Palmoplantar lichen planus • Pityriasis rubra pilaris • Acrokeratosis paraneoplastica • Keratoderma blennorrhagicum • Inherited palmoplantar keratodermas (see Ch. 58) • Palmoplantar keratoderma associated with hypothyroidism • Crusted scabies

Table 13.4 Differential diagnosis of dermatitis of the foot.

some scaling (Fig. 13.11), and often accompanied by painful cracks and fissures. The dorsa of the feet, the interdigital spaces, and the instep are typically spared. Less often, similar lesions are found on the hands.



Fig. 13.11 Juvenile plantar dermatosis in a child. Erythema and scaling of the plantar surface of the great toes and fifth toes as well as the ball of the foot bilaterally. Note the glazed appearance of the skin of the left foot. *Courtesy Kalman Watsky, MD.*

Pathology

Histologically, the features of a chronic eczematous dermatitis are seen (see section "Stasis dermatitis").

Differential diagnosis

Juvenile plantar dermatosis needs to be distinguished from *allergic contact dermatitis* to chemicals contained in leather (e.g. chromates, dyes) or rubber. However, the latter is uncommon in children and, if present, often involves the dorsa of the feet as well. *Tinea pedis* is equally uncommon in children, and the interdigital spaces are usually predominantly affected. Patch testing and KOH preparations may help in establishing the diagnosis.

Treatment

Juvenile plantar dermatosis is a chronic but self-limiting condition. Patients should be advised to avoid wearing impermeable socks and shoes, and the application of emollients, keratolytics, and/or paraffin-type ointments is beneficial. When shoes are removed, socks, if damp, should also be removed and replaced by dry socks.

Diaper Dermatitis

Key features

- Frequently, an irritant dermatitis of the diaper area due to occlusion and prolonged exposure to urine and feces
- Secondary infection with *Candida albicans* often occurs
- May be associated with seborrheic dermatitis and psoriasis

Epidemiology

Diaper dermatitis develops in at least 50% of infants, and it is responsible for a considerable percentage of dermatologic consultations in infants and toddlers. Seborrheic dermatitis is a predisposing factor.

Pathogenesis

Diaper dermatitis is the cumulative result of several factors, in particular dampness and exposure to urine and feces. In the past, ammonia derived from the urea in urine was held as primarily responsible for diaper dermatitis. More recently, the blame has been placed on the (alkaline) pH of the urine and the role of fecal bacteria. Enzymes produced by fecal bacteria, as well as residual pancreatic proteases and lipase in the stool, act as irritants and these enzymes are also activated in the

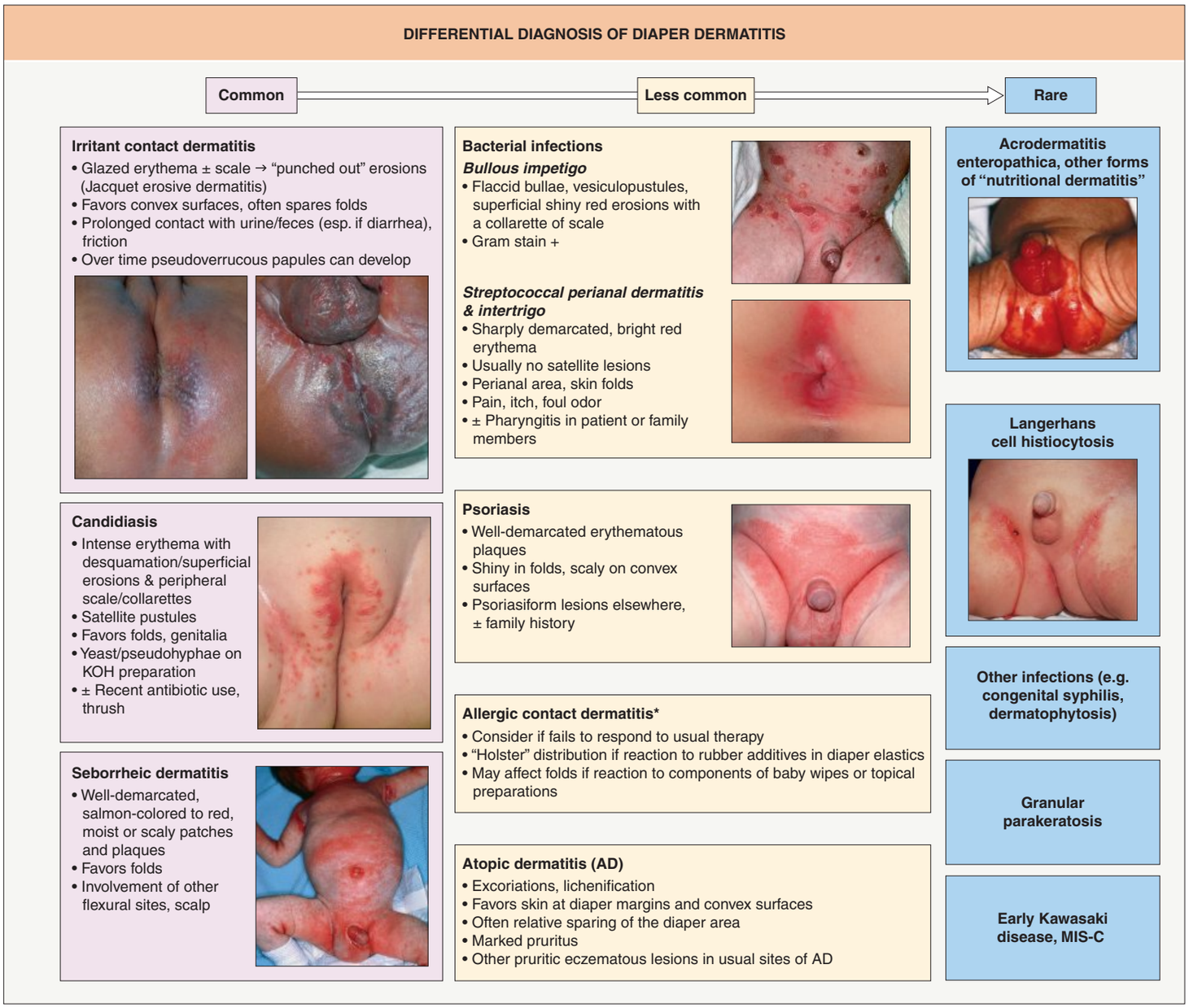


Fig. 13.12 Differential diagnosis of diaper dermatitis. While the most common etiologies are irritant contact dermatitis, cutaneous candidiasis and seborrheic dermatitis, patients often have a combination with one disorder superimposed on another. The spectrum of "erosive papulonodular dermatosis" due to chronic irritation in the diaper area includes granuloma gluteale infantum, pseudoverrucous papules, and Jacquet erosive dermatitis. Discrete papules or nodules are seen in scabies, whereas congenital syphilis often presents with erosions and even ulcerations, MIS-C, SARS-CoV-2-related multisystem inflammatory syndrome in children. *Potential allergens include sorbitan sesquioleate (an emulsifier in diaper balms), fragrances, disperse dyes, rubber additives (e.g. mercaptobenzothiazole), and preservatives in baby wipes (e.g. iodopropynyl butylcarbamate). *Insets: Courtesy Robert Hartman MD; Julie V. Schaffer, MD.*

alkaline milieu[63,64]. In addition, ureases are produced by fecal bacteria, resulting in a further increase of the urinary pH. This explains why diaper dermatitis is more likely to appear in cow milk-fed than in breast-fed infants: cow milk formulas are colonized by a greater number of urease-producing bacteria[65].

Prolonged use of diapers, dampness, and the factors detailed above lead to the breakdown of the horny layer barrier function. An alkaline pH also facilitates the development of secondary *C. albicans* infection.

As diaper dermatitis tends to be most prominent on the inner parts of the thighs, genitalia, and buttocks, friction between the skin and the diaper material likely acts as a physical factor that leads to further irritation. In addition, chemical constituents of the diaper and/or topical preparations and baby wipes may lead to contact sensitization.

Clinical features

Diaper dermatitis is strictly confined to the diaper area, presenting with mild to pronounced erythema, erosions, and scaling. In the common form due to irritant contact dermatitis, genitocrural folds are typically spared. Depending on whether there is a secondary infection or an underlying dermatosis (e.g. seborrheic dermatitis, psoriasis), the clinical picture can vary (Fig. 13.12).

Differential diagnosis

The differential diagnosis is outlined in Fig. 13.12.

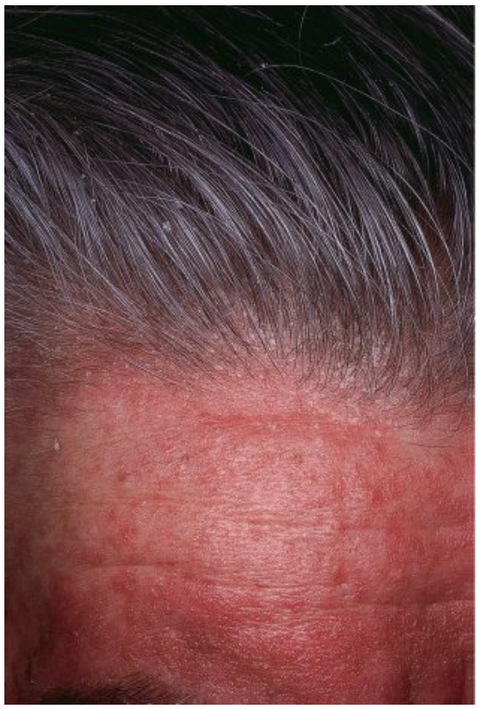
Treatment

In the acute phase, mild corticosteroid preparations are helpful. Topical imidazole creams are added for secondary infection with *Candida* spp. The major goal of long-term management is avoidance of the causative factors. Frequent changing of highly absorbent disposable diapers is associated with a lower incidence and severity of diaper dermatitis, and it leads to a more physiologic pH[66]. Emollients containing white paraffin (Vaseline®) or soft zinc pastes provide both protective and soothing effects.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 13.1 Adult seborrheic dermatitis of the face and scalp. Note the diffuse scaling of the scalp in addition to erythema of the forehead. *Courtesy Jean L. Bolognia, MD.*



eFig. 13.2 Seborrheic dermatitis of the scalp. Diffuse yellow scales are seen. *Courtesy Julie V. Schaffer, MD.*





eFig. 13.4 Asteatotic eczema (eczema craquelé). A The distal lower extremity has areas of dull erythema that contain a criss-cross pattern of superficial cracks and fissures said to resemble a dried river bed. **B** A close-up of the pattern.





eFig. 13.3 Seborrheic dermatitis-like presentation of Langerhans cell histiocytosis (A) and dermatomyositis (B). Note the extension onto the neck in the patient with dermatomyositis. *A, Courtesy Peter W. Heald, MD; B, Courtesy Jeffrey P. Callen, MD.*



eFig. 13.5 Asteatotic eczema. A It often flares in the winter, arises within areas of xerosis, and is exacerbated by an overuse of soap. **B** When widespread, there can be involvement of the trunk and proximal extremities. Along with the distal lower extremity, the area that surrounds the posterior axillary fold is a common site for asteatotic eczema. *A, Courtesy Kalman Watsky, MD; B, Courtesy Thomas Schwarz, MD.*



eFig. 13.6 Nummular dermatitis. Note the moist "wet" nature of the lesion. *Courtesy Luis Requena, MD.*



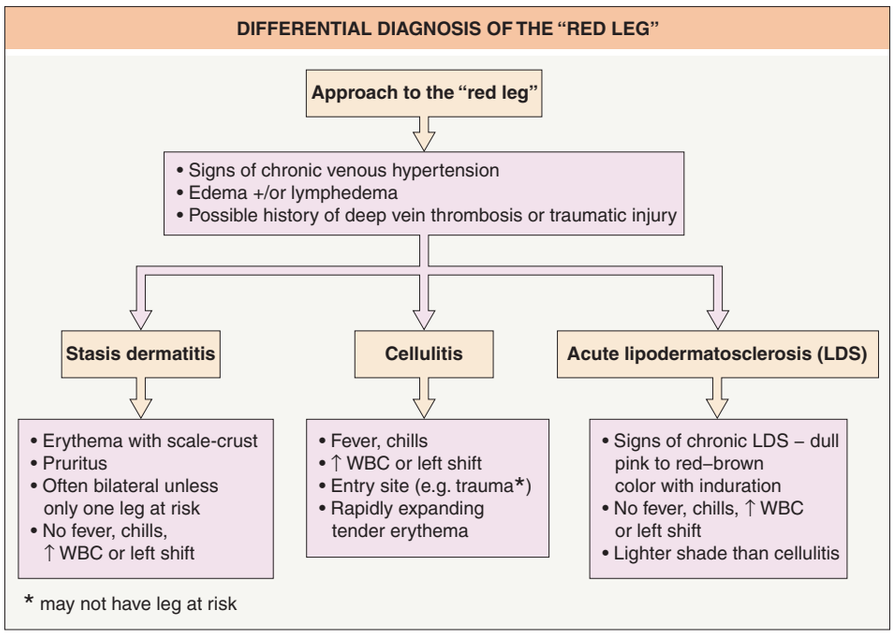
eFig. 13.7 Nummular dermatitis. Coin-shaped eczematous plaques with scale-crust. *Courtesy Boni Elewski, MD.*



eFig. 13.8 Nummular dermatitis in a child. The coin-shaped lesions are edematous and have scale-crust. *Courtesy Julie V. Schaffer, MD.*



eFig. 13.9 Pityriasis alba. Hypopigmented macules and patches on the cheek of a Black girl. *Courtesy Anthony J. Mancini, MD.*



eFig. 13.10 Differential diagnosis of the "red leg". In a patient with chronic lipodermatosclerosis (LDS), it can be difficult to distinguish partially treated cellulitis (e.g. oral antibiotics for several days and no white blood count [WBC] at time of initial presentation) versus superimposed acute LDS. *Courtesy Jean L. Bolognia, MD.*



eFig. 13.11 Dyshidrotic eczema. Firm papules and pseudovesicles on the palms and volar sides of fingers.



eFig. 13.12 Keratotic eczema of the central palm. Some clinicians view this as psoriasis, not dermatitis. A history of repeated rubbing of the site by the third and fourth fingers can sometimes be elicited.



eFig. 13.13 Infectious eczematous dermatitis. Crusting and scaling at the periphery of otitis externa due to *Staphylococcus aureus*.



eFig. 13.14 Acute irritant diaper dermatitis due to prolonged exposure to urine and feces. Glazed erythema with erosions that favors convex surfaces and often spares folds. *Courtesy Julie V. Schaffer, MD.*



eFig. 13.15 Pseudoverrucous perianal papules and nodules (Jacquet dermatitis). This 2-year-old child had frequent exposure to loose stool following a colostomy takedown. *Courtesy Julie V. Schaffer, MD.*

14 Allergic Contact Dermatitis

Kalman L. Watsky, Rosemary L. Nixon, Christen M. Mowad and James G. Marks Jr

Synonyms: ■ Contact dermatitis ■ Contact eczema

Key features

- Allergic contact dermatitis (ACD) is a pruritic, eczematous reaction
- Acute ACD and many cases of chronic ACD are well demarcated and localized to the site of contact with the allergen
- ACD can also have a diffuse or patchy distribution, depending on the allergen and/or the development of disseminated eczema (autosensitization dermatitis)
- The prototypic reactions are ACD caused by nickel, poison ivy, and related plants
- ACD may coexist with irritant contact dermatitis, contact urticaria, and different forms of endogenous eczema
- Patch testing remains the gold standard for accurate and consistent diagnosis unless the exposure is quite obvious as in poison ivy

INTRODUCTION

When the skin comes in contact with external agents, many adverse events can occur including contact dermatitis, which can be either allergic or irritant. Irritant contact dermatitis (ICD) accounts for ~80% of all contact dermatitis (see Ch. 15), with allergic contact dermatitis (ACD) accounting for the remainder[1]. ACD is a delayed-type hypersensitivity reaction that is elicited when the skin comes in contact with a chemical to which an individual has previously been sensitized.

The cutaneous responses of ACD are dependent on the particular chemical, the duration and nature of the contact, and individual host susceptibility. The chemicals that cause contact dermatitis may be found in jewelry, personal care products, plants, topical medications (prescription, over-the-counter or herbal), clothing, and home remedies, as well as chemicals the individual comes in contact with at work, during avocations, or via contact with another individual (e.g. consort contact dermatitis).

ICD and ACD, especially the chronic forms, can take on similar clinical appearances. The classic picture of contact dermatitis is a well-demarcated, erythematous, vesicular, and/or scaly patch or plaque with well-defined margins corresponding to the area of contact (Fig. 14.1A). The distribution can be linear, when an object such as a leaf or branch is rubbed against the skin (Fig. 14.1B), or localized to the site where there has been contact with the offending chemical or product, e.g. hand dermatitis caused by ACD to epoxy resin or foot dermatitis due to ACD to the components of shoes (Figs. 14.2–14.4). Because ICD and ACD are not always discernible clinically, patch testing is required to help identify an allergen or exclude an allergy to a suspected allergen. While patch testing remains the gold standard for diagnosing ACD, it is important to note that ICD and ACD may coexist.

Patients with the most common clinical presentations of ACD often do not seek medical attention. Those who have earring dermatitis or erythema and pruritus under a ring may simply diagnose themselves as having an allergy to jewelry. An individual who is gardening over the weekend may never present to a physician because the "poison ivy rash" is so familiar. Nickel (worldwide) and poison ivy (US; see Ch. 17) are among the most common etiologies of ACD and are often not further investigated because the cause is obvious. However, oftentimes, the clinical picture and history are not sufficiently specific to identify the causative allergen, and patch testing is then necessary. For example, the patient with chronic hand dermatitis or eyelid dermatitis who comes to the office for treatment is often unaware that a personal care product could be the cause of the problem. These are the patients who can be most helped by a thorough history and cutaneous examination, as well as the diagnostic procedure of patch testing.

HISTORY OF PATCH TESTING

Jadassohn has been credited with describing the technique of patch testing over 100 years ago. In 1931, Sulzberger and Wise[2] formally brought the technique to the US and described its use as a diagnostic tool for identifying a causative allergen responsible for dermatitis. This technique has been further developed over the years on a worldwide basis, with standardized allergens, testing devices, and protocols as well as numerous regional baseline series.

EPIDEMIOLOGY

ACD can affect individuals in all walks of life. It can affect the old, the young, and individuals of all races and both sexes. Differences between



Fig. 14.1 Allergic contact dermatitis (ACD). A This erythematous plaque with vesiculation developed in a 14-month-old boy following the application of neomycin ointment. **B** Erythematous streaks with linear vesicles caused by ACD to poison ivy. *A, Courtesy Anthony J. Mancini, MD; B, Courtesy Joyce Rico, MD.*



Fig. 14.2 Chronic allergic contact dermatitis (ACD). Chronic foot dermatitis due to ACD to rubber (mercaptobenzothiazole). *Courtesy Louis A. Fragola, Jr, MD.*



Fig. 14.3 Persistent hand dermatitis due to chronic allergic contact dermatitis. The allergen was epoxy resin.





Fig. 14.4 Allergic contact dermatitis to shoes – acute versus chronic. A Extremely pruritic erythematous papules and papulovesicles appeared within days of wearing new sneakers; note the distribution pattern. **B** Pebbled and lichenified plaques with both hypo- and hyperpigmentation. The patient had a positive patch test to potassium dichromate. *Courtesy Louis A. Fragola, Jr, MD.*

sexes may be seen but are generally based upon exposure patterns, such as nickel allergy occurring more frequently in women, presumably because of their greater exposure to jewelry[3]. Occupations and avocations also play an important role in the epidemiology of ACD (see Ch. 16). Allergens, and therefore patch test results, differ from region to region, e.g. preservatives used in personal care products can vary based on government legislation. While quaternium-15 is a cosmetic preservative that commonly causes ACD in the US, some have argued that it is not even needed in the European Baseline Series[4]. In addition, even in a particular locale, some allergens can increase in clinical importance over time while others decrease due to usage patterns, and new allergens are continually being introduced.

PATHOGENESIS

ACD is a delayed-type hypersensitivity response. It is an allergen-specific reaction that requires prior sensitization of the individual to the chemical in question. The pathogenesis of ACD involves an initial sensitization phase when the patient first comes in contact with the chemical, which penetrates the skin and then elicits a cascade of events that results in sensitization (see Fig. 4.13 for details). The subsequent re-exposure of the skin leads to the presentation of the responsible allergen to an already primed T cell milieu, causing the release of multiple cytokines and chemotactic factors and resulting in the clinical picture of eczema (see Fig. 4.14). Once sensitized, all that is needed to elicit a reaction is contact with a low concentration of the causative chemical.

CLINICAL FEATURES

In order to diagnose ACD and treat it adequately, the clinician needs to be familiar with its clinical presentations. The typical appearance is often a well-demarcated pruritic eczematous eruption, which may be acute (blistering, weeping and/or edema, e.g. Figs. 14.1, 14.5 & 14.6) or chronic (lichenified or scaly plaques, e.g. Figs. 14.2, 14.3, 14.4B, 14.7 & 14.8). This reaction is typically localized to the area of skin that comes in contact with the allergen (Fig. 14.9A,B). However, the clinician must also be aware that patchy or diffuse distributions can also be seen, depending on the nature of the causative allergen (Fig. 14.9C,D & 14.10). For example, body washes or shampoos that are rinsed over the body may cause a more patchy or diffuse clinical dermatitis. Other less common presentations of allergic contact dermatitis are listed in Table 14.1.

PATHOLOGY

Although the diagnosis of ACD is in large part a clinical one aided by the diagnostic procedure of patch testing, histology can sometimes be helpful. This is especially true when excluding other diagnoses, such as mycosis fungoides. The pathology of ACD is most helpful in acute





Fig. 14.5 Acute vesiculobullous allergic contact dermatitis (ACD). A The allergen was neomycin from a topical antibiotic ointment. **B** The allergen was urushiol in poison ivy; this distribution pattern is seen in patients who wear gloves. *A, Courtesy Jonathan Chan, MD.*





Fig. 14.6 Acute allergic contact dermatitis with a prominent component of edema. A Periorbital edema, in addition to crusted and weeping plaques, due to poison ivy. **B** Allergic contact dermatitis to methylisothiazolinone in a wet wipe used to remove make-up. *A, Courtesy Jean L. Bolognia, MD.*



Fig. 14.7 Allergic contact dermatitis due to aloe-containing cream. The degree of involvement on the upper and lower lips is similar, as opposed to actinic cheilitis. In the latter scale is predominantly on the lower vermilion lip.



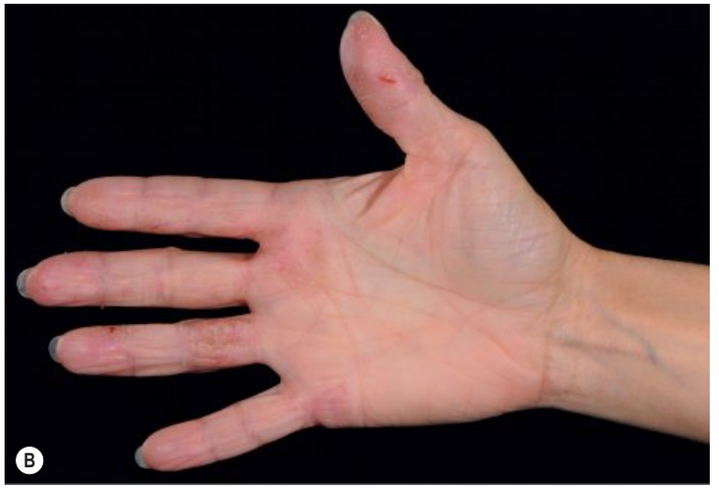


Fig. 14.8 Persistent hand dermatitis due to chronic allergic contact dermatitis. A In this machine operator, the allergen was black rubber. **B** The allergen was methylisothiazolinone in sanitary wet wipes.

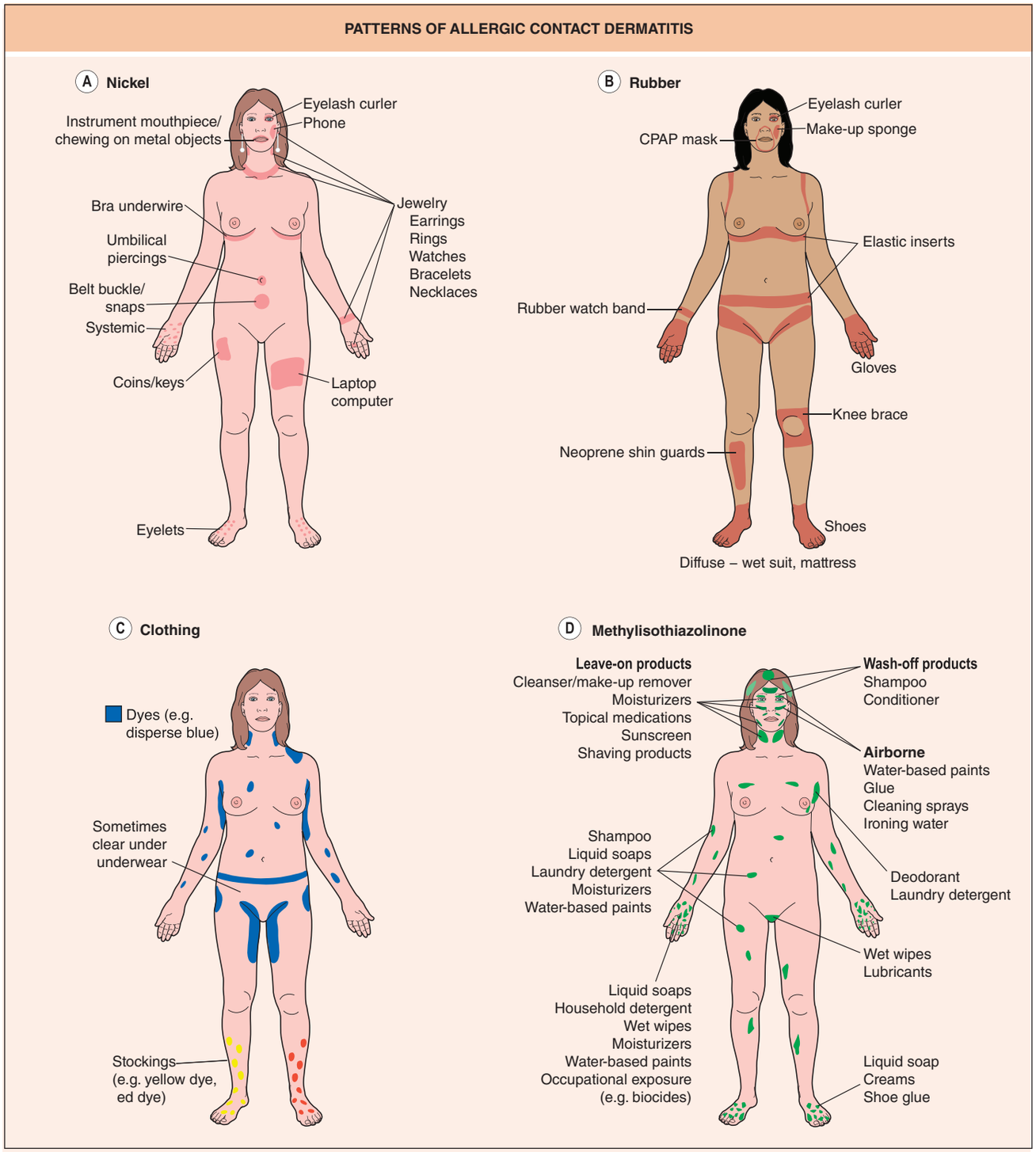


Fig. 14.9 Patterns of allergic contact dermatitis. A Due to nickel; lesions can also arise from metal braces and on the back at the site of bra clasps. **B** Due to rubber. **C** Due to dyes and resins in clothing. **D** Due to methylisothiazolinone. Some exposures can affect multiple sites and cause generalized dermatitis. CPAP, continuous positive airway pressure.

lesions, as subacute or chronic lesions often produce confusing patterns that are not diagnostic. Histologically, ACD is the prototype of spongiotic dermatitis. In the acute stage, there is a variable degree of spongiosis, with a mixed dermal inflammatory infiltrate containing lymphocytes, histiocytes, and a variable number of eosinophils. In moderate to severe reactions, marked spongiosis results in intraepidermal vesiculation (Fig. 14.11A). In subacute to chronic stages, epidermal hyperplasia, often psoriasiform, develops (Fig. 14.11B).

However, even when spongiotic dermatitis is present, clinicopathologic correlation is always required, as ACD is not the only cause of this reaction pattern. In addition, as with any dermatitis, the application of topical corticosteroids may alter the histologic findings. Occasionally, other histopathologic patterns are seen in ACD, as outlined in Table 14.1.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of ACD includes many other forms of dermatitis, such as ICD, protein contact dermatitis, atopic dermatitis, stasis dermatitis, and seborrheic dermatitis, as well as the erythematous form of rosacea. Hand and foot ACD also needs to be distinguished from endogenous dermatitis, psoriasis, and tinea (see Table 13.4 & Fig. 15.7). Of note, these conditions may coexist, which can make clinical assessment complicated. In general, when evaluating regional dermatoses (e.g. eyelid, hand, and foot), other disorders common to the area need to be considered as well as allergens specific to that area (Table 14.2). If there is widespread disease, either because of widespread contact with an allergen or autosensitization, additional causes of erythroderma (see Ch. 10), e.g. Sézary syndrome, enter the differential diagnosis.



Fig. 14.10 Allergic contact dermatitis due to cashew nut shell oil. This represented an occupational exposure.

RARE TO UNCOMMON PRESENTATIONS OF ALLERGIC CONTACT DERMATITIS	
Based primarily upon morphology	**Based primarily upon distribution and/or pathogenesis**
• Pigmented (e.g. fragrances, bactericides; often facial) • Lichenoid (e.g. color film developers, dental acrylates) • Erythema multiforme (e.g. tropical woods, *p*-phenylenediamine, poison ivy*) • Pigmented purpura (e.g. rubber diving suits) • Pseudolymphomatous (e.g. Compositae) • Granulomatous (e.g. zirconium) • Pustular (e.g. fragrances)	• Photoinduced (photoallergic contact dermatitis; see Ch. 87) • Airborne contact dermatitis • Systemic contact dermatitis (see Table 14.12) • Baboon syndrome – symmetric erythema of the gluteal and inguinal area in addition to other flexural sites†
*The lesions of erythema multiforme may favor sites previously unaffected by poison ivy. †Overlap with systemic contact dermatitis and clinical overlap with *s*ymmetrical *d*rug-*r*elated *i*ntertriginous and *f*lexural *e*xanthema (SDRIFE; see Table 21.14).	

Table 14.1 Rare to uncommon presentations of allergic contact dermatitis (ACD). Contact urticaria, both immunologic and non-immunologic, can also complicate the clinical picture.

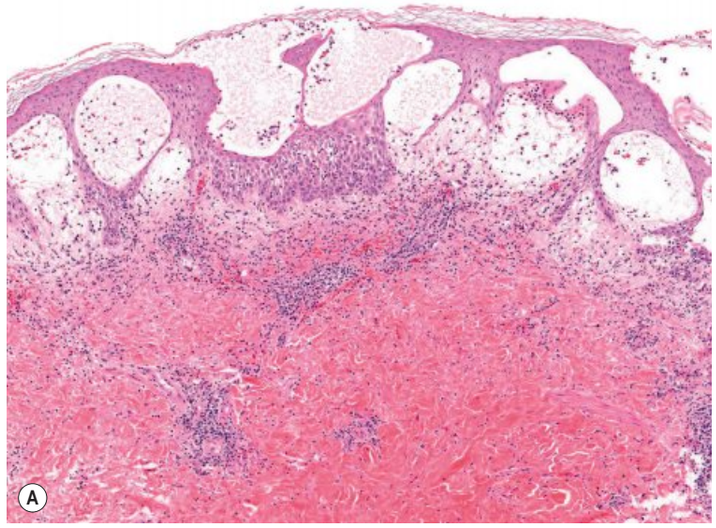




Fig. 14.11 Allergic contact dermatitis (ACD) – histologic features. A Acute ACD with marked spongiosis leading to intraepidermal vesiculation. There is a perivascular infiltrate of lymphocytes and eosinophils as well as exocytosis of these cells into the epidermis. **B** Chronic ACD with irregular psoriasiform epidermal hyperplasia and significantly less spongiosis. There is also a primarily perivascular infiltrate of lymphocytes admixed with eosinophils. *Courtesy Lorenzo Cerroni, MD.*

Deciphering and differentiating these diseases can sometimes be a challenge. Distribution and history can be helpful (see Figs. 14.1, 14.4, 14.5), as can simple tests such as a KOH preparation. In addition, dermatoses are sometimes multifactorial, and ACD may be superimposed on atopic dermatitis or stasis dermatitis. However, in order to diagnose ACD, the clinician must first consider the possibility, then ask the right questions, and, finally, use the appropriate allergens to diagnose this condition. What follows will hopefully provide the clinician with an outline to the appropriate questions to ask and procedures to use when investigating ACD.

Patch Testing

Patch testing is a deceptively simple office procedure upon which the diagnosis of ACD often rests. Although the procedure is straightforward, deciding when and what to patch test requires training and experience. Unfortunately, patch testing is still underutilized. In 2010 in the US, only 22% of dermatology program directors and 27% of chief residents reported having a specific patch testing rotation[5].

The T.R.U.E. TEST®, which is approved by the US Food and Drug Administration (FDA), consists of panels with pre-impregnated allergens, allowing for increased ease of use and perhaps resulting in increased patch testing. However, it currently screens for 35 allergens, in addition to a negative control, and although this is helpful, extended testing beyond these allergens has been shown to improve diagnostic accuracy[6–8]. With extended testing, 37%–76% more positive reactions were detected, and 47% of the patients had positive reactions *only* to non-screening allergens[6–8] (these latter allergens come in multi-use syringes or tubes [see Appendix]). Lastly, when patch testing was performed with 28 T.R.U.E. TEST® allergens, only 27.6% of patients had completely detected allergens[8].

Prior to the application of the patch tests, the clinician should ask questions about exposures both at home and at work, and attempt to understand the mechanics of the work environment. The effect of vacations and time away from work or home should also be ascertained. In addition, all personal care products should be inventoried and hobbies explored. The information gained can help to direct allergen selection more appropriately.

Technique

Although the T.R.U.E. TEST® now has 35 allergens (plus control) and the European Baseline Series[9] 30 allergens plus 13 recommended additions (Table 14.3), referral centers with patch test clinics routinely patch test to an "expanded" series of 60+ allergens. Such panels include the American Contact Dermatitis Society Series (updated in 2020)[10], the North American Contact Dermatitis Group 70 (which includes allergens "of interest" primarily for research purposes), and

EYELID DERMATITIS – DIFFERENTIAL DIAGNOSIS AND MOST COMMONLY ASSOCIATED ALLERGENS	
Differential diagnosis	
Endogenous	
• Atopic dermatitis – lichenification common • Seborrheic dermatitis – scaling of eyelid margins & accentuated in creases • Ocular rosacea – eyelid margin^ • Dermatomyositis >> cutaneous lupus – may have associated edema	
Exogenous	**Allergens most commonly associated with ACD of the eyelids***
• Allergic contact dermatitis (ACD) – occasionally airborne • Irritant contact dermatitis (ICD) – topical medications (e.g. for acne), anti-aging creams, cosmetics, occupational exposures	• Fragrances, including *Myroxylon pereirae* (balsam of Peru) • Preservatives – quaternium-15, DMDM hydantoin, methylchloroisothiazolinone, methyldibromoglutaronitrile • Topical antibiotics – neomycin • Metals – nickel, cobalt chloride, gold sodium thiosulfate • Surfactants – cocamidopropyl betaine, amidoamine

^May co-exist with periorificial dermatitis.
*Adapted from North American Contact Dermatitis Group (2003–2004). *Dermatitis*. 2007;18:78–81.

Table 14.2 Eyelid dermatitis – differential diagnosis and most commonly associated allergens. There is often a combination of endogenous plus exogenous causes. This nail salon technician had allergic contact dermatitis to 2-hydroxyethylmethacrylate (HEMA) which is found in nail polish and nickel; note the involvement of the fingertip.

COMPONENTS OF THE AMERICAN CONTACT DERMATITIS SOCIETY (ACDS) SCREENING SERIES (2020), THE T.R.U.E. TEST® SERIES, THE AUSTRALIAN BASELINE SERIES (2021), THE EUROPEAN BASELINE SERIES (2019), AND THE NORTH AMERICAN CONTACT DERMATITIS GROUP (NACDG) 70 (2017–18)

Allergen/hapten	Conc/vehicle	ACDS series (2020)	T.R.U.E. TEST®	Australian baseline 60	European baseline	NACDG 70
2-Bromo-2-nitropropane-1,3-diol (Bronopol®)	0.5% pet				*	
Bacitracin	20% pet					
Black rubber mix^	0.6% pet					
Budesonide	0.1% pet				0.01% pet	
Carba mix	3% pet					
Cobalt chloride	1% pet					
Colophony (colophonium)	20% pet					
Diazolidinyl urea	1% pet			2% pet	*	
Epoxy resin (bisphenol A)	1% pet					
Ethylenediamine dihydrochloride	1% pet					
Formaldehyde	2% aq					1% & 2% aq
Fragrance mix I	8% pet					
Gold sodium thiosulfate	2% pet					
Hydrocortisone-17-butyrate	1% pet					
Imidazolidinyl urea	2% pet				*	
Mercapto mix	1% pet			3.5% pet	2% pet	
Mercaptobenzothiazole (MBT)	1% pet			2% pet	2% pet	
Methylchloroisothiazolinone/methylisothiazolinone	110 ppm aq				200 ppm aq	200 ppm aq
Methyldibromoglutaronitrile	0.5% pet					2% pet**
Myroxylon pereirae resin (balsam of Peru)	25% pet					
Neomycin	20% pet					
Nickel sulfate	2.5% pet			5% pet	5% pet	
p-Phenylenediamine (PPD)	1% pet					
p-tert-Butylphenol formaldehyde resin	1% pet					
Paraben mix	12% pet				16% pet	
Parthenolide (sesquiterpene lactone)			0.003 mg/cm^2 PV			

^N-isopropyl-N′-phenyl PPD, N-cyclohexyl-N′-phenyl PPD, and N,N′-diphenyl PPD.
*Recommended additions to the European Baseline Series.
**Methyldibromoglutaronitrile combined with phenoxyethanol.

Table 14.3 Components of the American Contact Dermatitis Society (ACDS) Screening Series (2020), the T.R.U.E. TEST® Series, the Australian Baseline Series (2021), the European Baseline Series (2019), and the North American Contact Dermatitis Group (NACDG) 70 (2017–18). *Continued*

COMPONENTS OF THE AMERICAN CONTACT DERMATITIS SOCIETY (ACDS) SCREENING SERIES (2020), THE T.R.U.E. TEST® SERIES, THE AUSTRALIAN BASELINE SERIES (2021), THE EUROPEAN BASELINE SERIES (2019), AND THE NORTH AMERICAN CONTACT DERMATITIS GROUP (NACDG) 70 (2017–18)						
Allergen/hapten	**Conc/vehicle**	**ACDS series (2020)**	**T.R.U.E. TEST®**	**Australian baseline**	**European baseline**	**NACDG 70**
Potassium dichromate	0.25% pet			0.5% pet	0.5% pet	
Quaternium-15	2% pet			1% pet	1% pet	
Thiuram mix	1% pet					
Tixocortol-21-pivalate	1% pet				0.1% pet	
Benzocaine	5% pet					
Caine mix (benzocaine, tetracaine, dibucaine)			0.63 mg/cm^{2}PV		***	
Disperse blue 106			0.05 mg/cm^{2}PV			
Disperse blue 106/124 mix	1% pet					
Quinoline mix			0.19 mg/cm^{2}PV			
Thimerosal			0.007 mg/cm^2 HPC			
2-Ethylhexyl-4-methoxycinnamate	10% pet					
2-Hydroxy-4-methoxybenzophenone (benzophenone-3)	10% pet					
2-Hydroxy-4-methoxybenzophenone-5-sulfonic acid (benzophenone-4)	2% pet					10% pet
2,6-Ditert-butyl-4-cresol (BHT)	2% pet					
3-(Dimethylamino) propylamine (DMAPA)	1% aq					
4-Chloro-3-cresol (PCMC)	1% pet					
Amerchol L101	50% pet					
Amidoamine (stearamidopropyl dimethylamine)	0.1% aq					
Benzalkonium chloride	0.1% aq					
Benzoic acid	5% pet					
Benzyl alcohol	10% SOF					
Benzyl salicylate	10% pet					
Carmine	2.5% pet					
Cetyl steryl alcohol	20% pet					
Chlorhexidine digluconate	0.5% aq					1% aq
Chloroxylenol (PCMX)	1% pet					
Cinnamic aldehyde (cinnamal)	1% pet					
Clobetasol-17-propionate	1% pet					
Cocamide DEA (coconut diethanolamide)	0.5% pet					
Cocamidopropyl betaine	1% aq					
Compositae mix II	5% pet				2.5% pet*	6% pet
Decyl glucoside	5% pet				*	
Disperse orange 3	1% pet					
Disperse yellow 3	1% pet					
DL Alpha tocopherol	100%					
DMDM hydantoin	1% pet			2% aq		
Ethyl acrylate	0.1% pet					
Ethyl cyanoacrylate	10% pet					
Ethyleneurea melamine-formaldehyde	5% pet					
Ethylhexylglycerin	5% pet					
Fragrance mix II	14% pet					
Hydroperoxides of limonene	0.2% pet			0.3% pet	0.3 & 0.2% pet*	0.3% pet
Hydroperoxides of linalool	0.5% pet			1% pet	1 & 0.5% pet*	1% pet
Hydroxisohexyl 3-cyclohexene carboxaldehyde (Lyral®)	5% pet					
Hydroxyethyl methacrylate	2% pet					

Table 14.3 Components of the American Contact Dermatitis Society (ACDS) Screening Series (2020), the T.R.U.E. TEST® Series, the Australian Baseline Series (2021), the European Baseline Series (2019), and the North American Contact Dermatitis Group (NACDG) 70 (2017–18).

COMPONENTS OF THE AMERICAN CONTACT DERMATITIS SOCIETY (ACDS) SCREENING SERIES (2020), THE T.R.U.E. TEST® SERIES, THE AUSTRALIAN BASELINE SERIES (2021), THE EUROPEAN BASELINE SERIES (2019), AND THE NORTH AMERICAN CONTACT DERMATITIS GROUP (NACDG) 70 (2017–18)

Allergen/hapten	Conc/vehicle	ACDS series (2020)	T.R.U.E. TEST®	Australian baseline	European baseline	NACDG 70
Iodopropynyl butylcarbamate	0.1% pet			0.2% pet		0.5% pet
Jasminium officinale oil	2% pet					
Lanolin alcohol (wool alcohols)	30% pet		1000 mcg/cm^2 PV			
Lauryl polyglucose (glucosides)	3% pet				*	
Lavandula angustifolia oil (lavender oil)	2% pet					
Lidocaine	15% pet					
Mentha piperita oil (peppermint oil)	2% pet					
Methyl methacrylate	2% pet					
Methylisothiazolinone	0.2% aq					
Mixed dialkyl thioureas	1% pet					
N,N-Diphenylguanidine	1% pet					
Oleamidopropyl dimethylamine	0.1% aq					0.1% aq
Phenoxyethanol	1% pet					2% pet**
Polymyxin B sulfate	3% pet					
Pramoxine hydrochloride	2% pet					
Propolis	10% pet					
Propylene glycol	30% aq					100%
Sesquiterpene lactone mix	0.1% pet					
Shellac	20% alcohol					
Sodium benzoate	5% pet					
Sorbic acid	2% pet					
Sorbitan sesquioleate	20% pet					
Tea tree oil	5% pet					
Tosylamide formaldehyde resin	10% pet					
Triamcinolone	1% pet					
Ylang ylang oil	2% pet					
Ammonium persulfate	2.5% pet					
Betamethasone-17-valerate	1% pet					
Chloroacetamide	0.2% pet					
Citral	2.0% pet					
Geraniol	2.0% pet					
Isoeugenol	2.0% pet					
Methylchloroisothiazolinone (Kathon CG)	0.215% pet					
Methylprednisolone aceponate (Advantan)	1.0% pet					
Sodium metabisulphite	1.0% pet				*	
Textile dye mix (8 disperse dyes)	6.6% pet					5.6% pet (7 disperse dyes)
Toluene diamine	1.0% pet					
Toluene diamine sulphate	1.0% pet					
Benzisothiazolinone	0.1% pet				*	
N-Isopropyl-N-phenyl-4-phenylenediamine	0.1% pet					
Octylisothiazolinone	0.1% pet				*	0.025% pet
Carvone	5% pet					
Hydroquinone	1.0% pet					

*Recommended additions to the European Baseline Series.
**Methyldibromoglutaronitrile combined with phenoxyethanol.
***Benzocaine, cinchocaine, tetracaine.

Table 14.3 Components of the American Contact Dermatitis Society (ACDS) Screening Series (2020), the T.R.U.E. TEST® Series, the Australian Baseline Series (2021), the European Baseline Series (2019), and the North American Contact Dermatitis Group (NACDG) 70 (2017–18). The concentrations and vehicles are used in the ACDS Series unless otherwise noted. aq, aqueous; Conc, concentration; HPC, hydroxypropyl cellulose; pet, petrolatum; ppm, parts per million; PV, polyvidone; SOF, soluble organic fraction.

the Australian Baseline Series (updated in 2021). This is in addition to more specific allergen panels, e.g. the hairdressing tray, dental tray or florist tray, which contain allergens unique to a particular occupation. The companies from which these allergens and other supplies can be obtained are listed in the Appendix. Although these expanded series of allergens are not FDA-approved, they are often required to establish the precise etiology of the patient's dermatitis.

Substances brought by patients to the dermatologist should *not* be tested in a blinded fashion. The physician should be aware of the chemical ingredients of the product, or severe irritation such as a burn or ulceration could occur. Therefore, no unknown product or chemical should be applied as a patch test. Material safety data sheets (MSDS) can sometimes help in further evaluating the chemical. However, not all ingredients are listed on these forms: those chemicals that represent a small percentage and fall below a certain threshold do not need to be listed, even though they may be the causative allergens. Identification of the latter requires communication with the manufacturer, so that full disclosure of the chemical ingredients can be obtained.

When patients bring all their personal care products to the office for patch testing, special attention is required. The general rule regarding testing of these products is that products intended to be left on the skin (so-called "leave-on" products), such as moisturizers and make-up, may be tested "as is". Products that are intended to be diluted by water or rinsed off (so-called "rinse-off" products), such as soaps and shampoos, need to be diluted prior to patch testing (often to 1%–10% in water). There are helpful guides for determining appropriate patch test concentrations for numerous chemicals[11]. When these nonstandard allergens are tested, controls (including vehicles) must be tested to evaluate for the possibility of ICD.

After allergen selection has been finalized, appropriate technique is necessary to ensure adequate testing. The most common site is the upper back. The patient should not have a sunburn in this area and should not have applied topical corticosteroids to the sites of patch testing for 1 week[12,13]. Systemic and longer-lasting injectable corticosteroids should also be avoided for at least 1–2 weeks[14]. (If necessary for disease control, the daily oral AM dose of corticosteroids should not exceed the equivalent of 20 mg of prednisone during testing.) Any one of these factors may decrease the individual's ability to elicit a reaction when challenged by an allergen, resulting in a false-negative test[12–14]. Other immunosuppressants (e.g. methotrexate, mycophenolate mofetil) and targeted immune modulators ("biologics") may also impact patch testing results[15,16].

A nurse or technician in the office can be trained to apply the patches, and this leads to improved efficiency. Either the pre-packaged allergens are placed on the back as in the case of the T.R.U.E. TEST®, or the allergens are dispensed into chambers. There are a number of different patch test systems, including Finn Chambers® (SmartPractice®) which are adhered to Scanpor® tape (Norgesplaster, Norway; available in the US from SmartPractice®); allergEAZE® chambers (SmartPractice®; Fig. 14.12); and IQ, IQ Ultra™, or IQ Ultimate™ chambers (Chemotechnique Diagnostics; distributed by Dormer Laboratories, Inc.). These patches are applied to the back, reinforced with more Scanpor® tape if required, and the patient is sent home with instructions to keep the back dry and the patches secured until the second visit at 48 hours. Patients should also be told to avoid excessive sweating and to avoid heavy lifting, as the patches may come loose. Antihistamines can be prescribed, as they will not affect the outcome of the testing. A map of where the allergens were placed should be constructed for future reference.

When the patient returns at 48 hours, the patches need to be examined to ensure that the testing technique was adequate. Initial inspection can determine that the patches are still in place. Confirmation comes from observing whether the chambers have adhered adequately so as to leave an impression in the skin (see Fig. 14.14G). As the patches are removed, their sites of application should be marked in order to identify the location of the particular allergens (Fig. 14.13). Two types of marking pen are recommended for this procedure: either a permanent surgical marker or a fluorescent highlighter. Highlighters are less messy and do not rub off as easily as the permanent marker. Because of the latter property, permanent markers can soil clothing and make interpretations at the second reading more difficult. Any positive reactions are scored according to the International Grading System (Table 14.4; Fig. 14.14). The patient is again asked to keep the back dry until the second reading, which can be performed from 72 hours to 1 week after the initial application of patches.

When the patient returns for the second reading, the map is used to identify any positive reactions. If a fluorescent marker has been utilized, a Wood's lamp may be needed to identify the markings. Positive reactions are again graded according to the standard system (see Table 14.4). This later reading is necessary as patch test responses to some allergens such as gold, neomycin, and corticosteroids may be delayed. The actual products the patient uses in his or her work and/or home environment are examined and the ingredients compared with the positive reactions. In so doing, products can be divided into groups: those that are free of the suspected allergen(s) and are safe to use and those that contain these chemical(s) and should be avoided. There will usually be some products with no ingredients listed, and these will have to be further investigated by the patient or physician by contacting companies and inquiring about ingredients.

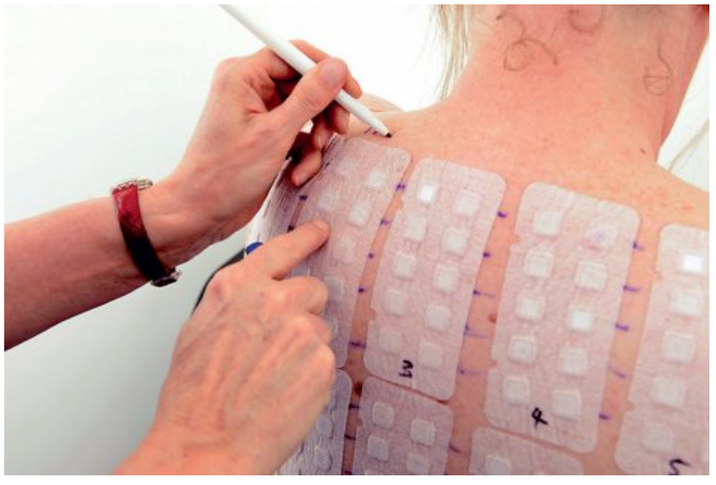


Fig. 14.12 Placement of allergens to the patient's back utilizing allergEAZE® chambers.



Fig. 14.13 Sites of specific patch tests labelled for future reference following removal of the chambers.

INTERNATIONAL GRADING SYSTEM FOR PATCH TESTS	
+/–	Doubtful reaction, faint macular erythema
+	Weak, non-vesicular reaction with erythema, infiltration and papules
++	Strong, vesicular reaction with erythema, infiltration and papules
+++	Spreading bullous reaction
–	Negative reaction
IR	Irritant reaction

Table 14.4 International Grading System for patch tests. See Fig. 14.14.

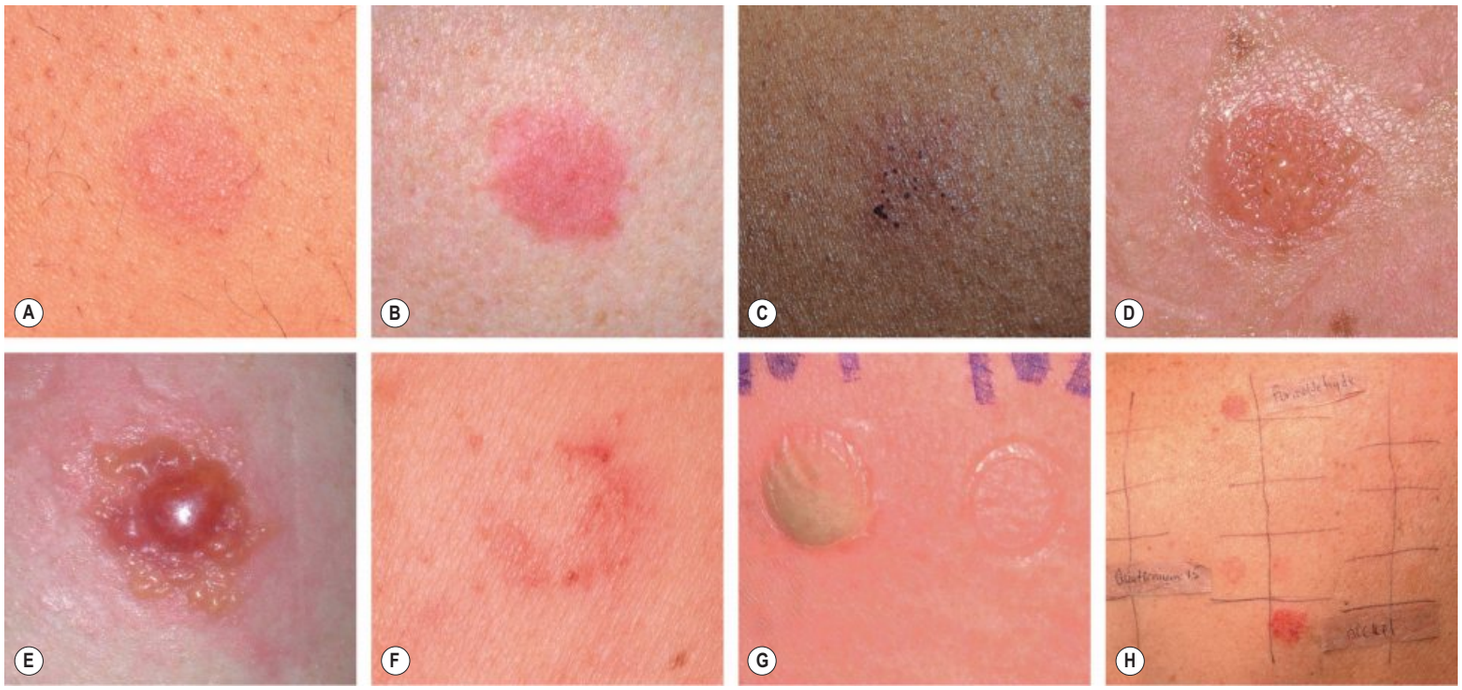


Fig. 14.14 Patch test reactions. A +/– to + reaction. **B, C** + reaction. **D** ++ reaction. **E** +++ reaction. **F** Erythematous papules at the edge of the Finn chamber application site (rim or edge effect). **G** Pustular irritant reaction at the site of the application of a metalworking fluid. The adjacent skin impression of a chamber reflects good adherence. **H** Three different patch test reactions: +/– to quaternium-15, + to formaldehyde, and ++ to nickel.

Interpreting the test

Through the process of reviewing exposures and products, the clinical *relevance* of positive test results can be determined. Allergens may have past relevance. For example, a patient who presents with a known allergy to nickel and reactions to costume jewelry is found on patch testing to have a positive reaction to nickel. The nickel may have past relevance to the patient's problem with costume jewelry but no current relevance to the chronic hand dermatitis. Relevance may also be determined to be current. For example, a positive reaction to tuliposidase A (see Ch. 17) in a florist who has hand dermatitis and contact with *Alstroemeria* when arranging flowers would have present relevance. In some individuals, relevance may be unknown, as in a patient with an eyelid dermatitis and a positive reaction to thimerosal but no history of current or past exposure; sensitization may have occurred from a vaccine.

TREATMENT AND PATIENT EDUCATION

Once allergens are positively identified, the patient should be given written information on all of these chemicals. The information sheets should contain data regarding the name of the chemical, possible synonyms, typical uses for the chemical, how to avoid exposure, and, when appropriate, substitutions. The sheets can be individually composed or obtained from books and copied for patient use[17]. In addition, the American Contact Dermatitis Society website (www.contactderm.org) is an excellent resource for allergen and product information, including patient information sheets (Table 14.5). The Contact Allergen Management Program (CAMP) is another feature of the website (available to members of the society): this allows the user to input the known allergens and the database assembles a list of products free of the allergens entered. With this CAMP-generated list, the patients can then purchase products that lack the ingredients to which they are allergic. In addition, this website contains a Contact Dermatitis Alternatives Database which assists both patients and physicians with regard to appropriate substitutions for known allergens.

The patient should also be instructed on how to read the labels of any new or old products not reviewed, in order to avoid future exposure. Each time the patient considers buying a product, he or she should utilize updated information sheets, because ingredients in a given product can change over time. In addition, ingredients in a particular product can change from location to location (e.g. between countries, or between the East and West Coast of the US) without a change in the packaging.

After identifying the substances to which the patient is allergic, the most important step a physician can take is to educate the patient regarding the names of the allergens and how to avoid them. This empowers the individual and allows the physician to transfer to the patient the responsibility for avoiding said chemicals. When trying to identify allergens in the patient's environment, one must also consider allergens transferred from other sources – so-called consort dermatitis (e.g. from spouse to spouse, such as the cologne on the husband causing a reaction on the face of his wife).

Treatment of ACD primarily involves identification of the causative allergens. Once the allergens have been identified, the physician should try to clear the dermatitis with appropriate treatments, such as topical or, if necessary, systemic corticosteroids. The educated patient then needs to be diligent in avoiding the identified allergens. It may take 6 weeks or more to see complete and prolonged clearing, even when allergens are being avoided (Fig. 14.15). If the ACD is superimposed upon another dermatosis (e.g. stasis dermatitis, atopic dermatitis, ICD), then the latter will also need to be addressed via appropriate skin care including avoidance of skin irritants and moisturizing creams.

If a patient is unable to undergo patch testing for some reason, or confirmation of patch test results is desired, a repeat open application test may be performed. This open use test, sometimes referred to as the "poor man's patch test", can prove useful. In an open use test, the patient applies the product in question to the same predetermined location (where there is no dermatitis) twice daily for 1–2 weeks; a common site is the antecubital fossa or flexor forearm. If dermatitis develops, it can be concluded that the patient is reacting to that product. Unfortunately, this type of testing does not allow the identification of individual ingredients. Repeat open application tests are also used to establish clinical relevance of the patch test results, e.g. a patient reacts to a fragrance, but the concentration of the fragrance in a particular product was so low that it did not react on initial patch testing.

ALLERGENS

The top 10 allergens, as identified by the North American Contact Dermatitis Group (NACDG) in 2017–2018 were nickel sulfate, methylisothiazolinone (MI), methylchloroisothiazolinone/MI, fragrance mix I, hydroperoxides of linalool, formaldehyde, benzisothiazolinone, *Myroxylon pereirae* (balsam of Peru), cobalt chloride, and *p*-phenylenediamine (Table 14.6)[7]. For patients with active dermatitis awaiting

METHYLCHLOROISOTHIAZOLINONE/METHYLISOTHIAZOLINONE		
Other names:		
5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one, Kathon CG, Euxyl K100, or Groton K		
What is it?		
Methylchloroisothiazolinone and methylisothiazolinone (MCI/MI) are used alone or together as preservatives. They are active against bacteria, yeast, fungi, and algae. They are widely used in personal, household, and industrial products.		
Where might it be found?		
Personal care products		
Shampoo	Facial cleanser, scrub, mask	Facial moisturizer, anti-aging
Hair conditioner, detangler	Make-up remover	Sunscreen, sunless tanner
Hair styling mousse, foam, gel	Moist towelettes, wet wipes	Foot scrub
Hair color	Baby wipes, baby shampoo	Bubble bath
Body or hand soap, cleanser	Moisturizer, cream, lotion	
Household care and other products		
Laundry detergent	Fountain, cooling tower water	Jet fuel, anti-static
Fabric softener, stain remover	Bubble blowing solutions	Pesticide, weed killer
Household shampoo, cleaners	Dehumidifier	Pet spray, pet shampoo
Pre-moistened mop, sponge	Adhesive, glue, binding agent	Printing ink, coloring agents
Wax, polish	Cutting fluid, metalworking	Paper mill anti-slime
Paint, enamel, primer, sealer	Milk sampling	
Latex emulsions	Flax spinning	
How to avoid it:		
• To avoid MCI/MI check the complete ingredient list of each product you use. For products already at home with no ingredient list, go to the store and inspect the original box or package. Some products' ingredient lists are available on the internet at the manufacturer's website or the store's website. • You may be exposed to MCI/MI by coming in contact with products your partner is using. • Ask your hairdresser, aesthetician, and others to avoid using MCI/MI in your care. • Tell your physician about your allergy. • Some prescriptions (e.g. halobetasol and crotamiton) may contain MCI/MI. • Some items with these brand names contain MCI: Eucerin, Nivea, Moisturel, Purpose, Aveeno, Neutrogena, Nu-Skin, Herbal Essences, Dove, Pantene, Suave, and Dep. • MCI is in Cottonelle, Kleenex, Wal-Mart, Walgreens, and CVS flushable wipes. • Safe wipes are Charmin Freshmates, Wet Ones, and White Cloud Unscented; be sure to check the ingredients list. • To identify possible workplace exposure, check the complete ingredient list of everything encountered. You may need to contact the manufacturer to find out if a commercial product contains this preservative; Material Safety Data Sheets may be incomplete. • If you must come into contact with MCI/MI in your work or care for children, elders, or pets, wear protective gloves made of rubber, nitrile, or vinyl.		

Table 14.5 American Contact Dermatitis Society (ACDS) exposure information sheets: methylchloroisothiazolinone(MCI)/methylisothiazolinone (MI). Patient information sheets for several common allergens as well as the Contact Allergen Management Program (for members) are available at www.contactderm.org.



Fig. 14.15 Allergic contact dermatitis to fragrance found in cologne. A Patient at the time of diagnosis. **B** Patient after avoidance of fragrances and his cologne.

TOP TEN ALLERGENS AS IDENTIFIED BY THE NORTH AMERICAN CONTACT DERMATITIS GROUP		
Test substance	**Allergic reactions (%)**	**Relevant reactions (%) (definite, probable, possible [combined])**
Nickel sulfate, 2.5% pet	16	49
Methylisothiazolinone, 0.2% aq	15	88
Methylchloroisothiazolinone/ methylisothiazolinone, 0.02% aq	11	90
Fragrance mix I, 8% pet	9	87
Hydroperoxides of linalool, 1% pet	9	87
Formaldehyde, 2% aq	7	78.5
Benzisothiazolinone, 0.1% pet	7	52
Myroxylon pereirae (balsam of Peru), 25% pet	7	85
Cobalt, 1% pet	7	46.5
p-Phenylenediamine, 1% pet	6	64.5
Data from DeKoven JG, Silverberg JI, Warshaw EM, et al. North American Contact Dermatitis Group Patch Test Results: 2017–2018. *Dermatitis*. 2021;32:111–23.		

Table 14.6 Top 10 allergens as identified by the North American Contact Dermatitis Group. aq, aqueous; pet, petrolatum.

patch testing, avoidance of common allergens such as these can be a useful temporizing measure[18]. Table 14.7 provides a list of additional important allergens (and the frequently identified routes of exposure). Of note, ACD in children is becoming increasingly recognized, and the most common allergens, as identified by the NACDG in this age group[19], are outlined in Table 14.8. The modern era has brought us new products and new exposures to allergens, e.g. isobornyl acrylate in glucose sensors, alkyl glucosides in leave-on and rinse-off personal care products, and cyanoacrylates in surgical glues[20–25]. Additional examples are outlined in Table 14.9, including exposure to the preservative MI (see Fig. 14.9D)[27]. MI has served as a substitute for older preservatives such as parabens; the latter were eliminated from many products due to concerns regarding non-cutaneous side effects, but as a reflection of the low allergenicity of parabens they were designated the 2019 (non) allergen of the year by the ACDS[28].

The following section will briefly discuss pertinent information regarding several key allergens.

Nickel

Nickel ranks as the most common allergen tested by the NACDG, with up to 20% of patch test clinic patients reacting to it. In patch test clinics worldwide, nickel is the most common allergen, but it is often not relevant to the dermatitis in question[19]. However, upon questioning, past relevance may be discovered (e.g. previous mid-abdomen dermatitis). Nickel is a strong silver-colored metal that is commonly used in jewelry, buckles, and snaps, as well as other metal-containing objects (Fig. 14.16).

It has been proposed that the high rate of nickel sensitivity, which in some patch test clinics approaches 30%–40%, can be attributed in large part to ear piercing. Studies have shown that the metal posts used in ear piercing release varying amounts of nickel, allowing for direct exposure to an injured cutaneous surface[29]. Traditionally, the prevalence of nickel sensitivity has been higher in women; however, with newer trends toward piercing multiple body sites by both men and women, a sex difference may become less apparent[3]. In Europe, there has been a significant reduction in nickel allergy as a result of legislation limiting nickel release from items in contact with the skin[30].

Clinically, nickel dermatitis most commonly occurs at sites of contact with earrings, necklaces, and the backs of watches (see Fig. 14.9A, Fig. 14.16A). Dermatitis of the mid-abdomen caused by a belt buckle or snap is common (see Fig. 14.16C) and eyelid dermatitis from metal eyelash curlers or eyeglasses can also be seen. Facial dermatitis due to ACD to nickel and chromate within cellular phones has been described as has a generalized eruption caused by nickel from an iPad[31].

Concomitant reactions to nickel and cobalt have been reported and may be due to the frequency with which the two metals are used in combination[32]. Of note, sweating can increase the amount of metal leached from a product. A useful test to determine whether a particular item contains nickel is the dimethylglyoxime test (see Appendix), which identifies objects that release nickel using a pink color indicator (see Fig. 14.16D).

Individuals with nickel allergy should avoid costume jewelry. They can usually wear jewelry made of stainless steel, platinum or gold, but not white gold. Some clinicians advocate coating nickel-containing surfaces such as snaps on jeans with clear nail polish (e.g. Beauty Secrets Hardener) to prevent leaching by sweat onto the skin. However, the nail polish can rub off and should be reapplied if it is effective.

Methylisothiazolinone (MI)

By 2014, patch test clinics around the world were reporting that MI was becoming their most common allergen[33]. MI was previously used in combination with methylchloroisothiazolinone (MCI) in a ratio of 3 : 1 in rinse-off products, and its concentration was <3.75 ppm. In 2005, however, regulatory changes allowed its concentration to increase to 100 ppm, and this was followed by the current epidemic. While there is increasing recognition that use of sanitary wet wipes can lead to ACD of the anogenital region and hands (see Fig. 14.8B), it should be noted that MI has also been found in make-up removal wipes (see Fig. 14.6B), sorbolene lotions, liquid soaps, shampoos, deodorants, and a number of other personal care items (see Fig. 14.9D)[34]. Paints containing MI have been associated with occupational ACD as well as airborne ACD[35].

Fragrance Mix

Fragrances are ubiquitous in our environment. They are used to provide a pleasant odor and have been used extensively for centuries. According to the NACDG, fragrances are a common allergen, with a rate of up to 12%[7].

The detection of a fragrance allergy was made easier with the introduction of a fragrance mix in the 1970s. Prior to that, fragrance allergy was identified primarily through testing with balsam of Peru, which detected only about 50% of those affected[36]. The current fragrance mix I contains eight different fragrance components (at 1% each; Table 14.10).

Fragrance mix I is the most useful tool for detecting fragrance allergy[37]. However, the composition of fragrance-containing products continually changes. Therefore, by including additional allergens such as those in fragrance mix II (see Table 14.10), the detection rate of fragrance allergy can be increased. It is estimated that ~25% of patients allergic to fragrance would be missed if fragrance mix II were not used[38].

In product formulations, fragrances can be used to provide a pleasant odor. However, they can also be used to mask an unpleasant odor – a so-called masking fragrance. This often occurs in products labeled "unscented". Patients who are identified as being allergic to fragrance must be instructed to read all labels and to avoid any product that lists a fragrance, is labeled "unscented", or has an obvious scent (see Fig. 14.15). They should be instructed to look instead for "fragrance-free" products. Unfortunately, there are several fragrance ingredients that have other purposes, i.e. they act as a preservative or emollient. These covert fragrances, e.g. balsam of Peru, benzylaldehyde, benzyl alcohol, bisabolol[39], can be used in a product and the product may still be labeled fragrance-free as long as the potentially allergenic ingredient has been identified as being used for a purpose other than fragrance. Obviously, this causes significant problems for the individual with fragrance allergy who is trying to avoid fragrances. Label reading may not always be enough unless the patient is educated about some of these practices. Complete disclosure on labels of all ingredients regardless of intended function would be helpful, but this is not yet part of industry practice in the US; by contrast, in Europe 26 fragrances must be included in the product label[40]. For the individual allergic to fragrances, repeat open application testing is very helpful in screening for an allergy to new or old products.

Hydroperoxides of Linalool and Limonene

Recently, the discovery that the hydroperoxides of linalool and limonene are more sensitizing than their parent chemicals has led to increased

ADDITIONAL IMPORTANT ALLERGENS	
Allergens	**Uses/found in**
Preservatives	
Iodopropynyl butylcarbamate	Preservative/cosmetics, personal care products
Parabens	Preservative/cosmetics, personal care products; rare allergen
Polyhexamethylene biguanide (polyaminopropyl biguanide, PHBG)	Preservative, disinfectant/cosmetics, wet wipes, wound dressings, cleaning agents (including contact lens solutions)
Preservatives – formaldehyde releasers	
2-Bromo-2-nitropropane-1,3-diol (Bronopol®)	Preservative/cosmetics, personal care products
Diazolidinyl urea	Preservative/same as above
Imidazolidinyl urea	Preservative/same as above
DMDM hydantoin	Preservative/same as above
Components of rubber products	
Carba mix	Rubber accelerator/especially gloves
Mercaptobenzothiazole (MBT), mercapto mix	Rubber accelerator/especially gloves
Thiuram mix	Rubber accelerator/especially gloves
Mixed dialkyl thioureas	Rubber accelerator/rubber, neoprene, photocopying, photography
Black rubber mix	Rubber additives (antioxidants)/black rubber products (household, sports)
Hair and nail allergens	
Glyceryl thioglycolate	Alters disulfide bonds/permanent wave solutions (“acid”, “heat”); can persist for months
Tosylamide formaldehyde resin	Film former/nail polish
Acrylates	Artificial nails/nail glues
Textile allergens	
Ethyleneurea/melamine formaldehyde resin	Thermosetting resin/permanent press clothing
Disperse blue 106 and 124	Textile dyes/darkly colored > lightly colored clothing
Adhesive allergens	
Colophony (colophonium)	Resin/adhesives, cosmetics, topical medications
Epoxy resin	Resin/adhesives
p-tert-Butylphenol formaldehyde resin	Resin/adhesives
Other	
Alkyl glucosides	Surfactants/leave-on and rinse-off cosmetics
Benzocaine	Anesthetic/topical preparations
Budesonide	Corticosteroid/topical creams, ointments
Cinnamic aldehyde	Fragrance/flavoring
Cocamidopropyl betaine	Surfactant/shampoos, cosmetics
Amidoamine	Contaminant of cocamidopropyl betaine
Dimethylaminopropylamine	Contaminant of cocamidopropyl betaine
Compositae mix	Includes *Tanacetum vulgare* (tansy) and *Ambrosia* spp. (ragweed)
DL-alpha tocopherol	Synthetic vitamin E/ointments, creams
Ethylenediamine dihydrochloride	Antihistamine/topical creams
Hydroxyethyl methacrylate	Dental restorative materials, lacquers, artificial nails, adhesives, teeth whiteners
Lanolin (wool alcohol)	Emollient/topical creams, lotions
Oleamidopropyl dimethylamine	Emulsifier/cosmetics, shampoos, baby lotions
Potassium dichromate	Metals, leather, cement
Propolis	Botanical/cosmetics, cosmeceutical, naturopathic, and homeopathic products
Propylene glycol	Emulsifier/cosmetics, topical medicaments, e-cigarettes
Sesquiterpene lactone mix	Screen for Compositae allergy
Shellac	Resin/varnishes, food coating, cosmetics
Sodium gold thiosulfate	Metal/jewelry, dental implants (clinical relevance can be difficult to determine)
Tixocortol-21-pivalate	Corticosteroid/topical creams, ointments

Table 14.7 Additional important allergens. See Table 14.6 for ‘Top 10’ allergens identified by the North American Contact Dermatitis Group.

TOP 20 ALLERGENS IN CHILDREN AND ADOLESCENTS (<18 YEARS OF AGE) AS IDENTIFIED BY THE NORTH AMERICAN CONTACT DERMATITIS GROUP	
Metals	Nickel sulfate Cobalt chloride* Potassium dichromate†
Preservatives	Quaternium-15 Formaldehyde Methylchloroisothiazolinone/methylisothiazolinone 2-Bromo-2-nitropropane-1,3-diol (Bronopol®)
Topical antibiotics	Neomycin sulfate Bacitracin
Fragrances	Fragrance mix I Fragrance mix II *Myroxylon pereirae* (balsam of Peru)
Components of rubber products	Carba mix
Other	Lanolin alcohol Propylene glycol *p*-Phenylenediamine Carmine Propolis Decyl glucoside (surfactant) Compositae mix

*Also contained in ceramics (see text).
†Also contained in leather.
Data from Zug KA, Pham AK, Belsito DV, et al. Patch Testing in Children From 2005–2012: Results from the North American Contact Dermatitis Group. *Dermatitis.* 2014;25:345–355.

Table 14.8 Top 20 allergens in children and adolescents (<18 years of age) as identified by the North American Contact Dermatitis Group.

recognition of the importance of these allergens in many fragranced products, and relatively high levels of relevant reactions have been reported (see Table 14.6). However, patch testing with these fragrances is also associated with a number of doubtful and irritant reactions[41–43].

Myroxylon pereirae

Myroxylon pereirae (balsam of Peru) is a naturally occurring fragrance and one of the more common allergens identified by the NACDG[7] (see Table 14.6); however clinical relevance is often lacking[44,45]. Because it is infrequently found in topical pharmaceuticals or fragrances, positive reactions usually relate to previous exposure to fragrances, with allergy to balsam of Peru most commonly observed in those with fragrance allergy[44,45].

Patients with a positive reaction to balsam of Peru should be counseled to avoid fragrances. Some patients suspected with clinical features of systemic contact dermatitis may benefit from a restrictive diet avoiding balsams, cinnamon, cloves, and vanilla[44].

Formaldehyde

Formaldehyde is ubiquitous. It is a colorless gas that can be found in the workplace as well as in cosmetics, medications, nail hardeners, textiles, paints, cigarette smoke, paper, and formaldehyde resins (e.g. plastic bottles)[46]. Formaldehyde can cause several different types of reactions, including ICD, ACD, contact urticaria, and mucous membrane irritation, especially of the conjunctiva and respiratory tract. Formaldehyde is present in the air, as it is released in cigarette smoke, automobile exhaust, and even hair-straightening products.

Today, formaldehyde is rarely used in personal care products or cosmetics. However, allergy to formaldehyde is commonly seen in association with other formaldehyde-releasing preservatives, such as quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, 2-bromo-2-nitropropane-1,3-diol, and tris(hydroxymethyl) nitromethane, and therefore formaldehyde-sensitive individuals should generally avoid these substances[46].

Textile dermatitis can be caused by formaldehyde resins, because the latter are used as a finish on "wash-and-wear" or wrinkle-resistant clothes. Of the various textiles, 100% polyester is believed to have the least amount of formaldehyde[17]. A study of many fabrics showed that some free formaldehyde was present in all of those tested[17]. Washing clothes, especially those that are "permanent press" or "drip dry", several times prior to wearing will decrease the amount of formaldehyde present but will not eliminate it.

As formaldehyde is so widespread, avoidance is often difficult. Clinical relevance can sometimes be difficult to determine.

ALLERGIC CONTACT DERMATITIS IN THE MODERN ERA		
Product(s)	**Allergen(s)**	**Clinical presentation**
Wet wipes, personal care products (including contact lens solution for PHMB)	Methylisothiazolinone, polyhexamethylene biguanide (PHMB)	Anogenital dermatitis (all ages) Hand dermatitis in caregivers (see Fig. 14.8B)
Glucose sensors, insulin pumps	Isobornyl acrylate, other acrylates, colophony	Dermatitis at the site of the device
Continuous positive airway pressure (CPAP) therapy	Dialkyl thioureas Components of cleansing agents	Dermatitis at edge of mask ICD more common
"Natural" botanical products resurgence plus grooming practices, e.g. beeswax-containing lip balm	Propolis	Cheilitis of both the upper and lower lip
Temporary tattoos	*p*-Phenylenediamine	Allergic reaction at site of temporary tattoo (see Fig. 14.17)
Sunscreen products	Benzophenone-3	Photoallergic contact dermatitis in sun-exposed areas, cheilitis
Surgical masks	Formaldehyde & formaldehyde releasers, nickel, rubber, aluminum, polypropylene	Facial and ear dermatitis ICD and flares of acne & rosacea more common
Personal electronic devices – mobile (cellular) phones, tablets, iPad, laptop computers, e-cigarettes	Nickel, chromate	Facial dermatitis, generalized dermatitis (see Fig. 14.9A)
Anti-mold sachets inside leather products to prevent mold formation during shipping (e.g. couches, chairs, shoes) [historical]	Dimethylfumarate	When heated, fumes are created which penetrate through leather and clothing, leading to dermatitis of the back, buttocks and posterolateral thighs if in furniture

Table 14.9 Allergic contact dermatitis in the modern era. For orthopedic implants, see Fig. 14.20. For hand dermatitis, especially in children, also consider ICD to homemade "slime"[26]. ICD, irritant contact dermatitis.

Quaternium-15

Quaternium-15 is a quaternium compound that is used as a preservative. It is an effective biocide against *Pseudomonas aeruginosa* and *P. cepacia*, as well as other bacteria and fungi. Although quaternium-15 is used in several industries, the incidence of associated occupational contact dermatitis is very low[46]. Quaternium-15 more typically plays a role as an allergen in personal care products such as shampoos, moisturizers, conditioners, and soaps. In the past, quaternium-15 and formaldehyde were reported to be the most common cosmetic preservatives to cause ACD in the US, but they have been overtaken by MI. The allergenicity of quaternium-15 can be due to its release of formaldehyde[47]. Studies have shown that up to 80% of those reacting to quaternium-15 are also formaldehyde-sensitive[44,48]. Allergy to quaternium-15 is often relevant to the patient's dermatitis[44,48].



Fig. 14.16 Allergic contact dermatitis to nickel. A On the earlobe at the site of a clip-on earring. **B** At sites of contact with nickel-containing eyeglass frames; note the erosions and linear configuration on the temple. **C** Excoriated pink plaques due to nickel within the belt buckle. **D** A positive dimethylglyoxime test in which the pink color indicates the presence of nickel, in this case in a metal clip on a badge. *C, Courtesy Julie V. Schaffer, MD.*

COMPONENTS IN FRAGRANCE MIX I AND FRAGRANCE MIX II	
Fragrance mix I	**Fragrance mix II**
• α-Amyl cinnamic aldehyde • Cinnamic aldehyde • Cinnamyl alcohol • Eugenol • Geraniol • Hydroxycitronellal • Isoeugenol • Oak moss absolute	• Citral • Citronellol • Coumarin • Farnesol • Hexyl cinnamic aldehyde • Lyral®

Table 14.10 Components in fragrance mix I and fragrance mix II. Lyral® is hydroxyisohexyl-3-cyclohexene carboxaldehyde.

In addition to coexisting with formaldehyde sensitivity, allergy to quaternium-15 can be seen in association with other formaldehyde-releasing preservatives, such as imidazolidinyl urea, diazolidinyl urea, 2-bromo-2-nitropropane-1,3-diol, DMDM hydantoin, and tris(hydroxymethyl)nitromethane[17,46,47,49]. Avoidance of quaternium-15 is possible through careful label reading. If the individual allergic to quaternium-15 is not allergic to the other formaldehyde-releasing preservatives mentioned above, they need only avoid quaternium-15. Obviously, avoidance of the other formaldehyde-releasing preservatives may be necessary depending on the patch test results. Quaternium-15, formaldehyde, diazolidinyl urea, and imidazolidinyl urea are present in T.R.U.E. TEST®. However, other formaldehyde-releasing preservatives may be missed if expanded patch testing beyond the T.R.U.E. TEST® is not performed (see Table 14.3). As a group, the quaternium amino compounds are infrequent sensitizers and the other quaternium compounds can be safely used in those allergic to quaternium-15[46].

p-Phenylenediamine

Paraphenylenediamine (PPD) is the most commonly used permanent hair colorant and it is recognized as a common cause of ACD. Once fully oxidized, the disperse dye is no longer allergenic, but in reality the chemical is not always fully oxidized. Since 1998, PPD has been found in some temporary tattoos in concentrations higher than those present in hair color products[50]. As a result, PPD has resurfaced as an allergen in a new population (Fig. 14.17). When ACD is due to PPD in permanent hair colorants, it involves primarily the forehead, neck and scalp.

Benzisothiazolinone

Isothiazolinone derivatives have potent bactericidal, fungicidal, and algicidal properties and are primarily used in non-personal care products such as household detergents and water-based paints. Of the isothiazolinone derivatives, sensitization potential is greatest for MCI > MI followed by benzisothiazolinone > octylisothiazolinone[51].

Cobalt

Cobalt is a metal that is often used in conjunction with other metals in order to add hardness and strength. It is frequently combined with nickel, chromium, molybdenum, and tungsten. This may be the explanation for the frequent finding of sensitization to cobalt in patients



Fig. 14.17 Allergic contact dermatitis to *p*-phenylenediamine in a temporary tattoo.

who are also allergic to either nickel or chromium. Specifically, ~80% of individuals with a cobalt sensitivity have a co-sensitivity to nickel (more common in women) or chromate (more common in men)[17].

Exposure to cobalt is typically through a metal, most often in jewelry, snaps, buttons, or tools. However, cobalt is also found in cosmetics, hair dyes, orthopedic implants, ceramics, and enamel as well as in cement, paints, and resins[17]. Exposure can come from hobbies such as pottery making and occupations such as bricklaying.

When patch testing to cobalt, one may see a particular reaction, described as "poral", that appears as erythematous to violaceous dots. This is not an allergic reaction but is believed to result from the allergen residing within the acrosyringia[48]. A cobalt spot test has recently been released, based on disodium-1-nitroso-2-naphthol-3,6-disulfonate[52].

Chromium

Allergic contact dermatitis to chromium occurs from two main sources, leather tanned with chromate and cement. European legislation mandating the addition of ferrous sulphate to cement has reduced the amount of hexavalent chromium in cement to less than 2 parts per million, with a dramatic decline in the number of cases of allergic contact dermatitis. Trivalent chromium is less soluble and has a low degree of skin permeation. Allergic contact dermatitis to chromium in cement has a notoriously bad prognosis[53].

Topical Antibiotics

Neomycin is an aminoglycoside that is prescribed as a topical rather than an oral medication because it has poor gastrointestinal absorption. It is the most commonly used topical antibiotic and is the most common sensitizer among the topical antibiotics[7,17]. Neomycin is found in many over-the-counter (OTC) preparations, including antibacterial ointments, hemorrhoid creams, and otic and ophthalmic preparations (see Table 14.2). It is frequently used in conjunction with other antibacterial agents, such as bacitracin and polymyxin B (e.g. Neosporin®)[49], as well as with topical corticosteroids.

Bacitracin is a topical antibiotic with activity against Gram-positive bacteria and spirochetes. It is also used in topical antibacterial creams or ointments as well as in otic and ophthalmic preparations. As noted previously, bacitracin is frequently combined with neomycin, and although the two antibacterial agents are chemically unrelated, they often show co-reactivity. This is believed to be due to sensitization to both, given how commonly they are combined in OTC products (e.g. Neosporin®)[49]. Another common combination is bacitracin plus polymyxin B (Polysporin®)[54]. In addition to ACD, bacitracin rarely causes anaphylaxis and/or contact urticaria[55].

Thimerosal

Thiosalicylic acid and ethylmercuric chloride are the two components that are combined to form thimerosal – sodium ethylmercurithiosalicylate – a preservative that is used in a few products. It is believed that the most likely cause of sensitization to thimerosal comes from its use as a preservative in vaccines[56]. Reports of sensitivity to ethylmercuric chloride and thiosalicylic acid have been published and both compounds have been found to be capable of inducing a delayed hypersensitivity reaction[56].

Many positive reactions to thimerosal are found on patch testing. Clinical relevance may be found in patients who use otic or ophthalmic drops, but in general relevance is low. Currently, thimerosal is in neither the NACDG 70 Series nor the European Baseline Series (see Table 14.3), but is still present in the T.R.U.E. TEST®.

Gold

Worldwide rates of positive gold reactions vary, and with routine testing they range from 0.8% to 10%[57,58]. In one NACDG series, 90% of gold-allergic patients were women, and there appeared to be a higher rate of nickel (33.5%) and cobalt allergies (18%) in patients with gold allergy than in the general population (14% and 9%, respectively)[59]. Similar findings have been reported in other studies[58].

When relevant, the most common clinical presentation is that of a hand, facial, or eyelid dermatitis[57,59]. One of the difficulties with gold patch testing is that the relevance of positive reactions is usually difficult to determine[57–59]. Gold sodium thiosulfate is currently not included in the NACDG 70 Series or the European Baseline Series[19].

Corticosteroids

Corticosteroids are administered in many different forms: topical, intralesional, oral, intramuscular, intravenous, inhalational, and intra-articular. They are anti-inflammatory agents and have been shown to cause ACD in 0.2%–6% of patients[60]. Corticosteroids have been reclassified into three groups based on patch test results and molecular modeling, with group 1 corticosteroids producing the most allergic reactions[61] (Table 14.11). It is suspected that ACD to these agents may be underdiagnosed, either because of insufficient testing to the allergens or perhaps owing to incomplete testing, as a later reading is often necessary because of the anti-inflammatory nature of these compounds[60]. Clinical scenarios that should raise the question of a possible allergy to topical corticosteroids include chronic dermatitis, failure to clear with topical corticosteroids, and exacerbation of dermatitis after use of topical corticosteroids.

The combination of tixocortol-21-pivalate and budesonide provides reasonable screening for corticosteroid allergy (see Table 14.11), with ~75% of corticosteroid allergic reactions detected with these allergens in one large study[60]. Positive patch test reactions to corticosteroids are often unexpected in routine testing, but are usually relevant. They are often seen with other positive reactions. Fig. 14.18 may help direct the clinician in approaching the patient suspected of having an ACD to topical corticosteroids.

In addition to the anti-inflammatory nature of corticosteroids complicating patch test interpretation, an edge effect has also been observed. During the first reading, there may be erythema only at the rim of the test chamber, with a clear center that may later become involved. This is believed to be due to the anti-inflammatory effect of corticosteroids. In the center, the corticosteroid may be concentrated, inhibiting a reaction, but be less concentrated at the rim, where a reaction may occur more readily[62].

TEXTILE DERMATITIS

Textile dye dermatitis often goes undetected because of low suspicion and a lack of routine testing with screening allergens. The allergens most likely to cause textile dermatitis are not the synthetic or natural fibers from which the textiles are made, but rather the dyes used to color them and the resins (e.g. ethyleneurea/melamine formaldehyde resin, dimethylol dihydroxyethyleneurea) used to make clothes less likely to wrinkle or shrink[63,64]. Textile dermatitis typically occurs in areas where clothing fits more tightly (see Fig. 14.9C), and it is more

CORTICOSTEROID CLASSES AND PATCH TEST CONCENTRATIONS	
Drug	**Concentration (%)***
Group 1: non-methylated, most often non-halogenated molecules (formerly A, D2, and budesonide)	
Budesonide†,‡	0.01
Cortisone acetate	25
Fludrocortisone acetate	
Hydrocortisone¶,†	2.5 ethanol (1, 2, 5, 10, 25, ethanol or petrolatum)
Hydrocortisone aceponate	
Hydrocortisone acetate¶	25
Hydrocortisone-17-butyrate†	
Hydrocortisone-21-butyrate	
Methylprednisolone aceponate	
Methylprednisolone acetate	10
Prednisolone	5 (10)
Prednisone	
Tixocortol pivalate†	
Triamcinolone	
Group 2: halogenated molecules with a C_{16}/C_{17} cis ketal/diol structure (formerly B)	
Amcinonide	0.5
Desonide	0.05
Flucinolone acetonide	0.5 (0.05, 1, 5, 10)
Flucinonide	1
Halcinonide	1
Triamcinolone acetonide†	1
Group 3: halogenated and C_{16}-methylated molecules (formerly C, D1)	
Alclometasone dipropionate	1
Betamethasone	
Betamethasone-17-valerate	1
Betamethasone dipropionate	5
Betamethasone–disodium phosphate	1
Clobetasone butyrate	0.5
Clobetasol propionate†	1
Desoximetasone	1
Dexamethasone	
Dexamethasone–disodium phosphate	1
Fluocortolone	
Fluticasone propionate	
Mometasone furoate	1 alcohol

*In petrolatum unless stated otherwise. Parentheses contain additional suggested concentrations or vehicles.
†Suggested screening agent (in *italics*); all but hydrocortisone are in the ACDS screening series (see Table 14.3).
‡Budesonide R-isomer may cross-react with acetonides in group 2.
¶Available without prescription in the US.

Table 14.11 Corticosteroid classes and patch test concentrations. Most allergic reactions are due to corticosteroids in Group 1. *Adapted from Immediate and delayed allergic hypersensitivity to corticosteroids: practical guidelines. Contact Dermatitis. 2012;66:38–45.*

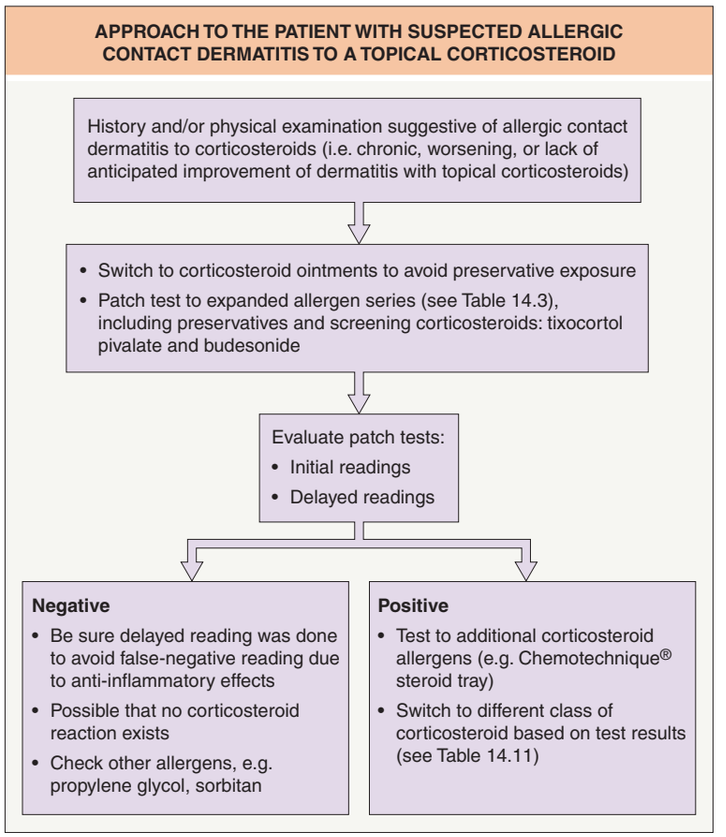


Fig. 14.18 Approach to the patient with suspected allergic contact dermatitis to a topical corticosteroid.

common in women[63]. Dyes, particularly disperse blue dyes 106 and 124, have been found to be a common cause of textile dermatitis and can be used as screening agents[63]. They frequently cross-react and positive patch test reactions can be delayed up to 7–10 days[64]. Although *p*-phenylenediamine is a disperse dye, it is not a good screening allergen for textile dye dermatitis[64]. Testing with an individual's moistened garment can also produce a relevant positive patch test reaction.

RUBBER CHEMICALS

Rubber accelerators are important causes of hand dermatitis caused by gloves, particularly in healthcare workers. Allergens include thiurams, carbamates, mercaptobenzothiazole and its derivatives, and thioureas. Of note, there is some evidence of declining frequencies of reactions to rubber accelerators[65]. ACD to rubber may coexist with an immediate hypersensitivity to natural rubber latex protein (see Ch. 16).

SYSTEMIC CONTACT DERMATITIS

Systemic exposure to a chemical may result in a widespread dermatitis. This reaction generally involves a chemical to which the patient has had a prior contact allergy; the patient is then exposed to the same chemical (or one that cross-reacts) via a systemic route, such as with an injection or oral, intravenous, or intranasal administration. This reaction is believed to be due to a delayed T cell-mediated immune response. Historically, one of the most common examples of systemic contact dermatitis was the patient with a history of ACD to ethylenediamine who then developed a diffuse dermatitis secondary to intravenous aminophylline, which contains ethylenediamine (Fig. 14.19).

Other causes of systemic contact dermatitis due to ingestion of allergens that have previously caused an ACD include antibiotics, corticosteroids, plants/plant products, propylene glycol, sorbic acid, and importantly, metals[66–73]. Marks et al.[66] reported the ingestion of cashews tainted with oil from the cashew nut shell resulting in a systemic contact dermatitis in patients with a prior history of poison ivy dermatitis. In addition, ingestion of a pesto sauce made with cashew nuts resulted in systemic contact dermatitis in the form of the "baboon syndrome" (symmetric, sharply demarcated erythema of the gluteal or inguinal area plus other intertriginous or flexural sites)[67]. Ingestion of both cashews and mangoes has been shown to cause reactions in patients sensitive to poison ivy and poison oak, as they are all members of the Anacardiaceae family (see Ch. 17).



Fig. 14.19 Systemic contact dermatitis. This patient, who was previously sensitized to ethylenediamine, received intravenous aminophylline.

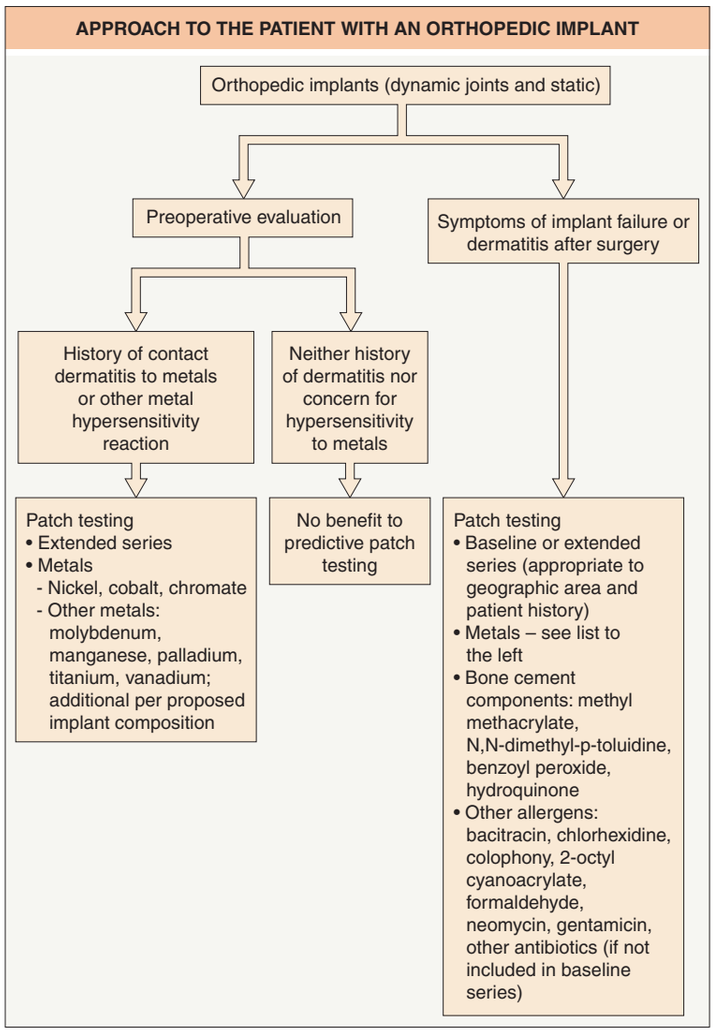


Fig. 14.20 Approach to the patient with an orthopedic implant. *Adapted from Schalock PC, Menné T, Johansen JD, et al. Contact Dermatitis. 2011;66:4–19.*

In the proper clinical setting, patch tests demonstrating a sensitivity to balsam of Peru or fragrance mixture can support the diagnosis of a systemic contact dermatitis due to balsam-related foods or spices. A diet avoiding such foods or spices may result in an improvement of the dermatitis[44,45,73].

The ingestion of metals can also cause systemic contact dermatitis, and nickel is the metal most commonly implicated[68,69]. However, the use of low-nickel diets to treat dermatitis in patients with positive patch tests to nickel is controversial, although there is increasing interest[74].

EXAMPLES OF TOPICAL ALLERGENS THAT MAY RESULT IN SYSTEMIC CONTACT DERMATITIS AFTER SYSTEMIC EXPOSURE	
Cutaneous allergen	**Systemic exposure**
Medications	
Ethylenediamine hydrochloride	Aminophylline (IV), hydroxyzine/cetirizine (po)
Quinolones	Quinolones (IV, po)
Ampicillin	Ampicillin-containing surgical solution
Neomycin	Gentamicin, streptomycin, kanamycin (IM, IV)
Topical corticosteroids	Systemic corticosteroids, e.g. prednisone, dexamethasone (IA, IL, IM, INH, IV, po)
Thiuram	Disulfiram
Metals	
Nickel and other metal salts	Nickel (and other metal salts) in food, nickel from catheter hub
Plants	
Poison ivy/oak	Cashews, mangoes
Sesquiterpene lactones	Herbal teas or food containing chamomile, chrysanthemum, wild feverfew (*Parthenium hysterophorus)*
Myroxylon pereirae (balsam of Peru)	Foods (tomatoes, citrus), sodas, spices, cough syrup, mouthwashes, toothpaste
Foods	
Formaldehyde	Aspartame (artificial sweetener)
Sorbic acid	Sorbic acid (preservative)
Propylene glycol	Emulsifier in foods and medications
Carmine[77]	Food coloring

Table 14.12 Examples of topical allergens that may result in systemic contact dermatitis after systemic exposure. IA, intraarticular; IL, intralesional; IM, intramuscular; INH, inhaled; IV, intravenous; po, oral.

The possibility of systemic contact dermatitis to metals in orthopedic implants has also been suggested, along with proposed screening recommendations (Fig. 14.20)[75]. Nonetheless, for several reasons, including the likelihood that immune reaction pathways are different for implants compared to the skin, the role of lymphocyte transformation testing remains unclear, and patch testing may neither predict future problems nor aid in the decision to remove an existing implant, this remains a topic of debate. Lastly, Fowler reported a patient with systemic contact dermatitis following ingestion of chromium picolinate, a nutritional supplement[76]. Patch testing was positive to potassium dichromate, and upon discontinuation of the chromium picolinate, the dermatitis subsided.

Examples of other cutaneous allergens and their common sources of systemic exposure are listed in Table 14.12. An extensive chapter on this subject is in *Fisher's Contact Dermatitis* textbook[68] and the reader is referred there for additional information.

AIRBORNE CONTACT DERMATITIS

When airborne allergens have contact with the skin, they may cause ACD or ICD, with a resemblance (or overlap) with photoallergic contact dermatitis and phototoxic contact dermatitis (see Fig. 87.15). Ragweed dermatitis, a good example of an airborne contact dermatitis, is most noticeable on the face (see Ch. 17)[78]. Prolonged and repetitive exposure to airborne allergens generally produces an ACD that is lichenified and dry and is predominantly located in the exposed portions of the skin: especially the eyelids, but also the face, V of the neck, arms, and legs[79]. The most common causative agents are plants, especially Compositae, fragrances, woods, rubber, preservatives, glues, metals, epoxy resins, and acrylates (Fig. 14.21A,B)[80,81].

While there are many common sources of airborne contact dermatitis, more obscure causes have been reported such as essential oils volatilized during aromatherapy or thyme dust in farmers[82–84]. There has been an increasing number of reactions to paints, especially to those



Fig. 14.21 Airborne contact dermatitis. A, **B** The allergen was an epoxy resin. Note the involvement of the eyelids. **C** The detected allergens were decyl glucoside, fragrance, thiuram, and carba mix.

containing MI or MCI[84,85], as well as to baby wipes[86]. Occupationally induced reactions appear to be the most common cause of airborne contact dermatitis. Dermatoses in exposed areas should raise the possibility of a possible airborne contact allergy, leading to a series of questions regarding possible exposure sources and to appropriate patch testing when indicated (Fig. 14.21C).

Additional figures and tables, on Simple interventions prior to patch testing, ACDS-composed exposure information sheet, and Alternatives to *p*-phenylenediamine (PPD) in hair dyes, available in our eBook (see inside front cover for access code).

APPENDIX	
Company	**Supplies**
SmartPractice Dermatology/Allergy 3400 E. McDowell Road Phoenix, AZ 85008–7899, USA Tel: (1) 800–878–3837 Fax: (1) 800–926–4568 Email: info@smartpractice.com Website: www.smartpractice.com	T.R.U.E. TEST® Finn Chambers® AllergEAZE® chambers Scanpor® tape Nickel spot test (dimethylglyoxime) Cobalt spot test (disodium-1-nitroso-2-naphthol-3, 6-disulfonate)
Chemotechnique Diagnostics Modemgatan 9 S-235 39 Vellinge Sweden Tel: +46–(0)40–46 60 77 Fax: +46–(0)40–46 67 00 E-mail: info@chemotechnique.se; order@chemotechnique.se Website: www.chemotechnique.se	ACDS Screening Series (NAE-80) NACDG Screening Series European Baseline Series Multiple national series Specific allergen panels, e.g. bakery, cosmetic, corticosteroid, dental, epoxy, hairdressing, plastic/glues, shoe, sunscreens, textile colors & finishes; photopatch series IQ, IQ Ultra™, IQ Ultimate™ chambers

APPENDIX	
Company	**Supplies**
Dormer Laboratories Inc. 5–91 Kelfield Street Toronto, Ontario M9W 5A3 Canada Tel: (1) 416–242–6167 Fax: (1) 416–242–9487 E-mail: info@dormer.com Website: www.dormer.com	Chemotechnique® products (see above)
SmartPractice Canada 720 28th Street NE Suite #210 Calgary, Alberta T2A 6R3 Canada Tel: (1) 866–903–2671 Fax: (1) 866–903–2672 Email: info@smartpracticecanada.com Website: www.smartpracticecanada.com	AllergEAZE® allergens and chambers NACDG Screening (Standard) Series Australian Baseline Series European, British, & Italian Baseline Series Japanese Standard Series Specific allergen panels (e.g. bakery, cosmetics, dental, eyelid, hairdressing, leg ulcer, photoallergens)

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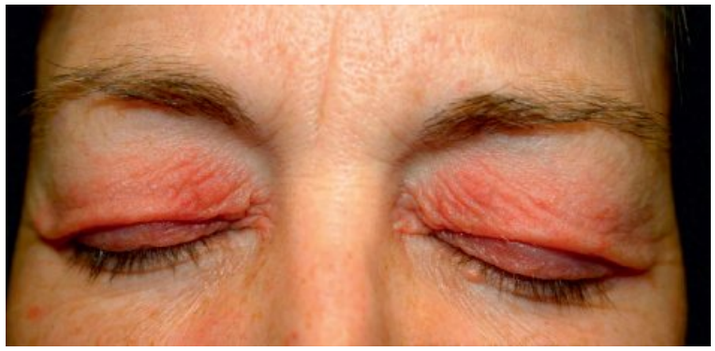
eFig. 14.1 Acute vesiculobullous allergic contact dermatitis (ACD). The culprit was the plant *Grevillea* Robyn Gordon which grows in Australia. *Courtesy Ian Hamann, MD.*



eFig. 14.2 Acute allergic contact dermatitis with a prominent component of edema. Obvious edema of the shaft of the penis plus subtle crusts of the glans due to application of tiger balm (contains extracts of several plants, including mint, clove, and Chinese cinnamon). *Courtesy Louis A. Fragola, Jr, MD.*



eFig. 14.3 Acute vesiculobullous allergic contact dermatitis (ACD). ACD to compound benzoin tincture; note the geometric shape. *Courtesy Louis A. Fragola, Jr, MD.*



eFig. 14.4 Allergic contact dermatitis to neomycin. Note the erythema and edema of the upper eyelids.



eFig. 14.5 Allergic contact dermatitis to 2-hydroxyethylmethacrylate (HEMA) in nail polish. A Dermatitis of the eyelids. **B** Positive patch test to HEMA.





eFig. 14.6 A, B Chronic allergic contact dermatitis leading to hand dermatitis. This golfer wore one leather glove and had positive patch tests to potassium dichromate and a piece of his glove.



eFig. 14.7 Persistent hand dermatitis due to chronic allergic contact dermatitis. In this bowler, the allergen was colophony contained within a tackifier. *Courtesy Ian Hamann, MD.*



eFig. 14.8 Chronic allergic contact dermatitis due to glutaraldehyde. The patient was an optometrist.



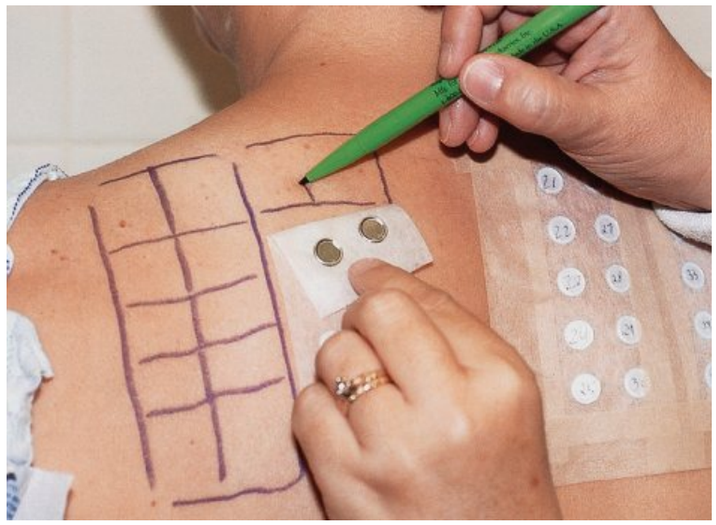
eFig. 14.9 Allergic contact dermatitis to methacrylates within shoes. *Courtesy Louis A. Fragola, Jr, MD.*



eFig. 14.10 Allergic contact dermatitis to thiuram within shoes.



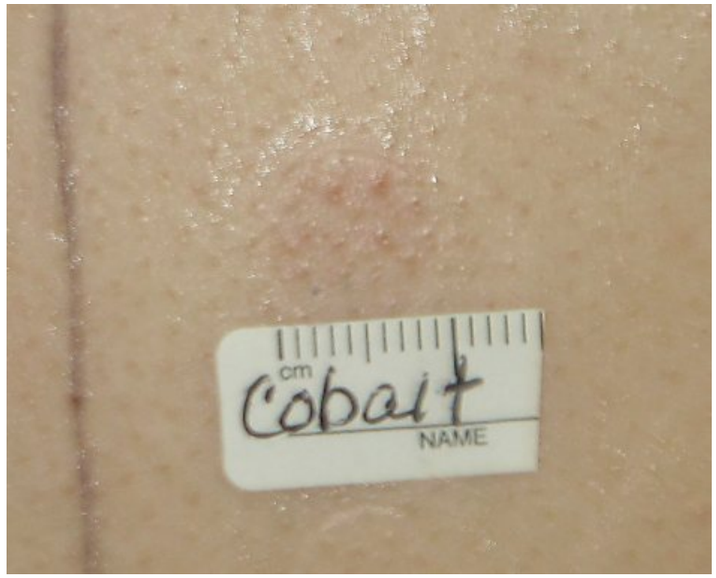
eFig. 14.11 Allergic contact dermatitis to methylisothiazolinone and cutting oil. There are multiple linear excoriations.



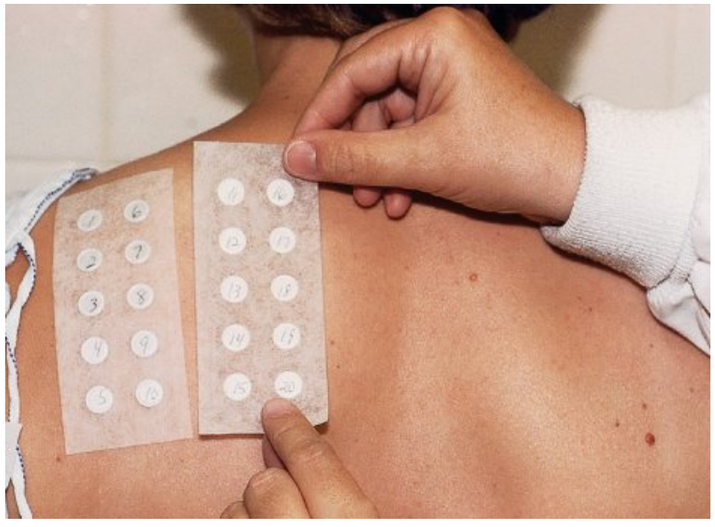
eFig. 14.14 Allergens being marked upon removal of Scanpor® tape.



eFig. 14.12 Allergens contained within syringes being placed by nurse into Finn chambers.



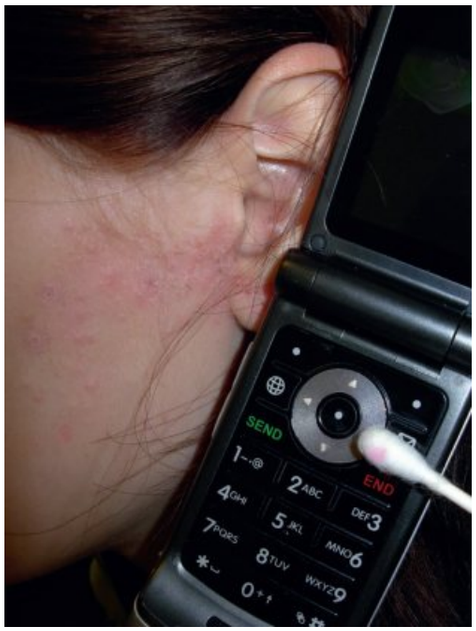
eFig. 14.15 Cobalt patch test – poral reaction. *Courtesy Lisa Garner, MD.*



eFig. 14.13 Fixing allergens to patient's back using Scanpor® tape.



eFig. 14.16 Allergic contact dermatitis to nickel within a belt buckle. An additional allergen was lanolin.



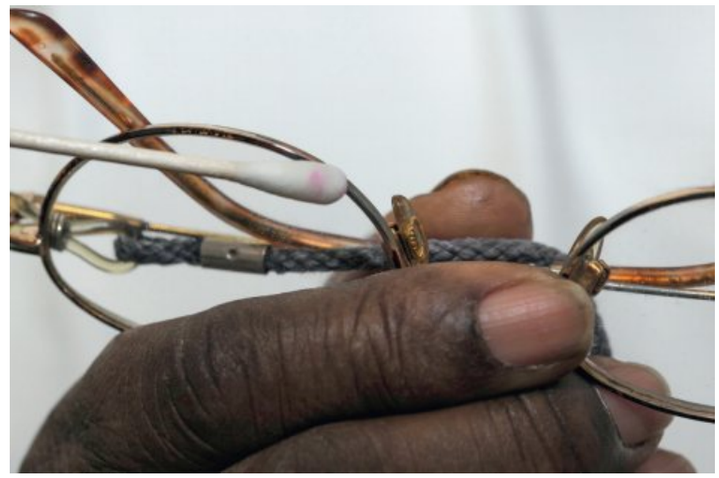
eFig. 14.17 Facial dermatitis due to nickel within a cellular phone. The latter is demonstrated by a positive dimethylglyoxime test (pink indicator).



eFig. 14.18 Allergic contact dermatitis to nickel within handcuffs. A positive dimethylglyoxime test.



eFig. 14.19 A positive dimethylglyoxime test in which the pink color indicates the presence of nickel within eyeglass frames.



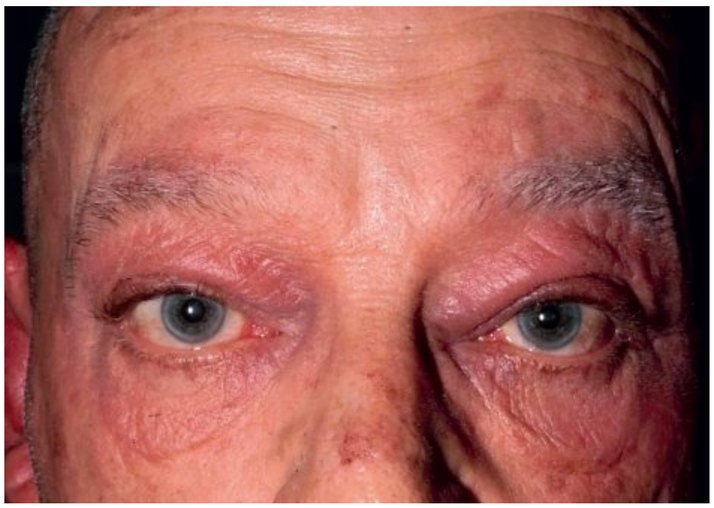
eFig. 14.20 A positive dimethylglyoxime test in which the pink color indicates the presence of nickel within eyeglass frames.



eFig. 14.21 Allergic contact dermatitis to *p*-phenylenediamine (PPD) in a temporary tattoo. *Courtesy Luis Requena, MD.*



eFig. 14.22 Allergic contact dermatitis to *p*-phenylenediamine (PPD) in permanent hair colorant. The most involved area was the border zone between the scalp and facial/retroauricular/nuchal skin. *Courtesy Jean L. Bolognia, MD.*



eFig. 14.23 Airborne contact dermatitis. Note the significant involvement of the eyelids. *Courtesy Joyce Rico, MD.*



eFig. 14.24 Airborne contact dermatitis to methylisothiazolinone.

SIMPLE INTERVENTIONS PRIOR TO PATCH TESTING FOR THE PATIENT WITH ACTIVE DERMATITIS
For all patients
• Instruct the patient to avoid the most common allergens (see Table 14.6), especially fragrance and methylisothiazolinone (e.g. switch to personal care products such as those made by Free & Clear™ or Vanicream™), and avoid irritants, especially in the occupational setting*.
• Fragrances may be found in perfumes, moisturizers, shampoos, deodorants, essential oils, diffusers, and hand washes and should be avoided where possible.
• Methylisothiazolinone may be found in shampoos, lotions, and hand washes and should be avoided where possible.
Specific tips for facial dermatitis
• Make the patient aware of the risk of airborne contact dermatitis (e.g. avoid hair sprays, scented candles, fragrance diffusers).
• Use open wet dressings followed by a medium potency, low allergenicity topical corticosteroid (group 3, formerly C & D1; see Table 14.11) for 1–2 weeks then taper.
• Ensure that the patient uses only white petrolatum as an emollient or another product that has been confirmed safe by repeat open application testing†.
• Patch test as soon as possible.
Specific tips for hand dermatitis
• Obtain an occupational and vocational history especially related to wet work and exposures; advise the patient to avoid wet work or use plastic gloves when wet work is unavoidable. Examine other sites, in particular the feet, to assess for endogenous dermatoses.
• Consider a course of oral antibiotics to treat secondary infection if fissures or crusts are present.
• Use high potency, low allergenicity topical corticosteroid (group 3, formerly C & D1; see Table 14.11) for 1–2 weeks nightly, preferably under occlusion with loose fitting plastic gloves‡; if tolerated, then taper.
• Ensure that the patient uses only white petrolatum as an emollient or another product that has been confirmed safe by repeat open application testing†.
• Patch test as soon as possible.
*See Tables 15.1 and 15.4. †Repeat open application testing (ROAT) consists of daily application of a small amount of the suspect product to an area of clear skin on the volar forearm or lateral neck for 1–2 weeks. Erythema at the site would represent a positive result that should be further evaluated by patch testing. ‡Two schools of thought regarding placing cotton gloves under plastic gloves.

eTable 14.1 Simple interventions prior to patch testing for the patient with active dermatitis.

ACDS-COMPOSED EXPOSURE INFORMATION SHEET: *MYROXYLON PEREIRAE* (BALSAM OF PERU)		
Other names		
Myroxylon pereirae, black balsam, *Toluifera pereirae* balsam, Honduras balsam, China oil		
This complex substance contains many potential allergens: benzoic acid, benzyl acetate, benzyl benzoate, benzyl cinnamate, cinnamic acid, cinnamic alcohol, cinnamic aldehyde, cinnamyl cinnamate, eugenol, farnesol, isoeugenol, nerolidol, and vanillin		
What is it?		
Balsam of Peru is a sweet-smelling natural substance derived from the bark of a tree native to Central America. For decades it has been added to topical preparations for its aroma and its antibacterial effect.		
Where might it be found?		
Hemorrhoid treatment	Rectal suppository	Diaper or medicated ointment
Burn treatment or wound spray	Analgesic rub, liniment	Baby powder
Antiseptic lotion or cream	Deodorant	Feminine hygiene spray
Chinese ointment, Tiger balm	Aromatherapy product	Consecrated oil, incense
Dental cement	Hair tonic or pomade	Shampoo, conditioner
Shaving lotion, aftershave	Perfume, cologne	Cosmetic with fragrance
Sunscreen, tanning lotion	Toothpaste, mouthwash	Lip balms, chewing gum
Cough medicine, lozenges	Scabies treatment	Tincture of benzoin
Scented cleaning product	Scented candle	Air freshener, deodorizer
Scented paper product	Pet care product	Pesticide
Violin rosin	Histology slide fixative	Scented tobacco, coffee, tea
How to avoid it:		
• Fragrances, flavorings, and natural substances are not always listed on ingredient labels. You may need to **avoid using any product with a scent or fragrance**. Be especially suspicious of things in your environment with a cinnamon, vanilla, or clove aroma. *Choose only "fragrance-free" products, since "unscented" ones may actually contain a masking fragrance*! • Read complete ingredient lists. Check the original box or package. Some products' ingredient lists can be found on the internet at the manufacturer's website or the store's website. • For possible workplace exposure, check the ingredient labels of all products encountered. Often commercial products contain a small amount of fragrance but do not list it. You may need to contact the manufacturer to find out. • Ask your doctor, nurse, attendant, hairdresser, masseuse, and others not to use fragranced products in your care. Be cautious of exposure from contact with a partner who uses fragranced products. If you must use fragranced products as you care for children, elders, or pets, wear protective rubber, nitrile, or vinyl gloves. • If there is a particular perfumed product you must use, ask your doctor how you can perform a repeat open application test (ROAT). • If you are not successful in clearing your skin rash by strictly avoiding contact with this allergen, your doctor may recommend you go on a special diet for one month to eliminate foods that may contain balsam of Peru in flavors and spices.		
Dietary restrictions to avoid *Myroxylon pereirae* (balsam of Peru)		
Avoid the following: **citrus fruits** and products that contain citrus flavor, peel, zest, or oil; **tomatoes** and tomato-containing products; **spices** such as cinnamon, cloves, vanilla, curry, nutmeg, allspice, anise and ginger as well as spicy condiments; **sweet flavorings**; **colas**, i.e. soft drinks, such as Dr Pepper, that may contain sweet flavorings and spices; and **liquors** such as wine, beer, gin and vermouth		
Related substances		
You may show a cross-reaction to some closely related substances that are derived from plants. If you are not successful in clearing your skin rash by strictly avoiding sources of balsam of Peru, you may also need to avoid these:		
Beeswax	Benzaldehyde	Benzoic acid
Benzoin	Benzyl salicylate	Colophony
Coniferyl alcohol	Coniferyl benzoate	Coumarin
Diethylstilbestrol	Resorcin monobenzoate	Resorcinol
Propolis	Storax	Tolu balsam
Wood tars		

eTable 14.2 American Contact Dermatitis Society (ACDS)-composed exposure information sheets: *Myroxylon pereirae* (balsam of Peru).

ALTERNATIVES TO *P*-PHENYLENEDIAMINE (PPD) IN HAIR DYES		
PPD-free (but may contain chemicals which can cross-react with PPD)	**Temporary dyes**	**Plant-based dyes (most include henna)**
Aveda Full spectrum protective (TDS, aminophenol)	*Truhair® by Chelsea Scott* Color & Lift	*As I am* Henna Happiness
Biokap® Nutricolor (TDS)	*Clairol* Natural Instincts (MePPD)	*Desert Shadow* Indigo shadow (indigo)
Hair Wonder Colour & care (TDS)	*ColorMark* Touch back	*Hairprint* True Color Grey Hair Restorer (no henna)
Hennaplus Long Lasting Colour (TDS, aminophenol)	*Goldwell* Elumen	*Matrix* Biolage Hair Color (henna)
Madison-Reed Radiant hair color (TDS, aminophenol)	*Hennaplus* Colour cream	*Light Mountain Natural* Hair Color (henna)
Napro Palette (TDS, aminophenol)	*SanoTint®* Reflex temporary natural hair dye	*Palette by Nature™* (henna, indigo)
L'Oreal Paris Casting crème (TD, aminophenol)	*Schwarzkopf* Keratin Color	*Sante* (indigo)
Schwarzkopf Brilliance luminance Live salon permanent Color ultime (TDS)	*Sebastian* Cellophanes	*Surya* (henna)
Wella Koleston perfect (MePPD)		**Other** (for men)
		Clubman Pinaud Black gel (beard) (iron oxides) Youthair (lead acetate) Youthair lead-free (bismuth citrate)
		Grecian Formula 16 liquid with conditioner (new formulation has bismuth citrate not lead acetate)

eTable 14.3. Alternatives to *p*-phenylenediamine (PPD) in hair dyes. MePPD, methyl-phenylenediamine; TD, toluenediamine; TDS, toluene diamine sulfate.

Irritant Contact Dermatitis 15

Emily C. Milam and David E. Cohen

Synonyms: ■ Irritant reaction ■ Irritant dermatitis ■ Irritant dermatitis syndrome ■ Irritant contact dermatitis syndrome ■ Toxic contact dermatitis ■ "Irritation" ■ "Chemical burn"

Key features

- Irritant contact dermatitis (ICD) is a localized, non-immunologically initiated, cutaneous inflammatory reaction. Its clinical characteristics are polymorphous and include erythema, scaling, edema, vesiculation, and erosions in acute cases, with erythema, lichenification, hyperkeratosis, and fissures in chronic cases
- ICD results from a direct cytotoxic effect due to single or repeated application of a chemical substance or physical insult to a cutaneous site
- ICD is a common disorder and represents an important spectrum of clinical presentations in both general and occupational dermatology, occurring when the normal epidermal barrier is disrupted and secondary inflammation develops
- Despite different pathogeneses, allergic contact dermatitis and ICD have similar clinical appearances, especially their chronic variants
- ICD is a multifactorial syndrome determined by the properties of the irritating substance as well as host and environmental factors; a dose–response relationship is related to exposure parameters such as concentration, pH, temperature, occlusion, repetition, and duration of contact
- Strong or absolute irritants such as strong acids and alkalis, as well as oxidants, produce erythema, edema, vesicles that may coalesce into bullae, oozing, and, in severe cases, necrosis and ulceration. The latter is vernacularly termed a "chemical burn"
- ICD is most often caused by cumulative exposure to weak irritants such as soap and water
- The clinical features of chronic ICD from repeated exposure to low-grade or marginal irritants (e.g. soaps, solvents, cleansers, weak acids and bases) include erythema, lichenification, excoriations, scaling, and fissures

INTRODUCTION

There are two major forms of contact dermatitis: irritant and allergic. Irritant contact dermatitis (ICD) is a cutaneous inflammatory disorder resulting from activation of the innate immune system by the direct cytotoxic effect of a chemical or physical agent, whereas allergic contact dermatitis is a delayed-type hypersensitivity immune reaction mediated by hapten-specific T cells[1].

Contact dermatitis is a matter of public health importance[1], with total direct costs exceeding an estimated $1.5 billion in the US in 2013[2]. Occupational contact dermatitis represents a significant cost to society when accounting for medical costs, workers' compensation, decreased productivity, and lost time from work[3–6]. A National Health Interview Survey suggested that in 2010, 15 million Americans were affected by occupational dermatitis[6], a figure 100-fold higher than in prior reports by the US Bureau of Labor Statistics. Overall, the impact of occupational skin diseases on both society and the individual is formidable in light of both prevalence and economic factors.

HISTORY

One of the earliest documented irritant skin reactions is in the writings of Celsus around 100 CE, who described skin ulceration resulting from corrosive metals[7]. The first accounts of occupational skin diseases focused on ill health among miners, and in 1556, Georg Agricola detailed the deep ulcers observed among metal workers. Eleven years later, Paracelsus discussed the etiology, pathogenesis, and therapy of skin changes caused by salt compounds. In 1700, Bernardino Ramazzini published a detailed treatise on the diseases of tradespeople in which he described skin disorders incurred by bath attendants, bakers, gilders, midwives, millers, and miners[7]. Physicians began to more widely recognize occupational irritant dermatitis during the Industrial Revolution with the development of new materials and chemicals, both natural and synthetic, for industrial and household use[8]. Germany and France were the first to enact laws compensating workers for industrial skin diseases.

EPIDEMIOLOGY

ICD is the most common form of occupational skin disease, estimated to constitute between 70% and 80% of all occupational skin disorders (Table 15.1)[9]. Data from the North American Contact Dermatitis Group indicate that in groups of patients with contact dermatitis, ICD (as a primary diagnosis) accounts for 9%–10% of those screened for allergic contact dermatitis via patch testing, and when hands are affected, ICD predominates over all other causes of contact dermatitis[10,11].

The US Bureau of Labor Statistics data show that occupational skin diseases accounted for a consistent 30%–45% of all patients with occupational illnesses from the 1970s through the mid-1980s. However, occupational skin disease rates have since fallen dramatically, e.g. from an average rate of 16.2 events/10 000 full-time workers in 1972 to 2.8 events in 2013[12].

Although skin disease accounted for only 17% of all recorded nonfatal occupational illnesses in 2007[13,14], it still ranks second and is only surpassed by musculoskeletal disorders. The incidence of occupational contact dermatitis in several other countries is similar to that in the US, with a range of 50 to 70 cases/100 000 workers/year[15]. In Europe, the decreasing incidence of occupational contact dermatitis has been attributed to more recently enacted legislation that limits occupational exposure to chemical agents, though a causal relationship has not been confirmed[16,17]. In 1996, the United Kingdom created a voluntary reporting system that combined information from the EPIDERM study with the occupational physicians' reporting activity (OPRA). The annual incidence of occupational contact dermatitis reported by dermatologists was 0.9 per 10 000 workers, and for occupational physicians, it was 3.1 per 10 000 workers[1,18].

In 2010, the National Institutes of Occupational Safety and Health sponsored the National Health Interview Survey which utilized a sample cohort of 27 157 individuals (to represent 229 million US civilian adults), the majority of whom were employed or recently employed[6]. The overall prevalence of dermatitis was 10.2%, ranging from 7.3% in those who never worked to 9.8% in currently employed workers to 11.8% in those recently, but not currently, employed.

In addition to manufacturing, industries with the highest nonadjusted and adjusted rates of dermatitis include healthcare and social assistance; arts, entertainment, and recreation; and accommodations and food services. Rubber chemicals, soaps and cleansers, wet work, resins, acrylics, and nickel are some of the more common sources for irritant and allergic contact dermatitis. Additional high-risk occupations are discussed in Chapter 16[1,18].

EXPOSURES TO IRRITANTS BY OCCUPATION	
Occupation	**Irritants**
Agriculture workers	Artificial fertilizers, disinfectants, pesticides, cleaners, gasoline, diesel oil, plants/grains
Artists	Solvents, clay, plaster
Automobile and aircraft industry workers	Solvents, cutting oils, paints, hand cleansers
Bakers and confectioners	Flour, detergents
Bartenders	Wet work, detergents
Bookbinders	Solvents, glues
Butchers	Detergents, meat
Cabinet makers and carpenters	Glues, detergents, thinners, solvents, wood preservatives
Cleaners	Detergents, solvents, wet work
Coal miners	Dust (coal, stone), wet conditions
Construction workers	Cement
Cooks and caterers	Detergents, vegetable juices, wet work
Dentists and dental technicians	Detergents, hand cleansers, wet work
Dry cleaners	Solvents
Electricians	Soldering fluxes
Electroplaters	Acids, alkalis
Floor layers	Solvents
Florists and gardeners	Manure, artificial fertilizers, pesticides, wet work
Hairdressers	Permanent wave solutions, shampoos, bleaching agents, wet work
Homemakers	Detergents, cleansers, foods, wet work
Hospital workers	Detergents, disinfectants, foods, wet work
Jewelers	Detergents, solvents
Mechanics	Oils, greases, gasoline, diesel fuel, cleaners, solvents
Metal workers	Cutting oils, solvents, hand cleansers
Nurses	Disinfectants, detergents, wet work
Office workers	Paper products, solvents in cleaners, adhesives, and photocopiers/toner
Painters	Solvents, thinners, wallpaper adhesives, hand cleansers
Photography industry workers	Solvents, wet work
Plastics workers	Solvents, acids, styrene, oxidizing agents
Printers	Solvents
Rubber workers	Solvents, talc, zinc stearate
Shoemakers	Solvents
Tannery workers	Acids, alkalis, reducing and oxidizing agents, wet work
Textile workers	Fibers, bleaching agents, solvents
Veterinarians and slaughterhouse workers	Disinfectants, wet work, animal entrails and secretions

Table 15.1 Exposures to irritants by occupation. *Adapted from Tovar R, Leikin JB. Irritants and corrosives. Emerg Med Clin North Am 2015;33:117–31.*

Clinical manifestations of ICD are highly variable and determined by the properties of the irritating substance as well as host and environmental factors. These include concentration, pH, mechanical pressure, temperature, humidity, and duration of contact. Low ambient humidity and cold are important factors in decreasing the water content of the stratum corneum and, consequently, increasing the permeability to irritants such as soaps, detergents, acids, bases, and solvents. Cold alone may also reduce the plasticity of the horny layer, with consequent cracking of the stratum corneum. However, in one study, the application of cold had a protective effect on the development of ICD if applied during the provocative exposure, in this case to sodium lauryl sulfate[19]. Occlusion, excessive humidity, and maceration increase the water content of the stratum corneum and compromise the stratum corneum's protective lipid bilayers, with consequent enhanced percutaneous absorption of water-soluble substances (Fig. 15.1)[20]. In addition, irritated skin may become more susceptible to superimposed allergic sensitization.

Important predisposing characteristics of the individual include age, sex, pre-existing skin disease, anatomic region exposed, and sebaceous activity. There are age-associated changes in the skin that can alter the skin's response to irritants. Both infants and the elderly are more often affected by ICD because of their less robust epidermal barrier, and they also develop more severe symptoms. While skin irritation may be seen more often on the upper extremities of women than men, this higher prevalence of ICD may be due to increased frequency of exposure rather than inherent sex differences. Genetic factors also play a role in the development of ICD, as shown in studies with monozygotic twins[21]. Patients with a history of atopic dermatitis have a 13.5 times greater risk of developing occupational dermatitis[22], and a reduction in epidermal filaggrin can reduce the inflammatory threshold for irritants[23]. Lastly, the most commonly affected sites are exposed areas such as the hands and the face, with hand involvement seen in ~80% of patients and facial involvement in 10%[15]. Excessive exposure to water, soaps and detergents, common causes of ICD, play a critical role given that wet work (immersion in water for >2 hours, occlusive protective gear, and/or hand washing >20 times/day) represents one of the most important risk factors for developing irritant dermatitis[24].

PATHOGENESIS

ICD is due to direct contact of a chemical or physical agent with the skin, which triggers activation of the innate immune response without the need for prior sensitization. Although the cellular mechanisms of ICD remain elusive, increasing evidence suggests that activated keratinocytes act as signal transducers in the control of host homeostatic responses to exogenous stimuli and they serve as key immunoregulators. An irritant chemical's ability to induce cutaneous damage may serve to trigger pattern recognition receptors (PRR), including Toll-like receptors, providing the necessary impetus to activate the innate immune system[25]. While other mediators such as prostaglandins, leukotrienes, and neuropeptides may possibly play a role, cytokines carry the most interest in ICD as they are the central mediators in T-cell recruitment and inflammation.

Several pathomechanisms have been associated with ICD, including denaturation of epidermal keratins, disruption of the permeability barrier (see Ch. 124), damage to cell membranes, and direct cytotoxic effects, with different mechanisms at work with different irritants



Fig. 15.1 Bilateral irritant contact dermatitis of the feet and ankles due to chronic occlusive footwear.

IRRITANTS AND MECHANISMS OF TOXICITY	
Irritant	**Mechanisms of toxicity**
Detergents	Barrier disruption, protein denaturation, membrane toxicity
Acids	Protein denaturation, cytotoxicity
Alcohols	Protein denaturation
Alkalis	Barrier lipid denaturation, cytotoxicity through cellular swelling
Oils	Disorganization of barrier lipids
Organic solvents	Solubilization of membrane lipids, membrane toxicity
Oxidants	Cytotoxicity
Reducing agents	Keratolysis
Water	If barrier is disrupted, cytotoxicity through swelling of viable epidermal cells

Table 15.2 Irritants and mechanisms of toxicity.

(Table 15.2). The mechanisms involved in the acute and chronic phases of ICD are fundamentally different. Acute reactions involve direct cytotoxic damage to keratinocytes, while repeated exposures to solvents and surfactants cause slower damage to cell membranes by removing surface lipids and water-retaining substances.

The pathogenic pathway in the *acute phase* of ICD, common to many chemically unrelated irritants, begins with penetration of the irritant through the permeability barrier (stratum corneum), mild damage or stress to keratinocytes, and the release of mediators of inflammation with resultant T cell activation[20]. In this manner, once activation is initiated via epidermal cells, continuous T cell activation independent of the exogenous agent may be maintained and barrier dysfunction perpetuated[26]. Tumor necrosis factor (TNF) and interleukin (IL)-1α are the major mediators, and they are capable of inducing production of other cytokines, chemokines, and adhesion molecules, leading to leukocyte recruitment to the site. Specifically, TNF, IL-6, and IL-1β upregulate expression of intercellular adhesion molecule-1 (ICAM-1)[27]. This is a predominant feature of ICD. In addition, IL-1 receptor antagonist (IL-1RA) and IL-8 increase substantially after exposure to the common irritant sodium lauryl sulfate.

In the *chronic phase* of ICD, the stratum corneum barrier is disrupted. Damage to the stratum corneum lipids (which mediate barrier function) is associated with loss of cohesion of corneocytes, desquamation, and an increase in transepidermal water loss (TEWL). TEWL is one of the triggering stimuli that promote lipid synthesis, keratinocyte proliferation, and transient hyperkeratosis during the restoration of the cutaneous barrier. However, damage with a solvent can disrupt this protective mechanism by occlusion and blockage of water evaporation, thus halting lipid synthesis and barrier recovery. After chronic exposure, the result is increased epidermal turnover manifested clinically by the chronic eczematoid irritant reaction[28].

CLINICAL FEATURES

Several different types of ICD have been described[29] (see below). Consequences of the myriad forms of ICD range from postinflammatory pigmentary changes to poorly healing ulcers (Table 15.3).

CLINICAL FEATURES SUGGESTING AN IRRITANT OR TOXIC ETIOLOGY		
Clinical feature	**Possible irritant or toxin**	
Ulcerations	Inorganic acids (chromic, hydrofluoric, nitric, hydrochloric, phosphoric, sulfuric) Strong alkalis (calcium oxide, sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, sodium metasilicate, sodium silicate, potassium cyanide, trisodium phosphate, sodium carbonate, potassium carbonate) Salts (arsenic trioxide, dichromates) Solvents (acrylonitrile, carbon bisulfide) Gases (ethylene oxide, acrylonitrile)	
Folliculitis or acneiform lesions	Oils and greases Tar and asphalt Chlorinated naphthalenes and polyhalogenated biphenyls Arsenic trioxide Glass fibers	
Miliaria	Occlusive clothing and overheating Adhesive tape Ultraviolet and infrared radiation Aluminum chloride	
Pigmentary changes		
• Hyperpigmentation	Any irritant or allergen, especially phototoxic agents such as psoralens, tar, asphalt, psoralen-containing plants Metals, such as inorganic arsenic (systemically), silver, gold, bismuth, mercury Radiation: ultraviolet, infrared, microwave, ionizing	
• Hypopigmentation	*p*-Tert-amylphenol	*p*-Cresol
	p-Tert-butylphenol	3-Hydroxyanisole
	Hydroquinone (HQ)	Butylated hydroxyanisole
	Monobenzyl ether of HQ	1-Tert-butyl-3, 4-catechol
	Monomethyl ether of HQ	1-Isopropyl-3, 4-catechol
	p-Tert-catechol	4-Hydroxypropriophenone
Alopecia	Borax Chloroprene dimers	
Urticaria	Animals (arthropods, caterpillars, corals, jellyfish, moths, sea anemones) *Myroxylon pereirae* (balsam of Peru) Cosmetics (e.g. sorbic acid) Drugs (alcohol [ethanol], benzocaine, camphor, capsaicin, chloroform, iodine, methyl salicylate, resorcinol, tar extracts) Foods (cayenne pepper, fish, mustard, thyme) Fragrances and flavoring agents (cinnamon oil, cinnamic acid and aldehyde, benzaldehyde) Metals (cobalt) Plants (seaweed, stinging nettles), woods Preservatives (benzoic acid) Textiles (e.g. blue dyes)	

Table 15.3 Clinical features suggesting an irritant or toxic etiology.

Acute Irritant Contact Dermatitis

Acute ICD, commonly seen with occupational accidents, develops when the skin is exposed to a potent irritant. The latter is capable of profound reactions on the skin surface: oxidation, reduction, desiccant, vesicant, or ion disruption[30]. The acute reaction reaches its peak quickly, usually within minutes to hours after exposure, and then starts to heal. This is termed the decrescendo phenomenon. Symptoms of acute ICD include burning, stinging, and soreness of the directly affected sites. Physical signs include erythema, edema, bullae, and possibly necrosis. These lesions are restricted to the area where the irritant or toxicant damaged the tissue, with sharply demarcated borders and asymmetry pointing to an exogenous cause. If there is no dermal injury, healing should be complete[31].

The potent irritants that most frequently lead to ICD are acids and alkalis, resulting in chemical burns.

Acute Delayed Irritant Contact Dermatitis

Acute delayed ICD is a retarded inflammatory response characteristic of certain irritants, such as anthralin (dithranol), benzalkonium chloride (preservative/disinfectant), and ethylene oxide. Adverse reactions to these chemicals are considered idiosyncratic, except when they are applied to previously injured skin, e.g. sites of xerosis or atopic dermatitis[31]. Clinically visible inflammation is not seen until 8 to 24 hours (or more) after exposure, and thus may mimic allergic contact dermatitis; however, the associated symptom is more frequently burning rather than pruritus. Sensitivity to touch and water is elicited. This form of ICD is commonly seen during diagnostic patch testing.

Irritant Reaction Irritant Contact Dermatitis

Irritant reaction ICD is a type of subclinical irritant dermatitis in individuals exposed to wet chemical environments, such as hairdressers, caterers, metal workers, or those with frequent exposures to soap and water. It is characterized by one or more of the following signs: scaling, redness, vesicles, pustules, and erosions, often beginning under occlusive jewelry (e.g. rings) and then spreading onto the fingers and then the hands and the forearms. It may simulate dyshidrotic dermatitis and ultimately result in cumulative ICD if exposure is prolonged; however, ICD tends to resolve if exposure is discontinued.

Cumulative Irritant Contact Dermatitis

Cumulative ICD is a consequence of multiple sub-threshold skin insults, without sufficient time between them for complete restoration of skin barrier function (see Fig. 16.4). It may be due to a variety of stimuli or frequent repetition of one factor, e.g. exposure to water both at the workplace and at home. Clinical symptoms develop only after the cumulative damage exceeds an individually determined manifestation or elicitation threshold, which may decrease with progression of the disease. Weak irritants do not lead to clinical ICD if they are encountered far enough apart to allow for restoration of skin barrier function. However, if the same irritant exposures follow each other closely in time, or when the manifestation threshold is reduced (e.g. in a patient with active atopic dermatitis), cumulative ICD can develop. The properties of the irritating substance, e.g. pH, solubility, detergent action, physical state, are also important. In contrast to acute ICD, the lesions of chronic ICD are less sharply demarcated. Pruritus and pain due to fissures of hyperkeratotic skin are symptoms of chronic ICD. Signs may include xerosis, erythema, and vesicles, but lichenification and hyperkeratosis predominate.

Asteatotic Dermatitis

Asteatotic dermatitis, also referred to as asteatotic eczema, eczema craquelé, or exsiccation eczematid ICD, is a special variant seen primarily during dry winter months. Elderly individuals who frequently bathe without remoisturizing are at particular risk of developing asteatotic dermatitis. Intense pruritus is common, with the skin appearing dry with ichthyosiform scale and characteristic patches of superficially cracked skin (see Ch. 13).

Traumatic Irritant Contact Dermatitis

Traumatic ICD may develop after acute skin trauma, such as from burns, lacerations, or acute ICD. Patients should be asked whether they have cleansed the skin with strong soaps or detergents. It is characterized by eczematous lesions, most commonly on the hands, that last for weeks to months with persistent redness, infiltration, scale, and fissuring in the affected areas.

Pustular and Acneiform Irritant Contact Dermatitis

Pustular and acneiform ICD results from exposure to certain irritants, such as metals, croton oil, mineral oils, tars, greases, cutting and metal working fluids, and naphthalenes (see Table 15.3 and Ch. 16). This syndrome should be considered in conditions in which folliculitis or acneiform lesions develop in settings outside of typical acne, particularly in patients with atopic dermatitis, seborrheic dermatitis, or prior acne vulgaris. The pustules are "sterile" and transient. Miliarial reactions, which may become pustular, can develop in response to occlusive clothing, adhesive tape, or ultraviolet and infrared radiation.

Non-erythematous Irritant Contact Dermatitis

Non-erythematous ICD may be defined as a subclinical form of ICD with early stages of skin irritation seen as changes in the stratum corneum barrier function without a clinical correlate.

Subjective or Sensory Irritant Contact Dermatitis

Subjective or sensory ICD is characterized by reports of a stinging or burning in the absence of visible cutaneous signs of irritation. Irritants capable of eliciting this reaction include propylene glycol, hydroxy acids, ethanol, and topical medications such as lactic acid, azelaic acid, benzoic acid, benzoyl peroxide, mequinol, and tretinoin. Sorbic acid, a preservative in concentrations of up to 0.2% in foods, cosmetics, and drugs, may also produce sensory irritation in predisposed individuals. This reaction to irritants such as lactic or sorbic acid may be reliably reproduced with dose responsiveness in double-blinded exposure tests.

Airborne Irritant Contact Dermatitis

Airborne ICD develops in irritant-exposed sensitive skin of the face and periorbital regions. While this often simulates photoallergic reactions, involvement of the upper eyelids, philtrum, and submental regions in patients with airborne ICD may aid in distinguishing between these two entities. Airborne ICD results from exposure to floating dusts, fibers (particularly fiberglass), fragrances, woods, and volatile solvents and sprays[32].

Frictional Irritant Contact Dermatitis

Frictional ICD is a distinct ICD subtype resulting from repeated low-grade frictional trauma. It is often acknowledged to also play an adjuvant role in allergic contact dermatitis and ICD. The frictional response includes hyperkeratosis, acanthosis, and lichenification, often progressing to hardening, thickening, and increased toughness. It often involves the fingers of the dominant hand. Frictional ICD has been associated with repetitive handling of paper, carbon, fabric and plastic bags; driving (due to repetitive gripping of the steering wheel and gear stick); and rubbing from clothing or sports equipment, as in golf and fishing[33].

Contact Urticaria

Contact urticaria is divided into non-immunologic and immunologic subtypes (see Ch. 16), with the former occurring more frequently and in the absence of previous exposure. Irritants that can produce *immunologic* contact urticaria include parabens (preservatives), henna, ammonium persulfate (oxidizing agent), and latex. *Non-immunologic* contact urticaria can be caused by a number of exposures, from caterpillars and jellyfish to stinging nettles and foods (see Table 15.3)[34]. Risk factors include atopy, hand dermatitis, previous mucosal exposure to latex (e.g. urinary catheterization), and allergies to fruits (e.g. kiwi, avocado; see Table 16.6).

PATHOLOGY

The histopathologic features of ICD vary according to the nature of the irritant, but often include variable spongiosis, necrosis of keratinocytes, and an inflammatory infiltrate rich in neutrophils. The combination of a neutrophil-rich superficial perivascular infiltrate plus widely scattered necrotic keratinocytes is most typical; sometimes there is even full-thickness epidermal necrosis and subepidermal clefting. Mild ICD can resemble allergic contact dermatitis. Over time, additional histologic findings include acanthosis with mild hypergranulosis and hyperkeratosis. In aggregate, these elements are not specific, and they cannot be confidently differentiated from either chronic allergic contact dermatitis or other types of chronic eczemas[35].

CLASSIFICATION OF IRRITANT CHEMICALS

Acids

A variety of both inorganic and organic acids can be corrosive to the skin. Acids cause epidermal damage via protein denaturation and cytotoxicity. Principally, all strong acids give the same clinical features, including erythema, vesication, and necrosis (Fig. 15.2).

Inorganic acids are commonly used in industry, especially hydrofluoric, sulfuric, hydrochloric, chromic, nitric, boric, and phosphoric acids (Table 15.4). Hydrofluoric acid and sulfuric acid cause the most severe



Fig. 15.2 Chemical burn due to hydrochloric acid. Development of erythema, edema, and bullae, some of which are hemorrhagic. *Courtesy Eugene Mirrer, MD.*

burns, even at low concentrations, and significant absorption may lead to systemic toxicity[36].

In general, organic acids tend to be less irritating. Among the organic acids, acetic, acrylic, formic, glycolic, benzoic, and salicylic acids are the most common irritants, particularly after prolonged exposure. The uses and properties of *acrylic acid* and *formic acid* are outlined in Table 15.4. *Acetic acid* is a constituent of vinegar, flavoring agents, and astringent mouthwashes, whereas *glycolic*, *benzoic*, and *salicylic acids* are mild irritants whose properties can be harnessed for therapeutic and cosmetic purposes, when used in low concentrations.

Alkalis

Alkalis or bases often cause more painful and severe damage than most acids, with the exception of hydrofluoric acid. There are generally no vesicles, but rather necrotic skin that first appears dark brown, then black, and ultimately becomes hard, dry, and cracked. Alkalis disrupt barrier lipids and denature proteins with subsequent fatty acid saponification, thus subjecting the cell to edema and resultant cytotoxicity. The emulsifying effect of soaps formed in the process facilitates the further penetration of the alkali into the deeper layers of the skin. Strong alkalis include sodium, ammonium, calcium, and potassium hydroxide; sodium and potassium carbonate; and calcium oxide, used primarily in the manufacture of bleaches, dyes, vitamins, pulp, paper, plastics, and soaps and detergents[37,38]. Calcium hydroxide is liberated from wet cement, which has an initial pH of 10–12 that rises to 12–14 as the cement sets (see Table 15.4).

Metal Salts

Metals represent an important and commonly encountered group of irritants, with irritant reactions to metal salts ranging from folliculitis and pigmentary changes to ulceration (see Table 15.4).

Solvents

A wide variety of solvents are used daily in processes such as chemical reactions, hydraulic systems, metal refining, dry cleaning, and metal degreasing. Nearly all are primary irritants to varying degrees (see Table 15.4), with only a few, such as turpentine, also being able to elicit allergic sensitization. Solvents act mainly by dissolving the intercellular lipid barrier of the epidermis, thereby substantially compromising barrier function. Prolonged skin contact can result in severe dermatitis as well as symptoms and even death from systemic absorption, making early recognition of skin manifestations important in the prevention of systemic toxicity. After repeated exposure, the hands, and occasionally the hands and face, develop erythema, scaling and dryness, eventually evolving into eczema (Fig. 15.3). The irritating capacity of organic solvents, attributed mainly to their lipophilicity, follows the order: aromatic > aliphatic > chlorinated > turpentine > alcohols > esters > ketones[39]. In the common clinical scenario of solvent then soap and water exposure, there is a synergistic degradation of epidermal barrier function, pointing to the importance of personal protection and hygiene[40].

Alcohols/Glycols

Alcohols are used widely as solvents, disinfectants, preservatives in cosmetics, and penetration enhancers in drug delivery systems; most have only mild irritating effects. Alcohols are the safest known topical antiseptic compounds, providing bactericidal activity against most Gram-positive and Gram-negative bacteria as well as many fungi and viruses. Most appropriate for this use are diluted solutions of ethyl alcohol, propyl alcohol, and isopropyl alcohol, which act by means of protein denaturation. In cosmetics, alcohol is used as a preservative to prevent microbial contamination and to decrease viscosity. The principal mechanism by which alcohols enhance percutaneous absorption is hypothesized to be the extraction of intercellular lipids from the stratum corneum[41,42].

Glycols, or diols, such as ethylene glycol and propylene glycol, are aliphatic alcohols commonly used in cosmetic products as solvents, emulsifiers, humectants, or keratolytics. Propylene glycol can produce both allergic and irritant contact dermatitis and sources of exposure include personal care products, topical corticosteroids, and other topical medications[43]. Of note, propylene glycol is typically used in cosmetics in concentrations <50%[44].

Detergents and Cleansers

A detergent includes almost any surface-active agent (surfactant) that concentrates at oil–water interfaces and holds both cleansing and emulsifying properties. Detergents most commonly cause chronic forms of ICD and are present in skin cleansers, cosmetics, and household cleaning products. With normal use, ICD is rare from skin cleansers, the exception being in individuals with susceptible skin. Detergents' cleansing actions are derived from their ability to lower the surface tension between two non-mixable phases due to their hydrophilic (polar head) and lipophilic (apolar tail) components. Skin toxicity arises from their damaging influence on the stratum corneum, which impairs barrier function (Fig. 15.4). Surfactants concomitantly bind to keratin and cause protein denaturation. When the stratum corneum is disrupted, detergents can damage viable epidermis and papillary dermal structures.

Irritancy from detergents is best evaluated by measuring TEWL since the latter represents the surrogate measurable change indicative of irritancy damage from this group of chemicals. As a group, anionic detergents such as alkyl sulfates and alkyl carboxylate salts (soap) are more irritating than are amphoteric and non-ionic groups. Sodium lauryl sulfate, an anionic detergent, is often used as a reference irritant in studies because of its consistent, non-allergic, rapid toxic response. Amphoteric surfactants such as *cocamidopropyl betaine* – which are used in therapeutic formulations, personal care products, and cosmetics – have the lowest irritation potential[45,46]. *Cocamide DEA* (diethanolamine), a non-ionic biodegradable surfactant, is used as a viscosity booster, stabilizer, and foam booster; it is found in hand soaps, liquid shampoos, detergents, and dishwashing liquids. Of note, cocamide DEA is one of the more irritating surfactants[47], and it is commonly involved in occupation-related contact dermatitis in North American healthcare workers[48]. In contrast, *cocamide MEA* is minimally irritating and can be used in a concentration of up to 10% in leave-on products[49].

Skin cleansers may be solid or liquid, based on soap and/or synthetic detergents, and may contain solvents or abrasives, depending on use requirements (see Ch. 153). Although the primary factor that determines skin irritancy is the detergent component, skin tolerance cannot be adequately predicted from the composition of products alone. Such an assessment is largely left to trial and error or repeated skin challenges in volunteer cohorts.

Disinfectants

Most disinfectants used to destroy pathogens in the environment act as weak toxic agents and cause chronic ICD as a result of cumulative doses of subclinical irritancy (Fig. 15.5). Various compounds may be used, such as alcohols (see above), aldehydes, phenolic compounds, halogenated

IRRITANT CHEMICALS: USES, PROPERTIES AND SIDE EFFECTS		
Compound	**Uses/exposures**	**Properties and side effects**
Inorganic acids		
Chromic acid	• Metal treatments (chrome plating, copper stripping, aluminum anodizing)	• Ulcerations known as "chrome holes" • Nasal septal perforation
Hydrochloric acid	• Production of fertilizers, dyes, paints, and soaps • Electroplating, oil refining, and food processing	• Erythema, vesication, and necrosis (Fig. 15.2)
Hydrofluoric acid	• Semiconductor industry (etching glass, metal, and stone; can dissolve silicon) • Household and commercial rust, stain, and lime-scale removers	• Extremely cytotoxic agent that can lead to severe tissue damage • Penetrates intact skin due to its limited dissociation constant • Painful penetration may continue for days after exposure • With low concentrations, the onset of symptoms may be delayed for up to a day • Intense pain is due to the capacity of fluoride ions to bind tissue calcium, thereby affecting nerve conduction • Hypomagnesemia and a fluoride-mediated increase in pulmonary vascular resistance may also play a role in toxicity
Nitric acid	• Production of fertilizers and explosives; metal etching and cleaning • Fuming nitric acid – a chemical intermediate used in rocket fuels and as a laboratory reagent	• Chemical burns • Irritant contact dermatitis • Distinctive yellow discoloration • Fuming nitric acid – highly corrosive
Phosphoric acid	• Phosphate fertilizer, pharmaceuticals, water treatment, animal feeds, soaps and detergents, and cotton dyeing	• Erythema, vesication, and necrosis
Sulfuric acid	• Manufacture of fertilizers, inorganic pigments, textile fibers, explosives, pulp, and paper • Occupational risk: jewelers, electroplaters, metal cleaners, and storage battery makers	• Erythema, vesication, and necrosis
Organic acids		
Acrylic acid	• Monomer for acrylic plastics, synthetic resins, dentures, artificial nails, adhesives, and paints	• Highly irritating and corrosive • Capable of penetrating rubber gloves • Also allergic contact dermatitis
Formic acid	• Neutralizer in leather manufacturing, an antiseptic in brewing, and a coagulant in the production of natural latex	• Greatest corrosive potential of the organic acids
Alkalis		
Cement (mixed with water)	• Construction	• Acute ulcerative damage as a result of the high alkalinity of wet cement (due to liberation of calcium hydroxide) • Necrotic skin changes appear 8–12 hours after exposure • Chronic irritant cement dermatitis – develops over months to years from continued exposure; can accompany allergic contact dermatitis to chromium • Most common locations – lower limbs (kneeling, contaminated footwear), hands (glove contamination)
Metal salts		
Arsenic compounds (including arsenic trioxide)	• Aerosolized during the smelting of copper, gold, lead and other metals • Manufacture of pesticides and herbicides • Semiconductor industry and smelting operations	• Persistent folliculitis • Potential for systemic toxicity (see Ch. 88)
Beryllium	• Production of hard, corrosion-resistant alloys	• Ulcerated granulomatous skin lesions (local reaction; see Ch. 94) • Sarcoidosis-like granulomas of the skin and lung (systemic reaction)
Calcium oxide (quicklime)	• Manufacture of pulp, steel, and paper	• Releases heat on contact with water, causing painful cutaneous ulcerations
Cobalt salts	• Alloys, ceramics, electroplating, electronics, magnets, paints, varnishes, and hair dyes	• Irritant and allergic contact dermatitis
Copper salts (e.g. sulfates, oxides, cyanides)	• Used as a biostatic surface and in wood preservatives and fungicides	• Impart a greenish-black color to hair, skin, and teeth if persistent exposure to dust forms • Inhalation of copper oxides (as well as magnesium and zinc oxides) can cause metal fume fever, a brief influenza-like illness usually associated with welding operations

Table 15.4 Irritant chemicals: uses, properties and side effects.

IRRITANT CHEMICALS: USES, PROPERTIES AND SIDE EFFECTS		
Compound	**Uses/exposures**	**Properties and side effects**
Mercury, inorganic	• Products containing inorganic mercury have been banned in US since 1990 • Imported skin-lightening creams* • Limited exposure possible from old cans of latex paint	• Bluish linear pigmentation of the tongue and gums, which may serve as a marker for systemic mercury poisoning
Mercury, organic	• Phenyl mercury salts are used as preservatives in cosmetics and vaccines, as fungicides, herbicides and pesticides in agriculture, and in dental restorative materials	• Although once used as skin disinfectants, both irritant and allergic contact dermatitis have restricted its use • Positive patch tests to mercury (as well as other metals such as gold) observed in patients with oral lichenoid reactions to dental materials (see Ch. 11)
Selenium compounds (including sulfide)	• Therapeutic shampoo (selenium sulfide)	• Skin irritation, conjunctivitis
Thimerosal	• Topical medicaments, vaccines, and cosmetics	• Common cause of both allergic and irritant patch-test reactions
Solvents		
Benzene	• Manufacture of polymers, plastics, resins, adhesives, rubber, lubricants, dyes, detergents, drugs, explosives, and pesticides	• Petechial eruption of the trunk, extremities, and mucous membranes • Petechiae considered to be a marker for aplastic anemia
Chlorinated hydrocarbons (e.g. carbon tetrachloride, trichloroethylene, tetrachloroethane, methylene chloride, ethylene chloride)	• Production of vinyl chloride, which is then converted to polyvinyl chloride • Pesticides • Dry cleaning	• Cutaneous irritation • Systemic effects: liver and kidney damage, CNS depression, and carcinogenesis • Methylene chloride can hydrolyze to form hydrochloric acid, thus leading to significant cutaneous irritation (see above) • "Degreaser's flush" – sudden erythema in extensive areas of the face, neck, and shoulders; caused by alcohol ingestion shortly before or during inhalation of trichloroethylene
Coal tar derivatives (e.g. toluene, xylene, ethyl benzene, cumene)	• Medications • Solvents	• Skin drying and defatting • Exposure solely to vapors can cause xerosis
Petrochemicals (e.g. gasoline, hexane, kerosene, Stoddard solvent)	• Fuels • Insecticides • Dry cleaning • Hexanes – gasoline, glues, and for extraction of cooking oils from seeds	• Irritant contact dermatitis • Absorption of hexane via inhalation or percutaneously can cause paresthesias, hypoesthesia, and motor weakness
Disinfectants		
Aldehydes (e.g. formaldehyde, glutaraldehyde, hexamethylene-tetramine)	• Disinfectants, biocides • Tissue fixative, embalming agent • Adhesives, resins	• More irritating than alcohols • Formaldehyde – high chemical reactivity with proteins; both allergen and irritant, even at low concentrations
Ethylene oxide	• Sterilization of medical equipment	• Oxidizing agent • Severe chemical burns
Halogens – Chlorines	• Disinfectants, including wounds† • Bleach (sodium hypochlorite) • Sanitizers for swimming pools, hot tubs	• Denature proteins via deaminating or chlorinating amino acids • Oxidizing agent (sodium hypochlorite) • Acute skin and mucosal irritant reactions, particularly at high temperatures
Halogens – Iodines	• Broad-spectrum antimicrobial and sporicidal agents • Surgical scrub, shampoo, and skin cleanser (povidone-iodine in a surfactant base)	• Inhibit DNA, RNA, and protein synthesis • Irritant contact dermatitis • Contact urticaria
Phenolic compounds (e.g. Lysol® [cresol and soap solution], pentachlorophenol, chloroxylenol)	• Disinfectants • Preservative in over-the-counter products (baby powders, shampoos), especially chloroxylenol	• Irritant contact dermatitis • Chemical leukoderma (amyl- and butyl-phenol compounds; see Table 15.3)
Quaternary ammonium salts (e.g. benzalkonium chloride)	• Cosmetics, medications (e.g. ophthalmic solutions) • Antiseptics (e.g. cleaning of surgical instruments) • Detergent	• Cationic surfactants that can precipitate or denature proteins and destroy microorganisms • Local skin irritation depends on the solution concentration • Benzalkonium chloride – irritant reactions frequent during patch testing (concentration, 0.1%); can also be an allergen (e.g. healthcare workers, leg ulcer patients) so clinical correlation required

*Rarely organic mercury.
†Dakin's solution contains sodium hypochlorite; EUSOL (Edinburgh solution of lime) contains chlorinated lime and boric acid.

Table 15.4 Irritant chemicals: uses, properties and side effects. Glycols/alcohols and detergents/cleansers are discussed in the text.



Fig. 15.3 Bilateral irritant contact dermatitis of the palms secondary to repeated contact with paint solvents. Extensive patch testing excluded allergic contact dermatitis in this professional paint and crayon illustrator. *Courtesy Kalman Watsky, MD.*



Fig. 15.4 Irritant contact dermatitis caused by playing with slime composed of school glue, food coloring, and laundry detergent. Note the involvement of the web spaces. Components of homemade slime typically include glue, dye, and sodium borate (borax powder or within detergents) or boric acid. *Courtesy Emily Berger, MD.*

compounds, and quaternary ammonium salts (see Table 15.4), in addition to dyes, oxidizing agents, and mercury compounds[50–52].

Dyes of the triphenylmethane family are extensively used as topical antiseptics; they are capable of producing phototoxic dermatitis but uncommonly cause irritant reactions. Benzoyl peroxide is a common *oxidizing agent* used as a topical antimicrobial medication that is capable of causing mild irritation. Most *mercury* compounds induce skin irritation by protein precipitation, but have fallen into disuse as a result of hazards of systemic toxicity.

Plastics

Plastics are synthetic macromolecular end-products consisting of large polymers formed by the linkage of small monomers into large chain-like units. A large number of plastic resins are commercially important and they can be divided into three categories:

- thermoplastics – polyacrylates, polyethylene, polystyrene, polyvinyl chloride, and saturated polyesters
- thermosettings – epoxy resins, phenol–formaldehyde resins, and polyurethanes
- elastomers – synthetic rubbers.

Skin damage is almost exclusively attributable to the monomer ingredients, hardeners, and other additives such as stabilizers. The final hardened plastic product is generally considered inert and non-hazardous to the skin, but residual non-polymerized monomers may be the offending agents. Both irritant and allergic contact dermatitis are common, and they may only be differentiated by patch testing[53].



Fig. 15.5 Irritant contact dermatitis of the hands due to chronic exposure to disinfectants. *Courtesy Antonio Torrelo, MD.*

Food and Plants

Food and food additives often contain compounds that elicit contact sensitivity and irritation, particularly in those working in agriculture, fishing, catering, and food processing industries. Much of the work in these sectors is done without gloves under damp working conditions with frequent hand washing – factors further aggravating skin irritation. Mechanical, thermal, and climatic factors also contribute. A large majority of exposed persons in food handling and fishing professions may be affected by chronic irritant hand dermatitis[54]. Slight irritant skin changes are often accepted as "normal" for the patient's occupation and medical advice is often not sought.

Examples of foods that can lead to ICD include pineapples, which contain the proteolytic enzyme bromelain (bromelin), and garlic, which contains allicin and diallyl disulfide. Irritant dermatitis and chemical burns have occurred from the homeopathic use of garlic as well as apple cider vinegar (contains acetic acid; see Fig. 90.7)[55]. Foods can also lead to contact urticaria (see Table 15.3) and protein contact dermatitis; both of these entities are discussed in detail in Chapter 16.

Additional food-associated and plant-derived irritants are outlined in Table 15.5 and the latter are discussed in Chapter 17.

Water

Water, the universal solvent, is a particularly ubiquitous skin irritant. Wet workers such as hairdressers, hospital cleaners, cannery workers, and bartenders have an increased incidence of hand eczema, with frequent exposure to water via hand washing directly correlating with the development of irritant hand dermatitis[24]. Several mechanisms such as osmolarity, pH, hardness, and temperature might account for the irritancy of water. Stratum corneum hydration may facilitate penetration of polar and non-polar substances through connections in the lacunar network (see Ch. 124) as well as support the overgrowth of pathogenic organisms. The irritancy of water is often exacerbated by occlusion, as it changes the barrier properties of the stratum corneum[56].

Bodily Fluids

Urine, feces (especially in the setting of diarrhea), and saliva can lead to ICD. In babies, irritant diaper dermatitis is a common problem and is often characterized by glazed erythema of convex surfaces and at the diaper margins, with sparing of the skin folds; edema, scaling, and superficial erosions may also be observed (see Fig. 13.12). Chronic diarrhea and incontinence can result in similar problems in the elderly[57].

CHEMICAL COMPOUNDS IN PLANTS RESPONSIBLE FOR CHEMICAL IRRITANT CONTACT DERMATITIS			
Irritant	**Mechanism of action**	**Clinical features**	**Example of plants**
Bromelain	Proteolytic activity	Cutaneous irritation	Pineapple
Capsaicin	Binds to vanilloid receptors on sensory neurons	Cutaneous burning and erythema	Hot pepper
Isothiocyanates (mustard oils)	Readily react with amino groups of proteins in the skin and mucosae	Short-lived cutaneous burning and erythema; urticarial Ocular irritation	Mustard, cabbage, brussels sprouts, broccoli, cauliflower, radishes
Nicotine	Antagonist for nicotinic receptors in the peripheral and central nervous systems	Cutaneous irritation	Tobacco
Phorbol esters	Bind to phospholipid-dependent membrane receptors	Cutaneous pain, erythema, edema, and blistering Conjunctivitis and even blindness	Texas croton, castor bean
Protoanemonin (ranunculol)	Disrupts disulfide bonds, resulting in subepidermal separation	Cutaneous burning and erythema Irritation of conjunctivae and nasal airway	Buttercups, columbine (when wounded)

Table 15.5 Chemical compounds in plants responsible for chemical irritant contact dermatitis. For additional causes, see Table 17.6.

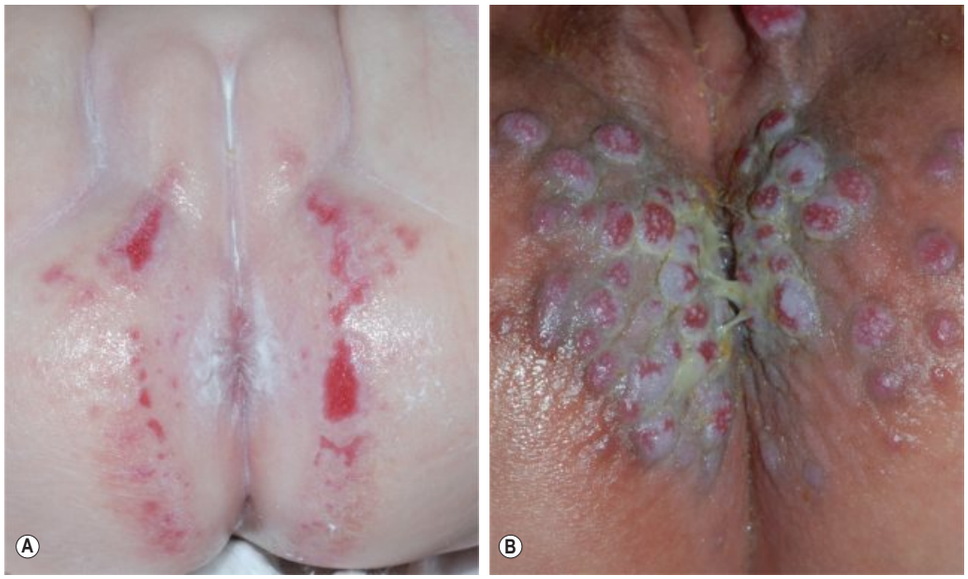


Fig. 15.6 Granuloma gluteale infantum, a form of chronic irritant contact dermatitis. Chronic exposure to urine and feces can lead to erosions and ulcerations (**A**); also referred to as Jacquet erosive dermatitis, as well as pseudoverrucous papules and nodules or erosive papulonodular dermatosis (**B**). *Courtesy Julie V. Schaffer, MD.*

In both children and adults, long-standing irritant dermatitis in the anogenital region can lead to papules and nodules (granuloma gluteale infantum [adultorum]; pseudoverrucous papules and nodules) as well as punched-out erosions and ulcerations (Jacquet erosive dermatitis) (Fig. 15.6)[58]. Predisposing factors, in addition to prolonged exposure to urine or stool, include occlusion, candidal infection, and topical corticosteroid use. Histologically, epidermal hyperplasia, a variably dense mixed inflammatory infiltrate in the dermis, and vascular proliferation are typically observed. The term erosive papulonodular dermatosis has been suggested as an overarching term to describe this spectrum of reactive changes. Of note, similar changes can be seen in submammary and peristomal skin. Although barrier creams and topical antifungal agents may have some benefit, the condition tends to persist until the irritant trigger is eliminated.

Children, more so than adults, develop the habit of lip licking. In these patients, irritant dermatitis may involve the perioral skin as well as the lips (Fig. 72.16A). In a series of 75 patients with cheilitis who were referred for patch testing, ICD was the most common cause of cheilitis[59,60]. Figure 72.15 outlines distinguishing features of the various forms of cheilitis, including that due to ICD. Periurethral ICD may be seen in patients with bladder-drained pancreatic allografts and in those receiving foscarnet.

DIFFERENTIAL DIAGNOSIS

Despite their different pathogeneses, allergic and irritant contact dermatitis, especially of the chronic type, show a remarkable similarity with respect to clinical appearance, histopathology, and immunohistology. Clinically, the reactions often look identical, with erythematous plaques, xerosis, scaling, fissures, and lichenification locally distributed and sharp borders delineating the areas of contact. In the clinical setting, the substance in question is often unknown, as is the concentration and duration of exposure. As a result, the diagnosis of ICD has remained a diagnosis of exclusion – when the dermatitis cannot be explained by a positive patch test to a known allergen. Another helpful, but not conclusive, clinical feature is the more frequent complaint of burning, pain, and stinging with ICD, in contrast to pruritus in areas of allergic contact dermatitis (Fig. 15.7).

PROGNOSIS

In many individuals, ICD resolves spontaneously even with continuous exposure, a process referred to as "accommodation" or "hardening"[61]. The exact mechanisms are still unclear, but the following changes have been observed after repetitive cutaneous exposure to irritants:

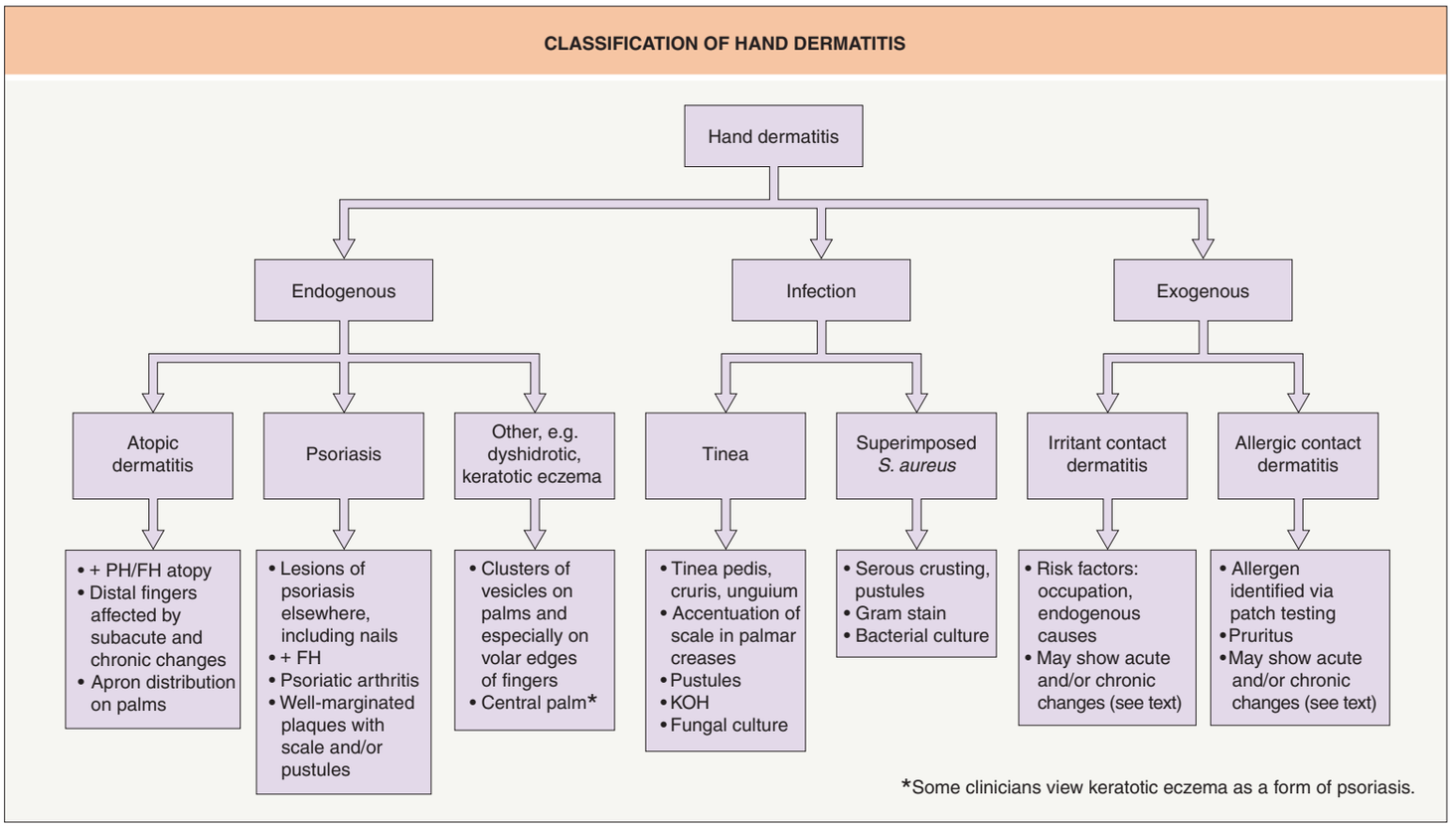


Fig. 15.7 Classification of hand dermatitis. More than one etiology may be present, e.g. atopic dermatitis plus irritant contact dermatitis. Keratolysis exfoliativa is usually not confused with hand dermatitis. Also see Figure 17.1. FH, family history; PH, personal history. (For further details, see Seidenari S, Giusti F, Pepe P, Mantovani L. Contact sensitization in 1094 children undergoing patch testing over a 7-year period. *Pediatr Dermatol.* 2005;22:1–5.)

- improvement of the physical barrier via formation of a thicker stratum corneum and a thicker stratum granulosum as well as increased production of ceramide 1
- increased skin permeability to irritants plus changes in vascular reactivity that allow faster removal of irritants
- immunologic alterations that favor an anti-inflammatory response to irritants, e.g. increased ratio of IL-1Ra (an anti-inflammatory cytokine) to IL-1α (a proinflammatory cytokine)
- a systemic hyporeactive state following repetitive exposure to low-dose irritants[61].

The time required for "accommodating" to the aggravating stimulus varies among individuals, and for some individuals, ICD can be a chronic and devastating problem. Poor prognosis is related to a previous history of atopy, female sex, and the presence of allergic contact dermatitis (as well as ICD). Factors that can potentially improve prognosis are early diagnosis, treatment, and patient knowledge about the disease[62].

TREATMENT

Avoidance of causative irritants in the home or the workplace is the primary treatment for ICD. Strategies in the prevention of ICD include the identification of irritants with appropriate substitution, the establishment of engineering controls to reduce exposure, the utilization of personal protective equipment such as gloves and special clothing, and barriers such as ointments, emollients, or creams. Other preventive strategies include emphasizing personal and occupational hygiene, establishing educational programs to increase awareness in the workplace, and providing health monitoring.

In the workplace, by far the most effective measure for reducing the incidence of contact dermatitis is technical avoidance. This can be accomplished via shielding and personal protection of the workers and limiting the use of potent irritants to closed or automated systems. Preventive skin care at the workplace may mitigate occupational hand dermatitis among vulnerable populations and involves regular use of protective creams to intact skin, removal of irritants by mild cleaning agents, and enhancement of barrier function generation by emollients or moisturizers[63,64]. Non-irritating fatty substances such as petrolatum preclude hydrophilic chemical penetration and restore barrier function. The efficacy of barrier creams for skin protection (as compared to bland emollients) remains a topic of debate[65]. In a randomized controlled trial, both barrier creams and moisturizing vehicles were found to positively influence skin status and hydration, without significant differences in efficacy[66]. Newer moisturizers containing ceramides can also improve barrier function, but further trials are necessary to ascertain their efficacy compared to traditional moisturizers[67,68]. Lastly, while new bioengineering techniques have been proposed for the assessment of individual irritant sensitivity, their value in predicting occupational ICD, especially of the cumulative type, remains unclear.

Protective gloves can reduce risk of irritant hand dermatitis when appropriately selected and worn; however, gloves worn incorrectly or produced with poor quality control can actually instigate or worsen ICD. Glove failure can result in penetration, permeation, or contamination of hazardous materials, with irritation further compounded by the gloves' occlusive environment[69,70].

The establishment of appropriate educational prevention programs is essential. A project in Finland showed a significantly better outcome for employees with occupational hand dermatitis attending an "eczema school"-like clinic run by a specialized nurse compared with an unschooled control group[71]. Another study found that most occupational skin diseases responded to effective secondary preventive measures, combining employee medical treatment with exposure analysis-based individual and group training in preventive measures[72]. Education was important in making the employees aware of initial skin changes, such as slight erythema and scaling in the interdigital folds, indicating the need to optimize skin protection and care measures in order to prevent exacerbation and chronicity.

The goal of treatment is to restore normal epidermal barrier function. Topical corticosteroids are frequently used, but their efficacy has

been controversial, as experimental studies have provided conflicting results[73]. In one double-blind, vehicle-controlled study, statistically lower values of erythema and TEWL were observed in sites irritated by sodium lauryl sulfate after 7 days of treatment with betamethasone valerate[74]. Systemic corticosteroids, although potentially helpful in reducing acute inflammation, are not useful in the treatment of chronic ICD unless corrective measures are taken to avoid the offending contactants. Narrowband ultraviolet B or photochemotherapy (PUVA) irradiation may be considered for chronic dermatitis that does not respond to any other form of therapy. Hyperkeratotic palmoplantar dermatitis from frictional or chronic ICD or a combination of dermatitis and psoriasis may benefit from the adjunctive use of systemic retinoids such as acitretin and alitretinoin or systemic immunomodulators such as methotrexate, cyclosporine, and possibly targeted immunomodulatory (biologic) therapy[75].

Additional figures and tables on Causes of cheilitis in patients who were referred for patch testing, The Hand Eczema Severity Index (HECSI), and The modified Total Lesion Symptom Score (mTLSS) for hand eczema, available in our eBook (see inside front cover for access code).

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eFig. 15.1 Moderately severe irritant contact dermatitis of the hands due to chronic exposure to disinfecting solutions and antiseptics. The results of patch testing, latex challenge testing, and RAST testing were negative in this practicing dentist.



eFig. 15.3 Irritant contact diaper dermatitis (Jacquet erosive dermatitis). Multiple punched out erosions and ulcerations. *Courtesy Julie V. Schaffer, MD.*



eFig. 15.2 Chemical burn from topical application of apple cider vinegar. There is sparing of the skin folds and this may be misdiagnosed as child abuse (see Ch. 90). *Courtesy Julie V. Schaffer, MD.*



eFig. 15.4 Irritant contact diaper dermatitis (granuloma gluteale infantum). Coalescing moist, pink papules on the vulva and suprapubic area of an infant. *Courtesy Julie V. Schaffer, MD.*

CAUSES OF CHEILITIS IN PATIENTS REFERRED FOR PATCH TESTING	
Irritant contact dermatitis Most frequent cause: lip licking	36%
Allergic contact dermatitis Most common allergens (% of patients in a second series[60]): fragrance mix, 30%; *Myroxylon pereirae* (balsam of Peru), 23%; nickel, 22%; gold, 13%; neomycin, 12%; cobalt, 10%; propylene glycol, 8%; lanolin, 7%; cinnamic aldehyde, 7%; bacitracin, 5%; benzophenone, 5%; methyldibromo glutaronitrile/phenoxyethanol, 5%; tea tree oil, 5%; budesonide, 5%	25%
Atopic dermatitis	19%
Eczema (cause unknown)	9%
Non-eczematous causes (angioedema, photosensitivity, psoriasis, erosive candidal cheilitis, functional)	9%
Seborrheic dermatitis	1%

eTable 15.1 Causes of cheilitis in patients who were referred for patch testing (n = 75). *Adapted from Freeman S, Stephens R. Cheilitis: analysis of 75 cases referred to a contact dermatitis clinic. Am J Contact Dermat. 1999;10:198–200 and Zug KA, Kornik R, Belsito DV, et al.; North American Contact Dermatitis Group. Patch-testing North American lip dermatitis patients: data from the North American Contact Dermatitis Group, 2001 to 2004. Dermatitis. 2008;19:202–8.*

THE HAND ECZEMA SEVERITY INDEX					
Clinical signs	**Location and intensity score**				
	Fingertips	*Fingers (except tips)*	*Palm of hands*	*Back of hands*	*Wrists*
Erythema	0–3	0–3	0–3	0–3	0–3
Infiltration/ papulation	0–3	0–3	0–3	0–3	0–3
Vesicles	0–3	0–3	0–3	0–3	0–3
Fissures	0–3	0–3	0–3	0–3	0–3
Scaling	0–3	0–3	0–3	0–3	0–3
Edema	0–3	0–3	0–3	0–3	0–3
Intensity sum (range)	0–18	0–18	0–18	0–18	0–18
Extent score of clinical symptoms (Ex)	0–4	0–4	0–4	0–4	0–4
Total HESCI Score =	Intensity sum × Ex +	Intensity sum × Ex +	Intensity sum × Ex +	Intensity sum × Ex +	Intensity sum × Ex

eTable 15.2 The Hand Eczema Severity Index (HECSI). The HECSI evaluates hand eczema severity based on 6 clinical signs and 5 locations. Each location is given a score from 0 to 3 for the *intensity* of clinical symptoms, graded on the following scale: *0, no skin changes; 1, mild disease; 2, moderate; and 3, severe*. For each location (in consideration of both hands) the affected area is given a score from 0 to 4 for *extent* of clinical symptoms (*0 = 0%; 1 = 1%–25%; 2 = 26%–50%; 3 = 51%–75% and 4 = 76%–100%)*. The score given for the extent for each location is multiplied by the total sum of the intensity of each clinical feature. The total score ranges from 0 to a maximum severity score of 360. A composite HECSI score of 0 to 11 corresponds to mild disease; scores of 12 to 27 correspond to moderate disease; scores of 28 or more correspond to severe disease. *Adapted from Held E, Skoet R, Johansen JD, Agner T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. Br J Dermatol. 2005;152(2):302-307; and Oosterhaven J a. F, Schuttelaar MLA. Responsiveness and interpretability of the hand eczema severity index. Br J Dermatol. 2020;182(4):932-939.*

THE MODIFIED TOTAL LESION SYMPTOM SCORE (MTLSS) FOR HAND ECZEMA	
Parameter	**Severity score***
Erythema	0 = Absent 1 = Faint erythema 2 = Prominent redness 3 = Deep intense red color
Scaling	0 = Absent 1 = Slight flaking over limited areas, mostly fine scales 2 = Flaking over widespread area(s), coarser scales 3 = Desquamation covering over 30% of the hand, with coarse thick scales
Lichenification/ hyperkeratosis	0 = Absent 1 = Mild thickening with exaggerated skin lines over limited areas 2 = Palpable thickening over widespread area(s) 3 = Prominent thickening over widespread area(s) with exaggeration of normal skin markings
Vesiculation	0 = Absent 1 = Scattered vesicles affecting up to 10% of hand, without erosion 2 = Scattered or clustered vesicles affecting up to 30% of hand, without visible erosion or excoriation
Edema	0 = Edema 1 = Dermal swelling over less than 10% of hands 2 = Definite dermal swelling over more than 10% of hand 3 = Dermal swelling with skin induration over widespread area(s)
Fissures	0 = Absent 1 = Cracked skin affected a small area of the hand 2 = Cracked skin affecting multiple areas of the hand and causing pain 3 = One or more deep fissures and causing bleeding or severe pain
Pruritus/pain	0 = Absent 1 = Occasional, slight discomfort a few times per day 2 = Intermittent, causing discomfort frequently during the day 3 = Persistent or interfering with sleep
*1 = mild; 2 = moderate; 3 = severe.	

eTable 15.3 The modified Total Lesion Symptom Score (mTLSS) for hand eczema. Composite scores range from 0 (no signs or symptoms) to 21 (more serious disease). *Adapted from Ruzicka T, Lynde CW, Jemec GBE, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. Br J Dermatol. 2008;158:808–17.*

Occupational Dermatoses 16

S. Mark Wilkinson and Faheem Latheef

INTRODUCTION

Given the diverse occupations that people pursue, there are thousands of chemicals and other potentially noxious insults that can impinge on the skin in many different ways[1]. Traditionally, the types of hazardous exposure are categorized as:

- mechanical – friction, pressure, vibration, mechanical disruption
- chemical – elements and chemical compounds (organic, inorganic, and proteins)
- physical – heat, cold, radiation (UV and ionizing)
- biological – organisms including viruses, bacteria, fungi, and parasites.

The types of dermatoses induced by exposure to these noxious occupational hazards can be grouped as outlined in Table 16.1. This chapter differs from most of the others in that it deals with diverse conditions, many of which are also covered in detail in specific chapters.

HISTORY

Occupational disease has existed for thousands of years. Hippocrates (c460–377 BCE) hypothesized that there were environmental causes of disease. One of the first written descriptions of occupational dermatoses was by the Italian Bernardino Ramazzini (1633–1714). He described diseases associated with a variety of occupations, including different types of ulcerations in fresh- and salt-water fishermen. During their long-distance voyages in the sixteenth century, Drake and Magellan experienced significant problems from scurvy due to the lack of vitamin C from fresh fruit and vegetables. In 1747, James Lind performed the first controlled trial demonstrating the protective effects of citrus fruits against scurvy. In 1795, the British Navy included lemon juice in ships' stores as one of the earliest forms of prevention for an occupational skin disease.

EPIDEMIOLOGY

In a UK household survey, a rate of occupational dermatosis of 15/10 000 for those who had ever been employed demonstrates the high frequency of affected individuals; in comparison, a rate of 5.1/10 000 has been reported by physicians in Denmark and Finland, where occupational disease is notifiable. Of the most common physical illnesses due to occupation, skin diseases (23%) rank second, after musculoskeletal disorders (45%)[2]. In the US in 2010 it was estimated that for private industry, the annual cost of occupational skin disease due to lost productivity, medical care, and disability payments was US$1.2 billion[3], and this accounted for 10.5% of the cost attributed to skin disorders from all causes. The average cost per claim for occupational dermatitis in the 1990s was US$3550 and the period of disability was 24 days[4]. More recently, the German statutory health insurance companies estimated the cost of hand eczema to be €9000 per case with an annual cost of €2128[1].

Based upon classification systems such as the International Standard Classification of Occupations (ISCO), the distribution of occupational skin disease reported by industry varies with the specialty of the physician (Fig. 16.1)[5]. The difference in incidence of neoplasia, as reported by dermatologists compared to occupational physicians, reflects the delay between exposure and development of disease and the fact that the majority of workers have left employment when the cancer develops. Differences in reporting also reflect the distribution of occupational health departments in industry: vehicle assembly, glass, and ceramic workers as well as scientific technicians are often seen by occupational physicians, whereas hairdressers, for example, are seen primarily by dermatologists. Over the past decade, there has been a consistent decline in the reported incidence of occupational dermatoses both in the US and in Europe[6].

THE OCCUPATIONAL DERMATOSES

Contact Dermatitis

Synonym: Contact eczema

Key features

- The most common causes of occupational *allergic* contact dermatitis are (in order of decreasing frequency): rubber, nickel, epoxy and other resins, and aromatic amines
- The most common causes of occupational *irritant* contact dermatitis are (in order of decreasing frequency): soaps, wet work, petroleum products, solvents, and cutting oils and coolants

Introduction

Contact dermatitis accounts for the majority of occupational skin disease that predominantly affects the hands. The prevalence of hand dermatitis in the population has been estimated at ~0.5%, rising in some studies to 10% when an industrial workforce has been examined. While most individuals will remain at work, over half will change jobs and a large proportion will be absent from work for a month or more.

History

In the first century CE, Pliny the Younger recorded dermatitis in individuals after they cut down pine trees, presumably representing allergic contact dermatitis to colophony in pine resin. Ramazzini in his 1700 treatise described irritant contact dermatitis of the hands and forearms in soap and laundry workers.

Epidemiology

An age-related increase in rates of occupational dermatitis is seen in men, but in women the peak age of incidence is 16–29 years with a decline thereafter. However, a comparison of rates by age within specific occupational groups suggests that the sexes follow a similar pattern. Among chefs and cleaners of either sex, higher rates are seen in young workers, whereas rates among machine tool operators increase with age, reflecting the type of occupational exposure. Materials giving rise to contact dermatitis in the United Kingdom (UK) are shown in Fig. 16.2, and the highest risk UK occupations in Fig. 16.3[7]. In contrast to the UK, in Finland and the US, the highest rate of skin disease is among agricultural workers.

Pathogenesis

The initial events of both irritant and allergic contact dermatitis (see Chs. 14 & 15) are similar. Depending upon the severity of the insult, the tissue response can reach a level at which it becomes clinically apparent as cutaneous inflammation (Fig. 16.4). If tissue perturbation is maintained via repeated insults, then chronic dermatitis ensues, while an early withdrawal of the insult may result in healing.

Clinical features

Contact dermatitis, both allergic and irritant, is morphologically indistinguishable from endogenous eczema (Fig. 16.5). Although most cases of dermatitis will result from direct exposure that leads to localized

CLINICAL CLASSIFICATION OF OCCUPATIONAL DERMATOSES
Contact dermatitis • Irritant - chemically induced - photoinduced - mechanical • Allergic
Chemical burn
Contact urticaria
Cancer • Sunlight/UV-induced • Ionizing radiation-induced • Chemically induced
Follicular disease • Acne • Folliculitis • Chloracne
Autoimmune connective tissue disease • Systemic sclerosis (silica; see Ch. 43) • Scleroderma-like (vinyl chloride, organic solvents; see Ch. 43) • Vibration-induced
Pigmentary disorders • Hypopigmentation (see Ch. 66) • Hyperpigmentation (see Ch. 67)
Foreign body reactions (see Ch. 94)
Infection • Viral • Bacterial • Fungal • Parasitic

Table 16.1 Clinical classification of occupational dermatoses.

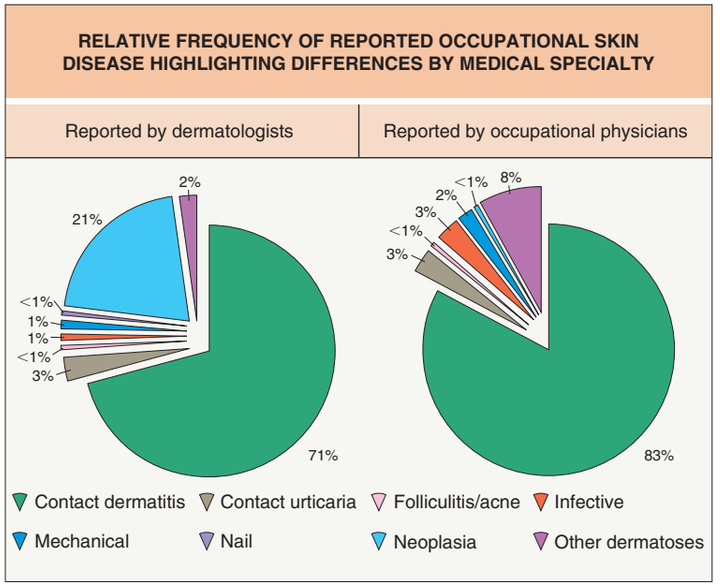


Fig. 16.1 Relative frequency of reported occupational skin disease highlighting differences by medical specialty. *Courtesy The Health and Occupation Research (THOR) network of the Centre for Occupational and Environmental Health (COEH) of the University of Manchester, UK.*

dermatitis, there are other routes of absorption that can lead to dermatitis. In the case of solvents, inhalation may result in widespread dermatitis, often with systemic involvement.

Diagnosis of an occupational cause is dependent on a thorough dermatologic and occupational history (Table 16.2), combined with

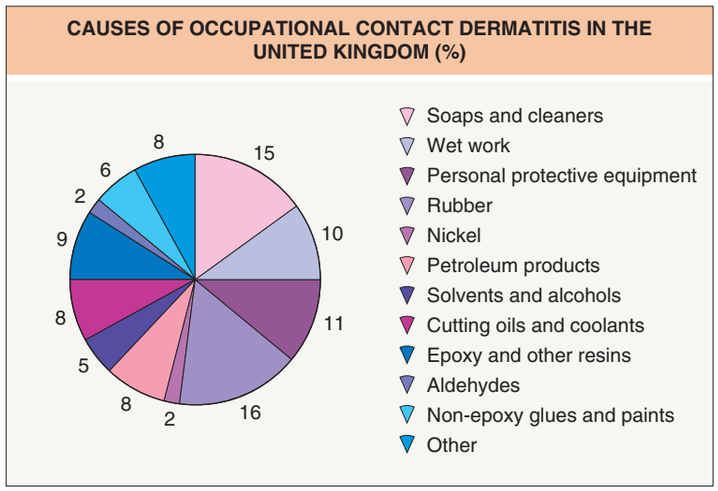


Fig. 16.2 Causes of occupational contact dermatitis in the United Kingdom (%).

examination of the entire skin. Material safety data sheets (MSDS) provide a guide to the nature of materials handled at work. They list the chemical composition and the hazards associated with the product, e.g. irritant, corrosive, contains a sensitizer. However, total reliance should not be placed on the MSDS as they may not list all ingredients of relevance, and communication with the manufacturer may prove helpful. When occupational dermatitis is suspected but a cause cannot be established from the history, a workplace visit may prove invaluable and may also elucidate the source of an allergen previously detected via patch testing.

Although the primary site is usually the hands, spread to *adjacent* areas of skin (even without primary contact) is relatively common. Spread to *distant* sites, such as the face and feet, is more frequently seen in allergic contact dermatitis than in irritant contact dermatitis. Notably, airborne allergens, e.g. from paint sprayers, can lead to a pattern of dermatitis that suggests this type of exposure. Covered areas such as the trunk and feet are unusual sites of onset of disease. Improvement of the dermatitis during periods away from work is an important clue to an occupational cause, but it should be remembered that endogenous eczema may also be exacerbated by workplace exposures. As the dermatitis becomes chronic, the relationship between work and exacerbations becomes less clear-cut.

Occupational contact dermatitis

Occupational contact dermatitis can be either irritant or allergic. Personal protective equipment (PPE) is defined as equipment that protects the wearer's body against health/safety risks at work. Although it is designed to help reduce the incidence of contact dermatitis at work, in some cases PPE itself can cause contact dermatitis. Hand dermatitis due to gloves is the most common PPE-related dermatitis, but non-glove exposures also occur[8]. Dermatitis associated with the use of face masks during the recent SARS-CoV-2 pandemic would be a prime example[9].

Allergic contact dermatitis (see Ch. 14)

Patch testing is essential for establishing the diagnosis and should be performed in any individual with a dermatitis that may be work-related or for whom a change of job is being contemplated. Testing with work materials is essential (Table 16.3) if contact allergy is not to be missed, as not all allergens are commercially available and the MSDS may not disclose all relevant ingredients. A guide to testing 5200 chemicals has been published[10]. When a reaction occurs to an unknown substance, the use of a dilutional series and the testing of ~20 controls can confirm that the reaction is allergic rather than irritant.

In an extensive surveillance report, the most common causes of occupational allergic contact dermatitis were rubber (23.4% of cases), nickel (18.2%), epoxy and other resins (15.6%), aromatic amines (8.6%), chromate (8.1%), fragrances and cosmetics (8.0%), and preservatives (7.3%)[7]. Recently, the more frequent use of long-lasting artificial nails has led to an increase in allergic contact dermatitis due to methacrylates in occupationally exposed, and sensitized, nail technicians[11].

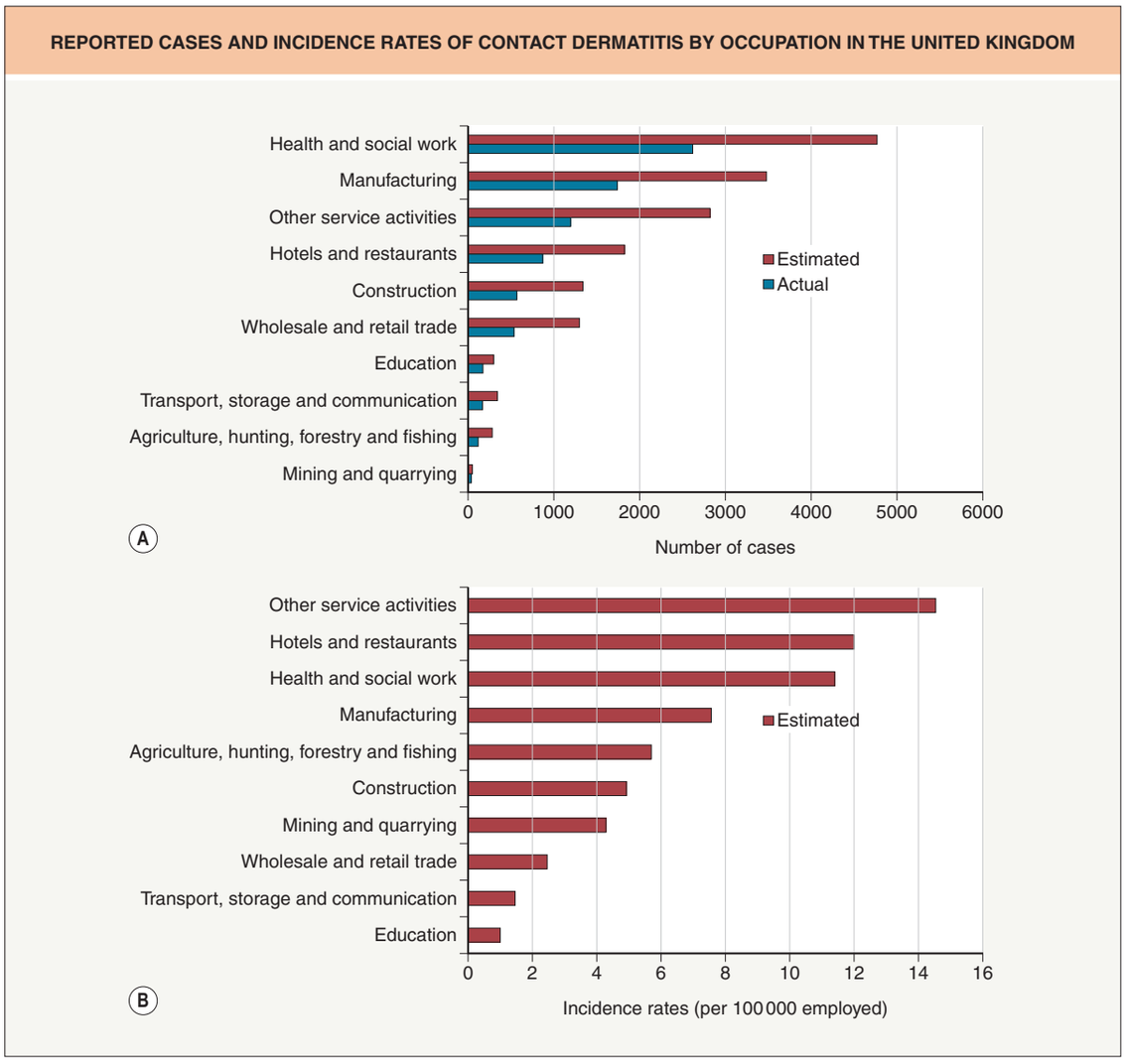


Fig. 16.3 Reported cases and incidence rates of contact dermatitis by occupation in the United Kingdom. A Actual and estimated cases of contact dermatitis, with crude data adjusted for sampling bias. **B** Contact dermatitis incidence rates (per 100 000 employed); crude data were adjusted for the size of the labor force by utilizing the labor force survey data (2002–2009) as the denominator. *Courtesy The Health and Occupation Research (THOR) network of the Centre for Occupational and Environmental Health (COEH) of the University of Manchester, UK.*

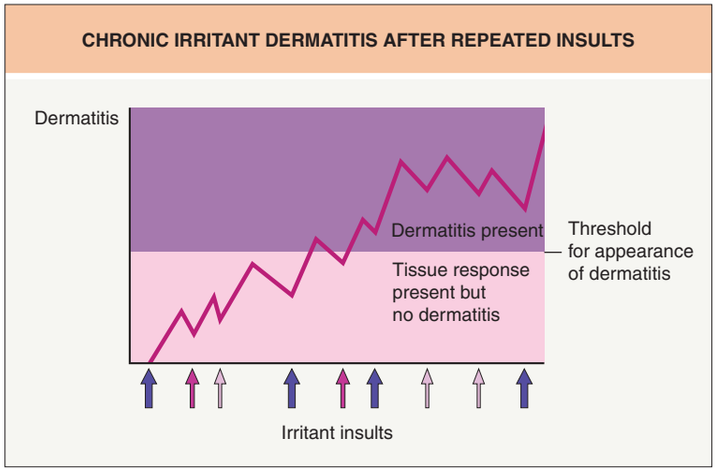


Fig. 16.4 Chronic irritant dermatitis after repeated insults. Initial subclinical response to tissue perturbation by an irritant becomes manifest as chronic irritant dermatitis after repeated insults. Each arrow represents an irritant insult of different intensity.



Fig. 16.5 Hand of a builder who presented with a dyshidrotic (pompholyx) pattern of eczema. Investigation demonstrated allergic contact dermatitis to chromate found in cement and contact urticaria to latex in the gloves he was using for hand protection.

POINTS TO CONSIDER WHEN TAKING AN OCCUPATIONAL HISTORY	
Primary (initial) site of disease • Time course	In 90%, it is the hands Is this consistent with work exposure as a cause? Does time off result in improvement?
Materials handled • Labels and material safety data sheets (MSDS) • Other persons affected • Protection provided	Irritant, corrosive, or sensitizing Suggests an irritant contact dermatitis Is it appropriate? Is there an allergy to personal protective equipment?
Previous skin disease or history of atopy	Is this a recurrence of a previous problem?
Known allergies	Is there unrecognized exposure?
Treatment	May cause allergic contact dermatitis
Hobbies	May be a more likely cause than occupation

Table 16.2 Points to consider when taking an occupational history.

Irritant contact dermatitis (see Ch. 15)

Most occupational dermatitis results from repeated exposures to weak irritants which cause cumulative damage to the skin (see Fig. 16.4). On the other hand, strong irritants are usually recognized and protection provided. Employees with previous atopic dermatitis, especially with hand involvement, are particularly at risk, as are those with mutations in the filaggrin gene[12].

Soaps (22% of cases), wet work (20%), petroleum products (9%), solvents (8%), and cutting oils and coolants (8%) are the most frequently cited causes of occupational irritant dermatitis[7].

Chemical burns

A chemical burn is an acute irritant reaction in which the injury to the skin is irreversible and cell death occurs. It can occur following a single exposure. Initial symptoms consist of burning and stinging with progressive development of erythema, blisters, erosions, and ulceration (see Fig. 15.2). Symptoms usually develop in close association with the exposure, but some chemicals, such as phenols and weak hydrofluoric acid, can have a delayed onset. Common occupational causes include[13]:

- **strong acids:** e.g. sulfuric, nitric, hydrochloric, chromic. Most coagulate skin proteins and as a result form a barrier that impedes further penetration. Hydrofluoric acid differs in that it causes a liquefactive necrosis: penetration, even down to bone, can continue for several days after exposure. Pain, which can last several days, is typical of hydrofluoric acid and other fluorides. If more than 1% of the body surface area is affected, systemic toxicity can develop
- **strong alkalis:** e.g. sodium, calcium, and potassium hydroxides; wet cement (Fig. 16.6); sodium and potassium cyanides. Degradation of lipids and saponification of the resulting fatty acids form soaps which aid the penetration of alkalis deeper into the skin. As a consequence, damage is more severe than with most acids (apart from hydrofluoric acid) and pain is also a feature
- **organic and inorganic chemicals:** e.g. dichromates; arsenates; phenolic compounds. Phenols and unhardened phenolic resins easily penetrate the skin. Nerve damage may cause anesthesia, but rarely in the absence of visible skin damage. Vasoconstriction may contribute to the necrosis that develops and following systemic absorption, shock and renal damage may ensue
- **solvents and gases:** e.g. acrylonitrile; ethylene oxide; carbon disulfide; mustine. Ethylene oxide gas is used to sterilize medical instruments, textiles, and plastic materials, and it can remain on these items for several days if not allowed to evaporate off prior to use. The possibility of exposure may therefore not be obvious.

SUGGESTED CONCENTRATIONS FOR PATCH TESTING SELECTED WORK MATERIALS		
Sample	**Dilution**	**Occupation(s)**
Personal care products		
• Leave on	As is	Hairdresser/beautician
• Wash off	1%–5% aqueous or open*	Hairdresser/beautician
Plants†		
Bulb, leaf, flower	As is	Gardener/florist Agriculture/vegetable processing
Woods – sawdust	As is/10% petrolatum	Joiner/woodworker
Dyes (clothing)	1% petrolatum	Textiles
• Cloth	As is – moistened	
Foods‡	As is	Catering/chef
Glue	10% aqueous/ petrolatum	Various
• Methacrylate monomer	1% petrolatum	Dentist/orthopedic surgeon
• Acrylate monomer	0.1% petrolatum	
• Epoxy resin	1% petrolatum	Painter – 2-part paints
• Epoxy hardener	0.1% petrolatum	
Ink	As is	Printing
• UV cured	1% petrolatum	
Oil		
• Cutting (coolant) – water miscible	10% aqueous or open	Metal machining
• Lubricant – immiscible with water	As is	Various-use machinery
Paint	10% aqueous/ petrolatum	Painter/decorator
Photographic chemicals	10% aqueous	Photographer
Solvents/thinners	10% acetone	Various

*Open test: apply the substance to a 3 cm diameter area of skin and allow to dry. Read as normal but do not occlude.
†Do not test unless the plant has been identified and is recognized not to be an irritant. There may be a risk of sensitization.
‡Prick testing is essential to exclude contact urticaria.

Table 16.3 Suggested concentrations for patch testing selected work materials. This is a guide only: the final decision must always be made in light of the information available in relation to the suspected material. Tests are usually performed on the upper back.

Fiberglass dermatitis

Glass fibers are subdivided into various types, depending on fiber diameter, and are used for their insulating (thermal, acoustic, and electrical), strengthening, and filtering abilities. They are chemically inert and the mechanism of skin injury is via direct penetration, which is directly proportional to the diameter (>3.5 microns) of the fiber and inversely proportional to its length. Histologically, eczematous changes including spongiosis are seen. Occasionally, granulomatous dermatitis is seen with birefringent fibers visible in polarized light.

Pruritus and tingling are the usual initial symptoms of fiberglass dermatitis. Subsequently, erythematous papules develop (often with follicular accentuation), either on exposed areas when there is airborne exposure or on the forearms when there is contamination of a work surface (Fig. 16.7)[14]. Contamination of clothing leads to involvement of sites where there is close contact with the skin, particularly flexural areas. Paronychia is common, and airborne exposure may also cause burning eyes, sore throat, and cough.

The diagnosis is often based on clinical findings, but can be confirmed by detecting the glass fibers either by tape stripping affected skin or by examining skin scrapings in 20% potassium hydroxide. The dermatitis resolves rapidly after cessation of exposure. In most individuals, hardening occurs and symptoms resolve over a few weeks despite continued



Fig. 16.6 Cement burns. Ulcerations on the fingertips of a construction worker exposed to wet cement. *Courtesy P. J. Coenraads, MD.*



Fig. 16.7 Fiberglass dermatitis. Multiple pruritic pink papules at the site of exposure.

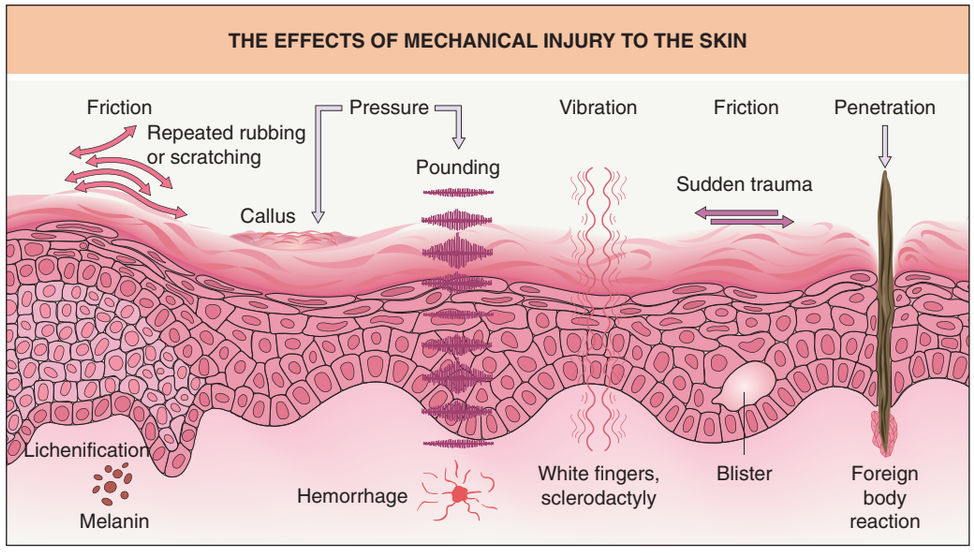


Fig. 16.8 The effects of mechanical injury to the skin. Both friction and pressure lead to callus formation. *Adapted from Adams RM. Occupational Skin Disease, 3rd ed. Philadelphia: WB Saunders, 1999:36.*

exposure; of note, the use of resins to bind glass fibers can result in an allergic contact dermatitis.

Phototoxic eruptions (see Ch. 87)

Most occupational photosensitivity is phototoxic in nature and resolves with hyperpigmentation. The most common scenario consists of outdoor workers exposed to plant-derived psoralens. This may result from direct contact or be airborne as in "strimmer" dermatitis when plant sap splatters the body of a worker inadequately protected when cutting down plants (see Ch. 17).

Coal tar and its products, including creosote, can cause a reaction known as tar/pitch smarts. A burning or stinging sensation develops after as little as 15 minutes of sun exposure.

Mechanical

Occupational marks are usually areas of lichenification or calluses and corns that develop at sites of friction and are specific to a particular job (Fig. 16.8). Mechanical injury to the skin is also thought to cause dermatitis analogous to irritant chemical damage. It may result in a keratotic hand dermatitis or post-traumatic eczema (Koebner phenomenon).

Pathology

The histopathologic features of allergic contact dermatitis and irritant contact dermatitis are discussed in Chapters 14 and 15, respectively.

Differential diagnosis

The etiology of occupational dermatitis is frequently multifactorial and coexisting endogenous eczema may contribute to the clinical appearance. Tinea manuum may resemble hand dermatitis, especially following treatment with topical corticosteroids, and scabies infestation of the interdigital spaces can simulate irritant dermatitis. Rarely, blistering of the dorsal hands due to porphyria cutanea tarda is misconstrued as contact dermatitis.

Psoriasis frequently affects the palms, resulting in keratotic plaques, sometimes with fissures. This can be difficult to distinguish from dermatitis when there are no lesions elsewhere. Furthermore, psoriasis may be exacerbated by repeated, work-related trauma leading to Koebner phenomena. Nail involvement and plaques over the interphalangeal joints are helpful clues.

Treatment

Occupational disease prevention is divided into primary, secondary, and tertiary measures (Table 16.4)[15]. During pre-employment screening, a history of severe childhood atopic dermatitis, particularly with hand involvement, indicates an individual at risk of developing dermatitis from exposure to irritants. Employment in a "dry" job should be recommended. In the workplace, the use of PPE and skin care preparations should be encouraged (Table 16.5). Use of protective creams prior to exposure may aid in the subsequent removal of irritants and application

HIERARCHY OF OCCUPATIONAL DISEASE PREVENTION	
Primary prevention	Avoid disease onset • Engineering measures • Chemical substitution • Workforce education in skin care
Secondary prevention	Detect presymptomatic or early disease • Health surveillance
Tertiary prevention	Treatment of active disease • Avoidance measures • Medical management

Table 16.4 Hierarchy of occupational disease prevention.

GUIDELINES AIMED AT PREVENTING CONTACT DERMATITIS		
Advice		**Explanation**
Do not wear rings		• Chemicals/water accumulate underneath
Hand washing	• Use lukewarm water and dry thoroughly	• Skin damage from detergent is reduced at a low temperature • Dermatitis often begins at sites that are missed, e.g. fingerwebs
Wear gloves	• For wet work	• Wet work is the major risk factor for contact dermatitis
	• For as short a time period as possible	• Glove occlusion also damages the skin
	• With a cotton inner liner if prolonged exposure	• Liners absorb moisture and reduce irritation
	• That are dry, clean, and intact	• Occlusion of chemicals inside gloves increases irritancy
Use moisturizer	• Frequently throughout the day	• Encourages barrier repair
	• To the whole hand	• Need to include web spaces
	• That is fragrance-free and preservative-free	• Prevents sensitization and development of ACD to common allergens
For antisepsis	• Use alcohol gel	• Less irritating than soaps or antiseptic detergents
Follow the same advice at home		• Domestic exposures are additive

Table 16.5 Guidelines aimed at preventing contact dermatitis. ACD, allergic contact dermatitis.

of emollients throughout the day may prevent the development of dermatitis. Education of the workforce in skin care has been shown to reduce the development of skin disease[16].

Treatment is discussed in Chapters 14 and 15. The most important aspect, however, is avoidance of the cause. Ideally, a change in the production process may avoid the need for exposure, but this may not be feasible. A practical compromise is the use of PPE and/or substitution of a particular chemical. Advice on appropriate glove type may be found on the MSDS or from glove manufacturers (e.g. www.ansellpro.com). Gloves need to be replaced regularly and each particular type of glove will have a penetration time for any given chemical. For example, acrylate glues (orthopedic surgeons, dentists), the hair dye para-phenylenediamine (hairdressers), and "acid perm" solutions containing glycerol monothioglycolate (hairdressers) rapidly penetrate latex gloves.

Initial treatment of chemical burns requires irrigation with large volumes of water. When the chemical is insoluble in water, a soap solution may be used instead. High pressures should not be used, in order to avoid splashing other areas of the body or bystanders with the corrosive material. For some chemicals, specific antidotes can then be used, e.g. 2.5% calcium gluconate gel for hydrofluoric acid; reduction of pain is a sign of successful treatment. When there is a risk of toxicity from systemic absorption, as with chromic acid, early debridement of necrotic areas reduces blood levels.

Several chemicals (e.g. hydrofluoric acid, phenolic compounds, chromic acid, gasoline) carry a significant risk of systemic toxicity even when the area of skin involved is small (~1% of body surface area). In these instances, regular monitoring of blood, liver, and kidney function plus appropriate supportive treatment (e.g. dialysis) is required. When the chemical is also a sensitizer, allergic contact dermatitis may subsequently appear on re-exposure to non-irritant concentrations, as burns and irritant dermatitis promote sensitization.

Once it has developed, the outlook for occupational contact dermatitis is poor[17], and patients frequently have persistent disease despite interventions. While a change of occupation is associated with a better prognosis, the possibility exists that the new workplace will have the same or similar chemical exposures. Prognosis is also worse when there is a contact allergy (delayed or immediate) to a chemical that is present in the domestic as well as the industrial environment. Some individuals (~10%) have persistent disease in the absence of any obvious cause, for which the term "persistent post-occupational dermatitis" has been coined.

Contact Urticaria

Synonyms: ■ Contact urticaria syndrome ■ Immediate contact reaction ■ Variant: protein contact dermatitis

Key features

- Pruritus and wheal-and-flare reaction
- Develops within 60 minutes of exposure and resolves within 24 hours
- The protein content of latex rubber is responsible for the associated contact urticaria
- In suspected cases of latex-induced contact urticaria, the specific IgE test may be negative, requiring prick testing with a commercial latex extract and a usage test

Introduction

Contact urticaria has been reported following exposure to a wide range of substances[18]. With regard to occupational skin disease, plant- and animal-derived proteins are recognized causes, especially among food handlers and agricultural, animal laboratory, and veterinary workers. In extreme circumstances, systemic symptoms (i.e. rhinoconjunctivitis, bronchospasm, and anaphylaxis) may be seen. With the introduction of universal precautions in the 1980s and increased use of natural rubber gloves, latex protein emerged as an important cause of contact urticaria, particularly in the healthcare setting.

History

Contact urticaria was first defined as a clinical entity during the 1970s but it had long been recognized.

Epidemiology

Based on official statistics, occupational causes of contact urticaria have been well classified in Finland[1]. The relative frequency of various urticants is shown in Fig. 16.9 and reflects the high prevalence of reactions in the farming community. The reactions to cow dander are probably the result of high exposure, as cattle are kept indoors from September to May/June. The prevalence varied from 140/100 000 for bakers to 2.1/100 000 for shop assistants and was higher in women, irrespective of occupation. Relative risk by occupation is shown in Fig. 16.10. The incidence of contact urticaria declines with age, and ~30% of individuals have coexistent contact dermatitis.

Pathogenesis

Contact urticaria is classified as either irritant/nonimmune-mediated or allergic/immune-mediated. An additional category includes those cases in which the mechanism is uncertain, exemplified by ammonium persulfate in hairdressing.

The mechanism of nonimmune contact urticaria is not well defined but involves the release of vasoactive mediators. It is inhibited by non-steroidal anti-inflammatory drugs but not by antihistamines, suggesting a role for prostaglandins. Symptoms develop in the majority of those exposed and are most often due to simple chemicals, e.g. sorbic acid.

Immunologic contact urticaria is mediated by allergen-specific IgE (see Ch. 18). Binding of antigen, usually protein, to mast cells in a previously sensitized individual results in degranulation and release of mast cell mediators, including histamine. Atopic individuals are at greater risk of this type of reaction.

Clinical features

Signs and symptoms range from nonspecific, i.e. pruritus, tingling and burning, to more typical urticaria with a wheal and flare, usually noted within 30 minutes of exposure at the site of contact. Resolution occurs within hours. Individuals with immunologically mediated urticaria[19] may also experience systemic symptoms with generalized urticaria, rhinoconjunctivitis, orolaryngeal and gastrointestinal symptoms, bronchospasm, and even anaphylaxis.

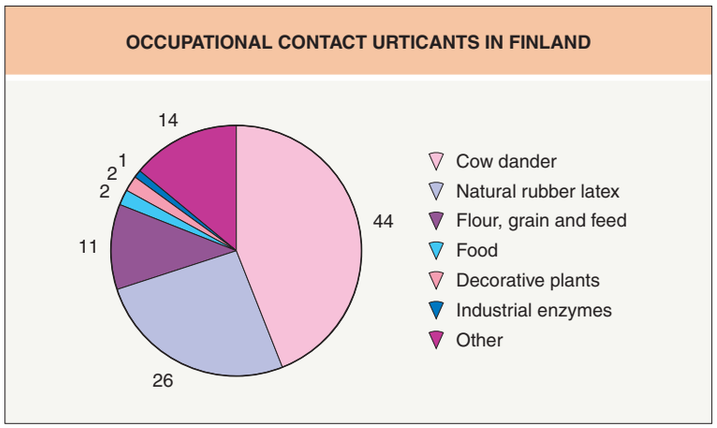


Fig. 16.9 Occupational contact urticants in Finland. Relative frequencies are represented. *Reproduced from Kanerva L, Elsner P, Wahlberg JE, et al. Handbook of Occupational Dermatology. Berlin: Springer Verlag, 2000.*

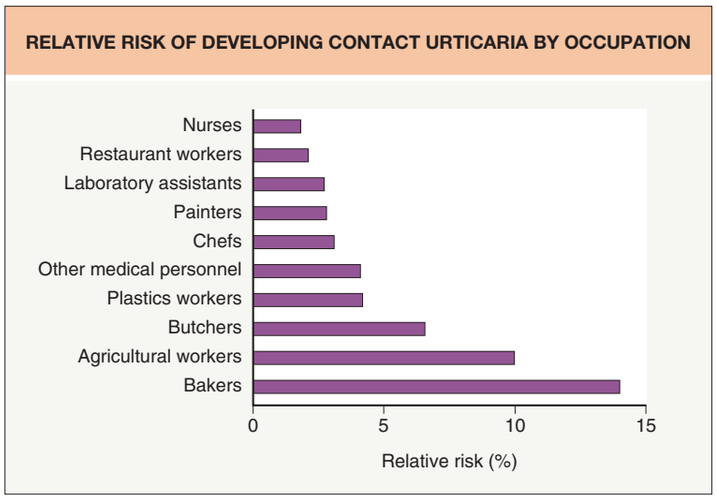


Fig. 16.10 Relative risk of developing contact urticaria by occupation. Based upon statistics from Finland. *Reproduced from Kanerva L, Elsner P, Wahlberg JE, et al. Handbook of Occupational Dermatology. Berlin: Springer Verlag, 2000.*

Foods

One of the more common causes of contact urticaria is foodstuffs, which can provoke either orolaryngeal symptoms when ingested or hand symptoms when handled (e.g. fish processors, slaughterhouse workers, individuals in the catering industry). There is a diverse range of responsible foods, including meats, fish, eggs, fruits, vegetables and flour, as well as associated enzymes such as α-amylase (found as an additive in flour). In Scandinavia, a strong association is seen between the incidence of birch pollen allergy and contact urticaria to fruits and vegetables, due to the presence of similar peptides. Birch pollen is a common aeroallergen in Scandinavia, whereas in the UK the most common aeroallergens are the house dust mite and grass pollen; this may explain why there are fewer reports of contact urticaria in food handlers in the UK. In the US, incidences of birch pollen allergy vary depending upon geographic region. If contact urticaria is confirmed, there are recognized cross-reactions between the various foodstuffs (Table 16.6)[20].

Latex

Contact urticaria to latex was first described in 1979. The term "latex" defines an aqueous dispersion of a rubber. The rubber obtained from latex by drying or coagulation is termed "latex rubber". Natural latex is derived from the sap of the tree *Hevea brasiliensis*. Natural latex contains polyisoprene (30%–40%) together with a variety of other plant chemicals, including proteins (2%).

After 1985, the demand for latex gloves for medical and dental use to prevent the transmission of infectious agents[21] more than doubled. Paralleling this rise in usage were reports of type I allergy to latex gloves. Occupational latex contact urticaria occurs more frequently in women, atopic patients (particularly those with hand eczema), and workers frequently exposed to latex gloves (e.g. hairdressers). Rates ranging from 3% to 16% have been reported among healthcare workers.

Most problems arise from items made by coating a mold with concentrated liquid latex, e.g. gloves, balloons, condoms. Nowadays, however, many gloves are manufactured by methods designed to leave lower levels of protein allergen in the final product. Latex that is allowed to dry before processing by compression molding or extrusion (e.g. syringe plungers, vial stoppers) causes fewer problems, due to degradation of the protein allergen during the manufacturing process. When latex protein is absorbed onto starch particles in gloves, it can become airborne and cause conjunctivitis, rhinitis, and asthma. Ideally, powder-free gloves should be used to avoid this risk.

In a subgroup of latex-sensitive patients, hypersensitivity reactions to bananas, avocados, chestnuts, kiwis and other fruits may also occur (see Table 16.6). Radioallergosorbent inhibition studies have shown that they contain a similar antigen. In some individuals, the primary

POTENTIAL CROSS-REACTIONS BETWEEN CAUSES OF CONTACT URTICARIA

Food/natural product	Risk (%)	Cross-reactions
Fruit (kiwi, avocado, banana)	10	Latex
Latex	35	Fruits (e.g. kiwi, avocado, banana)
A shellfish (e.g. crab)	75	Other shellfish (e.g. prawn, lobster)
A fish (e.g. salmon)	50	Other fish (e.g. swordfish, sole)
A grain (e.g. barley)	20	Other grains (e.g. wheat, rye)
A legume (e.g. peanut)	5	Other legumes (e.g. peas, beans, lentils)
Peach	55	Other Rosaceae fruit (e.g. apple, pear, cherry, plum)
Melon	90	Other fruits (e.g. watermelon, banana, avocado)

Table 16.6 Potential cross-reactions between causes of contact urticaria. If allergic to item in column 1, risk of cross-reacting with item in column 3.

sensitization is to the fruit, with latex sensitivity developing as a secondary phenomenon.

Common household sources of exposure to latex are gloves, balloons, latex contraceptives, latex mattresses and pillows, rubber bands, swimming caps, and baby pacifiers. The term "hypoallergenic glove" refers to latex gloves with reduced levels of accelerators and antioxidants (causes of allergic contact dermatitis); these gloves are not suitable for individuals allergic to latex (with immediate-type hypersensitivity).

Non-latex alternatives should be sought. Vinyl (PVC) gloves are suitable for home use. For those in the medical and dental professions, alternative gloves, typically nitrile (both sterile and non-sterile), are available from the major glove suppliers. Affected individuals should warn any doctor or dentist that they visit of their sensitivity so that measures can be taken to prevent a reaction. The most severe reactions have followed mucosal and parenteral exposures. Death has occurred following the use of a natural rubber latex cuff on a barium enema device and anaphylaxis after intraoperative, oral, or vaginal exposure to latex gloves. Use of a bracelet or necklace to alert medical professionals in the event of an emergency has been advocated.

Low-molecular-weight chemicals

Although rare, these chemicals can be important causes of occupational contact urticaria in the industrial setting. Some are also potential causes of occupational asthma. The diagnosis may prove difficult to establish because skin testing may require conjugation of the low-molecular-weight chemical with protein to form the allergen. Chemicals (and industries) associated with contact urticaria include: antibiotics (pharmaceutical industry); ammonium persulfate and para-phenylenediamine (hairdressing); phthalic anhydrides, epoxy resin systems, and polyfunctional aziridines (plastics and glue industry); and reactive dyes (textile workers).

Protein contact dermatitis

The term "protein contact dermatitis" was originally used to describe an eczematous reaction to protein-containing material in food handlers (see Table 12.5). The reactions were both allergic and non-allergic, although many had a positive prick test or the presence of specific IgE antibodies, implying an IgE-mediated mechanism. In some, positive patch tests pointed to the coexistence of delayed-type hypersensitivity. The clinical picture is usually that of a chronic eczema with episodic exacerbations following contact with the allergen[22].

Pathology

The histologic findings of contact urticaria are described in Chapter 18.

Differential diagnosis

After a detailed history and clinical examination, skin testing may be performed to confirm the diagnosis of contact urticaria. When the patient has experienced anaphylactic symptoms and a specific IgE test is available, the blood test may confirm the diagnosis, avoiding the risk of anaphylaxis as a result of skin testing. Skin testing should be performed with appropriate positive and negative controls. With an unknown allergen, exposure should be graded; an initial application test (open and subsequently occluded) is followed by a prick test and, if necessary, an intradermal test. If the patient has a positive test, control individuals should be tested; a positive response in the latter group points to the presence of a nonimmune contact urticant. While commercial allergen extracts are available, it should be remembered that, unless adequately standardized, they may not contain the relevant protein allergens, resulting in a false-negative test result. The gold standard for testing is a sample of fresh material. Skin tests should only be performed where resuscitation facilities are available.

In the case of latex, the specific IgE blood test is not sensitive and a negative test does not exclude the diagnosis (Fig. 16.11). While skin tests with glove extracts have been recommended, many gloves now contain low levels of latex protein and prick testing with these homemade extracts frequently leads to false-negative results. Prick test solutions of latex are commercially available, some of which claim >98% sensitivity and 100% specificity (Fig. 16.12). If a particular glove type appears to elicit symptoms, a so-called "prick to prick" test can be used: the suspected item itself is pricked with the lancet, after which the patient's skin is pricked with the antigen-"contaminated" lancet. The final arbiter is a usage test in which a patient wears the suspect glove on a moistened hand and is observed for any reaction.

In the absence of a latex allergy, localized symptomatic dermographism is a common cause of urticaria to gloves. Lastly, a proportion of individuals who have reactions to gloves have symptoms caused by irritation.

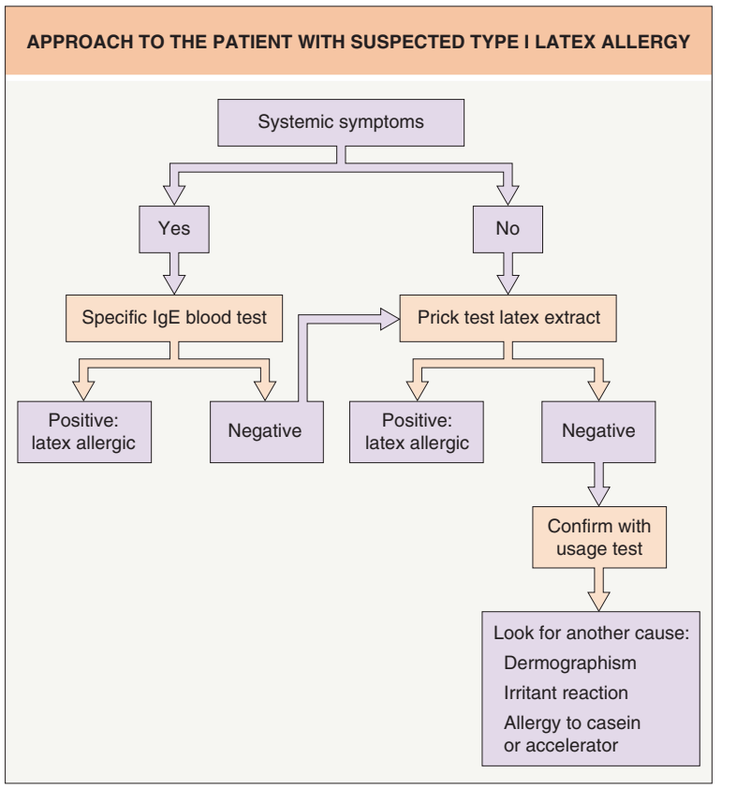


Fig. 16.11 Approach to the patient with suspected type I latex allergy. IgE-mediated immediate hypersensitivity is detected by prick tests, whereas delayed-type hypersensitivity, which manifests as allergic contact dermatitis, is detected by patch testing. In the open usage test, the patient wears the suspect glove on a moistened hand.



Fig. 16.12 Positive prick test with a commercial latex extract (L). Histamine (H; 10 mg/ml) and saline (C) controls are appropriately positive and negative. The histamine-positive control confirms that the effects of previous medications (including antihistamines) are no longer an issue and the negative control assesses for dermographism. When a standardized allergen is available for a prick test, a small drop is placed on the skin and the skin is pierced with a special lancet with a 1 mm tip. Surplus allergen is blotted off and a fresh lancet is used for each test substance to prevent cross-contamination. Reactions develop over 15 minutes and a wheal 3 mm larger than the negative control is considered positive.

Treatment

Management consists of avoidance, as desensitization for the majority of involved allergens is not available. Avoidance may be achieved by improved occupational hygiene and the use of PPE, but in extreme circumstances may necessitate a change of occupation. Treatment of the acute episode includes the use of systemic antihistamines and epinephrine (adrenaline), depending on the severity of the attack.

In the case of latex, the use of powder-free gloves containing low levels of protein has been shown to prevent the development of latex hypersensitivity by reducing the level of exposure in the at-risk population. There has also been a movement in healthcare facilities to use non-latex gloves.

Occupational Skin Cancer

Key features

- A skin cancer in which occupation has played a major etiological role
- In the workplace, the most important exposures are UV radiation, ionizing radiation, and carcinogenic chemicals (e.g. polycyclic hydrocarbons)

Introduction

Occupational skin cancers[23] have been estimated to account for <1% of all skin cancers. In a study of workers exposed to coal and diesel combustion products, the relative risk for developing non-melanoma skin cancer was 1.5%[24]. The tumor most frequently associated with occupational chemical exposure is squamous cell carcinoma (SCC).

History

The first association between occupation and cancer was made in 1775. Sir Percivall Pott, a surgeon at St Bartholomew's Hospital in London, described the occurrence of scrotal cancer in chimney sweeps. The carcinoma was often preceded by keratotic lesions known as soot warts. In 1873, von Volkmann described skin cancers from exposure to the distillation products of tar and pitch.

In the early 1800s, inorganic arsenic was associated with skin cancers, especially of the scrotum in smelter workers, but also from exposure in the mining industry and in users of end products (e.g. sheep dip). In the early twentieth century, ionizing radiation was recognized as a cause of radiodermatitis followed by skin cancer, particularly of the hands of medical workers administering radiotherapy.

Epidemiology

As carcinogens have become recognized and limits on occupational exposure introduced, solar UV exposure has risen to account for ~95% of cases of occupational skin cancer reported in the UK. In Australia, the most common cause of compensated occupational cancer (of all types) was UV exposure (22%), followed by asbestos (21%)[25]. It was estimated that 34 000 cases of non-melanoma skin cancer per year and 4% of cases of cutaneous melanoma in men were attributable to occupation. Recently, in Germany, actinic keratoses (AKs) and cutaneous SCCs were recognized and compensated as occupational diseases, provided in the case of AKs they cover at least 4 cm^2 or ≥5 separate AKs develop each year[26]. The SCCs must arise in sun-exposed skin and the worker must have been occupationally exposed to an additional 40% more UV than that of an indoor worker, e.g. at age 50 the worker would have to have spent 15 years in an outdoor occupation.

Occupations at high risk of occupational skin cancer include:

- outdoor workers, especially in agriculture and construction industries, and welders (UV exposure). Squamous cell carcinoma occurs with an odds ratio (OR) of 1.77 (95% confidence interval [CI] 1.40–2.22; p<0.001) and basal cell carcinoma with an OR of 1.43 (95% CI 1.23–1.66; p=0.0001) amongst outdoor workers[27]
- workers exposed to polycyclic hydrocarbons (e.g. tars, pitches, oil fractionation products); in addition to direct skin contact, fumes may be inhaled
- workers exposed to arsenic in glass production, copper, zinc or lead smelting, and the production of pesticides, herbicides, and semiconductors
- radiologists, dentists, X-ray technicians, and those who work with radioactive materials (ionizing radiation).

Pathogenesis

The major carcinogenic hazards include UV radiation, ionizing radiation, and carcinogenic chemicals. Occupationally induced cancers are not pathologically different from those which arise spontaneously. However, the former tend to occur at an earlier age than spontaneous tumors at the same anatomic site. They arise following repeated or continuous exposure to the carcinogen, and there is a long latency period between the exposure to the carcinogen and appearance of the tumor which can make it difficult to attribute causation.

There are two major classes of chemical carcinogens: (1) polycyclic aromatic hydrocarbons including benzo(a)pyrene; and (2) aromatic amines such as dichlorobenzidine, an intermediate in the dyestuffs industry. For many compounds, carcinogenic mechanisms are not well understood.

The molecular pathogenesis of UV radiation is discussed in Chapters 86 and 107.

Clinical features and diagnosis

In evaluating a patient with suspected UV-related occupational skin cancer, a careful history is required to establish the relative contributions of work and leisure exposure. The final judgment is essentially clinical.

With polycyclic aromatic hydrocarbons, a variety of skin changes may precede the development of cancer and aid in the clinical diagnosis. Associated changes include (in order of development) erythema and burning, folliculitis, poikiloderma, and keratotic papillomas (tar warts) within the poikilodermatous skin. The verrucous tumors may then develop into SCC, although basal cell carcinomas and keratoacanthomas also occur.

The clinical features and diagnosis of these cutaneous malignancies are discussed in detail in Chapters 108 and 113.

Pathology and treatment

The pathology and treatment of skin cancers are discussed in detail in Chapters 108 and 113.

Occupational Acne

Key features

- Open and closed comedones
- Non-inflamed nodules and cysts
- Inciting factors include exposures to oils, halogenated polycyclic hydrocarbons, and repeated frictional trauma

Introduction

Occupational acne is a form of acne resulting from various chemical exposures as well as environmental and physical factors. Chloracne is a rare acne-like skin condition caused by certain toxic chemicals and is a cutaneous sign of systemic exposure.

History

Chloracne was first reported in 1897. In 1949, the first descriptions of human exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)-contaminated chemicals were reported after a trichlorophenol reactor explosion in Nitro, West Virginia, USA. The majority of health effects have been reported among groups with high exposure, including occupational populations such as chemical production workers, pesticide applicators, and individuals who handled or were exposed to materials treated with 2,3,7,8-TCDD-contaminated pesticides. In addition, residents of communities contaminated with tainted waste oil (Missouri, USA) and industrial effluent (Seveso, Italy) have been affected[28]. During the Vietnam War, chloracne in US troops was ascribed to exposure to the defoliant Agent Orange. More recently, dioxin poisoning was implicated in the development of chloracne in the Ukrainian President Viktor Yushchenko.

Epidemiology

Oil acne is the most common form of occupational acne.

Pathogenesis

Continued exposure to oils results in reactive hyperkeratosis and subsequently follicular occlusion with typical manifestations of acne vulgaris.

Chloracne is caused by exposure to certain halogenated polycyclic hydrocarbons such as polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs)[29], which are most often found in fungicides, insecticides, herbicides, and wood preservatives. It occurs within 2 months of exposure to chloracnegens and can persist for years despite cessation of exposure. The condition is always a sign of systemic exposure to the causal agent(s), but entry may occur via percutaneous absorption as well as from inhalation or ingestion of the chemicals. After exposure of workers in a large chemical factory to hexachlorobenzene[30], blood levels in those with chloracne were compared to the levels in workers without chloracne. In the chloracne group, blood levels ranged from 1168 to 22 308 pg/g blood lipid. In the exposed but chloracne-free group, the range was from 424 to 662 pg/g. It was concluded that chloracne developed at blood levels between 650 and 1200 pg/g.

Clinical features

Oil acne and tar acne

Contact with acnegenic substances, such as creosote, oils and greases, can worsen existing acne. Oils used in industry, such as cutting oils (paraffin/oil mixtures), tars (pitch and creosote), and crude petroleum oils such as diesel oil, can all cause acne. Lesions may develop both in the usual sites for acne and in unusual sites, including beneath clothing that is saturated with oils (e.g. arms, abdomen). Oils mists can also induce acneiform eruptions.

Acne mechanica

Acne mechanica is a form of acne, usually inflammatory, that is exacerbated by repeated frictional trauma that occludes the follicle. It is localized to sites of pressure, e.g. the back in long-distance drivers, the neck in violinists, the chin in football players who wear helmets with chin straps, the face from mask-wearing during the SARS-CoV-2 pandemic[9].

Acne cosmetica

Certain cosmetic ingredients used by models and thespians, e.g. lanolin, petrolatum, some vegetable oils, can induce comedo formation.

Chloracne

Chloracne is distinguished from ordinary acne vulgaris by the predominance of open (over closed) comedones and a concentration of lesions over the malar crescent and behind the ears (Fig. 16.13). The first sign of chloracne may be excessive oiliness of the skin. This is accompanied or followed by the appearance of numerous open comedones. In mild cases, open comedones may be limited to the area around the eyes, extending across the temples to the ears. In more severe cases, they may appear more extensively on the body, especially in the malar region, other facial areas, behind the ears, and on the arms. The open comedones are usually accompanied by fluid-filled cysts and by an increased or darker growth of body hair.

As the disease progresses, milia form together with distinctive yellowish epidermoid inclusion cysts (some of which may become inflamed) on the face, behind the ears, and on the neck, buttocks, scrotum, and thighs. Some authors have proposed using the term "metabolizing acquired dioxin-induced skin hamartomas" for these dioxin-induced cysts[31]. The skin may become thicker and hyperpigmented and it may desquamate or peel. In severe cases, ulcerations and permanent scars appear. Chloracne fades slowly after exposure. Minor involvement may disappear altogether, but more severe disease may persist for years. This disorder is difficult to treat and can last for long periods without known additional exposure to chloracnegens.

In addition to conjunctivitis and "ophthalmic acne", there may be systemic manifestations including altered liver function (elevated transaminases), headaches, and peripheral neuropathy.

Acne due to halogens

Chemicals that contain iodides, bromides, and other halogens can induce an acneiform eruption similar to that due to corticosteroids (see Chs. 36 and 125); however, the iodide-induced eruptions (i.e. iododerma) may be more severe. Patients with bromoderma may also have lesions that resemble pyoderma gangrenosum.



Fig. 16.13 Chloracne. Note involvement of retroauricular skin with numerous comedones (primarily closed) and cysts. The clinical differential diagnosis includes folliculotropic mycosis fungoides.

Pathology

Histopathologic features of comedones are reviewed in Chapter 36. Small infundibular cysts and dilated infundibula filled with orthokeratotic plugs are seen in chloracne. A disappearance of sebaceous glands has been described[31].

Treatment

Treatment consists primarily of avoidance of the cause, although some forms can be persistent and require treatments designed for acne vulgaris, e.g. topical or oral retinoids (see Ch. 36). However, chloracne is particularly recalcitrant to therapy.

Vibration White Finger

Synonyms: ■ Hand–arm vibration syndrome ■ Dead finger

Key features

- Development of a white finger or fingers in response to cold
- Associated transient loss of sensation
- Possible permanent finger neuropathy and pain in the affected limb
- Associated with exposures to vibrations between 30 and 300 Hz
- Workers at risk include operators of chainsaws and pneumatic tools

Introduction

Vibration white finger is a relatively frequent disorder among operators of chainsaws, pneumatic tools, and hand grinders who work in cold climates[32]. Up to half of the exposed workforce can be affected.

History

Loriga first described the disorder in Italian marble-quarry workers in 1911. Six years later, this was followed by a description in sandstone cutters in Indiana, USA.

Epidemiology

Prevalence studies have suggested a relationship between symptoms and degree of exposure. This varies, however, with the type of tool and the work process involved. From 1972 to 1990, the prevalence amongst Finnish lumberjacks fell from 40% to 5%. This was attributed to a reduction in the weight and acceleration-induced vibration of their chainsaws[33].

It has been suggested that vibration white finger does not occur in countries with a warm climate. However, this may reflect the absence of cold temperatures that serve as a trigger for symptoms rather than the absence of vibration-induced vascular changes. In tropical countries, neurological symptoms predominate[34].

Pathogenesis

Vibrations between 30 and 300 Hz are most strongly associated with development of this disorder. While increased activity of the sympathetic nervous system is viewed as the major cause of vibration white finger, local factors are likely also important. Vibration-induced damage to endothelial vasoregulatory mechanisms with alteration in α-adrenoceptors and impaired release of nitric oxide have been described.

Smoking is known to contribute to the development of the disorder, presumably because of the vasoconstrictive effect of nicotine.

Clinical features

Onset may occur within 3 months of beginning work but more frequently it takes 2–3 years to develop. Typically, a white patch of skin develops in response to cold-induced vasospasm. It is well demarcated from surrounding areas. Reduction in sensation occurs because the touch receptors are unable to function without adequate blood supply and this results in reduced dexterity. Episodes cease upon rewarming, often with the development of reactive hyperemia. Although caused by vibrating tools, attacks are not usually triggered by work with the vibrating tool.

The condition is graded according to the severity and frequency of symptoms, starting on the tips of the fingers (stage 1) and spreading to affect the whole digit (stage 3). In the most severe form, there are trophic changes and ulceration (stage 4). To aid in the diagnosis, finger skin temperature and finger systolic blood pressure can be measured in response to cold exposure, but the results are not discriminatory.

Pathology

The histopathologic features of vibration white finger include a significant reduction in the number of unmyelinated nerve fibers containing the neuropeptide calcitonin gene-related peptide (CGRP). There also may be hypertrophy of arterial smooth muscle. However, histology is not routinely utilized in the diagnosis of vibration white finger.

Differential diagnosis

In contrast to the symmetric distribution seen in Raynaud disease, in vibration white finger the blanching is asymmetric and occurs only on those digits most exposed to vibration; the thumbs are usually spared.

OCCUPATIONAL INFECTIONS ACQUIRED FROM ANIMALS OR HUMANS WITH CUTANEOUS MANIFESTATIONS

Occupation	Infection	Organism	Animals/other humans
Healthcare Sex industry Laboratory worker	Herpetic whitlow	Herpes simplex virus	Humans
	Scabies	*Sarcoptes scabiei* var *hominis*	
	Syphilis	*Treponema pallidum*	
	AIDS	Human immunodeficiency virus	
	Hepatitis B and C viral infection	Hepatitis B virus, hepatitis C virus	
	Mpox	Orthopoxvirus	
Farmer Abattoir* worker Veterinarian	Orf	Parapoxvirus	Sheep, goats, reindeer
	Milker's nodule	Parapoxvirus	Cows
	Brucellosis	*Brucella suis*; *B. abortus*; *B. melitensis*	Pigs; cattle; sheep, goats
Farmer Wool sorter Dock worker Butcher	Anthrax	*Bacillus anthracis*	Cattle, sheep, goats, horses, buffalo, camels
Fisherman Tropical fish keeper Fish market worker	Fish tank granuloma	*Mycobacterium marinum*	Fish
Butcher Abattoir* worker Meat and fish packers	Butcher's warts	Human papillomavirus, most commonly type 7 (see Ch. 79)	Humans
	Impetigo	*Staphylococcus aureus*	
	Erysipelas	Group A streptococci	
Fisherman Abattoir* worker Farmer Butcher, cook Veterinarian	Erysipeloid	*Erysipelothrix rhusiopathiae (insidiosa)*	Shellfish, fish, birds and mammals (esp. pigs)
Fisherman	Cellulitis	*Vibrio vulnificus*	Salt water
Farmer Veterinarian	Tinea corporis, capitis, and barbae due to zoophilic species	*Microsporum canis*	Cats, dogs
		M. nanum	Pigs
		Trichophyton mentagrophytes	Small mammals
		T. verrucosum	Cattle
		M. (T.) gallinae	Chickens

*Slaughterhouse.

Table 16.7 Occupational infections acquired from animals or humans with cutaneous manifestations. Laboratory personnel can also acquire primary cutaneous forms of dimorphic fungal infections. AIDS, acquired immune deficiency syndrome.

However, Raynaud phenomenon can also result from repeated occupational trauma, particularly in those who use tools that require a squeezing action, e.g. farmers, mechanics.

The hypothenar hammer syndrome results from occlusion of the ulnar artery as a consequence of repeated trauma to the palms and may be misdiagnosed as Raynaud phenomenon.

Treatment

The prognosis for affected individuals is good: the disease regresses upon cessation of exposure. This is particularly true in the early stages, provided there are no other environmental or constitutional factors contributing to the disorder. As a consequence, no specific treatment may be required other than avoidance[35]. Therapeutically, topical nitroglycerin ointment or sustained-release glyceryl trinitrate patches are effective, but the condition relapses upon withdrawal. Various systemic agents used for Raynaud disease, e.g. calcium channel blockers, have also been used for symptom control (see Ch. 43).

Infections

Many occupations, particularly those involving contact with animals, are associated with exposure to infectious agents. For example, individuals with occupations that involve wet work combined with rough physical conditions, such as butchers, slaughterhouse workers, and meat and fish packers, commonly develop infections with pyogenic bacteria and human papillomavirus (butcher's warts) through cuts and abrasions. Epidemics of methicillin-resistant *Staphylococcus aureus* infection have also occurred in professional football players in the US[36].

In the metal working industry, staphylococcal folliculitis can develop as a result of exposure to contaminated work materials such as coolant fluid. In addition, outdoor workers are exposed to environmental pathogens either by direct contact or implantation with soil or plants (e.g. mycetoma, chromomycosis, sporotrichosis), as well as following inoculation, most commonly via insect bites (e.g. Lyme disease, tularemia, spotted fevers).

Common infections may also occur more frequently as a result of environmental factors in the workplace. Increased humidity may lead to bacterial and fungal infections (due to dermatophytes or *Candida* spp.) in flexural body sites along with maceration of the skin. Pitted keratolysis caused by *Corynebacterium* spp. or *Micrococcus sedentarius* occurs on the soles in association with the use of occlusive footwear.

Infectious organisms related to specific occupations are summarized in Table 16.7. Further information on these infections[37] can be obtained by reference to the relevant chapter in this book (see Section 12).

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Dermatoses Due to Plants 17

Thomas W. McGovern

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Key features

- Plant constituents cause a variety of adverse reactions, including many cases of allergic contact dermatitis
- Plant dermatoses are due to a small minority of plants
- Urticaria, mechanical and chemical irritant contact dermatitis, phytophotodermatitis, and allergic contact dermatitis are the most common plant dermatoses
- Two major plant allergens are urushiol (Anacardiaceae family which includes poison ivy) and sesquiterpene lactones (Asteraceae family which includes chrysanthemums)

Important botanical synonyms

New family name	Old family name
Apiaceae	Umbelliferae (Parsnip family)
Arecaceae	Palmae (Palm family)
Asteraceae	Compositae (Daisy family)
Brassicaceae	Cruciferae (Mustard family)
Fabaceae	Leguminosae (Pea family)
Lamiaceae	Labiatae (Mint family)
Poaceae	Gramineae (Grass family)

Rhus ≠ *Toxicodendron* or poison ivy (see text)

Non-immunologic urticaria = Toxin-mediated urticaria

INTRODUCTION

Contrary to the belief of patients, just because a product is "natural" and not "artificial", it doesn't mean it is safe. When patients discover that a "natural" skin care product is harming them, they are dumbfounded. The light only goes on in their minds when we point out that, "Poison ivy is natural, too." All the reactions described in this chapter are natural.

Plant reactions can be classified into urticaria (immunologic and toxin-mediated; see Chs. 16 & 18), irritant dermatitis (mechanical and chemical), phototoxic dermatitis (phytophotodermatitis), and allergic contact dermatitis. Table 17.1 lists the most common plant reactions.

Botanical Aspects

Becoming familiar with basic botanical nomenclature used for the over 390 000 plant species will help clinicians to better understand the literature that addresses plant-related dermatoses[1].

Poison ivy – just as allergenic despite a name change

It is occasionally necessary to change a plant's name. For example, the genus *Rhus* was once thought to be a cohesive, widespread genus that included poison ivy (previously known as *Rhus radicans* or *Rhus toxicodendron*). Research in the 1950s and 1960s revealed that poison ivy and its immediate relatives represented a distinct developmental lineage that should not be classified as *Rhus* but as a distinct genus, *Toxicodendron*, and thus the correct scientific name for common poison ivy is *Toxicodendron radicans*.

Binomial nomenclature

The nomenclatural scheme of botany and zoology gives every entity two names: a generic name followed by a specific epithet (e.g. *Toxicodendron radicans*). A reference to the person (authority) who first published the species name is often placed after the binomial name. The full binomial name of common poison ivy reads "*Toxicodendron radicans* (L.) O. Ktze". "(L.)" refers to Carl Linnaeus, who first named the plant with the specific epithet *radicans*. "O. Ktze" refers to Otto Kuntze, who transferred the epithet *radicans* from the genus *Rhus* into the genus *Toxicodendron*.

The genus, species, and any infraspecific epithets are called the "minor categories of nomenclature", and these names are used when citing a plant's name (Table 17.2). Genera are grouped into families, and if you know the family to which a plant belongs, you will probably be able to determine what kind of dermatologic manifestations (if any) it can cause.

Plant identification

The following recommendations should be followed to identify an unknown plant that you or your patient thinks is causing an eruption.

- *Collect specimens*. Herbs (low-growing plants with fleshy stems) should be collected in their entirety with their flowering and/or fruiting materials intact. For shrubs (low-growing plants with woody stems), the end of a branch (up to 60 cm) should be collected, with the leaves attached, as well as any flowering or fruiting materials present. You may press plants before submitting them for identification, or you can put them into a plastic bag with *no water added* and submit them with data on: (1) where that plant was collected; and (2) its habitat (cultivated in a garden; growing wild along a creek bank, in an open field, in high-elevation woodlands, etc.).
- *Involve a plant taxonomist*. Every US state and most Canadian provinces have an established mechanism for routine and rapid plant identification, and in most locales the service is free. In suburban and rural areas, the county or regional agricultural extension service or farm advisors are knowledgeable about the procedures for immediate plant identification, and they have access to the regional herbaria. Urban areas have similar services, usually accessed through the urban horticulturist of the state extension service, or through the local garden center or botanical garden. In other countries, look for a nearby herbarium housing a collection of flora of the region. A botanist who works there would likely be willing to help identify an unknown plant.

MOST COMMON PLANT DERMATOSES			
Binomial name	**Common name**	**Reaction type**	**Inciting agent**
Allium sativum	Garlic	ACD	Diallyl disulfide, allicin
		ICD	Probably the same
Alstroemeria spp.	Peruvian lily	ACD	Tulipalin A > B
Capsicum annuum	Hot peppers	Erythema/edema/burning	Capsaicin
Citrus latifolia	Persian lime	Phytophotodermatitis	Furocoumarins
Narcissus pseudonarcissus	Daffodils	ICD	Calcium oxalate
Opuntia spp.	Prickly pear and others	Mechanical irritant dermatitis	Glochids
Parthenium hysterophorus	Scourge of India, congress grass	ACD	Sesquiterpene lactones
Toxicodendron radicans	Poison ivy	ACD ICD (black-spot reaction)	Alkyl-catechols and resorcinols in urushiol
Toxicodendron diversilobum	Poison oak	ACD ICD (black-spot reaction)	Alkyl-catechols and resorcinols in urushiol
Tulipa spp.	Tulips	ACD	Tulipalin A > B
		ICD	Coarse hair on bulbs
Urtica dioica	Stinging nettle	Urticaria	Histamine
X *Dendranthema* cultivars	Chrysanthemums	ACD	Sesquiterpene lactones

Table 17.1 Most common plant dermatoses. These are admittedly biased by the anecdotal and unscientific observations as well as literature reviews of the author. ACD, allergic contact dermatitis; ICD, irritant contact dermatitis.

THE BASIC NOMENCLATURAL SCHEME FOR PLANTS, USING COMMON POISON IVY AS THE EXAMPLE	
Kingdom	**Plantae (Metaphyta)**
Division	Magnoliophyta (flowering plants)
Class	Magnoliopsida (dicotyledons)
Subclass	Rosidae
Order	Sapindales
Family	Anacardiaceae (sumac or cashew family)
Genus	*Toxicodendron*
Species	*radicans*
(Author's name)	(L.) O. Ktze

Table 17.2 The basic nomenclatural scheme for plants, using common poison ivy as the example. The distinctive ending for each category is underlined. Note that the minor categories of nomenclature have no special endings.

Patch Testing

Details of patch testing are beyond the scope of this chapter (see Ch. 14). The reader is also referred to the paper by Mitchell[2]. The most common allergenic plants and a proposed botanical screening tray are found in Table 17.3[3].

MOST COMMON RELEVANT BOTANICAL ALLERGENS AND PROPOSED BOTANICAL SCREENING TRAY		
Plant name	**Plant family**	**Test compound**
Achillea millefolium (yarrow) *Arnica* spp. *Chrysanthemum* cultivars *Matricaria chamomilla* (chamomile) *Tanacetum parthenium* (feverfew)	Asteraceae	Compositae mix II 6% in petrolatum, sesquiterpene lactones (SQLs) mix 0.1% in petrolatum, and parthenolide 0.1% in petrolatum
Alstroemeria spp.	Alstroemeriaceae	Alpha-methylene-gamma-butyrolactone 0.1% in petrolatum
Cananga odorata	Anonaceae	Cananga (ylang-ylang) oil 2% in petrolatum
Citrus aurantium var. *amara*	Rutaceae	Neroli oil 4% in petrolatum
Lavandula spp.	Lamiaceae	Lavender (absolute) 2% in petrolatum
Lichens (fungus–alga dual organisms)	Non-plant	Lichen acid mix 0.3% in petrolatum (contains usnic acid, atranorin, evernic acid)
Melaleuca alternifolia	Myrtaceae	Tea tree oil 5% in petrolatum
Mentha spp.	Lamiaceae	Spearmint oil 5% in petrolatum
Pelargonium cultivars	Geraniaceae	Geranium oil (Bourbon) 2% in petrolatum
Primula obconica	Primulaceae	2-methoxy-6-n-pentyl-4-benzoquinone (primin) 0.1% in petrolatum
Rosa damascena	Rosaceae	Rose oil (Bulgarian) 2% in petrolatum
Santalum album	Santalaceae	Sandalwood oil 2% in petrolatum
Taraxacum officinale	Asteraceae	Dandelion 2.5% in petrolatum

Table 17.3 Most common relevant botanical allergens and proposed botanical screening tray. This list may help to narrow down a potential botanical allergy in a patient who brings specimens into your office to examine[3]. Note this screening tray does not include urushiol. See Appendix in Chapter 14 for commercial sources of patch tests.

IMMUNOLOGIC CONTACT URTICARIA

Key features

- Atopy and frequent contact with fresh fruits and vegetables are risk factors
- May present as urticaria, pruritus, burning, or chronic dermatitis
- Oral allergy syndrome is mucosal contact urticaria caused by antigens similar to allergenic pollen
- Protein contact dermatitis represents an eczematous eruption arising from repeated urticarial reactions

Plant-induced urticarial reactions are divided into immune and non-immune (toxin-mediated [see next section]). Several cutaneous reaction patterns besides wheals are possible, e.g. erythema, dermatitis.

Epidemiology

Immunologic contact urticaria is rather uncommon. Approximately 95% of cases are work-related – long-time food handlers with underlying dermatitis are at greatest risk. However, fully half of patients with "protein contact dermatitis", a type IV eczematous eruption arising from repeated type I urticaria reactions, are not atopic.

Examples of reported urticants include common vegetables (e.g. celery, onions, potatoes, lettuce), fruits (e.g. tomatoes, bananas, lemons), herbs (e.g. parsley, dill) and nuts, as well as algae, lichens, shrubs, trees, and grasses.

Pathogenesis (see Ch. 18)

IgE-mediated release of vasoactive mediators from mast cells leads to local urticaria and, rarely, a "contact urticaria syndrome" that includes local wheals plus systemic symptoms involving the nose, throat, lungs, gastrointestinal tract, or cardiovascular system. The main cause seems to be histamine release, but prostaglandins, kinins, and leukotrienes probably augment the inflammatory response.

Clinical Features

Within 30 minutes of contact with certain fresh foods, affected individuals experience pruritus, erythema, urticarial swelling, and even dyshidrotic-like vesicles. Sometimes, individuals only develop burning or tingling without objective findings[4]. Theoretically, any plant can cause contact urticaria, especially with repeated exposures on the wet, macerated skin of food handlers. Cooking, processing, deep-freezing, or crushing fruits and vegetables generally reduces their allergenicity.

Some individuals become cross-sensitized to pollen and similar allergens in fruits or vegetables[5]. Upon eating a cross-reacting food, they experience sudden, IgE-mediated, oral cavity itching, stinging, and pain. Edema of the lips, tongue, palate, and pharynx typically ensue as the "oral allergy syndrome" (OAS) progresses. Gastrointestinal symptoms and anaphylaxis are possible if enough allergens are ingested. For example, 70% of European patients with immediate hypersensitivity to birch pollen develop OAS while eating apples, pears, cherries, peaches, plums, apricots, almonds, celery, carrots, potatoes, kiwis, hazelnuts, or mangoes. Pollen-associated foods are often, but not always, edible when heated.

The term "protein contact dermatitis" describes a chronic dermatitis in which patch tests are typically negative but prick tests to large protein allergens are positive[6]. Patients develop a chronic dermatitis – frequently on the hands and fingertips – that urticates within minutes of contact with the offending allergen (Fig. 17.1).

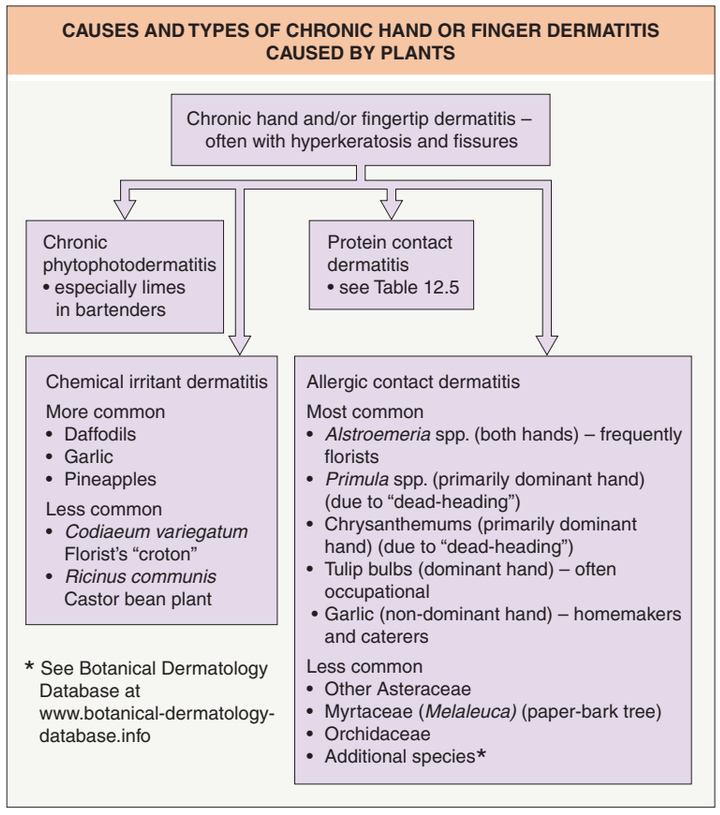


Fig. 17.1 Causes and types of chronic hand or finger dermatitis caused by plants.

Differential Diagnosis and Pathology

See Toxin-Mediated (Non-immunologic) Contact Urticaria and Chs. 16 & 18.

Treatment

Prevention is the preferred form of "treatment". Parenterally administered epinephrine (adrenaline) is required for anaphylactic reactions.

TOXIN-MEDIATED (NON-IMMUNOLOGIC) CONTACT URTICARIA

Key features

- Anyone can be affected
- Stinging nettles (*Urtica* spp.) are most common cause
- Reaction can be subjective only
- Sharp hairs on the plants can contain histamine, serotonin, and acetylcholine

History

Plants causing toxin-mediated urticaria have been used since antiquity as counterirritants in folk medicine, and Native Americans used stinging nettles to treat rheumatism, stomach upset, postpartum hemorrhage, paralysis, fevers, colds, and tuberculosis. Stinging nettle is used to produce homemade diuretics, and stem fibers were even used to make cloth until the early twentieth century.

Epidemiology

Urticaceae family members cause the majority of plant-induced contact urticaria. Because everyone exposed to the toxins develops urticaria, toxin-mediated urticaria is far more common than immunologic urticaria. Since few affected people seek medical attention, the true incidence of toxin-mediated urticaria is unknown. The most common culprit in the US is the stinging nettle (*Urtica dioica*; Fig. 17.2A)[7], which is widely scattered throughout the northern hemisphere (except in lowland tropical areas), especially in moist woods, roadsides, and on wasteland. Other common urticating plants are listed in Table 17.4.

Pathogenesis (see Ch. 18)

Inciting plants possess sharp hairs (trichomes) on leaves and stems (Fig. 17.2B,C). The proximal silicaceous hair is attached to a distal calcified portion that possesses a terminal bulb. When rubbed against, the bulb dislodges to reveal a beveled, hypodermic needle-like, hollow hair (Fig. 17.2D). The latter releases an irritant chemical cocktail (histamine, acetylcholine, serotonin) that supposedly serves as a defense mechanism against herbivores.

Clinical Features

Wheals achieve maximal size 3 to 5 minutes after contact, and erythema, burning, and pruritus last 1–2 hours. Paresthesias may last 12 hours or more. Although histamine, acetylcholine, and serotonin explain the early cutaneous reaction, they do not account for the persistent paresthesias.

Reactions to stinging nettle pale in comparison to those elicited by members of the *Dendrocnide* genus of the Urticaceae family. These trees grow up to 40 meters tall in eastern Australian rainforests. Young

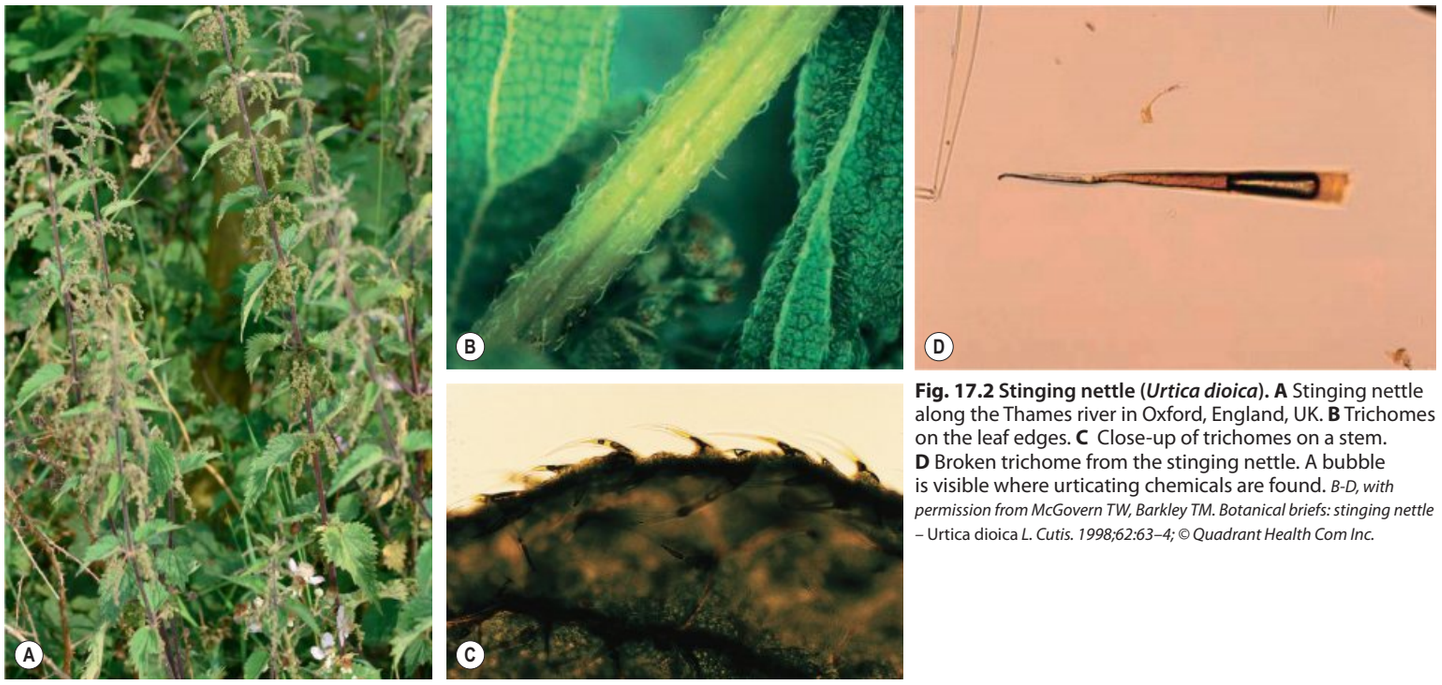


Fig. 17.2 Stinging nettle (*Urtica dioica*). A Stinging nettle along the Thames river in Oxford, England, UK. **B** Trichomes on the leaf edges. **C** Close-up of trichomes on a stem. **D** Broken trichome from the stinging nettle. A bubble is visible where urticating chemicals are found. *B-D, with permission from McGovern TW, Barkley TM. Botanical briefs: stinging nettle – Urtica dioica L. Cutis. 1998;62:63–4; © Quadrant Health Com Inc.*

THE MOST COMMON PLANTS CAUSING TOXIN-MEDIATED URTICARIA			
Family	**Genus**	**Species**	**Notes**
Urticaceae (nettle family)	*Urtica*	*dioica*, *urens*, *pilulifera*	Stinging nettles – worldwide
	Laportea	*canadensis*	"Wood nettle", 5-foot-tall perennial herb – NE USA
	Dendrocnide	*gigas*, *moroides*, *photinophylla*	Potentially deadly stinging trees – eastern Australian rainforests
Euphorbiaceae (spurge family)	*Acidoton*	*urens*	Tropical Americas
	Cnidoscolus	*stimulosus*	Spurge nettle – SE USA
		other species	Spurge nettles of tropical Americas
Hydrophyllaceae (water-leaf family)	*Wigandia*	*caracasana*, *urens*	Large-leafed shrubs – tropical Americas

Table 17.4 The most common plants causing toxin-mediated urticaria.

shoots are covered with stiff stinging hairs. Severe urticaria from these may last for weeks, and contact with water or cold objects reactivates the urticaria. Severe, intermittent, stabbing pains may follow the course of lymphatics. Human and animal deaths due to *Dendrocnide* contact have been documented.

Pathology (see Ch. 18)

Five minutes after contact with *Urtica dioica*, dermal edema and telangiectasias with or without mild spongiosis are seen. At 12 hours, the edema resolves but vasodilation persists. Some patients develop spongiosis in conjunction with a neutrophilic and/or lymphocytic infiltrate. Mast cells are observed within the papillary dermis at 12 hours, but not at 5 minutes.

Differential Diagnosis (see Ch. 18)

Although the evaluation of such patients is difficult, office testing of suspected allergens or toxin-containing plants may involve one of several methods[4]. The most sensitive tests for immunologic contact urticaria are the prick and scratch-chamber tests. For the scratch-chamber test, a 5-mm scratch is made on the back or forearm. Test material is applied and occluded with a Finn chamber for 15 minutes. The site is examined following Finn chamber removal and every 15 minutes for an hour. After reading, the chamber can be replaced for 48 hours to test for delayed hypersensitivity.

The open application test provides the most reliable way to test for toxin-mediated urticaria. Samples (0.1 ml) from a series of dilutions are each spread onto discrete 3 × 3 cm areas of skin. Sites are observed every 10–15 minutes for an hour. Maximal erythema and edema typically occur 30–40 minutes after application.

Treatment

Most stings are benign, self-limited, and require no treatment. Trichomes may be removed with glue and gauze as described in the next section. Topical pramoxine or oral analgesics may provide some symptomatic relief.

MECHANICAL IRRITANT DERMATITIS

Key features

- Large spines (modified leaves) and thorns (modified branches) cause penetrating injuries and secondary infection
- Small fishhook-shaped spines (glochids) can embed in the skin
- Prickly pears are a cause of glochid dermatitis

Epidemiology

Mechanical irritant dermatitis can affect anyone. Many plants, including most cacti, can inflict mechanical injury via small or large emergences. Generally, the amount of damage to the skin is inversely proportional to the size of the emergence. Many of the plant families that can cause mechanical irritant dermatitis are listed in Table 17.5.

COMMON PLANTS KNOWN TO CAUSE MECHANICAL IRRITANT REACTIONS		
Family	**Genus species**	**Notes**
Amaranthaceae	*Kali tragus*	Tumbleweed or Russian thistle – sharp-edged spines penetrate skin
Araliaceae	*Hedera helix*	Common ivy – leaf-borne stellate hairs detach as leaves age
Asteraceae	*Carduus* and *Cirsium* spp.	Thistles
	Lactuca serriola	Prickly lettuce
Boraginaceae	*Borago officinalis*	Borage – sharp, stiff leaf and stem hairs
Cactaceae	*Opuntia* spp.	Prickly pears; "Sabra dermatitis"
Liliaceae	*Tulipa* spp.	Coarse fibers on tulip bulb tunics cause irritant component of "tulip fingers"
Moraceae	*Ficus* spp.	Figs – abrasive bristles on leaves and fruit
	Morus spp.	Mulberries – abrasive bristles on leaves and fruit
Nyctaginaceae	*Bougainvillea*	Sharp spines on stems and spear-shaped crystals in trichomes on leaves (Brazil native)
Poaceae	Many spp.	Grasses – fine hairs, prickly spikes, and cutting leaf edges
Proteaceae	*Grevillea* spp.	Terminal, sharp points on leaves – Australia
Rosaceae	*Rosa* spp.	Thorns can cause penetrating injuries, tenosynovitis, and foreign body granulomata
Rubiaceae	*Galium aparine*	"Goosegrass" – hooked prickles on fruit, stems, leaves
Scrophulariaceae	*Verbascum thapsus*	"Mullein" or "flannel-plant" – woolly hairs on leaves used as facial rubefacient
Sterculiaceae	*Fremontodendron* spp.	"California glory" possesses stiff, stellate hairs

Table 17.5 Common plants known to cause mechanical irritant reactions. Although numerous plants possess irritant appendages, some of the well-known ones are listed here.

Pathogenesis

Whereas cacti possess large spines, their smaller glochids cause more notorious dermatologic problems. The glochids – tufts of hundreds of short, barbed or hooked hairs – arise from pincushion-like structures called "areoles", from which larger spines may also arise. The minute, barbed glochids (Fig. 17.3A) often point outward and backward like a fishhook and produce considerable irritation and pruritus after penetrating the skin. For example, *Opuntia microdasys* ("polka dot cactus", "bunny ears cactus"), a house and garden favorite, bears disarming-appearing "fluffy" clusters of 100–200 glochids on its pads (see Fig. 17.12).

Clinical Features

Prickly pear glochids from *Opuntia* spp. cause "Sabra dermatitis", a pruritic, papular eruption occurring among prickly-pear pickers and those who unwarily stumble into burglar-proof hedges of this native Mexican plant (Fig. 17.3B). The fruit contains the highest concentration of glochids (Fig. 17.3C), and the ensuing eruption can resemble fiberglass dermatitis or scabies. Prickly pears should be picked only when wetted, and harvesting should cease when it is windy, since the glochids can become airborne.

All 200 or so species of *Opuntia* are native to the New World, ranging from New England and British Columbia southward to the Straits of Magellan. Numerous species have become established in the Mediterranean basin, South Africa, South Asia, and Australia.

Spine and thorn injuries can be complicated by cutaneous inoculation of microorganisms such as *Clostridium tetani* and *Staphylococcus aureus*. Grasses, sphagnum moss, and rose thorns can transmit *Sporothrix schenckii*. Atypical mycobacteria such as *Mycobacterium kansasii* (blackberries), *M. marinum* (cactus spines), and *M. ulcerans* (spiky tropical vegetation) have also added infectious insult to mechanical injury.

Treatment

In a controlled study in rabbits, *Opuntia* glochids were most effectively removed by first detaching the larger clumps with tweezers and then applying glue and gauze to the affected area. After the glue dried, the gauze was grasped and peeled off, resulting in the removal of 95% of implanted glochids[8].

CHEMICAL IRRITANT DERMATITIS

Key features

- Calcium oxalate in daffodils is a major cause of plant-related irritant dermatitis in florists and horticulturalists
- Spurges (including poinsettias) contain irritant phorbol esters in latex
- Capsaicin in hot peppers affects cutaneous nerves, but not the skin



Fig. 17.3 Prickly pears (*Opuntia* spp.) and their glochids. A Microscopic appearance of glochids from *Opuntia microdasys*. **B** Prickly pear (*Opuntia ficus-indica*) habit. **C** Prickly pear (*Opuntia ficus-indica*) fruit. Fine spines and glochids are visible. *Courtesy Dirk Elston, MD.*

History

Plant-derived irritant chemicals have been recognized for centuries. Native Mexican Indians once used smoke from burning peppers (*Capsicum* [Solanaceae]) as a weapon against enemies, and latex from the manchineel tree (*Hippomane mancinella* [Euphorbiaceae]) was used by Caribbean people as poison for arrow tips.

Epidemiology

Several major plant families found throughout the world contain chemical irritants (Table 17.6).

Pathogenesis, Clinical Features, and Treatment (see Ch. 15)

Calcium oxalate, one of the most common chemical irritants, is found in *Dieffenbachia picta* (Araceae), a plant that decorates millions of homes and public places. Upon contact with a moist surface, the leaves release water-insoluble calcium oxalate. When leaves are chewed, salivation, burning, mucosal edema, and blistering follow. This causes hoarseness or aphonia, hence the common name "dumb cane". Treatment includes parenteral corticosteroids, antacid mouthwashes, and analgesics; antihistamines are of no benefit. The pain and edema wane over 4–12 days.

Calcium oxalate enhances the irritancy of other chemicals, including the proteolytic enzyme bromelain (bromelin) found in pineapples. Pineapple workers often develop cracks, fissures, fingerprint loss, and microhemorrhages on their hands. Calcium oxalate-induced microabrasions allow bromelain to exert its proteolytic effect on dermal blood vessels. Nitrile gloves can be worn for protection.

Bulb dermatitis, though less dramatic, is more common[9]. Daffodil sap, found not only in bulbs but also in stems and leaves, contains calcium oxalate and causes "daffodil itch", probably the most common dermatitis in florists. Dryness, scaling, fissures, and erythema develop on the fingertips, hands, and forearms. Bulbs of several other plants (e.g. tulips, hyacinths) also commonly cause dermatitis. Allergens found in garlic bulbs act as irritants at high concentrations leading to second- and third-degree burns as well as subungual hyperkeratosis and hemorrhage that can mimic nail psoriasis.

While spurges (Euphorbiaceae) are notorious for their irritant latex, they derive their common name from the purgative properties of their seeds. The milky latex contains irritant phorbol esters, diterpenes, and daphnane esters that may cause a painful, blistering dermatitis and even temporary blindness if the latex contacts the eye. Sitting under a manchineel tree in the Caribbean during a rainstorm will lead to intense cutaneous burning, erythema, and bullae, often accompanied by periocular swelling through transfer of the latex by rain. Manchineel fruit is known locally as the "apple of death". The latex of the best-known family member, the poinsettia (*Euphorbia pulcherrima*), is only mildly irritating.

Buttercups (Ranunculaceae) contain the glycoside ranunculin that is converted to protoanemonin after plant injury. Protoanemonin causes severe, linear vesiculation that may resemble early phytophotodermatitis, but no hyperpigmentation ensues. Because protoanemonin rapidly polymerizes to the non-irritant anemonin, only freshly damaged plants cause reactions.

"Chili burns" commonly occur among those who remove skins from large batches of roasted chili peppers (*Capsicum annuum*). When applied to skin, the active principle, capsaicin, depolarizes nerves causing vasodilation, smooth muscle stimulation, glandular secretion, and sensory nerve activation. Because only nerves are affected, there is erythema but no vesicles or bullae. Symptoms may be delayed and last hours to days. The best home remedy for chili burns is handwashing with soap and water followed immediately by 1 hour of immersion in vegetable oil to remove the fat-soluble capsaicin.

The "century plant" (*Agave americana*) grows in temperate, subtropical, and tropical climates and forms rosettes of tough, sword-shaped leaves with spiny margins. The marked pruritus and stinging that follows within five minutes of contact with the agave leaf is thought to be caused by latex-derived calcium oxalate crystals and saponins. Purpura may appear subsequently. Soldiers have been known to try to "earn" sick leave by rubbing broken leaves on their skin to induce a severe vesiculopustular irritant dermatitis, often accompanied by systemic symptoms[10].

PLANTS MOST COMMONLY IMPLICATED IN CAUSING CHEMICAL IRRITANT DERMATITIS

Family	Binomial name	Common name	Irritant chemical (location)
Agavaceae	*Agave americana*	Century plant	Calcium oxalate, saponins (latex throughout plant)
Alliaceae	*Allium sativum*	Garlic	Thiocyanates (bulbs)
Amaryllidaceae	*Narcissus* spp.	Daffodil, narcissus	Calcium oxalate (stems, leaves, bulbs)
Anacardiaceae	*Anacardium occidentale*	Cashew tree	Cashew nut shell oil (mesocarp [middle layer] of nut shell [irritant and allergenic])
Araceae	*Dieffenbachia picta*	Dumb cane	Calcium oxalate (leaves and fruits)
	Philodendron spp.	Philodendron	Calcium oxalate (leaves)
Brassicaceae	*Brassica nigra*	Black mustard	Thiocyanates (all parts)
	Raphanus sativus	Radish	
Bromeliaceae	*Ananas comosus*	Pineapple	Bromelain (stem > fruit) Calcium oxalate (all parts)
Euphorbiaceae	*Codiaeum variegatum*	Florist's "croton"	Phorbol esters (latex in stems, leaves, fruits)
	Euphorbia esula	Leafy spurge	
	Hippomane mancinella	Manchineel tree	Standing in rain beneath manchineel tree can transfer highly irritant latex and even cause blindness
	Euphorbia pulcherrima	Poinsettia	
Liliaceae	*Hyacinthus orientalis*	Hyacinth	Calcium oxalate (bulbs)
Polygonaceae	*Rheum rhaponticum*	Rhubarb (false, rhapontic)	Calcium oxalate (leaves)
Ranunculaceae	*Ranunculus* spp.	Buttercups	Protoanemonin (freshly damaged plant parts)
	Aquilegia spp.	Columbine	
	Caltha spp.	Marsh marigold	
Solanaceae	*Capsicum annuum*	Hot pepper	Capsaicin (placenta of fruit [no dermatitis, only erythema, edema, burning])

Table 17.6 Plants most commonly implicated in causing chemical irritant dermatitis.

PHYTOPHOTODERMATITIS

Key features

- Non-immunologic – it can happen to anyone
- Need UVA light plus topical or oral contact with photosensitizer
- Furocoumarins (psoralens and angelicins) are the most common photosensitizers
- Limes, celery, and rue (herb-of-grace) are the most common causes
- Potential photosensitizing plants of the family Apiaceae can be identified by umbel flower structure

Phytophotodermatitis connotes phototoxic reactions consisting of erythema (with or without blistering) and delayed hyperpigmentation following exposure to plants. Phototoxicity implies an inflammatory reaction caused by the combination of a topical or oral photosensitizing agent followed by exposure to the appropriate wavelength of UV radiation. Because this is not an immunologic reaction, no prior sensitization is necessary and anybody can be affected.

History

As early as 2000 BCE, vitiligo patients were encouraged to lie in the sun after picking *Ammi majus* from the Nile River valley and rubbing the juice on their skin. By 1400 BCE, Indian doctors were using boiled extracts of *Psoralea corylifolia* (scurf-pea, babchi), from which we derive the term "psoralen". Even nowadays in India, its seeds remain a source of psoralens for the treatment of vitiligo.

In 1897, Apiaceae-induced dermatitis was first reported, but the need for concomitant UV radiation went unnoticed. It would be another 40 years before Klaber introduced the term "phytophotodermatitis" to emphasize that a combination of plants ("*phyto-*") plus light ("*photo-*") is required for the reaction.

Epidemiology

Apiaceae (formerly Umbelliferae) and Rutaceae (citrus family) plants are the most common causes of phytophotodermatitis (Table 17.7 & 17.8). Members of the mulberry (Moraceae) and pea (Fabaceae) families also contain furocoumarins.

Apiaceae

A distinctive floral umbel makes family members easy to recognize: numerous small flowers form a simple umbel (a cluster of flowers on stalks of roughly equal length arising from a single point). Many small umbels can form "compound umbels" (Fig. 17.4A). Compound umbels may be umbrella-shaped or ball-shaped. The flower heads are sheathed at the base by one or more leaf-like bracts.

Common hogweed, also referred to as cow parsnip, is known by three species names: *Heracleum lanatum*, *H. maximum*, or *H. spondylium*. In North America, it naturally grows over 2 meters tall (Fig. 17.4B,C), with leaves up to 1 meter long. The larger giant hogweed (*H. mantegazzianum*) is a European native that has now invaded parts of North America. Both cause phytophotodermatitis. Fruits contain the highest concentrations of psoralens followed by leaves and stems. The greatest threat from hogweed occurs in the autumn, when the weather favors the development of many seeds. One severe case of occupational contact with giant hogweed during mid-summer roadside lawn mowing led to marked phytophotodermatitis-induced soft tissue necrosis of the leg and eventual below-the-knee amputation.

Rutaceae

The Rutaceae family includes tropical (*Citrus* spp.), subtropical, and temperate (*Ruta* spp.) plants and is the second most common plant family (after Apiaceae) that causes phytophotodermatitis (see Table 17.8). Many Rutaceae grow as shrubs or small trees and produce fleshy fruit. The rind of the Persian lime (*Citrus latifolia*), which contains ten times more 5-methoxypsoralen (5-MOP) than the pulp, is a major cause of phototoxic reactions in the US, especially in Florida and the desert Southwest. Outdoor bartenders commonly develop vesicles on their index and middle fingers from squeezing limes to make cocktails. Even the sweet orange (*Citrus sinensis*) can cause a phototoxic cheilitis after contact with the rind.

Garden rue (*Ruta graveolens*) is a bitter tasting and smelling sub-shrub native to the Mediterranean basin with a long history as a folk medicine

IMPORTANT MEMBERS OF THE APIACEAE FAMILY (FORMERLY UMBELLIFERAE) IMPLICATED IN PHOTOTOXIC REACTIONS		
Scientific name	**Common name(s)**	**Comments**
Ammi majus	False Bishop's weed	Historical and economic importance
Angelica archangelica	Angelica	Candied portions used in cakes; characteristic Benedictine flavor
Angelica sylvestris	Wild angelica	
Anthriscus sylvestris	Cow parsley, wild chervil	"Strimmer dermatitis"*
Apium graveolens	Celery	Fungus-infected plants produce more psoralens
Ficus carica	Fig	Widespread second-degree burns when used as tanning promoter (Turkey)
Foeniculum vulgare	Fennel	
Heracleum laciniatum	Tromsø palm	Scandinavia
Heracleum lanatum, H. maximum, H. sphondylium	Cow parsnip (common hogweed)	North America; most common cause of "strimmer dermatitis"*
Heracleum mantegazzianum	Giant (Russian) hogweed, wild rhubarb, hogweed tree	Giant weed naturalized and invasive across UK, Europe, Canada, US
Heracleum persicum	Persian hogweed	Iran, Iraq, Turkey
Notobubon galbanum	Blister bush	South Africa
Pastinaca sativa	Parsnip	Furocoumarins in leaves, roots, stem, fruits
Petroselinum crispum	Parsley	

*Strimmer = string trimmer, a garden tool for cutting weeds.

Table 17.7 Important members of the Apiaceae family (formerly Umbelliferae) implicated in phototoxic reactions.

PHOTOTOXIC MEMBERS OF THE FAMILY RUTACEAE	
Scientific name	**Common name(s)**
Citrus aurantiifolia	Key lime
Citrus latifolia	Persian lime or seedless lime
Citrus aurantium	Bitter orange
Citrus bergamia	Bergamot orange
Citrus sinensis	Sweet orange
Citrus limetta	Sweet lemon
Citrus limon	Lemon
Citrus paradisii	Grapefruit
Cneoridium dumosum	Coast spice bush, berry rue
Dictamnus albus	Burning bush, gas plant
Pelea anisata	Mokihana (berries used for lei in Hawaii)
Phebalium squamulosum	Blister bush, common in Western Australia
Ruta graveolens	Rue, herb-of-grace

Table 17.8 Phototoxic members of the family Rutaceae.

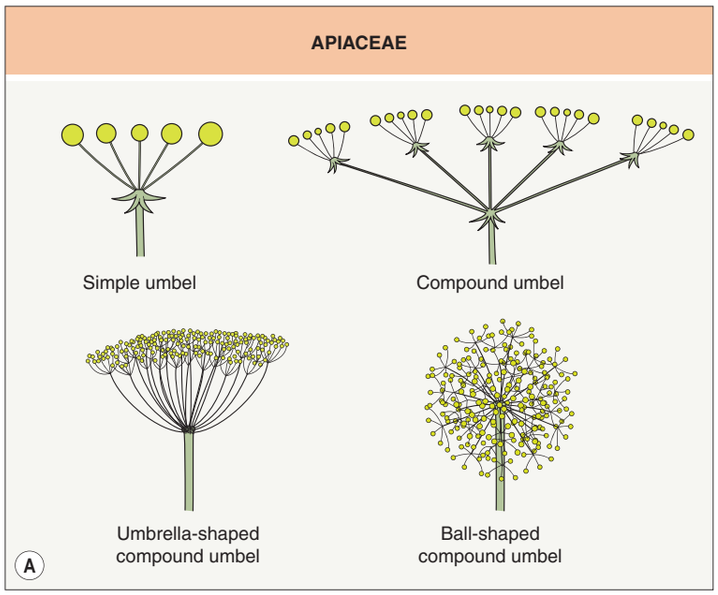






Fig. 17.4 Apiaceae. **A** Compound umbels can be umbrella-shaped or ball-shaped. **B** Cow parsnip (common hogweed; *Heracleum maximum*) habit, Mackinac Island, MI, USA. **C** Compound umbel of cow parsnip (common hogweed)



Fig. 17.5 Bullous phase of phytophotodermatitis. There was associated burning but no pruritus, and the linear bullae were replaced by hyperpigmentation. *Courtesy Jean L. Bolognia, MD.*

remedy and insect repellant. It contains 5-MOP, 8-MOP, and angelicins and is probably the most common cause of phototoxicity acquired in English gardens.

Dictamnus albus, the gas plant or burning bush, exudes an aromatic oil that can be ignited briefly without harming the plant. It has become a common yard plant in the US and Canada, and it grows wild in central and southern Europe, eastern Siberia and northern China. The seed pods have high concentrations of both 5-MOP and 8-MOP.

Moraceae

The mulberry family includes the fig tree (*Ficus carica*), a Middle Eastern native that has been widely cultivated throughout warm, temperate regions of the world. Psoralens are found chiefly in the sap of leaves and shoots but not in the fruit[11].

Other families

Eleven of 23 HIV-infected patients receiving systemic hypericin (from St John's wort, *Hypericum perforatum* [Hypericaceae]) as a potential antiretroviral agent developed severe cutaneous phototoxicity.

Pathogenesis

Furocoumarins possess linear (psoralens) or angular (angelicins) tricyclic structures (see Fig. 134.9). Bergapten (5-MOP), originally isolated from the southern European bergamot orange (*Citrus bergamia*), and 8-MOP (xanthotoxin), first isolated from the Nigerian prickly ash (*Fagara zanthoxyloides*), cause the most severe reactions.

In the presence of UVA (peak effectiveness at 320–340 nm), psoralens within the skin can interact with molecular oxygen and form reactive oxygen species that induce cytoplasmic vacuolization and membrane rupture of keratinocytes. Within 2 hours of UVA exposure, desmosomal plaques detach and degenerate leading to blister formation without the need for DNA damage[12].

UVA also excites intercalated psoralens to form covalent interstrand DNA cross-links by binding to pyrimidines (see Fig. 134.10). This leads to further keratinocyte cell death (apoptosis, "sunburn cells") and stimulates hyperpigmentation via increased melanocyte mitosis and dendricity, melanocyte hypertrophy, increased tyrosinase activity, larger melanosomal size, and enhanced distribution of melanosomes throughout the epidermis.

Furocoumarins appear necessary to defend plants from fungal attack. Healthy celery plants (*Apium graveolens*) contain 10–100 mcg/g wet weight of psoralens, but they may produce 320 mcg/g when infected with pink-rot fungus (*Sclerotinia sclerotiorum*). Disease-resistant celery unfortunately possesses high levels of furocoumarins concentrated in the leaf and stem sap.

Clinical Features

Cutaneous sensitivity to UVA light peaks 30–120 minutes after contact with furocoumarins. Bizarre configurations of erythema, edema, and bullae appear after 24 hours and peak at 72 hours (Fig. 17.5). These painful, non-pruritic reactions are more often seen in mid to late summer, when psoralen concentrations are highest in the offending plants and more skin is exposed to direct sunlight. To avoid misdiagnosis as poison ivy dermatitis, physicians must note that the initial erythematous and bullous reaction only occurs in sun-exposed areas. Hyperpigmentation appears 1–2 weeks later and lasts months to years (Fig. 17.6). Occasionally, low-dose UVA and/or psoralens cause hyperpigmentation without a preceding vesicular or erythematous eruption (see Ch. 67). Involved areas may remain hypersensitive to UV radiation for years. Wet skin, sweating, and heat enhance the phototoxic response.

Furocoumarin exposure occurs in many settings (Table 17.9). Modern power tools such as weed-whackers and strimmers (string trimmers) deliver a buckshot spray of weeds that may include phototoxic plants. "Strimmer dermatitis" appears 12–24 hours later as red, irregular

macules and papules, not bizarre linear and angular streaks, on the chest, arms, and legs if wearing shorts. Implicated species, especially in Europe, include common hogweed (cow parsnip; *Heracleum sphondylium*), giant hogweed (*Heracleum mantegazzianum*), and cow parsley (*Anthriscus sylvestris*). Berlock (or berloque, meaning trinket or charm) dermatitis is characterized by pendant-like streaks of pigmentation on the neck, face, arms, or trunk after the application of colognes containing 5-MOP.



Fig. 17.6 Phytophotodermatitis. Streaky hyperpigmentation due to contact with a psoralen-containing plant followed by exposure to sunlight. *Courtesy Lorenzo Cerroni, MD.*

Phytophotodermatitis has also been mistaken for child abuse (see Ch. 90). Parents who touch plants or fruit containing furocoumarins can transfer these chemicals to their children. A week or more later, the children may develop digitate hyperpigmentation in sun-exposed sites of parental hand contact. Multiple hues are not seen in the skin lesions, as in healing bruises. In addition, lime-induced phytophotodermatitis can be misdiagnosed as allergic contact dermatitis, impetigo, cellulitis, and infectious lymphangitis.

Celery harvesters and canners are at high risk for developing phytophotodermatitis. Only 1 mcg of 8-MOP/cm^2 of skin is necessary to produce blisters after 2.4 J/cm^2 (less than 10 minutes) of summer sunlight in Colorado. In one study of 320 randomly selected Michigan celery workers, 163 (51%) displayed various stages of vesicular and bullous dermatitis on the fingers, hands, and forearms[13]. In this study, the authors could not induce phytophotodermatitis except by using celery infected with pink-rot fungus. However, phototoxicity following the ingestion of naturally occurring psoralens is uncommon.

Phytophotoallergic Contact Dermatitis

Photoallergy due to plants is rare. A 20-year review of photopatch testing results from a tertiary medical center found reactions in eight of 69 patients, with reactions in only four patients thought to be clinically relevant[14].

Treatment

Prevention is the best treatment for phytophotodermatitis. Known furocoumarin-containing plants should not be planted near play areas. When using weed-whackers or strimmers, operators must cover their chest and extremities. If one has been in contact with a suspected phototoxic plant, prompt washing with soap and water may prevent a reaction.

ALLERGIC CONTACT DERMATITIS (SEE CH. 14)

Members of the Anacardiaceae and Asteraceae families represent the most common causes of allergic contact dermatitis due to plants.

RISK ACTIVITIES FOR PHYTOPHOTODERMATITIS	
Cosmetics	Tan promoters or perfumes containing bergamot oil (berlock [berloque] dermatitis) or a fig leaf decoction
Fruit and vegetable processing	Canning celery or stocking celery in grocery stores Making lemonade or limeade, especially if selling it outside Squeezing lime juice for margaritas and other drinks or guacamole Applying wild carrot decoction to treat foot swelling (China)
Gardening	Brushing against *Dictamnus* spp. ("gas plant/burning bush") (US, Europe, N China) or *Ruta* (UK) Cultivating celery, parsnip, or parsley Clearing weeds with a "weed whacker" (US) or "strimmer" (UK) Pruning or harvesting figs Growing *Angelica* for herbal medicine (Korea), cake decorating (when candied), tonic and flavoring in wines (esp. Benedictine, US)
Hiking	Through fields and riverbanks (*Heracleum* spp.) (Pacific NW, Europe) Hiking in southern California and Baja California (*Cneoridium dumosum*, coast spice bush [Rutaceae])
Ingestion	Ingestion of massive quantities of psoralens (esp. celery) before UVA tanning Eating selemez (wild spinach, *Chenopodium album* [Chenopodiaceae]) – native in Europe and Asia, cultivated widely; sensitizing chemical unknown
Medications	Excessive exposure to UV radiation after taking or applying psoralens for PUVA Application of rue (*Ruta* spp.) as an insect repellant
Play	Making peashooters with *Heracleum* spp. Playing among rue bushes or Apiaceae (see Table 17.7) Using psoralen-containing plants as "weapons" Wearing lei of *Pelea anisata* (Hawaii)

Table 17.9 Risk activities for phytophotodermatitis.

Epidemiology

Anacardiaceae and related families

Key features

- Poison ivy/poison oak plant identification
  - Compound leaves with three leaflets
  - Flowers or fruit arise from axillary position
  - Black dots of urushiol often present on leaves and fruit
  - Common poison ivy climbs as a vine with hairy aerial roots
- Allergens are long-chain catechols and resorcinols found in the urushiol oleoresin

Members of the Anacardiaceae family cause more allergic contact dermatitis than all other plant families combined. Most allergenic family members belong to the genus *Toxicodendron* (meaning "poison tree"). In the US, over a third of patients present during June or July[15].

Toxicodendron identification

Compound *Toxicodendron* leaves possess three or more odd-numbered leaflets[16]. Flowers and fruit arise in an axillary position in the angle between the leaf and the twig from which it arises (Fig. 17.7A,B). The leaf stalk is enlarged at its origin from the supporting twig and leaves a "U"- or "V"-shaped scar after it falls off. Green fruit turn off-white when mature. Plants cling to trees via "hairy" aerial rootlets (Fig. 17.7C,D).

Toxicodendron oleoresin contains urushiol and the enzyme laccase which oxidizes urushiol to form an insoluble, black, plastic-like polymer with great tensile strength. Black spots are commonly found on the leaves of plants (Fig. 17.7E), and the "black-spot test" helps identify toxic Anacardiaceae, but performing it also increases one's likelihood of contracting a nasty dermatitis! A stone is used to thoroughly crush plant contents, especially the leaf stalks, between folds of white paper. Urushiol turns dark brown within 10 minutes and black by 24 hours.

Allergenic Anacardiaceae

As noted in Table 17.10, there are two species each of poison ivy and poison oak and one species of poison sumac that are common to the US (Fig. 17.8). Some have multiple subspecies. Poison oak and poison ivy are weeds that grow along roads, trails, or streams; they possess three (or occasionally five) leaflets per leaf. Poison sumac contains 7–13 leaflets per leaf (see Fig. 17.7A). Young leaves are frequently red in color, and the mature fruit (drupes) are tan or cream-colored and hairless (young fruit has hair). Classically, poison ivy leaves have pointed tips and are ovate (widest point below the center). Poison oak leaves usually have rounded ends. Western poison oak has oval leaves, whereas Eastern poison oak has variable leaf appearances that can mimic white oak leaves.

Virtually all portions of the plant can induce dermatitis, even in the winter. The "winter" shape of poison ivy on fence posts resembles "Medusa heads" that are identifiable while driving down the highway. Strongly suspect any vine climbing by hairy aerial rootlets that is connected at the bottom to a tree or log. In snow, Western poison ivy grows so low to the ground that the upward, tine-like branches may be the only clue to its identification.

The cashew nut tree (*Anacardium occidentale*) grows in the tropics worldwide. The nut contains an oily, brown juice between the two layers of its shell. Contact with concentrated phenols in the nutshell and bark leads to immediate vesication. Any part of the tree, except the nut, can cause dermatitis.

Mango (*Mangifera indica*) is the most popular fruit tree in tropical and subtropical America, and some 35 species grow throughout Southeast Asia. The leaves, bark, stems, and fruit skin contain sensitizing resorcinols. Peeling the fruit before eating it typically prevents allergic contact dermatitis, although allergy to mango pulp has been demonstrated; the pulp allergens appear to be distinct from the resorcinols. Hawaiian natives rarely react to mango, perhaps because early oral exposure induces immunologic tolerance.

The Florida holly (*Schinus terebinthifolius*, Brazilian pepper tree) is probably the most common cause of allergic contact dermatitis in southern Florida. The sap and crushed berries possess a variety of sensitizing catechols and resorcinols.

Although the mango, cashew, and Brazilian pepper trees are incredibly common throughout Latin America, dermatitis to them there is rare, in contrast to the frequent reactions seen in US residents. The main allergens in toxicodendrons are catechols, whereas those in the listed trees are resorcinols, and catechols possess greater allergenicity than resorcinols. Early *cutaneous* exposure to catechols may allow

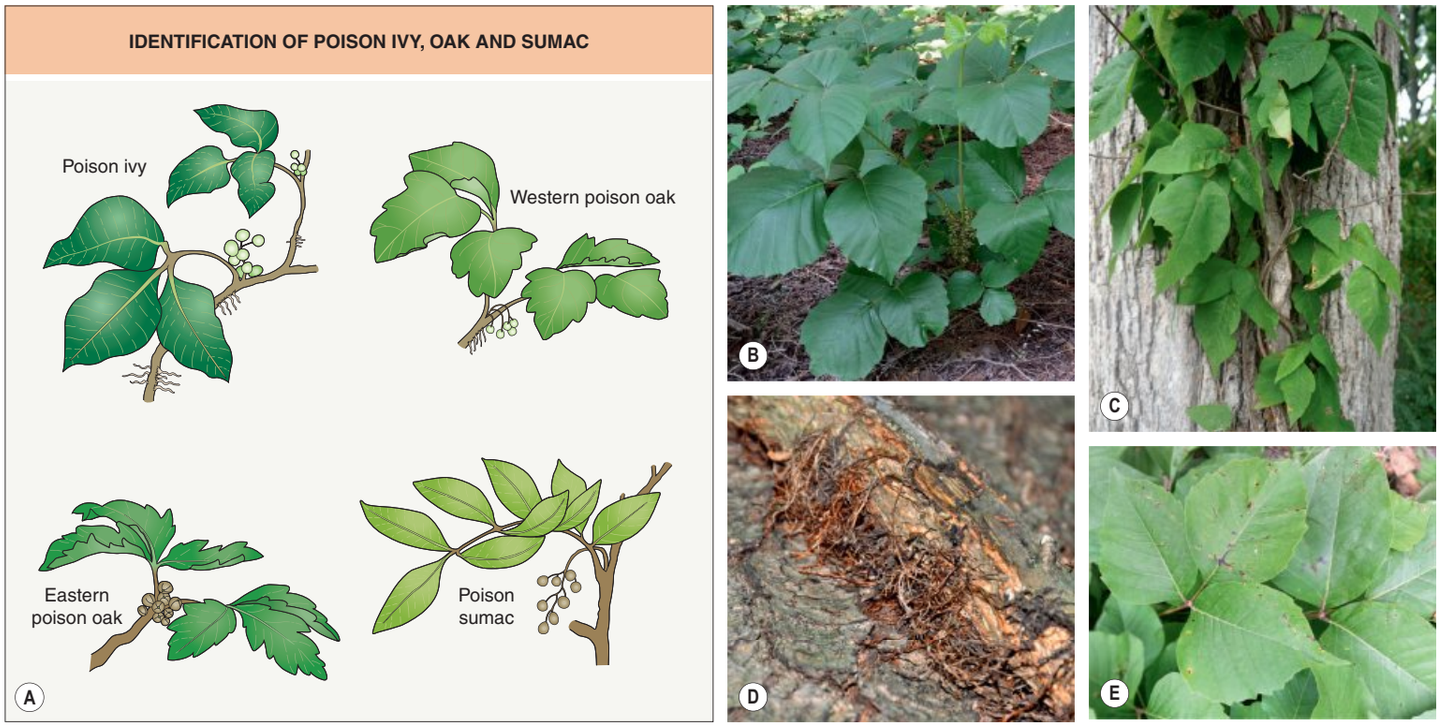


Fig. 17.7 Characteristic features useful for identifying poison ivy, poison oak and poison sumac. A Shapes and numbers of leaflets and appearance of fruit (drupes). **B** Shrub type poison ivy (*T. radicans*) with flowers arising from an axillary position just below point where leaf attaches to stem. Leaves possess three leaflets ("*Leaves of three, let them be*" or "*One, two, three, don't touch me*"). **C, D** Climbing vine of poison ivy (*T. radicans*) on an oak tree demonstrating aerial roots that anchor the vine to the tree; close-up of vine anchored to tree bark by fine hair-like aerial roots ("*Hairy rope, don't be a dope*"). **E** Shrub type poison ivy (*T. radicans*) with black spots on leaflets. Leaf trauma (e.g. wind, rain, trampling by animals or people) allows urushiol to reach the surface, oxidize, and turn black.

MOST COMMON ALLERGENIC MEMBERS OF THE ANACARDIACEAE FAMILY AND MEMBERS OF TWO OTHER PLANT FAMILIES THAT ALSO CONTAIN URUSHIOL CROSS-REACTING CHEMICALS		
Binomial name	**Common name**	**Notes**
Toxicodendron radicans	Common or Eastern poison ivy	Eastern half of USA Climbs trees with aerial rootlets Some subspecies in Mexico, Japan, China
Toxicodendron rydbergii	Northern or Western poison ivy	Western half of USA (except CA) and northern border states Non-climbing shrubs
Smodingium argutum	African poison ivy	South Africa
Toxicodendron pubescens	Eastern poison oak	Southeast USA
Toxicodendron diversilobum	Western poison oak	Pacific Coast of USA Usually a shrub but can climb
Toxicodendron vernix	Poison sumac	Eastern third of USA Not a weed Grows in standing water
Anacardium occidentale	Cashew nut tree	Tropical Americas Highest concentration of allergen in oil in middle layer of nut shell
Mangifera indica	Mango tree	Tropics (see text)
Metopium toxiferum	Poisonwood tree	Caribbean basin
Semecarpus anacardium	Indian marking nut tree	Southeast Asia, Pacific Islands, Australia Used to mark laundry in India ("dhobie mark dermatitis") and used topically as herbal remedy for dermatitis, tattoo removal
Toxicodendron verniciflua	Japanese lacquer tree Chinese lacquer tree	Japan and China Resin used to lacquer wood products
Gluta renghas	Rengas tree	Malaysia lumber source
Schinus terebinthifolius	Brazilian pepper tree or Florida holly	Native to South America, but now a problem in southern Florida, Hawaii, Central America, the Pacific Rim and Pacific Islands
Cross reactors		
Ginkgo biloba (Ginkgoaceae)	Ginkgo tree	Cultivated worldwide in temperate climates – only the seed coat is allergenic
Grevillea spp. (Proteaceae)	Spider flower, silk oak, Hawaiian tree, Kahili tree	Widely cultivated Australian natives

Table 17.10 Most common allergenic members of the Anacardiaceae family and members of two other plant families that also contain urushiol cross-reacting chemicals.

cross-reactions to other Anacardiaceae, whereas early *oral* exposure to resorcinols may induce a state of tolerance.

The 15- to 20-meter tall Japanese lacquer tree (*Toxicodendron verniciflua;* also referred to as the Chinese lacquer tree) produces a thick, self-melanizing, viscous bark sap used for varnishing wood. Because polymerized urushiol remains in the lacquer, it maintains its allergenicity for many years. Patients allergic to poison ivy usually react to Japanese lacquer tree catechols. In a survey of 232 lacquer craftsmen, 189 (81%) developed dermatitis from the lacquer, but 83% of these reactions resolved with continued lacquer exposure (natural hyposensitization)[17].

Other common urushiol-containing Anacardiaceae family members include *Smodingium argutum* (African poison ivy) in South Africa, *Toxicodendron striatum* (Manzanillo tree) in Colombia, and *Lithraea caustica* (Litre tree) in central Chile.

Cross-reactors from other families

The seed of the Ginkgo tree (*Ginkgo biloba*), the only living member of the family Ginkgoaceae, possesses the allergenic catechol ginkgolic acid. Because of the tree's large size, beauty, and resistance to air pollution, male ginkgo trees are widely grown in suburban North America and Europe. The yellowish seeds of female trees disintegrate and release rancid-smelling butyric acid. Contact with the soft outer layer (pulp) of the seed causes most allergic reactions. Dermatitis following contact with the seed kernel, seed shell, and leaves has been reported, but these parts likely only cause irritant reactions (Fig. 17.9). Handling the intact seed (without the seed pulp) does not cause dermatitis in sensitized individuals. The unique, fan-shaped leaf makes the ginkgo easy to recognize.

The genus *Grevillea* (Proteaceae) includes 250 plant species common to Australia that contain pentadecylresorcinol. Having no side-chain double bonds, it is less allergenic than poison ivy and poison oak allergens. The flower of the Hawaiian kahili tree (*Grevillea banksii*) is a significant cause of allergic contact dermatitis in Hawaii.

Asteraceae and related families

Key features

- Asteraceae (Compositae) identification
  - Flower head with all strap-like florets (e.g. dandelion)
  - Flower head with small, central tubular florets and peripheral strap-like florets (e.g. daisy, sunflower)
  - Leaf-like bracts surround undersurfaces of flowers
- Allergens are sesquiterpene lactones (SQLs)

Asteraceae identification

The compound flower heads in this largest of all plant families (~24 000 species) are composed of clusters of tiny flowers (florets) subtended by a whorl of leaf-like bracts (Fig. 17.10). In some plants, an inner "disc" of short, tubular florets is surrounded by long, strap-like "ray" florets (see Fig. 17.10A). In some plants, all the florets are similar (see Fig. 17.10C).

Allergenic Asteraceae

The daisy family includes many troublesome weeds, ornamentals, herbaceous perennials, and vegetables (Table 17.11).

In 1956, *Parthenium hysterophorus* ("congress grass"), a native of northeastern Mexico, accidentally traveled in a consignment of US wheat to India, where it found an inviting ecologic niche. It now infests approximately two million hectares within India as well as large areas of the Americas, South Africa, Madagascar, eastern Australia, and the Pacific Islands. Unlike South American *P. hysterophorus*, the Indian plant contains high concentrations of SQLs and is likely the most common cause of Asteraceae dermatitis in the world.

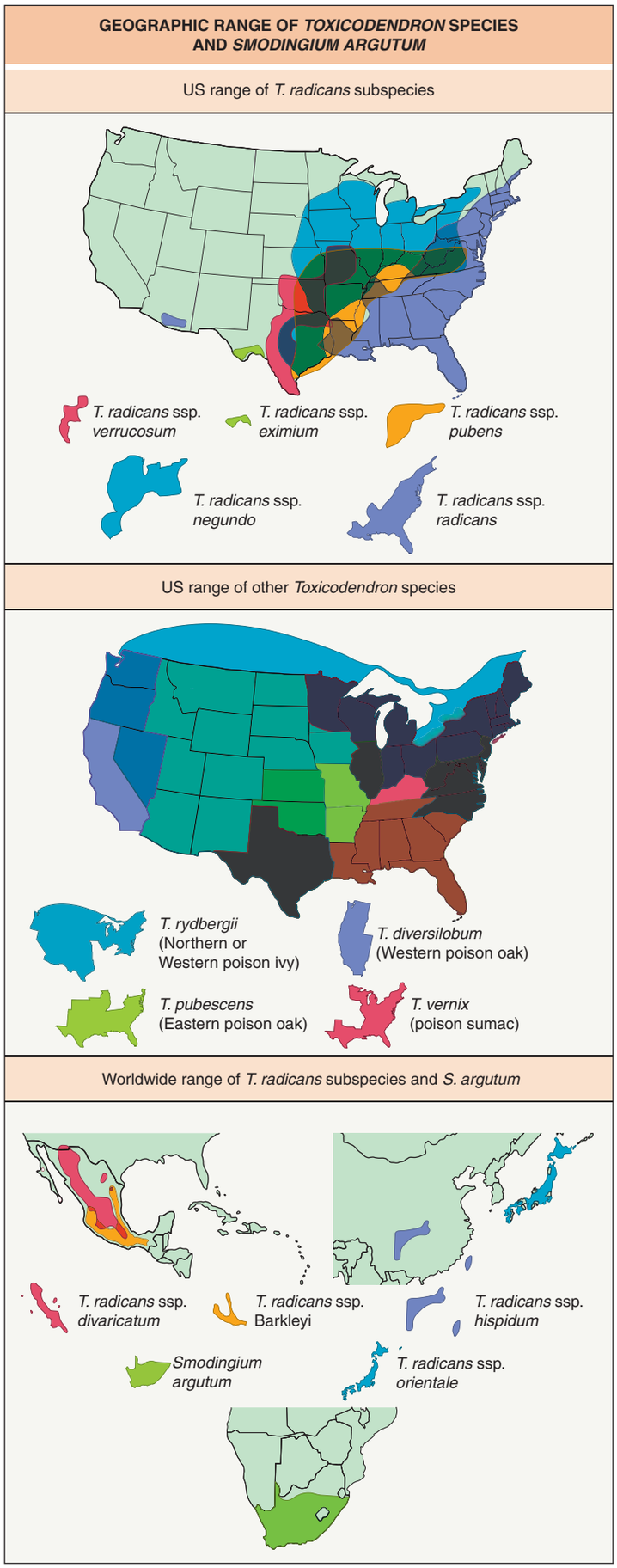


Fig. 17.8 Geographic range of *Toxicodendron* spp. and *Smodingium argutum* (African poison ivy).



Fig. 17.9 Leaves and seeds of *Ginkgo biloba*. Only the fresh seed covering contains the allergen, ginkgolic acid, which typically cross-reacts with urushiol.

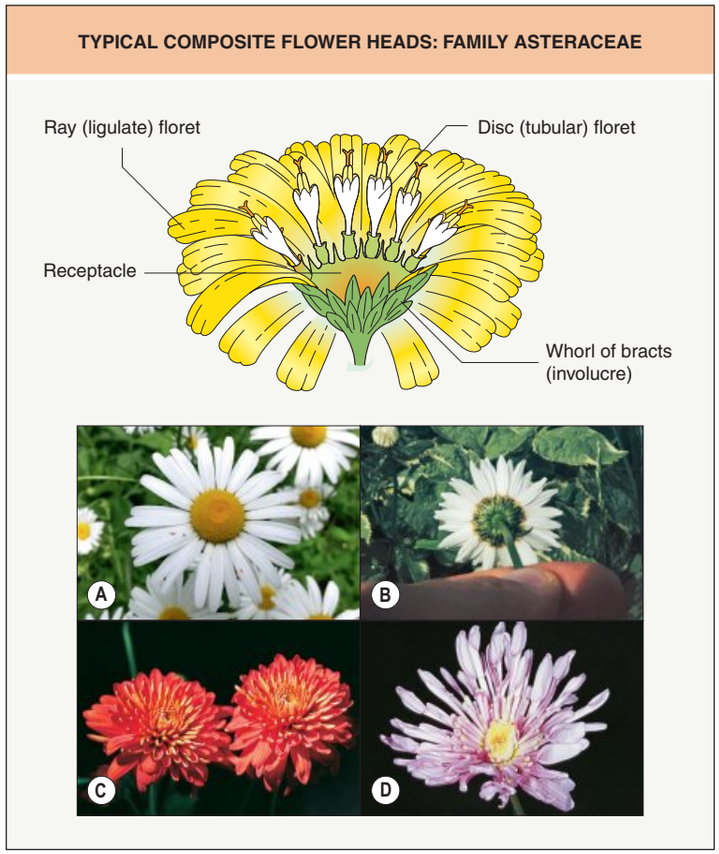


Fig. 17.10 Typical composite flower heads of members of the family Asteraceae (Compositae). Daisy (*Leucanthemum* spp.), demonstrating a composite flower head of numerous, tiny, yellow tubular florets centrally and white ray florets peripherally **(A)** as well as green leaf-like bracts beneath the flower head **(B)**, both of which are characteristic of flower heads of the family Asteraceae. **C** A cushion chrysanthemum (X *Dendranthema* cvs), demonstrating all ray, or strap-like, florets. **D** A composite chrysanthemum (X *Dendranthema* cvs), demonstrating central yellow tubular florets and peripheral ray florets.

Cross-reactors from other families

Allergic reactions to SQLs occur following contact with tulip poplar bark (*Liriodendron tulipifera*) and *Magnolia* trees (Magnoliaceae); liverworts (*Frullania* spp. [Jubulaceae]) in the Pacific Northwest; and leaves of the bay laurel tree (*Laurus nobilis* [Lauraceae]), a Mediterranean basin native.

Pathogenesis

Anacardiaceae allergens

The allergenic substance urushiol derives its name from the Japanese word for the sap (kiurushi) of the Japanese lacquer tree (*T. verniciflua*). It contains a mixture of catechols (1,2-dihydroxybenzenes) and resorcinols (1,3-dihydroxybenzenes) that avidly binds to skin[18].

Catechols and their alkyl side chains are immunologically inert. However, combining them produces potent sensitizers[19]. The

SOME OF THE MORE THAN 200 ALLERGENIC MEMBERS OF ASTERACEAE (COMPOSITAE) FOUND THROUGHOUT TEMPERATE WORLD CLIMATES			
Category	**Binomial name**	**Common name**	**Notes**
Wild flowers and weeds	*Achillea millefolium*	Yarrow, milfoil	A cause of allergic contact "strimmer" or "weed whacker" dermatitis
	Ambrosia spp.	American ragweeds	Allergic contact dermatitis throughout growing season; allergic rhinitis only during pollen season
	Arnica montana	Arnica, mountain tobacco	
	Artemisia vulgaris	Mugwort	Grows in temperate climates worldwide
	Helenium autumnale	Sneezeweed	
	Iva spp.	Marsh elder, sumpweed	
	Parthenium hysterophorus	Scourge of India, congress grass, wild feverfew	Probably most common cause of Asteraceae dermatitis worldwide; Australian "bush dermatitis"; parthenin is primary SQL
	Tanacetum cinerarilifolium	Pyrethrum	
	Tanacetum vulgare	Tansy	
	Tanacetum parthenium	Feverfew	Perhaps the best single plant to screen for SQL allergy
	Taraxacum officinale	Dandelion	Airborne contact dermatitis after mowing
Ornamental flowers	*Dahlia* spp.	Dahlia	
	X *Dendranthema* cultivars	Chrysanthemum	Common cause of SQL dermatitis; florists remove dead flowers ("dead-head") to encourage more blooms
	Helianthus annuus	Sunflower	Windblown trichomes can cause airborne contact dermatitis
	Rudbeckia hirta	Black-eyed Susan	
In herbal medicine*	*Calendula officinalis*	Pot marigold	
	Chamaemelum nobile	Sweet/Roman chamomile	
	Inula helenium	Elecampane	
Vegetables	*Cichorium endiva*	Endive	
	Cichorium intybus	Chicory	
	Cynara scolymus	Globe artichoke	
	Lactuca sativa	Lettuce	

*Also *Achillea millefolium*, *Arnica montana*, *Helianthus annuus*, *Tanacetum parthenium*, *Tanacetum vulgare*, *Taraxacum officinale*.

Table 17.11 Some of the more than 200 allergenic members of Asteraceae (Compositae) found throughout temperate world climates. SQL, sesquiterpene lactone.

immunologic activity of alkyl side chains results from weak van der Waals forces. Longer side chains increase irritancy and allergenicity; location of the catechol ring at position 3 increases antigenicity, but placement at position 6 induces tolerance. Although virtually all individuals who are allergic to poison ivy react to the C15 catechol with two double bonds (a diolefin), only 35% respond to the C15 catechol with an unsaturated side chain (pentadecylcatechol). Therefore, pentadecylcatechol, which is easily synthesized, is an inappropriate patch test allergen for Anacardiaceae sensitivity, because the diolefin is the major component in poison ivy and poison oak urushiols.

Asteraceae allergens

The major sensitizers, sesquiterpene lactones (SQLs), are found in the leaves, stems, and flowers, and they are composed of a sesquiterpene ($C_{15}H_{24}$) and a lactone ring (cyclic ester). Direct plant contact, botanical extracts in skin care products and cosmetics, and dry airborne plant parts including pollen can transfer SQLs to individuals. Over 5000 SQLs have been described, of which about 4000 are potentially allergenic. The composition of SQLs produced by any species varies according to location and weather.

Patch testing for SQL allergy has traditionally relied on the SQL mix consisting of three SQLs – costunolide, alantolactone, and dehydrocostus lactone – or the "Compositae mix" of non-standardized extracts from five species of Asteraceae. The SQL mix has a false-negative rate of 35%–65% in SQL-allergic patients, while the Compositae mix has a false-negative rate of at least 15%. The SQLs present in these mixtures poorly represent SQL structural diversity[20]. A combination of three commercially available patch tests – SQL mix, Compositae II mix, and parthenolide (also contained in Compositae II mix) – can be used as this combination detects 96% of known SQL allergic individuals[21]. Ideally, patients should be tested to portions of the suspect plant.

Clinical Features

Anacardiaceae dermatitis

Key features

- Urushiol is a partially water-soluble allergen that must be washed off quickly
- Treat for at least 2 weeks, otherwise rebound dermatitis commonly occurs
- Eruption "progresses" to "new areas" because of variability in antigen concentration and stratum corneum thickness

Lightly brushing against uninjured leaves is innocuous, since plants must be damaged to release urushiol (see Fig. 17.7E). However, in the late fall, plants spontaneously release urushiol. In addition, contaminated clothing, pets, lacquered furniture, sawdust, and smoke (potentially causing severe respiratory tract inflammation, dermatitis, and even temporary blindness) can transfer urushiol.

After urushiol contact, a sensitized person typically develops an erythematous, pruritic eruption within 2 days (range, 4–96 hours) that peaks within 1–14 days[22] . However, dermatitis may occur up to 3 weeks after primary contact or within hours of secondary contact. Streaks of erythema and edematous papules typically precede vesicles and bullae (Fig. 17.11A,B,E). If the antigen load is lower, only erythematous, edematous reactions may be seen (Fig. 17.11C,D). Although allergic contact dermatitis is the most common cause of such a streaky, vesicular dermatitis, plants may cause this picture by other means (e.g. chemical irritant dermatitis or the initial phase of phytophotodermatitis). Patch tests of bulla fluid are routinely negative. The illusion that

this fluid propagates the eruption results from variations in the time it takes for a clinical reaction to occur at different sites that have received differing antigen loads and have variable stratum corneum thicknesses.

Erythema multiforme appears to be an underreported sequela of severe poison ivy reactions that may appear 2 weeks following onset of the dermatitis (Table 17.12)[23]. Uncommonly, nephritis or eruptions resembling measles, scarlatina, or urticaria develop and are ascribed to immune complex deposition. Without treatment, poison ivy dermatitis lasts about 2–3 weeks. Prolonged postinflammatory hyperpigmentation may occur in individuals with darker skin phototypes.

Over 70% of the US population react to poison ivy allergens after patch testing, but only 50% react to plants in nature. Interestingly, only 15% of atopic persons are sensitive, and studies suggest that sensitivity is hereditary. Urushiol-sensitive AIDS patients with $CD4^+$ counts <200/mcl maintain sensitivity to poison ivy allergens[24] because the predominant effector T cells against poison ivy catechols are $CD8^+$.

In "black-spot" poison ivy dermatitis, urushiol acts as both irritant and allergen; an irritant contact dermatitis is superimposed on an allergic contact dermatitis[25,25a]. Oxidized resin creates a black discoloration on the skin (Fig. 17.11F). If urushiol stains clothing black, it cannot be washed off and will retain its allergenicity indefinitely. A more widespread spotted pattern in non-covered sites is seen if a patient has been weed-whacking areas of poison ivy (Fig. 17.11G).

Asteraceae dermatitis

Key features

- Caused by sesquiterpene lactones (SQLs)
- Most common cause for home gardeners is chrysanthemums
- Most common worldwide cause is *Parthenium hysterophorus*
- Often presents with an airborne contact pattern
- Patients frequently become photosensitive

Chrysanthemums probably cause more allergic contact dermatitis than any other home garden plant (Fig. 17.12). The flowers and leaves are more potent sensitizers than the stems, and contact is common when removing dead flowers to encourage further blooming ("dead-heading").

Middle-aged men with a history of outdoor exposure may develop Asteraceae allergy that resembles airborne contact dermatitis (ABCD) (Fig. 17.13). SQLs, though not volatile, are bound to airborne trichomes and dried leaves in sufficient concentrations to cause ABCD[26]. Typically, a single region of the body is involved for several years, flaring in the summer during the plant's growing season and disappearing during the winter. Later, all exposed areas develop a chronic pruritic and lichenified dermatitis. However, the eyelids, melolabial folds, retroauricular sulci and antecubital fossae are generally involved, unlike the situation in photosensitive dermatitis (see Fig. 87.15).

Ragweed (*Ambrosia artemisiifolia*) commonly causes ocular and airway immediate hypersensitivity reactions via pollen allergens, with the major allergen identified as Amb a 1. Although pollen can rapidly penetrate the skin[27], it contains no SQLs and has not been demonstrated to cause contact dermatitis. SQLs found in other parts of ragweed plants can induce ABCD (see above) and dyshidrotic eczema[28].

Parthenium hysterophorus allergic contact dermatitis accounts for 40% of all visits to contact dermatitis clinics in India and most commonly presents with an ABCD pattern (45%); 15% of patients have erythroderma while 10% develop chronic actinic dermatitis[29]. The remainder display a mixture of these three patterns. *Parthenium*-allergic patients sometimes demonstrate positive prick tests suggesting the

PLANTS AND PLANT PRODUCTS THAT CAN LEAD TO ERYTHEMA MULTIFORME IN THE SETTING OF SEVERE ALLERGIC CONTACT DERMATITIS

Common name (binomial name)	Family	Notes
Poison ivy, oak, sumac (*Toxicodendron* spp.)	Anacardiaceae	US and Canada
Tea tree oil (*Melaleuca alternifolia*)	Myrtaceae	Australia, exported products
Wild feverfew (*Parthenium hysterophorus*)	Asteraceae	India

Table 17.12 Plants and plant products that can lead to erythema multiforme in the setting of severe allergic contact dermatitis.

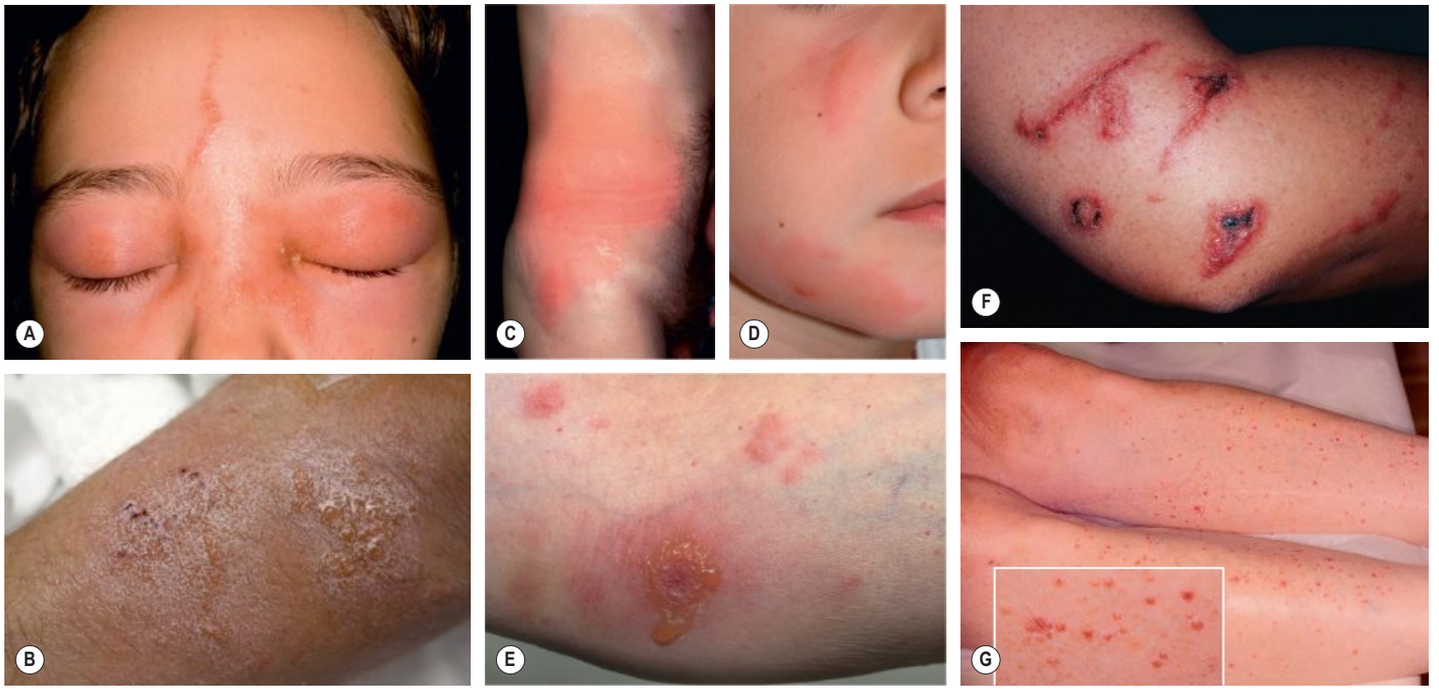


Fig. 17.11 Clinical manifestations of Anacardiaceae dermatitis. A Poison ivy (*Toxicodendron radicans*) dermatitis: acute streaks of erythema with superimposed vesicles and eyelid edema with serous crusting. **B** Poison ivy dermatitis: multiple vesicles and a few hemorrhagic crusts with superimposed zinc oxide from application of calamine lotion. **C** Widespread erythema and edema associated with intense pruritus after carrying logs of the poisonwood tree (*Metopium toxiferum*) of the family Anacardiaceae. **D** Pink edematous streaks on the face. **E** Compared to **B**, more obvious erythema in association with edema and multiloculated vesicles. **F** "Black-spot" poison ivy dermatitis: note the black discoloration in the central portion of the edematous plaques due to polymerized plant oleoresin. **G** Weed whacker dermatitis with widespread spotted pattern. *A, G, Courtesy Louis A. Fragola, Jr, MD; B, Courtesy Julia Pettersen Neckman, MD; D, Courtesy Julie V. Schaffer, MD; E, F, Courtesy Kalman Watsky, MD.*

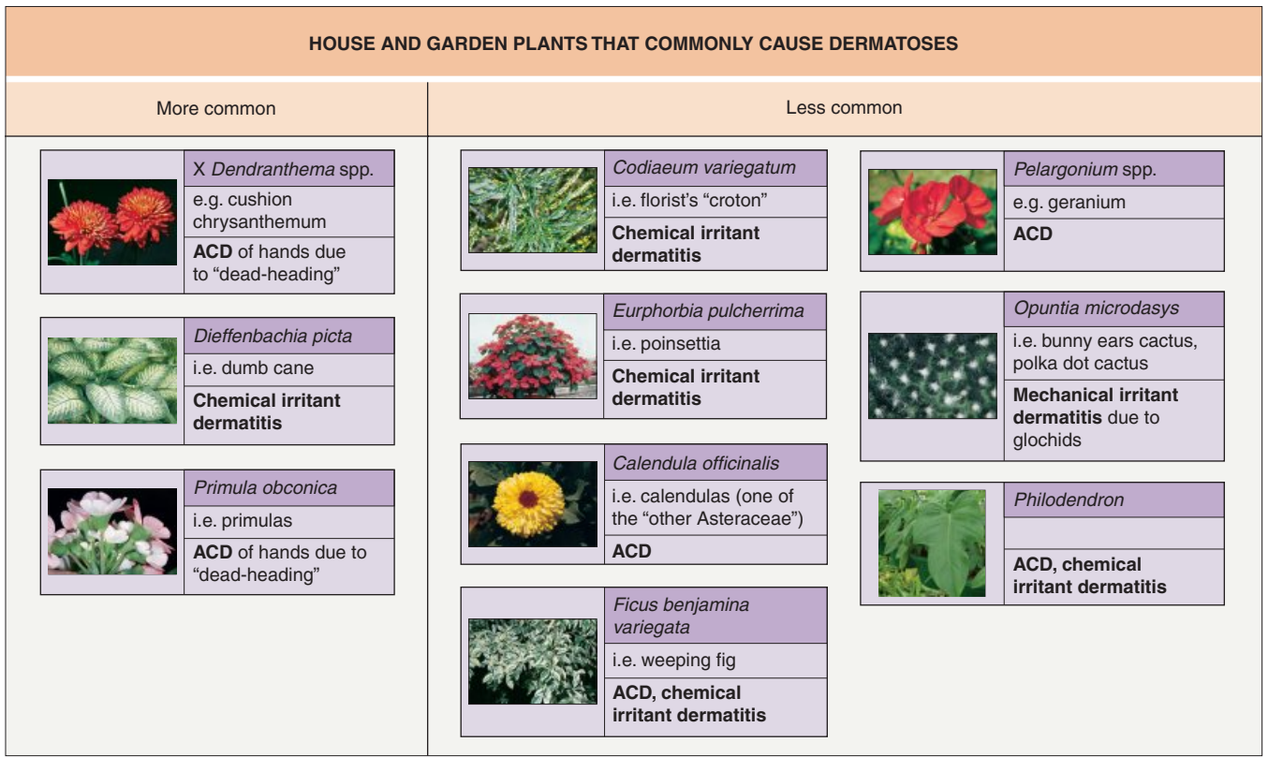


Fig. 17.12 House and garden plants that commonly cause dermatoses. ACD, allergic contact dermatitis. *Photograph of poinsettia courtesy Denver Botanical Gardens.*



Fig. 17.13 Airborne contact dermatitis. This farmer from Gujarat, India was allergic to the sesquiterpene lactones in *Parthenium hysterophorus*. *Courtesy Shyam Verma, MBBS, DVD, FRCP.*

coexistence of type I and type IV hypersensitivity reactions. Allergens found in Asteraceae plants have been shown to cause systemic allergic dermatitis which can involve both skin and mucosae[30]. Although patients are initially sensitized via skin contact, subsequent exposure to the allergen by other routes (e.g. intravenous, intramuscular, subcutaneous, inhalation, oral, mucosal) results in dermatitis in the absence of contact of the allergen with the skin.

Photosensitivity and Asteraceae allergy

SQLs possess neither phototoxic nor photoallergic properties, yet allergic patients often develop abnormally low minimal erythema and minimal phototoxic doses to wavelengths of 300–350 nm, and conversely, up to 85% of patients with chronic photosensitivity dermatoses react to Asteraceae allergens[31]. Chronic actinic dermatitis (CAD) that develops in some patients who are allergic to SQLs is thought to be an autoimmune photodermatosis mediated by sunlight-induced antigens in the skin (see Ch. 87). For example, the SQL isoalantolactone has been shown to be highly reactive with DNA in solution during UVA irradiation, and the UV action spectrum for CAD corresponds with the UV absorption peak for DNA. An interaction between SQLs and DNA in the presence of UV light may alter DNA to render it antigenic and trigger a CAD response[32].

Although α-terthienyl and various polyacetylenes with phototoxic properties have been found in some Asteraceae, no link has been established between their presence and dermatitis[32].

Treatment (Anacardiaceae and Asteraceae Dermatitis)

The primary goal of treatment is to relieve pruritus[22]. As soon as exposure to poison ivy or related plants is recognized, one approach is to thoroughly wash the entire body three times with liquid dishwashing soap and a damp washcloth – stroked in one direction, not back and forth – under very warm to hot running water[33]. If no dishwashing soap is available, washing with just water will still remove some resin.

Weepy lesions are best treated with tepid baths, wet-to-dry soaks, or bland shake lotions (calamine) that can dry the lesions. An astringent such as Burow's solution (aluminum acetate) works well to cool and dry lesions when applied as a wet-to-dry dressing or open wet dressing. Topical antihistamines, anesthetics containing benzocaine, and antibiotics should be avoided to prevent sensitization[34,34a].

Superpotent topical corticosteroids only help if applied during the earliest stages of the outbreak when vesicles and bullae are not yet present, and their abrupt discontinuation can lead to rebound inflammation. Topical calcineurin inhibitors are ineffective in treating urushiol-induced dermatitis. One surfactant product (Zanfel® wash) reportedly relieves redness and itching[35].

Systemic corticosteroids are extremely effective when indicated. Oral prednisone should be dosed at 1–2 mg/kg/day based upon ideal weight and gradually tapered over 2–3 weeks[34]. Six-day tapering courses of methylprednisolone (e.g. Medrol® Dosepak) are too short and too low dose to be effective; rebound commonly follows completion. The author routinely uses intramuscular long-acting triamcinolone acetonide (1 mg/kg) mixed with fast-acting betamethasone (0.1 mg/kg). Patients experience rapid relief and fewer side effects than with oral prednisone[34]. Such systemic treatment is also less expensive than application of high potency topical corticosteroids[15]. Soporific oral antihistamines often induce poor-quality sleep while doing nothing for the itch, since histamine is not responsible for the pruritus.

Hyposensitization programs for Anacardiaceae- and Asteraceae-allergic individuals have generally failed. Patients develop pruritus ani, generalized pruritus, or urticaria and comment that the "treatment is worse than the disease". It appears that hyposensitization after becoming cutaneously sensitized to the potent allergens in poison ivy and poison oak is difficult, but not impossible, as demonstrated by Japanese lacquer craftsmen (see above) and one study of *Parthenium*-allergic individuals in which 70% of patients who underwent oral hyposensitization improved symptomatically[29].

A recent study in guinea pigs suggests that vaccination may be possible. Intramuscular administration of water-soluble derivatives of certain urushiol components not only desensitized previously sensitized animals, but also prevented sensitization of naive animals[36].

Applying 5% quaternium-18 bentonite lotion before touching poison ivy reduces allergic reactions, but currently the once commercially available product is no longer available. Of note, toxicodendron allergens pass through rubber gloves, but not heavy-duty vinyl gloves.

In chronic actinic dermatitis or other widespread Asteraceae-induced dermatitis, potent topical corticosteroids and oral prednisone are relatively ineffective unless employed early (before year-round dermatitis occurs). Very-low-dose PUVA with initial oral corticosteroid coverage[37], azathioprine, or mycophenolate mofetil may be necessary to control the disease (see Ch. 87 for details).

Other Plant Families Causing Allergic Contact Dermatitis

Alliaceae

The genus *Allium* includes onions, garlic, and chives. Garlic is the most frequent cause of fingertip dermatitis in cooks. It typically presents on the thumb, index, and middle fingertips of the non-dominant hand with hyperkeratosis, desquamation, and fissuring. Patch testing to whole garlic should never be done because of its irritant properties. The most important irritant and allergen is diallyl disulfide. Onion (*Allium cepa*) dermatitis is rare. Common disposable gloves, such as vinyl, latex, polyethylene, and nitrile, do not protect sensitized individuals who handle garlic or onions. Reusable domestic rubber gloves are protective.

Alstroemeriaceae and Liliaceae

"Tulip fingers" is a combined allergic and irritant contact dermatitis caused by tulip bulbs (*Tulipa* spp.). Erythematous, scaly plaques appear on the fingertips and periungual skin, particularly on the first and second fingers of the dominant hand, but a diffuse, xerotic hand dermatitis often develops after prolonged exposure. Pulpitis, paronychia, and dissemination to the face, neck, arms, and anogenital area may ensue. Tuliposide A, a glycoside, is found in the white epidermis of bulbs. Acidic hydrolysis converts it to tulipalin A, the allergen. Tuliposide B is also found in tulips, but its hydrolytic product, tulipalin B, is a much weaker sensitizer.

Since their popularization in Holland in 1963, Peruvian lilies (*Alstroemeria aurantiaca* and *A. ligtu*) have become incredibly popular in floral arrangements. Handlers remove individual flowers, thread wire through the stems, and/or cut off leaves (Fig. 17.14A). These workers can develop erythema, fissuring, vesicles, hyperkeratosis, and exfoliation of the fingertips, greater on the dominant hand (Fig. 17.14B)[38]. Most often, allergic reactions present with non-inflamed distal finger fissuring and hyperkeratosis. Unfortunately, the allergen passes through vinyl (polyvinyl chloride) gloves[38]. Although nitrile (synthetic rubber) gloves are protective, few florists will wear them. Tuliposide A and B are found in virtually all portions of the plant. The flowers have more allergen than the stems, and the leaves have the least amount.

Myrtaceae

Since the early 1990s, oil distilled from the leaves of *Melaleuca alternifolia* (the Australian tea tree) has been increasingly reported as a cause of allergic contact dermatitis. At least two-thirds of Australians have been exposed to it, and between 2% and 7% of them are allergic to it. While tea tree oil possesses broad-spectrum antimicrobial, anti-inflammatory, and antihistaminic effects, at least 16 different constituents are strong sensitizers. Because most sensitizers are degradation products formed after exposure of tea tree oil to light, warmth, and moisture, fresh tea tree oil is a weak sensitizer[39].

Botanical products

Hundreds of botanical extracts are added to skin care products for fragrance and purported healing properties. Fifty to 60% of patients with a presumed contact allergy to botanical extracts display at least one relevant positive reaction[3,40]. In a 2004 report, the most common culprit was tea tree oil, followed by feverfew (Asteraceae family) and lichen acid mix (found in deodorants)[3]. A more recent analysis of allergic contact dermatitis due to the use of herbal remedies found that Asteraceae plants were the most common source of botanical allergens[40].

Balsam of Peru (*Myroxylon* spp.), fragrance mix, Compositae mix, and SQL mix are poor screens for botanical allergy in that they uncover only 33%, 30%, 20%, and 7% of relevant allergic reactions, respectively[3]. A *repeat open application test* performed by applying the suspected allergenic product to the antecubital fossa twice daily for seven days will help diagnose an allergy to botanical extracts.

Table 17.13 lists plant dermatoses most commonly observed by dermatologists in various countries from around the world.

OCCUPATIONAL PLANT DERMATOSES

Bakers

Bakers and food processors have high rates of immunologic contact urticaria[41]. Flours, grains, and feeds ranked third behind cow dander and latex as the causes of such urticaria[2]. Omalizumab has allowed at least one baker to maintain his job when protein contact dermatitis to wheat threatened his livelihood[42].

Florists and Horticulturalists[43–45]

Irritant dermatitis outweighs allergic contact dermatitis in frequency and importance. Estimates of hand dermatitis in florists range from an 8% point prevalence to a 25%–30% annual incidence to a nearly 50% lifetime incidence, especially amongst floral designers. Although most cases of hand dermatitis are mild, periodic, and self-limited, because florists' hands are often wet, primary irritant reactions may lead to sensitization over long periods of time.

For florists, the most common sensitizers are sesquiterpene lactones, tulipalin A, and primin (*Primula obconica*). Daffodil itch (caused by calcium oxalate), from handling stems and bulbs, is probably the most common cause of irritant contact dermatitis in florists. In one series,



Fig. 17.14 Allergic contact dermatitis in a florist. **A** Florist with fingertip *Alstroemeria* allergic contact dermatitis showing how he holds a Peruvian lily while cutting off the leaves. **B** Index finger of the same florist, showing the chronic, lichenified, hyperkeratotic dermatitis caused by allergy to Peruvian lily and tulipalin A. *Photos with permission from the American Journal of Contact Dermatitis 1999;10:172–6.*

10% of 250 horticultural workers were allergic to Asteraceae[45] and one-third developed urticaria. An atopic family history increased one's likelihood of developing urticaria[45].

Food Handlers

Food handlers are at increased risk for immunologic contact urticaria and protein contact dermatitis (see above)[46]. Of those who develop protein contact dermatitis, over 60% need to change jobs. Among grocery store workers, contact with fresh celery combined with indoor tanning increases the prevalence ratio for phytophotodermatitis to >40 as compared to those with neither risk factor.

Outdoor Workers

Among outdoor workers, poison ivy and poison oak (*Toxicodendron* spp.) are the main causes of occupational contact dermatitis. *Toxicodendron* contact accounts for 10% of all lost-time injuries for the US Department of Agriculture Forest Service. Foresters, especially when fighting forest fires, have virtually no control over avoiding these plants. Up to 25% of firefighters need to leave the fire line because of severe *Toxicodendron* dermatitis.

Forestry workers in the American and Canadian Pacific Northwest may develop "woodcutter's eczema", an allergic contact dermatitis caused by airborne or rainwater-dispersed SQLs from liverworts (*Frullania* spp.) growing on trees and rocks. The dermatitis is worse in wet winter months and presents in a pseudo-photodistribution, involving the upper eyelids while sparing the submental area.

DERMATOSES ERRONEOUSLY ASCRIBED TO PLANTS

Organisms that are neither animal nor plant belong to one of the following kingdoms:

- Monera – unicellular prokaryotes (anuclear); includes bacteria and blue-green algae (cyanobacteria)
- Fungi – multicellular, heterotrophic (absorb food) eukaryotes (possess nuclei); lack cilia or flagella
- Protista – unicellular eukaryotic protozoans and algae

Reactions to these organisms can be falsely ascribed as reactions to plants.

Lichen Dermatitis[47]

Lichens are composite organisms consisting of a fungus and a photosynthetic partner, usually a green or blue-green alga. In the Pacific Northwest, the fungal component of lichens growing on trees, rocks, or soil disperses usnic acid, atranorin, and everinic acid onto foresters or other passersby via either direct contact or rainwater. This leads to allergic contact dermatitis in a pseudo-photodistribution. These three lichen acids are found in the common fragrance constituent oak moss absolute, and they can also cause photoallergic contact dermatitis. Oak moss absolute is one of eight ingredients in the fragrance mix I and is responsible for almost 40% of positive reactions to this fragrance mix.

Chlorella Photodermatitis

Ingestion of *Chlorella*, a nutritional supplement grown in Taiwan and Japan, can cause photodermatitis. *Chlorella* is a single-celled green alga that produces pheophorbide A, a photosensitizing breakdown product of chlorophyll that has been used experimentally for photodynamic therapy.

Seaweed Dermatitis[48]

While there are over 3000 species of seaweed, the unicellular blue-green alga *Lyngbya majuscula* is the primary species that causes a chemical irritant contact dermatitis (due to aplysiatoxin and debromoaplysiatoxin). Usually growing in fine blackish-green to olive-green strands up to 30 cm long, it looks like matted hair or felt and can get caught under bathing or wet suits. Within minutes of contact, genitalia and buttocks develop erythema, pruritus, and edema. Pustules and several days of desquamation often follow.

Seaweed dermatitis is primarily a problem during algal blooms stimulated by pollution and overfishing. In temperate and tropical oceans around the world, *Lyngbya* has been observed in intertidal zones up to a depth of 30 meters.

Pseudo-Phytodermatitis From Plant Hitchhikers

Allergic and irritant chemical reactions may occur from insecticides and other chemicals used to prevent horticultural or agricultural damage. Contaminating arthropods such as the hay itch mite (*Pyemotes* spp.) found in grains can cause pruritic wheals in dock workers, farmers,

GLOBAL PERSPECTIVE – PLANT DERMATOSES MOST COMMONLY OBSERVED BY DERMATOLOGISTS IN VARIOUS COUNTRIES

Country	Plants/Types of reactions		
Australia	*Lyngbya majuscula* (seaweed dermatitis)/ICD	*Dendrocnide* tree/TMU	*Melaleuca* (tea tree oil)/ACD
Brazil	*Anacardium occidentale* (cashew nut tree)/ACD	*Mangifera indica* (mango tree)/ACD	*Schinus terebinthifolia(us)* (Brazilian peppertree)/ACD
Canada	Lichen (woodcutter's eczema)/ACD	*Frullania* (liverwort; woodcutter's eczema)/ACD	*Toxicodendron* spp. (poison ivy)/ACD
Chile	*Lithraea caustica* [Anacardiaceae]/ACD	*Ruta graveolens* (common rue)/PPD	*Urtica* spp. (stinging nettles)/TMU
China	*Toxicodendron vernicifluum*/ACD	*Mangifera indica* (mango tree)/ACD	*Ginkgo biloba* (Ginkgo tree)/ACD
Colombia	*Toxicodendron striatum* (manzanillo)/ACD	*Alstroemeria* spp./ACD	
India	*Parthenium hysterophorus*/ACD	*Chrysanthemum* spp./ACD	
Italy	*Ficus carica* (fig tree)/ICD, MID, PPD		
Japan	*Toxicodendron vernicifluum*/ACD	*Primula obconica*/ACD	
Lebanon	*Chrysanthemum* spp./ACD		
Philippines	*Lyngbya majuscula* (seaweed dermatitis)/ICD	*Anacardium occidentale* (cashew nut tree)/ACD	
South Africa	*Smodingium argutum* (African poison ivy)/ACD	*Alstroemeria spp.*/ACD	*Chrysanthemum* spp./ACD
United States	*Toxicodendron* spp. (poison ivy/oak)/ACD	*Alstroemeria* spp./ACD	*Chrysanthemum* spp./ACD
Uzbekistan	*Ficus carica* (fig tree)/ICD, MCD, PPD	*Solanum lycopersicum* (tomato leaves)/ACD, TMU	*Chelidonium majus* [Papaveraceae] (greater celandine)/ICD

Table 17.13 Global perspective – plant dermatoses most commonly observed by dermatologists in various countries. Note that *Lyngbya maluscula* is an alga. ACD, allergic contact dermatitis; ICD, irritant contact dermatitis; MID, mechanical irritant dermatitis; PPD, phytophotodermatitis; TMU, toxin-mediated urticaria.

packers and storers of grain (see Ch. 85). Paraphenylenediamine added to henna tattoos can induce allergic contact dermatitis. Allergic contact dermatitis due to normal plant tissue levels of nickel have been reported for *Euphorbia triangularis* (Euphorbiaceae) and the freshwater plant *Ludwigia repens* (Onagraceae).

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 17.1 Erythematous, burning, edematous scrotum from an irritant reaction after applying garlic (*Allium sativum*) to treat a "rash". *Courtesy Martin Giandoni, MD.*



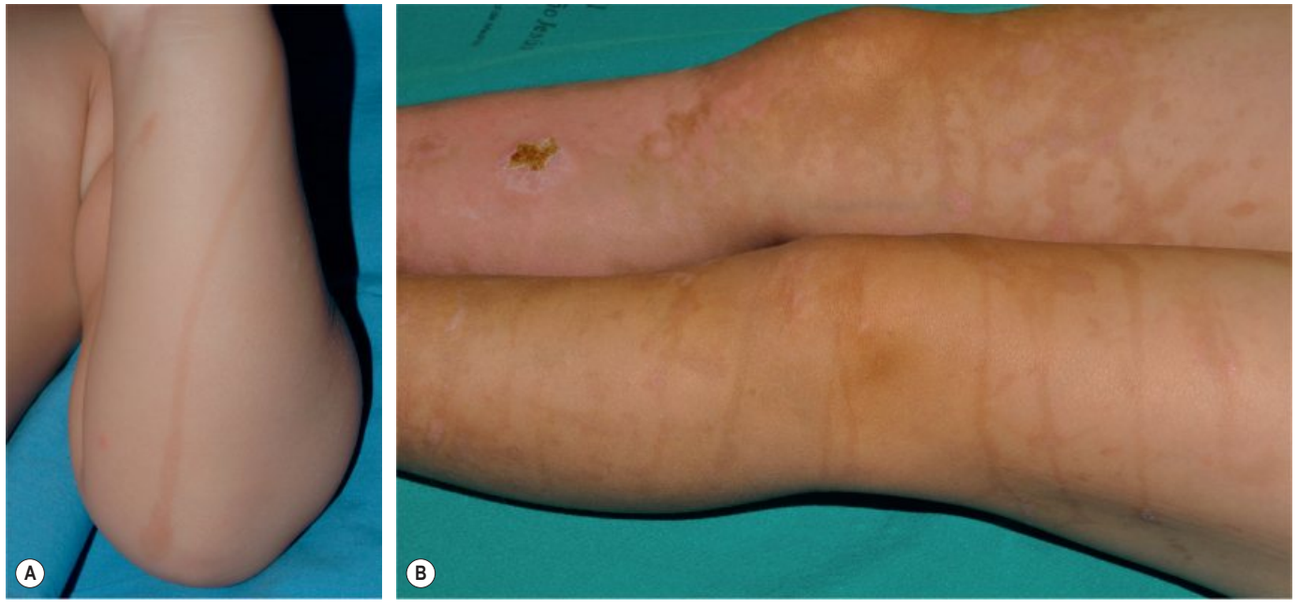
eFig. 17.2 "Chili burns" of the non-dominant hand after cutting jalepeño peppers. Capsaicin-induced depolarization of nerves leads to vasodilation and sensory nerve activation. As a result, the patient develops erythema accompanied by a burning sensation.



eFig. 17.4 Phytophotodermatitis. The patient was exposed to limes then sunlight while making guacamole dip. *Courtesy Kalman Watsky, MD.*



eFig. 17.5 Allergic contact dermatitis due to mangos. Note the linear lesion at 5 o'clock. *Courtesy Scott Norton, MD.*



eFig. 17.3 Phytophotodermatitis. A, B Linear hyperpigmented streaks are seen in addition to inflammation and crusting in **B.** *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Antonio Torrelo, MD.*



eFig. 17.6 Poison ivy (*Toxicodendron radicans*) dermatitis. Vesicles and bullae arising within areas of edematous erythema. Pruritus can be severe. *Courtesy Kalman Watsky, MD.*



eFig. 17.7 Allergic contact dermatitis due to poison ivy (*Toxicodendron radicans*). Pink, edematous streaks on the trunk. *Courtesy Julie V. Schaffer, MD.*





eFig. 17.8 Stinging nettle (*Urtica dioica*). A Habitat on the Kansas prairie. **B** Trichomes on both the stem and the leaf surfaces. *A, Courtesy Craig A. Freeman; with permission from McGovern TW, Barkley TM. Botanical briefs. Stinging nettle – Urtica dioica L. Cutis. 1998;62:63–4; ©1998 Quadrant Health Com Inc.*

Urticaria and Angioedema 18

Clive E.H. Grattan, Emek Kocatürk and Sarbjit S. Saini

Synonyms: ■ Wheals – hives, nettle rash ■ Angioedema – Quincke edema, angioneurotic edema

Key features

- Urticaria is characterized by transient skin or mucosal swellings due to plasma leakage. Superficial dermal swellings are wheals, and deep swellings of the skin or mucosa are termed angioedema. Wheals (hives) are characteristically pruritic and pink or pale in the center, whereas angioedema is often painful, less well-defined, and shows no color change
- There are several recognizable clinical patterns of urticaria and different causes. The latter include allergy, autoimmunity, drugs, dietary pseudoallergens, and infections. Many cases of spontaneous urticaria remain unexplained ("idiopathic") even after an extensive evaluation; they may also be multifactorial
- C1 esterase inhibitor deficiency and angiotensin-converting enzyme (ACE) inhibitors need to be considered as causes of recurrent angioedema without wheals
- Diagnosis is based primarily on the history and clinical examination. Determination of the etiology or triggers, as well as exclusion of other diagnoses, may require further investigations, including blood tests, physical and dietary challenges, skin tests, and skin biopsy
- Urticaria is a common disorder that may cause considerable distress and last for years, but the symptoms can usually be alleviated by appropriate management

INTRODUCTION

Urticaria is a common reason for patients to present to primary care practitioners, emergency rooms, dermatologists, and allergists. It is characterized by the rapidity of its fluctuation. As a rule, individual wheals last no more than 24 hours, but the entire affliction usually lasts much longer. With nearly all clinical patterns of urticaria, wheals may be accompanied by angioedema, but the occurrence of isolated angioedema (without wheals) is of special significance because some of these patients will have a deficiency of C1 esterase inhibitor (C1 inh). The latter is due to bradykinin formation rather than release of mast cell mediators. C1 inh deficiency is a rare disorder that is often inherited and because it can prove fatal without treatment must be considered in any patient with isolated angioedema. Urticarial vasculitis is an important disorder to exclude in patients with chronic urticaria. It is a systemic disease defined by damage to small blood vessels rather than transient vasodilation and vascular permeability (see Ch. 24). Urticarial vasculitis sometimes presents with wheals or angioedema that, without confirming a duration of more than 24 hours (by serial examination of marked lesions) and a lesional skin biopsy, can be indistinguishable from chronic spontaneous urticaria (CSU). While urticaria rarely progresses to anaphylaxis, wheals are often a feature of that condition. Good management of urticaria depends on a thorough understanding of etiologies, triggers, and aggravating factors, in addition to the most appropriate drug therapies.

Definition of Urticaria

Urticaria is often used as a descriptive term for recurrent wheaing of the skin, with angioedema being viewed as a physical sign. However, there is increasing acceptance that the term "urticaria" also defines an entity that may be acute or chronic. Thus, when viewed as a disease, urticaria may present with wheals, angioedema, or both.

Wheals are pruritic, pink or pale swellings of the superficial dermis that have an initial erythematous flare around them (Fig. 18.1). Lesions may be a few millimeters in diameter or as large as a hand, and the number can vary from a few to numerous. The hallmark of wheals is that, by definition, *individual* lesions come and go rapidly, generally within 24 hours. However, larger coalescing wheals may take longer to resolve.

Angioedema swellings occur deeper in the dermis and in the subcutaneous or submucosal tissue. They may also affect the oropharynx and rarely the bowel in hereditary angioedema. The areas of involvement tend to be normal or faint pink in color, painful rather than pruritic, larger, and less well-defined than wheals, and they often last for 2 to 3 days (Fig. 18.2).

EPIDEMIOLOGY

Depending on the age range and method of sampling, estimates of the lifetime prevalence of acute and chronic urticaria in the general population range from 8% to 22%[1]. In a recent meta-analysis, chronic urticaria had overall lifetime and point prevalence rates of 1.4% and 0.7%, respectively[2]. The prevalence of specific subtypes of chronic urticaria, e.g. the inducible urticarias, is lower[3].

Urticaria is a worldwide disease and may present at any age, with the peak incidence dependent upon etiology. The proportion of cases due to different etiologic agents is likely related to the frequency of environmental exposures, such as infections and allergens, in different countries, but estimates of this are not available. It is also often difficult to prove a cause and effect, and so an underlying condition may be inappropriately "blamed" for causing urticaria. Overall, urticaria is more common in women, with a female : male ratio of ~2 : 1 for CSU, but the ratio varies with the different physical urticarias. For example, women outnumber men in dermographism and cold urticaria, but more men develop delayed pressure urticaria. Hereditary angioedema has an autosomal dominant inheritance pattern and occurs in ~1 in 50 000 individuals, with a range that varies from 1 in 20 000 to 1 in 60 000.

PATHOGENESIS

The Mast Cell

Distribution and diversity

The mast cell is the primary effector cell of urticaria. Mast cells are widely distributed throughout the body but vary in their phenotype and response to stimulation. This may explain why systemic features, such as those seen in anaphylaxis, do not accompany the activation of cutaneous mast cells in urticaria. The majority of mast cells in the skin and intestinal submucosa contain the neutral proteases tryptase and chymase (MC_{TC}), whereas those in the bowel mucosa, alveolar wall, and nasal mucosa contain only tryptase (MC_T). Both types, however, express high-affinity IgE receptors (FcεRI) and are therefore capable of participating in IgE-dependent allergic reactions[4]. There is conflicting evidence on the number of cutaneous mast cells in chronic urticaria, but there is agreement that they may be more likely to degranulate in response to certain stimuli, such as intradermal codeine injection, and in this sense may be in general more "releasable". Little is known about the beneficial effects of mast cells, but there is evidence that they are involved in the innate immune response to infection, wound healing, and the neuroendocrine system. They have also been shown to help initiate the extracellular matrix formation and angiogenesis required for neurofibroma development.



Fig. 18.1 Wheals. A, B Wheals can vary in size from small to large as well as be annular, but they still retain the classic central pallor and erythematous flare. **C** Occasionally, more uniform edematous plaques are seen.



Fig. 18.2 Angioedema. The swelling is deeper than wheals and may affect mucosal surfaces. Note the swelling of the lips and periorbital region and the lack of erythema.

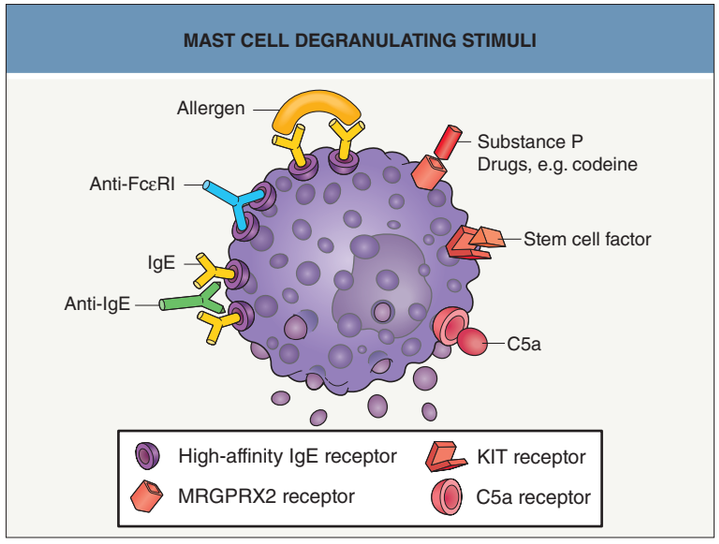


Fig. 18.3 Mast cell degranulating stimuli. Both immunologic and non-immunologic stimuli can lead to release of mediators. Substance P also binds to neurokinin 1 receptor; stem cell factor is also known as KIT ligand. MRGPRX2, MAS-related G-protein coupled receptor X2.

Degranulating stimuli

Cross-linking of two or more adjacent FcεRI on the mast cell membrane will initiate a chain of calcium- and energy-dependent steps leading to fusion of storage granules with the cell membrane and externalization of their contents. This is known as degranulation. Classic immediate hypersensitivity reactions involve binding of receptor-bound specific IgE by allergen. There are also several recognized immunologic degranulating stimuli that act through the IgE receptor, such as IgG anti-IgE and anti-FcεRI antibodies (Fig. 18.3).

Autoantibodies against FcεRI (IgG > IgM, IgA) are associated with disease markers of CSU[5], but the degree to which they mediate release of histamine from mast cells or basophils *in vitro* can vary. In addition, because anti-IgE and anti-FcεRI autoantibodies have been identified by immunoassays (but not functional assays) in patients with other diseases such as systemic lupus erythematosus[6] and occasionally in healthy controls, the role of autoantibodies in the pathogenesis of urticaria has been debated. Stimuli that can lead to mast cell degranulation independent of FcεRI activation include C5a, stem cell factor, and agents that bind MRGPRX2 (MAS-related G-protein coupled receptor X2; see Fig. 18.3); the latter include substance P and drugs such as opioids[7,8].

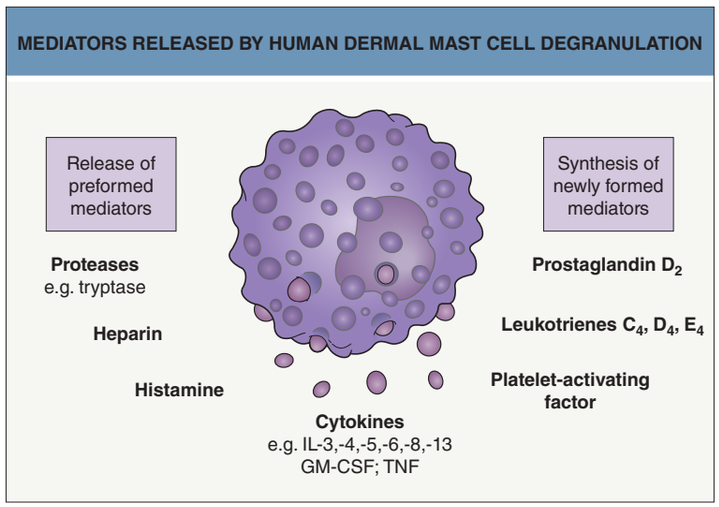


Fig. 18.4 Mediators released by human dermal mast cell degranulation. Both preformed and newly synthesized proinflammatory mediators are released from mast cells.

Proinflammatory mediators

Mast cell granules contain preformed mediators of inflammation, the most important of which is histamine (Fig. 18.4). A wide range of cytokines has been identified in human mast cells from different tissues, including tumor necrosis factor (TNF), interleukins (IL)-3, -5, -6, -8, and -13, and granulocyte–macrophage colony-stimulating factor (GM-CSF). Synthesis and secretion are upregulated following FcεRI stimulation. TNF is expressed constitutively in resting human cutaneous mast cells. Prostaglandins and leukotrienes are synthesized from arachidonic acid derived from cell membrane phospholipids. The

most important *proinflammatory* eicosanoids are prostaglandin (PG) D_2 and the leukotrienes (LT) C_4, D_4, and E_4 (slow releasing substance of anaphylaxis). PGE_2 has inhibitory effects on immunologic mast cell degranulation and may therefore have a protective role in urticaria. Increased levels of TNF, IL-1β, -6, -10, -12p70, -13, and B cell activating factor (BAFF) have been detected in the sera of urticaria patients[9].

Blood Vessels

Histamine and other proinflammatory mediators released upon degranulation bind receptors on postcapillary venules in the skin, leading to vasodilation and increased permeability to large plasma proteins, including albumin and immunoglobulins. Furthermore, histamine, TNF, and IL-8 upregulate the expression of adhesion molecules on endothelial cells, thereby promoting the migration of circulating inflammatory cells including eosinophils, basophils, neutrophils, and Th0 cells from the blood into the urticarial lesion[10].

Blood

Autoantibodies

Based upon *in vitro* assays, functional IgG autoantibodies that release histamine (and other mediators) from mast cells and basophils have been detected in the serum of 30%–50% of patients with CSU[11]. The *majority* of these autoantibodies bind the extracellular *α subunit of FcεRI*. Those recognizing the α_2 domain compete with IgE for the binding site, whereas non-competitive autoantibodies directed against the terminal α_1 domain are able to bind the receptor in the presence of IgE (Fig. 18.5). Increased serum levels of IgM anti-FcεRIα autoantibodies have also been found in patients with CSU and have been linked to features of autoimmune CSU[5]. Approximately 10% of chronic urticaria sera contain functional autoantibodies directed against the *Fc portion of IgE itself* (see Fig. 18.3). Binding of the autoantibodies to mast cells may initiate complement activation with the generation of C5a anaphylatoxin, which in turn facilitates or augments degranulation[12].

Circulating IgE autoantibodies directed against a range of autoantigens such as thyroid peroxidase (TPO), thyroglobulin, tissue factor, and IL-24 have been detected in patients with CSU[13–16]. However, healthy individuals and patients with disorders such as atopic dermatitis also have these IgE autoantibodies[17]. In patients with CSU and IgE anti-TPO antibodies, skin testing with recombinant TPO can elicit a wheal and flare reaction, indicating potential functionality, but it is still unclear as to why such patients develop only local wheals rather than systemic anaphylaxis[18].

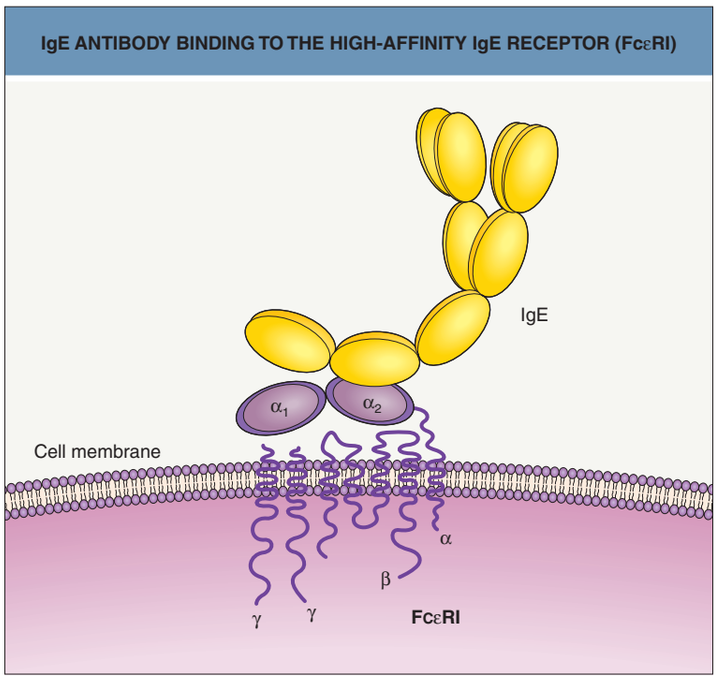


Fig. 18.5 IgE antibody binding to the extracellular α subunit of the high-affinity IgE receptor (FcεRI). Histamine-releasing autoantibodies directed against the terminal α_1 domain are able to bind the receptor in the presence of IgE and are therefore non-competitive, whereas those recognizing the α_2 domain compete with IgE for the binding site.

Other mast cell activating factors may also exist in urticaria sera, e.g. a non-IgG "mast cell-specific factor" has been described, although its identity remains unknown[19]. There is currently no evidence that characterized cytokines cause mast cell degranulation in urticaria. Evidence from small series of CSU patients treated with plasmapheresis[20] or cyclosporine[21] indicates that functional autoantibody levels correspond to disease severity.

Leukocytes

The importance of peripheral blood leukocytes in the pathogenesis of urticaria is becoming clearer. In general, blood ***basophils*** from CSU patients are less responsive *in vitro* to anti-IgE antibodies as an immunologic stimulus, possibly through desensitization, and these cells are reduced in number[22]. CSU patients can be further classified into responders and non-responders based upon the release of histamine by their basophils in response to anti-IgE antibodies or the flow cytometry-based basophil activation test (BAT). This basophil functional phenotype appears to remain stable during the course of the active illness, but then, during disease remission, the basophils become more responsive to anti-IgE antibodies[23]. Expression of the negative regulator SHIP (*s*rc *h*omology 2-containing *i*nositol *p*hosphatase) is increased in the basophils from anti-IgE non-responders[24], although the significance of this to the pathogenesis of chronic urticaria is unknown.

Evidence has emerged that basophils are recruited into urticaria wheals[25] and may sustain the inflammatory response by releasing histamine and other mediators, analogous to the delayed phase of immediate hypersensitivity reactions. A correlation between disease severity and the degree of reduction in circulating basophil counts has been observed[26]. This basopenia can normalize following successful treatment with omalizumab, providing support for the role of basophil migration into lesional skin during periods of disease activity[27].

In addition to basopenia, circulating eosinopenia may be present in those CSU patients who have greater disease activity and a lack of response to H1 antihistamines[28]. ***Eosinophils*** can contribute to the persistence of wheals by generating LTC_4, LTD_4, and LTE_4 and by releasing toxic granule proteins, including major basic protein (MBP); the latter can induce release of histamine from basophils and trigger mast cells via MRGPRX2[8]. Interactions between eosinophils and mast cells also include expression of tissue factor by eosinophils which then leads to activation of mast cells via protease activated receptors (PARs).

While ***lymphocyte*** numbers are normal in the peripheral blood of CSU patients, these cells are often present in biopsy specimens from spontaneous wheals. In one study, ~50% of the cells in the perivascular cellular infiltrates were T cells and ~20% were monocytes. Additional investigations in CSU patients noted the dermal infiltration of $CD4^+$ helper T cells, the majority of which co-expressed HLA-DR antigen; T cell activation in the peripheral blood as well as lesional and nonlesional skin; and increased expression of Th2-initiating cytokines in lesional skin[29]. Lastly, autoreactive $CD4^+$ T cells specific for FcεRIα were detected in the peripheral blood of patients with CSU[30].

Nerves

Substance P and other neuropeptides release histamine from mast cells *in vitro* and can induce a wheal and flare reaction in human skin when injected intradermally. Vasoactive intestinal polypeptide (VIP) caused a greater wheal reaction in those with chronic urticaria than did other skin-tested neuropeptides, but the relevance of this to urticaria is still uncertain. Elevated levels of brain-derived neurotrophic factor, β-endorphin, and substance P have been detected in patients with chronic urticaria[31–33]. Because several of these neuropeptides can bind MRGPRX2 on mast cells[34], the roles of neuro-immuno-cutaneous factors and neurotransmission in chronic urticaria require further clarification.

Mechanisms of Urticaria Formation

Mast cell-dependent urticaria

Potential mechanisms for mast cell-dependent urticaria are included in Table 18.1. Cross-linking of the Fab portion of specific IgE on mast

ETIOLOGIES AND PATHOMECHANISMS OF WHEALS AND/OR ANGIOEDEMA
Idiopathic
Immunologic
• Autoimmune (autoantibodies against FcεRI or IgE) • IgE-dependent (allergic) • Immune complex (vasculitic) • Kinin- and complement-dependent (C1 esterase inhibitor deficiency)
Non-immunologic
• Direct mast cell-releasing agents (e.g. opioids) • Vasoactive stimuli (e.g. nettle stings) • Aspirin, other nonsteroidal anti-inflammatory drugs, dietary pseudoallergens • Angiotensin-converting enzyme inhibitors

Table 18.1 Etiologies and pathomechanisms of wheals and/or angioedema. It is often difficult to know the exact pathogenesis of individual cases of urticaria, and many cases remain idiopathic after evaluation.

cells by percutaneous or circulating allergen undoubtedly accounts for some cases of acute or episodic urticaria, especially in children (see Fig. 18.3), but this is probably never the cause of adult chronic continuous urticaria. Examples of the former would be contact urticaria from natural rubber latex and acute urticaria from foods, including nuts, fish, and fruit. However, the majority of acute urticaria cases do not relate to allergen exposure.

IgE has been implicated in the pathogenesis of symptomatic dermographism, cold urticaria, and solar urticaria, but the mechanism by which it renders skin mast cells more sensitive to physical stimulation is not certain. It is proposed that the physical stimulus in these patients induces a neoantigen that reacts with specific IgE antibody bound to mast cells. An additional mechanism, such as neuropeptide release, could initiate or potentiate mast cell activation (see above). Using electron microscopy, localized platelet clumping has been demonstrated in cold urticaria, and the release of platelet mediators, including platelet-activating factor (PAF) and platelet factor 4/CXCL4, could contribute to wheal formation. A mutation in *F12*, which encodes the coagulation protein factor XII, has been identified in familial cold urticaria and a bradykinin-dependent, rather than mast cell-dependent, pathomechanism has been proposed (see below). Cold-induced urticarial lesions also occur in familial cold autoinflammatory syndromes (FCASs) due to mutations in *NLRP3, NLRP12*, or *PLCG2*, thus implicating a role for the cryopyrin inflammasome and its production of IL-1β (see Tables 45.2 & 45.7)[35].

Cholinergic urticaria develops in response to stimulation of cholinergic sympathetic innervation of the sweat glands. How release of acetylcholine from the nerve endings leads to mast cell activation and histamine release is unknown. An allergy to sweat has been demonstrated by one group of investigators[36]. It has been proposed that pressure-induced wheals may be due to a late-phase reaction, but an antigen has never been identified. In three Lebanese families with autosomal dominant vibratory urticaria, a missense gain-of-function variant was detected in *ADGRE2* which encodes adhesion G protein-coupled receptor E2. This was thought to lead to destabilization of the inhibitory interaction between the alpha and beta subunits of ADGRE2, leading to sensitization of mast cells to vibration-induced degranulation[37].

The initiating event for spontaneous urticaria wheals is unclear but may involve plasma leakage due to local factors such as heat or pressure, which allows the extravasation of autoantibodies or IgE-directed antigens that then activate the IgE receptor, thus leading to mast cell degranulation and a subsequent urticarial response. As functional autoantibodies cannot be detected in ~70% of chronic urticaria sera by currently available tests, other mechanisms may operate in "non-autoantibody" urticaria, which, nevertheless, has a similar clinical presentation[38]. Increased plasma levels of prothrombin fragment 1 + 2 (F 1 + 2) and D-dimer (a measure of fibrinolysis) have been demonstrated in CSU[39] and relate to disease severity, but the contribution of coagulation abnormalities to the pathogenesis remains unclear. There are other serum factors in CSU patients that can activate mast cell lines *in vitro* and lead to endothelial activation, independent of IgE receptors on mast cells and the presence of IgG[40].

A popular hypothesis is that dietary food additives and natural salicylates as well as nonsteroidal anti-inflammatory drugs (NSAIDs) may cause urticaria via the diversion of arachidonic acid metabolism from prostaglandin to leukotriene formation. How this leads to urticaria is not clear, but it is known that intradermal injections of LTC_4, LTD_4, and LTE_4 cause wheaing by a direct action on small blood vessels. There is some evidence from studies of rat peritoneal mast cells that PGE_2 can have inhibitory effects on immunologic mast cell degranulation[41], so a reduction in their formation may facilitate the latter. Aspirin can *aggravate* urticaria in up to 30% of patients with chronic disease, and while some clinical studies of dietary pseudoallergen avoidance have given encouraging results, the proportion of complete responders confirmed by rechallenge is small[42]. Aspirin allergy as a *cause* of urticaria is much less common, and the proportion of patients with urticaria due solely to pseudoallergens is probably low. Tolerance to NSAIDs is thought to be achievable in many CSU patients who are well controlled by H1 antihistamines[43].

Understanding "idiopathic" urticaria remains an important challenge. From a clinical perspective, it should be regarded as a multifactorial problem, and searching for aggravating factors is just as important as looking for causes.

Mast cell-independent urticaria

There are several recognized circumstances where angioedema or wheals are due to mechanisms that do not involve mast cells. These need special consideration because their management and prognosis are different. For example, prostaglandins are involved in the pathogenesis of some patterns of non-immunologic contact urticaria (e.g. to benzoic acid), and the latter can be suppressed by NSAIDs[44]. In the cryopyrin-associated periodic syndromes (CAPS; see below), patients often develop urticarial lesions. Systemic symptoms, such as fever, help to distinguish patients with autoinflammatory syndromes from those with CSU (see Ch. 45). The significant improvement that results from the administration of *anakinra*, an IL-1 receptor antagonist[45], *rilonacept*, a fusion protein that contains the extracellular domain of the IL-1 receptor and functions as an IL-1 trap[46], or *canakinumab*, a human anti-IL-1β monoclonal antibody[47], points to the role of the cryopyrin inflammasome and its production of IL-1β (see Figs. 4.2 & 45.13).

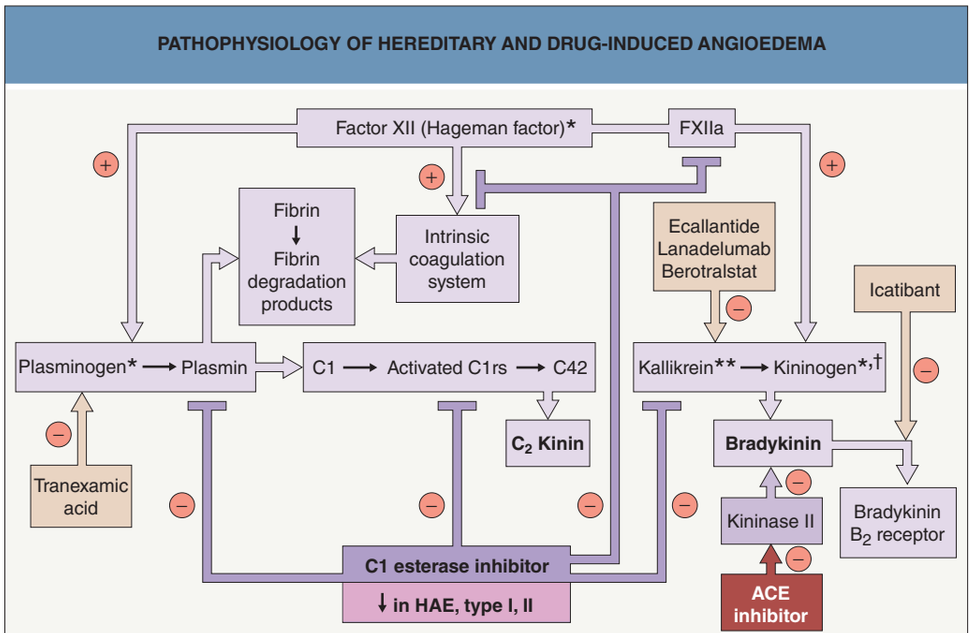
C1 esterase inhibitor (C1 inh) deficiency

C1 inh deficiency is usually hereditary but may be acquired. Two major forms of *hereditary* angioedema (HAE), types I and II, are primarily caused by mutations in one allele of the structural gene for C1 inh (*C1NH/SERPING1*) and are inherited in an autosomal dominant pattern. These mutations result in reduced levels of C1 inh (85% of cases; type I) or reduced C1 inh function (15% of cases; type II). Because these heterozygous mutations lead to levels that are 5%–30% of normal (rather than the expected 50%) in patients with type I HAE, it is thought that there is *trans* inhibition of the normal allele or increased catabolism of C1 inh. Rare families with autosomal recessive severe HAE and homozygous mutations have been reported.

Deficiency of C1 inh leads to loss of inhibition of factor XII (FXII; Hageman factor), resulting in the generation of bradykinin by the action of kallikrein on high-molecular-weight kininogen (Fig. 18.6). Activation of the C1 component of complement by proteolytic enzymes, including plasmin and FXIIa, leads to low levels of C4 in the serum, which is an almost constant feature between and during attacks in untreated patients.

HAE with normal C1 inh activity, also known as nC1-INH-HAE and previously referred to as type III HAE[48], is currently subclassified as HAE3 to HAE8 based upon underlying genetic mutations. HAE3 is due to *gain-of-function* mutations in one allele of the gene that encodes FXII, leading to increased formation of bradykinin (see Fig. 18.6). A positive feedback loop between kallikrein and FXII also contributes to the pathogenesis. One possible explanation for the preponderance of women with HAE3 is enhanced transcription of *F12* by estrogens. Mutations in *PLG*, *ANGPT1*, *KNG1*, *MYOF*, and *HS3St6* which encode plasminogen, angiopoietin-1, kininogen 1, myoferlin, and heparan sulfate 3-O-sulfotransferase 6 have also been described in HAE with normal C1 inh activity.

Acquired deficiency of C1 inh may result from activation of C1q and the complement cascade in patients with B cell lymphoproliferative disorders and plasma cell dyscrasias, or in those with autoimmune connective tissue diseases. This leads to *consumption* of C1 inh plus low



*HAE with normal C1inh is subdivided based upon molecular analysis with three groups having mutations in *F12*, *PLG*, or *KNG1* which encode factor XII, plasminogen, and kininogen 1, respectively; additional mutated genes in these patients include *ANGPT1*, *MYOF*, and *HS3St6* which encode angiopoietin 1, myoferlin, and heparan sulfate 3-O-sulfotransferase 6, with the seventh subgroup consisting of those without a known mutation.

**Kallikrein is formed from prekallikrein.
†High-molecular-weight.

Fig. 18.6 Pathophysiology of hereditary and drug-induced angioedema. Angiotensin-converting enzyme (ACE) inhibitor-induced urticaria is believed to result from the inhibition of endogenous kininase and a subsequent increase in bradykinin. Intravenous C1 inh concentrate (derived from human plasma) or recombinant C1 inh (derived from milk of transgenic rabbits), subcutaneous icatibant (a decapeptide that is a specific bradykinin B_2 receptor antagonist), and subcutaneous ecallantide (a 60-amino acid recombinant kallikrein inhibitor) are options for the *emergency* treatment of hereditary angioedema (HAE). Subcutaneous or intravenous C1 inh (every 3–4 days), subcutaneous plasma kallikrein inhibitor lanadelumab (every 2 weeks), and oral kallikrein inhibitor berotralstat (150 mg daily) are options for *prevention* of attacks. ACE, angiotensin-converting enzyme; HAE, hereditary angioedema; inh, inhibitor.

serum levels of C1q as well as C4 (acquired, type I) or the formation of *inhibitory autoantibodies* directed against the C1 inh (acquired, type II).

Angiotensin-converting enzyme (ACE) inhibitor-induced urticaria is believed to result from the inhibition of endogenous kininase II (also known as ACE), which leads to increased production of bradykinin via inhibition of its metabolism (see Fig. 18.6). It usually presents with angioedema, which is usually orofacial and may be life-threatening.

CLINICAL FEATURES

Clinical Diversity

It is important to distinguish *urticaria* from *urticarial dermatoses*, such as urticarial drug eruptions, eosinophilic cellulitis, and the urticarial phase of pemphigoid. The individual wheals of urticaria are "here today and gone tomorrow" (i.e. they generally last <24 hours), whereas with urticarial dermatoses, the individual lesions may last for days or longer. Although urticarial vasculitis is often included in classifications of urticaria because the wheals resemble urticaria, it is actually an urticarial dermatosis. Clinically, the lesions last longer than 24 hours (as determined by circling and observing individual wheals), and histologically there is evidence of leukocytoclastic vasculitis (see Ch. 24).

Wheals may be small or large, as well as single or multiple. In the physical urticarias, the distribution pattern and morphology can be helpful in separating the different clinical types (see Inducible Urticarias). Angioedema can merge with wheals and these two can be difficult to separate, especially around the eyelids. Angioedema may also be a feature of anaphylaxis, if the throat is involved. In this sense, wheals, angioedema, and anaphylaxis form parts of a clinical spectrum resulting from mast cell activation.

Classification

Because the etiology is often unknown at the time of the first consultation, the most practical classification of urticaria relies on clinical characteristics rather than etiology when defining groups of patients (Table 18.2). Mostly, spontaneous urticaria can be considered to behave in an ordinary manner (i.e. fluctuating wheals which may be accompanied by angioedema) whatever its etiology or duration, unless it has a predominantly physical trigger, has evidence of vasculitis, or is caused by exogenous contact. If no cause for spontaneous urticaria can be defined, it is called idiopathic, but the use of this label as an automatic prefix to chronic urticaria is no longer tenable as a significant number of these patients are considered to have an autoimmune etiology as evidenced by functional basophil histamine release and activation assays (Table 18.3) or flow cytometry-based BAT. Elevated thyroid antibodies are also suggestive of autoimmune urticaria. It is worth separating angioedema without wheals from the other patterns of urticaria, because some of these cases will be due to HAE, acquired C1 inh deficiency, or drug reactions (e.g. ACE inhibitors, NSAIDs), and these are managed differently.

URTICARIA – CLINICAL CLASSIFICATION AND DIFFERENTIAL DIAGNOSIS
Clinical classification

• Spontaneous urticaria (all urticarias not classified below)
• Inducible urticarias (see Table 18.4)
  • Physical, non-physical (e.g. aquagenic), and cholinergic urticarias
  • Contact urticaria (induced by percutaneous or mucosal penetration)*

Differential diagnosis
• Urticarial drug eruption • Urticarial vasculitis (defined histologically by leukocytoclastic vasculitis) • Angioedema without wheals (e.g. hereditary angioedema, ACEi-induced angioedema) • Urticarial syndromes (e.g. autoinflammatory syndromes)
*Included within the inducible urticarias in the EAACI/GA²LEN/EDF/WAO Guideline[90].

Table 18.2 Urticaria – clinical classification and differential diagnosis. All clinical patterns of urticaria can be acute, episodic, or chronic. ACEi, angiotensin-converting enzyme (ACE) inhibitor.

Acute Versus Chronic Urticaria

All urticarias are acute initially. Some will become chronic after a period of time that is usually defined as 6 weeks or more. In a study from Korea, only a small proportion (7.8%) of patients with new-onset urticaria developed chronic urticaria during a 10-year follow-up period[49]. The term "chronic urticaria" should only be applied to continuous urticaria

TESTS EMPLOYED FOR AUTOIMMUNE URTICARIA				
Test		**Method**	**Strengths**	**Weaknesses**
Functional				
Basophil activation	Histamine release	Incubation of CSU sera with healthy donor basophils	• Test of CSU serum functionality – assumed IgG autoantibodies against FcεRI or IgE • Commercially available • May predict good response to cyclosporine	• Not specific for autoantibodies • May be present in patients with other illnesses and healthy individuals
	Basophil activation (CD203c or CD63)	Incubation of CSU sera with healthy donor basophils	• Test of CSU serum functionality – assumed IgG autoantibodies against FcεRI or IgE • Not commercially available outside the US	• No proven predictive value for treatment response
Autologous serum skin test (ASST)	Red wheal response to *autologous* serum	Intradermal *autologous* serum injection	• Visual demonstration of circulating serum factors and skin reactivity during CSU disease activity	• Not specific for functional antibodies or CSU • Not predictive of treatment response • No longer widely used due to concerns about safety of unregulated skin testing with blood products
Non-functional (and functional)				
Immunoassays	ELISA	IgG, IgM, and IgA autoantibodies against FcεRI and IgE	• Specific for autoantibody isotype and target antigens in CSU • Detects functional and non-functional antibodies	• Present in patients with other illnesses and healthy individuals • No proven utility for predicting treatment response • Not commercially available

Table 18.3 Tests employed for autoimmune urticaria. CSU, chronic spontaneous urticaria; ELISA, enzyme-linked immunosorbent assay.

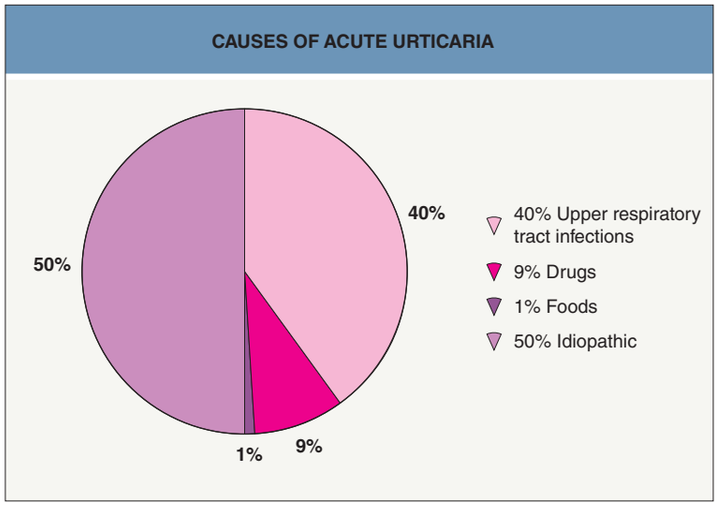


Fig. 18.7 Causes of acute urticaria. *Data from Zuberbier T, Iffländer J, Semmler C, Henz BM. Acute urticaria: clinical aspects and therapeutic responsiveness. Acta Derm Venereol 1996;76:295–7.*

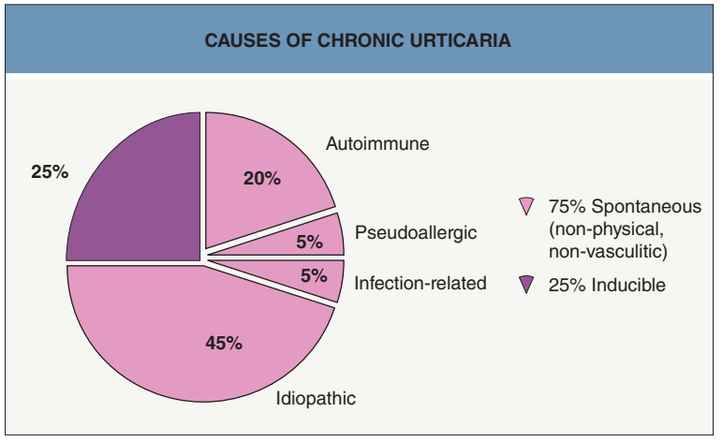


Fig. 18.8 Causes of chronic urticaria. Autoimmune represents those patients with functional autoantibodies against FcεRI or the Fc portion of IgE.

occurring at least twice a week off treatment. Urticaria occurring less frequently than this over a long period is better called episodic (or recurrent), because this presentation may be more likely to have an identifiable environmental cause.

The causes of *acute* urticaria in adults presenting to emergency dermatology clinics in one survey are shown in Fig. 18.7[50,51]. Most of these patients probably fall into the spontaneous category, because physical urticarias and urticarial vasculitis tend to persist beyond 6 weeks and contact urticarias would not normally present as an emergency. The high frequency of associated viral infections is notable, as is the lack of food allergy as a cause. The different clinical patterns of *chronic* urticaria and their causes (where known) are shown in Fig. 18.8. These data reflect the experience of specialist urticaria clinics in dermatology departments and may not represent the experience of other medical practitioners, such as those in general practice, internal medicine, pediatrics, or allergy.

Spontaneous Urticaria

The condition can present at any age. Acute urticaria is common in young atopic children but chronic urticaria peaks in the fourth decade. Multiple pruritic wheals of different sizes erupt anywhere on the body and then fade within 2–24 hours without bruising; angioedema may last up to 72 hours when severe. In literature reviews, isolated urticaria occurred in ~50% of patients, urticaria plus angioedema in ~40%, and angioedema alone in the remainder[52,53]. Wheals may occur at any time, but often appear in the evening or are present on waking. Irritation tends to be most intense at night and may disturb or prevent sleep. This, in turn, compounds the distress of the condition. Substantial impairment in quality-of-life measures, including self-image, sexual relationships, and social interactions, has been demonstrated. Women may describe premenstrual exacerbations. Systemic symptoms of fatigue, lassitude, sweats and chills, indigestion, myalgia, or arthralgia may occur with severe attacks[54], but the occurrence of pyrexia or arthritis should alert the clinician to another explanation, such as urticarial vasculitis or neutrophilic urticarial dermatosis due to Schnitzler syndrome, Still disease, or CAPS.

Associations and comorbidities

Chronic spontaneous urticaria has been associated with autoimmune thyroid disease[55] and other autoimmune conditions, including vitiligo, insulin-dependent diabetes, rheumatoid arthritis, and pernicious anemia[56]. Those chronic urticaria patients with demonstrable histamine-releasing autoantibodies have a very strong association with HLA DRB1*04 (DR4) and its associated allele DQB1*0302 (DQ8)[57]. A possible association between *Helicobacter pylori* gastritis and chronic urticaria was suggested by a systematic review of therapeutic studies,

which showed a higher frequency of urticaria remission when the infection was eradicated than when it was not[58]. Parasitic infections, in particular protozoa (e.g. *Blastocystis hominis*, *Giardia* spp.), are an uncommon cause of urticaria in high-income countries, but may be a significant problem where they are endemic. Acute urticaria due to gastric *Anisakis simplex* has been reported from Spain[59]. Possible associations between dental infections or gastrointestinal candidiasis and chronic urticaria have not been substantiated by large epidemiologic studies.

Although there have been anecdotal reports linking urticaria to malignancy[60], no statistically significant association was found in a Swedish survey[61]. However, an increased risk of hematologic malignancies, especially non-Hodgkin lymphoma, was noted in a large retrospective cohort study of a National Insurance database in Taiwan[62]. Atopic diseases[63], metabolic syndrome[64], and psychiatric disorders (especially anxiety and depression)[65] are reported comorbidities in chronic urticaria.

Inducible Urticarias (syn. Physical Urticarias)

These urticarias represent a distinct subgroup of urticaria that is induced by an exogenous stimulus rather than occurring spontaneously. This section discusses physical triggers while the next section reviews other chemical and protein stimuli. Because cholinergic urticaria is triggered by factors that lead to sweating (e.g. a rise in core body temperature, stress, spicy foods), rather than an external physical stimulus, it is often classified separately from other inducible urticarias. The inducible urticarias are classified by the predominant stimulus that triggers whealing, angioedema, or anaphylaxis[66] (Table 18.4). Of all the urticarias, they may affect the quality of life most severely, particularly delayed pressure urticaria and cholinergic urticaria[67]. While the lesions of most physical urticarias occur within minutes of provocation and generally resolve within 2 hours, a few physical urticarias (e.g. delayed pressure urticaria, delayed dermographism) develop after a delay of several hours and persist for 24 hours or longer.

The wheals are usually localized to the stimulated area of skin. However, sometimes the physical stimuli need to produce a systemic effect, e.g. a rise or drop in core body temperature, to induce urticaria of a reflex type. Thus, generalized heating of the body can induce cholinergic urticaria (which is common), and generalized cooling, cold reflex urticaria (which is rare). Here, multiple small wheals occur on widespread areas of the body.

Angioedema may be seen with all the physical urticarias except with symptomatic dermographism. Vibratory angioedema manifests with subcutaneous swellings but not wheals. Also, several forms of physical urticaria can coexist in the same patient. Common combinations include: (1) symptomatic dermographism and cholinergic urticaria; and (2) cold and cholinergic urticaria. In addition, delayed pressure urticaria may coexist with CSU. Some rare forms of physical urticaria, such as familial delayed cold urticaria, are beyond the scope of this chapter.

CLASSIFICATION OF INDUCIBLE URTICARIAS
Urticaria due to mechanical stimuli

Dermographism
• Immediate
  • Simple
  • Symptomatic
• Delayed
Delayed pressure urticaria
Vibratory angioedema
• Inherited
• Acquired

Urticaria due to temperature changes

Heat
• Heat contact urticaria
Cold
• Cold contact urticaria
  • Primary
  • Secondary (cryoproteins)

Urticaria due to sweating or stress
Cholinergic urticaria Adrenergic urticaria Exercise-induced urticaria • Exercise-induced anaphylaxis • Food- and exercise-induced anaphylaxis
Contact urticaria
Solar urticaria
Aquagenic urticaria
Rare variants are not shown here for simplicity.

Table 18.4 Classification of inducible urticarias by the eliciting stimulus.

Urticaria due to mechanical stimuli

Dermographism (literally "skin writing") (syn. dermatographism, factitious urticaria)

Immediate dermographism

This is divided into simple or symptomatic. *Simple* immediate dermographism occurs in at least 5% of the normal population in response to moderate stroking of the skin and may be regarded as an exaggerated physiologic response and is typically not pruritic.

Symptomatic immediate dermographism is the most common type of physical urticaria (Fig. 18.9). It manifests as pruritic linear wheals at sites of scratching or sites of friction, such as collars and cuffs of clothes. Whealing occurs after gentle stroking of the skin in response to a shearing force. Patients, most frequently young adults, often complain of pruritus before the wheals appear and may not associate them with scratching. It is worst in the evening and often occurs in bouts. The lesions usually resolve within an hour. Oral mucosal involvement does not occur, but vulvodynia and swelling during sexual intercourse has been reported[68].

The general course is unpredictable, but usually there is a gradual tendency towards improvement over several years. Symptomatic dermographism occasionally follows scabies infestation and penicillin allergy reactions. There is no association with systemic disease, atopy, food allergy, or autoimmunity.

Rarer forms of dermographism

These include delayed dermographism, which appears at least 30 minutes after a stroking stimulus, red dermographism (in response to rubbing, not stroking, the skin), localized dermographism, cholinergic dermographism, and Darier's sign (a localized dermographic response after gentle rubbing of cutaneous mastocytosis lesions). The blanching response seen in patients with atopic and other forms of dermatitis, known as white dermographism, is not a form of urticaria nor is black dermographism in which there is dark discoloration of the skin due to surface deposition of metallic particles.

Delayed pressure urticaria

Delayed pressure urticaria (DPU) is important because it can interfere severely with quality of life; it may be underdiagnosed and its treatment is difficult[69]. DPU is characterized by the development of deep



Fig. 18.9 Symptomatic immediate dermographism. Itchy wheals appear very soon after scratching. *Courtesy Jean L. Bolognia, MD.*



Fig. 18.10 Delayed pressure urticaria.



Fig. 18.11 Cold urticaria. Wheals developed on the forearm after placement of an ice cube for 10 minutes, followed by rewarming. *Courtesy Thomas Schwarz, MD.*

erythematous swellings at sites of sustained pressure to the skin, after a delay of 30 minutes to 12 hours (Fig. 18.10); sometimes it resembles angioedema. The swellings are usually pruritic, painful, or both, and may persist for several days, unlike the spontaneous wheals of ordinary urticaria. Sites frequently involved are the waistline after wearing tight clothing, below the elastic of socks, the feet in tight shoes, the palms after manual work, the soles after walking or climbing ladders, and the genitalia after intercourse.

Rarely, systemic features such as malaise, "flu-like" symptoms, and arthralgia may occur. If the swellings develop over joints, the resulting restriction of motion may be mistaken for arthritis. The prognosis is variable, but the mean duration in different series was 6–9 years. Up to 35% of patients with CSU attending a hospital specialist clinic had associated DPU. Conversely, nearly all patients with DPU have associated spontaneous wheals. Because of this association and the delayed onset, patients may not be aware of any relationship to pressure unless specifically questioned.

Vibratory angioedema

This is a very rare form of urticaria, where a vibratory stimulus induces localized swelling and erythema within minutes, lasting 30 minutes. Stimuli include jogging, vigorous rubbing with a towel, and the use of vibrating machinery such as lawnmowers and motorcycles. Avoidance of vibratory stimuli enables patients to live a normal life. Vibratory angioedema may be acquired or familial. The acquired form is often milder, and it may be associated with other physical urticarias such as DPU and symptomatic immediate dermographism. The familial form is dominantly inherited, has its onset during infancy, and intense vibratory stimuli may induce generalized erythema and systemic symptoms such as headaches[70]. Pathogenic variants in *ADGRE2*, which encodes adhesion G protein-coupled receptor E2, have been detected (see Pathogenesis).

Urticaria due to temperature changes

Heat exposure

Heat contact urticaria

This is one of the rarest forms of urticaria. Within minutes of contact with heat from any source, itching and whealing occur at the site of contact, lasting up to 1 hour. This must be distinguished from cholinergic urticaria. Patients can present after contact with hot water (e.g. washing dishes), but also after contact with radiant heat or warm sunlight. Systemic symptoms of faintness, headache, nausea, and abdominal pain have occurred when the urticaria is extensive. There is an even rarer delayed form[71].

Cold exposure

Cold urticaria represents a heterogeneous group of conditions in which whealing occurs within minutes of rewarming after cold exposure[72]. There are both typical and atypical forms, with the latter group constituting ~30% of cases and being characterized by negative provocation tests. Typical forms are primary cold contact urticaria and secondary cold contact urticaria, while atypical forms are systemic atypical acquired cold urticaria, cold-dependent dermographism, cold-induced cholinergic urticaria, delayed cold urticaria, and localized cold reflex urticaria[73].

Primary cold contact urticaria

The most commonly encountered form is primary cold contact urticaria; it accounts for at least 95% of cases (Fig. 18.11). Although cold urticaria may follow respiratory infections, arthropod bites or stings, and perhaps HIV infection, the cause of most cases remains unknown (idiopathic). It may occur at any age, but is most frequently seen in young adults. Itching, burning, and whealing occur in cold-exposed areas minutes after rewarming the skin. Commonly, primary cold contact urticaria occurs in rainy, windy weather and after contact with cold objects or drinking cold liquids. Patients often relate symptoms to changes in temperature as much as to the absolute external temperature. Systemic symptoms of flushing, headache, syncope, and abdominal pain can develop if large areas are affected. Cold baths and swimming should usually be avoided as there is a potential risk of anaphylaxis. The mean duration was 6–9 years in one series, though primary cold contact urticaria may be more transient if it follows a viral infection.

Secondary cold contact urticaria

Cases due to cryoproteinemia are rare, and they are associated with other manifestations such as Raynaud phenomenon or purpura. The wheals are usually similar to those of primary cold contact urticaria, but may last longer. The presence of circulating cryoglobulins should be determined and if detected, underlying causes, such as hepatitis B or C viral infections, lymphoproliferative disease, or infectious mononucleosis, should be excluded.

Reflex cold urticaria

In this form, generalized cooling of the body induces widespread whealing. Patients with this disorder can experience life-threatening reactions from exposures such as diving into a cold lake. The ice cube test is negative, but placing the patient in a cold room at 4°C can reproduce lesions; however, one should exert caution because anaphylaxis could occur.

Familial cold urticaria

Familial cold urticaria, also referred to as familial cold autoinflammatory syndrome (FCAS), belongs to the group of disorders known as cryopyrin-associated periodic syndromes (CAPS) (see Table 45.2). The patients with FCAS1 have mutations in *NLRP3*, which encodes the inflammasome protein cryopyrin, and they develop cold-induced urticaria wheals. FCAS2 and FCAS3 are due to mutations in *NLRP12* and *PLCG2*, respectively; the latter encodes a phospholipase (see Table 45.7). Lastly, *gain-of-function* mutations in *F12* have been detected in families with either HAE3 or cold-induced urticarial lesions and systemic symptoms[35].

Urticaria due to sweating or stress

Cholinergic urticaria

Cholinergic urticaria is characterized by multiple, transient, papular wheals that are 2–3 mm in diameter and surrounded by an obvious flare. They occur within 15 minutes of sweat-inducing stimuli, such as any form of physical exertion, hot baths, or sudden emotional stress (Fig. 18.12). Other eliciting stimuli include moving from a cold to a hot room, drinking alcohol, and eating spicy food. It occurs more frequently in young adults with an atopic diathesis and is unusual in the elderly. It may be associated with acquired generalized hypohidrosis (see Table 39.11)[74].

After the appropriate stimulus, pruritus is followed by the development of small, monomorphic wheals that are symmetrically distributed. They are most prominent on the upper half of the body, but can also affect the lower legs and forearms and even become generalized. Angioedema and systemic manifestations consisting of faintness, headache, palpitations, abdominal pain, and wheezing may occur. Reduced forced expiratory volumes (in the absence of respiratory symptoms) have been recorded by spirometry. In more severely affected individuals, cholinergic urticaria can cause severe personal and occupational disability.

Cold urticaria, symptomatic dermographism, or aquagenic urticaria may be associated with cholinergic urticaria. There is usually a gradual tendency towards improvement, but the condition may last for years. Rarer forms include cholinergic pruritus, cholinergic erythema (in which pruritic, symmetric, small erythematous macules appear to be persistent, but individual lesions actually last for up to 1 hour), and cholinergic dermographism. Severe exercise-induced cholinergic urticaria may sometimes progress to anaphylaxis.

Exercise-induced anaphylaxis (EIA)

This can occur without the typical wheals of cholinergic urticaria and appears to be a syndrome in its own right. Food- and exercise-induced anaphylaxis (FEIA) is an increasingly recognized syndrome[75]. In FEIA, angioedema and/or anaphylaxis occur within minutes of exercise if it follows either prior ingestion of a specific food (e.g. α-gliadin in wheat), or sometimes within 4 hours of a heavy meal. FEIA may be due to priming of the mast cell by either prior exposure to an allergen or an unknown mechanism. EIA is produced by exercise, but not by an increase in core temperature induced by other means capable of provoking cholinergic urticaria (e.g. passive overheating in a hot bath), and this distinction can be used to differentiate between the two conditions.

Adrenergic urticaria

Adrenergic urticaria can be distinguished from cholinergic urticaria by the presence of blanched vasoconstricted skin surrounding small pink wheals induced by sudden stress, as opposed to pale wheals surrounded by a pink halo. The lesions can be reproduced by intradermal injections of norepinephrine (noradrenaline).

Urticaria due to other exposures

Solar urticaria

Itching and whealing occur within minutes of exposure to ultraviolet or visible wavelengths of solar radiation specific to the patient (see Ch. 87).



Fig. 18.12 Cholinergic urticaria on the trunk after hot bath provocation.

Aquagenic urticaria

In aquagenic urticaria, contact with water of any temperature induces an urticarial eruption resembling a sparse form of cholinergic urticaria, with large flares around papular wheals. Lesions occur most frequently on the upper part of the body and last for less than an hour. Other physical urticarias must be excluded and the condition must be differentiated from aquagenic pruritus (see Ch. 6).

Contact Urticaria (see Ch. 16)

Contact urticaria is defined by the development of urticaria at the site(s) of contact with skin or mucosa but contact erythema and even burning and stinging without erythema are sometimes embraced in the definition[44]. Percutaneous or mucosal penetration of the urticant may have distant effects, including acute urticaria or even anaphylaxis. Contact urticaria may be more common than reported, as patients often do not present to the hospital or tertiary care clinics, because the diagnosis is usually self-evident.

Immunologic and non-immunologic forms are recognized, depending on whether the contact urticaria is due to allergen interaction with specific IgE or is IgE-independent. *Immunologic* (i.e. allergic) contact urticaria can be seen in children with atopic dermatitis who become sensitized to environmental allergens, such as grass, animals and foods, or in glove-wearers who are allergic to latex. In those individuals repeatedly exposed to latex via mucosal surfaces (e.g. urinary catheterization in spina bifida patients), allergic contact urticaria can be complicated by anaphylaxis. *Non-immunologic* (i.e. non-allergic) contact urticaria is due to direct effects of urticants on blood vessels, such as from exposure to either sorbic acid and benzoic acid in eye solutions and foods or cinnamic aldehyde in cosmetics; it may be mediated by PGD_2 and can be inhibited by NSAIDs. Percutaneous microinjection of histamine, acetylcholine, and/or serotonin by nettle stings as well as contact with histamine liberators that degranulate mast cells (e.g. dimethylsulfoxide, cobalt chloride) can result in contact urticaria.

Food contact hypersensitivity syndrome

The oral allergy syndrome, also referred to as pollen–food allergy syndrome, presents with itching and mild swelling of the mouth, tongue, and soft palate within minutes of eating fresh fruits such as apples, pears, peaches, and cherries, but not cooked fruit. It usually occurs in hay fever sufferers and represents a cross-reaction between fruit proteins and panallergens in grass (profilin) or birch pollen allergens, in particular Bet v 1, a member of the PR-10 family. Angioedema and anaphylaxis are fortunately very rare. The term "food contact hypersensitivity syndrome" was proposed to include all forms of immediate mucosal food contact reactions, including oral allergy syndrome[76].

Angioedema Without Wheals

Recurrent angioedema without wheals is in most instances idiopathic, but it is important to exclude a drug reaction and to consider the possibility of C1 inhibitor (inh) deficiency. The latter can be inherited or acquired (e.g. B cell lymphoproliferative disorders, plasma cell dyscrasias, autoantibodies against C1 inh).

Drug reactions

A number of drugs can cause angioedema without wheals. The most common are NSAIDs[77] and ACE inhibitors (see Fig. 18.6)[78]. Aspirin intolerance may present with angioedema alone, or with urticaria or anaphylaxis; cross-reactions with other NSAIDs can occur. A causative link to ACE inhibitors may be overlooked because angioedema can present over a year after starting the medication and occasionally even years later. An increased risk of ACE inhibitor-induced angioedema has been observed when the latter is coadministered with dipeptidyl peptidase-4 inhibitors ("gliptins") and mTOR inhibitors[79,80]. ACE inhibitors are contraindicated in patients with HAE and acquired C1 inh deficiency, and for practical purposes, ACE inhibitors should be discontinued in favor of other antihypertensive medications if angioedema occurs without wheals.

Angiotensin receptor blockers (ARBs) such as valsartan and losartan are also associated with development of angioedema. Depending upon the study, the risk of ARB-induced angioedema in patients with ACE inhibitor-induced angioedema varies from 0–15%. As a result, ARBs are

avoided in such patients. As with other drug eruptions, it is important to consider exposure via combination drugs, in this case sacubitril–valsartan, which is increasingly being used to treat congestive heart failure. Of note, an increased incidence has been reported in Black patients[81].

Hereditary angioedema (HAE), types I and II (inherited C1 inh deficiency)

The likelihood of inherited C1 inh deficiency as a cause of recurrent angioedema is increased if there is a family history or previous laryngeal edema or colicky abdominal pain (sometimes presenting as a surgical emergency). Trauma (emotional or physical) and estrogens can trigger attacks. The usual duration is 48–72 hours, and episodes are often followed by a refractory period. Some families with HAE describe a transient, prodromal erythematous eruption, but urticaria wheeling does not occur and so a history of recurrent wheals effectively excludes the disorder.

Hereditary angioedema (HAE) with normal C1 inh activity (nC1-INH-HAE; previously type III)

This form of HAE currently has seven subgroups, six of which are associated with mutations in the genes that encode factor XII, plasminogen, angiopoietin-1, kininogen 1, myoferlin, and heparan sulfate 3-O-sulfotransferase 6 (see above). The seventh group includes those whose genetic basis is unknown. Compared to patients with an inherited deficiency of C1 inh, the age of onset is later (usually in or after the second decade) and there is a higher frequency of facial angioedema.

Distinctive Syndromes with Urticarial Lesions

Hereditary periodic fever syndromes

Cryopyrin-associated periodic syndromes (CAPS)

The allelic disorders Muckle–Wells syndrome, familial cold autoinflammatory syndrome (familial cold urticaria), and neonatal-onset multisystem inflammatory disease (NOMID/CINCA) are all now known to be due to mutations in *NLRP3*, which encodes the protein cryopyrin (see Table 45.2)[82]. These patients can develop wheals from an early age that are resistant to antihistamines.

Other syndromes

In hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) due to partial mevalonate kinase deficiency as well as TNF receptor-associated periodic syndrome (TRAPS), erythematous and edematous urticarial plaques can occur in addition to periorbital edema (in TRAPS). The cutaneous lesions in familial Mediterranean fever are more erysipelas-like in appearance (see Table 45.2).

Acquired autoinflammatory syndromes

Schnitzler syndrome

Schnitzler and colleagues in 1974 described an unusual variant of chronic urticaria characterized by recurrent, non-pruritic wheals plus intermittent fevers, bone pain, arthralgia or arthritis, an increased ESR, and an IgM monoclonal gammopathy[83]. Occasionally, there is an IgG paraprotein. The Strasbourg validated diagnostic criteria for Schnitzler syndrome consist of two major criteria – urticarial rash and IgM or IgG monoclonal gammopathy – and four minor criteria – recurrent fever >38°C without any other cause, changes in bone structure visible in imaging ± bone remodelling, neutrophilic dermal infiltrate, and leukocytosis and/or elevated CRP. Confirming the diagnosis requires both major and at least two minor criteria (if IgM) or at least three minor criteria (if IgG). If the two major criteria are accompanied by only one minor criterion (if IgM) or two minor criteria (if IgG), the diagnosis is considered probable[84]. Some of the patients with Schnitzler syndrome will have an MYD88 L265P variant.

The clinical presentation overlaps with that of the CAPS group of inherited autoinflammatory disorders. While skin biopsy specimens usually show a neutrophil-predominant dermal infiltrate without edema, fully developed small vessel vasculitis is not seen. Some clinicians believe that these patients are best considered as having a variant of neutrophilic urticaria while others prefer the term neutrophilic urticarial dermatosis (see Table 45.6). Schnitzler syndrome responds very well to IL-1 blockade, e.g. anakinra, canakinumab, rilonacept.

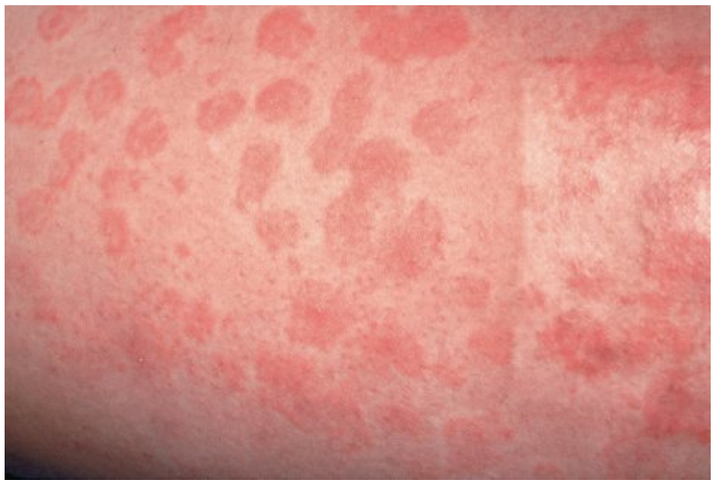


Fig. 18.13 Urticarial vasculitis. Lesions look like spontaneous urticaria but last longer and may bruise. An incidental finding is a skin graft donor site.

Adult-onset Still disease

This is a rare acquired autoinflammatory disorder in which patients present with fever, a sore throat, an often evanescent urticarial eruption, arthritis, lymphadenopathy, and hyperferritinemia (see Ch. 45).

Episodic angioedema with eosinophilia (Gleich syndrome)

A syndrome of episodic angioedema with hypereosinophilia, weight gain, and fever has been described. The cause is uncertain, but increased serum levels of IL-5 have been noted[85].

Systemic capillary leak syndrome

Also known as Clarkson syndrome, this rare acquired disorder is characterized by episodic massive plasma exudation from blood vessels, leading to potentially life-threatening hypotension, analogous to anaphylaxis. Angioedema may be a feature. It is associated with an IgG paraproteinemia. Medications, in particular IL-2, can also produce a systemic capillary leak syndrome.

Urticarial vasculitis (see Ch. 24)

Urticarial vasculitis is a clinicopathologic entity in which cutaneous lesions resemble urticaria clinically, but last longer than 24 hours and may resolve with postinflammatory hyperpigmentation or purpura (Fig. 18.13). Histologically, there is evidence of leukocytoclastic vasculitis. Extracutaneous manifestations, especially in the setting of hypocomplementemia, may include arthralgias, abdominal pain, obstructive pulmonary disease, glomerulonephritis, and uveitis or episcleritis.

PATHOLOGY

The histopathology of urticaria is characterized by upper dermal edema with a mild mixed perivascular infiltrate of lymphocytes, eosinophils, basophils, and some neutrophils (Fig. 18.14). A predominantly neutrophilic pattern has been described in a minority of patients (see below)[86]. Previous reviews of biopsy specimens from large series of patients with chronic urticaria have emphasized a spectrum of changes, ranging from mild lymphocytic infiltrates with rare neutrophils to occasionally showing fully developed leukocytoclastic vasculitis[87], pointing to some histopathologic overlap between chronic urticaria and urticarial vasculitis. Features of the latter include endothelial cell damage, a perivenular cellular infiltrate rich in neutrophils, swelling of vessel walls, and leukocytoclasis. Extravasation of erythrocytes and fibrinoid deposits in and around blood vessels may also be seen.

The term *neutrophilic urticaria* is sometimes used when biopsy specimens of urticaria contain predominantly neutrophilic dermal infiltrates but lack features of vasculitis[88]. Although this pattern did not appear to have clinical or etiologic significance[68], neutrophilic urticaria overlaps with *neutrophilic urticarial dermatosis*. This term is used to describe an aseptic, interstitial, perivascular, and peri-appendageal neutrophilic infiltrate with nuclear dust and neutrophils within dilated dermal blood vessels, but without vasculitis. The latter occurs

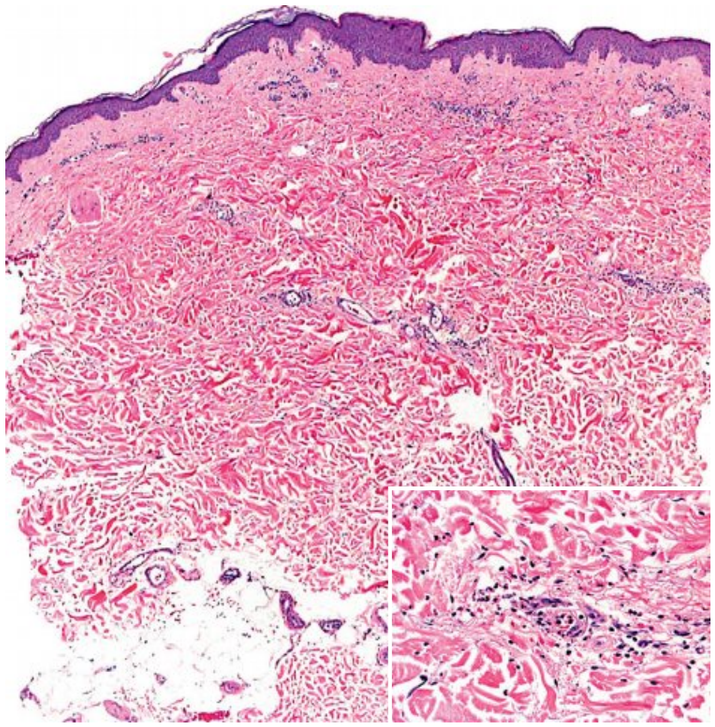


Fig. 18.14 Spontaneous urticaria – histologic findings. A sparse, mainly perivascular inflammatory infiltrate and scant edema within the superficial and mid dermis. Note several neutrophils and a few eosinophils (inset). *Courtesy Lorenzo Cerroni, MD.*



Fig. 18.15 Urticaria in a young child. This clinical presentation of urticaria is sometimes misdiagnosed as erythema multiforme because of the dusky centers, with some clinicians referring to it as urticaria multiforme. As lesions expand, central clearing can occur, which is not seen in erythema multiforme. *Courtesy Luis Requena, MD.*

in the setting of inherited acquired and inherited autoinflammatory syndromes (e.g. CAPS, Schnitzler syndrome, Still disease; see Table 45.6) as well as occasionally in systemic lupus erythematosus.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The differential diagnosis of urticaria includes all dermatologic conditions with an urticarial component, including insect bite reactions (papular urticaria), urticarial drug reactions, pre-bullous phase of pemphigoid (i.e. urticarial pemphigoid), urticarial vasculitis, autoinflammatory syndromes, eosinophilic cellulitis (Wells syndrome), polymorphic eruption of pregnancy, acute eyelid contact dermatitis (versus angioedema), and the urtication that may occur when lesions of urticaria pigmentosa are rubbed. In all these conditions, the urticarial component is part of a more prolonged inflammatory process (or mast cell proliferation in the case of mastocytosis) than in true urticaria and should be readily distinguishable by the prolonged duration of individual lesions or associated systemic findings. Especially in young children, urticaria may develop a dusky center (urticaria multiforme; Fig. 18.15; see Table 20.3) and be confused with erythema multiforme, serum sickness-like reaction, or hemorrhagic edema of infancy.

Diagnosis

A comprehensive history is essential in every patient with urticaria. It should cover the duration of disease, frequency of attacks, duration of individual lesions, medications, known allergies, past and family history including comorbidities, previous treatments and responses, occupation and leisure activities, and an assessment of the impact of the disease on the patient's quality of life. The use of a detailed questionnaire in conjunction with a complete blood count and ESR was found to be almost as good as a complete diagnostic evaluation[89]. A full physical examination looking for the morphology and duration (by circling individual lesions) of wheals, bruising, livedo reticularis, and signs of systemic disease should always be undertaken, but it is often normal. The patient's own photographs can often be useful because it is common for urticaria to have cleared by the time of consultation. Investigation should be targeted at specific features identified in the clinical assessment, as outlined below, and may include blood tests, skin biopsy (obtained in all patients with lesions consistently lasting more than 24 hours), challenges for physical urticarias, food additives, and drugs, and, infrequently as an extended investigation, skin tests for allergy and measurement of histamine-releasing autoantibodies[90]. Most patients with antihistamine-responsive urticaria do not need an extensive investigation. A diagnostic algorithm is given in Fig. 18.16.

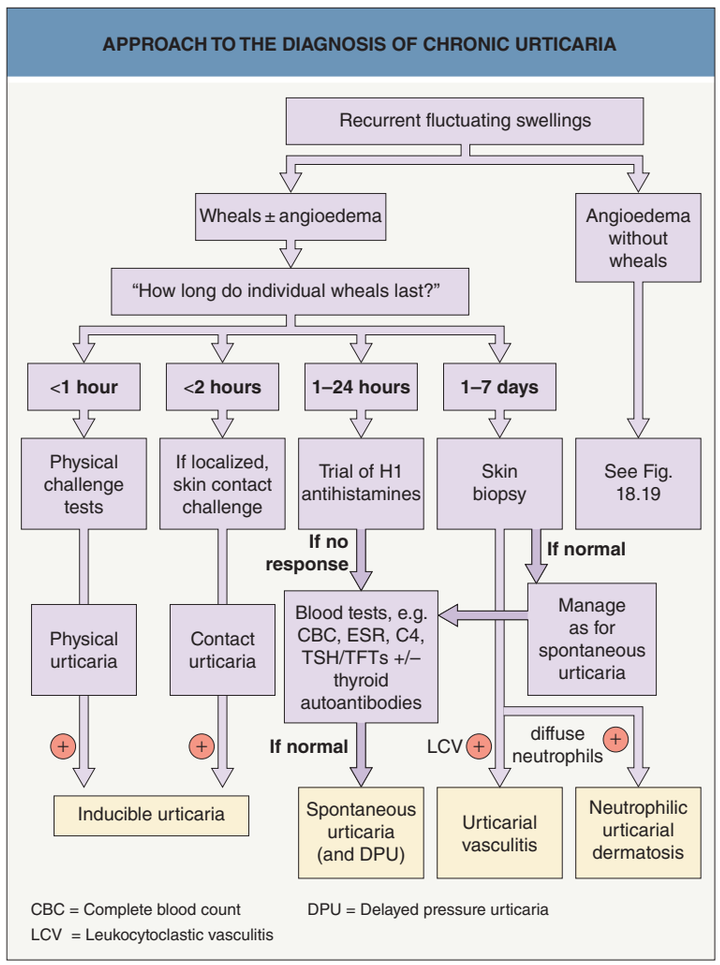


Fig. 18.16 Approach to the diagnosis of chronic urticaria.

Acute urticaria

No routine laboratory tests are recommended for acute urticaria but when a type 1 allergic reaction to environmental allergens is suspected as the cause of acute urticaria or contact urticaria, skin prick testing and measurement of specific IgE antibodies (e.g. ImmunoCAP®) can be performed.

Chronic urticaria

No investigations are routinely required for the majority of patients with mild disease that responds to antihistamines. A useful screening profile for non-responders with more severe disease could include a complete blood count with differential (for instance, to detect the eosinophilia of intestinal parasitosis) and ESR (usually normal in CSU). The ESR may be elevated in urticarial vasculitis, and it is consistently high in symptomatic acquired and genetic autoinflammatory syndromes in which patients also have an elevated C-reactive protein level (usually >30 mg/l). Measurement of thyroid autoantibodies and thyroid function tests should be performed if indicated clinically. The prevalence of thyroid autoantibodies is higher in patients with chronic urticaria than in controls and may be an indicator of autoimmune urticaria. Tests for helminths may be considered in the appropriate clinical setting. Although evidence is equivocal that *Helicobacter pylori* infection can be associated with CSU, patients with hyperacidity should be tested since eradication therapies may lead to urticaria remission.

Although the term "autoimmune" urticaria is increasingly being used for patients with evidence of functional serum autoantibodies (see Fig. 18.3 & Table 18.3), there is still a lack of agreement with regard to definitively establishing such a diagnosis. Demonstration of autoreactivity in the form of a localized wheal and flare response to intradermal injection of autologous serum (autologous serum skin test [ASST]) provides useful evidence of functional factors in the blood but is not specifically a test for functional autoantibodies[91] (Fig. 18.17). A negative test, however, has very good negative predictive value for the absence of functional autoantibodies[92]. However, stricter regulatory guidelines regarding the handling of blood products will increasingly limit performance of this assay.

Immunoassays for anti-FcεRI and anti-IgE antibodies do not necessarily correlate with basophil and mast cell histamine-releasing assays because non-functional as well as functional autoantibodies have been detected by Western blot and ELISA (see Table 18.3). Fig. 18.18 illustrates the overlap between: (1) autoreactivity by ASST; (2) functional autoantibodies as detected via basophil or mast cell activation assays; and (3) immunoassays ("immunoreactivity"). The most convincing evidence for an autoimmune etiology of urticaria is provided by demonstrating all three features, but some clinicians would accept a positive functional assay as providing sufficient proof of autoimmunity to guide therapies and prognosis. Because CSU patients can have increased rates of IgE sensitization to autoantigens such as thyroid peroxidase[18,93] and interleukin-24[94] and some have a very rapid response to anti-IgE antibody (e.g. omalizumab), the concept of autoallergic urticaria has been proposed.

Physical urticarias

International standards for the diagnosis of physical urticarias and definitions of challenge testing have been proposed[66]. *Symptomatic dermographism* can be tested for by stroking the skin of the back lightly with the rounded edge of a wooden spatula or a plastic device with round pegs that have different lengths (FricTest®). A calibrated instrument called a dermographometer, which is a spring-loaded stylus, the pressure of which can be adjusted to a predetermined setting, can be used to confirm the diagnosis of symptomatic dermographism (if ≤36 g/mm^2). *Delayed pressure urticaria* is confirmed if applying either a 2.5-kg weight to the thigh or back for 15 minutes (using a rod with a diameter of 1.5 cm) or a dermographometer set at 100 g/mm^2 for 70 seconds results in a palpable wheal at 30 minutes to 8 hours (usually at 6 hours).

Provocation tests for *cholinergic urticaria* include exercise to the point of sweating in an overheated environment, preferably on a treadmill or exercise bicycle, or partial immersion in a hot bath at 42°C for



Fig. 18.17 Autologous serum skin test (ASST). At 30 minutes, a red wheal response is present at the site of an intradermal injection of autologous serum, but not at that of a normal saline control. For the test to be positive, the wheal response at the serum injection site must be at least 1.5 mm greater in diameter than the control site. This criterion is a reasonably sensitive and specific screening test for functional autoantibodies as detected by the basophil release assay. Spontaneous wheals are also present at the venipuncture site and above the serum skin test.

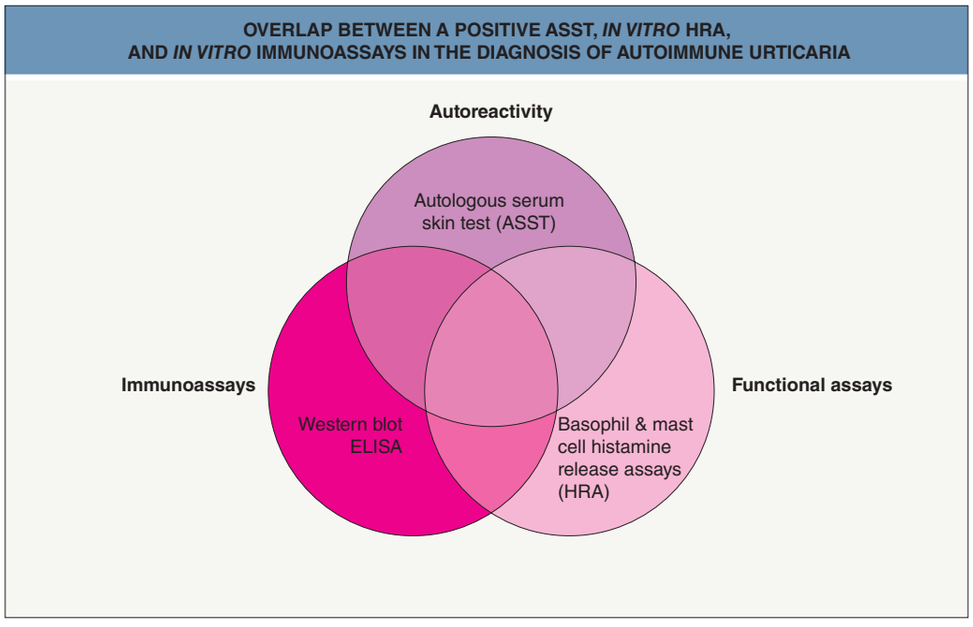


Fig. 18.18 Overlap between a positive autologous serum skin test (ASST), *in vitro* histamine release assays (HRA), and *in vitro* immunoassays in the diagnosis of autoimmune urticaria. The ASST will become increasingly difficult to perform in the future as regulations regarding blood products become more restrictive.

10 minutes. A positive hot bath test excludes exercise-induced anaphylaxis. *Cold contact urticaria* is confirmed either by the development of whealing at the site of application of a melting ice cube in a thin polyethylene bag or glove for 5 minutes (the most sensitive individuals may react after 30 seconds, with the least sensitive requiring up to 20 minutes of ice application; see Fig. 18.11) or by assessment of the critical temperature threshold by an instrument such as TempTest®.

Phototesting confirms the diagnosis of *solar urticaria*, with the development of wheals within minutes of exposure to natural or artificial radiation. The action spectra of the inducing wavelengths can be determined by narrowband monochromators (see Ch. 87). The diagnosis of *aquagenic urticaria* is made by inducing a limited number of small pruritic wheals with a large flare after a bath or shower at body temperature, or under wet gauze applied at body temperature for 20 minutes. *Heat contact urticaria* is confirmed by applying a heated cylinder (temperature increments up to 44°C) to the skin for 30 seconds to 5 minutes or assessment of the critical temperature threshold by an instrument such as TempTest®.

Urticarial vasculitis

Lesional skin biopsy is essential and should be undertaken if circled lesions consistently last >24 hours, in order to confirm the presence or absence of leukocytoclastic vasculitis histologically. The sampled lesion should have been present for 12–24 hours. Direct immunofluorescence microscopy for C3 and immunoglobulin deposits in blood vessels is generally uninformative and does not need to be performed routinely. Patients with urticarial vasculitis need a full vasculitis screen (see Ch. 24).

Angioedema without wheals

Detection of a low serum level of C4 is a very sensitive, but nonspecific, screening test for types I and II HAE and acquired C1 inh deficiency (the level is normal in nC1-INH-HAE). Measurement of the *amount* of C1 inh by immunochemical assay for type I HAE and C1 inh *function* to detect type II HAE should be performed if indicated by the history and supported by a low serum C4 level. Serum C1q levels are also reduced in acquired C1 inh deficiency (Fig. 18.19).

TREATMENT

Patients should be given advice and information on common precipitants, treatments, and prognosis. Antipruritic lotions and the avoidance of aggravating factors, including NSAIDs, may be sufficient for some, but many will need additional interventions, including systemic medications. These can be stratified into first-, second-, and third-line therapies (Fig. 18.20). The management of urticarial vasculitis is discussed in Chapter 24 and treatment of C1 inh deficiency is considered separately because its pathogenesis and therapeutic interventions differ. Patients must understand that although systemic corticosteroids may completely eliminate their lesions, recurrences often occur with tapering of the dosage and long-term use is unacceptable. In addition, H1 antihistamines and other drug combinations can nearly always control symptoms and significantly improve quality of life.

Acute, Chronic Spontaneous, and Inducible Urticarias

First-line therapies

H1 antihistamines are the mainstay of management for most patients with urticaria, although not all patients will respond and only about 40% of those attending tertiary care clinics will clear or almost clear at licensed doses. Antihistamines reduce pruritus, flatten wheals, shorten wheal duration, and reduce wheal numbers, even though they may not clear urticaria completely. It is worth discussing the relative benefit with patients who feel that "they haven't worked".

Antihistamines should be taken on a daily basis, the frequency depending on their half-life. In other words, they should not be taken only when the patient is symptomatic. As a general rule, antihistamines

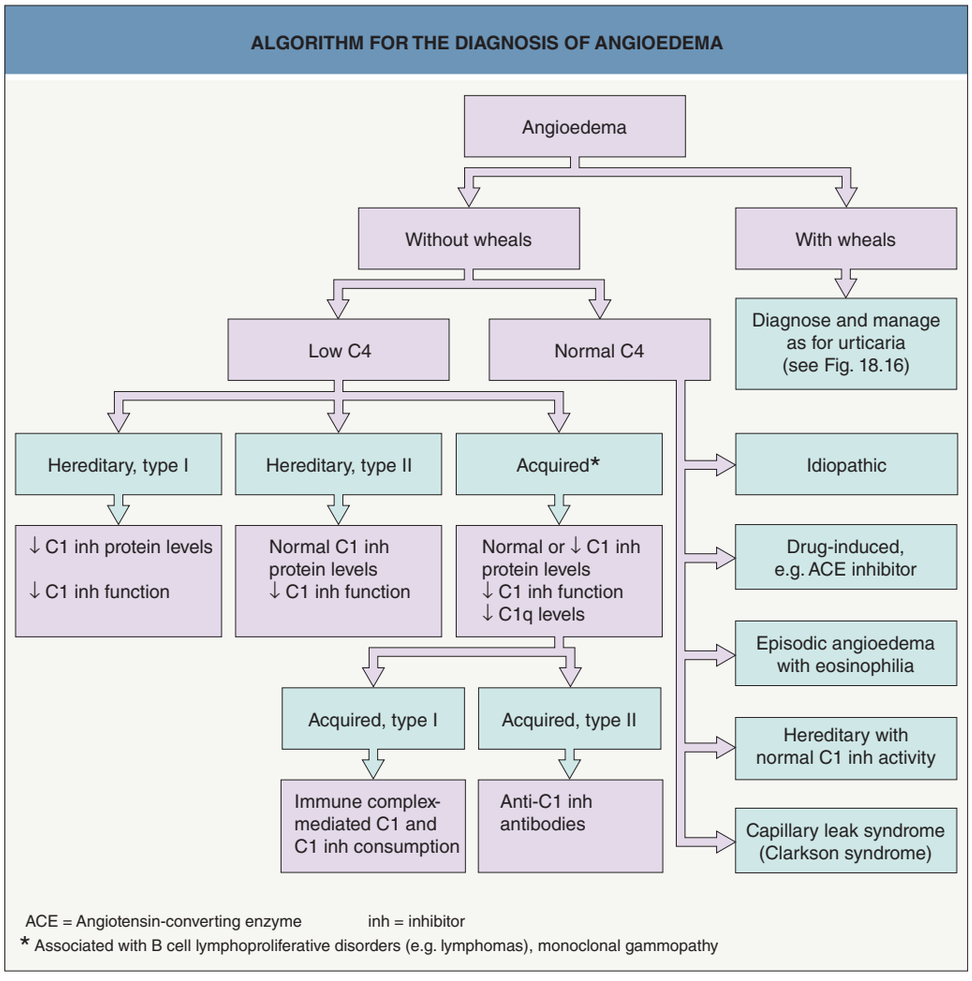


Fig. 18.19 Algorithm for the diagnosis of angioedema. Episodic angioedema with hypereosinophilia, along with weight gain and fever, is known as Gleich syndrome. There are currently 7 subgroups of HAE with normal C1 inh activity (nC1-INH-HAE, previously referred to as type III HAE); the six subgroups that have a known underlying genetic mutation are termed HAE3 to HAE8 (see Fig. 18.6), while the seventh subgroup includes those whose genetic basis is unknown.

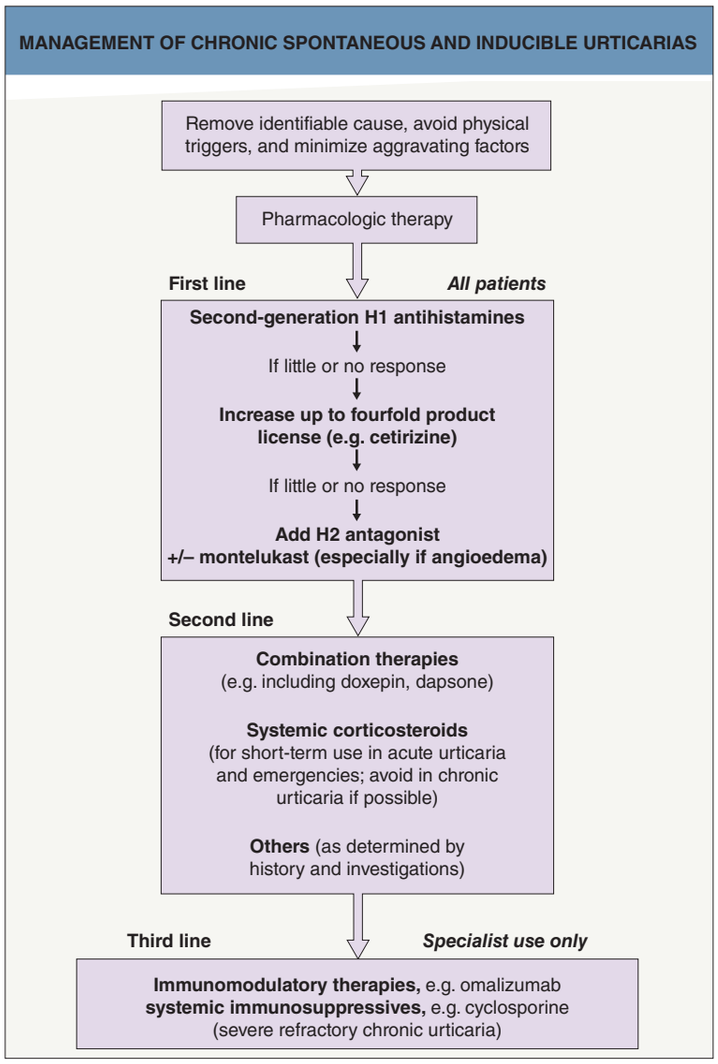


Fig. 18.20 Management of chronic spontaneous and inducible urticarias.

are safe and have few significant adverse effects. They can be grouped into first-generation (classic, sedating) antihistamines, second-generation (new generation, non- or minimally sedating) antihistamines and their derivatives, and the H2 antagonists (Table 18.5). The EAACI/GA^{2}LEN/EDF/WAO consensus guidelines on chronic urticaria strongly recommend *against* using sedating H1 antihistamines as monotherapy[90].

Classic antihistamines

Classic antihistamines are problematic because sedation and anticholinergic side effects are often dose-limiting. However, in combination with a daytime non-sedating antihistamine, they can be taken at night if sleep is disturbed by urticaria, but the following day they may interfere with skilled tasks (e.g. operating machinery and driving) or reduce the ability to concentrate at work or school.

Second-generation antihistamines

Second-generation antihistamines are usually well tolerated, with the majority of patients requiring only once-daily oral dosing (see Table 18.5). For chronic urticaria, there is probably little distinction between the second-generation antihistamines when they are taken at the licensed dosages. A consensus paper has recommended increasing the daily dose of second-generation H1 antihistamines up to fourfold for difficult urticaria[90]. It is possible that their additional anti-allergic and anti-inflammatory properties may be clinically beneficial at these higher doses, but direct evidence for this is lacking and they do represent unlicensed dosages.

Fexofenadine is licensed for urticaria at 180 mg daily. It is the active metabolite of terfenadine but does not appear to have the potential for ventricular arrhythmias as of its parent drug. Desloratadine (an active metabolite of loratadine) and levocetirizine (the active enantiomer of cetirizine) probably offer no clinical advantage over their parent drugs at equivalent doses.

Clinically important drug interactions are infrequent, but coadministration of mizolastine with systemic erythromycin and ketoconazole is contraindicated because of concern about possible cardiac arrhythmias. Caution is also recommended with regard to other hepatic cytochrome P450 3A4 inhibitors (e.g. cimetidine) or substrates (e.g. cyclosporine; see Ch. 131), which may be used for urticaria in special circumstances.

Addition of H2 antagonists to conventional H1 antihistamines

The addition of H2 antagonists to conventional H1 antihistamines may be helpful in some patients with chronic urticaria, although clinical trial evidence for combining H1 antihistamines and H2 antagonists is poor and not all authorities recommend this therapeutic approach. H2 antagonists have no effect on histamine-induced pruritus and should not be used as monotherapy. Nizatidine and famotidine have similar properties to ranitidine (currently unavailable) but have not been evaluated in clinical trials for chronic urticaria. They are preferable to cimetidine, which may interfere with hepatic metabolism of other drugs and is weakly anti-androgenic.

Antihistamines in pregnancy

No H1 antihistamine can be advertised as being safe during pregnancy, but recent urticaria guidelines suggest loratadine and cetirizine (previously FDA category B drugs) as preferred medications, especially in the second and third trimesters. Both drugs are also compatible with breastfeeding, but hydroxyzine is contraindicated because of reports of seizures in breastfed infants (see Ch. 27). Because of its lengthy prescription record, chlorphenamine has also been used, but it should be avoided close to parturition and during breastfeeding due to potential sedative effects in the child.

Second-line therapies (targeted interventions)

Second-line therapies may be considered when urticaria does not respond well to antihistamines, but high-quality evidence to support their use is lacking. They should usually be prescribed as additive therapies (to antihistamines) rather than as alternatives. The choice of second-line drugs should be guided by specific indications, summarized in Table 18.6. Here, the management of urticaria can be influenced considerably by a full clinical assessment and the experience of the clinician. It is unusual for children to need second-line therapies, except the occasional use of prednisolone for very severe acute exacerbations of chronic urticaria. Second-line drugs should be used with considerable care in pregnancy, and only after the risks have been carefully considered against the likely benefits. Non-drug interventions include diets (e.g. salicylate-free), phototherapy, and cold desensitization.

Drug therapies

Prednisone or *prednisolone* is effective for nearly all presentations of chronic urticaria, but often needs to be used at reasonably high doses (e.g. 30–50 mg daily in adults) to achieve good initial control of severe disease. It should be considered primarily for the short-term management of "crisis" urticaria and serious angioedema of the throat as a rescue medication, when, often, a single dose or several daily doses will be sufficient to re-establish control with regular full-dose antihistamines. Regular treatment with oral corticosteroids should be avoided because of the usually prolonged duration of chronic urticaria and because of their predictable long-term side effects (e.g. hypertension, weight gain, glucose intolerance, osteoporosis). Rebound is also a common problem and the long-term course of the urticaria is often not altered.

Epinephrine (adrenaline) by subcutaneous or intramuscular injection is the treatment of choice for anaphylactic shock or severe anaphylactoid reactions, whether due to an allergy, pseudoallergy, or inducible urticaria. Epinephrine may also be necessary for angioedema of the oropharynx in severe acute allergic urticaria and idiopathic angioedema, but it is rarely required for chronic urticaria and is not effective for HAE. Directing epinephrine mist from an aerosol inhaler onto mucosal angioedema may be helpful for minor episodes, but it is usually better to administer the drug intramuscularly or subcutaneously, if it is required. Side effects of epinephrine include tachycardia, anxiety, and headache. It should be used with caution in patients with hypertension, ischemic heart disease,

ANTIHISTAMINES FOR URTICARIA			
Class	**Examples**	**Plasma half-life (hours)**	**Daily adult dose***
Classic (sedating) H1 antihistamines	Chlorphenamine (1)	12–15	4 mg three times daily (up to 12 mg at night)
	Hydroxyzine (1)	7–20	10–25 mg three times daily (up to 75 mg at night)
	Diphenhydramine (2)	2.5–9	10–25 mg at night
	Doxepin† (1)	8–24	10–50 mg at night
Second-generation H1 antihistamines	Acrivastine‡ (1)	1.5	8 mg three times daily
	Cetirizine§ (1)	7–11	10 mg once daily
	Loratadine (1)	8–11	10 mg once daily
	Mizolastine¶ (1)	13	10 mg once daily
Newer second-generation H1 antihistamines	Bilastine¶	14.5	20 mg once daily
	Desloratadine (1)	27	5 mg once daily
	Fexofenadine (1)	11–15	180 mg once daily
	Levocetirizine (1)	7–10	5 mg once daily
	Rupatadine¶ (1)	6	10 mg once daily
H2 antagonists‖	Cimetidine (1)	2–3	400 mg twice daily
	Famotidine (3)	3	20 mg twice daily

*Current prescribing manuals should be consulted for details on doses in children; off-label, up to fourfold the approved doses of cetirizine and levocetirizine have been prescribed.
†Possesses potent H1 antihistaminic and H2 antagonist properties.
‡Only available in the US as a combination product with pseudoephedrine for seasonal allergic rhinitis.
¶Not available in the US.
§The active metabolite of hydroxyzine.
‖Used in combination with H1 antihistamines.

Table 18.5 Antihistamines for urticaria. A short-acting classic antihistamine may be added at night to a daily second-generation antihistamine, with or without the addition of an H2 antagonist for maximal antihistamine blockade. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

SECOND-LINE MEDICATIONS FOR CHRONIC SPONTANEOUS OR PHYSICAL URTICARIA				
Generic name	**Drug class**	**Route**	**Dose**	**Special indication/associated diseases**
Prednisone or prednisolone (2)	Corticosteroid	Oral	0.5 mg/kg daily	Severe exacerbations (days only) – "rescue" treatment
Epinephrine (2)	Sympathomimetic	Subcutaneous, IM (self-administered)	300–500 mcg	Idiopathic or allergic angioedema of throat/ anaphylaxis
Montelukast (3)	Leukotriene receptor antagonist	Oral	10 mg daily	Aspirin-sensitive urticaria, delayed pressure urticaria
Colchicine (3)	Neutrophil inhibitor	Oral	0.5/0.6–1.5/1.8 mg* daily	Neutrophilic infiltrates in lesional biopsy specimens or urticarial vasculitis
Dapsone (2)	Aminosalicylates	Oral	50–100 mg daily	Neutrophilic infiltrates in lesional biopsy specimens or urticarial vasculitis
Sulfasalazine (2)	Aminosalicylates	Oral	2–4 g daily	Delayed pressure urticaria

*Available in doses of 0.5 mg or 0.6 mg, depending upon the country.

Table 18.6 Some second-line medications for chronic or physical urticaria. Current prescribing manuals should be consulted for details on dose, drug interactions, and contraindications for individual patients. The stated doses represent guidelines only. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. IM, intramuscular.

cerebrovascular disease, and diabetes mellitus. Coadministration of epinephrine with tricyclic antidepressants (including doxepin) and β-blockers should be avoided. For reassurance, patients who are prone to severe acute allergic urticaria and idiopathic angioedema may carry a self-administered epinephrine pen and they need to be aware of side effects, drug interactions, and potential rebound phenomenon.

Doxepin is a tricyclic antidepressant with very potent H1 antihistaminic and H2 antagonistic properties. Although it has significant sedative and anticholinergic properties, it may be valuable, especially when dosed at night in adult patients with chronic urticaria. Monitoring of serum drug levels can prove helpful as clinical studies have frequently observed subtherapeutic levels (therapeutic range for doxepin plus *N*-desmethyldoxepin = 150–250 ng/mL)[95].

Montelukast, a leukotriene receptor antagonist (see Table 130.11), may be beneficial for aspirin-sensitive chronic urticaria due to the likely involvement of leukotrienes in its pathogenesis[96]. There have been anecdotal reports of responses in refractory chronic urticaria associated with delayed pressure urticaria, but clinical experience to date has been less encouraging. It may be useful in combination with H1 antihistamines for CSU patients with angioedema[97]. Side effects are uncommon, but urticaria, angioedema, and anaphylaxis have been reported when it has been given for other indications.

Dapsone has been shown in two randomized clinical trials as well as a larger retrospective medical record review to be an effective and well-tolerated second-line therapy for patients with refractory CSU, including the idiopathic and autoimmune subtypes[98]. Its precise mechanism of action in treating CSU is unknown but is thought to be related to its inhibition of prostaglandin and leukotriene activity, disruption of neutrophil adhesion molecules, suppression of neutrophil recruitment and activation, and interference with the release or functioning of neutrophil lysosomal enzymes (see Ch. 130). Dapsone can also be considered in DPU patients who are sensitive to NSAIDs.

Sulfasalazine may be helpful for chronic urticaria when delayed pressure urticaria (DPU) symptoms predominate, providing it is tolerated. Otherwise, these patients often require systemic corticosteroids. The drug should be avoided in patients with aspirin sensitivity and as with dapsone, glucose-6-phosphate dehydrogenase (G6PD) deficiency. For both medications, a complete blood count should be monitored every 2 weeks for the first 2 months and then regularly thereafter, along with hepatic enzymes. Side effects are reviewed in Chapters 31 and 130.

Colchicine may be beneficial for chronic urticaria when predominantly neutrophilic infiltrates are seen histologically ("neutrophilic urticaria") and it is also used for urticarial vasculitis. Potential side effects are outlined in Table 130.9. Patients receiving colchicine should avoid P-glycoprotein or strong CYP3A4 inhibitors.

Anabolic steroids, such as danazol and oxandrolone, may be useful for severe cholinergic urticaria, especially in male patients, but virilizing side effects and long-term concern regarding liver toxicity are disadvantages.

Miscellaneous drug therapies described for chronic urticaria include tranexamic acid, heparin, and warfarin, but convincing evidence for their use is lacking and there are no specific situations where they appear to be better than other treatments.

Non-drug therapies

Exclusion of food additives and natural salicylates from the diet has been advocated in a number of reports. The high success rates in some series may have been due in part to the natural history of remission in chronic urticaria, as <20% of patients responding to low-pseudoallergen diets flare after double-blind, placebo-controlled challenge with individual additives[99]. Diets nevertheless remain popular with CSU patients and are worth considering when antihistamines have failed and second-line drugs are inappropriate. There is general agreement that food allergy as a cause of adult chronic urticaria is exceptional, and that investigation for relevant immediate hypersensitivity reactions should not be undertaken without a strong lead from the history.

Induction of tolerance by repeated, frequent, graduated exposures to the precipitating physical factor can be helpful for cold urticaria, solar urticaria, and heat contact urticaria. The schedule is time consuming, not all patients can be rendered tolerant, and repeated daily exposures may be necessary to maintain tolerance.

Ultraviolet therapy and photochemotherapy (PUVA) have been used for chronic urticaria, but the reported results have been inconclusive. A retrospective survey suggested that narrowband UVB (NB-UVB) phototherapy might be effective. There is limited evidence that PUVA and NB-UVB are helpful for highly symptomatic dermographism at doses usually administered for psoriasis.

Autohemotherapy with whole blood or serum has been used in ASST-positive patients but strong evidence for this intervention is lacking[100].

Third-line therapies

Omalizumab (humanized anti-IgE monoclonal antibody) has been shown to be effective for chronic spontaneous/idiopathic urticaria in large phase III studies[101,102], as well as for associated angioedema[103] and H1 antihistamine-refractory CSU[104]. The most common dosage in adults is 300 mg monthly via subcutaneous injection. High baseline IgE levels appear to be a marker for early response[105] and early relapse[106]. In retrospective studies, patients with inducible urticarias also had a high rate of complete response of symptoms[107]. After six months of therapy, omalizumab is usually discontinued, while remaining on H1 antihistamines. Recurrences do occur and longer courses may be required.

Cyclosporine (3–4 mg/kg/day for 4–8 weeks) clears or substantially benefits approximately two-thirds of patients with chronic autoimmune urticaria refractory to antihistamines[21]. However, only 25% of responders remained clear or almost clear 4–5 months after discontinuing therapy. As a result, the risk of maintaining the "impossible to wean" patient on long-term cyclosporine is potentially considerable.

Other *immunosuppressive therapies*, including methotrexate, mycophenolate mofetil, and azathioprine, may be effective in some patients with severe CSU, if cyclosporine fails. For example, *methotrexate* has been beneficial in corticosteroid-dependent chronic urticaria patients with and without evidence of functional autoantibodies[108]. *Plasmapheresis* was used successfully in some patients with chronic autoimmune urticaria in a small, open, proof-of-concept study, but it is not recommended as monotherapy because of its expense and an early relapse of the urticaria[20]. *IVIg* infusions (total of 2 g/kg over 5 days) were beneficial in the majority of chronic autoimmune urticaria patients in another small open study, with remissions in some lasting at least three years; expense and potential side effects are concerns. Potential future therapies include other anti-IgE antibodies, Bruton tyrosine kinase inhibitors, anti-KIT monoclonal antibody, and eosinophil inhibitors.

C1 Esterase Inhibitor (C1 inh) Deficiency

The treatment of C1 inh deficiency differs from that of other types of angioedema. Intravenous C1 inh concentrate or recombinant C1 inh, subcutaneous icatibant (a specific bradykinin B_2 receptor antagonist), or subcutaneous ecallantide (a kallikrein inhibitor) should be given in an emergency, as this may prove to be life-saving (see Fig. 18.6). Fresh frozen plasma may be given as an alternative to C1 inh concentrate if the latter is unavailable. Antihistamines, corticosteroids, and epinephrine are not effective in patients with C1 inh deficiency[109]. To treat an acute life-threatening attack, patients with the acquired form of C1 inh deficiency often require much higher doses of C1 inh concentrate than the 20 units/kg recommended for HAE.

C1 inh concentrate may also be given intravenously for short-term prophylaxis 1 hour before elective surgery, especially when intubation or tooth extraction is necessary. For minor surgical procedures, oral tranexamic acid (1 g four times daily in adults or 500 mg four times daily in children) for 48 hours before and after the procedure, or an increase in established maintenance doses of tranexamic acid or danazol, can be effective prophylaxis.

Longer-term prophylaxis may be necessary for patients with symptomatic recurrent angioedema or abdominal colic due to bowel edema. Subcutaneous or intravenous C1 inh (every 3–4 days), the subcutaneous kallikrein inhibitor lanadelumab (every 2 weeks), and the oral kallikrein inhibitor berotralstat (150 mg daily) are therapeutic options. As a result, the use of anabolic steroids (see above) and tranexamic acid have declined. The latter is an inhibitor of the activation of plasminogen to plasmin and is contraindicated if there is a history of thrombosis; with chronic administration, regular eye examinations and liver function tests are recommended. Because HAE may be induced or exacerbated by estrogens in oral contraceptive pills or hormone replacement therapy, they should be avoided if possible.

PROGNOSIS

Most patients with chronic urticaria can expect to benefit symptomatically from treatment, but the prognosis for complete remission has probably changed little from that in a survey done over 50 years ago, which identified that 50% of patients attending a tertiary referral center with wheals alone were clear within a year, but that 20% with wheals and angioedema continued to have symptoms 20 years from the time of onset[110]. A mean duration of disease of slightly over six years has been reported[111].

Additional figures and table on Urticarial vasculitis, available in our eBook (see inside front cover for access code).

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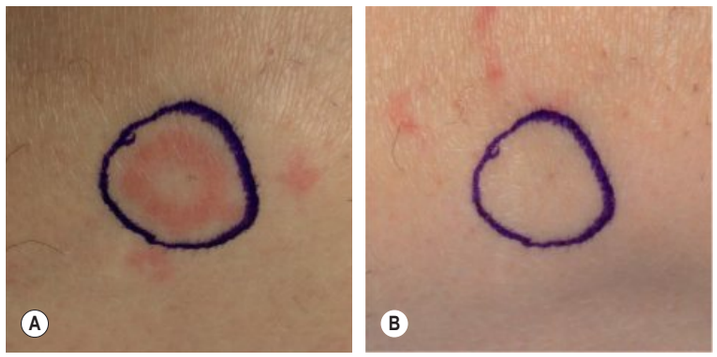
eFig. 18.1 Urticaria. Pink edematous papules and plaques that are transient and pruritic. *Courtesy Jeffrey P. Callen, MD.*



eFig. 18.2 Urticaria. Annular and arcuate lesions.



eFig. 18.3 Urticaria – annular and arcuate lesions. Note the pallor due to edema within the lesions.



eFig. 18.4 Spontaneous urticaria. A Given the transient nature of individual lesions, circling them with ink assists in the clinical diagnosis. **B** Hours later the lesion has resolved. *Courtesy Jacob Siegel, MD.*



eFig. 18.5 Urticaria in the setting of SARS-CoV-2 infection. *Courtesy Roni P. Dodiuk-Gad, MD.*



eFig. 18.6 Yellow-colored urticaria in a patient with hyperbilirubinemia secondary to hepatic cirrhosis. The arrow denotes the elevated pink border. *Courtesy Jonathan S. Leventhal, MD.*



eFig. 18.7 Neutrophilic urticarial dermatosis in a patient with systemic lupus erythematosus. Clinically, the lesions resemble urticaria but histologically the dermal infiltrate of neutrophils distinguishes this entity. *Courtesy Nour Kibbi, MD*.



eFig. 18.8 Viral-associated trichodysplasia in a renal transplant recipient receiving tacrolimus, mycophenolate mofetil, and prednisone. Numerous skin- to pink-colored folliculocentric papules, many with central spiny excrescences, developed on the nose and cheeks. This disorder is most commonly seen in the setting of immunosuppression due to systemic calcineurin inhibitors. *Courtesy Mark Kirchhof, MD, and Sheila Au, MD*.

URTICARIAL VASCULITIS	
Epidemiology	Favors middle-aged women
Characteristics of urticarial lesions	>24 hours in duration; painful & burning sensation as well as pruritus; residual purpura as they resolve
Sites of involvement	Often occur at pressure points
Concurrent angioedema	Up to 40% of patients
Extracutaneous manifestations (% of patients affected); more common in hypocomplementemic form*	Arthralgias (50%) – transient, migratory GI involvement (20%) – abdominal pain, nausea, vomiting, diarrhea Pulmonary obstructive disease (20%) Renal (5%–10%) – proteinuria, hematuria Ocular (unusual) – conjunctivitis, episcleritis, uveitis Other (unusual) – Raynaud phenomenon, livedo reticularis, splenomegaly, lymphadenopathy, idiopathic intracranial HTN, pericardial or muscle involvement
Associated disorders	Systemic lupus erythematosus Sjögren syndrome Serum sickness Cryoglobulinemia Infections – hepatitis B or C virus, Epstein–Barr virus Rarely, solar or cold urticaria, drugs, hypergammaglobulinemia
Laboratory evaluation	CBC with differential, platelet count; ESR, CRP; LFTs, BUN, creatinine Complement assays – C3, C4, CH50; if C4 low, C1q Urinalysis If indicated, pulmonary function tests, CXR Tests for associated disorders, e.g. ANA, anti-Ro Ab
Disease course	Average of 3 years
Treatment (primarily based upon small case series and case reports; see Table 24.10)	Antihistamines for associated pruritus NSAIDs – improvement in 50% of patients Colchicine, dapsone, hydroxychloroquine, methotrexate, plasmapheresis, omalizumab in normocomplementemic form Corticosteroids ± immunosuppressants†

*Higher incidence and greater severity in patients with hypocomplementemia.
†Especially for hypocomplementemic urticarial vasculitis.

eTable 18.1 Urticarial vasculitis. In a series of 132 patients, an elevated ESR (28%), hypocomplementemia (18%), and an ANA titer >1:160 (11%) were the more common abnormalities[e1]. Ab, antibodies; ANA, anti-nuclear antibodies; BUN, blood urea nitrogen; CRP, C-reactive protein; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HTN, hypertension; LFTs, liver function tests; NSAIDs, nonsteroidal anti-inflammatory drugs; PFTs, pulmonary function tests.

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19 Figurate Erythemas

Agustín España

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INTRODUCTION

Erythema represents a change in the color of the skin that is due to the dilation of blood vessels, especially those in the papillary and reticular dermis. The color, which is blanchable, can vary from pink to dark red to violaceous. Most erythemas last for days to months, but some may last only minutes (e.g. flushing). A very heterogeneous group of cutaneous disorders manifests as erythemas, ranging from palmar erythema of pregnancy to a diffuse scarlatiniform eruption. The erythemas discussed in this chapter all share a common feature – a figurate configuration.

In figurate erythemas, the lesions have an annular, arciform, or polycyclic appearance. While a wide range of cutaneous diseases can have an annular configuration (Table 19.1), there are four "classic" figurate erythemas: erythema annulare centrifugum, erythema marginatum, erythema migrans, and erythema gyratum repens.

ERYTHEMA ANNULARE CENTRIFUGUM

Synonyms: ■ Superficial or deep gyrate erythema ■ Erythema perstans ■ Palpable migrating (arciform) erythema

Key features

- Erythematous annular lesions that migrate centrifugally
- Superficial lesions can have the classic "trailing" white scale, while the deep gyrate erythemas have a more infiltrated border
- The disorder occurs more commonly in adults, and superficial lesions favor the thighs and hips
- Individual lesions usually last for several days to a few months
- Although often idiopathic in nature, it can be associated with infections (e.g. tinea pedis) and anecdotally with other disorders or exposures

Introduction

The term "erythema annulare centrifugum" (EAC) has come to encompass more than just annular erythematous plaques with trailing scale. One explanation for this is that once the other three major figurate erythemas (with specific etiologies; see below) and the disorders listed in Table 19.1 are excluded, EAC often becomes a "default" diagnosis. Unfortunately, this has led to some confusion, but until a specific "trigger" can be identified for each individual patient, this situation will persist. As a consequence, some authors have come to the conclusion that EAC, especially the deeper form, represents a clinical reaction pattern rather than a specific clinicopathologic entity[1]. Adding to the confusion is the school of thought in which the term EAC is reserved for only the superficial form.

History

In 1881, Colcott-Fox described persistent, ring-shaped lesions with pruritus, to which he gave the name "erythema gyratum perstans". The term "EAC" was introduced by Darier in 1916 while the name "erythema perstans" has been used by some authors to describe similar annular erythemas. It is now thought that all of these terms refer to clinical or pathologic variants of the entity now referred to as EAC[2]. However, Ackerman[3] preferred to call the two histologically different forms (superficial and deep) of EAC "superficial gyrate erythema" and "deep gyrate erythema", while Weyers et al.[4] believed that the superficial and deep forms of EAC were unrelated to one another and should not be referred to by the same name. These latter authors recommended that the term EAC be reserved for the superficial type, which in their opinion represented a specific clinicopathologic entity.

Epidemiology

Although EAC can appear in any age group, its peak incidence is in the fifth decade of life. There is no known sex difference. A rare autosomal dominantly inherited form of EAC, referred to as "familial annular erythema", has also been described[5].

Pathogenesis

It has been suggested that EAC, especially the superficial form with epidermal spongiosis histologically, represents a reaction pattern or "hypersensitivity" to one of many antigens[6]. EAC has been associated with infectious agents, particularly dermatophytes, but also with other fungi (e.g. *Candida*, *Penicillium* in blue cheese), viruses (e.g. poxvirus, EBV, varicella–zoster virus, HIV), bacteria (e.g. *Pseudomonas*, post-tonsillitis), parasites, and ectoparasites (e.g. *Phthirus pubis*). Less commonly, EAC has been linked to drugs (e.g. diuretics, nonsteroidal anti-inflammatory drugs, antimalarials, finasteride, amitriptyline, nivolumab, sorafenib, rituximab, pegylated interferon-α-2a plus ribavirin, ustekinumab [often as single case reports]), Crohn disease, pregnancy, autoimmune endocrinopathies, hypereosinophilic syndrome and, occasionally, neoplasms (e.g. lymphomas, leukemias, solid organ malignancies). The latter has been referred to as *p*araneoplastic *EAC e*ruption (PEACE)[7]. However, most of these associations are anecdotal, and, in the last group, Curth's postulates have not been consistently fulfilled (see Ch. 53). There are patients with EAC who noted resolution of their lesions after the diseases that presumably triggered the EAC were successfully treated. In one series, an associated disease was identified in only one-third of patients[8].

The peripheral migration of EAC lesions is thought to reflect localized production of proinflammatory cytokines and vasoactive peptides[9], but the precise mechanism is unknown.

Clinical Features

The initial lesions of EAC begin as firm pink papules that expand centrifugally and then develop central clearing. An individual lesion can enlarge to greater than 6 cm in diameter over a period of 1 to 2 weeks. If expansion of the annular plaque is not uniform, incomplete arcs appear, as do polycyclic lesions, or simply festooned bands. In the *superficial* form, the lesions are minimally elevated, and there is desquamation at the inner margin, i.e. trailing scale (Fig. 19.1A,B). The scale may not be present in all the lesions in a particular patient (Fig. 19.2A). There may be associated pruritus, especially in lesions that histologically show spongiosis.

DIFFERENTIAL DIAGNOSIS OF FIGURATE ERYTHEMA			
Disorders	**Clinical features**	**Histopathologic findings**	**Cross references**
Transient individual lesions (typically lasting <24 hours)			
Urticaria	Transient and recurrent wheals; pruritus	Dermal edema with sparse perivascular infiltrate of eosinophils and lymphocytes; occasionally neutrophils	Ch. 18
Urticaria multiforme (a variant of annular urticaria)	Annular and polycyclic wheals, often with central ecchymosis that should not be confused with necrosis; pruritus; edema of the face, hands, feet; absence of mucous membrane erosions or crusts; recent viral or bacterial infection	Indistinguishable from other forms of urticaria	
Serum sickness-like reaction	Annular and polycyclic wheals often have a purpuric component; acral edema; high fevers, arthralgias, lymphadenopathy; drug exposure (e.g. cefaclor, penicillins, minocycline)	Similar to urticaria; unlike serum sickness (e.g. due to equine- or rabbit-derived antithymocyte globulin), leukocytoclastic vasculitis is usually absent	
Erythema marginatum	Polycyclic erythematous eruption; antecedent group A streptococcal infection; additional manifestations of acute rheumatic fever, e.g. arthritis and carditis	Superficial perivascular infiltrate of neutrophils and lymphocytes; occasionally eosinophils	See text
Erythema marginatum-like lesions of hereditary angioedema	Transient polycyclic erythematous eruption; favors trunk; precedes or accompanies episodes of angioedema	Minimal to no inflammatory infiltrate	Ch. 18
African trypanosomiasis	Annular erythematous patches on the trunk associated with fever spikes	Perivascular lymphocytic infiltrate with many plasma cells; parasites are occasionally seen within the dermis	Ch. 83
Erythrokeratodermia variabilis et progressiva	Transient gyrate or circinate erythematous patches (usually fade/migrate within a few hours); also fixed figurate hyperkeratotic plaques; *GJB3, GJB4* > *GJA1* mutations	Scant perivascular lymphocytic infiltrate; dilated capillaries; psoriasiform acanthosis and mild hyperkeratosis (fixed plaques)	Ch. 57
Urticarial lesions lasting >24 hours			
Allergic urticarial eruption	Annular edematous plaques; favors trunk	Edema; superficial and deep lymphocytic infiltrate with eosinophils	
Wells syndrome	Edematous erythematous plaques, often annular or arcuate with a greenish color centrally; pruritus; peripheral eosinophilia	Diffuse infiltrate of eosinophils; flame figures	Ch. 26
Eosinophilic annular erythema	Recurrent annular edematous erythematous plaques; pruritus; some authors view as a subtype of Wells syndrome but peripheral eosinophilia is typically absent; originally described in children where overlap with eosinophilic form of annular erythema of infancy	Superficial and deep perivascular, periadnexal and interstitial lymphohistiocytic infiltrate with abundant eosinophils	
Annular erythema of infancy (including neutrophilic figurate erythema of infancy)	Recurrent annular erythematous plaques, usually lasting a few days; typically affects infants 3–11 months of age (see Fig. 19.4A); neutrophilic form can have purpura and vesicles and affect adults (see Fig. 19.4B)	Perivascular lymphocytes and eosinophils; sometimes a predominantly neutrophilic infiltrate	
Urticarial vasculitis	Urticarial plaques, often annular, that may have a purpuric or petechial component; pain, burning, and/or pruritus; systemic manifestations, especially in hypocomplementemic form	Leukocytoclastic vasculitis	Ch. 24
Erythema migrans	Erythema slowly migrates from site of tick bite; influenza-like syndrome; secondary distant lesions	Superficial and deep perivascular lymphohistiocytic infiltrate; eosinophils and plasma cells in some cases of erythema migrans; mucin and clusters of CD123+ plasmacytoid dendritic cells in LE tumidus; mucin in annular erythema of Sjögren syndrome	See text and Ch. 74
Erythema annulare centrifugum (deep)	Annular erythema with raised borders		See text
Lymphocytic infiltrate of Jessner	Annular erythematous plaques; favors face and upper trunk		Ch. 121
LE tumidus	Annular erythematous plaques; favors face, upper trunk > extensor forearms		Ch. 41
Annular erythema of Sjögren syndrome*	Annular erythematous plaques; favors face, arms, upper trunk; most common in Asian patients; anti-Ro antibodies		Ch. 45
Granulomatous lesions			
Granuloma annulare	Skin-colored to pink annular and arcuate plaques with borders composed of multiple papules; favors acral and extensor sites	Palisading granulomas with altered collagen and mucin	Ch. 93
Annular elastolytic giant cell granuloma	Pink annular plaques with atrophy and hypopigmentation centrally; favors sites of chronic sun exposure	Granulomatous infiltrate with elastophagocytosis by giant cells (border of lesion); absence of elastic fibers (center of lesion)	Ch. 93
Interstitial granulomatous dermatitis (IGD); interstitial granulomatous drug reaction (IGDR) (also referred to as reactive granulomatous dermatitis)	Annular erythematous plaques (or, in IGD, linear cords); favors axillae, groin, lateral trunk and legs; associated arthralgia/arthritis; IGDR is most often due to antihypertensive and lipid-lowering medications	Interstitial infiltrate of histiocytes with "rosetting" around collagen fibers and histiocytes surrounding single fibers of collagen; eosinophils may be present in IGDR	Ch. 93

Table 19.1 Differential diagnosis of figurate erythema.

DIFFERENTIAL DIAGNOSIS OF FIGURATE ERYTHEMA			
Disorders	**Clinical features**	**Histopathologic findings**	**Cross references**
Sarcoidosis	Red-brown annular plaques and papules; favors face; systemic manifestations	Sarcoidal granulomas ("naked tubercles")	Ch. 93
Borderline or tuberculoid leprosy	Annular plaques with raised erythematous borders and (in tuberculoid lesions) central hypopigmentation; asymmetric distribution; hypoesthesia, alopecia	Non-caseating granulomas with fragmentation of nerve fibers (tuberculoid leprosy); less well-defined granulomas (borderline leprosy)	Ch. 75
Papulosquamous lesions			
Erythema annulare centrifugum (superficial)	Annular lesions with trailing scale; favors thighs, hips and trunk	Superficial perivascular lymphocytes with focal spongiosis and parakeratosis; focal hemorrhage and exocytosis of lymphocytes in pityriasis rosea	See text
Erythema gyratum repens	Concentric erythematous rings with wood-grain appearance; erythema moves ~1 cm per day; associated with cancer		See text and Ch. 53
Pityriasis rosea	Herald patch on trunk; oval annular papules and plaques with central fine scaling and/or a collarette of trailing scale; Christmas-tree distribution on posterior trunk		Ch. 9
Pityriasis rubra pilaris	Appears as the primary "classic" lesions resolve; resembles erythema gyratum repens	Epithelial hyperplasia; alternating vertical and horizontal ortho- and parakeratosis; follicular plugging with shoulders of parakeratosis	See text and Ch. 9
Tinea corporis	Annular plaques with scale (exception: tinea incognito); pustules in border; concentric lesions in tinea imbricata; KOH-positive	Dermatophytes in the stratum corneum	Ch. 77
Lichen planus (LP), annular and actinic variants	Violaceous annular plaques; gray-brown to brown hyperpigmentation centrally; mucosal involvement; photodistribution in actinic LP	Hypergranulosis, band-like lymphocytic infiltrate at dermal–epidermal junction, necrotic keratinocytes	Ch. 11
Annular LE (subacute > discoid), *neonatal LE*, mothers of boys with chronic granulomatous disease	Photosensitivity; favors face (discoid), extensor upper extremities/upper trunk (SCLE), periorbital area (neonatal LE); anti-Ro antibodies (SCLE, neonatal LE); erythema gyratum atrophicans transiens neonatale is considered a variant of neonatal LE	Vacuolar interface dermatitis; variably dense periadnexal lymphohistiocytic inflammation with clusters of CD123+ plasmacytoid dendritic cells	Ch. 41
Seborrheic dermatitis	Erythematous annular plaques with scaling; favors face and central chest	Psoriasiform epithelial hyperplasia, spongiosis, perivascular lymphocytes	Ch. 13
Psoriasis	Annular scaly plaques with slow expansion	Psoriasiform epithelial hyperplasia, parakeratosis, diminished granular layer, elongated rete ridges, neutrophils migrating into epidermis	Ch. 8
Ichthyosis linearis circumflexa of Netherton syndrome	Serpiginous or circinate erythematous plaques bordered by double-edged scale; trichorrhexis invaginata; atopic diathesis, elevated serum IgE	Psoriasiform features with hyperkeratosis and a well-developed granular layer	Ch. 57
Lesions with absence or variable presence of scale			
Annular lichenoid dermatitis of youth	Red-brown annular patches or thin plaques with central hypopigmentation; favors groin and flanks; affects children and young adults	Lichenoid infiltrate; marked keratinocyte necrosis limited to the tips of rete ridges	Ch. 11
Erythema papulatum centrifugum	Usually a single, large annulus on the trunk whose border is 2–6 cm in width and composed of small erythematous papules, papulovesicles or crusted papules; favors Japanese men	Mononuclear infiltrate around eccrine ducts within the epidermis and dermis; spongiosis	
Secondary syphilis	Annular plaques with central hyperpigmentation; favors face; influenza-like symptoms; additional mucocutaneous manifestations; positive for RPR and FTA-ABS	Perivascular and interstitial infiltrate with plasma cells; also lichenoid or granulomatous infiltrate, exocytosis; bacilli can be identified by immunohistochemistry	Ch. 82
Mycosis fungoides	Annular erythematous or hypopigmented plaques, some with scale; admixed with classic lesions; often pruritic	Band-like infiltrate of lymphocytes in the papillary dermis with epidermotropism	Ch. 120
Neutrophilic sebaceous adenitis	Annular, indurated, erythematous plaques that favor the face and upper trunk of young adults; may be exacerbated by sun exposure	Focal necrosis of sebocytes; neutrophils within sebaceous glands; superficial and deep lymphocytic infiltrate	Ch. 25
Pustular lesions			
Pustular psoriasis (annular pattern)	Rapid expansion with erythematous borders studded with pustules	Subcorneal and spongiform pustules; neutrophils in the epidermis	Ch. 8
Sneddon–Wilkinson disease, IgA pemphigus	Pustules in a circinate pattern; peripheral expansion with central clearing; axillae, groin, inframammary areas	Subcorneal pustules; neutrophils in the epidermis; intercellular epidermal IgA deposition in IgA pemphigus	Chs. 8 & 29
Eosinophilic pustular folliculitis (Ofuji disease)	Grouped follicular pustules and papulopustules in an annular or serpiginous configuration; favors the face, trunk and arms	Infundibular eosinophilic pustules	Ch. 38

Table 19.1 Differential diagnosis of figurate erythema.

Continued

DIFFERENTIAL DIAGNOSIS OF FIGURATE ERYTHEMA			
Disorders	**Clinical features**	**Histopathologic findings**	**Cross references**
Erosive/vesiculobullous lesions			
Erythema multiforme (EM), Stevens–Johnson syndrome	Association with HSV and *Mycoplasma* vs drugs, respectively; target lesions more common in EM; mucosal involvement	Necrotic keratinocytes, vacuolar degeneration of the basal layer and variable inflammation	Ch. 20
Necrolytic migratory erythema	Erosion and crusting of advancing edge; periorificial involvement; glossitis; association with glucagonoma or liver/GI disorders (pseudoglucagonoma); constitutional symptoms	Pallor and edema of the upper epidermis; variable erosion	Ch. 53
Bullous pemphigoid, pemphigoid gestationis	Annular urticarial plaques; tense bullae; pruritus; peripheral eosinophilia	Subepidermal bullae with eosinophils > neutrophils; linear deposits of IgG and/or C3 in BMZ	Chs. 27 & 30
Linear IgA bullous dermatosis	Annular urticarial plaques; vesicles and bullae within border ("string of pearls"); pruritus	Subepidermal bullae with neutrophils > eosinophils; linear deposits of IgA in BMZ	Ch. 31
Epidermolysis bullosa simplex (especially generalized severe subtype [formerly Dowling–Meara subtype])	"Herpetiform" blisters in figurate array; episodic flares of migratory circinate erythema and blistering; *KRT5* or *KRT14* mutations	Intraepidermal split; eosinophilic inclusions within the keratinocytes	Ch. 32
Annular/cyclic epidermolytic ichthyosis	Migratory, annular or polycyclic, erythematous plaques with superficial blistering/peeling and scaling at the border; episodic flares; *KRT1* or *KRT10* mutations	Epidermolytic hyperkeratosis	Ch. 57
Purpuric lesions†			
Purpura annularis telangiectoides	"Cayenne pepper" petechiae and telangiectasias in annular configuration; favors trunk and legs	Capillary dilation and tight perivascular infiltrate of lymphocytes; extravasated erythrocytes; siderophages	Ch. 22
Acute hemorrhagic edema of infancy	Annular or targetoid, edematous, erythematous plaques that become purpuric; favors face, ears and extremities; febrile but non-toxic-appearing child <2 years of age	Leukocytoclastic vasculitis; perivascular IgA deposition in fewer than one-third of cases	Ch. 24
Perforating lesions‡			
Elastosis perforans serpiginosa	Peripheral edge composed of keratotic papules; favors neck and other flexural areas	Excess of degenerated elastic fibers in clumps in the superficial dermis with transepidermal elimination	Ch. 96

*Considered by some authors to be a form of SCLE.
†Purpura can also occur in urticarial vasculitis.
‡Giant variant of acquired perforating dermatosis can be annular.

Table 19.1 Differential diagnosis of figurate erythema. Key clinical features and histologic findings are provided. Disorders in *italics* favor children or childhood onset. Additional conditions that can present with figurate erythema include Kawasaki disease (may be erythema marginatum-like), hereditary periodic fever syndromes (especially *T*NF *r*eceptor-*a*ssociated *p*eriodic syndrome [TRAPS]; see Table 45.2), relapsing polychondritis, polymorphous light eruption, inflammatory vitiligo (including a papulosquamous variant), eosinophilic vasculitis, Sweet syndrome, neutrophilic eccrine hidradenitis, pyoderma vegetans (expanding pustular lesions), leukemia cutis, symmetric acral annular erythema, and porokeratosis. There is also an annular variant of acute generalized exanthematous pustulosis (e.g. due to terbinafine) and a generalized pustular figurate erythema associated with hydroxychloroquine. BMZ, basement membrane zone; FTA-ABS, fluorescent treponemal absorption; GI, gastrointestinal; LE, lupus erythematosus; RPR, rapid plasma reagin; SCLE, subacute cutaneous LE.

Occasionally, vesicles develop within the peripheral margin. In *deep* gyrate erythema, the advancing edges are obviously elevated (Fig. 19.1C) and there is usually no associated scale or pruritus.

As lesions resolve, there is no residual scarring, but postinflammatory hyperpigmentation can be seen and, on occasion, purpura. Although the lesions of EAC may be localized or generalized, they rarely, if ever, involve the palms, soles, scalp or mucous membranes. Individual lesions can persist for weeks to months, but associated systemic manifestations are uncommon. While new lesions can appear just as older ones resolve, there may be prolonged intervals of time between flares. Compared to the deep variant, the superficial form tends to recur more frequently but the individual lesions are often shorter-lived. The total duration of the disorder ranges from days to decades[2], and an unusual form of EAC has been described that recurs annually.

When EAC is due to an underlying disorder, flares of the former may correlate with recurrences of the latter. However, most patients with EAC do not have an identifiable underlying disorder, nor can the onset, fluctuations, or duration be related to a specific antigen.

Pathology

In *superficial* lesions of EAC, the findings are nonspecific, with mild spongiosis and microvesiculation plus associated focal parakeratosis, as well as a mild superficial perivascular lymphohistiocytic infiltrate. These histologic features correspond to the scale on the inner margin of the advancing erythematous arc. Characteristically, the inflammatory cells form a fairly tight aggregate around vessels, the so-called "coat sleeve" appearance (Fig. 19.1D). Rarely, eosinophils are found in the perivascular infiltrate. The advancing edge, which is slightly raised, may also show edema in the papillary dermis. The central area of clearing may contain dermal melanophages.

In *deep* lesions of EAC, the epidermis is usually unremarkable, and a mononuclear cell infiltrate with a sharply demarcated perivascular arrangement is present primarily within the mid and lower dermis. For this reason, the lesions are generally elevated and are more indurated than in the superficial form of EAC, and they do not have trailing scale.

Differential Diagnosis

EAC must be differentiated from other annular erythematous lesions (see Table 19.1)[10], particularly tinea corporis and annular psoriasis, when there is associated scale. Additional entities to consider include annular urticaria (Fig. 19.2B), allergic urticarial eruption, symmetric acral annular erythema, cutaneous lymphoid hyperplasia (pseudolymphoma), and lymphoma cutis. Patients with autoimmune disorders, including linear IgA bullous dermatosis, bullous pemphigoid, Sjögren

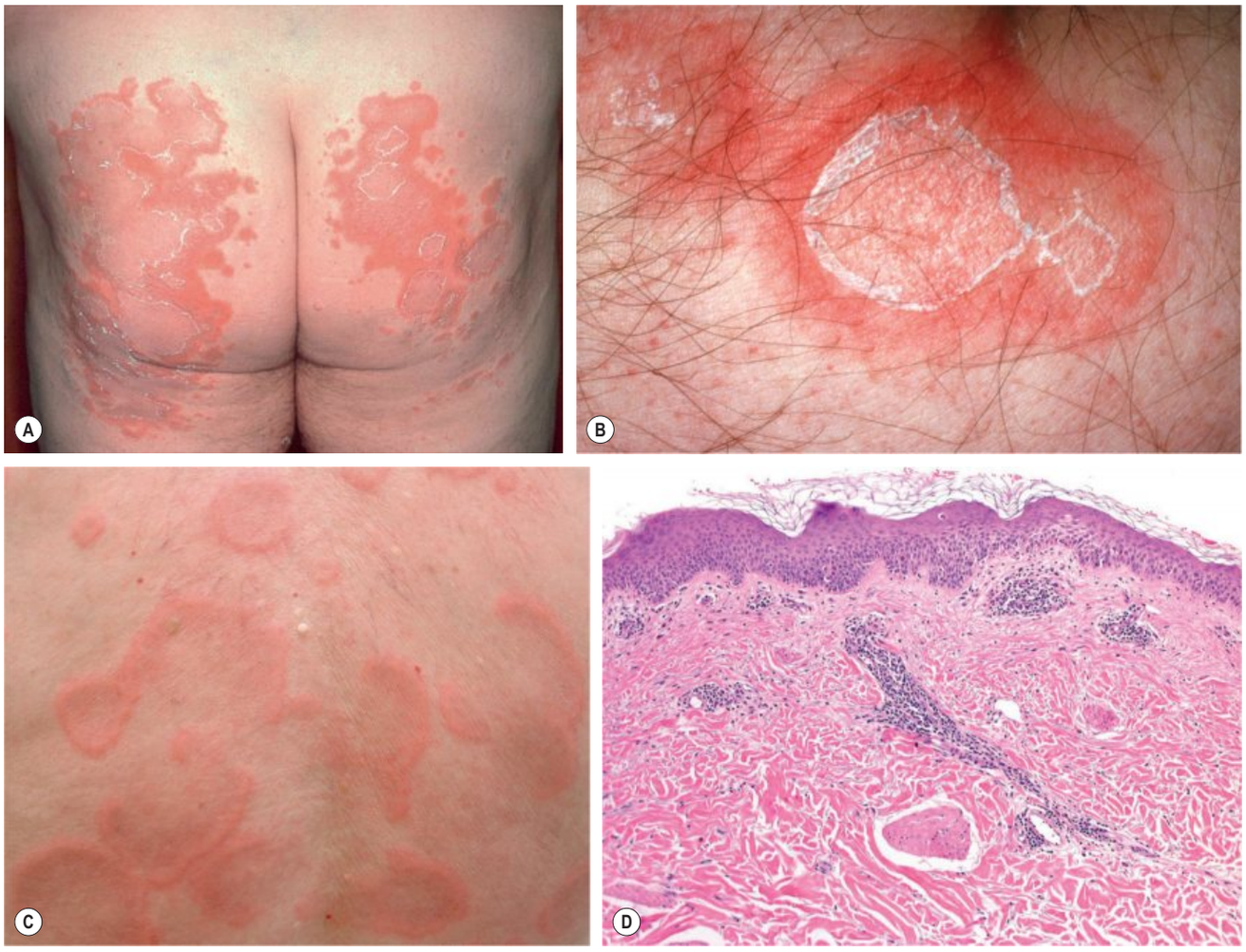


Fig. 19.1 Erythema annulare centrifugum. A, B Superficial form, with polycyclic plaque and delicate scale on the inner margin of the advancing edge (trailing scale). The scale is detached centrally. **C** Deep form, with obvious elevation of advancing edges and without trailing scale. **D** Photomicrograph of the superficial form with dermal perivascular lymphohistiocytic infiltrates; note the tight "coat sleeve"-like appearance of the infiltrate. *D, Courtesy Lorenzo Cerroni, MD.*



Fig. 19.2 A comparison of erythema annulare centrifugum and urticaria. The lesions in **A** have no scaling and may be confused with annular urticaria (**B**). However, individual lesions of urticaria are evanescent. Placement of an ink circle around a lesion, followed by longitudinal observation, allows this distinction.

syndrome, and lupus erythematosus (LE tumidus, subacute cutaneous LE, neonatal LE), can also have erythematous annular, arciform, and polycyclic lesions.

Treatment

If EAC is due to an underlying disorder, the skin lesions will usually resolve once the latter has been successfully treated. Topical corticosteroids applied to the advancing border of the lesions may be of benefit. Topical antipruritics and sedating antihistamines can be prescribed if there is associated pruritus. Even in the absence of an identifiable cause, some authors have advocated the empiric use of antibiotics (e.g. macrolides) or antifungal agents. Although systemic corticosteroids can induce a clinical remission, recurrences are common when the medication is discontinued. Based solely on case reports, the following have been reported as beneficial: topical tacrolimus, topical calcipotriene (calcipotriol), NB-UVB, oral metronidazole, apremilast, subcutaneous etanercept, and subcutaneous interferon-α. However, systemic therapies are seldom necessary.

ERYTHEMA MARGINATUM

Synonyms: ■ Erythema marginatum rheumaticum ■ Erythema annulare rheumaticum

Key features

- Migratory, annular and polycyclic, erythematous eruption
- Cutaneous manifestation of acute rheumatic fever
- Associated findings include carditis, migratory polyarthritis, Sydenham chorea, and subcutaneous nodules
- Seen more commonly in children than in adults

Introduction

Rheumatic fever (RF) is characterized by an abnormal immunologic response to a preceding infection with group A β-hemolytic streptococci and by the triad of fever, arthritis, and carditis. Cutaneous manifestations include erythema marginatum and subcutaneous nodules, but they are seen in a minority of patients. The diagnostic criteria of RF were recently revised in 2015 by the American Heart Association[11]: major criteria in low-risk populations are carditis or valvulitis (by echocardiography), polyarthritis, Sydenham chorea, erythema marginatum, and subcutaneous nodules. Minor criteria include fever, polyarthralgia, elevated acute phase reactants (ESR ≥60 mm, C-reactive protein ≥3 mg/dL), and prolonged PR interval on ECG. To establish the diagnosis of acute RF, two major or one major and two minor criteria must be accompanied by evidence of an antecedent group A streptococcal infection, e.g. a positive culture, an elevated or rising antistreptolysin O or anti-DNase B titer. In moderate- to high-risk populations, monoarticular arthritis is also considered a major criterion, with monoarthralgia and an ESR ≥30 mm representing additional minor criteria[11].

History

In 1831, Bright noted the presence of annular erythematous lesions in patients with RF. In 1889, Cheadle proposed the name "erythema marginatum rheumaticum"[12]. Carol and van Krieken first described the histopathologic findings in 1935. Two years later, Perry reported that rapid migration of the lesions was a characteristic finding[13]. In 1944, Jones established criteria for diagnosing RF[14].

Epidemiology

Attacks of acute RF are associated with antecedent group A β-hemolytic streptococcal infections of the pharynx. Approximately 3% of patients with untreated infections can develop acute RF. It is estimated that in high-income countries, i.e. low-risk populations, the incidence is 5 per 100 000, whereas in low-income countries, it ranges from 100 to 1000 per 100 000. Erythema marginatum is seen in less than 10% of patients with acute RF. The higher incidence of erythema marginatum in children (as compared to adults) reflects the predominance of RF during childhood; the peak age-related incidence is between 5 and 15 years[15].

Pathogenesis

The mechanisms that underlie erythema marginatum are unknown. Presumably, there is an abnormal humoral and cellular immune response to one or more antigens associated with group A β-hemolytic streptococci (e.g. M protein)[16]. Antigenic mimicry may play a role in that epitopes that cross-react with group A streptococcal antigens have been identified in human myosin, actin, tropomyosin, keratin, laminin, N-acetylglucosamine, and vimentin[17]. Specific characteristics of certain strains of group A β-hemolytic streptococci, such as higher M protein content and mucoid colony formation, may facilitate the development of acute RF[18]. Enhanced expression of genes that encode cysteine proteases (e.g. *Streptococcus pyogenes* exotoxin B [SpeB], immunoglobulin G degrading enzyme of *Str. pyogenes* [IdeS]) is thought to contribute to cardiotoxicity and virulence[19]. The role of host genetic factors is currently under investigation via genome-wide association studies[20].

Clinical Features

Following the initial episode of streptococcal pharyngitis, there is usually a latency period of 2–5 weeks before the development of the acute attack of RF. The lesions of *erythema marginatum* begin as erythematous macules that spread peripherally and become patches or plaques with no scale. Erythema marginatum can also have a polycyclic arrangement (Fig. 19.3). The lesions are usually asymptomatic, and, over a period of 12 hours, they can migrate from 2 to 12 mm; in areas of previous involvement, the skin may appear pale or lightly pigmented[15]. As with other erythemas, exposure to heat can accentuate lesions.



Fig. 19.3 Erythema marginatum. Polycyclic and evanescent annular lesions are seen on the trunk of this young patient.

The most common locations for erythema marginatum are the trunk, axillae and proximal extremities, with sparing of the face. New lesions usually last from a few hours to a few days and are often most noticeable during the afternoon. Recurrent crops can occur over a number of weeks. Erythema marginatum is associated primarily with the active phase of RF, and, in general, it is seen in conjunction with carditis. Of note, children less than 5 years of age appear to have a higher incidence of erythema marginatum as well as carditis and arthritis[21].

Subcutaneous nodules appear primarily over bony prominences, especially the wrists, elbows, knees and ankles, in patients with long-standing disease. The nodules are usually painless and are rare during the initial attack of RF. Similar nodules can be seen in patients with polyarticular juvenile idiopathic arthritis (see Ch. 45). In addition to the major and minor criteria (see above), patients may also have malaise, chest or abdominal pain, epistaxis, tachycardia and anemia, as well as a nonspecific urticarial eruption[18].

Pathology

An interstitial and perivascular infiltrate composed predominantly of neutrophils without vasculitis is observed. Occasionally, eosinophils are seen and in later stages, there can be extravasation of erythrocytes. Direct immunofluorescence microscopy for immunoglobulin and complement deposits is negative. These histologic findings are not unique to erythema marginatum, and overlapping features with the neutrophilic variant of annular erythema of infancy (neutrophilic figurate erythema of infancy) and the neutrophilic urticarial dermatosis seen in several autoinflammatory disorders may be observed.

Differential Diagnosis

The clinical differential diagnosis includes primarily annular urticaria (including urticaria multiforme) and annular erythema of infancy (Fig. 19.4A), as well as its variant neutrophilic figurate erythema of infancy[22]. Occasionally, neutrophilic figurate erythema is seen in adults and can be accompanied by vesicles and purpura (Fig. 19.4B). Less often, Still disease, hereditary periodic fever syndromes (particularly *T*NF *r*eceptor-*a*ssociated *p*eriodic *s*yndrome [TRAPS]; see Table 45.2), EAC, Kawasaki disease, and other entities listed in Table 19.1 need to be considered. Annular erythema with an appearance similar to erythema marginatum may precede or accompany episodes of hereditary angioedema[23] and is seen only occasionally in patients with cat scratch disease or psittacosis[24,25]. The angioedema-associated figurate erythema may be related to deposits of bradykinin within the dermis while the latter may reflect an overlap between erythema



Fig. 19.4 Annular erythema of infancy and neutrophilic figurate erythema. A Expanding annular urticarial plaques in a 6-month-old boy. Lesions are typically asymptomatic, expand slowly, and then resolve over a few days. New plaques may continue to appear for several months. **B** A neutrophilic variant occurs in both infants and adults and in the latter, there can be striking purpura within the lesions. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Lorenzo Cerroni, MD.*

marginatum and EAC. In a patient receiving sorafenib, figurate lesions with associated scale-crust and hemorrhage developed and the name "erythema marginatum hemorrhagicum" was proposed, but clinically these lesions can easily be distinguished from erythema marginatum[26].

Treatment

There is no specific therapy for this dermatosis. In general, its clinical course is unaltered by treatment of the underlying acute RF; however, symptoms are usually mild and lesions resolve spontaneously.

ERYTHEMA MIGRANS

Synonyms: ■ Erythema chronicum migrans ■ Lyme borreliosis (early stage) ■ Lyme disease (early stage)

Key features

- Annular erythema develops at the site of the bite of a *Borrelia*-infected tick
- Several species of *Ixodes* ticks are infected with different genospecies of *Borrelia burgdorferi*
- Erythema migrans represents the initial cutaneous manifestation of Lyme disease and is seen in 60%–80% of patients diagnosed with the disease
- Multiple secondary lesions that may be smaller in size can occur as a result of spirochetemia or lymphatic spread

Introduction

Lyme disease (LD) is an infection due to *Borrelia burgdorferi* spirochetes that are transmitted by bites from several species of *Ixodes* ticks (e.g. *I. scapularis*, *I. pacificus*, *I. ricinus*; see Chs. 76 & 85). Erythema migrans represents the initial cutaneous manifestation.

History

The first report of an annular erythema developing after a tick bite was by Afzelius in 1909 and he coined the term "erythema migrans". Lipschütz then referred to these cutaneous lesions as "erythema chronicum migrans". In the US, Steere described an epidemic form of childhood arthritis preceded by erythema migrans in several communities in the vicinity of Lyme, Connecticut. In the 1980s, Burgdorfer isolated a new spirochete in lesions of erythema migrans and the organism was subsequently named *B. burgdorferi*[27].

Epidemiology

Although LD has a worldwide distribution, it is seen most commonly in the US (Northeast, mid-Atlantic, and Great Lakes regions) and in northern and eastern Europe. The competent hosts that serve as a reservoir for *Borrelia* include mice, chipmunks and birds, with deer playing a role in sustaining the life cycle[28]. In temperate regions, the peak incidence for LD is during the spring and the summer, and it occurs more commonly in those who spend time outdoors in or near fields and woods. Approximately 30 000 cases of Lyme disease are currently reported to the CDC each year, with 95% of confirmed cases coming from 14 states (www.cdc.gov/lyme/). Based upon recent US insurance claim data, an estimated 475 000 people were treated yearly for Lyme disease, but this number obviously includes noninfected individuals. In Europe, ~320 000 cases of LD are diagnosed each year, but the incidence varies depending upon the country[29,30]. Not all patients who have positive serologic tests for *B. burgdorferi* develop LD.

Pathogenesis

In mice, *B. burgdorferi* has been shown to usurp a tick salivary protein, Salp15, as a means of enhancing transmission[31]. By binding to the outer surface protein C (OspC) of *B. burgdorferi*, Salp15 provides protection against antibody-mediated killing. In addition, Salp15 inhibits adaptive immune responses against both *Borrelia* and tick antigens[32]. Of note, one of the proposed strategies for preventing LD is the development of anti-tick vaccines that utilize tick salivary proteins.

Once the *Borrelia* organisms have entered the body, spirochetal lipoproteins trigger an innate immune response, with cytokines being produced by macrophages[33]. In addition, a Th1 response is triggered and B cell responses facilitate the synthesis of antibodies against different antigens of *B. burgdorferi*. Spirochetemia is present in ~45% of patients at the time of their presentation with erythema migrans[34], and organisms can disseminate widely due to their ability to resist elimination by macrophages, evade complement, adhere to brain and epithelial cells, penetrate into the cytoplasm via intracellular junctions, and induce TNF production[35].

Even though the lesion expands centrifugally, *B. burgdorferi* organisms have been found both in the center and at the periphery of lesions

of erythema migrans. The persistence of the spirochete in the skin after the tick bite may be due to an absence of the production of interferon-γ and an ineffective immune response[33]. Also, different immune responses to the various genospecies of the *B. burgdorferi* sensu lato complex (*B. burgdorferi* sensu stricto, *B. afzelii, B. garinii*) may lead to different clinical presentations (e.g. borrelial lymphocytoma in Europe but not the US; see Ch. 74)[36]. More recently, an additional genospecies was identified in the upper midwestern US, *B. mayonii*, which may lead to a more severe clinical presentation due to an unusually high spirochetemia[37].

Clinical Features

LD is divided into three clinical stages: (1) early localized disease; (2) early disseminated disease; and (3) chronic disease (Table 19.2). Erythema migrans is an important clinical feature of early disease. Typically, 7–15 days (range, 3–30 days) after tick detachment, an erythematous, expanding, circular or annular plaque appears that may have a lighter-colored central area or a bull's-eye appearance (Fig. 19.5). The eventual diameter is usually at least 5 cm, and the center may become darker red to violaceous in color, crusted, or even vesicular. Lesions of primary erythema migrans favor the trunk, axilla, groin, and popliteal fossa. Untreated, the lesions usually last less than 6 weeks (median, 4 weeks). In 20%–25% of patients, multiple lesions can appear due to multiple tick bites or as a result of disseminated disease secondary to spirochetemia. Disseminated lesions tend to be smaller in size and less pronounced and usually appear days to weeks after the appearance of the primary erythema migrans (Fig. 19.6)[38].

Erythema migrans is seen in 60%–80% of patients diagnosed with LD. In the US, the systemic manifestations of this initial phase tend to be acute, with influenza-like symptoms, including fatigue, headache, arthralgia, myalgia and fever, as well as lymphadenopathy, conjunctivitis or hepatitis (see Table 19.2)[39]. In Europe, this initial clinical phase is usually less severe, and the lesions of erythema migrans tend to last longer. If untreated, ~60% of patients will go on to have monoarticular or oligoarticular arthritis (usually the knee) within weeks to months after the initial infection; ~10%, neurologic manifestations (most commonly facial nerve palsy); and ~5%, cardiac complications (usually varying degrees of atrioventricular block)[34]. For a discussion of borrelial lymphocytoma and acrodermatitis chronica atrophicans, see Chapter 74.

Depending upon the geographic region, *Ixodes* ticks can be co-infected with the following microbes (in addition to *B. burgdorferi*): *Babesia microti* (babesiosis)[40], *Anaplasma phagocytophilum* (anaplasmosis), *Borrelia miyamotoi*, or Powassan virus. Co-infections should be considered when patients with LD have prolonged or severe manifestations of infection, cytopenias, or an unusually high or persistent fever[28].

Pathology

The histologic features of erythema migrans are similar to those of a deep gyrate erythema (Fig. 19.7). While routine histology is often not specific, many specimens will show superficial and deep lymphoid infiltrates admixed with a few eosinophils and plasma cells. Immunohistochemical studies have shown a reduction in the number of Langerhans cells; in the dermis, the inflammatory infiltrate contains macrophages, $CD4^+$ T helper cells and $CD45RO^+$ memory T cells[41]. PCR analysis of tissue specimens can be performed to confirm the presence of *Borrelia* spirochetes within a lesion.

Differential Diagnosis

The 2022 revised CDC case definition for LD now includes three categories: "confirmed", "probable", and "suspected" (Table 19.3)[42]. These categories are based upon laboratory evidence and whether a person resides in a low-incidence versus high-incidence jurisdiction (state). Confirmatory laboratory evidence consists of one of the following: (1) isolation of *B. burgdorferi* sensu stricto or *B. mayonii* in culture; (2) detection of *B. burgdorferi* sensu stricto or *B. mayonii* in a clinical specimen by a *B. burgdorferi* group-specific nucleic acid amplification test (NAAT) assay; (3) detection of *B. burgdorferi* group-specific antigens by immunohistochemical assay on biopsy or autopsy tissues; or (4) positive serologic tests in a two-tier or equivalent format. The latter includes either: (1) the standard two-tier test (STTT) - a positive or equivocal first-tier screening assay, often an enzyme immunoassay (EIA) or immunofluorescence assay (IFA) for IgM, IgG or combination, followed by a concordant positive IgM or IgG immunoblot; or (2) modified two-tier test (MTTT) - positive or equivocal first-tier screen, followed by a different sequential positive or equivocal EIA in lieu of an immunoblot[42]. In 2019, the MTTT methodology was introduced in which an FDA-cleared second EIA (e.g. for VlsE1-IgG and pepC10-IgM) could be used in place of the Western immunoblot[44]. *Presumptive* laboratory evidence consists of a positive IgG immunoblot, interpreted by established criteria, without positive or equivocal first-tier screening.

Of note, the peak specific IgM response (usually directed against the 41 kDa flagellar antigen) occurs 3–6 weeks into the infection[35]. As a result, serologic testing has a low sensitivity, e.g. only 25%–40% of patients with erythema migrans during the acute phase (but without evidence of dissemination) have positive test results, with a slightly higher percentage in those with dissemination (~50%)[28]. During convalescence following antibiotic therapy, positive test results are still only observed in approximately half of those who did not have dissemination, presumably reflecting eradication of the spirochetes[28].

STAGES AND MAJOR ORGAN MANIFESTATIONS OF LYME DISEASE

Organ	Early localized disease	Early disseminated disease	Chronic disease
Skin	Erythema migrans		Acrodermatitis chronica atrophicans (Europe)
	Disseminated erythema migrans Borrelial lymphocytoma (Europe)		
Nervous system		Lymphocytic meningitis Cranial neuritis Bell palsy Radiculoneuropathy	Encephalopathy Encephalomyelitis Neuropathy
Musculoskeletal system		Arthralgia, arthritis Myositis	Chronic arthritis
Heart		Atrioventricular block Myopericarditis, pancarditis	
Lymphatic	Regional lymphadenopathy	Regional or generalized lymphadenopathy	
Other		Conjunctivitis, iritis Hepatitis Non-productive cough Microscopic hematuria or proteinuria	

Table 19.2 Stages and major organ manifestations of Lyme disease. Patients with erythema migrans may also have influenza-like symptoms, including fatigue, headache, myalgia, and fever. *Adapted from Müllegger RR. Dermatological manifestations of Lyme borreliosis. Eur J Dermatol. 2004;14:296–309.*







Fig. 19.5 Erythema migrans. A, B Annular erythema that spreads centrifugally; the peripheral erythematous border may or may not be sharply demarcated and is usually 1–2 cm in width. Concentric rings can form, leading to a bull's-eye appearance, but some lesions of EM have a more uniform color. Vesiculation centrally can also be seen (**B**). **C** The center may become violaceous in color. Patients may not report a history of a tick bite. *A, Courtesy Department of Dermatology, Medical University of Graz; C, Courtesy Dennis Cooper, MD.*



Fig. 19.6 Disseminated erythema migrans. Multiple pink circular and oval-shaped thin plaques with coalescence. Patients often have influenza-like symptoms. *Courtesy Ian W. Tattersall, MD, PhD.*

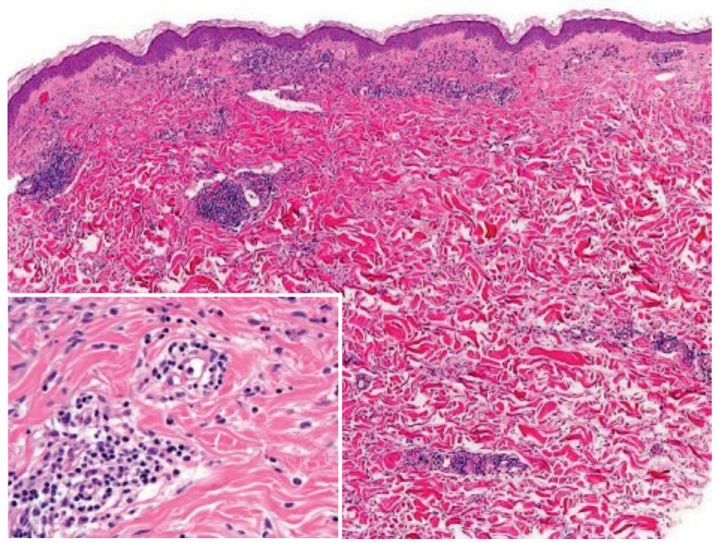


Fig. 19.7 Erythema migrans. A superficial and deep perivascular infiltrate is present within the dermis as well as a scattered interstitial pattern. The infiltrate is composed of lymphocytes and plasma cells (inset). *Courtesy Lorenzo Cerroni, MD.*

Although culture of tissue from the perimeter of erythema migrans lesions is essentially 100% specific and can distinguish live from dead organisms, it requires special agar (modified Barbour–Stoenner–Kelly medium) and prolonged observation, making it impractical in the standard clinical setting. As noted previously, detection of *B. burgdorferi* in skin biopsy specimens of erythema migrans via PCR is possible.

Erythema migrans must be distinguished from exaggerated local arthropod reactions (including to the tick bite), erysipelas, cellulitis, allergic contact dermatitis and non-pigmented fixed drug eruption, and less often, other entities outlined in Table 19.1. An erythema migrans-like skin lesion can be seen in southern tick-associated rash illness (STARI or Masters disease) which follows the bite of the lone star tick, *Amblyomma americanum* (see Ch. 85).

Treatment

Recommended antibiotic regimens are outlined in Table 19.4[43]. It is estimated that even in highly endemic areas, the risk of disease transmission from a recognized tick bite is low (1%–3%)[45]. This may be due to the observation that in general transmission from infected nymph ticks requires 36–48 hours of attachment and for adult ticks, ≥48 hours of attachment[28]. Therefore, routine treatment of tick bites with 2- to 3-week courses of antibiotics is not recommended. In patients from endemic areas (>20% of ticks infected) in whom the tick, identified as a nymphal or adult *I. scapularis*, has been attached for >36 hours and prophylaxis can be started within 72 hours of tick removal, a single 200 mg dose of doxycycline may decrease the risk of developing LD (from 3.2% in the placebo group to 0.4% in the treatment group in one study)[46].

ABRIDGED 2022 CDC LYME DISEASE SURVEILLANCE CASE DEFINITION
Definition of Erythema Migrans (EM)
A skin lesion that typically begins as a red macule or papule and expands over a period of days to weeks to form a large round lesion, often with partial central clearing. A single primary lesion must reach ≥5 cm in diameter. Secondary lesions also may occur. Annular erythematous lesions occurring within several hours of a tick bite represent hypersensitivity reactions and do not qualify as EM. EM may be accompanied by influenza-like symptoms (see text) and the diagnosis of EM must be made by a health care provider
Additional clinical criteria
• Recurrent, brief attacks of objective joint swelling in one or a few joints • Lymphocytic meningitis, cranial neuritis (particularly facial palsy [unilateral or bilateral]), radiculoneuropathy, or, rarely, encephalomyelitis • Acute onset of high-grade (2nd-degree or 3rd-degree) atrioventricular conduction defects that resolve in days to weeks and are sometimes associated with myocarditis
Laboratory criteria
• See text for details
Confirmed, probable, or suspect*
• High-incidence jurisdiction† - suspect if presumptive laboratory evidence • Low-incidence jurisdiction‡ - confirmed if confirmatory laboratory evidence and probable if presumptive laboratory evidence
*See website for details. †A jurisdiction with an average Lyme disease incidence of at least 10 confirmed cases/100 000 for the previous three reporting years [www.cdc.gov/lyme/stats/tables.html]. ‡A jurisdiction with an average Lyme disease incidence of <10 confirmed cases/100 000 for the previous three reporting years [www.cdc.gov/lyme/stats/tables.html].

Table 19.3 Abridged 2022 CDC Lyme disease surveillance case definition. CDC, Centers for Disease Control and Prevention. https://ndc.services.cdc.gov/case-definitions/lyme-disease-2022/

ERYTHEMA GYRATUM REPENS

Synonym: ■ Gammel disease

Key features

- A figurate erythema that is migratory and composed of concentric rings with a wood-grain appearance
- It represents a paraneoplastic phenomenon and the most common underlying neoplasm is carcinoma of the lung
- The lesions may have associated pruritus and scale, and they characteristically exhibit rapid migration (up to 1 cm per day)
- The cutaneous lesions resolve when the neoplasm is successfully treated

Introduction

In the vast majority of patients, erythema gyratum repens (EGR) represents a paraneoplastic figurate erythema. In theory, the cutaneous lesions arise as a result of an immune reaction against tumor-associated antigens with the subsequent recognition of similar antigens in the skin.

History

EGR was first reported by Gammel in 1952, and his original description clearly identified its key clinical features.

TREATMENT OPTIONS FOR LYME DISEASE				
Manifestation	**Drug**	**Dose (pediatric dose*)**	**Duration (days)**	**Comments**
Erythema migrans	Doxycycline	100 mg (2 mg/kg) po BID	14 (range, 10–21)	• Not preferred in children <8 yrs of age†, or pregnant or lactating women • Good CNS penetration • Also treats human granulocytic anaplasmosis
	Amoxicillin	500 mg (16 mg/kg) po TID	14 (range, 14–21)	
	Cefuroxime axetil	500 mg (15 mg/kg) po BID	14 (range, 14–21)	
	Azithromycin^	500 mg (10 mg/kg) po daily	7 (range, 5–10)	
Manifestation	**Drugs**		**Duration (days)**	**Comments**
Meningitis	Ceftriaxone (IV), cefotaxime (IV)		14 (range, 10–28)	
Cranial nerve palsy (without meningitis)	Same drugs and dosing as for erythema migrans		14 (range, 14–21)	• May not affect outcome of facial palsy
Carditis	If symptomatic, initiate treatment with parenteral antibiotic (e.g. ceftriaxone) then based upon clinical response, finish course with oral agents		14 (range, 14–21)	• Advanced heart block may require a pacemaker
Arthritis	Same parenteral agents as for meningitis and same oral agents as for erythema migrans		28	• If persists or recurs, a second course of antibiotics
*The maximum pediatric dose is the adult dose. †The American Academy of Pediatrics considers use of doxycycline for ≤21 days to be acceptable in children <8 years of age. ^For patients intolerant of both doxycycline and β-lactam antibiotics.				

Table 19.4 Treatment options for Lyme disease[43]. A Jarisch–Herxheimer-like reaction with an increase in systemic symptoms and in the size or intensity of the inflammation of the erythema migrans lesion occurs in ~15% of patients within 24 hours after the initiation of antimicrobial therapy. If all three antibiotics for erythema migrans are contraindicated, then macrolides (e.g. clarithromycin, erythromycin, azithromycin) can be prescribed but the cure rates are ~80% rather than 90% with recommended antibiotics[28]. BID, twice daily; IV, intravenous; po, orally; TID, three times daily; yrs, years.



Fig. 19.8 Erythema gyratum repens. Multiple gyrate erythematous plaques, showing a wood-grain pattern. *Courtesy Agustin Alomar, MD.*

Epidemiology

EGR is a very rare disorder seen primarily in adults. Risk factors parallel those for the underlying neoplasms.

Pathogenesis

A leading hypothesis is that EGR represents an immune reaction in which there is a cross-reaction between tumor and cutaneous antigens[47]. In a few patients, direct immunofluorescence (DIF) has demonstrated deposits of IgG and C3 in the basement membrane zone (BMZ) of the skin, and, in isolated cases, similar deposits were seen in the associated neoplasm[48]. However, this could simply represent a nonspecific finding. Caux et al.[48] suggested that the tumor produces a modification in its basement membrane and this subsequently induces an immune response. Recognition of similar antigens in the BMZ of the skin then leads to the cutaneous eruption. The responsible antigen(s) is not known, but a curious finding is an accumulation of active Langerhans cells in the upper layers of the epidermis[49]. Recently, a link between glutamine metabolism within the skin and the distinct pattern of EGR lesions was proposed[50].

Clinical Features

Patients usually have multiple, annular or polycyclic, erythematous lesions that develop scale at their edges and advance at a rapid rate (up to 1 cm per day)[51]. This rate of peripheral spread is significantly faster than that of EAC. Lesions have a wood-grain or zebra-like pattern, due to the development of "rings within rings" (Fig. 19.8). In some patients, the eruption is also pruritic. Additional findings in patients with EGR include acquired ichthyosis, palmoplantar keratoderma, and peripheral eosinophilia.

In at least 70% of patients, EGR is associated with an underlying neoplasm, most commonly of the lung then breast, esophagus or stomach[52]. The cutaneous lesions usually develop between 1 year prior to 1 year after the diagnosis of the neoplasm. EGR may coincide with underlying pulmonary tuberculosis, and patients with other disorders (see below) can also develop EGR-like lesions. Occasionally, no underlying disorder or malignancy can be identified.



Fig. 19.9 Resolving pityriasis rubra pilaris. The lesions can resemble erythema gyratum repens. *Courtesy Irwin Braverman, MD.*

Pathology

The histopathologic findings are nonspecific and include hyperkeratosis, focal parakeratosis, moderate patchy spongiosis and a mild, perivascular lymphohistiocytic infiltrate. In some cases, variable numbers of eosinophils are seen in the dermis.

Differential Diagnosis

In addition to excluding the other types of figurate erythema, EGR-like lesions may be seen in patients with erythrokeratodermia variabilis et progressiva and resolving pityriasis rubra pilaris (Fig. 19.9) as well as autoimmune bullous diseases, in particular bullous pemphigoid (both paraneoplastic and classic) and epidermolysis bullosa acquisita[52,53]. Similar appearing lesions can occasionally be seen in mycosis fungoides, resolving psoriasis, hypersensitivity reactions to azathioprine, urticarial vasculitis, and autoimmune connective tissue diseases, primarily lupus erythematosus (subacute variant [also referred to as LE gyratus repens] or an associated neutrophilic dermatosis or small vessel vasculitis), and Sjögren syndrome. In certain regions of the world (e.g. maritime and mainland Southeast Asia), tinea imbricata would also be included in the differential diagnosis.

Treatment

EGR resolves when the associated neoplasm is successfully treated. There may be a return of cutaneous lesions in association with the development of metastases or local recurrences of the malignancy.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 19.1 Annular and arcuate urticaria. A, B Individual lesions of urticaria are evanescent.



eFig. 19.2 Erythema marginatum. Evanescent arciform and circular lesions can be clinically subtle. *Courtesy Eugene Mirrer, MD.*



eFig. 19.3 Erythema migrans. Annular erythema that spreads centrifugally. The peripheral erythematous border is usually 1–2 cm in width. Centrally, vesiculation is present.



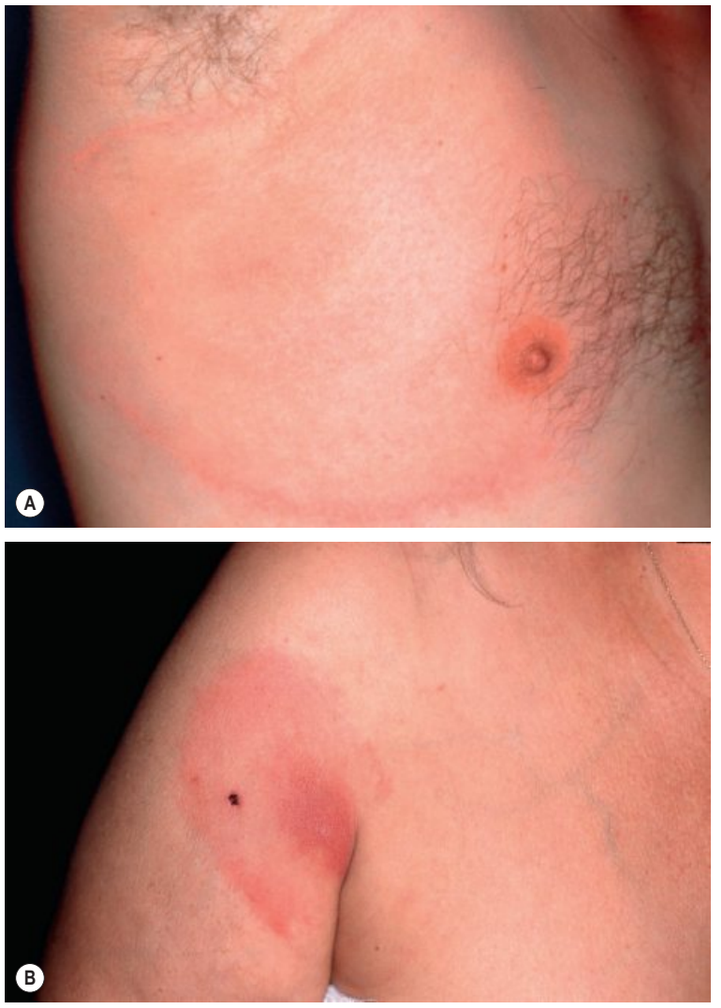
eFig. 19.4 Erythema migrans. Two expanding circular pink plaques on the leg. *Courtesy Alicia Little, MD.*



eFig. 19.5 Disseminated erythema migrans. Multiple circular and a few annular plaques are scattered on the lower extremities as well as the trunk (not shown). *Courtesy Thomas Schwarz, MD.*



eFig. 19.6 Disseminated erythema migrans. Multiple circular pink plaques on the thigh and knee. Patients often have flu-like constitutional symptoms.



eFig. 19.7 Erythema migrans. A Annular erythema that spreads centrifugally; the peripheral erythematous border may or may not be sharply demarcated and is usually 1-2 cm in width. **B** Sometimes an arciform plaque is seen and the site of the tick bite may have more intense inflammation. A previous biopsy has been performed. *A, Courtesy Lorenzo Cerroni, MD; B, Courtesy Department of Dermatology, Medical University of Graz.*



eFig. 19.8 Eosinophilic annular erythema. Annular plaques on the lower extremities without secondary changes. Histopathologically, a dermal infiltrate of eosinophils is seen. Some authors view this entity as a subtype of Wells syndrome. *Courtesy Jonathan S. Leventhal, MD.*

Erythema Multiforme, Stevens–Johnson Syndrome, and Toxic Epidermal Necrolysis

20

Wolfram Hötzenecker, Anna Oschmann and Lars E. French

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ERYTHEMA MULTIFORME

Synonym: ■ Erythema multiforme minor – erythema multiforme von Hebra

Key features

- A self-limited but potentially recurrent disease
- Abrupt onset of papular "target" lesions, with the vast majority of lesions appearing within 24 hours
- Two types of target lesions are recognized: (1) typical, with at least three different zones; and (2) atypical papular, with only two different zones and/or a poorly defined border
- Target lesions favor acrofacial sites
- Erythema multiforme minor: typical and/or occasionally atypical papular target lesions with little or no mucosal involvement and no systemic symptoms
- Erythema multiforme major: typical and/or occasionally atypical papular target lesions with severe mucosal involvement and systemic features
- A preceding herpes simplex virus (HSV) infection is the most common precipitating factor; occasionally, there are other preceding infections or, rarely, drug exposure
- Diagnosis of erythema multiforme requires clinicopathologic correlation and is not based solely on histologic findings
- Erythema multiforme does not carry the risk of progressing to toxic epidermal necrolysis

Introduction

Erythema multiforme (EM) is an acute, self-limited skin disease characterized by the abrupt onset of symmetric fixed red papules, some of which evolve into typical and/or occasionally "atypical" papular target lesions[1,2]. The eruption is often precipitated by an infection, particularly HSV. Two forms of EM are recognized – EM minor and EM major. Both are characterized by the same type of elementary lesions (targets), but are distinguished by the presence or absence of mucosal involvement and systemic symptoms (Table 20.1). In the vast majority of patients, EM can be distinguished clinically from Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) based upon the type of elementary skin lesions and their distribution[2,3].

History

EM was first described by the Austrian dermatologist Ferdinand von Hebra in 1860[4,5]. The disease he described was mild with a sudden onset of hundreds of red papules. By daily observation, von Hebra recognized that some of the original papules evolved into lesions with concentric zones of color change, which he termed "target" lesions. Some of the target lesions resembled a "herpes iris". However, von Hebra described neither a prodrome nor the presence of mucosal lesions. He recognized that the condition could be recurrent and mentioned a "typus annuus" which recurred every spring.

In 1950, Bernard Thomas further subdivided EM into EM minor and EM major[6]. Thomas considered von Hebra's disease to be EM minor, and severe mucosal necrosis with "EM-like" cutaneous lesions to be EM major. Since 1950, much confusion has developed regarding the definition of EM, in part because some authors, especially in the US, have stated that EM major includes SJS. However, recent investigations have clarified the situation by providing strong evidence that the term "EM minor" should be reserved for von Hebra's disease and the term "EM major" should be used for EM associated with mucosal lesions and systemic symptoms, but not for describing SJS, because SJS and EM major are distinct clinical disorders[2,3]. That said, because these are biologic processes, there can be patients where the distinction proves challenging.

Epidemiology

EM is predominantly observed in young adults and is very uncommon during childhood[3,7]. There is a slight male preponderance, but no racial predilection. The exact incidence rate of EM is not known.

Pathogenesis

Current understanding suggests that EM is most likely a mucocutaneous immune reaction that occurs in the setting of an infection in certain "predisposed" individuals. HSV is clearly the most commonly associated infectious agent, with *Mycoplasma pneumoniae* (which also may be associated with SJS), *Histoplasma capsulatum*, and parapoxvirus (orf) observed less frequently (Table 20.2)[8]. Histoplasmosis-associated EM may occur more often in patients with concomitant erythema nodosum. To date, evidence for EBV as a precipitating factor is inconclusive[7]. Rarely, EM has been associated with drugs or systemic disease (see Table 20.2). Consequently, the possibility of SJS, generalized bullous fixed drug eruption, polymorphous exanthematous drug eruption, or urticaria multiforme should be strongly considered if the presumed diagnosis is drug-induced EM[7,9]. Of note, several physical agents such as trauma, cold, and UV and orthovoltage irradiation have been described as triggers for outbreaks of EM related to infectious agents, drugs, or systemic disease.

To date, there is no clearly defined genetic predisposition for the development of EM. Several small studies of HLA alleles have found different associations: HLA-DQw3 (specifically the DQB1*301 split), DRw53, and Aw33[10,11]. These HLA associations differ from those reported for SJS and TEN (see below).

Herpes simplex virus and Mycoplasma pneumoniae

In the majority of children and adults with EM, the disease is precipitated by HSV types 1 and 2[12,13]. Preceding herpes labialis is noted in ~50% of patients with EM[12,13]. Herpes labialis may precede the onset of the cutaneous lesions, occur simultaneously, or be evident after the target lesions of EM have appeared. Most commonly, herpes labialis precedes target lesions of EM by 3–14 days. It is presumed that most cases in children and young adults are due to HSV type 1, but documented cases of HSV type 2 in adolescents and young adults have been reported[12,13].

Most of our current knowledge regarding EM is related to the study of HSV-associated EM. Not only are HSV-encoded proteins found within affected epidermis[12,13], but HSV DNA can be detected within the early red papules or the outer zone of target lesions in 80% of individuals with EM[5]. The presence of fragments of HSV DNA (most often comprised of sequences that encode its DNA polymerase) within the cutaneous lesions, as well as the expression of virally encoded antigens

COMPARISON OF ERYTHEMA MULTIFORME (EM) MINOR, EM MAJOR, STEVENS–JOHNSON SYNDROME (SJS), SJS/TOXIC EPIDERMAL NECROLYSIS (TEN) OVERLAP, AND TEN						
	Type of skin lesions	**Distribution**	**Mucosal involvement**	**Systemic symptoms**	**Progression to TEN**	**Precipitating factors**
EM minor (Fig. 20.1 & 20.2)	• Typical targets • ± *Papular* atypical targets	Extremities (especially elbows, knees, wrists, hands), face	Absent or mild	Absent	No	• Herpes simplex virus • Other infectious agents
EM major (Fig. 20.3)	• Typical targets • ± *Papular* atypical targets • Occasionally bullous lesions	Extremities, face	Severe	Usually present • Fever • Arthralgias	No	• Herpes simplex virus • *Mycoplasma pneumoniae* • Other infectious agents • Rarely, drugs
SJS (Fig. 20.7 & 20.14)	• Dusky and/or dusky red *macules* with epidermal detachment and erosions • *Macular* atypical targets • Bullous lesions • <10% BSA detachment	Isolated lesions Confluence (+) Trunk, face	Severe	Usually present • Fever • Lymphadenopathy • Hepatitis • Cytopenias	Possible	• Drugs • Occasionally, *Mycoplasma pneumoniae** • Rarely, immunizations
SJS/TEN overlap (Fig. 20.11)	• Similar to SJS • 10%–30% BSA detachment	Isolated lesions Confluence (++) Trunk, face, neck	Severe	• Same as SJS	Likely	• Drugs
TEN (Fig. 20.8 & 20.9)	• Similar to SJS • >30% BSA detachment	Confluence (+++) Isolated lesions rare Trunk, face, neck, elsewhere	Severe, with involvement of respiratory and gastrointestinal mucosa	• Same as SJS plus nephritis		• Drugs
*Occasionally, also subcorneal pustules.						

Table 20.1 Comparison of erythema multiforme (EM) minor, EM major, Stevens–Johnson syndrome (SJS), SJS/toxic epidermal necrolysis (TEN) overlap, and TEN. BSA, body surface area; TEN, toxic epidermal necrolysis.

PRECIPITATING FACTORS IN ERYTHEMA MULTIFORME	
Infections (~90% of cases)	
Viral	• **Herpes simplex virus (HSV-1, HSV-2)** • Parapoxvirus (orf) • Vaccinia (smallpox vaccine) • Varicella zoster virus (chickenpox) • Adenovirus • Epstein–Barr virus • Cytomegalovirus • Hepatitis B & C viruses • Coxsackievirus • Parvovirus B19 • Human immunodeficiency virus
Bacterial	• ***Mycoplasma pneumoniae**** • *Chlamydophila* (formerly *Chlamydia*) *psittaci* (ornithosis) • *Salmonella* spp. • *Mycobacterium tuberculosis*
Fungal	• *Histoplasma capsulatum* • Dermatophytes
Drugs (unusual)	
Primarily	• Nonsteroidal anti-inflammatory drugs • Sulfonamides • Anticonvulsants, most commonly aromatic • Other antibiotics, e.g. aminopenicillins • Allopurinol
Exposures (unusual)	
	• Poison ivy • Vaccines (e.g. diphtheria & tetanus, hepatitis B virus)
Systemic disease (unusual to rare)	
	• Lupus erythematosus† (Rowell syndrome) • Inflammatory bowel disease • Behçet disease†
*Also precipitating factor for Stevens–Johnson syndrome and *Mycoplasma*-induced rash and mucositis (MIRM)/reactive infectious mucocutaneous eruption (RIME). †May be a pattern of cutaneous lesions in the disease rather than a precipitating factor.	

Table 20.2 Precipitating factors in erythema multiforme. This is a *non-exhaustive* list based primarily on case reports and small series of cases. The most common causes are in **bold**.

on keratinocytes, may be interpreted as evidence for replicating HSV within affected skin sites[12–14]. However, replication must be at a low level, because usually HSV cannot be cultured from EM lesions.

The inflammation within cutaneous lesions is believed to be a part of an HSV-specific host response[13]. Individuals with HSV-associated EM have normal immunity to HSV, but may have difficulty clearing the virus from infected cells; within sites of cutaneous lesions, HSV DNA may persist for 3 months after a lesion has healed[14]. Development of cutaneous lesions is initiated by the expression of HSV DNA sequences within the skin, followed by the recruitment of virus-specific T helper type 1 (Th1) cells that produce interferon-γ in response to viral antigens within the skin[15]. An "autoimmune" response is then thought to result from the recruitment of T cells that respond to autoantigens released by lysed/apoptotic viral antigen-containing cells. More recently it was shown that the HSV DNA fragments described above are transported (by peripheral blood $CD34^+$ Langerhans cell precursors) to the sites where EM skin lesions will develop prior to each eruption[16].

While HSV is the predominant cause of EM, there are other associated infectious agents. In particular, a severe acro-mucosal presentation with mucositis, conjunctivitis, and targetoid or bullous skin eruptions can be seen in patients with *M. pneumoniae* infections, primarily community-acquired pneumonia (see below). This variant occurs most commonly in young boys and adolescents. *M. pneumoniae* has been cultured from the bullae in patients with EM-like skin reactions, suggesting an etiologic role[17]. However, this association could also be explained by autoimmune molecular mimicry, as in *M. pneumoniae*-related Guillain–Barré syndrome[18].

Clinical Features

Due to a certain degree of clinical similarity, EM minor, EM major, SJS and TEN have, until recently, all been considered to be part of a single disease spectrum. However, as discussed previously, there is now strong evidence to support the concept that EM is a disease distinct from SJS and TEN at several levels – clinical, prognostic, and etiologic. Clinical criteria allow the distinction of both forms of EM from SJS/TEN in the vast majority of patients[2,3]. These clinical criteria are as follows: (1) the type of elementary skin lesion; (2) the distribution of skin lesions (topography); (3) the presence or absence of overt mucosal lesions; and (4) the presence or absence of systemic symptoms (see Table 20.1).

Elementary skin lesions (Fig. 20.1)

The characteristic elementary skin lesion of EM is the *typical target lesion*. The latter measures <3 cm in diameter, has a regular round shape and a well-defined border, and consists of at least three distinct zones, e.g. two concentric rings of color change surrounding a central circular zone that has evidence of damage to the epidermis in the form of bulla formation or crust[2]. Frequently, this central circular zone has a dusky appearance and over time, the lesion may resemble a "bull's eye".

While early target lesions often have a central dusky zone and a red outer zone ("iris" lesion), they can evolve to three zones of color change. Each concentric ring within the target lesion most likely represents one of a sequence of events of the same ongoing pathologic process. This may explain why some patients have only a limited number of fully developed, typical targets amidst a number of target lesions that are not yet typical or fully evolved, while in others all the lesions are at the same stage of development, thus creating a monomorphic clinical appearance. Given the possibility that only a few typical target lesions may be present, a complete skin examination is essential.

In EM, elevated *atypical papular target lesions* can either accompany typical target lesions or constitute the primary cutaneous lesion. These particular lesions are defined as round, edematous, palpable, and reminiscent of EM, but with only two zones and/or a poorly defined border. They must be distinguished from the flat (macular) atypical targets that are seen in SJS or TEN, but not EM. These macular lesions are defined as round lesions that are also reminiscent of EM, but with only two zones and/or a poorly defined border, as well as being non-palpable (with the exception of a potential central vesicle or bulla).

Distribution of skin lesions (topography)

Although there is considerable variation from individual to individual, numerous lesions are usually present[7]. In general, lesions of EM develop preferentially on the extremities and the *face*; target lesions favor the *upper extremities*, as does the entire eruption of EM[7,14,19]. The dorsal aspects of the hands and the forearms are the most frequently involved sites, but the palms, neck, face, and trunk are common locations as well (Fig. 20.2)[19]. Involvement of the legs is seen less frequently. EM lesions may also appear within areas of sunburn[7]. In addition, lesions tend to be grouped, especially on the elbows or knees.[7]

The Koebner phenomenon may be observed, with target lesions appearing within areas of cutaneous injury such as scratches[7] (see Fig. 20.1F) or as erythema and swelling of the proximal nail folds at sites of chronic self-trauma. The injury must precede the onset of the EM eruption because the Koebner phenomenon does not occur once the EM lesions have appeared.

Mucosal lesions

Severe mucosal involvement is characteristic of EM major. Mucosal involvement is usually absent in EM minor, and, when present, lesions are few in number and mildly symptomatic[3,7,12,13,19]. The primary mucosal lesions of EM are vesiculobullous and rapidly develop into painful erosions that involve the buccal mucosa and lips (Fig. 20.3), and less commonly the ocular and genital mucosae. On the lips, the erosions rapidly become covered by painful crusts. Erosions of the anogenital mucosa are often large and polycyclic with a moist base.

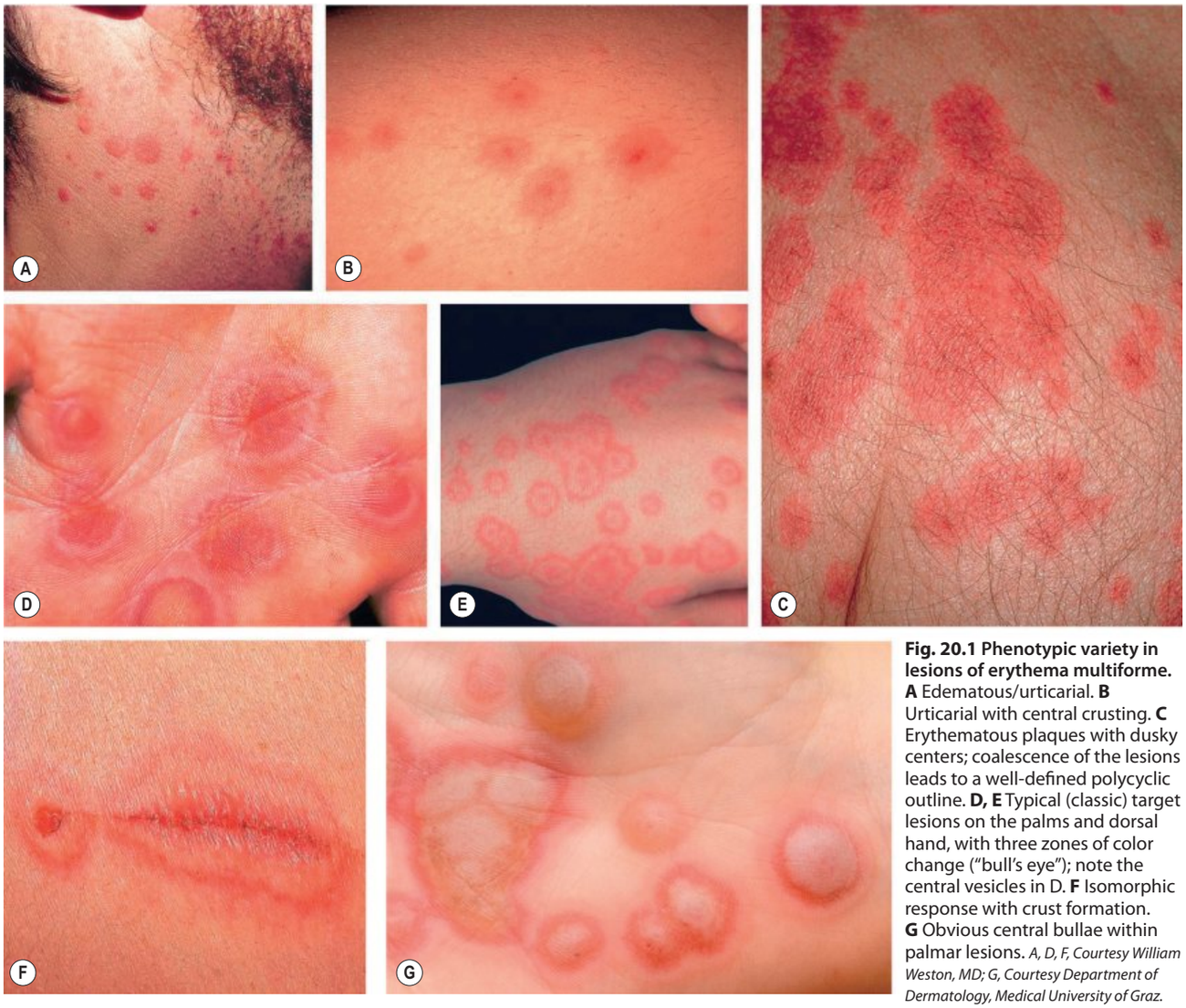


Fig. 20.1 Phenotypic variety in lesions of erythema multiforme. **A** Edematous/urticarial. **B** Urticarial with central crusting. **C** Erythematous plaques with dusky centers; coalescence of the lesions leads to a well-defined polycyclic outline. **D, E** Typical (classic) target lesions on the palms and dorsal hand, with three zones of color change ("bull's eye"); note the central vesicles in D. **F** Isomorphic response with crust formation. **G** Obvious central bullae within palmar lesions. *A, D, F, Courtesy William Weston, MD; G, Courtesy Department of Dermatology, Medical University of Graz.*



Fig. 20.2 Multiple lesions of erythema multiforme (EM) on the trunk. The dusky or crusted centers within the papules help to differentiate EM from a morbilliform drug eruption.



Fig. 20.3 Mucosal involvement in erythema multiforme major. A Typical target lesions are seen as well as serous crusting of the vermilion lips and eyelid margin. At the margin of the serous crusting of the lip, there are two zones of color with a polycyclic outline. **B** Erosions and hemorrhagic crusting of the lips in a child with the acro-mucosal variant associated with *Mycoplasma pneumoniae* infection, also referred to as MIRM (*Mycoplasma pneumoniae*-induced rash and mucositis) or RIME (reactive infectious mucocutaneous eruption). *B, Courtesy Julie V. Schaffer, MD.*

Systemic symptoms

Systemic symptoms are almost always present in EM major and absent or limited in EM minor. In EM major, the systemic symptoms that usually precede and accompany the skin lesions are fever and asthenia of varying degrees. Arthralgias with joint swelling have occasionally been described, as has pulmonary involvement resembling atypical pneumonia. Whether the latter is due to a pulmonary manifestation of EM versus an associated primary infection such as *Mycoplasma* pneumonia is unclear. Renal, hepatic, and hematologic abnormalities in the context of EM major are rare[20]. By integrating these four clinical criteria, a distinction can be made between EM minor, EM major, and SJS (see Table 20.1).

Natural history

In EM, almost all of the lesions appear within 24 hours and full development has occurred by 72 hours.[7,20] Pruritic or burning sensations within the lesions may be described. Individual lesions remain fixed at the same site for 7 days or longer[4,5,21].

For most individuals with EM, the episode lasts 2 weeks and heals without sequelae[7,20]; one possible rare exception is ocular damage in the setting of EM major, which may occur if adequate eye care is not promptly instituted. Occasionally, postinflammatory hyper- or hypopigmentation is seen. Patients with EM usually have an uncomplicated clinical course, although recurrences, in the case of HSV-associated EM, are quite common[7,20]. One recurrence each spring, as described by von Hebra, may occur[4]. Most individuals with recurrent HSV-associated EM have one or two episodes a year, with an exception being patients receiving immunosuppressive drugs[20,22,23]. The use of immunosuppressive agents such as oral corticosteroids may be associated with more frequent and longer episodes of EM[7,20]. These individuals may have five or six episodes per year or even almost continuous overlapping disease in which one attack has not completely resolved before another occurs. The incidence of secondary bacterial infections also increases in the setting of prolonged corticosteroid use[7,20]. Rarely, patients experience persistent EM with a months-long protracted course.

Pathology

EM is a clinicopathologic, not a purely histologic, diagnosis. Histologic findings are characteristic, but not specific, and are most useful for excluding entities in the differential diagnosis such as lupus erythematosus (LE) and vasculitis[7,20,22]. In EM, the keratinocyte is the target of the inflammatory insult, with apoptosis of individual or clusters of keratinocytes being the earliest pathologic finding (Fig. 20.4)[22]. As the process evolves, mild spongiosis and focal vacuolar degeneration of basal keratinocytes are observed. Superficial dermal edema and a perivascular infiltrate of lymphocytes with exocytosis into the epidermis are also seen.

Immunofluorescence findings are nonspecific[7]. Granular deposits of IgM and C3 around superficial blood vessels and focally at the dermal–epidermal junction have been described. Specific HSV antigens have been detected within keratinocytes by immunofluorescence, and HSV genomic DNA has been detected by PCR amplification of skin biopsy specimens[12,14].

Compared to SJS, the dermal inflammation component is more prominent in EM and the epidermal "necrolysis" component is more discrete[24]. Large areas of full-thickness epidermal necrosis are not seen in EM.

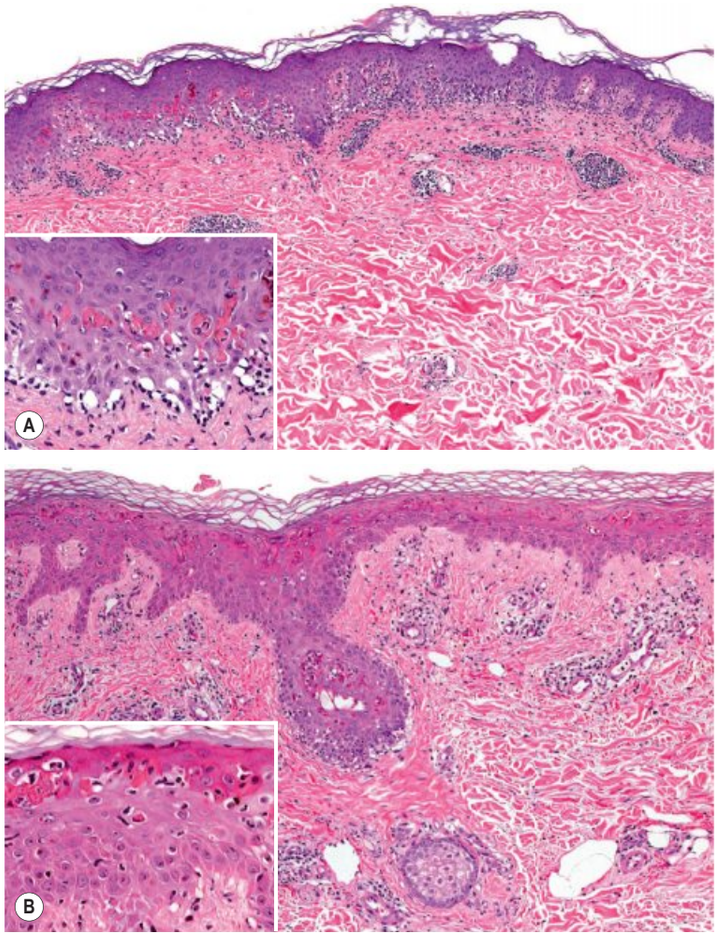


Fig. 20.4 Erythema multiforme – histopathologic features. A Early lesion – focal sites of apoptosis of keratinocytes with an interface dermatitis and vacuolar degeneration of the basal layer (inset). A perivascular lymphocytic infiltrate is also present. **B** Late lesion – more confluent necrosis of keratinocytes within the upper layers of the stratum spinosum (inset). The hair follicle still has evidence of an interface dermatitis. *Courtesy Lorenzo Cerroni, MD.*



Fig. 20.5 Acute annular urticaria (urticaria multiforme) in an infant misdiagnosed as erythema multiforme. These migratory, annular plaques are markedly edematous. Some of the lesions have an erythematous or dusky center while others have central clearing with two shades of peripheral rings. There are no crusts or blisters. The term "urticaria multiforme" has been used to describe these skin findings, which are often preceded by a viral or bacterial infection and accompanied by angioedema of the face, hands, and/or feet. *Courtesy Julie V. Schaffer, MD.*

COMPARISON OF URTICARIA AND ERYTHEMA MULTIFORME	
Urticaria	**Erythema multiforme**
Central zone is normal skin or transient duskiness*	Central zone is damaged skin (dusky, bullous, or crusted)
Individual lesions are transient, lasting <24 hours†	Individual lesions "fixed" for at least 7 days
New lesions appear daily	All lesions appear within first 72 hours
May be associated with swelling of face, hands, or feet (angioedema)	No edema

*May be referred to as urticaria multiforme.
†Can be documented by circling individual lesions with ink then observing over time.

Table 20.3 Comparison of urticaria and erythema multiforme.

Differential Diagnosis

Non-dermatologists often overdiagnose EM by labeling individuals with giant annular urticaria as having EM (Fig. 20.5)[9]. This is further highlighted by the term "urticaria multiforme", which represents a variant of urticaria that is often misdiagnosed as erythema multiforme or a serum sickness-like reaction in children[25]. This emphasizes the need to apply clinical criteria to distinguish EM from urticaria (Table 20.3)[7]. These include the presence of symmetrical fixed red papules or atypical papular target lesions, at least some of which evolve into typical target lesions. Particular attention should be given to the duration of individual lesions at a specific site and to epidermal damage in the center of the target lesions. EM papules are "fixed" at the same skin site for at least 7 days, whereas urticarial lesions last <24 hours at a particular site. The center of EM lesions demonstrates epithelial damage in the form of crusting or vesicles, whereas the center of giant urticaria is characterized by normal skin or erythema without epidermal damage. Administration of subcutaneous epinephrine (adrenaline) will clear urticaria within 20 minutes, but will not change EM lesions. Edema of the face, hands, and feet can be associated with urticaria, but is usually not observed in EM[7,9,20].

A number of other conditions can sometimes have "target-like" lesions and mimic EM, including fixed drug eruptions, Kawasaki disease, erythema annulare centrifugum, Sweet syndrome, and several forms of vasculitis[26]. A skin biopsy to exclude these entities is helpful. However, there is significant clinical and histologic overlap between EM and generalized bullous fixed drug eruption. The total number of lesions is helpful, especially when there are hundreds, but it is also important to try to determine the number of lesions present in the initial episode (i.e. fewer lesions in fixed drug eruption).

Recurrent EM during childhood may mimic polymorphous light eruption or juvenile spring eruption in that it may be sun-induced and develop with the first significant sun exposure in the spring[27]. In patients with systemic LE, occasional individual lesions can mimic true target lesions of EM, but other lesions characteristic of systemic LE are usually present[7]. That said, patients with Rowell syndrome may only have EM-like lesions as can children with Kawasaki disease. Early lesions of vasculitis, particularly urticarial vasculitis, may mimic target lesions of EM. Histologic examination assists in distinction; additional clues include an elevated ESR, autoantibodies, and low serum complement levels[7].

Whether *Mycoplasma pneumoniae*-induced rash and mucositis (MIRM) is a distinct disorder or within the spectrum of EM major or SJS remains a matter of debate (Table 20.4). More recently, as additional bacterial and viral triggers were identified, the term reactive infectious mucocutaneous eruption (RIME) was proposed[28].

Treatment

Therapeutic options include topical and systemic treatment of the acute eruption as well as prophylactic treatment of recurrent disease. Topical therapy includes topical antiseptics for eroded skin lesions and antiseptic/antihistamine rinses and local anesthetic solutions for oral lesions (see Ch. 72). Administration of topical ophthalmic preparations should be done in conjunction with an ophthalmologist.

There are no double-blind or open trials of systemic therapies for the acute episode of EM[7,20]. When a precipitating factor can be identified (e.g. HSV, *M. pneumoniae*), specific therapy should be instituted; in the case of HSV, this represents chronic suppressive antiviral therapy



KEY FEATURES OF *MYCOPLASMA PNEUMONIAE*-INDUCED RASH AND MUCOSITIS (MIRM)/ REACTIVE INFECTIOUS MUCOCUTANEOUS ERUPTION (RIME)



Children and adolescents >> adults
Prodromal symptoms (cough, malaise, fever) precede the eruptions by approximately one week
Predominance of mucosal involvement • Severe mucositis • Typically ≥2 mucosal sites (e.g. oral, ocular, anogenital, nasal) Absent or sparse polymorphic cutaneous involvement (<10% body surface area) • Typically vesiculobullous or atypical target lesions • Occasionally subcorneal pustules
For MIRM, clinical and/or laboratory evidence of *Mycoplasma pneumoniae* infection • PCR of pharyngeal swab • IgM and IgG serologies* For RIME, clinical and/or laboratory evidence of triggering infection, most often respiratory (see legend)
Often benign clinical course with excellent prognosis (<5% require intensive care but up to 10% may develop ocular sequelae) Supportive care and pain management similar to SJS with systemic antimicrobials if infectious trigger Systemic corticosteroids (e.g. 5–7 days of prednisone 1 mg/kg/day) – optional if severe†
*Serial measurements may be required to detect elevated IgM titers and are required to detect four-fold increase in IgG titers; enzyme-linked immunoabsorbent spot (ELISpot) assay of *Mycoplasma*-specific IgM antibody-secreting cells (ASCs) can improve diagnostic specificity and sensitivity. †Also case reports of etanercept, IVIg, and cyclosporine.

Table 20.4 Key features of *Mycoplasma pneumoniae*-induced rash and mucositis (MIRM)/reactive infectious mucocutaneous eruption (RIME). The terms MIRM then RIME were proposed to distinguish these infection-related eruptions from EM major and SJS/TEN. Prior to this distinction, patients were usually diagnosed as having incomplete, atypical or acro-mucosal SJS, *Mycoplasma*-associated EM major, *Mycoplasma*-associated SJS, Fuchs syndrome, or *Mycoplasma pneumoniae*-associated mucositis. Because other bacterial (e.g. *Chlamydophila pneumoniae*) and viral infections, especially respiratory (e.g. adenovirus, enteroviruses, human metapneumovirus, influenza B, parainfluenza virus type 2, rhinovirus, SARS-CoV-2), have been associated with similar mucocutaneous eruptions, this led to the term RIME. *Photographs: Courtesy Katherine G. Ligtenberg, MD, Jean L. Bolognia, MD, and Julie V. Schaffer, MD.*

(see below). As a rule, antiviral therapy has minimal impact if given after the appearance of the acute episode of EM. In most cases of EM, especially EM minor, symptomatic treatment will suffice. Oral antihistamines for 3 or 4 days may reduce the stinging and burning of the skin. In severe EM with functional impairment, early therapy with systemic corticosteroids (e.g. prednisone [0.5–1 mg/kg/day for 3–5 days] or pulse methylprednisolone [20 mg/kg/day for 3 days]) should be considered, despite the absence of controlled studies and the long-existing controversy regarding increasing the risk of infectious complications[29].

In individuals with HSV-associated EM with frequent recurrences, prophylaxis for at least 6 months with oral valacyclovir (500–1000 mg/day, with dose depending upon frequency of recurrences), famciclovir (250 mg twice daily), or acyclovir (10 mg/kg/day in divided doses) should be considered. A double-blind, placebo-controlled study in young adults with EM demonstrated the efficacy of acyclovir prophylaxis[23]. In addition to reducing the frequency of recurrences, occasionally the beneficial effect can continue even after the antiviral drug is discontinued. In non-responsive patients, the dose of the medication may be doubled, or a substitution made of the antiviral drug. However, as stated previously, treatment with acyclovir or valacyclovir after symptoms appear is ineffective[20]. Obviously, in those patients in whom EM is precipitated by factors other than reactivation of HSV, antivirals will be of no benefit.

In patients with recurrent EM that is resistant to prophylactic antiviral therapy, especially severe cases, several therapeutic approaches have been described; however, none have been validated by controlled trials and none have been consistently effective or free of side effects. Among these are: azathioprine (100 mg/day for several months), prednisone (0.5 mg/kg/day for several months), thalidomide, dapsone, cyclosporine, mycophenolate mofetil, and PUVA[20,30–33]. JAK inhibitors may be considered for persistent EM.

STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Synonym: ■ Toxic epidermal necrolysis – Lyell syndrome

Key features

- Prodrome of upper respiratory tract symptoms, fever, and painful skin
- Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two rare, potentially fatal, adverse cutaneous drug reactions of differing severity, characterized by mucocutaneous tenderness and erythema as well as extensive exfoliation
- SJS is characterized by <10% body surface area of epidermal detachment, SJS/TEN overlap by 10%–30%, and TEN by >30%
- The medications most frequently incriminated are allopurinol, nonsteroidal anti-inflammatory drugs, antibiotics, and aromatic anticonvulsants; TEN and SJS usually occur 7–21 days after initiation of the responsible drug
- The average mortality rate is 5% for SJS and 15%–25% for TEN; the mortality rates are often higher in the elderly and those with a very large surface area of epidermal detachment
- Exfoliation is due to extensive death of keratinocytes via apoptosis; the latter is mediated via the cytotoxic secretory protein granulysin and interaction of the death receptor–ligand pair Fas–FasL
- Optimal medical management of SJS and TEN requires early diagnosis, immediate discontinuation of the causative drug(s), and rapid initiation of supportive care
- Additional therapies include TNF inhibitors (e.g. etanercept), IVIg, cyclosporine, and pulse corticosteroids, but to date there is no consensus as to the most effective treatment

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute, and life-threatening mucocutaneous diseases that are nearly always drug-related. They are a consequence of extensive keratinocyte cell death that results in the separation of significant areas of skin at the dermal–epidermal junction, producing the appearance of scalded skin. This extensive cell death also results in mucous membrane detachment, and it contributes to the characteristic symptoms of SJS and TEN, which include: high fever, moderate to severe skin pain, anxiety, and asthenia. The disease runs an unpredictable course. An initially benign-appearing dermatosis can progress rapidly, and once overt skin detachment has occurred, it is difficult to determine when it will end. Several studies have addressed the clinical signs of SJS and TEN, and there is now a framework of diagnostic criteria. Mortality risk can be calculated by applying a severity-of-illness score specifically developed for predicting the clinical outcome of TEN (SCORTEN; see below).

As prognosis is correlated with the speed at which the culprit drug is identified and withdrawn, it is crucial to establish the correct clinical diagnosis rapidly, so the causal drug(s) can be discontinued and appropriate medical treatment begun as soon as possible. Although TEN, and especially SJS, were historically considered to be part of a spectrum of diseases that included EM major (all of which have clinically similar mucosal lesions), these disorders should now be distinguished, as their cause, management, and/or prognosis are usually distinct (see Table 20.1). SJS and TEN should also be distinguished from dermatoses such as staphylococcal scalded skin syndrome, generalized bullous fixed drug eruption, drug-induced linear IgA bullous dermatosis, toxic erythema of chemotherapy, and acute generalized exanthematous pustulosis, as their management and prognosis can vary significantly.

High-quality supportive treatment, ideally in intensive care units with modern equipment and trained nursing staff, is the current standard of care and can improve outcome. To date, one randomized prospective trial has been conducted with 96 patients in which etanercept was compared to prednisolone (see below). The lack of additional large prospective, controlled clinical studies can be explained in part by the low incidence of SJS and TEN as well as their life-threatening potential which make randomized clinical trials difficult to perform.

History

In 1922, two US physicians, Stevens and Johnson, described an acute mucocutaneous syndrome in two young boys. The condition was characterized by severe purulent conjunctivitis, severe stomatitis with extensive mucosal necrosis, and "EM-like" cutaneous lesions. It became known as Stevens–Johnson syndrome (SJS) and was recognized as a severe mucocutaneous disease with a prolonged course and occasional fatalities[2,3]. SJS was later designated as EM major by Bernard Thomas in 1950.[6] However, recent clinical investigations have made it clear that the term "EM major" should not be used to describe SJS as they are distinct disorders (see Table 20.1)[2,3].

In 1956, Alan Lyell described four patients with an eruption "resembling scalding of the skin objectively and subjectively", which he called "toxic epidermal necrolysis". "Toxic" referred to toxemia – circulation of a toxin – which was thought to be responsible for the constitutional symptoms and epidermal necrosis. Lyell coined the term "necrolysis" by combining the key clinical feature "epidermolysis" with the characteristic histopathologic feature "necrosis". He also described an attack on the mucous membranes as part of the syndrome, and noted that there was very little inflammation in the dermis, a feature that was later referred to as "dermal silence"[34]. This feature contrasted with the obvious inflammatory infiltrate of other blistering disorders such as EM, dermatitis herpetiformis, and bullous pemphigoid. TEN was considered at the time to be a cutaneous reaction pattern to multiple stimuli, including drugs (e.g. sulfonamides) and microbes (e.g. *Staphylococcus*)[35].

The description of a subgranular epidermal split in neonatal mice following exposure to phage group II *S. aureus*, the subsequent discovery of a new staphylococcal exotoxin called epidermolytic toxin, and the absence of overt keratinocyte necrosis led to the distinction between TEN and what would come to be known as "staphylococcal scalded skin syndrome" (SSSS; see Ch. 74)[36]. It should be noted here that one of Lyell's original patients actually represented SSSS, and although by that time he had already noted the histologic differences between TEN and SSSS, they were attributed to different degrees of injury.

As more patients with TEN were reported in the years following Lyell's treatise, it became clear that certain drugs such as sulfonamides, pyrazolones (e.g. phenylbutazone), barbiturates, and aromatic anticonvulsants were principally associated with TEN. At the same time, drugs were increasingly being incriminated as a cause of EM associated with severe stomatitis. Hence, EM epidermal type (as defined by Orfanos et al.[37] in the mid 1970s), SJS and TEN were, at the time, considered to be part of a continuous spectrum of cutaneous reactions. It was clear, however, that HSV was the major cause of EM, and that this virus was not associated with cases of TEN. In the late 1990s, the group of Jean-Claude Roujeau clarified this issue by providing clinical evidence that EM and SJS were clinically distinct disorders with different causes and prognoses[3]. Increasingly, SJS and TEN are considered to be two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions, differing by the extent of skin detachment (see Table 20.1).

Epidemiology

SJS and TEN are rare diseases that affect women more often than men. Certain patient groups have an increased risk of developing SJS/TEN, including those who metabolize drugs at a decreased rate (slow acetylator genotypes), are immunocompromised (e.g. HIV infection), are undergoing radiotherapy while concomitantly receiving anticonvulsants, or have specific human leukocyte antigen (HLA) alleles (Table 20.5; see Table 21.3). Examples of the latter are HLA-B*15:02 in Asians and East Indians who are exposed to carbamazepine and HLA-B*58:01 in Han Chinese exposed to allopurinol. Consequently, the FDA recently recommended genotyping of all Asians for the allele HLA-B*15:02 prior to the administration of carbamazepine. In Europe, ~5% of the patients with SJS/TEN are infected with HIV[43].

STEVENS–JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN): EPIDEMIOLOGY AND RISK FACTORS	
Annual incidence	1.2–6 per million (SJS)
	0.4–1.2 per million (TEN)
Ratio women : men	1.5 : 1
Risk factors	Slow acetylator genotypes
	Immunosuppression (e.g. HIV infection, lymphoma)
	Concomitant administration of radiotherapy and aromatic anticonvulsants (most commonly, those with brain tumors)
	HLA-B*15:02 – Asians (in particular Han Chinese, Thai, Malaysian populations)† and East Indians exposed to carbamazepine
	HLA-B*15:02 – Taiwanese/lamotrigine
	HLA-B*15:02 – Han Chinese/phenytoin
	HLA-A*31:01 – Europeans/carbamazepine
	HLA-B*58:01 – Han Chinese/allopurinol

†The background prevalence of HLA-B*15:02 varies from 4% to 15% in affected populations but is extremely rare in Northern Europeans (<0.01%).

Table 20.5 Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN): epidemiology and risk factors. Table 21.3 contains additional HLA associations. *Data from refs 38–42.*

Death rates reported in large case series in which only supportive therapy was used are quite variable, and it is known that these rates are heavily dependent on factors such as patient age and extent of epidermal detachment. In the past, mortality rates were reported to be ~10% for SJS, 30% for SJS/TEN, and 50% for TEN[43,44], but these rates have decreased over the past few decades. A USA-based study that analyzed nationwide inpatient records from 2009 to 2012 reported a mean mortality of 5%, 19%, and 15% for SJS, SJS/TEN, and TEN, respectively[45]. The mortality risk is lower in children who have TEN.

Use of medications is reported in over 95% of patients with TEN. A strong association between drug ingestion and development of the cutaneous eruption is observed in 80% of cases. Other rare causes include infections and immunizations. The literature reflects a less clear relationship between drugs and SJS, as only 50% of reported SJS cases are attributed to drug exposure. This is certainly an underestimation, however, and most likely is due, in part, to the confusion that previously existed regarding the diagnostic distinction between SJS and EM, especially EM major.

More than 100 drugs have been identified to date as being associated with SJS/TEN. The most frequently implicated drugs are listed in Table 20.6 and consist primarily of allopurinol, antibiotics, nonsteroidal anti-inflammatory drugs, and aromatic anticonvulsants. Among the antibiotics, sulfonamides are the most strongly associated with SJS/TEN; other antimicrobials include aminopenicillins, quinolones, cephalosporins, and tetracyclines as well as antiretrovirals. In general, the risk of developing SJS/TEN is reported to be highest during the initial week(s) of therapy. For the aromatic anticonvulsants, the risk is greatest during the first two months of treatment[46]. Furthermore, drugs with long half-lives are more likely to cause drug reactions and a fatal outcome than those with short half-lives, even if they are chemically related[47].

Pathogenesis

To date, the precise sequence of molecular and cellular events that lead to the development of SJS/TEN is only partially understood. The proposed pathogenesis must take into account the rarity of the reaction and the involvement of specific types of drugs.

Compelling evidence suggests that SJS/TEN is associated with an impaired capacity to detoxify reactive intermediate drug metabolites. It is thought to be initiated by an immune response to an antigenic complex formed by the reaction of such metabolites with certain host

MEDICATIONS MOST FREQUENTLY ASSOCIATED WITH STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS
• Allopurinol
• Aminopenicillins
• Amithiozone (thioacetazone)*,†
• Antiretroviral drugs, especially NNRTIs (e.g. nevirapine, efavirenz, etravirine)
• Barbiturates
• Carbamazepine
• Cephalosporins
• Chlormezanone*,‡
• Immune checkpoint inhibitors (e.g. ipilimumab, nivolumab)¶
• Phenytoin anticonvulsants
• Lamotrigine (risk may be increased when co-administered with valproic acid)
• Phenylbutazone*,§
• Piroxicam and other NSAIDs (e.g. diclofenac)
• Quinolones
• Sulfonamide antibiotics, including sulfamethoxazole‖, sulfadiazine*,†
• Sulfasalazine
*Not available in the US.
†Antibacterial.
‡Sedative/hypnotic.
¶SJS/TEN-like eruptions may also occur with a delayed onset and favorable response to systemic corticosteroids.
§Nonsteroidal anti-inflammatory drug.
‖Usually in combination with trimethoprim.

Table 20.6 Medications most frequently associated with Stevens–Johnson syndrome and toxic epidermal necrolysis. NNRTIs, non-nucleoside reverse transcriptase inhibitors. For a complete updated list of drugs associated with SJS and TEN, refer to: Shear N. *Litt´s Drug Eruption and Reaction Manual*, 28th edn. London: CRC Press, 2022.

tissues[44,48–50]. Currently, three different concepts exist regarding how the neoantigenic drug–tissue complex is formed: (1) covalent binding of the drug to a cellular peptide (hapten/pro-hapten concept); (2) non-covalent, direct interaction of the drug with a specific MHC class I molecule or T cell receptor (p-i concept); and (3) presentation of an altered-self repertoire by direct drug–MHC I molecule interaction (altered peptide concept). Whereas the well-known hapten model is less likely to be HLA-restricted, the other two concepts favor specific HLA phenotypes. According to these models, drugs directly bind to specific HLA molecules and/or T cell receptors without being processed by an antigen-presenting cell. In the p-i concept, the mere pharmacologic interaction of certain drugs with immune receptors is sufficient to elicit a drug hypersensitivity reaction[51]. In contrast, more recent reports have shown that the drugs abacavir and carbamazepine modify the HLA-peptide repertoire resulting in enhanced presentation of self-peptides and autoimmune reactivity (altered peptide model)[52,53]. Of note, because of the increased risk of DRESS, patients are often screened for HLA-B*57:01 prior to receiving abacavir (see Table 21.3).

In line with the concept of HLA-restricted drug presentation are reports of specific drug-related HLA alleles as major susceptibility genes for the development of SJS and TEN (see Table 20.5)[38,39,54]. Notably, in Taiwan, HLA-B*15:02 screening prior to administration of carbamazepine decreased the risk of drug-induced SJS/TEN[55]. In addition to the alleles listed in Table 20.5, the HLA-DQB1*06:01 allele has been reported in a significantly disproportionate number of White patients with SJS *and* ocular complications, suggesting that this allele may confer an increased risk for this specific clinical phenotype[56].

Cytotoxic T cells expressing the skin-homing receptor, cutaneous lymphocyte-associated antigen (CLA), are seen early in the development of cutaneous lesions[57]. These are likely to be drug-specific cytotoxic T cells[58]. Important cytokines such as interleukin (IL)-6, TNF, interferon-γ, IL-18, and Fas ligand (FasL) are also present in the lesional epidermis and/or blister fluid of patients with TEN, and their actions could explain some of the constitutional symptoms of TEN as well as the frequently observed discrepancy between the extent of epidermal damage and the paucity of the inflammatory infiltrate[59,60]. Lastly, the typical interval between the onset of drug therapy and SJS/TEN is between 1 and 3 weeks, suggesting a period of sensitization and providing further support for the role of the immune system in disease pathogenesis. This period ("memory") is considerably shortened in patients who are unfortunately re-exposed to a drug that previously resulted in SJS or TEN.

The tissue damage described by pathologists as epidermal necrolysis is a reflection of massive keratinocyte cell death via apoptosis[61]. The apoptosis of individual keratinocytes is a hallmark of the early stages of SJS and TEN, and it is the first clear morphologic sign of specific tissue damage. The more classic histologic image of extensive epidermal "necrolysis" is, in fact, the aftermath of keratinocyte apoptosis. Indeed, the apoptotic state of cells is transient in nature, and it is followed by necrosis if the apoptotic cells are not rapidly phagocytosed. In SJS and TEN, within hours keratinocyte apoptosis becomes very abundant in lesional skin, thus rapidly overwhelming the phagocytic capacity of the affected skin. Over a period of hours to days, these apoptotic keratinocytes become necrotic and lose their cohesion to adjacent keratinocytes as well as the basement membrane. The entire epidermis then loses viability, creating the familiar histologic image of full-thickness epidermal necrolysis.

Fas ligand (FasL, CD95L), a member of the TNF family of cytokines, has the ability to induce apoptosis by binding to its specific cell surface receptor, the Fas (CD95, Apo-1) death receptor[62]. Such death receptors function as cell surface sensors that detect the presence of specific extracellular death signals and rapidly trigger cellular destruction by apoptosis (Fig. 20.6, pathway A). Notably, keratinocyte apoptosis within lesional skin of patients with TEN is associated with highly increased expression of keratinocyte FasL, together with conserved levels of keratinocyte Fas expression[59,62–64]. Overlaying cryostat sections of lesional skin with Fas-sensitive cells as targets has demonstrated that keratinocyte FasL is cytolytically active in TEN; cytolysis can be prevented by monoclonal antibodies that block the interaction of Fas and FasL.

Subsequently, the cytotoxic molecule granulysin was shown to play a role in the keratinocyte apoptosis observed in SJS/TEN (see Fig. 20.6D)[65]. High concentrations of granulysin, a secreted, cationic, cytolytic protein produced by cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, and natural killer T (NKT) cells, were found in blister fluid from patients with SJS/TEN. Moreover, injection of recombinant granulysin into mouse skin induced epidermal necrolysis and an inflammatory cell infiltrate. More recently, it was demonstrated that necroptosis of keratinocytes (a form of programmed necrosis) can be triggered by the interaction of annexin A1 and formyl peptide receptor 1 (FPR1) and this may contribute to the pathogenesis of SJS/TEN (see Fig. 20.6C).[66] In SJS/TEN patients, data suggest that exposure to the causative drug induces annexin A1 secretion from monocytes. Annexin A1 in turn binds to FPR1 and induces FPR1 expression in keratinocytes, resulting in cell death via a necroptosis pathway. Lastly, the perforin/granzyme pathway can also induce keratinocyte apoptosis (see Fig. 20.6B). Following the binding of CTLs and NK cells to their target cells, they secrete granules containing perforin and granzyme B. Perforin allows granzyme B to transverse the cell membrane and activate the intrinsic apoptotic pathway[67]. Of interest, circulating levels of IL-15 appear to be associated with the severity and mortality rate of SJS/TEN[68].

In summary, the current model for the pathogenesis of SJS/TEN is as follows: upon exposure to certain types of drugs (see Table 20.6), an individual with particular predisposing factors (see Table 20.5) mounts a specific immune reaction to the drug or one of its metabolites. As a result of an interplay of cell types and cytokines that remains to be totally defined, there is a strong expression of the cytolytic molecule FasL on keratinocytes as well as secretion of granulysin from CTLs, NK cells and NKT cells and annexin A1 from monocytes. This leads to FasL-, granzyme B-, and granulysin-mediated apoptosis and/or annexin-dependent necroptosis of keratinocytes and subsequent epidermal necrosis and detachment (see Fig. 20.6).

Clinical Features

Initial symptoms of both TEN and SJS can be fever, stinging eyes, and pain upon swallowing, any of which can precede cutaneous manifestations by 1 to 3 days. Skin lesions tend to appear first on the trunk, spreading to the neck, face, and proximal upper extremities. The distal portions of the arms as well as the legs are relatively spared, but the palms and soles can be an early site of involvement. Erythema and erosions of the buccal, ocular, and genital mucosae are present in >90% of patients (Fig. 20.7). The epithelium of the respiratory tract is involved in 25% of patients with TEN, and gastrointestinal lesions

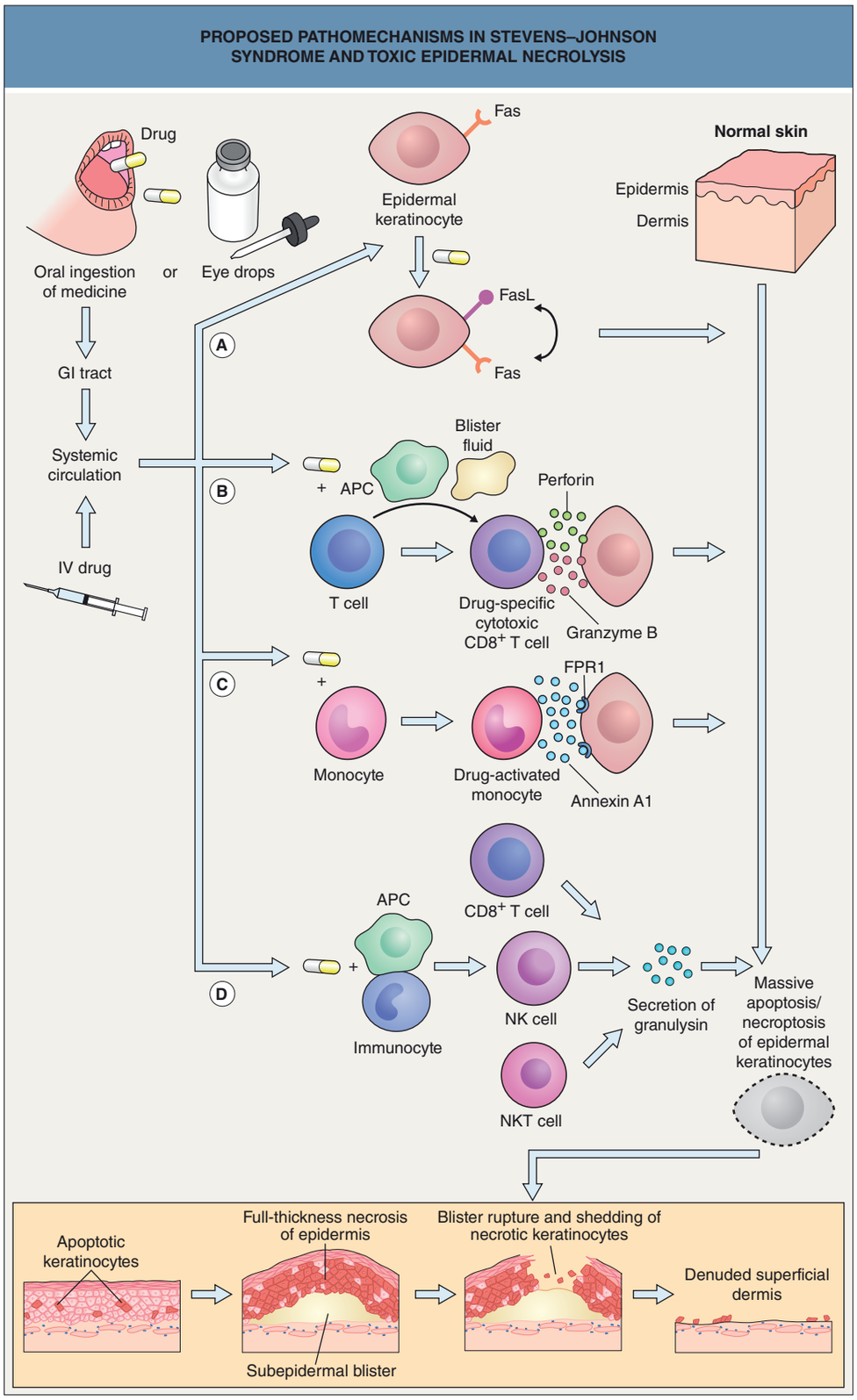


Fig. 20.6 Proposed pathomechanisms to explain apoptosis of epidermal keratinocytes in Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). A number of medications can trigger widespread apoptosis of epidermal keratinocytes in individuals with SJS or TEN, leading to skin blistering and denudation. Several theories have been proposed for this condition: (**A**) the medication might induce upregulation of FasL by keratinocytes constitutively expressing Fas, leading to a death receptor-mediated apoptotic pathway; (**B**) the drug might interact with MHC class I-expressing cells and then drug-specific $CD8^+$ cytotoxic T cells accumulate within epidermal blisters, releasing perforin and granzyme B that kill keratinocytes; (**C**) drug-activated monocytes could secrete annexin A1, which induces necroptosis in keratinocytes via binding to formyl peptide receptor 1 (FPR1); and (**D**) the drug may also trigger the activation of $CD8^+$ T cells, NK cells and NKT cells to secrete granulysin, with keratinocyte death not requiring cell contact. IVIg contains antibodies against Fas that can block the binding of FasL to Fas. FPR1, formyl peptide receptor 1. *Adapted from Nickoloff BJ. Saving the skin from drug-induced detachment. Nat Med 2008;14:1311–13, with permission of Nature Publishing Group.*

(e.g. esophagitis, diarrhea) can also occur[69]. The skin lesions are usually tender, and mucosal erosions are very painful. Additional systemic manifestations include fever, lymphadenopathy, hepatitis, cytopenias, and cholestasis due to vanishing bile duct syndrome.

The morphology of the skin lesions has been studied in detail. First, lesions appear as erythematous, dusky red, or purpuric *macules* of irregular size and shape, and they have a tendency to coalesce (Fig. 20.8). At this stage, and in the presence of mucosal involvement and tenderness, the risk of rapid progression to SJS or TEN should be strongly suspected. In the absence of spontaneous epidermal detachment, a Nikolsky sign should be sought by exerting tangential mechanical pressure with a finger on several erythematous zones. This sign is considered positive if dermal–epidermal cleavage is induced. In some patients, the macular lesions observed at the onset can have a dusky center, giving them a target-like appearance. However, such lesions lack the three concentric rings characteristic of typical target lesions (as originally described by Hebra) and are not papular as in atypical target lesions of EM.

As the epidermal involvement progresses toward full-thickness necrosis, the dusky red macular lesions take on a characteristic gray hue. This process can be very rapid (hours), or take several days.





Fig. 20.7 Mucosal involvement in Stevens–Johnson syndrome. A Erythema and conjunctival erosions. **B** Erosions of the genital mucosa.



Fig. 20.8 Cutaneous features of toxic epidermal necrolysis (TEN). Characteristic dusky red color of the early macular eruption in TEN. Lesions with this color often progress to full-blown necrolytic lesions with dermal–epidermal detachment.

The necrotic epidermis then detaches from the underlying dermis, and fluid fills the space between the dermis and the epidermis, giving rise to bulla formation. The blisters have special features: they break easily (flaccid) and can be extended sideways by slight pressure of the thumb as more necrotic epidermis is displaced laterally (Asboe–Hansen sign). The skin resembles wet cigarette paper as it is pulled away by minimal trauma, often revealing large areas of raw and bleeding dermis, which is referred to as "scalding" (Fig. 20.9). These patients must therefore be handled with extreme care. Tense blisters are usually seen only on the palmoplantar surfaces, where the epidermis is thicker and, therefore, more resistant to mild trauma.

When evaluating such patients, the extent of necrolysis constitutes a major prognostic factor. The rules characteristically used to evaluate the surface area of thermal burns are appropriate for this purpose (see Ch. 88). Experience has shown that the extent of skin detachment is easily overestimated. Measurements should include detached and detachable epidermis (positive Nikolsky sign) but not purely erythematous areas (negative Nikolsky sign)[2]. The extent of skin detachment allows classification of the patient into one of three groups (Fig. 20.10; see Table 20.1):

- SJS: <10% of body surface area (BSA)
- SJS/TEN overlap (an intermediate category): 10%–30% of BSA (Fig. 20.11)
- TEN: >30% of BSA.

Mucosal erosions are present in >90% of patients (see above). Patients may describe photophobia and painful micturition.

It is also important to distinguish between SJS and EM, which are now considered to be different illnesses with different prognoses (see EM History)[3]. Their histologic features are similar and, therefore, not helpful in distinguishing between the two diseases. Differentiation is based primarily on clinical characteristics, especially the appearance of the target lesions and their distribution. To retain the diagnosis of EM, typical target lesions need to exist, whereas SJS should be considered if target lesions are atypical (see Table 20.1). Unfortunately, criteria for predicting which patients with SJS are likely to progress to TEN are currently unavailable. Recently, a case report form for SJS/TEN has been created by an NIH working group to help standardize the collection of patient information[70].

In TEN, factors correlated with poor outcome include increasing age and extent of epidermal detachment. In addition, the number of medications, elevation of serum urea, creatinine and glucose levels, neutropenia, lymphopenia, and thrombocytopenia have been statistically linked to poor outcome. Late withdrawal of the causative drug is also associated with a less favorable outcome. It has been estimated that prompt withdrawal of the offending drug reduces the risk of death by 30% per day[47]. SCORTEN is a severity-of-illness score for TEN, in which seven parameters with equal weight have been integrated to predict outcome (Table 20.7)[71]. However, one study suggested that it may underestimate mortality risk[73].

In 2019, a second mortality prediction model was introduced – the ABCD-10 score (*a*ge ≥50 years [1 point], serum *b*icarbonate level <20 mmol/l [1 point], active *c*ancer [2 points], *d*ialysis prior to admission [3 points], and epidermal detachment >*10%* body surface area [1 point]). Dialysis represented the strongest predictor of in-hospital mortality, but overall the predictability of the ABCD-10 score did not differ significantly from SCORTEN and needs further validation[72]. Recently, a cohort study involving 196 Asian patients suggested that SCORTEN was superior in predicting mortality rates when compared to ABCD-10[74].

On average, death occurs in every third patient with TEN, and it is mainly due to infections (*S. aureus* and *Pseudomonas aeruginosa*). Massive transepidermal fluid loss associated with electrolyte imbalance, inhibition of insulin secretion, insulin resistance, and onset of a hypercatabolic state can also be contributive factors. All these complications of TEN (that can also be observed in SJS) are best managed in intensive care units. They can unfortunately culminate in adult respiratory distress syndrome and multiple organ failure despite adequate supportive therapy.

Healing of areas of detached epidermis through re-epithelialization usually starts within days, and it is complete in most cases within 3 weeks. This process results from proliferation and migration of keratinocytes from "reservoir" sites, such as healthy epidermis surrounding denuded areas and hair follicles within the areas of detachment. Due to this conserved capacity for re-epithelialization, skin grafting is not required in SJS or TEN. Unfortunately, however, healing can be imperfect, and survivors may have both ocular (symblepharon, conjunctival synechiae, entropion, ingrowth of eyelashes) and cutaneous sequelae (scarring, dyspigmentation, eruptive melanocytic nevi), as well



Fig. 20.9 Clinical features of toxic epidermal necrolysis (TEN). A Detachment of large sheets of necrolytic epidermis (>30% body surface area), leading to extensive areas of denuded skin. A few intact bullae are still present. **B** Extensive symmetric hemorrhagic crusting of the face with areas of denudation. **C** Epidermal detachment of palmar skin. **D** Note the rolled and folded sheets of detached epidermis at the edge of denuded skin in addition to widespread erythema and intact bullae. *D, Courtesy Luis Requena, MD.*

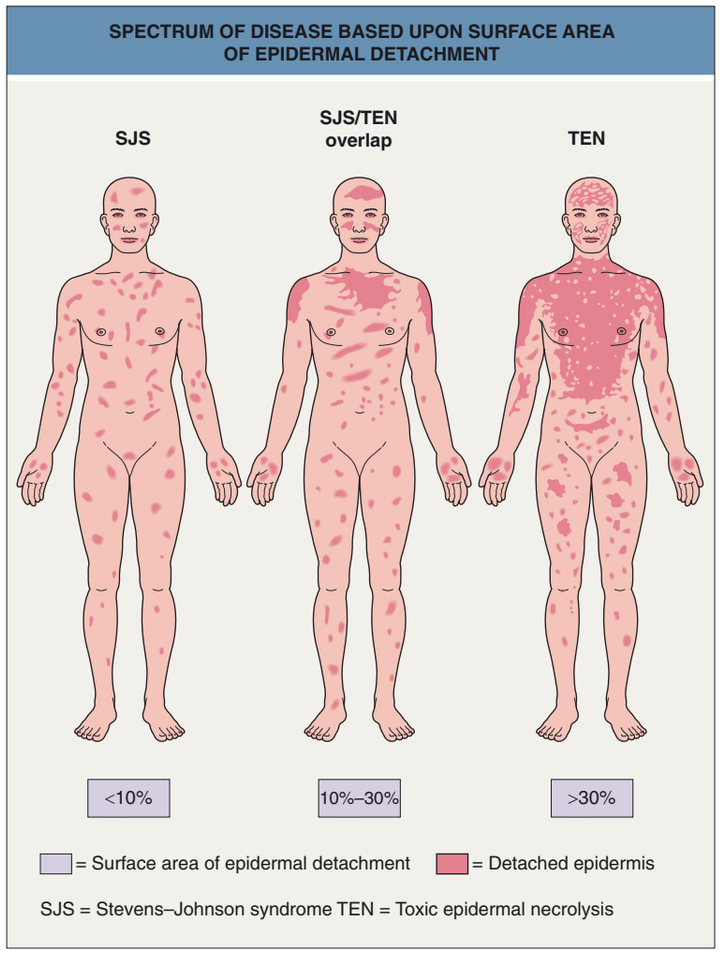


Fig. 20.10 Spectrum of disease based upon surface area of epidermal detachment.

as persistent erosions of the mucous membranes, urethral stenosis, phimosis, vaginal synechiae and stenosis with dyspareunia or hematocolpos, nail dystrophy, and diffuse hair loss (Fig. 20.12). These can often be minimized by optimizing skin care (see below), but, in TEN, up to 35% of survivors can have ocular symptoms ranging from sicca syndrome to blindness[44]. While amniotic membranes can be used acutely, scleral lenses (e.g. PROSE) assist in long-term care. Hypogeusia, dysphagia, progressive membranous glomerulonephritis, depression, and post-traumatic stress disorder represent additional sequelae.

Identification of the offending drug is an important and difficult task, but it should be among the first priorities. As noted previously, delayed withdrawal of the causative drug(s) is associated with increased mortality. Currently, there is no reliable *in vitro* test for the rapid identification of causative drugs. Patch testing shows weak sensitivity in SJS/TEN and is not appropriate for identification purposes; re-exposing the patient to the proposed causative drug is obviously not an acceptable option in severe drug reactions. The clinician, therefore, has to rely on previously reported associations and determine the probability (unlikely, possible, plausible, probable, very probable) for each medication based on the intrinsic ability of a particular drug to cause SJS/TEN (see Table 20.6 and reference therein) and extrinsic factors such as the initiation of a given medication with respect to the onset of SJS/TEN. SJS and TEN usually occur 7–21 days after initiation of the causative drug if it is the first exposure to the drug, but can occur within 2 days in the case of re-exposure to a drug that previously caused SJS or TEN. In general, the medication list of patients with SJS and TEN should be reduced to a strict minimum, appropriate substitutions made, and drugs with short half-lives favored. In an attempt to identify the culprit drug, ALDEN (algorithm of drug causality for epidermal necrolysis) and other causality assessment tools (CATs) have been developed which consider factors such as drug administration before and during disease progression, medication notoriety, and previous adverse reactions[75]. Unfortunately, available CATs, including ALDEN, have demonstrated poor reliability and validity[76].

Pathology

Histopathologic examination of lesional skin is a very useful tool for confirming the diagnosis of SJS and TEN, as the morphologic findings are distinct from those observed in SSSS (subcorneal blister with cleavage located in the granular layer of the epidermis) and acute generalized exanthematous pustulosis (AGEP; a neutrophil-rich infiltrate, superficial epidermal pustules and spongiosis, but no full-thickness epidermal necrolysis). Immediate analysis of frozen cryostat sections may be sufficient for this purpose.

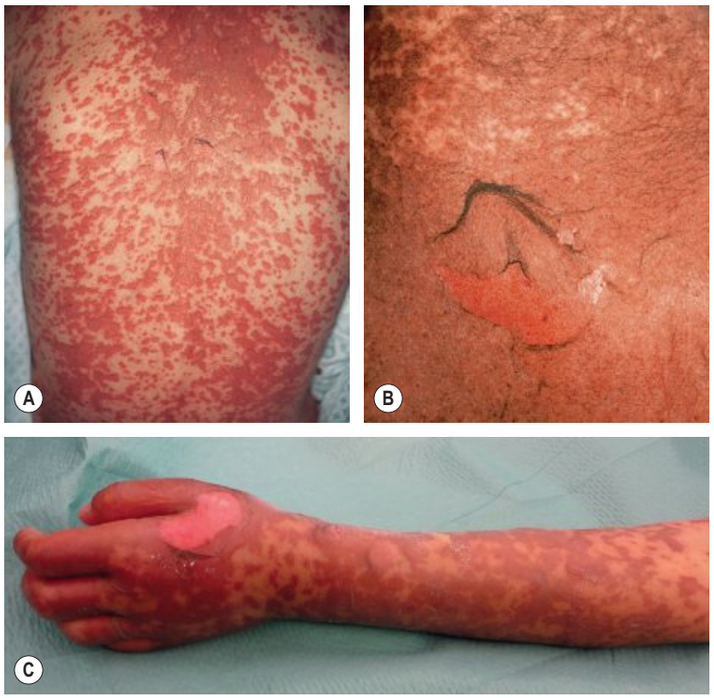


Fig. 20.11 Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) overlap and early TEN. A In addition to mucosal involvement and numerous dusky lesions with flaccid bullae, there are areas of coalescence and multiple sites of epidermal detachment. Because the latter involved >10% body surface area, the patient was classified as having SJS/TEN overlap. **B** Close-up of epidermal detachment, the appearance of which has been likened to wet cigarette paper. **C** A child with early TEN due to diclofenac. There is coalescence of the dusky lesions as well as detached epidermis and denudation. *C, Courtesy Lisa Weibel, MD.*

SCORTEN	
Prognostic factors	**Points**
Age ≥40 years*	1
Heart rate ≥120 bpm	1
Cancer or hematologic malignancy*	1
BSA involved on day 1 >10%*	1
Serum urea level (>10 mmol/l)	1
Serum bicarbonate level (<20 mmol/l)*	1
Serum glucose level (>14 mmol/l)	1
SCORTEN	**Mortality rate (%)**
0–1	3.2
2	12.1
3	35.8
4	58.3
≥5	90

*Parameters also included in the ABCD-10 scoring system, but age ≥50 years, 2 points for active cancer, and 3 points for dialysis prior to admission. The predicted mortality rates varied from 2.3% (score = 0) to 84% (score = 6)[72].

Table 20.7 SCORTEN. A prognostic scoring system for patients with toxic epidermal necrolysis. The score is based upon seven prognostic factors. Some investigators also determine the red cell distribution width to hemoglobin ratio. BSA, body surface area. *Adapted from ref 71.*



Fig. 20.12 Sequelae of toxic epidermal necrolysis. A Symblepharon, erosion of lower lateral eyelid margin and sparse eyelashes; the patient also had entropion with an ingrowth of eyelashes and pebble-like scarring of facial skin. **B** Larger irregular areas of hypopigmented scarring. **C** Nail dystrophy consisting of longitudinal ridging and fissuring, fragility, and distal notching.

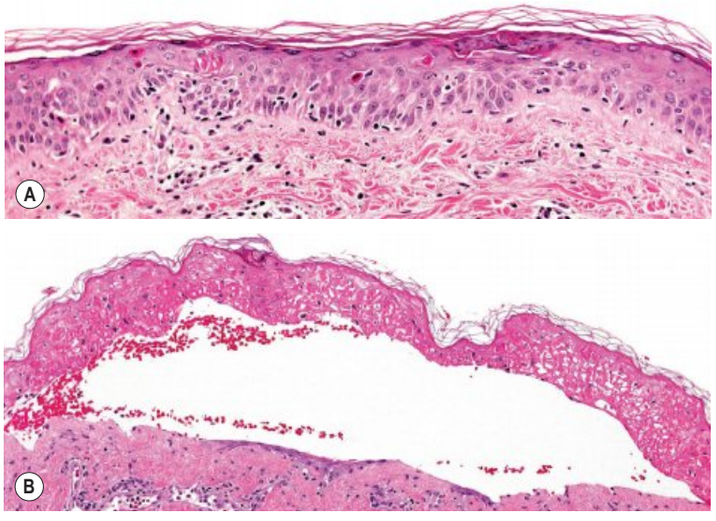


Fig. 20.13 Toxic epidermal necrolysis – histopathologic features. A Early lesions are characterized by apoptotic keratinocytes present individually and in clusters within the epidermis. Subtle vacuolar changes along the basal layer are accompanied by minimal inflammation, with scattered lymphocytes within the epidermis. **B** In later stages, a subepidermal blister with full-thickness necrosis of the overlying epidermis is seen. *Courtesy Lorenzo Cerroni, MD.*

In early lesions of SJS and TEN, apoptotic keratinocytes are observed scattered in the basal and immediate suprabasal layers of the epidermis (Fig. 20.13A). This is most likely the histologic correlate of the dusky to gray color that clinicians familiar with SJS/TEN consider as a warning sign of impending full-blown epidermal necrolysis and detachment. At later stages, lesional biopsy specimens show a subepidermal blister with overlying confluent necrosis of the entire epidermis and a sparse perivascular infiltrate composed primarily of lymphocytes (Fig. 20.13B). At an immunopathologic level, variable numbers of lymphocytes (usually $CD8^+$) and macrophages are observed within the epidermis, whereas lymphocytes in the papillary dermis are primarily $CD4^+$ cells[57].

DIFFERENTIAL DIAGNOSIS OF TOXIC EPIDERMAL NECROLYSIS	
Disease	**Clinical and histologic features**
Erythema multiforme and Stevens–Johnson syndrome	• See Table 20.1
Generalized bullous fixed drug eruption (see Ch. 21)	• When there are numerous mucocutaneous lesions • Timing post drug exposure differs • Microscopically, significant overlap
Acute generalized exanthematous pustulosis (AGEP; see Ch. 21)	• Numerous small, non-follicular pustules; can coalesce leading to large areas of exfoliation • Peripheral neutrophilia • *Microscopically, subcorneal pustules; no full-thickness epidermal necrosis*
Drug reaction with eosinophilia and systemic symptoms (DRESS; see Ch. 21)	• In addition to widespread erythema, vesiculobullae and pustules can develop • Facial edema; peripheral eosinophilia (most patients) • *Microscopically, changes are variable and sometimes nonspecific; necrosis usually absent; relatively dense dermal inflammatory infiltrate, often admixed with eosinophils*
Toxic erythema of chemotherapy (TEC; see Ch. 21)	• Exposure to particular chemotherapeutic or targeted agents • Symmetric dusky erythema, often involving skin folds, hands and feet and less often elbows and knees • Can be generalized but bullae less fragile • *Microscopically, usually minimal necrosis and presence of enlarged, atypical-appearing keratinocytes ("busulfan" cells)*
Drug-induced linear IgA bullous dermatosis (LABD), paraneoplastic pemphigus (PNP), bullous pemphigoid (see Chs. 29–31)	• Exposure to high-risk drugs, e.g. vancomycin for LABD • *Findings by routine histology and direct and indirect (PNP) immunofluorescence microscopy allow distinction*
Lupus erythematosus (Rowell syndrome; see Ch. 41)	• Usually resembles EM but can have TEN-like presentation • Appears *de novo* or as therapy tapered • Microscopically, significant overlap
Severe acute GVHD (stage/grade IV; see Ch. 52)	• Recipient of allogeneic hematopoietic stem cell transplant • Rare nowadays due to use of prophylactic GVHD therapies • Exposure to high-risk drugs for TEN and TEC is common • Microscopically, significant overlap
Staphylococcal scalded skin syndrome (SSSS; see Ch. 74)	• Children and occasionally adults • Split is more superficial so base is eroded epidermis not dermis • Perioral and periorbital accentuation with radial scale-crusts; no intraoral lesions • *Microscopically, subcorneal split with a normal underlying epidermis*
Invasive fungal dermatitis (see Ch. 34)	• Very-low-birth-weight newborns • Widespread erythema with erosions resembling a thermal burn • Usually due to candidal infection
Disseminated intravascular coagulation/purpura fulminans	• Bullae are hemorrhagic • Acral ischemia/necrosis • *Microscopically, fibrin thrombi within vessels in the dermis, with hemorrhage and minimal inflammation; necrosis of the epidermis, if present, is secondary to vascular occlusion*

Table 20.8 Differential diagnosis of toxic epidermal necrolysis. Distinctive histopathologic findings are in *italics*. In DRESS and AGEP, EM-like lesions can also be seen, including in the annular form of AGEP due to terbinafine.





Fig. 20.14 Early Stevens–Johnson syndrome. A In this child, there are individual erythematous lesions on the lower face, but coalescence on the cheeks. The two fresh bullae on the cheek are still intact. **B** This patient was originally diagnosed as a severe morbilliform drug eruption to penicillin, but then areas of epidermal detachment due to friction developed. *A, Courtesy Julie V. Schaffer, MD.*

Differential Diagnosis

The differential diagnosis of SJS consists primarily of EM (especially EM major), MIRM/RIME, autoimmune bullous diseases, and Kawasaki disease while the differential diagnosis for both SJS and TEN includes SSSS, drug-induced linear IgA bullous dermatosis (LABD), LE, generalized bullous fixed drug eruption, and the other entities outlined in Table 20.8. During the first 24–36 hours, SJS (as well as EM) may be diagnosed as a morbilliform drug reaction (Fig. 20.14).

Treatment

Optimal medical management of SJS and TEN requires early diagnosis, immediate discontinuation of the causative drug(s), and supportive care (Fig. 20.15).

Supportive care is similar to that performed for severe thermal burns, and it is aimed at limiting associated complications, which are the main cause of mortality. These include hypovolemia, electrolyte imbalance, renal insufficiency, and sepsis. Careful daily wound care, hydration, and nutritional support are essential and, preferably, done in an

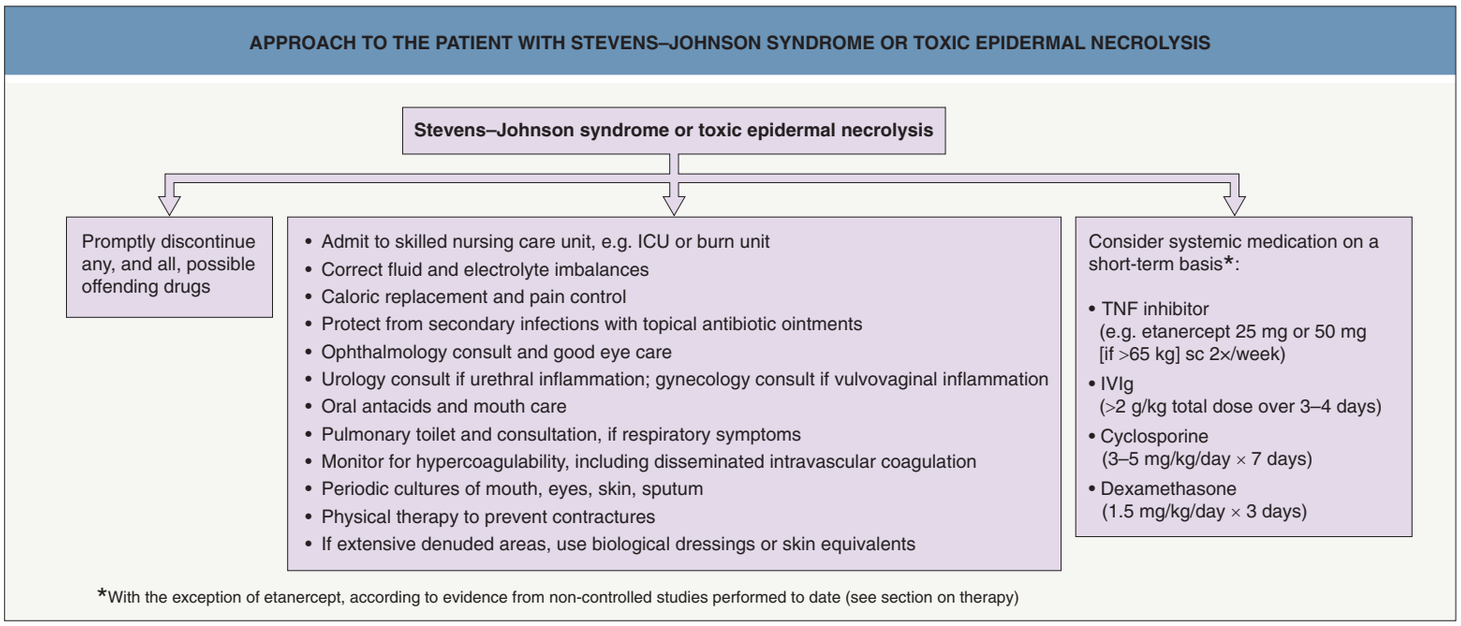


Fig. 20.15 Approach to the patient with Stevens–Johnson syndrome or toxic epidermal necrolysis. ICU, intensive care unit; sc, subcutaneous.

intensive care unit if there is epidermal detachment involving 10%–20% (or more) of BSA[77]. Use of a controlled pressure, thermoregulated bed and an aluminum survival sheet, instead of a regular bed and sheets, is recommended. All patient manipulations should be performed sterilely, and venous catheters should be placed, if possible, in a region of non-involved skin.

Wound care is best performed once daily with the help of, or in the presence of, a dermatologist. The patient should be manipulated as little as possible, as every movement is a potential cause of epidermal detachment. Cutaneous care should concentrate on the face, eyes, nose, mouth, ears, anogenital region, axillary folds, and interdigital spaces. Non-detached areas are kept dry and not manipulated. Detached areas, particularly on the back and pressure sites in contact with the bed, should be covered with Vaseline® gauze until re-epithelialization has occurred (see Ch. 145). For the face, serous and/or bloody crusts can be cleaned daily with isotonic sterile sodium chloride solution. An antibiotic ointment (e.g. mupirocin) or petrolatum ointment (if the patient is on systemic antibiotics) should be applied around orifices, e.g. ears, nose, mouth. Silicone dressings can be used to cover erosive denuded areas of skin. The silicone dressing does not need to be changed and can be left in place until re-epithelialization occurs, but its surface must be cleansed daily with isotonic sterile sodium chloride solution. Another option is to place a large non-adherent layered dressing (e.g. Exu-Dry™) over the patient and on the bed.

For the eyes, regular examination by an ophthalmologist is recommended. Eyelids should be gently cleansed daily with isotonic sterile sodium chloride solution, and an ophthalmic antibiotic ointment applied to the eyelids. In addition, antibiotic eyedrops should be administered three times a day to the cornea to reduce bacterial colonization, which can lead to scarring. Nostrils should be cleaned daily with a sterile cotton swab, moistened with isotonic sterile sodium chloride solution, and then the same procedure used to apply a little antibiotic (e.g. mupirocin) or petrolatum ointment. The mouth should be rinsed several times a day using a syringe with isotonic sterile sodium chloride solution, and then aspirated if the patient is unconscious. In the anogenital region and interdigital spaces, cutaneous care is performed daily by short applications of silver nitrate solution (0.5%) in the case of maceration, or simply sterile sodium chloride solution if there is no maceration.

In addition to supportive care, the most commonly employed systemic therapies have been TNF inhibitors, IVIg, cyclosporine, and corticosteroids. In a prospective, randomized, controlled trial involving 96 patients with SJS and TEN, etanercept was compared to intravenous prednisolone with the former resulting in shorter skin healing time (14 vs 19 days; $p = 0.01$) and less gastrointestinal hemorrhage[78]. However, to date, no additional large prospective, randomized, controlled clinical trials have been performed due in part to the low prevalence of these disorders. In general, therapy for severely affected patients with SJS has mirrored therapy for TEN, while those patients with milder non-progressive forms of SJS may receive only supportive care.

Although systemic corticosteroids have been a mainstay of therapy for decades, their use remains controversial[79]. A more recent study reported efficacy when the corticosteroids were administered acutely and over a short period of time as pulse therapy (intravenous dexamethasone 1.5 mg/kg for three consecutive days)[80]. In 2021, a network meta-analysis suggested that a combination of corticosteroids plus IVIg could reduce mortality in patients with SJS/TEN overlap and TEN[81]. Conflicting results have been observed with regard to the use of cyclosporine. A meta-analysis of 256 patients with SJS/TEN found significantly improved survival in patients treated with cyclosporine while a monocentric retrospective study of 174 patients did not see an advantage of cyclosporine over supportive care alone[82,83].

In 1998, IVIg was administered to a series of 10 patients, based upon the observation that IVIg contains antibodies that can block the binding of FasL to Fas (see Fig. 20.6A)[59]. High doses (0.75 g/kg/day for four consecutive days) were employed and blockage of the progression of epidermal detachment was observed[59]. Since then multiple published case series have been summarized in several meta-analyses[81,84–86]. While total doses of <2 g/kg may be insufficient for obtaining an optimal therapeutic effect[84], higher doses of IVIg (≥2 g/kg) correlated with an increased survival rate and lower mortality rate[85,87]. Relative contraindications for IVIg include a hypercoagulable state, IgA deficiency, and less so renal disease as the current products have less of an osmotic load.

In case reports and small uncontrolled series, several treatments have been reported as successful including cyclophosphamide (100–300 mg/day), plasmapheresis, and N-acetylcysteine (2 g/6 h)[88–90]. On the other hand, a controlled study using thalidomide was interrupted because of higher mortality in the thalidomide group compared with the placebo group[91].

Addressing the long-term complications of SJS/TEN clearly requires a multi-disciplinary approach.

Additional figures available in our eBook (see inside front cover for access code).

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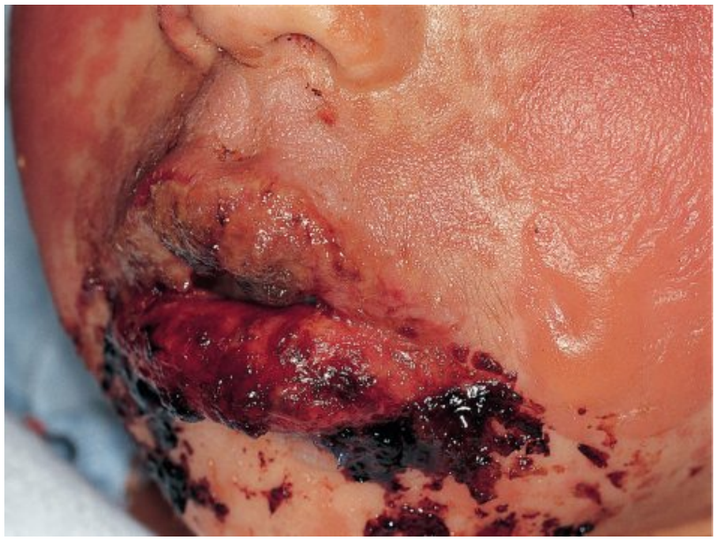
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eFig. 20.1 Erythema multiforme-like lesions in two patients, one of whom had systemic lupus erythematous (A) and the other Sweet syndrome (B). *A, Courtesy Kalman Watsky, MD; B, Courtesy Dennis Cooper, MD.*



eFig. 20.2 Childhood Stevens–Johnson syndrome secondary to trimethoprim–sulfamethoxazole therapy. Note the hemorrhagic crusts and denudation of the lips as well as bullous cutaneous lesions. *Courtesy William Weston, MD.*



eFig. 20.3 Stevens–Johnson syndrome (SJS) due to ipilimumab that progressed to toxic epidermal necrolysis. The initial clue to the diagnosis of SJS was the fragility of the skin overlying the scapula (circled). *Courtesy Marianna Freudzon, MD.*



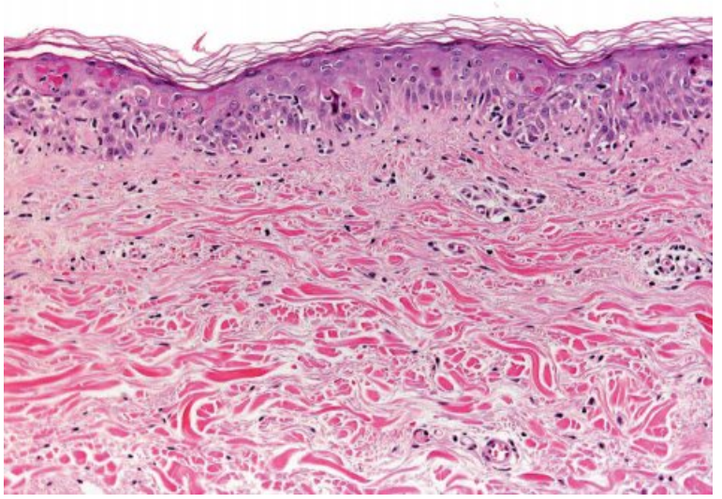
eFig. 20.4 Stevens–Johnson syndrome/toxic epidermal necrolysis overlap due to trimethoprim–sulfamethoxazole. Multiple dusky plaques with central blister formation that have coalesced on the mid and upper back. In the latter areas, the skin is fragile with obvious sloughing of the epidermis. *Courtesy Katherine Hunt, MD.*



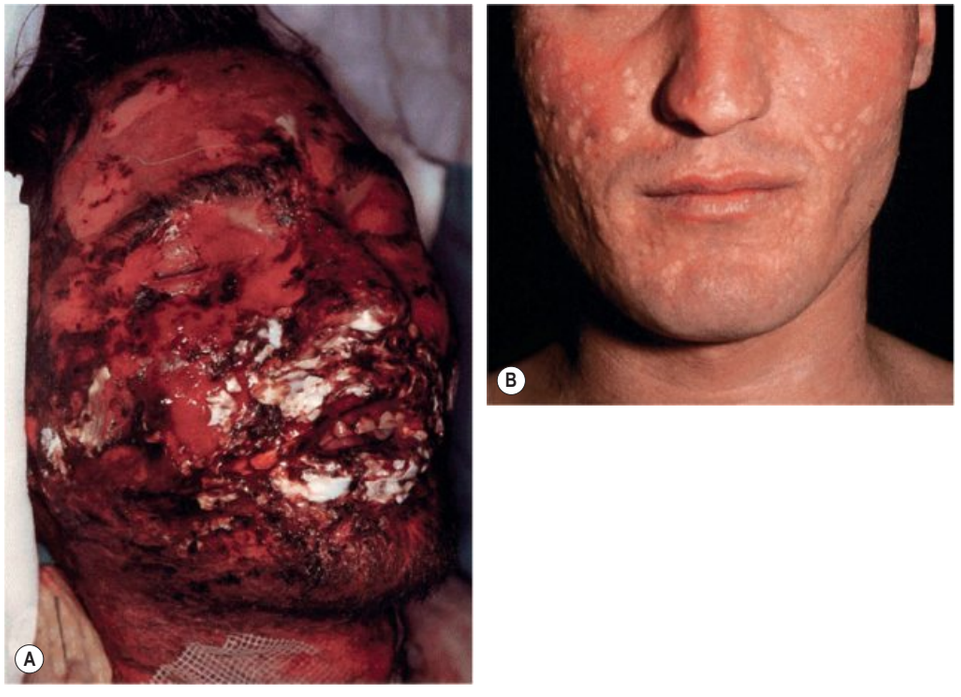
eFig. 20.5 Toxic epidermal necrolysis due to an antimalarial drug. The epidermis is no longer present on the majority of the back. *Courtesy Rosemarie Moser, MD.*



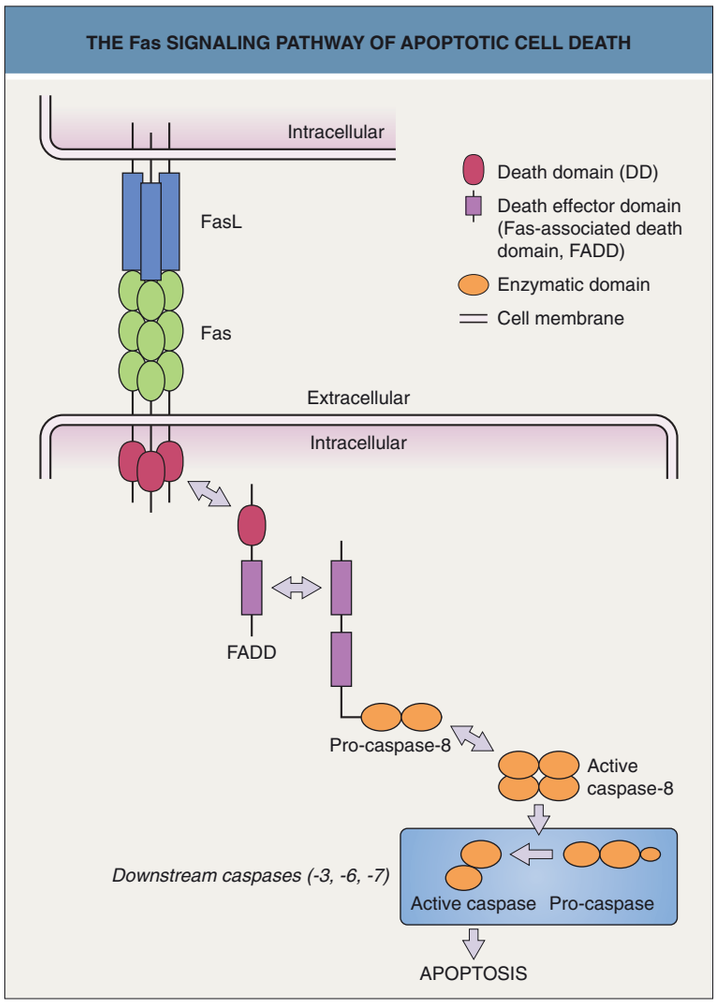
eFig. 20.6 Toxic epidermal necrolysis. Multiple hemorrhagic crusts with mucosal involvement.



eFig. 20.7 Toxic epidermal necrolysis – histopathologic features. Early lesions are characterized by apoptotic keratinocytes present individually and in clusters within the epidermis. Subtle vacuolar changes along the basal layer are accompanied by minimal inflammation, with scattered lymphocytes within the epidermis. *Courtesy Lorenzo Cerroni, MD.*



eFig. 20.8 Treatment of toxic epidermal necrolysis (TEN). Facial involvement of a patient with TEN (50% body surface area involvement) before (**A**) and 3 weeks after (**B**) treatment with IVIg (0.75 g/kg/day for 4 days).



eFig. 20.9 The Fas signaling pathway of apoptotic cell death. The death receptor Fas and its ligand FasL are transmembrane proteins. Fas signaling is triggered in the target cells by receptor tri(multi)-merization, induced upon contact with membrane-bound FasL from an adjacent cell. Subsequently, recruitment of intracellular signaling proteins FADD and pro-caspase-8 leads to autoactivation of the protease caspase-8 as well as apoptosis due to subsequent activation of downstream effector caspases (caspases-3, -6, -7), which cause cellular disintegration and death. Stimuli that induce apoptosis include cellular stress, growth factor withdrawal, DNA damage and cytokines.

21 Drug Reactions

Christina Bergqvist, Saskia Ingen-Housz-Oro and Olivier Chosidow

Key features

- The skin is one of the most common targets for adverse drug reactions
- To determine the cause of the eruption, a rigorous approach based on clinical characteristics, chronologic factors, and a literature search is required
- Exanthematous (morbilliform) eruptions and urticaria are the two most common forms of cutaneous drug reactions
- When an exanthematous eruption is associated with fever, lymphadenopathy, and/or edema of the face, drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) should be considered and an evaluation for systemic involvement conducted
- Less common drug reactions include fixed, lichenoid, pustular, granulomatous, pseudolymphomatous, acneiform, bullous, photosensitivity, and vasculitic reactions, as well as Stevens–Johnson syndrome and toxic epidermal necrolysis
- Introduction of targeted therapies and immune checkpoint inhibitors to treat cancer has led to a wide range of cutaneous adverse reactions
- Early withdrawal of all potentially responsible drugs is essential, particularly in the case of severe cutaneous adverse reactions (SCARs)

INTRODUCTION

The skin is one of the most common sites for adverse drug reactions[1]. Although eruptions are usually observed in 0.1% to 1% of patients enrolled in pre-marketing trials of most systemic drugs, up to 5% of patients treated with antibiotics or aromatic anticonvulsants may develop a cutaneous eruption. Even higher incidences have been reported with newer targeted therapies and immune checkpoint inhibitors (ICIs) to treat cancer. In the mid 1990s, it was estimated that 1 of every 1000 hospitalized patients had a serious cutaneous drug reaction[1]. Introduction of the term SCARs (*s*evere *c*utaneous *a*dverse *r*eactions [to drugs]) reinforced the need for prompt identification followed by discontinuation of the most likely culprit drug(s) thereby decreasing both morbidity and mortality (Table 21.1)[2].

It may be tempting to consider most eruptive cutaneous drug reactions, especially the severe ones, as various presentations of a "hypersensitivity state". However, it is more precise to examine the specificity of the clinical, pathologic, and biologic patterns, thus allowing linkage of each type of adverse cutaneous reaction with a well-defined mechanism[3].

This chapter focuses on adverse cutaneous reactions due to systemically administered drugs. In addition, several specific types of cutaneous adverse reactions (CARs) are discussed in other chapters (Table 21.2).

SEVERE CUTANEOUS ADVERSE REACTIONS (SCARs)
Anaphylaxis
Anticoagulant-induced skin necrosis
Acute generalized exanthematous pustulosis (AGEP)
Drug rash with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS)
Generalized bullous fixed drug eruption
Stevens–Johnson syndrome and toxic epidermal necrolysis

Table 21.1 Severe cutaneous adverse reactions (SCARs). Trimethoprim-sulfamethoxazole-associated sudden conjunctivitis, lymphopenia, and rash combined with hemodynamic changes (SCoRCH) is a rare disorder.

EPIDEMIOLOGY

CARs to drugs occur in up to 8% of hospitalized patients[4]. In departments of dermatology, they represent 2% of consultations and ~5% of the admissions to an inpatient dermatology service. The incidence of fatalities due to drug reactions (systemic and cutaneous) among inpatients is between 0.1% and 0.3%[2]. There are multiple risk factors for developing an adverse drug reaction, including immunosuppression (e.g. HIV-infected individuals have a 10- to 50-fold greater risk of developing an exanthematous eruption to sulfamethoxazole) and specific HLA alleles (Table 21.3)[5].

Epidemiology of common CARs is still evolving. As a result, the incidence of drug reactions is difficult to establish precisely. Generally speaking, pre-marketing clinical trials, conducted before a new drug is licensed, include a limited number of patients, thus preventing a clear estimate of the true incidence. It is usually after several months or years of greater utilization that a more precise profile of the side effects of a newly released drug is established. Moreover, available information should be interpreted with caution, depending upon the method of data collection.

ADDITIONAL REVIEWS OF SPECIFIC TYPES OF CUTANEOUS ADVERSE REACTIONS TO DRUGS	
Type of cutaneous adverse reaction	**Chapter or table**
Acneiform/folliculitis	Tables 36.1 & 38.1
Bullous pemphigoid and pemphigus	Chapters 29 & 30
Cutaneous lymphoid hyperplasia (pseudolymphoma)	Table 121.1
Erythroderma	Table 10.3
Gingival enlargement	Table 72.2
Granulomatous (interstitial)	Table 93.7
Hyper- and hypohidrosis	Tables 39.2 & 39.9
Hyperpigmentation and dyschromatosis	Tables 67.5 & 67.11
Hypopigmentation (skin and hair)	Table 66.9
Lichenoid	Table 11.2
Linear IgA bullous dermatosis	Table 31.5
Lipodystrophy	Chapter 101
Lupus erythematosus (systemic and cutaneous)	Chapter 41
Nail abnormalities	Table 71.9
Panniculitis	Chapter 100
Phototoxic and photoallergic	Table 87.5
Pityriasis rosea-like	Chapter 9
Pseudoporphyria	Table 49.5
Psoriasiform	Chapters 8 & 128
Sarcoidal	Chapter 93
Stevens–Johnson syndrome and toxic epidermal necrolysis	Table 20.6
Ulcerations, lower extremities	Chapter 105
Urticaria	Chapter 18
Vasculitis	Table 24.4
Warfarin- and heparin-induced necrosis	Chapter 23

Table 21.2 Additional reviews of specific types of cutaneous adverse reactions to drugs.

SPECIFIC HLA ALLELES THAT INCREASE THE RISK OF CUTANEOUS DRUG REACTIONS			
Drug	**Higher risk population(s)**	**HLA allele**	**Type of drug reaction**
Abacavir	White, African-Americans	**B*57:01**	DRESS > SJS/TEN
Allopurinol	Asians (Han Chinese) > White	**B*58:01**	SJS/TEN
	Asians (Taiwanese) > White	**B*58:01**	DRESS
β-Lactam antibiotics	Chinese	C*04:06 C*08:01 DRB1*04:06	Exanthematous eruption DRESS SJS
Carbamazepine	Han Chinese and other Asian populations	**B*15:02**	SJS/TEN
	Han Chinese, Koreans, Japanese	B*15:11	SJS/TEN
	White	B*57:01	SJS/TEN
	Europeans, Han Chinese, Spanish	A*31:01	DRESS
	Northern Europeans, Japanese, Koreans	A*31:01	DRESS/SJS/TEN
	Japanese	B*59:01	SJS/TEN
	Spanish	B*38:01	SJS/TEN
Dapsone	Chinese	B*13:01	DRESS
Feprazone (NSAID)	Scandinavians	B22	FDE
Lamotrigine	Taiwanese	B*15:02	SJS/TEN
	White	B*38 B*58:01 A*68:01 Cw*07:18	SJS/TEN
	Koreans	A*31:01	SJS/TEN
	Spanish	A*24:02	DRESS/SJS/TEN
Nevirapine	Hispanics, Africans, Australians	DRB1*01:01	DRESS
	Thai	B*35:05	DRESS
	Sardinians, Japanese	B*14:02 Cw*08:01 Cw*08:02	Hypersensitivity syndrome
	Malawians	C*04:01	DRESS/SJS/TEN
Phenytoin	Southeast Asians	B*15:02 B*13:01 B*51:01 A*33:03 B*38:02 B*56:02 B*58:01 C*14:02	SJS/TEN
Phenobarbital	Han Chinese	B*15:02	SJS/TEN
Raltegravir	Africans, Hispanics	B*53:01	DRESS
Trimethoprim–sulfamethoxazole	Turkish	B55	FDE
	Japanese	A*11:01	SJS/TEN Hypersensitivity syndrome
Vancomycin	Europeans	A*32:01	DRESS

Table 21.3 Specific HLA alleles that increase the risk of cutaneous drug reactions. A number of HLA alleles also increase the risk of liver injury, including from penicillin derivatives. Highest relative risks are in **bold**. DRESS, drug reaction with eosinophilia and systemic symptoms; FDE, fixed drug eruption; NSAID, nonsteroidal anti-inflammatory drug; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Reaction rates to commonly administered drugs have been confirmed by several prospective studies; however, the latter have been limited to inpatients[4]. In one series, adverse skin reactions occurred in 2.7% of 48 000 patients hospitalized over a 20-year period on a general internal medicine service; maculopapular exanthems (91.2%), urticaria (5.9%), and vasculitis (1.4%) were the reactions most commonly observed. The primary responsible drugs were penicillins, sulfonamides, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Except for studies in hospitalized populations and those focusing on the most severe reactions, data regarding the incidence of cutaneous drug reactions in the general population are minimal, in part due to the absence of comprehensive post-marketing surveillance programs. In a retrospective cohort study from the Netherlands of 13 679 patients from general practices, the most frequently reported skin reactions to antimicrobials were due to trimethoprim–sulfamethoxazole (2.1% of users), fluoroquinolones (1.6%), and penicillins (1.1%).

PATHOGENESIS

Drug-induced skin reactions are mediated by either an immunologic or a non-immunologic mechanism (Table 21.4). In the former, drugs or their metabolites act as haptens, inducing a specific cell-mediated or humoral response. In the latter, some of the reactions are predictable given their relationship to the dose and/or the pharmacologic properties of the drug. However, the responsible pathophysiology may be difficult to identify simply on the basis of clinical appearance as the skin responds to a wide variety of stimuli through a limited number of morphologic reaction patterns. This may explain, at least in part, why the underlying mechanism of many cutaneous drug eruptions is still unknown.

Immunologically Mediated Drug Reactions

- *IgE-dependent drug reactions* (formerly type I, Gell–Coombs classification): urticaria, angioedema, and anaphylaxis.
- *Cytotoxic drug-induced reactions* (antibody against a fixed antigen; formerly type II): petechiae secondary to drug-induced thrombocytopenia.
- *Immune complex-dependent drug reactions* (formerly type III): vasculitis, serum sickness, and certain types of urticaria.
- *Delayed-type, cell-mediated drug reactions* (activation of $CD4^+$ and $CD8^+$ T cells; formerly type IV)[3]: exanthematous, fixed, and lichenoid drug eruptions, as well as Stevens–Johnson syndrome (SJS) and TEN. This group has been further subdivided into the following:
  - Th1 immune reaction (IVa): monocytes are preferentially recruited and activated by IFN-γ, leading to $CD8^+$ T cell activation and a proinflammatory response (TNF, IL-12)
  - Th2 immune reaction (IVb): eosinophils are preferentially recruited and activated in part by IL-4, -5, -13, and eotaxin, as in drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), hereafter referred to as DRESS in the text

MECHANISMS OF CUTANEOUS DRUG-INDUCED REACTIONS	
Immunologic mechanism (unpredictable)	• IgE-dependent drug reactions • Cytotoxic drug-induced reactions • Immune complex-dependent drug reactions • Cell-mediated reactions
Non-immunologic mechanisms (sometimes predictable)	• Overdose • Pharmacologic side effects • Cumulative toxicity • Delayed toxicity • Drug–drug interactions • Alterations in metabolism • Exacerbation of disease
Idiosyncratic with a possible immunologic mechanism (unpredictable)	• DRESS/DIHS • SJS/TEN • Drug reactions in the setting of HIV infection • Drug-induced lupus erythematosus

Table 21.4 Mechanisms of cutaneous drug-induced reactions. DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; HIV, human immunodeficiency virus; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

- Cytotoxic immune reaction (IVc): involves $CD4^+$ and $CD8^+$ T cells with release of perforin and granzyme B and/or Fas–FasL interactions, as in SJS/TEN (see Fig. 20.6)
- Neutrophil and T cell-based immune reaction (IVd): mediated via chemokines (e.g. CXCL8) and cytokines (e.g. GM-CSF), as in acute generalized exanthematous pustulosis (AGEP)

Several immunologic mechanisms have been proposed to explain SCARs including: (1) the *hapten/pro-hapten concept* – the drug or its metabolite covalently binds to an endogenous peptide and the resultant hapten is recognized by a highly restricted major histocompatibility complex (MHC); (2) the *pharmacoimmune reaction* ("p-i concept") – drugs induce formation of HLA–drug complexes that can directly activate T cell immune responses without the need for a specific peptide ligand[3]; and (3) *direct HLA–drug interactions* – certain drugs such as carbamazepine, abacavir, and sulfamethoxazole bind non-covalently within the peptide groove of a specific HLA and modify the antigen-binding cleft, thereby altering the endogenous peptide repertoire[6–9]. Interestingly, adoptive transfer of T cells expressing a public αβ T cell receptor to *HLA-B*15:02* transgenic mice receiving oral carbamazepine has been shown to induce a SCAR-like reaction[10].

Genetic factors

Specific HLA alleles have emerged as important genetic risk factors for SCARs, especially SJS/TEN and DRESS (see Table 21.3)[5,11,12]. Given the strong associations between HLA-B*15:02 and carbamazepine-triggered SJS/TEN in Asians and between HLA-B*57:01 and abacavir-triggered DRESS, pretreatment genetic testing is systematically performed in some countries in order to reduce the risk of SCARs. In patients with HLA-B*15:02 who are also carriers of CYP2C9*3 (portends intermediate or poor drug metabolizing phenotype), phenytoin should not be used as a therapeutic alternative to carbamazepine.

Non-immunologic Mechanisms (see Table 21.4)

Overdose

The clinical manifestations of a drug overdose are predictable and represent an exaggeration of the medication's pharmacologic actions. It may occur as a consequence of a prescribing error, deliberate or inadvertent excess by the patient, or altered absorption, metabolism, or excretion[13]. For example, overdose-related methotrexate toxicity can occur in patients with reduced renal function or in patients who erroneously take methotrexate daily instead of once weekly (Fig. 21.1).

Pharmacologic side effects

These reactions include undesirable or toxic effects that cannot be separated from the desired pharmacologic actions of the drug. An example would be alopecia and mucositis due to chemotherapeutic agents that target more rapidly dividing cells.

Cumulative toxicity

Prolonged exposure to a medication or its metabolites may lead to cumulative toxicity. For example, methotrexate can lead to hepatic fibrosis and accumulation of minocycline, hydroxychloroquine, amiodarone, or rarely levofloxacin within the skin can lead to cutaneous discoloration.

Delayed toxicity

This corresponds to a toxic, dose-dependent effect that occurs months to years after the discontinuation of a medication. Examples include squamous cell carcinomas and palmoplantar keratoses following exposure to arsenic and acute leukemia due to alkylating agents.

Drug–drug interactions

Interactions between two or more drugs administered simultaneously may occur at several different steps: (1) intestinal drug interactions; (2) displacement from binding proteins or receptor sites; (3) enzyme stimulation or inhibition; and (4) altered drug excretion (see Ch. 131). Examples of each include the interactions between tetracycline and calcium, methotrexate and sulfonamides, cyclosporine and azoles, and methotrexate and probenecid. A different scenario is a morbilliform eruption or TEN following the administration of both a common culprit drug (e.g. cephalosporin) and an immune checkpoint inhibitor (e.g. nivolumab) whereas re-exposure to just the immune checkpoint inhibitor does not lead to a CAR.

Alterations in metabolism

Drugs may induce cutaneous changes by their effects on the nutritional or metabolic status of the patient. Bexarotene may induce severe hypertriglyceridemia and eruptive xanthomas, while isoniazid may be associated with pellagra-like changes.

Exacerbation of disease

A variety of drugs can exacerbate pre-existing dermatologic diseases, such as androgens in patients with acne vulgaris, interferons in patients with sarcoidosis and psoriasis, or paradoxically TNF inhibitors in patients with psoriasis.

Photosensitivity

Systemically administered drugs in combination with light (ultraviolet or visible) may cause cutaneous photosensitivity, classically either phototoxicity (e.g. doxycycline, quinolones) or photoallergy (e.g. quinine, sulfonamide antibiotics). Topical medications may also lead to photosensitizing reactions (e.g. ketoprofen-induced photoallergic dermatitis). In addition, drugs can act as photocarcinogens, even after short use (e.g. voriconazole-induced squamous cell carcinomas). Oral medications may even induce systemic (e.g. hydralazine, minocycline) and cutaneous lupus erythematosus (e.g. terbinafine, hydrochlorothiazide).



Fig. 21.1 Methotrexate toxicity. Increased serum levels of methotrexate secondary to decreased renal excretion can lead to epidermal necrosis. **A** Large erosions and areas of epidermal necrosis with a shellac-like appearance in a patient with rheumatoid arthritis. **B** Epidermal necrosis limited to psoriatic plaques. *A, Courtesy Kalman Watsky, MD.*

Idiosyncratic With a Possible Immunologic Mechanism (see Table 21.4)

The pathophysiology of drug-induced skin reactions such as exanthematous drug eruptions, DRESS, AGEP and TEN, as well as the increased susceptibility of HIV-infected patients, may be partially explained by an interplay between a virus with its subsequent immune mechanisms and genetic predisposition.

DIAGNOSTIC FEATURES

Drug eruptions, both suspected and unsuspected, frequently lead to a dermatologic consultation, and it is often (although not always) possible to categorize a drug as having a high, medium, or low probability of being the culprit. A rigorous approach begins with an accurate description of the skin lesions and their distribution, in addition to associated signs and symptoms (Table 21.5). Data regarding all the drugs taken by the patient, including prescription, non-prescription/over-the-counter, and complementary or alternative treatments, as well as the dates of administration and doses need to be collected on a timeline[2]. The chronology of drug administration is of paramount importance (Table 21.6). The time between initiation of the drug and the onset of the skin eruption is a key element in identifying the culprit drug, as most immunologically mediated reactions occur 7 to 21 days after initiation of a new medication.

Evolution after drug withdrawal may be helpful, as common cutaneous eruptions (e.g. exanthematous) often clear when the suspected drug is discontinued. However, this assessment may prove difficult in the case of drugs with a long half-life or "persistent" drug reactions such as lichenoid and photoallergic eruptions, drug-induced pemphigus foliaceus and subacute cutaneous lupus erythematosus, or even SCARs, once the disease process has been definitively triggered.

The culprit drug should be withdrawn as soon as possible. The usual practice is to discontinue all other drugs that are non-essential. However, in some instances, it is necessary to weigh the risks versus the benefits of each drug and to determine if a similar-acting, but non-cross-reactive, drug is available as a substitute.

In the process of identifying the responsible drug, access to drug databases or drug agency websites is very helpful[5,6,14]. However, new or unusual drug reactions may not be identified. Moreover, the drug most frequently associated with adverse reactions may be innocent in a particular patient, and the physician dealing with a suspected drug reaction must remain open-minded.

RIGOROUS APPROACH TO DETERMINE THE CAUSE OF A DRUG ERUPTION	
Drug responsibility assessment	
Clinical characteristics	• Type of primary lesion (e.g. urticaria, erythematous papule, pustule, purpuric papule, vesicle, or bulla) • Distribution and number of lesions • Mucous membrane involvement, facial edema • Associated signs and symptoms: fever, pruritus, lymph node enlargement, visceral involvement
Chronological factors	• Document all drugs to which the patient has been exposed (including OTC and complementary) and the dates of administration • Date of eruption • Time interval between drug introduction (or reintroduction) and skin eruption • Response to removal of the suspected agent • Consider excipients (e.g. soybean oil) • Response to rechallenge*
Search of databases	• Bibliographic research (e.g. PubMed, Micromedex, Litt's Drug Eruption and Reaction Database) • MedWatch (fda.gov/medwatch) • Data collected by pharmaceutical companies • In the case of more recently released medications, extrapolation based on the class of drug and in particular the first drug released in the class
*Often inadvertent.	

Table 21.5 Rigorous approach to determine the cause of a drug eruption.
OTC, over-the-counter.

With the exception of assays for IgE antibodies, diagnostic or confirmatory assays to establish the responsible drug are not readily available. A number of *in vitro* tests have been designed, including the histamine release test, migration inhibition factor test, lymphocyte toxicity assay, lymphocyte transformation test, and basophil degranulation test[7]. However, their sensitivity and specificity have not been assessed in a reliable way with relevant controls. As a result, they are of limited value in the clinical setting.

Results of patch testing, in which drugs (usually with petrolatum or alcohol as the vehicle) are applied to the upper back for 48 hours, vary depending upon the responsible drug and the type of eruption[15] (Table 21.7). Prick and intradermal tests can be performed in patients with urticaria and angioedema, but they are contraindicated in SJS/TEN due to the risk of relapse. Of note, delayed reading of prick, intradermal, and patch tests is particularly important in the case of amoxicillin-induced morbilliform eruptions. Unfortunately, investigations involving series of patients with several different types of drug reactions have shown heterogeneous results. In general, these tests, when positive, may be helpful in preventing re-administration of the culprit drug, but with the exception of prick and intradermal tests in patients with urticaria and perhaps patch tests in a few disorders (see Table 21.7), their specificity and/or sensitivity are still controversial. Of note, delayed intradermal testing is increasingly being performed in patients with DRESS when there is uncertainty regarding the responsible drug and pretest probability is high.

Rechallenge carries the risk of inducing a more severe reaction, thus it is contraindicated after SCARs. In critical situations, rechallenge may be useful, e.g. a patient with active tuberculosis who develops a rash while receiving a cocktail of antituberculous drugs; a step-by-step reintroduction may be performed in specialized centers. However, the recurrence rate is not 100% with rechallenge and a negative result may give an erroneous sense of security.

CLINICAL FEATURES

Urticaria (see Ch. 18 for details)

Urticaria presents as transient, pruritic, erythematous, and edematous papules and plaques that may appear anywhere on the body. Lesions can vary significantly in size and number and may assume a figurate configuration (Fig. 21.2).

Although drugs are thought to be responsible for <10% of all cases of urticaria, they are more often associated with acute rather than chronic urticaria. Drug-induced urticaria may either occur immediately, i.e. less than one hour after drug intake (see below), or have a delayed appearance (late urticaria)[16]. Of note, patients with chronic urticaria should avoid acetylsalicylic acid (ASA; aspirin), as well as other NSAIDs, as they can lead to an exacerbation.

In IgE-mediated urticaria, lesions typically appear within minutes to less than an hour after drug administration, especially when there has been prior sensitization. Both immunologic assays, such as radioallergosorbent tests (RAST) that detect specific IgE antibodies, and skin tests (prick tests) are useful in confirming the diagnosis. Unfortunately, US commercial RAST panels only test for a limited number of drugs. Prick tests should be performed under appropriate medical supervision due to the risk of an anaphylactic reaction. Of note, in some series, only 10%–20% of patients who reported a history of penicillin allergy were truly allergic when assessed by skin testing.

Drugs that most frequently produce immunologically based urticaria are antibiotics, especially penicillins and cephalosporins, and less often, sulfonamides and minocycline. As the use of monoclonal antibodies for neoplastic and inflammatory diseases increases, so will cases of urticaria (and vasculitis; see below) due to these exogenous proteins (see Ch. 128).

In anaphylactoid reactions, which are not IgE-mediated but resemble anaphylaxis clinically, vasodilation results from the liberation of large amounts of histamine, bradykinin, and/or leukotrienes. Acetylsalicylic acid is the classic example of a drug that induces an anaphylactoid reaction and it does so via cyclooxygenase inhibition and subsequent accumulation of leukotrienes. The majority of urticarial reactions to radiocontrast media are also non-immunologic (Table 21.8), as are many, but not all, reactions to NSAIDs (e.g. ibuprofen, naproxen). Infusion of chemotherapy (e.g. taxanes) can also result in anaphylactoid reactions.

CHARACTERISTICS OF MAJOR DRUG-INDUCED ERUPTIONS				
Clinical presentation	**Percentage that are drug-induced (%)**	**Time interval**	**Mortality (%)**	**Selected responsible drugs**
Exanthematous (morbilliform) eruption	Child: 10–20 Adult: 50–70	4–14 days	0	Aminopenicillins Sulfonamides Cephalosporins Anticonvulsants (aromatic) Allopurinol Abacavir Nevirapine
Urticaria	<10	Minutes to hours	0	Penicillins Cephalosporins NSAIDs* Monoclonal antibodies Radiocontrast media*
Anaphylaxis	30	Minutes to hours	5	
Fixed drug eruption (FDE)	100	First exposure: 1–2 weeks Re-exposure: <48 hours, usually within 24 hours	0	Acetaminophen TMP-SMX NSAIDs Tetracyclines Pseudoephedrine†
Acute generalized exanthematous pustulosis (AGEP)	70–90	<4 days	1–2	β-Lactam antibiotics Macrolides Calcium channel blockers Clindamycin
Drug reaction with eosinophilia and systemic symptoms (DRESS)/ drug-induced hypersensitivity syndrome (DIHS)	70–90	15–40 days	5–10	Anticonvulsants (aromatic) Lamotrigine (especially in combination with valproate) Sulfonamides Abacavir Allopurinol Dapsone Minocycline Nevirapine Vancomycin
Stevens–Johnson syndrome (SJS)	70–90	7–21 days	5	Sulfonamides, β-lactam antibiotics Anticonvulsants (aromatic) Lamotrigine Allopurinol NSAIDs NNRTIs, e.g. nevirapine
Toxic epidermal necrolysis (TEN)			30	
*Often anaphylactoid reaction. †Non-pigmenting.				

Table 21.6 Characteristics of major drug-induced eruptions. See Chs. 18 and 20 for additional details. NNRTIs, non-nucleoside reverse transcriptase inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; TMP-SMX, trimethoprim–sulfamethoxazole (co-trimoxazole).

CUTANEOUS DRUG ERUPTIONS – USE OF PATCH TESTING TO IDENTIFY THE RESPONSIBLE DRUG		
Type of cutaneous drug reaction	**% Patch test positivity***	**Comments**
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)	50–80	Positive results most frequently observed with β-lactam antibiotics, clindamycin, erythromycin, pseudoephedrine, contrast agents > allopurinol, H1 blockers
Acute generalized exanthematous pustulosis (AGEP)	50–60	Positive results most frequently observed with β-lactam antibiotics and pristinamycin > carbimazole/metamizole, ciprofloxacin, clindamycin, diltiazem, metronidazole, morphine, NSAIDs, and pseudoephedrine
Fixed drug eruption	>40	*In situ* patch test recommended, i.e. at the site of a previous lesion
Drug reaction with eosinophilia and systemic symptoms (DRESS)	30–60	Should be performed at least 6 months after clinical resolution Positive results primarily observed with abacavir, β-lactam antibiotics, carbamazepine, proton pump inhibitors, and antituberculous drugs
Exanthematous (morbilliform) drug eruption	10–40	If patch test negative, prick tests can be discussed to increase positivity, depending upon disease severity
SJS/TEN	10–25	Reports of positive results with β-lactam antibiotics, carbamazepine, trimethoprim–sulfamethoxazole, and pseudoephedrine
*Range because results often depend upon particular drug.		

Table 21.7 Cutaneous drug eruptions – use of patch testing to identify the responsible drug. Patch tests are placed on the upper back for 48 hours and read at 3–7 days as with standard patch testing (see Ch. 14). Vehicles are usually petrolatum or alcohol and concentrations are either predetermined (commercially available products) or based upon literature review. SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.



Fig. 21.2 Urticaria secondary to penicillin. Several of the lesions have a figurate appearance.

ADVERSE REACTIONS TO RADIOCONTRAST MEDIA
Iodinated
Immediate (<1 hour)
Urticaria (usually non-immunologic), angioedema
Anaphylactoid reaction
Delayed (1 hour to 1 week)
Exanthematous (morbilliform) eruption
Acute generalized exanthematous pustulosis (AGEP)
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)
Iododerma (also >1 week)
DRESS/DIHS (iodinated > gadolinium)
Gadolinium
Urticaria, erythema (rare)
Anaphylactoid reactions, anaphylaxis (rare)
Nephrogenic systemic fibrosis (in the setting of renal insufficiency; see Ch. 43)

Table 21.8 Adverse reactions to radiocontrast media. DRESS/DIHS, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome.

The most important step in the treatment of drug-induced urticaria is withdrawal of the causative agent. Treatment consists primarily of H1 antihistamines. Additional therapeutic options are discussed in Chapter 18 as is the differential diagnosis which includes the immune complex-mediated disorders urticarial vasculitis and serum sickness.

Angioedema (see Ch. 18 for details)

Angioedema is a consequence of transient edema of the deep dermal, subcutaneous, and submucosal tissues. It is associated with urticaria in 50% of cases and may be complicated by life-threatening anaphylaxis. Angioedema occurs in 1 to 2 per 1000 new users of angiotensin-converting enzyme (ACE) inhibitors and is due to an accumulation of bradykinin (see Fig. 18.6). The most severe cases of angioedema may start within a few minutes after drug administration. However, in the case of ACE inhibitor-induced angioedema, lesions may appear from 1 day to several years after starting the drug; most appear within the first year. Blacks and women are at increased risk for developing ACE inhibitor-induced angioedema.

The most common clinical presentation is an acute, asymmetric, pale or pink, subcutaneous swelling involving the face. Involvement of the oropharynx, larynx, and epiglottis can lead to impaired swallowing and stridor. Occasionally, there is edema of the intestinal wall with abdominal pain, nausea, vomiting, and diarrhea.

The major drugs implicated in angioedema, besides penicillins and ACE inhibitors, are NSAIDs, radiographic contrast media, and more recently, monoclonal antibodies (see Ch. 128). Although angiotensin II receptor antagonists do not increase levels of bradykinin, they are also associated with angioedema, albeit less frequently. It is important to note that drug-induced angioedema may actually represent an unmasking of another cause for angioedema, e.g. acquired C1 inhibitor deficiency due to autoimmune or lymphoproliferative disorders.

Anaphylaxis

Anaphylaxis consists of an acute life-threatening reaction that occurs within minutes of drug administration, usually parenteral. It occurs in about 1 per 5000 exposures to penicillin and combines skin signs (urticaria and/or angioedema) with systemic manifestations such as hypotension and tachycardia. Occasionally, there is hypotension in the absence of cutaneous lesions. In severe cases, the patient becomes unconscious as a result of cardiovascular shock. Prompt discontinuation of the culprit drug is mandatory, as is strict avoidance of the drug in the future. Subcutaneous epinephrine (adrenaline) is the primary treatment for life-threatening angioedema and anaphylaxis, along with careful monitoring. Systemic corticosteroids and H1 antihistamines are also beneficial. Of note, patients taking β-blockers may have a limited response to epinephrine.

The most frequently incriminated drugs are antibiotics, in particular the penicillins/aminopenicillins but also cephalosporins and quinolones, muscle relaxants, NSAIDs, and gadolinium-based contrast media[17]. Anaphylaxis can also be seen following exposure to latex (see Ch. 16) while anaphylactoid reactions are usually seen with NSAIDs and radiocontrast media (see Table 21.8).

Exanthematous Drug Eruptions

Synonyms: ■ Morbilliform drug eruption ■ Maculopapular drug eruption ■ Urticarial drug eruption

Exanthematous or morbilliform eruptions are the most common adverse drug reactions affecting the skin. They are often referred to as maculopapular drug eruptions or, in the case of non-dermatologists, "drug rashes".

The primary underlying pathomechanisms are most likely immunologic, complex, and cell-mediated. Several mechanisms have been proposed (see above) in which the drug or drug-peptide hapten presented by dendritic cells to T lymphocytes can either bind covalently or non-covalently to MHC molecules[9]. $CD4^+$ and $CD8^+$ T cells that strongly express perforin and granzyme are then recruited and their cytotoxic activity leads to death of keratinocytes.

Overall, most drug classes can induce an exanthematous eruption in ~1% of treated patients. Higher risk medications (>3% of treated patients) include aminopenicillins, allopurinol, sulfonamides, cephalosporins, and anticonvulsants (aromatic and lamotrigine). Certain viral infections are also known to increase the incidence of drug reactions. Depending upon the series, the frequency of aminopenicillin-induced exanthematous eruptions in patients with infectious mononucleosis ranges from 33% to 100% (see Ch. 80). One theory is that reactive drug metabolites disturb the balance between cytotoxic and regulatory immune responses, leading to a cytotoxic reaction that targets virally infected keratinocytes.

A morbilliform eruption classically begins 4 to 14 days after the initial drug administration, but appears earlier (less than 2 days) in the case of rechallenge[16]. Symmetrically distributed erythematous macules, papules, and/or urticarial lesions initially appear on the trunk and upper extremities; over time they can become confluent (Fig. 21.3A). Sometimes, the lesions on the distal lower extremities become petechial or purpuric (Fig. 21.3B). Mucous membranes are usually spared but pruritus and a low-grade fever are often present. There may also be annular plaques (Fig. 21.3C) or atypical "target" lesions, leading to a misdiagnosis of erythema multiforme. Once the culprit drug is discontinued, the eruption gradually resolves over one to two weeks, without complications and/or sequelae. However, for 1 to 3 days immediately following discontinuation of the responsible medication, an increase in extent and intensity may be observed.

Signs and symptoms that point to the possibility of a more severe drug-induced eruption (see Table 21.1) include skin pain, edema of the face, pustules, vesicles, purpuric macules, skin fragility (Nikolsky sign), mucous membrane involvement, and/or marked peripheral blood eosinophilia. Histologically, nonspecific findings are typically seen in morbilliform drug eruptions, i.e. a mild superficial perivascular and interstitial

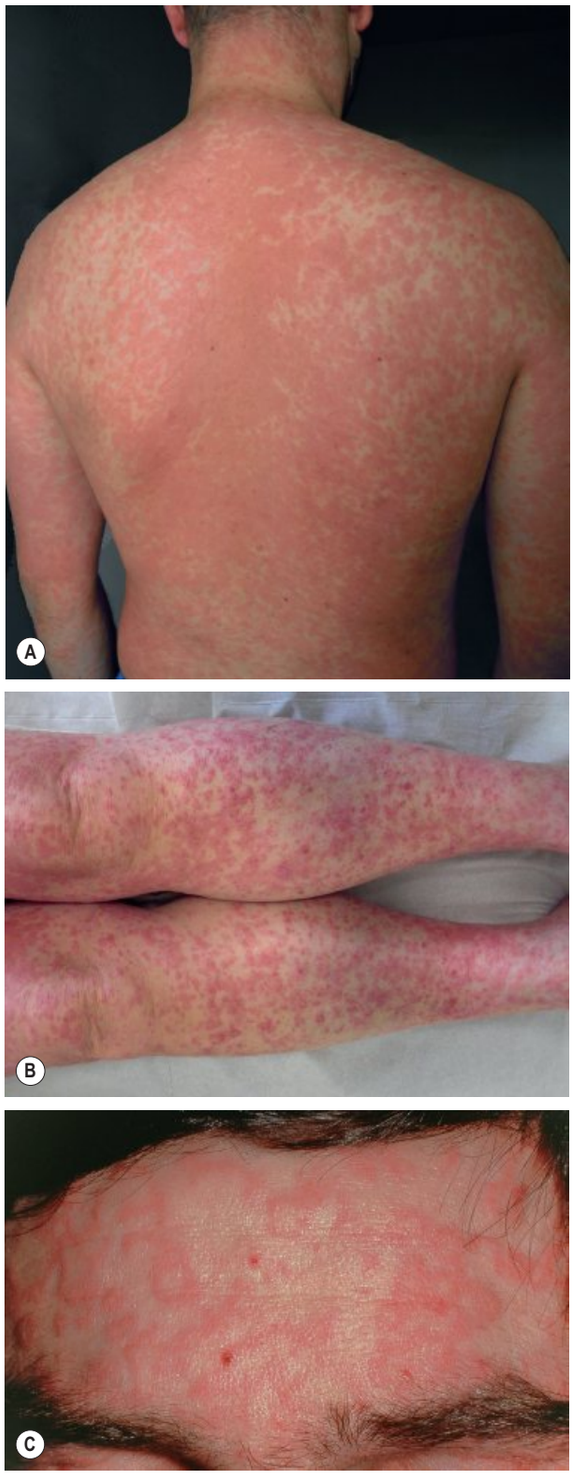


Fig. 21.3 Morbilliform (exanthematous) drug eruptions. A Erythematous papules and urticarial lesions with confluence on the midback induced by amoxicillin. **B** Due to dependency, lesions on the distal lower extremities can become petechial or purpuric. **C** Pink papules and annular lesions on the forehead due to phenobarbital. *A, B, Courtesy Laurence Valeyrie-Allanore, MD.*

lymphocytic infiltrate that may contain eosinophils (up to 70% of cases) in addition to interface changes.

The major entity in the differential diagnosis of a morbilliform drug eruption is a viral exanthem (e.g. Epstein–Barr virus [EBV], enterovirus, adenovirus, early HIV infection, human herpesvirus type 6 [HHV-6]; see Fig. 81.2). Peripheral blood eosinophilia and a polymorphous appearance point to a drug eruption, and in the absence of definitive evidence, drug eruptions are favored in adults whereas viral exanthems are favored in children. Occasionally, there is a viral infection that might enhance the risk of developing a drug eruption (see above)[9]. However, "idiopathic" exanthematous eruptions still remain a frequent occurence[18]. Toxic shock syndrome, scarlet fever, acute GVHD, Kawasaki disease, and SCARs should be excluded on the basis of associated clinical features (Fig. 21.4).

Treatment is supportive. Topical steroids may help to alleviate pruritus and reduce erythema. Discontinuing the culprit agent is the first therapeutic intervention. "Treating through", i.e. continuing the drug despite the cutaneous eruption, can be considered when there are no diagnostic criteria for a SCAR, the suspected drug is of paramount importance for the patient, and there is no satisfactory substitute drug. Desensitization may be considered in HIV-infected patients who require sulfonamides. Unfortunately, *in vitro* assays (see above) and patch testing (see Table 21.7) are of limited clinical utility.

RegiSCAR SCORING SYSTEM FOR DRESS			
Criteria	**No**	**Yes**	**Unknown/ unclassifiable**
Fever (≥38.5°C)	–1	0	–1
Lymphadenopathy (≥2 sites; >1 cm)	0	1	0
Circulating atypical lymphocytes	0	1	0
Peripheral hypereosinophilia	0		0
0.7–1.499 × 10^9/L - *or* - 10–19.9%*		1	
≥1.5 – 10^9/L - *or* - ≥20%*		2	
Skin involvement			
• Extent of cutaneous eruption >50% BSA	0	1	0
• Cutaneous eruption suggestive of DRESS†	–1	1	0
• Biopsy suggests DRESS	–1	0	0
Internal organs involved‡	0		0
One		1	
Two or more		2	
Resolution in ≥15 days	–1	0	–1
Laboratory results negative for at least three of the following (and none positive): (1) ANA; (2) blood cultures; (3) HAV/HBV/HCV serology; and (4) *Chlamydia* and *Mycoplasma* serology	0	1	0
Final score: <2, no case; 2–3, possible case; 4–5, probable case; >5, definite case			
*If leukocytes <4.0 × 10^9/L. †At least two of the following: edema, infiltration, purpura, scaling. ‡Liver, kidney, lung, muscle/heart, pancreas, or other organ and after exclusion of other explanations.			

Table 21.9 European Registry of Severe Cutaneous Adverse [Drug] Reactions (RegiSCAR) scoring system for DRESS (drug reaction with eosinophilia and systemic symptoms)[20]. This scoring system has been validated, but the resolution criterion is not helpful at the time of the initial diagnosis and the laboratory results criterion is in need of re-evaluation in the opinion of the editors. ANA, anti-nuclear antibody; BSA, body surface area; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)

Synonyms: ■ Drug-induced hypersensitivity syndrome (DIHS) ■ Drug-induced delayed multi-organ hypersensitivity syndrome (DIDMOHS)

DRESS is an unusual, potentially life-threatening, multi-organ adverse drug reaction[2]. Its incidence has been estimated to be between 1 in 1000 and 1 in 10 000 exposures to drugs such as aromatic anticonvulsants (e.g. phenytoin, carbamazepine, phenobarbital) and sulfonamides[19]. Additional names for this syndrome have arisen in part because not all patients have peripheral blood eosinophilia[19,20]. To aid in the clinical diagnosis of this disorder, two accepted scoring systems have been proposed as outlined in Tables 21.9 and 21.10[21].

Although the precise pathogenesis of DRESS is still not fully understood, several underlying mechanisms have been proposed, including a specific alteration in the metabolism of particular drugs. For example, genetic polymorphisms that affect detoxification of anticonvulsants and sulfonamides have been identified in patients recovering from DRESS. For aromatic anticonvulsants, the inability to detoxify toxic arene oxide metabolites is probably a key factor and would provide an explanation for the cross-reactivity between phenytoin, carbamazepine, and phenobarbital which has been well documented, both *in vivo* and *in vitro*[22].

Distinct HLA alleles have been associated with a significantly increased risk of developing *drug-specific* DRESS in certain populations (see Table 21.3)[23–26]. In addition, IL-5 plays a role in the generation of eosinophilia and drug-specific T cells that are activated in the skin and internal organs serve to mediate the disorder.

Also implicated in the pathogenesis of DRESS is reactivation of human herpes viruses, primarily HHV-6 and HHV-7, but also CMV and EBV[27]. In patients with DRESS, transmission of HHV-6 to skin-infiltrating $CD4^+$ T cells (and subsequent replication) was found to require recruitment of HHV-6^+ peripheral monomyeloid cells to damaged skin[28]. A study of 40 patients with DRESS noted reactivation of EBV, HHV-6, or HHV-7 in 76% of patients; activated circulating $CD8^+$ T cells with cutaneous homing markers secreted large amounts of TNF and IFN-γ, especially in those with the most severe visceral involvement. In patients' EBV-transformed B cells, culprit drugs triggered the production of EBV.

Clinically, DRESS develops 2 to 8 weeks after drug initiation, i.e. later than most other immunologically mediated skin reactions. With re-exposure and perhaps depending upon the particular drug, there can be a shorter time to onset. Fever and a cutaneous eruption are the most

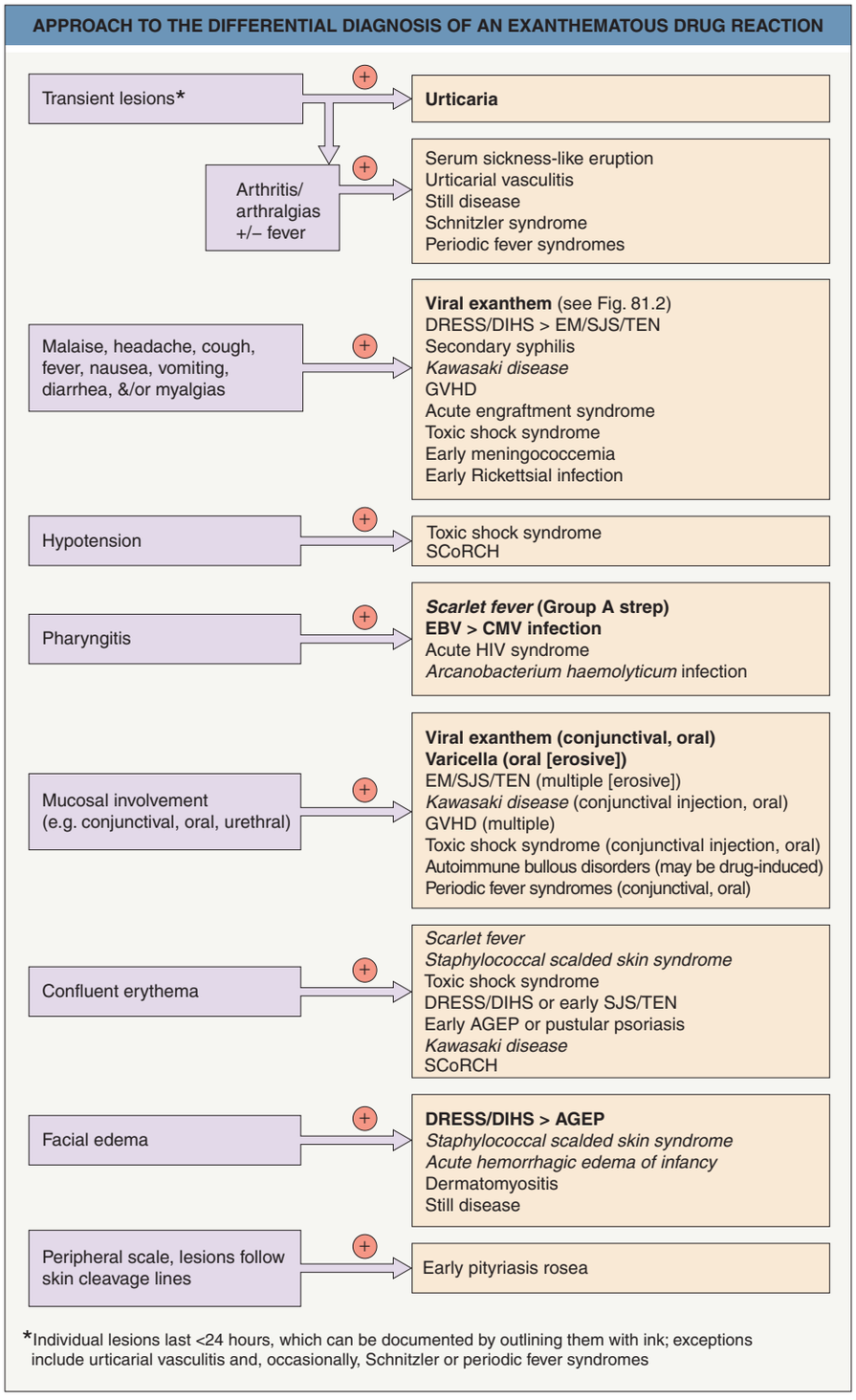


Fig. 21.4 Approach to the differential diagnosis of an exanthematous drug reaction. With a few exceptions (e.g. pityriasis rosea, drug-induced autoimmune bullous disorders), patients with these entities may be febrile. *Entities in italics occur primarily in children* and most common entities are in **bold**. Toxic shock syndrome can be staphylococcal or streptococcal (see Ch. 74). Drug-induced autoimmune bullous disorders: bullous pemphigoid or linear IgA bullous dermatosis > drug-induced pemphigus. Trimethoprim-sulfamethoxazole-associated sudden conjunctivitis, lymphopenia, and rash combined with hemodynamic changes (SCoRCH) is a rare disorder that presents with generalized sunburn-like erythema, fever, hypotension, and mild facial and acral edema as well as kidney and/or liver involvement; it can appear within a day if prior exposure and between 4 to 11 days if no prior exposure.

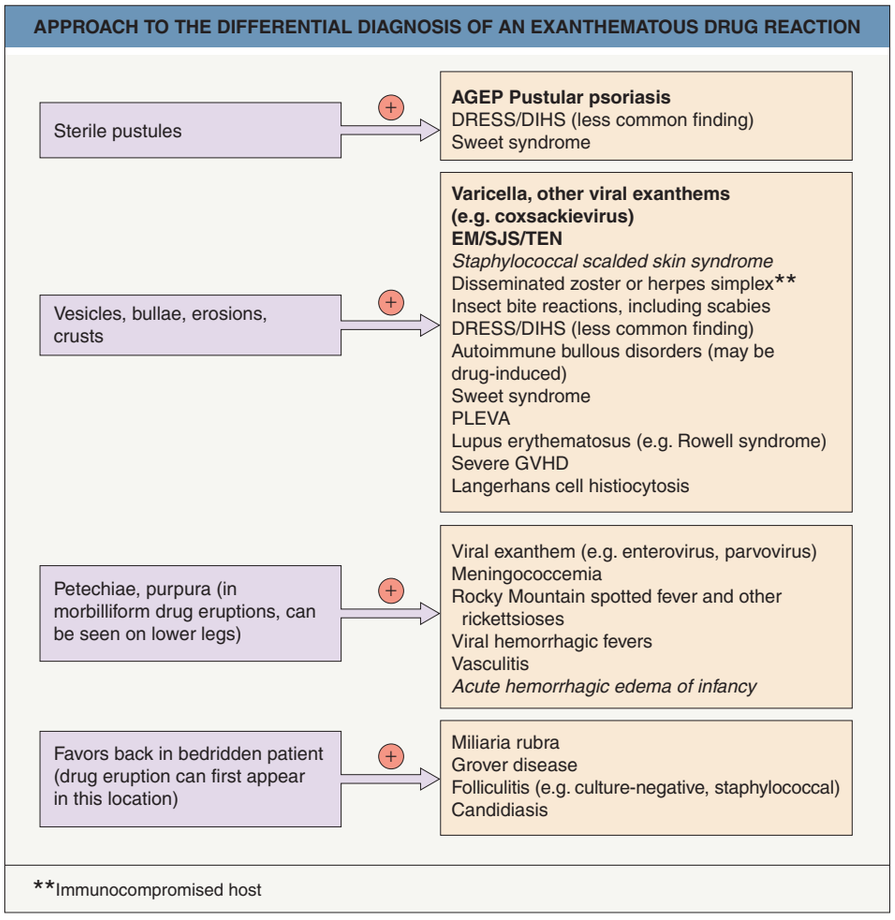


Fig. 21.4 Approach to the differential diagnosis of an exanthematous drug reaction. AGEP, acute generalized exanthematous pustulosis; CMV, cytomegalovirus; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein–Barr virus; EM, erythema multiforme; GVHD, graft-versus-host disease; PLEVA, pityriasis lichenoides et varioliformis acuta; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

J-SCAR DIAGNOSTIC CRITERIA FOR DRESS/DIHS
1. Maculopapular rash developing >3 weeks after starting therapy with a limited number of drugs
2. Prolonged clinical symptoms after discontinuation of the causative drug
3. Fever (>38°C)
4. Liver abnormalities (ALT >100 U/L)*
5. Leukocyte abnormalities (at least one present): (a) leukocytosis (>11 × 10^9/L); (b) atypical lymphocytes (>5%); and (c) eosinophilia (>1.5 × 10^9/L)
6. Lymphadenopathy
7. HHV-6 reactivation
*This can be replaced by other organ involvement (e.g. renal).

Table 21.10 Japanese Research Committee on Severe Cutaneous Adverse [Drug] Reactions (J-SCAR) diagnostic criteria for DRESS (drug reaction with eosinophilia and systemic symptoms)/DIHS (drug-induced hypersensitivity syndrome). Typical DIHS is defined as the presence of all 7 criteria, while atypical DIHS is defined as the presence of only the first 5 criteria.

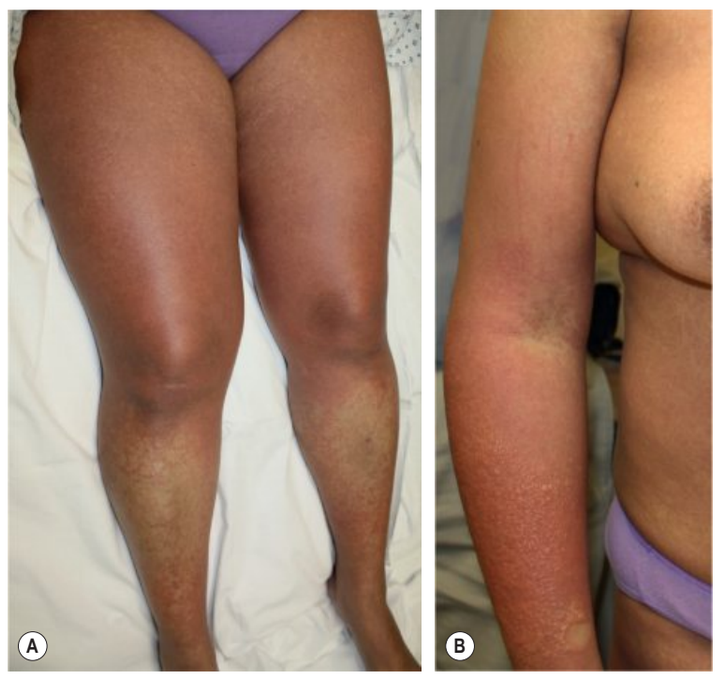


Fig. 21.5 Drug reaction with eosinophilia and systemic symptoms (DRESS) due to carbamazepine. A Exanthematous eruption with confluence on the thighs. **B** Edema and vesiculation on the forearm. *Courtesy Alicia Little, MD.*

common symptoms, seen in 85% and 75% of patients, respectively[21,29]. Cutaneous involvement usually begins as a morbilliform eruption (Fig. 21.5A), which later becomes edematous and oftentimes more extensive and sometimes erythrodermic. Less common manifestations include vesicles (Fig. 21.5B), follicular or non-follicular pustules (~20% of patients, overlapping with AGEP), and erythema multiforme-like or purpuric lesions. The face, upper trunk, and extremities are usually the initial sites of involvement. Edema of the face is a frequent finding and is a hallmark of DRESS whereas mucosal involvement, if present, is mild.

The major internal manifestations include lymphadenopathy and hepatitis (~80% of patients); rarely, the latter may become life-threatening (see Tables 21.9 and 21.10). Patients may also develop renal involvement (e.g. interstitial nephritis), myocarditis, interstitial pneumonitis, myositis, thyroiditis, and even infiltration of the brain by eosinophils. Of note, DRESS has overlap with and/or may progress to hemophagocytic lymphohistiocytosis. The cutaneous and visceral involvement may persist for several weeks or months after drug withdrawal, and additional sites of involvement (e.g. cardiac, thyroid) may develop weeks or months later, including following a taper of corticosteroids. Overall mortality due to DRESS ranges from 2% to 10%[21]. Possible predictors of more severe disease include a higher fever (>38.5°C), purpura, erythema multiforme-like lesions, and histologic features of severe dyskeratosis, interface dermatitis, and an intense lymphocytic infiltrate with atypical lymphocytes.

ASSESSMENT AND LONGITUDINAL EVALUATION OF PATIENTS WITH DRESS (DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS)
Basic laboratory screening during the acute phase with recommended repetitive tests *in italics**
• *CBC with differential, platelet count*, peripheral smear for atypical lymphocytes • *BUN, creatinine, urinalysis*, spot urine for protein : creatinine ratio† • *LFTs, creatine kinase (CK)*, lipase, CRP • *TSH, free T4* (repeat at 3 months, 1 year, and 2 years) • Fasting glucose (in anticipation of systemic corticosteroids)
Additional testing
• ECG, troponin T, baseline echocardiogram • Quantitative PCR for HHV-6, HHV-7, EBV, CMV • Wright stain of urine for eosinophilia (prior to instituting corticosteroids) • ANA, blood cultures (exclusion criteria in RegiSCAR scoring system) • If hemophagocytic lymphohistiocytosis suspected (see Ch. 91)‡: ferritin, triglycerides, LDH, BM examination
Further testing based upon laboratory abnormalities or signs and symptoms‡
• Liver – PT, PTT, albumin • Renal – albumin, renal ultrasound (if laboratory abnormalities) • Cardiac – ECG, troponin T, echocardiogram • Neurologic – brain MRI • Pulmonary – CXR, PFTs • Gastrointestinal – endoscopy • Pancreas – amylase, lipase, CT abdomen; rarely type I diabetes mellitus
*Testing is more frequent during the acute phase (e.g. twice weekly) with frequency also a reflection of disease severity. Longitudinal evaluation is recommended for at least one year. †Allows for immediate assessment for proteinuria. ‡Including during longitudinal evaluation.

Table 21.11 Assessment and longitudinal evaluation of patients with DRESS (drug reaction with eosinophilia and systemic symptoms). BM, bone marrow; BUN, blood urea nitrogen; CBC, complete blood count; CK, creatine kinase; CRP, C-reactive protein; LDH, lactic dehydrogenase; LFTs, liver function tests; PFT, pulmonary function test; PT, prothrombin time; PTT, partial thromboplastin time; TSH, thyroid stimulating hormone.

DRUGS ASSOCIATED WITH DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)	
Drug category	**Specific drugs**
Anticonvulsants	**Carbamazepine, lamotrigine*, phenobarbital, phenytoin**, oxcarbazepine, zonisamide > gabapentin, valproic acid
Antimicrobials	Amoxicillin, ampicillin, azithromycin, cefotaxime, **dapsone**, ethambutol, isoniazid, levofloxacin, linezolid, metronidazole, **minocycline**, piperacillin/tazobactam, pyrazinamide, quinine, rifampin, streptomycin, **sulfasalazine**, teicoplanin, **trimethoprim–sulfamethoxazole**, **vancomycin****
Antiretrovirals	**Abacavir**, **nevirapine**, zalcitabine
Analgesics/NSAIDS	Acetaminophen, celecoxib, diclofenac, ibuprofen
Antidepressants	Bupropion, fluoxetine
Antihypertensives	Amlodipine, captopril
Direct acting antivirals for hepatitis C	Boceprevir, telaprevir
Immune checkpoint inhibitors	Durvalumab, **ipilimumab**, nivolumab
Targeted therapies for cancer	Imatinib, sorafenib, **vemurafenib†**, vismodegib
Miscellaneous	**Allopurinol‡**, azathioprine, fluindione, hydroxychloroquine, lenalidomide, mexiletine, omeprazole, olanzapine, phenindione, ranitidine, strontium ranelate, ziprasidone; radiocontrast media
*Especially when coadministered with valproic acid. **Higher trough levels and re-exposure may be risk factors. †Increased risk after immune checkpoint inhibitor therapy and may have earlier onset. ‡Full doses in the setting of renal dysfunction a risk factor.	

Table 21.12 Drugs associated with drug reaction with eosinophilia and systemic symptoms (DRESS). Most commonly associated drugs are in **bold**. NSAIDs, nonsteroidal anti-inflammatory drugs.

Histologically, various inflammatory patterns can be seen, including eczematous, interface dermatitis, AGEP-like, and erythema multiforme-like. Prominent peripheral blood eosinophilia is common and is a very characteristic feature. It is often accompanied, and sometimes replaced, by mononucleosis-like atypical lymphocytosis. Elevation of hepatic enzymes can be a worrisome finding and requires serial evaluation. Thyroid and cardiac dysfunction (as detected by an ECG and echocardiogram) may develop as delayed complications and patients should therefore undergo longitudinal evaluation (Table 21.11).

The major entities in the differential diagnosis include other cutaneous drug eruptions, viral infections, hypereosinophilic syndrome, lymphoma (especially angioimmunoblastic T cell lymphoma), and pseudolymphoma (e.g. HIV-related $CD8^+$ cutaneous pseudolymphoma)[27]. Involvement of multiple internal organs differentiates DRESS from the more common morbilliform eruptions. In addition to the most common etiologies – the aromatic anticonvulsants (phenobarbital, carbamazepine, and phenytoin), lamotrigine (especially when coadministered with valproic acid), and sulfonamides – vancomycin, minocycline, allopurinol, and dapsone may also induce this syndrome, as well as drugs used to treat HIV infection (e.g. abacavir) and targeted therapies for cancer (e.g. vemurafenib; Table 21.12).

Early withdrawal of the culprit drug is mandatory, but this may not result in a rapid complete recovery. Although guidelines for the treatment of DRESS are still lacking, systemic corticosteroids (oral or intravenous) typically represent first-line therapy, at least in moderate-to-severe DRESS. Because relapse can occur when the dosage is reduced, a slow taper of corticosteroids over a period of 3 to 6 months is required[30]. In milder cases of DRESS, even in the setting of mild hepatitis, topical high-potency corticosteroids may be helpful and may lead to less viral reactivation[29]. In a recent trial of IVIg (without corticosteroids), there was an increased risk of complications, and little therapeutic benefit. There are also reports of successful treatment with cyclosporine or JAK inhibitors[30a,30b]. To date, antiviral strategies have only been proposed in case reports[31].



Fig. 21.6 Serum sickness due to antithymocyte globulin. The purpuric lesions are due to small vessel vasculitis in this patient with aplastic anemia. *Courtesy Jean L. Bolognia, MD.*

Serum Sickness-Like Eruption

This syndrome is more commonly observed in children and typically includes fever, arthralgias, arthritis, rash (urticarial, morbilliform), and lymphadenopathy[2]. It occurs 1 to 3 weeks after drug exposure. Unlike in "true" serum sickness due to non-human proteins (e.g. antithymocyte globulin, tositumomab, infliximab; Fig. 21.6), hypocomplementemia, circulating immune complexes, vasculitis, and renal disease are absent. This reaction occurs in approximately 1 in 2000 children given

cefaclor. Other drugs associated with serum sickness-like reactions are penicillins, NSAIDs, bupropion, phenytoin, sulfonamides, minocycline, and propranolol.

Vasculitis (see Ch. 24)

Drug-induced cutaneous small vessel vasculitis (CSVV) accounts for ~10% of all cases of CSVV and typically involves small vessels and in some patients medium-sized vessels. Drug-induced CSVV may be either a type II (cytotoxic) or a type III (immune complex) drug reaction.

Clinically, drug-induced CSVV usually presents as purpuric papules, primarily on the lower extremities. Urticaria-like lesions, hemorrhagic blisters, pustules, digital necrosis, and ulcers may also be seen. Systemic involvement is unusual, but suggestive symptoms are fever, myalgias, arthralgias, and/or headache. Internal manifestations include arthritis, nephritis, peripheral neuropathy, and gastrointestinal bleeding. Histopathologic examination demonstrates leukocytoclastic vasculitis.

Vasculitis usually develops 7 to 21 days after drug administration and within 3 days if a rechallenge. Systemic corticosteroids may benefit patients with systemic involvement; otherwise, discontinuing the culprit drug is usually sufficient. Additional management options are discussed in Chapter 24.

The primary medications associated with drug-induced CSVV include penicillins, NSAIDs (both oral and topical), sulfonamides, and cephalosporins; additional drugs are propylthiouracil, thiazide diuretics, furosemide, allopurinol, quinolones, levamisole, bortezomib, and systemic immunomodulators (e.g. granulocyte and granulocyte–macrophage colony-stimulating factors [G-CSF, GM-CSF], interferons, TNF inhibitors). ANCA-positive vasculitis with anti-myeloperoxidase antibodies has been associated with several drugs, including propylthiouracil, hydralazine, levamisole, and minocycline, and polyarteritis nodosa has been observed following hepatitis B vaccination[32] and in patients receiving minocycline.

Neutrophilic Drug Eruptions

Acute generalized exanthematous pustulosis

Synonyms: ■ Pustular drug eruption ■ Toxic pustuloderma

Acute generalized exanthematous pustulosis (AGEP) is an acute febrile drug eruption characterized by numerous small, primarily non-follicular, sterile pustules arising within large areas of edematous erythema. More than 90% of cases of AGEP are drug-induced. Occasionally, AGEP is due to other causes, e.g. enteroviral infection, exposure to mercury.

HLA-B5, -DR11, and -DQ3 have been found more frequently in patients with AGEP[33], and mutations in *IL36RN* may be a risk factor as well[34]. Prior sensitization (including contact sensitization) would explain the short interval (<4 days) between drug administration and the onset of the eruption, as this suggests an immunologic recall phenomenon. The percentage of positive patch tests to an incriminated drug is relatively high (50%–60%) (Fig. 21.7A)[15]. Blood neutrophilia and the accumulation of neutrophils within the lesions suggest the release of neutrophil-activating cytokines by drug-specific T lymphocytes (e.g. IL-3, IL-8, IL-17, G-CSF), but the precise underlying mechanisms of AGEP are still unknown.

Clinically, AGEP is characterized by a high fever, with skin lesions beginning on the face or in the major intertriginous zones (i.e. axillae and groin), followed by dissemination over a few hours. Numerous small (<5 mm), primarily non-follicular, sterile pustules arise within large areas of edematous erythema (Fig. 21.7B,C). There may be associated burning and/or pruritus. Lesions typically last from 1 to 2 weeks and are followed by superficial desquamation. In a series of 58 patients, systemic involvement was detected in a minority (17%) of patients, with the primary sites being the liver and kidneys followed by the lungs (acute respiratory distress)[34]. A validation score developed

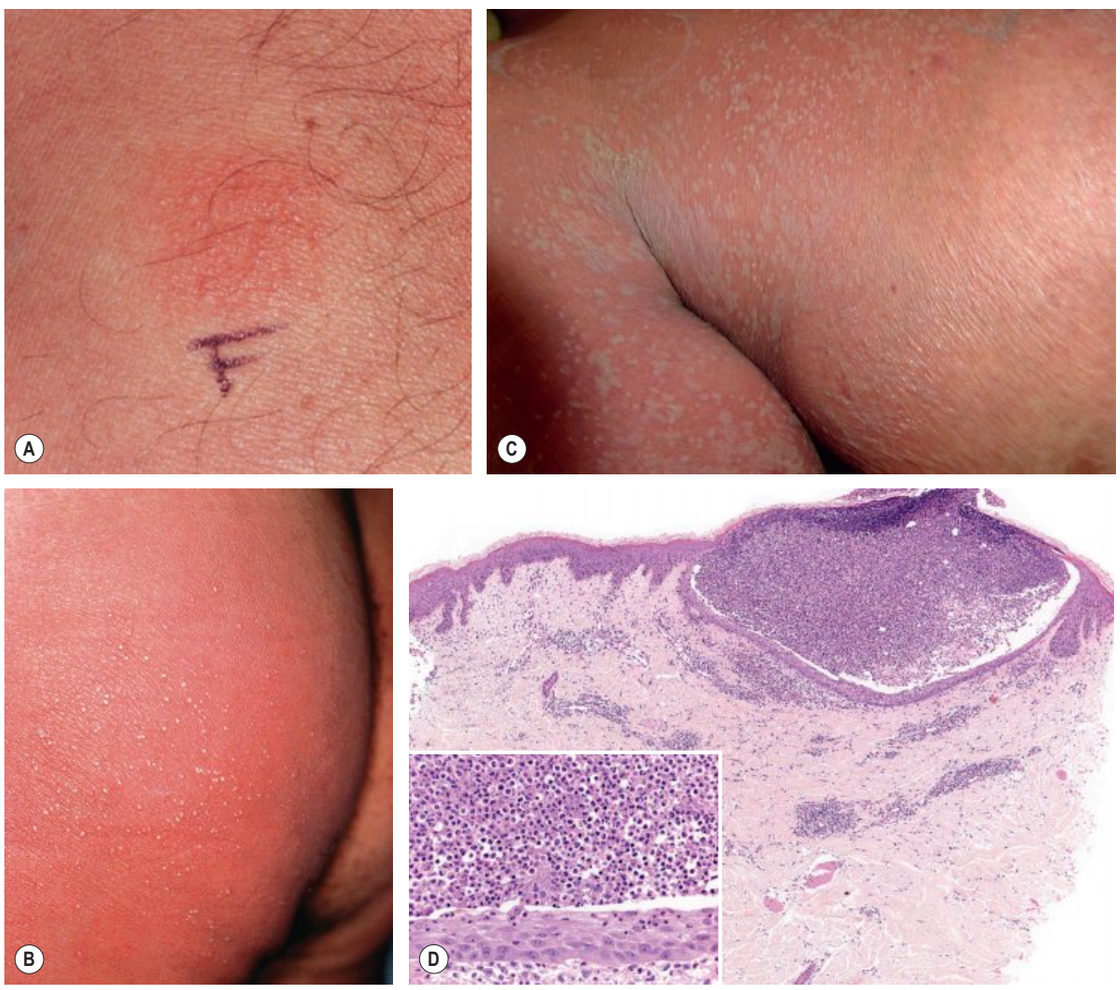


Fig. 21.7 Acute generalized exanthematous pustulosis (AGEP). **A** Positive patch test result 4 days following the application of 0.75% metronidazole in a patient with a previous pustular drug eruption to that medication. **B** Diffuse erythema of the buttock with multiple small sterile pustules due to a cephalosporin. **C** Numerous sterile pustules with superficial epidermal detachment in areas where the pustules have become confluent in a patient receiving amoxicillin. **D** Subcorneal pustule composed of neutrophils as well as scattered neutrophils within the epidermis (inset). *A, Courtesy Kalman Watsky, MD; C, Courtesy Laurence Valeyrie-Allanore, MD; D, Courtesy Lorenzo Cerroni, MD.*

AGEP – MOST COMMONLY ASSOCIATED MEDICATIONS	
• Acetaminophen • Antibiotics **Penicillins, aminopenicillins** Carbapenems **Cephalosporins** Chloramphenicol **Clindamycin** Gentamicin Isoniazid Macrolides Metronidazole **Pristinamycin** Quinolones **Sulfonamides** Tetracyclines Vancomycin	• Antimalarials, especially hydroxychloroquine • Antimycotics Amphotericin B Fluconazole Griseofulvin Itraconazole Ketoconazole Nystatin **Terbinafine** • Calcium channel blockers, especially **diltiazem** • Carbamazepine • Cetirizine • Herbal medicines • NSAIDs, including oxicam derivatives and COX-2 inhibitors • Proton pump inhibitors

Table 21.13 Acute generalized exanthematous pustulosis (AGEP) – most commonly associated medications. An annular variant can also occur, in particular with terbinafine and hydroxychloroquine, and the onset may be delayed. Common culprits are in **bold**.

by the EuroSCAR study group assists in categorizing cases as definite, probable, possible, or no AGEP[35].

Rarely, a localized variant of AGEP, referred to as acute localized exanthematous pustulosis (ALEP), occurs. There is involvement of a single site, most commonly the face, neck, or trunk, with ALEP most often due to b-lactam antibiotics. Fever and peripheral neutrophilia are associated findings.

Histologically, spongiform pustules are seen within the superficial layers of the epidermis (Fig. 21.7D). Edema of the papillary dermis and a perivascular mixed infiltrate with neutrophils and some eosinophils are usually present. A complete blood count typically reveals a marked leukocytosis with an elevated neutrophil count.

AGEP must be differentiated from acute pustular psoriasis of the von Zumbusch type; no personal history of psoriasis, rapid appearance, and recent drug exposure all favor AGEP. In severe forms of AGEP, the confluence of the pustules and subsequent superficial epidermal detachment may lead to confusion with TEN. However, the presence of subcorneal pustules in biopsy specimens allows one to distinguish between the two entities. In addition to facial edema, pustules may also be observed in DRESS, but the prolonged evolution, atypical lymphocytosis, marked hypereosinophilia, and common visceral involvement usually permit differentiation. That said, a true overlap drug reaction with features of both AGEP and DRESS may be observed[36].

Medications that most frequently induce AGEP include: (1) antibiotics, e.g. aminopenicillins, cephalosporins, clindamycin, and outside of the US, pristinamycin; and (2) calcium channel blockers, e.g. diltiazem. Additional associated drugs are listed in Table 21.13[37]. Withdrawal of the responsible drug is the major therapeutic intervention, in conjunction with topical corticosteroids and antipyretics.

Sweet syndrome (acute febrile neutrophilic dermatosis) (see Ch. 25)

Drug-induced Sweet syndrome is increasingly being recognized, but still remains a relatively unusual condition[38]. Sweet syndrome is characterized by fever, peripheral blood neutrophilia, and painful erythematous plaques that favor the face and upper extremities and contain dense neutrophilic dermal infiltrates. Neutrophilic infiltrates can be seen elsewhere, including the muscles and lung. In drug-induced Sweet syndrome, the lesions usually develop about a week after initial drug administration and neutrophilia is often absent. The latter finding most likely reflects the fact that drug-induced Sweet syndrome is frequently due to granulocyte growth factors used to reverse chemotherapy-induced neutropenia.

The list of drugs associated with drug-induced Sweet syndrome continues to expand. It includes granulocyte growth factors (G-CSF, GM-CSF, pegfilgrastim), all-*trans*-retinoic acid, other antineoplastic medications (e.g. bortezomib, FLT3 inhibitors, immune checkpoint inhibitors, imatinib, decitabine, azacitidine), antibiotics (e.g. trimethoprim–sulfamethoxazole, minocycline, quinolones), abacavir, azathioprine, furosemide, hydralazine, interferon-α, and NSAIDs[38]. Following withdrawal of the responsible drug, the fever abates in 1 to 3 days and the lesions disappear within 3 to 30 days. Systemic corticosteroids may be required in severe cases. Of note, when these medications are used to treat Sweet syndrome-associated disorders or treatment-associated neutropenia, timing of the eruption and degree of control of the underlying disorder need to be considered when determining underlying etiology.



Fig. 21.8 Iododerma. Edematous erythematous vesiculopustules on the buttocks with central crusts.

Halogenoderma

Bromoderma, fluoroderma, and iododerma are rare dermatoses that develop following exposure to bromides, fluorides, iodides, and iodine-containing compounds. The latter two groups are used as radiation protectants, in combination therapy for hyperthyroidism, and as expectorants (saturated solution of potassium iodide; SSKI). Systemic exposure to iodine-containing contrast media, irrigation of wounds with povidone-iodine, ingestion of iodide-containing supplements, and the use of amiodarone are additional causes of iododerma. One important risk factor for the development of these reactions is acute or chronic renal failure.

Halogens classically induce acneiform eruptions and pustules, but granulomatous or vegetative plaques, ulcers, and even bullae can be seen (Fig. 21.8). Although cutaneous lesions often appear after long-term exposure, they can appear in as quickly as a few days. Histologically, accumulation of neutrophils within the dermis is seen and exocytosis of neutrophils into the epidermis can lead to intraepidermal abscesses. In longer-standing lesions, papillomatosis develops. Histologic evaluation and measurement of blood levels of iodine and bromide aid in establishing the diagnosis. Halogenodermas may persist for weeks after drug withdrawal because of the slow elimination rate of iodides and bromides. Topical and systemic corticosteroids, in addition to diuretics, may hasten resolution, and, in severe cases, cyclosporine may be administered.

Other Neutrophilic Eruptions

Neutrophilic eccrine hidradenitis (NEH) is characterized by erythematous, often painful papules and plaques due to neutrophilic infiltrates around and within eccrine glands (Fig. 21.9). Common sites of involvement include the face, upper trunk, and dorsal aspect of the hands. NEH is most frequently seen 7–14 days after initiating chemotherapy, in particular cytarabine plus an anthracycline (e.g. idarubicin, mitoxantrone) for acute myelogenous leukemia; additional culprit drugs include bleomycin, imatinib, and G-CSF (see Ch. 39). Facial pustular neutrophilic eruption can be seen following SARS-CoV-2 vaccine administration.

Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDRIFE)

In SDRIFE, sharply demarcated, symmetrical areas of erythema develop in the anogenital region following exposure to a systemically administered drug, most commonly amoxicillin or another β-lactam antibiotic. Often based upon case reports, it has also been associated with other antimicrobials, radiocontrast media, and H2 blockers as well as the



Fig. 21.9 Neutrophilic eccrine hidradenitis. Erythematous plaques on the leg, which may be confused with Sweet syndrome. *Courtesy Laurence Valeyrie-Allanore, MD and Jean Revuz, MD.*

SYMMETRICAL DRUG-RELATED INTERTRIGINOUS AND FLEXURAL EXANTHEMA (SDRIFE) – CLINICAL CRITERIA AND REPORTED CULPRIT DRUGS	
Clinical criteria	
• Exposure to a *systemically* administered drug*, occurring with either the initial or a repeated dose (excluding contact allergens) • Sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area • Involvement of at least one other intertriginous site/flexural fold • Symmetry of affected areas • Absence of systemic symptoms and signs	
Reported culprit drugs and vaccines	
Antimicrobials	HCTZ/telmisartan
Azoles	IVIg
β-Lactams	Mitomycin
Clindamycin	NSAIDs (e.g. celecoxib)
Macrolides	Oxycodone
Metronidazole	Progestin/estrogen vaginal ring
Terbinafine	Proton pump inhibitors
Tetracyclines	**Radiocontrast media**
Valacyclovir	Risperidone
Acetaminophen	Tacrolimus
Allopurinol	Traditional Chinese medicine
EGFR inhibitors (e.g. cetuximab, gefitinib)	TNF inhibitors
Everolimus	Zoledronic acid
H2 blockers (e.g. cimetidine, famotidine)	SARS-CoV-2 vaccine
*Not a chemotherapeutic agent so as to not confuse with toxic erythema of chemotherapy.	

Table 21.14 Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) – clinical criteria and reported culprit drugs. This entity is also referred to as drug-induced intertrigo, flexural drug eruption, and baboon syndrome. The latter term is also used to describe a form of systemic contact dermatitis. More common culprit drugs are in **bold**. *Adapted from Häusermann P, Harr TH, Bircher AJ. Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? Contact Derm 2004;51:297–310.*

medications listed in Table 21.14. Typically, there is involvement of at least one other flexural site. Confusion arises because some patients with systemic contact dermatitis may have erythema of the buttocks and upper inner thighs, with both the latter clinical presentation – as well as SDRIFE – sometimes referred to as baboon syndrome. The differential diagnosis also includes fixed drug eruption and toxic erythema of chemotherapy, but the history of chemotherapy administration 2–4 weeks earlier permits distinction.

Bullous Eruptions

Fixed drug eruption

In fixed drug eruption (FDE), lesions develop from a few days to two weeks after the initial exposure. With subsequent exposures, they usually appear within 24 hours. However, because the first episode is often undiagnosed or underdiagnosed, a brief time interval is most commonly observed. Clinically, one or a few round to oval, sharply demarcated, erythematous to dusky violet plaques are seen (Fig. 21.10A,B). Associated edema varies and vesiculobullae may develop centrally (bullous FDE), followed by erosions due to epidermal detachment (Fig. 21.10B–E).

Lesions can appear anywhere on the body, as well as the mucous membranes (Fig. 21.10F), with common sites being the lips, face, hands, feet, and genitalia. Over several days, the lesions fade and often, but not always, leave residual postinflammatory brown pigmentation (Fig. 21.10G,H). Upon readministration of the causative drug, lesions recur in exactly the same sites. With each subsequent recurrence, additional sites of involvement may appear or the number of lesions may remain constant. The presence of numerous lesions, involving more than two or three anatomical sites, is referred to as generalized bullous FDE (GBFDE; see Fig. 21.10D,E), and it may be difficult to distinguish from TEN (especially when the oral mucosa is also involved), but an asymmetric distribution pattern and large skip areas point to GBFDE. GBFDE occurs more commonly in older patients, and prognosis correlates with the extent of skin detachment[39].

A non-pigmenting variant of FDE, characterized by large erythematous edematous plaques, has also been described. It occurs primarily after administration of pseudoephedrine, but has been observed with other drugs, e.g. NSAIDs, acetaminophen, tetrahydrozoline (eye drops). Linear FDE is a rare variant that may be confused with linear lichen planus. The proposed pathogenic events in FDE are depicted in Fig. 11.3.

Histopathology reveals a lichenoid infiltrate composed of lymphocytes admixed with eosinophils, and sometimes neutrophils. There are usually scattered necrotic keratinocytes in the epidermis (Fig. 21.11A) or rarely extensive epidermal necrosis that is indistinguishable from SJS/TEN (Fig. 21.11B); deeper extension of the infiltrate and more prominent melanin incontinence point to FDE. Dermal melanophages are often the only histologic finding in non-inflammatory lesions.

The drugs most frequently associated with FDE include antibiotics (sulfonamides, tetracyclines > β-lactams, fluoroquinolones, macrolides), NSAIDs, acetaminophen, aspirin, barbiturates, dapsone, proton pump inhibitors, and azole antifungal drugs[40]. In some patients, the responsible drug can be readministered without inducing an exacerbation, and there may be a refractory period after the occurrence of a fixed eruption. Provocation via patch testing in a previously *involved* site may be useful in determining the responsible drug (as long as not performed during the refractory period; see Table 21.7).

If there is a single lesion, the differential diagnosis includes a spider or arthropod bite reaction whereas when there are multiple lesions, it includes erythema multiforme and TEN. Genital and periungual lesions may be misdiagnosed as a recurrent HSV infection or paronychia, respectively.

Linear IgA bullous dermatosis

Linear IgA bullous dermatosis (LABD) is an autoantibody-mediated subepidermal blistering disease that may be drug-induced. Tense vesicles and bullae appear 24 hours to 15 days after the culprit medication is begun. The blisters often have an annular configuration, as in the idiopathic form of the disease (see Ch. 31), but there can also be a TEN-like clinical presentation, especially when due to vancomycin[41]. Histologic examination shows subepidermal bullae with neutrophils in the dermis. Direct immunofluorescence reveals linear deposition of IgA (+/– IgG, C3) within the basement membrane zone. Most patients lack circulating IgA autoantibodies. Resolution occurs within 2 to 5 weeks of discontinuation of the responsible medication. Vancomycin is the most common cause of drug-induced LABD; less often β-lactam antibiotics, captopril, NSAIDs, phenytoin, sulfonamide antibiotics, amiodarone, furosemide, lithium, rifampin, and G-CSF are the inciting drugs (see Table 31.5)[41]. The origin of the drug exposure may initially be obscure as in vancomycin-loaded bone cement spacers.



Fig. 21.10 Fixed drug eruptions. A An oval, well-demarcated red–brown plaque with a more erythematous border. **B** Multiple round violet-colored lesions with central bullae. **C** Erosive lesion of the penis due to epidermal detachment; this clinical presentation is sometimes misdiagnosed as recurrent HSV infection. **D, E** Generalized bullous FDE with involvement of the genitalia and intertriginous zones; erosions are seen following rupture of the bullae. Because of its more widespread distribution, this variant can be confused with TEN. **F** In the mouth, mucosal detachment leads to erosions. **G** As the inflammation resolves, the lesion acquires a brown hue. **H** Once inflammation is completely resolved, circular or oval areas of hyperpigmentation are commonly seen. Responsible drugs were phenolphthalein (**A**), acetaminophen (**B**), ciprofloxacin (**C**), naproxen (**D**), pseudoephedrine (**E**), allopurinol (**F**), metronidazole (**G**), and trimethoprim–sulfamethoxazole (**H**). *B, Courtesy Jeffrey P. Callen, MD, and Tyler Geers, MD; C, F, G, Courtesy Kalman Watsky, MD; D, Courtesy Sara Perkins, MD; E, Courtesy Edward W. Cowen, MD; H, Courtesy Mary Stone, MD.*

Drug-induced bullous pemphigoid

Drug-induced bullous pemphigoid (BP) may occur up to months after initial administration of a new medication. The clinical presentation is similar to the spontaneous form of this autoimmune disorder. Three major classes of inducers have been identified – diuretics (e.g. furosemide, spironolactone), neuroleptics (e.g. phenothiazine), and more recently, dipeptidyl peptidase 4 inhibitors ("gliptins") that function as hypoglycemic agents[42,43]. Anti-PD-1/PD-L1 antibodies have also been recognized as triggers of BP (see Ch. 30)[44]. The histologic and direct immunofluorescence findings are similar to those observed in BP, and the possibility of drug-induced disease should always be considered.

Drug-induced pemphigus vulgaris and pemphigus foliaceus are discussed in Chapter 29.

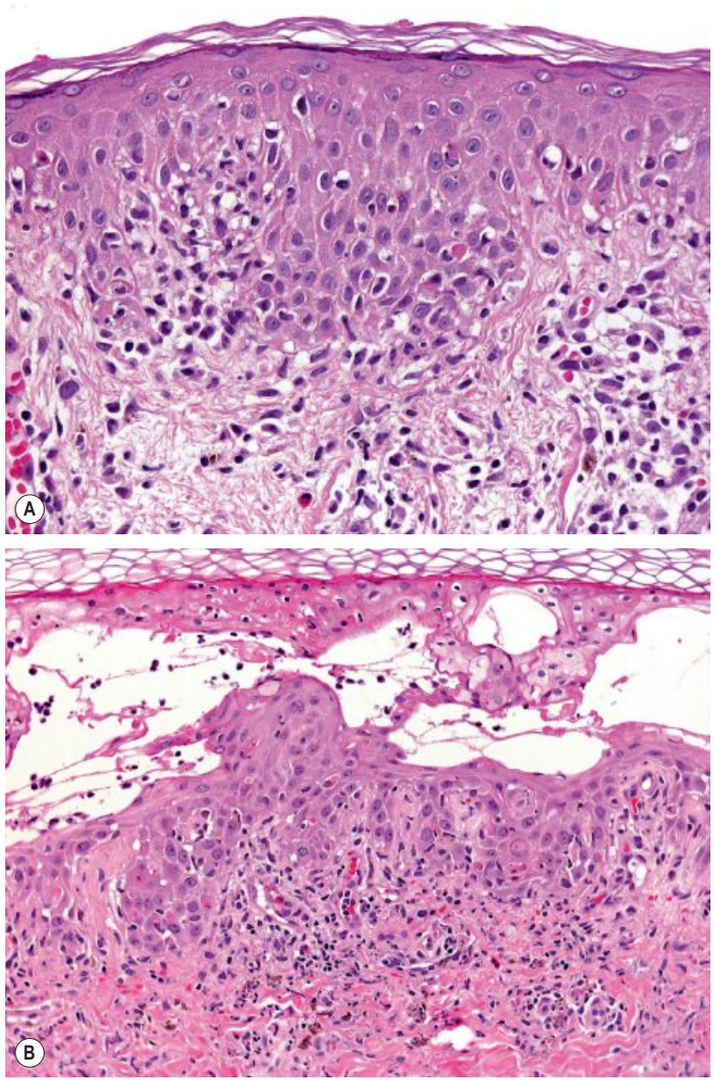


Fig. 21.11 Fixed drug eruptions – histopathologic features. A A few necrotic keratinocytes, mild vacuolar changes at the dermal–epidermal junction, papillary dermal edema, and melanophages can be seen as well as a mixed infiltrate with neutrophils and an occasional eosinophil. **B** Sometimes there is more extensive epidermal necrosis. *Courtesy Lorenzo Cerroni, MD.*

Stevens–Johnson syndrome and toxic epidermal necrolysis (see Ch. 20)

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered rare, life-threatening, drug-induced skin reactions within a clinical spectrum[45] and early detection is essential[2]. During the acute phase, the mean mortality rate is ~15% and depends upon body surface area involved as well as the level of supportive care[46,47].

These diseases are discussed in detail in Chapter 20.

Photosensitivity (see Ch. 87)

Cutaneous photosensitivity may be idiopathic, due to endogenous photosensitizers (e.g. porphyrins), or result from exogenous photosensitizers (e.g. medications). The combination of light (ultraviolet or visible) plus drug can lead to a range of cutaneous findings, but classically photosensitivity drug reactions are divided into two major types – phototoxic and photoallergic[48]. The former is more common than the latter.

Phototoxicity

Phototoxic drug reactions are usually predictable. They occur immediately after exposure to ultraviolet radiation (UVR) and are often dependent on the dose of the drug and/or UVR. There is a direct interaction of UVR with the drug (or its metabolite) within the skin such that an unstable singlet or triplet state is created, leading to the generation of reactive oxygen species. The latter are responsible for cellular damage.



Fig. 21.12 Phototoxic reaction in a patient receiving methotrexate. The erythema and bullae are obviously limited to sun-exposed sites and resemble an exaggerated sunburn. Patients on methotrexate can also experience a "sunburn-recall" phenomenon.



Fig. 21.13 Photolichenoid drug eruption due to hydrochlorothiazide. The lesions favored the extensor surfaces of the forearms.

Clinically, a phototoxic drug reaction usually resembles an exaggerated sunburn limited to sun-exposed sites (Fig. 21.12) and is often followed by postinflammatory hyperpigmentation. Histologically, necrotic keratinocytes are present as well as variable degrees of edema and vasodilation and a sparse lymphocytic infiltrate within the dermis.

Photo-onycholysis and pseudoporphyria are less common clinical presentations. In the former, the nail plate separates from the nail bed of several digits, with minimal nail bed changes. Fragility, erosions, and vesicles of the dorsal hands and face are observed in pseudoporphyria, but plasma porphyrins are normal (see Ch. 49).

The drugs most commonly responsible for phototoxic reactions contain ringed chemical structures and include doxycycline, quinolones, NSAIDs, thiazide diuretics, amiodarone, voriconazole, chlorpromazine, and vemurafenib[48] (see Table 87.5). Pseudoporphyria is most frequently linked to naproxen (see Table 49.5). For drugs with a short half-life, administration of the drug in the evening may decrease the risk below the clinical threshold for phototoxicity.

Photoallergy

Photoallergic drug reactions occur as a result of cell-mediated hypersensitivity to an allergen activated or produced by the effect of light on a drug (or its metabolite). UVR is required to convert the drug into an immunologically active compound (photoallergen) that induces the immune response. These reactions are idiosyncratic and can be maintained in the absence of excessive sun exposure.

Clinically, the lesions are pruritic and resemble eczema or lichen planus (Fig. 21.13); they are primarily in sun-exposed sites but may extend to

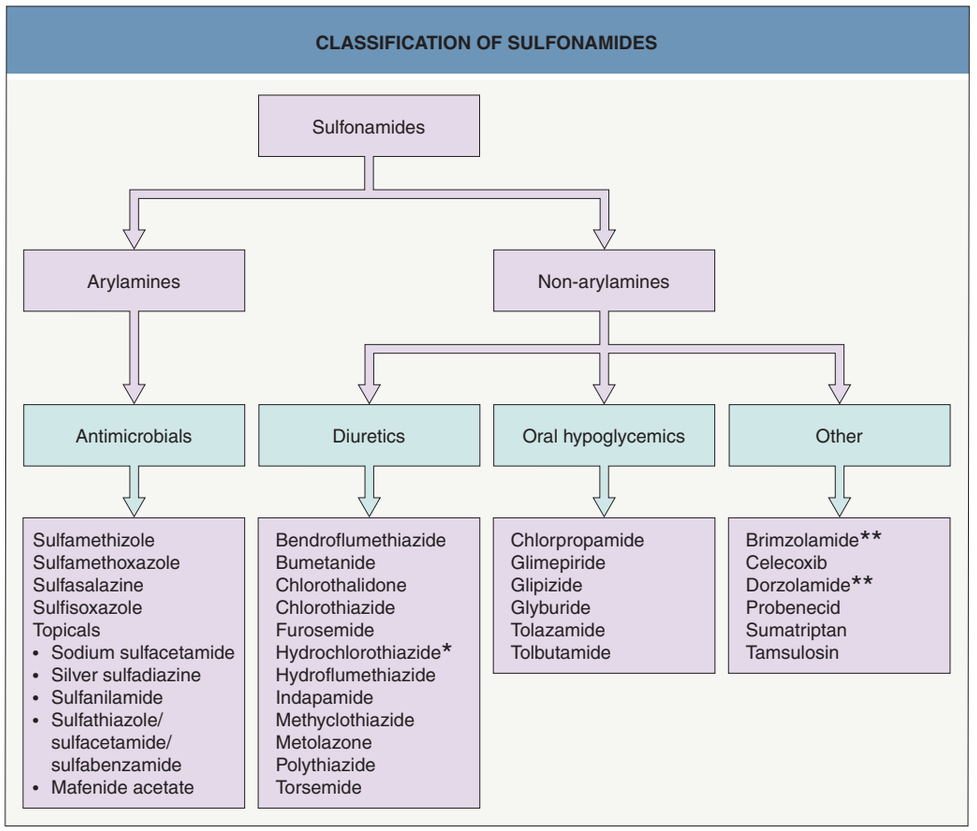


Fig. 21.14 Classification of sulfonamides. Approximately 10% of the patients with a history of a drug reaction to antimicrobial sulfonamides will also react to the non-arylamine sulfonamides. However, this is thought to be a reflection of a predisposition to allergic reactions rather than cross-reactivity. *Often combined with other antihypertensives, e.g. triamterene, angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II receptor blockers. **Eyedrops.

non-sun-exposed areas. Chronic exposure to photoallergic drugs can, in an occasional patient, lead to extreme photosensitivity that persists for months to even years after the responsible drug is eliminated. These patients then fall within the spectrum of chronic actinic dermatitis (see Ch. 87). Photopatch testing can be useful in the clinical evaluation.

Classes of drugs commonly associated with photoallergic reactions include thiazide diuretics, sulfonamide antibiotics, sulfonylureas, and phenothiazines, all of which contain a sulfur moiety (Fig. 21.14). Additional medications that have been reported as photoallergens include quinine, quinidine, tricyclic antidepressants, griseofulvin, and both oral and topical NSAIDs. For example, topical ketoprofen is a frequent cause of photoallergic contact dermatitis.

In photoallergic reactions, drug withdrawal is recommended, given the risk of exacerbation even with relatively low-dose exposures to UVR and the risk of chronicity. Topical corticosteroids are a mainstay of therapy, along with physical barriers, reduced sun exposure, and broad-spectrum sunscreens.

Reactions to Anti-Neoplastic Agents – Chemotherapy, Targeted Therapy, and Immunotherapy

This group of medications can induce cutaneous reactions that range from benign to life-threatening[49], and their occurrence continues to rise as new antineoplastic agents are introduced.

Chemotherapy

Alopecia

One of the most common adverse reactions to chemotherapy is alopecia due to anagen effluvium in which there is an abrupt cessation of mitotic activity (Table 21.15)[50]. The alopecia involves primarily the scalp hairs, but other sites may be affected, such as the eyebrows and axillary and pubic regions. The hair loss is typically reversible, and the severity of alopecia depends primarily upon the specific drugs administered. However, drugs such as taxanes and busulfan can lead to irreversible diffuse thinning of scalp hair. Occasionally, patients with straight hair will develop curly hair when it regrows.

Scalp cooling during chemotherapy administration may diminish alopecia[51]. Possible mechanisms include local vasoconstriction of blood vessels, decreased follicle cell metabolic rate, reduced delivery of chemotherapy, and reduced cellular drug uptake. Cooling is begun 30 minutes prior to administration of chemotherapy and continued for at least 90 minutes following conclusion of the chemotherapy infusion. While scalp cooling is generally well tolerated, there are possible side effects including patient discomfort (feeling cold) and headache. In addition, it is to be avoided in patients with head and neck, CNS, or hematologic malignancies.

Stomatitis

Mucositis of the oral and gastrointestinal mucosae is a major, often dose-limiting, toxic effect of chemotherapy and it can be particularly severe when chemotherapy is combined with radiotherapy. Stomatitis occurs in over 40% of patients receiving chemotherapy and can be explained by:

- Direct drug-induced cytotoxic effects on the oral epithelial cells, which have a high mitotic index (Fig. 21.15).
- Indirect effects on the oral mucosa due to superimposed infections (e.g. *Candida*, herpes simplex virus) and/or hemorrhage, reflections of bone marrow suppression. These effects are typically observed at the therapeutic nadir of the white blood cell count. However, the prophylactic use of antivirals (e.g. acyclovir) and antifungals (e.g. fluconazole) as well as colony-stimulating factors (which reduce the duration of neutropenia) have decreased the impact of this second mechanism.

Dental evaluation and treatment prior to administering chemotherapy can reduce the risk of oral infections. Preventive measures include maintaining oral hygiene via the use of soft toothbrushes and rinsing with water and sodium bicarbonate. In addition to specific antimicrobial agents, topical anesthetics and anti-inflammatory agents may be helpful; in some patients, systemic analgesics are required. Occasionally, palifermin is prescribed, but its use can lead to white coating of the tongue and transient keratoses.

Additional reactions

Chemotherapeutic agents are also responsible for other mucocutaneous reactions such as ulcerations at sites of extravasation of intravenous

MUCOCUTANEOUS SIDE EFFECTS OF ANTINEOPLASTIC AGENTS	
Reactions	**Responsible drugs**
Alopecia, reversible	Alkylating agents: cyclophosphamide, ifosfamide, mechlorethamine (nitrogen mustard) Anthracyclines: daunorubicin, doxorubicin, idarubicin, mitoxantrone Endocrine therapy for breast cancer (pattern alopecia similar to androgenetic): tamoxifen, aromatase inhibitors (e.g. anastrozole, letrozole) Taxanes: paclitaxel, docetaxel Topoisomerase 1 inhibitors: topotecan, irinotecan Other: actinomycin D, busulfan, etoposide, gemcitabine, methotrexate, vincristine, vinblastine
Alopecia, irreversible	Busulfan, cyclophosphamide, thiotepa (conditioning regimens); docetaxel, paclitaxel
Mucositis	Anthracyclines (e.g. daunorubicin, doxorubicin), cyclophosphamide, etoposide, melphalan (high-dose), methotrexate (high-dose), taxanes, topotecan, continuous infusions of 5-FU, and prodrugs of 5-FU (e.g. capecitabine)
Extravasation reactions (e.g. chemical cellulitis, ulceration)	Anthracyclines, bendamustine, carmustine, 5-FU (irritant), mechlorethamine (vesicant), mitomycin C, vinblastine, vincristine, vinorelbine (vesicant)
Chemotherapy recall (tender sterile inflammatory nodules at sites of previous chemotherapy extravasation or administration)	Anthracyclines (e.g. doxorubicin, epirubicin), 5-FU, mitomycin C, paclitaxel
Hyperpigmentation (see Ch. 67)	Alkylating agents: bendamustine, busulfan, cisplatin, cyclophosphamide, mechlorethamine, melphalan Antimetabolites: capecitabine (5-FU prodrug), 5-FU, hydroxyurea, methotrexate Antitumor antibiotics: bleomycin, doxorubicin
Serpentine supravenous hyperpigmentation	Docetaxel, doxorubicin, 5-FU, fotemustine, vinorelbine; actinomycin D + vincristine, cisplatin + pemetrexed
Mucosal hyperpigmentation	Busulfan, cyclophosphamide, doxorubicin, 5-FU, hydroxyurea
Nail hyperpigmentation	Anthracyclines (e.g. daunorubicin, doxorubicin), bleomycin, cyclophosphamide, 5-FU, hydroxyurea, methotrexate
Onycholysis +/– subungual hemorrhage	Taxanes (e.g. paclitaxel, docetaxel [along with photosensitivity]); doxorubicin + cyclophosphamide
Radiation recall	Anthracyclines (e.g. daunorubicin, doxorubicin), capecitabine (5-FU prodrug), 5-FU, gemcitabine, taxanes > actinomycin D, dacarbazine, endocrine therapy (e.g. tamoxifen, letrozole), etoposide, hydroxyurea, melphalan, methotrexate, pemetrexed
Radiation enhancement	Doxorubicin, etoposide, 5-FU, gemcitabine, hydroxyurea, methotrexate, taxanes
Photosensitivity	5-FU and 5-FU prodrugs (e.g. capecitabine, tegafur), methotrexate, taxanes > dacarbazine, hydroxyurea, mitomycin C
Inflammation of "keratoses"	*Actinic keratoses*: 5-FU and 5-FU prodrugs (e.g. capecitabine), pentostatin, taxanes *Seborrheic keratoses*: cytarabine, taxanes *Disseminated superficial actinic porokeratosis:* 5-FU and 5-FU prodrugs, taxanes
Toxic erythema of chemotherapy: • Acral erythema (HFS) • Eccrine squamous syringometaplasia	 Anthracyclines, busulfan, clofarabine, cisplatin, cytarabine, fludarabine, 5-FU (prolonged infusions) and 5-FU prodrugs, methotrexate, taxanes (dorsal hands) Busulfan, carmustine, cyclophosphamide, cytarabine, taxanes
Neutrophilic eccrine hidradenitis	Anthracyclines, bleomycin, cyclophosphamide, cytarabine, topotecan
Ulcerations	Hydroxyurea (lower extremities), methotrexate (e.g. psoriatic plaques)
Nodulosis	Methotrexate (but usually in patients with rheumatoid arthritis)
Flushing	Asparaginase, high-dose BCNU, mithramycin
Periorbital edema	Pemetrexed (plus conjunctivitis and lower extremity edema)
Others:	*Acquired cutaneous adherence:* doxorubicin (plus ketoconazole*) *Dermatomyositis-like eruption:* hydroxyurea *Eccrine poromatosis*: polychemotherapy *Exanthematous eruption:* bleomycin, carboplatin, cladribine, cytarabine, doxorubicin, gemcitabine, methotrexate, paclitaxel, pemetrexed *Palmoplantar hyperkeratosis:* capecitabine, tegafur *Paraneoplastic pemphigus-like:* fludarabine *Pseudocellulitis and acute lipodermatosclerosis-like reaction:* gemcitabine *SJS/TEN:* bendamustine, bleomycin, busulfan, cyclophosphamide, docetaxel, doxorubicin, etoposide, methotrexate *Scleroderma-like reaction (especially extremities):* bleomycin, gemcitabine, pemetrexed, taxanes *SCLE:* taxanes, 5-FU and 5-FU prodrugs, doxorubicin + cyclophosphamide, gemcitabine *Urticaria:* asparaginase, bleomycin, chlorambucil, cyclophosphamide, daunorubicin *Vasculitis:* busulfan, cyclophosphamide, gemcitabine, hydroxyurea, levamisole, pemetrexed
*Rarely used nowadays.	

Table 21.15 Mucocutaneous side effects of antineoplastic agents. The mucocutaneous side effects of targeted therapies are reviewed in Table 21.16. Cutaneous squamous cell carcinomas are most commonly associated with fludarabine, hydroxyurea, and topical BCNU. Related side effects are shaded. 5-FU, 5-fluorouracil; HFS, hand–foot syndrome; SCLE, subacute cutaneous lupus erythematosus; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

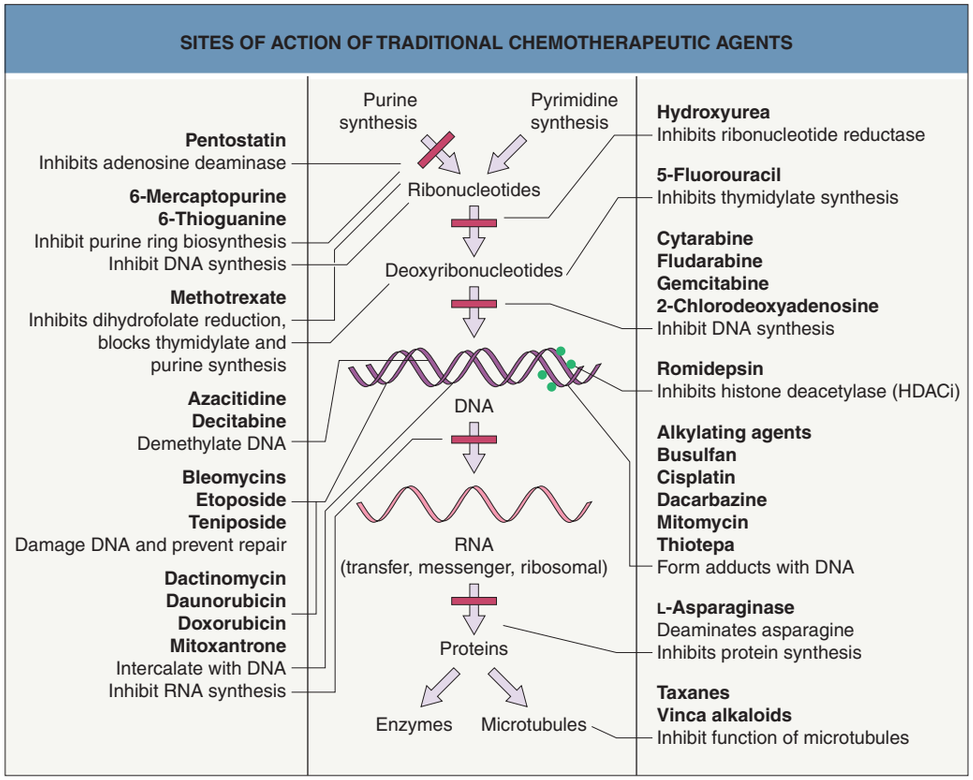


Fig. 21.15 Sites of action of chemotherapeutic agents. *Adapted with permission from Brunton L, Lazo J, Parker K (eds.). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th edn. New York: McGraw-Hill Medical, 2005.*

medications; skin, oral, and nail hyperpigmentation (Fig. 21.16A); and acral erythema (Fig. 21.16C,D), also known as erythrodysesthesia. The frequency of extravasations has been markedly reduced by the use of "permanent" central venous catheters, whereas the incidence of acral erythema has increased in the setting of prolonged infusions of drugs and the chronic use of oral multi-kinase inhibitors (see below).

A variety of terms have been used to describe the cutaneous toxic effects of chemotherapy, e.g. "palmoplantar erythrodysesthesia", "hand–foot syndrome", "eccrine squamous syringometaplasia", "intertrigo eruption of chemotherapy", "malignant intertrigo", and "epidermal dysmaturation", creating some confusion. There is considerable overlap in the appearance of the symmetric erythematous to dusky patches which can develop edema, desquamation, and/or purpura (depending on the patient's platelet count), whether they favor acral sites, intertriginous zones, the scrotum, or the elbows and knees (Fig. 21.17). "Toxic erythema of chemotherapy" has been suggested as an encompassing term that allows simplification (Fig. 21.18). Treatment options include reduction of the chemotherapy dose, analgesia, topical medications (e.g. corticosteroids), high-dose vitamin D, low-dose acitretin for hyperkeratosis, and perhaps regional cooling as a preventive measure.

Additional reactions to chemotherapy include radiation recall or enhancement; photosensitivity (see Fig. 21.12); inflammation of pre-existing actinic or seborrheic keratoses (Fig. 21.16B); necrosis of plaques of psoriasis (see Fig. 21.1B) or mycosis fungoides; Raynaud phenomenon with digital necrosis (Fig. 21.16E); flagellate erythema or hyperpigmentation (Fig. 21.16F); and neutrophilic eccrine hidradenitis (see Fig. 21.9). Long-term administration of hydroxyurea is associated with the development of painful ulcerations of the malleolar region of the lower extremities as well as the development of cutaneous malignancies (see Fig. 105.20F). The ulcers may be difficult to heal unless the hydroxyurea is discontinued.

Targeted therapy

The use of targeted therapies that act on cell-surface receptors and intracellular signaling pathways is rapidly increasing[52]. Examples include specific inhibitors of VEGFR and EGFR and multi-kinase inhibitors that target the KIT receptor and mitogen-activated protein (MAP) kinase pathway (see Ch. 113). The side effects of targeted therapies and newer antineoplastic agents are outlined in Tables 21.16 and 21.17, respectively. Hand–foot skin reaction (HFSR), presenting with acral hyperkeratosis, erythema and occasionally blisters, is particularly prevalent with certain multi-kinase inhibitors (e.g. sorafenib, regorafenib). It can be treated with topical corticosteroids and keratolytics, avoidance of heat, trauma and irritants, and a drug holiday followed by dose reduction in severe cases.

Immunotherapy

As with targeted agents, the use of immunotherapies is expanding exponentially. ICIs are being used for common malignancies such as non-small-cell lung cancer as well as metastatic melanoma. The side effects of anti-CTLA-4 (e.g. ipilimumab), anti-PD-1 (e.g. nivolumab), and anti-PD-L1 (e.g. atezolizumab) antibodies are outlined in Table 21.18. The skin is the most common site for *i*mmune-*r*elated *a*dverse *e*vents (irAEs; Fig. 21.19) and often is the initial site, with an onset within six weeks. However, appearance of cutaneous side effects can be delayed and may even appear after discontinuation of the immunotherapy. Along with pruritus, morbilliform, psoriasiform, eczematous, and lichenoid dermatoses are most frequently observed and they are usually managed with topical therapies and continuation of immunotherapy (see Ch. 11). Less often, patients develop bullous pemphigoid or SCARs (e.g. SJS/TEN, DRESS). The appearance of irAEs, in particular vitiligo-like depigmentation in patients with melanoma, has been associated with improved tumor response rate and survival[53].

Drug-Induced Adverse Reactions Involving Hair and Mucosae

Hair

A considerable number of medications induce hair loss[51]. They affect the hair follicles via two major mechanisms: anagen effluvium (abrupt interruption of the active growth phase) and telogen effluvium (an increased number of hairs in the resting phase). In the former, hair loss occurs within 2 to 3 weeks of drug administration as with cytotoxic chemotherapy, whereas in telogen effluvium, there is usually a delay of 2 to 4 months. Clinically, both are diffuse non-scarring alopecias (see Ch. 69). The hair loss is usually reversible after discontinuation of the responsible agent. Diagnosis of drug-induced telogen effluvium can be difficult and requires observation of improvement after the suspected drug has been withdrawn. Table 21.19 lists a number of the drugs associated with alopecia, including β-blockers, lithium, retinoids, and heparin.



Fig. 21.16 Cutaneous side effects and complications of chemotherapeutic agents. A Horizontal melanonychia due to 5-fluorouracil. **B** Inflammation surrounding a seborrheic keratosis in a patient receiving paclitaxel. **C** Toxic erythema of chemotherapy (TEC) due to cytarabine, with obvious painful acral erythema involving the plantar surface. **D** TEC, also referred to as hand–foot syndrome when localized, due to capecitabine; diffuse glazed erythema and mild hyperkeratosis of palmoplantar skin. **E** Raynaud phenomenon and digital necrosis due to systemic bleomycin. **F** Multiple linear (flagellate) erythematous urticarial plaques in a patient receiving systemic bleomycin for Hodgkin lymphoma. **G** Chemical cellulitis due to extravasation of enfortumab vedotin (anti-Nectin-4 antibody attached to monomethyl auristatin, a cytotoxic microtubule inhibitor). *A–C, Courtesy Jean L. Bolognia, MD; D, F, Courtesy Kalman Watsky, MD; G, Courtesy Katherine Given, MD.*



Fig. 21.17 Toxic erythema of chemotherapy. Symmetric involvement of intertriginous zones and the scrotum. There is central desquamation and some of the lesions have a dusky color. The patient was receiving fludarabine plus intravenous busulfan. *Courtesy Leonard Kristal, MD.*

With regard to drug-induced hair growth, it is important to distinguish between hypertrichosis and hirsutism. The associated medications for both entities are discussed in Chapter 70.

Mucosal ulcerations

Stomatitis with erosions and ulcerations may occur either as part of a drug-induced mucocutaneous syndrome (e.g. FDE, SJS/TEN) or as a side effect of chemotherapy (see above & Table 21.15)[49]. In addition to cytotoxic drugs (e.g. methotrexate), several drug classes can cause oral ulcerations, including calcineurin inhibitors, anticholinergic bronchodilators, NSAIDs including acetylsalicylic acid, antihypertensives (e.g. β-blockers), antiretrovirals (e.g. protease inhibitors), bisphosphonates, platelet aggregation inhibitors, and vasodilators (e.g. nicorandil). Medications more commonly prescribed in the past such as metamizole, phenylbutazone, D-penicillamine, and gold salts can also produce oral ulcers. Additionally, allergic reactions to dental materials and exposure to metals such as mercuric chloride or copper sulfate may cause stomatitis. Irritation secondary to drugs excreted in the urine, such as foscarnet, can lead to penile ulceration.

Other Drug-Induced Cutaneous Reactions

Acneiform eruptions (including folliculitis)

Acneiform eruptions represent ~1% of drug-induced skin eruptions. Clinically, papules and/or pustules are seen primarily on the face and upper trunk, the same sites favored by acne; comedones are usually absent unless androgens are the cause. The interval between drug

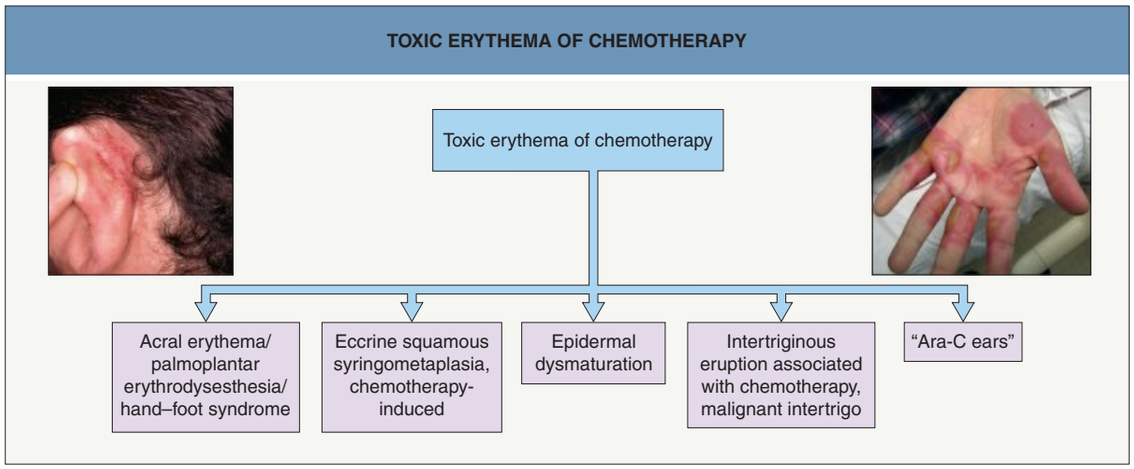


Fig. 21.18 Toxic erythema of chemotherapy. Use of a number of terms (especially those based on histologic findings), including palmoplantar erythrodysesthesia, eccrine squamous syringometaplasia and epidermal dysmaturation, has created some confusion for clinicians. There is considerable overlap in the appearance of the symmetric erythematous to dusky patches which can develop edema, erosions, desquamation or purpura, whether they favor acral sites, intertriginous zones, or the elbows and knees. "Toxic erythema of chemotherapy" has been suggested as an encompassing term that allows simplification. In addition, there is no need to implicate additional diagnoses when lesions are not limited to the hands and feet. Insets: Erythema of the ears due to cytarabine (cytosine arabinoside), sometimes referred to as "Ara-C ears"; the petechiae are due to thrombocytopenia. Dusky edematous plaques of the palm, some of which have developed sterile bullae. *Courtesy Jean L. Bolognia, MD and Boni Elewski, MD.*

MUCOCUTANEOUS SIDE EFFECTS OF SELECTED TARGETED THERAPIES

Drug	**Cetuximab[Ab] Necitumumab[Ab] Panitumumab[Ab] Amivantamab[bispecific Ab] Erlotinib[1st gen] Gefitinib[1st gen] Afatinib[2nd gen] Dacomitinib[2nd gen] Lapatinib[2nd gen] Neratinib[2nd gen] Osimertinib[3rd gen]**	**Dabrafenib Encorafenib Vemurafenib**	**Binimetinib Cobimetinib Selumetinib Trametinib**	**Pertuzumab Trastuzumab**	**Bosutinib Dasatinib Imatinib Nilotinib Ponatinib Avapritinib Ripretinib**	**Bevacizumab Ramucirumab Ranibizumab**
Selected targets	EGFR (monoclonal antibodies, 1st generation, 3rd generation) EGFR, HER2 (2nd generation) EGFR, MET (bispecific monoclonal antibody)	BRAF V600E (vemurafenib) BRAF V600E/K (dabrafenib, encorafenib)	MEK 1/2	HER-2	BCR-ABL, Src (bosutinib) BCR-ABL, Src, KIT, EphA2, PDGFRβ (dasatinib) BCR-ABL, KIT, PDGFR (imatinib) BCR-ABL, PDGFR, DDR1 (nilotinib) BCR-ABL, VEGFR, PDGFR, FGFR, Src, KIT, RET, Tie2, Flt3 (ponatinib) PDGFRα, KIT (avapritinib, ripretinib)	VEGF (bevacizumab, ranibizumab) VEGFR2 (ramucirumab)
Alopecia	√ (non-scarring and scarring)	√	√	√ (mild)	√	
Folliculitis* (acneiform)	√	√	√	√	√	√
Acral erythema/ hyperkeratosis† (HFSR)	√	√			√ (uncommon)	
Paronychia‡	√¶		√¶	√		
Stomatitis	√	√ (hyperkeratotic)	√		√	√
Photosensitivity	√	√			√	
Exanthematous (morbilliform) eruption		√ (often folliculocentric)	√	√	√	√
Pruritus	√	√	√	√	√	
Xerosis	√ (with digital fissures)	√	√	√ (with digital fissures)	√	
Dermatitis: Asteatotic	√		√		√	

Table 21.16 Cutaneous side effects of selected targeted therapies. Entities in **bold** or shaded are more commonly observed. *Continued*

MUCOCUTANEOUS SIDE EFFECTS OF SELECTED TARGETED THERAPIES						
Dermatitis: Psoriasiform						
Dermatitis: Seborrheic	√	√	√			
Keratosis pilaris		√			√ (especially dasatinib and nilotinib)	
SCARs	√ (afatinib)	√ (DRESS, SJS/TEN; especially vemurafenib, increased after ICI therapy)			√ (AGEP, DRESS, SJS/TEN)	
Other	**Purpuric pustular eruptions, trichomegaly,** acquired perforating dermatosis, blepharitis, enhanced radiation dermatitis, hirsutism, erythema dyschromicum perstans-like, necrolytic migratory erythema-like	**Squamous proliferations (verrucae, KAs, SCCs), eruptive/ changing nevi, primary melanoma,** curly hair, epidermal cysts, erythema nodosum-like panniculitis, Grover disease, HS, sarcoidal reaction	Curly hair, panniculitis	Nail changes (onycholysis, brittle nails)	**Cutaneous + hair hypo- > hyperpigmentation (imatinib), periorbital edema (imatinib), lichenoid eruption including lichen planopilaris-like (dasatinib, nilotinib),** hyperhidrosis, ichthyosiform eruption (ponatinib), peripheral edema, PRP-like eruption (ponatinib), pseudolymphoma, psoriasis flare (imatinib), Sweet syndrome, urticaria	**Disturbed wound healing, muco-cutaneous hemor-rhage**, geographic tongue, radiation recall, ulcerated striae
Notes	Folliculitis (papulopustular eruption) is most common Cutaneous side effects are less common and less severe with osimertinib (3rd generation)	Addition of MEK inhibitor markedly reduces cutaneous side effects, particularly SCCs/KAs	Similar profile to EGFR inhibitors	Generally milder side effects with HER2 compared to EGFR [HER1] and MEK inhibitors	Exanthematous (morbilliform) eruptions and keratosis pilaris are most common	Less frequent compared to VEGFR/ PDGFR multi-kinase inhibitors
Drug	**Axitinib Cabozantinib Lenvatinib Pazopanib Regorafenib Sorafenib Sunitinib Vandetanib**	**Acalabrutinib Ibrutinib Zanubrutinib**	**Abemaciclib Palbociclib Ribociclib**	**Erdafitinib Infigratinib Rogaratinib**	**Alectinib Brigatinib Ceritinib Crizotinib Entrectinib Lorlatinib**	**Alpelisib Copanlisib Duvelisib Idelasib**
Selected targets	VEGFRs, PDGFRβ (axitinib) RET, MET, VEGFRs, KIT, Axl (cabozantinib) VEGFRs, FGFRs, PDGFR, KIT, RET (lenvatinib) VEGFRs, PDGFRα/β, FGFR, KIT (pazopanib) VEGFRs, Tie2, BRAF, KIT, FGFR, PDGFRα/β, RET (regorafenib) B/C-RAF, KIT, VEGFRs, PDGFRβ (sorafenib) PDGFRα/β, VEGFRs, KIT (sunitinib) EGFRs, VEGFRs, RET (vandetanib)	BTK	CDK4/6	FGFR 1–4	ALK (lorlatinib) ALK, RET (alectinib) ALK, ROS1, IGF-1R, Flt3, EGFR (brigatinib) ALK, IGF-1R, InsR, ROS1 (ceritinib) ALK, c-MET, ROS1, MST1R (crizotinib) ALK, TRKA/B/C, ROS1 (entrectinib)	PI3K
Alopecia	√ (most commonly sorafenib)		√	√		√
Folliculitis* (acneiform)	√	√	√	√	√	√ (uncommon)
Acral erythema/ hyperkeratosis† (HFSR)	√ (especially sorafenib and regorafenib)			√		
Paronychia‡	√¶ (vandetanib)			√		√
Stomatitis	√		√	√		√

Table 21.16 Cutaneous side effects of selected targeted therapies. Entities in **bold** or shaded are more commonly observed. *Continued*

MUCOCUTANEOUS SIDE EFFECTS OF SELECTED TARGETED THERAPIES						
Photosensitivity	√ (vandetanib)	√			√ (crizotinib)	
Morbilliform exanthem	√		√	√	√	√ (may progress to erythroderma)
Pruritus	√	√	√		√	
Xerosis	√	√	√	√		
Dermatitis: Asteatotic	√	√				
Dermatitis: Psoriasiform						√
Dermatitis: Seborrheic						
Keratosis pilaris	√ (especially sorafenib)					
SCARs	√ (AGEP, SJS/TEN)		√ (SJS)		√ (EM, SJS/TEN)	√ (DRESS, SJS/TEN, EM)
Other	**Genital eruption including scrotal > vulvar ulcers (cabozantinib, pazopanib, sorafenib, sunitinib), yellow skin discoloration (sunitinib), reversible hair depigmentation (sunitinib, pazopanib, cabozantinib),** acquired perforating dermatosis (sorafenib), angioedema (sorafenib), blue–gray macules (vandetanib), cutaneous vasculopathy (axitinib), eruptive nevi (sorafenib), facial edema (sunitinib, pazopanib), pyoderma gangrenosum, scalp pruritus (sorafenib), squamous proliferations (KAs, SCCs) (sorafenib), subungual splinter hemorrhages (sorafenib, sunitinib, pazopanib)	**Increased bleeding, petechiae and ecchymoses, palpable purpuric eruptions,** cutaneous staphylococcal infections, hair texture changes, nail changes (brittle nails, onycholysis), neutrophilic panniculitis	Bullous dermatitis, drug-induced lupus (SCLE, DLE), radiation enhancement, small vessel vasculitis, vitiligo	**Calcinosis cutis, calciphylaxis (associated hyperphosphatemia),** nail changes (onycholysis with or without subungual hemorrhage, onychomadesis), xerostomia	Lichenoid eruption, peripheral edema	Urticarial hypersensitivity reaction
Notes	HFSR is the most common	Petechiae, palpable purpuric eruptions, and folliculitis are most common Side effects are more common with ibrutinib	Alopecia (especially with endocrine therapy) and stomatitis are most common	Alopecia, stomatitis, and nail changes are most common	Uncommon	Exanthematous (morbilliform) eruptions are most common (particularly with alpelisib ~50%)

*Also referred to as papulopustular eruption; can be associated with secondary *Staphylococcus aureus* infection or *Demodex* infestation.
†May be bullous.
‡Topical β-blockers, such as timolol 0.5% gel twice daily under occlusion, may be effective in the treatment of pyogenic granuloma-like lesions.
¶(Pseudo)pyogenic granulomas may occur.

Table 21.16 Cutaneous side effects of selected targeted therapies. Entities in **bold** or shaded are more commonly observed. See following tables for the side effects of vismodegib and sonidegib (Table 108.10), mTOR and proteasome inhibitors (Table 21.17), and checkpoint inhibitors (Table 21.18). Brentuximab, alemtuzumab, and mogamulizumab are reviewed in Chapter 120; rituximab and other anti-tumor monoclonal antibodies are reviewed in Chapter 128. Monoclonal antibodies conjugated to cytotoxic agents (e.g. enfortumab vedotin, loncastuximab tesirine) are associated with a range of bullous reactions including toxic erythema of chemotherapy and SJS/TEN. Ab, antibody; AGEP, acute generalized exanthematous pustulosis; ALK, anaplastic lymphoma kinase; BTK, Bruton's tyrosine kinase; CDK, cyclin-dependent kinase; DLE, discoid lupus erythematosus; EGFR, epidermal growth factor receptor; EM, erythema multiforme; FGFR, fibroblast growth factor receptor; FLT3, FMS-related tyrosine kinase 3; gen, generation; HER2, receptor tyrosine-protein kinase erbB-2; HFSR, hand–foot skin reaction; HS, hidradenitis suppurativa; ICI, immune checkpoint inhibitor; KAs, keratoacanthomas; MEK, mitogen-activated protein kinase kinase; MET, mesenchymal epithelial transition factor; PI3K, phosphoinositide 3-kinase; PDGFR, platelet-derived growth factor receptor; PRP, pityriasis rubra pilaris; RAF, name derived from ability of 3611–MSV virus to induce "*ra*pidly growing *f*ibrosarcomas" in mice; RET, rearranged during transfection; SCARs, severe cutaneous adverse reactions; SCCs, squamous cell carcinomas; SCLE, subacute cutaneous lupus erythematosus; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor. *Adapted from Robert C, et al. Lancet Oncol 2005;6:491–500; Macdonald JB, et al. J Am Acad Dermatol 2015;72:203–18; Ransohoff J, Kwong B. Clin Lymphoma Myeloma Leuk 2017;17:834–51.*

MUCOCUTANEOUS SIDE EFFECTS OF mTOR AND PROTEOSOME INHIBITORS		
	Sirolimus (rapamycin), everolimus, temsirolimus	**Bortezomib, carfilzomib, ixazomib**
Target	mTOR	Proteasome
Stomatitis, including aphthous	+	+/–
Facial hair growth and/or eyelash trichomegaly	+	–
Paronychia	+	–
Periorbital edema	+	–
Flushing	+	–
Exanthematous (morbilliform) eruption (Fig. 21.19)	+	+
Pruritus	+	+
Acneiform eruptions, hidradenitis	+	+*
EM-like/SJS/TEN	–	+
Acute febrile neutrophilic dermatosis (Sweet syndrome)	–	+
Small vessel vasculitis	+	+
Other	Xerosis and eczematous eruptions, yellow fragile nails, angioedema, bruising, peripheral edema and leg ulcers	Increased risk of herpes zoster; erythematous nodules and plaques that favor the trunk (bortezomib), cutaneous lupus

*Folliculitis and follicular nodules.

Table 21.17 Mucocutaneous side effects of mTOR and proteosome inhibitors.



Fig. 21.19 Exanthematous (morbilliform) drug reaction to lenalidomide with accentuation at sites of bortezomib injections. *Courtesy Dennis Cooper, MD.*

MUCOCUTANEOUS AND EXTRACUTANEOUS SIDE EFFECTS OF IMMUNE CHECKPOINT INHIBITORS
Mucocutaneous – most common*

• Eruptions (Fig. 21.20B,D)
  • morbilliform
  • lichenoid
  • psoriasiform
  • eczematous
• Pruritus
• Vitiligo-like depigmentation,including poliosis (Fig. 21.20C)†

Mucocutaneous – less common*
• Acute generalized exanthematous pustulosis, DRESS (including with radiation), erythema multiforme (minor and major), Stevens–Johnson syndrome, toxic epidermal necrolysis (Fig. 21.20A) • Bullous pemphigoid, pemphigus • Dermatomyositis, subacute cutaneous lupus erythematosus • Generalized lichen nitidus, lichen sclerosus, lichen planopilaris, PLEVA, PLC-like, lichen planus pemphigoides • Vogt–Koyanagi–Harada-like syndrome, alopecia areata, alopecia universalis • Sarcoidosis and sarcoidal lesions (including subcutaneous), granuloma annulare • Radiation sensitivity, photosensitivity • Atypical squamous proliferations, eruptive keratoacanthomas, and squamous cell carcinomas‡ • Eosinophilic fasciitis, morpheaform and sclerodermoid reactions • Erythema nodosum-like panniculitis • Acquired generalized lipodystrophy • Sjögren syndrome, vasculitis • Neutrophilic dermatoses, in particular Sweet syndrome • Oral ulcers, xerostomia, nail dystrophy (may occur with lichenoid or psoriasiform eruptions) • Acneiform eruption, papulopustular rosacea, Grover disease, urticaria
Extracutaneous
• Enteritis/colitis (diarrhea, nausea, vomiting), hepatitis • Adrenal insufficiency • Arthritis (primarily seronegative inflammatory arthritis) • Autoimmune thyroiditis (hypothyroidism ≫ hyperthyroidism) • Flare of existing autoimmune disorder (e.g. rheumatoid arthritis, systemic lupus) • Hypophysitis, hypopituitarism • Myocarditis • Nephritis, hyperkalemia • Neurotoxicity, including Guillain–Barré syndrome, PRES • Pancreatitis • Pneumonitis • Sarcoidosis (pulmonary, lymph nodes) • Type 1 diabetes, acute onset with severe hyperglycemia, ketoacidosis • Uveitis, episcleritis • Vasculitis
*More than one morphology may be seen in a patient. †May be intraoral, genital, or accentuated in sun-exposed sites. ‡May be driven by lichenoid inflammation.

Table 21.18 Mucocutaneous and extracutaneous side effects of immune checkpoint inhibitors. These include anti-CTLA-4 (e.g. ipilimumab, tremelimumab), anti-PD-1 (e.g. nivolumab, pembrolizumab, cemiplimab), and anti-PD-L1 (e.g. atezolizumab, avelumab, durvalumab) antibodies. Certain reactions are more commonly associated with anti-PD-1/PD-L1 antibodies (e.g. lichenoid eruption, bullous pemphigoid, psoriasiform eruption), and combination anti-CTLA-4/-PD-1 therapy is associated with increased frequency and severity of immune-related adverse events. Rarely, subcutaneous fat necrosis, circumoral plasmacytosis, and repigmentation of gray hair have been observed. DRESS, drug reaction with eosinophilia and systemic symptoms; PLEVA, pityriasis lichenoides et varioliformis acuta; PLC, pityriasis lichenoides chronica; PRES, posterior reversible encephalopathy syndrome.

exposure and the acneiform eruption depends on the responsible agent. Major drugs implicated in acneiform eruptions include corticosteroids, androgens, hydantoins, lithium, halogenides, and oral contraceptives (more often those that contain progestins with androgen-like effects) (see Table 36.1). Less commonly, JAK inhibitors, azathioprine, quinidine, and adrenocorticotropic hormone are the culprits.

DRUG-INDUCED ALOPECIA	

Telogen phase	• Amphetamines
	• **Anticoagulants:** heparin > warfarin
	• Anticonvulsants: carbamazepine, lamotrigine, phenytoin, valproic acid
	• Antidepressants: desipramine, fluoxetine, imipramine, maprotiline,
	• Antihypertensive agents:
	  • **β-Blockers:** acebutolol, propranolol, timolol
	  • ACE inhibitors: captopril, enalapril, ramipril
	  • Diuretics: spironolactone
	• Antimicrobials: fluconazole, gentamicin, isoniazid, terbinafine, thiamphenicol
	• Antithyroid drugs: carbimazole, thiouracils
	• Colchicine
	• **Interferons**
	• Lipid-lowering agents: cholestyramine, clofibrate
	• **Lithium**
	• NSAIDs: ibuprofen, indomethacin, naproxen, piroxicam
	• Oral contraceptives (discontinuation > initiation or change)
	• Endocrine therapies (e.g. **tamoxifen**, letrozole > anastrozole, goserelin, leuprolide)
	• **Retinoids** (acitretin > isotretinoin)
	• Others: allopurinol, bromocriptine, buspirone, cimetidine, L-dopa, pyridostigmine

Anagen phase	• Antineoplastic agents (see Tables 21.15 & 21.16) • Others: arsenic, bismuth, gold, thallium

Table 21.19 Drug-induced alopecia. The more commonly incriminated medications are in **bold**. ACE, angiotensin-converting enzyme.

With the introduction of EGFR and MEK inhibitors (Fig. 21.21A), there has been an increase in drug-induced follicular eruptions, inasmuch as papulopustular eruptions can occur in up to 80% of patients receiving these medications, in particular 1st and 2nd generation EGFR inhibitors (see Table 21.16). Lesions often appear within a few weeks of administration but may not develop until several months later. Areas rich in sebaceous glands, in particular the central face, scalp and trunk, are most commonly affected (Fig. 21.21B,C). Symptoms include stinging, pruritus, and pain. Although the initial pustules are sterile, secondary infection by *Staphylococcus aureus*, herpes simplex virus, and dermatophytes may occur as well as an increased density of *Demodex folliculorum*. Late-onset papulopustular acneiform eruptions that favor the lower extremities may appear months into therapy as can non-follicular purpuric papulopustular eruptions.

It has been suggested that papulopustular eruptions are a surrogate marker for efficacy of EGFR inhibitors as several studies have reported an association with increased overall response rate or survival. Of note, at the initiation of EGFR or MEK inhibitor therapy, some clinicians prescribe a prophylactic regimen consisting of oral doxycycline or minocycline plus low- to mid-potency topical corticosteroids[54]. Severe or recalcitrant papulopustular disease can be treated with higher potency topical corticosteroids, oral corticosteroids, or low-dose oral isotretinoin.

Anticoagulant-induced skin necrosis

Anticoagulant-induced skin necrosis is a rare, potentially life-threatening reaction induced by warfarin or heparin. *Warfarin-induced* necrosis typically begins 2 to 5 days after therapy is initiated and coincides with



Fig. 21.20 Spectrum of cutaneous reactions to immune checkpoint inhibitors (immune-*r*elated *a*dverse *e*vents). A SJS/TEN overlap due to ipilimumab. **B** Lichenoid dermatitis of the palms in a patient receiving pembrolizumab for metastatic colon cancer. **C** Vitiligo-like leukoderma in a patient with metastatic melanoma receiving nivolumab. **D** Widespread eruption of erythematous papules due to ipilimumab; many of the lesions are crusted. *A, Courtesy Marianna Freudzon, MD; B, Courtesy Jonathan Leventhal, MD. C, Courtesy Jean L. Bolognia, MD; D, Courtesy Miriam Totonchy, MD.*

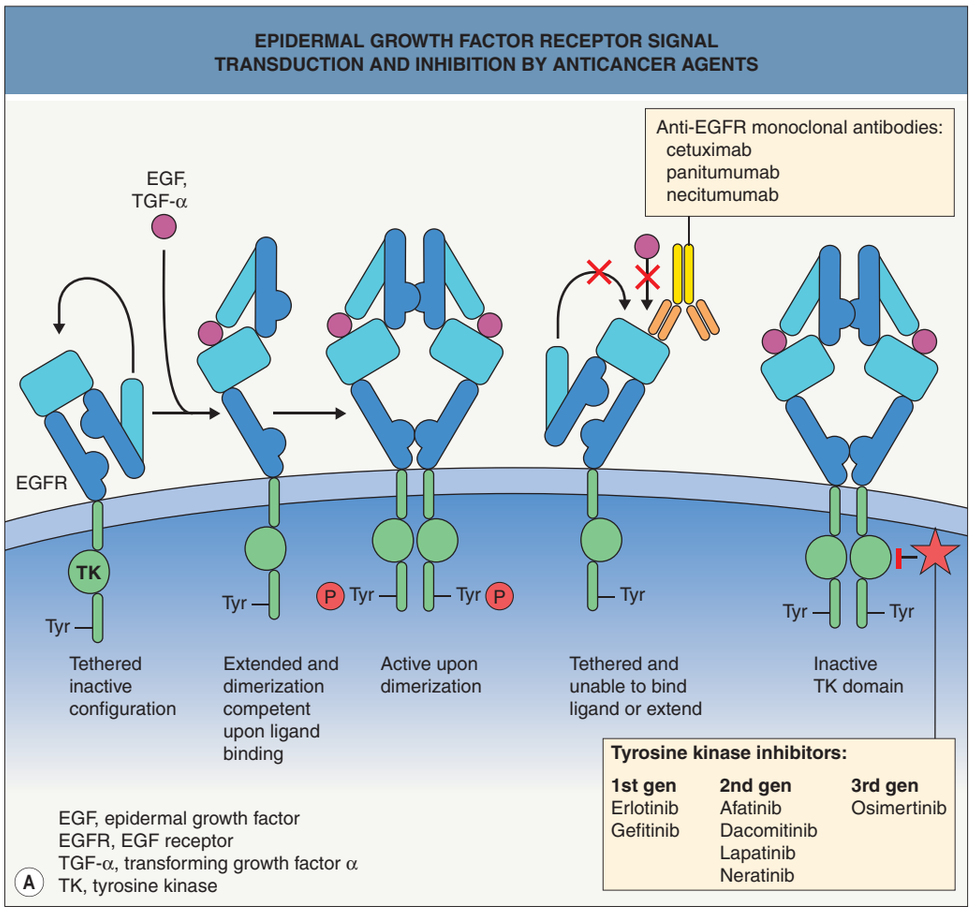


Fig. 21.21 Papulopustular (acneiform) reactions to epidermal growth factor receptor (EGFR) inhibitors. **A** EGFR signal transduction and sites of action of inhibitors. In addition to the tyrosine kinase inhibitors listed, there are drugs that block EGFR plus other targets such as ALK or VEGFR (e.g. vandetanib). **B** Numerous pustules on an erythematous base with coalescence on the central upper back. **C** Multiple follicular papulopustules, hyperpigmented scars, and a large multiloculated inflamed cyst on the cheek. gen, generation; P, phosphorylation; Tyr, tyrosine. *B, Courtesy Lauren Levy, MD, and Jonathan Leventhal, MD; C, Courtesy Kalman Watsky, MD.*

the expected early drop in protein C function (see Ch. 22). One in every 10 000 individuals who receives warfarin will develop this side effect, with middle-aged obese women and those with a hereditary deficiency of protein C being at highest risk.

Clinically, erythematous painful plaques evolve into hemorrhagic blisters and necrotic ulcers as a consequence of ischemic infarcts. The latter are due to occlusive thrombi within blood vessels of the skin and subcutaneous tissue[1]. The most common sites of involvement are areas with greater subcutaneous fat such as the breasts, thighs, abdomen, and buttocks. Therapy includes discontinuing warfarin and administering vitamin K, heparin (as the anticoagulant), and intravenous infusions of protein C concentrate. Warfarin necrosis should not be confused with anticoagulant-induced cholesterol emboli, which, despite the name "warfarin blue toe syndrome", is not restricted to this medication.

Heparin-induced cutaneous necrosis is due to antibodies that bind to complexes of heparin and platelet factor 4 and induce platelet aggregation and consumption (see Ch. 23). Platelet counts are usually depressed, but, unless the baseline platelet count is known, this may not be appreciated. In addition to relative thrombocytopenia, heparin can induce thrombosis and cutaneous necrosis, both at the site of injection and at distant sites (Fig. 21.22) as well as in internal organs (e.g. CNS). This is sometimes referred to as heparin-induced thrombocytopenia (HIT) syndrome. Discontinuation of the heparin and administration of anticoagulants, such as argatroban or bivalirudin, is recommended.

Granulomatous reactions

Granulomatous drug reactions can mimic interstitial granulomatous dermatitis and granuloma annulare and are discussed in Chapter 93. In addition, sarcoidal reactions have been seen in patients with hepatitis C viral infections who received interferon-α and ribavirin as well as immune checkpoint inhibitors.

Drug reactions in HIV infection

Patients with HIV infection are at increased risk for drug eruptions, especially when the $CD4^+$ count is between 100 and 400/mm^3 (see Ch. 78). As an example, the incidence of SJS/TEN in HIV-infected patients is 1/1000 per year (versus 1/1 000 000 per year in the general population). One possible explanation for this increased risk is a loss of skin-protective





Fig. 21.22 Heparin-induced thrombocytopenia (HIT) syndrome. **A** Ischemia and necrosis of the foot. **B** Petechiae due to thrombocytopenia and an irregular area of cutaneous necrosis due to thrombosis. *A, Courtesy Kalman Watsky, MD; B, Courtesy Jean L. Bolognia, MD.*

$CD4^+/CD25^+$ T regulatory cells in that HIV-infected patients were found to have an increased ratio of $CD8^+$:$CD4^+$ T cells within TEN lesions as well as a decreased number of skin-directed $CD4^+$ T cells[55].

The major culprit drugs include TMP-SMX, aminopenicillins, dapsone, abacavir, nevirapine, antituberculous drugs, and anticonvulsants. For example, up to 40% of HIV-infected patients may develop a "rash" during treatment with TMP-SMX. These adverse cutaneous reactions, especially when severe, necessitate discontinuation of the drug. In the case of mild reactions, "treating through", i.e. continuing the drug despite the cutaneous eruption, is possible and has been followed by the disappearance of the rash. Corticosteroids may lower the rate of reactions to sulfonamides in AIDS patients. Desensitization has been performed in these patients with varying results.

Drug-induced lupus erythematosus (LE)

A range of medications can induce systemic LE (SLE) and cutaneous LE, most commonly subacute cutaneous LE (SCLE) and occasionally discoid lupus erythematosus (DLE). In drug-induced SLE, patients may develop fever, malaise, polyarthritis, and serositis from drugs such as hydralazine, minocycline, and procainamide[56], but associated acute cutaneous LE is rare. Although symptoms typically appear at least one month after drug initiation and resolve days to weeks after discontinuation of the responsible medication, the skin lesions of SCLE are sometimes more persistent. Tables 41.2 and 41.10 review the drugs that have been reported to induce SLE and SCLE.

The pathogenesis of drug-induced SLE is not well understood, but one possibility is that reactive drug metabolites, interacting with nuclear histones, could act as haptens and activate the complement cascade. For example, procainamide-induced SLE occurs more frequently in patients who are slow acetylators as compared to rapid acetylators.

While drug-induced SLE is characterized by the presence of antihistone antibodies in up to 95% of cases, these antibodies are not specific and may be seen in patients with idiopathic SLE. Antibodies against double-stranded DNA are typically absent, with the exception of TNF inhibitor-induced SLE. The seroconversion from negativity to positivity for anti-nuclear antibodies alone is not sufficient to discontinue a particular medication, but if symptoms develop, the culprit drug should be withdrawn. However, the anti-nuclear antibodies may persist for 6 to 12 months.

In drug-induced SCLE, anti-SSA/Ro and anti-SSB/La antibodies are often present and the cutaneous and histologic findings are indistinguishable from those seen in the idiopathic form of the disease. It therefore behooves the clinician to carefully review all medications in patients with the diagnosis of SCLE, in particular terbinafine, thiazide diuretics, proton pump inhibitors, calcium channel blockers, and taxanes (see Table 41.2). Of note, patients receiving TNF inhibitors may develop cutaneous lesions of chronic (discoid), subacute, or acute cutaneous LE as well as anti-nuclear and anti-DNA antibodies.

Lymphomatoid drug reaction (see Ch. 121)

Synonyms: ■ Pseudolymphomatous drug reaction ■ Drug-induced cutaneous lymphoid hyperplasia

A lymphomatoid drug reaction has a benign biological behavior and does not satisfy the criteria for non-Hodgkin lymphoma[57]. Although this disorder was originally thought to represent a hypersensitivity reaction, current evidence indicates that the responsible drugs may depress immunologic functions and impair immunosurveillance, leading to an abnormal clonal or non-clonal proliferation of B cells or T cells.

Lymphomatoid drug reactions develop insidiously over a period of months or even years after initial administration of the culprit drug. Cutaneous lesions may be solitary or multiple, localized or generalized, and consist of erythematous to violet papules, plaques, or nodules. Numerous widespread tumors are rare as is an erythroderma simulating Sézary syndrome. There is often associated lymphadenopathy, but it may be the sole finding.

Histologically, a dense lymphocytic infiltrate is seen within the dermis that can mimic a T or B cell lymphoma. In some patients, the lymphocytic infiltrate is band-like, resembling mycosis fungoides, while in others there is a B cell pattern with reactive germinal centers.

Lesions resolve within weeks to months following withdrawal of the responsible medication. The majority of lymphomatoid drug reactions have been reported with anticonvulsants (phenytoin, phenobarbital, carbamazepine, lamotrigine), antipsychotics (e.g. chlorpromazine), and imatinib (see Table 121.1).

Pigmentary changes (see Ch. 67)

Drug-induced cutaneous hyperpigmentation may result from a variety of mechanisms, including: (1) enhanced melanin production; (2) deposition of drugs or their metabolites – sometimes complexed with melanin or iron and in some instances better described as discoloration; and (3) simply postinflammatory changes. The hyperpigmentation may be more pronounced in sun-exposed areas. The drugs most commonly implicated in cutaneous hyperpigmentation (or discoloration) include minocycline, antimalarials, amiodarone (Fig. 21.23), oral contraceptives, imipramine, chemotherapeutic agents, clofazimine, zidovudine, and less often fluoroquinolones. Exposure to heavy metals such as silver and gold as well as arsenic may also induce darkening of the skin, and bleomycin can lead to linear "flagellate" hyperpigmentation.

Hypopigmentation can occur with the chronic use of several topical medications, including retinoic acid and corticosteroids; depigmentation is associated primarily with the application of monobenzyl ether of hydroquinone and imiquimod or exposure to catechols, phenols, and quinones (i.e. contact or occupational leukoderma; see Ch. 66). Cutaneous hypopigmentation can result from oral tyrosine kinase inhibitors, in particular imatinib and cabozantinib.

A few drugs are capable of changing the color of hair. For example, chloroquine, imatinib, dasatinib, and sunitinib can lead to lightening or even depigmentation (see Table 21.16). Imatinib can also lead to darkening of the hair.

Drug-induced psoriasis

Drugs may be associated with a precipitation or exacerbation of psoriasis. The clinical manifestations of drug-induced psoriasis span the spectrum of psoriasis, from limited or generalized plaques to erythroderma and pustulosis of the palms and soles. Nail changes and scalp



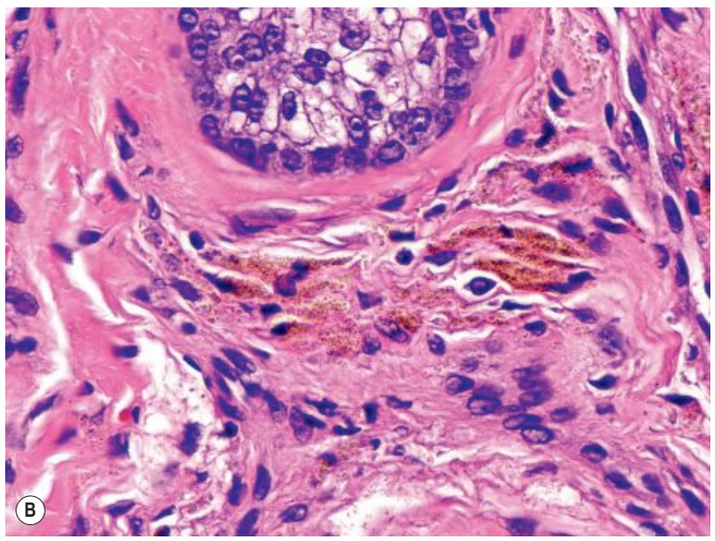


Fig. 21.23 Cutaneous discoloration due to amiodarone. A Gray–violet discoloration of the face. Note sparing of the lower eyelid. **B** Biopsy specimens demonstrate yellow–brown granules within dermal macrophages. *A, Courtesy Jean L. Bolognia, MD; B, Courtesy Luis Requena, MD.*

involvement may also be seen as well as plaques at the sites of injections (e.g. interferon). While a wide range of drugs have been implicated, those with the strongest causal relationship include lithium, β-blockers, NSAIDs (oral and topical), TNF inhibitors (especially infliximab), and interferons. Its association with additional medications (e.g. antimalarials, GM-CSF, potassium iodide) has been debated.

Lesions of drug-induced psoriasis usually regress within weeks to a few months of discontinuing the inciting drug. However, psoriasiform eruptions, including palmoplantar pustulosis, may be more persistent in patients receiving TNF inhibitors (see Ch. 128). The latter occur not just in individuals with psoriasis or rheumatoid arthritis, but also in patients being treated for other conditions, e.g. GVHD or inflammatory bowel disease, who have no personal or family history of psoriasis (Fig. 21.24). These eruptions may or may not follow a reduction in immunosuppression.

Histologic findings are similar to those in conventional psoriasis or pustular psoriasis. However, medications may induce more than one type of skin lesion, e.g. eczematous as well as psoriasiform in patients receiving TNF inhibitors, and this is reflected in the histologic findings.

The mainstay of treatment is recognition and discontinuation of the culprit drug when possible. If the psoriatic lesions fail to improve following discontinuation of the suspected drug, routine therapies for psoriasis are initiated. For mild TNF inhibitor-induced disease, a "treat through" approach can be considered, along with the addition of other anti-psoriatic treatments (e.g. methotrexate). In the case of moderate to severe TNF inhibitor-induced paradoxical psoriasis, switching to a different TNF inhibitor (moderate disease) or completely different class of immunomodulators ("biologics") is recommended.

Additional uncommon drug reactions

Examples of such drug reactions are outlined in Table 21.20.



Fig. 21.24 Psoriasiform eruption due to TNF inhibitor. Sterile pustulosis of the plantar surface developed in this patient with rheumatoid arthritis who had received infliximab for the previous 5 years. There was no reduction in immunosuppression prior to the onset of the psoriasiform eruption. *Courtesy Chris Bunick, MD.*

UNCOMMON ADVERSE MUCOCUTANEOUS DRUG REACTIONS	
Adverse reaction	**Drugs**
Bullous hemorrhagic dermatosis (intraepidermal hemorrhagic bullae at distant sites)	Enoxaparin Heparin
Eczematous drug reaction	Calcium channel blockers Intravenous immunoglobulins (including pompholyx) TNF inhibitors Ustekinumab, anti-IL-17 antibodies Immune checkpoint inhibitors EGFR inhibitors ACE inhibitors HMG-CoA reductase inhibitors (statins)*
Genital ulcers Scrotal Penile	 All-trans-retinoic acid†, anti-angiogenic multikinase inhibitors (e.g. cabozantinib, sunitinib) Foscarnet
Eosinophilic granulomatosis with polyangiitis	Montelukast Mesalazine
*Also xerosis. †Also oral ulcers.	

Table 21.20 Uncommon adverse mucocutaneous drug reactions. Drug-induced acanthosis nigricans is reviewed in Fig. 53.16. EGFR, epidermal growth factor; TNF, tumor necrosis factor.

Cutaneous Side Effects of Vaccines and Injected Medications

Vaccine-induced reactions

With the discontinuation of vaccinations for smallpox in the general population, the incidence of significant cutaneous side effects due to vaccines had markedly decreased. However, the introduction of lipid nanoparticle-encapsulated mRNA-based SARS-CoV-2 vaccines has led to a resurgence. Local inflammatory reactions consisting of erythema, swelling, and tenderness can be seen, as well as urticaria, angioedema, and anaphylaxis; in the past, the latter occurred primarily with live measles vaccines. Excessive limb swelling, mimicking cellulitis, has also been described, particularly with vaccines containing a pertussis component (Table 21.21). Lichenoid eruptions, erythema multiforme, and occasionally autoimmune reactions, e.g. polyarteritis nodosa, bullous pemphigoid, have been observed, with a wide range of reactions reported after the SARS-CoV-2 vaccine, from petechial exanthems to inflammatory reactions to hyaluronic acid soft tissue fillers. In addition, the commonly administered influenza vaccine has been associated with a serum sickness-like reaction, acute febrile neutrophilic dermatosis, and linear IgA bullous dermatosis.

REACTIONS LOCALIZED TO SITES OF INJECTIONS OF MEDICATIONS AND VACCINES	
Medication or vaccine	**Cutaneous reaction**
Medication	
Adalimumab*	Erythematous or urticarial plaques
Anakinra	Erythematous or urticarial plaques
Anti-sense oligonucleotides	Erythema accompanied by pruritus or pain, necrosis, ulceration
Bortezomib	Erythematous or urticarial plaque (Fig. 21.19), necrosis, spider-like or reticulated erythema
Corticosteroids	Deposits of drug (Fig. 125.8), dermal atrophy (Fig. 125.7 A), hypopigmentation (Fig. 125.7B), lipoatrophy, telangiectasias
Desensitization injections	Subcutaneous sarcoidosis
Enfuvirtide	Erythematous or morpheaform plaque
Etanercept*	Erythematous plaques (Fig. 128.8), eosinophilic cellulitis, vasculitis
Glatiramer acetate	Fibrosis, lipoatrophy, Nicolau syndrome†, panniculitis, vasospasm
GM-CSF*, G-CSF*	Pustular reaction, urticarial plaque (Fig. 128.3)
Heparin	Ecchymosis, erythematous plaques, necrosis, urticaria (see Ch. 23)
Hyaluronic acid, silicone	Granulomatous reaction (see Ch. 94), swelling
Interferon*	Development of plaque of psoriasis, lupus-like reaction, vasculopathy with necrosis
Interleukin-2	Granulomas, lobular panniculitis
Iron	Brown discoloration, hyperpigmentation
Low-molecular-weight, calcium-containing heparin	Calcinosis cutis
Meglumine antimoniate	Pruritic erythematous plaque, occasionally necrosis
Rituximab/hyaluronidase human	Erythematous plaque
SCI_g	Erythematous plaque
Vitamin B_{12}	Morpheaform plaque, pruritus
Vitamin K	Erythematous plaque, often annular (Fig. 21.25), morpheaform plaque (Texier disease)
Vaccine‡	
Aluminum-containing vaccine	Foreign body reaction, nodules
SARS-CoV-2 mRNA vaccine	Tender or pruritic erythematous plaque, either within one week or delayed (larger and primarily with Moderna vaccine); occasionally vesicular or multiple plaques
Thimerosal-containing vaccine	Allergic contact dermatitis

*Discussed in Chapter 128.
†Uncommon complication of intramuscular (and also intra-articular or subcutaneous) drug injection characterized by severe pain and erythematous–ecchymotic livedoid skin discoloration at the injection site leading to variable degrees of ischemic necrosis of the surrounding skin and deeper tissues.
‡Generalized reactions to vaccines can also occur, including anaphylaxis, Sweet syndrome, acute generalized exanthematous pustulosis, bullous pemphigoid, linear IgA bullous dermatosis, lichenoid eruptions, and erythema multiforme.

Table 21.21 Reactions localized to sites of injections of medications and vaccines (in addition to extravasation of those administered intravenously). See Table 21.22 and Table 89.4 for reactions to insulin and illicit drugs, respectively. Local injection site reactions consisting of an erythematous plaque and induration can be seen with systemic immunomodulators including ustekinumab, secukinumab, ixekizumab, risankizumab, and dupilumab. CSF, colony-stimulating factor; G, granulocyte; GM, granulocyte–macrophage; SCIg, subcutaneous immunoglobulin.

CUTANEOUS SIDE EFFECTS OF INSULIN INJECTIONS
Immediate hypersensitivity
Local reaction (erythema, pruritus)
Urticaria, angioedema
Anaphylaxis (rare)
Delayed hypersensitivity
Reaction at injection sites (erythema, induration)
Exanthematous (morbilliform) eruption (rare)
Acute generalized exanthematous pustulosis (AGEP) (rare)
Exfoliative dermatitis (rare)
Localized lipodystrophy
Lipoatrophy* (occurs less frequently with rapidly absorbed analogue insulins, e.g. insulin lispro)
Lipohypertrophy
Localized skin infections
Cellulitis and abscesses, most commonly due to *Staphylococcus aureus*
Granulomatous nodules, e.g. due to atypical mycobacteria
Ulcers
Localized acanthosis nigricans
Localized insulin-derived amyloidosis (subcutaneous amyloid mass)
*Rarely occurs at distant sites.

Table 21.22 Cutaneous side effects of insulin injections. Use of an insulin pump also carries the risk of scarring and allergic contact dermatitis to isobornyl acrylate in the adhesive.

Vaccination with BCG can lead to a benign, self-limited local reaction consisting of a plaque, pustule, or even ulcer (see Ch. 75). Occasionally, local abscess formation may follow vaccination of strongly reactive individuals, administration of a large amount of vaccine, or a deep injection. Delayed type hypersensitivity to a vaccine's aluminum adjuvant can appear weeks to months following vaccination, presenting as persistent erythema, a sterile abscess, or subcutaneous nodules.

Localized reactions to injected medications

In addition to the cutaneous reactions to vaccines discussed previously, Table 21.21 outlines cutaneous reactions that are localized to the sites of injections of medications and Table 21.22 reviews the side effects of insulin injections.

Treatment

A limited number of drug eruptions are life-threatening or lead to disabling sequelae. Management begins with the withdrawal of the suspect drug as soon as possible. Frequently, however, several drugs may be incriminated. As there is no clinical or laboratory test which permits identification of the culprit agent with certainty, the decision is usually made to discontinue all drugs that are non-essential as well as the "high-probability" drugs. Medications in the same chemical family are avoided as substitutions. Additional evaluation can be done, e.g. patch tests, prick, and intradermal tests, but results often return after decisions regarding drugs to discontinue have been made.

For mild drug eruptions, topical corticosteroids and oral antihistamines may be helpful. In the case of "acute skin failure" as in TEN, management must be undertaken in specialized intensive care units. Supportive interventions include warming of the environment, correction of electrolyte disturbances, high caloric supplementation, and prevention of sepsis[58].

The presumed immunologic etiology for drug eruptions has led to the use of systemic corticosteroids, immunosuppressive, and anticytokine therapies. There is minimal evidence for the usefulness of systemic corticosteroids, either as a preventive or as a therapeutic agent, in the most common forms of drug reactions (e.g. exanthematous) or SJS/TEN. However, topical or systemic corticosteroids represent the cornerstone of treatment for DRESS. In patients with mild exanthematous drug eruptions that occur during the treatment of a severe disease, it is sometimes possible to "treat through" the rash and continue the incriminated drug. That said, there is no agreement regarding this clinical approach and, in the case of severe reactions, resumption of the culprit drug, including chemically similar ones, is contraindicated. An allergy card and a detailed list of drugs to avoid *ad infinitum* should be given to the patient, with modifications made based upon additional testing (see above).



Fig. 21.25 Local reactions to vitamin K injections. A This patient was originally diagnosed as having erythema multiforme. **B** Large pink–violet plaque with areas of hemorrhage in an infant. *B, Courtesy Julie V. Schaffer, MD.*

Public health and drug policies should focus on the avoidance and prevention of SCARs at the population level. These measures include: (1) pharmacogenetic tests to identify patients at risk for SCARs in specific subpopulations (see Table 21.3); and (2) pharmacovigilance, which requires systematic reporting of culprit drugs to health authorities, pharmaceutical companies, and independent registries. Guidelines should be followed when prescribing drugs, especially allopurinol and trimethoprim–sulfamethoxazole[59], and both pharmaceutical companies and government agencies should avoid allowing look-alike and sound-alike drugs that could result in dispensing errors[60].

Additional figures and tables on Skin reactions to "drugs" received by at least 1000 patients, Drugs received by more than 1000 patients with no skin reactions (rates estimated to be ≤3 per 1000), Features that suggest a severe cutaneous adverse reaction (SCAR) to a drug, Frequency of clinical and laboratory features in drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), Severity score of drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), and Management of immune checkpoint inhibitor cutaneous side effects, available in our eBook (see inside front cover for access code).

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eFig. 21.1 Exanthematous drug eruptions. A Numerous pink papules on the trunk due to a cephalosporin. **B** Confluence of the lesions on the trunk secondary to phenobarbital.

DRUG ERUPTION CHART – SAMPLE

Drugs	Pre-hospital Duration (years)	6/15	6/16	6/17	6/18	6/19	6/20	6/21 (Rash onset)	6/22 (Derm consult)	6/23	6/24 (Rash worse)	6/25	6/26	6/27	6/28	6/29 (Rash better)
Dates drug(s) administered																
Aspirin	x 10	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Heparin SC			×	×	×	×	×	×	×	×	×	×	×	×	×	×
Famotidine		×	×	×	×	×	×	×	×							
Insulin	x 5	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Digoxin	x 8	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Diltiazem	x 6	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Multi-vitamin	x 5	×	×	×	×	×	×	×	×							
Thiamine		×	×	×												
Folate		×	×	×	×	×	×	×	×							
Lorazepam		×	×	×	×	×	×	×	×	×	×	×				
Zolpidem		×	×		×	×		×								
Acetaminophen		×	×													
Ibuprofen				×	×											
Tramadol HC						×	×	×								
Maalox®			×	×	×											
Lactulose						×	×	×								
Diphenhydramine								×	×	×	×	×	×			
Ampicillin/sulbactam		×	×													
Vancomycin				×	×	×	×	×	×							
Ceftazidime				×	×	×	×	×	×							
Levofloxacin										×	×					
Linezolid												×	×	×	×	×
Laboratory																
WBC		20.2	16.5	7.0	7.6	8.1	10.2	11.3	11.5	11.2	11.5	10.5	9.2	7.0	7.0	6.5
% Eosinophils		0%	0%	<1%	<1%	3%	5%	7%	9%	9%	8%	7%	5%	3%	1%	1%
% Atypical lymphocytes		0%	→													
Platelets		nl	→													
AST		nl	→													
ALT		nl	→													
BUN/Cr		nl	→													
Temperature (°C)		40			38			38.3		38.5			37.5			
Physical exam*		nl	→													
Type of rash								Morbilliform →		Confluence						

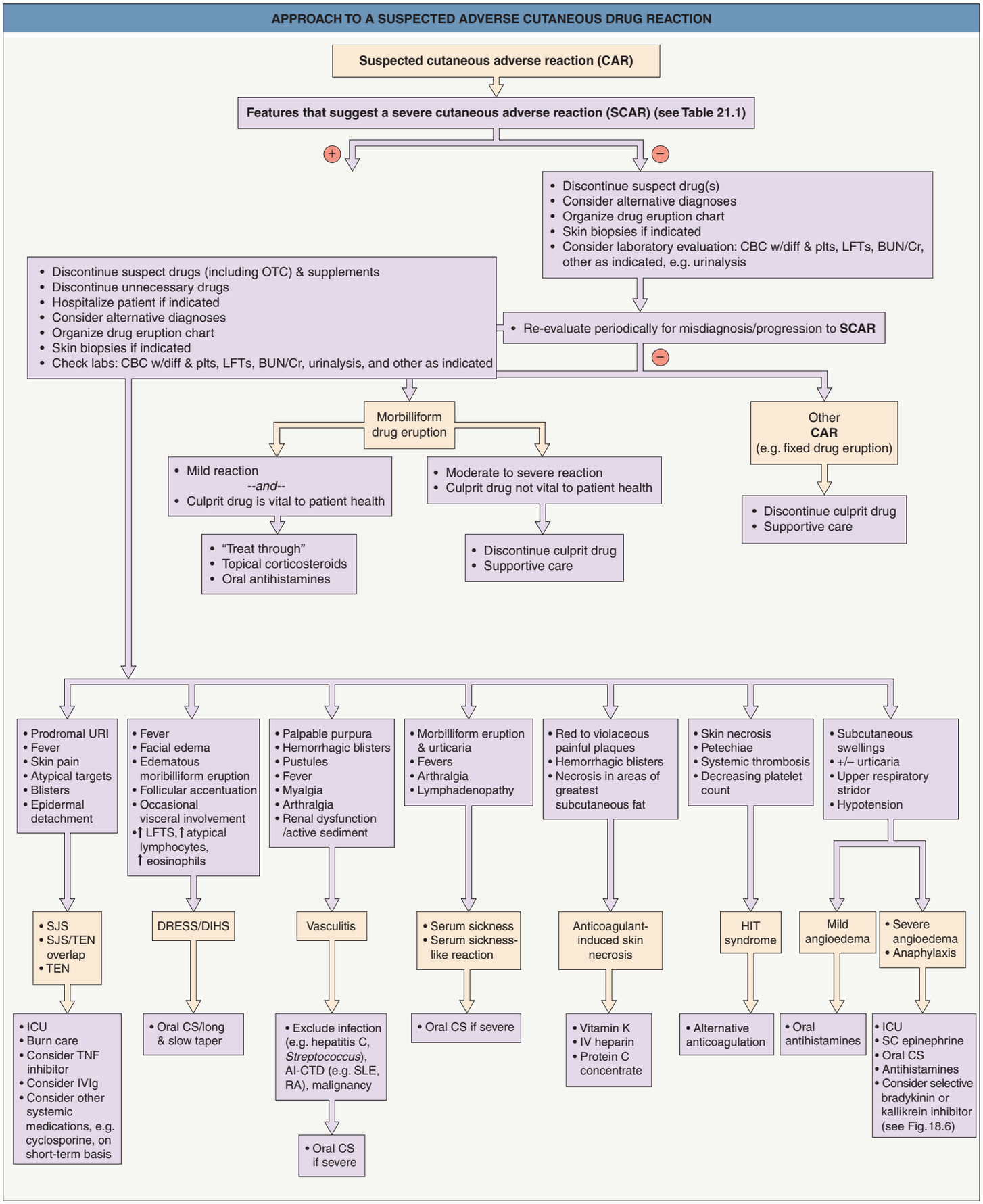
(A) * Checking for the presence of lymphadenopathy, arthritis, wheezing, hypotension

eFig. 21.2 Drug eruption chart. A Sample chart. This is a helpful working template for organizing all of the available patient information into one document for a patient with a suspected cutaneous adverse reaction (CAR). **Step 1:** Compile all of the recently consumed or administered drugs (including prescription, over-the-counter, and supplements) into the chart. **Step 2:** Review and list the pertinent laboratory information and physical findings at the bottom of the chart. **Step 3:** Exclude a **severe cutaneous adverse reaction** (SCAR) and categorize the type of CAR. **Step 4:** Based on time intervals and the most and least likely drugs to cause CAR (see Table 21.6), begin to formulate the most likely culprit drugs and recommend their discontinuation. In addition, discontinue unnecessary drugs. **Step 5:** Longitudinal evaluation of the patient is necessary to (1) exclude progression to a SCAR, (2) determine the response upon discontinuation of the culprit drug (noting that it might "get worse before it gets better"), and (3) provide supportive care to the patient. In this sample patient, the most likely culprit drugs are ceftazidime > ampicillin/sulbactam > vancomycin; however, the multi-vitamin, folate, famotidine, zolpidem, acetaminophen, ibuprofen, tramadol, Maalox®, and lorazepam (must taper off and not abruptly stop) were also discontinued. Note that the discontinuation of levofloxacin by the primary physicians was not necessary. **B** A blank template of the drug eruption chart. AST, aspartate aminotransferase; ALT, alanine aminotransferase; SC, subcutaneous; WBC, white blood cell count. *Courtesy Karynne O. Duncan, MD.*

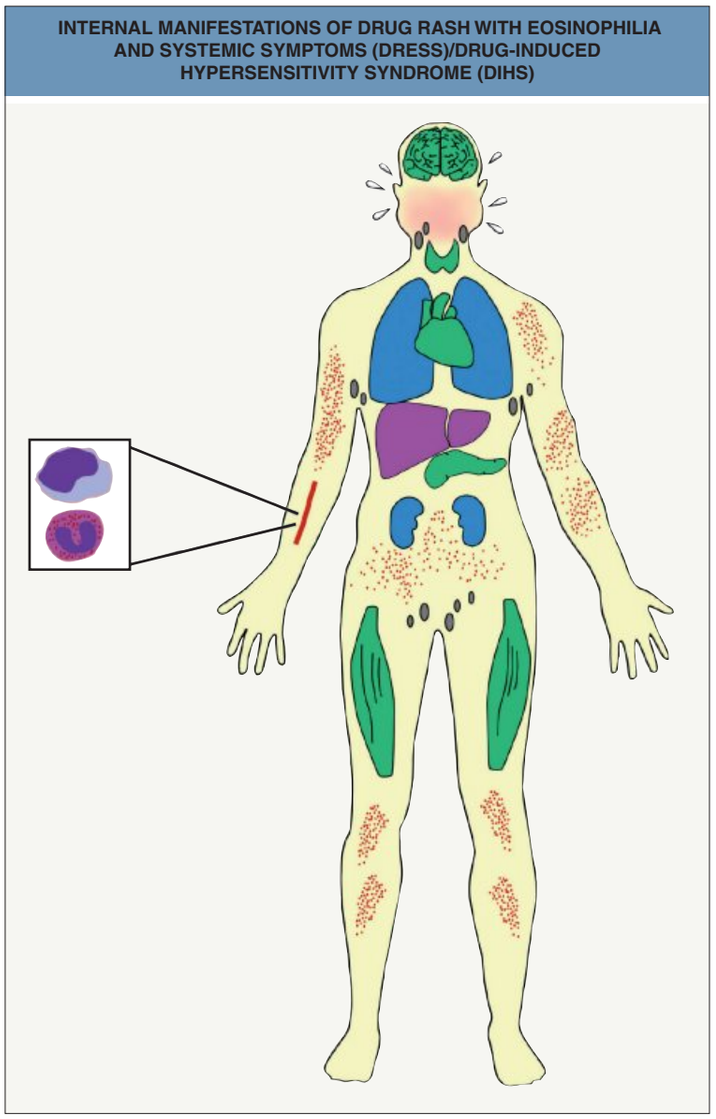
DRUG ERUPTION CHART

	Dates drug(s) administered															
Drugs	Pre-hospital / Duration (years)															
Laboratory																
WBC																
% Eosinophils																
% Atypical lymphocytes																
Platelets																
AST																
ALT																
BUN/Cr																
Temperature (°C)																
Physical exam*																
Type of rash																

B * Checking for the presence of lymphadenopathy, arthritis, wheezing, hypotension



eFig. 21.3 Approach to a suspected adverse cutaneous drug reaction. OTC, over-the-counter; CBC, complete blood count; diff, differential; plts, platelets; LFTs, liver function tests; BUN/Cr, blood urea nitrogen/creatinine; URI, upper respiratory illness (including sore throat); SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; ICU, intensive care unit; SC, subcutaneous; IV, intravenous; DRESS, drug reaction with eosinophilia and systemic symptoms; DIHS, drug-induced hypersensitivity syndrome; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; HIT, heparin-induced thrombocytopenia.



eFig. 21.4 Schematic of the internal manifestations of drug rash with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS). In addition to peripheral eosinophilia and atypical lymphocytes, there can be fever, lymphadenopathy, and systemic involvement including the liver, kidneys, heart, lungs, muscles, CNS, and pancreas. *Courtesy Jean L. Bolognia, MD.*



eFig. 21.5 Acute generalized exanthematous pustulosis (AGEP). Diffuse erythema of the face with numerous pustules due to metronidazole. *Courtesy Kalman Watsky, MD.*



eFig. 21.6 Acute generalized exanthematous pustulosis (AGEP) due to ipilimumab. *Courtesy Anna Eisenstein, MD.*



eFig. 21.7 Iododerma in a patient with late-stage chronic kidney disease.
Courtesy Christine Warren, MD.



eFig 21.10 Generalized bullous fixed drug eruption (GBFDE). Due to naproxen; note the "wet cigarette paper" appearance at the site of a ruptured bulla inferiorly. *Courtesy Sara Perkins, MD.*



eFig. 21.8 Fixed drug eruption due to metronidazole. Red–brown, well-defined, round patch. *Courtesy Edward Cowen, MD.*



eFig. 21.11 Fixed drug eruption due to naproxen. Coalescing red–brown plaques with a central dusky violaceous hue due to naproxen.



eFig. 21.9 Bullous fixed drug eruption.



eFig. 21.12 Fixed drug eruption due to acetaminophen. As lesions start to resolve, a brown hue can begin to appear within the areas of inflammation.



eFig. 21.13 Vesicular fixed drug eruption of the glans penis due to trimethoprim–sulfamethoxazole. *Courtesy Kalman Watsky, MD.*



eFig. 21.14 Stevens–Johnson syndrome. Flaccid bullae leading to epidermal detachment (<10% body surface area).



eFig. 21.15 Paclitaxel-induced onycholysis with subungual hemorrhage. All of the fingernails were involved. *Courtesy Jonathan S. Leventhal, MD.*



eFig. 21.16 Lichenoid dermatitis due to anti-PD-1 antibody therapy. Pink–violet papules and plaques with white scale on the back. *Courtesy Jonathan S. Leventhal, MD.*



eFig. 21.17 Inflammation of actinic keratoses in a patient receiving intravenous interleukin-2. *Courtesy Jean L. Bolognia, MD.*



eFig. 21.19 Papulopustular (acneiform) eruption due to cetuximab, an epidermal growth factor receptor (EGFR) inhibitor. *Courtesy of Jean L. Bolognia MD.*



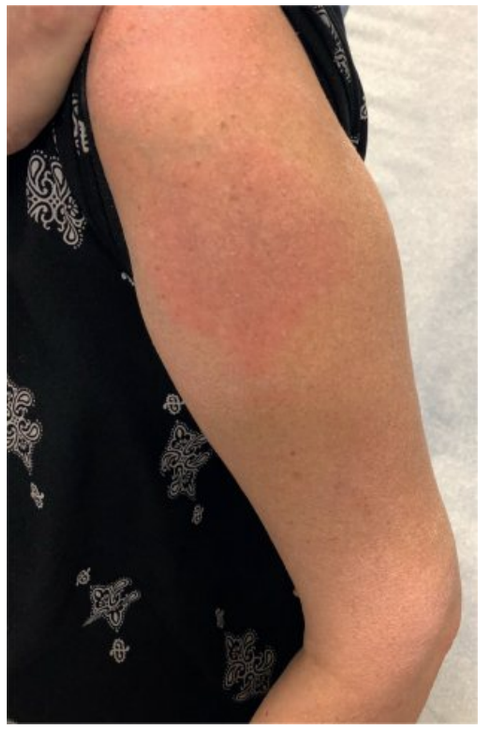
eFig. 21.18 Papulopustular (acneiform) reaction to an epidermal growth factor receptor (EGFR) inhibitor. Pustules and numerous crusted papules on the face. *Courtesy Diane Thiboutot, MD.*



eFig. 21.20 Papulopustular (acneiform) eruption due to erlotinib, an epidermal growth factor receptor (EGFR) inhibitor. There are multiple fine pustules and hemorrhagic crusts. *Courtesy Edward Cowen, MD.*



eFig. 21.21 Epidermal growth factor receptor inhibitor-associated paronychia and (pseudo)pyogenic granuloma-like lesions. Friable granulation tissue developed within the lateral nail folds following administration of cetuximab. Silver nitrate application plus topical timolol led to improvement. *Courtesy Jonathan S. Leventhal, MD.*



eFig. 21.22 Erythematous plaque at the site of injection of lipid nanoparticle-encapsulated SARS-CoV-2 mRNA-1273 vaccine (Moderna). This has been referred to as "Moderna arm". *Courtesy Dennis Cooper, MD.*

SKIN REACTIONS TO "DRUGS" RECEIVED BY AT LEAST 1000 PATIENTS	
Drugs	**Reaction rate (per 1000 recipients)**
Ampicillin	52
Penicillin G	16
Cephalosporins	13
Packed red blood cells	8.1
Heparin	7.7
Nitrazepam	6.3
Barbiturates	4.7
Chlordiazepoxide	4.2
Diazepam	3.8
Propoxyphene	3.4
Guaifenesin	2.9
Furosemide	2.6
Phytonadione	0.9
Flurazepam	0.5
Chloral hydrate	0.2

eTable 21.1 Skin reactions to "drugs" received by at least 1000 patients. Arndt KA, Jick H. Rates of cutaneous reactions to drugs. *J Am Med Assoc*. 1976;235:918–923.

DRUGS RECEIVED BY MORE THAN 1000 PATIENTS WITH NO SKIN REACTIONS (RATES ESTIMATED TO BE ≤3 PER 1000)
• Potassium chloride • Milk of magnesia • Digoxin • Meperidine hydrochloride • Dioctyl sodium sulfosuccinate • Magnesium hydroxide • Aluminum hydroxide • Acetaminophen • Multivitamins • Bisacodyl • Diphenhydramine hydrochloride • Aspirin • Aminophylline • Prochlorperazine • Ferrous sulfate • Thiamine • Prednisone • Atropine • Codeine • Vitamin B complex and ascorbic acid • Pentazocine • Hydrochlorothiazide* • Phosphate enema • Castor oil • Tetracycline* • Morphine • Regular insulin • Warfarin • Spironolactone
*Notably phototoxic reactions were not included.

eTable 21.2 Drugs received by more than 1000 patients with no skin reactions (rates estimated to be ≤3 per 1000). Arndt KA, Jick H. Rates of cutaneous reactions to drugs. *J Am Med Assoc*. 1976;235:918–923.

FEATURES THAT SUGGEST A SEVERE CUTANEOUS ADVERSE REACTION (SCAR) TO A DRUG		
Cutaneous features	**Systemic features**	**Laboratory findings**
• Skin pain • Confluent erythema • Facial edema • Blisters or epidermal detachment • Mucosal erosions • Necrosis • Palpable purpura • Urticaria • Swelling of lips/tongue	• High fever • Lymphadenopathy • Arthralgia/arthritis • Shortness of breath, wheezing, stridor, hypotension • Other visceral involvement	• Marked eosinophilia • Lymphocytosis with atypical lymphocytes • Leukopenia • Abnormal liver or renal function tests • Thrombocytopenia • Neutrophilia

eTable 21.3 Features that suggest a severe cutaneous adverse reaction (SCAR) to a drug. *Adapted from Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272–85.*

FREQUENCY OF CLINICAL AND LABORATORY FEATURES IN DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)/DRUG-INDUCED HYPERSENSITIVITY SYNDROME (DIHS)	
Clinical and laboratory features	**Percentage of patients**
Mucocutaneous	
Skin Extent of rash >50% BSA Maculopapular rash Facial edema Purpura Pustules	 45–80 60–100 40–85 10–30 15–30
Mucosae Mouth/throat/lips Eyes	50–60 50 10–15
Laboratory	
Eosinophilia	30–95
Atypical lymphocytes	30–65
Systemic	
Fever	70–100
Lymphadenopathy	30–90
Internal organ involvement 1 organ 2 or more organs	90 35–85 15–55
Liver	50–100
Kidney	5–55
Lung	5–35
Heart	≤15
Spleen	15
Pancreas	5

eTable 21.4 Frequency of clinical and laboratory features in drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS). BSA, body surface area.

SEVERITY SCORE OF DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)/DRUG-INDUCED HYPERSENSITIVITY SYNDROME (DIHS)		
Parameters	**Grade/extent**	**Score**
Fixed		
Age, years	≤40 / 41–74 / ≥75	–1 / 0 / 2
Duration of drug exposure after onset, days	0–6 / ≥7	0 / 1
Allopurinol exposure	Yes	1
Variable		
Pulsed prednisone	Yes	2
Skin involvement Erythema, % BSA Erosion, % BSA	 <70 / ≥70 / erythroderma <10 / 10–29 / ≥30	 0 / 1 / 2 0 / 1 / 3
Fever ≥38.5°C, duration in days	0 or 1 / 2–6 / ≥7	0 / 1 / 2
Appetite loss (≤70% of regular food intake), days	0–4 / ≥5	0 / 1
Renal dysfunction (creatinine, mg/dL)	<1 / 1–2 / ≥2.1 or HD	0 / 1 / 3
Liver dysfunction (ALT, IU/L)	<400 / 400–1000 / >1000	0 / 1 / 2
C-reactive protein (mg/dL)	≤2 / <2–<10 / ≥10–<15 / ≥15	–1 / 0 / 1 / 2

eTable 21.5 Severity score of drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS). Scores ≥4 were associated with the later development of cytomegalovirus (CMV) disease and complications and therefore early intervention with anti-CMV agents should be considered. ALT, alanine aminotransferase; BSA, body surface area; HD, hemodialysis. *Adapted from Mizukawa Y, et al. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms severity score: a useful tool for assessing disease severity and predicting fatal cytomegalovirus disease. J Am Acad Dermatol 2019;80:670–8.e672.*

MANAGEMENT OF IMMUNE CHECKPOINT INHIBITOR CUTANEOUS SIDE EFFECTS			
Inflammatory eruptions (morbilliform, lichenoid, eczematous and psoriasiform)			
Grade	***Clinical findings***	***Treatment recommendations***	***Immune checkpoint inhibitor management and preventive measures***
1	Symptoms without impact on QOL or controlled with "simple treatment" (topical regimen and/or oral antipruritic)	Simple treatment: Emollients, mild-to-moderate potency topical CS, oral antipruritics*	Continue ICI Avoid skin irritants Minimize sun exposure
2	Impact on QOL and requires intervention	Same as Grade 1 but higher potency CS Consider oral CS (e.g. prednisone 1 mg/kg tapered over at least 4 weeks) *Narrowband UVB, acitretin, apremilast*	Consider holding ICI and assess weekly until return to Grade 1
3	Fails to respond to Grade 2 treatment	Same as Grade 2 but consider higher dose of oral CS (e.g. (methyl)prednisolone 1–2 mg/kg) tapering over at least 4 weeks *Systemic immunomodulators depending upon type of eruption, e.g. anti-IL-4/-13 for eczematous, anti-IL-23 or -17 for psoriasiform*	Hold ICI & assess in conjunction with dermatologist when to resume
4	Severe, intolerable, fails to respond to Grade 2/3	Hospitalization & IV CS (e.g. methylprednisolone 1–2 mg/kg) with slow taper when the toxicity resolves	Same as Grade 3 Consider alternative therapy
Bullous eruptions (autoimmune bullous dermatoses and bullous drug reactions)			
Grade	***Clinical findings***	***Treatment recommendations***	***Immune checkpoint inhibitor management and preventive measures***
1	No symptoms, blisters covering <**10% BSA**, no erythema	Local care Consider other etiology	Continue ICI
2	Symptomatic blisters or erosions, impacting QOL **10%–30% BSA**	Local care & class I topical CS *Doxycycline +/– nicotinamide* Low threshold for oral CS (e.g. prednisone 0.5–1 mg/kg tapered over ≥4 weeks) *Dupilumab, methotrexate, omalizumab*	Hold ICI Evaluation for autoimmune bullous dermatosis & observe for progression to SCAR†
3	Blisters or erosions >**30% BSA** plus pain and ADLs impacted	Hospitalization & IV CS (e.g. methylprednisolone 1–2 mg/kg) with slow taper; if BP, consider rituximab or IVIg *Dupilumab, methotrexate, omalizumab*	Hold ICI & assess in conjunction with dermatologist regarding appropriateness of resuming
4	Blisters or erosions >**30% BSA** plus fluid or electrolyte abnormalities	Same as Grade 3	Permanently discontinue ICI
Severe cutaneous adverse reactions (including SJS/TEN, AGEP, and DRESS)			
Grade	***Clinical findings***	***Treatment recommendations***	***Immune checkpoint inhibitor management***
1	NA‡	Monitor closely for improvement or worsening	
2 DRESS	Morbilliform eruption **10%–30% BSA** plus systemic symptoms, lymphadenopathy, or facial swelling	Emollients, oral antihistamines, and moderate-to-high dose topical CS Consider oral CS (e.g. prednisone 0.5–1 mg/kg tapered over at least 12–24 weeks)	Consider holding ICI and assess every 3 days until return to Grade 1
3 SJS	Skin sloughing <**10% BSA** plus mucosal involvement	Hospitalization and IV CS (e.g. methylprednisolone 0.5–1 mg/kg initially then switch to oral and taper over at least 4 weeks) +/– *IVIG, cyclosporine or TNF inhibitor*	Hold ICI, consider alternative therapy
4 SJS/ TEN DRESS	Skin erythema & blistering/sloughing ≥**10% BSA** *or* concerning lab abnormalities	Hospitalization and IV CS (e.g. methylprednisolone 1–2 mg/kg), with taper when toxicity resolves to normal +/– IVIG or cyclosporine *or TNF inhibitor*	Permanently discontinue ICI

*Oral antipruritics include sedating and non-sedating antihistamines for mild itch; gabapentinoids, aprepitant, or dupilumab may be helpful for more severe itch.
†Includes Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).
‡For SCARs, there is no Grade 1; if limited body surface area involvement with bullae or erosions, there should remain a high concern that this reaction will progress to Grade 3 or 4.

eTable 21.6 Management of immune checkpoint inhibitor cutaneous side effects. Additional skin-directed treatments in *italics* were not in guidelines; for Grade 2 bullous eruptions, skin "sloughing" was changed to "blisters or erosions" for consistency. ICI therapy is typically held until the rash is grade 1 or the prednisone dose ≤10 mg daily. ADL, activities of daily living; AGEP, acute generalized exanthematous pustulosis; BP, bullous pemphigoid; BSA, body surface area; CS, corticosteroids; DRESS, drug reaction with eosinophilia and systemic symptoms; ICI, immune checkpoint inhibitor; IV, intravenous; IVIg, intravenous immunoglobulin; NA, not available; QOL, quality of life; SCAR, severe cutaneous adverse reactions; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; UVB, ultraviolet B. *Adapted from Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36:1714–68 and Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol. 2021;39:4073–4126.*

Purpura: Mechanisms and Differential Diagnosis

22

Warren W. Piette

INTRODUCTION

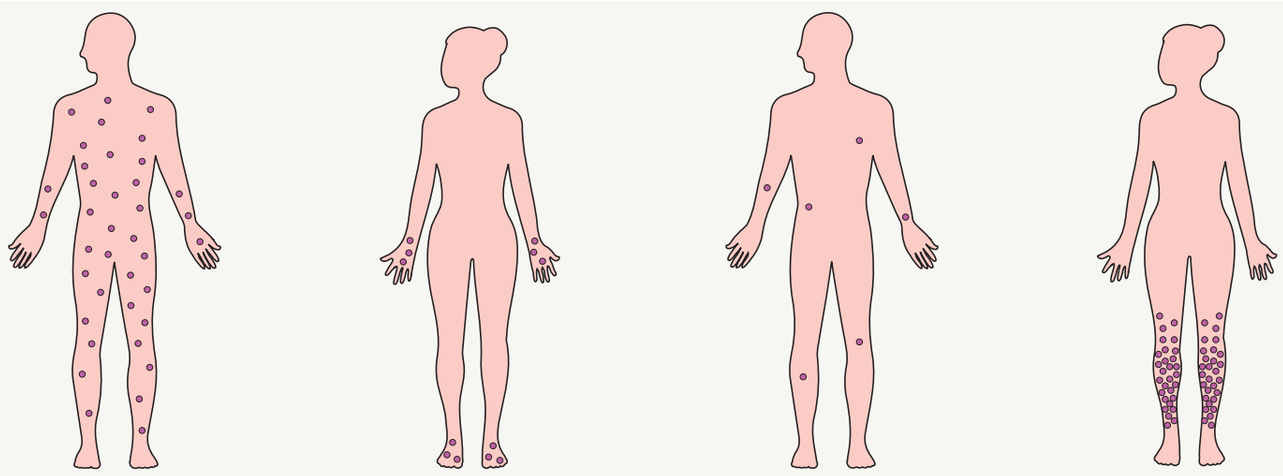
This chapter addresses the evaluation and classification of patients presenting with purpura, defined as visible hemorrhage within the skin or mucous membranes. The differential diagnosis presented in this chapter is directed toward syndromes of primary purpura, where the hemorrhage is an integral part of lesion formation, rather than hemorrhage secondary to causes such as trauma and scratching or hemorrhage into established lesions due to dependency (e.g. stasis dermatitis, eczema craquelé).

This chapter outlines a diagnostic approach based upon lesion number and distribution pattern, with a further focus on the morphology of the purpuric lesions. The initial goal is to identify the most plausible of three broad categories: simple hemorrhage (vascular breach), inflammatory hemorrhage (vessel-directed inflammation), or microvascular occlusion/ischemia. Assigning the patient to one of these three major categories facilitates a more directed, efficient, and accurate evaluation to prove or disprove the suspected pathomechanism and it serves to narrow the list of possible diagnoses.

Figure 22.1 illustrates this diagnostic approach based upon lesion number and distribution pattern. Interpretation of these clinical findings is then modified by lesional morphology, extracutaneous findings, and clinical context. For example, petechiae appearing in a generalized pattern requires exclusion of severe thrombocytopenia or perhaps thrombotic thrombocytopenic purpura, but they are most often due to a viral or drug eruption.

When *widespread*, purpuric lesions in a severely ill patient raise concern for serious drug eruptions (e.g. Stevens–Johnson syndrome) or some vasculitides whereas generalized retiform purpura in the setting of multi-organ disease suggests fulminant microvascular disease (e.g. catastrophic antiphospholipid syndrome) or sepsis-associated disseminated intravascular coagulation (DIC) with purpura fulminans. *Predominantly acral* lesions are divided into two subsets: (1) involvement of the ears and nose as well as the hands and feet, typically triggered by cold exposure; and (2) a more widespread distribution pattern with prominent involvement of the hands and feet, typically in the absence of cold exposure. A *pauci-random* distribution pattern is typical

APPROACH TO THE PATIENT WITH PURPURIC LESIONS BASED UPON NUMBER OF LESIONS AND DISTRIBUTION PATTERN



Multiple and generalized/widespread	Predominantly acral	Pauci-random	Multi-dependent
• Viral exanthem • Drug eruption • If only petechiae, severe thrombocytopenia • If retiform purpura & systemically ill patient, - Purpura fulminans - Sepsis/DIC - Catastrophic APLS - Fulminant ANCA-associated vasculitides	A) Multiple acral sites; typically cold-induced & retiform purpura due to vascular occlusion • Cryoglobulinemia, primarily type I • Rarely due to cryofibrinogens or cold agglutins B) Predominantly hands & feet • Viral exanthem, e.g. parvovirus • Erythema multiforme, including RIME/MIRM variant • Sepsis/DIC with hypotension; thromboses localized to vasoconstricted sites	• Usually <25 lesions • ANCA-associated vasculitides • Lymphomatoid papulosis • Occasionally, cutaneous PAN (more commonly pauci-dependent) • If favors areas with increased adipose tissue, - Warfarin-induced skin necrosis - Calciphylaxis	• 25–100 lesions • If macular & non-blanching, - Thrombocytopenia - Hypergammaglobulinemic purpura of Waldenström - Pigmented purpura - Occasionally, immune complex vasculitis* • If palpable & partially blanchable, - Immune complex vasculitis* - Occasionally, pigmented

*Presents similarly whether skin-limited or systemic, so clinical and laboratory evaluation of extracutaneous signs and symptoms required (see Ch. 24).

Fig. 22.1 Approach to the patient with purpuric lesions based upon number of lesions and distribution pattern. APLS, antiphospholipid antibody syndrome; DIC, disseminated intravascular coagulation; MIRM, *Mycoplasma*-induced rash and mucositis; RIME, reactive infectious mucocutaneous eruption; PAN, polyarteritis nodosa.



Fig. 22.2 Clinical examples of petechiae and purpura. A Round to oval petechiae, <3 mm in diameter. **B** Solar (actinic) purpura in sites of actinic damage plus trauma. **C** Palpable purpura due to cutaneous small vessel vasculitis (inflammation plus hemorrhage). **D** Non-inflammatory (bland) retiform purpura as well as hemorrhagic bullae in a patient with disseminated intravascular coagulation (DIC). *B, Courtesy Kalman Watsky, MD; D, Courtesy Judit Stenn, MD.*

of ANCA-associated vasculitides, various microvascular occlusive diseases, or lymphomatoid papulosis, and occasionally cutaneous polyarteritis nodosa (PAN). *Multi-dependent* patterns can result from severe thrombocytopenia but in the practice of dermatology is most commonly due to cutaneous small vessel vasculitis (see Ch. 24).

In 1989, the term *retiform purpura* was coined to describe a sign of certain vasculitic subsets, but nowadays it is generally used to denote a frequent marker of thrombotic or occlusive microvascular disease[1–3]. The morphologies of purpuric lesions are divided into two major subsets: (1) exclusively macular, whose shapes can be round, oval, irregular, or geometric; and (2) palpable and/or retiform. The macular group consists of petechiae (Fig. 22.2A, Table 22.1)[2], macular purpura (Table 22.2), and macular ecchymoses (Fig. 22.2B, Table 22.3). The palpable and/or retiform group consists of palpable purpura (Fig. 22.2C, Table 22.4), non-inflammatory retiform purpura (Fig. 22.2D; Table 22.5), and inflammatory retiform purpura (Table 22.6). In this chapter, lesions in the macular group are categorized on the basis of size and are defined as non-blanching and non-palpable; those in the palpable and/or retiform group can range in size from a few millimeters to several centimeters in diameter, may be palpable, and may partially blanch with pressure. The relevance of these morphologic subsets when sorting through the differential diagnosis is depicted in Figure 22.3.

Two major causes of purpura – microvascular occlusion syndromes and vasculitis – are discussed in Chapters 23 and 24[4]. Occlusion is important to recognize because it may mimic vasculitis but requires a very different approach to determine its etiology and appropriate therapy. The most typical presentation of microvascular occlusion syndromes is retiform purpura (see Table 22.5).

Livedo reticularis is a reflection of the physiologic anatomy of slow flow states. The three-dimensional structure and flow regulation of the dermal and subcutaneous vasculature give rise to the net-like pattern of livedo reticularis (see Fig. 106.1). The diameter of the almost-circular to polygonal individual units within the net-like grid varies from 2 cm or larger on the back to 5 mm or less on the palms or soles.

Retiform purpura morphology results from involvement of the same vessels that produce the livedo reticularis pattern. While the former was traditionally considered a component of livedo reticularis, the two should be distinguished based upon the presence or absence of purpura, hence the term "retiform purpura"[1,2]. Given the size of dermal vessels, the clot within the vessel is too small to be seen grossly. What is actually observed is hemorrhage around the dermal vessels, presumably due to ischemia with hemorrhage prior to complete occlusion of the vessel. A complete reticulate pattern is seen infrequently. Instead, the morphology of retiform purpura is composed of "puzzle pieces" of the livedo reticularis pattern. While some lesions have a branching appearance, very few, if any, are truly stellate, i.e. a central area of necrosis or hemorrhage with a radiating star-like pattern composed of straight lines.

Retiform lesions can be inflammatory or non-inflammatory, but the age of the lesion may blur this morphologic distinction, so in practice both groups of diagnoses need to be considered (see Tables 22.5 & 22.6). Inflammatory retiform purpura is accompanied by peripheral erythema, but the wound healing response can eventually lead to erythema and leukocytoclasis in lesions initiated by non-inflammatory occlusion (Fig. 22.4). As a corollary, vasculitis sometimes produces lesions that have minimal early erythema and lesions lose erythema during resolution.

Lastly, the retiform lesions of immune complex vasculitis are invariably sparse in number and are accompanied by many round purpuric lesions. In addition, these retiform lesions are typically more finely branched than either occlusive or ANCA-associated retiform purpura. However, when within confluent areas of purpura, they may have more intense branching hemorrhage or necrosis. Of note, vasculitic retiform lesions do not simply represent the crowding or collision of more classic round purpuric lesions, and they may occur with or without cutaneous arteritis.

The presence of a multi-dependent round and retiform pattern (many round/few retiform lesions) is seen most commonly with three types of immune complex vasculitis: (1) IgA-predominant; (2) autoimmune connective tissue disease-associated; and (3) mixed cryoglobulinemia. This pattern of round and retiform purpuric lesions may occasionally

DIFFERENTIAL DIAGNOSIS OF MACULAR PETECHIAE (≤4 MM IN DIAMETER)
Hemostatically relevant thrombocytopenia (<10 000–20 000/mm³)*
Major etiologies†

• Idiopathic thrombocytopenic purpura
• Thrombotic thrombocytopenic purpura
• Other acquired thrombocytopenias, including drug-related
  • Peripheral destruction (e.g. quinine, quinidine)
  • Drug-induced decreased production, idiosyncratic or dose-related (e.g. chemotherapy)
  • Bone marrow infiltration, fibrosis, or failure
• Disseminated intravascular coagulation (early sign)

Abnormal platelet function
Major etiologies†

• Congenital or hereditary platelet function defects
• Acquired platelet function defects
  • Aspirin, NSAIDs
  • Renal insufficiency
  • Monoclonal gammopathy (uncommon)
• Thrombocytosis secondary to myeloproliferative disorders (often >1 000 000/mm³)

Non-platelet etiologies
Major etiologies†

• Spiking elevations of intravascular venous pressure (Valsalva maneuver-like, e.g. repetitive vomiting, childbirth, paroxysmal coughing, seizure)
• Fixed increased pressure (e.g. stasis, ligatures) or intermittent pressure (e.g. blood pressure cuff – Rumpel–Leede sign)
• Trauma (often linear)
• Fat embolism syndrome
• Perifollicular (vitamin C deficiency)
• Mildly inflammatory conditions
  • Pigmented purpuric eruptions
  • Hypergammaglobulinemic purpura of Waldenström

*Platelets provide factors necessary for hemostasis of endothelial cell junctions. When counts fall below 10 000–20 000/mm³, inadequate platelet support leads to degradation of junction function, increased permeability, and hemorrhage³. †Partial list.

Table 22.1 Differential diagnosis of macular petechiae (≤4 mm in diameter). NSAIDs, nonsteroidal anti-inflammatory drugs.

DIFFERENTIAL DIAGNOSIS OF INTERMEDIATE MACULAR PURPURA (5–9 MM)
Major etiologies*
• Hypergammaglobulinemic purpura of Waldenström • Infection/inflammation in patients with thrombocytopenia • Rarely, minimally inflamed cutaneous small vessel vasculitis (usually dependent distribution)
*Partial list.

Table 22.2 Differential diagnosis of intermediate macular purpura (5–9 mm).

be seen in microscopic polyangiitis or granulomatous polyangiitis, but the lesions are fewer in number and more randomly distributed. The combination of many round/few retiform lesions is not seen with simple hemorrhage or microvascular occlusive disease.

THE TIME COURSE OF PURPURA

The three subsets of macular (non-palpable) purpura (see Tables 22.1–22.3) typically develop via simple hemorrhage, with extravasated red blood cells and minimal inflammation observed in biopsy specimens. These lesions simply evolve from initial hemorrhage to steady clearing of red blood cells and hemoglobin. Clinically this correlates with fading of lesions and, in larger lesions, transition of color from red–blue or purple to green, yellow, or brown before complete fading.

In syndromes of inflammatory hemorrhage, such as cutaneous small vessel vasculitis, as well as in microvascular occlusion, the evolution and

DIFFERENTIAL DIAGNOSIS OF MACULAR ECCHYMOSES (≥1 CM)
Procoagulant defect plus minor trauma
Major etiologies*
• Anticoagulant use • Hepatic insufficiency with poor procoagulant synthesis • Vitamin K deficiency • Disseminated intravascular coagulation (some)
Poor dermal support of vessels plus minor trauma
Major etiologies*
• Solar (actinic, senile) purpura • Corticosteroid therapy, topical or systemic • Vitamin C deficiency (scurvy) • Systemic amyloidosis (light chain-related, transthyretin-related; see Tables 47.1 & 47.2) • Ehlers–Danlos syndrome
Platelet disorders plus minor trauma
Major etiologies*
• Platelet function defects, including von Willebrand disease and those induced by medications and metabolic diseases • Acquired or congenital thrombocytopenia
Miscellaneous
• Papular purpuric gloves and socks syndrome
*Partial list.

Table 22.3 Differential diagnosis of macular ecchymoses (≥1 cm).

PALPABLE PURPURA: INFLAMMATORY PURPURA WITH PROMINENT EARLY ERYTHEMA
Leukocytoclastic vasculitis due to immune complex disease (see Fig. 24.1)
Small vessels only
• Idiopathic, infection- or drug-associated IgG or IgM complexes • Idiopathic IgA complexes (HSP), or IgA complexes associated with drugs or infection • Hypergammaglobulinemic purpura of Waldenström • Urticarial vasculitis: often minimally purpuric • Pustular vasculitis (e.g. bowel bypass syndrome)
Small- and medium-sized (macroscopic) vessels may be involved
• Mixed cryoglobulinemia • Rheumatic vasculitides (LE, RA, Sjögren syndrome)
Pauci-immune leukocytoclastic vasculitis (see Fig. 24.1)
ANCA-associated
• Granulomatosis with polyangiitis • Microscopic polyangiitis • Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
Other
• Erythema elevatum diutinum • Sweet syndrome (vasculitis unusual)
***Not* leukocytoclastic vasculitis**
Small vessels only
• Erythema multiforme • Pityriasis lichenoides et varioliformis acuta (PLEVA) • Pigmented purpuric eruptions • Hypergammaglobulinemic purpura of Waldenström (although some lesions have histologic evidence of leukocytoclastic vasculitis)
Classic target lesion – usually erythema multiforme, but can be small vessel vasculitis, especially IgA-associated

Table 22.4 Palpable purpura: inflammatory purpura with prominent early erythema. HSP, Henoch–Schönlein purpura; LE, lupus erythematosus; RA, rheumatoid arthritis.

DIFFERENTIAL DIAGNOSIS OF NON-INFLAMMATORY RETIFORM PURPURA
Occlusion primarily due to platelet-related thrombopathy
Major etiologies*
• Heparin-induced thrombocytopenia syndrome (HITS) • Thrombocytosis secondary to myeloproliferative disorders • Paroxysmal nocturnal hemoglobinuria • Thrombotic thrombocytopenic purpura (though platelet plugs form primarily in visceral vessels, and skin hemorrhage is due more often to thrombocytopenia)
Cold-related precipitation or agglutination
Major etiologies*
• Cryoglobulinemia, usually monoclonal (early lesions of mixed cryoglobulinemia are more often inflammatory and leukocytoclastic due to immune complex deposition) • Cryofibrinogenemia (though most cryofibrinogens are incidental findings in hospitalized patients) • Cold agglutinins (rarely cause occlusion; usually cause hemolysis or are asymptomatic)
Occlusion due to organisms growing in vessels
Major etiologies*
• Vessel-invasive fungi (e.g. *Mucor* spp., *Aspergillus* spp.; usually in immunocompromised patients) • Ecthyma gangrenosum (often *Pseudomonas* spp. or other Gram-negative bacilli proliferating in adventitia of subcutaneous arterioles) • Disseminated strongyloidiasis • Lucio phenomenon of Hansen disease • Rocky Mountain spotted fever, other rickettsial spotted fevers
Systemic alteration in control of coagulation
Major etiologies*

• Disseminated intravascular coagulation, often in the setting of sepsis
• Protein C- and S-related
  • Homozygous protein C or protein S deficiency (neonatal purpura fulminans)
  • Acquired protein C deficiency (some patients with sepsis-associated DIC)
  • Warfarin necrosis† (protein C dysfunction)
  • Postinfectious purpura fulminans (protein S dysfunction)
• Antiphospholipid antibody, lupus anticoagulant
• Levamisole-adulterated cocaine‡

Vascular coagulopathy
• Livedoid vasculopathy/atrophie blanche (may also have a systemic prothrombotic component) • Malignant atrophic papulosis/Degos disease (antiphospholipid antibody syndrome can mimic this disease) • Sneddon syndrome (can be related to antiphospholipid antibody syndrome) • Deficiency of adenosine deaminase 2 (ADA2)
Embolization or crystal deposition
Major etiologies*
• Cholesterol emboli • Oxalate crystal deposition (rare) • Marantic endocarditis, atrial myxoma, crystal globulins, hypereosinophilic syndrome (all rare)
Reticulocyte, red blood cell occlusion
• Sickle cell disease • Severe malaria (usually *Plasmodium falciparum*)
Miscellaneous
• Cutaneous calciphylaxis • Brown recluse (*Loxosceles*) spider bite reaction • Intravascular B cell lymphoma • Hydroxyurea (rare)
*Partial list. †Also referred to as Coumadin® necrosis. ‡Early lesions primarily thrombotic, but vasculitis can also occur; retiform purpura can be inflammatory.

Table 22.5 Differential diagnosis of non-inflammatory retiform purpura. DIC, disseminated intravascular coagulation; RBC, red blood cell; vWF, von Willebrand factor.

clearing of lesions is more complicated. This is outlined in Figure 22.4. Because of the different evolution of these two processes, it is possible for a biopsy specimen of a late lesion of vasculitis to resemble an early lesion of occlusion histologically. Conversely, a late lesion of occlusion with some resulting dermal necrosis may on histologic examination show features characteristic of leukocytoclastic vasculitis (LCV). This means that *both* the clinical morphology and the histopathology of a purpuric lesion must be interpreted within the context of the lesion's age and clinical setting.

HEMOSTASIS/COAGULATION

Primary hemostasis consists of adhesion, activation, and aggregation of platelets at the site of vascular injury. This leads to the formation of a platelet plug sufficient for routine minor injuries to the microvascular system. Platelets are also essential for maintaining the integrity of small blood vessels. There is molecular signaling crosstalk between megakaryocytes and endothelial cells, with platelets delivering megakaryocytic factors that are important for endothelial health.

Petechial hemorrhage due to severe thrombocytopenia (typically platelets <20 000/mcl) results from reduced delivery of these megakaryocyte/platelet factors to the endothelium, thereby impairing endothelial cell function and widening of the gaps between endothelial cells[5]. This probably also explains why platelet dysfunction does not typically result in petechial hemorrhage, since platelet number and factor delivery remain normal, but rather ecchymoses develop because platelet plugs fail to form at sites of injury.

When a platelet plug is inadequate due to the size of the vessel or the size of the injury, **secondary** hemostasis with clot formation is needed. Secondary hemostasis classically includes the intrinsic and extrinsic coagulation pathways that then converge into a common pathway, driving the formation of fibrin from fibrinogen via stepwise amplifications (Fig. 22.5)[6,7]. The *intrinsic* (contact activation) pathway is the longer of the two; it begins with factor XII activation, typically due to injury-related exposure of endothelial collagen. This pathway is assessed by the activated partial thromboplastin time (aPTT). The *extrinsic* pathway is triggered by tissue factor released from endothelial and other cells, which converts factor VII to factor VIIa, and then as the extrinsic pathway converges with the intrinsic pathway to form the common pathway, factor X is converted to factor Xa. The extrinsic pathway is monitored by the prothrombin time (PT).

Whereas insufficient clotting can lead to death via hemorrhage, inappropriate clotting produces thrombosis, embolus, and/or necrosis. Uncontrolled clotting with fibrinolysis can produce both thrombosis and hemorrhage, as in DIC. Ideally, a thrombus should form rapidly at sites of injury, but should not extend beyond where it is needed. Clotting factors that escape the local injury site must be prevented from triggering clotting at distant sites. As might be expected for a system that requires exquisite regulation to perform properly, the control of coagulation is multifaceted. Basal coagulation encompasses the constant low-level activation of some components of the procoagulant, natural anticoagulant, and fibrinolytic pathways, so that these systems are primed for a rapid response when needed. While Figure 22.5 appears complicated enough for a dermatologist, there are additional modifiers of coagulation including prekallikrein, C1 esterase inhibitor (see Fig. 18.6), factor XIII, and protein Z/protein Z-dependent protease inhibitor[6].

The initiation phase of clotting is down-regulated by *tissue factor pathway inhibitor* (TFPI) and *antithrombin III* (ATIII). TFPI and ATIII are bound to heparan sulfate molecules on the surface of endothelial cells (see Fig. 22.5). Their presence in close proximity to sites of desired clot formation allows them to capture activated clotting factors and prevent them from leaving the area. ATIII can neutralize thrombin as well as factors IXa, Xa, and XIIa; this process is greatly enhanced by heparan sulfate or heparin binding to ATIII.

The *thrombomodulin/protein C/protein S* system is the other major natural anticoagulant pathway. While both ATIII and protein C pathways

DIFFERENTIAL DIAGNOSIS OF INFLAMMATORY RETIFORM PURPURA
Vasculitis
Primarily dermal vessels
• IgA vasculitis
Dermal and subcutaneous vessels usually involved
• Mixed cryoglobulinemia • Rheumatic vasculitides (LE, RA) • Polyarteritis nodosa • Microscopic polyangiitis • Granulomatosis with polyangiitis • Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
Dermal vessel inflammation/occlusion/constriction
• Livedoid vasculopathy • Septic vasculitis • Chilblains (pernio) • Pyoderma gangrenosum

Table 22.6 Differential diagnosis of inflammatory retiform purpura. LE, lupus erythematosus; RA, rheumatoid arthritis.

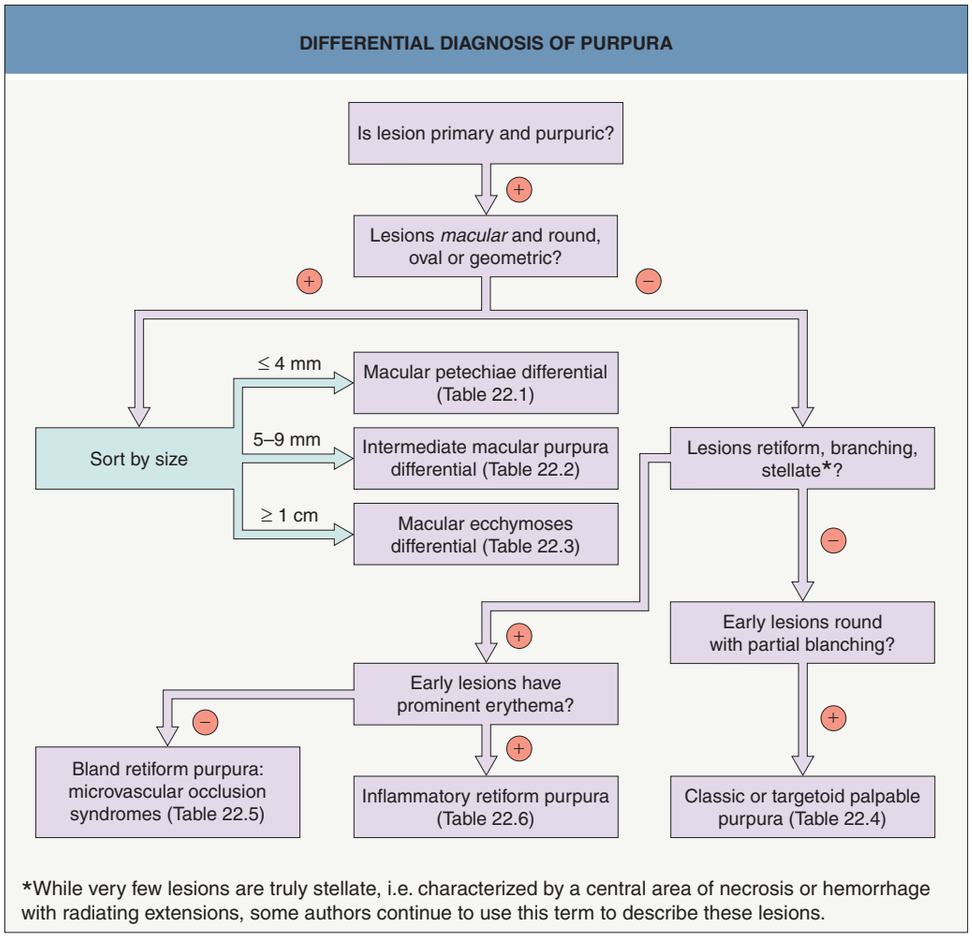


Fig. 22.3 Differential diagnosis of purpura. Morphology can be used as a primary sorting method, but combining morphology with an initial pattern approach as depicted in Figure 22.1 can improve accuracy. When discrepancies between the two arise, additional investigation is warranted.

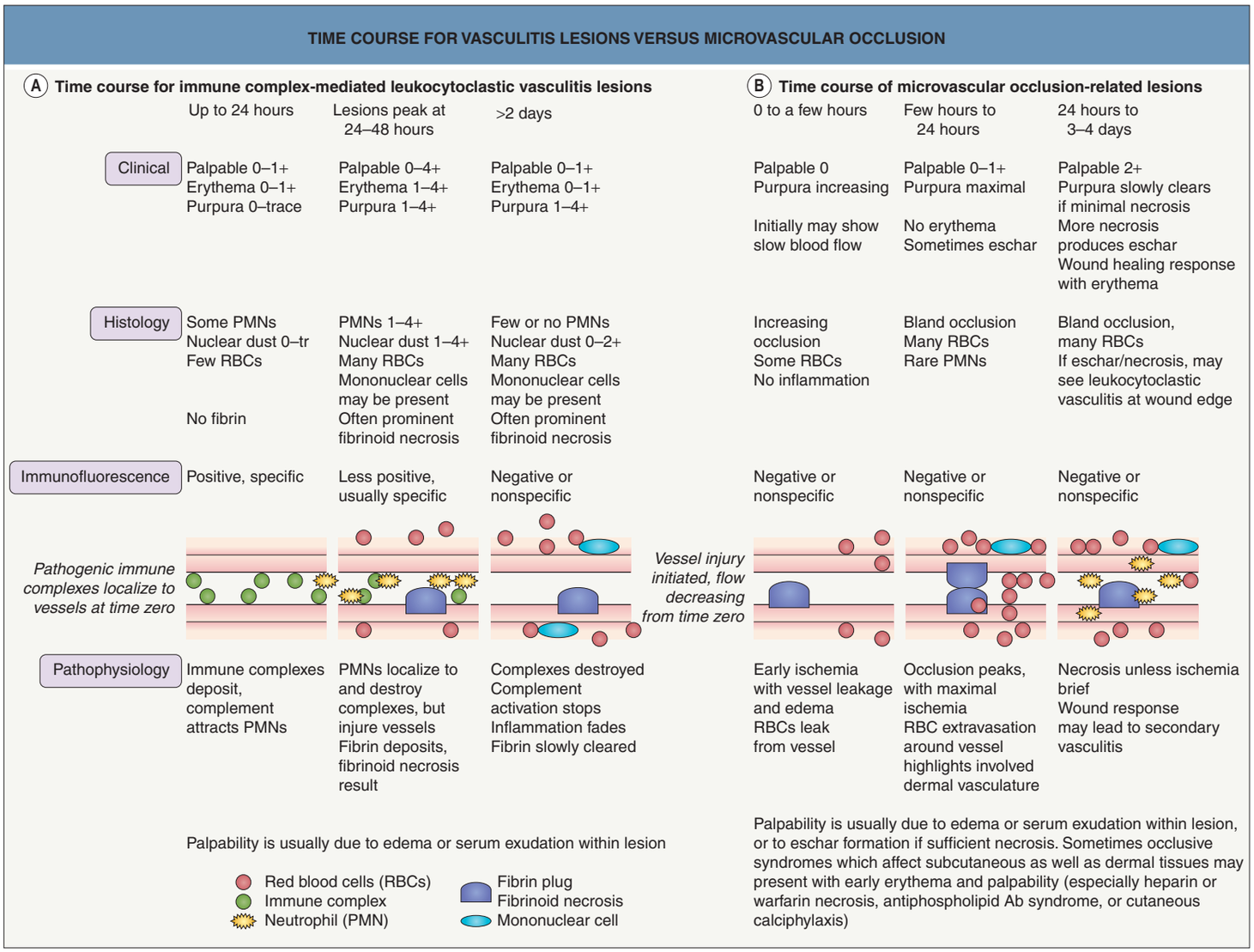


Fig. 22.4 Time course for skin lesions due to vasculitis versus microvascular occlusion. A Time course for lesions due to immune complex-mediated leukocytoclastic vasculitis. **B** Time course for lesions due to microvascular occlusion. Ab, antibody; tr, trace.

are important in large vessels, the protein C system seems to be critical for normal function of the microvasculature. Thrombin that escapes the clot site can bind to thrombomodulin on the endothelial cell surface. Once bound to thrombomodulin, thrombin no longer activates procoagulant factors, but instead avidly binds and activates protein C, a vitamin K-dependent anticoagulant protein (see Fig. 22.5). The anticoagulant function of activated protein C is enhanced by binding to a phospholipid surface, a high-density lipoprotein (HDL), and protein S (another vitamin K-dependent anticoagulant). This complex then inactivates factors Va and VIIIa. The factor V Leiden mutation is a single amino acid change at the site of cleavage by activated protein C, and this change renders it much more resistant to inactivation, thus explaining the associated prothrombotic state. In other patients, a polymorphism in the prothrombin gene, specifically 20210A within an untranslated region, increases the level of prothrombin and can lead to a prothrombotic state.

OVERLAP OF COAGULATION AND INFLAMMATORY VESSEL DISEASE

Hemostasis is one aspect of the host response to injury. It is clear that inflammatory injury can lead to fibrin deposition in vessels, as exemplified by fibrinoid necrosis in vasculitis (see Fig. 22.4). Both platelets and coagulation factors play an important role in vascular integrity, innate immunity, inflammatory responses, and wound healing[8,9]. For example, thrombin is a procoagulant factor, but it also acts to promote monocyte, fibroblast, and endothelial cell migration into an area of recent injury to begin removal of damaged tissue and initiate wound repair. Thrombin bound to thrombomodulin activates protein C, which in addition to its potent anticoagulant action also has important anti-inflammatory properties. In addition, a powerful angiogenesis inhibitor, angiostatin, is a cleavage product of plasminogen. Thromboinflammation is an expanding concept that recognizes the complex and vital integration of coagulation, inflammation, and wound healing pathways[8,9].

TESTS FOR COAGULATION

A thorough history (including family history) and physical examination are important in the proper selection and interpretation of tests measuring coagulation and anticoagulation parameters. A basic laboratory assessment of clotting includes a platelet count, PT, and aPTT (Table 22.7). Platelet function tests (e.g. bleeding time, ristocetin-induced platelet aggregation studies) are performed in settings suggesting platelet function defects unexplained by medications (e.g. aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs]) or metabolic disorders such as renal failure. Another example would be the platelet dysfunction observed in Hermansky–Pudlak syndrome. Laboratory tests that are employed in the evaluation of thrombophilia/hypercoagulability are outlined in Table 105.9.

ANTIPLATELET AND ANTICOAGULANT AGENTS

Antiplatelet agents are used in specific clinical settings to reduce the risk of thrombosis. Medications that dermatologists are most likely

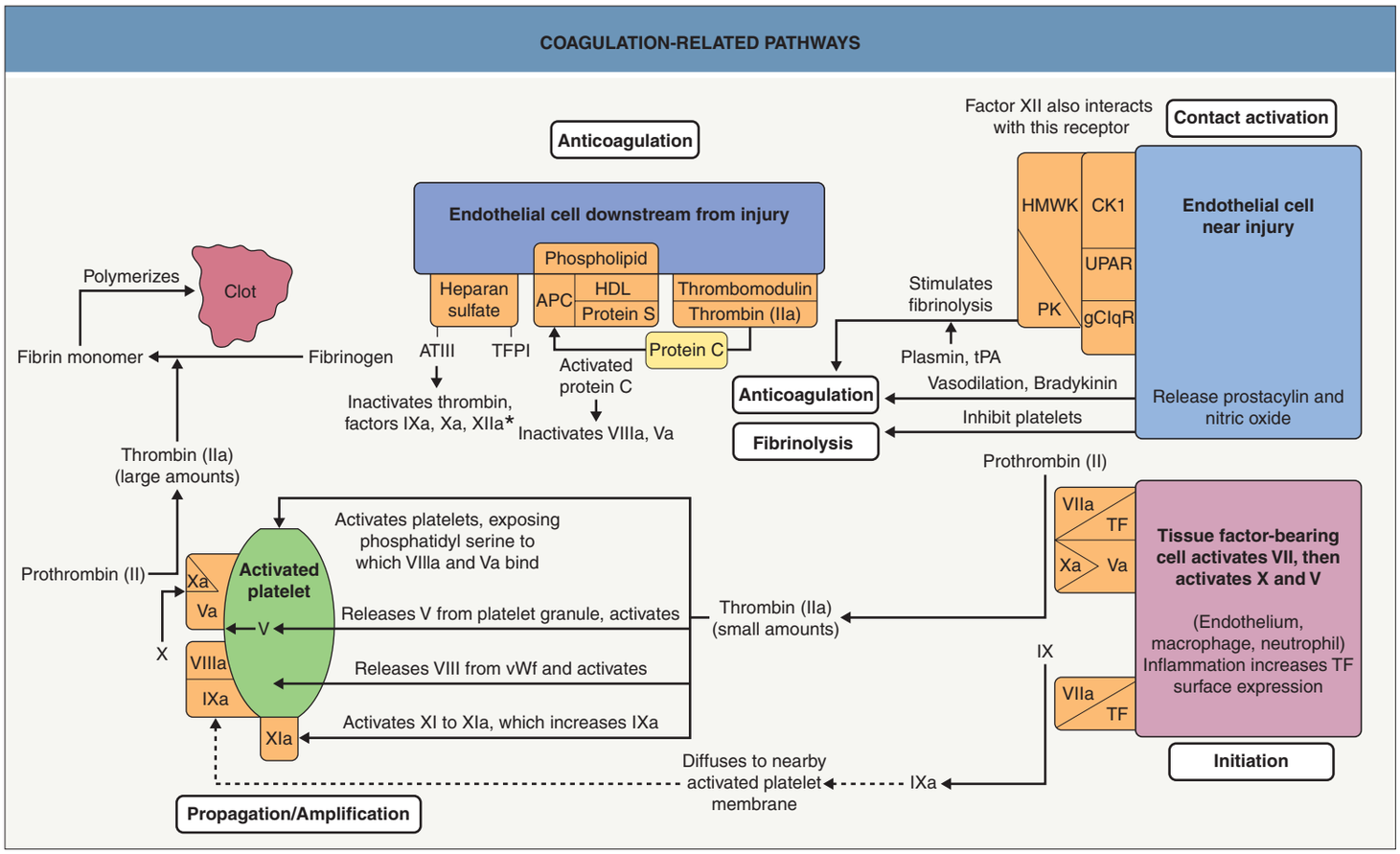


Fig. 22.5 Coagulation-related pathways. TFPI can inactivate factor Xa, and the TFPI–factor Xa complex can inhibit VIIa. *Enhanced by binding of heparin to ATIII. APC, activated protein C; ATIII, antithrombin III; CK1, cytokeratin 1; gC1qR, globular head of the C1q receptor; HDL, high-density lipoprotein; HMWK, high-molecular-weight kininogen; PK, prekallikrein; TF, tissue factor; TFPI, tissue factor pathway inhibitor; tPA, tissue plasminogen activator; UPAR, urokinase plasminogen activator receptor; vWF, von Willebrand factor.

INTERPRETATION OF PROTHROMBIN TIME (PT) AND ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)	
Coagulation test results	**Most likely etiologies**
Normal PT, prolonged aPTT	Heparin administration Lupus anticoagulant* Acquired factor VIII inhibitor von Willebrand disease (defective platelet adhesion and functional deficiency of factor VIII) Significant deficiency of one of following: • Factor VIII, IX, XI, or XII • High-molecular-weight kininogen (HMWK) • Prekallikrein
Prolonged PT, normal aPTT	Factor VII deficiency Low-dose oral anticoagulant
Prolonged PT and prolonged aPTT	Deficiency or inhibitor of: • Fibrinogen • Prothrombin • Factor V or X Combined deficiency of multiple procoagulant factors: • Severe vitamin K deficiency • High-dose oral anticoagulant
*Other tests, such as the dilute Russell viper venom time, may help confirm the presence of lupus anticoagulant activity.	

Table 22.7 Interpretation of prothrombin time (PT) and activated partial thromboplastin time (aPTT). Repeating the test using a 1:1 mixture of the patient's plasma and normal plasma will usually normalize the time if there is a factor deficiency, but the time will remain prolonged if an inhibitor is present.

to use to treat microvascular involvement in livedoid vasculopathy or antiphospholipid antibody syndrome include acetosalicylic acid (ASA, aspirin; inhibits cyclooxygenase), dipyridamole or pentoxifylline (both increase cAMP), and clopidogrel (blocks ADP). *Anticoagulant* medications are listed by their mechanisms of action in Table 22.8[10–12], and their sites of interaction are illustrated in Figure 22.6. Unlike warfarin, dabigatran and direct oral anticoagulants (DOACs) that inhibit thrombin or factor Xa, respectively, do not require monitoring of the international normalized ratio (INR), i.e. prothrombin ratio[10]. Given their popularity, specific reversal agents became a priority and are now commercially available while others are in development (see Table 22.8)[11–14]. In addition to LWMH, DOACs are now being used more frequently for select syndromes with prominent microvascular cutaneous involvement such as livedoid vasculopathy.

SELECTED PURPURA SYNDROMES

Some syndromes that are not traditionally discussed in chapters on microvascular occlusion (Ch. 23) or vasculitis (Ch. 24) will be addressed here.

Pigmented Purpuric Dermatoses

Synonyms: ■ Pigmented purpuric eruptions ■ Capillaritis ■ Purpura pigmentosa chronica ■ Purpura simplex ■ Majocchi–Schamberg disease

Variants:
- ■ Schamberg disease: Schamberg purpura, progressive pigmentary dermatosis of Schamberg, purpura pigmentosa progressiva
- ■ Purpura annularis telangiectodes of Majocchi: Majocchi's disease
- ■ Pigmented purpuric lichenoid dermatitis of Gougerot and Blum
- ■ Eczematid-like purpura of Doucas and Kapetanakis: eczematoid purpura, itching purpura
- ■ Lichen aureus: lichen purpuricus

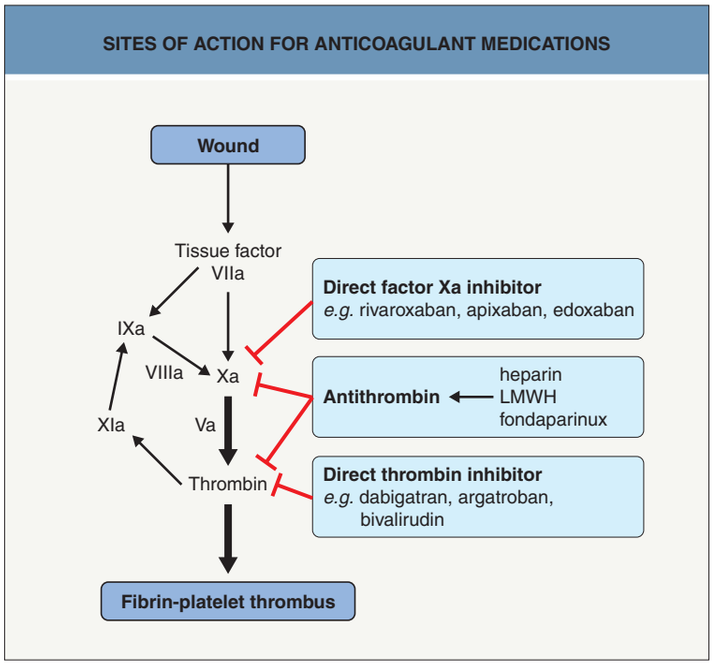


Fig. 22.6 Sites of action for anticoagulant medications. LMWH, low-molecular-weight heparin.

ANTICOAGULANTS		
Agent	**Route of administration**	**Reversal agent**
Interact with antithrombin to primarily inhibit factor IIa (thrombin) and/or factor Xa		
Unfractionated heparin	IV	Protamine sulfate
Enoxaparin (LMWH)	SC	Protamine sulfate (partial)
Dalteparin (LMWH)	SC	Protamine sulfate (partial)
Tinzaparin (LMWH)	SC or IV	Protamine sulfate (partial)
Fondaparinux (synthetic pentasaccharide)	SC	
Inhibit gamma carboxylation of vitamin K dependent factors: II, VII, IX, X, protein C, & protein S		
Warfarin	Oral	Vitamin K Urgent reversal: PCC, FPP, or recombinant factor VIIa
Direct thrombin inhibitor		
Dabigatran (NOAC*)	Oral	Idarucizumab
Argatroban	IV	Can be hemodialyzed
Bivalirudin (synthetic hirudin analogue)	IV	Can be hemodialyzed
Direct factor Xa inhibitor (DOAC)		
Rivaroxaban	Oral	Specific: Andexanet† Nonspecific: PCC
Apixaban	Oral	Specific: Andexanet† Nonspecific: PCC
Edoxaban	Oral	Nonspecific: PCC
Betrixaban	Oral	Nonspecific: PCC
Binds factor XI and XIa		
Abelacimab**	SC or IV	

*NOACs include DOACs plus dabigatran.
**Currently under investigation.
†Under evaluation for broader use.

Table 22.8 Anticoagulants. Ciraparantag is being evaluated as a possible reversal agent for heparin, LMWH, fondaparinux, and DOACs. DOAC, direct oral anticoagulant; FPP, fresh frozen plasma; IV, intravenous; LMWH, low-molecular-weight heparin; NOAC, novel oral anticoagulant or non-vitamin K oral anticoagulant; PCC, prothrombin complex concentrate; SC, subcutaneous.

Key features

- Clustered petechial hemorrhage
- Often a background of yellow–brown discoloration due to hemosiderin deposition
- The location and pattern depends on the particular variant

Introduction

Pigmented purpuric eruptions represent a group of diseases characterized by petechial hemorrhage thought to be secondary to capillaritis[15–18]. These diseases have no systemic findings, but they occasionally lead to a patient evaluation to exclude thrombocytopenia or vasculitis because of the purpuric (usually petechial) nature of the lesions and clinical misdiagnosis, especially of the rarer forms.

Pathogenesis

These diseases all result from minimal inflammation and hemorrhage of superficial papillary dermal vessels, usually capillaries. The reason for the inflammation is unknown.

Clinical features

The characteristics of the various forms of pigmented purpuric eruptions are outlined in Table 22.9 and illustrated in Figures 22.7 and 22.8. This disorder occurs in both children and adults[18].

Pathology

Histopathologic features include red cell extravasation, endothelial cell swelling, a perivascular lymphocytic infiltrate, and hemosiderin-containing macrophages (Fig. 22.9). The lichen aureus and Gougerot–Blum variants are characterized by a lichenoid infiltrate, and epidermal spongiosis with patchy parakeratosis is often observed in the latter as well as in eczematid-like purpura of Doucas and Kapetanakis. A rare granulomatous variant has also been described[17].

Differential diagnosis

The clinical picture is often sufficient for diagnosis, but a biopsy specimen may be required to distinguish the lichenoid variant from cutaneous small vessel vasculitis. Although usually on one extremity, angioma serpiginosum may occasionally be misdiagnosed as pigmented purpura. Lesions resembling capillaritis have been reported in patients with mycosis fungoides; allergic contact dermatitis (e.g. due to rubber or azo dyes); non-allergic reactions to topical medications (e.g. fluorouracil or eutectic mixture of local anesthetics [EMLA]); drug eruptions (e.g. carbromal, meprobamate, acetaminophen, infliximab, bezafibrate, glipizide, pseudoephedrine, NSAIDs, diuretics, creatine supplementation, medroxyprogesterone injections) based primarily on case reports; suction-induced purpura (e.g. cupping); rheumatoid arthritis; lupus erythematosus; hypergammaglobulinemic purpura of Waldenström; and perhaps due to diet (e.g. apple–cherry fruit spritzer)[16].

Pigmented purpuric eruptions on the legs must be differentiated from dermal hemorrhage secondary to venous hypertension, which presents with petechiae superimposed on diffuse hemosiderosis (Fig. 22.7B) rather than the discrete yellow–brown patches that characterize Schamberg disease. It also needs to be distinguished from exercise-induced vasculitis, also known as golfer's vasculitis, hiker's rash or ankle heat rash, which occurs with prolonged exercise in hot weather[19]. Histologically, findings in exercise-induced vasculitis range from urticarial vasculitis to frank LCV. Since exercise or prolonged standing may also induce recurrent macular vasculitis (see below), it is possible that there is some overlap between these two disorders.

Treatment

Topical corticosteroid therapy is occasionally helpful, especially in patients who report pruritus or have more evident erythema. Effective treatment of more extensive pigmented purpuric eruptions with narrowband UVB and PUVA has been described. Successful therapy with ascorbic acid (500 mg twice daily) plus rutoside (50 mg twice daily) has also been reported. While multiple treatments have been recommended, to date none have proven to be reproducibly effective.

TYPES OF PIGMENTED PURPURIC DERMATOSES			
Type	**Age/Sex**	**Morphology**	**Location**
Schamberg disease	• Most common form • Can occur in children • Peak frequency in middle-aged to older men	• Yellow–brown patches with an oval to irregular outline (Fig. 22.7A) • Pinpoint petechiae within patches – likened to "cayenne pepper" • Successive crops	• Favors lower legs • Can also involve thighs, buttocks, trunk, and arms
Purpura annularis telangiectodes of Majocchi	• Uncommon • Adolescents and young adults, especially women	• 1–3 cm annular plaques that may slowly expand • Punctate telangiectasias and petechiae within the border (Fig. 22.8A)	Trunk, proximal lower extremities

Pigmented purpuric lichenoid dermatitis of Gougerot and Blum	• Rare
	• Middle-aged to older men
		• Admixture of two types of lesions:
		  • Schamberg-like
		  • Purpuric red–brown lichenoid papules
		• Chronic
		• Occasionally pruritic
			On lower extremity, may be confused with cutaneous small vessel vasculitis

Eczematid-like purpura of Doucas and Kapetanakis	• Rare • Middle-aged to older men	• Scaly petechial or purpuric macules, papules, and patches (Fig. 22.8B) • Pruritic	Primarily lower extremities
Lichen aureus	• Rare	• Solitary patch • Color varies from golden to rust to purple–brown	Usually lower extremity, often over a perforator vein
Linear pigmented purpura	• Rare • Can occur in children and adolescents	• Linear array, usually unilateral (Fig. 22.8C) • Individual lesions similar in appearance to lichen aureus or Schamberg disease	Often a single extremity
Granulomatous pigmented purpura	• Very rare	• Brown patches with superimposed hemorrhagic papules*	Lower legs

*Histologically, hemorrhagic granulomatous inflammation in upper dermis.

Table 22.9 Types of pigmented purpuric dermatoses. Rarely, the first two types are familial.

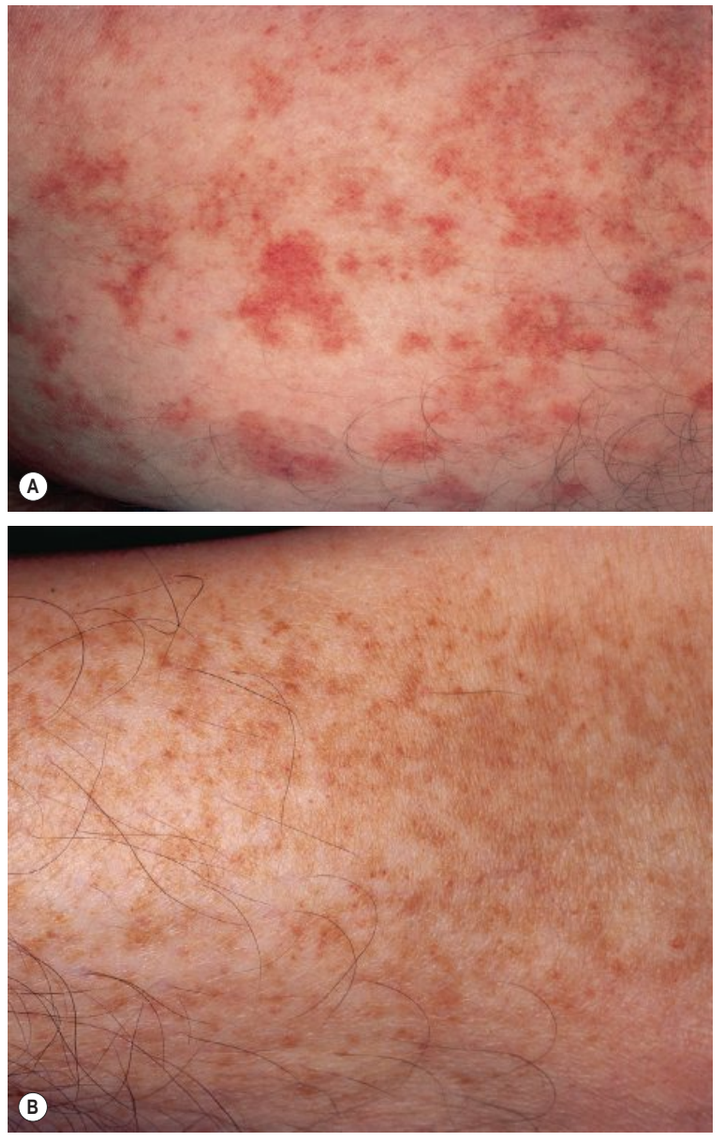


Fig. 22.7 Schamberg disease versus petechiae and hemosiderin secondary to venous hypertension. A Discrete yellow–brown and yellow–pink patches with superimposed petechiae in Schamberg disease. **B** Petechiae superimposed on more diffuse hemosiderin deposits in venous hypertension, referred to as "stasis purpura". *B, Courtesy Jean L. Bolognia, MD.*

Benign Hypergammaglobulinemic Purpura of Waldenström

Synonym: ▪ Recurrent macular vasculitis in hypergammaglobulinemia

Key features

- Usually affects women
- Recurrent crops of petechiae and larger purpuric macules on the lower extremities, which often burn or sting
- Patients typically have polyclonal hypergammaglobulinemia and may have elevated IgG or IgA rheumatoid factor (RF), but not necessarily IgM RF (the standard RF test)
- An autoimmune connective tissue disease develops in a subset of patients

Introduction

This syndrome was first described in 1943 by Waldenström, who reported three women with chronic relapsing purpura, hypergammaglobulinemia, an elevated ESR, and mild anemia. Hypergammaglobulinemic purpura of Waldenström is often associated with an autoimmune connective tissue disease (AI-CTD), especially Sjögren syndrome. In the most recent cutaneous vasculitis classification, this disorder has been renamed *recurrent macular vasculitis in hypergammaglobulinemia*[4].

Pathogenesis

Although associated with hypergammaglobulinemia, a strong argument can be made that a more specific feature of this condition is the presence of small circulating immune complexes, which often contain IgG or IgA rheumatoid factor (RF). Complexes of this size have also been identified in individuals with a clinical presentation that fits this syndrome but who lacked polyclonal hypergammaglobulinemia[20,21]. IgG and IgA RFs are highly soluble, which might explain the rapidity with which lesions appear and then resolve. The presence of monoclonal RF early on in the disease in some patients as well as the tendency of affected individuals to develop autoimmune and (less often) lymphoproliferative disorders supports the presence of a mild immune dysregulation syndrome.







Fig. 22.8 Less common forms of pigmented purpuric eruptions (capillaritis). **A** Purpura annularis telangiectodes of Majocchi characterized by annular plaques with cayenne pepper petechiae in the border. **B** Eczematid-like purpura that often presents with pruritus. **C** Linear pigmented purpuric dermatosis in which there is a linear array of yellow–brown macules and patches with superimposed petechiae and small, red–brown purpuric papules on the arm of a child. The eruption had been present for several months and was limited to this segment of skin. *B, Courtesy Kalman Watsky, MD; C, Courtesy Julie V. Schaffer, MD.*

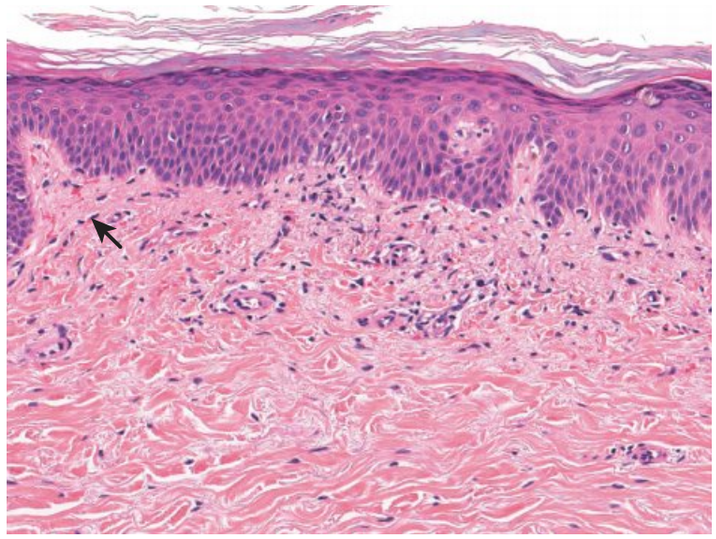


Fig. 22.9 Pigmented purpuric eruption – histopathologic features. Minimal perivascular lymphocytic infiltrate with extravasation of red blood cells (arrow) and hemosiderin deposits. *Courtesy Lorenzo Cerroni, MD.*



Fig. 22.10 Hypergammaglobulinemic purpura of Waldenström. This young woman with Sjögren syndrome had recurrent crops of petechiae on her lower legs. Note the hemosiderin deposition at sites of older lesions. *Courtesy Julie V. Schaffer, MD.*

Clinical features

The purpura is often preceded by a slight itch, mild tingling or burning, and it may be aggravated by tight-fitting garments, prolonged standing, and heat. Macular hemorrhage (e.g. petechiae or larger purpuric macules) on the lower extremities represents the most common presentation, but the lesions may be fleeting (Fig. 22.10). Some patients have palpable purpura with histologic evidence of vasculitis (see below), which has led many authors to classify this entity as a subset of cutaneous small vessel vasculitis[22].

Recurrent macular vasculitis can be primary or secondary[22]. In younger patients it is usually primary, but over time some patients develop evidence of an AI-CTD, most frequently Sjögren syndrome and occasionally rheumatoid arthritis or lupus erythematosus. Much less often, a monoclonal gammopathy or very rarely, a lymphoma or multiple myeloma develops. Children with recurrent macular vasculitis frequently have an associated AI-CTD and it may also develop in patients with cystic fibrosis[23].

Laboratory evaluation typically reveals polyclonal hypergammaglobulinemia and an elevated ESR. Standard RF assays identify only IgM RF, so they will not detect the IgG and IgA RFs that are frequently found in this syndrome (although specific tests for IgG and IgA RF can be performed). Anti-SSA/Ro and -SSB/La antibodies are commonly present and may predict a higher likelihood of developing an associated AI-CTD.

Pathology

Simple hemorrhage is most frequently seen. Occasionally a mild perivascular lymphocytic infiltrate or rarely LCV may be present.

Differential diagnosis

The clinical picture is often characteristic. Some patients develop palpable purpura mimicking classic cutaneous small vessel vasculitis syndromes, but most patients present with recurring crops of burning or stinging macular hemorrhage. Exercise-induced vasculitis is also in the differential diagnosis[19].

Treatment

Some agents used to treat this syndrome, such as aspirin or support stockings, have also been reported to exacerbate the condition. Avoidance of precipitating factors such as alcohol and prolonged

standing may be helpful. In secondary cases, treatment is aimed at the underlying disease. When there is evidence of LCV histologically, treatment with colchicine or dapsone can be considered.

Gardner–Diamond Syndrome

Synonyms: ■ Psychogenic purpura ■ Autoerythrocyte sensitization

Key features

- Typically affects girls and young women with an underlying psychiatric illness and triggering stressors
- Painful, swollen ecchymoses occur spontaneously or at trauma sites

Introduction

In 1955, Gardner and Diamond described four women with an abnormal response to bruising characterized by the development of painful ecchymoses at sites of trauma followed by progressive erythema and edema.

Clinical features

This condition is seen almost exclusively in girls and young women, and in the majority of patients, it has been associated with psychiatric illnesses, especially depression[24,25]. Individuals report a sudden onset of painful, swollen bruises of variable size in any area of the body. Sometimes there are also prodromal symptoms. The lesions most commonly involve the extremities (lower > upper), usually resolve within a 2-week period, and typically recur. Original reports described appearance of these atypical purpuric lesions at sites of injection of a patient's own blood or other agents, hence the term autoerythrocyte sensitization. However, more recent reports have challenged the reproducibility of this finding.

Pathology

The histologic features of early lesions consist of edema, a minimal perivascular mononuclear infiltrate, and extravasated red blood cells in the upper dermis.

Differential diagnosis and treatment

Gardner–Diamond syndrome is a diagnosis of exclusion. Both child abuse and domestic abuse need to be considered[25]. Some clinicians view this disorder as a factitial disease, but proving a factitial origin is generally difficult. Gentle probing for an underlying, and potentially treatable, psychiatric condition may prove more productive than confronting the patient. Laboratory evaluation is generally unremarkable and histologic findings non-diagnostic. Patients may develop a lesion at the site of an intradermal injection of autologous washed erythrocytes. Some series report a high degree of success with psychological therapy, coupled with medications, most commonly selective serotonin reuptake inhibitors (SSRIs).

Paroxysmal Finger Hematoma

Synonyms: ■ Acute blue finger ■ Achenbach syndrome

Key features

- Recurrent acute episodes of painful ecchymoses on the palmar surface of one or more fingers

Clinical features

This idiopathic syndrome shares some similarities with Gardner–Diamond syndrome as it occurs primarily in females and may be preceded by prodromal symptoms such as pain, tingling, or itching. However, it has an older mean age of onset (48 years).

Recurrent painful ecchymoses develop on the palmar surface of the hand, primarily the fingers[26–28]. The right index finger is the most common site of involvement, and swelling may precede or accompany the ecchymoses. Evaluation is routinely negative, including Doppler ultrasonography, and is usually not indicated.

Differential diagnosis

Trauma, pernio, acrocyanosis, Raynaud phenomenon, and vascular insufficiency are often suspected, but the history, localization to the palmar surface, and time course aid in excluding these entities.

Treatment

While a variety of therapies have been tried, there is no specific successful treatment. The bleeding generally stops spontaneously, but pressure may be helpful. Typically, there is resolution within two weeks.

Onyalai

Onyalai is a Bantu name for a disease that often presents with hemorrhagic blisters in the mouth. It results from the consumption of sorghum grains contaminated with the fungus *Epicoccum sorghinum*. This fungus produces compounds which inhibit platelet aggregation and angiogenesis[29]. Onyalai may run a course indistinguishable from acute immune thrombocytopenic purpura (ITP). Literature regarding Onyalai is limited, treatment is unclear, and it appears to be less responsive to corticosteroids than is ITP.

Mondor Disease

Synonym: ■ Mondor syndrome of superficial thrombophlebitis

Key features

- Superficial thrombophlebitis affecting the anterolateral thoracoabdominal wall
- Pathogenic factors include trauma, surgical procedures, infections, and breast carcinoma
- Presents with the sudden onset of chest pain and subsequent appearance of a cord-like thrombosed vein

Introduction

Mondor disease is characterized by superficial thrombophlebitis of subcutaneous veins within the anterolateral thoracoabdominal wall, i.e. lateral thoracic, thoracoepigastric, and superior epigastric veins. Though previously reported by others, Henry Mondor provided a very detailed description of this condition in 1939[30]. A similar cord-like superficial thrombophlebitis can occur in other sites (e.g. the upper and lower extremities, abdomen, groin, penis).

Pathogenesis

Common pathogenic factors in chest wall thrombophlebitis include trauma, excessive physical activity, a surgical procedure on the breast, mastitis, a breast abscess, and pendulous breasts[30]. Up to 10% of patients with Mondor syndrome have an underlying breast carcinoma. Occasionally, the condition is associated with rheumatoid arthritis, filariasis, pregnancy, oral contraceptive use, intravenous drug use, intravenous catheters, a non-breast malignancy, or a hypercoagulable state (e.g. hereditary protein C deficiency, anti-cardiolipin antibodies).

Clinical features

A sudden onset of chest pain followed by the appearance of one or more visible or palpable cords (representing thrombophlebitic veins) typify this syndrome. Associated findings include tenderness, a sensation of tension, erythema, ecchymosis, pruritus, arthralgia, and rarely fever. Symptoms worsen on pulling the skin or elevating the breast and the ipsilateral upper extremity. The condition is usually unilateral and is three times more common in women than in men.

Pathology

A biopsy is rarely required. The process may involve arteries and lymphatic vessels as well as veins. Sclerosing endophlebitis with complete

or partial obliteration of the lumen by thrombus and inflammatory cells is typical. The time period between the onset of the condition and ultimate recanalization of the affected vessels varies from 2 weeks to more than 6 months.

Differential diagnosis

The clinical presentation is unique, and etiologic factors should be identified. Recurrent superficial thrombophlebitis (migratory thrombophlebitis) is frequently associated with an underlying malignancy (Trousseau syndrome; most often pancreatic or lung carcinoma), a hypercoagulable state (inherited or acquired), or an inflammatory condition (e.g. Behçet disease).

Treatment

The disease is usually benign and self-limited, except when associated with breast cancer. Aching pain typically ends within 10 days, but the cord often persists for weeks to months and may be tender. Local heat, rest of the arm, and breast support can improve symptoms. The rate of recurrence is ~5%.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 22.1 Pigmented purpuric dermatosis (capillaritis). Schamberg disease with pinpoint petechiae within lesions. *Courtesy Kalman Watsky, MD.*



eFig. 22.2 Linear pigmented purpura. Linear array of yellow–brown macules. Clinically, the pinpoint hemorrhages were subtle but easily seen by dermoscopy. *Courtesy Jean L. Bolognia, MD.*



eFig. 22.3 Purpura annularis telangiectodes of Majocchi. Annular plaques with pinpoint petechiae within the border. *Courtesy Frank Samarin, MD.*



eFig. 22.4 Purpura annularis telangiectodes of Majocchi. Annular plaques with petechiae within the border. *Courtesy Julie V. Schaffer, MD.*



eFig. 22.5 Capillaritis. Because the lesions were plaques and the patient was elderly, the possibility of a capillaritis-like presentation of mycosis fungoides was excluded. *Courtesy Kalman Watsky, MD*.



eFig. 22.6 Retiform purpura with bullae formation due to disseminated intravascular coagulation in association with *Klebsiella* pneumonia (A, B).

Cutaneous Manifestations of Microvascular Occlusion Syndromes

23

Warren W. Piette

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INTRODUCTION

The differential diagnosis of microvascular syndromes involving the skin is extensive. It is critical to distinguish between inflammatory injury and *non-inflammatory occlusive injury* to vessels. The diagnosis of occlusive syndromes in the skin is greatly facilitated by recognizing the telltale lesions of retiform purpura or non-inflammatory (bland) necrosis.

Diseases that produce skin lesions secondary to microvascular occlusion have often been lumped with cutaneous vasculitic syndromes or discussed primarily as systemic diseases with little attention paid to cutaneous findings. While there is some overlap in the pathogenesis of deep venous thrombosis and pulmonary emboli and the pathogenesis of cutaneous microvascular occlusion syndromes, the two can differ substantially with respect to disease etiology and treatment.

The differential diagnosis for occlusive syndromes is best approached through major pathophysiologic categories (Table 23.1). These categories frequently have sufficiently distinctive clinical settings that a minimal history and physical examination plus laboratory findings quickly allows for an efficient sorting of the most likely diagnoses (Fig. 23.1). This is especially important in life-threatening situations when making timely decisions is crucial. A reasonable panel of initial laboratory tests is listed in Table 23.2.

It must be emphasized that some inflammatory syndromes capable of producing retiform purpura may occasionally present with lesions that have minimal inflammation (see Ch. 22). In particular, this may occur with the anti-neutrophil cytoplasmic antibody (ANCA)-positive syndromes of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), as well as ANCA-negative cutaneous polyarteritis nodosa.

Because treatment depends on pathogenesis (see Fig. 22.4), accurate diagnosis is critical prior to instituting appropriate therapy. The use of anti-inflammatory therapy for occlusive disease may not only be useless but actually harmful, and the same may be true for anticoagulant therapy in most vasculitides.

DISORDERS OF PLATELET-RELATED THROMBOPATHY

Heparin-Induced Thrombocytopenia (HIT) Syndrome

Key features

- Exposure to heparin, most often unfractionated
- Decreasing platelet counts (>50% of recent highest count) 5–10 days after heparin exposure
- Risk of arterial, venous, and microvascular occlusion
- Heparin-induced skin necrosis typically presents as retiform purpura or non-inflammatory necrosis
- Cutaneous lesions may arise locally at sites of heparin infusion/injection or at distant sites
- Detection of anti-platelet factor 4-heparin complex antibodies via ELISA has a very high negative predictive value (when absent) but low positive predictive value (when present)
- Non-necrotic hemorrhage and bullae are not signs of heparin-induced skin necrosis

Introduction

Heparin-induced thrombocytopenia (HIT) syndrome occurs in <0.1%–7% of adults exposed to heparin, with a third to half of these patients developing thrombosis[1,2]. Despite its rarity, it is an important iatrogenic cause of potential limb- and life-threatening disease.

HIT and heparin-induced skin necrosis were first recognized in the early 1970s. They may occur after subcutaneous or intravenous heparin administration, including the trace amounts injected to keep infusion lines open. Of note, the same pathogenic cascade may be activated without heparin exposure (see below) and HIT-like syndromes have also been described as vaccine-induced thrombotic thrombocytopenia (VITT).

Epidemiology

The risk of developing HIT is highest with unfractionated heparin, lower with low-molecular-weight heparin, and negligible with the synthetic pentasaccharide fondaparinux (see Table 22.8). Risk is higher following major surgery, especially orthopedic, coronary artery bypass grafting, or major arterial, as well as significant trauma. It is more frequently observed in women (but rare during pregnancy) and in individuals >50 years of age.

Pathogenesis

The innate immunity pathway in which binding of platelet factor 4 (PF4) to polyanions on the surface of bacteria leads to their phagocytosis can be compared to the pathologic pathway that underlies HIT. The latter involves the binding of PF4 to a polyanion, usually unfractionated heparin, to form ultralarge complexes (ULCs) consisting of multiple PF4 molecules bound to single heparin chains. This binding exposes an epitope on the quadrameric PF4 molecule, which then becomes the target of naturally occurring IgM antibodies[2] with subsequent complement activation and deposition of C3 on the ULCs. Presentation of these modified ULCs to splenic marginal B cells triggers synthesis of

DIFFERENTIAL DIAGNOSIS OF CUTANEOUS MICROVASCULAR OCCLUSION BASED ON PATHOPHYSIOLOGY
Platelet-related thrombopathy
• Heparin-induced thrombocytopenia syndrome • Thrombocytosis secondary to myeloproliferative neoplasms • Paroxysmal nocturnal hemoglobinuria • Primary thrombotic microangiopathies (TTP, STEC-HUS, CM-HUS)
Cold-related precipitation or agglutination
• Cryoglobulinemia (type I) • Cryofibrinogenemia • Cold agglutinins
Vessel-invasive organisms
• Ecthyma gangrenosum (primarily Gram-negative bacteria) • Opportunistic fungi (e.g. *Aspergillus* spp., *Rhizopus* spp.) • Disseminated strongyloidiasis • Lucio phenomenon of Hansen disease (leprosy) • *Rickettsia* spp.
Embolization
• Cholesterol embolus • Oxalate embolus • Atrial myxoma • Marantic endocarditis • Libman–Sacks endocarditis (lupus, often in association with antiphospholipid antibodies) • Infective endocarditis (acute, fungal) (rare)* • Crystalglobulin vasculopathy • Hypereosinophilic syndrome
Systemic coagulopathies
• Neonatal purpura fulminans • Warfarin† necrosis • Warfarin†-associated venous limb gangrene • Purpura fulminans of sepsis/disseminated intravascular coagulation • Postinfectious purpura fulminans • Antiphospholipid antibody/lupus anticoagulant syndrome
Vascular coagulopathies
• Sneddon syndrome/idiopathic livedo reticularis with CVAs • Livedoid vasculopathy • Hydroxyurea-associated vasculopathy • Interferon-induced vasculopathy • Benign and malignant atrophic papulosis/Degos disease • Levamisole/cocaine vasculopathy/vasculitis • Cutaneous calciphylaxis
Disorders of cell-related vascular occlusion
• Red blood cell occlusion • Intravascular cellular occlusion • Intravascular histiocytosis (occlusion with erythema but no purpura)
Miscellaneous/unknown mechanism
• *Loxosceles* (spider bites) • Large hematoma occlusion syndrome • SARS-CoV-2 infection
*Usually inflammatory. †Sometimes referred to by its trade name Coumadin®.

Table 23.1 Differential diagnosis of cutaneous microvascular occlusion based on pathophysiology. Entities are listed as they appear in the text. CM-HUS, complement-mediated hemolytic uremic syndrome; CVAs, cerebrovascular accidents; STEC-HUS, Shiga toxin-producing *E. coli* hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

pathogenic IgG antibodies which bind to PF4 complexed with glycosaminoglycans on platelets; this leads to platelet activation and aggregation. Other cells, especially monocytes, neutrophils, and endothelial cells, also interact with these complexes and enhance thrombosis[2].

Occasionally pathogenic antibodies persist after heparin cessation and anamnestic antibody responses can occur upon re-exposure to heparin. Since the antigen trigger is the exposed epitope on bound PF4, PF4 could potentially bind to endogenous polyanions with exposure of the same epitope. This would explain the rare instances of spontaneous or autoimmune HIT syndrome in the absence of heparin administration.

Clinical features

HIT usually occurs between days 5 and 10 of heparin therapy[1]. In patients exposed to heparin within the past 90–100 days, HIT may develop within hours after re-exposure. Occasionally, there is an anaphylactoid reaction within 30 minutes of a heparin bolus[1]. A delayed-onset form of heparin-induced skin necrosis has been described in which lesions can occur up to 3 weeks after exposure to heparin, including short chain variants[3,4]. Of note, heparin-dependent antibodies usually do not reappear if subsequent heparin use is *after* 100 days.

There are additional unusual clinical scenarios in which HIT can develop. In patients receiving *chronic* heparin, e.g. for renal dialysis, major surgery may trigger HIT within 5–10 days. Even in the absence of exposure to heparin, major surgery or bacterial infections can trigger a spontaneous or autoimmune HIT syndrome (see above).

Cutaneous lesions are usually tender, sharply demarcated, non-inflammatory, and purpuric or necrotic, often with a retiform morphology. Large necrotic areas with or without branching margins can also be seen. Lesions may occur at the site of subcutaneous injections (Fig. 23.2) or may develop at sites distant to the heparin infusion (see Fig. 21.22)[3,4]. Although consumption of platelets is part of this syndrome, absolute thrombocytopenia is often not present in patients with significant vascular occlusion. A decline in the platelet count of >50% from the most recent highest value prior to the administration of heparin (preferably from the day heparin is begun) should prompt consideration of HIT. All limbs and organs are at risk for vascular occlusion, including the CNS.

Heparin may also induce bullous hemorrhagic dermatosis that lacks necrosis (see Ch. 21). This adverse reaction is unrelated to HIT and is not associated with an increased risk of thrombosis[5].

Pathology

In HIT-associated thrombosis, there is non-inflammatory occlusion of blood vessels and ischemic necrosis. Microvascular as well as venous or arterial occlusion can be seen, both in the skin and internal organs.

Differential diagnosis

A recent history of heparin administration should prompt consideration of this diagnosis in any patient who develops retiform purpura or bland necrosis, whether or not the patient is thrombocytopenic. However, a decrease in the platelet count is a common incidental finding in patients who are ill and coincidently receiving heparin and so it can be unrelated to the development of this syndrome. Conversely, a normal platelet count does not exclude the diagnosis. Other cutaneous occlusion syndromes associated with thrombocytopenia include antiphospholipid antibody syndrome, purpura fulminans secondary to sepsis, and thrombotic thrombocytopenic purpura (although skin lesions due to microvascular occlusion are rare in the latter syndrome).

Detection of anti-PF4–heparin complex antibodies by ELISA has a 98%–99% negative predictive value but low positive predictive value[1]. While specialized testing can confirm the presence of anti-PF4–heparin complex antibodies, a clinical diagnosis is often needed before the results of this test are known. The 4Ts score based upon acute *t*hrombocytopenia, *t*iming of onset, *t*hrombosis, and absence of other causes of *t*hrombocytopenia is often used to estimate the likelihood of HIT syndrome. This score can be combined with functional assays (e.g. C-serotonin release assay, PF4-enhanced platelet activation assay) to greatly improve accuracy[6,7].

Treatment

Treatment requires cessation of heparin therapy and initiation of therapeutic anticoagulation. Argatroban and bivalirudin, direct thrombin inhibitors, are FDA-approved for the treatment of HIT and for patients with HIT undergoing cardiovascular procedures, respectively. Although not FDA-approved for these indications, subcutaneous fondaparinux is also effective. Whereas patients with HIT and thrombosis require therapeutic anticoagulation for at least three months, treatment duration for patients with only HIT has not been standardized.

Vitamin K antagonists (e.g. warfarin) are contraindicated during the acute phase because of an increased risk of developing venous limb gangrene secondary to decreased protein C levels[8]. Patients with delayed or spontaneous HIT should be anticoagulated with non-heparin agents (e.g. argatroban, bivalirudin). Based upon observational studies, direct oral anticoagulants (DOACs) may also be effective, although isolated cases of heparin necrosis-like skin lesions have been reported with rivaroxaban and apixaban[9]. For refractory and autoimmune HIT, IVIg and plasma exchange have been used[1,2].

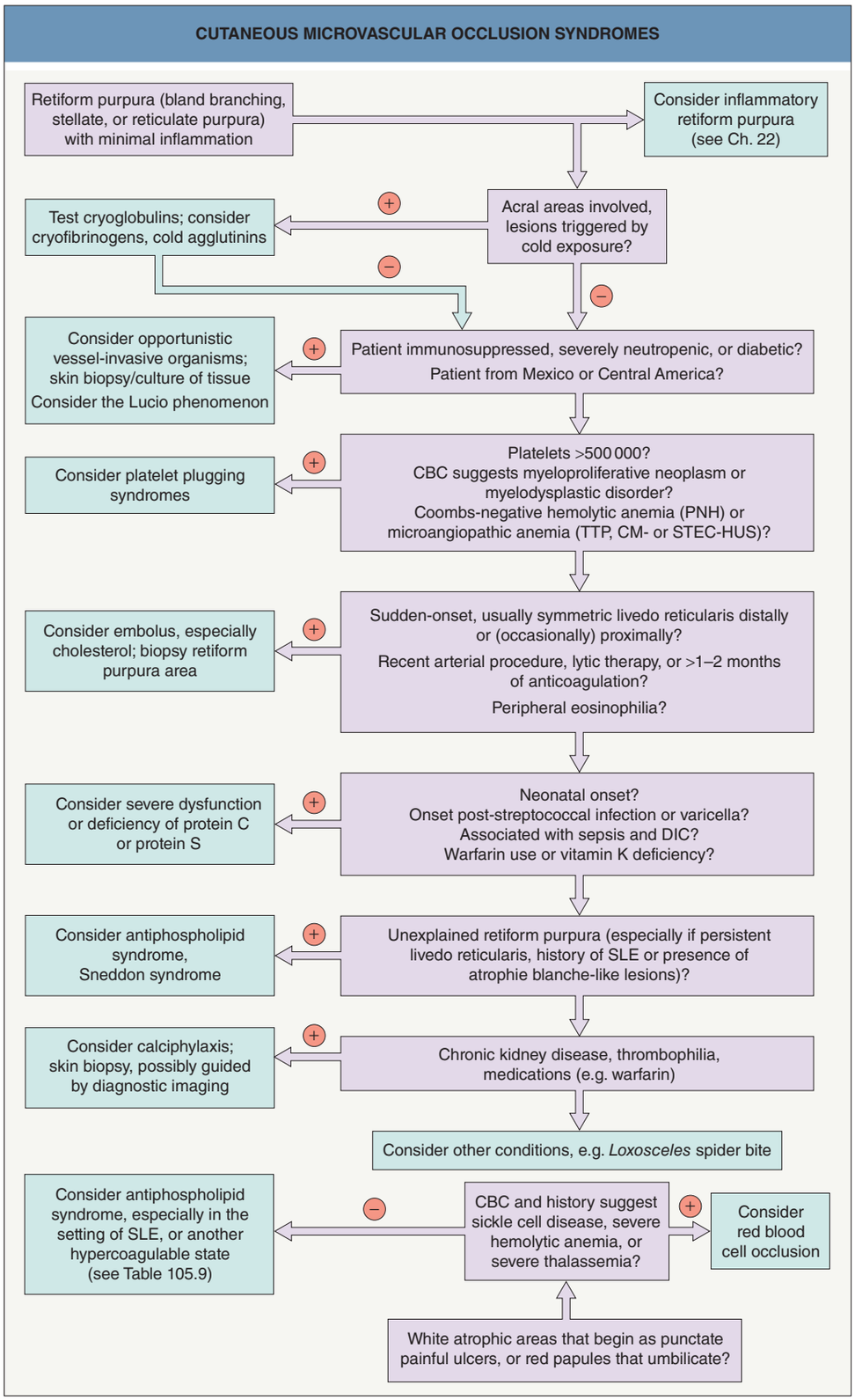


Fig. 23.1 Cutaneous microvascular occlusion syndromes. CM-HUS, complement-mediated hemolytic uremic syndrome; DIC, disseminated intravascular coagulation; PNH, paroxysmal nocturnal hemoglobinuria; SLE, systemic lupus erythematosus; STEC-HUS, Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

Philadelphia Chromosome-Negative Myeloproliferative Neoplasms

Key features

- Philadelphia chromosome-negative myeloproliferative neoplasms include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF)
- 90% of patients have somatic phenotypic driver mutations in *JAK2* (V617F), *CALR*, or *MPL*
- Thrombosis, vascular events (e.g. stroke), and bleeding can occur in all three disorders

Introduction

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic disorders whose manifestations depend on the type of stem cell affected, with some patients eventually developing myelodysplastic syndrome or acute myelogenous leukemia. The Philadelphia chromosome-negative MPNs (which exclude most chronic myelogenous leukemias) are clonal disorders driven by mutations in *JAK2*, *CALR*, or *MPL* in all but the 10% of patients who are "triple-negative". These genes encode a tyrosine kinase, calreticulin, and the thrombopoietin receptor, respectively. Many patients have additional non-driver mutations, typically involving epigenetic regulator genes (e.g. *TET2, DNMT3A*), chromatin

BASIC SCREENING TESTS FOR OCCLUSIVE SYNDROMES
Complete blood count with differential, platelet count, and blood smear

• Polycythemia or anemia, granulocytosis, thrombocytosis, poikilocytosis
  • May be sign of myeloproliferative neoplasms or myelodysplastic syndromes
• Evidence of red cell fragmentation (schistocytes) and microangiopathy, consider:
  • TTP–hemolytic uremic syndrome
  • Purpura fulminans with DIC, occasionally
  • Antiphospholipid antibody syndrome, occasionally
• Thrombocytopenia, consider:
  • Heparin-induced thrombocytopenia (HIT) syndrome
  • Purpura fulminans with DIC
  • TTP–hemolytic uremic syndrome
  • Antiphospholipid antibody syndrome, some patients
• Severe neutropenia
  • Immunocompromised; opportunistic infections very likely
• Eosinophilia
  • Cholesterol emboli
  • Hypereosinophilic syndrome (rare)

Partial thromboplastin time (PTT)
• Minimally prolonged in TTP–hemolytic uremic syndrome • Prolonged in purpura fulminans and DIC • Prolonged if lupus anticoagulant activity present and assay sensitive
Cryoglobulins (occasionally cryofibrinogen and cold agglutinins) when location and history suggest cold occlusion syndrome
Biopsy
• Confirms occlusion (e.g. due to thrombi) versus other mechanisms of vessel injury • May suggest cryoglobulin or cryofibrinogen precipitation • May diagnose calciphylaxis • May suggest cholesterol, oxalate, or crystalglobulin occlusion • Special stains for organisms in immunocompromised hosts, when appropriate
Basic hepatic and renal function screens
• Hepatic function can affect vitamin K-dependent factors and warfarin metabolism • Renal disease moves cutaneous calciphylaxis higher in the differential diagnosis, even though non-uremic calciphylaxis can occur
ANCA
• To evaluate for the uncommon non-inflammatory retiform purpura presentation of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) • ANCA may be available before permanent histologic sections

Table 23.2 Basic screening tests for occlusive syndromes. Elevated levels of fibrin degradation products, including D-dimers, are seen in purpura fulminans with DIC. TTP and hemolytic uremic syndrome are considered types of thrombotic microangiopathy. ANCA, anti-neutrophil cytoplasmic antibody; DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura.

regulator genes (e.g. *ASXL1*, *EZH2*), and splicing machinery genes (e.g. *SF3B1*), leading to variable disease expression[10].

Thrombosis, vascular events (e.g. stroke, pulmonary emboli), and hemorrhage are the most common causes of morbidity and mortality in PV and ET. The frequency of thrombosis is highest in PV, followed by PMF and ET, while bleeding complications are highest in PMF followed by ET and PV. The *JAK2* V617F, mutation is associated with an increased risk of thrombotic complications whereas *CALR* mutations have a lower risk.

Pathogenesis

In that thrombosis in ET has been attributed to platelet dysfunction/number and platelet-driven events appear important in patients with ET and other MPNs, these disorders are discussed under platelet-related thrombopathies. However, the degree of thrombocytosis does not correlate with thrombotic and vascular complications. For example, patients with ET and extreme thrombocytosis are at greater risk of bleeding than thrombosis[10].



Fig. 23.2 Heparin necrosis at site of subcutaneous heparin injection. Note branching or retiform pattern of intense hemorrhage and necrosis in the center of the lesion. *From Robson K, Piette W. Adv Dermatol 1999;15:153–82, used with permission.*

In both myeloproliferative and myelodysplastic disorders, platelets can function abnormally, leading to occlusion and/or hemorrhage. When the platelet count is $400–1000\times10^9$/L, thromboembolism is common, whereas both thrombosis and bleeding may occur with a platelet count of $1000–2000\times10^9$/L; bleeding predominates when the platelet count is $>2000\times10^9$/L[11]. Acquired von Willebrand syndrome may develop when the platelet count is $>1000\times10^9$/L, providing an explanation for the associated hemorrhage. When the platelet count is within the normal range in the setting of an MPD, the risk of thrombosis is uncertain.

Of the three most frequently associated genes (see Introduction), mutations in *MPL* and *CALR* occur more commonly in ET and PMF and only rarely in PV. A single mutation, *JAK2* V617F, is present in 90%–95% of PV patients and 50%–70% of those with ET and PMF. The *JAK2* mutations lead to activation of the JAK–STAT pathway (see Fig. 128.11)[10].

Epidemiology

Both PV and ET occur more often in women. They are uncommon before the age of 50 years, but the incidence increases almost exponentially after age 60 years.

Clinical features

Cutaneous lesions occur in ~20% of patients with ET, including purpura, hematomas, livedo reticularis and racemosa, erythromelalgia, Raynaud phenomenon, urticaria, cutaneous small vessel vasculitis, leg ulcers, gangrene, and recurrent superficial thrombophlebitis. An important subset of these cutaneous lesions is due to microvascular occlusion.

Erythromelalgia is a syndrome that can occur as a primary (idiopathic) or a secondary phenomenon (see Ch. 106). It is characterized by intense burning and paroxysmal bright erythema of the distal extremities. Most closely associated with ET, and less often with PV, erythromelalgia can occur with any myeloproliferative or myelodysplastic disorder if the platelet count is sufficiently elevated[12,13]. Because this form of secondary erythromelalgia is caused by platelet-mediated acral vasodilation, inflammation, and microvascular occlusion, patients can also develop discrete areas of purpura or necrosis, often retiform, as a unique manifestation. This version of erythromelalgia typically responds dramatically to aspirin administration, whereas idiopathic and other secondary forms generally show minimal or no benefit from aspirin.

Other clinical features of patients with MPNs depend on the diagnosis, e.g. PV patients may have a ruddy cyanosis and experience severe pruritus following exposure to warm water[14], while neutrophilic dermatoses (pyoderma gangrenosum, Sweet syndrome) have been reported with MPNs.

Pathology

Microvascular occlusion of dermal vessels or subcutaneous arterioles is found in biopsy specimens from retiform purpura or necrotic lesions.

Differential diagnosis

Useful findings which suggest an MPN include anemia or elevated hematocrit, an abnormal white blood cell count or differential, and an abnormal platelet count or platelet morphology. The differential diagnosis of reactive thrombocytosis, especially due to iron deficiency, post-splenectomy, infection or malignancy, must be considered when assessing the significance of an elevated platelet count.

Treatment

Low-risk patients with PV and ET may be treated with low-dose aspirin. Traditionally administered once daily, more recent data suggests 100 mg twice daily may be more beneficial[15]. In PV, control of the hematocrit is usually achieved via phlebotomy. In higher risk patients, options include cytoreductive therapy (typically hydroxyurea), pegylated interferon-α, or JAK inhibitors such as ruxolitinib[14,16]. Prompt and lasting relief of burning pain by low-dose aspirin is a characteristic finding in thrombocythemic ET while refractory pruritus in PV may respond to paroxetine (20 mg/day), interferon-α, UVB phototherapy, or ruxolitinib[14].

Paroxysmal Nocturnal Hemoglobinuria

Key features

- Coombs-negative intravascular and extravascular hemolytic anemia due to *PIG-A* mutations
- Cytopenias and thrombosis
- Cutaneous lesions are uncommon, but may be extensive

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematopoietic stem cell disorder that is associated with an increased risk of thrombosis.

Pathogenesis

This disease is due to a somatic mutation in *PIG-A* (*p*hosphatidyl *i*nositol *g*lycan class *A*) in hematopoietic stem cells. This X-linked gene encodes a glycosylphosphatidylinositol (GPI)-anchored protein that is required for the cell membrane attachment of several important membrane proteins. Some of these proteins are responsible for protecting blood cells and platelets from complement-mediated injury.

The alternate complement pathway is part of the innate immune system, with chronic low-level activation of complement by a process termed C3 tickover. This results in C3 and C5 convertase amplification (involving Factors B and D) and formation of membrane attack complex (MAC) on the antigen. Normal red cells are protected from this attack by the presence of both CD55 (decay decelerating factor), which stabilizes these convertases, and CD59 (membrane inhibitor of reactive lysis), which inhibits MAC formation. These protective proteins are unable to anchor to cells lacking the GPI anchor protein[17]. The lack of protection leads to red cell lysis and activation of platelets.

The cause of venous thrombosis is multifactorial and is due in part to microparticle formation from platelets and other blood component membranes as well as depletion of nitric oxide related to hemolytic release of free hemoglobin.

Clinical features

This acquired clonal hematologic disorder classically presents with intravascular hemolysis, deficient hematopoiesis, and a thrombotic tendency. It may also occur in the setting of hematologic disorders such as aplastic anemia and myelodysplastic syndrome where it is often subclinical because of a limited number of mutated clones[17,18]. Thrombotic events are the most common cause of death, and venous thromboses (e.g. Budd–Chiari syndrome) are more common than arterial. Depletion of nitric oxide related to chronic hemolysis can lead to smooth muscle dystonia with dysphagia, abdominal pain, and erectile dysfunction[17]. There is also a six-fold increased risk of chronic kidney disease.

A variety of cutaneous findings have been reported in PNH, including hemorrhagic bullae, petechiae, leg ulcers, non-inflammatory retiform purpura, and a purpura fulminans-like presentation[19].

Pathology

Biopsy specimens reveal microvascular occlusion, typically fibrin thrombi. Detection of an absence or severe deficiency of GPI-anchored protein in ≥2 cell lineages (e.g. WBCs, RBCs) by flow cytometry of peripheral blood is diagnostic of PNH.

Differential diagnosis

The differential diagnosis of the various skin lesions that can occur in PNH is broad. The presence of hemolytic anemia plus pancytopenia should suggest the diagnosis.

Treatment

In the past, treatment was largely supportive, consisting of transfusions, iron and folic acid supplementation, and anticoagulation when needed. Nowadays, patients can receive life-long IV therapy with eculizumab or ravulizumab which inhibit the terminal phase of the complement cascade at the C5 stage and can reduce intravascular hemolysis and venous thrombosis[20]. Crovalimab, a C5 inhibitor which can be administered subcutaneously, has shown noninferiority to eculizumab; its prolonged half-life, as well as that of ravulizumab, is based upon SMART-Ig technology which allows prolonged recirculation. Because C5 inhibition does not prevent extravascular hemolysis[21], agents that inhibit C3 activation (e.g. pegcetacoplan) have been FDA approved for PNH or are in clinical trials (e.g. danicopan, iptacopan)[20,21].

Since complement inhibitors can increase the risk of meningococcemia via C5 inhibition, patients under 45 years of age should ideally receive the meningococcal vaccine at least 2 weeks before instituting therapy. However, patients still have a >1000-fold increased risk of *Neisseria* infections, leading to consideration of prophylactic chronic penicillin administration[20].

Primary Thrombotic Microangiopathy

Key features

- Thrombotic microangiopathy (TMA) is characterized by microangiopathic hemolytic anemia (RBC fragmentation with schistocyte formation) and thrombocytopenia
- The focus here will be the three primary TMAs: thrombotic thrombocytopenic purpura (TTP), Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome (STEC-HUS), and complement-mediated HUS (CM-HUS)
- Round, macular petechiae are seen in inherited or acquired ADAMTS13-related TMA (i.e. TTP), most likely due to simple hemorrhage
- Skin lesions are not observed in STEC-HUS while patients with CM-HUS occasionally develop distal necrosis or purpuric/necrotic lesions

Introduction

TMA is a syndrome characterized by microangiopathic hemolytic anemia and thrombocytopenia and it can be primary or secondary. The differential diagnosis can be challenging, especially since most of these syndromes evolve rapidly, leading to significant morbidity and mortality[22–24]. Within the larger spectrum of all TMAs, *primary* TMA includes three entities: TTP, HUS-STEC, and CM-HUS. The latter is also referred to as atypical HUS.

Pathogenesis

Hereditary TTP (Upshaw–Schulman syndrome) is due to biallelic mutations of *ADAMTS13*. Its protein product is an enzyme responsible for cleaving ultra-large multimers of von Willebrand factor (vWF). However, for 90% of patients, TTP is an acquired disorder that develops during adulthood and is immune-related with antibodies that reduce the function of ADAMTS to <10% of normal[25]. Complement activation is thought to contribute to acute TTP, with vWF multimers possibly acting as scaffolding to support alternative pathway activation. In acute TTP, complement activation has been associated with increased mortality[25].

HUS was initially recognized in association with *Shigella* dysentery, but can also be caused by Shiga toxin-producing enterohemorrhagic *E. coli*; STEC-HUS includes both etiologies. Historically, CM-HUS was referred

to as atypical HUS because of the absence of diarrhea. However, mutations that lead to complement dysfunction (e.g. increased complement activation due to deficiencies of alternate complement pathway inhibitory molecules) have been detected in at least 50% of patients with CM-HUS[25,26].

Clinical features

The complete syndrome of classic TTP is characterized by fever, petechiae, thrombocytopenia, microangiopathic hemolytic anemia (schistocytes or fragmented red cells prominent on peripheral smear), renal disease, and neurologic symptoms (most commonly headache and confusion). The macular petechiae usually reflect simple hemorrhage, but occasionally may be attributed to platelet plugging. While platelet occlusion occurs primarily in visceral organs, very few papers have addressed the histology of cutaneous lesions. Currently, the classic syndrome of TTP would be classified as within the spectrum of ADAMTS13 deficiency-mediated TMA, either inherited or acquired/immune[25].

The HUS syndromes may mimic the findings in TTP, but hemolysis and renal involvement predominate. STEC-HUS is typically associated with diarrhea in children, less so in adults, and is not associated with skin hemorrhage. The fatality rate in children is <3%, rising to 15%–30% in frail or elderly adults. Long-term sequelae are seen in a third of children and up to 50% of adults[26]. CM-HUS rarely leads to digital necrosis or scattered necrotic skin lesions[27].

Pathology

Microvascular occlusion of visceral terminal arterioles and capillaries is expected but is rare in the cutaneous microvasculature. Petechial (cutaneous) hemorrhage is most likely due to simple hemorrhage, but documentation is limited. In the rare lesions of CM-HUS, microvascular occlusion may be seen. Immunofluorescent staining of normal skin in patients with CM-HUS may be positive for MAC factors C5–9 in vessels, supporting but not confirming the diagnosis of CM-HUS[28].

Differential diagnosis

Traditionally, *primary* TMA requires exclusion of other causes of TMA, such as disseminated intravascular coagulation (DIC), sepsis, or other infections; pre-eclampsia, eclampsia, scleroderma renal crisis, or malignant hypertension; catastrophic antiphospholipid antibody syndrome; and HELLP syndrome of pregnancy (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelet count)[22–25]. Both toxic and immune drug-induced TTP-HUS also need to be excluded, e.g. cyclosporine, tacrolimus, VEGF inhibitors, gemcitabine, oxaliplatin, and quinine can trigger TMA[24]. In addition, an HUS-like syndrome that involves a VEGFR2 pathway can occur in infants with diacylglycerol kinase epsilon deficiency[24,29].

DIC is characterized by evidence of clot activation (prolonged prothrombin time [PT] and partial thromboplastin time [PTT]) as well as clot lysis (significant elevation of fibrin split products or D-dimers; marked decrease of plasma fibrinogen). Such findings are absent in the primary TMAs. A normal or minimally elevated PT plus profound thrombocytopenia strongly favors primary TMA over DIC.

Treatment

Since *TTP* is usually due to acquired antibodies to ADAMTS13, total plasma exchange represents first-line therapy, leading to a reduction in mortality of up to 90%. Corticosteroids are also helpful in reducing antibody production and in refractory cases, rituximab has been used. For patients with severe disease poorly responsive to plasma exchange, chronic relapsing disease, or congenital disease with absence of ADAMTS13, caplacizumab – a humanized anti-vWF antibody that interferes with platelet–vWF interactions – can reduce thromboembolic complications[25,30–32]. However, initial use of standard first-line therapy may lead to a more rapid response[33].

Treatment of hereditary TTP has traditionally been plasma infusions during flares and then routine prophylactic infusions in patients with frequent recurrences or serious complications[34]. In addition to caplacizumab, recombinant ADAMTS13 may represent a future therapy[34].

For *STEC-HUS*, treatment is primarily directed at eliminating the toxin-producing bacteria and providing supportive care. To restore more normal complement function, the C5 inhibitor eculizumab is currently first-line therapy for *CM-HUS*[35]. Selective C5aR1 blockade, which reduces C5a-induced platelet aggregation while preserving C5–9 formation and thus reducing the risk of serious infections from C5a inhibition (see above), may represent a future approach[36].

DISORDERS OF CRYOPRECIPITATION OR CRYOAGGLUTINATION

Key features

- Retiform purpura most often in an acral location
- Due to cryoglobulins and rarely cryofibrinogens or cold agglutinins
- Cold-induced cryoprecipitation and vascular occlusion most commonly associated with type I cryoglobulins
- In acute lesions, eosinophilic hyaline deposits occluding blood vessels may be present

Introduction

Cryoglobulins are immunoglobulins that are present in both serum and plasma and reversibly precipitate with cold exposure[37]. *Cryofibrinogens* are fibrinogens which precipitate in the cold, are consumed in clotting, and are therefore detectable only in plasma samples[38]. *Cold agglutinins* are antibodies which promote agglutination of red cells on exposure to cold, often leading to a brisk hemolytic anemia[39]. All three groups can cause occlusive syndromes in the skin that are triggered by cold exposure. While cryofibrinogens and cold agglutinins can be detected in many patients in association with a variety of illnesses, they are rarely the cause of cold-related occlusion syndromes directly due to cryoprecipitation or cryoagglutination.

Pathogenesis

Cryoglobulins cause disease via two mechanisms: occlusion (usually type I) or immune complex-mediated vasculitis (usually types II, III; see Table 24.6)[37]. Type I cryoglobulin is a monoclonal antibody, most often IgM, less often IgG, and rarely IgA. Because type I cryoglobulins are not part of an immune complex, they typically affect vessels via induction of hyperviscosity or precipitation in the cold. The possibility of secondary vasculitic changes in older occlusive lesions (see Fig. 22.4) needs to be considered in any reports of type 1 cryoglobulin-induced vasculitis[40].

Cryoglobulins change their configuration in the cold and become water-insoluble, but plasma proteins, pH, and salt concentrations (e.g. in renal glomeruli) can also induce conformational changes[37] as many of these proteins transform only at refrigerator temperatures, not at skin temperatures typically seen with cold exposure of acral areas. Simple occlusion with minimal early inflammation and often retiform purpura/necrosis develops when cryoproteins precipitate upon cold exposure. Intravascular deposits of type 1 cryoglobulins are subdivided into: (1) amorphous deposits – account for most cryo-occlusive syndromes; (2) gelatinous forms – lead to hyperviscosity; and (3) cryocrystals – rarest form with dense linear or herringbone-like arrays[41]. The presence of monoclonal immunoglobulins (IgG, IgM ≫ IgA, light chains), including type I cryoglobulins, points to an underlying plasma cell dyscrasia or lymphoproliferative disorder[37,42,43].

Cryofibrinogen precipitates are composed of fibrinogen, fibrin, fibronectin, and occasionally albumin, immunoglobulins, or other plasma proteins. *Cold agglutinins* bind to red cells in the cold, often triggering complement activation and red cell lysis. Because of their ability to bind multiple red blood cells, pentameric IgM antibodies more readily agglutinate these cells, leading to occlusion.

Epidemiology

The prevalence of cryofibrinogenemia varies from 2% to 9% in healthy individuals and from 8% to 13% in hospitalized patients[38]. Its female:male ratio is 1.4:1. Cryofibrinogenemia may be essential or secondary to a wide spectrum of disorders including infections, autoimmune diseases, and carcinomas. When a cryopathy has been suspected, cryofibrinogenemia was observed in 10%–50% of patients, although usually not in isolation.

Clinical features

The cardinal sign of cold occlusion, including that due to *cryoglobulinemia*, is purpuric or necrotic lesions, often retiform, at sites of cold exposure that are typically acral (Fig. 23.3). Other cutaneous findings include acral cyanosis, Raynaud phenomenon, and livedo reticularis.

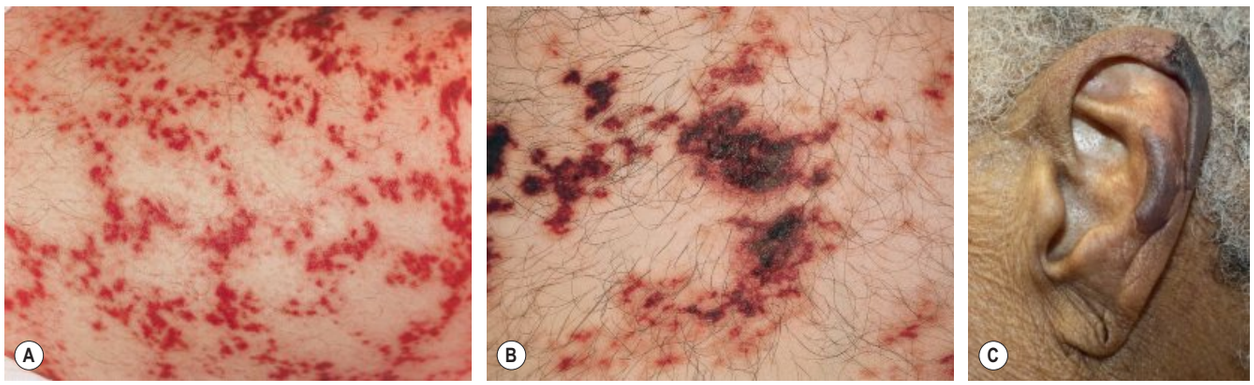


Fig. 23.3 Type I cryoglobulinemia in two patients with multiple myeloma (IgG type). A Retiform purpura of the lower extremity. **B** Areas of necrosis within the areas of retiform purpura. **C** Purpuric lesions of the antihelix and helix of the ear. *A,B, Courtesy Jean L. Bolognia, MD; C, Courtesy Jonathan Leventhal, MD.*

Although some reports describe cutaneous small vessel vasculitis in patients with type I cryoglobulins, it is likely that this finding is often a secondary leukocytoclastic vasculitis that occurs following occlusive necrosis or ulceration (see Fig. 22.4). Mixed (types II and III) cryoglobulins may cause occlusion if they are unstable at close to body temperature, but more frequently they induce lesions via immune complex mechanisms, with clustering of classic palpable purpura in dependent areas.

Because of the prevalence of *cryofibrinogenemia* (see above), clinical correlation is critical in judging the significance of its presence. Cutaneous findings are similar to those induced by cryoglobulins and include both venous and arterial occlusion.

Cold agglutinins are frequently asymptomatic incidental findings, as in *Mycoplasma* infections. When symptomatic, cold agglutinins lead to hemolysis post cold exposure, which can be severe[39,44]. Very rarely, cold exposure in patients with cold agglutinins can induce red cell agglutination, sludging, and vascular occlusion in cold-exposed sites[45]. Lesions may develop at infusion sites following administration of cold blood products. Although skin lesions due to vascular occlusion are unusual, in one study 90% of patients with primary cold agglutinin disease had symptoms, ranging from moderate acrocyanosis to severe Raynaud phenomenon precipitated by even slight cold exposure[44].

Pathology

In type I cryoglobulinemia, occlusion of small dermal vessels is a typical finding (Fig. 23.4). Types II and III cryoglobulinemia show features of an acute cutaneous small vessel vasculitis and are only rarely associated with intraluminal thrombi. Necrosis may be evident in older lesions of all types of cryoglobulinemia, along with secondary vasculitis. In patients with skin lesions due to vascular occlusion, deposits of cold agglutinins are seen as intravascular amorphous eosinophilic material admixed with red blood cells.

Differential diagnosis

The sudden onset of acral disease with cold exposure should suggest this group of disorders. Occasionally, syndromes of distal occlusion (e.g. cholesterol emboli, acral antiphospholipid antibody syndrome, sepsis with DIC and hypotension) may have a similar appearance, but without the history of cold exposure and usually with sparing of the nose and ears. Chilblains (pernio) must also be considered, but lesions are usually slow in onset and seldom progress to significant purpura or necrosis.

Treatment

Management of *cryoglobulin* occlusion is primarily directed at minimizing cold exposure and controlling the underlying plasma cell dyscrasia or lymphoproliferative disorder in order to reduce the titer of monoclonal cryoglobulin. Plasmapheresis or plasma exchange provides only short-term improvement. Patients with Waldenström macroglobulinemia and symptomatic hyperviscosity syndrome should not be treated with rituximab until the hyperviscosity is addressed, usually by plasmapheresis and other systemic therapy (e.g. ibrutinib)[46].

Treatment of *cryofibrinogenemia* also includes minimizing cold exposure. Beyond that, there is little evidence to guide treatment of cutaneous disease. Stanozolol, low-dose aspirin, corticosteroids, fibrinolytics, and immunosuppressives have been suggested, although a rationale for their use is not clear[38,47]. Anticoagulants are only recommended for patients with arterial or venous thrombosis. For secondary cryofibrinogenemia, therapy is aimed at the associated disease. Over time, some patients with "essential" cryofibrinogenemia may develop a lymphoma[47].

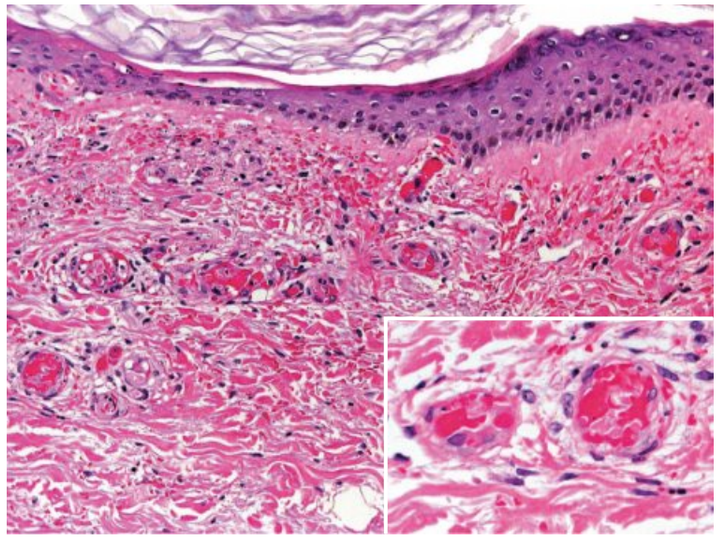


Fig. 23.4 Thrombotic vasculopathy due to type I cryoglobulinemia. In the dermis, there are eosinophilic thrombi within several blood vessels (inset) with hemorrhage and only a minimal inflammatory infiltrate. *Courtesy Lorenzo Cerroni, MD.*

In *cold agglutinin* disease, cold avoidance is recommended but often ineffective. When no secondary cause is identified (e.g. Epstein–Barr virus), most patients are assumed to have a low-grade lymphoproliferative disorder and are treated with rituximab therapy. Sutimlimab, a C1s inhibitor, can reduce hemolysis due to antibody-induced complement activation[44], but since it does not affect antibody levels, patients may still experience cold-related acral cyanosis and vascular occlusion.

DISORDERS OF OCCLUSION BY OPPORTUNISTIC ORGANISMS PROLIFERATING WITHIN VESSELS

Key features

- Retiform purpura or non-inflammatory necrosis
- Often associated with administration of immunosuppressive agents or severe neutropenia
- Poorly controlled diabetes mellitus is a risk factor for mucormycosis

Introduction/pathogenesis

These syndromes share the feature of vessel invasion by organisms (see Chs. 74 & 77), and usually occur in severely immunocompromised patients. All but disseminated strongyloidiasis can have organism growth within the endothelium or vascular wall. The immunocompromised

state is usually due to severe neutropenia and/or to the administration of multiple potent immunosuppressive agents, but may be due to chronic disease or malnutrition.

Clinical features/pathology

Ecthyma gangrenosum is the syndrome of occlusion by organisms (usually bacterial) proliferating in the adventitia of subcutaneous blood vessels. The classic organism is *Pseudomonas aeruginosa*, but ecthyma gangrenosum-like skin lesions have also been described with other organisms, including other *Pseudomonas* spp. (*P. cepacia, P. maltophilia), Serratia marcescens, Aeromonas hydrophila, Klebsiella pneumoniae, Vibrio vulnificus, Moraxella* spp., *Morganella morganii, Escherichia coli*, and *Staphylococcus aureus*; these lesions may also be due to fungal organisms, e.g. *Candida albicans, Mucor* spp., *Aspergillus fumigatus, Fusarium* spp., and *Neoscytalidium dimidiatum*[48,49].

Ecthyma gangrenosum begins as erythematous, painless macules, but typically progresses to purpuric or escharotic lesions which may be bullous or pustular, and frequently show retiform or branching features. There is extensive bacillary infiltration of the media, adventitia, and perivascular regions of blood vessels, typically with sparing of the lumen and intima. As the bacteria proliferate, gradual compression of the vessel wall narrows and then ultimately occludes the lumen of a subcutaneous arteriole that supplies an overlying cone of skin. This is followed by clot formation within many blood vessels in that skin zone. Immediate antibiotic therapy is crucial, although the prognosis is poor if the neutropenia persists, antimicrobial agents are ineffective, or the disease process is advanced. Of note, many authors include cutaneous lesions and histopathologic findings in this category which might more properly be classified as septic vasculitis due to bacteremia from Gram-negative rods, when sufficient neutrophils exist to provide a local response.

In severely immunocompromised patients, *vessel-invasive fungi* can result in necrotic lesions secondary to vessel invasion and thrombosis[48,49]. The most common opportunistic fungi in this group are *Aspergillus, Rhizopus*, *Mucor*, *Rhizomucor*, and *Lichtheimia* (formerly *Absidia*) spp. The latter four are causes of mucormycosis. In diabetic patients, mucormycosis may present in the central face with cutaneous necrosis, presumably originating from a sinus cavity infection. Opportunistic fungi that produce retiform purpura tend to proliferate and invade from within the lumen into the vessel wall and into vascular branches. Thrombus develops around the hyphal elements within the vessels and presumably also on the altered endothelium.

Disseminated strongyloidiasis can occur in patients infected with the human nematode *Strongyloides stercoralis*. Reticulated purpuric lesions, especially in the periumbilical region, have been described with dissemination, although such lesions are rare (see Ch. 83); their appearance has been likened to thumbprints (see Fig. 83.21). Histologically, the purpuric lesions demonstrate extravasated erythrocytes and larvae within capillaries and between collagen bundles. The mortality rate in disseminated disease is high.

Lucio phenomenon is common in Mexico and Central America, but rare in other areas. The associated thrombotic lesions are distinguished from erythema nodosum leprosum (an immune complex-mediated neutrophilic vasculitis with variable involvement of the panniculus) by an absence of fever, leukocytosis, and tenderness; a poor response to thalidomide; and restriction to patients with the diffuse non-nodular lepromatous form of Hansen disease. Some acute lesions present as retiform purpura, and these lesions frequently progress to chronic ulcers (see Fig. 75.10D)[50]. Extensive blanchable livedo reticularis of the extremities may also be present[51] and concomitant antiphospholipid antibody syndrome has been reported. Histologically, some cases have endothelial swelling and thrombus formation within dermal and some subcutaneous vessels whereas others show features of leukocytoclastic vasculitis in the superficial and mid-dermis with overlying epidermal necrosis.

Of the rickettsial infections (see Ch. 76), widespread cutaneous lesions with hemorrhage are most commonly observed in Rocky Mountain spotted fever. Initially, the eruption is not hemorrhagic, but by day 5, petechiae usually develop within lesions due to vascular hyperpermeability[52]. Progression of hemorrhage beyond 3–4 mm is typically associated with severe disease. Early petechial lesions may be comma-shaped or linear, reflecting hemorrhage following the microvasculature. Due to endothelial injury, DIC can develop later in the disease course, resulting in cutaneous necrosis that is often in a retiform pattern. Other spotted fevers that often have a hemorrhagic component are Brazilian spotted fever, boutonneuse fever, and Japanese spotted fever (see Ch. 76).

Differential diagnosis

The differential diagnosis includes other causes of non-inflammatory purpura due to cutaneous microvascular occlusion (see Table 23.1).

Treatment

Treatment is directed at mitigating the immunocompromised state where possible, and by selecting appropriate antimicrobial therapy based on identification of the invading organism. Ivermectin is the treatment of choice for disseminated strongyloidiasis.

DISORDERS OF OCCLUSION BY EMBOLI

Cholesterol Embolus

Key features

- Usually abrupt onset
- Livedo reticularis is usually much more prominent than retiform purpura
- Distal extremities, especially the legs, are the most likely site of cutaneous involvement

Introduction

Cholesterol embolus is primarily a disease of men 50 years of age or older. Common comorbidities include diabetes mellitus, hyperlipidemia, hypertension, tobacco use, and peripheral artery disease[28,53]. In autopsy studies, cholesterol embolism was observed in 15%–20% of patients older than 60 who had a history of atherosclerotic disease, and in up to 3% of unselected autopsies[53,54]. Given the relatively low frequency rate of the clinical diagnosis of cholesterol embolus, this figure suggests that cholesterol emboli are frequently undiagnosed or asymptomatic.

Pathogenesis

Since fragmentation of ulcerated atheromatous plaques is the cause of cholesterol emboli, affected patients usually have severe (but often unrecognized) atherosclerotic disease. Although spontaneous fragmentation of plaques can occur, there are three, possibly four, clinical settings known to prompt embolization. The first is *arterial or coronary catheterization*, which may disrupt a plaque, leading to emboli within hours to days of catheterization. The second is *acute thrombolytic therapy* given for myocardial infarction or stroke. Embolization may occur within hours to days of lytic therapy but a true causal relationship has been questioned. A third recently described trigger for cholesterol embolus is the *Heimlich maneuver*[55]. The fourth, *prolonged anticoagulation*, which typically occurs after 1 to 2 months of therapy, is also a matter of debate. Theoretically, anticoagulation slowly lyses the clot which may be reinforcing a friable plaque, leaving exposed areas of the plaque subject to the shear stress of arterial flow. This "warfarin blue toe syndrome" is not restricted to warfarin anticoagulation and should not be confused with warfarin necrosis[56]. Of note, ~20% of patients with cholesterol emboli have no known inciting event[54].

Clinical features

Clinical findings include fever, weight loss, myalgias, altered mental status, and a sudden onset of arterial hypertension. Transient ischemic attacks, strokes, renal failure, gastrointestinal ulcerations, and hemorrhagic pancreatitis may also occur. Patients with multisystem involvement can have significant morbidity and occasionally may die from embolic complications.

Cutaneous findings are reported in 35%–90% of patients with cholesterol embolization and they include: livedo reticularis (50%–75%), cyanosis/blue toes (30%–75%), ulceration (15%–40%), multiple sites of peripheral gangrene (0–35%), nodules (~10%), and purpura (~10%) (Fig. 23.5A–D)[57]. Because retiform purpura represents a purpuric accentuation of the livedo reticularis pattern, it may be described as livedo reticularis in some reports. Upper extremity lesions can appear if the plaque originated



Fig. 23.5 Cholesterol emboli. A Livedo reticularis is seen proximally on the thigh. **B** Both livedo reticularis and retiform purpura are seen distally. **C** Purpura of the digits. **D** Several irregularly shaped ulcers with eschars surrounded by retiform purpura on the thigh. **E** Histologically, intravascular clefts are seen which are due to dissolution of cholesterol crystals during fixation. *A,B,E, Courtesy Norbert Sepp, MD; D, Courtesy Kalman Watsky, MD.*

from the aortic arch. Rarely, cholesterol emboli occur more proximally (buttocks, thighs, flanks) and may mimic calciphylaxis or antiphospholipid antibody-related necrosis (Fig. 23.5D)[58]. Of note, an initial diagnosis of cholesterol emboli is made in only 35%–40% of patients[57].

Peripheral blood eosinophilia is observed in 15%–80% of recognized cases[57]. Other laboratory findings include decreased complement levels, leukocytosis, pyuria, eosinophiluria, elevations in the ESR, CRP, serum creatinine, BUN and amylase, and heme-positive urine or stool[57].

Pathology

A biopsy of the livedo reticularis is most informative when it consists of an elliptical incision centered on the blanched portion of the livedo reticularis and is deep enough to include fat (see Fig. 106.1). Areas of retiform purpura usually provide diagnostic findings in punch biopsy specimens and should be the first choice for biopsy when present.

Histologically, cholesterol emboli produce elongated clefts within lumina of small vessels (Fig. 23.5E), often in association with thrombi[53]. The clefts are created by dissolution of cholesterol crystals during the fixation process. The affected arteriole is usually at the dermal–subcutaneous junction. Neutrophils, eosinophils, and mononuclear cells may be seen in arterial walls within 24–48 hours in an experimentally produced cholesterol embolus, followed by multinucleated histiocytes within 3 to 6 days, and sometimes intimal fibrosis. Lesions of different ages may be found in the same patient, consistent with recurrent showers of emboli.

Differential diagnosis

The abrupt onset of distal livedo reticularis should prompt consideration of cholesterol or oxalate embolism. Retiform purpura, especially when it occurs distally in concert with more extensive distal livedo reticularis, is especially suggestive of this diagnosis. Acral cold occlusion syndromes (see above) need to be considered when distal lesions are present, as well as antiphospholipid antibody syndrome. Proximal cholesterol emboli mimicking calciphylaxis have been reported[58].

Treatment

Treatment is mainly supportive, unless surgical bypass or endovascular stent grafting can eliminate the source of embolism. Aspirin and other antiplatelet agents, HMG-CoA reductase inhibitors ("statins"), discontinuation of warfarin (per package insert), initiation of anticoagulation in patients with severe renal damage, systemic corticosteroids, iloprost, and hyperbaric oxygen have all been advocated as effective in occasional patients, but no therapeutic standard exists.

Oxalate Embolus

Introduction

Oxalate embolism is a rare event, usually occurring in association with primary hyperoxaluria. Three types of *primary* hyperoxaluria result from rare enzyme deficiencies in which there is increased hepatic production of oxalic acid[59]. This leads to hyperoxalemia and calcium oxalate deposition within tissues[59,60]. *Secondary* hyperoxaluria, and occasionally hyperoxalemia, usually reflects increased gut absorption of oxalate due to: (1) increased dietary intake of oxalate (e.g. rhubarb, spinach and green smoothies, almonds) or oxalate precursors (e.g. ascorbic acid, ethylene glycol, naftidrofuryl oxalate); (2) fat malabsorption leading to calcium binding by fatty acids in the gut and increased absorption of free oxalate; or (3) decreased intestinal oxalate degradation due to a change in gut microbiota[59].

Clinical features

Type 1 primary hyperoxaluria (oxalosis) is the most common and most severe form, usually presenting during childhood with recurrent urolithiasis. The kidney is the major site of oxalate deposition until progressive renal insufficiency develops, at which time clinical signs of deposition in other organs become evident. Therefore, oxalate embolus typically occurs after the development of renal failure. Death by the age

of 20 years is not unusual in patients with childhood onset. Types 2 and 3 primary hyperoxaluria are less severe and often do not present until adulthood[59].

Cutaneous findings in systemic oxalosis include acrocyanosis, Raynaud phenomenon, peripheral gangrene, acral cutaneous necrosis and infarcts, livedo reticularis, erythematous ulcerated nodules, miliary calcified deposits, and a cutaneous calciphylaxis-like presentation[60,61]. The calciphylaxis-like presentation can be misleading, not only because of lesional similarity, but also because both oxalate embolus and calciphylaxis typically occur in the setting of renal failure.

Pathology

Skin biopsy specimens demonstrate yellow–brown, birefringent crystals in a rectangular or radial pattern within and around vessels in the deep dermis and subcutaneous tissue. Crystals are yellow to golden-brown in routinely stained sections and birefringent under polarized light[61]. They also stain with alizarin red S at pH 7.0 but not at pH 4.2. Foreign body giant cells may be present. Although clinical lesions may mimic those of cutaneous calciphylaxis, calcium deposition in vessels is not a characteristic finding in cutaneous oxalate emboli.

Differential diagnosis

This disorder is most likely to be confused with cholesterol embolus or cutaneous calciphylaxis in a patient with renal failure, but the differential diagnosis includes other causes of retiform purpura and livedo reticularis. A history of renal calculi in a patient with sudden-onset livedo reticularis or retiform purpura suggests hyperoxaluria as a prime diagnostic possibility. Brawny, woody fibrosis of the distal upper and lower extremities, suggestive of nephrogenic systemic fibrosis, has also been described[60].

Treatment

In patients with primary hyperoxaluria without renal failure, therapeutic options include massive fluid intake and calcium oxalate crystallization inhibitors[59]. Oral pyridoxine may be helpful in type 1 oxalosis. Liver transplantation is the only "curative" treatment[59]. Renal transplantation is contraindicated without correction of the underlying abnormality, since the transplanted kidney will be damaged by continued oxalate deposition. Lumasiran, a small interfering RNA (siRNA), is approved for type 1 hyperoxaluria[59].

Other Embolus-Associated Syndromes

In addition to emboli from acute bacterial or fungal endocarditis (which are usually inflammatory in nature), cutaneous emboli or thrombi have been rarely described in patients with atrial myxomas, marantic endocarditis, crystalglobulins, and hypereosinophilic syndrome. Emboli from these disorders may produce retiform purpura, but cutaneous findings are diverse.

Atrial myxomas are rare, typically present between the third and sixth decades of life, and may be associated with symptoms or signs secondary to: (1) intracardiac obstruction – dyspnea, chest pain, syncope; (2) cytokine release by the tumor – fever, myalgias, arthralgias; and (3) extracardiac embolism – most often to the CNS but occasionally to skin[62]. Cutaneous findings of myxomatous emboli include acral papules (with claudication), purpuric, serpiginous or annular violaceous fingertip lesions, splinter hemorrhages, livedo reticularis, Raynaud phenomenon, toe necrosis, a red–violet malar flush, and distal petechiae[48,53,62]. Carney complex (NAME/LAMB syndromes) is associated with multiple, early-onset cardiac myxomas and may have other cutaneous findings such as lentigines and blue nevi, unrelated to the emboli. Treatment of atrial myxoma consists of surgical removal.

Marantic endocarditis results in focal deposits of fibrin and other blood elements on heart valves, similar to Libman–Sacks (antiphospholipid antibody-related) or acute rheumatic endocarditis[63]. Portions of these loose sterile deposits may occasionally embolize. Vegetations of *infective endocarditis* may also embolize. Emboli are more likely to occur with acute bacterial endocarditis, whereas cutaneous lesions in subacute bacterial endocarditis are more likely to result from immune complex disease, not embolization, despite frequent localization to hands.

Crystalglobulin vasculopathy is a rare syndrome of usually IgG or light chain paraproteins which spontaneously crystallize intravascularly. The crystalglobulinemia syndrome presents with rapidly progressive renal failure, polyarthropathy, peripheral neuropathy, cutaneous ulcerations, petechiae, and ecchymoses. Skin biopsies show intravascular crystalline deposits and thrombosis[53,64].

In the *hypereosinophilic syndrome*, an intracardiac mural thrombus can form, and thrombi in smaller vessels are not uncommon at autopsy in patients with this syndrome[53,65]. Clinical findings described to date include splinter hemorrhages, "non-blanching livedoid discoloration" (retiform purpura), digital gangrene, Raynaud phenomenon, and necrotic or blistering skin lesions, but some features may also be due to thrombosis or vasculitis related to the eosinophilia[7,53].

SYSTEMIC COAGULOPATHIES WITH CUTANEOUS MANIFESTATIONS

Disorders of the thrombomodulin, protein C, and protein S pathways may lead to fulminant microvascular occlusion syndromes. Antiphospholipid antibodies are also a major cause of microvascular occlusion, including the catastrophic antiphospholipid antibody syndrome. Many different pathways of antiphospholipid antibody-enhanced coagulation are known or suspected; some include interference with protein C or S function.

Protein C and S Disorders, Congenital and Acquired

Relevant associations:

- Neonatal purpura fulminans – congenital severe protein C or S deficiency
- Warfarin necrosis – acquired protein C dysfunction
- Purpura fulminans in children during recovery from streptococcal or varicella infections – severe acquired protein S dysfunction, probably antibody-mediated

Key feature

- Retiform, branching, or stellate purpura in one of the above clinical settings

Introduction

The term "purpura fulminans" was first used in the late 1800s to describe a syndrome of extensive purpura in severely ill patients, usually children, in the setting of an acute or convalescent infection. This term now includes at least three different syndromes (see below), including septic patients with widespread purpura of any type (petechiae, ecchymoses, palpable purpura, or retiform purpura). It would be more helpful to restrict the term *purpura fulminans* to the subset of patients (either neonatal or septic) with clinical features of DIC and occlusion, including retiform, branching, or necrotic purpura, and/or bland thrombi as the primary histologic finding.

Pathogenesis/clinical features

Despite some overlap in pathophysiology, the differential diagnosis for cutaneous microvascular occlusion is quite different from that of deep venous thrombosis (DVT) or pulmonary emboli (PE). With respect to skin, the protein C–protein S–thrombomodulin pathway is critically important (see Fig. 22.5).

Neonatal purpura fulminans

While severe congenital deficiency of antithrombin III may result in repeated DVT or PE, the only cutaneous finding is venous stasis ulcers from DVT-induced venous insufficiency. In contrast, homozygous (or compound heterozygous) deficiency or severe dysfunction of either protein C or protein S leads to neonatal purpura fulminans within a few hours to 5 days after birth, and it is fatal unless treated[66,67]. Clinically, non-inflammatory retiform purpura is seen until confluence results in large-scale cutaneous and limb necrosis (Fig. 23.6). Ultimately, there is visceral organ involvement. In addition, such infants are often born with cerebral thrombosis or retinal vessel occlusion with congenital blindness. Acquired neonatal purpura fulminans is most commonly due to group B streptococcal infections[67].



Fig. 23.6 Protein C deficiency in an infant. Large purpuric plaques, with development of bullae and necrotic ulcerations within those on the lower extremities. Note the retiform purpura surrounding the heel ulcer. *Courtesy Luis Requena, MD.*



Fig. 23.7 Warfarin (Coumadin®) necrosis. Striking areas of purpura and ischemia on the scrotum (**A**) and pannus (**B**). Note the branching outline of the purpura and central necrosis in the lesions on the abdomen. The differential diagnosis would include calciphylaxis (see Fig. 106.5). *A, Courtesy Kenneth Greer, MD; B, Courtesy Jean L. Bolognia, MD.*

For patients with congenital protein C deficiency, intravenous protein C concentrate or fresh frozen plasma (FFP) is used as initial therapy and then warfarin or low-molecular-weight heparin is begun, followed by tapering of factor replacement. Anticoagulation is continued for life. Liver transplantation is an option for restoring protein C activity[66,67]. Treatment of purpura fulminans due to congenital protein S deficiency is primarily replacement with FFP.

Warfarin necrosis

Warfarin therapy results in abnormal γ-carboxylation of the vitamin K-sensitive factors (II, VII, IX, X, protein C, protein S) by the liver; severe vitamin K deficiency results in a similar dysfunction. Of these factors, the two with the shortest half-life are factor VII and protein C. Factor VII is needed primarily to switch the idling coagulation system into progressive amplification of clotting, and there is considerable redundancy of the procoagulant cascade. In contrast, protein C is critical for preventing the distal spread of clot from the initial point of coagulant activation. In warfarin necrosis, the *pro*coagulant system takes significantly longer to reach its low-point equilibrium than does the protein C-dependent *anti*coagulant activity.

Warfarin necrosis usually develops within 2–5 days of warfarin initiation in the absence of heparin, and it is much more likely to occur if loading doses of warfarin are used[8,68,69]. This coincides with the expected early drop of protein C function. Reversal of warfarin necrosis via replacement with protein C concentrates and laboratory confirmation of very low functional levels of protein C in this setting support this pathomechanism. The incidence of warfarin necrosis is four times higher in women, with a peak incidence in the sixth and seventh decades of life. Although up to one-third of cases of warfarin necrosis may involve inherited partial deficiency of protein C, the disorder occurs more commonly in individuals without inherited defects in protein C. Late-onset warfarin necrosis, occurring up to 6 months after initiating therapy, has been attributed to poor compliance or inappropriate dosing, alterations in the synthetic function of the liver, or drug–drug interactions[69].

Affected sites usually overlie areas of abundant subcutaneous fat, such as the breast, hip, buttock, or thigh. Pain is often the presenting sign, followed by well-demarcated erythema, which rapidly becomes hemorrhagic and then necrotic (Fig. 23.7). Partial retiform or branching purpura typically can be seen within or at the margin of the cutaneous lesions. Biopsy specimens reveal bland (non-inflammatory) thrombosis of most of the dermal vessels[53]. Treatment consists of warfarin discontinuation and administration of vitamin K and heparin. Use of protein C replacement, if available, should also be strongly considered.

Warfarin-associated venous limb gangrene

Synonym: ■ Warfarin-induced venous limb ischemia/gangrene

Severe venous limb ischemia and gangrene is a catastrophic complication of warfarin therapy and there are two predisposing clinical settings – malignancy (often occult) and HIT syndrome (see above)[8]. In patients with a malignancy, there is platelet consumption and ongoing consumptive coagulopathy; administration of heparin leads to an increase in platelet counts while discontinuation of heparin leads to a decline. There is also evidence of persistent thrombin generation despite anticoagulation. Another characteristic finding is warfarin-associated supratherapeutic international normalized ratios (INRs).

Purpura fulminans with sepsis

Acquired purpura fulminans is most notably associated with meningococcal infection, perhaps due to the meningococcus' ability to bind directly to endothelial receptors via its type IV pili. However, it can also occur in association with sepsis from a variety of bacteria, including *S. aureus*, groups A and B β-hemolytic streptococci, *Streptococcus pneumoniae, Haemophilus influenzae*, and *H. aegyptius*[70,71]. In neonates, it is most often due to group B streptococcus.

In a septic patient with DIC, development of retiform purpura can be the first sign of microvascular thrombosis, possibly due to an inability of the protein C–thrombomodulin pathway to prevent propagation of clot[72]. Support for this hypothesis comes from a study in pediatric patients with purpura fulminans in whom early use of protein C correlated with improved survival[73]. However, in adults with septic shock, use of activated protein C did not confer survival benefit and increased the risk of bleeding[74]. While some authors support the use of protein C (as well as antithrombin) for sepsis with purpura fulminins[75], to date definitive studies in which native or activated protein C supplementation is administered to patients with new-onset retiform purpura in the setting of sepsis and DIC have not been done.

Purpura fulminans postinfection

While protein C abnormalities seem to correlate with acquired purpura fulminans in the setting of sepsis in both children and adults, a second clinical presentation has been recognized in children which occurs during the recovery period from group A streptococcal infections including scarlet fever, varicella–zoster, or rarely rubella or human herpesvirus 6 infection[76]. These patients acquire an antibody that can inhibit protein S function[76,77]. The development of postinfectious purpura fulminans ~7–10 days after the onset of the initial infection correlates with the production of infection-triggered antibodies. It is known that protein S requires phospholipid binding for full activity

and transient antibodies to phospholipids or coagulation proteins can develop in children with varicella–zoster viral infections. However, the presence of these antibodies is not predictive of thrombotic complications[77]. Because protein S is an important cofactor for tissue factor pathway inhibitor (which ordinarily acts to suppress tissue factor : factor VIIa-triggered coagulation; see Ch. 22), a reduction in its activity could enhance thrombosis via this mechanism[78].

Treatment of postinfectious purpura fulminans is challenging because there is no commercially available protein S concentrate and it is significantly more difficult to overcome antibody-mediated inhibition of protein S than to restore a deficiency of protein S. Therapeutic options include plasma exchange, plasmapheresis, or plasma replacement in combination with corticosteroids, low-molecular-weight heparin, and sometimes IVIg[76–79].

Antiphospholipid Antibody/Lupus Anticoagulant Syndrome

Key features

- Livedo reticularis, bland necrosis, retiform purpura, or atrophie blanche-like lesions are typical
- The definite diagnosis of antiphospholipid antibody syndrome requires at least one clinical and one laboratory criterion (Table 23.3)
- Pathogenicity of antibodies depends more on binding to certain proteins than to phospholipid binding alone

Introduction

The reagin test for syphilis developed by Wasserman in 1905 was the first antiphospholipid (aPL) antibody test[80]. Some of these antibodies were subsequently associated with thrombotic and obstetric syndromes. Despite their designation as aPL antibodies, it wasn't until the 1990s that co-binding of aPL antibodies to a protein was recognized as essential for pathogenicity[80].

Epidemiology

Antiphospholipid antibody syndrome (APS) is estimated to affect 0.3%–1% of the population[81]. In a 1000-patient cohort of individuals with APS, there was a strong female predominance (82%) and the mean age was 42 ± 14 years at study entry. Fifty-three percent of the patients had primary APS, 36% had APS secondary to systemic lupus erythematosus (SLE), and the remaining 11% had other associated diseases[82]. Thrombosis occurred in a third of patients, most commonly cerebrovascular accidents, transient ischemic attacks, DVTs, and PE. The most frequent obstetric and fetal complications were early pregnancy loss (~15% of pregnancies), premature birth (~50%), and intrauterine growth restriction (~25% of total live births). Mortality was ~10%, usually due to thrombosis (35%) or infection (30%).

Catastrophic APS (CAPS) occurred in 0.9% of this 1000-patient cohort and 55% of those affected died[82]. In a study of 500 patients with CAPS and thrombosis of multiple small vessels, the majority were female (70%), the mean age was 38 years, and the mortality was ~35%[83]. Autoimmune disease was present in 40%, primarily SLE (75%). Organs involved were kidneys (70%), lungs (60%), brain (55%), heart (50%), and skin (50%). Malignancy was a trigger primarily in older patients, whereas infection was a common trigger in younger patients. Lupus patients with CAPS were more likely to have severe cardiac and brain involvement, resulting in a higher mortality (50%).

Pathogenesis

The majority of, if not all, pathogenic aPL antibodies recognize cell surface proteins attached to plasma membrane phospholipids[81,84,85]. The three APS criteria antibody groups are: (1) IgM and IgG anti-β_2-glycoprotein I (β_2GPI) antibodies; (2) anti-cardiolipin (aCL) antibodies; and (3) lupus anticoagulant (LA) (see Table 23.3). The latter is most strongly associated with thrombosis and adverse pregnancy outcomes[85]. Antibodies against β_2GPI bind directly to this protein, which is not a phospholipid, and then may bind to phospholipids on cell membranes. β_2GPI is a unique five domain protein with anticoagulant, antiplatelet, and procoagulant actions (see Table 23.3). β_2GPI, along with C-reactive protein and thrombomodulin, are the only three proteins that have the dual capability of regulating the complement and coagulation systems both up and down depending on external stimuli[8].

Anticardiolipin antibodies are not pathogenic unless their binding is dependent on co-binding to a protein (usually β_2GPI). Likewise, LA is not pathogenic (prothrombotic) unless its binding is co-dependent on either β_2GPI or prothrombin[85]. Of note, pediatric patients with LA that targets prothrombin can rarely develop hypoprothrombinemia and present with bleeding rather than thrombosis. In addition, some forms of LA can punch holes in the annexin 5 shield, leading to phospholipid exposure and thrombosis vulnerability, including in placental vessels.

Different molecular mechanisms may underlie the obstetric versus thrombotic APS subsets[81,85]. Purified IgG from patients with obstetric, but not thrombotic, manifestations of APS were capable of inhibiting trophoblast invasion, while in thrombotic APS, neutrophils produced spontaneous neutrophil extracellular traps (NETs) which incorporated into thrombi[81,85]. Of note, aPL antibodies can also bind to β_2GPI receptors on platelets leading to platelet activation and aggregation, resulting in thrombocytopenia in roughly a third of patients with APS[85].

Vascular findings such as prominent and persistent livedo racemosa or reticularis are unlikely to be due solely to thrombotic mechanisms; they may be related in part to aPL antibodies binding to receptors on endothelial cells with inhibition of endothelial nitric oxide synthase. This would lead to impairment of nitric oxide production and release, inducing endothelial dysfunction and potentially endothelial cell proliferation and intimal hyperplasia[84,85].

Clinical features

APS is one of the more commonly acquired causes of hypercoagulability, presenting as thrombosis (arterial, venous, microvascular) and pregnancy morbidity (miscarriages, late intrauterine fetal demise, severe pre-eclampsia)[85]. Cutaneous findings associated with the APS are listed in Table 23.4. In one large study, the incidence of cutaneous findings were: livedo reticularis, 25%; leg ulcers, 6%; pseudovasculitic lesions, 4%; digital gangrene, 3%; cutaneous necrosis, 2%; and splinter hemorrhages, 0.7%[86] (Fig. 23.8). Cutaneous lesions may also develop indirectly, i.e. by embolization from heart valve vegetations (see embolus section).

ANTIPHOSPHOLIPID ANTIBODY SYNDROME: SAPPORO–SYDNEY CRITERIA

At least one clinical criterion and one laboratory criterion required*

Clinical criteria

1. Vascular thrombosis
   - One or more objectively confirmed episodes of arterial, venous, or small vessel thrombosis occurring in any tissue or organ
2. Pregnancy morbidity
   - One or more unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation – *or* –
   - One or more premature births of morphologically normal neonates at or before the 34th week of gestation because of eclampsia, pre-eclampsia, or placental insufficiency – *or* –
   - Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation

Laboratory criteria – present on two or more occasions at least 12 weeks apart*

1. Anti-cardiolipin antibodies, IgG or IgM [>40 GPL or MPL – *or* – >99th percentile as measured by a standardized ELISA]
2. Lupus anticoagulant [detected according to the guidelines of the International Society on Thrombosis and Haemostasis]
3. Anti-β_2-glycoprotein I† antibodies, IgG or IgM [>99th percentile as measured by a standardized ELISA]

*Patients who do not meet these criteria may still have antiphospholipid antibody syndrome.
†β_2-glycoprotein I binds to ApoER2 receptor, affecting Factor XI effect on platelets and protein C activation, inhibits plasmin generation via direct binding to thrombin, impairs platelet aggregation, inhibits both activated protein C and the activation of protein C by thrombomodulin/thrombin complexes, and inhibits the anticoagulant effect of annexin V.

Table 23.3 Antiphospholipid antibody syndrome (APS): Sapporo–Sydney criteria. The criteria allow for standardization of patients enrolled in clinical studies. GPL, IgG phospholipid units; MPL, IgM phospholipid units. *Adapted from refs 52 and 54.*

CUTANEOUS FINDINGS IN PATIENTS WITH THE ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)
• Livedo reticularis, with or without retiform purpura
• Cholesterol embolus-like proximal livedo reticularis with distal retiform purpura
• Acral livedo reticularis
• Sneddon syndrome
• Livedoid vasculopathy or Degos-like lesions
• Anetoderma-like lesions with microthrombosis
• Raynaud phenomenon
• Vasculitis-like lesions
• Pyoderma gangrenosum-like ulcers
• Nail fold ulceration
• Splinter hemorrhages
• Widespread cutaneous necrosis, typically as part of catastrophic APS
• Pseudo-Kaposi sarcoma (acroangiodermatitis)
• Superficial thrombophlebitis migrans

Table 23.4 Cutaneous findings in patients with the antiphospholipid antibody syndrome (APS).



Fig. 23.8 Antiphospholipid antibody syndrome. **A** Purpura and ischemia of the distal portion of the foot. The purpuric lesions have irregular borders (marked with ink). **B** Purpura and milder ischemia of the distal fingers. *A, Courtesy Jean L. Bolognia, MD.*

In addition to the skin, many other organ systems may be involved, with DVT/PE and CNS disease the most common extracutaneous manifestations. CAPS is uncommon and precipitating factors include infection (often younger patients), surgical procedures, drugs (e.g. sulfur-containing diuretics, captopril, oral contraceptives), discontinuation of anticoagulant therapy, and malignancy, especially in older individuals. These patients often present with multi-organ failure; the majority present with renal involvement as well as evidence of acute respiratory distress syndrome. In a series of 65 patients with CAPS and skin involvement, the cutaneous findings included livedo racemosa (45%), necrotic or ulcerated lesions (42%), splinter hemorrhages (29%), apparent distal inflammatory edema (hands, feet, face; 23%), and purpura (14%)[86a]. Complement activation appears to play a role in CAPS and up to 60% of patients with CAPS have germline mutations in complement regulatory genes[87].

Pathology and laboratory findings

As noted previously, LA is most strongly associated with thrombosis and adverse pregnancy outcomes[85]. Detection of LA activity requires a 3-step process: (1) screening assay, e.g. dilute Russell viper venom test, sensitive activated PTT – required because of heterogeneous nature of LA; (2) mixing 1–2 : 1 patient plasma : normal plasma – determines if factor deficiency (corrects prolonged clotting detected in screening assay) or the presence of an inhibitor; and (3) if no correction, determine if inhibitor is phospholipid-sensitive[85].

Tests for aCL and anti-β_2GPI antibodies depend on ELISA assays. In general, patients with triple positivity, i.e. all three antibody groups (see Table 23.3), are considered at highest risk for thrombosis. Additionally, some patients may fit an APS profile but be seronegative for criteria antibodies. The non-criteria antibody most strongly associated with the presence of LA and thrombosis is the anti-phosphatidylserine/prothrombin complex antibody. Of note, this antibody has been highly associated with skin-predominant polyarteritis nodosa, primarily in Japan[88]. In lupus patients, IgM aCL is not associated with thrombosis risk, but the non-criteria IgA aCL appears to be[85].

Histologic features of early lesions typically reveal non-inflammatory thrombosis of small dermal vessels; later lesions may show inflammation following necrosis or with wound healing. In CAPS, there can be arterial and venous occlusion as well as microvascular occlusion in multiple organs including the skin. Complement activation and NETosis can lead to inflammation of blood vessels.

Differential diagnosis

The differential diagnosis of APS includes many of the syndromes discussed in this chapter plus the diseases or syndromes associated with the cutaneous findings in Table 23.4. The presence of persistent or widespread livedo reticularis or livedo racemosa, especially in association with SLE, points to Sneddon syndrome or APS. Complement-mediated HUS (CM-HUS) and sepsis-associated purpura fulminans/DIC can mimic CAPS, but the latter does not typically result in prolonged PT/PTT or elevated fibrinolysis, as in DIC.

Treatment

Therapy for APS normally consists of heparin followed by a vitamin K antagonist to maintain an INR = 2.0–3.0[85,89]. In CAPS, treatment options include heparin, methylprednisolone, IVIg, plasmapheresis, and more recently C5 inhibitors (e.g. eculizumab)[85,90]. Rituximab, cyclophosphamide, and other immunosuppressive agents have been used for both refractory APS and for CAPS[85,91]. In general, direct-acting oral anticoagulants (DOACs) are not recommended[85,89]. Controversy surrounds the use of low-dose aspirin; while multiple lupus trials showed no benefit except for arterial thrombosis[85], it may have a role as preventive therapy in asymptomatic non-lupus patients with aPL antibodies. Hydroxychloroquine, HMG CoA reductase inhibitors ("statins"), and vitamin D replacement may be considered as adjunctive therapies.

DISORDERS OF VASCULAR COAGULOPATHIES WITH CUTANEOUS MANIFESTATIONS

Sneddon Syndrome

Synonym: ■ Idiopathic livedo reticularis with cerebrovascular accidents

Key features

- Usually affects young women
- Persistent livedo reticularis or livedo racemosa
- Labile hypertension
- Recurrent neurologic symptoms due to cerebrovascular disease

Introduction

This uncommon syndrome was first described in 1965[91]. An estimated four new cases of Sneddon syndrome occur per million inhabitants per year, with a prevalence of 0.26% in a hospital-based cohort of strokes from all causes[91].

SNEDDON SYNDROME AND CUTANEOUS/NEURAL MIMICS
Vasculopathies with livedo reticularis or racemosa plus cerebrovascular or CNS involvement
Sneddon syndrome • Idiopathic • Antiphospholipid (aPL) antibody-associated • NOTCH-3 pathway mutations • Adenosine deaminase 2 (ADA2) deficiency due to mutations in *ADA2*/*CECR1*
Primarily adult-onset
Systemic lupus erythematosus (may be associated with aPL antibodies)
Primarily pediatric-onset (selected)
Moya-moya angiopathy Alagille syndrome Susac syndrome (encephalopathy, retinal artery occlusion, hearing loss) Type I interferonopathies, including SAVI (STING-associated *v*asculopathy with onset in *i*nfancy; see Table 45.9) Majewski osteodysplastic primordial dwarfism type II Homocystinuria, hyperhomocysteinemia
Vasculopathies/vasculitis with livedo reticularis or racemosa or livedo-like macular hyperpigmentation, sometimes with peripheral neuropathy
Cryoglobulinemia, especially mixed Cutaneous predominant polyarteritis nodosa Lymphocytic thrombophilic arteritis/macular arteritis Livedoid vasculopathy Cold agglutinin disease

Table 23.5 Sneddon syndrome and cutaneous/neural mimics. CECR1, cat eye syndrome chromosome region, candidate 1; STING, *st*imulator of *in*terferon *g*enes. See references 91–98.

Pathogenesis

Sneddon syndrome is characterized by the association of persistent livedo reticularis or livedo racemosa with an increased risk of transient ischemic attacks (TIAs) and cerebrovascular accidents (CVAs). Underlying risk factors include aPL antibodies, mutations in the NOTCH3 signaling pathway, and adenosine deaminase 2 deficiency (Table 23.5)[91–95]. As in APS, vascular dysfunction of arterioles within the subcutis may drive the livedo reticularis or racemosa pattern, rather than thrombophilia.

Clinical features

Patients with Sneddon syndrome have persistent and usually widespread livedo reticularis or racemosa (see Fig. 106.2), labile systolic hypertension, and CNS disease. There is a strong female predominance (~80%) and the median age at diagnosis is ~40 years[91,92]. A history of fetal loss and Raynaud phenomenon are other recognized features[91]. Of note, the livedo reticularis or racemosa may precede neurologic symptoms by several years.

Neurologic complications tend to occur in three phases[91]: (1) headaches and vertigo (dizziness), which may precede the appearance of livedo reticularis; (2) recurrent TIAs and CVAs; and (3) cognitive decline and dementia. Seizures and chorea have also been reported, especially in aPL antibody-positive patients, as have ophthalmic complications including amaurosis fugax.

In one series of 53 patients, aPL antibody-negative patients were more likely to have CNS events (e.g. seizures, recurrent CVAs) and non-valvular cardiac defects (e.g. atrial septal defect), while aPL antibody-positive patients were more likely to have deep venous thromboses and positive ANAs (70% vs 20%)[92]; Libman–Sacks endocarditis was only seen in aPL antibody-positive patients. However, other studies have shown no differences in valvular disease, CVAs, or recurrent spontaneous abortions. One explanation is that in this series cardiovascular risk factors were much higher than in the normal population and this might have affected the rates of complications[92].

In addition to livedo reticularis or racemosa and Raynaud phenomenon, other occasionally reported cutaneous findings include acrocyanosis, angiomatosis, annular atrophic lichen planus, and peripheral gangrene[91].



Fig. 23.9 Livedo racemosa of the arms in a patient with the autosomal recessive disorder adenosine deaminase 2 deficiency. *Courtesy Edward Cowen, MD.*

Pathology

When standardized biopsies were performed (i.e. three biopsies from the center of livedo reticularis or racemosa rings that included subcutis; see Fig. 106.1), intimal proliferation with subtotal or total obliteration of the lumen of an arteriole or a small artery was found in 80% of cases. A single biopsy versus two biopsies showed the diagnostic features in 27% versus 50% of patients, respectively. These features could be observed only in a small minority of biopsies taken from the circular livedo segment[92]. Because similar biopsy findings were occasionally noted in control patients, these histologic findings are said to be supportive, but not diagnostic, of Sneddon syndrome[92].

In addition to frequently positive aPL antibodies, thrombocytopenia may be present. When the previously cited series of 53 patients was tested for thrombophilia, seven were positive – factor V Leiden mutation (3), protein S deficiency (2), protein C deficiency (1), and prothrombin mutation (1)[91,92].

Differential diagnosis

In addition to Sneddon syndrome, several other vasculopathies may present with persistent livedo reticularis/racemosa and CNS disease and whose onset is most often during infancy or childhood (see Table 23.5)[91–96]. Two disorders that may be on a continuum, cutaneous polyarteritis nodosa (cPAN) and lymphocytic thrombophilic arteritis (LTA), can have peripheral neuropathy plus livedo reticularis/racemosa (see Fig. 106.3)[97,98]. The latter may become hyperpigmented, but CNS involvement is not seen in either entity. Pediatric-onset livedo racemosa and stroke with or without PAN-like findings should prompt consideration of adenosine deaminase 2 deficiency (Fig. 23.9). While screening for the presence of aPL antibodies is important when evaluating patients with signs and symptoms of Sneddon syndrome, patients with cPAN may have anti-phosphatidylserine–prothrombin complex antibodies (see Ch. 24), which could lead to confusion with aPL-related Sneddon syndrome[88].

Treatment

Antiplatelet and antithrombotic agents, aspirin or clopidogrel and warfarin, respectively, are used for secondary stroke prophylaxis[91]. Patients with aPL antibodies are treated as those with primary APS (see above). In aPL antibody-negative patients, antiplatelet agents may be preferable due to a lower risk of bleeding and lack of clear evidence favoring antithrombotic agents. There are case reports of healing of ulcers following intravenous infusion of alprostadil, a synthetic analogue of prostaglandin E1.

Livedoid Vasculopathy

Synonyms: ■ Atrophie blanche ■ Livedo reticularis with summer ulceration ■ Segmental hyalinizing vasculitis ■ Livedoid vasculitis

Key features

- Favors the distal lower extremities, especially the ankles
- Female predominance
- Painful, punched-out ulcers
- White, round, or stellate scars with peripheral telangiectasias
- Livedo reticularis or racemosa in some patients

Introduction

Livedoid vasculopathy is an unusual disorder characterized by small, punctate, painful ulcers that sometimes cluster, are usually on the lower extremities near the ankles, and may be surrounded by reticulated erythema or hemorrhage[99,100]. Resolution classically results in small atrophic white macules with surrounding telangiectasias, referred to as atrophie blanche (see Fig. 105.7). Unfortunately, this term has also been used to describe similar lesions that can arise in the setting of venous insufficiency but are not preceded by small painful ulcerations, leading to variable analyses of etiologies and treatment outcomes.

Epidemiology

Based upon four retrospective series from different countries with a total of just over 200 patients[99–102], the ratio of women : men ranged from 2 : 1 to 5.2 : 1. Although most patients were middle-aged at disease onset, there was a wide range (6 to 67 years)[100]. In one study, flares were reported during the spring and summer in ~80% of patients, supporting previous reports of seasonal variation[102].

Pathogenesis

The precise pathogenesis of livedoid vasculopathy is not known, but it is thought to involve an alteration in endothelial function and/or in coagulation with formation of fibrin thrombi focally within superficial dermal blood vessels. A number of prothrombotic factors have been associated with this syndrome, including hyperhomocysteinemia, elevated lipoprotein (a), aPL antibodies, protein C and S abnormalities, factor V Leiden and prothrombin mutations, antithrombin III deficiency, sticky platelet syndrome, and excess plasminogen activator inhibitor (PAI-1; see Table 105.9)[99–102]. Because data from age-matched controls are frequently lacking and genetic polymorphisms for some of these thrombotic factors are relatively common (e.g. PAI-1), determination of their pathogenic role can be challenging.

Clinical features

Painful, persistent, and often punched-out ulcerations on the legs, especially over the malleoli and in women, should suggest this diagnosis (Fig. 23.10A), as should atrophic white scars with peripheral telangiectasias. Some patients, particularly those with prominent livedo surrounding these ulcers, may develop retiform or stellate purpura or ulcer extension.

In one study, peripheral neuropathy was documented in 10 of 20 evaluated patients, a finding which had been previously noted in the literature[100]. In all four retrospective series from different countries, a spectrum of associated prothrombotic laboratory findings were detected but they neither affected response to treatment nor predicted development of thrombotic complications such as venous thrombosis[99–102]. Of note, even in patients with DVTs/PE, routine screening for coagulation disorders may not be beneficial in directing therapy or predicting risk of recurrence[103].

Pathology

The characteristic histologic findings in livedoid vasculopathy are mild perivascular lymphocytic infiltrates and extravasated red cells surrounding superficial dermal vessels with hyalinized walls and luminal fibrin deposition[99–102] (Fig. 23.10B). Immunofluorescence findings are frequently positive (40%–100%), most often C3 and IgM deposits in blood vessel walls[102]. In a recent study of 62 patients, 95% had positive findings, usually for a combination of immunoreactants (C3 and IgM > IgA > IgG)[102a].

Differential diagnosis

Table 23.6 outlines other disorders that can present with painful, punched-out, vasculopathic ulcers, sometimes with surrounding livedo reticularis[104–110]. Porcelain white macules in the setting of venous insufficiency, but without antecedent punctate ulcerations, should be considered an unrelated entity.



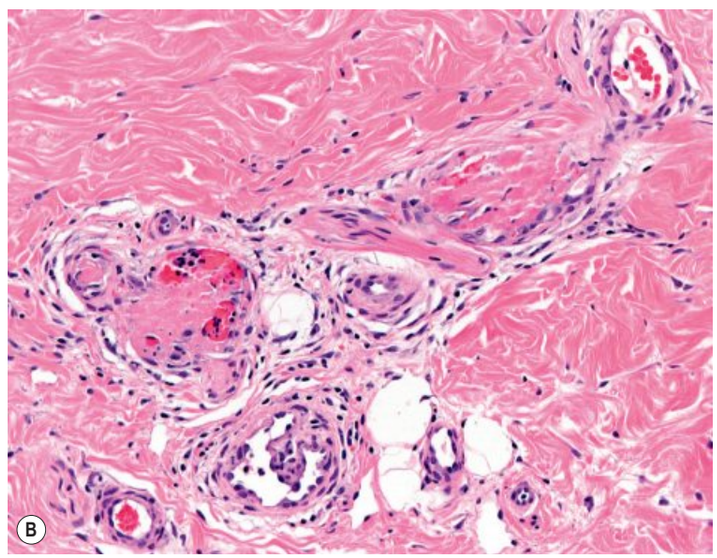


Fig. 23.10 Livedoid vasculopathy. A Punched-out ulcers are seen on the ankle as well as multiple stellate purpuric macules. **B** Thrombi are seen within two dermal blood vessels in addition to a mild perivascular lymphocytic infiltrate. *B, Courtesy Lorenzo Cerroni, MD.*

Treatment

In a systematic review of reported treatments for livedoid vasculopathy (n = 339 patients)[111], those best studied with good clinical outcomes were anticoagulants (e.g. DOACs, heparin)[99–101], pentoxifylline, antiplatelet agents (e.g. aspirin), anabolic steroids, and IVIg. However, there was insufficient evidence to recommend any one particular therapy[111]. Additional options include immunosuppressives (e.g. prednisone) and hyperbaric oxygen therapy. Given the risks of anticoagulation[100], some clinicians begin with the other treatments outlined above, alone or in combination, and then move to anticoagulants if disease control is not achieved. There are also case reports of the successful use of JAK inhibitors (e.g. tofacitinib) for refractory disease.

Hydroxyurea-Associated Vasculopathy

Patients with myeloproliferative disease and sickle cell disease can develop occlusion-related painful ulcerations, but hydroxyurea use in these disorders can occasionally increase the risk of painful ulcer development, usually in the perimalleolar region (see Fig. 105.20F)[112,113].

DISORDERS THAT MAY MIMIC LIVEDOID VASCULOPATHY
Antiphospholipid antibody syndrome
Atrophie blanche-like cutaneous polyarteritis nodosa
Autoimmune connective tissue diseases • SLE and rheumatoid arthritis (sometimes associated antiphospholipid antibodies) • Dermatomyositis vasculopathy, especially MDA-5 antibody-associated • Punctate ischemic ulcerations of systemic sclerosis
Degos disease
Hydroxyurea–associated ulcers
IgA-predominant cutaneous vasculitis
Interferonopathies (see Table 45.9)
Hypertensive (Martorell) ulcers
Non-infected ulcers of sickle cell disease

Table 23.6 Disorders that may mimic livedoid vasculopathy. These entities can present with painful, punched-out, ulcers and those in *italics* are discussed in the chapter. Porcelain white macules in the setting of venous insufficiency, but without antecedent punctate ulcerations, are an unrelated entity. SLE, systemic lupus erythematosus. *From references 104–110.*



Fig. 23.11 Degos disease and antiphospholipid antibody syndrome – similar cutaneous lesions. Multiple papules and small plaques with porcelain white centers surrounded by an erythematous rim with telangiectasias in a patient with malignant atrophic papulosis. Similar-appearing lesion in a lupus patient with antiphospholipid antibody syndrome (inset). *Courtesy Edward Cowen, MD.*

Ulcers may resemble those of livedoid vasculopathy or they can be larger and more shallow[114]. The pathogenesis of these ulcers is unclear, but healing typically requires discontinuing the hydroxyurea. There is some evidence that ulceration is dependent on duration of treatment (≥1 year), daily dose (0.5–1 g), and cumulative dose (≥510 g)[53,113]. Histologically, vascular findings range from leukocytoclastic vasculitis to sometimes thrombotic occlusion[115]. Fibrosis, lymphocytic infiltration, and/or thickening of vessel walls may also be seen[53,112].

Interferon-Induced Vasculopathy/Cutaneous Necrosis

Atrophie blanche-like ulcers have been reported during interferon-α adjuvant therapy for melanoma[116]. In addition, a number of cutaneous findings have been reported at interferon-β injection sites, including microvascular occlusion and evidence of cutaneous necrosis or necrotic panniculitis clinically (see Fig. 128.1)[117,118]. While some blood vessels may have prominent perivascular inflammation, thromboses are typically noted in the deep dermis or fat, often without inflammation. Systemic thrombotic microangiopathy has also been reported[119].

Benign and Malignant Atrophic Papulosis

Synonyms: ■ Degos disease ■ Kohlmeier–Degos disease

Introduction

Described by Kohlmeier in 1941 and Degos in 1942 as malignant atrophic papulosis, this disorder typically occurs between the second and fourth decades of life and has a slight female predominance. In some patients, it may be familial.

Pathogenesis

There are two forms of atrophic papulosis – benign (skin-limited; BAP) and malignant (systemic; MAP). Risk factors or triggers of this small vessel vasculopathy include genetic predisposition (especially with the benign form), coagulation disorders, viral infections, and autoimmunity[118–121]. In addition to lymphocytic vasculitis and endothelial dysfunction, there is some evidence to support a role for dysregulated interferon-α and the C5–9 membrane attack complex in the underlying endothelial injury[122].

Clinical features

Atrophic papulosis is a rare vasculopathy that may affect only the skin (benign) versus other organs (malignant). The latter occurs more often, with the gastrointestinal tract (~70%) and CNS (~45%) the most commonly involved sites, and less often the lungs or eyes. In a recent systematic review (n = 347 patients), the mean age of onset was 34 years, 64% had systemic findings, and the mortality rate was 57% in the "malignant" form[118].

Cutaneous lesions are usually asymptomatic and begin as scattered crops of small erythematous papules (2–10 mm) on the trunk (~60%) or extremities (~60%)[118–120]. These evolve over 2 to 4 weeks, with the development of a central depression and ultimately a porcelain white scar (Fig. 23.11), often with a rim of telangiectasias and an appearance similar to atrophie blanche. Cutaneous findings typically precede systemic manifestations by 2 years, but this may range from 0 to 28 years[118]. Gastrointestinal lesions can lead to bowel perforation, and, along with CNS manifestations (e.g. CVAs), are the leading causes of death[118,120].

Pathology

Skin lesions are characterized histologically by a wedge-shaped area of ischemic dermis with a sparse perivascular lymphohistiocytic infiltrate at the edge of the ischemic area and an atrophic but slightly hyperkeratotic overlying epidermis. Edema and mucin deposition are found within the ischemic dermis, and in later stages sclerosis may be observed. The base of the lesion shows vascular damage with thrombosis, but examination of deeper tissue sections may be required for detection[123,124].

Differential diagnosis

It is important to consider other systemic diseases, especially SLE, dermatomyositis and APS, as possible causes of malignant atrophic papulosis-like lesions (Fig. 23.11, *inset*)[118,121]. Localized lesions can occur when due to interferon-α injections.

Treatment

Some studies recommend semi-annual evaluations for the first 7 years after diagnosis and then annually[120]. This is based on the observation that the likelihood of the benign variant increases to >95% after 7 years of skin-limited disease[120].

In the systematic review, surgery (especially bowel resection) was the most commonly reported intervention for MAP, but the therapeutic goal should be to prevent serious events requiring surgery[118]. Antiplatelet monotherapy was the most common pharmacologic treatment for BAP and MAP, with complete response rates of 42% and 20%, respectively. These results support an underlying coagulopathy. When antiplatelet agents were combined with other therapies, the complete response rate in BAP was similar to that achieved with antiplatelet monotherapy while the complete response rate in MAP was halved (9%). This suggests that antiplatelet monotherapy was more often prescribed for milder cases, whereas patients with more aggressive disease received multiple therapies that were unable to achieve complete resolution.

The C5 inhibitor eculizumab, which blocks vascular C5b-9 deposition, has also shown benefit in the treatment of MAP[118]. Complete and partial resolution of both variants has been reported with corticosteroids and other immunosuppressants, antimalarial drugs, and IVIg.

Levamisole-Adulterated Cocaine-Induced Vasculopathy/Vasculitis

Levamisole, an immunomodulatory and antiparasitic drug, is a frequent adulterant of illicit cocaine and it can induce a serious vasculopathy/vasculitis (see Ch. 89). In the US, levamisole is only approved for veterinary use.

Clinical features

A recent systematic review (n = 192 patients) found women to be more frequently affected (2 : 1), even though men are more likely to use the drug, suggesting a sex-based predisposition[124]. Median age at presentation was 44 years. The skin is frequently involved (95% of patients), typically with retiform purpura and necrotic lesions on the face, ears, and lower extremities more often than on the upper extremities or trunk (see Fig. 89.13)[124,125]. Approximately 20%–30% of patients have fever and arthralgias, with myalgias, acute renal failure, and pulmonary involvement in ~10% of patients.

Pathology and laboratory findings

Laboratory findings include leukopenia and/or neutropenia (40%–50% of patients), agranulocytosis (10%), ANCAs (95%), and both anti-myeloperoxidase and anti-proteinase antibodies in half of those with ANCAs; <5% of patients have only cANCA positivity. In addition, aPL antibodies are present in ~70% of patients and an ANA titer >1 : 80 in ~50%. Autoantibodies resolve after discontinuation of levamisole.

Histologically, both leukocytoclastic vasculitis (~50%) and thrombotic vasculopathy (~40%) can be seen. Sometimes there is an angiocentric neutrophil-rich infiltrate in the superficial and deep plexus[53]. Variation in the age of the thrombi, ranging from a fibrinous plug to organized fibrotic thrombi with focal recanalization, may be a clue to recurrent use of levamisole-adulterated cocaine. Direct immunofluorescence may show immune complexes and complement deposition in the vessel walls[53].

Differential diagnosis

The lesions of levamisole-induced vasculopathy tend to be more widespread than the acral lesions of cryoprotein-induced disorders. In the setting of sepsis and hypotension, purpura fulminans is a more likely diagnosis. Given the high incidence of ANCAs, aPL antibodies and ANAs, in concert with cytopenias, ANCA-associated vasculitides, systemic lupus, and APS need to be considered, especially in the presence of renal or pulmonary involvement. Since cANCA positivity is rare in this syndrome[124], its singular presence requires strong consideration of a primary ANCA-associated vasculitis. Of note, this syndrome is distinct from cocaine-induced vasculitis.

Treatment

In a review of 151 patients, 28 improved with drug cessation alone while 85 improved following additional interventions, most often prednisone at a median dose of 60 mg/day. Less often, cyclophosphamide, rituximab, methotrexate, thalidomide, and plasmapheresis are employed. Occasionally, surgery is required to remove necrotic tissue[124].

Calciphylaxis

Synonyms: ■ Calcific arteriolopathy ■ Calcific uremic arteriolopathy

The cutaneous manifestations of calciphylaxis are reviewed in Chapters 50 and 106. This section focuses on the mechanisms that underlie the associated thrombotic vasculopathy. While calcification in vessels or peri-eccrine areas within the subcutis is considered the gold standard for the diagnosis of cutaneous calciphylaxis, identical calcification has been demonstrated in normal skin in ~40% of patients with end-stage and chronic renal disease without calciphylaxis as well as in 18% of a small sample of control patients without renal disease undergoing elective surgery[126].

In one study, patients whose skin biopsies fulfilled the histologic criteria for calciphylaxis also had areas of thrombosis within vessels without evidence of calcification[127]. This raised the question of whether calcification is a driver of occlusion, an incidental factor, or a consequence of an underlying vascular dysfunction distinct from calcification (subcutaneous thrombotic vasculopathy). More recently, at least half of patients with uremic and non-uremic calciphylaxis were found to have lupus anticoagulant, offering an explanation for vascular dysfunction[128].

The elevated calcium × phosphate product, association of calciphylaxis with administration of vitamin D, and calciphylaxis in individuals without chronic kidney disease treated with teriparatide (PTH agonist for osteoporosis), suggests that calcium plays a triggering or synergistic role in this disease[129]. Vitamin K is thought, at least in part, to play a role in the pathogenesis of the vascular calcification. There are two forms of vitamin K: (1) K1 (phylloquinone), stored primarily in the liver, is an essential cofactor for synthesis of the procoagulant factors II, VII, IX, and X as well as the anticoagulant proteins C and S; and (2) K2 (metaquinone), stored primarily in vessels and bones, is essential for carboxylation of multiple inhibitors of vascular calcification, especially Gas6 (growth arrest-specific 6) and MGP (matrix Gla) proteins[130]. Chronic renal disease leads to depletion of vascular stores of vitamin K2, resulting in accelerated atherogenesis with arterial calcification and presumably increases the risk of cutaneous vessel calcification[130]. This may also explain why warfarin is associated with a greater risk of calciphylaxis, as warfarin or other vitamin K antagonists further interfere with impaired K2-dependent carboxylation of Gas6 and matrix Gla proteins.

DISORDERS OF CELL-RELATED VASCULAR OCCLUSION

Red Blood Cell (RBC) Vascular Occlusion: Sickle Cell Disease (SCD)

Introduction and pathogenesis

Cell-free hemoglobin, arginase-1, and RBC metabolites interfere with nitric oxide availability and contribute to vasculopathy in SCD[131]. Slow flow results in local hypoxemia, triggering further sickling, providing an explanation for lower extremity ulcerations[131]. In addition, cell-free hemoglobin and heme serve as danger signals, prime the innate immune system, and trigger a proinflammatory endothelial environment[131]. Adherent neutrophils often undergo NETosis which increases RBC entrapment as do activated platelets[131–133]. Damaged RBC-derived microparticles, which are found in large numbers in patients with SCD, also trigger a proinflammatory phenotype on endothelial cells[134]. Lastly, coagulation activation may play a role as inhibitors of thrombin or factor Xa improve microvascular stasis in a mouse model[135,136].

Clinical features

In SCD, the overall incidence of leg ulcers is 8%–10% and they most frequently develop during the second decade of life[137]. The incidence does vary widely by geographic location, from 1% in Saudi Arabia to 25% in the US to up to 75% in Jamaica. Ulcers may be triggered by trauma or edema, are frequently punched-out in appearance, and usually measure <10 cm^2 (see Fig. 105.20C)[137].

Treatment

Hydroxyurea reduces hemolysis and lowers exposure to phosphatidylserines on damaged RBC-derived microparticles, abolishing their proinflammatory properties[134]. There is a reduction in vaso-occlusive crises (VOCs) and presumably the risk of ulceration, but as noted previously hydroxyurea can independently cause ulcerations[137]. Additional potential therapies include L-glutamine (reduces oxidative stress), voxelotor (stabilizes oxygenated hemoglobin S)[133], and crizanlizumab (reduces VOCs via binding to P-selectin on endothelial cells and platelets)[133].

Allogeneic hematopoietic stem cell transplant can be effective in treating SCD, but only 15% of affected individuals have matched donors[133]. In the future, gene therapy may be an option. For example,

LentiGlobin™ for SCD (bb111) consists of a lentiviral vector with a modified β-globin gene that encodes an adult hemoglobin which sterically inhibits polymerization of hemoglobin S and can lead to prevention of severe VOCs[138]. Clinical trials are also underway utilizing CRISPR technology (see Fig. 3.13).

Red Blood Cell (RBC) Vascular Occlusion/Ischemia: Thalassemia

Approximately half of patients with severe β-thalassemia, particularly those in Southeast Asia, have hemoglobin E (HbE). Leg ulcers occur in ~20% patients with HbE β-thalassemia[139]. Ulcers are usually located on the medial or lateral malleoli and often follow minor trauma. They are thought to be due to tissue hypoxia, tend to become chronic, and are severely painful. RBC transfusions, zinc supplementation, and hydroxyurea, either alone or in combination with recombinant human erythropoietin, can accelerate healing. Hyperbaric oxygen and platelet-rich plasma may lead to improvement[139].

Red Blood Cell (RBC) Vascular Occlusion/ Ischemia: Other

Occasionally, other severe hemolytic anemias such as hereditary spherocytosis have been associated with leg ulcers[140]. Splenectomy, which reduces hemolysis and results in normalization of the reticulocyte count, may lead to ulcer resolution.

Intravascular Cellular Occlusion

Although chronic lymphocytic leukemia is the most common cause of a marked elevation of circulating atypical leukocytes, these cells are fragile and do not lead to vascular occlusion syndromes. Reduced perfusion of various organ systems may accompany high blast counts, nearly always of myelogenous origin. Cutaneous bland leukemic occlusion syndromes have not been reported, although repeated arterial occlusion from myeloblasts has been described (e.g. retinal artery, cerebral arteries)[141]. Leukemic vasculitis in the skin has been described[142], as has a case of T cell prolymphocytic leukemia with a cutaneous presentation that mimicked livedoid vasculopathy[143].

Intravascular lymphoma (B cell > T cell) is a very rare syndrome which is frequently diagnosed *post mortem*, usually because of vague clinical findings. CNS involvement is often the most severe clinical manifestation. Skin lesions are commonly observed (40% of patients) but nonspecific and include erythematous, sometimes painful plaques or nodules and macular or telangiectatic lesions[144]. The lower extremities are the most common location (often in association with edema), followed by the trunk. Occasionally, it may present as retiform purpura (Fig. 23.12). The histopathologic finding of intraluminal occlusion by atypical lymphocytes can be missed on initial interpretation (see Fig. 119.14).



Fig. 23.12 Intravascular B cell lymphoma. The clinical presentation in this patient was retiform purpura and necrosis with livedo reticularis. *Courtesy Lucinda Buescher, MD.*

Cutaneous intralymphatic histiocytosis is characterized by dilated lymphatic vessels filled with histiocytes, leading to overlying erythematous patches without purpura (see Fig. 121.6). This entity was previously referred to as cutaneous intravascular histiocytosis, until it was recognized that only lymphatic vessels are involved. It is often associated with chronic inflammation, rheumatoid arthritis, joint replacements, or metal implants[145].

DISORDERS OF OCCLUSION, MISCELLANEOUS

Loxosceles Spider Bites

Clinical and histologic features as well pathogenesis and treatment options are discussed in Chapter 85. At the site of the bite, edema, erythema, and a painful reddish blister develop that is surrounded by a cyanotic bluish discoloration with ischemic borders and then intensely erythematous halo. This results in a characteristic blue–white–red concentric pattern[146]. The cyanotic area can darken and enlarge over a few days, sometimes becoming geographic or retiform in appearance with central necrosis.

Systemic symptoms include fever, nausea, headache, shivering, weakness, myalgias, and arthralgias. Rarely, patients can develop hemolytic anemia, thrombocytopenia, disseminated intravascular coagulation, hemoglobinuria, myoglobinuria, acute renal failure, and gangrene[146].

Hematoma-Associated Retiform Purpura

Retiform purpura with necrosis, best explained by compression of subcutaneous arterioles by large trauma-induced hematomas, may rarely occur, including in patients with hemophilia[147].

SARS-CoV-2 Purpuric Syndromes

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with a diminished type I interferon response during its early phase[148,149]. Resultant viral replication contributes significantly to septal capillary compromise within the lung as well as extrapulmonary pseudovirion dissemination with extrapulmonary vascular sequelae[148]. Spike glycoprotein and other viral capsid proteins localize to microvasculature expressing angiotensin-converting enzyme 2 (ACE2), the receptor utilized by spike glycoprotein[148]. The primary localizations of viral capsid/spike protein and its ACE2 receptor are the septal capillaries of the lung, deeper dermal and subcutaneous capillaries and venules of both diseased and normal-appearing skin, and the microvessels of the brain[148]. There is little evidence to support viral proliferation in tissues beyond the nasal epithelium and lung; evidence instead suggests that pseudovirions or spike proteins that disseminate from the lung and localize to sites of ACE2 receptors are important in disease expression. Differently modulated immune responses appear to correlate with observed patterns of vascular inflammation and coagulopathy.

Pernio/chilblains-like disease ("COVID toes")

Individuals with this disorder, more often children, are usually antibody- and PCR-negative for SARS-CoV-2, leading many authors to question whether there is a true association. Patients typically present with tender or pruritic red–purple papules on the toes > fingers which may blister or ulcerate[148,149]. Although the overall histologic features are similar to those of idiopathic pernio (see Ch. 88), a distinguishing feature is the presence of occlusion of some blood vessels within the reticular dermis. By immunostaining, there is increased MxA expression in the epidermis, eccrine coils, endothelia, T cells, and plasmacytoid dendritic cells, pointing to a robust type I interferon response[148,149].

One theory advanced in support of a true association is that a very brisk innate immune type I interferon response clears the virus quickly, without enough viral proliferation to trigger a humoral antibody response to SARS-CoV-2. This brisk response still allows vascular dissemination of pseudovirions (but not intact virus) which bind to ACE2 receptors, leading to a second wave of local type I interferon responses beyond the window of viral detection. However, this explanation is not universally accepted.

The relationship between pernio and interferon dysregulation is supported by the clinical findings in two inherited interferonopathies – familial chilblain lupus and Aicardi–Goutières syndrome (see Table 45.7)[149]. The theory that spike protein or RNA segments in

the absence of intact virions can trigger a type I interferon response is supported by reports of pernio-like lesions following SARS-CoV-2 vaccination[149]. A high density of eccrine glands on hands and feet might partially explain the favored location for this reaction.

Immune complex vasculitis and antiphospholipid antibodies

Skin-limited leukocytoclastic vasculitis (LCV), including one with mixed cryoglobulinemia, has been observed in patients with mild to moderately severe SARS-CoV-2 infection[148]. SARS-CoV-2-associated IgA LCV and IgA nephropathy have also been reported, as have IgA LCV and nephropathy following SARS-CoV-2 vaccination[150–152]. In skin-limited idiopathic IgA vasculitis, it is known that hypoglycosylated IgA becomes a target antigen for formation of immune complexes and for binding to renal mesangium[153]. Whether this is true of SARS-CoV-2-associated IgA vasculitis is not yet known.

Antiphospholipid antibodies have also been associated with SARS-CoV-2 infection. However, data suggest that most aPL antibodies are transient with many, if not all, instances likely representing a consequence of vascular injury rather than its cause[154,155].

Retiform thrombotic purpura

A hypercoagulable state and organ failure, particularly progressive acute respiratory distress syndrome (ARDS) and acute renal insufficiency, qualify as critical SARS-CoV-2 infection. In both affected and normal skin of patients with critical infections, there is evidence of complement activation in the ACE2-positive microvascular beds that have bound viral capsid protein (but not active viral replication)[148]. The mannan-binding lectin (MBL) pathway has been implicated as the driver of vascular damage that leads to thrombosis and coagulopathy, with possible augmentation by the alternate complement activation pathway. C5b-9 deposition and vascular injury are similar to that seen in CM-HUS. The MBL pathway is also implicated as an inducer of the overproduction of various cytokines (e.g. tumor necrosis factor, interleukin-6) by activated endothelium.

Histologically, there is a pauci-inflammatory thrombogenic vasculopathy affecting dermal capillaries and venules, and in half of the patients with retiform purpura, the arterioles and small arteries are also involved. This finding is associated with a higher risk of stroke and death. Degenerative endothelial cell changes with sloughing is more conspicuous in the deeper dermis and subcutaneous fat, along with secondary ischemic necrosis of eccrine coils[148].

SARS-CoV-2-related systemic coagulopathy

Malignancy-associated DIC frequently leads to bleeding with significant fibrinolysis while sepsis tends to suppress fibrinolysis and favor thrombosis, termed sepsis-induced coagulopathy (SIC)[156,157]. The coagulopathy of SARS-CoV-2 infection resembles SIC, but because it manifests in a distinct manner, the term COVID-19-associated coagulopathy (CAC) is often employed[156–158]. For example, a decreased platelet count and prolonged PT, hallmarks of SIC, are uncommon in the early phase of CAC. Symmetrical peripheral gangrene can occur due to microthromboses, and acute hepatic dysfunction (shock liver) appears to predispose to this complication[157].

Systemic thromboembolic events include PE, DVT, ischemic stroke, myocardial infarction, and systemic arterial embolism[159]. SARS-CoV-2 infection-associated DIC is an unusual but potentially lethal complication, reported in ~2% of hospitalized patients.

Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)

Synonym: ■ Variant of thrombosis with thrombocytopenia syndrome (TTS)

Thrombosis with thrombocytopenia syndrome (TTS) has been used synonymously with vaccine-induced immune thrombotic thrombocytopenia, but TTS is more broadly applied to post-vaccination syndromes related to differing mechanisms[160,161]. VITT is specifically due to anti-platelet factor 4 (anti-PF4) antibodies that are induced primarily by adenoviral vector vaccines and, very rarely, SARS-CoV-2 mRNA vaccines. VITT strongly resembles spontaneous "heparin-induced" thrombocytopenia or classic HIT (see above). Unlike classic HIT, spontaneous HIT results from an anti-PF4 antibody that does not require co-binding to a long chain polyanion such as heparin and occurs in the absence of exposure to heparin.

The rate of this complication from SARS-CoV-2 viral vector vaccines is 3.83 per million doses versus 0.00855 per million with the mRNA vaccines, a 450-fold difference in frequency. The possibility exists that the rate in the mRNA vaccine group represents the background incidence of spontaneous HIT in the US. Compared to HIT, VITT appears to target a different antigenic site on PF4, which is shared with neutrophil activating peptide-2 (NAP2). NAP2 is one of the most abundant chemokines released from activated platelets and is known to be involved in the initiation and propagation of the immunothrombotic response[162].

Clinical features include cerebral venous (sinus) thrombosis (55%), PE (40%), extremity DVT (40%), and abdominal vein thrombosis (30%), with one sixth of the patients developing arterial thrombosis, mirroring the frequency seen in spontaneous HIT[160,161]. Characteristic laboratory findings include a moderate-to-severe thrombocytopenia and evidence of DIC with D-dimer elevation and hypofibrinogenemia.

Additional figures available in our eBook (see inside front cover for access code).

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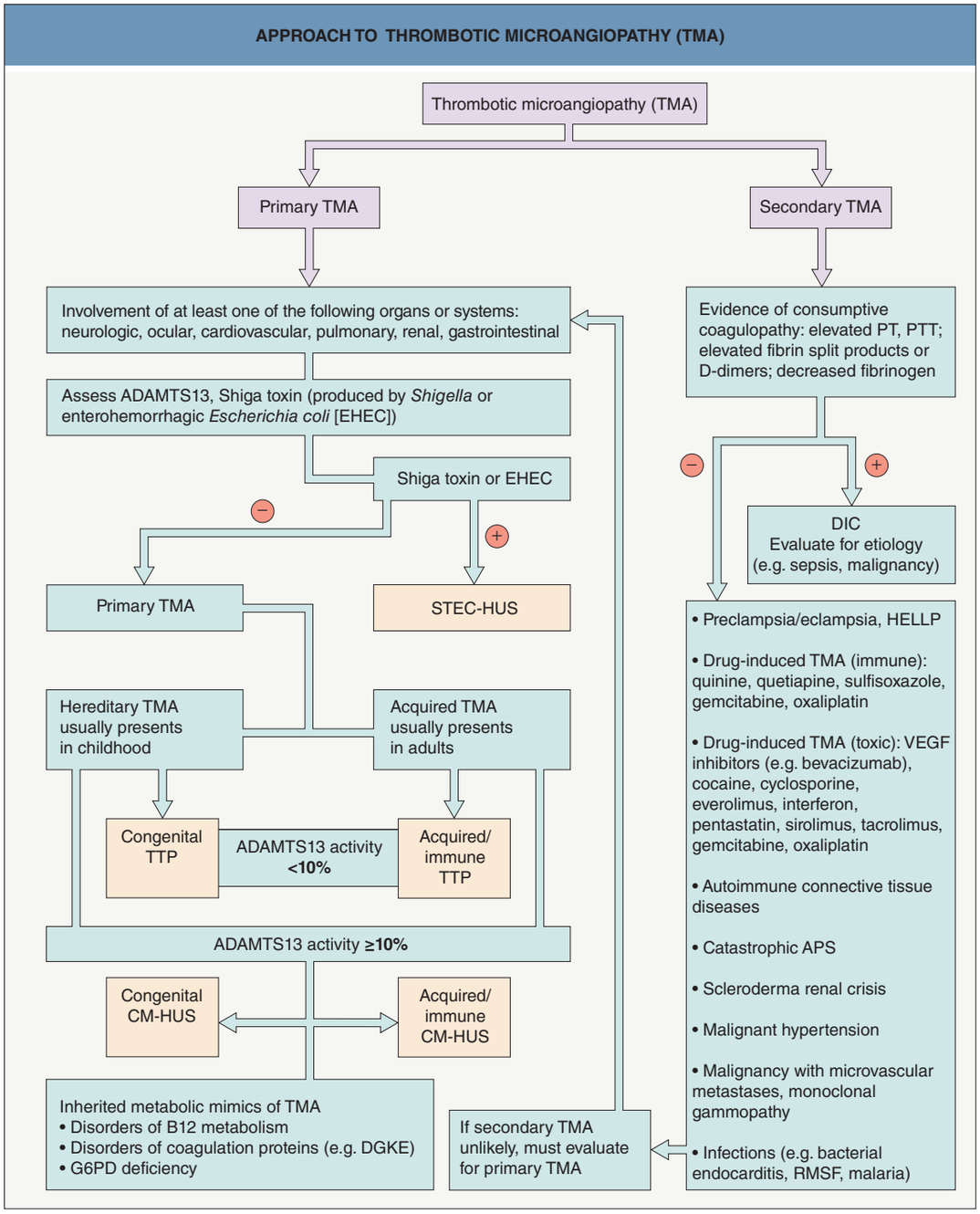
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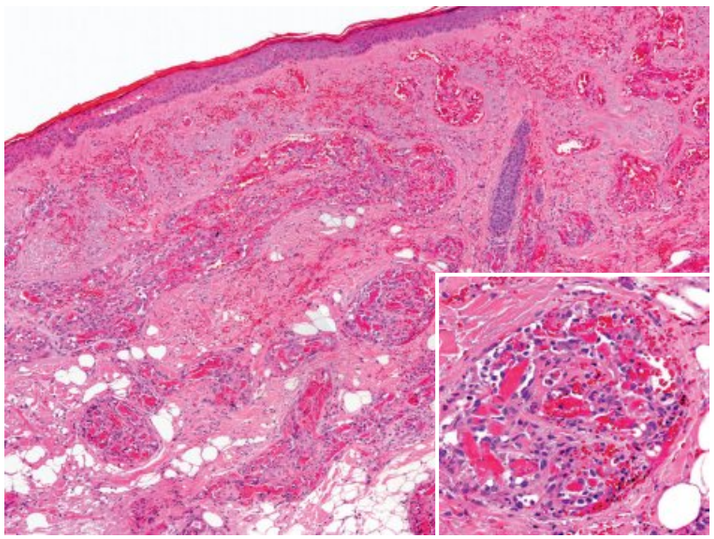
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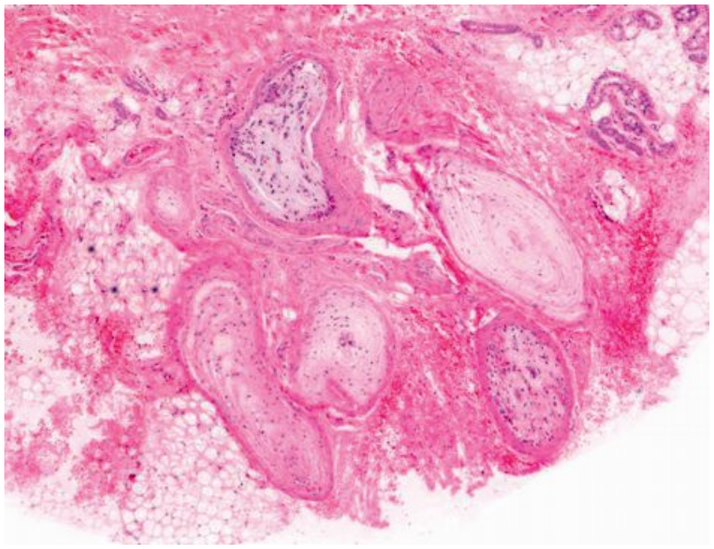
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eFig. 23.1 Thrombotic microangiopathies (TMAs) – primary and secondary. TMA is characterized by microangiopathic hemolytic anemia (red blood cell fragmentation with schistocyte formation) and thrombocytopenia. CM-HUS is also referred to as atypical HUS and is due to increased complement activation or reduced complement regulation secondary to deficiencies or dysfunction of alternate complement pathway inhibitory molecules or dysregulation resulting from altered function of other molecules such as thrombomodulin. APS, antiphospholipid antibody syndrome; CM-HUS, complement-mediated hemolytic uremic syndrome; DGKE, diacylglycerol kinase-epsilon; DIC, disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; HELLP syndrome of pregnancy (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelet count); PT, prothrombin time; PTT, partial thromboplastin time; RMSF, Rocky Mountain spotted fever; STEC-HUS, Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; VEGF, vascular endothelial growth factor.



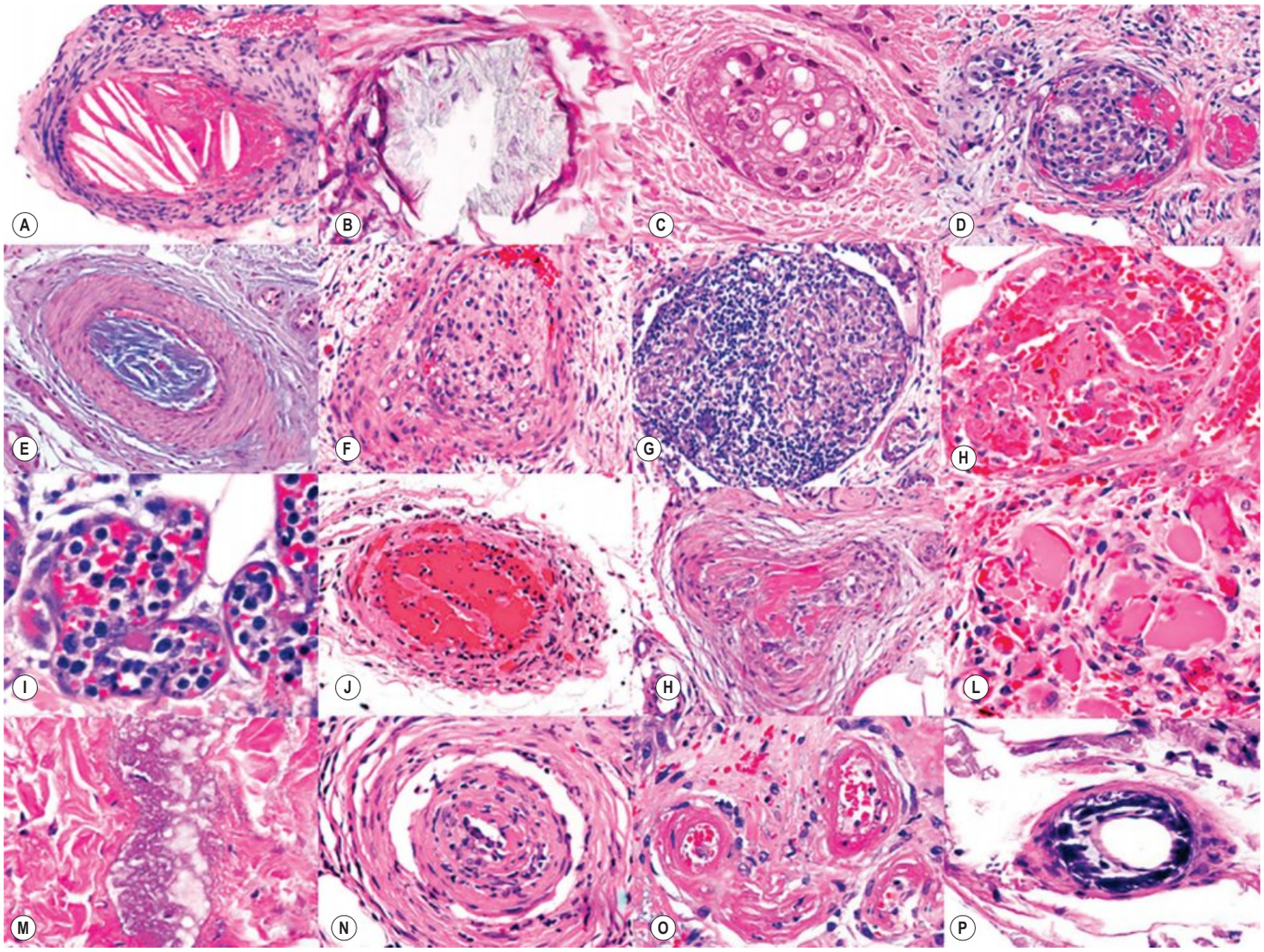
eFig. 23.2 Cold agglutinin disease – histopathologic findings. Within the entire thickness of the dermis, there are dilated blood vessels with an intravascular proliferation of endothelial cells. Deposits of cold agglutinins are seen as intravascular amorphous eosinophilic material admixed with many red blood cells (inset). There is also hemorrhage within the dermis. *Courtesy Luis Requena, MD.*



eFig. 23.3 Cutaneous emboli from an atrial myxoma. An arteriole within the deeper dermis has its lumen occluded by mucinous material. *Courtesy Luis Requena, MD.*



eFig. 23.4 IgA vasculitis mimicking livedoid vasculopathy. This middle-aged women had a two-year history of small painful ulcers on her arms that healed with macular atrophy; biopsies two years apart showed classic findings of livedoid vasculopathy. Subsequently, she developed these lesions with a retiform pattern of ulceration and new-onset progressive sensory neuropathy and microscopic hematuria. Histologically, leukocytoclastic vasculitis with prominent IgA deposition was seen and low-dose dapsone led to clinical improvement. Hematuria was diagnosed as IgA mesangial glomerulopathy.



eFig. 23.5 Histopathology of various cutaneous emboli, thrombi, and vasculopathies. A Cholesterol embolus. **B** Oxalate embolus. **C** Metastatic inflammatory breast carcinoma. **D** Metastastic telangiectatic breast carcinoma. **E** Atrial myxoma embolus. **F** Embolus of an intracardiac angiosarcoma. **G** Intralymphatic histiocytosis. **H** Cold agglutinin syndrome. **I** Intravascular lymphoma. **J** Heparin-induced skin necrosis. **K** Essential thrombocytosis **L** Monoclonal cryoglobulinemia. **M** Ecthyma gangrenosum. **N** Sneddon syndrome. **O** Livedoid vasculopathy (atrophie blanche). **P** Cutaneous calciphylaxis. *Courtesy Luis Requena, MD*.

24 Cutaneous Vasculitis

Robert G. Micheletti

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Key features

- The morphology of cutaneous lesions of vasculitis correlates with the size of the affected blood vessels, facilitating disease classification and diagnosis
- Cutaneous vasculitis can be a manifestation of a systemic vasculitis, a skin-limited or skin-predominant variant of a systemic vasculitis, or single-organ vasculitis with no detectable systemic involvement
- The diagnosis of cutaneous vasculitis requires careful clinicopathologic correlation and differentiation from mimickers, assessment for internal organ involvement and underlying disorders, and evaluation of features that point to a particular vasculitis subtype

INTRODUCTION

Vasculitis is defined as inflammation and destruction of blood vessels with resultant downstream ischemic tissue damage. Any organ system can be affected, and clinical manifestations correlate with the size of affected blood vessels, such that disorders are generally classified according to vessel size. Cutaneous vasculitis may represent: (1) a manifestation of a systemic vasculitis; (2) a skin-limited or skin-predominant variant of a systemic vasculitis; or (3) a single-organ vasculitis with no detectable systemic involvement[1].

Vasculitis can affect small, medium-sized, or large vessels of the arterial and/or venous systems (Table 24.1). Small vessels include arterioles, capillaries, and postcapillary venules, which are found in the superficial and mid dermis of the skin. Medium-sized vessels refer to the small arteries and veins that reside within the deep dermis or subcutis. Large vessels include the aorta and named arteries. Cutaneous involvement occurs almost exclusively with vasculitis of small and medium-sized vessels; therefore, the large vessel vasculitides are discussed only briefly or mentioned in Table 24.1.

Terminology

In this chapter, "*cutaneous vasculitis*" generally refers to vasculitis with any underlying etiology and affecting any sized vessel in which the clinical manifestations include, but are not necessarily limited to, the skin. *Cutaneous small vessel vasculitis* (CSVV), on the other hand, is a term defined as a single-organ, skin-limited type of vasculitis involving small blood vessels. *Leukocytoclastic vasculitis* (LCV) is a histopathologic term for vasculitis involving the small postcapillary venules of the dermis with neutrophilic inflammation. Patients whose cutaneous lesions have histologic findings of LCV may have skin-limited vasculitis, but this is not always the case; a careful and systematic evaluation is required to identify a particular vasculitis subtype and/or etiology. In summary, these three terms are not synonymous and should not be used interchangeably without appropriate clarification.

CLASSIFICATION

The 2012 revised International Chapel Hill Consensus Conference Nomenclature, which is based upon expert consensus, provides standardized terminology and disease definitions for the various types of vasculitis[2]. A 2018 dermatologic addendum to the Chapel Hill Nomenclature further classifies cutaneous vasculitides[1]. In addition, the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS), a large, multinational observational study that utilized patient data, aims to develop and validate evidence-based diagnostic and classification criteria for use in practice and clinical trials. These data are the basis of revised ACR-EULAR classification criteria for large vessel vasculitis and ANCA-associated vasculitis[3].

Because a system based upon the *predominant* size of the involved blood vessels is conceptually useful and helps to predict the clinical presentation and corresponding histopathologic findings, this type of classification scheme will be employed in this chapter (see Table 24.1). Additional features that aid in classifying cutaneous vasculitis are systemic manifestations, direct immunofluorescence studies, and the presence or absence of pertinent laboratory findings, e.g. anti-neutrophil cytoplasmic antibodies (ANCAs) (see Fig. 24.16). Despite descriptions of distinct vasculitic syndromes, unique diagnostic criteria are often lacking and clinicopathologic correlation is always required.

EPIDEMIOLOGY

The annual population-based incidence of biopsy-proven LCV is ~45 per million. Of note, this figure includes various subtypes such as urticarial vasculitis, cryoglobulinemic vasculitis, and ANCA-associated vasculitis, any of which may demonstrate LCV histologically[4]. Cutaneous vasculitis occurs in all age groups (mean age in adults, 47 years; mean age in children, 7 years), has a slight female predominance[5,6], and is much more common in adults than in children. The most common type of vasculitis in children is IgA vasculitis (Henoch–Schönlein purpura).

PATHOGENESIS

Cutaneous small vessel vasculitis as well as other subtypes of small vessel vasculitis involving the skin are mediated by immune complexes that form in the presence of antigen excess. After their deposition within postcapillary venules, these complexes lead to complement-mediated chemotaxis of neutrophils (Fig. 24.1A). In ANCA-associated vasculitis, vessel wall damage is directly mediated by neutrophils rather than by immune complex deposition (Fig. 24.1B), hence the term "pauci-immune" vasculitis.

GENERAL CLINICAL FEATURES

The skin lesions of CSVV usually appear 7–10 days after the inciting event; rarely, drug-induced CSVV may appear within hours of administration of the responsible drug. In systemic vasculitis, systemic symptoms often precede the appearance of associated cutaneous lesions (average, 6 months), but the interval is variable and cutaneous findings can certainly be a presenting manifestation[5]. As noted, the cutaneous findings of vasculitis depend upon the predominant size of the vessels involved. CSVV typically presents with palpable or macular purpura,

CUTANEOUS VASCULITIS CLASSIFICATION SCHEME			
Caliber of the predominantly affected vessel	**Classification**	**Subclassification or etiologies**	**Morphology of cutaneous lesions**

Small	Small vessel vasculitis of the skin	• Cutaneous small vessel vasculitis (CSVV)
		• IgA vasculitis, including Henoch–Schönlein purpura
		• Acute hemorrhagic edema of infancy
		• Urticarial vasculitis
		• Erythema elevatum diutinum
		• Secondary causes of CSVV (see Table 24.4):
		  • Drug exposure
		  • Infections (septic vasculitis)
		  • AI-CTD
		  • Malignancies, most often hematologic
			• Palpable purpura (most common)
			• Petechiae
			• Macular purpura
			• Urticarial papules
			• Vesicles
			• Pustules
			• Targetoid papules and plaques
			• Round ulcers

Small and medium-sized ("mixed")	Cryoglobulinemic vasculitis (types II and III)	• Secondary to an underlying infection (e.g. HCV), AI-CTD, or lymphoplasmacytic disorder • Primary/idiopathic	• Petechiae • Palpable purpura • Livedo racemosa • Retiform purpura • Ulcers • Subcutaneous nodules • Digital necrosis
	ANCA-associated	• Granulomatosis with polyangiitis (formerly Wegener granulomatosis) • Microscopic polyangiitis • Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) • Drug-induced	
	Secondary causes	• Infections • Inflammatory disorders (e.g., AI-CTD)	
Medium-sized	Polyarteritis nodosa (PAN)	• Classic (systemic) PAN • Cutaneous PAN (cutaneous arteritis)	• Livedo racemosa • Retiform purpura • Ulcers • Subcutaneous nodules • Digital necrosis
Large*	Temporal (giant cell) arteritis		• *Early* – erythematous or cyanotic skin, alopecia, purpura, tender nodules on frontotemporal scalp • *Late* – ulceration and/or gangrene of frontotemporal scalp or tongue
	Takayasu arteritis		• Erythematous subcutaneous nodules ± ulceration, pyoderma gangrenosum-like lesions on the extremities (lower > upper) • May have evidence of small and/or medium-sized vessel vasculitis
*Cutaneous manifestations are rare.			

Table 24.1 Cutaneous vasculitis classification scheme. In patients with Behçet disease, there can be involvement of small, medium-sized, and large vessels. AI-CTD, autoimmune connective tissue diseases; ANCA, anti-neutrophil cytoplasmic antibodies.

but urticarial papules, pustules, vesicles, petechiae, or targetoid lesions can be seen (Fig. 24.2 & 24.3). The lesions favor dependent sites, as well as areas under tight-fitting clothing, reflecting the influence of hydrostatic pressure and stasis on immune complex deposition. In general, the lesions are asymptomatic, but they may itch, burn, or sting.

In medium-sized vessel vasculitis, the affected blood vessels reside within the reticular dermis or subcutis. As a result, it typically presents with livedo racemosa, retiform purpura, ulcers, subcutaneous nodules, and/or digital necrosis. In general, the presence of larger ulcerations or necrosis suggests deeper arterial involvement. The combination of purpuric macules and papules plus features of medium-sized vessel disease points to a "mixed" pattern of vasculitis with involvement of both small and medium-sized vessels, as in cryoglobulinemic vasculitis and ANCA-associated vasculitis (see Table 24.1).

Common manifestations of systemic vasculitis include inflammatory arthritis as well as constitutional symptoms, such as fever, weight loss, and malaise. These common findings can be seen in virtually any type of systemic vasculitis, whereas other signs and symptoms (e.g. motor neuropathy, sinusitis) are more often associated with specific disease states. As in the skin, systemic manifestations tend to correlate with the size of the affected blood vessels; for example, glomerulonephritis is a manifestation of small vessel disease, while renal artery aneurysms and renovascular hypertension are features of medium-sized vessel vasculitis[6]. In a population-based study of 84 patients with biopsy-proven LCV, 39 patients (46%) had systemic manifestations, with renal involvement most commonly observed (17 of 39 patients)[4].

PATHOLOGY

Timing and appropriate sampling of the most likely involved vessels increase the diagnostic yield of a skin biopsy. Ideally, lesions should be biopsied for routine processing within the first 24 to 48 hours of appearance. When small vessel vasculitis is suspected, a biopsy specimen for direct immunofluorescence (DIF) should be obtained, as the presence of certain immunoglobulins (e.g. IgA) may suggest a particular diagnosis and prognosis. Biopsies for DIF should also be obtained from lesions of recent onset, ideally those that are only hours old. In general, punch biopsies are adequate for the diagnosis of small vessel vasculitis, while an incisional deep biopsy may be required to diagnose vasculitis of larger vessels.

In cutaneous vasculitis, the histologic findings vary depending upon the type and age of the sampled lesion in addition to the size of the affected vessel. The classic histopathologic features of CSVV are referred to as LCV and consist of transmural infiltration of the walls of small vessels (primarily postcapillary venules) by neutrophils undergoing karyorrhexis of their nuclei, as well as fibrinoid necrosis of the vessel walls (Fig. 24.4). Other findings include leukocytoclasia (degranulation and fragmentation of neutrophils, leading to the production of nuclear dust), extravasated erythrocytes, and signs of endothelial cell damage. However, lesions present for greater than 48 to 72 hours may have a predominantly mononuclear rather than neutrophilic infiltrate. In the case of palpable purpura, the most common clinical lesion of CSVV,

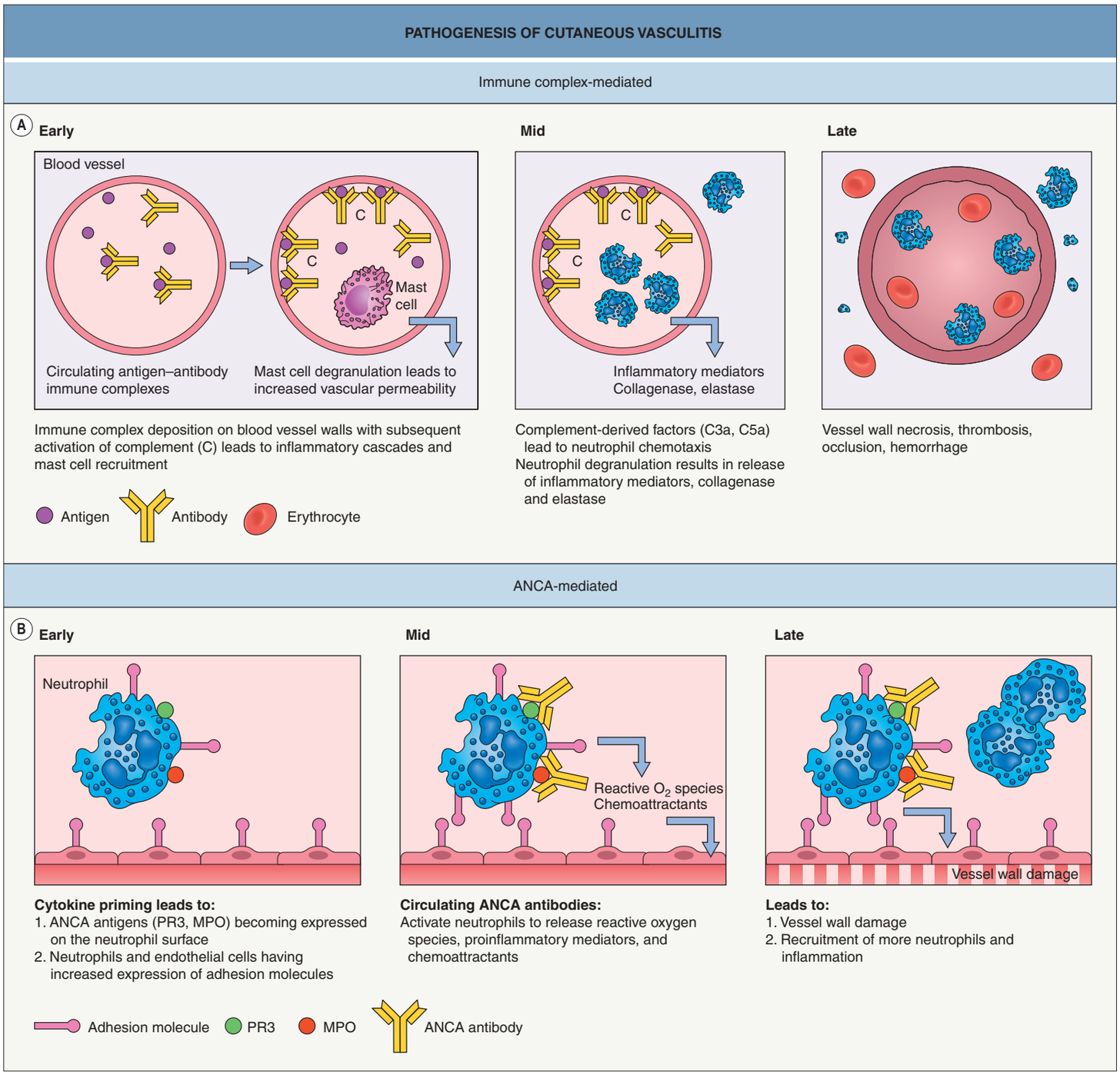


Fig. 24.1 Pathogenesis of cutaneous vasculitis – immune complex- versus anti-neutrophil cytoplasmic antibody (ANCA)-mediated. A In immune complex-mediated vasculitis, circulating antigens (e.g. infectious agents, medications, neoplasms) induce antibody formation. Binding of antibodies to circulating antigens creates immune complexes. Immune complex deposition within postcapillary venules activates complement and subsequently leads to an increase in adhesion molecule expression on the endothelium. Complement split products (C3a and C5a) induce mast cell degranulation and neutrophil chemotaxis. Mast cell degranulation leads to increased vascular dilation and permeability, enhancing immune complex deposition and leukocyte tethering to endothelium. Increased adhesion between inflammatory cells (especially neutrophils) and the endothelium is mediated by elevated expression of selectins (E-selectin, P-selectin) and members of the immunoglobulin superfamily (ICAM-1, VCAM-1, PECAM-1) on endothelial cells in concert with the upregulation of their corresponding ligands and receptors/adhesion molecules on leukocytes (e.g. P-selectin glycoprotein ligand-1, LFA-1, Mac-1) (see Ch. 102 for details). Neutrophils release proteolytic enzymes (such as collagenases and elastases) and free oxygen radicals that damage the vessel wall. In addition, formation of the membrane attack complex (C5–C9) on the endothelium leads to the activation of the clotting cascade and the release of cytokines and growth factors with ensuing thrombosis, inflammation, and angiogenesis. **B** In ANCA-mediated vasculitis, following primary activation by cytokines such as tumor necrosis factor (TNF), intracellular proteins from neutrophils (e.g., proteinase 3 [PR3], myeloperoxidase [MPO]) become expressed on the cell surface. After formation of ANCAs that recognize these antigens, binding of the autoantibodies to neutrophils leads to increased neutrophil adhesion to vessel walls and subsequent cellular activation. Neutrophils then release reactive oxygen species and other toxic mediators that result in vessel wall damage (see **A**). Because the vessel damage in ANCA-positive vasculitides is directly mediated by neutrophils rather than by immune complexes, they are referred to as "pauci-immune" vasculitides. Formation of ANCAs may be related to an impairment in neutrophil apoptosis which results in a prolonged opportunity for autoantibody development.

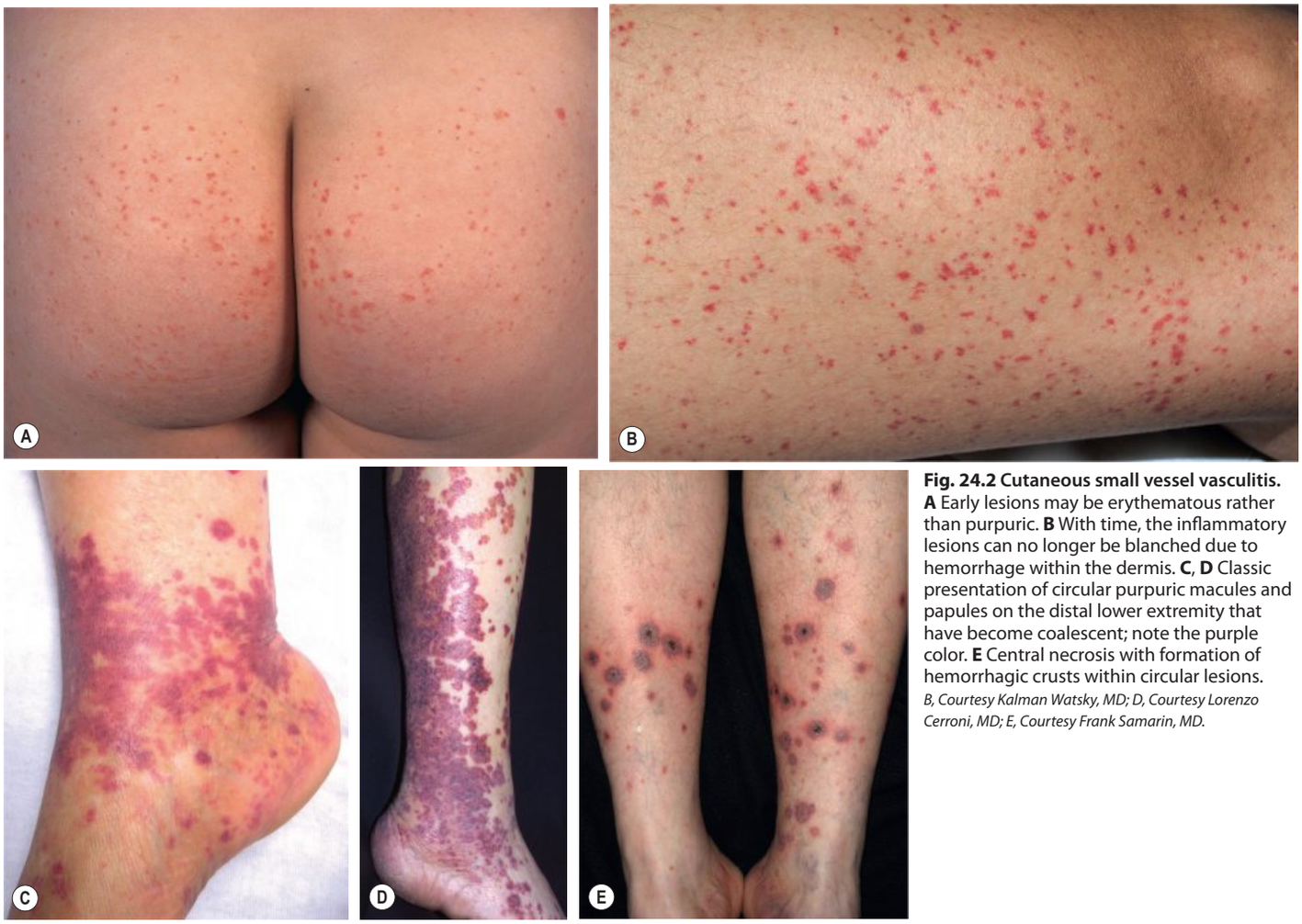


Fig. 24.2 Cutaneous small vessel vasculitis. **A** Early lesions may be erythematous rather than purpuric. **B** With time, the inflammatory lesions can no longer be blanched due to hemorrhage within the dermis. **C**, **D** Classic presentation of circular purpuric macules and papules on the distal lower extremity that have become coalescent; note the purple color. **E** Central necrosis with formation of hemorrhagic crusts within circular lesions. *B, Courtesy Kalman Watsky, MD; D, Courtesy Lorenzo Cerroni, MD; E, Courtesy Frank Samarin, MD.*

the small vessel involvement accounts for the small size of the lesions, the inflammatory response for the palpability and symptomatology (e.g. burning pain, pruritus), the red blood cell extravasation from damaged blood vessels for the non-blanching purpura, and the effect of gravity on immune complex deposition for the distribution of lesions on the lower legs and other dependent areas.

Some studies suggest that additional histologic findings may provide clues to the underlying etiology, e.g. eosinophils in drug-induced CSVV[7], thrombi in patients exposed to levamisole-tainted cocaine, and thrombi plus dense dermal inflammation in septic vasculitis. Involvement of deeper dermal vessels can alert the clinician to look for an underlying etiology rather than presuming the CSVV is idiopathic[8].

Vasculitis of medium-sized blood vessels is characterized by similar changes involving the vessels (e.g. small arteries) of the deep reticular dermis and subcutaneous fat. Neovascularization of the adventitia, in the form of small capillaries, is commonly seen in older lesions of medium-sized vessel vasculitis.

In ~80% of cases of small vessel vasculitis of the skin, DIF demonstrates deposition of C3, IgM, IgA, and/or IgG (generally in that order of frequency) in a granular pattern within the vessel walls[5]. Immunoglobulin deposition is highest (up to 100%) in skin lesions present for ≤48 hours[5]. On the other hand, in 30% of samples obtained 48–72 hours after lesion onset, the DIF will be negative for immunoglobulins, and only C3 will be detected in lesions present for >72 hours[5]. In patients with ANCA-associated vasculitis, the DIF of lesional skin is usually negative. After controlling for duration, it is preferable to biopsy more proximal lesions for DIF in order to avoid nonspecific vascular fluorescence that can occur at sites of increased hydrostatic pressure.

As stated previously, the term LCV is a histologic designation. Terms used to describe additional histologic forms of cutaneous vasculitis include "lymphocytic" and "granulomatous" (see below)[9]. Use of the term lymphocytic vasculitis requires clarification, as it does not represent a conventional type of vasculitis but rather a histologic finding seen in a number of non-vasculitic disorders such as pernio and pityriasis lichenoides et varioliformis acuta (Table 24.2).

DIFFERENTIAL DIAGNOSIS

Several disorders can present with skin lesions that resemble the various cutaneous manifestations of vasculitis; the most common entities in the differential diagnosis are listed in Table 24.3. Similarly, histologic findings of vasculitis may be seen in other conditions which are not types of primary vasculitis, including arthropod bites, neutrophilic dermatoses, and cutaneous ulceration. Careful clinicopathologic correlation is necessary to differentiate these vasculitis mimickers.

SMALL VESSEL VASCULITIS

Synonyms: ■ IgM/IgG immune complex vasculitis ■ Cutaneous leukocytoclastic vasculitis ■ Cutaneous leukocytoclastic angiitis ■ Hypersensitivity vasculitis ■ Cutaneous necrotizing venulitis

Key features

- A single-organ, skin-limited vasculitis involving small blood vessels
- Presents with palpable purpura, urticarial lesions, and/or hemorrhagic macules or vesicles; less common findings include targetoid lesions, pustules, and round ulcerations
- Lesions favor the lower extremities and other dependent areas or pressure points
- Histologically, there is leukocytoclastic vasculitis involving small vessels, primarily postcapillary venules
- Must be differentiated from vasculitis with extracutaneous involvement



Fig. 24.3 Clinical variants of cutaneous small vessel vasculitis. A Targetoid appearance that can resemble erythema multiforme. **B** Hemorrhagic vesicles in addition to palpable purpura. **C** Hemorrhagic crusts in an annular configuration. **D** Lesions involving the upper extremities. **E** Purpuric macules and papules with areas of confluence that resemble a purpuric morbilliform drug eruption. **F** Coalescence of palpable purpura as well as edema and an ulcer with a thick black eschar; petechiae are also present and in the instep resemble pinpricks. *B, Courtesy Kalman Watsky, MD; D, Courtesy Lindy Fox, MD, and Kanade Shinkai MD; E, Courtesy David A. Wetter, MD; F, Courtesy Jean L. Bolognia, MD.*

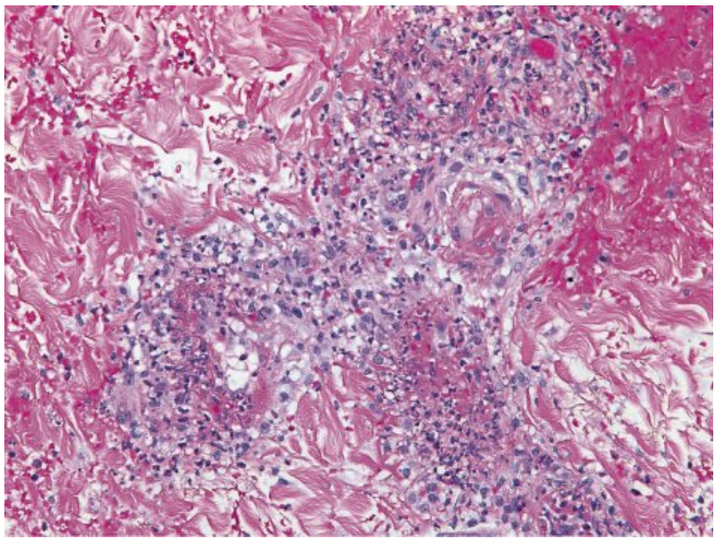


Fig. 24.4 Cutaneous small vessel vasculitis – histopathologic features. Angiocentric segmental inflammation with endothelial swelling, a neutrophilic infiltrate with leukocytoclasia, red blood cell extravasation, and fibrinoid necrosis of blood vessel walls. The neutrophils are present around and within the walls of the small dermal blood vessels. *Courtesy David F. Fiorentino, MD.*

LYMPHOCYTIC VASCULITIS

• Defined histologically as a perivascular lymphocytic dermal infiltrate with associated damage to the walls of small blood vessels; findings may range from extravasated RBCs and swelling or hyperplasia of endothelial cells to fibrin deposition and fibrinoid necrosis of the vessel wall
• Most commonly seen in:
  • **Pernio**
  • **Pityriasis lichenoides et varioliformis acuta (PLEVA)**
  • Rickettsial, viral infections
  • Autoimmune connective tissue diseases, e.g., lupus erythematosus, relapsing polychondritis
  • Behçet disease
  • Hypercoagulable disorders, e.g., Sneddon syndrome
  • Lymphocytic thrombophilic arteritis (macular arteritis)
  • Panniculitis, including lupus

Table 24.2 Lymphocytic vasculitis. This topic is one where there is ongoing debate. Most common entities in **bold**. Angiocentric infiltrates of atypical lymphocytes, sometimes with angiodestruction, may also be observed in some cutaneous lymphomas. RBC, red blood cell.

CLINICAL DIFFERENTIAL DIAGNOSIS OF CUTANEOUS VASCULITIS	
Clinical presentation	**Differential diagnosis**
Purpuric papules/plaques	Arthropod bites Morbilliform drug eruptions with hemorrhage in dependent sites Erythema multiforme Pityriasis lichenoides et varioliformis acuta Infectious emboli (septic vasculitis) due to bacteria (e.g., *Neisseria meningococcus* [acute meningococcemia]), rickettsiae, fungi (e.g., *Rhizopus*) Pigmented purpura (e.g. lichenoid capillaritis) Cellulitis
Purpuric macules/patches	**Hemorrhage** • Trauma • Solar (actinic) purpura* • Medication-related (i.e. aspirin, topical or systemic corticosteroids)* • Thrombocytopenia and platelet dysfunction • Coagulopathies* • Viral exanthems (e.g., enterovirus, parvovirus B19) • Scurvy • Primary systemic amyloidosis **Thromboses** • Thrombophilia/hypercoagulable state (e.g., antiphospholipid antibody; see Table 105.9) • Livedoid vasculopathy • Purpura fulminans (e.g., due to sepsis/DIC) • Heparin necrosis • Warfarin (Coumadin®) necrosis • Thrombotic microangiopathy • Paroxysmal nocturnal hemoglobinuria **Emboli** • Cholesterol • Cardiac (infective endocarditis ≫ myxomatous or marantic) • Fat • Air **Cold-related gelling** • Cryoglobulins (primarily type I) **Inflammation** • Pigmented purpura (capillaritis) • Hypergammaglobulinemic purpura of Waldenström (recurrent macular vasculitis in hypergammaglobulinemia) **Infection** • Lucio phenomenon (Hansen disease) • Strongyloidiasis
Urticarial lesions	Urticaria (including neutrophilic urticaria) Arthropod bites and papular urticaria Urticaria multiforme Serum sickness-like reaction Neutrophilic urticarial dermatosis Autoinflammatory diseases (e.g., periodic fevers; see Table 45.2) Still disease, including adult-onset Schnitzler syndrome Viral exanthems Kawasaki disease Sweet syndrome Urticarial phase of bullous pemphigoid
Ulcers ± atrophie blanche	Venous hypertension or peripheral arterial disease Pyoderma gangrenosum Livedoid vasculopathy Thrombophilia/hypercoagulable state (e.g., antiphospholipid antibodies; see Table 105.9) Calciphylaxis Infections (e.g., bacterial, mycobacterial, dimorphic or opportunistic fungal, protozoal) Hemoglobinopathies Factitial Halogenodermas Degos disease See Fig. 105.1 for additional entities
Nodules	Panniculitis Superficial migratory thrombophlebitis Dermal neoplasms Infections (e.g., bacterial, mycobacterial, dimorphic or opportunistic fungal)
Livedo reticularis	See Chapter 106

Table 24.3 Clinical differential diagnosis of cutaneous vasculitis.

Continued

CLINICAL DIFFERENTIAL DIAGNOSIS OF CUTANEOUS VASCULITIS	
Clinical presentation	**Differential diagnosis**
Digital gangrene	Arterial occlusive disease, including atherosclerosis Diabetes mellitus Thromboangiitis obliterans (Buerger disease) Systemic sclerosis Emboli (e.g., cholesterol, septic) Cryoglobulinemia (type I) > cryofibrinogenemia or cold agglutinin disease Thrombosis (e.g., antiphospholipid syndrome, purpura fulminans, myeloproliferative thrombocytosis) Calciphylaxis Hypereosinophilic syndrome Paraneoplastic acral vascular syndrome (e.g., with lung or ovarian carcinoma)
*Element of trauma.	

Table 24.3 Clinical differential diagnosis of cutaneous vasculitis. DIC, disseminated intravascular coagulation.

Introduction

CSVV is a type of single-organ, skin-limited vasculitis that involves primarily the dermal postcapillary venules and is characterized histologically by LCV. The dermatologic addendum to the Chapel Hill Consensus Conference Nomenclature proposes the term "IgM/IgG immune complex vasculitis" to further characterize this entity[1]. Because clinical manifestations of small vessel vasculitis of the skin (e.g. palpable purpura) and histologic findings of LCV may be seen in other disease entities (e.g. IgA vasculitis), systematic evaluation and consideration of other types of vasculitis involving small cutaneous vessels is necessary before establishing the diagnosis of CSVV (see Table 24.1). CSVV is often idiopathic in nature, but it may be secondary to an underlying cause such as an infection, medication, or autoimmune connective tissue disease (Table 24.4). Within the spectrum of small vessel vasculitis of the skin are several entities whose rather unique epidemiologic and clinical features warrant subclassification (see Table 24.1) and separate discussion (following sections).

Epidemiology

CSVV occurs in both sexes and at all ages[10], but it is more common in the adult population. It is estimated that ~10% of those affected are children. The annual population-based incidence of CSVV (excluding those with a distinct clinical subtype of small vessel vasculitis) is 21 cases per million[4].

Pathogenesis

CSVV is mediated by immune complex deposition (see Fig. 24.1A).

Clinical features

CSVV typically presents spontaneously, or after exposure to an inciting agent, with a crop of lesions consisting of non-blanching purpuric macules and papules, petechiae, urticarial lesions, or hemorrhagic vesicles ranging in size from 1 mm to several centimeters (see Fig. 24.2 & 24.3). Lesions often begin with erythema and then rapidly become purpuric; larger lesions arise via coalescence of papules. Occasionally, pustules, targetoid lesions, and round ulcerations are seen. CSVV favors dependent areas, as well as areas affected by trauma (Koebner phenomenon) or under tight-fitting clothing. Prolonged sitting or standing, as well as exercise, in particular walking or hiking in hot weather, can induce CSVV on the lower extremities. Although they may be asymptomatic, lesions can be associated with burning pain or pruritus and may be psychologically distressing. Residual postinflammatory hyperpigmentation can persist for months after the primary process resolves.

By definition, CSVV is skin-limited, or skin-predominant, so it is appropriate to apply this label to patients with small vessel vasculitis of the skin in whom there is no evidence of systemic vasculitis. That said, patients with CSVV commonly have low-grade constitutional symptoms and arthralgias which may accompany flares of skin vasculitis. Because of a lack of clarity regarding terminology and disease definitions in the literature, estimates of the prevalence of systemic symptoms in CSVV vary. Available data suggest that systemic symptoms occur in 5%–25% of patients with CSVV, with arthralgias and arthritis occurring most commonly (15%–65%), followed by genitourinary signs or symptoms (3%–7%), and gastrointestinal involvement (3%–5%)[11]. A population-based study demonstrated systemic symptoms in 11 of 38 patients (29%) with CSVV[4]. *In general, more overt signs or symptoms of systemic disease, such as marked constitutional symptoms, inflammatory arthritis, and gastrointestinal, renal, or neurologic involvement should increase the clinical suspicion for a systemic vasculitis*. In one study, the presence of paresthesias or fever were identified as risk factors for an associated systemic disease[12]. A stepwise approach to evaluation, guided by the presenting signs and symptoms, is recommended to help identify those patients with systemic manifestations of vasculitis or important underlying disorders (see Fig. 24.19)[13].

Approximately 90% of patients with CSVV will have spontaneous resolution of cutaneous lesions within several weeks or a few months, while another 10% will have chronic or recurrent disease at intervals of months to years[14]. In the latter group, the average duration of disease activity is reported to be ~24–28 months[4,5]. The presence of arthralgias or cryoglobulinemia and an absence of fever may portend chronicity[12]. An underlying cause for the CSVV, such as an autoimmune connective tissue disease or neoplasm, also affects prognosis.

Differential diagnosis

In addition to determining if the patient has a particular subtype of small vessel vasculitis (see Table 24.1) or has cutaneous vasculitis as a manifestation of a systemic vasculitic syndrome, causes of secondary cutaneous vasculitis also need to be considered (see Table 24.4; Fig. 24.5 & 24.6). Entities listed in Table 24.3, especially the first three categories, may mimic cutaneous vasculitis and need to be included in the clinical differential diagnosis.

Treatment

The initial intervention in CSVV consists of supportive care and elimination of potential triggers. The need for and choice of pharmacotherapy depends on the chronicity and severity of the cutaneous involvement and any potential underlying disease state. In cases of small vessel vasculitis of the skin where systemic involvement is identified, the choice of therapy must appropriately address those manifestations. Specific therapeutic options are outlined in Table 24.10.

CSVV often resolves without any specific treatment. Because it is usually self-limited as well as skin-limited, supportive measures (e.g. rest, leg elevation, compression) or symptomatic therapy (e.g. antihistamines, NSAIDs) may be sufficient.

Chronic (lasting >4 weeks) or severe cutaneous disease generally requires more aggressive systemic therapy. There is a dearth of high-quality data to guide management, but a number of agents, including colchicine, dapsone and azathioprine, appear to be effective for skin and joint manifestations in some patients and are usually well tolerated (see Table 24.10). A randomized trial is currently underway to assess the efficacy of these agents for skin-limited vasculitis[15].

Patients with severe, ulcerating, or progressive cutaneous disease who require rapid control of symptoms can be treated with a short course of high-dose oral corticosteroids (e.g. up to 1 mg/kg/day of prednisone). Because of adverse effects associated with long-term corticosteroid use, a taper over 4 to 6 weeks should be attempted. If the patient develops recurrent CSVV as the dosage is decreased, addition of a steroid-sparing agent is warranted. However, corticosteroids do not represent an appropriate long-term plan for chronic or recurrent CSVV. In addition to the oral medications listed previously, methotrexate (<25 mg weekly), mycophenolate mofetil, and rituximab have been reported to be useful in recalcitrant CSVV[16].

UNDERLYING CAUSES OF SECONDARY CUTANEOUS VASCULITIS				
Association	**Incidence**	**Agent/Disease**		
		Common	**Uncommon**	**Rare**
Idiopathic	50%			
Infection	15%–20%	**Bacterial**		
		Beta-hemolytic streptococci, especially group A *Mycobacterium leprae*	*Neisseria meningococcus* (in chronic meningococcemia) *Mycobacterium tuberculosis* Atypical mycobacteria	*Mycoplasma pneumoniae* *Chlamydophila pneumoniae, Chlamydia trachomatis* *Brucella* *Bartonella henselae* *Salmonella* *Campylobacter* *Yersinia enterocolitica* *Treponema pallidum*
		Septic vasculitis*		
		Infective endocarditis	*Neisseria meningitidis* (acute) *Neisseria gonorrhoeae* *Staphylococcus aureus* Rickettsiae Gram-negative rods *Escherichia coli* *Klebsiella* *Pseudomonas* Disseminated fungal infections (immunocompromised hosts) *Candida* *Aspergillus* *Fusarium* *Mucor*	*Francisella tularensis*
		Viral		
		Upper respiratory tract infection Hepatitis C > B ≫ A, including vaccines	HIV Parvovirus B19	Cytomegalovirus Varicella zoster virus Influenza virus, including vaccine
Inflammatory disorders	15%–20%	Autoimmune connective tissue diseases • Rheumatoid arthritis† • SLE • Sjögren syndrome • Overlap SLE/Sjögren syndrome	Inflammatory bowel disease Behçet disease Hypergammaglobulinemic purpura of Waldenström Seronegative spondyloarthropathies	Sarcoidosis Cystic fibrosis§ Primary biliary cirrhosis Bowel-associated dermatosis–arthritis syndrome Gluten enteropathy Hidradenitis suppurativa Systemic sclerosis Dermatomyositis
Drug exposure¶	10%–15%	***Antibiotics, esp. β-lactams*** Penicillins Cephalosporins, esp. cefaclor Sulfonamides Minocycline§ Quinolones Macrolides ***Cardiovascular*** Thiazides Hydralazine§ Quinidine ***Other*** Allopurinol Bortezomib D-penicillamine G-CSF NSAIDs Propylthiouracil/other antithyroid agents§ Serum (e.g. ATG) Streptokinase	***Antimicrobials*** Quinine Vancomycin ***Cardiovascular*** ACE inhibitors Beta-blockers Furosemide ***Other*** Cocaine adulterated with levamisole§ COX-2 inhibitors Interferons Leukotriene inhibitors§,‖ Methotrexate Oral contraceptives Phenytoin Retinoids Sirolimus Sulfonylureas TNF inhibitors Warfarin	***Antimicrobials*** Mefloquine ***Cardiovascular*** Amiodarone ***Neuropsychiatric*** Atypical antipsychotics Gabapentin Phenothiazines SSRIs ***Other*** Insulin Leflunomide Metformin Methamphetamine 3,4-methylenedioxymethamphetamine Rituximab SSKI Tocolytics (e.g. ritodrine, terbutaline) ***Miscellaneous*** Radiographic contrast media Food/drug additives Vitamins
Neoplasms	2%–5%	Plasma cell dyscrasias • Monoclonal gammopathies • Multiple myeloma Myelodysplasia Myeloproliferative disorders Lymphoproliferative disorders Hairy cell leukemia	Solid organ carcinomas (IgA vasculitis in adults ≫ other forms of CSVV)	

Table 24.4 Underlying causes of secondary cutaneous vasculitis.

Continued

UNDERLYING CAUSES OF SECONDARY CUTANEOUS VASCULITIS				
Association	**Incidence**	**Agent/Disease**		
		Common	**Uncommon**	**Rare**
Genetic disorders	Rare	Alpha-1 antitrypsin deficiency		Immunodeficiency syndromes (see Table 60.1) Familial Mediterranean fever and other periodic fever syndromes (see Table 45.2)

*Histopathology varies and includes leukocytoclastic vasculitis, organisms within the vessel wall, and non-inflammatory thrombotic purpura.
†Rheumatoid vasculitis typically occurs in seropositive patients with elevated inflammatory markers; cutaneous vasculitis is the most common presentation, followed by vasculitic neuropathy.
¶Peripheral blood eosinophilia may be present in up to 80% and 20% of patients with systemic and skin-limited diseases, respectively[6].
§May be associated with anti-neutrophil cytoplasmic antibodies (ANCAs).
‖Associated with eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome).

Table 24.4 Underlying causes of secondary cutaneous vasculitis. ACE, angiotensin-converting enzyme; ATG, antithymocyte globulin; COX, cyclooxygenase; CSVV, cutaneous small vessel vasculitis; G-CSF, granulocyte colony-stimulating factor; HIV, human immunodeficiency virus; HSP, Henoch–Schönlein purpura; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; SSKI, saturated solution of potassium iodide; SSRI, selective serotonin reuptake inhibitor; TNF, tumor necrosis factor. *List of associated drugs adapted from Lotti T, et al. J Am Acad Dermatol 1998;39:667–87; ten Holder SM, et al. Ann Pharmacother 2002;36:130–47; and Ortiz-Saniuan F, et al. J Rheumatol. 2014;41:2201–7.*

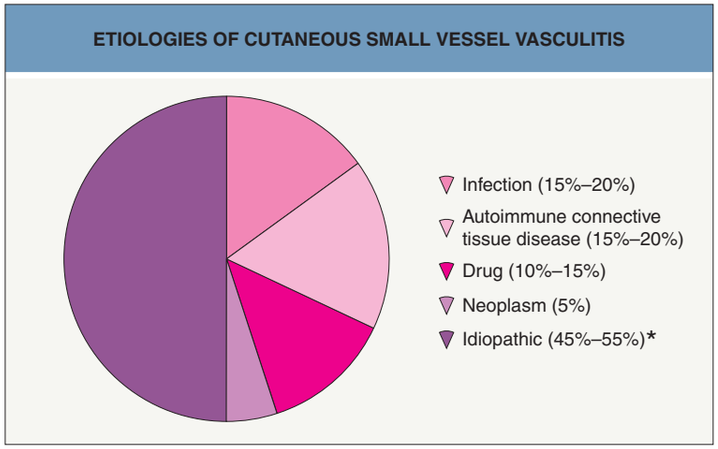


Fig. 24.5 Etiologies of cutaneous small vessel vasculitis (CSVV). *CSVV was idiopathic in 76% of cases in a population-based study from Olmsted County, Minnesota[4].

IgA Vasculitis (Henoch–Schönlein Purpura)

Synonyms: ■ Schönlein–Henoch purpura ■ Anaphylactoid purpura ■ Purpura rheumatica ■ Cutaneous small vessel vasculitis secondary to IgA immune complexes

Key features

- Most common form of vasculitis in children <10 years of age
- Frequently preceded by an upper respiratory tract infection
- Intermittent palpable purpura on the extremities with IgA-dominant immune deposits in the walls of small blood vessels
- Systemic involvement, in particular gastrointestinal, joint, and renal, is often observed, but IgA vasculitis may be skin-limited
- In adults (men > women), rarely associated with an underlying malignancy

Introduction

IgA vasculitis (IgAV), also referred to as Henoch–Schönlein purpura (HSP), is a type of vasculitis affecting small blood vessels in which vascular IgA deposition is a key diagnostic and pathophysiologic feature. This particular type of vasculitis occurs more commonly in children than in adults. The classic tetrad consists of palpable purpura, arthritis, abdominal pain, and hematuria. However, IgAV may be skin-limited or skin-predominant, with either no associated symptoms or mild arthralgias and/or constitutional symptoms.



Fig. 24.6 Cutaneous small vessel vasculitis associated with systemic disorders. The underlying diseases were Sjögren syndrome (**A**), rheumatoid arthritis (**B**), relapsing polychondritis with myelodysplasia (**C**), and endocarditis due to *Streptococcus mitis* (**D**). Note the Koebner phenomenon in **A** and rheumatoid nodules in **B**. Cutaneous vasculitis in association with relapsing polychondritis and myelodysplasia points to a likely diagnosis of VEXAS syndrome. *C, Courtesy Jean L. Bolognia, MD; D, Courtesy David A. Wetter, MD.*

Epidemiology

IgAV is the most common form of vasculitis in children, with an incidence of 30 to 270 cases per million children per year[17]. The average age of onset is 6 years, and 90% of cases occur in children <10 years of age[18,19]. In adults, the incidence of HSP is 8 to 18 cases per million[17], and the population-based incidence of biopsy-proven cutaneous IgA

vasculitis is 13 cases per million per year[4]. The disorder follows a seasonal pattern, with a peak occurrence during the winter. HSP has a slight male predominance in both children and adults.

Pathogenesis

IgAV frequently presents 1 to 2 weeks following an upper respiratory tract infection, especially in children. Although several studies have reported that 20%–50% of HSP patients have positive antistreptolysin O (ASO) titers[18], no causal role for group A β-hemolytic streptococci has been demonstrated. IgAV may be triggered by a medication or rarely it is a paraneoplastic phenomenon.

IgA (specifically IgA1) is thought to play a fundamental role in the pathogenesis of IgAV. IgA deposits in the postcapillary venules of the skin and mesangium and, less commonly, circulating IgA-containing immune complexes and increased serum levels of IgA have been demonstrated in patients with IgAV[19]. In a case series of over 400 patients with IgAV, increased serum IgA levels were found in ~30%[20]. Altered glycosylation of the hinge region of IgA1 may promote the formation of macromolecular complexes that lodge within the mesangium and activate the alternate complement pathway[18].

Certain genetic polymorphisms may predispose to more severe disease[21]. For example, HLA-B35 positivity may predispose to renal disease, while patients who do not have the ICAM-1 469 K/E variant have less severe gastrointestinal involvement[19].

Clinical features

IgAV classically presents with palpable purpura in association with arthritis, abdominal pain, and/or nephritis. Cutaneous lesions begin as erythematous macules or urticarial papules and evolve into palpable purpura ranging in size from pinpoint to several millimeters (Fig. 24.7). Urticaria, vesicles, bullae, targetoid lesions, and foci of necrosis can also be seen as well as lower extremity edema. Typically, lesions are symmetrically distributed on the lower extremities and buttocks but may also involve the trunk, upper extremities, and face. Individual lesions usually regress within 10 to 14 days, with resolution of cutaneous involvement over a period of several weeks to months. Recurrences of skin disease are observed in 5%–10% of patients[14].

Extracutaneous manifestations of IgAV are common. *Arthritis* occurs in up to 75% of patients with IgAV and most commonly affects the joints of the lower extremities (knees and ankles). *Gastrointestinal* involvement (50%–75% of patients) may precede the purpura and presents with colicky abdominal pain (65%), gastrointestinal bleeding (30%), and/or vomiting. Intussusception and bowel perforation are rare complications.

Renal involvement occurs in 40%–50% of patients and typically presents with microscopic hematuria (40%), often accompanied by proteinuria (25%). The appearance of cutaneous lesions generally precedes the development of nephritis. When it occurs, renal involvement usually appears within the first month of diagnosis (85%) and develops within six months in >95% of patients[22]. Therefore, close observation, with frequent urinalyses, is recommended during this time period[18]. In pediatric patients, risk factors for the development of nephritis include male sex, age >10 years at onset, severe gastrointestinal symptoms, arthritis/arthralgia, persistent or recurrent purpura, and several laboratory abnormalities (leukocytosis, thrombocytosis, elevated ASO titer, low C3)[23]. Depending upon the series, persistent renal disease has been observed in 8%–50% of patients[20], emphasizing the need for



Fig. 24.7 IgA vasculitis (Henoch–Schönlein purpura). A, B Early inflammatory lesions that are beginning to develop a hemorrhagic component. Sites of previous involvement on the shins are now dull pink patches. **C** More developed lesions with central necrosis. **D** Less common vesiculobullous variant. **E** Purpuric macules and papules of the buttocks with coalescence into a retiform configuration on the upper left; inflammatory retiform purpura can be seen in some forms of vasculitis, especially IgA vasculitis (see Table 22.6). **F** Accentuation of lesions at the sock lines due to increased pressure. *A, D, E, Courtesy David A. Wetter, MD; F, Courtesy Carlo Mainetti, MD.*

longitudinal monitoring until all abnormalities resolve. Fortunately, only 1%–3% of children develop long-term renal impairment[18]. Poor prognostic factors include renal failure at the time of onset, nephrotic syndrome, hypertension, and decreased factor XIII activity[5].

In young boys, *orchitis* is a rare manifestation of systemic disease. The *lung* is also a rare site of involvement, presenting as hemoptysis and/or pulmonary infiltrates due to diffuse alveolar hemorrhage[24].

Adult patients with IgAV present with clinical signs and symptoms similar to those in children. However, adults are more likely than children to: develop chronic renal insufficiency (up to 30%)[25]; have diarrhea and leukocytosis; require more aggressive therapy; and have a longer hospital stay[26]. Compared to younger adults, those >65 years of age are more likely to develop a 50% increase in serum creatinine and less likely to achieve clinical remission[27]. Lastly, adult patients with IgAV may have an underlying malignancy, most often cancer of a solid organ, in particular the lung[28]. Because 90% of the latter group are men, older male patients should be current with cancer screening guidelines and undergo symptom-based screening. However, there is no consensus regarding the recommended extent of the screening or the need for repeated screening.

Pathology

Histologically, LCV of the small dermal blood vessels is seen. In one series of adults with IgA vasculitis (age >40 years), an absence of dermal eosinophils was associated with an increased risk of renal involvement[29]. The presence of perivascular IgA deposition by DIF is the defining pathologic feature of IgAV (Fig. 24.8). Other immunoglobulins (C3, IgM, IgG) may be seen but are generally not as prominent as IgA and are considered nonspecific deposits. A few small studies have suggested that the presence of other findings, such as perivascular C3 or IgM deposits and papillary dermal edema, may be associated with an increased risk of renal involvement[30]. Of note, endothelial deposits of IgA are ~80% sensitive and specific for IgAV. Therefore, patients with signs and symptoms concerning for IgAV should be followed closely and treated appropriately for suspected systemic complications even if the DIF is negative for IgA[31].

Differential diagnosis

The clinical differential diagnosis includes any of the vasculitides involving small blood vessels (see Table 24.1), particularly CSVV, since the cutaneous findings in IgAV and CSVV can be indistinguishable. Several entities listed in Table 24.3, especially the first three categories, are also in the clinical differential diagnosis. Because vascular IgA deposition is not 100% sensitive or specific[32], the diagnosis of IgAV is supported by the presence of IgA in the appropriate clinical setting.

Treatment

As with other types of vasculitis, management of IgAV is dictated by the extent and severity of systemic and cutaneous manifestations. Because IgAV is generally self-limited, resolving over the course of weeks to months, treatment may be primarily supportive. For skin-limited IgAV, dapsone or colchicine may decrease the duration of cutaneous lesions and frequency of recurrences (see Table 24.10)[33]. Systemic corticosteroids are effective in treating associated arthritis and abdominal pain, as well as reducing the gastrointestinal complications and duration of skin lesions, but they do not prevent recurrences of purpura and are not suitable as a long-term therapy[34,35]. In adults, the following factors may predict relapsing disease: age >30 years, persistent purpura >1 month, abdominal pain, hematuria, an underlying systemic disorder, and absence of IgM on DIF[36].

In patients with renal involvement (e.g. microscopic hematuria, proteinuria), referral to a nephrologist is indicated. Corticosteroids have not been shown to be effective in preventing renal disease due to IgAV and are therefore not recommended. For example, a Cochrane review of interventions for preventing and treating IgAV nephritis found no difference in the risk of persistent kidney disease (up to 12 months following treatment) in children who received prednisone for 2–4 weeks at the time of presentation, as compared to placebo or supportive therapy[37]. In a randomized, double-blind, placebo-controlled trial involving 352 children with new-onset IgAV, early treatment with 14 days of prednisolone did not reduce the prevalence of proteinuria 12 months after disease onset[38]. For those who do develop evidence of IgAV nephritis, the treatment approach depends on disease severity and whether the patient is a child or adult. Individuals with limited evidence of renal involvement, mild proteinuria (<1 g/day), and normal serum creatinine warrant close monitoring and consideration for treatment with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Those with more significant proteinuria (≥1 g/day), elevated serum creatinine, or crescentic glomerulonephritis on kidney biopsy should initially receive, in addition to an ACEi or ARB, high-dose systemic corticosteroids. In sum, the current consensus is that corticosteroids do not prevent renal disease but should be used to treat severe nephritis[19].

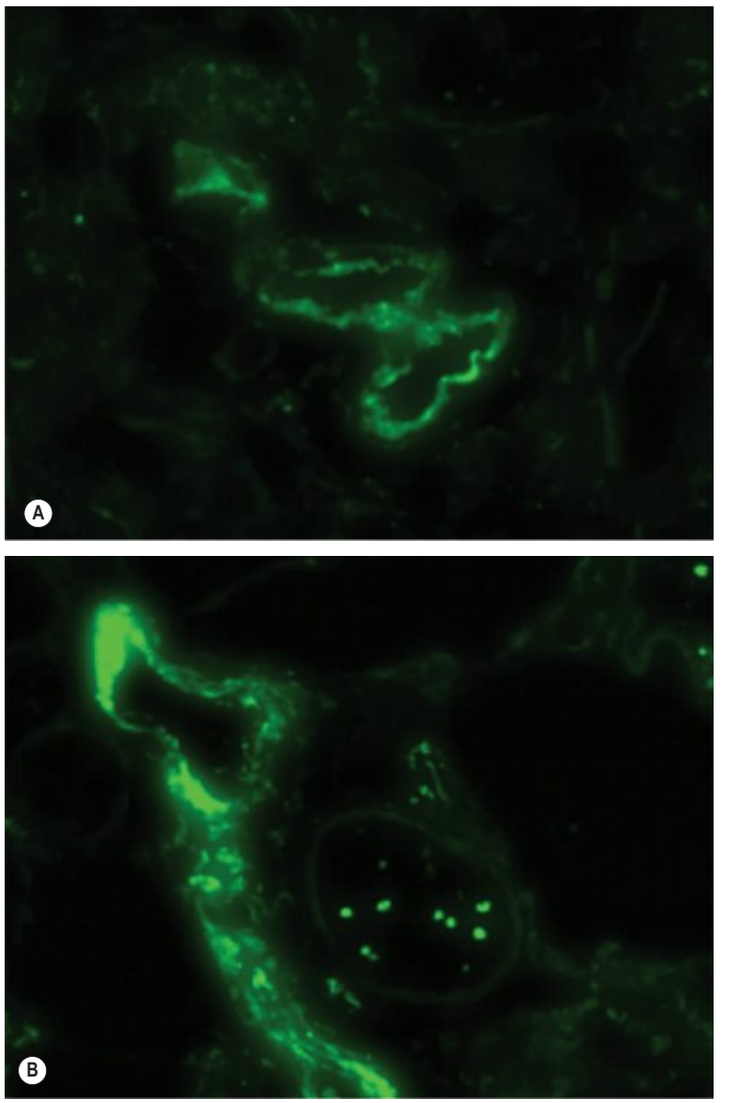


Fig. 24.8 Direct immunofluorescence microscopy of IgA vasculitis (Henoch–Schönlein purpura). A, B Strong staining for IgA within the walls of dermal blood vessels. *Courtesy Laura Najera, MD.*

Acute Hemorrhagic Edema of Infancy

Synonyms: ■ Acute hemorrhagic edema of childhood ■ Infantile acute hemorrhagic edema ■ Finkelstein disease ■ Seidlmayer syndrome ■ Finkelstein–Seidlmayer disease ■ Purpura en cocarde avec edema ■ Postinfectious cockade purpura

Key features

- Seen primarily in children between 4 and 24 months of age
- Annular, circular, or targetoid purpuric plaques on the face and extremities
- Tender, non-pitting edema of acral sites
- The child is well-appearing, and extracutaneous involvement is unusual
- Benign clinical course with spontaneous resolution within 1 to 3 weeks

Introduction

Acute hemorrhagic edema of infancy (AHEI) is an unusual form of small vessel vasculitis that usually affects children 4 to 24 months of age. Cutaneous lesions typically begin as plaques with variable degrees of hemorrhage and favor the head and extremities. They subsequently become edematous and targetoid in appearance. Previously considered a benign form of Henoch–Schönlein purpura (HSP), AHEI is now recognized as its own clinical entity.

Epidemiology

AHEI is a relatively rare disorder. It affects children <2 years of age, with ~70% of cases occurring in boys[39]. A seasonal variation is observed, with a peak incidence during the winter months.

Pathogenesis

Although the etiology of AHEI is unknown, up to 85% of patients have an associated infection, drug exposure, or immunization[40]. An infectious prodrome is observed in two-thirds of patients, most commonly a respiratory tract infection (80%), diarrheal illness (12%), or urinary tract infection (6%)[39]. There are multiple reported triggers, and they are listed in Table 24.5. As with other forms of small vessel vasculitis involving the skin, the pathogenesis of AHEI is thought to be due to immune complex deposition in response to an antigenic trigger.

TRIGGERS AND ASSOCIATIONS IN ACUTE HEMORRHAGIC EDEMA OF INFANCY AND URTICARIAL VASCULITIS	
Acute hemorrhagic edema of infancy – triggers	
Infections	
• Adenovirus	• Rotavirus
• Coxsackievirus	• Varicella zoster virus
• Cytomegalovirus	• *Campylobacter* spp.
• Epstein–Barr virus	• *Escherichia coli*
• Herpes simplex virus	• *Mycobacterium tuberculosis*
• Hepatitis A virus	• *Streptococcus* spp.
• Measles	
Medications	
• Acetaminophen	• Trimethoprim–sulfamethoxazole
• Penicillins	• NSAIDs
• Cephalosporins	
Urticarial vasculitis – associations	
Autoimmune connective tissue diseases (SLE, Sjögren syndrome)	
Serum sickness	
Cryoglobulinemia	
Infections	
• Hepatitis B virus	• Epstein–Barr virus
• Hepatitis C virus	• Lyme disease
	• SARS-CoV-2
Medications	
• Cimetidine	• Methotrexate
• Cocaine	• NSAIDs
• Diltiazem	• Potassium iodide
• Etanercept	• Procainamide
• Fluoxetine	• Procarbazine
• Infliximab	
Vaccines	
• Influenza (e.g. H1N1)	• SARS-CoV-2
Hematologic malignancies	
• Plasma cell dyscrasias (IgM, IgG, IgA)	
• Leukemias	
• Lymphomas	
• Castleman disease	
Solid organ malignancies – rare	
• Colon carcinoma	
• Renal cell carcinoma	

Table 24.5 Triggers and associations in acute hemorrhagic edema of infancy and urticarial vasculitis. NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

Clinical features

Children typically do not appear ill, although fever is present in ~45% of patients. The typical interval between the inciting event and the onset of disease is 1–2 weeks[41]. Cutaneous involvement presents abruptly with large erythematous patches or urticarial lesions that evolve into annular or targetoid purpuric plaques. The latter favor the cheeks, ears, and extremities (Fig. 24.9), but truncal involvement may also occur. Lesions may be asymptomatic, painful, or, less commonly, pruritic. Arcuate, polycyclic, scalloped, or rosette-shaped lesions and vesicobullae occur less commonly, as does healing with atrophic scars[41]. Tender, non-pitting edema of the face, ears, extremities (including the hands and feet), and scrotum is characteristic. Although mucosal and visceral involvement is unusual, oral petechiae, conjunctival injection, abdominal pain, arthralgias, glomerulonephritis, and intussusception (<1%) may occur[39,40,42]. The course is benign, with spontaneous and complete resolution without sequelae within 1 to 3 weeks. Although exacerbations may occur, once a remission has lasted 2 weeks, relapses as a rule are not observed[39].

Pathology

Leukocytoclastic vasculitis involving the capillaries and postcapillary venules of the upper and mid dermis is observed. Direct immunofluorescence reveals vascular deposition of a range of immunoreactants, including fibrinogen, C3, IgG, IgM, IgA, and IgE. IgA deposition is seen in ~10%–35% of cases[39].

Differential diagnosis

While AHEI was historically considered a variant of HSP, the distinct clinical presentation and infrequent presence of endothelial IgA deposits are distinguishing features. In young children with urticarial lesions and acrofacial edema, urticaria multiforme should be considered[43]. The differential diagnosis also includes erythema multiforme, urticaria, urticarial drug eruption, serum sickness-like reaction, Kawasaki disease, urticarial vasculitis, and Sweet syndrome. Given the significant cutaneous hemorrhage, trauma, acute meningococcemia, and purpura fulminans are sometimes considered. Routine laboratory tests are nonspecific, and the diagnosis is based on appropriate clinicopathologic correlation.

Treatment

Treatment is supportive (see Table 24.10). Antibiotics should be given to treat concurrent bacterial infections, if present. Antihistamines may be useful for symptomatic relief. Systemic corticosteroids have not been shown to alter the course of the disease, but they may be useful for ameliorating acute manifestations when severe[44].

Urticarial Vasculitis

Synonyms/Variants: ■ Normocomplementemic urticarial vasculitis ■ Hypocomplementemic urticarial vasculitis ■ Hypocomplementemic urticarial vasculitis syndrome ■ Anti-C1q vasculitis ■ McDuffie syndrome

Key features

- Recurrent urticarial lesions lasting >24 hours and resolving with bruise-like discoloration
- Two major subtypes: normocomplementemic and hypocomplementemic; low serum complement levels suggest systemic disease
- Clinical manifestations include constitutional symptoms, arthritis, and obstructive lung disease
- Associated with autoimmune connective tissue disease, especially systemic lupus erythematosus

Introduction

Urticarial vasculitis is a clinicopathologic entity consisting of persistent urticarial lesions that demonstrate the histopathologic features of LCV. Its association with autoimmune connective tissue disease and potential overlap with systemic lupus erythematosus (SLE) distinguish this disorder from typical CSVV. Although the relationship between urticarial vasculitis and neutrophilic urticaria is an area of debate, these and other related conditions (e.g. Still disease) may occur within a

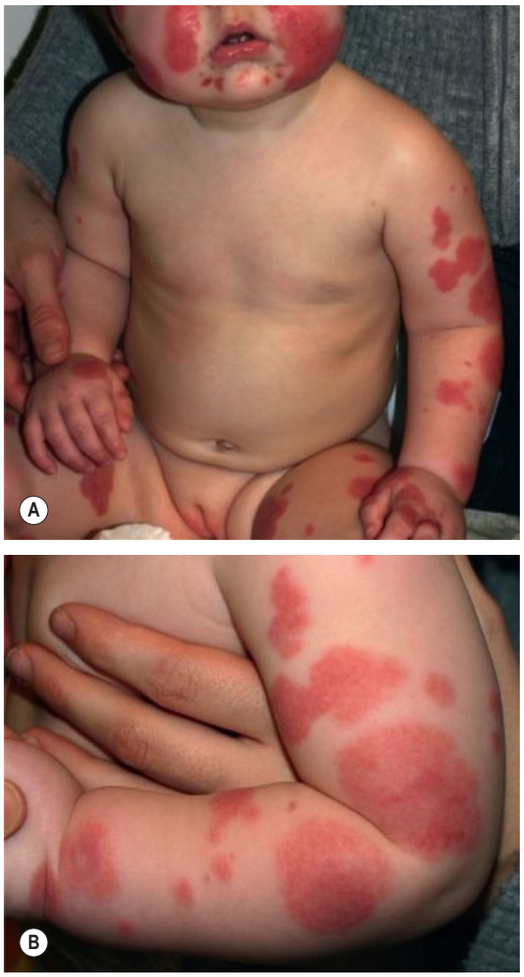


Fig. 24.9 Acute hemorrhagic edema of infancy. A, B Multiple edematous erythematous plaques on the face and extremities of a toddler. Some of the lesions have begun to become dusky. *Courtesy Ilona J. Frieden, MD.*



Fig. 24.10 Urticarial vasculitis. A Urticarial papules and purpuric macules in a patient with hypocomplementemic urticarial vasculitis. **B** Arcuate, dull violet plaques of the lower extremities. *B, Courtesy David A. Wetter, MD.*

spectrum (see below). For this chapter, the definition of urticarial vasculitis is as follows: urticarial lesions that histopathologically demonstrate vasculitis, as defined by a *minimum of leukocytoclasia with vessel wall necrosis*, with or without fibrinoid deposits, perivascular inflammation, or red blood cell extravasation[45].

Epidemiology

The population-based incidence of urticarial vasculitis is 5 cases per million per year[4]. In patients with chronic urticaria in whom a strict definition of urticarial vasculitis (see above) is applied, the prevalence of urticarial vasculitis is said to be ~5%[45], although this is likely an overestimation. The peak incidence is during the fifth decade, and 60%–80% of patients with urticarial vasculitis are female. The hypocomplementemic form occurs almost exclusively in women[46]. Approximately 70%–80% of cases of urticarial vasculitis are normocomplementemic, and they follow a benign course with an average duration of 3 years.

Pathogenesis

The pathogenesis of urticarial vasculitis is similar to that of typical CSVV. In urticarial vasculitis, it is thought that complement activation triggers mast cell release of inflammatory mediators such as TNF that in turn increase the expression of ICAM on mast cells (important for eosinophil transmigration) and E-selectin on endothelial cells[45].

Although urticarial vasculitis is most often idiopathic, it can be associated with autoimmune connective tissue diseases (especially SLE and Sjögren syndrome), serum sickness, cryoglobulinemia, infections, medications, and hematologic malignancies (see Table 24.5).

Clinical features

Lesions of urticarial vasculitis consist of erythematous, indurated wheals (Fig. 24.10), with or without angioedema, that favor the trunk and proximal extremities. Urticarial vasculitis is distinguished from chronic urticaria by the persistence of individual lesions beyond 24 hours, burning pain rather than pruritus, and the presence of purpura and/or postinflammatory hyperpigmentation. Blanching of the skin via diascopy may reveal a central red–purple or brown macule, suggesting vasculitis. However, these features are not always present. Rarely, bullae, erythema multiforme-like lesions, livedo reticularis, Raynaud phenomenon, and laryngeal edema are clinical manifestations of urticarial vasculitis[45].

When evaluating patients with urticarial lesions that histologically demonstrate features of LCV, the most important prognostic feature is the presence or absence of hypocomplementemia. Patients with normal complement levels tend to have skin-limited disease and are perhaps best considered to have a subset of CSVV with hive-like lesions. Those with hypocomplementemia are much more likely to have systemic manifestations, including gastrointestinal, joint, or renal involvement, and to meet diagnostic criteria for SLE[47]. The hypocomplementemic urticarial vasculitis syndrome (HUVS) is typically a more severe syndrome defined by specific diagnostic criteria[45]:

- *Two major criteria*: (1) urticaria for 6 months; and (2) hypocomplementemia – *plus* –
- *Two or more minor criteria*: (1) vasculitis on skin biopsy; (2) arthralgia or arthritis; (3) uveitis or episcleritis; (4) glomerulonephritis; (5) recurrent abdominal pain; or (6) positive C1q precipitin test with a low C1q level.

Patients with hypocomplementemia who do not meet the criteria for HUVS are considered to have hypocomplementemic urticarial vasculitis but not HUVS.

Musculoskeletal involvement is the most common extracutaneous manifestation of urticarial vasculitis. Arthralgias of the hands, elbows, knees, ankles, and feet occur in half of all patients with urticarial vasculitis, but up to 50% of patients with HUVS have frank arthritis[45]. Up to 20% of patients with HUVS have *pulmonary* symptoms which can

resemble asthma or chronic obstructive pulmonary disease (COPD) and include cough, dyspnea, hemoptysis, laryngeal edema, and pleural effusions[14]. COPD is especially severe in smokers with urticarial vasculitis, and it is worse than would be expected due to smoking alone; therefore, patients should be told to avoid smoking. *Renal* involvement, manifesting as proteinuria or microscopic hematuria, occurs in up to 15% of patients with HUVS[45]. *Gastrointestinal* manifestations (abdominal pain, nausea, vomiting, diarrhea) occur in up to 30% of patients. Cardiac and central nervous system involvement are rare but reported. HUVS shares features with SLE, but distinctive clinical findings in HUVS include *ocular* inflammation (30%; conjunctivitis, episcleritis, iritis, uveitis), angioedema (50%), and COPD-like symptoms (20%)[45]. In a study of 57 patients with hypocomplementemic urticarial vasculitis, various systemic manifestations were observed, including ocular (56%), pulmonary (19%), gastrointestinal (18%), and renal (14%)[47].

In patients with urticarial vasculitis, the most common abnormal laboratory studies are an elevated ESR, low serum C3 and C4 levels, and a positive ANA. HUVS is usually marked by low serum complement levels (which may vary from non-detectable to normal, even during flares) plus the presence of anti-C1q precipitin and depressed C1q levels. Although up to a third of patients with SLE have circulating anti-C1q antibodies, and up to half of patients with HUVS have a positive ANA, patients with HUVS rarely have anti-dsDNA or anti-Sm antibodies[45].

Pathology

Histologically, urticarial vasculitis is defined as the presence of leukocytoclasia with vessel wall necrosis, with or without fibrinoid deposits, perivascular inflammation, or red blood cell extravasation[45]. In one series, an interstitial neutrophilic infiltrate was more commonly observed in patients with the hypocomplementemic form of urticarial vasculitis[46]. Eosinophils may also be noted. Although findings can be subtle and consist only of interstitial neutrophils or perivascular lymphocytes with extravasated erythrocytes (especially in older lesions), these findings alone do not fulfill the histologic criteria for the diagnosis of urticarial vasculitis.

By DIF, 70% of lesions demonstrate deposits of immunoglobulin, C3, or fibrinogen around blood vessels. A granular pattern of immunoreactants along the basement membrane zone occurs in ~80% of lesions and, when accompanied by hypocomplementemia, suggests the diagnosis of SLE. Basement membrane immunoreactants have also been associated with renal disease[45].

Differential diagnosis

The main entity in the differential diagnosis is urticaria (including delayed pressure urticaria, in which lesions can last longer than 24 hours). Urticarial vasculitis should also be distinguished from neutrophilic urticaria, which, although considered by some to be within the spectrum of urticarial vasculitis, is not associated with hypocomplementemia or autoimmune disease and is better thought of as a subset of urticaria that histologically demonstrates a neutrophilic infiltrate without vasculitis. The differential diagnosis also includes disorders that clinicopathologically present with urticarial lesions and an interstitial neutrophilic infiltrate (i.e. neutrophilic urticarial dermatosis)[48], including Schnitzler syndrome, adult-onset Still disease, and cryopyrin-associated periodic syndromes (see Ch. 45). Additional entities to consider are the urticarial phase of bullous pemphigoid, atypical erythema multiforme, urticaria multiforme[43], Sweet syndrome, tumid lupus erythematosus, SLE (see above), and rheumatoid neutrophilic dermatitis. For lesions of angioedema, the differential diagnosis includes acquired and inherited forms of angioedema (see Ch. 18).

Treatment

No randomized clinical trials have been performed to evaluate possible therapeutic options for urticarial vasculitis. Antihistamines may reduce the swelling and pain associated with cutaneous lesions but do not alter the course of the disease. Oral corticosteroids are effective, but the duration of use should be kept to a minimum (see Ch. 125). Indomethacin, dapsone (with or without pentoxifylline), colchicine, hydroxychloroquine, and mycophenolate mofetil have all been reported to be beneficial (see Table 24.10). Rituximab, omalizumab, anakinra, and canakinumab have been reported to improve recalcitrant hypocomplementemic urticarial vasculitis[49].

Erythema Elevatum Diutinum

Key features

- Symmetric, red–violet to red–brown papules and plaques
- Persistent lesions develop on extensor surfaces
- Fibrosing leukocytoclastic vasculitis

Introduction

Erythema elevatum diutinum (EED) is a rare, chronic dermatosis characterized by red–violet to red–brown papules, plaques, and nodules that favor extensor surfaces. Histopathologic features consist of LCV in early lesions, followed by fibrotic replacement of the dermis in older lesions.

Epidemiology

EED is rare, with descriptions of several hundred cases in the literature. The disease can develop at any age but is more common in middle-aged and older adults (ages 30–60 years). An earlier onset occurs more often in the setting of HIV infection[50]. The male-to-female ratio is approximately equal, and no racial predilection has been observed[51].

Pathogenesis

Although the etiology of EED is unknown, circulating immune complexes, with repeated deposition, associated inflammation and partial healing, are thought to represent the underlying pathogenesis[50]. Immune complex deposition results in complement activation, neutrophilic infiltration, and the release of destructive enzymes. The latter results in fibrin deposition in and around small dermal vessels during the later stages of the disease.

EED has been described in association with a number of systemic diseases, including infections, autoimmune diseases, and both benign and malignant hematologic disorders, especially IgA monoclonal gammopathy. Associated infections include β-hemolytic streptococci, HBV, HIV, tuberculosis, and syphilis[50]. Lesions identical to EED, both clinically and histologically, have been reproduced by the intradermal injection of streptococcal antigen into non-lesional skin of patients with EED[51]. In patients with HIV infection, EED may be due to either HIV-related antigen–antibody complexes directly damaging small blood vessels or HIV-induced immunosuppression allowing other infectious agents to serve as the antigenic stimulus.

Autoimmune or inflammatory conditions associated with EED include granulomatosis with polyangiitis (formerly Wegener granulomatosis), inflammatory bowel disease, celiac disease, relapsing polychondritis, SLE, and rheumatoid arthritis. In addition to plasma cell dyscrasias (especially IgA monoclonal gammopathy), associated hematologic disorders include myelodysplasia, myeloproliferative disorders, and hairy cell leukemia.

Clinical features

The typical cutaneous lesions of EED are violaceous, red–brown or yellowish papules, plaques, or nodules that are symmetrically distributed. They favor acral and periarticular sites, in particular the extensor surfaces of the elbows, knees, ankles, hands, and fingers (Fig. 24.11). Additional sites of involvement include the face, retroauricular area, trunk, axillae, buttocks, and genitalia[52]. Initially, the lesions are erythematous, but with time they become red–brown or violaceous in color as well as doughy or firm to palpation due to fibrosis.

In general, the lesions are asymptomatic, but they can be associated with a burning sensation or pruritus, especially early on[50]. Annular plaques with a raised border[52] and verrucous plaques on the soles[53] have also been described. Nodular lesions, primarily palmoplantar, that progress to form bulky masses are characteristic of EED in the setting of HIV infection[54]. Arthralgias may develop in underlying joints[51], but extracutaneous involvement, with the exception of ocular disease, is extremely rare. There have been reports of associated peripheral keratitis, nodular scleritis, panuveitis, and blindness[55,56]. The disease is chronic and has a relapsing and remitting course; the majority of cases resolve spontaneously over a period of 5 to 10 years, but the disease can last up to 40 years[51].

In patients presenting with EED, evaluation for an associated infection (e.g. streptococcal, viral hepatitis, HIV, syphilis), monoclonal

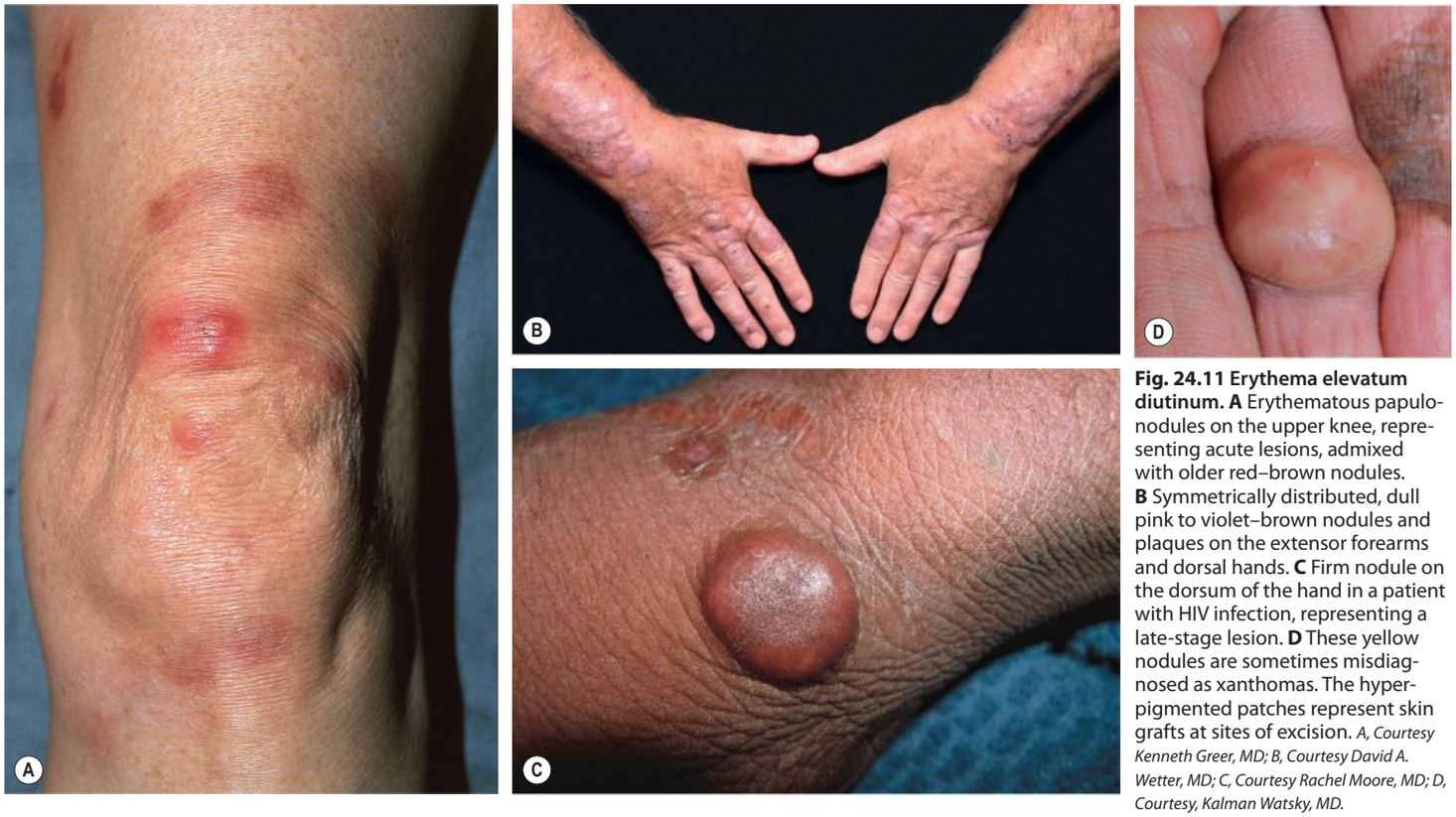


Fig. 24.11 Erythema elevatum diutinum. A Erythematous papulonodules on the upper knee, representing acute lesions, admixed with older red–brown nodules. **B** Symmetrically distributed, dull pink to violet–brown nodules and plaques on the extensor forearms and dorsal hands. **C** Firm nodule on the dorsum of the hand in a patient with HIV infection, representing a late-stage lesion. **D** These yellow nodules are sometimes misdiagnosed as xanthomas. The hyperpigmented patches represent skin grafts at sites of excision. *A, Courtesy Kenneth Greer, MD; B, Courtesy David A. Wetter, MD; C, Courtesy Rachel Moore, MD; D, Courtesy, Kalman Watsky, MD.*

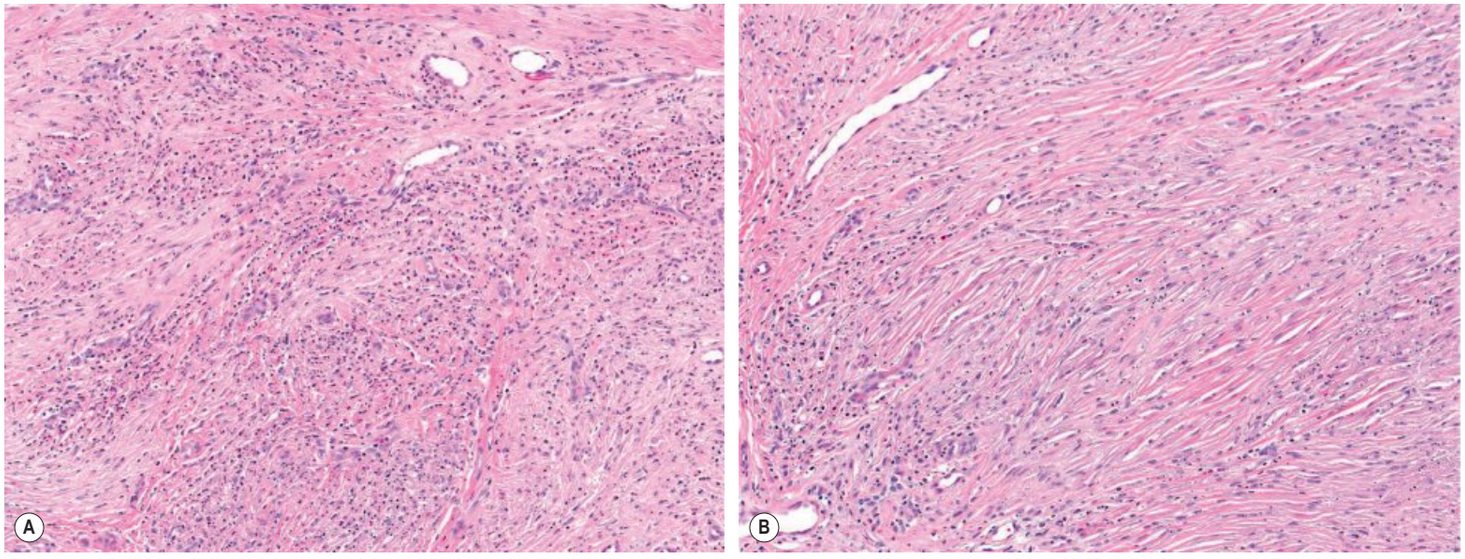


Fig. 24.12 Erythema elevatum diutinum – histopathologic features. A An early-stage lesion: dense neutrophilic infiltrates with focal leukocytoclastic vasculitis. **B** A late-stage lesion: a sparser inflammatory infiltrate and marked fibrosis. *Courtesy Lawrence E. Gibson, MD.*

gammopathy (serum immunofixation electrophoresis), or autoimmune disorder (see above) should be considered, based upon the clinical context.

Pathology

Early lesions of EED demonstrate the changes of LCV, with a neutrophilic infiltrate within the upper and mid dermis (Fig. 24.12A), admixed with some eosinophils. Involvement of the papillary and perifollicular adventitial dermis (without a grenz zone) is observed in more mature lesions[57]. The latter are also characterized by the presence of granulation tissue and perivascular, concentric, or storiform fibrosis plus mixed inflammation that is composed predominantly of neutrophils. In the late stage, capillary walls may have fibrinoid necrosis or fibrosis (Fig. 24.12B); vertically oriented capillaries can also be seen, and it may be difficult to discern the features of vasculitis. Intracellular lipidosis, previously termed "extracellular cholesterolosis", is a classic finding in late-stage lesions[58].

Differential diagnosis

The clinical differential diagnosis depends upon the stage of the lesion. For earlier lesions, one can consider neutrophilic dermatoses (e.g. Sweet syndrome, rheumatoid neutrophilic dermatitis) and palisaded neutrophilic and granulomatous dermatitis. Late-stage lesions may be confused primarily with tuberous xanthomas, granuloma annulare, rheumatoid nodules, fibroid nodules of *Borrelia*, and multicentric reticulohistiocytosis. Other granulomatous disorders (e.g. sarcoidosis, Hansen disease [leprosy], necrobiotic xanthogranuloma) are sometimes in the differential diagnosis, and for an isolated lesion, dermatofibroma or dermatofibrosarcoma protuberans (DFSP). Occasionally, lesions with a prominent vascular component, especially in an HIV-infected patient, might be mistaken for Kaposi sarcoma or bacillary angiomatosis.

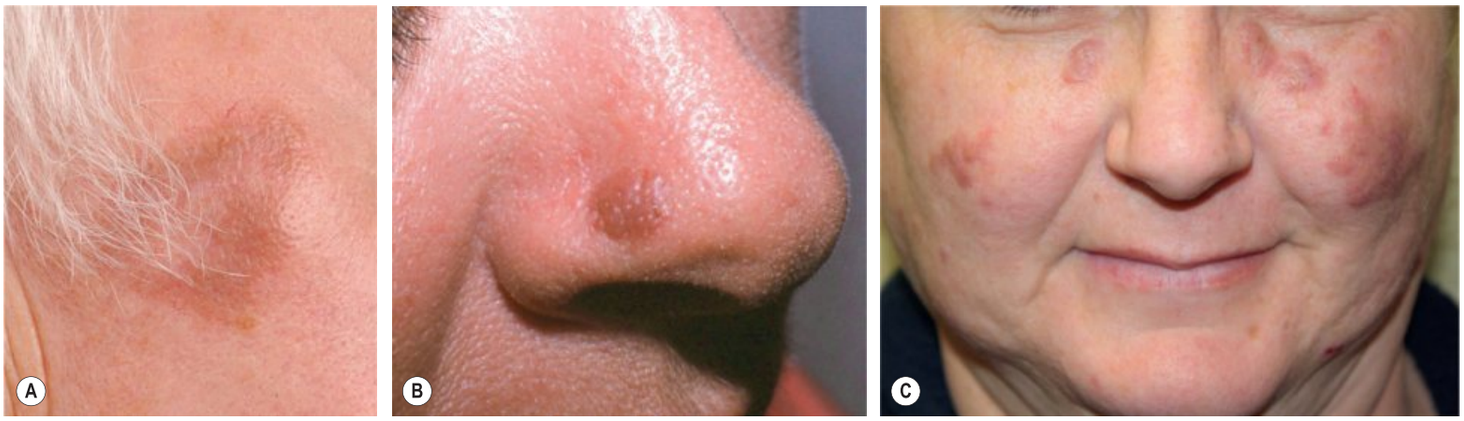


Fig. 24.13 Granuloma faciale. A Single light brown plaque of the lateral malar cheek. **B** Single red–brown papule of the nose. Clues to the diagnosis include prominent follicular openings and a lack of secondary changes such as scale. **C** Less commonly, patients present with multiple lesions. *A, Courtesy Department of Dermatology, Medical University of Graz; B, Courtesy Cloyce L. Stetson, MD; C, Courtesy Jeffrey P. Callen, MD.*

Histologically, the earliest lesions may share features with the neutrophilic dermatoses, but foci of LCV help to distinguish EED. Granuloma faciale may also be considered, but a predominance of eosinophils and plasma cells and the presence of a grenz zone are distinguishing features, as is the localization of lesions to the face. The differential diagnosis of later lesions includes tuberous xanthomas, fibrotic disorders or tumors (e.g. DFSP; see Chs. 98 & 116), and, occasionally, fibroid nodules of *Borrelia*, Kaposi sarcoma, and bacillary angiomatosis[50].

Treatment

Dapsone is the mainstay therapeutically[59], but relapses frequently occur upon discontinuation. If present, treatment of any associated infection or underlying systemic disorder is also recommended. Other therapies include NSAIDs, niacinamide, tetracyclines, chloroquine, colchicine, and plasmapheresis (see Table 24.10). Intralesional corticosteroids may be helpful for mild cases, but systemic corticosteroids are rarely indicated.

Granuloma Faciale

Key features

- Firm red–brown or violaceous plaques or nodules, often solitary and most commonly on the face
- Histologic features of small vessel vasculitis, with dense dermal infiltrates of neutrophils, lymphocytes and plasma cells, admixed with numerous eosinophils; the inflammation spares the upper papillary dermis (grenz zone), and fibrosis may be present

Introduction

Granuloma faciale is a chronic inflammatory dermatosis characterized by red–brown to violaceous plaques or nodules. The face is the most common site of involvement and lesions are more often solitary than multiple. Because histologic features of vasculitis are frequently present, the disease can be classified as a subtype of skin-limited vasculitis.

Epidemiology

Granuloma faciale occurs predominantly in middle-aged White men but has been observed in Black and Asian men as well as women.

Pathogenesis

While the precise pathogenesis remains unknown, granuloma faciale is thought to be a localized form of skin-limited small vessel vasculitis. Direct immunofluorescence (DIF) microscopy demonstrates granular deposition of IgG, IgA, IgM, and/or C3 in blood vessel walls, a nonspecific finding that suggests a role for immune complex-mediated vascular damage. Interferon-γ and increased IL-5 production have been implicated as potentially important disease mediators[60]. An increased ratio of IgG4-:IgG-bearing circulating plasma cells and/or relative increases of IgG4-positive plasma cells in skin lesions has been observed, but patients do not typically meet consensus criteria for IgG4-related disease[61].

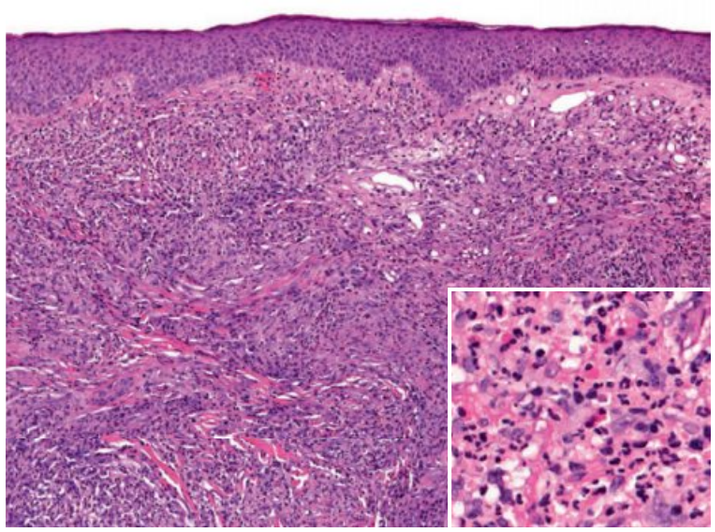


Fig. 24.14 Granuloma faciale – histopathologic features. Dense diffuse dermal inflammation with a grenz zone. Inset shows mixed infiltrate of lymphocytes, eosinophils, neutrophils, and plasma cells. *Courtesy Lorenzo Cerroni, MD.*

Clinical features

Granuloma faciale usually presents as a solitary, asymptomatic, red–brown or violaceous plaque on the face, with a predilection for the forehead, cheek, and preauricular area (Fig. 24.13A,B). Less often, multiple papules or plaques may be present (Fig. 24.13C); in one retrospective analysis of 66 patients, one-third had more than one lesion[62]. Uncommon locations for granuloma faciale include the ears, scalp, trunk, and extremities; in the previously cited study, 7% of patients had extrafacial involvement. The individual lesions tend to persist and only occasionally resolve spontaneously. Granuloma faciale has not been associated with systemic disease.

Pathology

In the dermis, there are perivascular and interstitial infiltrates of neutrophils, lymphocytes, and plasma cells, admixed with numerous eosinophils. Characteristically, the inflammation spares the upper papillary dermis, resulting in a "grenz zone" (Fig. 24.14). Features of leukocytoclastic vasculitis are most prominent early on, with older lesions tending to have fewer neutrophils and more eosinophils and plasma cells, as well as fibrosis. Because of the presence of eosinophils, IgG4-bearing plasma cells, and lamellar fibrosis, granuloma faciale can resemble IgG4-related disease histologically (see Table 26.2)[63].

Differential diagnosis

The clinical differential diagnosis of granuloma faciale includes cutaneous lymphoma, persistent arthropod bite reactions, angiolymphoid hyperplasia with eosinophilia, tumid lupus erythematosus, and

several granulomatous disorders (e.g. sarcoidosis, Hansen disease, granulomatous rosacea). The histopathology of granuloma faciale may have features in common with rheumatoid neutrophilic dermatitis, neutrophilic dermatosis associated with lupus erythematosus, epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia), or arthropod bite reaction. Granuloma faciale may also resemble erythema elevatum diutinum (EED), both clinically and histopathologically. However, EED presents as multiple red–brown papules, plaques, or nodules in a symmetric distribution on the extensor aspects of the extremities, with a predilection for skin that overlies joints. Fibrosis also tends to be more pronounced, and lipid-laden macrophages may be seen in EED, but not in granuloma faciale.

Treatment

Because of the facial location, treatment is often desired. Unfortunately, granuloma faciale is frequently resistant to therapy. Topical or intralesional corticosteroids (e.g. triamcinolone suspension 2.5–5 mg/ml) and topical calcineurin inhibitors (pimecrolimus, tacrolimus) are first-line therapeutic options. Prolonged therapy (e.g. 3–6 months) may be necessary for improvement. As with other recalcitrant dermatoses, there are several alternatives with reported efficacy, including topical and oral dapsone (50–150 mg daily), topical ruxolitinib, hydroxychloroquine, clofazimine (300 mg daily), topical PUVA, and TNF inhibitors[64].

Cryosurgery[65], electrosurgery, surgical excision, dermabrasion, and CO_2 or pulsed dye laser therapy may be effective, but each carries a risk of scarring given the depth of inflammation. In addition, recurrence after excision has been reported. Laser therapy targeting the prominent vascular component (e.g. 595 nm pulsed dye laser, 532 nm potassium titanyl phosphate laser) has led to improvement in a number of patients.

PREDOMINANTLY SMALL AND MEDIUM-SIZED VESSEL VASCULITIDES

Cryoglobulinemic Vasculitis

Synonyms: ■ Type II or III cryoglobulinemia ■ Mixed cryoglobulinemia ■ Cryoglobulinemic purpura ■ Essential cryoglobulinemic vasculitis

Key features

- Associated with mixed cryoglobulinemia (IgM and IgG), most commonly in the setting of hepatitis C virus (HCV) infection
- Palpable purpura, typically on the lower extremities
- Myalgias and arthralgias
- Peripheral neuropathy and glomerulonephritis

Introduction

Cryoglobulins are cold-precipitable immunoglobulins that can be divided into three subtypes, all of which have cutaneous manifestations (Table 24.6). Type I cryoglobulinemia, composed primarily of monoclonal IgM (and less frequently IgG > IgA), results in microvascular occlusion without vasculitis (see Ch. 23). In contrast, vasculitis is seen with type II and III cryoglobulins, also referred to as "mixed cryoglobulins," because they are composed of polyclonal IgGs – the autoantigens – and monoclonal or polyclonal IgMs, respectively. The IgM autoantibodies bind other antibodies and therefore have rheumatoid factor activity. Approximately 15% of patients with circulating mixed cryoglobulins present with symptoms due to cryoglobulinemic vasculitis[14]. Cryoglobulinemic vasculitis typically affects the skin, joints, peripheral nervous system, and kidneys.

Epidemiology

The frequency of mixed cryoglobulinemia varies according to geographic location; e.g. there is a higher prevalence in Southern Europe than in Northern Europe or North America[66]. In northwest Spain, the annual incidence was determined to be 4.8 cases per million. Geographic variations in the frequency of mixed cryoglobulinemia likely reflect differences in the prevalence of HCV infection. While 40%–60% of patients with HCV infection have cryoglobulinemia, overt cryoglobulinemic vasculitis develops in ~5%–30% of these individuals[67].

Pathogenesis

Mixed cryoglobulinemia occurs in the setting of specific infections, autoimmune connective tissue diseases, and hematologic malignancies[66] (see Table 24.6). When the association between HCV infection and mixed cryoglobulinemia was discovered in 1989, a cause for 80%–90% of "essential" cryoglobulinemia became apparent. Only 5% of cases are associated with HBV infection, and occasionally, HIV, EBV, cytomegalovirus, *Leishmania*, and *Treponema* spp. have been implicated[68]. In a minority of patients, mixed cryoglobulinemia has been associated with autoimmune connective tissue diseases, in particular Sjögren syndrome, SLE, and rheumatoid arthritis. Approximately 5% of the patients with mixed cryoglobulinemia have a lymphoproliferative disorder (e.g. B cell non-Hodgkin lymphoma, chronic lymphocytic leukemia, macroglobulinemia).

It is thought the underlying infectious, autoimmune, or lymphoproliferative disease causes B cell stimulation and proliferation, resulting in expansion of cryoglobulin-producing B cell clones. A significant percentage of lymphocytes in HCV-infected individuals possess a t(14;18) translocation that results in a rearrangement of *bcl-2*, whose protein product has an anti-apoptotic function; this can lead to B lymphocyte proliferation and may contribute to production of cryoglobulins. In HCV-infected patients who do not possess this *bcl-2* rearrangement, B cell activation and subsequent cryoglobulin and autoantibody production is believed to result from chronic immune stimulation by the virus[66]. For these reasons, patients with mixed cryglobulinemia are at increased risk of developing B cell non-Hodgkin lymphoma[69,70].

Cryoglobulinemic vasculitis occurs when immune complexes form from circulating cryoglobulins and deposit within the walls of small blood vessels. As with other forms of immune complex-mediated vasculitis, this immune complex deposition initiates complement activation and vascular inflammation. The presence of the hepatitis C virion (in association with IgM and IgG antibodies) within vessel walls raises the possibility that viral particles are a component of the cryoprecipitate[66].

CLASSIFICATION OF CRYOGLOBULINS				
Subtype	**Molecular composition**	**Associations**	**Pathophysiology**	**Clinical manifestations**
I	Monoclonal IgM > IgG*	Plasma cell dyscrasias, lymphoproliferative disorders	Vascular occlusion	Raynaud phenomenon, retiform purpura, gangrene, acrocyanosis
II†	Monoclonal IgM‡ (>IgG‡) against polyclonal IgG	HCV ≫ HBV, HIV; autoimmune connective tissue diseases (e.g. Sjögren syndrome); lymphoproliferative disorders (e.g. B cell non-Hodgkin lymphoma, CLL); subacute bacterial endocarditis	Vasculitis	Small and medium-sized vessel vasculitis: palpable purpura, livedo reticularis, retiform purpura, necrosis, and ulceration Arthralgias, peripheral neuropathy, glomerulonephritis
III†	Polyclonal IgM‡ against polyclonal IgG			

*Rarely IgA.
†Referred to as "mixed" cryoglobulins because either monoclonal or polyclonal immunoglobulins bind to polyclonal immunoglobulins.
‡Typically have rheumatoid factor activity (i.e. are directed against the Fc portion of IgG).

Table 24.6 Classification of cryoglobulins. See Chapter 23 for discussion of type I cryoglobulinemia. CLL, chronic lymphocytic leukemia; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Clinical features

Cutaneous involvement occurs in nearly all patients with cryoglobulinemic vasculitis, most commonly manifesting as palpable purpura of the lower extremities (Fig. 24.15). Other cutaneous findings include livedo reticularis, retiform purpura, necrosis, and ulceration, reflecting a mixture of small and medium-sized vessel vasculitis. Skin lesions are not typically cold-induced, in contrast to the vascular occlusive lesions seen in type I cryoglobulinemia. The condition usually has a chronic course[71], but in those with HCV-associated disease, more effective direct-acting viral agents for treating HCV may be curative (see below).

Common extracutaneous findings at the time of presentation include weakness (80%), arthritis or arthralgias (70%), peripheral (typically sensory) neuropathy (60%), gastrointestinal disease or hepatitis (60%), and membranoproliferative glomerulonephritis (20%)[71]. The hepatitis reflects the underlying viral infection or an associated autoimmune hepatitis and is not a direct result of the cryoglobulinemia. Occasionally, patients have xerostomia or xerophthalmia, as seen in Sjögren syndrome.

The most commonly associated infections, autoimmune connective tissue diseases, and hematologic disorders are listed in the Pathogenesis section. B cell non-Hodgkin lymphoma is the most common associated malignancy. Rarely, solid tumors such as hepatocellular carcinoma and papillary thyroid carcinoma have been reported to have a relationship with cryoglobulinemic vasculitis.

Tests for circulating cryoglobulins are often falsely negative. Specimens should be drawn during a flare using collection tubes prewarmed to 37°C without anticoagulants. The specimen should be kept at 37°C and transported directly to the laboratory to prevent cryoprecipitation. If clinical suspicion remains high, negative tests should be repeated. By contrast, rheumatoid factor is frequently positive in patients with mixed cryoglobulinemia (~70% of patients), often at high levels. Patients typically have low serum complement levels, often with low or undetectable C4 levels; however, complement levels do not necessarily correlate with the severity of the disease[66]. HBV, HCV, and HIV serologies should be evaluated, followed by a determination of viral load if there is evidence of infection. Up to 15% of patients with mixed cryoglobulinemia have a monoclonal gammopathy as detected by serum protein electrophoresis and/or immunofixation electrophoresis[14].



Fig. 24.15 Cryoglobulinemic vasculitis. A Palpable purpura of the lower extremities. **B** Purpuric papules and retiform plaques with central necrosis and ulceration in a patient with type II cryoglobulinemia secondary to hepatitis C viral infection. These cutaneous manifestations reflect a "mixed" pattern of both small and medium-sized vessel vasculitis. The patient also had an elevated rheumatoid factor, decreased C4, and an IgM monoclonal gammopathy.
B, Courtesy David A. Wetter MD.

Pathology

Histologically, features of LCV are seen. DIF reveals granular deposits consisting predominantly of IgM and C3 in a vascular pattern in the papillary dermis[5].

Differential diagnosis

The differential diagnosis of cryoglobulinemic vasculitis includes all forms of vasculitis affecting small or medium-sized vessels (see Table 24.1). Cryoglobulinemic vasculitis can be differentiated from these disorders based upon the appropriate context and by the detection of circulating mixed cryoglobulins. Patients with Sjögren syndrome can also have arthralgias, arthritis, xerostomia/xerophthalmia, and the presence of rheumatoid factor and/or mixed cryoglobulins; however, they are typically SSA (Ro)/SSB (La)-positive, have distinct histopathologic findings in salivary gland biopsies, and less frequently are found to have hepatitis, glomerulonephritis, or hypocomplementemia[66].

Treatment

The treatment of mixed cryoglobulinemia should be directed at any underlying disease. In patients with mild manifestations of vasculitis, that may be sufficient. In general, those with moderate or severe disease should first receive immunosuppressive therapy until they have stabilized clinically, then therapy for the underlying condition can be initiated. All patients with HCV-associated mixed cryoglobulinemia should be treated with antiviral therapy (see Table 24.10). Direct-acting antiviral agents are significantly more effective and better tolerated than previous interferon-containing regimens. Observational studies suggest antiviral regimens are effective in attaining a sustained virologic response, as well as improving vasculitic symptoms among those with HCV-associated cryoglobulinemic vasculitis. In a study of 148 patients, >95% had a complete or partial clinical response, with a median follow-up of 15.3 months[72]. While rates of clinical improvement are high, correlating with sustained virologic response, clonal production of cryoglobulins persists in some patients, leading to relapses of vasculitis.

Patients with mild manifestations of cryoglobulinemic vasculitis (e.g. purpura, arthralgias, mild sensory neuropathy) may respond to agents such as colchicine or dapsone and/or symptomatic management with nonsteroidal anti-inflammatory drugs (NSAIDs) or gabapentin. Those with moderate to severe disease should receive high-dose systemic corticosteroids in combination with rituximab. Evidence from randomized trials and cohort studies demonstrate the efficacy and safety of this regimen compared to conventional therapy with systemic corticosteroids, either alone or in combination with cyclophosphamide[73,74]. In addition, plasma exchange should be considered in those with acute life-threatening disease, including pulmonary hemorrhage, rapidly progressive crescentic glomerulonephritis, and hyperviscosity syndrome. As expected, prognosis depends on the severity of organ involvement and the underlying disease[75]. In non-infectious mixed cryoglobulinemic vasculitis, predictors of early relapse include purpura, cutaneous necrosis, and articular involvement[76].

ANCA-Associated Vasculitides

Introduction

The ANCA-associated vasculitides (AAVs) are characterized by vasculitis of small to medium-sized vessels, the presence of ANCAs, and an overlapping spectrum of organ involvement, with each having distinguishing clinical and laboratory features. New ACR-EULAR classification criteria for these diseases have been proposed[3]. The three AAVs discussed here are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (Table 24.7).

ANCAs are predominantly IgG autoantibodies directed against components of both primary granules of neutrophils and monocyte lysosomes, and they likely have an important role in the pathogenesis of AAVs via interactions with primed neutrophils and endothelial cells. By immunofluorescent staining, there are two vasculitis-relevant patterns: (1) cytoplasmic (c)-ANCAs – directed against the antigen proteinase

ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA)-ASSOCIATED VASCULITIDES			
Disorder	**Cutaneous and oral findings**	**Extracutaneous manifestations**	**Histologic findings¶**

Granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis) [most often *c-ANCA/anti-PR3 antibody*]	• Purpuric macules and papules
	• Friable, papular gingivae ("strawberry gums"), oral ulcers
	• PNGD*
	• Subcutaneous nodules
	• Pyoderma gangrenosum-like ulcers
		• **Upper respiratory**:
		  • *bloody nasal discharge, nasal crusting, or sino-nasal congestion*
		  • *cartilaginous involvement (e.g. saddle nose)*
		  • *conductive or sensorineural hearing loss*
		  • *inflammation or consolidaton of nasal/paranasal sinuses on imaging*
		  • subglottic stenosis
		• **Pulmonary**: *nodules, mass, or cavitation*†
		• **Renal**: *pauci-immune glomerulonephritis*
		• **Ocular:** proptosis, scleritis
		• Less often neurologic, GI, and cardiac involvement
			• *Granulomatous inflammation*
			• Vasculitis of small ± medium-sized vessels

Microscopic polyangiitis (MPA) [most often p-ANCA/anti-MPO antibody]	• Purpuric macules and papules • Erythematous macules, urticarial or purpuric plaques • Livedo racemosa, ulcers, splinter hemorrhages	• **Renal**: *pauci-immune glomerulonephritis* • **Pulmonary**: capillaritis/hemorrhage, *lung fibrosis or interstitial lung disease* • **Neurologic**: mononeuritis multiplex • *Absence of sino-nasal symptoms or signs*; cardiac, GI, or ocular involvement	• Vasculitis of small ± medium-sized vessels • No granulomas

Eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg–Strauss syndrome‡) [most often ANCA-negative or p-ANCA/anti-MPO antibody]	• Purpuric macules and papules
	• PNGD*
	• Subcutaneous nodules
	• Urticarial plaques
	• Livedo racemosa, retiform purpura, ulcers
		• **Upper respiratory**: paranasal sinusitis†, allergic rhinitis§, *nasal polyps*§
		• **Pulmonary**:
		  • *obstructive airway disease* (asthma)§
		  • non-fixed infiltrate†
		• **Hematologic**: *peripheral eosinophilia (>10%)*, elevated IgE
		• **Neurologic**: *mononeuritis multiplex*
		• **Cardiac**: myo- or pericarditis
		• Less often renal, GI, and ocular involvement
			• *Extravascular eosinophils*
			• Granulomatous inflammation
			• Vasculitis of small ± medium-sized vessels

*Palisaded neutrophilic and granulomatous dermatitis, which typically presents with umbilicated, crusted papulonodules on extensor surfaces (e.g., elbows) or the face (especially in GPA).
†Evidence via computed tomography (CT).
‡Occasionally triggered by leukotriene inhibitors or omalizumab and/or rapid discontinuation of corticosteroid therapy (see text).
¶May be observed in biopsies of the skin, mucosa, respiratory tract, kidney, or nerve.
§Usually the initial manifestations.

Table 24.7 Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs). See Fig. 24.16 for frequencies of specific ANCAs in each of these disorders. As in other forms of vasculitis, patients often have constitutional symptoms (e.g., fevers, malaise, weight loss), arthralgias, and arthritis. Features included in evidence-based classification criteria for each disorder are *italicized*; the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria are weighted criteria which have been validated for use in research. GI, gastrointestinal; MPO, myeloperoxidase; PR3, proteinase 3.

3 (PR3); and (2) perinuclear (p)-ANCAs – directed against the antigen myeloperoxidase (MPO), with other antigens (e.g. lactoferrin, cathepsin G, elastase) serving as targets in the setting of nonspecific inflammation. ANCAs are useful diagnostically and for monitoring disease activity[77]. However, these autoantibodies are also found in patients receiving certain medications (e.g. propylthiouracil, hydralazine) and who have underlying chronic infections, rheumatologic or inflammatory disorders, and malignancies (see Table 40.6)[77].

In order to improve specificity with regard to AAVs, an indirect immunofluorescence (IIF) test should be used as a screening evaluation to detect perinuclear versus cytoplasmic staining, followed by an ELISA that specifically detects anti-PR3 and anti-MPO antibodies. However, up to 5% of serum samples are positive by ELISA only, so when there is a high index of suspicion for AAV, the ELISA should be performed even if the IIF screening test is negative. Because neither anti-PR3 ANCA nor anti-MPO ANCA is specific for a particular AAV and patients with AAV may be ANCA-negative, clinicopathologic correlation is required when evaluating a patient with suspected AAV (Fig. 24.16). Semi-quantitative analysis may allow for disease monitoring and response to treatment since the persistence of ANCAs following remission has been associated with disease relapse[78]. Furthermore, there is growing recognition that ANCA type (anti-PR3 versus anti-MPO) is perhaps more clinically and prognostically meaningful than is disease type (GPA versus MPA), such that experts and clinical trialists increasingly refer to AAV by ANCA type and stratify clinical trial enrollment accordingly.

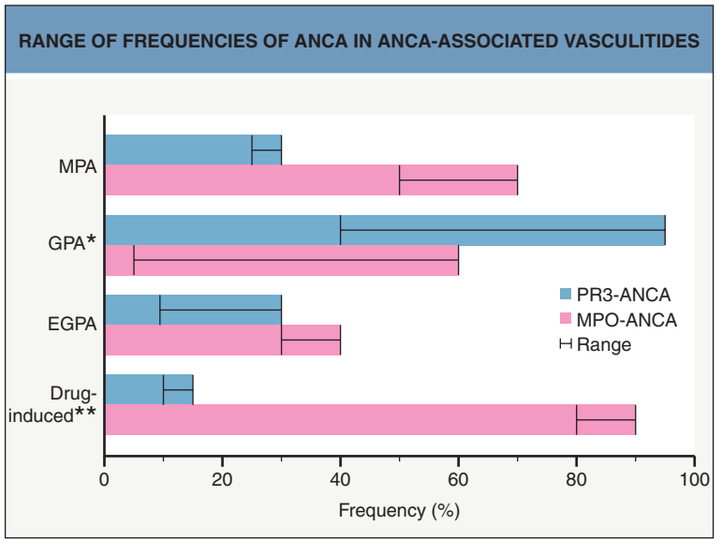


Fig. 24.16 Range of frequencies of ANCA in ANCA-associated vasculitides. Variability reflects differences in cohorts studied, disease extent and severity at time of assays, diagnostic criteria, and cutoff values of various ANCA assays. Negative ANCA testing does not exclude the presence of an ANCA-associated vasculitis, as overall frequencies for ANCA positivity are 90% (generalized GPA), 60% (limited GPA), 90% (MPA), and 50% (EGPA), respectively. *MPO-ANCAs are overrepresented in Chinese patients with GPA; 10% of non-Chinese patients with GPA have MPO-ANCAs[72]. **Examples include propylthiouracil, minocycline, hydralazine, and levamisole-tainted cocaine (see Tables 24.4 and 40.6). Note that other ANCA specificities may be detected in drug-induced vasculitis. ANCA, anti-neutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3. *Adapted from Wiik AS, Rheum Dis Clin NA. 2010;36:479–89.*

Epidemiology

In a population-based study of biopsy-proven small vessel vasculitis of the skin, the annual incidence of an underlying AAV was 4 cases per million[4], i.e. ~10% of the patients had an AAV, emphasizing the importance of considering this group of disorders. Conversely, cutaneous manifestations are a common presenting feature of AAV, occurring in a third of patients[79].

Pathogenesis

The pathogenesis of AAV, depicted in Fig. 24.1B, is complex and includes genetic as well as environmental factors. Key elements include: autoreactive B-lymphocytes that produce ANCAs; abnormal T-regulatory function which allows persistent T cell activation, especially of Th17 cells; neutrophils that cause tissue damage via injury to vascular epithelium; and activation of the alternative complement pathway, namely C5a, and neutrophil extracellular traps (NETs) which drive vascular inflammation[80].

Natural history, clinical features, and treatment

The morbidity and mortality of AAVs are relatively high, stemming from associated end-organ damage as well as complications of immunosuppressive therapy[81]. Delay in diagnosis, renal impairment, propensity for relapse, the presence of ANCAs, and older age are risk factors for reduced survival. The three major AAVs are discussed in the following sections, including clinicopathologic features (see Table 24.7)[82], as well as treatment options (see Table 24.10).

Granulomatosis With Polyangiitis

Synonym: ▪ Wegener granulomatosis (historical)

Key features

- Necrotizing granulomatous inflammation of the upper and lower respiratory tracts
- Pauci-immune glomerulonephritis
- Systemic vasculitis that can involve the skin and oral mucosa
- c-ANCA and anti-PR3 antibodies most commonly detected

Introduction

Granulomatosis with polyangiitis (GPA) is classically described as the triad of granulomatous inflammation of the upper and lower respiratory tracts, systemic necrotizing vasculitis, and pauci-immune glomerulonephritis. Patients with GPA exist along a spectrum of severity, depending upon the number of organs involved and the degree of functional impairment. Those with organ- or life-threatening disease have a high mortality rate if left untreated, while patients without organ- or life-threatening GPA have primarily airway disease without constitutional symptoms or systemic vasculitis. The initial evaluation of patients with GPA should establish the extent of organ involvement, as evidence supports distinct treatment approaches based upon disease severity[81]. However, because this disorder can evolve over time, patients initially without organ- or life-threatening disease must still be closely monitored.

Epidemiology

The incidence of GPA varies widely by geographic region and is estimated to be 0.4 to 12 cases per million per year. The disease occurs most often in White individuals, with a peak age of onset of 45–65 years.

Pathogenesis

The pathophysiology of GPA is reflected in two clinicopathologic hallmarks of the disease – granuloma formation and small to medium-sized vessel vasculitis. Activity of alpha-1 antitrypsin, a proteinase inhibitor, has been found to be markedly reduced in patients with GPA[83], while ANCAs, environmental factors, and genetic polymorphisms (e.g. *PTPN22* 620W allele) all contribute to immune dysregulation.

Although the specific pathogenic roles of PR3 or anti-PR3 antibodies remain unclear, surface expression of PR3 on apoptotic and/or activated neutrophils may stimulate dendritic cell maturation and proinflammatory cytokine release by antigen-presenting cells, thereby favoring development of Th1-mediated granuloma formation (termed "*neutrophil priming*"). Expression of PR3 on the cell surface of neutrophils may impede phagocytosis by macrophages, thus prolonging the opportunity for autoantibody development. In turn, ANCAs binding to PR3 on neutrophils result in vessel damage (e.g. pauci-immune or nonimmune complex-mediated vasculitis; see Fig. 24.1B)[77,84]. Neutrophil priming may occur as a result of certain infections, such as *Staphylococcus aureus*. Of note, nasal carriage of *S. aureus* is associated with relapse of GPA, and treatment of nasal carriage with antibiotics improves outcomes.

Clinical features

Patients with GPA typically present with nonspecific symptoms such as fever, malaise, weight loss, arthralgias, and myalgias. In one-third of patients, mucocutaneous involvement is a presenting feature[79]. While the most common lesions are petechiae and purpuric macules and papules that may be painful, subcutaneous nodules, nonspecific rashes, and ulcerations that can resemble pyoderma gangrenosum may also be seen (Fig. 24.17). Papulonecrotic lesions are common and usually occur on extensor surfaces, particularly the elbows. They are sometimes referred to as Churg–Strauss nodules. Cutaneous involvement may be prognostically important, as it has been associated with an increased risk of severe systemic manifestations of GPA, including glomerulonephritis and alveolar hemorrhage[79].

The *upper or lower respiratory tracts* are involved in up to 90% of patients with GPA. Nasal, sinus, tracheal, and ear involvement represent the presenting complaints in >70% of patients. Suggestive symptoms and signs include recurrent epistaxis, mucosal ulcerations, nasal septal perforation, and saddle nose deformity. Patients with pulmonary involvement typically present with dyspnea, cough, hemoptysis, or pleuritis, and chest X-rays demonstrate irregular infiltrates or nodules. *Renal disease* is present in only 20% of patients at presentation, but ~75% of patients eventually develop glomerulonephritis[85]. Other organ systems commonly affected by necrotizing vasculitis in GPA include musculoskeletal (70%), ocular (30%–60%), neurologic (20%–50%), gastrointestinal (5%–10%), and cardiac (5%–40%).

Laboratory findings are consistent with an inflammatory process, including elevated acute phase reactants (ESR, C-reactive protein), anemia, and leukocytosis. The frequencies of ANCAs are depicted in Fig. 24.16 and vary depending upon disease activity and severity. Patients with GPA most frequently have circulating c-ANCAs and anti-PR3 antibodies. Those with renal involvement may have proteinuria, hematuria, or an active urine sediment with red blood cell casts, as well as progressive renal failure. Additional diagnostic testing that assists in assessing for systemic involvement and excluding alternative diagnoses is outlined in Table 24.8.

Pathology

The diagnosis of GPA should be confirmed or corroborated histologically whenever possible. In one large series of patients with GPA, skin biopsies were performed in only a minority (29%) of patients, but they were thought to be diagnostic of vasculitis in 82%[79]. Histologic findings may be nonspecific (e.g. perivascular lymphocytic infiltrates), or they may demonstrate LCV and/or granulomatous inflammation. Biopsies of the papulonecrotic lesions (Churg–Strauss nodules) show a palisading neutrophilic dermatitis with areas of granulomatous inflammation surrounding foci of basophilic necrobiosis, i.e. palisaded neutrophilic and granulomatous dermatitis (PNGD; see Ch. 93).

Differential diagnosis

The primary differential diagnosis for GPA includes the other AAVs, given the shared and overlapping features of these diseases. Additional disorders and their distinguishing features are outlined in Table 24.9.

Treatment

Treatment of GPA consists of an initial induction regimen followed by maintenance therapy, with the goal of inducing and maintaining a long-term, relapse-free remission. The standard therapy for patients with organ- or life-threatening disease (e.g. active glomerulonephritis, pulmonary hemorrhage) is systemic corticosteroids (e.g. 1 mg/kg/day of prednisone) in conjunction with either rituximab or cyclophosphamide (see Table 24.10). There is some practice variation regarding which of the two is chosen. The combination of corticosteroids and oral cyclophosphamide results in a complete remission in up to 75% of patients and a ~90% survival rate[85]. However, two seminal randomized trials demonstrated comparable efficacy for rituximab-based regimens[86,87]. Given the more favorable side-effect profile of rituximab, many authors now prefer this agent for initial therapy. With regard to corticosteroids, a reduced-dose, 4- to 6-month tapering regimen is recommended for



Fig. 24.17 Granulomatosis with polyangiitis. A Ulceration on the leg, which may be misdiagnosed as pyoderma gangrenosum. **B** Ulceration of the tongue. **C** Subungual digital infarcts. **D** Purpuric macules and papules with central crusts due to small vessel vasculitis (leukocytoclastic vasculitis). **E** Papules and papulonodules with central scale-crust on the elbow (also referred to as Churg–Strauss nodules). **F** Friable papules of the gingivae ("strawberry gums"). *A, Courtesy David A. Wetter MD; E, Courtesy Jeffrey Gelhausen, MD and Nan Ring, MD.*

POSSIBLE ADDITIONAL DIAGNOSTIC TESTING FOR PATIENTS WITH SUSPECTED ANCA-ASSOCIATED VASCULITIDES								
	Chest X-ray and/or chest CT scan	**Electromyogram/ nerve conduction studies**	**Lung, nerve, or kidney biopsy**	**Upper respiratory tract or muscle biopsy**	**ECG, echocardiogram**	**CT scan of sinuses**	**Serum IgE level**	**Consider GI and ophthalmologic examination**
Granulomatosis with polyangiitis (GPA)	√	√	√*	√*	√	√		√
Microscopic polyangiitis (MPA)	√	√	√					
Eosinophilic granulomatosis with polyangiitis (EGPA)	√	√	√		√	√	√	√
*Depends upon signs and symptoms.								

Table 24.8 Possible additional diagnostic testing for patients with suspected ANCA-associated vasculitis. This is in addition to the general evaluation outlined in Fig. 24.19. ANCA, anti-neutrophil cytoplasmic antibody; CT, computed tomography; ECG, electrocardiogram; GI, gastrointestinal.

most patients; this is based upon randomized trial data demonstrating similar remission rates and fewer adverse events when compared to standard regimens[88,89]. Following induction of a remission, a maintenance regimen is initiated to try to prevent disease relapse. Although rituximab is generally favored for maintenance therapy[90], azathioprine, methotrexate, and mycophenolate mofetil may be reasonable alternatives depending on various patient-specific factors. Risk factors for relapse include PR3-ANCA positivity. The typical duration of maintenance therapy is 1 to 2 years.

Those *without* organ- or life-threatening disease as well as no renal dysfunction may receive weekly methotrexate (20–25 mg) as initial therapy and later as maintenance therapy, in combination with lower starting doses of corticosteroids (0.5 mg/kg/day prednisone equivalent). This regimen successfully induces a remission in most patients, but it is associated with a higher relapse rate[91]. Rituximab is also a reasonable option for these patients.

Recent work has led to a shift away from broader, more profound immunosuppression towards more targeted agents, resulting from improved understanding of disease pathophysiology. A phase III study evaluating the safety and efficacy of avacopan (an oral C5a inhibitor) as maintenance therapy found a higher sustained remission rate in the avacopan group than in the prednisone group, with similar rates of serious adverse events and approximately one-third the mean total dose of corticosteroids[92].

Additional alternative treatment regimens are summarized in Table 24.10.

Microscopic Polyangiitis

Synonym: ■ Microscopic polyarteritis

Key features

- Vasculitis of capillaries, venules, and medium-sized arteries
- Constitutional symptoms, crescentic necrotizing glomerulonephritis, and alveolar hemorrhage
- Purpura, livedo reticularis, and livedo racemosa
- p-ANCA and anti-MPO antibodies most commonly detected
- Absence of granuloma formation

KEY DISORDERS IN THE DIFFERENTIAL DIAGNOSIS OF ANCA-ASSOCIATED VASCULITIS AND THEIR DISTINGUISHING FEATURES		
ANCA-positive vasculitic syndrome	**Disorder in differential diagnosis**	**Distinguishing features of the disorder in the differential diagnosis**
Granulomatosis with polyangiitis (GPA)	Eosinophilic granulomatosis with polyangiitis	• Eosinophilia • Asthma • Lower incidence of severe renal disease
	Microscopic polyangiitis	• Absence of granulomatous inflammation
	NK/T cell lymphoma	• Destructive nasal midline lesion (see Table 45.3) • Characteristic histology
	Tuberculosis (lupus vulgaris), Hansen disease	• Destructive nasal midline lesion • Characteristic histologic features and laboratory findings
	Cocaine-induced destructive nasal midline lesion	• By ELISA, ANCAs are positive for both human neutrophil elastase and proteinase 3 • Neutropenia
	Goodpasture syndrome	• Kidney-bound or circulating anti-glomerular basement membrane antibodies
	SLE or rheumatoid vasculitis	• Distinct rheumatologic serologies • Develops in individuals with longstanding, poorly controlled disease
Microscopic polyangiitis (MPA)	Eosinophilic granulomatosis with polyangiitis	• Eosinophilia • Asthma and sinus disease • Increased incidence of cardiac involvement
	Granulomatosis with polyangiitis	• Granulomatous inflammation • Increased incidence of ocular and severe upper respiratory tract involvement
	Polyarteritis nodosa	• Absence of glomerulonephritis • Vasculitis of renal arteries with renovascular hypertension • Lower incidence of pulmonary involvement • ANCA-negative
	Goodpasture syndrome, SLE, rheumatoid vasculitis	• See above
Eosinophilic granulomatosis with polyangiitis (EGPA)	Microscopic polyangiitis	• No granulomatous inflammation • No history of asthma • No hypereosinophilia
	Granulomatosis with polyangiitis	• Increased incidence of glomerulonephritis • Lower incidence of cardiac or peripheral nerve involvement
	Hypereosinophilia, secondary	• Absence of vasculitic manifestations • Due to medications, parasitic infections, allergic disease, malignancy
	Hypereosinophilic syndrome	• Absence of vasculitic manifestations • Diagnosis of exclusion

Table 24.9 Key disorders in the differential diagnosis of ANCA-associated vasculitis and their distinguishing features. ANCAs, anti-neutrophil cytoplasmic antibodies; ELISA, enzyme-linked immunosorbent assay; SLE, systemic lupus erythematosus.

THERAPEUTIC LADDER FOR PATIENTS WITH VASCULITIS						
Disorder	**First-line treatment**	**Evidence levels**	**Second-line treatment**	**Evidence levels**	**Third-line treatment**	**Evidence levels**
Cutaneous small vessel vasculitis	Discontinue incriminated drugs Supportive care Treat underlying infections, neoplasms NSAIDs Antihistamines	 3 3	Colchicine (0.6 mg BID–TID) Dapsone (50–200 mg/day) CS	2[e1] 3[e2] 2[e3], 3[14]	AZA (2 mg/kg/day) MMF MTX IVIg CSA CYC Rituximab PEX	3[e4] 3[e5] 3[e6] 3[14] 3[14] 3[14] 3[e7] 3[14]
IgA vasculitis (Henoch–Schönlein purpura)	Supportive care		Dapsone Colchicine CS AZA ± CS CYC ± CS CSA ± CS Antihistamines	2[e8] 3 1[35,38], 2[e9] 2[e10–e12] 2[e10,e13,e14] 3[e13,e15,e16]	IVIg Rituximab MMF CS + tacrolimus ACA PEX	3[e17] 3[e18] 2[e19–e22] 3[e13] 2[e23] 2[e24], 3[e25,e26]

Table 24.10 Therapeutic ladder for patients with vasculitis.

Continued

THERAPEUTIC LADDER FOR PATIENTS WITH VASCULITIS						
Disorder	**First-line treatment**	**Evidence levels**	**Second-line treatment**	**Evidence levels**	**Third-line treatment**	**Evidence levels**
Acute hemorrhagic edema of infancy	Supportive care	3[e27]			CS	3[44,e27]
Urticarial vasculitis	Antihistamines Indomethacin Dapsone (100–200 mg/day) ± pentoxifylline CS	3[49] 3[49] 2[49,e28] 2[49]	Colchicine (0.6 mg BID–TID) HCQ AZA MTX	2[49,e29] 2[49,e30] 2[49] 2[49]	MMF IVIg Rituximab CSA PEX Canakinumab Tocilizumab Omalizumab CYC	2[49,e31] 3[49,e32,e33] 2[49,e34] 3[49] 3[49,e35] 2[e36] 3[e37] 3[e38] 2[47]
Erythema elevatum diutinum	NSAIDs Intralesional CS Dapsone	3 3 3[59]	Colchicine Chloroquine Tetracyclines	3 3 3	Niacinamide PEX	3 3
Cryoglobulinemic vasculitis (+ HCV)	CS + rituximab Direct-acting antivirals (e.g. sofosbuvir-velpatasvir)*	1[73,74,e39,e40] 1[67,72,e40,e41]	CS + CYC CS	3[e41,e42] 3[e41,e42]	Colchicine Dapsone IVIg PEX	3[e43] 3 3[e44] 3[e41,e42]
Cutaneous polyarteritis nodosa (cutaneous arteritis)	NSAIDs CS (topical, intralesional or oral)	3[e45] 2[e46,e47]	Dapsone Colchicine AZA MTX (15–25 mg/wk)	3[e45] 3[e45] 3[e46,e47] 3[e48]	Pentoxifylline HCQ IVIg MMF TNF inhibitors	3[e45] 3[e45] 3[e49] 3[e46,e47] 3
Systemic polyarteritis nodosa	CS CS + PEX + antiviral therapy (e.g. entecavir)	2[106] 2[112,121,e50,e51]	CS + CYC MTX (15–25 mg/wk) AZA	2[106,e51] 3 2[120]	IVIg	3
Granulomatosis with polyangiitis Microscopic polyangiitis (induction regimen)	CS + rituximab CS + CYC CS + MTX (non-life-threatening disease only)	1[86,87] 1[85] 1[91,e52]	CS + CYC + PEX CS + rituximab + CYC	1[89] 1[87]	MMF IVIg PEX Infliximab	3[e53] 3[e54] 3 2[e55,e56]
Granulomatosis with polyangiitis Microscopic polyangiitis (maintenance regimen)	Rituximab	1[90]	AZA MTX	1[e57,e58] 1[e57]	MMF CS + CYC TMP-SMX Leflunomide	2[e59,e60] 2[85] 1[e61] 1[e62]
Eosinophilic granulomatosis with polyangiitis	CS	2[106,108]	CS + CYC or rituximab (severe disease) Mepolizumab	2[106,107] 1[109]	IVIg ± PEX Rituximab AZA MMF MTX IFN-α	2[e63] 3[e64,e65] 2[e66,108] 3[e67] 3[e66,108] 3[e68,e69]

*Long-term control of HCV-associated mixed cryoglobulinemia can only be achieved via a treatment regimen that incorporates anti-hepatitis C viral therapy.

Table 24.10 Therapeutic ladder for patients with vasculitis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. ACA, aminocaproic acid; AZA, azathioprine; BID, two times daily; CS, corticosteroids; CYC, cyclophosphamide; CSA, cyclosporine; HBV, hepatitis B virus; HCQ, hydroxychloroquine; HCV, hepatitis C virus; IFN, interferon; IVIg, intravenous immunoglobulin; MTX, methotrexate; MMF, mycophenolate mofetil; NSAIDs, nonsteroidal anti-inflammatory drugs; PEX, plasmapheresis; TID, three times daily; TMP–SMX, trimethoprim–sulfamethoxazole; TNF, tumor necrosis factor. Additional references cited in this table (e) are available in the online content.

Introduction

Microscopic polyangiitis (MPA) is a systemic vasculitis involving small and medium-sized blood vessels that most commonly affects the skin, lungs, and kidneys. More than 90% of patients are ANCA-positive (most commonly p-ANCA and anti-MPO antibodies), but granulomatous inflammation is usually absent. Because the clinical features of MPA and GPA overlap considerably, it may at times be difficult to differentiate between these two entities. Given these similarities, most therapeutic trials of AAV include both patients with MPA and those with GPA or stratify enrollment by ANCA type (anti-MPO or anti-PR3 antibodies).

Epidemiology

The estimated annual incidence of MPA is 0.5 to 24 cases per million. The condition occurs most commonly in East Asia. The reported mean age of onset is 57 years, with a peak incidence between the ages of 65 and 75 years[93].

Pathogenesis

Similar to GPA, the etiology of MPA is largely attributed to the presence of autoreactive ANCAs, which form in the presence of proinflammatory cytokines and recognize exposed neutrophilic antigens. In MPA, ANCAs bind primarily to MPO, resulting in vascular damage. The precise role of predisposing genetic, environmental, and other factors is unknown[94] (see general Pathogenesis).

Clinical features

Most patients with MPA initially experience constitutional symptoms, such as fever, weight loss, arthralgias and myalgias, for months to years before other symptoms appear. Depending upon the series, 20%–70% of patients will have cutaneous involvement, most commonly petechiae and purpura (Fig. 24.18). Livedo reticularis and livedo racemosa are more often seen in MPA than in GPA or EGPA[79]. Other cutaneous findings may include a nonspecific rash, painful papules or nodules, and ulcers or gangrene[95]. Skin involvement is associated with higher rates of neurologic and musculoskeletal vasculitic manifestations but lower rates of renal and pulmonary complications[79].

Renal involvement occurs in nearly all patients with MPA (>90%); a pauci-immune, crescentic, necrotizing glomerulonephritis is the primary pathology, as in GPA. *Pulmonary* capillaritis (with dyspnea and pulmonary infiltrates) occurs in 30%–50% of patients and can result in diffuse alveolar hemorrhage (10%). Interstitial lung disease can also develop, occurring more often in MPA than in GPA[96]. *Neurologic* involvement is commonly observed and it usually presents as a peripheral neuropathy or mononeuritis multiplex in up to one-third of patients. Upper respiratory tract involvement occurs as well, but it is less common and less destructive than in GPA. The progressive clinical course of MPA typically leads to renal failure and/or pulmonary hemorrhage.

Anti-MPO antibodies (55%–65% of patients) are detected more often than anti-PR3 antibodies (20%–30%) (see Fig. 24.16). Uncommonly, patients may be ANCA-negative. Additional diagnostic testing for systemic involvement is outlined in Table 24.8, and Fig. 24.19 outlines an approach to the patient with suspected vasculitis.





Fig. 24.18 Microscopic polyangiitis. **A** Petechiae and purpuric macules on the lower extremity; some of the lesions have central hemorrhagic crusts. Histologically, leukocytoclastic vasculitis was seen. **B** Petechiae and multiple purpuric macules with central necrosis on the plantar surface. *A, Courtesy David A. Wetter, MD; B, Courtesy Cara Whitney Hannon, MD and Robert Swerlick, MD.*

Pathology

The characteristic histologic findings include a segmental necrotizing vasculitis of small blood vessels (capillaries, venules, and arterioles) and, less often, a vasculitis of small and/or medium-sized arteries[79]. Granulomatous inflammation is absent.

Differential diagnosis

MPA frequently presents with petechiae and purpura and constitutional symptoms. If no additional internal organ involvement is evident at initial presentation, it may be difficult to distinguish MPA from CSVV or other types of vasculitis involving small blood vessels. The differential diagnosis includes the entities listed in Table 24.9.

Treatment

The treatment approach for MPA is the same as that for GPA, consisting of both an induction phase and a maintenance phase. As stated previously, because these two conditions are related, with overlapping features and outcomes, recent clinical trials have included patients with both diseases. To induce remission in patients with organ- or life-threatening disease such as active glomerulonephritis or pulmonary hemorrhage, corticosteroids (e.g. initial prednisone dose of 1 mg/kg/day) plus either rituximab (usually preferred) or cyclophosphamide are recommended (see Table 24.10)[86]. A reduced-dose, tapering regimen of corticosteroids should be employed, if possible. Maintenance therapy with rituximab should be initiated after remission has been achieved; alternatives include azathioprine, methotrexate, or mycophenolate mofetil[90]. Those *without* organ- or life-threatening disease may be treated with corticosteroids and weekly methotrexate or rituximab. The role of plasma exchange in the initial management of GPA and MPA is controversial[89].

Patients with MPA have a lower risk of relapse compared to those with GPA. In both disorders, the presence of anti-PR3 antibodies and persistent or rising ANCA titers are associated with an increased risk of relapse after remission.

Eosinophilic Granulomatosis With Polyangiitis

Synonyms: ■ Churg–Strauss syndrome ■ Churg–Strauss vasculitis ■ Allergic angiitis and granulomatosis

Key features

- Prodromal asthma and allergic rhinitis are followed by eosinophilic and vasculitic phases
- Peripheral eosinophilia and ANCA-positivity in half of patients (usually p-ANCA and anti-MPO antibodies)
- Cutaneous manifestations in ~50% of patients
- Most commonly pulmonary, neurologic, renal, and cardiac involvement
- Histologic features consist of eosinophils, extravascular granulomas, and vasculitis

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), also referred to as Churg–Strauss syndrome, is characterized by vascular and extravascular granulomas, eosinophil-rich pulmonary infiltrates, and necrotizing vasculitis that involves small to medium-sized vessels within multiple organ systems. It is distinguished by an association with asthma and eosinophilia.

Epidemiology

Although the true incidence of EGPA is unknown due to uncertainties surrounding its diagnosis, it is thought to be the least common of the ANCA-associated vasculitides. EGPA has an estimated incidence ranging from 0.5 to 2.7 cases per million per year[97]. The mean age at diagnosis is 40 years, and it has no sex predominance. The incidence of EGPA in patients with asthma ranges from 35 to 65 per million per year.

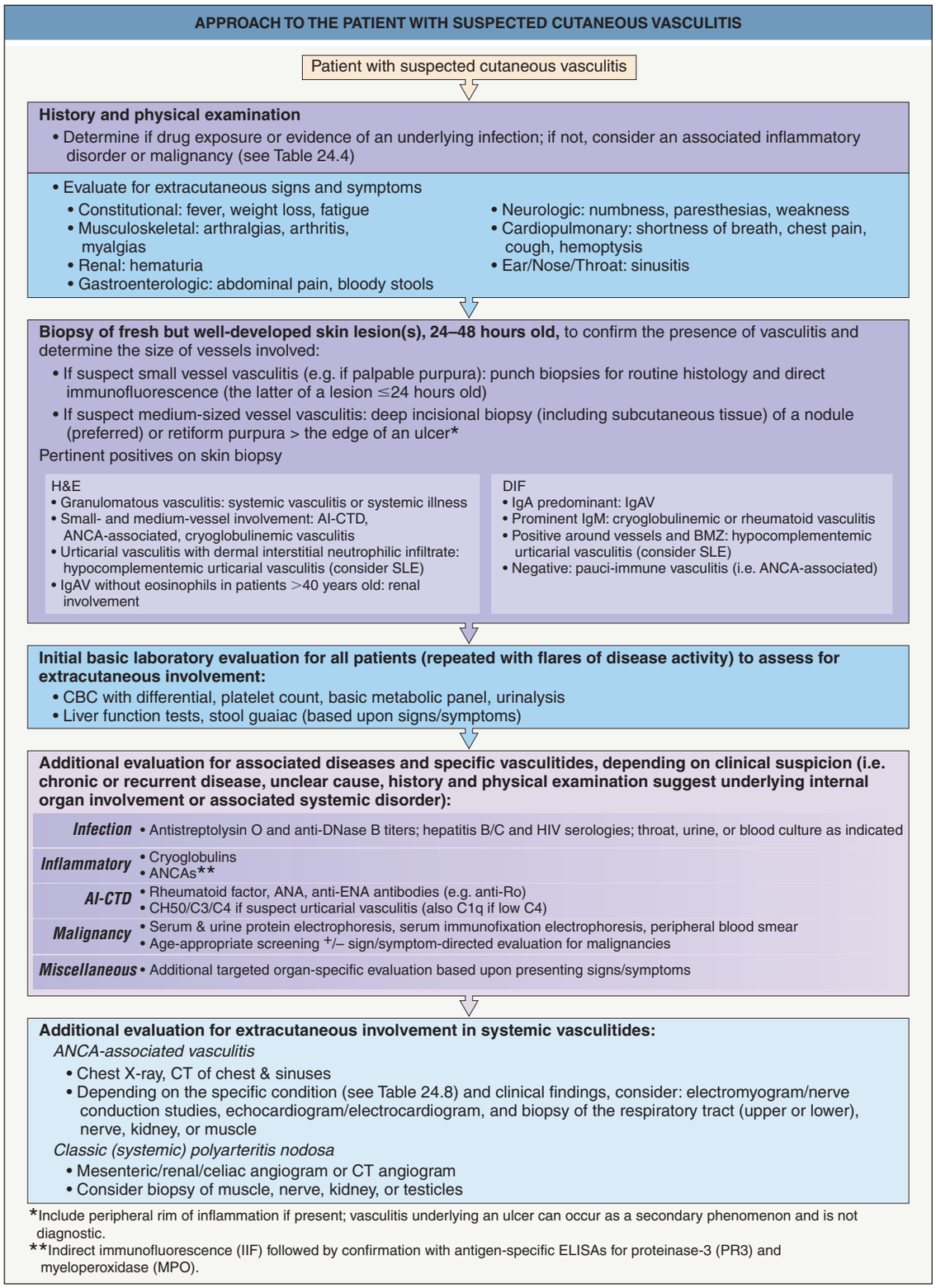


Fig. 24.19 Approach to the patient with suspected cutaneous vasculitis. AI-CTD, autoimmune connective tissue disease; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; BMZ, basement membrane zone; BUN, blood urea nitrogen; CBC, complete blood count; CT, computerized tomography; DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; H&E, hematoxylin and eosin; HIV, human immunodeficiency virus; Ig, immunoglobulin; IgAV, IgA vasculitis (Henoch–Schönlein purpura); SLE, systemic lupus erythematosus. *Adapted from Goeser MR, et al. Am J Clin Dermatol 2014;15:299–306.*

Pathogenesis

The onset of symptoms has been associated with various triggering factors, including vaccination, desensitization therapy, leukotriene inhibitors, omalizumab, and rapid discontinuation of corticosteroids. However, in some patients, this may more accurately represent an "unmasking" of the disease. T lymphocytes, eosinophils, and ANCAs all play a role in disease pathogenesis. Tissue infiltration and degranulation of eosinophils can lead to tissue injury, while T cells, both Th1 and Th2, are postulated to contribute to granuloma formation and allergic features, respectively. ANCA-dependent activation of neutrophils results in vasculitis (see Fig. 24.1B).

Two subsets of EGPA have been identified in which several risk genes (e.g. *HLA-DQ*) are associated with ANCA-positivity, while variants in *GPA33* and *IL5* are associated with ANCA-negative EGPA. The former group of patients is more likely to develop glomerulonephritis and neuropathy while the latter group more often has cardiomyopathy and pulmonary infiltrates.

Clinical features

The clinical presentation can be divided into three successive phases: (1) prodromal phase – symptoms of allergic rhinitis, nasal polyps, and asthma, which may persist for years; (2) eosinophilic phase – peripheral

eosinophilia and eosinophilic infiltration of internal organs, especially the lungs and gastrointestinal tract; and (3) vasculitic phase – systemic necrotizing vasculitis with granulomatous inflammation, which can occur several years to decades after the initial symptoms. Asthma, frequently severe, affects almost all patients and often precedes the onset of additional systemic manifestations by a decade or more[98]. Otitis media, allergic rhinitis, nasal polyposis, and sinusitis are also exceedingly common.

Cutaneous findings occur in 40%–75% of patients, typically during the third phase of the disease, but are the presenting sign in ~15% of patients[99]. Although petechiae and purpura are most often seen, a variety of nonspecific, non-vasculitic manifestations are also frequently observed. The latter include "rash", pruritus, and urticaria. Because these "allergic" skin findings occur more frequently in EGPA than in other types of ANCA-associated vasculitides, recognizing them as potentially consistent with EGPA in the right clinical setting is important[79]. Subcutaneous nodules, livedo racemosa, retiform purpura, and papulonecrotic lesions, particularly on the extensor surfaces (i.e. Churg–Strauss nodules, PNGD), may also be seen[100] (Fig. 24.20).

In addition to the respiratory tract, patients with EGPA often have neurologic and cardiac involvement, presenting as mononeuritis multiplex and cardiomyopathy, pericarditis, or an arrhythmia. Peripheral neuropathy affecting more than one site (mononeuritis multiplex) is seen in up to 75% of patients and may result in pain, numbness, or weakness[101]. Cardiac manifestations occur in up to half of patients, developing more often in those with higher peripheral blood eosinophil counts, and are the leading cause of death[102,103]. Necrotizing glomerulonephritis and pulmonary capillaritis resulting in diffuse alveolar hemorrhage occur less commonly than in the other AAVs. Musculoskeletal, gastrointestinal, and ocular involvement can also occur.

There are no specific laboratory findings, but peripheral eosinophilia (≥1500 cells/microL or ≥10% of the total leukocyte count) should prompt suspicion in the right clinical context. In addition, patients frequently have elevated serum IgE levels. ANCAs are present in roughly half of those with EGPA, with 75% of these antibodies p-ANCA and anti-MPO (see Fig. 24.16). ANCA positivity has been associated with a higher risk of vasculitic features, including peripheral neuropathy, glomerulonephritis, and histologic findings of vasculitis, as well as higher rates of disease relapse. On the other hand, cardiac involvement is more commonly observed in ANCA-negative patients[104].

Pathology

The histopathologic hallmarks are infiltrates of eosinophils, formation of extravascular granulomas, and necrotizing vasculitis of small to medium-sized vessels; both arteries and veins are affected. Biopsy specimens obtained from papulonecrotic lesions demonstrate a palisading dermatitis with eosinophil infiltration, granuloma formation, and eosinophilic necrobiosis.

Differential diagnosis

EGPA is suspected on the basis of its typical clinical findings of asthma, rhinosinusitis, and peripheral eosinophilia in addition to manifestations of vasculitis (e.g. cutaneous, neurologic, renal), biopsy findings of vasculitis, and/or ANCA positivity (if present). Due to the tendency









Fig. 24.20 Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome). A Purpuric macules and papules on the buttocks due to small vessel vasculitis (leukocytoclastic vasculitis). **B** Purpuric dermal plaques on the palm that histologically demonstrated vasculitis of a small muscular artery. **C** Crusted, firm papules on the elbow (Churg–Strauss nodules; palisaded neutrophilic and granulomatous dermatitis). **D** A few scattered purpuric papules, some of which have central pinpoint crusts, on the ankles. *A, B, Courtesy Lindy Fox, MD and Kanade Shinkai, MD; C, Courtesy Kalman Watsky, MD.*

for this disease to evolve over time or to lack one or more of these features, diagnosis can be challenging and delayed. As with GPA and MPA, revised EULAR/ACR diagnostic criteria have been published[3,105].

The differential diagnosis of EGPA includes other vasculitides (see Table 24.9), other causes of secondary hypereosinophilia (e.g. parasitic infections), and hypereosinophilic syndrome (HES; see Ch. 26)[98], as well as chronic eosinophilic pneumonia and allergic bronchopulmonary aspergillosis.

Treatment

Systemic corticosteroids (usually 0.5–1 mg/kg/day prednisone equivalent) are the mainstay of therapy, and >90% of patients respond to treatment with corticosteroids alone. However, relapse is common, and patients with more severe internal organ involvement (e.g. cardiac, renal, gastrointestinal, CNS) generally require additional immunosuppressive therapy. In such patients, either cyclophosphamide or rituximab is typically added to the corticosteroid. The five-factors score (FFS), which is based on the presence or absence of various clinical factors associated with worse prognosis, can be used for risk stratification[106,107]. Guidelines recommend cyclophosphamide in those who have active cardiac involvement and in those who are ANCA-negative and have severe neurologic or gastrointestinal manifestations. Rituximab may be preferred in those with: ANCA positivity, active glomerulonephritis, prior cyclophosphamide treatment, or risk of gonadal toxicity. For patients with active, non-severe EGPA, corticosteroids combined with the anti-IL-5 monoclonal antibody mepolizumab are recommended. Alternative options for patients without organ-threatening disease include methotrexate or azathioprine plus corticosteroids[108].

Once remission has been achieved, corticosteroids should be tapered over ~12–18 months. However, many patients will need to continue low-dose corticosteroids (e.g. ≤10 mg/day prednisone) long-term. In addition, cyclophosphamide or rituximab can be replaced by less toxic immunosuppressive drugs such as azathioprine, methotrexate, or mycophenolate mofetil[108]. The data supporting azathioprine and other second- and third-line agents (e.g. methotrexate, leflunomide) for treatment of relapsed or refractory EGPA are limited (see Table 24.10)[103]. Of note, mepolizumab is FDA-approved for the treatment of EGPA based on a randomized trial in which increased rates of remission and reduced corticosteroid use were observed in patients with relapsing or refractory non-severe disease. Still, only about half of patients who received mepolizumab achieved remission[109]. Clinical trials of other anti-IL-5 drugs are ongoing.

PREDOMINANTLY MEDIUM-SIZED VESSEL VASCULITIS

Polyarteritis Nodosa

Synonyms: ■ Periarteritis nodosa ■ Panarteritis nodosa

Key features

- Segmental vasculitis of predominantly medium-sized arteries
- Both cutaneous and systemic (classic) forms
- Skin findings include livedo racemosa, subcutaneous nodules, retiform purpura, ulcerations, and peripheral gangrene
- Extracutaneous manifestations of the systemic variant include fever, arthralgias, myalgias, paresthesias, abdominal pain, orchitis, and renovascular hypertension
- The cutaneous variant has a chronic course and may be accompanied by mild systemic symptoms, primarily myalgias, arthralgias, and peripheral neuropathy

Introduction

Polyarteritis nodosa (PAN) is a multisystem vasculitis characterized by segmental necrotizing vasculitis involving predominantly medium-sized blood vessels. Some authors view cutaneous PAN as a "skin-predominant" variant, which typically follows a benign yet chronic course with relapses. Although these two entities are discussed together in this section, there is an alternative view that cutaneous PAN represents a distinct disorder (with occasional muscle or nerve involvement) rather than a skin-restricted variant of PAN[110]. Recently, the term *cutaneous arteritis* has been introduced as a synonym for cutaneous PAN.

Epidemiology

The incidence of classic PAN ranges from 4 to 16 cases per million, with a male:female ratio of 1.5:1. PAN can occur at any age but typically affects middle-aged adults (40–60 years). The true incidence of cutaneous PAN is unknown, but it may represent ~10% of all cases of PAN and is the most common form of PAN in children[111].

Pathogenesis

Although most cases of PAN are idiopathic, it may be associated with infections, inflammatory diseases (e.g. inflammatory bowel disease), malignancies (especially hairy cell leukemia), and medications. HBV infection is strongly linked to PAN, with prevalence depending on the regional frequency of HBV infection. Fortunately, widespread administration of the HBV vaccine has led to a significant reduction in HBV-associated PAN. Clinical features are the same as in idiopathic PAN, but disease onset generally occurs within six months of HBV infection and small studies suggest a higher risk of gastrointestinal, neurologic, and renal involvement[112]. Cutaneous PAN has been associated with other infections, particularly group A *Streptococcus* (especially in children), as well as long-term administration of minocycline[113].

A subset of children presenting with a PAN-like vasculitis have recessive loss-of-function mutations in *CECR1*, the gene encoding adenosine deaminase 2 (ADA2), suggesting a genetic susceptibility in some patients (see Ch. 45)[114,115]. Additionally, some adult patients with PAN have been diagnosed with the recently described autoinflammatory disorder VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome[116].

Clinical features

Extracutaneous disease is the rule in classic PAN, and patients usually experience constitutional symptoms, such as weight loss and fever, as well as multi-organ involvement. Common symptoms include arthralgias, sensory and/or motor neuropathy (mononeuritis multiplex), myalgias (due to myopathy), and abdominal pain. Kidney involvement is common and occurs at the level of the interlobar renal arteries, resulting in renovascular hypertension and renal failure, but not glomerulonephritis. In male patients, orchitis frequently occurs, especially in association with HBV infection. Stroke, ischemic cardiomyopathy, and mesenteric ischemia with bowel infarction and perforation are rare, but devastating, complications of classic PAN; they result from thrombotic microangiopathy or vasculitic arterial occlusion. Gastrointestinal involvement heralds a poor prognosis, with a 1-year survival rate of <50%[112]. Classically, the lungs are spared.

In a series of 348 patients with *classic (systemic) PAN*, ~50% had cutaneous findings[111]. The lower legs are involved in the vast majority of patients. Common manifestations include tender erythematous nodules, livedo racemosa, inflammatory retiform purpura, and ulceration, findings indicative of medium-sized vessel vasculitis. Palpable purpura also occurs, indicating that there is vasculitis of small blood vessels and not just medium-sized vessels. Occasionally, atrophie blanche-like lesions are seen. Severe cutaneous complications of PAN include deep ulcerations and digital infarcts. Skin involvement in PAN is associated with joint disease and higher rates of relapse[111].

In systemic PAN, laboratory evaluation demonstrates nonspecific inflammation with leukocytosis, an elevated ESR, and thrombocytosis. Microscopic hematuria can be seen, but evidence of glomerulonephritis is absent. Microaneurysms of the renal, mesenteric, and/or celiac arteries detected by traditional, computed tomography (CT), or magnetic resonance (MR) angiography are highly suggestive of classic PAN.

Cutaneous PAN, a skin-predominant form of the disease, represents about 10% of PAN cases. The majority of patients present with patchy, focal livedo racemosa (so-called "starburst" livedo), and tender subcutaneous nodules on the lower legs (Fig. 24.21). Lesions appear less often on the arms and trunk. Ulcerations occur in up to half of patients[117] and may serve as a predictor for recurrences. Patients frequently report

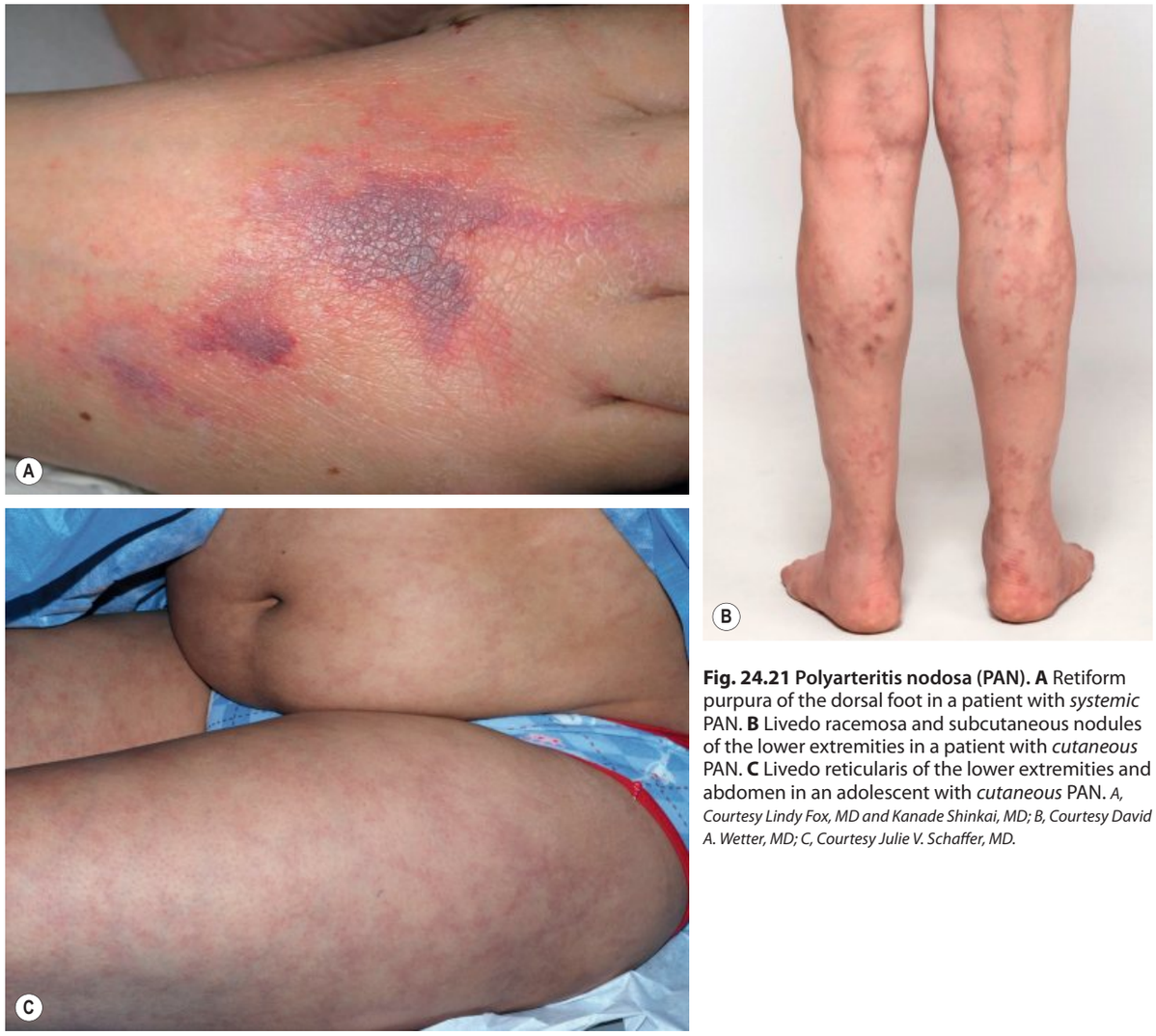


Fig. 24.21 Polyarteritis nodosa (PAN). A Retiform purpura of the dorsal foot in a patient with *systemic* PAN. **B** Livedo racemosa and subcutaneous nodules of the lower extremities in a patient with *cutaneous* PAN. **C** Livedo reticularis of the lower extremities and abdomen in an adolescent with *cutaneous* PAN. *A, Courtesy Lindy Fox, MD and Kanade Shinkai, MD; B, Courtesy David A. Wetter, MD; C, Courtesy Julie V. Schaffer, MD.*

mild systemic symptoms, consisting of fever, myalgias, arthralgias, and peripheral neuropathy localized to areas of skin involvement[118]. Although the latter can make differentiation of cutaneous versus systemic PAN more difficult, true cutaneous PAN should have neither prominent visceral manifestations nor muscle or nerve symptoms remote from skin lesions. In cutaneous PAN, a chronic, relapsing clinical course is typical[119], but progression to systemic PAN rarely, if ever, occurs. In two large series, only one patient was reported to have evolved from cutaneous to systemic PAN during the course of the disease[110,117].

While no diagnostic laboratory test for PAN exists, laboratory testing is helpful in determining the extent of organ involvement and narrowing the differential diagnosis. Measurement of serum creatinine and liver function tests as well as a urinalysis and HBV and HCV serologies should be performed. The presence of anti-PR3 or -MPO antibodies strongly argues in favor of an AAV and against a diagnosis of PAN.

Pathology

The histology of PAN is characterized by segmental necrotizing vasculitis of medium-sized muscular arteries (Fig. 24.22). Focal areas of involvement, with disruption of the elastic laminae, result in vessel wall weakening and necrosis, leading to aneurysmal dilation and/or stenosis. In the skin, affected medium-sized vessels are located within the deep dermis and subcutaneous fat[117], although overlying small blood vessels and nearby fat lobules may be secondarily involved. DIF, if performed, may show deposits of C3, IgM, and fibrin within or around vessel walls, but this is of uncertain significance.

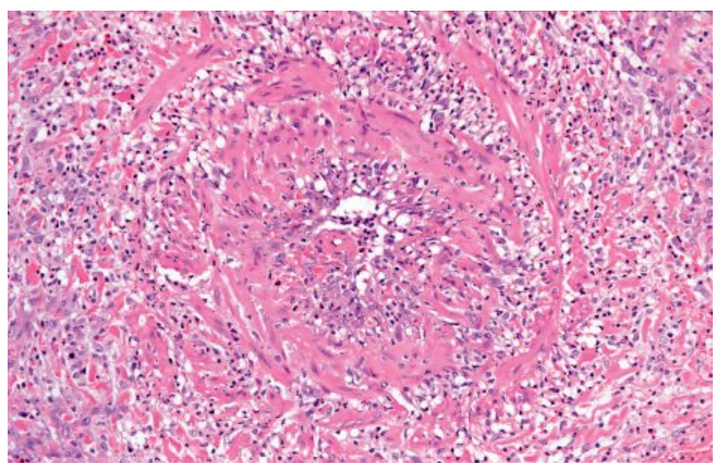


Fig. 24.22 Cutaneous polyarteritis nodosa (cutaneous arteritis) – histopathologic features. Vasculitis of a medium-sized vessel situated deep in the dermis. Neutrophils, neutrophilic debris, and fibrin within the arteriolar wall are seen. *Courtesy Lorenzo Cerroni, MD.*

Differential diagnosis

The diagnosis of PAN should be suspected based on characteristic symptoms, physical findings, and laboratory results. Biopsy of an involved organ (e.g. skin, muscle, nerve, kidney, testicle) to confirm

the presence of medium-sized vessel vasculitis should be performed whenever possible. Alternatively, detection of aneurysmal dilation and narrowing of renal and/or mesenteric vessels via angiography (conventional, CT, or MR) is often diagnostic.

The differential diagnosis of PAN is broad and includes cryoglobulinemic vasculitis, vasculitis secondary to autoimmune connective tissue disease (e.g. rheumatoid vasculitis), and AAV (see Table 24.9). In general, AAV can be distinguished from PAN by the presence of glomerulonephritis and pulmonary involvement in association with circulating ANCAs. There are several non-vasculitic diseases where aneurysmal dilations can be seen by angiography, including fibromuscular dysplasia, atherosclerosis, SLE, cholesterol emboli, Ehlers–Danlos syndrome, and emboli from infective endocarditis and left atrial myxoma.

The major entity in the differential diagnosis of cutaneous PAN is systemic PAN. A careful review of systems, angiography to assess involvement of visceral vessels, and diligent longitudinal evaluation are essential. Various panniculitides including erythema induratum (nodular vasculitis), calciphylaxis, cholesterol emboli, antiphospholipid syndrome, and other vasculopathies may have a similar presentation with livedo reticularis or racemosa, nodules, and ulcerations. Another entity to consider is lymphocytic thrombophilic arteritis (macular arteritis), which is characterized by livedo racemosa and reticulated hyperpigmentation on the lower extremities (see Fig. 106.3). Although histologic findings may be indistinguishable from cutaneous PAN, lymphocytic thrombophilic arteritis follows an indolent course and is rarely symptomatic. It may best be considered a forme fruste of cutaneous PAN and currently is not classified as an independent subtype of vasculitis[1].

When cutaneous lesions of PAN and livedo racemosa appear during childhood, the possibility of adenosine deaminase 2 (ADA2) deficiency should be considered; early-onset strokes are a serious manifestation of this disorder (see Table 45.7)[115]. A second autoinflammatory disorder, VEXAS syndrome (see above), is also in the differential diagnosis.

Treatment

Patients with mild *systemic PAN* should be treated with oral corticosteroids (e.g. 1 mg/kg/day of prednisone up to a maximum of 60–80 mg/day), tapered over 6 months. Approximately one-half of patients will achieve remission or cure with corticosteroids alone[106,120]. Azathioprine and methotrexate are commonly used steroid-sparing agents. Those with severe or refractory disease should receive corticosteroids plus cyclophosphamide for up to 12 months as initial therapy[106]. Treatment of HBV-associated PAN focuses first on eradication of the virus via antiviral agents[121]. Therapeutic alternatives are listed in Table 24.10.

Although it is often chronic and relapsing, *cutaneous PAN* follows a benign clinical course. Nevertheless, symptomatic disease generally warrants systemic therapy. Colchicine, dapsone, and azathioprine are commonly used and have favorable risk profiles[121a]. Case reports and expert opinion support a range of therapeutic alternatives as listed in Table 24.10. For mild disease, symptomatic relief may be achieved with NSAIDs alone.

TEMPORAL ARTERITIS (GIANT CELL ARTERITIS)

Rarely, cutaneous ulcers, primarily of the frontolateral scalp and tongue, can develop due to large vessel vasculitis (Fig. 24.23; see Table 24.1). Patients may have a history of headaches, jaw claudication, tenderness along the course of the temporal artery, and visual disturbances. They may also experience the muscle weakness associated with polymyalgia rheumatica. Cranial duplex ultrasound of the temporal artery is a non-invasive, but operator-dependent, option for initial diagnosis. In some centers, it has replaced temporal artery biopsy as the preferred initial diagnostic procedure. High-resolution MRI of cranial arteries is an alternative imaging modality with good sensitivity and specificity[122]. Plasma interleukin (IL)-6 levels may represent a marker of disease activity, and tocilizumab, an anti-IL-6 receptor antibody, is approved for the treatment of large vessel vasculitis[123]. High-dose corticosteroids are also employed as first-line therapy. In a phase 2 trial, mavrilimumab, an IgG4 monoclonal antibody which blocks GM-CSF signaling, demonstrated efficacy in maintaining clinical remission[123a].



Fig. 24.23 Temporal arteritis. Two ulcerations of the scalp in association with alopecia and scarring in an elderly patient. *Courtesy Steve Feldman, MD.*

DIAGNOSTIC APPROACH TO A PATIENT WITH SUSPECTED VASCULITIS

An approach to the patient with suspected cutaneous vasculitis is outlined in Figs. 24.19 and 24.24. Proper management includes clinicopathologic correlation and diagnosis, determination of any associated conditions, investigation for systemic involvement, and treatment.

History and Physical Examination

The clinician should assess the duration and acuity of symptoms and inquire about antecedent illnesses or exposures (e.g. medications). A history of autoimmune connective tissue disease or malignancy may be evident, but patients can present with cutaneous vasculitis as the initial sign of these diseases. The presence of systemic involvement (suggested by fever, weight loss, arthralgias, abdominal pain, paresthesias, cough, sinusitis, epistaxis, hematuria, or other focal symptoms) should be assessed via a thorough review of systems (see Fig. 24.19).

The cutaneous examination may be helpful in identifying the predominant vessel size affected (see Table 24.1 & Fig. 24.24). A complete head and neck, cardiopulmonary, abdominal, musculoskeletal, and neurologic examination should be performed in any patient in whom systemic vasculitis is suspected.

Laboratory Evaluation

A skin biopsy is necessary to assist in excluding entities that can mimic cutaneous vasculitis (see Table 24.3) and to identify the size of vessels involved. A fresh but well-developed lesion, e.g. one with both purpura and erythema, should be sampled in order to maximize the chance of obtaining characteristic histologic changes. If medium-sized vessel involvement is suspected, a deep punch, double-trephine ("telescoping") punch[124], or incisional biopsy that includes sufficient subcutaneous tissue should be performed. Biopsies obtained from nodules tend to have a higher diagnostic yield for medium-sized vessel vasculitis than those taken from an ulcer edge or livedo racemosa. Ulcers should be biopsied at their edge and include the peripheral rim of inflammation (if present), as incidental vasculitis can often be found underlying ulcers and is not a diagnostic finding. DIF should be routinely performed if immune complex-mediated small vessel vasculitis is suspected. Because immune complexes are degraded quickly by the inflammatory response, it is best performed on an early lesion.

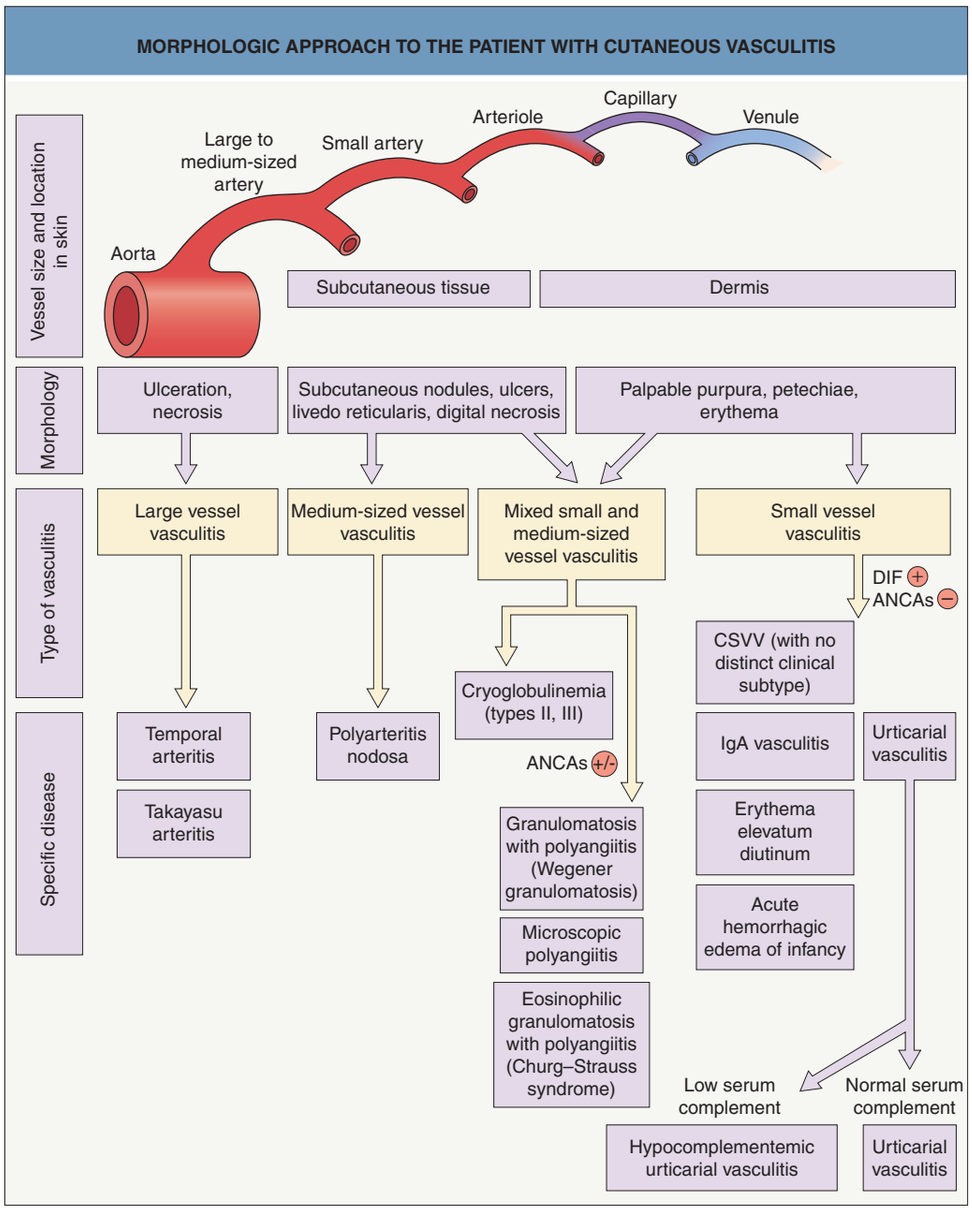


Fig. 24.24 Morphologic approach to the patient with suspected cutaneous vasculitis. ANCAs, anti-neutrophil cytoplasmic antibodies; CSVV, cutaneous small vessel vasculitis; DIF, direct immunofluorescence.

The laboratory evaluation of a patient with cutaneous vasculitis is outlined in Fig. 24.19. Basic testing should include a complete blood count, basic metabolic panel, and urinalysis. In straightforward initial episodes of small vessel vasculitis of the skin, in which the review of systems is negative, these studies may be all that are required. Additional tests can be performed in a stepwise fashion, based upon the suspected vasculitic syndrome or associated disease and as indicated by the patient's history, review of systems, and examination[13] (see Fig. 24.19 & Table 24.8). Laboratory tests to determine the extent of disease should be repeated with each subsequent episode of vasculitis. Tests for associated diseases are performed at baseline and only repeated if dictated by new information.

Treatment

The first step in the treatment of patients with cutaneous vasculitis is to determine whether the vasculitis is skin-limited or systemic as well as whether it is idiopathic or due to an associated disorder (e.g. autoimmune connective tissue disease) that must be addressed. Treatment is then based on the extent and severity of cutaneous and systemic involvement. Specific and detailed therapeutic approaches are discussed in conjunction with each disease and are outlined in Table 24.10. Along with an enhanced understanding of vasculitis pathogenesis has come a shift away from broad immunosuppression towards more targeted therapies[125].

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Additional figures and references available in our eBook (see inside front cover for access code).

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eFig. 24.1 Cutaneous small vessel vasculitis. Annular purpuric lesions on the inner thigh. *Courtesy Kalman Watsky, MD.*



eFig. 24.2 Cutaneous small vessel vasculitis. Digital infarcts.



eFig. 24.3 Vesiculobullous variant of cutaneous small vessel vasculitis. *Courtesy Lorenzo Cerroni, MD.*



eFig. 24.4 IgA vasculitis (Henoch–Schönlein purpura). In addition to purpuric macules and papules of the buttocks and lower extremities, there is evidence of accentuation at sites of pressure from socks.



eFig. 24.5 Multiple ulcerations due to IgA vasculitis (Henoch–Schönlein purpura). *Courtesy Julie V. Schaffer, MD.*



eFig. 24.6 IgA vasculitis with renal involvement in an adult. Many of the lesions have become vesicular.



eFig. 24.8 Hemorrhagic Sweet syndrome in a patient with acute myelogenous leukemia. The circular purpuric papules may initially be diagnosed clinically as cutaneous small vessel vasculitis.



eFig. 24.7 IgA vasculitis in an adult. A, B Clusters of erythematous papules with central hemorrhage on the foot and the thigh.



eFig. 24.9 Acute hemorrhagic edema of infancy. Multiple erythematous plaques on the thigh and sole in a toddler. Some of the lesions are edematous, while others have a targetoid appearance.



eFig. 24.10 Cutaneous vasculitis due to mixed cryoglobulinemia. Macular purpura mimicking Cullen sign in a patient with hepatitis C infection. *Courtesy Lindy Fox, MD and Kanade Shinkai, MD.*



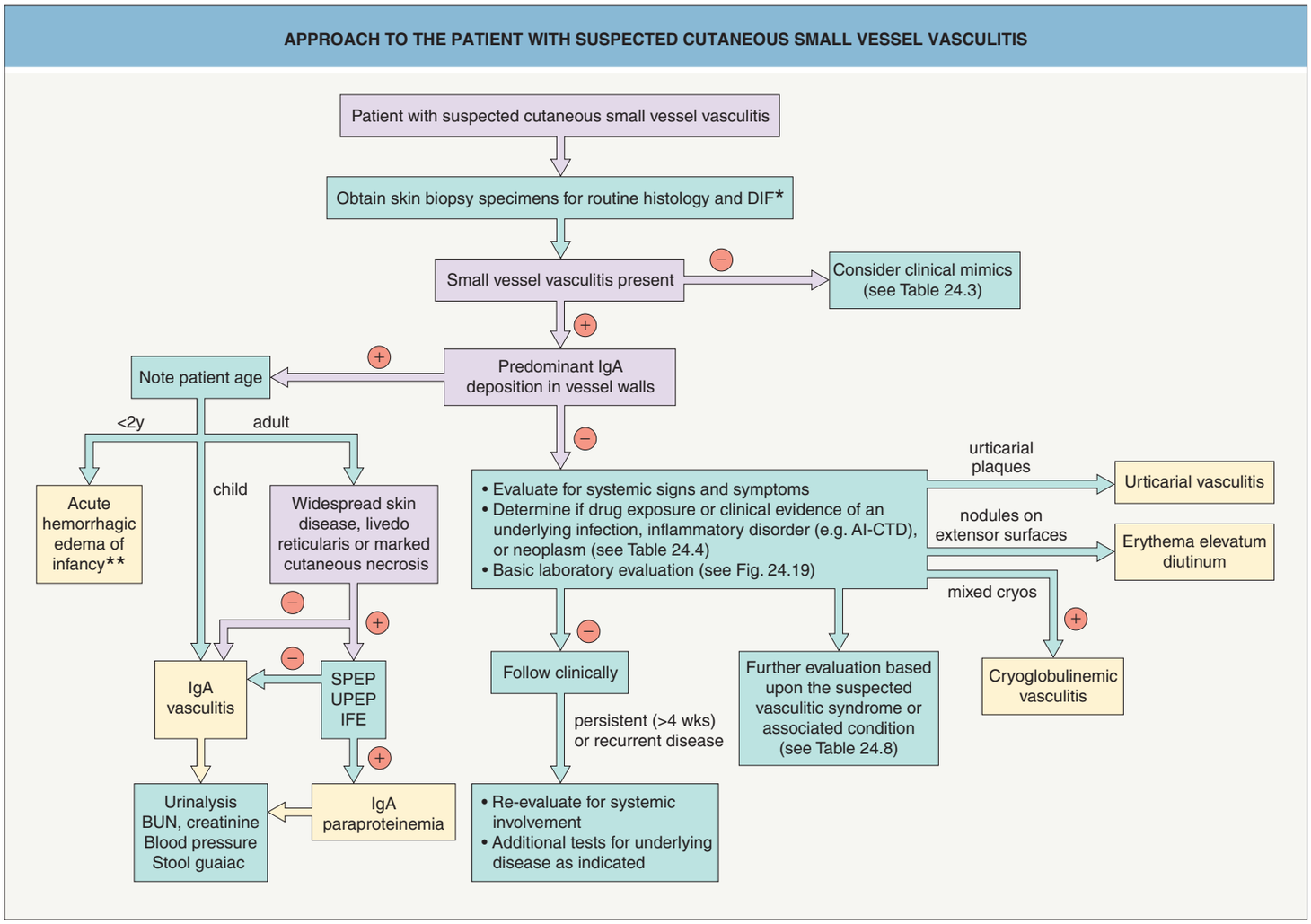
eFig. 24.11 Granulomatosis with polyangiitis. Sharply demarcated ulcer on the distal lower extremity, sometimes misdiagnosed as pyoderma gangrenosum. *Courtesy Irwin Braverman, MD.*



eFig. 24.12 Granulomatosis with polyangiitis. Crusted papules on the elbows (Churg–Strauss nodules).



eFig. 24.13 Lymphocytic thrombophilic arteritis (macular arteritis). A, B Asymptomatic, hyperpigmented, reticulated patches on the lower legs.



eFig. 24.14 Approach to the patient with suspected cutaneous small vessel vasculitis. *Best performed on an early lesion. **Vascular IgA deposits are found in less than one-third of cases. AI-CTD, autoimmune connective tissue disease; BUN, blood urea nitrogen; cryos, cryoglobulins; DIF, direct immunofluorescence; IFE, immunofixation electrophoresis; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

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25 Neutrophilic Dermatoses

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INTRODUCTION

The neutrophilic dermatoses constitute a heterogeneous but linked spectrum of diseases[1], with significant overlapping histopathologic findings and similar pathogenic mechanisms and therapeutic approaches. They are often associated with underlying systemic diseases. Histologically, these disorders are characterized by perivascular and diffuse dermal or subcutaneous neutrophilic infiltrates without identifiable infectious agents (Fig. 25.1). The cutaneous manifestations vary, from urticarial plaques and vesiculopustules to nodules and ulcers. It is noteworthy that there may be several different types of clinical lesions in the same patient, simultaneously or sequentially. Cutaneous lesions may be localized or widespread, and in some patients, sterile neutrophilic infiltrates may occur in other organs including the lungs, eyes, joints, bones, heart, and kidneys. Peripheral neutrophilia may be present. Distinct entities have been defined by the nature of their clinical and histopathologic presentations as well as their associated diseases.

Patients with autoinflammatory disorders may develop neutrophilic dermatoses, from sterile pustules in DIRA (*d*eficiency of *I*L-1 *r*eceptor *a*ntagonist) to pyoderma gangrenosum in PAPA (*p*yogenic [sterile] *a*rthritis, *p*yoderma gangrenosum, and *a*cne) and PASH (*p*yoderma gangrenosum, *a*cne, and *s*uppurative *h*idradenitis) syndromes (see Tables 45.6 and 45.7). There is also overlap between neutrophilic dermatoses and neutrophilic urticaria (see Table 45.6).

NEUTROPHIL BIOLOGY

Granulocytes (neutrophils, eosinophils, and basophils) are cells essential to our defense against microbes as well as other inflammatory responses. The neutrophil is a terminally differentiated, non-dividing cell which is packed with granules whose contents kill and degrade target microorganisms. Recent advances in our understanding of neutrophil biology include the molecular and cellular mechanisms responsible for their production and release from the bone marrow (e.g. chemokine CXC receptor 4 [CXCR-4]; see Ch. 60); their recruitment, priming, and activation within inflamed tissues (Table 25.1); and the events resulting in their removal.

Granulocytes, including neutrophils, originate in the bone marrow from pluripotent cells where granulocyte colony-stimulating factor (G-CSF) plays a critical role in regulation of neutrophil development. To supply sufficient numbers of circulating cells, neutrophils are produced within the bone marrow at a prodigious baseline rate (>5–10 $\times$ 10^{10} neutrophils daily). The bone marrow also has the capacity to upregulate granulocyte production sharply in response to a number of stresses such as infection. Mature neutrophils appear to circulate in the peripheral bloodstream anywhere from 6 hours to up to 6 days before migrating into tissues; within such tissues the neutrophils survive for an additional 2 to 3 days. Senescent neutrophils, unlike platelets and erythrocytes, appear to be removed from the circulation following a return to the bone marrow where they undergo apoptosis.

Transcriptional profiling studies suggest that granulocytes arise via the selective expression of a subset of transcription factors (e.g. STAT3), granulocyte proteins (e.g. neutrophil elastase), and receptors (e.g. N-formyl-methionyl-leucyl-phenylalanine [fMLP]). Differentiation from pluripotent stem cells requires 7–10 days, and during this period, under the influence of cytokines, neutrophils acquire their characteristic appearance and granules (primary, secondary, and tertiary). The following stages of myeloid maturation are recognized: myeloblast, promyelocyte, myelocyte, metamyelocyte, band, and, finally, the segmented neutrophil. The progressive gain of differentiated characteristics is accompanied by a loss in the potential to proliferate, i.e. beyond the myelocyte stage, the cells are non-dividing. The intracellular granules acquired during maturation contain enzymes that mediate the oxidative and non-oxidative killing functions of the neutrophil[2]:

1. primary (azurophilic) granules – acquired at the promyelocyte stage and their contents include myeloperoxidase, lysozyme, neutrophil elastase, defensins, proteinase 3, cathepsin 3, and bactericidal/permeability-increasing protein
2. secondary granules – acquired at the transition to the myelocyte stage and their contents include lactoferrin, neutrophil collagenase, neutrophil gelatinase-associated lipocalin, and lysozyme
3. tertiary granules – acquired during later stages of neutrophil maturation and contain gelatinase B (matrix metalloproteinase 9) and leukolysin.

While much remains to be discovered about the pathophysiology of neutrophilic dermatoses, contributing factors include genetic predisposition, aberrant cell signaling and effector molecules, and ultimately abnormal neutrophil activity. Proinflammatory cytokines that play a key role in neutrophilic inflammation include IL-1β, TNF, and IL-17[2a]. The latter upregulates G-CSF activity, which is important for neutrophil differentiation and release, and it enhances production of IL-8. In addition to being a potent neutrophil chemoattractant, IL-8 has synergistic effects when combined with TNF. Under normal conditions, phagocytosis of neutrophils limits IL-23 secretion, and this in turn limits IL-17 activity[2b]. The response of neutrophilic dermatoses to inhibitors of IL-17, TNF, and IL-1 lends support to this proposed pathogenesis.

Inflammation

A critical role of inflammation is to deliver neutrophils and other leukocytes to a site of injury and then activate these cells to perform their function of protecting the host against infection. Neutrophils are among the first cells to arrive at sites of inflammation. Reasons for this include their abundance in the bloodstream and their rapid response to chemokines. When activated, neutrophils move at speeds up to 30 microns/min – the fastest cell in the body.

The motile responses of neutrophils to microbial infection include emigration out of the vasculature and movement toward the source of the inflammatory chemoattractant. This culminates in the phagocytic ingestion of opsonized microbes. In order to arrive at the site of infection, leukocytes must migrate out of the vasculature via margination, rolling, activation, and tight adhesion (see Ch. 102). They then move toward the site of injury or infection (see Table 25.1) and eventually undergo degranulation then apoptosis.

The price to be paid for the defensive potency of neutrophils for destroying microbes and necrotic tissues is that they can injure normal tissue. During activation and phagocytosis, neutrophils release products (e.g. lysosomal enzymes, reactive oxygen intermediates, products of arachidonic acid metabolism [prostaglandins and leukotrienes]) not just within

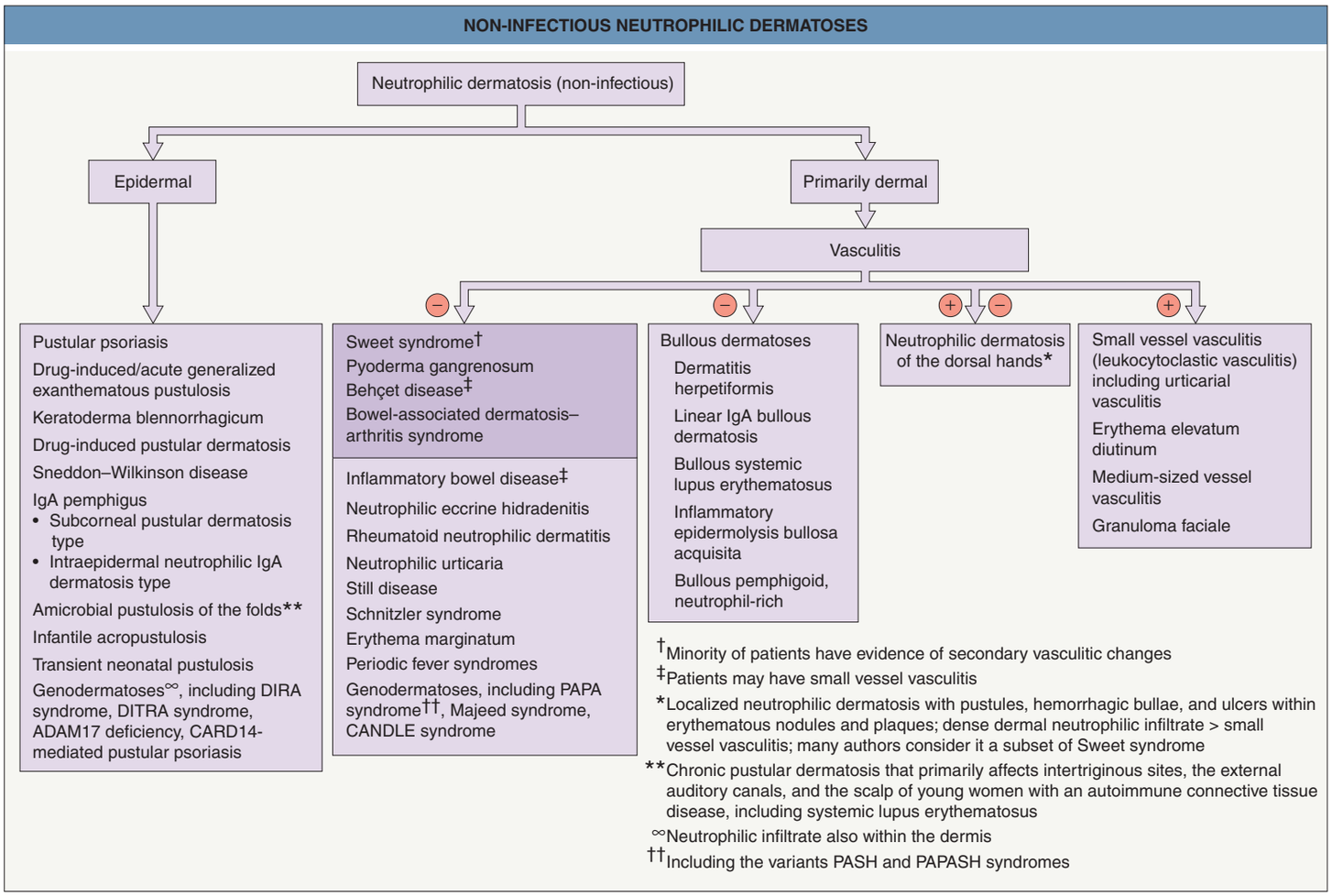


Fig. 25.1 Non-infectious neutrophilic dermatoses. Entities in the darker box are discussed in this chapter. CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; DIRA, deficiency of the interleukin-1 receptor antagonist; DITRA, deficiency of the interleukin-36 receptor antagonist; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; PAPASH, pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis; PASH, pyoderma gangrenosum, acne, and suppurative hidradenitis.

the phagolysosome, but also into the extracellular space. Endothelial injury and tissue damage ensue, thus contributing to a number of acute and chronic diseases that affect the skin as well as other organs.

SWEET SYNDROME

Synonym: ■ Acute febrile neutrophilic dermatosis

Key features

- Constitutional signs and symptoms such as fever and malaise
- Clinically, erythematous plaques that are occasionally bullous
- Histologically, dense perivascular neutrophilic infiltrate, edema and, infrequently, bullae; leukocytoclasia with minimal to no evidence of vasculitis
- Associated conditions include infections, malignancies (especially acute myelogenous leukemia), inflammatory bowel disease, autoimmune disorders (e.g. systemic lupus erythematosus [SLE]), drugs, and pregnancy

History

The prototype of the neutrophilic dermatoses is Sweet syndrome. In 1964, Sweet[3] described eight middle-aged women who had an acute onset of fever and erythematous plaques associated with a nonspecific infection of the respiratory tract or gastrointestinal tract. Histologically, the skin lesions were characterized by a neutrophilic infiltrate. He named this constellation of findings "acute febrile neutrophilic dermatosis". In 1968, Whittle and colleagues reported a similar case and named it "Sweet's syndrome".

Epidemiology

Sweet syndrome is an uncommon disease, with a worldwide distribution and no obvious racial predilection, although the disorder appears to be more frequent in Japan. The average age of onset is 30–60 years, but infants, children, and the elderly may be affected; there is a female predominance of 4 to 1. At least half of patients have an identifiable associated disorder or trigger: 15%–30% have an internal malignancy (hematologic ≫ solid organ), ~25% a preceding infection, and ~10% exposure to a potentially causative drug (Table 25.2)[4–7]. While the epidemiologic statistics in part reflect associated underlying disorders including internal malignancies, inflammatory bowel disease, and autoimmune connective tissue diseases such as SLE[8], they do not completely explain the female predominance.

Pathogenesis

The pathogenesis of Sweet syndrome is poorly understood, but the association with underlying diseases suggests a hypersensitivity reaction. Local and systemic dysregulation of cytokine secretion, including inflammasome activation, has been observed. Implicated cytokines include IL-1, tumor necrosis factor (TNF), G-CSF,

NEUTROPHILS – THEIR RELATIONSHIP TO SITES OF INFLAMMATION
Intravascular adhesion, activation and migration
• Neutrophils are activated by chemoattractants (bacterial-derived and host-produced), ligands of selectins, immune complexes, and activated complement components to express β_2 integrins (e.g. LFA-1) that then adhere to ICAM-1 on endothelial cells (see Fig. 102.11) • Endothelial cells can be activated by thrombin, histamine, cytokines (e.g. IL-1β, TNF, IL-17), LPS/endotoxin, and immune complex–C1q aggregates to express adhesive molecules (e.g. P-selectin, E-selectin, ICAM-1, VCAM-1) • PSGL-1 and L-selectin on the neutrophil surface are critical for tethering of neutrophils to the vessel wall followed by rolling then firm adhesion via β_2 integrins (see above) • Diapedesis represents migration of cells through inter-endothelial spaces towards a chemical concentration gradient, i.e. towards a site of infection or injury
Migration within tissue
• Leukocytes adhere to matrix proteins and follow chemotactic gradients • In response to the binding of chemoattractants (e.g. fMLP, C5a, PAF, LTB_4), neutrophils change their shape and crawl by alternating the extrusion and retraction of frontal lamellipodia, where chemokine and phagocytic receptors are concentrated
Activation within tissue
• Upon arrival at the site of injury or infection, neutrophils become activated via several signaling pathways (e.g. MAPK/ERK, PKC, phospholipase A2, cytosolic $[Ca^{2+}]$) and surface receptors are expressed (e.g. Toll-like receptors, receptors for cytokines, opsonins) • Activation results in degranulation and secretion of lysosomal enzymes, activation of the oxidative burst, production of arachidonic acid metabolites, and secretion of cytokines
Phagocytosis
• Recognition and attachment of the particle to be ingested by the neutrophil is greatly enhanced by opsonization (coating by opsonins such as antibodies, complement or lectins), which targets it for phagocytosis • Binding of the particle to phagocytic neutrophil receptors initiates engulfment of the particle, which then fuses with a lysosomal granule, forming a phagolysosome
Degranulation
• Microbes are killed preferentially by oxygen-dependent, rather than oxygen-independent, mechanisms with formation of reactive oxygen intermediates • With discharge of the granule's contents into the phagolysosome, the neutrophil becomes degranulated • NETosis also occurs, representing the process of setting *n*eutrophil *e*xtracellular *t*raps; these traps are composed of histones and antimicrobial granular and cytoplasmic proteins • Neutrophils then rapidly undergo apoptosis and are ingested by macrophages

Table 25.1 Neutrophils – their relationship to sites of inflammation[2]. ERK, extracellular signal-regulated kinase; fMLP, N-formyl-methionyl-leucyl-phenylalanine (bacterial-derived formylated tripeptide); ICAM, intercellular adhesion molecule; IL, interleukin; LFA, lymphocyte function-associated antigen; LPS, lipopolysaccharide; LT, leukotriene; MAPK, mitogen-activated protein kinase; PAF, platelet-activating factor; PKC, phosphokinase C; PSGL-1, P-selectin glycoprotein ligand-1; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

granulocyte–macrophage CSF (GM-CSF), and interferon-γ. A familial form of Sweet syndrome due to heterozygous mutations in *MEFV* (e.g. S242R) has been described[9]. Of note, this gain-of-function mutation in *MEFV* differs from those seen in familial Mediterranean fever. The term *pyrin-associated autoinflammatory disease* has been applied to these patients. As in PG and a murine model of neutrophilic dermatoses, the possibility that splice variants in *PTPN6* play a role in Sweet syndrome has been raised[10].

In hematologic malignancy-associated Sweet syndrome, the neutrophils in the cutaneous infiltrate and the malignant myeloid clone appear to share a clonal progenitor. This was observed when the skin lesions were present at the time of diagnosis as well as when they developed during treatment[11]. Thus, the inciting factors for malignancy-associated and familial Sweet syndrome likely differ from those of "classic" or drug-induced disease. However, downstream effectors presumably overlap with an end result of aberrant activation of neutrophils.

Clinical Features

The initial cutaneous lesions are tender, non-pruritic, erythematous plaques or papules, which may enlarge or coalesce to form plaques with an uneven mammillated surface (Fig. 25.2 & 25.3). Because of the pronounced associated edema, the lesions may have a pseudovesicular or pseudopustular appearance; however, some patients actually develop vesiculation, bullae, or pustules within their plaques. Occasionally, the plaques have a central yellowish discoloration creating a targetoid appearance. A facial erysipelas-like appearance has also been described as has a giant cellulitis-like variant. A relapsing localized variant can develop within areas of lymphedema or at sites of orthopedic implants[12]. The vesiculobullous variant, which is most frequently associated with acute myelogenous leukemia, can progress to ulceration resembling superficial pyoderma gangrenosum (PG). In this form, there may be a single lesion or multiple, asymmetrically distributed lesions.

The cutaneous eruption of Sweet syndrome favors the head, neck, and upper extremities (including the dorsal aspect of the hands), but can occur anywhere. In true malignancy-associated cases, the lesions tend to have a more widespread distribution. Papulonodules involving the lower legs may resemble erythema nodosum and although erythema nodosum has been reported in patients with Sweet syndrome, such nodules more likely represent a neutrophilic panniculitis. When isolated, the latter is often referred to as subcutaneous Sweet syndrome. A subset of patients, often with systemic involvement, can develop lesions that mimic necrotizing fasciitis, referred to as necrotizing neutrophilic dermatosis[13]; such lesions are also seen in patients with PG.

As with PG, specific lesions may be initiated by wounding injuries such as needle sticks, thermal burns, and surgical incisions. This phenomenon is known as pathergy. Oral lesions are uncommon, except in patients with hematologic disorders; initially they appear pseudopustular, and later ulcerate and appear as aphthae. The cutaneous eruption of Sweet syndrome usually resolves spontaneously within 5–12 weeks but recurs in up to 30% of patients.

An upper respiratory tract infection or flu-like illness frequently precedes the development of the syndrome. Fever occurs in 40%–80% of patients and can be intermittent. Extracutaneous involvement is also frequently seen (Fig. 25.4; Table 25.3).

Associated Diseases

These are summarized in Table 25.2 and should guide the history, including all medications, physical examination, and focused laboratory evaluation[4].

SWEET SYNDROME – ASSOCIATED DISORDERS AND TRIGGERS	
Infections	
• Viruses: **upper respiratory tract infections**, cytomegalovirus, hepatitis B virus, hepatitis C virus, HIV • Bacteria: *Yersinia*, streptococci • Mycobacteria: atypical mycobacteria, BCG vaccination, *M. tuberculosis*, *M. leprae* • Fungi: dimorphic, including sporotrichosis and coccidioidomycosis	
Malignancies	
• Hematologic (10%–20% of cases*), in particular **acute myelogenous leukemia** • **Myelodysplasia**, including VEXAS syndrome • Solid organ, predominantly the more common primary carcinomas	
Gastrointestinal disorders	
• **Inflammatory bowel disease: Crohn disease, ulcerative colitis**	
Drugs	
Most common	
• Colony stimulating factors (e.g. G-CSF, GM-CSF, pegfilgrastim)	• All-*trans*-retinoic acid (ATRA) > other retinoids
• Azathioprine	• Proteosome inhibitors (e.g. bortezomib)
Less common	
• Antibiotics (e.g. minocycline > TMP-SMX, quinolones)	• DNA hypomethylating drugs (e.g. decitabine, azacitidine)
• Hydralazine**	• FLT3 inhibitors
• NSAIDs (e.g. celecoxib)	• TNF inhibitors (e.g. adalimumab)
Uncommon (selected)	
• Abacavir	• BRAF inhibitors (e.g. vemurafenib)
• Furosemide	• Imatinib
• Immune checkpoint inhibitors (e.g. ipilimumab)	• Interferons
• Lenalidomide	• Oral contraceptives
• Propylthiouracil	• Vaccinations (e.g. BCG, pneumococcal)
Autoimmune disorders	
• Autoimmune connective tissue diseases (e.g. systemic lupus erythematosus [SLE]†, rheumatoid arthritis, dermatomyositis, relapsing polychondritis, Sjögren syndrome), autoimmune thyroid disease • Sarcoidosis • Behçet disease	
Immunodeficiencies	
• Anti-interferon-γ autoantibodies	
• Common variable immunodeficiency	
*Includes acute and chronic myelogenous leukemia, chronic lymphocytic leukemia, non-Hodgkin disease, Hodgkin disease, myeloma, and other myeloproliferative disorders. **Can simultaneously induce ANCA-positive vasculitis. †Some authors use the terms non-bullous neutrophilic LE or neutrophilic dermatosis in conjunction with LE rather than Sweet syndrome associated with SLE.	

Table 25.2 Sweet syndrome – associated disorders and triggers. The most common associations are in **bold**. BCG, bacillus Calmette–Guérin; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage CSF; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs; TMP-SMX, trimethoprim–sulfamethoxazole; TNF, tumor necrosis factor; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.



Fig. 25.2 Sweet syndrome. A Scattered edematous pink papules and plaques on the chest. **B** The edema can be quite marked as seen in these lesions on the upper back. *B, Courtesy Kalman Watsky, MD.*



Fig. 25.3 Sweet syndrome. A The periocular lesion demonstrates how some lesions can mimic cellulitis (pseudocellulitis). This patient also had neutrophilic esophageal ulcerations and subsequently developed colon cancer. **B** The plaques can have a pseudomammillated appearance due to the associated edema. **C** Hemorrhagic crusts may develop within the papules and plaques and in patients with acute leukemia and/or neutropenia, infectious etiologies are often the initial clinical diagnosis. *C, Courtesy Kalman Watsky, MD.*



Fig. 25.4 Sweet syndrome – ocular involvement. Obvious erythema and hemorrhage involving the sclera and conjunctiva. *Courtesy Kalman Watsky, MD.*

SYSTEMIC MANIFESTATIONS OF SWEET SYNDROME
Common (≥50%)
Fever Leukocytosis
Less common (20%–50%)
Arthralgias Arthritis: asymmetric, non-erosive, sterile, favors knees and wrists Myalgias Ocular involvement: conjunctivitis, episcleritis, limbal nodules, iridocyclitis
Uncommon
Neutrophilic alveolitis: cough, dyspnea and pleurisy; radiographic findings include interstitial infiltrates, nodules, pleural effusions Multifocal sterile osteomyelitis, a subtype of SAPHO (see Table 25.18) Renal involvement (e.g. mesangial glomerulonephritis): hematuria, proteinuria, renal insufficiency, acute renal failure
Unusual/rare
Acute myositis Hepatitis, pancreatitis, ileitis, colitis Aseptic meningitis, encephalitis, bilateral sensorineural hearing loss Other: aortitis, oral aphthae, pharyngitis, pharyngeal edema

Table 25.3 Systemic manifestations of Sweet syndrome[5,6]. SAPHO, synovitis, acne, pustulosis, hyperostosis and osteitis.

Pathology

The histopathologic features are contingent upon the type of cutaneous lesion sampled. The characteristic histologic presentation is a dense, diffuse dermal nodular and perivascular neutrophilic infiltrate without evidence of vasculitis (Fig. 25.5), although occasionally leukocytoclastic vasculitis (LCV) can be observed[14]. Leukocytoclasia with endothelial swelling, but without the fibrinoid necrosis that fulfills the criteria for LCV, is the usual finding. Occasionally, the dermal infiltrate may extend into the subcutis, creating a septal or, less frequently, a lobular panniculitis. Isolated neutrophilic panniculitis has been described.

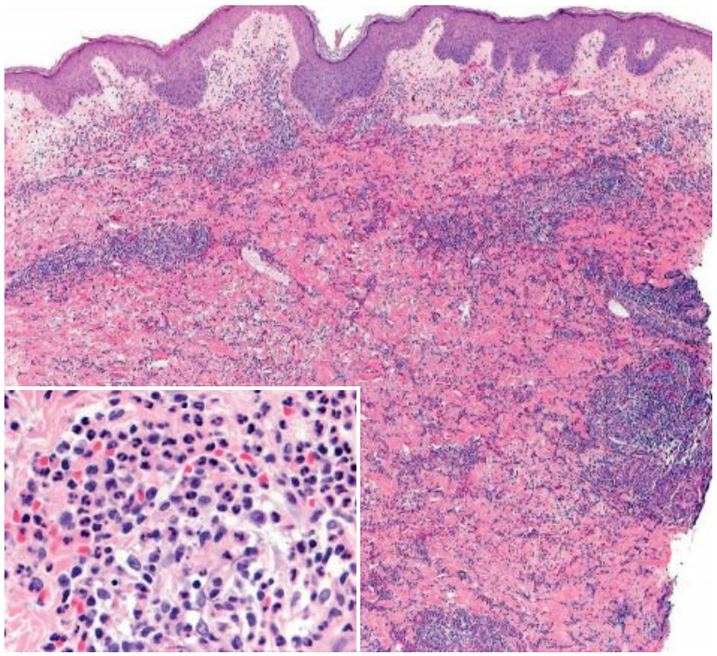


Fig. 25.5 Sweet syndrome – histopathologic features. Mild edema in the papillary dermis and a rather dense dermal infiltrate composed predominantly of neutrophils (inset). *Courtesy Lorenzo Cerroni, MD.*

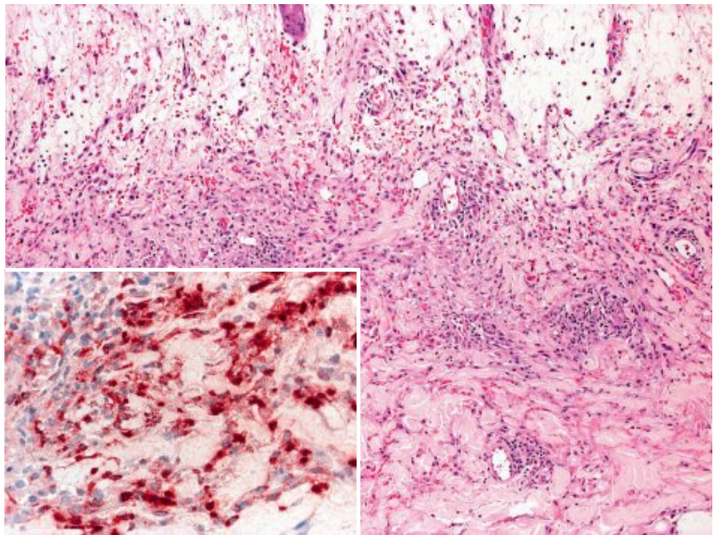


Fig. 25.6 Histiocytoid Sweet syndrome – histopathologic features. There is edema in the papillary dermis as well as a dermal infiltrate composed of histiocytoid cells admixed with neutrophils, a few eosinophils, and hemorrhage. The histiocytoid cells represent immature myeloid cells and therefore have stained positively for myeloperoxidase (inset). *Courtesy Lorenzo Cerroni, MD.*

In general, epidermal changes are not significant. However, neutrophils occasionally invade the epidermis, producing subcorneal pustules, and they may also infiltrate the adnexa. In the setting of significant edema, there can be epidermal spongiosis and sometimes reticular degeneration as well as intraepidermal and subepidermal vesiculation.

Three histologic variants of Sweet syndrome, histiocytoid, lymphocytic and eosinophilic, have been increasingly recognized. The histiocytoid variant is characterized by a dermal, and sometimes subcutaneous, infiltrate composed of histiocyte-like immature myeloid cells. These cells have myeloperoxidase activity (Fig. 25.6) and must be distinguished from those of leukemia cutis (bearing in mind that cells related to the malignant clone have been identified in some cases of histiocytoid Sweet syndrome associated with myelogenous leukemia). The lymphocytic variant is often associated with, and sometimes precedes, underlying myelodysplasia[15,16]. More recently, an eosinophilic variant has been described[17]. In a retrospective review, patients with the histiocytoid variant or subcutaneous involvement were more likely to have malignancy-associated disease[18].

CRITERIA FOR DIAGNOSIS OF SWEET SYNDROME
Major criteria
1. Abrupt onset of typical cutaneous lesions 2. Histopathology consistent with Sweet syndrome
Minor criteria
1. Preceded by one of the associated infections or vaccinations; accompanied by one of the associated malignancies or inflammatory disorders; associated with drug exposure or pregnancy 2. Presence of fever and constitutional signs and symptoms 3. Leukocytosis 4. Excellent response to systemic corticosteroids

Table 25.4 Criteria for diagnosis of Sweet syndrome. Both of the major and two minor criteria are needed for the diagnosis. *Reprinted with permission from Cutis. 1986;37:167–74. ©1986, Frontline Medical Communications Inc.*

Diagnosis and Differential Diagnosis

Although there are no specific diagnostic findings in this disease, a peripheral leukocytosis with neutrophilia and an elevated ESR and C-reactive protein (CRP) are frequently seen. In patients with an associated hematologic malignancy or myelodysplasia, there may be a high or low white cell count, lymphocytosis or lymphopenia, and thrombocytosis or thrombocytopenia. Although elevated serum levels of anti-neutrophil cytoplasmic antibody (ANCA) have been reported[19], in particular pANCA or an atypical ANCA, there is no strong evidence that it is a serologic marker for this disease.

In 1986, Su and Liu[20] proposed two major and four minor criteria for the diagnosis of Sweet syndrome, which have been widely accepted and are shown with minor revisions in Table 25.4. The differential diagnosis of the syndrome depends on the nature and age of the lesions and on the associated disorder (Table 25.5; see Fig. 25.1).

Patients with *neutrophilic dermatosis of the dorsal hands* develop tender, erythematous to violaceous plaques that may become bullous or ulcerative (Fig. 25.7)[21–23]. There is a spectrum of associated histologic features, from pustular vasculitis to those of PG or Sweet syndrome. Hence, some authors consider this to be a variant of Sweet syndrome.

In patients with hematologic malignancies, especially acute myelogenous leukemia, several neutrophilic dermatoses, e.g. Sweet syndrome, atypical (bullous) PG, and neutrophilic eccrine hidradenitis, can occur alone or in combination. The approach to such a patient is presented in Table 25.6.

In patients with rheumatoid arthritis, the possibility of rheumatoid neutrophilic dermatitis, including the uncommon annular variant, needs to be considered[24,25]. As noted in Table 25.5, Sweet syndrome can also mimic soft tissue infections, including cellulitis and necrotizing fasciitis[26,27]. This distinction can prove challenging, especially in immunocompromised hosts.

Treatment

When limited to the skin, Sweet syndrome is a benign condition which, if left untreated, may persist for weeks or months. Cutaneous lesions then involute spontaneously, rarely leaving scars. However, recurrences develop in ~30% of patients (with or without treatment) and occur even more often in those with hematologic disorders (~50%). Although the initial clinical presentation often suggests sepsis, antibiotics, in general, are ineffective. However, when the disease is associated with a recognized infection, treatment of the underlying infection may result in improvement.

The most effective therapy for Sweet syndrome is oral prednisone (0.5–1.0 mg/kg/day) for 2–6 weeks. There is prompt relief of not only the cutaneous, but also the extracutaneous, manifestations. In some patients, prolonged low-dose prednisone for an additional 2–3 months may be necessary to suppress recurrences. When the lesions are few and localized, topical superpotent or intralesional corticosteroids may prove helpful.

THE DIFFERENTIAL DIAGNOSIS OF SWEET SYNDROME
Inflammatory dermatoses
• *Pyoderma gangrenosum (bullous)* • *Neutrophilic dermatosis of the dorsal hands** • Neutrophilic eccrine hidradenitis • Rheumatoid neutrophilic dermatitis (dermatosis) • Palisaded neutrophilic and granulomatous dermatitis, especially early lesions • Other neutrophilic dermatoses (see Fig. 25.1) • Neutrophilic urticaria (e.g. Schnitzler syndrome) • Autoinflammatory diseases (see Tables 45.6 & 45.7) • Periodic fever syndromes (see Table 45.2) • Erythema multiforme • Urticarial vasculitis • Erythema elevatum diutinum • *Behçet disease* • *Bowel-associated dermatosis–arthritis syndrome* • Panniculitis, including erythema nodosum • Halogenoderma (iododerma or bromoderma) • Eosinophilic dermatoses (e.g. exaggerated arthropod bite reactions, Wells syndrome) • Autoimmune connective tissue diseases – acute, subacute, and neonatal lupus erythematosus • Interstitial granulomatous dermatitis
Infections
• Cellulitis, pyoderma, furunculosis • Septic vasculitis • Cryptococcosis† and dimorphic fungal infections • Mycobacterial infections
Neoplasms
• Leukemia cutis > lymphoma cutis
*Most authors consider this a variant of Sweet syndrome. †In cryptococcoid Sweet syndrome, the histopathologic findings can mimic cutaneous cryptococcosis.

Table 25.5 The differential diagnosis of Sweet syndrome[5,6]. Entities discussed in this chapter are in *italics*.

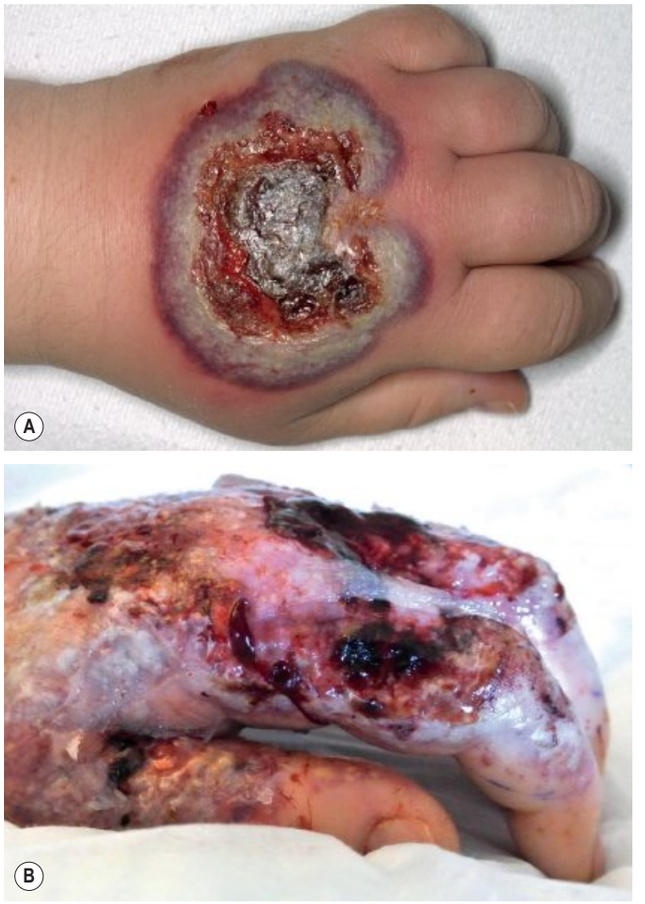


Fig. 25.7 Neutrophilic dermatosis of the dorsal hands. A Clinically and histologically, there is overlap with Sweet syndrome and bullous pyoderma gangrenosum. **B** More extensive necrotizing disease can be confused with an infectious process such as necrotizing cellulitis or necrotizing fasciitis.

NEUTROPHILIC DERMATOSES ASSOCIATED WITH HEMATOLOGIC MALIGNANCIES			
	Sweet syndrome	**Atypical (bullous) pyoderma gangrenosum**	**Neutrophilic eccrine hidradenitis**
Clinical manifestations			
• Cutaneous	Painful plaques and nodules with occasional blisters and pustules within lesions	Hemorrhagic bullae and superficial ulcerations	Erythematous edematous plaques and papules which may be painful, infrequent pustules
	Favors face, upper extremities and trunk	Favors face and upper extremities (especially dorsal hands)	Favors face, extremities, trunk
	Can recur (30%–50% of patients)	Can recur	Resolves spontaneously over ~2 weeks without scarring Can recur
• Systemic	Fever, arthralgia or arthritis Multiorgan involvement (Table 25.3) Neutrophilia Elevated ESR	Systemic features usually absent	Fever, neutropenia*
Histopathology	Papillary edema with dense dermal neutrophilic infiltrate Histiocytoid variant – histiocyte-like immature myeloid cells Lymphocytic variant – in the setting of myelodysplasia	Subepidermal hemorrhagic bullae Pustules with neutrophilic dermal infiltrate	Neutrophilic† infiltrate around and within eccrine glands, necrosis of eccrine epithelium, and sometimes eccrine squamous syringometaplasia
Associations	Infections, hematologic malignancies > solid tumors, IBD, autoimmune diseases, pregnancy, G-CSF, all-*trans*-retinoic acid (see Table 25.2)	Hematologic disorders, especially acute myelogenous leukemia, IgA monoclonal gammopathy and myelodysplasia, IBD, G-CSF	Leukemia with or without chemotherapy; post-chemotherapy for lymphoma and solid tumors; G-CSF; rarely infections
Primary treatment (in addition to treatment of underlying disease)	Systemic corticosteroids (0.5–1 mg/kg/day for 4–6 weeks), potassium iodide (900 mg/day), dapsone (100–200 mg/day), colchicine (1.0–1.5 mg/day or 1.2–1.8 mg/day‡) (see Table 25.11)	Systemic corticosteroids (see Table 25.11)	None (spontaneous resolution)
*Usually in setting of chemotherapy. †May be lymphocytic in setting of chemotherapy-induced neutropenia. ‡In the US, tablets are 0.6 mg; in other countries, tablets can be 0.5 mg.			

Table 25.6 Neutrophilic dermatoses associated with hematologic malignancies[6,18]. G-CSF, granulocyte colony-stimulating factor; IBD, inflammatory bowel disease.

The major alternative drugs are potassium iodide (900 mg/day; see Table 100.6), dapsone (100–200 mg/day), and colchicine (1–1.5 mg/day or 1.2–1.8 mg/day, depending upon dosage of commercially available tablets). They can also be used as corticosteroid-sparing agents. Nonsteroidal anti-inflammatory drugs (e.g. indomethacin, naproxen, sulindac), cyclosporine, thalidomide, lenalidomide, anakinra, methotrexate, and rituximab have also been reported to lead to improvement of Sweet syndrome. Evidence for any of these therapeutic regimens is based on case reports or small case series. Of note, while TNF inhibitors have been used to treat refractory Sweet syndrome, they can also be a cause of drug-induced Sweet syndrome.

PYODERMA GANGRENOSUM

Key features

- Four major clinical forms: ulcerative, bullous, pustular, and superficial granulomatous; additional variants include mucosal, peristomal, postsurgical, and necrotizing neutrophilic dermatosis
- Initial lesion is often a pustule on an erythematous or violaceous base, an erythematous nodule, or a bulla
- Characteristic lesion is an expanding ulcer with a necrotic undermined border; the base may be purulent or vegetative
- Histologically, a sterile dermal or adnexal abscess (without a vasculopathy) is seen in active, untreated, expanding lesions
- Associated illnesses include inflammatory bowel disease, arthritis, monoclonal gammopathies, and other hematologic disorders

Introduction

Pyoderma gangrenosum (PG) is an uncommon, chronic, recurrent, cutaneous ulcerative disease with a distinctive morphologic presentation. The laboratory and histopathologic findings can vary and therefore the diagnosis requires clinicopathologic correlation. This neutrophilic dermatosis is frequently associated with systemic disease[28–31].

History

In 1908, Brocq described a series of patients with skin ulcers he called "geometric phagedism". Two decades later, Brunsting, Goeckerman, and O'Leary coined the term "pyoderma gangrenosum" and advanced the theory that it had an infectious etiology (streptococci and staphylococci)[29].

Epidemiology

PG is a global disease. It can occur at any age but most commonly afflicts women between 20 and 50 years of age. Nearly half of the patients have an underlying systemic disease, most commonly inflammatory bowel disease, arthritis, or a hematologic disorder (e.g. IgA monoclonal gammopathy, acute myelogenous leukemia, myelodysplasia). Approximately 4% of cases of PG occur in infants and children. PG is also a cutaneous manifestation of several monogenic autoinflammatory diseases (see Tables 45.6 and 45.7).

Pathogenesis

Although the disease is idiopathic in 25%–50% of patients, an underlying immunologic abnormality is currently favored, given its frequent association with systemic diseases that have a suspected autoimmune pathogenesis. The association of PG with several autoinflammatory diseases points to aberrant activation of the innate immune system. In particular, enhanced activity of the IL-1 pathway is thought to play a role, as it does in several autoinflammatory disorders (see Fig. 4.2)[32]. In lesional skin biopsies, overexpression of IL-1α, IL-1β, and the IL-1 receptor as well as IL-8, IL-17, and TNF has been reported. Elevated serum levels of IL-1β have also been observed, and clinical improvement of PG following administration of the anti-IL-1β antibody canakinumab provides additional support for this proposed pathogenesis.

The adaptive immune system may also play a role as cytokines involved in the Th1/Th17 pathways (e.g. IL-23) and the JAK/STAT pathway have been implicated in the pathogenesis of PG. Pathergy is seen in 20%–30% of patients with PG and not only does this phenomenon lead to new cutaneous lesions but it can also aggravate them. Overexpression of IL-8 and IL-36 may contribute to this reaction to minor trauma.

Additional insights into the pathogenesis of PG should come from a better understanding of the monogenic primary immunodeficiencies and autoinflammatory disorders associated with PG (see below). As noted previously, based upon findings from a murine model of neutrophilic dermatoses, splice variants in *PTPN6* may play a role in PG as well as Sweet syndrome[10].

Clinical Features

Although the classic morphologic clinical presentation of PG is an ulcer, there are several variants (bullous, pustular, and superficial granulomatous/vegetative) which differ by their clinical presentation, location, and associated diseases (Table 25.7; Fig. 25.8 & 25.9)[28]. Cutaneous lesions are painful and most frequently occur on the lower extremities in patients with typical (classic) PG, especially the pretibial area (Fig. 25.10A,B,D), but they can occur anywhere (Fig. 25.10C,E), including

CLINICAL VARIANTS OF PYODERMA GANGRENOSUM
Vesiculobullous (also referred to as atypical or bullous PG)
• Lesions favor the face and upper extremities, especially the dorsal hands • Clinical appearance overlaps with the superficial bullous variant of Sweet syndrome (Fig. 25.8) • Occurs most commonly in the setting of acute myelogenous leukemia, myelodysplasia, IgA monoclonal gammopathy, and myeloproliferative disorders such as chronic myelogenous leukemia
Pustular
• Multiple, small, sterile pustules • Lesions usually regress without scarring, but can evolve into classic PG • Most commonly observed in patients with inflammatory bowel disease • Similar eruption may be seen in patients with Behçet disease or bowel-associated dermatosis–arthritis syndrome
Superficial granulomatous
• Localized, superficial vegetative or ulcerative lesion, which favors the trunk and usually follows trauma (e.g. surgery); may have verrucous border • Histologically, a superficial granulomatous response with a less intense neutrophilic infiltrate • Responds to less aggressive anti-inflammatory therapy • Controversy as to whether it is a variant of PG, a separate disorder, or related to granulomatosis with polyangiitis
Pyoderma/pyostomatitis vegetans
• Chronic, vegetative pyoderma of the labial and buccal mucosa (Fig. 25.9A) • May be associated with vegetative or ulcerative cutaneous PG (Fig. 25.9B) • Large verrucous plaques that may be studded with pustules • Seen in patients with inflammatory bowel disease

Table 25.7 Clinical variants of pyoderma gangrenosum (PG). Additional variants include peristomal, postsurgical/postoperative, and necrotizing neutrophilic dermatosis.



Fig. 25.8 Bullous pyoderma gangrenosum. This patient had ulcerative colitis.

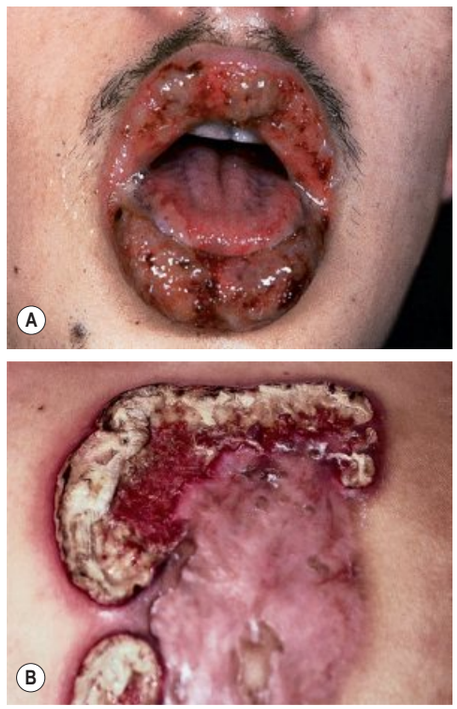


Fig. 25.9 Variants of pyoderma gangrenosum. **A** Pyostomatitis vegetans in a patient with ulcerative colitis. **B** Vegetative form following trauma to the skin. *Courtesy Samuel L. Moschella, MD.*



Fig. 25.10 Pyoderma gangrenosum (PG) – clinical presentations. A, B Typical (classic) form in which the ulcer has an undermined and overhanging violet–gray edge as well as a surrounding violaceous border. **C** Grouped sterile pustular nodules. **D** Central ulceration surrounded by inflammatory papules and pustules. **E** Deeper ulcer with vegetative and pustular base. **F** Centrally, there is healing with cribriform (sievelike) scarring.

on mucous membranes and peristomal sites (Fig. 25.11A). A vulvovaginal variant has been observed in patients who have received rituximab.

The lesions of PG usually begin as a tender papulopustule (Fig. 25.12) with surrounding erythematous or violaceous induration, an erythematous nodule, or a bulla on a violaceous base; the papulopustule may be follicular. All these lesions then undergo necrosis leading to a central shallow or deep ulcer; loss of tissue can expose underlying tendons or muscles. When fully developed, the ulcer has a purulent base with an irregular, undermined and overhanging, gunmetal-colored border which extends centrifugally (see Fig. 25.10A,B). This border may have surrounding erythema. Re-epithelialization occurs from the margins and the ulcers heal with atrophic cribriform pigmented scars (Fig. 25.10F).

In PG, the number of ulcers can vary from one to over a dozen, and sometimes they coalesce (Fig. 25.11B). Although the ulcers are classically described as rapidly expanding, some are less inflammatory and expand more slowly. The latter may require less aggressive therapeutic interventions.

In patients with hematologic disorders or in drug-induced cases, the clinical course is often characterized by an acute onset of hemorrhagic or purulent bullous lesions, with a more widespread distribution that can include the upper extremities, particularly the dorsal hands, as well as the face. These lesions rapidly necrose and are often associated with fever and signs of toxicity. In those patients with associated inflammatory diseases, such as inflammatory bowel disease or arthritis, the more characteristic presentation is a chronic, slowly enlarging ulcer with excessive granulation tissue in its base and sometimes with evidence of spontaneous regression.

Clinical variants have been described based on the clinical presentation (see Table 25.7) or the location of the lesion (e.g. peristomal[33], mucosal including the genitalia) or the age of the afflicted[30]. While the clinical appearance of PG in children is similar to that in adults, the lesions more frequently involve the head and anogenital region[34]. As with Sweet syndrome, extracutaneous sterile neutrophilic infiltrates have been reported in the bones, lung, liver, pancreas, spleen, kidneys, and CNS of patients with PG[35].

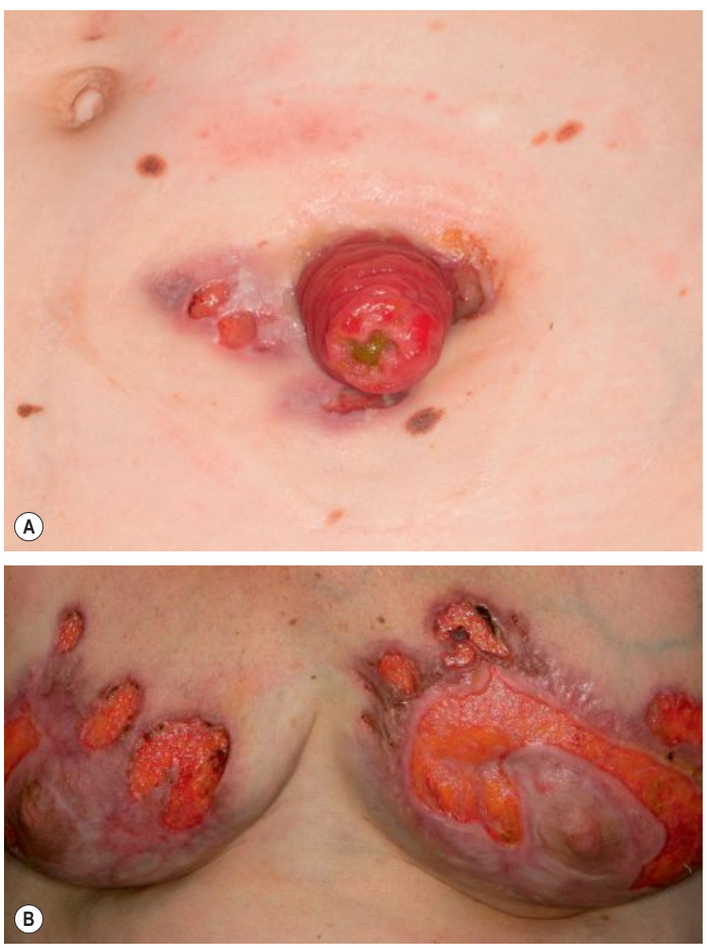


Fig. 25.11 Peristomal and postsurgical pyoderma gangrenosum (PG). **A** Several ulcers surround an ileostomy in a patient who had a total proctocolectomy performed because of refractory chronic ulcerative colitis. **B** Multiple ulcerations of the breasts following breast reduction. Because the original diagnosis postoperatively was soft tissue infection, multiple debridements had been performed and systemic antibiotics administered.

Associated Diseases

Between 50% and 70% of patients with PG have an antecedent, coincident, or subsequent associated disease or condition. The most common associations are inflammatory bowel disease (ulcerative colitis or Crohn disease [20%–30%]), arthritis (seronegative arthritis, spondylitis of inflammatory bowel disease or rheumatoid arthritis [20%]), and hematologic disease (in particular, acute > chronic myelogenous leukemia, myelodysplasia, hairy cell leukemia, and monoclonal gammopathy [15%–25%]). The monoclonal gammopathy is often composed of IgA.

Individuals with the autoinflammatory PAPA (*p*yogenic [sterile] *a*rthritis, *P*G and *a*cne) syndrome have been shown to have mutations in *PSTPIP1*, which encodes a CD2-binding protein, presumably leading to abnormal inflammatory responses (Fig. 25.13). PG-like lesions are also seen in patients with PASH and PAPASH syndromes (see Table 45.6), as well as in primary immunodeficiencies, e.g. leukocyte adhesion deficiency-1, common variable immunodeficiency due to *NFKB1* mutations (see Table 60.1).

Other neutrophilic dermatoses that have been reported in association with PG are subcorneal pustular dermatosis, Behçet disease, and Sweet syndrome.



Fig. 25.12 The earliest clinical lesion in pyoderma gangrenosum is a pustule with an inflammatory base. This patient had Crohn disease.



Fig. 25.13 Pyoderma gangrenosum in a patient with PAPA syndrome. Individuals with this monogenic autoinflammatory disorder have pyogenic sterile arthritis, pyoderma gangrenosum and acne. *Courtesy Maria Chanco Turner, MD.*

Pathology

The histopathology of PG can be nonspecific, especially when the disease is partially treated or minimally inflamed, and therefore be nondiagnostic. In early lesions, there is a neutrophilic vascular reaction, which can be folliculocentric. Neutrophilic infiltrates, often with leukocytoclasia, are seen in active, untreated, expanding lesions (Fig. 25.14). In fully developed ulcers, there is marked tissue necrosis with surrounding mononuclear cell infiltrates. In most patients with typical PG, chronic ulcers have fibrosing inflammation at the edge of the ulcer bed. Although biopsy specimens of PG may show nonspecific changes, histopathologic examination, often accompanied by tissue culture, assists in excluding other entities that can mimic PG[31].

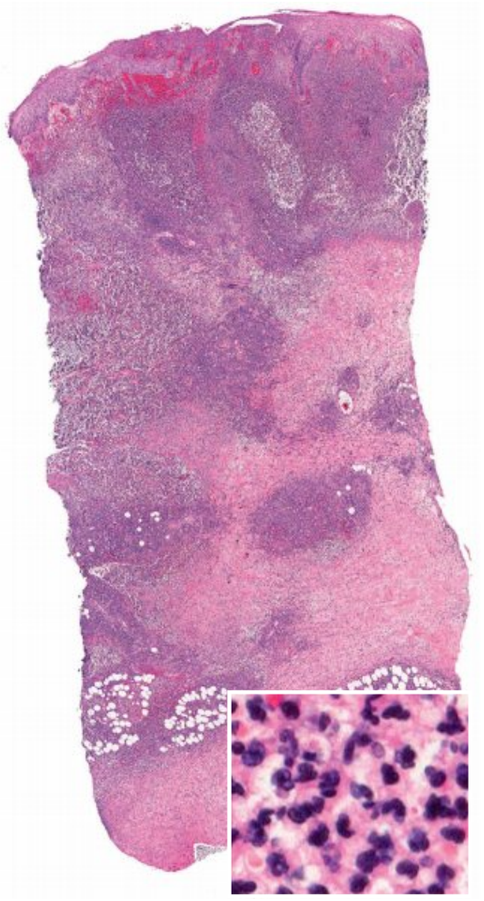


Fig. 25.14 Pyoderma gangrenosum. In expanding untreated lesions, a diffuse infiltrate of neutrophils (inset) is present at the edge of an ulceration. *Courtesy Lorenzo Cerroni, MD.*

Differential Diagnosis

Since there are no specific or diagnostic laboratory tests or histopathologic features and some of the associated conditions may not have declared themselves, the physician often needs to exclude other causes of cutaneous ulceration and search for a treatable associated disease. PG can be misdiagnosed: of 157 consecutive patients seen at one tertiary care medical center with a referral diagnosis of resistant ulcers due to PG, 15 (~10%) were found not to have PG[36]. To assist the clinician, three validated diagnostic schemes have been proposed (Table 25.8)[37]; all emphasize that no single criterion should be used in isolation. The evaluation of a patient with presumed PG is summarized in Table 25.9.

The differential diagnosis clearly depends on the evolutionary stage of the process – the initial inflammatory process characterized by erythematous papules, pustules, plaques, and nodules versus the later characteristic vegetative or ulcerative lesions (Table 25.10). Failure to establish the correct diagnosis can have serious consequences, including continued aggressive debridement and even amputation[38].

EVALUATION OF A PATIENT WITH PRESUMED PYODERMA GANGRENOSUM
• Thorough history and physical examination; review medications (e.g. rituximab), illicit drugs (e.g. cocaine) • Skin biopsy of *active* skin lesion with sufficient depth (panniculus) and sufficient tissue for special stains, culture, and/or PCR (bacterial, mycobacterial, fungal, viral, and occasionally parasitic). Possibility of future additional biopsies for immunofluorescence studies • Gastrointestinal tract studies – stool for occult blood and parasites, colonoscopy, biopsy, radiography, liver function tests, and if indicated, hepatitis evaluation • Hematologic studies – complete blood and platelet count, peripheral blood smear, and if indicated, bone marrow examination • Serologic studies – serum protein electrophoresis, immunofixation electrophoresis, anti-nuclear antibodies, anti-phospholipid antibodies, ANCA, VDRL • Chest X-ray and urinalysis

Table 25.9 Evaluation of a patient with presumed pyoderma gangrenosum[28–31]. ANCA, anti-neutrophil cytoplasmic antibodies.

THREE MAJOR PYODERMA GANGRENOSUM (PG) DIAGNOSTIC CRITERIA: SU CRITERIA, PARACELSUS SCORE, AND DELPHI CONSENSUS CRITERIA		
Su Criteria	**PARACELSUS Score**	**Delphi Consensus Criteria**
Diagnosis of PG requires both major criteria plus at least two minor criteria	*Highly likely PG requires score >10 points*	*Diagnosis of PG requires major criterion plus at least 4 of 8 minor criteria*
Major criteria	**Major criteria (3 points)**	**Major criterion**
• Rapid progression of a painful, necrolytic cutaneous ulcer with an irregular, violaceous, and undermined border • Other causes of cutaneous ulceration have been excluded	• Progressive course • Reddish-violaceous wound border • Absence of relevant differential diagnoses	• Biopsy with neutrophilic infiltrate
Minor criteria	**Minor criteria (2 points)**	**Minor criteria**
• History suggestive of pathergy or clinical finding of cribriform scarring • Systemic diseases associated with PG • Histopathological findings (sterile dermal neutrophilia, ± mixed inflammation, ± lymphocytic vasculitis) • Treatment response (rapid response to systemic steroid treatment)	• Amelioration due to immunosuppressant • Characteristically bizarre ulcer shape • Extreme pain >4 (VAS) **Additional criteria (1 point)** • Suppurative inflammation in histopathology • Undermined wound margins • Associated systemic disease	• Exclusion of infection on histology • Pathergy • PH of IBD or inflammatory arthritis • Papule, pustule, or vesicle that rapidly ulcerates • Peripheral erythema, undermining border, and tenderness at the site of ulceration • Multiple ulcerations (at least 1 occurring on an anterior lower leg) • Cribriform or wrinkled paper scars at healed ulcer sites • Decrease in ulcer size after immunosuppressive treatment

Table 25.8 Three major pyoderma gangrenosum (PG) diagnostic criteria: Su Criteria, PARACELSUS Score, and Delphi Consensus Criteria. These criteria are best applied to untreated disease, not disease partially treated by immunosuppressants. IBD, inflammatory bowel disease; PH, personal history; VAS, visual analogue scale for pain. *Adapted from Haag C, Hansen T, Hajar T, et al. Comparison of three diagnostic frameworks for pyoderma gangrenosum. J Invest Dermatol. 2021;141:59–63.*

DIFFERENTIAL DIAGNOSIS OF PYODERMA GANGRENOSUM
Early inflammatory non-ulcerative stage (papules, pustules, plaques, or nodules)
• Follicular infections (folliculitis, furuncle, carbuncle of bacterial, fungal, or viral origin) • Cellulitis or soft tissue infection (bacterial, mycobacterial, or fungal origin) • Insect bite reaction • Cutaneous T and B cell lymphomas • Halogenoderma (iododerma or bromoderma) • Panniculitides (inflammatory, infectious, metabolic, neoplastic) • Cutaneous polyarteritis nodosa • Sweet syndrome (see Table 25.5 for additional entities) • Behçet disease • Bowel-associated dermatosis–arthritis syndrome
Later ulcerative or vegetative stage
• Infections – streptococcal synergistic gangrene, ecthyma gangrenosum, atypical and typical mycobacterial infections, cutaneous lesions of the deep mycoses (e.g. blastomycosis, coccidioidomycosis, paracoccidioidomycosis, chromomycosis), cutaneous diphtheria, botryomycosis, gummatous treponemal ulcers • Parasitic infections – leishmaniasis, amebiasis, schistosomiasis • Vascular diseases – ulcerations due to venous hypertension, arterial insufficiency, non-septic emboli, hemoglobinopathies, thrombosis (secondary to hypercoagulability; see Ch. 105), or levamisole-induced vasculopathy/vasculitis • Vasculitis – cutaneous polyarteritis nodosa, microscopic polyangiitis, granulomatous vasculitides (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis [Churg–Strauss syndrome], temporal arteritis), autoimmune connective tissue disease (systemic lupus erythematosus, rheumatoid arthritis), Behçet disease • Malignancy – squamous cell carcinoma, basal cell carcinoma, cutaneous T and B cell lymphoma • Miscellaneous – brown recluse spider bite, ulcerative necrobiosis lipoidica, pemphigus vegetans of the Hallopeau or Neumann type, blastomycosis-like pyoderma*, non-healing surgical wound, factitious ulcers, idiopathic granulomatous mastitis, ulcers in patients with primary immunodeficiencies (e.g. leukocyte adhesion deficiency-1; see Table 60.1)
*Growth of at least one pathogenic bacteria from culture of tissue.

Table 25.10 Differential diagnosis of pyoderma gangrenosum (PG)[28–31]. In a series of 95 patients misdiagnosed with PG, the most common etiologies were vascular (venous or arterial; 28), vasculitis (21), malignancy (16), infection (14), and drug-induced or exogenous tissue injury (13)[36].

Treatment

There is neither specific nor uniformly effective therapy for PG. The nature and intensity of the therapeutic approach depend on the number, size and depth of the lesions, the rate of expansion and appearance of new lesions, the associated disorder, the medical status of the patient, and the risk and patient tolerance of prolonged therapy. Prior to instituting treatment, evaluation for an associated disease is recommended and this assessment may be guided by the age of the patient[39].

The therapeutic goals are to reduce the inflammatory process of the wound, thereby promoting healing and reducing pain, and to control the contributing underlying disease (especially leukemias and inflammatory bowel disease), while producing the least adverse side effects. The standard medical treatment of PG is local or combined local and systemic corticosteroid therapy, with or without adjunctive systemic therapy; based upon an evidence-based review, cyclosporine is also considered first-line therapy[40].

When delivered in adequate dosage, systemic corticosteroids have generally been the most predictable and effective medication. Unfortunately, the more resistant lesions require more protracted therapy (>3 months) at a higher than desirable dosage, thus inviting adverse side effects. Such patients should be closely monitored and should receive supplemental calcium (1500 mg/day), vitamin D (800 IU/day) and, in most instances, bisphosphonates (see Ch. 125). Additional therapies, e.g. classic steroid-sparing agents, JAK, TNF and IL-12/23 inhibitors, are outlined in Table 25.11[41]. Once the inflammation is under control, gentle debridement of necrotic debris may be performed, but a test area, as with intralesional corticosteroids, allows for assessment of pathergy.

BEHÇET DISEASE

Key features

- A multisystem, polysymptomatic disease
- Diagnosis is based on International Study Group criteria of recurrent oral ulceration, recurrent genital ulceration, ocular abnormalities (e.g. uveitis, retinal vasculitis), and cutaneous lesions
- Cutaneous findings range from sterile papulopustules and palpable purpura to erythema nodosum-like lesions
- Histologically, a neutrophilic angiocentric infiltrate with leukocytoclastic (early) or lymphocytic (late) vasculitis is the characteristic finding

Introduction

Behçet disease is a multisystem, polysymptomatic disease with unpredictable exacerbations and remissions[42–45]. All organs of the body can be affected concomitantly or consecutively. As a result, all subspecialties can be involved in the care of these patients.

History

In the fifth century BCE, Hippocrates first described the symptomatology of this disease, and in 1936, Behçet reported a patient with eye disease and orogenital ulcers.

Epidemiology

Most patients are from regions along the ancient Silk Route, which stretched from the Korean peninsula and Japan to the Mediterranean Sea. Turkey has the highest prevalence, at 80 per 100 000. In Japan, it is 10 per 100 000; in the UK, 0.64 per 100 000; and in the US, 0.12 per 100 000[43]. In Japan and Korea, the incidence of Behçet disease is greater in women, but in Middle Eastern countries it is seen more frequently in men. The peak incidence is between 20 and 35 years of age. The familial form usually comprises 2%–5% of cases, except in the Middle East, where it represents 10%–15%.

Pathogenesis

Epidemiologic evidence suggests that genetic and environmental factors contribute to the development of this disease. More than 80% of Asian patients have the HLA-B51 allele, but it is present in only about 15% of White individuals from Western countries; thus, the allele appears to be an important risk factor for those who live along the Silk Route.

Earlier theories of pathogenesis entertained the possibility of an infectious etiology (viral or bacterial), but subsequent evidence failed to substantiate this hypothesis. Among the infectious agents investigated were HSV, hepatitis C virus, parvovirus B19, and streptococci[43]. These infections may potentially trigger an immunoregulatory defect in a genetically predisposed individual.

The pathomechanisms of Behçet disease involve vascular injuries and autoimmune responses. Circulating immune complexes and neutrophils appear to be responsible for the mucocutaneous lesions that are characterized histologically by a neutrophilic vascular reaction or even leukocytoclastic vasculitis. The neutrophils of Behçet disease produce an increased amount of superoxides and an excess of lysosomal enzymes, and they have enhanced chemotaxis, all of which lead to tissue injury. The elevated circulating levels of TNF, IL-1β, and IL-8 may result in activation of neutrophils and augmentation of cellular interactions between neutrophils and endothelial cells. Clonal expansion of autoreactive T cells that recognize a peptide derived from heat shock protein 60 has also been described. More recent genome-wide association studies found that single nucleotide polymorphisms in IL-10 and IL-23R regions were associated with the disease.

THERAPEUTIC LADDER FOR THE TREATMENT OF PYODERMA GANGRENOSUM		
Treatment	**Dose**	**Level of evidence**
Inflammatory disease		
Mild disease and/or adjunctive therapy		
Superpotent topical corticosteroids		1
Intralesional corticosteroids		2
Topical tacrolimus		1
Oral antibiotics (e.g. sulfonamides, minocycline)		2
Colchicine	0.5 or 0.6 mg po BID to TID*	3
Dapsone	50–150 mg po daily	2
Combination colchicine/dapsone		3
Other (e.g. oral potassium iodide, intralesional cyclosporine, topical timolol, topical cromolyn sodium, nicotine patch or cream)		3
More severe disease		
Prednisone/prednisolone	0.5–1.5 mg/kg/day	1
TNF inhibitors‡	Infliximab 5 mg/kg IV weeks 0, 2, and 6 then every 6-8 weeks; adalimumab 160 mg sc (initial dose) then 80 mg at week 2 and then 40 mg sc weekly or every other week; etanercept 25–50 mg sc twice a week	1 (infliximab§); 1 (adalimumab); 3 (etanercept)
Cyclosporine	2.5–5 mg/kg po daily	1
Tacrolimus	0.1–0.2 mg/kg po daily	3
Methylprednisolone	1 g daily for 3–5 days (IV pulse) for aggressive/recalcitrant disease¶¶	3
IL-12/23 antagonists	Ustekinumab 45–90 mg sc weeks 0 and 4, then every 8–12 weeks	3
Interleukin (IL)-1, IL-1R antagonists	Anakinra 100 mg sc daily then decrease; canakinumab 150 mg sc weeks 0, 2, 8 (depending on response)	2
Methotrexate¶	5–25 mg po, sc, or IM weekly	3
Azathioprine¶	50–150 mg po daily	3
Mycophenolate mofetil¶	1–1.5 g po twice daily	2
Thalidomide†	50–150 mg po nightly	2
IVIg	1–2 g/kg IV monthly (given over 2–5 consecutive days)	3
JAK inhibitors	Tofacitinib, 5 mg po BID or 11 mg XR po daily; ruxolitinib 5 mg then 10 mg po BID; baricitinib 2–4 mg po daily	3
Apremilast	30 mg po twice daily after initial escalation	3
IL-36R inhibitor	Spesolimab 900 mg IV; may repeat at one week	3
Granulocyte +/– monocyte apheresis, plasmapheresis		3
Total colectomy (severe chronic ulcerative colitis)**		3
Non-inflammatory disease (“cold”)		
Bio-occlusive dressings Compression, limb elevation		

*In the US, tablets are 0.6 mg; in other countries, tablets can be 0.5 mg.
†Especially in patients with Behçet disease.
‡Especially in patients with inflammatory bowel disease.
¶Often used in combination with other agents or as maintenance therapy.
§50%–70% response rate.
¶¶Followed by daily oral prednisone.
**PG can also occur post colectomy.

Table 25.11 Therapeutic ladder for the treatment of pyoderma gangrenosum[40,41,41a,41b]. Based upon case reports, anti-interleukin (IL)-23 and -17 antibodies have also been used. For severe disease associated with IgA monoclonal gammopathy, bortezomib, dexamethasone, ± cyclophosphamide. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

Clinical Features and Differential Diagnosis

Mucocutaneous involvement

Aphthous stomatitis, the major criterion, is frequently the first symptom of Behçet disease (65%–70% of patients), and it is almost always present during the course of the disease. The aphthosis may precede the other manifestations by many years, but a dramatic increase in severity often occurs in concert with the onset of other features. Oral ulcers begin as an erythematous papule, which develops a yellowish pseudomembrane and then forms a painful usually non-scarring ulcer (Fig. 25.15A,B); it heals over a period of weeks. The ulcers are indistinguishable from those that occur with complex aphthosis or inflammatory bowel disease and they must be differentiated from other causes of oral ulcers, e.g. pemphigus vulgaris, Marshall syndrome. The latter patients also have periodic fevers, pharyngitis, and cervical adenitis[46].

The genital aphthae involve primarily the scrotum and penis in men and the vulva in women. Compared to oral lesions, the anogenital

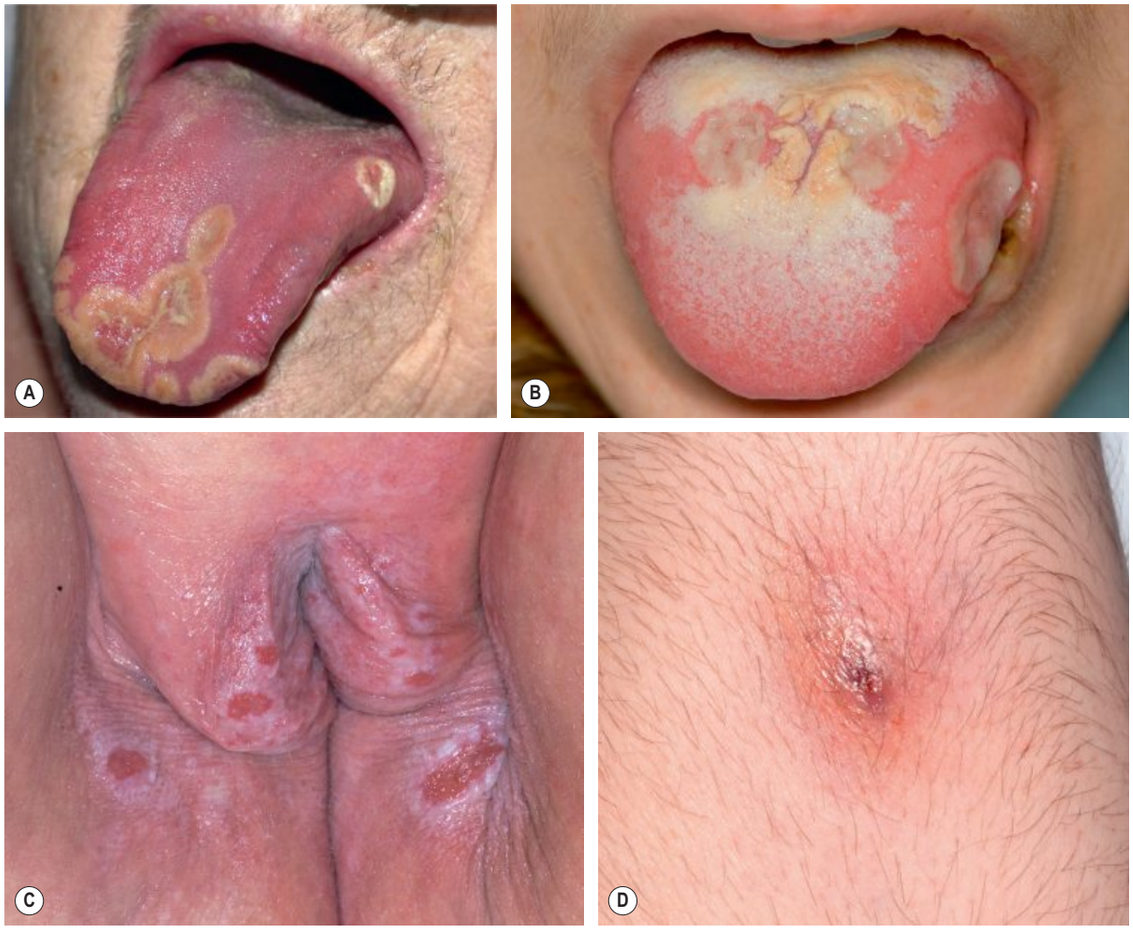


Fig. 25.15 Behçet disease – mucocutaneous lesions. A, B Oral aphthosis involving the tongue and lip; the ulcerations can be deep. These ulcers may be diagnosed as infectious (e.g. due to herpes simplex virus) or neoplastic rather than inflammatory. **C** Aphthae of the vulva and inguinal region. **D** Pathergy – a papulopustule appeared at the site of insertion of an intravenous catheter.

aphthae tend to be larger with irregular margins, but can vary in size (Fig. 25.15C); they are more painful. Distinction of genital lesions from lesions of HSV requires PCR, viral culture, or direct fluorescent antibody stain. Both immunobullous diseases (e.g. mucous membrane pemphigoid) and erosive lichen planus can also lead to oral and genital ulcerations.

Among the primary cutaneous lesions are acral and facial sterile vesiculopustules as well as pustular and/or purpuric papules[47]. Although the papulopustular lesions are usually not folliculocentric, they have nonetheless been described as acneiform, leading to some confusion (see Pathology below). The panniculitic erythema nodosum-like lesions favor women and appear on their legs and buttocks, and less often on the face and neck; they have to be differentiated from both superficial thrombophlebitis (which occurs in 30% of patients with Behçet disease) and erythema nodosum (which can develop in patients with Behçet disease). Pathergy also occurs (Fig. 25.15D), as in PG. Patients with features of both Behçet disease and relapsing polychondritis have been described and reported as MAGIC (*m*outh *a*nd *g*enital *u*lcers with *i*nflamed *c*artilage) syndrome (see Ch. 45)[48].

Patients with A20 haploinsufficiency, also referred to as familial Behçet-like autoinflammatory syndrome, can also have oral and genital ulcers as well as Sweet-like and erythema nodosum-like lesions and pustular eruptions (palmoplantar, folliculitis, pseudofolliculitis). This disorder is due to *TNFAIP3* mutations.

Systemic involvement

Systemic manifestations are summarized in Table 25.12 and distinctions between Behçet disease with bowel involvement and inflammatory bowel disease are outlined in Table 25.13.

Pathology

The histopathology of the cutaneous lesions is nonspecific. Vasculitic changes, which can involve all sizes of blood vessels within the dermis and subcutis, are probably secondary to the intense inflammation observed[49]. Both leukocytoclastic and lymphocytic vasculitis may be seen, and the affected vessels are sometimes occluded by fibrin thrombi.

The histologic features of the erythema nodosum-like lesions can vary from a neutrophilic lobular panniculitis to a septal and lobular panniculitis with a mixed inflammatory infiltrate, fat necrosis, and evidence of vasculitis.

Diagnosis

Since Behçet disease has no diagnostic test and is characterized by a complex constellation of signs and symptoms, various sets of clinical criteria have been created to assist in the diagnosis. Among the reported diagnostic criteria are those of the Japanese (1974), O'Duffy (1974), Zhang (1980), James (1986), and the International Study Group (ISG; 1990)[50]. The latter are presented in Table 25.14.

The development of the ISG criteria was based on the discriminating performance of various criteria-grouped combination sets, and the ISG criteria exhibited the highest sensitivity, specificity, and relative value. Controversy exists, however, about the failure of these criteria to require exclusion of inflammatory bowel disease.

Treatment

The management of the disease is difficult because of its variable course and the lack of sufficient double-blind studies. The therapeutic approach is a symptomatic one and is dictated by the nature of the mucocutaneous and visceral involvement. Because of the frequent vital organ involvement, e.g. the eye, and the tendency for the disease to recur, early and aggressive treatment is vital. CNS and large artery and vein involvement respond less favorably to therapy. There are multiple drugs available, both topical and systemic, that can be used as monotherapy or as combination therapy (Table 25.15)[51–53]. Evidence for many of the therapies is based on case-series data.

SYSTEMIC MANIFESTATIONS OF BEHÇET DISEASE
Ocular (leading cause of morbidity)[42–45]
• Occurs in 90% of patients; favors men, in whom it is more severe • Can be painful and may lead to blindness • Retinal vasculitis (more frequently associated with blindness) • Posterior uveitis (most characteristic ocular finding) • Anterior uveitis (Fig. 25.16), hypopyon • Secondary glaucoma, cataracts • Conjunctivitis, scleritis, keratitis, vitreous hemorrhage, optic neuritis
Joints
• Approximately 50% of patients develop arthritis • In majority (~80% of patients), duration of attacks is <2 months • Mono- or polyarthritic and non-erosive • Most commonly knees, wrists, and ankles
Gastrointestinal
• Abdominal pain and/or hemorrhage may be difficult to distinguish from IBD (see Table 25.13) • Ulcerations* develop within the small bowel (in particular the ileocecal region) as well as the transverse and ascending colon and esophagus; perforation can occur
Neurologic
• Usually appears later during the evolution of the disease • Associated with a poor prognosis • Acute meningo-encephalitis which may resolve spontaneously • Cranial nerve palsies • Brainstem lesions that can induce swallowing difficulties, laughter and crying • Pyramidal or extrapyramidal signs
Vascular
• Aneurysmal or occlusive arterial disease • Superficial or deep venous thrombosis
Cardiopulmonary
• Coronary arteritis, valvular disease, myocarditis • Recurrent ventricular arrhythmias • Pulmonary artery aneurysms
Renal
• Glomerulonephritis
*Resemble anogenital aphthae.

Table 25.12 Systemic manifestations of Behçet disease. IBD, inflammatory bowel disease.

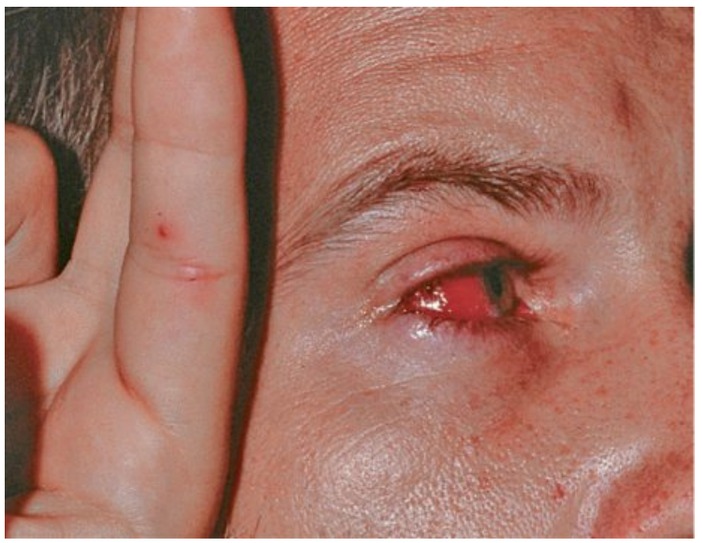


Fig. 25.16 Behçet disease – systemic involvement. Iritis and cutaneous pustular vasculitis. *Courtesy Samuel L. Moschella, MD.*

BOWEL-ASSOCIATED DERMATOSIS–ARTHRITIS SYNDROME

Synonyms: ■ Bowel bypass syndrome ■ Bowel bypass syndrome without bowel bypass ■ Intestinal bypass arthritis–dermatitis syndrome

Key features

- Constitutional signs and symptoms are serum sickness-like
- Cutaneous lesions include erythematous and purpuric papules and vesiculopustules as well as nodular panniculitis
- Associated polyarthritis and tenosynovitis
- Histopathology includes dermal perivascular nodular neutrophilic infiltrates and edema as well as a lobular neutrophilic or septal panniculitis

Introduction

Bowel-associated dermatosis–arthritis syndrome (BADAS) is characterized by diarrhea with resultant malabsorption, arthritis, and skin lesions. It is seen in patients who have undergone intestinal bypass surgery, have blind loops of bowel following surgery, had biliopancreatic diversion, or have gastrointestinal disorders (Table 25.16)[54,55].

History

During the 1960s and 1970s, morbid obesity began to be treated surgically by jejunoileal bypass surgery and 20% of these patients developed a syndrome initially referred to as bowel bypass syndrome. In the 1980s, a similar syndrome was described in patients with inflammatory bowel disease or with blind loops of bowel after intestinal surgery[55].

Pathogenesis

In bowel-associated dermatosis–arthritis syndrome, there is usually bacterial overgrowth in a blind loop of bowel. It is postulated that resultant immune complexes containing bacterial antigens are then deposited within the skin and synovium[56]. The pathogenic role of bacteria in this syndrome is supported by the disappearance of the disease with antibiotic therapy or surgery.

Clinical Features

Bowel-associated dermatosis–arthritis syndrome is characterized clinically by constitutional flu-like symptoms, skin lesions[57], and a variety of systemic complications (see below). It can occur from 1 to 6 years after the responsible bowel surgery. Constitutional symptoms, which are usually present and may precede the cutaneous eruption, are similar to those of serum sickness, e.g. fever, chills, malaise, arthralgias and myalgias.

The characteristic skin lesions are erythematous macules which progress to papules and purpuric vesiculopustules within 48 hours and last for 2–4 weeks; they may recur at 4- to 6-week intervals. The lesions may be few or many (Fig. 25.17), and they favor the proximal extremities and trunk.

Recurrent, tender, erythematous subcutaneous nodules are also seen in these patients and may be associated with fever. They are due to either a nodular, non-suppurative, lobular neutrophilic panniculitis (involving both the trunk and extremities and healing with depressed scars) or erythema nodosum (generally involving only the lower extremities), two entities which differ clinically and histologically[58]. Among the more common non-cutaneous findings are tenosynovitis and non-destructive polyarthritis. Associated systemic complications include electrolyte imbalance from persistent diarrhea, hepatic dysfunction and failure, renal calculi composed of calcium oxalate, gallstones, zinc deficiency, vitamin A deficiency, beriberi, hyperuricemia, and emotional disturbances.

NEUTROPHILIC DERMATOSES ASSOCIATED WITH BOWEL DISORDERS				
		Behçet disease	**Bowel-associated dermatosis–arthritis syndrome**	**Inflammatory bowel disease**
Cutaneous lesions	Aphthosis	+ (oral and anogenital)	+ (oral)	+ (oral)
	Vesiculopustular dermatosis	+	+	+
	Sweet syndrome-like dermatosis	+	–	+
	Pyoderma gangrenosum	+	–	+
	Pyostomatitis vegetans	–	–	+
	Pyoderma vegetans	–	–	+
	Vasculitis	+	±	+ (including cutaneous polyarteritis)
	Superficial thrombophlebitis	+	–	+
	Erythema nodosum	+	+	+
	Neutrophilic lobular panniculitis	+	+	+
	Pathergy	+	–	+
Systemic signs and symptoms	Fever/flu-like syndrome	+	+	+ (fever)
	Ocular involvement	+	–	+ (iritis)
	Arthritis	+	+ (plus tenosynovitis)	+
	Neurologic involvement	+	–	–
Gastrointestinal pathology		Typical aphthae can occur in the esophagus and throughout the stomach and intestine and can produce severe, cramping pain; ulcerations similar in appearance to chronic ulcerative colitis	Blind loop of bowel	Ulcerations in Crohn disease are superficial or deep, linear, and segmental or diffuse and on biopsy reveal granulomatous disease

Table 25.13 Neutrophilic dermatoses associated with bowel disorders. Pyoderma vegetans is also referred to as pyodermatitis vegetans.

INTERNATIONAL STUDY GROUP CRITERIA FOR THE DIAGNOSIS OF BEHÇET DISEASE	
Major criterion	**Required features**
Recurrent oral ulceration	Aphthous (idiopathic) oral ulceration observed by physician or patient, recurring at least three times in a 12-month period
Plus any two of the following minor criteria:	
Recurrent genital ulceration	Aphthous genital ulceration or scarring, observed by physician or patient
Eye lesions	Anterior or posterior uveitis; cells in the vitreous by slit lamp examination; or retinal vasculitis observed by ophthalmologist
Cutaneous lesions	Erythema nodosum-like lesions observed by physician or patient; papulopustular lesions or pseudofolliculitis; or characteristic acneiform nodules observed by physician in postadolescent patient not on corticosteroids
Pathergy test*	Interpreted at 24–48 h by physician
*Pathergy test is performed on the flexor forearm by obliquely inserting a 20–22-gauge sterile hypodermic needle to a depth of 5 mm ± an intradermal injection of 0.1 ml of normal saline. A positive reaction is defined as the development of a papule or pustule.	

Table 25.14 International Study Group criteria for the diagnosis of Behçet disease[50]. *Adapted from International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet. 1990;335:1078–80.*

Pathology

The characteristic lesions exhibit a perivascular, nodular neutrophilic infiltrate with nuclear dust and papillary and reticular dermal edema[57]. The infiltrate may be admixed with lymphocytes and histiocytes and may extend into the mid dermis and panniculus. A similar neutrophilic vascular pattern is seen in lesions of Sweet syndrome, Behçet disease, and the early phase of PG.

Differential Diagnosis

The papular eruption must be differentiated from that seen in urticarial vasculitis and erythema multiforme, whereas the pustular vasculitic lesions must be distinguished from other causes of small vessel vasculitis, disseminated gonococcemia (septic vasculitis), systemic candidiasis, subacute bacterial endocarditis, and Behçet disease. Pustular lesions may be misdiagnosed as folliculitis or arthropod bites (e.g. fire ants).

THERAPEUTIC LADDER FOR THE TREATMENT OF BEHÇET DISEASE		
Treatment	**Dose**	**Level of evidence**
Mucocutaneous disease		
Viscous lidocaine, topical sucralfate and other symptomatic treatments		3
Topical and inhalant corticosteroids		2
Tacrolimus (swish and spit)	1 mg in 0.5 liter of water; swish for 2 minutes BID	3
Intralesional corticosteroids		3
Colchicine	0.5–0.6 mg po thrice daily	1
Dapsone	50–150 mg po daily (or sulfapyridine equivalent)	1
Combination oral colchicine plus dapsone		3
Apremilast	30 mg po twice daily (oral ulcers)	1
Severe mucocutaneous disease		
Thalidomide	50–150 mg po nightly	1
Methotrexate	5–25 mg po, sc, or IM weekly	3
Prednisone, intermittent with taper	40–80 mg po daily usual starting dose	2
Interferon-α-2a	Variable dose (3–9× 10^6 IU sc 3× weekly)	1
TNF inhibitors	Infliximab 5 mg/kg IV at weeks 0, 2, and 6 then every 6–8 weeks; adalimumab 80 mg sc as initial dose then 40 mg sc weekly or every other week; etanercept 25–50 mg sc twice a week	1 (etanercept)
IL-12/23 inhibitors	Ustekinumab 45–90 mg sc week 0, week 4, and then once every 12 weeks	2
Systemic disease		
Prednisone	60–120 mg po daily usual starting dose (including split-dose), with taper to alternate days	2
Methylprednisolone acetate	40 mg IM 3× weekly	2
Azathioprine	50–150 mg po daily	1
Cyclophosphamide	Variable oral dose (50–200 mg daily) or IV pulse (500–1000 mg monthly then 500–1000 mg every 3 months)	3
Mycophenolate mofetil	1–1.5 g po twice daily	3
Cyclosporine	Variable doses (2–10 mg/kg po daily)	1
Tacrolimus	0.1–0.2 mg/kg po daily	2
IVIg	1–2 g/kg IV monthly (given over 2–5 consecutive days)	3
TNF inhibitors	See above for severe mucocutaneous disease	2
Interleukin(IL)-1, IL-1R antagonists	Anakinra, canakinumab (see Table 25.11)	3

Table 25.15 Therapeutic ladder for the treatment of Behçet disease[51–53]. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

CONDITIONS ASSOCIATED WITH BOWEL-ASSOCIATED DERMATOSIS–ARTHRITIS SYNDROME	
Surgical	**Medical**
• Gastric resection • Jejunoileal bypass • Blind loops of bowel following surgery • Biliopancreatic diversion	• Inflammatory bowel disease • Diverticulitis • Peptic ulcer disease • Cystic fibrosis

Table 25.16 Conditions associated with bowel-associated dermatosis–arthritis syndrome.

Treatment

Surgically, either revision of the bowel bypass or surgical resection of the blind loop of bowel is curative. Medically, systemic prednisone can produce significant symptomatic improvement of the cutaneous and rheumatologic manifestations, but it is not curative[55]. It is inadvisable to administer systemic corticosteroids as a long-term therapy. Antibiotics that have proven to be beneficial are listed in Table 25.17.

SYNOVITIS, ACNE, PUSTULOSIS, HYPEROSTOSIS, AND OSTEITIS (SAPHO) SYNDROME

Key features

- Presence of osteoarticular lesions, often in conjunction with an aseptic pustular dermatosis
- Usually a gradual onset of painful, multifocal osteoarticular lesions, especially of the anterior chest and axial skeleton
- The course of the osteoarticular lesions oscillates and is protracted, with gradual improvement that can be hastened by anti-inflammatory drugs

Introduction

SAPHO syndrome consists of a wide spectrum of aseptic neutrophilic dermatoses in association with aseptic osteoarticular lesions that have distinctive histologic and radiographic features[59,60]. Recognition of SAPHO syndrome is important so as to avoid misdirected therapies and unnecessary invasive procedures.



Fig. 25.17 Bowel-associated dermatosis–arthritis syndrome. A, B Papules and papulopustules can be erythematous or violaceous and purpuric. The number of lesions varies from a few to many.

THERAPEUTIC APPROACHES FOR BOWEL-ASSOCIATED DERMATOSIS–ARTHRITIS SYNDROME
Mild clinical expression
• Oral antibiotics to reduce bacterial overgrowth (4–8 weeks): tetracycline (500 mg 2–4 times daily), doxycycline (100 mg once to twice daily), minocycline (100 mg once to twice daily), clindamycin (600 mg daily), metronidazole (250–500 mg twice daily) • Aseptic neutrophilic inhibiting drugs (4–8 weeks): colchicine (0.6 mg thrice daily), dapsone (50–100 mg daily), thalidomide (50–200 mg daily)
Severe clinical expression
• Potent anti-inflammatory and immunomodulatory drugs (2–3 months): prednisone (40–60 mg daily then tapered), cyclosporine (200–300 mg daily), azathioprine (50–150 mg daily), mycophenolate mofetil (500 mg twice daily) • Surgical restoration of normal bowel anatomy • Possible role for TNF inhibitors (e.g. infliximab, adalimumab, etanercept)
Treatments based upon small case series and case reports.

Table 25.17 Therapeutic approaches for bowel-associated dermatosis–arthritis syndrome.

SAPHO SYNDROME
Osteoarticular manifestations (aseptic/sterile)
• Inflammatory synovitis • Arthrosteitis – inflammation of the osseous structures of a joint • Hyperostosis or osteitis, most often anterior chest wall (sternum, clavicles, ribs) and axial skeleton (spine*, pelvis) • Subtype: chronic recurrent multifocal osteomyelitis (CRMO) – frequent involvement of metaphyses of tubular bones and seen primarily in children
Associated cutaneous disorders
• **Palmoplantar pustulosis**, including TNF inhibitor-induced • Pustular psoriasis, including CARD14-mediated • Sneddon–Wilkinson disease (subcorneal pustular dermatosis) • Psoriasis • Follicular occlusion tetrad, in particular **acne conglobata** and hidradenitis suppurativa • **Acne fulminans** • Linear IgA bullous dermatosis • Behçet disease • Sweet syndrome • Pyoderma gangrenosum
Differential diagnosis (primarily genetic disorders)
• DIRA (deficiency of the interleukin-1 receptor antagonist) syndrome [*IL1RN* mutations] • PAPA (pyogenic [sterile] arthritis, pyoderma gangrenosum and acne) syndrome and its variant, PAPASH syndrome [*PSTPIP1* mutations] • Majeed syndrome (congenital dyserythropoietic anemia, CRMO, Sweet syndrome or cutaneous pustulosis [*LPIN2* mutations]) • Pyrin-associated autoinflammatory disease [*MEFV* mutations]
*Spondylitis or spondylodiscitis.

Table 25.18 SAPHO syndrome. SAPHO – synovitis, acne, pustulosis, hyperostosis and osteitis. Most common associated cutaneous disorders are in **bold**. PAPASH, *p*yogenic *a*rthritis, *p*yoderma gangrenosum, *a*cne, and *s*uppurative *h*idradenitis; TNF, tumor necrosis factor.

History

In 1972, chronic recurrent multifocal osteomyelitis was described as a rare chronic inflammatory musculoskeletal process in children and adults. Although cutaneous pustulosis and acne were reported in association with osteomyelitis and arthritis in the 1960s, it was not until 1987 that the acronym SAPHO (synovitis, *a*cne, *p*ustulosis, *h*yperostosis and *o*steitis) syndrome was coined to describe this clinicoradiologic entity that involves skin, bone, and joints.

Epidemiology

This is a rare and under-recognized syndrome that primarily affects children and young and middle-aged adults. It rarely presents after 60 years of age. There is no sex predilection, with the exception of a male predominance in those with acne. It has been observed most frequently in Japan, less often in Scandinavia, Germany and France, and infrequently in the US and Canada.

Pathogenesis

The pathogenesis of SAPHO appears to be multifactorial. Some hypothesize that it is the result of an autoimmune response triggered by low-virulence microorganisms and enhanced chemotaxis of neutrophils.

Clinical Features

The essential element is osteoarticular lesions, with pustular dermatoses noted in ~30% of children and ~85% of adults. The neutrophil is the "tie that binds" the clinical manifestations of this syndrome. Table 25.18 outlines the osteoarticular lesions of SAPHO. The affected bones are tender and the swollen joints are painful. Patients may be febrile with a leukocytosis and elevated ESR or CRP.

Bone scintigraphy demonstrates an increased uptake at involved sites[61]. MRI is very sensitive in assessing joint and tissue involvement and it helps in monitoring the disease. The osteoarticular involvement is intermittent with periodic exacerbations and remissions and there is no correlation with the activity of the associated sterile neutrophilic dermatosis. SAPHO is also associated with inflammatory bowel disease and is regarded as one of the seronegative spondyloarthropathies.

Pathology

Early in the process, medullary bone contains an inflammatory cellular infiltrate, consisting primarily of neutrophils, osteoclasts, and osteoblasts. Later on, cicatricial fibrosis surrounded by hypertrophic inactive bone is seen.

Differential Diagnosis

The differential diagnosis of the bone lesions includes classic bacterial osteomyelitis, primary bone tumors, metastases, and Langerhans cell histiocytosis. The possibility of a genetic syndrome with similar cutaneous and osseous manifestations also needs to be considered (see Table 25.18).

Treatment

Since precise knowledge of the pathogenesis of SAPHO syndrome is lacking, a variety of anti-inflammatory therapies have been tried. Although isotretinoin is used to treat associated severe acne, there are scattered case reports of isotretinoin-associated flares of SAPHO. Treatment options include NSAIDs and intra-articular corticosteroids for the arthritis; bisphosphonates for bone involvement; and systemic corticosteroids, other immunosuppressive medications (e.g. azathioprine, methotrexate), TNF antagonists (e.g. etanercept, adalimumab, infliximab), IL-1 antagonists (e.g. anakinra), and IL-12/23, IL-23, IL-17 or JAK inhibitors for both skin and bone disease. Of note, paradoxical induction of SAPHO was observed in a patient with inflammatory bowel disease treated with infliximab.

EROSIVE PUSTULAR DERMATOSIS

Synonym: ■ Erosive pustular dermatosis of the scalp

Key features

- Sterile pustules plus erosions and superficial ulcerations with keratotic crusts
- Most commonly develops within photodamaged atrophic skin of the midline scalp
- Can occur in other locations where the skin is atrophic or fragile, including sites of injury

History

In 1979, Pye et al.[62] described six elderly women with pustular and crusted lesions of the scalp that improved with potent topical corticosteroids.

Epidemiology

Erosive pustular dermatosis (EPD) occurs most commonly on the scalp of older adults with photodamaged skin. It has also been observed on the lower legs of individuals with venous insufficiency and at sites of injury, including in neonates.

Pathogenesis

It is unknown. The causes of erosive pustular dermatosis are not only limited to traumatic injuries but also include medications, comorbid conditions, and several dermatological procedures.

Significant cumulative photodamage in the setting of androgenetic alopecia and local mechanical trauma are risk factors, but how this leads to pustules and erosions is not known. Additional types of trauma include previous herpes zoster and thermal burns. There is a possible association with autoimmune disorders such as autoimmune thyroiditis.

Clinical Features

EPD is characterized by pustules, along with erosions and keratotic crusting, within atrophic or fragile skin. Tenderness is a common symptom and there may be associated pain or pruritus as well as drainage. The most common site of involvement is the photodamaged skin of the midline scalp in an elderly adult. Additional locations include the lower extremities in the setting of venous hypertension and at sites of injury, e.g. from thermal burns, surgical procedures, and skin graft placement. There have been a few reports of EPD in neonates following scalp injuries.

EPD can slowly progress and may eventually lead to scarring alopecia. Occasionally, there is secondary infection.

Pathology

The histopathologic findings are nonspecific. Regenerating epidermis in sun-damaged skin may show enlarged keratinocytes and should not be misinterpreted as actinic keratosis. Intraepidermal or subcorneal pustulation is usually observed.

Differential Diagnosis

The differential diagnosis for scalp lesions includes primarily hypertrophic actinic keratoses and squamous cell carcinomas. Additional entities to consider include folliculitis, pyoderma, cicatricial pemphigoid, EFGR inhibitor-induced pustular dermatosis and also, if at other sites, pustular psoriasis.

Treatment

In case series or case reports, topical therapies – corticosteroids (initially potent), calcineurin inhibitors, vitamin D analogues, dapsone – have been reported as successful treatments. Silicone gels or sheeting as well as photodynamic therapy (PDT) are additional therapeutic options. Topical and systemic antibiotics, including mupirocin and doxycycline, respectively, can also led to improvement. Severe EPD may benefit from oral retinoids, dapsone, or zinc sulfate. Supplementing medical therapy with mild debridement of the crusted areas via curettage may accelerate the response[63].

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eFig. 25.1 Sweet syndrome. The neck, upper trunk and upper extremities are common sites of involvement. Sometimes, edematous lesions have a targetoid appearance.



eFig. 25.2 Sweet syndrome. Grouped pink papules coalescing into plaques on the neck of a patient with acute myelogenous leukemia.



eFig. 25.3 Histiocytoid Sweet syndrome. Widespread eruption of edematous papulonodules in a patient with acute myelogenous leukemia. *Courtesy Nour Kibbi, MD.*



eFig. 25.4 Pyoderma gangrenosum. Inflammatory rim and violaceus overhanging border. *Courtesy Mark D. P. Davis, MD.*



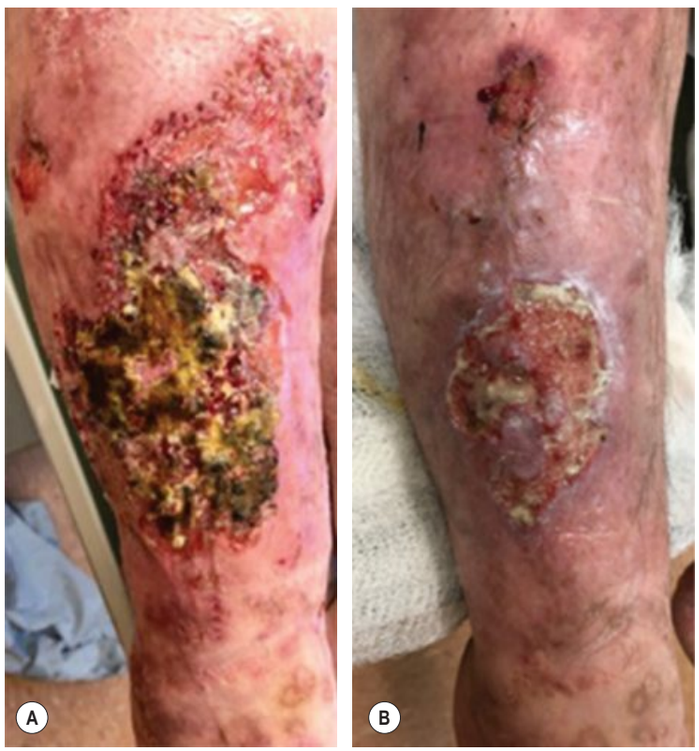
eFig. 25.5 Pyoderma gangrenosum. Inflammatory rim and violaceus overhanging border. *Courtesy Frank Samarin, MD.*



eFig. 25.6 Pyoderma gangrenosum. The ulcer has a vegetative base with a pustular exudate.



eFig. 25.7 Classic ulcerative pyoderma gangrenosum. The edge of this ulceration on the shin is undermined with a violet–gray color as well as an inflammatory rim. Note the central scarring.



eFig. 25.8 Pyoderma gangrenosum in a patient with IgA monoclonal gammopathy. A Persistent disease despite high-dose corticosteroids, mycophenolate mofetil, and intravenous immunoglobulin. **B** Institution of therapy for multiple myeloma (cyclophosphamide, bortezomib, decadron [CyBorD]) resulted in significant improvement. Of note, the patient had not met the criteria for IgA multiple myeloma. *Courtesy Jonathan S. Leventhal, MD.*



eFig. 25.9 Peristomal and postsurgical pyoderma gangrenosum (PG). Multiple ulcers surround an ileostomy (following a total proctocolectomy) in a patient with refractory chronic ulcerative colitis. While peristomal PG occurs most commonly following intestinal resection of inflammatory bowel disease, it can also follow resection of gastrointestinal or bladder carcinoma.



eFig. 25.10 Neutrophilic dermatosis of the dorsal hands. This entity has overlapping clinical and histologic features with both Sweet syndrome and pyoderma gangrenosum. Some patients have an associated pustular vasculitis. *Courtesy Jean L. Bolognia, MD.*



eFig. 25.11 Pathergy in a patient with pyoderma gangrenosum. The lesion appeared at the site of an intravenous catheter. *Courtesy Samuel L. Moschella, MD.*



eFig. 25.12 Behçet disease: mucocutaneous lesions. Perianal aphthosis. *Courtesy Samuel L. Moschella, MD.*



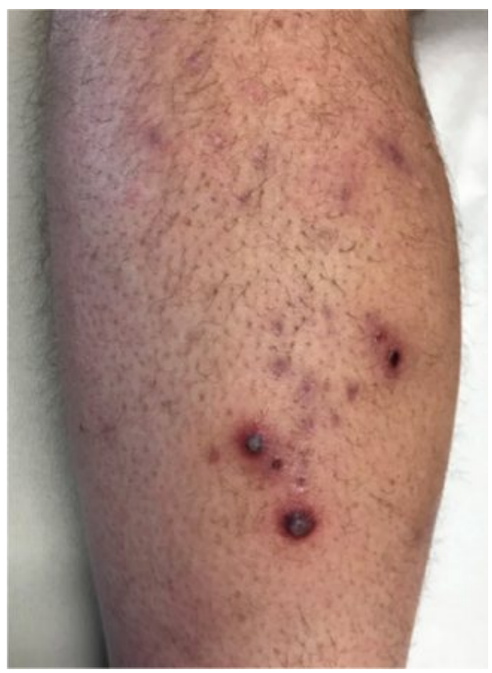
eFig. 25.13 Behçet disease. Multiple ulcerations of the lower extremities, some of which are small and punched-out with hemorrhagic crusts (inset). *Courtesy Luis Requena, MD.*



eFig. 25.14 Behçet disease. Ulcerations of the soft palate, uvula, and tongue.



eFig. 25.15 Bowel-associated dermatosis–arthritis syndrome. Multiple papulopustules on the upper extremity. *Courtesy Joseph L. Jorizzo, MD.*



eFig. 25.16 Pustular variant of pyoderma gangrenosum on the leg. Multiple, recurring, small sterile pustules and hemorrhagic crusts on a violaceous base. Note the punctate scarring and postinflammatory hyperpigmentation from previous lesions. Although this variant is most often seen in patients with underlying inflammatory bowel disease, this patient was diagnosed with autoimmune hepatitis. *Courtesy Karynne O. Duncan, MD.*

26 Eosinophil-Associated Dermatoses

Brendon Verhave and Lisa A. Beck

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Key features

- Infiltration of eosinophils into the skin is not uncommon; therefore, clinicopathologic correlation is important to arrive at the correct clinical diagnosis
- Eosinophil-associated dermatoses include arthropod bite reactions and drug eruptions ("bugs and drugs"), atopic dermatitis, Wells syndrome, hypereosinophilic syndromes, autoimmune blistering diseases, and parasitic infections
- Activated eosinophils lose their morphologic integrity as they deposit toxic granule proteins and other inflammatory mediators in tissues; the absence of intact eosinophils may not be an accurate reflection of their relevance to a disease state
- In patients with persistent peripheral blood eosinophilia, as observed with hypereosinophilic syndromes, tissue infiltration and eosinophil-derived mediators may cause significant end-organ damage

EOSINOPHIL BIOLOGY

The eosinophil is a leukocyte ~10–16 microns in diameter that possesses a segmented (usually bi-lobed) nucleus. It is produced in the bone marrow and circulates transiently (8–18 hours) in the peripheral blood. Under normal conditions, circulating eosinophil counts range from 0 to 500 cells/mcl of human blood. Except for the bone marrow, gastrointestinal tract (distal to the esophagus), and lymphoid tissues (spleen, thymus, and lymph nodes), eosinophils are limited to diseased tissues.

In 1879, Paul Ehrlich named the "eosinophil" because of the intense staining of its distinctive cytoplasmic granules with the acidic dye, eosin. Ultrastructurally, eosinophils are characterized by membrane-bound, cytoplasmic granules that have an electron-dense core and less dense matrix (Fig. 26.1). The eosinophil produces multiple factors that make it a highly proinflammatory and pro-fibrotic leukocyte[1–3]. It also expresses a number of receptors on its cell surface that are important for activation[4,5], prolonged survival, and targeted migration into tissue compartments (see Fig. 26.1)[1–4,6].

Eosinophils are attracted into tissues by the coordinated actions of: (1) eosinophil activating cytokines (commonly referred to as "priming" cytokines); (2) tissue-released chemokines; and (3) endothelial adhesion molecules[7]. Eosinophils express receptors for granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3, and IL-5 which are important for bone marrow production, maturation, activation, and prolonged survival[1,3,8]. Several lines of investigation indicate that eosinophils are recruited to and activated within tissues by cytokines that largely come from a type 2 immune response (IL-33) or from Th2 cells (IL-4, IL-5, and IL-13). Natural killer cells also produce IL-5, and mast cell-derived cytokines contribute indirectly to eosinophil activation via induction of IL-5 and GM-CSF.

Eosinophils themselves elaborate important inflammatory and regulatory cytokines, including IL-1α, TGF-α and TGF-β_1, GM-CSF, IL-3, IL-5, IL-6, IL-8, TNF, and macrophage inflammatory protein 1α (CCL3; see Fig. 26.1). As a result, eosinophil activation also occurs in an autocrine manner. In cytotoxicity assays, eosinophils are maximally activated by GM-CSF, followed by IL-3, IL-5, TNF and IL-4, in order of potency[3,8]. Eosinophil numbers in the circulation and tissues is a function of balance of mediators that prolong survival versus those that induce apoptosis, like glucocorticoids. Glucocorticoids can counteract the prolonged survival induced by IL-3, IL-5 and GM-CSF, which may in part explain their therapeutic efficacy in most eosinophil-driven conditions. More recently, the surface receptors sialic acid-binding immunoglobulin-like lectins (Siglec) -8 and -10, which are expressed on eosinophils and mast cells, have been shown to mediate apoptosis[4].

Several members of the C-C chemokine gene superfamily are chemotactic for eosinophils, including the eotaxins 1, 2, and 3 (CCL11, CCL24, and CCL26). These chemokines signal primarily through C-C chemokine receptor (CCR)-3, which is highly expressed on eosinophils. In addition to their chemotactic properties, these chemokines also induce the release of reactive oxygen species. Eotaxins are produced by tissue resident cells positioning them as upstream mediators of cutaneous inflammation[9].

Eosinophils enter tissues by traversing blood vessels. Similar to other leukocytes, this transmigration involves adhering to endothelial adhesion molecules within the selectin and immunoglobulin supergene families[1,3]. In particular, eosinophils constitutively express very late antigen (VLA)-4, the ligand for vascular cell adhesion molecule (VCAM)-1; the latter is a cytokine-inducible endothelial adhesion molecule (see Fig. 102.11). After entering tissues, eosinophil activity is influenced by interactions between integrins on the eosinophil cell surface and both extracellular proteins (fibronectin, laminin, or collagen) and glycosaminoglycans (hyaluronic acid or chondroitin sulfate), which are induced under inflammatory conditions.

Granular Contents

Upon activation, eosinophils release their granular contents into the extracellular spaces by three mechanisms[1]: cytolytic degranulation, piecemeal degranulation, and regulated secretion. Cytolytic degranulation is characterized by organelle rupture, chromatolysis of nuclei with loss of morphologic integrity, and extensive deposition of eosinophil granules and granule products within tissue[1,3]; this process occurs in many inflammatory disorders, including atopic dermatitis, as well as in affected organs (including the skin) in patients with hypereosinophilic syndromes (HES).

Eosinophil major basic protein 1 (eMBP1), the constituent of the granules' crystalline cores (see Fig. 26.1), directly damages helminths and mammalian cells, exemplified by its ability to cause exfoliation of bronchial epithelial cells. In addition, eMBP1, but none of the other eosinophil granule proteins, induces basophil histamine release. Furthermore, eMBP1 stimulates neutrophils, leading to the release of superoxides and lysozyme. *Eosinophil cationic protein* (ECP or RNase3) and *eosinophil-derived neurotoxin* (EDN or RNase2) are members of the RNase family. ECP is a potent toxin for parasites through a different mechanism than eMBP1 and is more effective at killing certain helminths than eMBP1. EDN, as its name implies, is a neurotoxin and also has antiviral activity against RNA viruses.

Eosinophil peroxidase (EPO) kills numerous microorganisms in the presence of hydrogen peroxide (generated by eosinophils and other phagocytes) and halides. This combination of products also initiates mast cell secretion. Binding of EPO to microbes, including *Staphylococcus aureus*, greatly potentiates their killing by phagocytes. Similarly, EPO-coated tumor cells are spontaneously lysed by activated macrophages, and eMBP1 is also toxic to tumor cells. EPO and eMBP1 are potent platelet agonists that lead to release of 5-hydroxytryptamine (serotonin) and promote clotting.

In summary, the highly basic granule proteins released by activated eosinophils have evolved to not only protect us from parasitic helminths but also some bacteria and viruses, and they may in some settings possess anti-tumor properties.

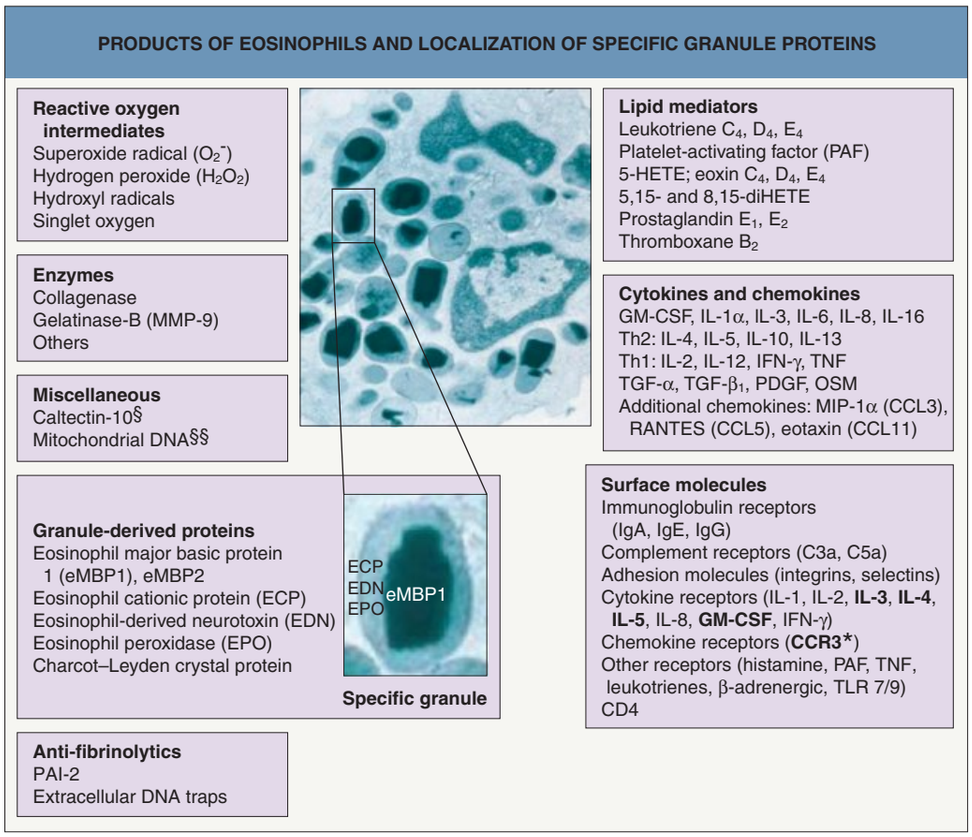


Fig. 26.1 Products of eosinophils and localization of specific granule proteins. The eosinophil produces myriad products that determine its role in inflammation. Specific granules contain major basic protein 1 and 2 (in the electron-dense core) and other toxic proteins (in the matrix). *Receptor for eotaxins and RANTES. §Charcot–Leyden crystal protein. §§Forms mitochondrial DNA traps with ECP and eMBP1. CCL, chemokine ligand; CCR, CC chemokine receptor; GM-CSF, granulocyte–macrophage colony-stimulating factor; HETE, *h*ydroxy*e*icosa*t*etra*e*noic acid; IFN, interferon; IL, interleukin; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; OSM, oncostatin M; P2X4, P2X purinoceptor 4; PAI-2, plasminogen-activator inhibitor; PDGF, platelet-derived growth factor; RANTES, *r*egulated on *a*ctivation, *n*ormal *T* cell *e*xpressed and *s*ecreted; Siglec, sialic acid-binding immunoglobulin-type lectins; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor.

EOSINOPHIL-ASSOCIATED DERMATOSES	
Diagnosis	**Clinical clues**
Common entities	
Allergic contact dermatitis (Ch. 14)	History of exposure; suggestive distribution; positive patch test
Arthropod bite/sting reactions (Ch. 85)	Primarily involves exposed skin; mosquitoes, fleas, spiders, ticks, and mites; exaggerated reactions in patients with CLL
Atopic dermatitis (Ch. 12)	History of atopy; pruritus; flexural accentuation; lichenification
Drug eruptions (Ch. 21)	Drug history, especially new drugs within the previous 2 weeks or up to 6 weeks for DRESS/DIHS Histopathologically, eosinophils are present in ~50% of cutaneous drug reactions
Erythema toxicum neonatorum (Ch. 34)	Newborn with erythematous macules, papules and pustules, often with prominent erythematous flare
Parasitic infections, particularly helminths (Ch. 83)	Cysticercosis, dirofilariasis, larva migrans, gnathostomiasis, onchocerciasis, schistosomiasis, and others
Scabies (Ch. 84)	Marked nocturnal pruritus; web-space, umbilical and groin involvement; close physical contact
Urticaria (Ch. 18)	Pruritic, migratory, transient wheals; individual lesions last <24 hours
Less common entities	
Annular erythema of infancy[58] (Ch. 19)	Annular or serpiginous non-pruritic plaques in infants
Autoimmune bullous dermatoses (Chs. 29–32; see Table 29.4 for differential diagnosis of eosinophilic spongiosis)	Pemphigoid (particularly bullous pemphigoid, gestational pemphigoid) > pemphigus, linear IgA bullous dermatosis, dermatitis herpetiformis, epidermolysis bullosa acquisita
Eosinophilic dermatosis associated with hematological disorders (eosinophilic dermatosis of hematologic malignancy; Ch. 33)	Most common in patients with CLL, but reported in patients with other hematologic malignancies; severe insect bite reactions as well as insect bite-like reactions
Eosinophilic fasciitis (Shulman syndrome; Ch. 43)	Acute onset of symmetrical induration of skin and subcutaneous tissues of the limbs; peripheral blood eosinophilia
Eosinophilic granulomatosis with polyangiitis (EGPA; Ch. 24)	Palpable purpura and tender papulonodules; peripheral blood eosinophilia; pulmonary (e.g. asthma), neurologic (e.g. mononeuritis multiplex), and cardiac involvement; prominent IgG4 and IgE responses

Table 26.1 Eosinophil-associated dermatoses.

EOSINOPHIL-ASSOCIATED DERMATOSES	
Diagnosis	**Clinical clues**
Eosinophilic (pustular) folliculitis (Ch. 38)	*Immunosuppression, including HIV infection and post-transplant*:* severe pruritus and papules on the face and upper trunk
	Ofuji disease: chronic, recurrent follicular pustules in a seborrheic distribution with a tendency to form circinate plaques; most commonly observed in east Asia
	Pediatric: follicular pustules on the scalp of an infant
Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy (EPPER)[59]	Local and generalized pruritus; erythematous papules and sometimes vesicles
Eosinophilic vasculitis (histopathologic reaction pattern rather than specific dermatosis)[60]	Pruritic urticarial and purpuric papules, angioedema; juvenile temporal arteritis (see below)
Eosinophilic ulcer of the oral mucosa (Ch. 72)	Rapidly enlarging nodule that develops ulceration; tongue most common site
Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia; Ch. 114)	Single or multiple nodules of the face, scalp, and/or ears
Granuloma faciale (Ch. 24)	Red-brown plaque(s), often with prominent follicular openings; lesions favor the face
Hypereosinophilic syndromes (HESs)	See text
Incontinentia pigmenti (Ch. 62)	Vesicles and bullae along the lines of Blaschko in neonate (stage I); peripheral blood eosinophilia
Juvenile temporal arteritis	Nodule in the temporal region in an older child or young adult due to eosinophilic vasculitis
Juvenile xanthogranuloma (Ch. 91)	Yellow to red–brown papules or nodules on the head and neck, upper trunk or proximal extremities; early lesions may have numerous eosinophils
Kimura disease (Ch. 114)	Subcutaneous masses and lymphadenopathy of the head and neck region; peripheral blood eosinophilia, increased serum IgE levels
Langerhans cell histiocytosis (especially eosinophilic granuloma; Ch. 91)	Disseminated pink and yellow–brown papules (often with crusts); intertriginous involvement; occasionally, nodules
Lymphoproliferative disorders of the skin, benign and malignant (Chs. 119–121)	Presentation varies depending upon specific type; variable number of eosinophils seen in entire spectrum of lymphoproliferative disorders and commonly observed in LyP and cutaneous ALCL
Cutaneous mastocytosis (Ch. 118)	Pink–tan to red–brown macules, papules and plaques that urticate with stroking (Darier sign)
Papuloerythroderma of Ofuji (see Ch. 10)	Most commonly in elderly men; widespread, pruritic, red–brown papules that may become more confluent with characteristic sparing of the skin folds ("deck-chair" sign); peripheral blood eosinophilia and elevated serum IgE level; can be associated with malignancies (especially CTCL), infections, or drugs
Polymorphic eruption of pregnancy (PEP; also referred to as pruritic urticarial papules and plaques of pregnancy [PUPPP]; Ch. 27)	Primigravida in third trimester; urticarial papules and plaques, especially in striae
Pruritic papular eruption of HIV disease[61] (Ch. 78)	Pruritic non-follicular papules in a symmetric distribution; HIV infection; may be an exaggerated reaction to arthropod antigens but without a recognized history of bites
Seabather's eruption (e.g. larvae of *Linuche unguiculata* and *Edwardsiella lineata*; Ch. 85)	Pruritic papules of skin covered by swimsuit; occurs after ocean swimming
Small vessel vasculitis (leukocytoclastic vasculitis; Ch. 24)	Palpable purpura that favors the lower extremities; eosinophils more commonly observed in drug-induced variant
Swimmer's itch or cercarial dermatitis (larvae of avian and mammalian schistosome species; Ch. 83)	Pruritic papules on uncovered skin; occurs after fresh-water swimming
Urticarial allergic eruption	Annular or gyrate urticarial plaques that persist >24 hours
Wells syndrome	See text
Less well-defined entities, with overlapping features	
Papular dermatitis (itchy red bump disease)	Markedly pruritic pink to red papules; may be associated with eczematous patches and/or dermographism; spongiotic dermatitis often seen histologically
Urticarial dermatitis	Very pruritic, urticarial and/or eczematous lesions involving the trunk and proximal extremities; favors the elderly (chronic eczematous eruption of aging) and may reflect immunosenescence; often requires UVB phototherapy, dapsone or systemic immunosuppressives (e.g. MTX, dupilumab) for control
Exudative discoid and lichenoid chronic dermatosis of Sulzberger and Garbe (oid-oid disease)[62]	Middle-aged men; pruritic lesions commonly involving genitals; progressive stages: discoid → exudative → lichenified; peripheral blood eosinophilia; possible variant of nummular dermatitis
Pachydermatous eosinophilic dermatitis[63]	South African Black teenage girls with generalized pruritic papules, hypertrophic genital lesions and peripheral blood eosinophilia; dapsone-responsive; possibly a variant of hypereosinophilic dermatitis of Nir–Westfried

*Hematopoietic stem cell or solid-organ.

Table 26.1 Eosinophil-associated dermatoses. *It should be emphasized that variable numbers of eosinophils may be encountered in a large number of inflammatory, neoplastic, and infectious skin disorders, in addition to those listed in this table.* ALCL, anaplastic large cell lymphoma; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T cell lymphoma; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; LyP, lymphomatoid papulosis; MTX, methotrexate.

TISSUE EFFECTS AND INNATE IMMUNITY

The presence of eosinophils in healthy tissues such as the gastrointestinal tract suggests that they may also have a homeostatic function. In addition, eosinophil infiltration is associated with tissue remodeling and fibrosis. Although cytokines, including IL-5 and eotaxins, are known to mediate eosinophil development and survival, mechanisms underlying the basal regulation of eosinophils, including their circadian cycling, remained largely unknown until the identification of innate lymphoid cells (ILCs). Long-lived type 2 ILCs, also known as ILC2s, are resident in peripheral tissues and regulate basal eosinophilopoiesis and tissue eosinophil accumulation via constitutive and stimulated cytokine expression[10–12]. ILC2s secrete IL-5 constitutively and are induced to co-express IL-13 during type 2 inflammation, resulting in localized eotaxin production and eosinophil accumulation.

Studies of the interactions of skin ILCs with other cell types demonstrated that dermal ILCs interact selectively and strongly with mast cells[12,13]. Type 2 innate lymphocytes have been designated part of the "Th2 franchise", and a broad role for ILC2s is emerging for both eosinophils and metabolic homeostasis, e.g. in atopic dermatitis[10], in glucose metabolism within adipose tissue[14] and adipose tissue remodeling[15], and in allergic respiratory disease[16]. Interactions of eosinophils with nerves may in part explain pruritus and other neurophysiological changes (e.g. white dermographism) observed in eosinophil-infiltrated tissues[17,18].

Eosinophils may act as antigen-presenting cells for microbial (including staphylococcal superantigens), viral, and parasitic antigens, promoting T cell proliferation. They also play a role in the regulation of mast cell function. Activation of eosinophils via toll-like receptors (TLR) 7 and TLR9 affects several eosinophil functions, with the overall response influenced by a Th2-like cytokine milieu[19]. In addition, eosinophils can generate mitochondrial DNA traps that contain ECP and eMBP1 which have antimicrobial activity and can promote thrombosis. In summary, eosinophils participate in innate and acquired immunity[2] and their functional diversity has numerous ramifications for both homeostasis and disease pathogenesis[1].

EOSINOPHIL-ASSOCIATED DERMATOSES

"Eosinophil-associated dermatoses" encompass a wide range of diseases characterized by the presence of a few to many eosinophils and/or evidence of eosinophil degranulation in skin and/or mucous membranes. Disorders characteristically associated with eosinophil infiltration include arthropod bite reactions and ectoparasite infestations (see Chs. 84 & 85), drug eruptions (see Ch. 21), atopic dermatitis (see Ch. 12), helminth infections (see Ch. 83), and Wells syndrome (Fig. 26.2). However, there are a number of other skin diseases where tissue eosinophilia may be present, including bullous pemphigoid, urticaria, and eosinophilic granulomatosis with polyangiitis (EGPA; Churg–Strauss syndrome) (Table 26.1). In addition, tissue eosinophilia can be observed in a wide range of skin disorders, from inflammatory to infectious to neoplastic.

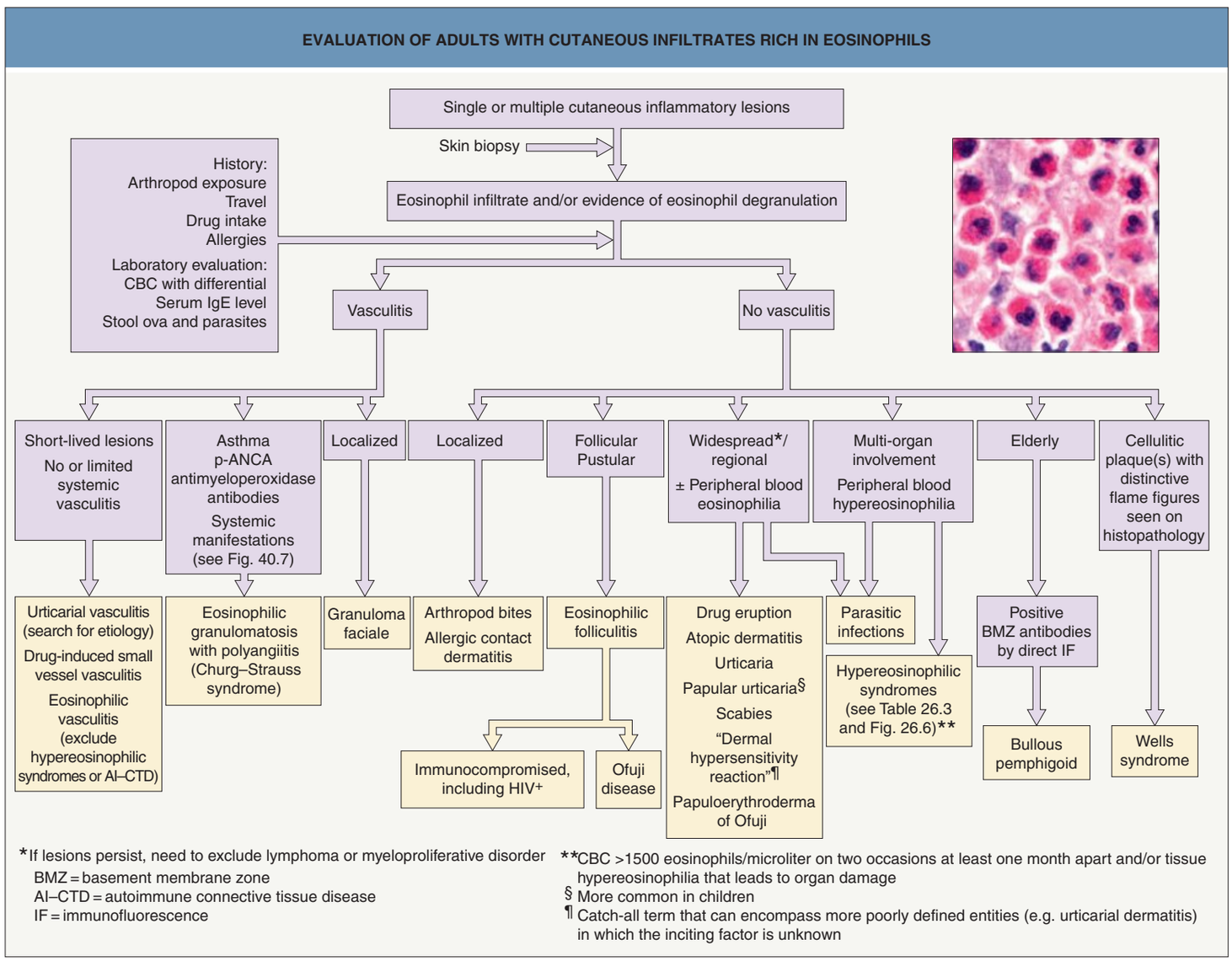


Fig. 26.2 Evaluation of adults with cutaneous infiltrates rich in eosinophils. These disorders are characterized histologically by eosinophil infiltration and/or eosinophil granule protein deposition. Peripheral blood eosinophilia occurs in some patients. Of note, systemic corticosteroids can significantly reduce the peripheral blood eosinophil count. *Photomicrograph, courtesy Lorenzo Cerroni, MD.*

More recently, it has been noted that mild to moderate peripheral eosinophilia (up to 35%–40%), along with tissue infiltration, is a key feature of IgG4-related disease (IgG4-RD[20]; Table 26.2)[20]. Initially described as a pancreatic disorder with increased serum IgG4 levels and numerous IgG4-positive plasma cells in affected tissues, the spectrum of IgG4-RD has been expanded to include any organ, including skin. Proposed cutaneous manifestations are granuloma faciale and lesions that resemble angiolymphoid hyperplasia with eosinophilia (see Table 26.2 & Ch. 24).

Wells Syndrome

Synonym: ■ Eosinophilic cellulitis

Key features

- The characteristic presentation is recurrent, painful and/or pruritic, edematous to indurated plaques
- Histologically, a diffuse dermal infiltrate composed of eosinophils and histiocytes is seen as are foci of amorphous/granular material, termed "flame figures", which reflect localized degranulation of eosinophils
- Flame figures are a characteristic but are not diagnostic feature, as they can be observed in a wide range of eosinophil-rich dermatoses
- Distinction between Wells syndrome as a specific entity and a reaction pattern occurring in the setting of another dermatosis may be difficult
- Dramatic improvement after administration of systemic corticosteroids

Introduction

Wells syndrome is a cutaneous disorder of unknown etiology characterized by one or more edematous (early) to indurated (late) plaques that resemble well-demarcated cellulitis. The classic histopathologic findings consist of a diffuse dermal infiltrate of eosinophils plus characteristic "flame figures".

History

Wells described the first patient in 1971 as "recurrent granulomatous dermatitis with eosinophilia". He later renamed the disease "eosinophilic cellulitis"[21]. Spigel and Winkelmann[22] proposed the eponym, Wells syndrome, in 1979.

Epidemiology

Over 100 cases of Wells syndrome have been reported to date, ranging from newborns to patients over 70 years of age.

Pathogenesis

The pathogenesis of Wells syndrome is unknown. Local hypersensitivity due to "triggers" has been proposed, including insect bites or stings, drugs, allergic contact dermatitis, an underlying malignancy, and infections (e.g. dermatophytes, viruses, *Toxocara canis*)[23,24]. Of note, peripheral lymphocytes isolated from patients with Wells syndrome were reported to have exaggerated responses to mosquito salivary gland extracts[25]. Activated eosinophils clearly play a major role in the pathophysiology of Wells syndrome and it is thought that Th2 cells, and IL-5 in particular, are responsible for eosinophil recruitment and activation in this disease[26].

Clinical features

In Wells syndrome, there are recurrent episodes of prodromal itching or burning, accompanied by markedly edematous plaques. The latter may have an annular or arcuate configuration[27], and vesicles and bullae can also be seen. Initially, the lesions are bright red, and then they fade to a pink–brown or slate-gray color (Fig. 26.3). The plaques may become indurated, and lesions usually resolve over 4 to 8 weeks. Less common clinical presentations include papules and hemorrhagic bullae. The extremities are most frequently affected, but involvement of the trunk can also be seen. The most common systemic complaint is malaise, with fever in less than a quarter of patients. Peripheral blood eosinophilia is common. Patients are often misdiagnosed as having erysipelas or acute cellulitis. Precipitating events, including arthropod bites and stings or vaccinations, have been described in a minority of patients[28].

Pathology

An interstitial dermal infiltrate of eosinophils, admixed with lymphocytes and histiocytes is seen (Fig. 26.4). The infiltrate is most prominent in the mid to deep dermis, with occasional involvement of the subcutaneous fat, fascia, and skeletal muscle. The superficial dermis may have massive papillary dermal edema to the point of subepidermal bulla formation. Intraepidermal vesiculation, with eosinophilic spongiosis, may also be present.

IgG4-RELATED DISEASE (IgG4-RD) AND CUTANEOUS DISORDERS THAT MAY HAVE INCREASED LESIONAL IgG4$^+$ PLASMA CELLS	
Characteristic findings (not present in all patients)	

• Clinical: swelling or mass(es) in one or more organ(s)/tissue(s)
• Blood: increased serum IgG4 level; increased serum IgE level; eosinophilia or hypereosinophilia
• Histopathology of affected organ(s)/tissue(s):
  • Dense infiltrates of lymphocytes and plasma cells
  • Fibrosis (typically storiform pattern)
  • IgG4$^+$ to IgG$^+$ plasma cells >40%; >10 IgG4$^+$ plasma cells/hpf
  • Eosinophil infiltrates
  • Obliterative phlebitis	

Affected organs/tissues and/or manifestations – emerging spectrum	
• Pancreas (autoimmune pancreatitis)	• Sclerosing cholangitis
• Lacrimal glands (bilateral)	• Salivary glands (often submandibular; bilateral; Mikulicz disease)
• Retroperitoneal fibrosis (previously viewed as idiopathic)	• Sinonasal eosinophilic angiocentric fibrosis
• Thyroid (Riedel thyroiditis, fibrous variant of Hashimoto thyroiditis)	• Aorta (aortitis, periaortitis)
• Orbit (pseudotumor, proptosis)	• Lung, pleura, pericardium, kidney (tubulointerstitial nephritis), prostate, stomach (lymphoplasmacytic gastritis), breast (sclerosing mastitis, pseudotumor)
Cutaneous disorders that may have increased lesional IgG4$^+$ plasma cells	
• Granuloma faciale	• Angiolymphoid hyperplasia with eosinophilia
• Kimura disease	• Rosai–Dorfman disease
• Cutaneous plasmacytosis	

Table 26.2 IgG4-related disease (IgG4-RD) and cutaneous disorders that may have increased lesional IgG4$^+$ plasma cells[64,65]. Corticosteroids represent the first-line treatment for systemic involvement, with anti-CD20 or anti-CD19 antibodies, Bruton tyrosine kinase inhibitors, and anti-SLAMF7 antibodies as potential additional therapies. hpf, high power field.

In addition to intact eosinophils, extracellular eosinophil granules are present in the dermis. The characteristic brightly eosinophilic flame figures consist of collagen fibers coated with eosinophil granule proteins[29] (Fig. 26.4, inset). Utilizing indirect immunofluorescence assays, extracellular eMBP1 from eosinophil granules has been localized to flame figures[30]. In addition, a palisade of histiocytes and a few multinucleated giant cells partially surround these flame figures. While flame figures are considered a hallmark of Wells syndrome, they are not a specific finding[31]. Flame figures can also be seen in other disorders in which degranulation of eosinophils occurs including arthropod bite and sting reactions, scabies, and less often, parasitic infections (e.g. onchocerciasis), bullous pemphigoid, pemphigus vegetans, and EGPA.



Fig. 26.3 Wells syndrome – clinical features. A Large edematous, erythematous plaque on the leg surrounded by several smaller plaques and nodules. This presentation may be misdiagnosed clinically as infectious cellulitis. **B** More mature dull pink nodules and plaques. *A, Courtesy Luis Requena, MD.*

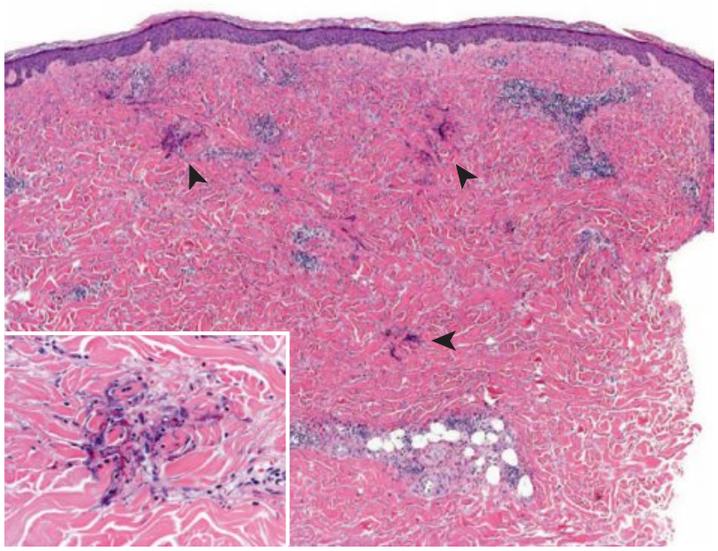


Fig. 26.4 Wells syndrome – histopathologic features. Perivascular and interstitial inflammatory infiltrates that contain eosinophils. There are several flame figures at sites of degranulated eosinophils (arrowheads; inset). *Courtesy Lorenzo Cerroni, MD.*

Differential diagnosis

Wells syndrome often has a striking clinicopathologic presentation[32]. Early on, bacterial cellulitis and erysipelas are the most common clinical mimics. The histopathologic findings of both erysipelas and bacterial cellulitis can also include significant edema, but neutrophils are the predominant inflammatory cell in these soft tissue infections. Other causes of pseudocellulitis, including exaggerated reactions to arthropod bites, should be considered (see Table 74.10).

Toxocara canis and other parasitic infections can present with clinical and pathologic findings resembling Wells syndrome. When a parasitic infection is suspected, laboratory evaluation including stool examinations, specific parasite serologies, and even PCR of stool may be necessary. Other disorders that may present with urticarial plaques due to infiltrates of eosinophils are listed in Table 26.1. Late (mature) lesions of Wells syndrome may clinically, but not histologically, resemble morphea.

Eosinophilic annular erythema (EAE) is also in the differential diagnosis, but this entity is considered by many to be a subset of Wells syndrome. EAE is a figurate erythema that presents with annular and polycyclic skin lesions due to dermal infiltrates of eosinophils. However, flame figures are uncommon. EAE has been observed in patients with a number of conditions including malignancy, autoimmune thyroid disease, borreliosis, chronic gastritis caused by *Helicobacter pylori* infection, diabetes mellitus, hepatitis C virus, chronic kidney disease, thymoma, and autoimmune pancreatitis[33].

Treatment

Initial therapy with prednisone 10–80 mg daily results in dramatic improvement within a few days in most patients[34]. Tapering the dose over one month is generally well tolerated. Flares or recurrence may be treated with additional courses of prednisone. Steroid-sparing medications, including minocycline, colchicine, antimalarials, dapsone,

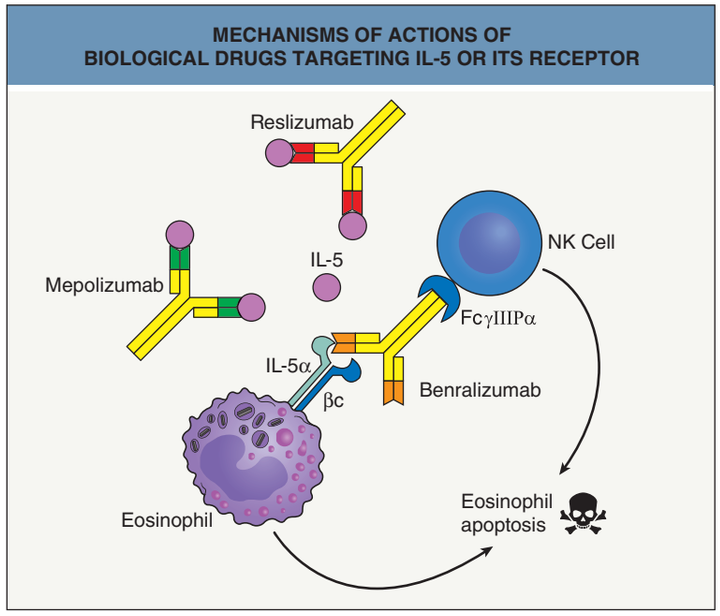


Fig. 26.5 Mechanisms of action of monoclonal antibodies that target IL-5 and IL-5Rα monoclonal antibodies. Anti-IL-5 antibodies inhibit its biological effects on eosinophils. Benralizumab interacts, via its Fab region, with the α subunit of the IL-5 receptor, thereby neutralizing IL-5 bioactivity. In addition, its Fc region binds to the FcγIIIRa on NK cells which induces apoptosis of eosinophils. See Ch. 138 for discussion of monoclonal antibodies that target the IL-4 receptor and IL-13. *From Pelaia C, Paolett G, Puggioni F, et al. Interlukin-5 in the pathophysiology of severe asthma. Front Physiol 2019;10:1514.*

griseofulvin, interferon-α and antihistamines, have limited evidence of efficacy. Recent reports suggest benefit with dupilumab, omalizumab (anti-IgE), mepolizumab (anti-IL-5), and benralizumab[35–37] (anti-α chain of IL-5R) (Fig. 26.5). For milder cases, potent topical corticosteroids may be sufficient[35–37].

HYPEREOSINOPHILIC SYNDROMES

Key features

- Mucocutaneous lesions occur in over 50% of patients with hypereosinophilic syndromes (HESs), most commonly presenting as pruritic erythematous papules or nodules, urticaria, angioedema, and/or mucosal ulcers
- Classification and treatment of HESs became more precise with discovery of the *FIP1L1-PDGFRA* fusion gene, whose protein product is a constitutively activated tyrosine kinase; additional chromosomal rearrangements have been identified that involve *PDGFRA*, *PDGFRB*, *FGFR1*, and *PCM1-JAK2* which encode platelet-derived growth factor receptor (PDGFR)-α, PDGFR-β, fibroblast growth factor receptor 1, and pericentriolar material 1/Janus kinase 2, respectively
- Based upon recently adopted terminology and classification criteria, primary (neoplastic) and secondary (reactive) forms of HES have been more clearly defined
- The *FIP1L1-PDGFRA* fusion gene and other genetic abnormalities (see above) are present in patients with primary (neoplastic) HES, which includes eosinophilic leukemia
- The lymphocytic (lymphoid) subtype of secondary (reactive) HES is characterized by a clonal proliferation of T cells with increased production of Th2 cytokines, particularly IL-5
- End-organ damage may occur from sustained tissue eosinophilia, including life-threatening endomyocardial fibrosis and/or thrombosis

Introduction

The term "hypereosinophilic syndrome" or "HES" was coined in the late 1960s to refer to a spectrum of eosinophil-associated diseases with common clinical features, including peripheral eosinophilia (>1500 cells/mcl) and internal organ involvement. In the 1990s, a subset of patients with HES was found to have a clonal proliferation of T cells, with increased production of IL-5. In 2003, it was discovered that some patients with the HES variant that responded to imatinib had a *FIP1L1-PDGFRA* fusion gene due to a chromosomal translocation[38]. Its protein product is a constitutively activated tyrosine kinase that is 100 times more sensitive to inhibition by imatinib than the BCR-ABL kinase present in chronic myelogenous leukemia (CML) patients. Since then, additional genetic abnormalities have been identified[8] and a number of HES variants have been described (Table 26.3)[39], leading to more tailored treatment recommendations (Fig. 26.6)[11,40].

History

The term "hypereosinophilic syndromes (HESs)" was first coined in 1968 with the diagnostic criteria initially proposed in 1975[41]. This was followed by the description of two major variants of HES – lymphocytic (LHES) and myeloproliferative (MHES). In 2011, experts from multiple disciplines came to a consensus regarding terminology and classification criteria during the Working Conference on Eosinophil Disorders and Syndromes[4,32,39]. The currently recognized clinical variants are outlined in Table 26.3[40]. Of note, the World Health Organization's definition of HES excludes myeloid variants associated with molecular abnormalities[42].

Epidemiology

Up to 25% of patients have associated HES (see Table 26.3), which has an equal sex distribution, while MHES (*FIP1L1-PDGFRA*- or other mutation-positive HES) has a striking male predominance (>90%). HES can affect all age groups, but the majority are adults. While individuals with the *FIP1L1-PDGFRA* fusion gene may be regarded as having chronic eosinophilic leukemia, there are rare patients who develop more aggressive disease with transformation to acute leukemia[8]. Patients with LHES are at risk for developing lymphoma.

Clinical Features

Patients present with signs and symptoms related to the organ systems affected by eosinophilic infiltrates. The most common mucocutaneous findings are pruritic erythematous macules, papules, plaques or nodules on the trunk and extremities or urticaria and angioedema[43,44]. Other cutaneous manifestations include erythema annulare centrifugum-like lesions, livedo reticularis, retiform purpura, and superficial thrombophlebitis, with the thrombotic entities occurring almost exclusively in primary HES.

Since eosinophils have been implicated as the primary cause of end-organ damage in all forms of HES, clinical improvement usually parallels a decrease in both blood and tissue eosinophilia[45]. However, the underlying pathogenesis of variants other than MHES and LHES still remains unclear[39]. Occasionally, patients with episodic angioedema with eosinophilia (Gleich syndrome) or the *n*odules, *e*osinophilia, *r*heumatism, *d*ermatitis and *s*welling (NERDS) syndrome may develop T cell clones and fulfill the diagnostic criteria for LHES (see Table 26.3). Therefore, as outlined in Figure 26.6, patients who cannot be classified as either MHES or LHES should continue to be monitored for cytogenetic abnormalities or T cell clonality[46,47].

Pathology

The histopathology of cutaneous lesions of HES is nonspecific and varies depending upon the type of skin lesion biopsied. Urticarial lesions have findings similar to ordinary urticaria, i.e. perivascular > interstitial infiltrates of lymphocytes, eosinophils, and occasional neutrophils. Biopsies from papules or plaques occasionally exhibit spongiosis in addition to the dermal infiltrate that usually contains at least a few eosinophils. Flame figures are occasionally present. When studied with immunohistochemical or immunofluorescence stains for specific eosinophil granule proteins, HES mucosal ulcers show extensive deposition of granule proteins in the absence of morphologically identifiable intact eosinophils. Thrombosis of dermal blood vessels has been observed in biopsy specimens from retiform purpura and necrotic skin lesions in HES patients.

Differential Diagnosis

The clinical and histopathologic differential diagnosis of HES includes other eosinophil-associated dermatoses (see Table 26.1), along with other dermatoses in which eosinophil degranulation occurs but infiltrates of intact eosinophils are not observed. The footprint of eosinophil participation is deposition of granular contents (e.g. eMBP1), which remain in the tissue while the cell itself is not morphologically identifiable, although parts of the eosinophil may be recognizable by electron microscopy. However, most other eosinophil-associated dermatoses will not be associated with peripheral blood hypereosinophilia of >1.5 cells × 10^9/L.

In contrast to Wells syndrome, patients with primary HES tend to be more systemically ill, with signs and symptoms of multi-organ involvement. Occasionally, dermal flame figures are seen in skin lesions of HES. EGPA can resemble HES clinically and is considered by some authors to be an HES-associated disease. Patients with EGPA have asthma as well as prominent IgG4 and IgE responses (see Ch. 24)[48]. While patients with EGPA have vasculitis of small and medium-sized vessels, vasculitis is an uncommon feature of HES. However, thromboembolic phenomena may produce lesions that mimic vasculitis (see Ch. 22).

Parasitic infections and infestations may closely resemble HES. A history of travel to endemic areas or a suggestive dietary history implicates helminthiasis. In such patients, serologic testing for anti-*Strongyloides* antibodies and three stool samples for ova and parasites should be obtained. A total serum IgE level >500 IU/ml is often seen in helminth infections. Inappropriate treatment of *Strongyloides stercoralis* with systemic corticosteroids or other immunosuppressives may result in severe sequelae, including death.

DIAGNOSTIC CRITERIA AND CLASSIFICATION OF HYPEREOSINOPHILIC SYNDROMES (HESs) AND OTHER ENTITIES WITH HYPEREOSINOPHILIA		
Three diagnostic criteria		
1. Peripheral blood hypereosinophilia – defined as >1.5 eosinophils × 10^9/L blood [>1500 eosinophils/mcl]* on two examinations at an interval of one month or greater† – and/or – Tissue hypereosinophilia defined by the following: • Percentage of eosinophils in bone marrow section exceeds 20% of all nucleated cells – and/or – • Pathologist is of the opinion that tissue infiltration by eosinophils is extensive – and/or – • Marked deposition of eosinophil granule proteins is found in the absence or presence of major tissue infiltration by eosinophils 2. Organ damage and/or dysfunction attributable to tissue hypereosinophilia 3. Exclusion of other disorders or conditions as major reason for organ damage		
Variants of HES (end-organ damage attributable to hypereosinophilia)		
Myeloid HES (MHES, neoplastic, primary) – 15%–20%	***Lymphocytic HES (LHES, secondary)***	***Overlap HES – eosinophilic disease restricted to a single organ – or – a defined eosinophilic syndrome that overlaps in clinical features with idiopathic HES***
• Underlying neoplasm of stem cells, myeloid cells, or eosinophils (WHO classification) • Eosinophils are considered (or shown) to be clonal‡ • Male predominance • In addition to typical skin lesions (see text), signs of cutaneous thromboses (e.g. retiform purpura) • Mucosal ulcers poor prognostic sign • Fever, weight loss, malaise, subendocardial fibrosis, restrictive cardiomyopathy, mitral or tricuspid valve insufficiency, hepatosplenomegaly, neutrophilia • Some patients have high serum tryptase and vitamin B_{12} levels, tissue fibrosis, splenomegaly, and bone marrow biopsies with increased numbers of $CD25^+$ atypical spindle-shaped mast cells¶	• Hypereosinophilia is thought to be cytokine-driven, due to clonal T cells§ producing Th2 cytokines (IL-5, -4, -13) • Skin is most commonly affected organ (severe pruritus, dermatitis, erythroderma, urticaria, angioedema) • Lymphadenopathy • Serum IgE and TARC (CCL17) levels are typically elevated (likely due to actions of IL-4, -13) • T cell clone often remains stable for years, but transformation to lymphoma can occur	• Episodic angioedema with eosinophilia (Gleich syndrome)‖ • *N*odules, *e*osinophilia, *r*heumatism, *d*ermatitis and swelling (NERDS) syndrome‖ • Eosinophilic granulomatosis with polyangiitis (EGPA) • Eosinophilia myalgia syndrome and toxic oil syndrome (both historic)
Associated HES (secondary, reactive)		***Overlap HES (eosinophilic disease restricted to an organ other than the skin)***
• HES in the setting of a known secondary cause • Hypereosinophilia cytokine-driven (IL-3, IL-5, GM-CSF), but not due to clonal T lymphocytes • Associated with underlying primary immunodeficiencies (e.g. Omenn syndrome, hyper IgE syndrome [*STAT3* or *DOCK8* mutations]), atopic diseases, helminth or other infections, drug hypersensitivity or other inflammatory disorders (e.g. chronic GVHD), hematologic or solid-organ malignancies • Systemic mastocytosis, including with an associated hematologic (non-mast cell lineage) neoplasm • Hypereosinophilia also seen in patients with cholesterol emboli, inflammatory bowel disease, and sarcoidosis		• Eosinophilic *gastrointestinal* diseases – eosinophilic esophagitis, gastroenteritis, colitis, pancreatitis, and hepatitis; eosinophilic ascites • Eosinophilic *pulmonary* diseases – eosinophilic asthma, bronchitis, pneumonia, pleuritis, rhinosinusitis (and nasal polyposis) • Eosinophilic *genitourinary* diseases – nephritis, cystitis, endometritis, myometritis • Other eosinophilic diseases – mastitis, myocarditis, synovitis, ocular disorders

*Eosinophilia is defined as 0.5–1.5 eosinophils × 10^9/L blood.
†In the case of evolving life-threatening end-organ damage, the diagnosis of HES can be made immediately to avoid delay in treatment.
‡*FIP1L1-PDGFRA* fusion gene (>80% of patients) and other rarer fusion genes or rearrangements involving *PDGFRB*, *FGFR1* or *PCM1-JAK2*, which encode platelet-derived growth factor receptor-β, fibroblast growth factor receptor-1, and pericentriolar material 1/Janus kinase 2, respectively; includes patients with eosinophilic leukemia, who may have other cytogenetic abnormalities. Point mutations in *JAK2* may also be seen.
¶In the WHO classification of mastocytosis, such patients (who have the *FIP1L1-PDGFRA* fusion gene) are designated as having systemic mastocytosis with associated clonal hematological non-mast cell-lineage disease (AHNMD).
§Some patients have phenotypically abnormal lymphocyte populations with unique surface phenotypes (e.g. $CD3^+CD4^-CD8^-$, $CD3^-CD4^+$).
‖May develop T cell clones.

Table 26.3 Diagnostic criteria and classification of hypereosinophilic syndromes (HESs) and other entities with hypereosinophilia. Two additional clinical variants are ***idiopathic*** and ***familial***[40]; the latter is rare and may have an autosomal dominant transmission pattern (with one case mapped to chromosome 5q where the IL-5 gene cluster resides) and it is sometimes asymptomatic[6]. *Data from references 52–55.*

In patients with HES and isolated urticarial plaques with or without angioedema, the differential diagnosis includes ordinary urticaria. In such patients, demonstration of internal organ involvement favors HES. In addition, HES with episodic angioedema may resemble hereditary or acquired angioedema clinically, but complement studies help to distinguish these entities (see Fig. 18.19). Furthermore, patients with hereditary angioedema often have a family history of the disease and rarely are their peripheral blood eosinophil counts as high as in HES.

Treatment

If patients do not present with life-threatening manifestations, high-dose corticosteroids (e.g. prednisone 1 mg/kg/day), if indicated, can be initiated after the evaluation is complete (see Fig. 26.6). Patients should be administered ivermectin if there has been exposure to *Strongyloides*.

If *FIP1L1-PDGFRA* or other genetic abnormalities involving *PDGFRA* or *PDGFRB* are present, imatinib therapy is warranted (see Fig. 26.6)[46,47]. As a tyrosine kinase inhibitor, imatinib prevents autophosphorylation of the fusion protein and phosphorylation of other substrates, resulting in termination of the signaling cascade that induces genes related to eosinophil proliferation and activation. Patients respond to varying doses of imatinib, depending upon an individual patient's sensitivity and ability of the given dosage to suppress the mutant clone. Imatinib doses ranging from 400 mg daily to 100 mg weekly or less have proven effective. However, maintenance therapy is required to avoid relapse. Because endomyocardial disease may worsen during the first several days of imatinib administration, serum levels of troponin and

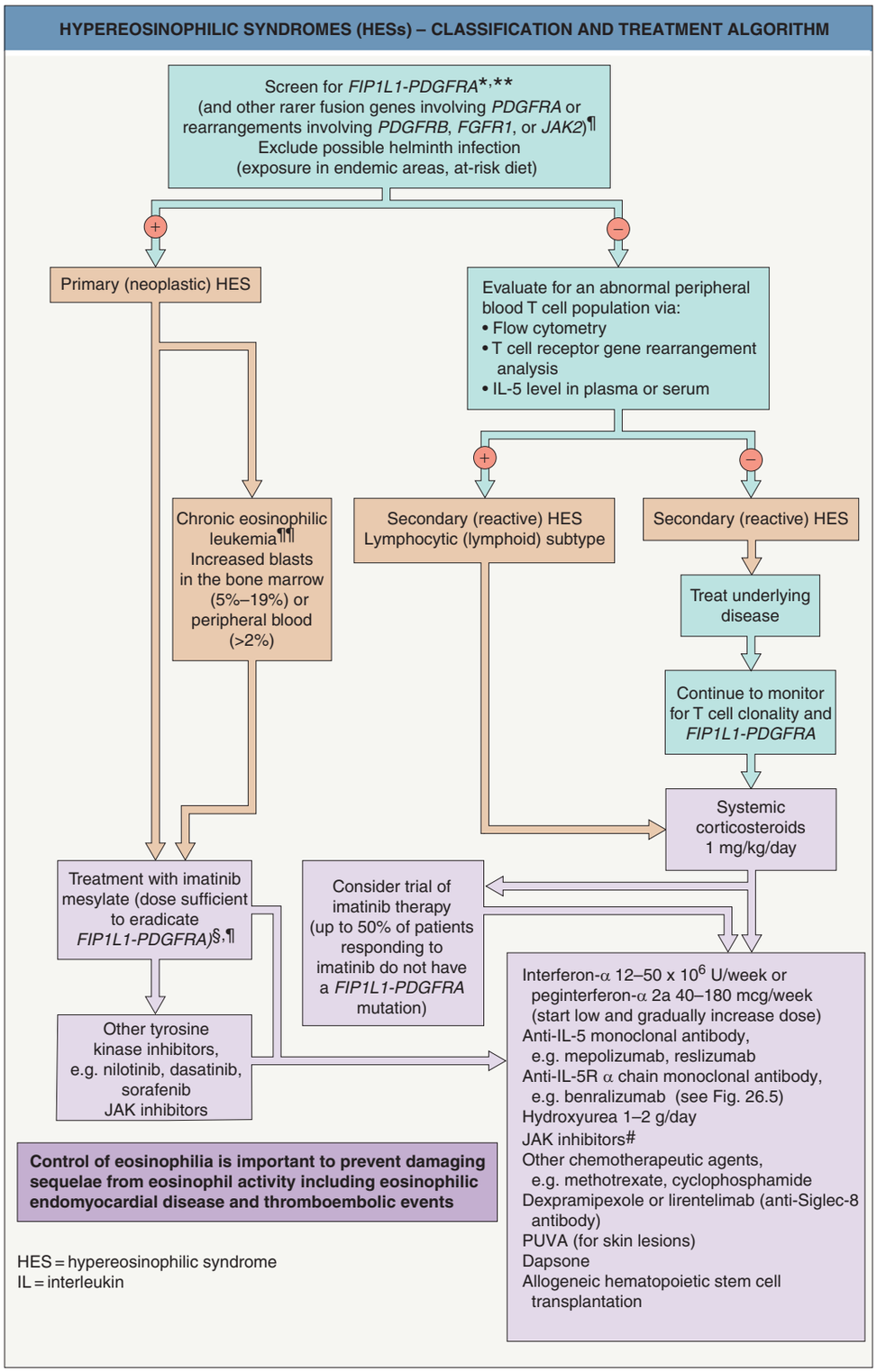


Fig. 26.6 Hypereosinophilic syndromes (HESs) – classification and treatment algorithm. *An 800 kb deletion on chromosome 4 produces a fusion gene composed of a portion of the *PDGFRA* (platelet-derived growth factor receptor α) gene that encodes its kinase domain linked to a previously uncharacterized gene that resembles *Fip1*, which encodes an essential component of the *Saccharomyces cerevisiae* polyadenylation machinery. The resultant product is a constitutively activated tyrosine kinase that is a target of the tyrosine kinase inhibitor, imatinib. Screening can be performed on a peripheral blood sample via reverse transcriptase-PCR or fluorescence *in situ* hybridization (FISH). **Bone marrow biopsy with cytogenetic studies should be done to exclude hematologic disorders that are accompanied by eosinophilia. Increased bone marrow mast cells and increased serum tryptase may be observed. ¶*PDGFRB*, *FGFR1*, and *JAK2* encode platelet-derived growth factor receptor-β, fibroblast growth factor receptor-1, and Janus kinase 2, respectively; patients with genetic abnormalities involving *PDGFRA* and *PDGFRB* typically respond to imatinib but not those involving *FGFR1*. Patients may become resistant due to new mutations (during blast crisis) or tandem mutations (during chronic phase). ¶¶May have other clonal cytogenetic and molecular genetic abnormalities; in the presence of eosinophilia, considered sufficient for diagnosis even in the absence of excess blasts. §Plus systemic corticosteroids if cardiac involvement. #Including those with *JAK2* mutations. *Data from refs 40,52–57.*

N-terminal pro-brain natriuretic peptide (NT-proBNP) should be monitored. Preemptive and concurrent treatment with corticosteroids is also recommended to maintain cardiac function. Other kinase inhibitors (nilotinib, dasatinib, and sorafenib) may also be useful in patients who do not respond to imatinib or become resistant as a consequence of mutations such as T674I in *FIP1L1-PDGFRA*[49].

Secondary HES is best managed by treating the underlying disease, once determined. When the underlying disease fails to respond to first-line therapies and the patient lacks *PDGFRA* or *PDGFRB* fusion genes, then corticosteroids are begun, usually prednisone at 1 mg/kg/day; ~70% of patients will respond, with the peripheral eosinophilia returning to normal levels. For patients who fail corticosteroid monotherapy or develop significant long-term side effects, there are several other therapeutic options (see Fig. 26.6). For example, patients with no detectable *FIP1L1-PDGFRA* fusion gene have achieved partial remission from imatinib, although the mechanism of response in these patients is unclear. Perhaps some patients had diagnostically occult *PDGFRA* or *PDGFRB* rearrangements[49]. Thus, imatinib represents a reasonable therapeutic option, given its relative safety.

Interferon (IFN)-α (12–50 × 10^6 U/week) has been beneficial in patients with both primary and secondary HES. Its mode of action is likely via myelosuppression but may include effects on Th2 helper cells by changing the cytokine milieu (including a decrease in IL-5 levels). For some patients, pegylated interferon (peginterferon-α 2a), administered weekly, is better tolerated. One concern regarding the use of IFN-α, based upon the findings of an *in vitro* study in which IFN-α acted as a growth factor for $CD3^-CD4^+$ cells, is probably minimized by concomitant corticosteroid therapy.

Two monoclonal antibodies against human IL-5 approved for the treatment of asthma, mepolizumab and reslizumab, and a monoclonal antibody directed against the alpha chain of the IL-5R, benralizumab, have been used to treat HES in clinical trials (see Fig. 26.5). Analyses of cytokine production by lymphocytes before and after treatment with mepolizumab showed a striking reduction in Th2 cytokine production (IL-13, IL-10) in addition to the expected IL-5 reduction[50]. In a randomized, double-blind, placebo-controlled trial involving *FIP1L1-PDGFRA*-negative patients who were already receiving prednisone (20–60 mg/day), administration of mepolizumab (750 mg IV every 4 weeks for 9 cycles) led to twice as many individuals (84% vs 43%) being successfully tapered to a stable prednisone dose of ≤10 mg/day[51].

The main treatment goals via single- or multiple-agent regimens are relief of symptoms and maintaining the peripheral eosinophil count in the range of $1–2 \times 10^9$/L blood or less[40]. HES patients also need to be routinely monitored for organ involvement, particularly cardiac disease, in addition to progression to lymphoma or leukemia. Patients who fail corticosteroid monotherapy have a worse prognosis.

Additional table on entities in which flame figures may be seen, available in our eBook (see inside front cover for access code).

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ENTITIES IN WHICH FLAME FIGURES MAY BE SEEN
Angiolymphoid hyperplasia with eosinophilia
Arthropod bite and sting reactions
Autoimmune bullous diseases (e.g. pemphigoid, gestational pemphigoid, pemphigus vegetans)
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
Eosinophilic pustular folliculitis
Hypereosinophilic syndromes
Incontinentia pigmenti
Kimura disease
Mastocytoma
Parasitic infections (e.g. ascariasis, onchocerciasis, gnathostomiasis, onchocerciasis, toxocariasis)
Wells syndrome

eTable 26.1 Entities in which flame figures may be seen.

27 Pregnancy Dermatoses

Christina M. Ambros-Rudolph

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INTRODUCTION AND BACKGROUND

For decades, the specific dermatoses of pregnancy represented a confusing group of overlapping entities, understood largely through anecdotes and case reports. However, more recent reviews have simplified and condensed the list of pregnancy-specific dermatoses (Table 27.1)[1–3]. For example, impetigo herpetiformis is now generally recognized as pustular psoriasis, perhaps induced by the relative hypocalcemia of pregnancy (see Ch. 8). Also, prurigo annularis, first reported in 1941 (without histology or laboratory information), and linear IgM disease of pregnancy (described in 1988) have not been subsequently reported yet are frequently perpetuated in reviews.

Much of the confusion can be dispelled by reviewing the original articles: Besnier (1904) first used the term "prurigo gestationis" to include all patients with pregnancy-related dermatoses, other than those with pemphigoid gestationis. Costello (1941) subsequently referred to these patients as "prurigo gestationis of Besnier" and estimated an incidence of 2% of all pregnancies. Bourne (1962) characterized a subset of patients with intensely pruritic papules or urticarial plaques that tended to appear during the later part of the third trimester, coining the term "toxaemic rash of pregnancy". Initial lesions typically developed within the abdominal striae of short women who experienced excessive weight gain during pregnancy. However, he offered no histopathologic or laboratory details.

Spangler et al. (also 1962) reported on a series of women with intensely pruritic, widely scattered, excoriated papules. Initial onset was during the second or third trimester and all patients suffered recurrences during subsequent gestations. The hallmarks of Spangler's cases were biochemical: elevated urinary human chorionic gonadotropin (HCG), decreased plasma hydrocortisone, and decreased serum half-life of hydrocortisone. Liver function tests and histopathology were not reported, and immunofluorescence (IF) was not yet available. Most notably, Spangler's papular dermatitis was associated with high fetal wastage, a finding now thoroughly discredited.

Nurse (1968) cited all of the above literature but ignored it, dividing patients with (non-pemphigoid gestationis) pregnancy eruptions into "early" and "late" forms. The late papular/urticarial form clearly overlapped with Bourne's "toxaemic rash of pregnancy", and has since been described as "pruritic urticarial papules and plaques of pregnancy" (PUPPP), "toxic erythema of pregnancy", and, most recently, "polymorphic eruption of pregnancy" (PEP). Nurse's "early-onset" patients and Spangler's "papular dermatitis" patients were undoubtedly drawn from the same clinical spectrum, and subsequently these entities were reclassified as forms of "prurigo of pregnancy" (see Table 27.1).

Pruritic folliculitis of pregnancy was added to the list of pregnancy-specific diseases in 1981, yet all six of the original patients were thought to have papular dermatitis clinically. They were classified as having a different entity based solely upon shared histologic features, that is, sterile folliculitis. In spite of their clinical similarity to the patients reported by Spangler, none had appropriate biochemical investigations. In 1998, an adaptation of the Holmes and Black classification scheme (1983)[2] was published[3] and listed pruritic folliculitis as a variant of prurigo of pregnancy (see Table 27.1).

Introduction of the term "atopic eruption of pregnancy (AEP)" represents the most recent revision to the classification of dermatoses of pregnancy[1]. Based upon an analysis of over 500 pregnant women with pruritus[1], significant overlap, both clinical and histologic, was noted amongst those patients with the diagnoses of prurigo of pregnancy, pruritic folliculitis of pregnancy, and eczema in pregnancy (~50% of the patients in this series)[4]. AEP was thought to be a useful diagnostic term that encompassed these three disorders and reminded the clinician that the eczema was more likely to be of new onset as opposed to a flare of previously diagnosed atopic dermatitis.

Because of the lack of primary lesions, intrahepatic cholestasis of pregnancy (ICP) had long been omitted from the list of pregnancy dermatoses. However, failure to appreciate ICP in a pregnant woman with widespread excoriations or even prurigo nodularis surely, in retrospect, accounts for some of the confusion in terminology. Furthermore, ICP is the most important diagnosis to exclude in a pregnant patient with pruritus, as it is associated with significant fetal risk (see below).

GESTATIONAL PEMPHIGOID

Synonyms: ■ Pemphigoid gestationis ■ Herpes gestationis

Key features

- Rare, pruritic, vesiculobullous eruption that develops during late pregnancy or the immediate postpartum period
- Linear C3 deposition along the basement membrane zone (BMZ) by direct IF
- IgG1 autoantibodies are directed against a transmembrane hemidesmosomal protein (BP180; BPAG2; collagen XVII)
- Increased risk of prematurity and small-for-gestational age neonates; the risk correlates with disease severity
- Commonly recurs in subsequent pregnancies

Introduction

Gestational pemphigoid is a rare, self-limited, autoimmune bullous disease. It is the most clearly characterized dermatosis of pregnancy and the only one that may also affect the skin of the newborn.

History

Milton first coined the term "herpes gestationis" in 1872 and Bulkley (1874) canonized the term "as embodying the clinical characters of the eruption and signifying at the same time the sex and state of the body in which it appears". Little additional insight was gained until IF techniques revealed complement deposition along the BMZ in 1973, a feature now accepted as essential for the diagnosis of gestational pemphigoid.

Epidemiology

The incidence of gestational pemphigoid has been estimated at 1:1700–1:50 000 pregnancies[5,6], correlating with the prevalence of

CLASSIFICATION OF THE DERMATOSES OF PREGNANCY	
Classification	**Synonym(s)**
Gestational pemphigoid	Pemphigoid gestationis* Herpes gestationis†
Polymorphic eruption of pregnancy (PEP)	Pruritic urticarial papules and plaques of pregnancy (PUPPP)*,† Toxic erythema of pregnancy Late-onset prurigo of pregnancy Toxemic rash of pregnancy
Intrahepatic cholestasis of pregnancy (ICP)	Cholestasis of pregnancy† Obstetric cholestasis Cholestatic jaundice of pregnancy Pruritus/prurigo gravidarum
Atopic eruption of pregnancy (AEP)	Prurigo of pregnancy*,† Prurigo gestationis (Besnier) Early-onset prurigo of pregnancy (Nurse) Papular dermatitis of pregnancy (Spangler) Pruritic folliculitis of pregnancy* Linear IgM disease of pregnancy Eczema in pregnancy

*Former classification by Holmes & Black (1983)[2].
†Former classification by Shornick (1998)[3].

Table 27.1 Classification of the dermatoses of pregnancy[1]. The preferred terms are in bold.

HLA-DR3 and -DR4 in different populations. While occurring primarily during pregnancy and the immediate postpartum period, gestational pemphigoid has rarely developed in association with trophoblastic tumors (hydatidiform mole, choriocarcinoma). However, no case of a pemphigoid-like disease has been reported in men with choriocarcinoma, who have a biochemically similar yet entirely syngenic tumor; of note, the nuclear genome in placental tissue (and hence choriocarcinoma in women) is primarily paternal in origin. Patients with a history of gestational pemphigoid appear to be at increased risk for the development of Graves disease[7].

Pathogenesis

Historically, gestational pemphigoid was thought to be caused by an anti-BMZ "serum factor" (the "herpes gestationis [HG] factor") that induces C3 deposition along the dermal–epidermal junction. This factor is now known to be complement-fixing autoantibodies of the IgG1 subclass directed against a 180 kDa transmembrane hemidesmosomal protein (BP180; BPAG2; collagen XVII). As in patients with bullous pemphigoid (BP), it is the non-collagenous (NC) segment closest to the plasma membrane of the basal keratinocyte, NC16A, that constitutes the immunodominant region of BP180 (see Fig. 31.9). Circulating antibodies are almost exclusively directed against this domain, as demonstrated by ELISA and immunoblot studies of maternal or neonatal sera.

What initiates the production of autoantibody remains enigmatic. Because the antibodies also bind to amniotic basement membrane[8] (a structure derived from fetal ectoderm and antigenically similar to skin), attention has focused on immunogenetics and potential cross-reactivity between placental tissue and skin. Immunogenetic studies have revealed a marked increase in HLA antigens DR3 or DR4, and, curiously, nearly 50% of patients have the simultaneous presence of both. There is essentially a 100% incidence of anti-HLA antibodies in patients with a history of gestational pemphigoid[9]. Since the only source of disparate HLA antigens is typically the placenta (which is primarily of paternal origin), the universal finding of anti-HLA antibodies implies a high frequency of immunologic insult during gestation. Women with gestational pemphigoid also have increased expression of MHC class II antigens (DR, DP, DQ) within the villous stroma of their chorionic villi. It has therefore been proposed that gestational pemphigoid is a disease, initiated by the aberrant expression of MHC class II antigens (of paternal haplotype), that serves to initiate an allogeneic response to placental BMZ, which then cross-reacts with skin[10].



Fig. 27.1 Gestational pemphigoid. A Intact tense bullae arising within areas of edematous erythema as well as erosions due to ruptured bullae; lesions typically involve the umbilical region. **B** Confluent crusted erythematous plaques studded with small vesicles; umbilical involvement is again noted. Dusky urticarial lesions are also present on the thighs. *B, Courtesy Luis Requena, MD.*

Clinical Features

Gestational pemphigoid may develop during any trimester as well as immediately postpartum, but classically it presents during late pregnancy. There is an abrupt onset of cutaneous lesions on the trunk, in particular the abdomen and often within or immediately adjacent to the umbilicus (Fig. 27.1). Rapid progression to a generalized pemphigoid-like eruption then occurs, with pruritic urticarial papules and plaques, followed by clustered (herpetiform) vesicles or tense bullae on an erythematous base. The eruption may involve the entire body, sparing only the mucous membranes. While the clinical presentation and course may vary considerably, spontaneous improvement during late gestation is common. This is followed, however, by a flare at the time of delivery in 75% of patients. Such flares may be dramatic, with an explosive onset of blistering within hours.

Most disease activity spontaneously remits during the weeks to months following delivery, but there are isolated reports of a protracted course postpartum. Flares and/or recurrences in association with menstruation are common, and in 25%–50% of patients, they may also be induced by oral contraceptives (Table 27.2). Gestational pemphigoid may not develop during the patient's first pregnancy, but once established, it is quite likely to recur in subsequent pregnancies, usually with

DERMATOSES OF PREGNANCY – FETAL RISK, INVOLVEMENT OF NEWBORN SKIN, AND RISK OF RECURRENCE			
Dermatosis	**Fetal risk**	**Newborn skin involvement**	**Risk of recurrence**
Gestational pemphigoid	Increased risk of prematurity and small-for-gestational age neonates; risk correlates with disease severity	Mild and transient lesions of gestational pemphigoid in up to 10%	Commonly recurs ("skipped" pregnancies in only 5%–8% of women); recurrences induced by oral contraceptives in 25%–50%
Polymorphic eruption of pregnancy	None	None	Usually does not recur
Intrahepatic cholestasis of pregnancy	Increased risk of premature labor (20%–60%), intrapartal fetal distress (20%–30%), and stillbirths (1%–2%)	None	Recurrence in 45%–70% of subsequent pregnancies; may be triggered by oral contraceptives
Atopic eruption of pregnancy	None	None	Commonly recurs due to atopic diathesis

Table 27.2 Dermatoses of pregnancy – fetal risk, involvement of newborn skin, and risk of recurrence.

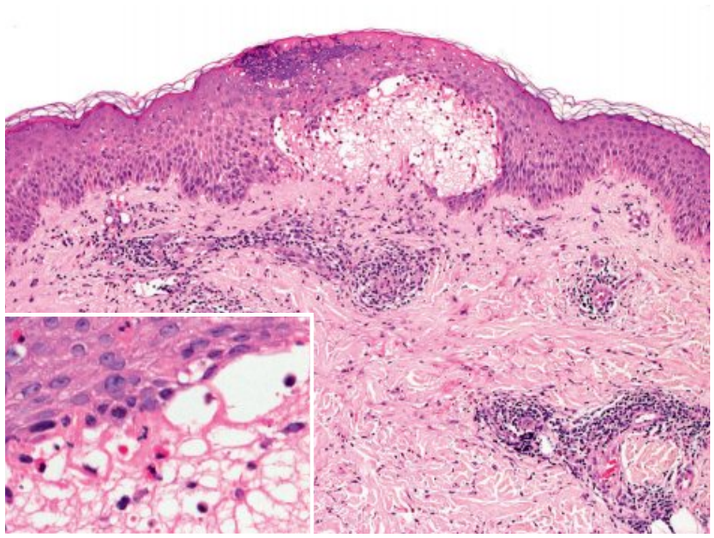


Fig. 27.2 Gestational pemphigoid – histopathologic features of an early lesion. Focal subepidermal vesicle accompanied by a superficial and mid dermal perivascular and interstitial mixed inflammatory infiltrate. Eosinophils are seen within the blister cavity and the epidermis (inset). *Courtesy Lorenzo Cerroni, MD.*

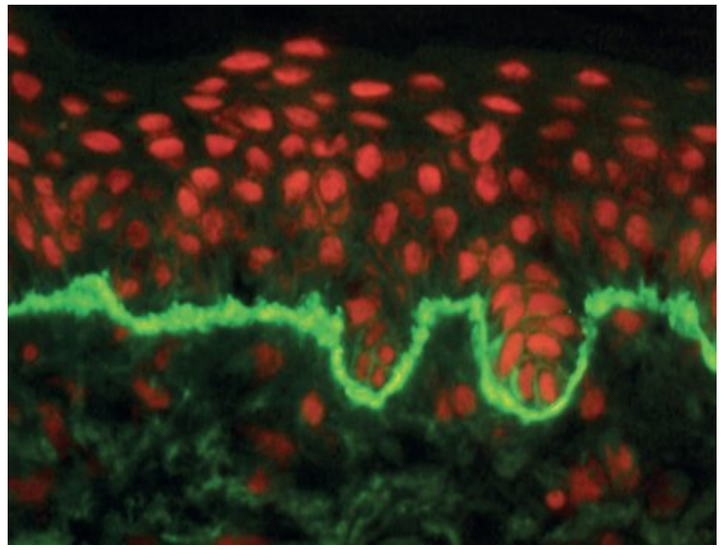


Fig. 27.3 Gestational pemphigoid – direct immunofluorescence (IF) microscopy. Linear deposits of C3 are seen along the basement membrane zone. *Courtesy Immunofluorescence Department, St John's Institute of Dermatology, St Thomas' Hospital, London, UK.*

an earlier onset and more severe course. "Skipped" pregnancies have been observed in 5%–8% of women.

Approximately 10% of newborns develop mild skin involvement due to passive transfer of maternal antibodies and this resolves spontaneously within days to weeks (see Ch. 34). There seems to be an increased risk of prematurity and small-for-gestational age neonates, presumably due to chronic placental insufficiency. More recently it was shown that this risk correlates with disease severity, i.e. occurrence of blistering and early onset, and not with the use of systemic corticosteroids[11].

Pathology

The classic histologic finding of a subepidermal vesicle is seen in the minority of patients. Instead, a nonspecific mixed cellular infiltrate containing a variable number of eosinophils is more common. The presence of eosinophils is the most constant histologic feature of gestational pemphigoid (Fig. 27.2).

The essential component for the diagnosis of gestational pemphigoid is a linear deposition of C3 along the BMZ of perilesional skin by direct IF microscopy (Fig. 27.3). This is observed in 100% of patients, and linear IgG deposition is seen in 30% of patients. When salt-split skin specimens are employed for *conventional* indirect IF, deposition of IgG along the bottom of the epidermal fragment is observed in 30% of patients. However, *complement-added* indirect IF reveals the circulating anti-BMZ IgG1 autoantibodies in essentially all patients. Determination of antibody titers via BP180-NC16A ELISA may be helpful in following disease activity and monitoring therapy.

An increased incidence of anti-thyroid antibodies has been documented, but clinically apparent thyroid dysfunction is uncommon[7]. Routine laboratory investigations are normal.

Differential Diagnosis

The most frequent considerations in the differential diagnosis are PEP and drug eruptions. PEP is a particularly challenging exclusion, given the difficulty of distinguishing PEP and urticarial lesions of gestational pemphigoid. Direct and indirect IF and, more recently, the BP180-NC16A ELISA are key to the differentiation and are especially relevant in helping the patient plan for future pregnancies.

Treatment

The primary goal in treating this self-limited disease is to relieve pruritus and suppress blister formation. In mild cases, the use of potent topical corticosteroids combined with emollients and systemic antihistamines may be adequate. However, systemic corticosteroids remain the cornerstone of therapy (Table 27.3). Most patients respond to 0.5 mg/kg of prednisolone daily; the dose is tapered as soon as blister formation is suppressed. The common flare associated with delivery usually requires a temporary increase in dosage. Those rare patients with refractory disease may benefit from plasmapheresis during pregnancy. Persistent disease after delivery is uncommon and is treated like BP.

Anecdotal alternatives to corticosteroids (dapsone, doxycycline, or minocycline ± nicotinamide, pyridoxine, cyclosporine) or adjuvants (methotrexate, cyclophosphamide, gold, IVIg) have been tried.

SPECIAL CONSIDERATIONS FOR CORTICOSTEROID AND ANTIHISTAMINE USE DURING PREGNANCY	
Corticosteroids	
Topical	• Recent large, population-based studies and a Cochrane review have *not* shown an increased risk of malformations, including oral cleft palate, or preterm delivery • Because fetal growth restriction has been reported with extensive use of potent corticosteroids (CS), particularly >300 g during the pregnancy, mild to moderate CS are recommended over potent CS • If potent CS are required, the treatment period should be limited in duration • Can add to risk of developing striae distensae
Systemic	• Prednisolone is the systemic corticosteroid of choice for dermatologic indications as it is largely inactivated in the placenta (mother : fetus = 10 : 1) • Use of the lowest effective corticosteroid dose is recommended • During the first trimester, particularly between weeks 8 and 11, a possible slightly increased risk of cleft lip/cleft palate has been debated, especially if high doses prescribed and for >10 days, but this was not substantiated by a recent large population-based case–control study • If use is long-term and extends late into gestation, fetal growth should be monitored and the risk of adrenal insufficiency in the newborn should be addressed
Antihistamines	
Systemic	• During the first trimester, the classic sedating agents (e.g. chlorpheniramine, diphenhydramine, clemastine, dimethindene) are preferred because of the preponderance of safety data • If a non-sedating agent is requested, loratadine is the first choice and cetirizine the second choice; both are considered safe throughout pregnancy

Table 27.3 Special considerations for corticosteroid and antihistamine use during pregnancy[30–33].

None of these medications, with the possible exception of cyclosporine and IVIg, are safe prior to term and thus should be avoided.

POLYMORPHIC ERUPTION OF PREGNANCY

Synonyms: ■ Pruritic urticarial papules and plaques of pregnancy (PUPPP) ■ Bourne's "toxaemic rash of pregnancy" ■ Nurse's "late-onset prurigo" of pregnancy ■ Toxic erythema of pregnancy

Key features

- Urticarial papules and plaques that usually first appear within striae distensae during the latter portion of the third trimester or immediately postpartum
- Development of polymorphous features (vesicles, erythema, target and eczematous lesions) with disease progression
- Most frequent in primiparous women
- Nonspecific histologic features, negative IF, and normal routine laboratory evaluation
- No maternal or fetal risks; usually does not recur

Introduction

Polymorphic eruption of pregnancy (PEP), formerly known as PUPPP, is a common gestational dermatosis. It is characterized by a typical clinical presentation, normal laboratory tests, and negative IF or ELISA.

History

The term PUPPP, introduced by Lawley et al.[12] in 1979, focuses on the initial clinical findings in this disorder but overlooks its later polymorphous features. In order to encompass the entire clinical spectrum, the term "polymorphic eruption of pregnancy" was introduced[3] and is now generally accepted.

Epidemiology

The incidence is ~1 in 160 deliveries[13]. It is seen predominantly in primiparous women and tends not to recur in subsequent pregnancies. There is neither an autoimmune diathesis nor an association with a specific HLA type.

Pathogenesis

The cause of PEP is unknown. Reference has been made to increased maternal weight gain and an increased frequency of multiple-gestation pregnancies[14,15]. It has therefore been suggested that rapid, late stretching of abdominal skin may lead to damage of connective tissue and elicitation of an allergic-type reaction, resulting in the initial appearance of the eruption within striae[16]. The lesions then become generalized as the inflammatory response develops cross-reactivity to collagen in otherwise normal-appearing skin. Immune tolerance during subsequent pregnancies might prevent recurrence. Additional theories include increased levels of progesterone in association with multiple gestations and peripheral chimerism (deposition of fetal DNA) that favors skin with increased vascularity and damaged collagen.

Clinical Features

Pruritic erythematous and edematous papules and plaques usually first appear within the abdominal striae, typically with periumbilical sparing (Fig. 27.4). Onset is most often during the latter part of the third trimester (85%) or in the immediate postpartum period (15%)[15]. The eruption typically spreads over a matter of days, but in general spares the face, palms, and soles. While pruritic urticarial papules are the initial lesions in almost all patients, approximately half will develop more polymorphic features as the disease evolves, including widespread erythema, target lesions, tiny vesicles, and eczematous plaques (Fig. 27.5). Irrespective of whether the eruption starts during pregnancy or postpartum, lesions resolve over an average of 4 weeks.

There are no maternal or fetal morbidities, and recurrences are unusual except for subsequent multiple-gestation pregnancies. To date, only a single possible case of newborn skin involvement has been described; however, the possibility of gestational pemphigoid was not excluded by IF studies[17]. Thus, it is generally agreed that neonatal skin is not affected by PEP.

Pathology

Skin biopsy specimens reveal nonspecific findings. Epidermal changes vary from modest spongiosis to acanthosis with hyperkeratosis and parakeratosis, depending upon the stage of the disease. The dermis shows a nonspecific perivascular lymphocytic infiltrate with a variable degree of dermal edema and a variable number of neutrophils and/or eosinophils. Early lesions may resemble arthropod bite reactions, with a deeper dermal infiltrate and an absence of epidermal changes (Fig. 27.6). The histologic correlate of microvesiculation is severe epidermal spongiosis and/or dermal edema. Direct IF reveals no relevant abnormalities and indirect IF is negative. Routine laboratory evaluation is normal.

Differential Diagnosis

Since lesions of PEP may show microvesiculation, contact dermatitis must be considered. Drug eruptions, urticaria, or viral exanthems may also be in the clinical differential diagnosis. The most important entity to exclude is urticarial gestational pemphigoid, whose lesions tend to appear earlier during gestation, have no association with abdominal striae and often involve the umbilicus, along with positive IF of perilesional skin.







Fig. 27.4 Polymorphic eruption of pregnancy. A, B On the abdomen, the edematous urticarial lesions favor the striae while sparing the umbilicus; note how skin phototype influences the color of the lesions. **C** Although there is periumbilical involvement, the umbilicus itself is spared and the edematous striae point to PEP.

Treatment

The majority of patients benefit from topical corticosteroids and oral antihistamines. More severe disease with a distressing degree of pruritus can be safely treated with a short course of systemic corticosteroids (see Table 27.3). Since the disease is self-limited and without serious sequelae, a conservative approach is justified.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Synonyms: ■ Cholestasis of pregnancy ■ Obstetric cholestasis ■ Cholestatic jaundice of pregnancy ■ Pruritus/prurigo gravidarum

Key features

- Pruritus without primary skin lesions with an onset during the third trimester
- Secondary changes correlate with disease duration and vary from subtle excoriations to severe prurigo nodularis
- Elevated total serum bile acid levels are diagnostic; histology is nonspecific and IF is negative
- Increased risk of prematurity, intrapartum fetal distress, and stillbirths
- Recurs in 45%–70% of subsequent pregnancies

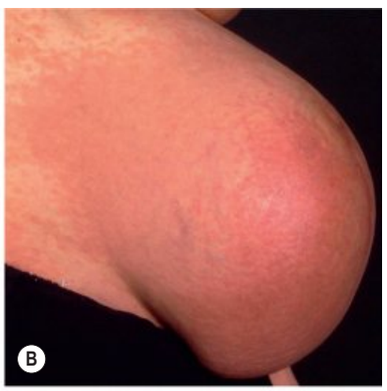
Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a rare form of genetically linked, hormone-dependent, reversible cholestasis. It typically presents late during pregnancy with dramatic pruritus. Although maternal prognosis is usually good (a small minority may develop steatorrhea and vitamin K deficiency), fetal risk is significant. As a result, ICP is the most important pruritic gestational condition to consider then promptly diagnose and treat in order to prevent fetal impairment.

History

ICP was first described in 1907 by Kehrer. In the past, much of the confusion arose from applying descriptive names such as "pruritus









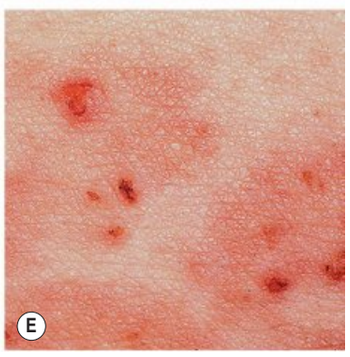


Fig. 27.5 Polymorphic eruption of pregnancy. The clinical spectrum includes: **A** urticarial papules and plaques, some of which demonstrate a steal phenomenon; **B** macular erythema, which can be widespread; **C** targetoid lesions; **D** tiny vesicles due to marked epidermal spongiosis or dermal edema; and **E** eczematous plaques, especially as lesions age.

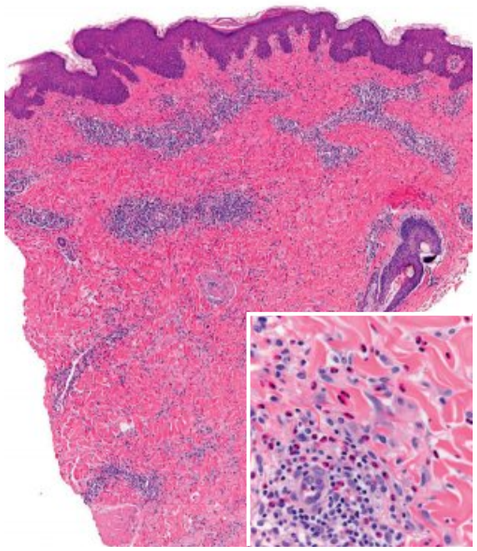


Fig. 27.6 Polymorphic eruption of pregnancy – histopathologic features. In this early lesion, a superficial and deep perivascular and interstitial lympho-histiocytic infiltrate is seen within the dermis. Numerous eosinophils are also present (inset).

gravidarum" for ICP without skin changes or "prurigo gravidarum" if skin lesions associated with scratching were present. While the first term was often combined with the mild unexplained pruritus that occurs in many women during pregnancy (most likely related to an atopic diathesis), the latter was confused with "prurigo of pregnancy" (see below). Because laboratory evaluation, including measurement of serum bile acid levels, was performed in only a minority of women, ICP was often missed.

Epidemiology

There are striking geographic and ethnic differences in the incidence of ICP. For example, it is most commonly observed in South America, with the highest incidence rates in Bolivia and Chile (9%–16%), particularly among Araucanian Indian women (~30%). In contrast, rates of 0.1% to 1.5% have been described in Europe and North America, with relative "hot spots" in Scandinavia and the Baltic states (1%–2%)[18]. Some of the variance is probably explained by different reporting criteria; however, endemic clustering and a positive family history in up to 50% of those affected point towards a genetic predisposition. A higher incidence of ICP is also seen in multiple-gestation pregnancies, which may be related to higher hormonal levels (e.g. estrogen) in these patients.

Pathogenesis

The key element is reduced excretion of bile acids, which leads to increased serum levels. This not only provokes severe pruritus in the mother, but also may have deleterious effects on the fetus. Toxic bile acids crossing the placenta can lead to acute fetal anoxia due to abnormal uterine contractility and vasoconstriction of chorionic veins as well as impaired fetal cardiomyocyte function[18]. One predisposing factor is mutations in genes (e.g. *ABCB4*, *ABCB11*, *ABCC2*) that encode bile transporter proteins[19,20]. While mild dysfunction of these canalicular transporters may not lead to clinical symptoms in non-pregnant individuals, when the transporters' capacity to secrete substrates is exceeded (as occurs in the setting of high levels of sex hormones during pregnancy), signs and symptoms of cholestasis can develop. Other contributing factors are the cholestatic effect of estrogen and progesterone metabolites, which peak late during pregnancy, and hepatitis C viral infection (see below). Furthermore, dietary factors such as selenium deficiency and increased intestinal permeability ("leaky gut") have been suggested as possible triggers.

Clinical Features

Patients typically present during their last trimester with a sudden onset of intense, generalized pruritus that often starts on the palms and soles. No primary skin lesions are seen, and secondary changes due to scratching vary from subtle excoriations early on to pronounced prurigo nodularis in those with pruritus of longer duration (Fig. 27.7).



Fig. 27.7 Intrahepatic cholestasis of pregnancy. Marked pruritus leads to secondary skin lesions that vary based on disease duration, from subtle linear excoriations and prurigo simplex early on (**A**) to pronounced prurigo nodularis when the pruritus is longstanding (**B**). *From Ambros-Rudolph CM, Glatz M, Trauner M, et al. The importance of serum bile acid level analysis and treatment with ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a case series from central Europe. Arch Dermatol 2007;143:757–62. © (2006) American Medical Association. All rights reserved.*

The extensor surfaces of the extremities, buttocks, and abdomen are usually most severely affected.

Although jaundice is often mentioned as a common finding in ICP, it actually occurs in only 10% of patients. Jaundice is usually a complication in those with the most severe and prolonged episodes of ICP. In such patients, concomitant extrahepatic cholestasis may be associated with steatorrhea and subsequent vitamin K deficiency, leading to an increased risk of intra- and postpartum hemorrhage.

Pruritus typically persists until delivery and then it resolves spontaneously within days. A protracted course is very unusual and should prompt one to exclude other liver diseases, especially primary biliary cirrhosis. Recurrence during subsequent pregnancies occurs in 45%–70% of patients, and recurrence with oral contraceptives is routine. No detectable abnormalities are generally present between gestations.

ICP is associated with significant fetal risk, in particular an increase in premature births (20%–60%), intrapartum fetal distress (20%–30%;

e.g. meconium staining of amniotic fluid, abnormal fetal heart rate), and fetal loss (1%–2%)[18]. Fetal risk correlates with the elevation in serum bile acid levels, especially when levels exceed 40 μmol/l[21]. Thus, prompt diagnosis and treatment is essential, as is close obstetric surveillance.

Pathology

Histologic findings in the skin and the liver are nonspecific and direct IF of perilesional skin is negative. The diagnosis is confirmed by an increase in total serum bile acid levels (>11 μmol/l in a pregnant woman; normal range in non-pregnant women, 0–6 μmol/l). Levels may range from 3 to 100 times normal. During pregnancy, alkaline phosphatase levels typically increase (placental origin) even in the absence of ICP, and γ-glutamyl transferase levels are usually lower than in the non-pregnant state. Serum levels of transaminases are usually elevated in those with ICP, but may be normal in 30% of patients[22]. In women with jaundice, conjugated (direct) bilirubin levels are increased and the prothrombin time may be prolonged. Hepatic ultrasonography generally is normal but may reveal gallstones in jaundiced patients, who are at increased risk for their development.

Differential Diagnosis

In the absence of primary lesions, the clinical differential diagnosis includes other causes of primary pruritus (see Ch. 6), including those that lead to cholestatic pruritus. Viral hepatitis is a common disorder and should be excluded by appropriate serologies. Of note, a history of hepatitis C viral infection is considered a risk factor for the development of ICP, and in one study, 20% of the women who were HCV RNA-positive developed ICP[23].

Treatment

Since fetal prognosis correlates with disease severity, the therapeutic goal is reduction of serum bile acid levels. This allows prolongation of the pregnancy and lessens both fetal risk and maternal symptoms. To date, the only successful agent has been oral ursodeoxycholic acid (UDCA)[18,22,24,25]. It is a naturally occurring, hydrophilic, non-toxic bile acid that has been used for a variety of cholestatic liver diseases. Although the exact mechanism of action in ICP is still not fully understood, there is evidence that UDCA corrects the maternal serum bile acid profile, decreases the passage of maternal bile acids to the fetoplacental unit, and improves the function of the bile acid transport system across the trophoblast. In a recent systematic review and individual participant data meta-analysis, prenatal UDCA was associated with a reduction in stillbirth in combination with preterm birth[26]. The authors concluded that UDCA should be prescribed, especially in women whose disease onset was before 37 gestational weeks and whose serum bile acid concentrations were ≥40 μmol/l.

UDCA is safe for mother and fetus, with its only side effect being mild diarrhea. Use of UDCA for ICP is off-label as it is only approved for primary biliary cirrhosis. The recommended oral dose is 15 mg/kg daily or, independent of body weight, 1 g daily. It should be started as early as possible and administered until delivery.

The use of S-adenosylmethionine, dexamethasone, epomediol, silymarin, phenobarbital or activated charcoal is not recommended as none have been shown to decrease fetal risk. Cholestyramine is contraindicated as it can further reduce vitamin K absorption and increase the risk of bleeding[25]. In jaundiced patients, the prothrombin time should be monitored, and intramuscular vitamin K administered as necessary. Close interdisciplinary collaboration with the obstetrician is essential and close monitoring of the fetus is recommended.

ATOPIC ERUPTION OF PREGNANCY

Synonyms: ■ Prurigo of pregnancy ■ Besnier's "prurigo gestationis" ■ Nurse's "early-onset prurigo" of pregnancy ■ Spangler's "papular dermatitis of pregnancy" ■ Pruritic folliculitis of pregnancy ■ Eczema in pregnancy

Key features

- Eczematous and/or papular skin lesions in a patient with an atopic diathesis in whom other specific dermatoses have been excluded
- Most common pruritic disorder during pregnancy
- Generally appears earlier than other pregnancy-related dermatoses (75% before the third trimester)
- Nonspecific histology; negative direct IF; elevated serum IgE levels in up to 70% of patients
- No maternal or fetal risks; commonly recurs in subsequent pregnancies

Introduction

Atopic eruption of pregnancy (AEP) is defined as either an *exacerbation* or the *first occurrence* of eczematous and/or papular skin changes during pregnancy in atopic individuals. As the majority of patients belong to the second group, the atopic link is often overlooked, leading to a number of different diagnoses, as evidenced by the many synonyms.

History

In retrospect, an association with atopy dates back to the first reports. When Besnier described the disorder "prurigo gestationis" in 1904, "prurigo" was the term dermatologists used for atopic dermatitis (Besnier was the first to note the association between atopic dermatitis, allergic rhinitis, and asthma). Nurse, in 1968, described accompanying eczematous features in most of the 31 patients in his "early-onset" prurigo group. In 1983, Holmes and Black were the first to suggest that "prurigo of pregnancy" could simply result from pregnancy-related pruritus in women with an atopic diathesis rather than being a distinct entity[3].

Epidemiology

AEP is by far the most common pruritic disorder in pregnant women and it tends to appear earlier than the other pregnancy-related dermatoses[1]. Its incidence is not known but may be as high as 1 in 5 to 1 in 20.

Pathogenesis

To prevent fetal rejection, a normal pregnancy is characterized by a lack of strong maternal cell-mediated immune function and reduced Th1 cytokine production (e.g. IL-12, interferon-γ) as well as a dominant humoral immune response with increased Th2 cytokine production (e.g. IL-4, IL-10). This natural switch towards a dominant Th2 response, which worsens the imbalance already present in most atopic patients, is thought to favor the development of AEP[1].

Clinical Features

In contrast to the other specific dermatoses of pregnancy, AEP appears earlier, often during the first trimester, with 75% of patients presenting before the third trimester. Approximately 20% of women experience an exacerbation of pre-existing atopic dermatitis, while the remaining 80% develop atopic skin changes for the first time during pregnancy. Two-thirds of patients present with eczematous lesions (Fig. 27.8), often involving "atopic sites" such as the face, neck, and flexural aspects of the extremities. One-third develop a papular eruption on the trunk and extremities, composed of either classic prurigo lesions or small erythematous papules (Fig. 27.9). Findings typically include xerosis (often marked) and other signs of the underlying atopic diathesis (see Ch. 12). Fetal and maternal prognoses are excellent and recurrences in subsequent pregnancies are common.

Pathology

Depending on the stage of the lesion, histologic features can vary. Epidermal changes include spongiosis, acanthosis, and erosions; the dermal infiltrate is composed of lymphocytes and usually admixed

eosinophils. If the histologic section includes a hair follicle, there may be sterile follicular inflammation. Direct IF is negative. Serum IgE levels may be elevated in up to 70% of patients, usually to a mild degree.

Differential Diagnosis

Of the specific pregnancy dermatoses, PEP and ICP are the ones that in particular need to be excluded. In AEP, the eruption starts significantly earlier during gestation and has no association with striae; serum bile acid levels are also normal. Furthermore, other pruritic dermatoses not specifically associated with pregnancy (e.g. scabies, viral exanthems, drug eruptions, contact dermatitis) must be considered.

Treatment

Cutaneous lesions respond rapidly to topical corticosteroids with or without systemic antihistamines. Topical tacrolimus may be used for sites such as face and intertriginous zones. Emollients, humectants, and topical antipruritic agents also play a role, as they do in non-pregnant patients with atopic dermatitis. Topical urea (10%), polidocanol, pramoxine, and menthol are considered safe during pregnancy. UVB irradiation is very helpful for severe disease. Secondary bacterial infection may require systemic antibiotics (e.g. penicillins, cephalosporins).



Fig. 27.8 Atopic eruption of pregnancy – eczematous lesions. The eczematous lesions often involve flexural areas and friction sites (**A,B**), as well as the breasts and abdomen (**B**). These changes are seen in approximately two-thirds of patients.

APPROACH TO THE PREGNANT WOMAN WITH PRURITUS

Pruritus is the major symptom in all four of the pregnancy-related dermatoses, but it may also be associated with coincidental dermatoses (e.g. scabies, urticaria, pityriasis rosea). A pregnant woman with severe pruritus and skin lesions requires urgent clinicopathologic assessment, given the possibility of associated fetal risks. Figure 27.10 is an algorithm that has proven helpful in distinguishing amongst the various pruritic dermatoses of pregnancy[1]. Primiparity and multiple gestations are significantly linked to PEP, while a history of identical skin findings in past pregnancies (recurrence) suggests ICP. An early presentation (75% before the third trimester) is typical for AEP, while the other disorders present late during pregnancy or postpartum. Abdominal location of skin lesions is characteristic of gestational pemphigoid and PEP, involvement of the trunk and extremities of AEP, and predominant involvement of the extremities of ICP. Pruritus as the sole presenting symptom followed by exclusively secondary cutaneous lesions due to scratching is only seen in ICP.

DERMATOSES INFLUENCED BY PREGNANCY

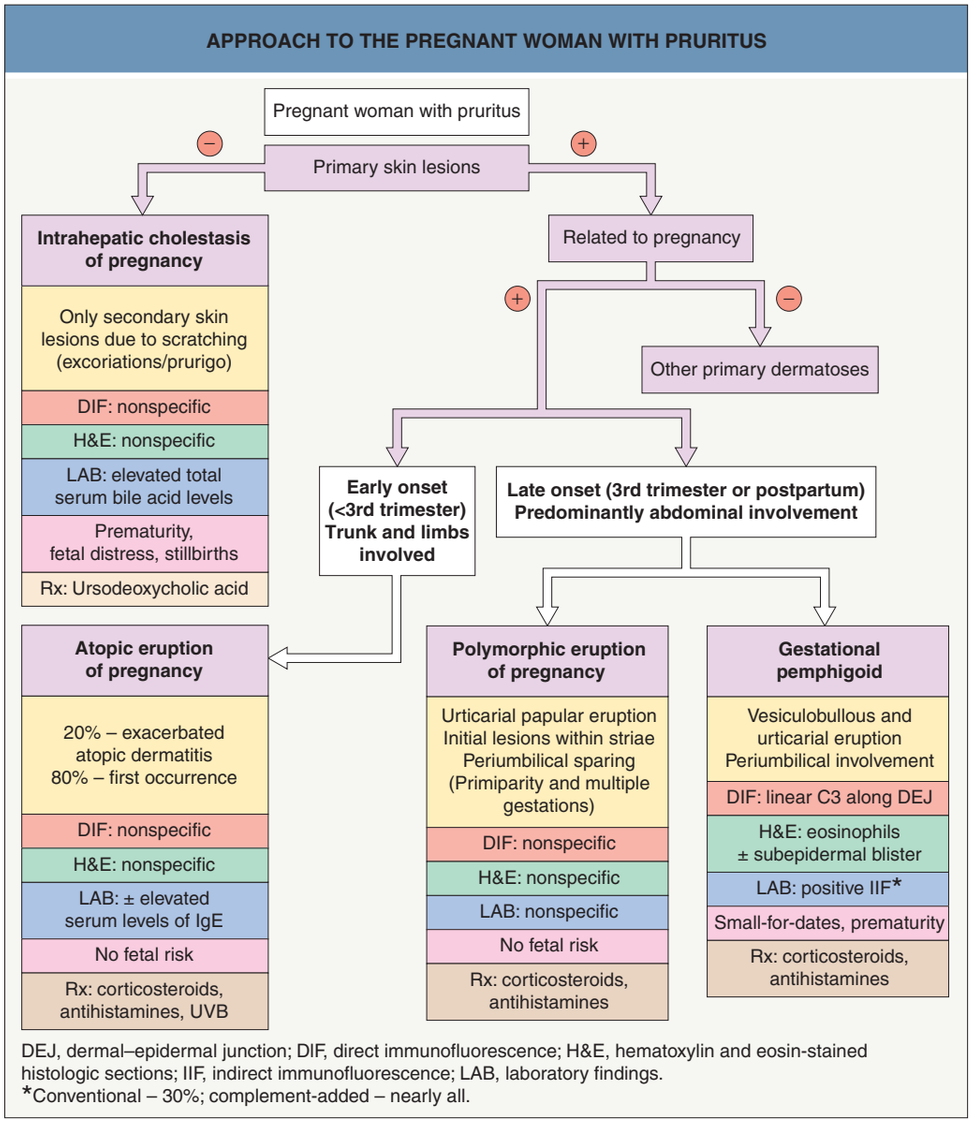
Pregnancy can have positive, as well as negative, effects on the status of pre-existing skin diseases[27]. Examples of pregnancy-influenced dermatoses are outlined in Table 27.4.

PHYSIOLOGIC CHANGES DURING PREGNANCY

Table 27.5 outlines many of the physiologic changes that have been associated with pregnancy. While some are very common, such as hyperpigmentation, others are more loosely associated, for example, nail changes. The majority of changes spontaneously regress following delivery[27].



Fig. 27.9 Atopic eruption of pregnancy – papular eruption. Scattered small erythematous papules (**A**) or excoriated prurigo lesions (**B**) favor the abdomen and extremities. These changes are seen in approximately one-third of patients. Note the absence of striae distensae.



DEJ, dermal–epidermal junction; DIF, direct immunofluorescence; H&E, hematoxylin and eosin-stained histologic sections; IIF, indirect immunofluorescence; LAB, laboratory findings.
*Conventional – 30%; complement-added – nearly all.

Fig. 27.10 Approach to the pregnant woman with pruritus[1]. Patients with refractory gestational pemphigoid may benefit from plasmapheresis during pregnancy. See Table 27.3 for special considerations regarding the use of corticosteroids (topical and oral) and antihistamines during pregnancy.

DERMATOSES INFLUENCED BY PREGNANCY	
Psoriasis	• Commonly improves during pregnancy, then flares within 6–12 weeks following delivery • Explanation: down-regulation of Th1 immune response during a normal pregnancy • May present as impetigo herpetiformis (generalized pustular psoriasis of pregnancy)
Atopic dermatitis Systemic lupus erythematosus Pemphigus vulgaris	• Usually worsens during pregnancy and then improves after delivery • Explanation: physiologic shift towards a strong Th2 immune response with an increase in Th2 cytokines (e.g. IL-4, IL-10)
Acne	• Can improve or flare; persistent acne often improves during pregnancy • The flares in women with acne gravidarum can be severe, in particular late in pregnancy due to hyperandrogenemia
Rosacea	• Often worsens during pregnancy, presumably due to immunologic, endocrine, and vascular changes • May present as rosacea fulminans
Melanocytic nevi	• With the exception of symmetric enlargement of nevi on the breasts and abdomen due to distention, changes in benign nevi are minimal; by dermoscopy, a symmetric peripheral rim of globules may be seen, which reverses after delivery • Nevi may darken during pregnancy, but those with worrisome features, clinically or by dermoscopy, should be biopsied

Table 27.4 Dermatoses influenced by pregnancy[27].

AUTOIMMUNE PROGESTERONE DERMATITIS

Although autoimmune progesterone dermatitis is not a specific dermatosis of pregnancy, it can first appear during pregnancy or postpartum[28]. Classically, there are recurrent cyclic flares of dermatitis that correspond to the luteal phase of the menstrual cycle, when progesterone levels increase. In addition to eczematous changes, lesions can vary from urticaria to papulovesicles to erythema multiforme-like. Some patients have primarily pruritus or oral erosions. At sites of intradermal injection of progesterone (e.g. 50 mg/ml), the vast majority of affected patients develop a cutaneous reaction characterized by urticaria (immediate [30 min]) and/or erythema and induration (delayed [24–48 h])[28]. Injections of saline and estrogen (e.g. estrone [1 mg/ml]) are often done concurrently, to serve as a control and to examine for

PHYSIOLOGIC CHANGES DURING PREGNANCY	
Pigmentary	
Hyperpigmentation (e.g. areolae, linea nigra; Fig. 27.11A) Melasma	• Hyperpigmentation (up to 90% of patients) and melasma (up to 70% of patients) are presumably of hormonal etiology • Melasma tends to persist postpartum in those with darker skin phototypes
Hair	
Hirsutism Postpartum telogen effluvium Postpartum androgenetic alopecia	• Some hirsutism is normal and typically regresses postpartum • Telogen effluvium may last up to 15 months • Postpartum patterned alopecia may or may not revert to normal
Nail	
Subungual hyperkeratosis Distal onycholysis Transverse grooving Brittleness	• There are no pathognomonic nail changes
Glandular	
Increased eccrine function (except palms) Increased sebaceous function Decreased apocrine function	• Eccrine sweating may increase (except on the palms) later in pregnancy and result in hyperhidrosis • The effect on apocrine function and sebaceous gland activity is incompletely understood
Connective tissue	
Striae distensae/gravidarum	• Develop in up to 90% of patients and often resolve • Both hormonal factors and physical stretching of the skin appear to be relevant in their development
Vascular	
Spider angiomas Palmar erythema (Fig. 27.11B) Non-pitting and pitting edema Varicosities Vasomotor instability Purpura Gingival hyperemia or hyperplasia Pyogenic granulomas (Fig. 27.11C) Hemorrhoids	• Vascular changes result from distention, instability, and new vessel formation • Clinically obvious changes are most pronounced during the third trimester and most changes regress spontaneously following delivery

Table 27.5 Physiologic changes during pregnancy[34]. *Adapted from Kroumpouzos G, Cohen LM. Dermatoses of pregnancy. J Am Acad Dermatol 2001;45:1–19.*

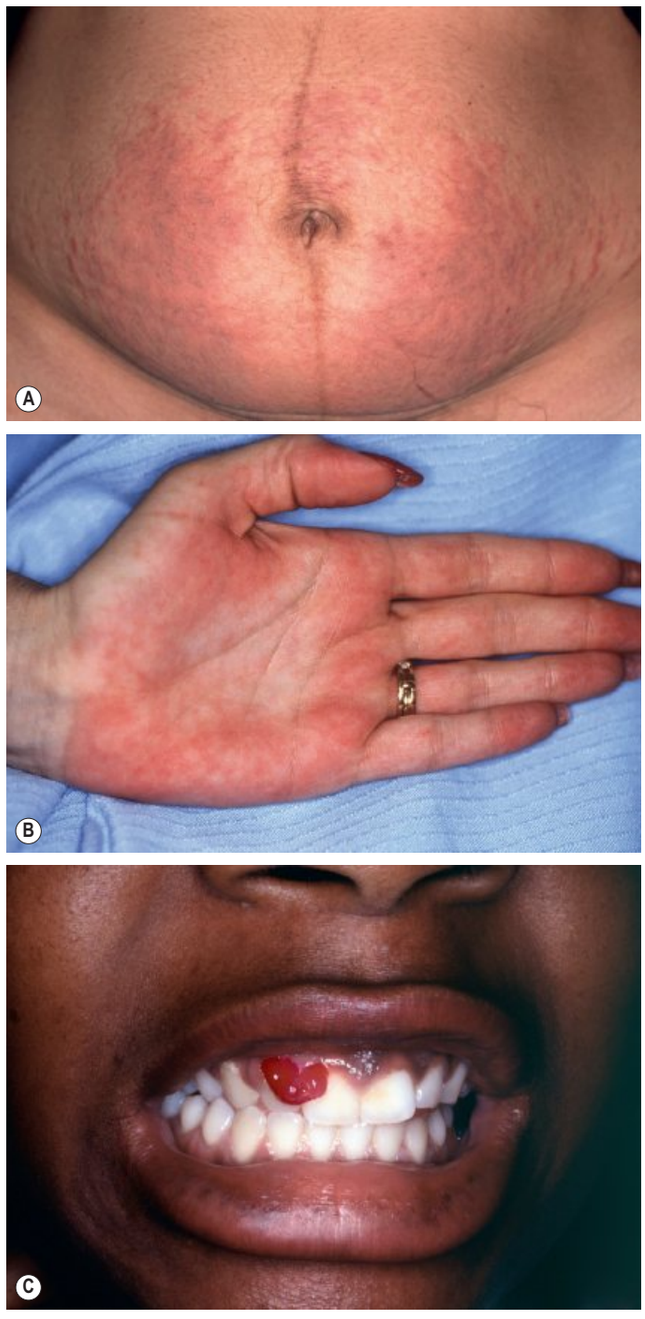


Fig. 27.11 Physiologic changes during pregnancy. A Well-demarcated linea nigra in a patient with polymorphic eruption of pregnancy. **B** Palmar erythema. **C** Gingival pyogenic granuloma.

evidence of estrogen dermatitis[29], respectively. Both oral and intramuscular progesterone have been used as a challenge test in patients with delayed reactions. Treatment consists primarily of inhibiting ovulation via estrogen-containing preparations. Anecdotally, additional reported therapies include tamoxifen and danazol, each possibly suppressing ovulation via interaction with the hypothalamic–pituitary axis. Of note, some patients have had remissions during pregnancy.

Acknowledgment

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Additional figures and table on An overview of the use of dermatologic drugs during pregnancy and lactation available in our eBook (see inside front cover for access code).

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eFig. 27.1 Gestational pemphigoid. Urticarial papules with central duskiness.

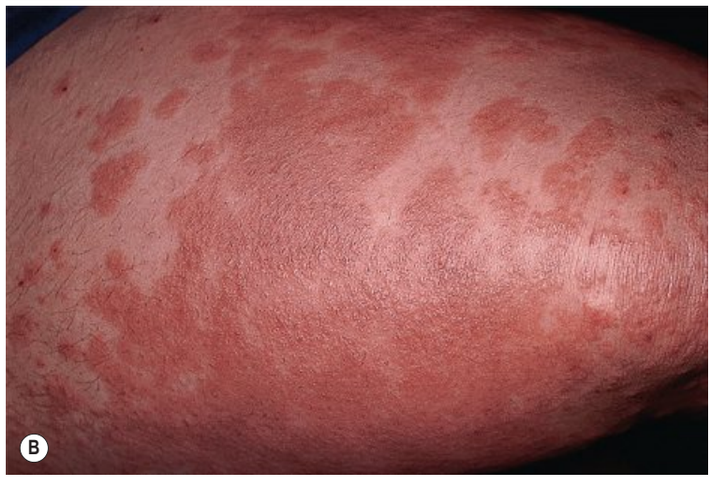


eFig. 27.3 Polymorphic eruption of pregnancy (PEP). Urticarial lesions as well as pseudovesicles on the hand.



eFig. 27.2 Gestational pemphigoid. Tense bullae arising within urticarial plaques, reminiscent of bullous pemphigoid. *Courtesy Luis Requena, MD.*





eFig. 27.4 Polymorphic eruption of pregnancy (PEP). A,**B** Edematous and urticarial lesions of the upper thighs. Note the pink color in a woman with skin phototype II (**A**) versus the red–brown color in a patient with a darker skin phototype (**B**).

AN OVERVIEW OF THE USE OF DERMATOLOGIC DRUGS DURING PREGNANCY AND LACTATION	
Dermatologic Medication	**Pregnancy**
Acne & Hair – Topical	
Azelaic acid	No well-controlled studies in pregnant women. Embryo-fetal toxicity at 3–32× MRHD in animal studies. About 4% systemic absorption with topical application. **Limited use is safe** in pregnancy[e1].
Benzoyl peroxide	No well-controlled studies in pregnant women and no animal studies conducted. About 5% systemic absorption with topical application and metabolized to a food additive, benzoic acid. **Limited use is safe** in pregnancy[e2].
Salicylic acid	No well-controlled studies in pregnant women. Teratogenic in animal studies. Low systemic absorption with topical application. **Limited use is safe** in pregnancy. Avoid occlusive dressings[e1].
Adapalene	No well-controlled studies in pregnant women. Anophthalmia and agenesis of the optic chiasma reported in an infant whose mother used topical adapalene during pregnancy[e4]. Teratogenic and fetotoxic with oral use at 32× MRHD in animal studies. Low systemic absorption with topical application. **Limited use is likely safe if medically necessary** during pregnancy[e2].
Minoxidil	No well-controlled studies in pregnant women. Fetal hypertrichosis and congenital anomalies (brain, heart, and vascular malformations, caudal regression) reported in infants whose mothers used oral and topical minoxidil during pregnancy. No teratogenicity in animal studies. About 1.4% systemic absorption with topical application. Crosses lipid barriers. Brain and fetal concentrations may be higher than in plasma. **Limited use is likely safe if medically necessary** during pregnancy[e1].
Tretinoin	No well-controlled studies in pregnant women. Congenital malformations (holoprosencephaly, craniofacial defects, ear, eye, cardiac, and neural abnormalities, diaphragmatic hernia, limb defects, fetal growth restrictions) reported in infants whose mothers used topical tretinoin during the first trimester. Larger studies indicate no associated increased risk for congenital abnormalities (including retinoid embryopathy), live births, or miscarriages with topical application in the first trimester[e6]. Teratogenic (hydrocephaly, retinoid malformations) and fetotoxic (skeletal variations) in animal studies. Low systemic absorption after topical application. **Limited use is likely safe if medically necessary** during pregnancy[e2].
Tazarotene	Healthy deliveries have been reported with topical tazarotene use. Teratogenic (retinoid malformations, spina bifida, hydrocephaly, heart defects) and embryotoxic (reduced fetal body weight and skeletal ossification) in animal studies. Less than 6% systemic absorption with topical application[e7]. Highly bound to plasma (>99%). Placental transfer unlikely[e6]. **Contraindicated** in pregnancy; embryo-fetal toxicity warning.
Acne & Hair – Systemic	
Spironolactone	No reports of major malformations. Anti-androgenic effects (feminization of male fetus) and endocrine dysfunction in animal studies. Crosses the placenta. **Use with caution** in pregnancy due to male fetal feminization and hypospadias risk[e2].
Isotretinoin	Congenital defects (cleft palate, microphthalmia, small/absent external auditory canals, skull, cerebral and cerebellar malformations, hydrocephalus, microcephaly, cardiac defects, thymus and parathyroid gland abnormalities), low IQ score, premature birth, and spontaneous abortion have been reported. **Contraindicated** in pregnancy. If pregnancy occurs, discontinue isotretinoin immediately. Must register with iPLEDGE Program. Women of childbearing potential must be on two forms of contraception or abstinence one month before, during, and one month after therapy. Must have two negative pregnancy tests prior to initiation and one negative test monthly.
Finasteride	Abnormalities of the external genitalia of a male fetus have been shown in animal studies. Teratogenic effects may occur due to the ability of type II 5α-reductase inhibitors to inhibit the conversion of testosterone to dihydrotestosterone. **Contraindicated** in pregnancy.
Minoxidil	Fetal hypertrichosis and congenital anomalies (brain, heart, and vascular malformations, caudal regression) reported in infants whose mothers used oral and topical minoxidil during pregnancy. Neonatal hypertrichosis has been observed in animal studies. There are no well-controlled studies in pregnant women. **Use with caution** in pregnancy.
Anesthetics	
Lidocaine(& epinephrine [adrenaline])	No well-controlled studies in pregnant women. Most of the information comes from anesthetic use in obstetrics. No association with malformations with first trimester exposure in one study. No adverse effects in animal studies. Crosses the placenta within minutes. Fetus and infants are capable of metabolizing lidocaine[e6]. Addition of epinephrine may lead to placental vasoconstriction, fetal tachycardia, and low placental blood flow, but may be neglected with dosage used for dermatological interventions. Vasoconstriction prolongs anesthetic effects and reduces placental transfer of lidocaine. **Safe** in pregnancy as a local anesthetic[e2].
Antibiotics – Topical	
Bacitracin	No well-controlled studies in pregnant women or animal reproduction studies conducted. Poorly absorbed after topical application. **Safe** in pregnancy[e6].
Mupirocin	No well-controlled studies in pregnant women. Rapid metabolism and elimination suggests clinical levels will not reach fetus[e6]. No teratogenicity in animal studies. Less than 1% systemic absorption with topical application[e6]. **Safe** in pregnancy. Topical antibiotic of choice[e1].

eTable 27.1 An overview of the use of dermatologic drugs during pregnancy and lactation.

Lactation	Female Fertility	Male Fertility	Former FDA Category
Excretion into breast milk is not known. **Likely compatible** with breastfeeding[e1].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Excretion into breast milk not known. **Likely compatible** with breastfeeding[e2].	Limited safety data.	Limited safety data.	C
Excretion into breast milk not known. **Compatible** with breastfeeding[e3].	No adverse effects on fertility[e1].	No adverse effects on fertility[e1].	C
Excretion into breast milk not known. **Likely compatible** with breastfeeding.	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	C
Likely excreted in breast milk. Hypertrichosis was not evident in nursing infant[e5]. **Compatible** with breastfeeding[e2].	Decrease in conception rate at 1× and 5× MRHD with oral administration in animal studies.	Decrease in conception rate at 1× and 5× MRHD with oral administration in animal studies.	C
Likely excreted in breast milk in low amounts. **Likely compatible** with breastfeeding[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	C
Excreted into breast milk in low amounts[e2]. **Likely compatible** with breastfeeding. Should not be used on >20% body surface area[e2].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	X
Active metabolite, canrenone, excreted in breast milk in low amounts. No adverse effects reported with breastfeeding. Intense diuresis may suppress lactation. **Compatible** with breastfeeding[e3].	No adverse effects on fertility in animal studies.	Decreased testosterone may lead to gynecomastia, impotence, and reduced sperm motility at >100 mg/day. Decreased sperm concentration, but not fertility, in animal studies[e8].	C
Excreted in breast milk. Highly lipid soluble. Concentrations in breast milk would be significant. **Contraindicated** with breastfeeding[e3].	No adverse effects on fertility in animal studies.	No infertility reported. Increased sperm density and motility in one study[e8].	X
Excretion into breast milk is not known. **Not recommended** in women by the manufacturer.	No adverse effects on fertility in animal studies.	Male infertility and poor seminal quality have been reported and may be reversible upon discontinuation of finasteride.	X
Excretion in breast milk has been reported. **Not recommended** in nursing women by the manufacturer.	Decrease in conception rate at 1× and 5× MRHD with oral administration in animal studies.	Decrease in conception rate at 1× and 5× MRHD with oral administration in animal studies.	C
Excreted in breast milk in low amounts. **Compatible** with breastfeeding[e3].	Limited safety data.	Limited safety data.	B
Compatible with breastfeeding[e6].	Limited safety data.	Limited safety data.	C
Compatible with breastfeeding. Topical antibiotic of choice[e1].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B

AN OVERVIEW OF THE USE OF DERMATOLOGIC DRUGS DURING PREGNANCY AND LACTATION	
Dermatologic Medication	**Pregnancy**
Silver sulfadiazine	No well-controlled studies in pregnant women. Not teratogenic in animal studies. Extensive area application of silver sulfadiazine should be avoided in pregnant women with burns because absorption of sulfonamides can lead to kernicterus. **Use with caution** in late-term pregnancy due to kernicterus risk in burns.
Antibiotics – Systemic	
Cephalosporins	No adequate well-controlled studies in pregnant women. No associated congenital abnormalities with cephalexin, cefaclor, cefamandole, cefoperazone, cefotaxime, ceftibuten, and cefuroxime use in a large study. Four birth defects (3 cardiovascular defects) reported in infants with ceftriaxone exposure, but mothers had additional contributing factors. No adverse effects have been reported with second trimester or third trimester use[e6]. No teratogenicity or embryo-fetal toxicity in animal studies. **Safe** in pregnancy. Older cephalosporins preferred. Eliminated more quickly in pregnancy; may require dose adjustments[e2].
Clindamycin	No well-controlled studies in pregnant women during the first trimester. No associated congenital abnormalities when taken orally in the first trimester[e6]. No teratogenicity in animal studies. **Safe** in pregnancy. Second-line to beta-lactams due to potential for pseudomembranous colitis[e2].
Metronidazole	No well-controlled studies in pregnant women. No associations with congenital abnormalities were found in multiple studies, although one population-specific study found an association with cleft lip, cleft palate, and polysyndactyly[e6]. Crosses placental barrier and enters fetal circulation rapidly. No fetotoxicity in animal studies. Lower systemic absorption with topical administration. **Safe** in pregnancy[e2].
Penicillin	No well-controlled studies in pregnant women. No associations with congenital abnormalities were found in multiple studies. Rapidly enters fetal circulation. No adverse effects in animal studies. **Safe** in pregnancy[e6]. Antibiotic of choice[e1]. Eliminated more quickly in pregnancy, therefore, may need dose adjustment[e2].
Trimethoprim–sulfamethoxazole	No well-controlled studies in pregnant women. Associations with congenital malformation (neural tube defects, cardiovascular abnormalities, urinary tract defects, oral clefts, and club foot) in some, but not all studies. Trimethoprim interferes with folate metabolism. Teratogenic (cleft palate) and fetotoxic (fetal loss) at 6× RHD in animal studies. **Use with caution** in pregnancy due to potential adverse fetal effects. Avoid use near delivery due to potential risk for neonatal hyperbilirubinemia. Supplement with folic acid in first trimester to lower risk for neural tube defects[e2].
Dapsone	No well-controlled studies in pregnant women. No congenital anomalies reported with use. Measure G6PD levels before use to reduce risk for maternal anemia, neonatal hyperbilirubinemia, and hemolytic anemia. No teratogenicity in animal studies[e2]. **Use with caution** in pregnancy due to potential adverse fetal effects. Regarding infections for pregnancy, use recommended only for leprosy, malaria, and *P. carinii* infections during pregnancy[e6].
Ciprofloxacin	No associations with congenital abnormalities or musculoskeletal defects in multiple studies[e6]. No adverse effects in animal studies. Causes arthropathy in immature animals when administered directly. **Use with caution** in pregnancy due to potential adverse fetal effects. Use recommended only for complicated or resistant infections during pregnancy due to potential risk for cartilage damage[e2].
Doxycycline	No associations with congenital malformations with first trimester use[e2]. Discoloration of teeth (yellow–gray–brown) and bone growth inhibition reported in infants with exposure in second and third trimesters[e6]. Crosses placenta and found in fetal tissue. Embryo-fetal toxicity in animal studies. **Contraindicated** in the second and third trimesters due to potential for teeth discoloration, bone growth inhibition, and maternal hepatitis[e2].
Antifungals – Topical	
Clotrimazole	No adverse effects with topical use in pregnancy. No associations with congenital defects were found in multiple studies. Very minimal absorption with topical or intravaginal application[e6]. No adverse effects in animal studies. **Safe** in pregnancy. Topical antifungal of choice[e2].
Nystatin	No associations with congenital malformations[e6]. No animal reproduction studies conducted. Very minimal absorption with topical or vaginal application. **Safe** in pregnancy. Topical antifungal of choice for *Candida* infections[e1].
Ciclopirox	No well-controlled studies in pregnant women. No reports of congenital abnormalities after use. No teratogenicity in animal studies. About 1.3% absorbed after topical application[e6]. **Likely safe** in pregnancy[e2].
Terbinafine	No increased risk of major malformations or spontaneous abortions in topical or oral use in one study[e9]. No teratogenicity or embryo-fetal toxicity in animal studies. Less than 5% systemic absorption after topical application. **Limited use is likely safe if medically necessary** in pregnancy[e2].
Antifungals – Systemic	
Terbinafine	No increased risk of major malformations or spontaneous abortions in topical or oral use in one study[e9]. No teratogenicity or embryo-fetal toxicity in animal studies. Less than 5% systemic absorption after topical application. **Limited use is likely safe if medically necessary** in pregnancy[e2].

eTable 27.1 An overview of the use of dermatologic drugs during pregnancy and lactation.

Lactation	Female Fertility	Male Fertility	Former FDA Category
Sulfonamides are excreted into human milk and increases the possibility of kernicterus. **Use not recommended** with breastfeeding unless medically necessary.	Limited safety data.	Limited safety data.	B
Excreted in breast milk in low concentrations (<1%). **Compatible** with breastfeeding[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Excreted in breast milk. Bloody stools with negative stool cultures reported in a nursing infant whose mother was exposed to clindamycin; discontinued when clindamycin was stopped. **Compatible** with breastfeeding[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Excreted in breast milk. Diarrhea reported in a nursing infant whose mother was exposed to oral metronidazole[e6]. **Compatible** with breastfeeding[e1].	Limited safety data.	Infertility at high doses with oral administration in animal studies.	B
Excreted in breast milk in low levels. Diarrhea and rash reported in nursing infants[e1]. **Compatible** with breastfeeding[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Excreted in breast milk in low amounts. Potential risk for bilirubin displacement from albumin leading to kernicterus. Hemolytic reactions can occur in neonates without glucose-6-phosphate dehydrogenase (G6PD) deficiency as soon as 8 days after birth. **Compatible** with breastfeeding. **Use not recommended** in infants with G6PD deficiency, premature infants, or neonates with hyperbilirubinemia[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	C
Excreted in breast milk in substantial amounts. Hemolytic reaction reported in nursing infant. **Use not recommended** in infants with G6PD deficiency[e3].	No adverse effects reported by women. Reduced viable embryos and number of implantations at 127× MRHD in animal studies.	Reduced sperm motility at 15× MRHD in animal studies.	C
Excreted in human milk in low amounts. *Clostridium difficile* toxin reported in the stool of a nursing infant whose mother developed pseudomembranous colitis after taking ciprofloxacin[e6]. **Compatible** with breastfeeding. Monitor infant for diarrhea[e1].	No adverse effects on fertility in animal studies.	Decreased spermatogenesis and impaired fertility at 13× MRHD in animal studies[e6].	C
Excreted in breast milk in low amounts due to calcium chelation. Potential risk of tooth discoloration and bone growth inhibition in nursing infant, but unlikely in short-term use. **Compatible** with short-term use for breastfeeding. **Use not recommended** for longer than 3 weeks due to potential for infant dental staining[e3].	No adverse effects on fertility in animal studies.	*In vitro* study showed impaired sperm movement and decreased sperm viability. This was reversible after 20 minutes of doxycycline discontinuation[e8].	D
Compatible with breastfeeding. Topical antifungal of choice[e1].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Compatible with breastfeeding[e3].	Limited safety data.	Limited safety data.	C (vaginal: A)
Excretion into breast milk not known, but likely negligible[e6]. **Likely compatible** with breastfeeding[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Excreted in breast milk in low amounts. **Use not recommended** with breastfeeding unless medically necessary[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Excreted in breast milk in low amounts. **Use not recommended** with breastfeeding unless medically necessary.[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B

AN OVERVIEW OF THE USE OF DERMATOLOGIC DRUGS DURING PREGNANCY AND LACTATION	
Dermatologic Medication	**Pregnancy**
Griseofulvin	Two conjoined twins reported in infants with first trimester exposure[e6]. Teratogenic and embryotoxic at 4× MRHD in animal studies. Crosses placenta. **Contraindicated** in pregnancy. Effective contraception recommended in women of child-bearing potential due to griseofulvin interaction with estrogen-containing oral contraceptives, which may increase risk for unintended pregnancies.
Fluconazole	No well-controlled studies in pregnant women. Congenital anomalies (cleft palate, craniofacial and bone abnormalities, cardiovascular defects) reported in infants with first trimester exposure. Spontaneous abortions and birth defects were reported in larger studies, but no patterns have been identified[e6]. Teratogenic (cleft palate) and embryotoxic (supernumerary ribs, delayed ossifications) in animal studies. **Avoid** in pregnancy (especially 1st trimester) per manufacturer, unless treating severe or potentially life-threatening fungal infections. **Limited use likely safe** in low doses and in the short-term for vaginal candidiasis. Obtain fetal ultrasound with first trimester exposure[e2].
Ketoconazole	No well-controlled studies in pregnant women. Cardiovascular, skeletal, craniofacial, and neural defects reported in infants with first trimester exposure[e2]. No major birth defects observed with oral exposure in the first trimester in a large study[e6]. Serum testosterone is lowered at 800 mg/day and is absent at 1600 mg/day. Teratogenic and embryotoxic (syndactyly and oligodactyly) at 10× MRHD with oral use in animal studies. **Avoid** in pregnancy. **Limited use likely safe** only after the first trimester at low doses. Obtain fetal ultrasound with first trimester exposure[e2].
Itraconazole	No well-controlled studies in pregnant women. Cardiovascular, skeletal, craniofacial, and neural defects reported in infants with first trimester exposure[e2]. Teratogenic (skeletal defects, encephaloceles, macroglossia) and embryotoxic at 5–20× MRHD in animal studies. **Avoid** in pregnancy. **Limited use likely safe** only after the first trimester at low doses. Obtain fetal ultrasound with first trimester exposure[e2].
Immunomodulators – Topical	
Calcipotriene (calcipotriol)	No well-controlled studies in pregnant women. Calcium imbalance, skeletal and bone ossification abnormalities in animal studies. **Safe** in pregnancy with topical application of doses <100 g/week[e2].
Corticosteroids (hydrocortisone, triamcinolone, fluocinonide, clobetasol)	No well-controlled studies in pregnant women. No associations with malformations with topical corticosteroid use in large studies. Fetal growth restriction reported only with extensive use of potent topical corticosteroids in the third trimester and with extensive use (particularly >300 g)[e10]. Stria may form, especially with higher potency corticosteroids and occlusive dressings. Halogenation, especially fluorination, of corticosteroids determines risk profile due to its ability to pass through the placenta. Methylprednisolone aceponate is a potent topical corticosteroid used in Europe, but has limited side effects due to lack of halogenation. **Limited use is safe** in pregnancy. Mild-to-moderate potency corticosteroids are preferred over potent corticosteroids, but may use potent corticosteroids for a limited period of time[e2].
Tacrolimus	No well-controlled studies in pregnant women. Cardiac defects and dysfunction, neonatal hyperkalemia, renal dysfunction, premature birth, and low birth weight have been reported in infants with oral maternal administration during pregnancy[e6]. Teratogenic and embryotoxic (late resorptions, decreased live births, decreased weight and viability) with oral use and high maternal doses in animal studies. Crosses placenta. Poor systemic absorption with topical application. **Limited use is safe** with topical application in pregnancy[e2].
Pimecrolimus	No well-controlled studies in pregnant women. Embryo-fetal toxicity (skeletal variations) with oral use and high maternal doses in animal studies. Congenital anomalies, neonatal hyperkalemia, low birth weight, and premature delivery have been reported with oral maternal administration during pregnancy, though association was complicated by medically complex history. Poor systemic absorption with topical application due to large molecular size. **Limited use is safe** with topical application in pregnancy.
Crisaborole	No adequate and well-controlled studies in pregnant women. No teratogenicity with oral administration in animal studies. Systemic absorption after topical application[e1]. **Use with caution** due to limited safety data.
Immunomodulators – Systemic	
Prednisone	No well-controlled studies in pregnant women. Increased risk for orofacial clefts 4 weeks before conception and 12 weeks after conception, premature delivery, premature membrane rupture, intrauterine growth restriction, gestational diabetes, and maternal hypertensive disorders[e2]. Teratogenic (cleft palate) in animal studies. Barely crosses placental barrier (mother-to-child ratio 10:1). **Limited use is likely safe**. During first trimester, particularly between weeks 8 and 11, increased risk of cleft lip/cleft palate has been debated with high doses and for >10 days but could not be substantiated by recent large population-based case–control study[e11]. If use is long-term and extends late into gestation, fetal growth should be monitored and the risk of adrenal insufficiency in the newborn should be addressed.
Intravenous immunoglobulin	Healthy deliveries reported in mothers with pemphigus vulgaris and gestational pemphigoid. No animal studies conducted. Crosses placenta increasingly after 30 weeks of gestation. Hypertension and thrombosis may occur with immunoglobulins, especially in the setting of a hypercoagulable state due to pregnancy. **Use recommended** for active pemphigus and severe gestational pemphigoid during pregnancy.
Hydroxychloroquine	No associations with congenital, neurologic, or auditory abnormalities in studies. No similar risk of retinopathy in fetuses as seen with adults. **Use recommended** for active lupus during pregnancy. Reduces risk for cardiac neonatal lupus[e2].

eTable 27.1 An overview of the use of dermatologic drugs during pregnancy and lactation.

Lactation	Female Fertility	Male Fertility	Former FDA Category
Use not recommended with breastfeeding due to potential for tumorigenicity[e3].	Limited safety data.	Sperm abnormalities not detected in humans. Males should wait at least 6 months after therapy completion before fathering a child. Suppressed spermatogenesis in animal studies.	C (Microsize: X)
Excreted in breast milk. No adverse effects reported with use. **Compatible** with breastfeeding[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	C (low dose for vaginal candidiasis); D (all other)
Excreted in breast milk. **Likely compatible** with breastfeeding[e3].	Decreased pregnancy rates and ovulation at high doses in animal studies. Discontinue prior to conception planning[e1].	Decreased testosterone levels and oligospermia in one study[e8]. Discontinuation prior to conception planning[e1].	C
Excreted in breast milk. Itraconazole has the potential to concentrate in breast milk. No adverse effects reported with use. **Use not recommended** with breastfeeding[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	C
Vitamin D is a normal component of breast milk and excreted in low amounts. **Compatible** with breastfeeding. Limit doses to <10 000 IU/day due to potential for excess calcium in infant[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	C
Corticosteroids are normally present in breast milk. Iatrogenic hypertension reported in infant after high potency (class I) topical corticosteroid application to nipple. **Safe** with breastfeeding. **Use not recommended** on nipple area. Rinse off before using[e3].	Limited safety data.	Limited safety data.	C
Present in breast milk in low amounts. No adverse effects, increased infections, or developmental concerns reported in nursing infants. **Use with caution** due to limited safety data. **Use not recommended** on nipple area since oral consumption by the infant could be significant. Rinse off before using[e3].	No adverse effects on fertility in animal studies. Higher pre-implantation loss and adverse effects on estrous cycle in animal studies.	Reduced sperm function at high doses in animal studies[e1].	C
Present in breast milk in low amounts. **Use with caution** due to limited safety data. **Use not recommended** on nipple area since oral consumption by the infant could be significant. Rinse off before using[e3].	Adverse effects on estrus cycles and post-implantation loss at high oral doses in animal studies.	Reduced sperm function at high oral doses in animal studies.	C
Excretion in breast milk is not known. **Use with caution** due to limited safety data.	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	N/A
Systemic corticosteroids and metabolite prednisolone are excreted in breast milk. No adverse effects reported in nursing infants. High doses may cause temporary loss of milk supply. **Likely compatible** with breastfeeding. Delay breastfeeding until 3–4 hours after administration of high doses only (>1 g)[e3].	Limited safety data. Used in fertility treatments[e1].	Possible reversible decreased sperm count and motility. No need to discontinue while trying to conceive[e1].	C
Excreted in breast milk. **Compatible** with breastfeeding[e3].	Improved fertility in *in vitro* fertilization results[e2].	No adverse effects[e1].	C
Excreted in breast milk in low amounts. Eliminated slowly, which increases risk for toxicity. Observation of exposed breastfed infants over 1 year of age showed no adverse effects on growth, vision, or hearing. **Compatible** with breastfeeding[e3].	Limited safety data.	Limited safety data.	N/A

AN OVERVIEW OF THE USE OF DERMATOLOGIC DRUGS DURING PREGNANCY AND LACTATION	
Dermatologic Medication	**Pregnancy**
Azathioprine	No well-controlled studies in pregnant women. Sporadic anomalies (preaxial polydactyly, cardiac defects, neural defects), preterm delivery, pancytopenia, immunosuppression, and cytomegalovirus infection reported in infants exposed during pregnancy. Large upper lumbar myelomeningocele, bilateral dislocated hips, and talipes equinovarus reported in an infant whose father was on long-term therapy. Other studies have not found associations with congenital defects. No clear patterns have been established[e6]. Teratogenic (skeletal malformations and visceral abnormalities) in animal studies. **Use with caution** in pregnancy due to potential adverse fetal effects. Half the dose if mother is leukopenic in the third trimester to prevent infant leukopenia. Avoid intrauterine devices (IUDs) for contraception, as azathioprine interferes with the efficacy of IUDs[e2].
Mycophenolate mofetil	Fetal losses and congenital malformations (cleft lip and palate, hypertelorism, microphthalmos, colomba, micrognathia, external ear abnormalities, polydactyly, syndactyly, cardiac defects, esophageal atresia, spina bifida) reported in infants with first trimester exposure. Teratogenic and embryo-fetal toxic in animal studies. **Contraindicated** in pregnancy; embryo-fetal toxicity warning. Non-hormonal contraception recommended and avoid blood donation until 6 weeks after therapy completion. Blood products might be administered to pregnant woman[e2].
Rituximab	B cell lymphocytopenia in infants exposed during pregnancy, but returned to baseline in less than 6 months. Decreased lymphoid B cells in animal studies. No patterns of congenital anomalies identified in one study[e12]. Monoclonal antibodies are actively transferred across placenta in third trimester[e6]. **Contraindicated** in pregnancy. Effective contraception recommended during therapy and for 1 year after therapy completion[e2].
Omalizumab	No associations with major birth defects or miscarriage in infants with first trimester exposure. Women with poorly controlled asthma may have increased risk for prematurity, low birth weight, small for gestational age in neonate. No teratogenicity embryotoxicity in animal studies. Monoclonal antibodies are actively transferred across placenta in third trimester[e6]. **Use with caution** due to limited safety data.
Dupilumab	No associations with major birth defects or adverse outcomes identified with maternal exposure. Monoclonal antibodies are actively transferred across placenta in third trimester[e6]. Women with poorly controlled asthma may have increased risk of prematurity, low birth weight, and small for gestational age in neonate. No teratogenic effects, embryo-fetal toxicity, immunologic impairment in animal studies. **Use with caution** in pregnancy due to limited safety data.
Tralokinumab	No well-controlled studies in pregnant women. Monoclonal antibodies are actively transferred across placenta in third trimester. No teratogenic effects, embryofetal toxicity, immunologic impairment in animal studies. **Use with caution** due to limited safety data.
Psoriasis (also see eTable 8.1 for additional medications)	
Certolizumab	Negligible placental transfer. Risk for adverse effects (fetal loss, preterm delivery, low birth weight) are correlated to maternal disease activity rather than certolizumab. No adverse effects in animal studies. **Likely safe** in pregnancy. Preferred choice of biologic because pegylation of antibody prevents placental transfer[e1].
Etanercept	No significant difference in spontaneous abortions or congenital malformations in women with psoriasis exposed to biologics in one study[e13]. VACTERL syndrome (vertebral anomalies, cardiac anomalies, tracheoesophageal fistula, esophageal atresia, renal abnormalities, and limb anomalies) and spontaneous abortions reported in infants with first trimester exposure. However, no clear patterns have been established in multiple studies, and it is currently thought that there is no teratogenic risk[e1]. No teratogenic effects or embryo-fetal toxicity in animal studies. **Use recommended** for severe, recalcitrant disease during pregnancy. Preferred over other non-pegylated TNF inhibitors due to fusion protein makeup which allows etanercept to cross by simple diffusion in lower levels[e1]. Uncertain if routine use is recommended due to limited safety data. Avoid live vaccines in exposed infants for the first 6 months of life[e2].
Adalimumab	No significant difference in spontaneous abortions or congenital malformations in women with psoriasis exposed to biologics in one study[e13]. Lack of pattern of major birth defects was found in infants exposed during pregnancy from a registry of pregnant women with rheumatoid arthritis or Crohn disease. Spontaneous abortions and multiple healthy deliveries have been reported[e2]. No teratogenic effects or embryo-fetal toxicity in animal studies. Monoclonal antibodies are actively transferred across placenta in third trimester[e6]. **Use recommended** for severe, recalcitrant disease during pregnancy. Consider discontinuation after 30 weeks of gestation. Uncertain if routine use is recommended due to limited safety data. Avoid live vaccines in exposed infants for the first 6 months of life[e2].
Cyclosporine	No well-controlled studies in pregnant women. Low birth weight, premature birth, spontaneous abortions, and musculoskeletal hypoplasia reported in infants exposed in early pregnancy[e6]. No renal, neural, or immune effects observed when followed to early childhood. Most of the data are from transplant patients who take higher doses than dermatologic patients. Crosses placenta. Embryo-fetal toxicity (reduced fetal weight, skeletal growth delay) at maternally toxic doses, but no teratogenic effects in animal studies. **Use recommended** only for severe maternal disease[e2].
Apremilast	No associations with congenital defects or adverse outcomes in studies. Embryo-fetal toxicity (fetal loss and incomplete skeletal ossification) at higher than MRHD, but no teratogenicity in animal studies. **Use with caution** in pregnancy due to potential adverse fetal effects and limited safety data.
Methotrexate	Associated with spontaneous abortions, congenital malformations (skull anomalies, facial dysmorphisms, central nervous system abnormalities, limb abnormalities, cardiac anomalies), and intellectual impairment with first trimester exposure. Associated with intrauterine growth restriction and functional abnormalities with second and third trimester exposure. Potential risk in fetus with preconception exposure. No animal studies that meet current standards. Benzyl alcohol is a preservative in the formulation that can cross the placenta. **Contraindicated** in pregnancy for non-neoplastic diseases; embryo-fetal toxicity warning. Use effective contraception during and 6 months after final dose. If administered intramuscularly, use preservative-free formulations, when possible, to avoid benzyl alcohol toxicity.

eTable 27.1 An overview of the use of dermatologic drugs during pregnancy and lactation.

Lactation	Female Fertility	Male Fertility	Former FDA Category
Azathioprine and metabolites are excreted in breast milk at low levels and are undetectable in infant serum. Mild asymptomatic neutropenia in infants reported, however not seen in more recent cases. **Likely compatible** with breastfeeding due to more recent reports. Wait 4 hours after taking medication. Monitor infant blood count[e3].	Limited safety data.	No infertility cases reported in humans. Normal fertility and normal semen analysis in one study[e8]. Temporary depression in spermatogenesis and reduction in sperm count in animal studies.	D
Excreted in milk in animal studies. Potential risk for infection and lymphoma in nursing infants and affects neonatal development. No reported adverse effects in nursing infants. **Contraindicated** in breastfeeding[e3].	No adverse effect on fertility in animal studies.	No adverse effects on fertility in animal studies. Men should not donate semen during therapy and for 3 months after discontinuation.	D
Excreted in breast milk in low amounts. Healthy nursing infants reported with exposure. **Use not recommended** with breastfeeding. If mother chooses to breastfeed, monitor infant for infant B cell count[e3].	Limited safety data.	Limited safety data.	C
Excreted in human milk in very low amounts. Omalizumab is a large molecule and likely destroyed in infant's gastrointestinal tract. No associations with increased infections or infestations in nursing infants. **Use with caution** due to limited safety data.	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Known that maternal IgG present in human milk. Low expected systemic exposure in infant (large molecule and degraded in infant gastrointestinal tract). **Use with caution** due to limited safety data.	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	N/A
Known that maternal IgG present in human milk. Low expected systemic exposure in infant (large molecule and degraded in infant gastrointestinal tract). **Use with caution** due to limited safety data.	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	N/A
Excreted in breast milk in exceedingly low amounts. No adverse effects reported. **Likely compatible** with breastfeeding[e1].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	N/A
Excreted in breast milk in low amounts, and minimally absorbed by infant due to large molecular weight of etanercept. No adverse effects reported with use. **Likely compatible** with breastfeeding[e3].	No adverse effects on fertility[e1].	No adverse effects on fertility.[1]	B
Excreted in breast milk in low levels. Low expected systemic exposure in infants (adalimumab is a large molecule and is likely degraded in infant gastrointestinal tract). No adverse effects in nursing infants reported. **Likely compatible** with breastfeeding[e3].	No adverse effects on fertility[e1].	No adverse effect of TNF inhibitors on fertility[e8].	B
Excreted in breast milk. Mostly undetectable levels in infant serum. No reports of adverse effects on growth, development or kidney function in nursing infants. **Use not recommended** with breastfeeding. If mother chooses to breastfeed, monitor infant for toxicity (edema, tremor, hirsutism, hypertension, seizure, and infant plasma levels)[e3].	No adverse effects on fertility in animal studies.	No reported infertility cases. Normal semen parameters and testicular function in one human study. Depressed sperm count, fertility, and testosterone in animal studies[e8]. No need to discontinue while trying to conceive[e1].	C
Excreted in animal breast milk. **Use with caution** due to limited safety data.	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	C
Excreted in breast milk in low amounts. Potential risk for infant toxicity due to retention in neonatal gastrointestinal cells and ovarian cells. **Contraindicated** in breastfeeding[e3]. Avoid breastfeeding for at least 1 week after last dose.	Reported infertility and menstrual dysfunction during and after therapy cessation. **Discontinue** 3 months prior to planning pregnancy[e1].	Risk of oligospermia and sterility, reversible 3 months after discontinuation. **Discontinue** 3 months prior to planning pregnancy[e8].	X

AN OVERVIEW OF THE USE OF DERMATOLOGIC DRUGS DURING PREGNANCY AND LACTATION	
Dermatologic Medication	**Pregnancy**
Secukinumab	No significant difference in spontaneous abortions or congenital malformations in women with psoriasis exposed to biologics in one study[e13]. No clear patterns of congenital abnormalities or spontaneous abortions were identified in pregnant women with psoriasis, psoriatic arthritis, and ankylosing spondylitis in recent post-market surveillance data[e14]. No teratogenicity or embryo-fetal toxicity in animal studies. Monoclonal antibodies are actively transferred across placenta in third trimester[e6]. **Use with caution** due to limited safety data.
Ustekinumab	No significant difference in spontaneous abortions or congenital malformations in women with psoriasis exposed to biologics in one study[e13]. No adverse effects reported in 24 infants exposed during pregnancy[e15]. No teratogenicity, embryo-fetal toxicity or adverse developmental effects in animal studies. Monoclonal antibodies are actively transferred across placenta in third trimester[e6]. **Use with caution** due to limited safety data.
Ixekizumab	No significant difference in spontaneous abortions or congenital malformations in women with psoriasis exposed to biologics in one study[e13]. Neonatal deaths due to early delivery, trauma, or congenital defects at 19× MRHD in animal studies. Monoclonal antibodies are actively transferred across placenta in third trimester[e6]. **Use with caution** due to limited safety data.
Guselkumab	No significant difference in spontaneous abortions or congenital malformations in women with psoriasis exposed to biologics in one study[e13]. Neonatal deaths at 6× and 30× MRHD in animal studies. Monoclonal antibodies are actively transferred across placenta in third trimester[e6]. **Use with caution** due to limited safety data.
Antipruritic	
Diphenhydramine	Increased risk for cleft palate in 1 study, but no associations with teratogenicity in other large studies. No adverse effects in animal studies. **Safe** in pregnancy. First line antihistamine during pregnancy. First generation antihistamines preferred over second generation[e2]. Avoid use near delivery due to sedating effects on the infant.
Cetirizine	No well-controlled studies in pregnant women. No associations with teratogenicity in large studies. No teratogenicity in animal studies. **Safe** in pregnancy. Second choice of non-sedating antihistamine in pregnancy[e2]. First generation antihistamines preferred over second generation.
Loratadine	Associated with hypospadias in one study, but not others. No teratogenicity in animal studies. Best studied antihistamine with >5000 exposed pregnancies. **Safe** in pregnancy. First choice of non-sedating antihistamine[e2]. First generation antihistamines preferred over second generation.
Hydroxyzine	Hypotension, myoclonus and movement disorders, hypoxia, central nervous system depression, and urinary retention reported in infants exposed during second half of pregnancy. Associated with a slightly increased risk of congenital anomalies with first trimester use[e2]. Crosses placenta. **Use with caution** in pregnancy due to potential adverse fetal effects.
Antiviral	
Acyclovir	Birth defects approximated general population with first trimester exposure in one study. No teratogenicity in animal studies. **Safe** in pregnancy. Use recommended for herpes simplex virus (HSV) and varicella–zoster virus during pregnancy. Use for HSV prophylaxis at 36 weeks of gestation. First choice antiviral for herpes at 400 mg 3 times daily for 7–14 days[e2].
Lice & Scabies	
Permethrin	No adverse effects reported with use. No adverse fetal effects in animal studies. Less than 2% absorbed with topical application and rapid metabolism to inactive metabolites. **Safe** in pregnancy. Use recommended for scabies (first line during pregnancy) and lice (second line during pregnancy)[e2].
Ivermectin	No well-controlled studies in pregnant women. No adverse effects reported with use. Teratogenic (cleft palate) and embryo-fetal toxic (carpal flexure, decreased fetal weight) in higher than MRHD in some, but not all, animal studies. Behavioral development abnormalities were seen at all doses in animal studies. **Use recommended** for scabies if topical therapies are ineffective[e1].
Warts	
Imiquimod	No well-controlled studies in pregnant women. No teratogenicity reported in humans. Teratogenic (exencephaly, protruding tongue, low-set ears) and embryo-fetal toxic (increased resorption, decrease fetal weight, delay in skeletal ossification, bent limb bones) at maternally toxic doses. **Use with caution** due to potential adverse fetal effects[e2].

eTable 27.1 An overview of the use of dermatologic drugs during pregnancy and lactation. (M)RHD, (maximum) recommended human dose. **Green**: Use or limited use of drug is safe in pregnancy. **Peach:** Limited use is likely safe if medically necessary or is recommended for specific indications. **Blue:** Use with caution in pregnancy due to potential adverse fetal effects. **Red:** Use is contraindicated in pregnancy. **Yellow:** Use with caution in pregnancy due to limited safety data.
Courtesy Heidi Bai, MD, and Jenny Murase, MD.

Lactation	Female Fertility	Male Fertility	Former FDA Category
Excretion in breast milk not known. Likely very low due to large molecule size and destruction in infant's gastrointestinal tract. **Use with caution** due to limited safety data.	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Undetectable or detectable at very low levels in breast milk. Likely destroyed in infant's gastrointestinal tract. **Use with caution** due to limited safety data.	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Excreted in animal breast milk. Likely very low due to large molecule size and destruction in infant's gastrointestinal tract. **Use with caution** due to limited safety data.	No adverse effects on reproductive organs or menstrual cycles in animal studies.	No adverse effects on reproductive organs or sperm in animal studies.	N/A
Excretion in breast milk is unknown. Likely very low due to large molecule size. Not excreted in animal breast milk. **Use with caution** due to limited safety data.	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	N/A
Excreted in breast milk. Short-term drowsiness and irritability reported in breastfed infants whose mothers were taking diphenhydramine, but no other adverse effects were found. **Likely compatible** with breastfeeding. Monitor infant for sedation. Second generation antihistamines preferred over first generation due to less-sedating effects[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Excreted in breast milk. **Compatible** with breastfeeding. Second generation antihistamines preferred over first generation due to less-sedating effects[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Loratadine and metabolite, descarboethoxyloratadine, excreted easily in breast milk. **Compatible** with breastfeeding. Second generation antihistamines preferred over first generation due to less-sedating effects[e3].	No adverse effects on fertility in animal studies.	Reported decrease in fertility, low sperm motility, and gynecomastia with chronic use. Reversible 3 months after discontinuation[e1].	B
Hydroxyzine metabolite, cetirizine, is excreted in breast milk. Seizures reported in breastfed infants. **Contraindicated** in breastfeeding.	Limited safety data.	Limited safety data.	C
Excreted in breast milk with oral administration. Topical application away from breast should pose negligible risk to infant. No adverse effects reported with use. **Compatible** with breastfeeding[e3].	No adverse effects on fertility in animal studies.	Reversible adverse effects on spermatogenesis in animal studies[e1].	B
No adverse effects in nursing infants over 2 months of age. **Compatible** with breastfeeding[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B
Poorly excreted in breast milk with oral administration. Neonatal toxicity in nursing animal studies, likely due to poorly developed blood–brain barriers in rats. **Compatible** with breastfeeding if topical therapies are ineffective[e3].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	C
Excretion in breast milk is not known. Not expected to cause adverse effects. **Likely compatible** with breastfeeding[e2].	No adverse effects on fertility in animal studies.	No adverse effects on fertility in animal studies.	B

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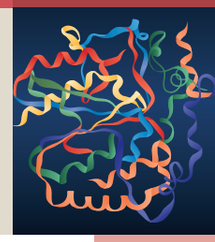
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The Biology of the Basement Membrane

28



Kim B. Yancey

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Synonyms: ■ Bullous pemphigoid antigen 1: BP230; dystonin ■ Bullous pemphigoid antigen 2: BP180; type XVII collagen ■ Laminin 311: laminin 6 ■ Laminin 332: laminin 5; epiligrin; kalinin; nicein; GB3 antigen; BM600 ■ Laminin 511: laminin 10 ■ Type VII collagen: the epidermolysis bullosa acquisita antigen ■ Nidogen: entactin

Key features

- Basement membranes serve as: (1) a substrate for cell attachment; (2) a template for tissue repair; (3) a matrix for cell migration; (4) a foundation for an infrastructure that influences differentiation, morphogenesis, and apoptosis of epithelial cell layers; and (5) a permeability barrier for cells and macromolecules
- The ultrastructural subregions of the epidermal basement membrane are: (1) basal keratinocytes with their cytoskeletons, hemidesmosomal plaques, and plasma membranes; (2) the lamina lucida, an electron-lucent region containing anchoring filaments; (3) the lamina densa; and (4) the sublamina densa region of the papillary dermis
- In the "laminated" model of the epidermal basement membrane, keratin intermediate filaments within basal keratinocytes attach to hemidesmosomes at the basal plasma membranes. Anchoring filaments connect hemidesmosomes to the lamina densa. The lamina densa is tethered to the dermis by anchoring fibrils that begin and end on the underside of the lamina densa, forming ultrastructural loops that also serve as attachment sites for fibrillar proteins in the papillary dermis
- Acquired or inherited abnormalities in structural proteins within the epidermal basement membrane often result in a disease phenotype characterized by blister formation

INTRODUCTION

Basement membranes are specialized structures located between cells and their underlying stroma or between different cell types[1]. Basement membranes of various tissues differ ultrastructurally, biochemically, and functionally. All basement membranes contain an electron-dense, somewhat granular matrix of variable thickness called the lamina densa. Major components of the lamina densa include type IV collagen, laminins, and heparan sulfate proteoglycans. Other components of the lamina densa vary depending upon the tissue type.

Basement membranes serve a variety of functions that are manifest in a tissue-specific manner. Functions common to virtually all basement membranes include (1) substrates for cell attachment; (2) templates for tissue repair; (3) matrices for cell migration; (4) substrata that influence differentiation, morphogenesis, and apoptosis of epithelial cell layers; and (5) permeability barriers for cells and macromolecules. In the skin, the two major basement membrane complexes are found at the epidermal–dermal interface and around the dermal microvasculature. This chapter will deal largely with the epidermal basement membrane.

The epidermal basement membrane is a highly specialized structure that contains numerous tissue-specific elements (Table 28.1). The first characterization of this ultrastructural region in the skin was made via electron microscopy, which identified four distinct subregions of the epidermal basement membrane (Fig. 28.1). From superior to inferior, they are:

- basal keratinocytes with their cytoskeletons, hemidesmosomal plaques, and plasma membranes;
- the lamina lucida, an electron-lucent region that contains delicate anchoring filaments; the latter connect hemidesmosomes (HDs) in basal keratinocytes to the underlying lamina densa;
- the lamina densa; and
- the sublamina densa region that contains anchoring fibrils, anchoring plaques, and filamentous proteins of the papillary dermis.

These subregions of the epidermal basement membrane, readily identified in fixed skin samples by transmission electron microscopy, have served as a useful conceptual model of a highly complex adhesion unit that preserves the integrity of the skin (Fig. 28.2). Interestingly, specialized transmission electron microscopy studies of cryopreserved skin have suggested that the lamina lucida may actually represent an artifact of tissue dehydration[2]. Nonetheless, the classic laminated model of the epidermal basement membrane serves as a useful framework for understanding its structure, function, and impairment in disease.

ORIGIN OF THE EPIDERMAL BASEMENT MEMBRANE

The epidermal basement membrane is comprised of proteins derived from both keratinocytes of ectodermal origin and dermal fibroblasts of mesodermal origin. *Basal keratinocytes* produce hemidesmosomal components such as plectin, the epidermal isoform of bullous pemphigoid antigen 1 (BPAG1e), bullous pemphigoid antigen 2 (BPAG2; collagen XVII), and integrin subunits α_6 and β_4; they also contribute CD151 tetraspan, types IV and VII collagen, laminins 332 and 311, and heparan sulfate proteoglycans to the epidermal basement membrane. *Dermal fibroblasts* produce nidogen, types IV and VII collagen, and other proteins that are translocated to the plasma membranes of basal keratinocytes where they condense and are incorporated within the basement membrane. Integrins and other proteins within the plasma membrane of basal keratinocytes provide key localization and organizational cues that facilitate the incorporation of fibroblast-derived proteins into the basement membrane. The major proteins of the epidermal basement membrane are described below (Fig. 28.3).

BASAL KERATINOCYTES: HEMIDESMOSOME-ANCHORING FILAMENTS AND INTEGRINS

Plectin

Plectin is a 500 kDa, dumbbell-shaped, dimeric protein associated with the cytoplasmic plaque of HDs[3]. Like BPAG1, desmoplakin, periplakin, and envoplakin (see Ch. 29), plectin is a member of the plakin family. Plakins are large, multidomain cytolinkers that connect cytoskeletal networks to each other and to adhesive junctions such as desmosomes and HDs[4].

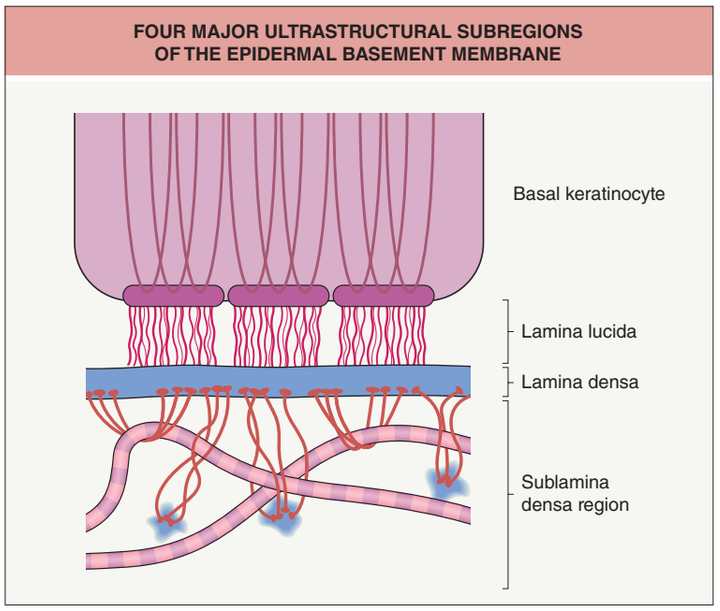


Fig. 28.1 Four major ultrastructural subregions of the epidermal basement membrane. The major ultrastructural subregions of the epidermal basement membrane consist of the following: (1) cytoskeleton, hemidesmosomal plaques, and plasma membranes of basal keratinocytes; (2) electron-lucent lamina lucida; (3) lamina densa; and (4) sublamina densa region of the papillary dermis.

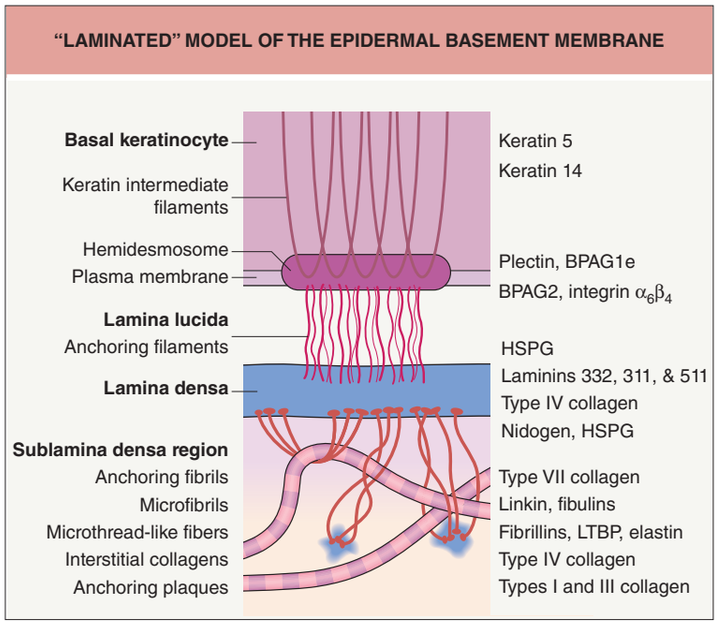


Fig. 28.2 "Laminated" model of the epidermal basement membrane. In the laminated model, keratin intermediate filaments attach to electron-dense hemidesmosomes on the basal plasma membranes of keratinocytes. Hemidesmosomes connect to the underlying lamina densa by small thread-like strands termed anchoring filaments. The lamina densa and the overlying epidermis are tethered to the papillary dermis by anchoring fibrils, a series of looping elements along the underside of the lamina densa that serve as attachment sites for fibrillar proteins in the papillary dermis. HSPG, heparan sulfate proteoglycans; LTBP, latent TGF-β-binding proteins.

The carboxy terminus of plectin binds keratin and vimentin intermediate filaments, whereas its amino terminus contains domains that bind the cytoplasmic tail of integrin subunit β_4, BPAG2, and actin. Mutations in the gene encoding plectin underlie forms of epidermolysis bullosa (EB) simplex that may be associated with muscular dystrophy or pyloric atresia (see Ch. 32). In mice, targeted inactivation of the gene encoding plectin impairs the cytoarchitecture of skin, muscle, and heart[5].

REPRESENTATIVE ADHESION PROTEINS IN THE EPIDERMAL BASEMENT MEMBRANE
Cytoskeleton of basal keratinocytes
• Keratin 5 • Keratin 14
Hemidesmosome-anchoring filament complexes
• Plectin • Bullous pemphigoid antigen 1e • Bullous pemphigoid antigen 2 (type XVII collagen) • Integrin subunit α_6 • Integrin subunit β_4 • Tetraspan CD151 • Laminin 332
Lamina densa
• Heparan sulfate proteoglycans (e.g. perlecan) • Laminin 332 (formerly laminin 5) • Laminin 311 (formerly laminin 6) • Laminin 511 (formerly laminin 10) • Nidogen • Type IV collagen
Sublamina densa region
• Type VII collagen • Type IV collagen • Elastin • Fibulins (glycoproteins found in microfibrillar bundles in the papillary dermis) • Fibrillins (large proteins that form an integral part of the microfibril structure) • Latent TGF-β-binding proteins • Linkin (main component of microthread-like fibers that comprise a delicate mesh-like network in the upper papillary dermis) • Type III collagen • Type I collagen

Table 28.1 Representative adhesion proteins in the epidermal basement membrane. TGF-β, transforming growth factor β.

Bullous Pemphigoid Antigen 1

Circulating autoantibodies from patients with bullous pemphigoid (BP) were used to define two autoantigens that reside in HDs of basal keratinocytes. The first of these autoantigens characterized, BPAG1e, is a 230 kDa plakin protein localized to the cytoplasmic plaque of HDs[6,7]. It has a central coiled-coil α-helical rod domain that contains a regular periodicity of acidic and basic amino acid residues. Studies showing that the periodicities of these residues are 180 degrees out of phase suggested that these proteins may self-aggregate by ionic interactions. The globular carboxy terminus of BPAG1e contains acidic and basic amino acids with a periodicity that promotes association with keratin intermediate filaments. The amino terminus of BPAG1e associates with the cytoplasmic domain of BPAG2, integrin subunit β_4, and ERBIN. The ERBIN protein interacts with the transmembrane tyrosine kinase receptor Erb-B2, thus serving as a potential link between HD biology and Erb-B2 signaling[4].

Consistent with the role that BPAG1e plays in cytoskeletal organization, BPAG1 knockout mice show signs of epithelial fragility in basal keratinocytes[8]. Unexpectedly, these mice also demonstrate neurologic impairment characterized by dystonia and ataxia, which results from concomitant inactivation of neuronal isoforms of BPAG1 (BPAG1n). The amino termini of BPAG1n differ from their epidermal counterpart in that BPAG1n contains actin- or microtubule-binding domains essential for maintaining the cytoarchitecture of neurons. Homozygous nonsense *BPAG1* mutations that affect only BPAG1e underlie a form of EB simplex[9].

Bullous Pemphigoid Antigen 2

BPAG2 (collagen XVII) is a transmembrane collagen associated with HD-anchoring filament complexes in basal keratinocytes[10]. The cytoplasmic amino terminus of BPAG2 consists of ~500 amino acid residues, with several potential phosphorylation sites within its central

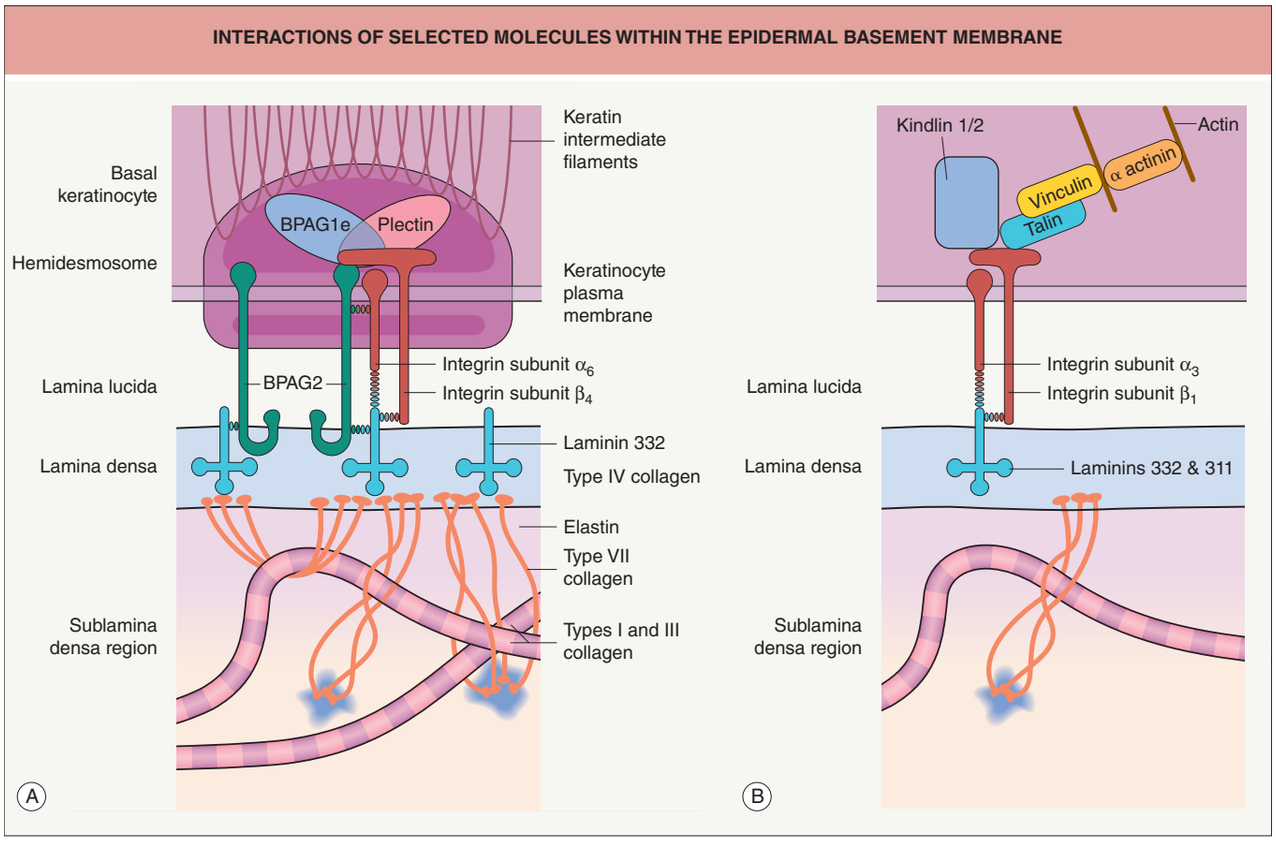


Fig. 28.3 Interactions of selected molecules within the epidermal basement membrane. A Important molecular interactions include: (1) plakin family members, BPAG1e and plectin, with keratin intermediate filaments; (2) plakin family members with BPAG2 and integrin $\alpha_6\beta_4$ (specifically, the large cytoplasmic domain of integrin subunit β_4); (3) the cytoplasmic domains of BPAG2 with integrin subunit β_4; (4) the extracellular domains of BPAG2 with integrin subunit α_6 and laminin 332; (5) integrin $\alpha_6\beta_4$ in hemidesmosomes with laminin 332 in the lamina densa; (6) laminin 332 with type VII collagen; (7) type VII collagen with type IV collagen, fibronectin, and type I collagen in the sublamina densa region. **B** In focal adhesion complexes, laminins 332 and 311 bind integrin $\alpha_3\beta_1$, which is associated with intracellular proteins such as kindlins, talin, vinculin, and, in turn, the actin microfilament network.

portion. The extracellular domain of BPAG2 contains 15 interrupted repeats that have multiple glycine-X-Y amino acid sequences; these are characteristic of collagen family proteins and therefore referred to as collagenous domains (coll 1–15; see Fig. 31.9). By rotary shadowing, the intracytoplasmic domain of BPAG2 appears as a globular head and the extracellular region as a central rod (coll 15) with a flexible tail (coll 1–14)[11]. Immunoelectron microscopy studies suggest that the coll 15 rod domain of BPAG2 inserts into the lamina densa and that its carboxy-terminal tail then loops back through the lamina densa into the lamina lucida (see Fig. 28.3)[12,13].

BPAG2 occurs in two forms[14]: (1) a 180 kDa full-length protein; and (2) a 120 kDa extracellular domain that is shed from plasma membranes of basal keratinocytes via proteolysis. Proteolytic processing of BPAG2 is mediated by "sheddases" of the *a d*isintegrin *a*nd *m*etalloproteinase (ADAM) family, in particular ADAM metallopeptidase domain 17 (ADAM17). Phosphorylation of BPAG2 by ecto-casein kinase 2 inhibits its proteolysis by ADAM17, a mechanism whereby the adhesion and motility of adjacent basal keratinocytes may be modulated[15].

In the epidermal basement membrane, the extracellular domain of BPAG2 is found as a homotrimer in which the collagenous domains form a cross-linked triple helix. The helix forms independently of amino acid sequences in the amino terminal portion of BPAG2 and is organized in a 5′ to 3′ orientation using the 16th *n*on-*c*ollagenous portion of the protein (NC16) as a nucleation site[16]. The cytoplasmic domain of BPAG2 associates with BPAG1e, integrin subunit β_4, and plectin[4]. The first extracellular segment of BPAG2 (NC16) contains 73 amino acid residues that bind integrin subunit α_6[17]. Immunogold electron microscopy studies have suggested that the carboxy-terminal portion of BPAG2 interacts with laminin 332 at the interface of these two proteins near the junction of the lamina lucida and the lamina densa (see Fig. 28.3)[12].

BPAG2 is targeted by autoantibodies from patients with BP, gestational pemphigoid, mucous membrane pemphigoid (MMP), and linear IgA bullous dermatosis (LABD)[18]. Autoantibodies from patients with BP, gestational pemphigoid, and LABD typically target the NC16A domain of BPAG2 (see Fig. 31.9). In contrast, the autoantibodies responsible for MMP tend to target the distal carboxy terminus of BPAG2, which extends deeper into the basement membrane, as well as NC16A. Patients with less severe subtypes of junctional EB often possess null mutations in the gene encoding BPAG2 (*COL17A1*) (Table 28.2). These individuals characteristically demonstrate a complete lack of BPAG2 in their epidermal basement membrane, along with a tendency for skin fragility, subepidermal blister formation, alopecia, dystrophic nails, and dental enamel hypoplasia[19]. Interestingly, *COL17A1* mutations resulting in deletion of the intracellular domain of BPAG2 that associates with BPAG1e, plectin, and integrin subunit β_4 result in a phenotype characterized by intraepidermal as well as junctional blister formation[20].

Integrins

Integrins are heterodimeric transmembrane receptors that promote cell–cell and cell–matrix interactions[21]. Ligand binding to integrin receptors modulates cell adhesion and growth, signal transduction, gene expression, and other fundamental biologic processes. All integrins are αβ-heterodimers. Numerous α- and β-subunits have been identified; several of these have alternatively spliced cytoplasmic domains (e.g. α_1, α_3, α_4, α_6, α_{11b}). Although some of the α-subunits can associate with more than one β-subunit, the number of heterodimers formed is limited.

Both α- and β-integrin subunits are glycoproteins with a single hydrophobic *transmembrane* domain and a *cytoplasmic* domain that is typically composed of ≤50 amino acid residues, although integrin subunit β_4 has a larger cytoplasmic domain of >1000 amino acid residues. Cytoplasmic domains of integrins typically interact with the actin cytoskeleton (see below) and other intracellular proteins. The

TARGETS COMMON TO AUTOIMMUNE AND INHERITED BLISTERING DISEASES			
Protein	**Structure**	**Autoimmune disease**	**Genetic disease**
BPAG1e	HD	BP	Recessive EB simplex
Type XVII collagen (BPAG2)	HD-anchoring filament complexes	BP, PG, MMP, linear IgA bullous dermatosis	Junctional EB (often milder)
Integrin subunit β_4	HD-anchoring filament complexes	Ocular MMP	Junctional EB with pyloric atresia
Laminin 332	Lamina lucida–lamina densa interface	Anti-epiligrin MMP	Junctional EB (often more severe)
Type VII collagen	Anchoring fibrils	EB acquisita Bullous eruption of SLE	Dystrophic EB (dominant and recessive)

Table 28.2 Targets common to autoimmune and inherited blistering diseases. BP, bullous pemphigoid; EB, epidermolysis bullosa; HD, hemidesmosome; MMP, mucous membrane (cicatricial) pemphigoid; PG, pemphigoid gestationis; SLE, systemic lupus erythematosus.

cytoplasmic domains and associations of integrin $\alpha_6\beta_4$ represent an exception to this model in that they are concentrated within HDs of epithelial cells[21].

The *extracellular* domains of integrin subunits associate to form heterodimers. The α- and β-subunits form a pocket that serves as a specific ligand-binding site, and switching either subunit can change ligand specificity. Particular integrin heterodimers can often bind to more than one ligand, and similarly, individual ligands are often recognized by more than one integrin. Integrins usually bind specific peptide sequences in a given group of adhesion molecules, such as the Arg-Gly-Asp (RGD) sequence in fibronectin and vitronectin. Integrin ligand binding is dependent on divalent cations (e.g. Ca^{2+}, Mg^{2+}, Mn^{2+}), and the cations can affect the affinity and the ligand specificity of the integrin.

Integrin-mediated cell–cell and cell–matrix adhesion triggers clustering of integrins and the assembly of signaling and adapter proteins at their cytoplasmic domains. This process creates an "outside in" signaling complex that conveys biochemical messages to different cellular compartments and links the integrin adhesion site to the actin cytoskeleton. In addition, an "inside out" signaling process fine-tunes affinity for extracellular ligands by altering the conformation of integrin ectodomains. Proteins that serve as major "inside out" integrin activators include talins and kindlins[22]. In basal keratinocytes, kindlin-1 and -2 and other proteins such as vinculin can form integrin-tethered macromolecular complexes termed *focal adhesions* through which the actin cytoskeleton connects to the extracellular matrix (see Fig. 28.3B).

Mutations in *FERMT1*, which encodes kindlin-1, are responsible for Kindler EB (Kindler syndrome), an autosomal recessive disease characterized by trauma-induced blistering, photosensitivity, poikiloderma, variable mucosal involvement, and increased risk of mucocutaneous squamous cell carcinoma (see Ch. 32)[23]. Lack of kindlin-1 in human keratinocytes results in defective signaling by Rho GTPases involved in remodeling the actin cytoskeleton and impaired adhesion due to reduced activity of the β_1 integrin subunit. Loss of kindlin-1 in mouse keratinocytes leads to decreased $\alpha_v\beta_6$ integrin-mediated transforming growth factor-β (TGF-β) activation and increased Wnt signaling, thereby stimulating cutaneous stem cell proliferation and contributing to skin cancer risk and cutaneous atrophy due to stem cell exhaustion[24].

Hemidesmosome-associated integrin $\alpha_6\beta_4$

The large cytoplasmic tail of integrin subunit β_4 contains sequences required for HD assembly; the membrane-proximal region directly associates with plectin, while the distal carboxy-terminal region binds BPAG2 (see Fig. 28.3)[21]. The proximal extracellular domain of integrin subunit α_6 binds the NC16A region of BPAG2[17]. Laminins 111 and 332 serve as the preferred ligands for this HD-integrin[25].

Patients harboring biallelic mutations in genes encoding either α_6 or β_4 integrin subunits develop junctional EB with pyloric atresia. They typically have subepithelial blistering of the oral and respiratory epithelia as well as the skin. Targeted deletions of genes encoding integrin subunits α_6 or β_4 in mice result in subepithelial blisters of the same tissues. The degeneration of basal keratinocytes observed in β_4-null mice suggests that this integrin subunit also plays a role in cell survival[26]. Transgenic mice carrying a targeted deletion of the cytoplasmic domain of integrin subunit β_4 have a proliferative defect of stratified and simple epithelia[27]. However, deletion of integrin subunit α_6 does not lead to developmental deficiencies in mouse epithelia.

Plasma membrane-associated integrins

Non-hemidesmosomal integrins expressed in basal keratinocytes include integrins $\alpha_2\beta_1$ and $\alpha_3\beta_1$. Both of these integrins are found along the lateral and apical aspects of these cells' plasma membranes, with additional basal localization for $\alpha_3\beta_1$[21]. Integrins bind the actin cytoskeleton and play a key role in cell–cell adhesion. Keratinocytes in culture utilize integrin $\alpha_3\beta_1$ to mediate initial adhesion to extracellular matrix via interaction with laminin 332.

Although integrin $\alpha_3\beta_1$ does not play a role in HD assembly, it provides key signals that regulate cytoskeletal assembly, function of integrin $\alpha_6\beta_1$, and the establishment and maintenance of basement membrane integrity[28]. Mice with targeted deletion of integrin subunit α_3 have disorganized basement membranes in the kidney as well as in the skin and exhibit mild blistering[29]. In these mice, the lamina densa appears normal beneath HDs but is missing (or sparse) between HDs. Homozygous mutations in the gene encoding the α_3 integrin subunit underlie a human disorder characterized by basement membrane disruption resulting in congenital nephrotic syndrome, interstitial lung disease, and a mild form of EB[30].

Tetraspan CD151

CD151 is a cell surface protein that belongs to the tetraspan superfamily, named for their four membrane-spanning domains. These proteins form "web-like" networks with other membrane proteins and regulate a variety of cellular processes. CD151, which is concentrated in HDs, associates with integrins $\alpha_6\beta_4$ in HDs and $\alpha_3\beta_1$ in the basolateral plasma membrane of basal keratinocytes.

In integrin subunit β_4-deficient keratinocytes, CD151 clusters with $\alpha_3\beta_1$ at the basal cell surface. Introduction of integrin subunit β_4 into the latter cells yields $\alpha_6\beta_4$ integrins that become incorporated into $\alpha_3\beta_1$–CD151 clusters, where they presumably induce the formation of HDs. Soon thereafter, the amount of $\alpha_3\beta_1$ integrins in such clusters diminishes, and CD151 becomes predominantly associated with $\alpha_6\beta_4$ integrins within HDs. CD151 is therefore considered to be a component of pre-HDs whose recruitment is regulated by integrin $\alpha_6\beta_4$. CD151 is also thought to provide a framework for the spatial organization of different HD components[31].

THE LAMINA DENSA

Laminins

Laminins are a family of heterotrimeric glycoproteins composed of at least 15 members in mammals[32]. Laminins consist of three subunits (α, β, and γ) that are joined and stabilized by interchain disulfide bonds and other associations (Fig. 28.4). Each laminin subunit is encoded by a different gene. To date, five α-, four β-, and three γ-subunits have been characterized[32]. Of note, the laminin α3 subunit gene (*LAMA3*) encodes two transcripts, α3A (short variant) and α3B (long variant).

Different laminin isoforms are created by the pairing of various α-, β-, and γ-subunits. In the current laminin nomenclature, each isoform's name reflects the numbers of its α-, β-, and γ-subunits (e.g. α3, β3, and γ2 in laminin 332, formerly termed laminin 5). Laminin isoforms are distributed in a tissue-specific manner, each having a variety of biologic functions. Laminins within basement membranes serve as ligands for overlying cell surface receptors (e.g. integrins), thereby providing key signals regarding the epithelial microenvironment.

The predominant laminins in epidermal basement membranes are 332 (α3β3γ2), 311 (α3β1γ1), and 511 (α5β1γ1). The overall structure of laminins is presented in Fig. 28.4 using laminin 111 (α1β1γ1), a primary component of dermal microvascular (but not epidermal)

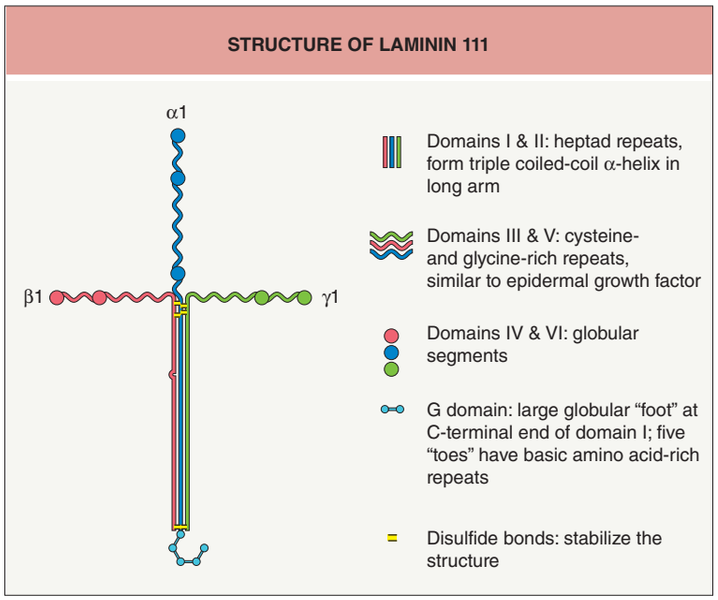


Fig. 28.4 Structure of laminin 111. Laminin 111 (laminin 1) serves as a prototype for the other laminin isoforms, which have similar structure and organization. Laminins consist of three subunits (α, β, γ), each encoded by a different gene and composed of six primary domains (domains I to VI).

basement membranes, as a prototype. The salient features of the laminin isoforms are summarized in Table 28.3[32–38].

The essential role that laminin 332 plays in the epidermal basement membrane is exemplified by inherited disruptions in the genes that encode its subunits (*LAMA3, LAMB3, LAMC2*), which lead to subtypes of junctional EB characterized by subepidermal blister formation and often early death in the more severe forms[19]. Moreover, patients with one form of mucous membrane pemphigoid (MMP) have IgG anti-basement membrane autoantibodies against laminin 332[39,40]. Passive transfer of rabbit anti-laminin 332 IgG to mice or patient IgG to grafts of human skin on immunodeficient mice elicit non-inflammatory subepithelial blisters with clinical, histologic, and immunopathologic features like those seen in patients with this form of MMP[41,42].

Type IV Collagen

Type IV collagen is a unique macromolecule that is specifically localized within basement membranes[1,43]. The structure of type IV collagen most closely resembles a procollagen, an intracellular form that retains globular domains at its amino and carboxy termini. Accordingly, type IV collagen links head-to-head rather than in parallel. Like all collagens, type IV collagen consists of three α-chain subunits; these subunits can be identical or genetically distinct but structurally related. To date, six type IV collagen α-chain subunits have been identified – polypeptides α_1(IV)–α_6(IV), with the corresponding genes *COL4A1–COL4A6*. The subunits of type IV collagen appear to be distributed in three major networks: (1) α_1 and α_2 in skin, smooth muscle, and glomerular basement membranes; (2) α_3, α_4, and α_5 in the glomerular basement membrane; and (3) α_5 and α_6 in skin and smooth muscle basement membranes.

Like all collagens, the α-chain subunits of type IV collagen associate to form a triple-helical structure[1]. The stability of this triple helix is dependent upon characteristic repeating glycine-X-Y amino acid sequences, accompanying residues rich in proline, and post-translational hydroxylation to hydroxyproline (see Ch. 95). The resulting triple helix has an extended, somewhat rigid conformation that is resistant to "ordinary" proteases (e.g. trypsin) and sensitive to specialized proteases (i.e. collagenases). Unlike classic fibrillar collagens, type IV collagen is not helical through its entire length. Short discontinuities in glycine-X-Y repeats within its α-subunits create non-helical domains that confer increased flexibility to this macromolecule as well as sites susceptible to damage by "ordinary" proteases.

The procollagen-like retained globular domains at the ends of type IV collagen are the 7S domain at the amino terminus and the smaller non-collagenous 1 (NC1) domain at its carboxy terminus[1]. The macromolecular structure of type IV collagen resembles a "hockey stick", where the blade of the stick corresponds to the amino-terminal 7S domain, the handle corresponds to the largely continuous triple-helical portion of the molecule, and the handle grip corresponds to the short globular NC1 domain at its carboxy terminus[1]. This model is particularly useful when one relates the lattice structure of type IV collagen matrices to an arrangement of hockey sticks created by: (1) the overlapping of four 7S blades to create a type IV collagen "spider" in which the handles are oriented at roughly right angles to each other; and (2) the subsequent polymerization of "spiders" at sites of their abutting carboxy termini (the handle grips/ends of the spiders' "legs") (Fig. 28.5). Such end-to-end, antiparallel interactions result in a two-dimensional type IV collagen lattice that serves as a key matrix within the lamina densa.

Defective type IV collagen underlies several diseases of basement membranes. For example, most patients with Alport syndrome (characterized by hematuria, progressive renal failure, sensorineural hearing loss, and occasionally ocular abnormalities) have mutations in *COL4A5* which encodes α_5(IV). In addition to this X-linked form of Alport syndrome, an autosomal recessive form is caused by mutations in *COL4A3* or *COL4A4*, and a rare autosomal dominant variant by mutations in *COL4A3*.

Goodpasture disease, a potentially lethal autoimmune disorder characterized by pulmonary hemorrhage and glomerulonephritis, is caused by anti-basement membrane antibodies directed against the NC1 domain of α_3(IV) and α_5(IV)[44]. Exposure of potentially pathogenic epitope(s) within α_3(IV) and/or α_5(IV) by infections or other events may represent an essential element in the development of this disease. Interestingly, antibodies against α_5(IV) ± α_6(IV) can cause a rare disorder characterized by subepidermal blisters and glomerulonephritis[45].

Fragments of type IV collagen α-chain subunits have important biologic activities. Canstatin, a basement membrane-derived fragment of α_2(IV), inhibits angiogenesis, lymphangiogenesis, and tumor growth[46]. Another example is tumstatin, a matrikine derived from the NC1 domain of α_3(IV) that possesses antiangiogenic and proapoptotic activities. Of note, peptides liberated by partial proteolysis of extracellular matrix macromolecules are termed matrikines[47].

Nidogen

Nidogen is a dumbbell-shaped 150 kDa glycoprotein localized to the lamina densa of basement membranes (see Fig. 28.5). Nidogen binds laminin isoforms containing the γ1-subunit (e.g., laminins 111, 311, 511; see Table 28.3) with high affinity. More specifically, the G3 domain at the carboxy terminus of nidogen binds the cysteine-rich, epidermal growth factor-like repeat in domain III of the γ1-subunit[34]. In addition, the G2 domain at the amino terminus of nidogen binds with high affinity to type IV collagen. Complexes of nidogen and laminin can also bind the core protein of heparan sulfate proteoglycans (HSPGs) such as perlecan as well as fibulins 1 and 2. Nidogen is therefore thought to stabilize various macromolecules within the lamina densa. Although traditionally nidogen has been postulated to link type IV collagen and laminin networks, more recent studies have found that perlecan (see below) may have a more important role in this connection[48] (see Fig. 28.5).

A second form of nidogen (nidogen 2) has ~45% identity with classic nidogen and is thought to link fibulins to HSPGs as well as to types I and IV collagen[49]. No autoimmune or inherited blistering diseases have been linked to nidogen, and mice engineered to lack nidogen 1 have no obvious abnormalities.

Heparan Sulfate Proteoglycans

Heparan sulfate proteoglycans (HSPGs) are a diverse group of macromolecules that are ubiquitous components of basement membranes. They are found within, immediately above, and just below the lamina densa of the epidermal basement membrane[1]. HSPGs consist of a central core protein that is lined with laterally emanating glycosaminoglycans in a so-called "bottle-brush" configuration (see Ch. 95)[1]. Different basement membranes contain HSPGs of various types and configurations. HSPGs interact with multiple components of the lamina densa and self-polymerize to contribute to the basement membrane matrix. The high sulfate content of HSPGs confers a negative charge to basement

FEATURES OF SELECTED LAMININS						
Laminin isoform (αβγ)*	**Previous numerical name†**	**Other names**	**Molecular weight, KDa**	**Processing, structure and assembly**	**Distribution**	**Interactions and functions**
111	1	EHS laminin, "classic" laminin	~800 (α: ~400; β: ~220; γ: ~210)	• Asymmetric cross: 3 short arms, 1 long arm (see Fig. 28.4) • Self-assembles into a network *in vitro*	• Dermal microvascular BMs • Little or none in epidermal BM	• Diverse biologic functions, largely mediated by interactions with integrin receptors
332	5	Epiligrin, kalinin, nicein, GB3 antigen, BM600	~410 (α: 200 for precursor/165 post processing; β: 140; γ: 155 for precursor/105 post processing)	• Cell-associated precursors of the α3- & γ2-subunits are processed following secretion • α3-subunit is truncated, lacks key N-terminal domains, and has a small G domain • β3-subunit is homolog of β1-subunit but does not undergo processing after secretion and has a truncated short arm • γ2-subunit's aa sequence has ~50% identity to that of the γ1-subunit, but the former's domains are truncated (I, II, III, IV, V) or absent (VI) • *Not* able to self-assemble into networks	• Found at interface of lamina lucida and lamina densa in epidermal BM • Produced and secreted by growing/migrating keratinocytes • Also in BMs of the trachea, gastrointestinal tract and amnion	• Attaches keratinocytes to the epidermal BM • γ2-subunit *lacks* domain that binds nidogen; instead, N-terminus of laminin 332 covalently associates with the branch points of the short arms of laminins 311 and 511, forming a complex that contains binding sites for nidogen (on γ1-subunit) and polymerization (on β_1-, β_2-, & γ_1-subunits) (see Fig. 28.5) • α3-subunit's G domain (positioned superiorly in epidermal BM) binds integrins $\alpha_6\beta_4$ (in HDs; see Fig. 28.3) and $\alpha_3\beta_1$ (in plasma membrane) • β3- or γ2-subunits of monomeric laminin 332 can bind the N-terminal NC1 domain of type VII collagen of anchoring fibrils (see Fig. 28.3) • Thereby links HD-anchoring filament complexes with underlying anchoring fibrils
311	6		~600 (α: 200 for precursor/165 post processing; β: ~220; γ: ~210)	• See above for processing and structure of α3-subunit	• As for laminin 332	• Joined with laminin 332 in a disulfide-bonded complex (see above) • Connected to type IV collagen and other molecules in the lamina densa via nidogen bound to the γ1-subunit (see Fig. 28.5)
511	10		~640–880 (α: 450 for precursor/210–380 post processing; β: ~220; γ: ~210)	• α5-subunit is thought to be processed	• BMs of many tissues	• Interacts with integrin $\alpha_3\beta_1$ and α-dystroglycan • Expressed in basement membranes of the interfollicular epidermis and dermal microvascular endothelial cells • Crucial for hair morphogenesis

*Each isoform's name reflects the numbers of its α-, β- and γ-subunits.
†Numbers reflect the order of the isoforms' discovery.

Table 28.3 Features of selected laminins[32–38]. aa, amino acid; BM, basement membrane; C-terminal, carboxy-terminal; EHS, Engelbreth–Holm–Swarm (a mouse tumor from which laminin 111 was initially isolated); G domain, globular segment at C-terminal end of domain I; HD, hemidesmosome; NC1, non-collagenous 1; N-terminal, amino-terminal.

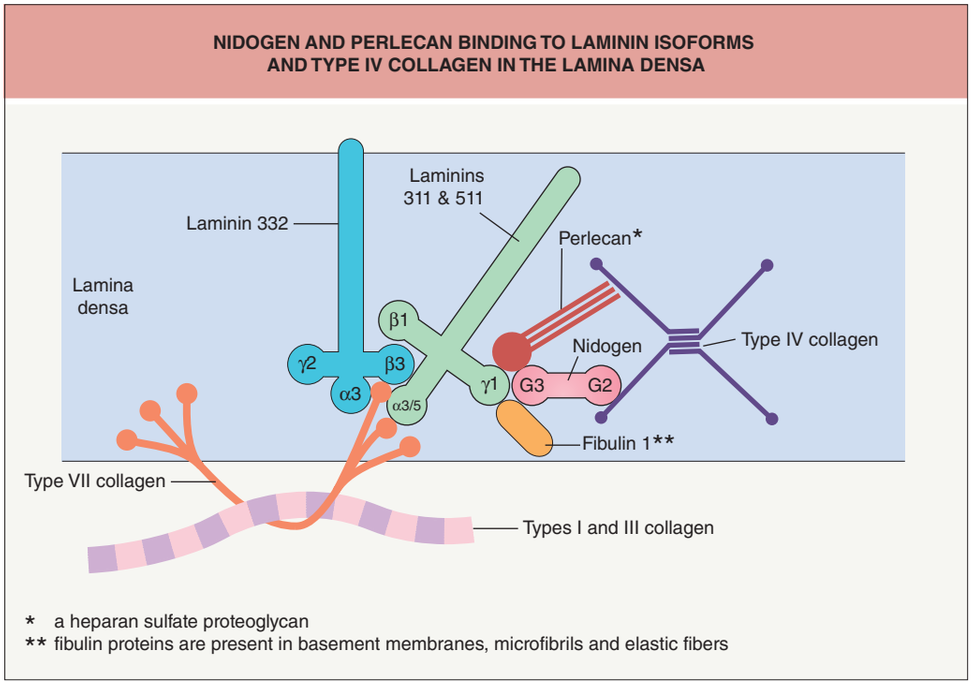


Fig. 28.5 Nidogen and perlecan binding to laminin isoforms and type IV collagen in the lamina densa. Nidogen binds both the γ-subunit of laminin 311 and type IV collagen, while nidogen–laminin complexes bind fibulins and heparan sulfate proteoglycan (HSPG) core proteins. Perlecan, an HSPG, is thought to have an important role in "spot welding" laminin and type IV collagen networks together. Laminin 332, which lacks the γ-domain required for nidogen binding, is stably bound to the basement membrane via a covalent association with the branch points of the short arms of laminin 311. A type IV collagen tetramer "spider" is created by the overlap of four amino terminal "hockey stick blade" domains. Such tetramers polymerize via their carboxy termini to create a macromolecular lattice within the lamina densa. Note that this figure is not drawn to scale.

membranes and thereby restricts their permeability. Perlecan is the best-characterized basement membrane HSPG and it is thought to "spot weld" laminin- and collagen IV-containing networks together (see Fig. 28.5)[48].

ANCHORING FIBRILS AND THE SUBLAMINA DENSA REGION

Type VII Collagen

Type VII collagen is restricted to the basement membrane of stratified squamous epithelia, where it localizes to the sublamina densa region[1]. It is the major component of anchoring fibrils and consists of three identical α-chains, each with a molecular weight of ~290 kDa[50]. Type VII collagen contains two non-collagenous domains: (1) the large, globular NC1 at its amino terminus; and (2) the smaller NC2 at its carboxy terminus (see Ch. 95).

The assembly of anchoring fibrils initiates when NC2 "tails" of individual type VII collagen molecules align in an antiparallel fashion and unite via disulfide bonds[1]. Once these tail-to-tail dimers form, the NC2 domain is proteolytically cleaved, leaving a long thread-like macromolecule characterized by a central rod with large globular NC1 domains at each end. Newly formed type VII collagen dimers then aggregate laterally with other dimers to form bundles resembling "wheat-stacks", which are termed anchoring fibrils (see Fig. 28.2). The globular NC1 domains in anchoring fibrils bind the lamina densa at one end, and the other end either loops back into the lamina densa or connects to electron-dense elements in the sublamina densa region termed anchoring plaques (see Fig. 28.2). Anchoring plaques are thought to represent portions of the lamina densa that have "dropped out" and fallen into the sublamina densa region as a consequence of basement membrane remodeling[51]. On a molecular level, specific subdomains within the NC1 domains of type VII collagen demonstrate affinity for type I fibrillar collagen in the dermis as well as type IV collagen in the lamina densa and anchoring plaques[52,53]. Type VII collagen also interacts with laminin 332, as outlined in Table 28.3[38]. The network of looping bands and tethers formed by anchoring fibrils connects the lamina densa with a series of fibrillar elements in the sublamina densa region.

The gene encoding type VII collagen, *COL7A1*, contains 118 exons but is compact due to its small introns. Mutations in *COL7A1* cause both dominant and recessive forms of dystrophic EB[54] (see Ch. 32). Patients with severe recessive dystrophic EB typically have mutations that lead to premature termination codons and nonsense-mediated mRNA decay, resulting in no detectable type VII collagen. Accordingly, these patients have no anchoring fibrils and manifest extreme skin fragility, mutilating scars, and an increased risk for cutaneous squamous cell carcinomas. Carriers of recessive dystrophic EB harbor only one mutant allele and produce sufficient amounts of type VII collagen from their normal allele to maintain basement membrane integrity and a normal skin phenotype. In contrast, patients with dominant dystrophic EB usually have a missense mutation in one *COL7A1* allele that creates a dominant-negative effect on protein derived from their other, normal *COL7A1* allele. Most dominant-negative *COL7A1* mutations result in glycine substitutions at critical points in the collagenous portion of type VII collagen. These abnormal proteins are incorporated (together with normal α-chains subunits) into type VII collagen trimers and disrupt their function. Consequently, patients with dominant dystrophic EB produce abnormal-appearing and/or reduced numbers of anchoring fibrils and demonstrate a blistering phenotype that is usually less severe than that seen in patients with recessive dystrophic EB.

EB acquisita (EBA) is an autoimmune subepidermal bullous disease in which blisters form in the sublamina densa region, usually as the result of mechanical trauma[55]. The antigen targeted in EBA is type VII collagen, and anti-type VII collagen IgG antibodies from most EBA patients bind four immunodominant epitopes within the NC1 domain of this protein[56,57]. Passive transfer of anti-type VII collagen IgG into mice can elicit lesions with clinical, histologic, and immunopathologic features like those in patients with EBA[58,59]. Of note, the bullous eruption of systemic lupus erythematosus (SLE), which tends to be more inflammatory, is caused by IgG autoantibodies directed against the same four immunodominant epitopes in type VII collagen that are recognized by autoantibodies from patients with EBA[57].

Microfibrils

Elastic fibers have two distinct components: (1) an amorphous component composed of the protein elastin; and (2) a microfibrillar component that has a regular diameter of 10–12 nm and consists primarily of fibrillins, which are associated with other proteins such as microfibril-associated glycoproteins, fibulins, and latent TGF-β-binding proteins (see Ch. 95). In the papillary dermis, microfibrillar elements insert vertically into the lamina densa and comprise what has classically been referred to as oxytalan fibers. At their inferior aspect, oxytalan fibers merge with microfibrillar elements oriented parallel to the skin's surface. These parallel microfibrillar elements contain an amorphous component, and they have been designated elaunin fibers. The network of oxytalan and elaunin fibers is contiguous with elastic fibers within the reticular dermis, which consist of microfibrillar elements associated with substantial amounts of elastin. The gradient of increasing amorphous component deeper in the dermis has been suggested to reflect maturation of elastic fibers in a top-down manner within the skin.

BASEMENT MEMBRANE REMODELING

The epidermal basement membrane is not only a physical barrier between the epidermis and the underlying dermis, but is also a dynamic structure that is constantly being remodeled. For example, the epidermal basement membrane is routinely penetrated by Langerhans cells trafficking into and out of the epidermis under normal physiologic conditions. Lymphocytes also cross the epidermal basement membrane in both inflammatory and neoplastic diseases. However, nonimmune and non-malignant cells rarely cross this ultrastructural barrier, with an absence of basement membranes in tumors correlating with malignancy and propensity for metastasis.

Metalloproteinases expressed by immune or malignant cells enable penetration of basement membranes. Such proteases also have important functions in remodeling epidermal and other basement membranes during morphogenesis, development, and other physiologic processes such as modification of mammary epithelia during pregnancy and lactation. In addition, metalloproteinases play a key role in alterations (e.g. thinning) of the epidermal basement membrane in aged and photoaged skin.

THE EPIDERMAL BASEMENT MEMBRANE IN BULLOUS DISEASES

Patients with acquired immunobullous diseases have autoantibodies directed against components of the epidermis (e.g. in pemphigus) or epidermal basement membrane (e.g. in various forms of pemphigoid). By utilizing autoantibodies from such patients, multiple autoantigens were identified thus demonstrating that individuals with a specific immunobullous disease have autoantibodies directed against a particular protein or proteins with important structural roles in the skin. Furthermore, the genes encoding these proteins often harbor mutations in patients with various forms of EB. Hence, either acquired or inherited alterations in key adhesion proteins in the skin result in disease phenotypes characterized by blister formation (see Table 28.2). The biology of the epidermal basement membrane in patients with autoimmune or inherited blistering diseases is briefly summarized below, and further details are provided in Chapters 30, 31, and 32.

Autoimmune Subepidermal Blistering Diseases

The autoantigens recognized in patients with subepidermal immunobullous diseases are outlined in Table 28.4. Once classified solely by their clinical and histologic features, these disorders are now also defined by their characteristic autoantigen–autoantibody pairings (Fig. 28.6). Profiling patients' autoantibodies to classify their bullous diseases has not only improved diagnostic accuracy but also increased recognition of the polymorphic nature of these conditions. For example, while EBA was once largely considered to be a diagnosis of exclusion for a rare, acquired skin fragility disorder, it is now recognized as a disease that may clinically resemble classic BP or mucous membrane pemphigoid (MMP) as well as dystrophic EB.

WELL-CHARACTERIZED SUBEPIDERMAL IMMUNOBULLOUS DISEASES			
Disease	**Antigen**	**Size (kDa)**	**Localization**
Bullous pemphigoid	BPAG1e	230	Intracytoplasmic plaque of hemidesmosomes
	BPAG2	180	Hemidesmosome-anchoring filament complexes
Pemphigoid gestationis	BPAG2	180	Hemidesmosome-anchoring filament complexes
Linear IgA bullous dermatosis	BPAG2	120→97	Hemidesmosome-anchoring filament complexes
Mucous membrane (cicatricial) pemphigoid	BPAG2	180	Hemidesmosome-anchoring filament complexes
Anti-epiligrin mucous membrane pemphigoid	Laminin 332	400–440	Lamina lucida–lamina densa interface
EB acquisita	Type VII collagen	290	Anchoring fibrils
Bullous eruption of systemic lupus erythematosus	Type VII collagen	290	Anchoring fibrils

Table 28.4 Well-characterized subepidermal immunobullous diseases. BPAG, bullous pemphigoid antigen; EB, epidermolysis bullosa.

LOCALIZATION OF AUTOANTIGENS IN SUBEPIDERMAL IMMUNOBULLOUS DISEASES AND MUTATED PROTEINS IN EPIDERMOLYSIS BULLOSA

Epidermal basement membrane	Autoantigens in immunobullous diseases	Mutated proteins in epidermolysis bullosa (EB)
Basal keratinocytes — Keratins 5 & 14		EB simplex
Lamina lucida — BPAG1e, plectin; BPAG2, integrin $\alpha_6\beta_4$	Bullous pemphigoid, pemphigoid gestationis LABD, mucous membrane pemphigoid	EB simplex, including subtypes with MD or PA Junctional EB, including subtype with PA
Lamina densa — Laminin 332	Anti-epiligrin mucous membrane pemphigoid	Junctional EB
Sublamina densa — Type VII collagen	Epidermolysis bullosa acquisita Bullous eruption of systemic lupus erythematosus	Dystrophic EB

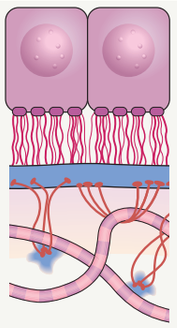


Fig. 28.6 Localization of autoantigens in immunobullous diseases and mutated proteins in epidermolysis bullosa. BPAG, bullous pemphigoid antigen; LABD, linear IgA bullous dermatosis; MD, muscular dystrophy; PA, pyloric atresia.

CLEAVAGE PLANE IN SALT-SPLIT SKIN AND USUAL SITES BOUND BY AUTOANTIBODIES IN INDIRECT IMMUNOFLUORESCENCE STUDIES

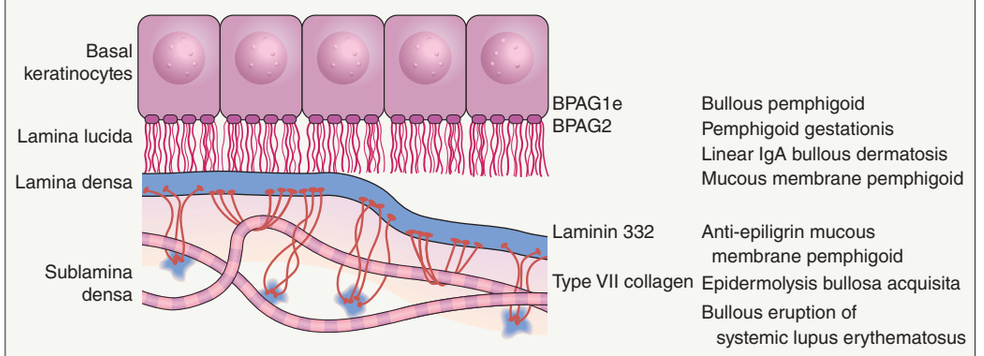


Fig. 28.7 Cleavage plane in salt-split skin and usual sites bound by autoantibodies in indirect immunofluorescence studies. The cleavage plane in 1 M NaCl salt-split skin is in the lower portion of the lamina lucida. Circulating autoantibodies from patients with various subepidermal immunobullous diseases bind to different sites, e.g. the epidermal versus dermal side of the split.

Advances in our understanding of the epidermal basement membrane and how it is targeted in various immunobullous diseases have also led to the development of immunopathologic techniques that have great clinical utility. One example of these techniques is the use of 1 M NaCl salt-split skin, cleaved within the lamina lucida, in immunofluorescence (IF) microscopy studies of patient sera and skin[60–62] (Fig. 28.7; Table 28.5). Indirect IF studies of salt-split skin first gained attention when it was shown that patients with an inflammatory form of EBA and those with classic BP could be distinguished by their IgG anti-basement membrane autoantibodies binding dermal and epidermal sides, respectively, of salt-split skin[60]. When it was found that IgG anti-basement membrane autoantibodies from patients with one form of MMP bound the dermal side of salt-split skin but showed no reactivity to type VII collagen, the search began for a previously unrecognized autoantigen, which was then identified as laminin 332 (epiligrin)[39,40].

For individuals who lack detectable circulating anti-basement membrane autoantibodies, the direct salt-split skin technique has been applied to studies of patient skin[61,62] (Table 28.5). In this technique, skin from a patient is split in the laboratory with 1 M NaCl then studied by direct IF microscopy to determine where immunoreactants localize *in situ*. For example, patients with EBA and anti-laminin-332 MMP have deposits of IgG that localize to the dermal side of salt-split skin. In contrast, patients with BP have deposits of IgG that localize to the epidermal (or both) side(s) of salt-split skin. The pattern of immunoreactant deposition as seen by direct IF microscopy can provide additional information, e.g. a u-serrated pattern distinguishes disorders in which type VII collagen is targeted from other subepidermal immunobullous diseases[63].

LOCALIZATION OF IMMUNOREACTANTS IN IMMUNOFLUORESCENCE MICROSCOPY STUDIES OF 1 M NaCl SALT-SPLIT SKIN		
Indirect immunofluorescence microscopy studies		
Disease	***Localization***	
Bullous pemphigoid	IgG characteristically epidermal; occasionally both sides with higher titer against the epidermal side	
Pemphigoid gestationis	IgG characteristically epidermal; occasionally both sides with higher titer against the epidermal side	
Linear IgA bullous dermatosis	IgA characteristically epidermal; rare patients with "IgA EBA" bind the dermal side	
MMP	IgG characteristically epidermal; occasionally both sides with higher titer against the epidermal side	
Anti-epiligrin MMP	IgG against dermal side of substrate	
EB acquisita	IgG against dermal side of substrate	
Anti-p200 pemphigoid (anti-laminin γ1 pemphigoid)	IgG against dermal side of substrate	
Anti-p105 pemphigoid	IgG against dermal side of substrate	
Direct immunofluorescence microscopy studies*		
Disease	***Localization of IgG***	***Localization of C3***
Bullous pemphigoid	Epidermal	Epidermal, dermal, or both
Pemphigoid gestationis	Epidermal	Epidermal, dermal, or both
Anti-epiligrin MMP	Dermal	Dermal
EB acquisita	Dermal	Dermal
*These studies utilize patient skin after it is split with 1 M NaCl.		

Table 28.5 Localization of immunoreactants in immunofluorescence microscopy studies of 1 M NaCl salt-split skin. EB, epidermolysis bullosa; MMP, mucous membrane (cicatricial) pemphigoid.

REPRESENTATIVE FORMS OF EPIDERMOLYSIS BULLOSA (EB)			
Disease	**Gene**	**Protein**	**Localization**
EB simplex	*KRT5*	Keratin 5	Intermediate filament cytoskeleton of basal keratinocytes
	KRT14	Keratin 14	Intermediate filament cytoskeleton of basal keratinocytes
EB simplex with muscular dystrophy	*PLEC*	Plectin	Intracytoplasmic plaque of hemidesmosomes
EB simplex, intermediate (former Ogna subtype)			
EB simplex with pyloric atresia			
Recessive EB simplex	*DST*	BPAG1	Intracytoplasmic plaque of hemidesmosomes
Junctional EB	*COL17A1*	BPAG2 (type XVII collagen)	Hemidesmosome-anchoring filament complexes
	ITGB4	β_4 integrin	Hemidesmosome-anchoring filament complexes
	LAMA3	Laminin 332, α3 subunit	Lamina lucida–lamina densa interface
	LAMB3	Laminin 332, β3 subunit	Lamina lucida–lamina densa interface
	LAMC2	Laminin 332, γ2 subunit	Lamina lucida–lamina densa interface
Junctional EB with pyloric atresia	*ITGA6*	α_6 integrin subunit	Hemidesmosome-anchoring filament complexes
	ITGB4	β_4 integrin subunit	Hemidesmosome-anchoring filament complexes
Dominant dystrophic EB	*COL7A1*	Type VII collagen	Anchoring fibrils
Recessive dystrophic EB			

Table 28.6 Representative forms of epidermolysis bullosa (EB). Homozygous mutations in the gene encoding the α3 integrin subunit can lead to congenital nephrotic syndrome, interstitial lung disease, and EB30. Additional forms of EB result from mutations in the genes encoding exophilin 5, kelch-like protein 24, CD151 antigen, and kindlin-1 (see Ch. 32). BPAG1, bullous pemphigoid antigen 1.

Inherited Subepidermal Blistering Diseases

The study of patients with various forms of EB has contributed to advances in our understanding of the epidermal basement membrane[64] (Table 28.6; see Fig. 28.6). Likewise, advances in cutaneous immunopathology facilitated the study of patients with EB. For example, because patients with EB simplex display cleavage within the cytoplasm of their basal keratinocytes, BPAG1e and type IV collagen localize to the dermal side of their blistered skin. In patients with various forms of junctional EB, BPAG1e localizes to the epidermal side of blistered skin, while type IV collagen remains attached to the dermis. Lastly, in patients with dystrophic EB, both BPAG1e and type IV collagen localize to the epidermal side of the cleavage plane, which sits within the sublamina densa region.

In addition to classifying patients with various forms of EB based upon mapping the plane of blister formation, studies of the immunoreactivity and ultrastructure of skin from EB patients have provided key insights regarding pathophysiology. For example, monoclonal antibodies against various subunits of laminin 332 generally fail to bind the skin of patients with severe junctional EB. Similarly, monoclonal antibodies against type VII collagen almost always fail to bind the skin of patients with severe recessive dystrophic EB.

SUMMARY

The basement membranes of various tissues differ in their ultrastructure, biochemical composition, and biological function. The epidermal basement membrane contains many highly specialized structures that are largely tissue-specific. Cell–matrix interactions between keratinocytes and the epidermal basement membrane provide key positional and environmental cues that directly modulate tissue morphogenesis, homeostasis, differentiation, wound healing, and acquisition of specialized functions.



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29 Pemphigus

Masayuki Amagai

Synonyms: ■ Fogo selvagem: endemic pemphigus foliaceus; Brazilian pemphigus ■ Pemphigus erythematosus: Senear–Usher syndrome ■ IgA pemphigus: intercellular IgA dermatosis; intraepidermal neutrophilic IgA dermatosis; intercellular IgA vesiculopustular dermatosis ■ Paraneoplastic pemphigus: paraneoplastic autoimmune multi-organ syndrome

Key features

- Pemphigus is a group of autoimmune blistering diseases of the skin and mucous membranes that is characterized by:
  - histologically, intraepidermal blisters due to the loss of cell–cell adhesion of keratinocytes
  - immunopathologically, the finding of *in vivo* bound and circulating IgG autoantibodies directed against the cell surface of keratinocytes
- Pemphigus is divided into three major forms: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus
- The functional inhibition of desmogleins, which play an important role in cell–cell adhesion of keratinocytes, by IgG autoantibodies results in blister formation
- Patients with pemphigus vulgaris and pemphigus foliaceus have IgG autoantibodies against desmoglein 3 and desmoglein 1, respectively, while patients with paraneoplastic pemphigus also have IgG autoantibodies against plakin molecules as well as a T cell-mediated autoimmune reaction that leads to an interface dermatitis
- IgA pemphigus is characterized by IgA, but not IgG, autoantibodies directed against keratinocyte cell surfaces and is divided into two major subtypes: intraepidermal neutrophilic (IEN) type and subcorneal pustular dermatosis (SPD) type
- Systemic corticosteroids are a mainstay of therapy in pemphigus vulgaris, given the rapidity of clinical response, but because of their potential side effects at effective doses, they are combined with steroid-sparing agents
- These additional therapies include immunosuppressive medications such as mycophenolate mofetil, high-dose IVIg (non-immunosuppressive), and anti-CD20 monoclonal antibodies
- Rituximab represents a first-line, FDA-approved therapeutic option for moderate-to-severe pemphigus and can also benefit patients who do not achieve clinical remission with systemic corticosteroids and/or other adjuvant immunosuppressive drugs

INTRODUCTION

The term pemphigus stems from the Greek *pemphix*, meaning blister or bubble, and it describes a group of chronic blistering skin diseases in which autoantibodies are directed against the cell surface of keratinocytes, resulting in the loss of cell–cell adhesion of keratinocytes through a process called acantholysis[1]. Pemphigus can be divided into three major forms: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus (Table 29.1).

Pemphigus vulgaris and pemphigus foliaceus are the originally characterized, classic forms of pemphigus[2]. All patients with pemphigus vulgaris have mucosal membrane erosions, and more than half will also have cutaneous blisters and erosions. The blisters of pemphigus vulgaris develop within the deeper portion of the epidermis, just above the basal cell layer. Patients with pemphigus foliaceus only have cutaneous involvement without mucosal lesions, and the splits occur in the superficial portion of the epidermis, mostly at the granular layer. Pemphigus vegetans is a variant of pemphigus vulgaris, and pemphigus erythematosus and fogo selvagem represent localized and endemic variants of pemphigus foliaceus, respectively.

Paraneoplastic pemphigus is distinct from the classic forms of pemphigus[3], as it consists of both humoral and cellular autoimmune reactions. Patients with paraneoplastic pemphigus have a known or occult associated neoplasm, usually of lymphoid tissue. Painful, severe oral and conjunctival erosions are a prominent feature of paraneoplastic pemphigus.

HISTORY

The modern history of pemphigus began with the discovery by Beutner and Jordon in 1964 of circulating antibodies directed against the cell surface of keratinocytes in the sera of pemphigus vulgaris patients[4] (Fig. 29.1). This was followed by the finding of *in vivo* IgG deposition on the cell surface of keratinocytes in patients' skin. These discoveries formed the basis of our understanding of pemphigus as a tissue-specific autoimmune disease of the skin and mucous membranes. In the late 1970s and early 1980s, pemphigus autoantibodies were shown to be pathogenic, i.e. they could induce blister formation in skin organ-culture systems as well as by passive transfer of patients' IgG to neonatal mice[5]. In the mid and late 1980s, the target antigens of pemphigus were characterized by immunochemical methods, such as immunoprecipitation and immunoblotting[6]. In the early 1990s, the isolation of cDNA for pemphigus antigens demonstrated that pemphigus is an anti-cadherin autoimmune disease[7].

EPIDEMIOLOGY

The prevalence of pemphigus vulgaris and pemphigus foliaceus in men and women is approximately equal. The mean age of onset of disease is 50 to 60 years, although the range is broad and disease arising in the elderly and in children has been described. Pemphigus can be found all over the world. Although limited data are available regarding the incidence of pemphigus, in general, it ranges from 0.76 to 5 new cases per million per year, with a higher incidence observed in the Middle East, Southeast Europe, and India. However, the incidence is much higher (16 to 32 cases per million per year) in those of Jewish ancestry, particularly Ashkenazi Jews. Occasionally, this ancestry may not be readily apparent, as in the descendants of the *conversos* (Jews from the Iberian peninsula who were forced to convert to Catholicism), who currently reside in the southwestern USA and Latin America.

In most countries, pemphigus vulgaris is more common than pemphigus foliaceus; exceptions include Finland, Tunisia, and Brazil. For example, in Japan (incidence of pemphigus: 3.5 cases per million per year), the ratio of pemphigus vulgaris to pemphigus foliaceus is 2 : 1. In France (incidence: 1.7 cases per million per year), pemphigus vulgaris accounts for the majority of all cases (~75%), as it does in Bulgaria. In contrast, in Finland (incidence: much lower at 0.76 cases per million per year) and in Tunisia (incidence: 6.7 cases per million per year), pemphigus foliaceus is twice as common as pemphigus vulgaris. More interestingly, the female-to-male ratio in Tunisia is 4 : 1, and the incidence is higher in young women ages 25 to 34 years (15.5 cases per million per year). In addition to Brazil, Tunisia may have endemic foci of pemphigus foliaceus as may the Mt. Kilimanjaro area.

CLASSIFICATION OF PEMPHIGUS

• Pemphigus vulgaris
  • Pemphigus vegetans
• Pemphigus foliaceus
  • Pemphigus erythematosus: localized
  • Fogo selvagem: endemic
• Herpetiform pemphigus
• Drug-induced pemphigus*
• Paraneoplastic pemphigus
• IgA pemphigus

*ACE inhibitors (e.g. captopril), penicillamine > gold, pyritinol, antibiotics (especially β-lactams), immune checkpoint inhibitors (e.g. pembrolizumab), nifedipine, phenobarbital, piroxicam, propranolol, pyrazolone and topical imiquimod.

Table 29.1 Classification of pemphigus.

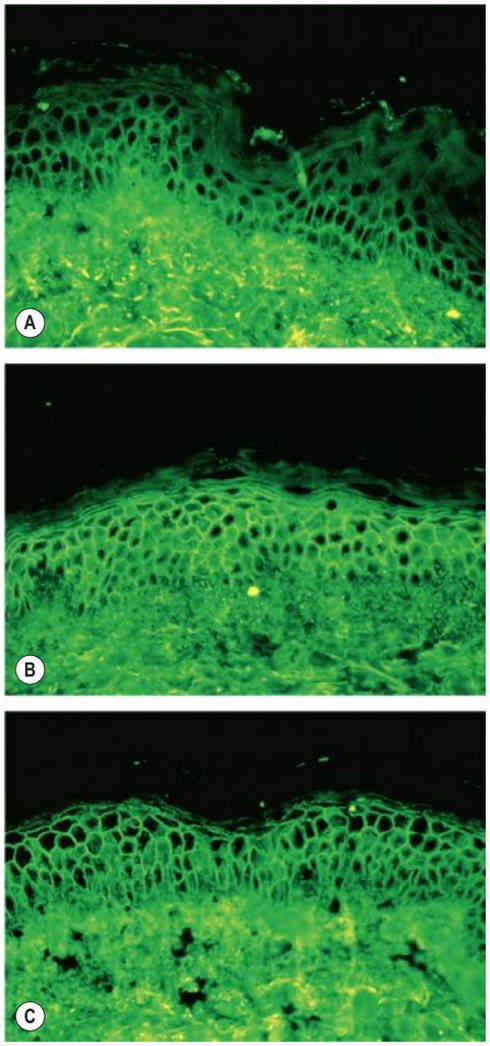


Fig. 29.1 Indirect immunofluorescence of pemphigus sera with normal human epidermis as a substrate. The hallmark of pemphigus is the finding of IgG autoantibodies directed against the cell surface of keratinocytes. **A** Pemphigus vulgaris sera containing anti-desmoglein 3 (anti-Dsg3) IgG alone stain predominantly the cell surfaces in the lower epidermis. **B** Pemphigus vulgaris sera containing both anti-Dsg3 IgG and anti-Dsg1 IgG stain the cell surfaces throughout the epidermis. **C** Pemphigus foliaceus sera, which contain only anti-Dsg1 IgG, stain the cell surfaces throughout the epidermis, but more intensely in the superficial layers.

Fogo Selvagem

Patients with fogo selvagem are clinically, histologically, and immunopathologically similar to patients with sporadic pemphigus foliaceus. However, fogo selvagem occurs in an endemic fashion in certain regions of Brazil and is thought to be caused by an environmental factor(s). Unlike sporadic pemphigus foliaceus, which is a disease of mostly middle-aged and older patients, fogo selvagem affects young adults and children of either sex or any race who are exposed to the local ecology in rural areas, and the incidence gradually decreases as the area is developed. The majority of patients live close to rivers and within the 10–15 km flying range of black flies (*Simulium* spp.), which may be the vector that precipitates the disease. There is also a high frequency of hematophagous insects (bedbugs and kissing bugs) in the homes of patients with fogo selvagem. Of note, a salivary protein from the sand fly *Lutzomyia longipalpis* was shown to induce cross-reactive antibodies to Dsg1[8].

Fogo selvagem frequently occurs in genetically related family members, although it is not contagious, and, to date, spread by blood products or body fluids has not been documented. In rural Brazil, the ratio of pemphigus foliaceus to pemphigus vulgaris is a remarkable 17:1. The prevalence in some rural areas of Brazil is as high as 3.4% of the population[9]. Furthermore, in these areas, more than 50% of normal individuals have anti-desmoglein 1 (anti-Dsg1) IgG autoantibodies, and it has been shown that the onset of the disease is preceded by a sustained antibody response consisting of non-pathogenic IgG1 and IgG4 antibodies. In certain genetically predisposed individuals, predominant IgG4 antibodies directed against the N-terminal extracellular EC1 and EC2 domains of Dsg1 are responsible for inducing disease (Fig. 29.2)[10]. Certainly, fogo selvagem provides a fascinating model for understanding the pathophysiologic and immunologic mechanisms involved in triggering an autoimmune response against skin components.

PATHOGENESIS

Pathogenic Autoantibodies in Pemphigus

The hallmark of pemphigus is the finding of IgG autoantibodies against the cell surface of keratinocytes (see Fig. 29.1)[4]. The pemphigus autoantibodies found in patients' sera play a primary pathogenic role in inducing the loss of cell adhesions between keratinocytes, and subsequent blister formation. Neonates of mothers with pemphigus vulgaris may have a transient disease caused by maternal IgG that crosses the placenta.[11] As maternal antibody is catabolized, the disease subsides. IgG fractions from patients can induce blister formation in the absence of complement or inflammatory cells in a skin organ-culture system[5]. Furthermore, passive transfer of patients' IgG to neonatal mice results in blisters in the mice with typical histologic findings[5]. Even monovalent Fab' fragments of IgG from patients with pemphigus foliaceus are sufficient to cause blisters in neonatal mice, indicating complement activation and surface cross-linking may not be essential in keratinocyte detachment[12].

Desmogleins as Pemphigus Antigens

Immunoelectron microscopy localized both pemphigus vulgaris and pemphigus foliaceus antigens to the desmosomes, the most prominent cell–cell adhesion junctions in stratified squamous epithelia[13]. Immunochemical characterization of pemphigus antigens by immunoprecipitation or immunoblotting with extracts from cultured keratinocytes or epidermis demonstrated that the pemphigus vulgaris and foliaceus antigens were 130 kDa and 160 kDa transmembrane glycoproteins, respectively (Table 29.2)[7,14]. By comparative immunochemical studies using anti-desmoglein 1 (Dsg1) monoclonal and polyclonal antibodies, the 160 kDa protein recognized by pemphigus foliaceus sera was subsequently shown to be identical to Dsg1. An 85 kDa plaque protein, plakoglobin, was co-immunoprecipitated with the 130 kDa and 160 kDa pemphigus antigens, demonstrating that plakoglobin forms a molecular complex with pemphigus vulgaris and foliaceus antigens[15].

Molecular cloning of cDNA encoding Dsg1 and pemphigus vulgaris antigens indicated that both molecules were members of the cadherin supergene family[7,16]. Thus, pemphigus was discovered to be an anti-cadherin autoimmune disease. The pemphigus vulgaris antigen was termed desmoglein 3 (Dsg3). The basic pathophysiology of pemphigus is as follows: autoantibodies inhibit the adhesive function of desmogleins and lead to the loss of the cell–cell adhesion of keratinocytes, resulting in blister formation.

Cadherins are a family of calcium-dependent cell–cell adhesion molecules that play an important role in the formation and maintenance of complex tissue integrity[17]. Based on sequence similarity, cadherins have two major subgroups: *classic* cadherins (e.g. E-, P-, N-cadherins) and *desmosomal* cadherins (desmogleins and desmocollins). All members of the cadherin family contain conserved repeated amino acid sequences (cadherin repeats) with calcium-binding motifs in their extracellular domains (see Fig. 29.2). When classic cadherins were introduced by gene transfection into non-adhesive mouse fibroblast L cells, the cells acquired strong cell adhesion activity mediated by a homophilic type of

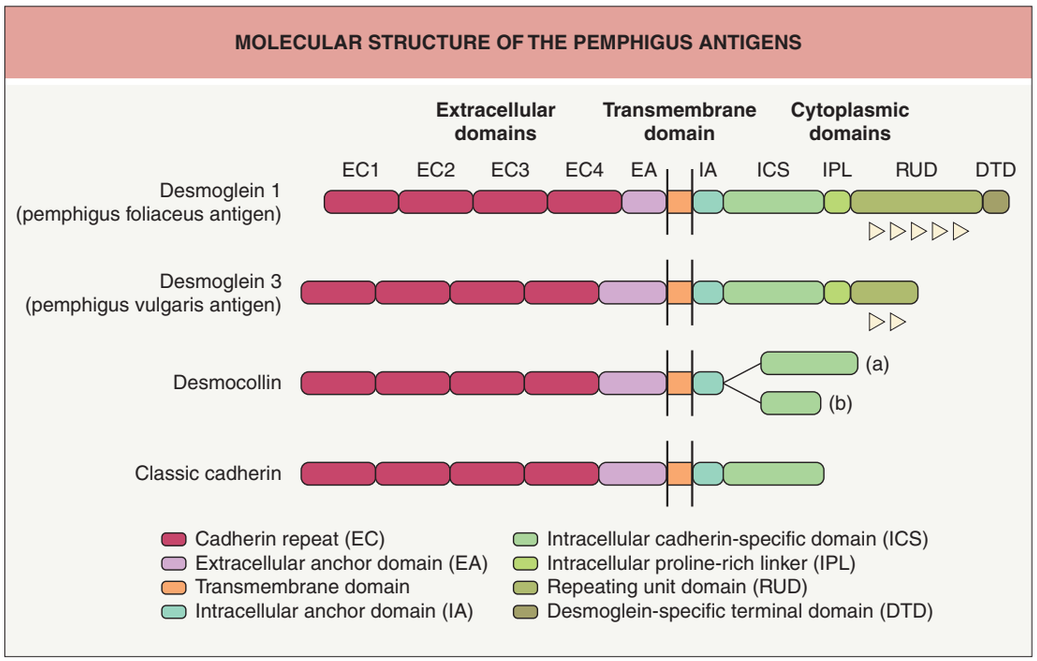


Fig. 29.2 Molecular structure of the pemphigus antigens. The extracellular (EC) region has four cadherin repeats, which have calcium-binding motifs. The intracellular cadherin-specific (ICS) domain is well conserved among cadherins and it is responsible for interactions with β-catenin or plakoglobin (see Fig. 29.3). Desmogleins have their own unique sequences (repeating unit domain [RUD]) of repeats of 29 ± 1 residues (arrowheads). Each desmocollin isotype has two products (a and b) derived from alternatively spliced transcripts of a single gene.

TARGET ANTIGENS IN PEMPHIGUS

Disease	Autoantibodies	Antigens	MW (kDa)
Pemphigus vulgaris			
Mucosal-dominant type	IgG	Desmoglein 3	130
Mucocutaneous type	IgG	Desmoglein 3	130
		Desmoglein 1	160
Pemphigus foliaceus	IgG	Desmoglein 1	160
Paraneoplastic pemphigus	IgG	Desmoglein 3	130
		Desmoglein 1	160
		Plectin*	500
		Epiplakin*	500
		Desmoplakin I*	250
		Desmoplakin II*	210
		BPAG1*	230
		Envoplakin*	210
		Periplakin*	190
		A2ML1	170
		Transglutaminase 1	90
Drug-induced pemphigus	IgG	Desmoglein 3	130
		Desmoglein 1	160
IgA pemphigus			
Subcorneal pustular dermatosis type	IgA	Desmocollin 1	110/100
Intraepidermal neutrophilic type	IgA	?	?
Pemphigus foliaceus type	IgA	Desmoglein 1	160
Pemphigus vulgaris type	IgA	Desmoglein 3	130
Pemphigus vegetans type	IgA	Desmoglein 3	130

*Members of plakin family.

Table 29.2 Target antigens in pemphigus. A minority of patients with classic pemphigus vulgaris and pemphigus foliaceus also have IgA autoantibodies and are classified as pemphigus vulgaris and pemphigus foliaceus. A2ML1, alpha-2-macroglobulin-like-1 protease inhibitor; BPAG1, bullous pemphigoid antigen 1.

interaction. Cadherins require their well-conserved cytoplasmic domains in order to associate with the plaque proteins, α-catenin, β-catenin and plakoglobin, which mediate and regulate binding to the cytoskeleton network (Fig. 29.3). As a consequence of these interactions, cadherins produce strong cellular adhesion and morphologic changes in the cells. Cadherin molecules form dimers as their functional unit, with the distal extracellular domain (EC1) of the cadherin from one cell binding to the same region of a second cadherin from an opposing cell[18].

Two major types of adhering junctions of epithelial cells are commonly distinguished: adherens junctions and desmosomes (see Fig. 29.3). The *adherens junction* anchors bundles of actin microfilaments and contains classic cadherins as its transmembrane components and α-catenin, β-catenin, and plakoglobin as its cytoplasmic components. In contrast, the *desmosome* anchors intermediate filaments like keratins and contains desmosomal cadherins as its transmembrane components and plakoglobin, plakophilin, and desmoplakin

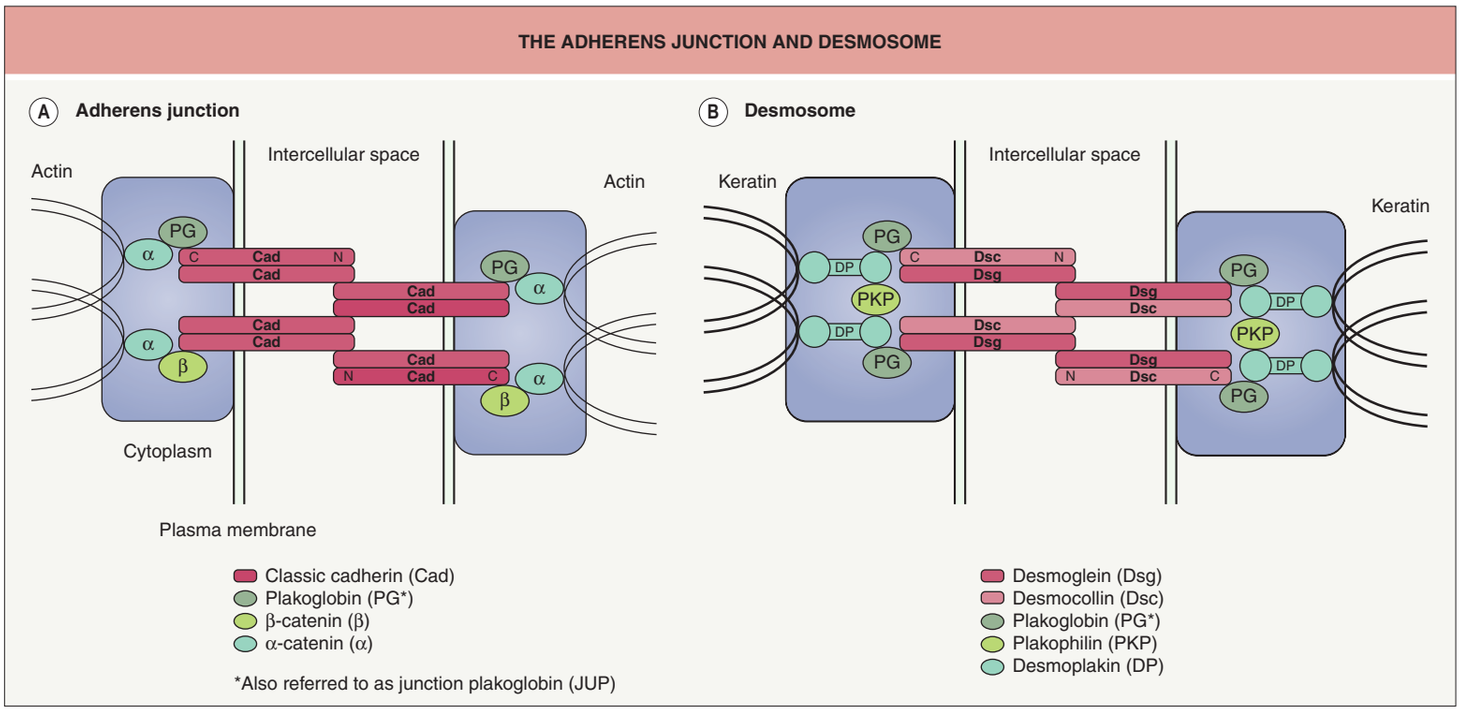


Fig. 29.3 The adherens junction and desmosome. A The adherens junction complex contains classic cadherins as transmembrane constituents and α-catenins, β-catenins, and plakoglobin as cytoplasmic constituents. A classic cadherin is directly coupled through its cytoplasmic tail to β-catenin or plakoglobin, which in turn is linked to α-catenin, which binds to actin. **B** The desmosome complex includes desmogleins and desmocollins as transmembrane constituents, and plakoglobin, plakophilin, and desmoplakin as cytoplasmic constituents. Desmogleins and desmocollins form heterodimers as a functional adhesive unit and associate with plakoglobin, which in turn binds to desmoplakin which links keratin to the membrane. C, carboxy terminus; N, amino terminus.

as its cytoplasmic components. In general, adherens junctions mediate quick but weak cellular adhesion, whereas desmosomes mediate slow but strong cellular adhesion.

Desmogleins have four cadherin repeats in their extracellular domain, as do classic cadherins (see Fig. 29.2). Desmogleins have four isoforms (Dsg1–4). Expression of Dsg1 and Dsg3 is basically restricted to stratified squamous epithelia, where blisters are formed in pemphigus, while Dsg2 is expressed in all desmosome-possessing tissues, including simple epithelia and myocardium. Dsg4 plays an important adhesive role primarily in hair follicles, and mutations in *DSG4* can lead to abnormal hair development (e.g. localized autosomal recessive hypotrichosis)[19].

Desmocollins are another group of transmembrane glycoproteins within desmosomes and they have three isoforms (Dsc1–3). Each isoform has two products derived from alternatively spliced mRNA of a single gene. Desmosomes always have desmoglein and desmocollin as a pair, with Dsg:Dsc heterodimers representing the fundamental adhesive unit of desmosomes and thus providing a structural framework for understanding desmosome assembly[20].

Plakoglobin and plakophilin, together with β-catenin, are members of the armadillo family of nuclear and junctional proteins, which are not only simple anchoring molecules but also dynamic regulators of cellular adhesion and proliferation. Desmoplakin is a dumbbell-shaped molecule composed of three domains: a central α-helical coiled-coil rod, flanked by globular carboxy- and amino-terminal domains that interact with intermediate filaments and armadillo family members, respectively (see Fig. 29.3). Desmoplakin has two products derived from alternatively spliced mRNA of a single gene: desmoplakin I (250 kDa) and II (210 kDa) (see Table 29.2). Desmoplakin, a member of the plakin family, plays an important role in the anchorage of the cytoskeleton to filament attachment sites on desmosomes.

Compelling evidence has accumulated that IgG autoantibodies against Dsg1 and Dsg3 are pathogenic and play a primary role in inducing the blister formation in pemphigus. Essentially, all patients with pemphigus have IgG autoantibodies against Dsg1 and/or Dsg3, depending on the subtype of pemphigus[21,22]. When anti-desmoglein IgG autoantibodies are removed from the sera of patients with pemphigus vulgaris, pemphigus foliaceus or paraneoplastic pemphigus (by immunoadsorption with recombinant desmoglein proteins), the sera are no longer pathogenic in inducing blister formation[23,24]. Furthermore, anti-desmoglein IgG autoantibodies that have been affinity-purified from pemphigus sera via desmoglein recombinant proteins can cause blisters when injected into neonatal mice[24,25]. Some pemphigus sera react with Dsg4 due to cross-reactivity of a subset of anti-Dsg1 IgG, although Dsg4/Dsg1-cross-reacting IgG has no demonstrable pathogenic effect[26]. IgG autoantibodies against non-desmoglein molecules, such as acetylcholine receptors or annexin-like molecules, have also been detected, but their pathogenic relevance in pemphigus remains to be determined.

Desmoglein Compensation Theory as Explanation for Localization of Blisters

The sites of blisters in pemphigus vulgaris and foliaceus are explained logically by the desmoglein compensation theory: Dsg1 and Dsg3 compensate for each other when they are coexpressed in the same cell (Fig. 29.4)[27,28]. While patients with pemphigus foliaceus have only anti-Dsg1 IgG autoantibodies, individuals with the mucosal-dominant type of pemphigus vulgaris have only anti-Dsg3 IgG autoantibodies. Those with the mucocutaneous type of pemphigus vulgaris have both anti-Dsg3 and anti-Dsg1 IgG autoantibodies. Of note, the intraepithelial expression pattern of Dsg1 and Dsg3 differs between the skin and mucous membranes. In the skin, Dsg1 is expressed throughout the epidermis, but more intensely in the superficial layers (see Fig. 29.1C), whereas Dsg3 is expressed in the lower portion of the epidermis, primarily in the basal and parabasal layers (see Fig. 29.1A). In contrast to the skin, Dsg1 and Dsg3 are expressed throughout the squamous layer of mucosa, but Dsg1 is expressed at a much lower level than Dsg3 (see Fig. 29.4B).

When sera contain only anti-Dsg1 IgG (which interferes with the function of Dsg1), blisters appear only in the superficial epidermis of the skin because that is the only area in which Dsg1 is present without coexpression of Dsg3. The splits occur between the second (SG2) and the third (SG3) layers of the stratum granulosum (SG) because IgG does not go beyond the tight junctions present between SG2 cells[29]. In the unaffected deep epidermis, the presence of Dsg3 compensates for the loss of function of Dsg1. Although the anti-Dsg1 IgG binds to mucosa, no blisters are formed, because of the coexpression of Dsg3.

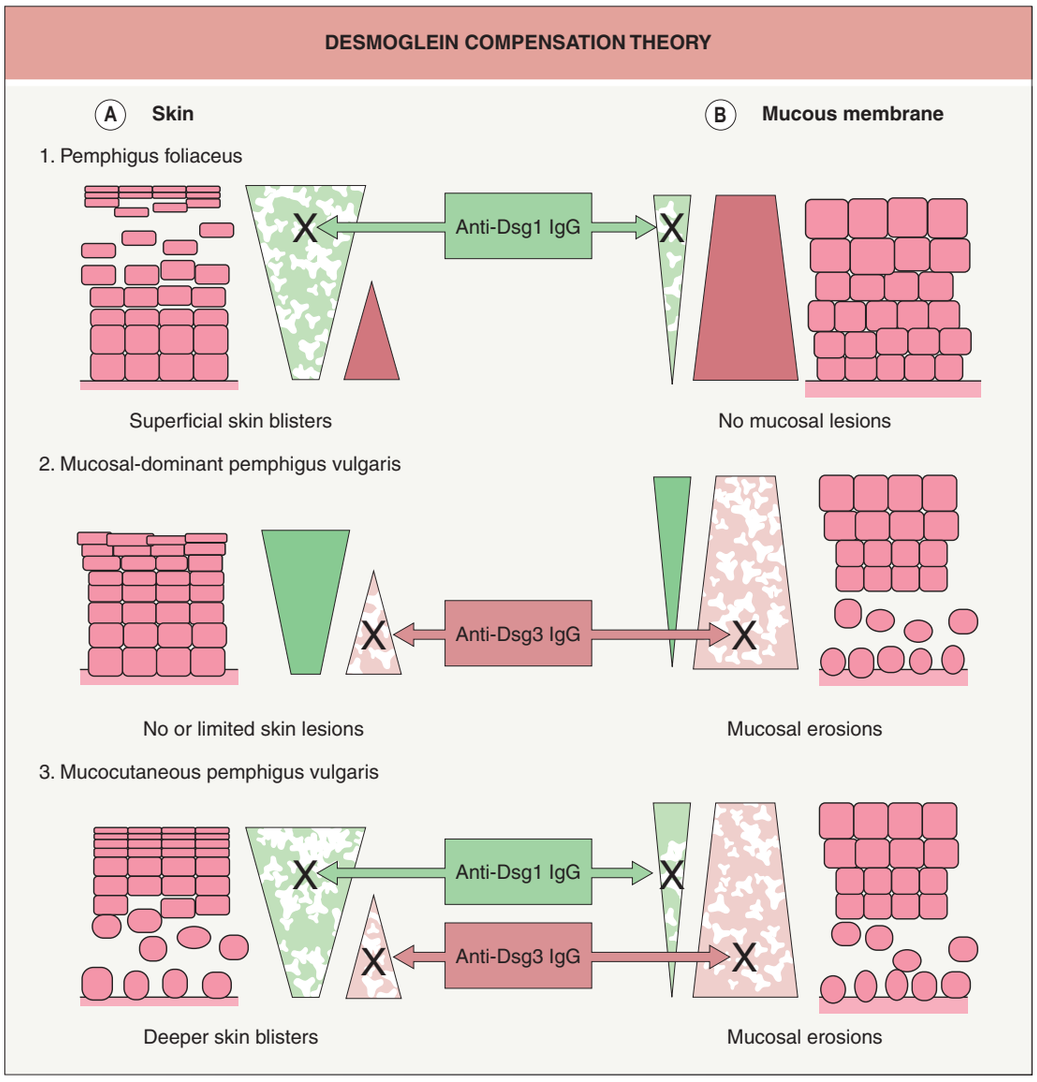


Fig. 29.4 Logical explanation for the localization of blister formation in classic pemphigus by desmoglein compensation theory. The colored triangles represent the distribution of desmoglein 1 (Dsg1, green) and desmoglein 3 (Dsg3, pink) in the skin (**A**) and mucous membranes (**B**). Pemphigus foliaceus sera contain only anti-Dsg1 IgG, which causes superficial blisters in the skin because Dsg3 functionally compensates for the impaired Dsg1 in the lower part of the epidermis (A1), whereas those antibodies do not cause blisters in the mucous membranes because cell–cell adhesion is mainly mediated by Dsg3 (B1). Sera containing only anti-Dsg3 IgG cause no or only limited blisters in the skin because Dsg1 compensates for the loss of Dsg3-mediated adhesion (A2); however, these sera induce separation in the mucous membranes, where the low expression of Dsg1 will not compensate for the loss of Dsg3-mediated adhesion (B2). When sera contain both anti-Dsg1 and anti-Dsg3 IgG, the function of both Dsgs is compromised and blisters occur in both the skin and mucous membranes (A3, B3). In neonatal skin, the situation is similar to that shown here for mucous membranes.

Thus, sera containing only anti-Dsg1 IgG cause superficial blisters in the skin without mucosal involvement, as is seen in patients with pemphigus foliaceus (see Fig. 29.4).

When sera contain only anti-Dsg3 IgG, they are inefficient in producing cutaneous blisters because coexpressed Dsg1 compensates for the impaired function of Dsg3, resulting in no, or only limited, skin lesions. However, in the mucous membranes, Dsg1 cannot compensate for the impaired Dsg3 function because of its low expression. Therefore, sera containing only anti-Dsg3 IgG cause oral erosions without apparent skin involvement, as is seen in patients with the mucosal-dominant type of pemphigus vulgaris (see Fig. 29.4).

When sera contain both anti-Dsg1 and anti-Dsg3 IgG, they interfere with the function of both Dsg1 and Dsg3, resulting in extensive blisters and erosions of the skin as well as the mucous membranes, as is seen in patients with the mucocutaneous type of pemphigus vulgaris. Possible explanations for why splits appear just above the basal layer, rather than the whole epithelium falling apart, include: (1) cell–cell adhesion in the basal and parabasal layers may be weaker than in other parts of the epithelium; and (2) autoantibodies, which penetrate from the dermis, might have better access to the lower part of the epithelia.

In pregnant women with pemphigus, autoantibodies cross the placenta and bind to the fetal epidermis. However, neonates develop blisters if the mother has pemphigus vulgaris, but very rarely if she has pemphigus foliaceus. This confusing observation is also explained by the desmoglein compensation theory[30]. The distribution of Dsg3 within neonatal epidermis is unlike that in adult epidermis; it is found on the surface of keratinocytes throughout the epidermis, which is similar to its distribution in mucous membranes (remember, neonatal skin is bathed in amniotic fluid). Therefore, pemphigus foliaceus sera containing only anti-Dsg1 IgG cannot efficiently induce blisters in neonatal skin.

As an extension of this compensation theory, exfoliative toxins, which are produced by *Staphylococcus aureus* and lead to bullous impetigo as well as staphylococcal scalded skin syndrome, specifically cleave Dsg1[31]. Inactivation of Dsg1 by this toxin induces superficial blisters in the epidermis that are clinically and histologically similar to those seen in pemphigus foliaceus.

In pemphigus, the disruption of cell–cell adhesion is currently thought to be mediated via the combined effects of direct inhibition by antibodies plus subsequent signal transduction induced by antibody binding[32]. The direct inhibition is mediated by steric hindrance, i.e. the binding of autoantibodies to desmogleins spatially interferes with the adhesive interaction of desmogleins between cells. This proposed pathogenesis is supported by the following observations: (1) in pemphigus vulgaris and foliaceus, dominant epitopes are localized to the functionally important N-terminal regions of desmogleins[25,33]; and (2) pathogenic anti-Dsg3 mouse or human monoclonal antibody, but *not* non-pathogenic monoclonal antibodies, recognizes the N-terminal adhesive surface of Dsg3 (see Fig. 29.3B)[33,34]. The phenotype of the *Dsg3* null mouse (whose *Dsg3* gene is genetically deleted) closely resembles that of human pemphigus vulgaris patients[35]. The role of signal transduction induced by antibody binding is supported by the *in vitro* observation that IgG from pemphigus vulgaris sera (when added to the media of cultured keratinocytes) causes a transient increase in intracellular calcium and/or inositol 1,4,5-triphosphate, activation of protein kinase C, or phosphorylation of Dsg3. Furthermore, with desmosomal disassembly, Dsg3 is internalized or endocytosed from the cell surface in association with keratin retraction[36].

Humoral and Cellular Autoimmunity in Paraneoplastic Pemphigus

Patients with paraneoplastic pemphigus develop characteristic IgG autoantibodies against multiple antigens[3], including Dsg3 and/or Dsg1[24], multiple members of the plakin family (plectin, epiplakin, desmoplakins I and II, bullous pemphigoid antigen 1, envoplakin, and periplakin), the protease inhibitor alpha-2-macroglobulin-like-1[37,38], and transglutaminase 1[38a] (see Table 29.2). Anti-desmoglein antibodies play a role in inducing the loss of cell adhesion of keratinocytes and initiate blister formation, while the pathophysiologic relevance of the anti-plakin autoantibodies is unclear, in that plakin molecules are intracellular and IgG cannot penetrate cell membranes. In addition to humoral autoimmunity, cell-mediated cytotoxicity is involved in the pathogenesis of paraneoplastic pemphigus, in which more severe and refractory oral erosions and stomatitis as well as more polymorphic skin eruptions are seen, in comparison with classic forms of pemphigus. It was demonstrated in mice that Dsg3-specific T cells not only help B cells produce anti-Dsg3 IgG (which causes acantholysis), but also directly infiltrate into the epidermis and induce an interface dermatitis[39]. Clarification of the exact roles of autoimmune T cells should provide valuable insights into the pathophysiology of paraneoplastic pemphigus.

Immunologic Mechanism of Pathogenic Autoantibody Production in Pemphigus

In contrast to the significant progress since the late 1980s in understanding the pathophysiologic mechanisms of blister formation in pemphigus, it is still unclear why patients with pemphigus begin to produce the pathogenic autoantibodies.

Pemphigus autoantibodies are composed of IgG isotypes, which may be produced after isotype switching, and they have a high affinity towards the antigen, which may be a result of affinity maturation of the antibodies. In addition, pemphigus sera recognize several distinct epitopes on desmogleins[40], and the presence of autoantibodies is associated with specific HLA class II alleles, including DRB1*0402, DRB1*1401, and DQB1*0302 in White individuals[41] and DRB1*14 and DQB1*0503 in Japanese. All of these features suggest that autoantibody production in pemphigus is T cell-dependent. More recently, T cells reactive against Dsg3 were shown to be present in peripheral blood from patients with pemphigus vulgaris as well as healthy individuals[42–44]. Certain peptides from Dsg3, predicted to fit into the DRB1*0402 pocket, were able to stimulate T cells from the pemphigus patients.

Another advance that will allow the study of T cells and B cells is the development of an active disease mouse model for pemphigus vulgaris[45]. This model is valuable not only for dissecting the cellular and molecular mechanisms involved in antibody production but also for developing novel therapeutic strategies.

CLINICAL FEATURES

Pemphigus Vulgaris

Essentially all patients with pemphigus vulgaris develop painful erosions of the oral mucosa. More than half of the patients also develop flaccid blisters and widespread cutaneous erosions. Pemphigus vulgaris is therefore divided into two subgroups: (1) the *mucosal-dominant* type with mucosal erosions but minimal skin involvement; and (2) the *mucocutaneous* type with extensive skin blisters and erosions in addition to mucosal involvement (see Fig. 29.4).

Mucous membrane lesions usually present as painful erosions (Fig. 29.5). Intact blisters are rare, probably because they are fragile and break easily. Although scattered or extensive erosions may be seen anywhere in the oral cavity, the most common sites are the buccal and palatine mucosae. The erosions are of different sizes with an irregular and ill-defined border, which, when extensive or painful, may result in decreased oral intake of food or liquids. The diagnosis of pemphigus vulgaris tends to be delayed in patients presenting with only oral involvement, as compared to patients with skin lesions.

The lesions may extend out onto the vermilion lip and lead to thick, fissured hemorrhagic crusts. Involvement of the throat produces hoarseness and difficulty in swallowing. The esophagus also may be involved and sloughing of its entire lining in the form of a cast has been reported. The conjunctivae, nasal mucosa, vagina, labia, penis and anus

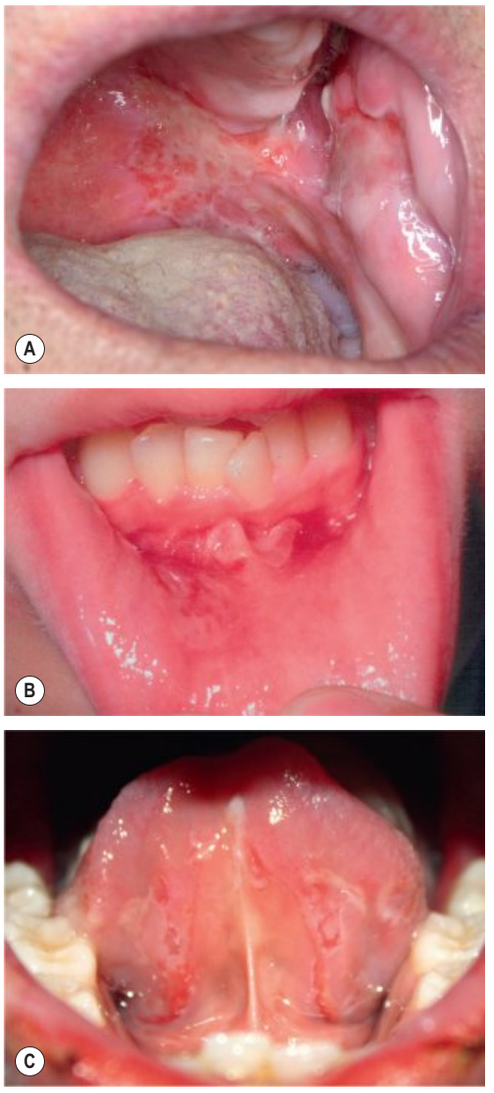


Fig. 29.5 Pemphigus vulgaris – oral involvement. Essentially all patients develop painful oral mucosal erosions. The most common sites are the buccal (**A**) and palatine mucosae, but lesions can also develop on the gingivae (**B**) and tongue (**C**). *A, Courtesy Lorenzo Cerroni, MD; B,C, Courtesy Jeffrey P. Callen, MD.*

can develop lesions as well. Cytology of vaginal cells may be misread as a malignancy when vaginal lesions are present.

The primary skin lesions of pemphigus vulgaris are flaccid, thin-walled, easily ruptured blisters (Fig. 29.6). They can appear anywhere on the skin surface and arise on either normal-appearing skin or erythematous bases. The fluid within the bullae is initially clear but may become hemorrhagic, turbid, or even seropurulent. The blisters are fragile and soon rupture to form painful erosions that ooze and bleed easily. These erosions often attain a large size and can become generalized. The erosions soon become partially covered with crusts that have little or no tendency to heal. Those lesions that do heal often leave hyperpigmented patches with no scarring. Associated pruritus is uncommon. Table 29.3 outlines more unusual clinical presentations of pemphigus vulgaris.

Because of an absence of cohesion within the epidermis, its upper layers easily move laterally with slight pressure or rubbing in patients with active disease (Nikolsky sign). The lack of cohesion of the skin may also be demonstrated with the "bulla-spread phenomenon" – gentle pressure on an intact bulla forces the fluid to spread under the skin away from the site of pressure (Asboe–Hansen sign, also referred to as the "indirect Nikolsky" or "Nikolsky II" sign). Without appropriate treatment, pemphigus vulgaris can be fatal because a large portion of the skin loses its epidermal barrier function, leading to the loss of body fluids or to secondary bacterial infections.

Pemphigus Vegetans

Pemphigus vegetans is a rare vegetative variant of pemphigus vulgaris, and it is thought to represent a reactive pattern of the skin to the autoimmune insult of pemphigus vulgaris.



Fig. 29.6 Pemphigus vulgaris – cutaneous involvement. A Flaccid blisters and an erosion due to rupture of a bulla. **B**, **C** Multiple erosions and hemorrhagic crusts of the back that can become extensive. Secondary bacterial infections are a potential complication. **D** A vegetative response can occasionally be seen in chronic recalcitrant lesions; the patient has a Cushingoid appearance due to use of chronic systemic corticosteroids. **E** The dyshidrosiform variant is uncommon. *A, D, Courtesy Luis Requena, MD; B, C, Courtesy Lorenzo Cerroni, MD; E, Courtesy Louis A. Fragola, Jr, MD.*

UNUSUAL CLINICAL PRESENTATIONS OF PEMPHIGUS VULGARIS
• Isolated crusted plaque on face or scalp
• Paronychia and/or onychomadesis
• Foot ulcers
• Dyshidrotic eczema or pompholyx
• Macroglossia
• Gingival hyperplasia

Table 29.3 Unusual clinical presentations of pemphigus vulgaris.

Pemphigus vegetans is characterized by flaccid blisters that become erosions and then form fungoid vegetations or papillomatous proliferations, especially in intertriginous areas and on the scalp or face (Fig. 29.7). Pustules rather than vesicles characterize early lesions, but these soon progress to vegetative plaques. The tongue may show cerebriform-like changes. Two subtypes are recognized: the severe Neumann type and the mild Hallopeau type. Occasionally, a vegetative response may also be seen in lesions of pemphigus vulgaris that tend to be resistant to therapy and remain for long periods of time in one location (see Fig. 29.6D).

Pemphigus Foliaceus

Patients with pemphigus foliaceus develop scaly, crusted cutaneous erosions, often on an erythematous base, but they do not have clinically apparent mucosal involvement even with widespread disease.



Fig. 29.7 Pemphigus vegetans. Large, thick, vegetating, papillomatous plaques arising in conjunction with erosions. Healed lesions have residual postinflammatory hyperpigmentation.

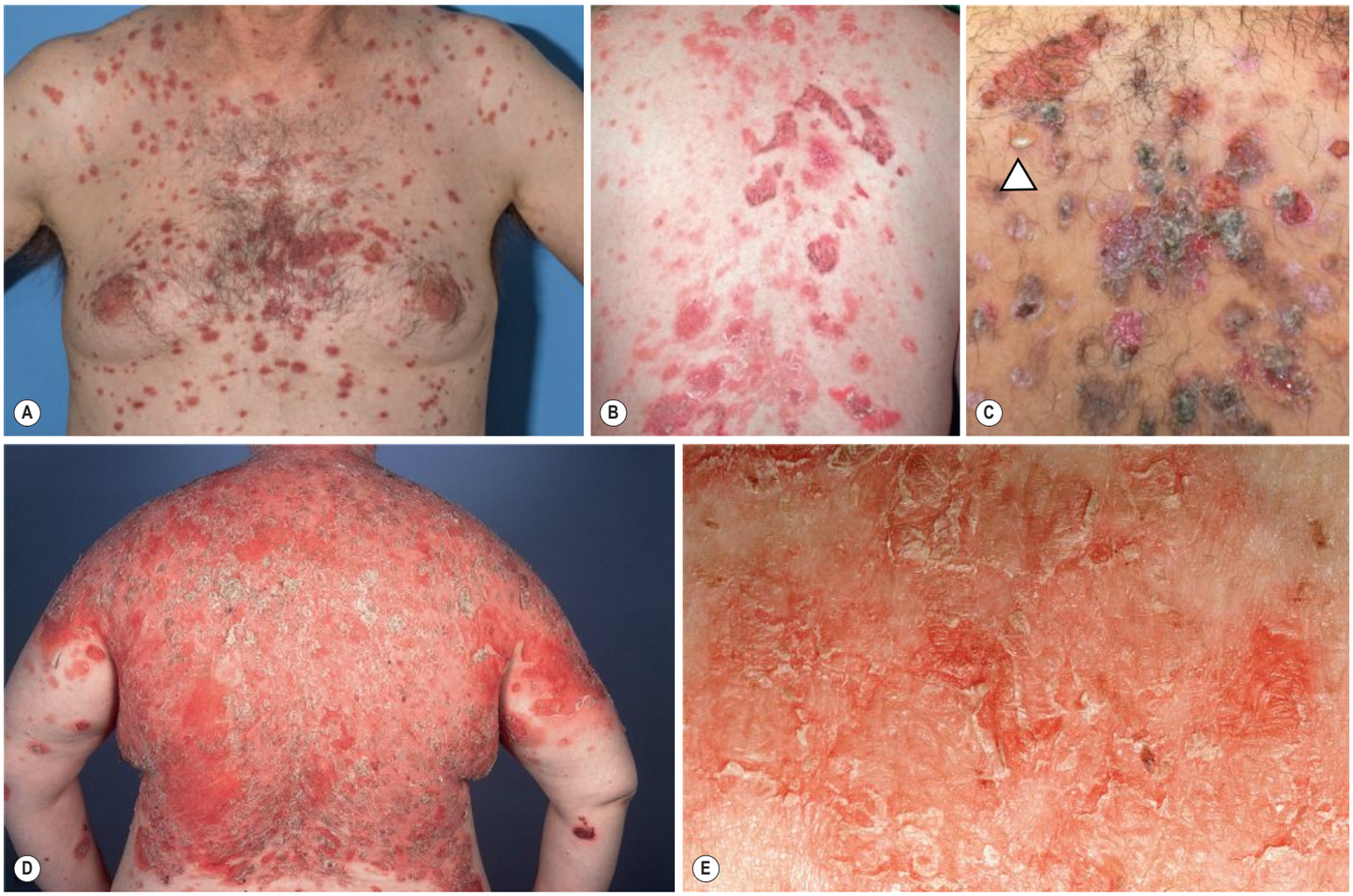


Fig. 29.8 Pemphigus foliaceus. A, B Multiple superficial erosions arising on an erythematous base on the trunk, a common site of involvement. Larger erosions as well as the characteristic scale-crusts are seen in **B**. **C** Thicker scale-crusts in addition to large erosions and one flaccid vesicle with seropurulent fluid where pus has settled in the lower half due to gravity similar to hypopyon ("half-half" blisters) (arrowhead). **D** As the disease progresses, the lesions become confluent, but because the vesicles are fragile and rupture easily, only erosions with scale-crust are observed. **E** The scales have been likened to cornflakes. *A, Courtesy Edward Cowen, MD; C, Courtesy Kalman Watsky, MD.*

The onset of disease is often subtle, with a few scattered crusted lesions that are transient and are frequently mistaken for impetigo. They are usually well demarcated and have a seborrheic distribution, i.e. they favor the face, scalp, and upper trunk (Fig. 29.8A–C). Because the vesicle is so superficial and fragile, often only the resultant crust and scale are seen (Fig. 29.8D, E). The disease may stay localized for years or it may rapidly progress, in some cases to generalized involvement and an exfoliative erythroderma (see Ch. 10). The Nikolsky sign is present. In contrast to the extensive oral lesions in pemphigus vulgaris, it is extremely rare, if ever, for patients with pemphigus foliaceus to develop mucosal involvement. Generally, patients with pemphigus foliaceus are not severely ill. However, they can experience burning and pain in association with the skin lesions.

Pemphigus Erythematosus (Senear–Usher Syndrome)

Pemphigus erythematosus is simply a localized variant of pemphigus foliaceus. Typical scaly and crusted lesions of pemphigus foliaceus appear in the malar region of the face (Fig. 29.9) and in other "seborrheic" areas. Originally, the term "pemphigus erythematosus" was introduced to describe patients with immunologic features of both lupus erythematosus (LE) and pemphigus, i.e. *in vivo* IgG and C3 deposition on cell surfaces of keratinocytes as well as the basement membrane zone, in addition to circulating anti-nuclear antibodies[46]. However, only a few patients have been reported to actually have the two diseases concurrently.

Herpetiform Pemphigus

Most patients with herpetiform pemphigus have a clinical variant of pemphigus foliaceus and the remainder may have a variant of pemphigus vulgaris. This disorder is characterized by: (1) erythematous urticarial plaques and tense vesicles that present in a herpetiform arrangement; (2) eosinophilic spongiosis and subcorneal pustules with minimal or no apparent acantholysis histologically; and (3) IgG autoantibodies directed against the cell surfaces of keratinocytes[47]. The target antigen is Dsg1 in most cases and Dsg3 in the remainder[48]. Some patients with herpetiform pemphigus will have features of pemphigus foliaceus or vulgaris during the course of their disease, and some patients will evolve into having pemphigus foliaceus or vulgaris. It is assumed that the pathogenic blister-inducing activity of the IgG autoantibodies



Fig. 29.9 Pemphigus erythematosus. Erythematous plaques with scale-crust and erosions on the nose and malar area of the face. *Courtesy Ronald P. Rapini, MD.*

in herpetiform pemphigus might be weaker than that seen in classic forms of pemphigus. Although often clinically less severe than pemphigus vulgaris, the course may be more chronic.

Drug-Induced Pemphigus

There are sporadic cases of pemphigus associated with the use of drugs, in particular penicillamine and captopril (see Table 29.1)[49]. In patients receiving penicillamine, pemphigus foliaceus is seen more commonly than pemphigus vulgaris, with a ratio of approximately 4:1. Although most patients with drug-induced pemphigus are shown to have autoantibodies against the same molecules involved in sporadic pemphigus, evidence suggests that some drugs may induce acantholysis without the production of antibodies. Both penicillamine and captopril contain sulfhydryl groups that are speculated to interact with the sulfhydryl groups in Dsg1 and Dsg3. This interaction may modify the antigenicity of the desmogleins, which may lead to autoantibody production, or their interaction may directly interfere with the adhesive function of the desmogleins. Imiquimod-induced pemphigus has also been reported as has a flare or recurrence of pemphigus due to immune checkpoint inhibitors. Most, but not all, patients with drug-induced pemphigus go into remission after the offending drug is discontinued.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is associated with underlying neoplasms, both malignant and benign. The most commonly associated neoplasms are non-Hodgkin lymphoma and chronic lymphocytic leukemia, followed by Castleman disease, malignant and benign thymomas, sarcomas, and Waldenström macroglobulinemia[3]. Non-Hodgkin lymphoma and chronic lymphocytic leukemia together account for two-thirds of patients. Castleman disease, a very rare lymphoproliferative disorder, is the third most commonly associated neoplasm in adults and the most commonly associated tumor in children and adolescents; its association with paraneoplastic pemphigus is strikingly disproportionate to its general occurrence. The absence of common tumors, such as adenocarcinomas of the breast or colon and squamous cell carcinomas, is notable.

The most constant clinical feature of paraneoplastic pemphigus is the presence of intractable stomatitis. Severe stomatitis is usually the earliest presenting sign and, after treatment, it is the one that persists and is extremely resistant to therapy. This stomatitis consists of erosions and ulcerations that affect all surfaces of the oropharynx and characteristically extend onto the vermilion lip (Fig. 29.10). Most patients also have a severe pseudomembranous conjunctivitis, which may progress to scarring and obliteration of the conjunctival fornices. Nasopharyngeal, esophageal, vaginal, labial, penile, and perianal lesions may also be seen.

Cutaneous findings are quite polymorphic and may present as erythematous macules, flaccid blisters and erosions resembling pemphigus vulgaris, tense blisters resembling bullous pemphigoid, erythema multiforme-like lesions, and lichenoid eruptions. The occurrence of blisters and erythema multiforme-like lesions on the palms and soles is often used to differentiate paraneoplastic pemphigus from pemphigus vulgaris, in which lesions on the palms and soles are unusual. In the chronic form of the disease, a lichenoid eruption may predominate over blistering lesions. Some patients with paraneoplastic pemphigus develop bronchiolitis obliterans, which can be fatal as a result of respiratory failure[50]. Although its pathophysiologic mechanism is still unclear, ectopic expression of epidermal antigens in the setting of squamous metaplasia is thought to render the lung a target organ[51]. Of note, a chest X-ray or CT scan obtained at the onset of bronchiolitis obliterans may be normal but pulmonary function tests will show small airway obstruction that does not reverse with bronchodilators.



Fig. 29.10 Paraneoplastic pemphigus. A The characteristic clinical feature is severe intractable stomatitis with multiple erosions; there may be a resemblance to erosive oral lichen planus. **B** The erosions, along with hemorrhagic crusts, can extend onto the vermilion lip and involve the nasal mucosa. **C** Papulosquamous lichenoid lesions, reflecting an interface dermatitis, can also be present. *A, Courtesy Luis Requena, MD; C, Courtesy Jennie Clarke, MD.*

IgA Pemphigus

IgA pemphigus represents a more recently characterized group of autoimmune intraepidermal blistering diseases presenting with a vesiculopustular eruption, neutrophilic infiltration of the skin, and *in vivo* bound and circulating IgA autoantibodies against the cell surface of keratinocytes; no IgG autoantibodies are present. IgA pemphigus usually occurs in middle-aged or elderly persons. Two distinct types of IgA pemphigus have been described: the *subcorneal pustular dermatosis type* and the *intraepidermal neutrophilic type*. Patients with both types of IgA pemphigus present with flaccid vesicles or pustules on either erythematous or normal skin (Fig. 29.11A). In both types, the pustules tend to coalesce to form an annular or circinate pattern with crusts in the center of the lesion (Fig. 29.11B), although a sunflower-like configuration of pustules is a characteristic sign of the intraepidermal neutrophilic type.

The most common sites of involvement are the axilla and groin, but lesions can also develop on the trunk and proximal extremities. Mucous membrane involvement is rare, and pruritus is often a significant symptom. In some patients, there is an underlying associated disorder such as IgA myeloma or ulcerative colitis. Because the subcorneal pustular dermatosis type of IgA pemphigus is clinically and

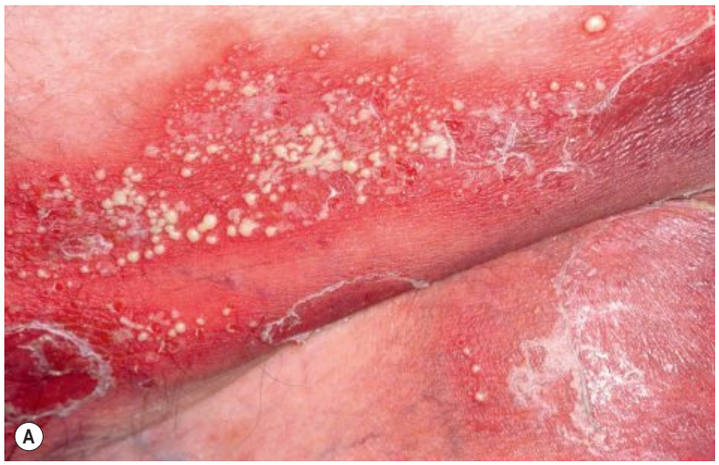




Fig. 29.11 IgA pemphigus – subcorneal pustular dermatosis (SPD) type. A Numerous superficial pustules arising within areas of erythema; these pustules rupture easily. The desquamation has a figurate configuration and overall there is a resemblance to pustular psoriasis. **B** Pustules tend to coalesce to form an annular or figurate pattern with crusts present centrally. Note the accumulation of the pustular component in the dependent portion of the vesiculopustule. *A, Courtesy Luis Requena, MD.*

histologically indistinguishable from classic subcorneal pustular dermatosis (Sneddon–Wilkinson disease; see Ch. 8), immunologic evaluation is essential to differentiate the two diseases.

IgA deposition on cell surfaces of epidermal keratinocytes is present in all cases, as shown by direct immunofluorescence (DIF) microscopy, and many patients have detectable circulating IgA autoantibodies, as shown by indirect immunofluorescence (IIF) microscopy. In the subcorneal pustular dermatosis type, IgA autoantibodies tend to react against upper epidermal surfaces, while in the intraepidermal neutrophilic type, IgA autoantibodies are found throughout the entire epidermis. The subclass of IgA autoantibodies is exclusively IgA1. IgA autoantibodies in the subcorneal pustular dermatosis type were shown to recognize desmocollin 1[52], while the autoimmune targets of the intraepidermal neutrophilic type remain to be identified. A subset of IgA pemphigus patients have IgA autoantibodies directed against Dsg1 or Dsg3, making the autoimmune targets of IgA pemphigus more heterogeneous. Besides the two major forms of IgA pemphigus, some authors include three additional forms of IgA pemphigus – IgA pemphigus foliaceus, IgA pemphigus vulgaris, and IgA pemphigus vegetans. The exact pathogenic role of IgA autoantibodies in inducing pustular formation in IgA pemphigus remains to be elucidated.

PATHOLOGY

For routine histology, it is best to perform biopsies of early lesions. If the vesicle or edematous papule is small enough, the entire lesion can be removed. Otherwise, the biopsy specimen should include the edge of a fresh vesicle or bulla plus the inflammatory rim (Fig. 29.12). Examination of perilesional, rather than lesional, skin is recommended for DIF in order to avoid negative staining due to secondary degeneration of target antigens and immunoreactants. In patients with only mucosal lesions, the biopsy specimen should consist of the active border of a denuded area, since intact blisters are rarely encountered. Cytologic examination (Tzanck smear) is useful for the rapid demonstration of acantholytic epidermal cells within the blister cavity. However, this bedside test merely represents a preliminary diagnostic tool and it should not supplant histologic examination. This is because acantholytic keratinocytes are occasionally seen in various non-acantholytic vesiculobullous or pustular diseases as a result of secondary acantholysis.

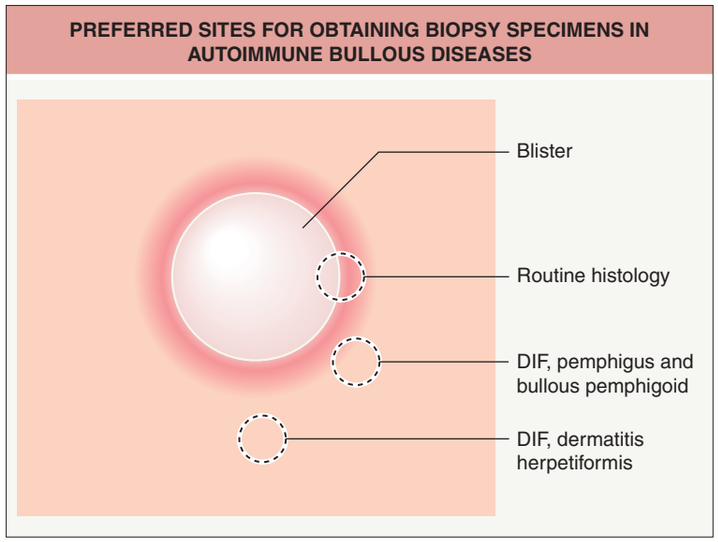


Fig. 29.12 Preferred sites for obtaining biopsy specimens in autoimmune bullous diseases. If the lesion is small enough, the entire vesicle can be removed for routine histology. If the lesions are not small, the edge of a fresh vesicle or bulla plus the inflammatory rim is recommended. For direct immunofluorescence (DIF) for various forms of pemphigus and bullous pemphigoid, perilesional skin is preferred, whereas nearby normal skin is recommended in dermatitis herpetiformis.

Pemphigus Vulgaris

The characteristic histologic finding in this form of pemphigus is intraepidermal blister formation due to a loss of cell–cell adhesion of keratinocytes (acantholysis) without keratinocyte necrosis (Fig. 29.13A). Whereas acantholysis usually occurs just above the basal cell layer (suprabasilar acantholysis), intraepithelial separation may occasionally be higher in the stratum spinosum. A few rounded-up (acantholytic) keratinocytes as well as clusters of epidermal cells are often seen within the blister cavity. Although the basal cells lose lateral desmosomal contact with their neighbors, they maintain their attachment to the basement membrane via *hemidesmosomes*, thus giving the appearance of a "row of tombstones" (Fig. 29.13B). The acantholytic process may involve hair follicles.

The dermal papillary outline is usually maintained and, frequently, the papillae protrude into the blister cavity. The blister cavity may contain a few inflammatory cells, notably eosinophils, and in the dermis there is a moderate perivascular mononuclear cell infiltrate with conspicuous eosinophils. In rare instances, the earliest histologic finding consists of eosinophilic spongiosis (Table 29.4), in which eosinophils infiltrate a spongiotic epidermis with little or no evidence of acantholysis.

In pemphigus vegetans, suprabasilar acantholysis is seen, in addition to considerable papillomatosis and acanthosis. Characteristically, there is an intense inflammatory cell infiltrate containing numerous eosinophils, and intraepidermal microabscesses of eosinophils are often seen.

Pemphigus Foliaceus

The histologic changes of pemphigus foliaceus, pemphigus erythematosus, and fogo selvagem are identical. Early blisters in pemphigus foliaceus have acantholysis in the upper epidermis, within or adjacent to the granular layer (Fig. 29.14). Because the blisters are superficial and fragile, it is often difficult to obtain an intact lesion for histologic examination. As a result, acantholysis is sometimes difficult to detect, but usually a few acantholytic keratinocytes can be found attached to the roof or floor of the blister. Of note, these cells are often almond- or spindle-shaped rather than round. When the blisters form within the granular layer, a "missing" horny layer with a few acantholytic keratinocytes

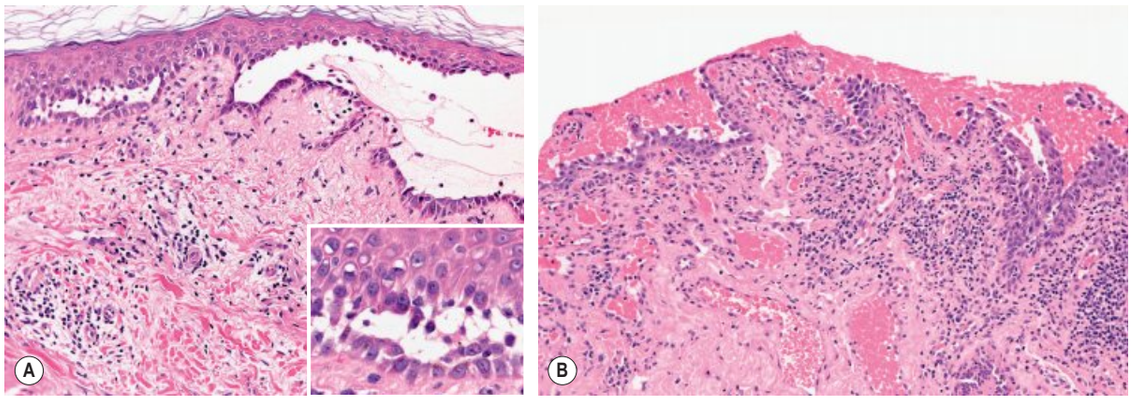


Fig. 29.13 Pemphigus vulgaris – histopathologic features. **A** Blisters in the skin show suprabasilar acantholysis with a few acantholytic cells in the blister cavity (inset). **B** Because blisters in the mouth rarely remain intact, the blister roof is often not seen in oral biopsy specimens. Nonetheless, the diagnosis can be made by the location of the split within the epithelium, the presence of acantholytic cells, and the "tombstones" appearance of the basal cells. *Courtesy Lorenzo Cerroni, MD.*

CAUSES OF EOSINOPHILIC SPONGIOSIS	
• Pemphigus vulgaris and its variants • Pemphigus foliaceus • Bullous pemphigoid and its variants • Pemphigoid gestationis (herpes gestationis) • Mucous membrane (cicatricial) pemphigoid • Linear IgA bullous dermatosis	• Arthropod-bite reactions, including scabies • Drug eruptions • Id reactions • Wells syndrome • Polymorphic eruption of pregnancy • Erythema toxicum neonatorum • Incontinentia pigmenti (first stage) • Atopic dermatitis • Contact dermatitis • Eosinophilic folliculitis • Mycosis fungoides • Prurigo pigmentosa • Still disease

Table 29.4 Causes of eosinophilic spongiosis.

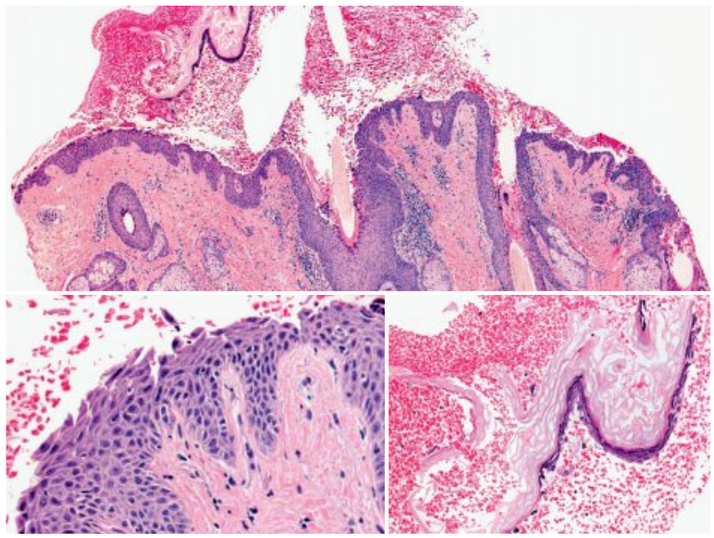


Fig. 29.14 Pemphigus foliaceus – histopathologic features. Because of the fragility of the blisters, the blister roof may become detached (right inset). The split is in the upper spinous layer of the epidermis and acantholytic cells are readily apparent (left inset). *Courtesy Lorenzo Cerroni, MD.*

may be the only histopathologic finding (the horny layer detaches as a consequence of superficial acantholysis). Although the deeper epidermis usually remains intact, secondary clefts may develop, leading to detachment of the epidermis in its midlevel, but rarely giving rise to limited areas of separation right above the basal layer.

These superficial blisters are histologically indistinguishable from those seen in staphylococcal scalded skin syndrome or bullous impetigo, because Dsg1 is targeted in both of these diseases[31]. Sometimes the blister cavity contains numerous acute inflammatory cells, particularly neutrophils. Eosinophilic spongiosis can be also seen in very early lesions of pemphigus foliaceus (see Table 29.4). The dermis shows a moderate number of inflammatory cells, among which eosinophils are often present.

Paraneoplastic Pemphigus

The histologic findings of cutaneous lesions in paraneoplastic pemphigus show considerable variability, reflecting the polymorphism seen clinically. The lesions show a unique combination of pemphigus vulgaris-like, erythema multiforme-like, and lichen planus-like histologic features, sometimes in the same specimen (Fig. 29.15). Intact cutaneous blisters demonstrate suprabasilar acantholysis and individual keratinocyte necrosis as well as lymphocytes within the epidermis. In addition, features of an interface dermatitis can be seen, including basal cell liquefactive degeneration or a dense band-like lymphocytic infiltrate in the upper dermis. Eosinophils are rare. Biopsy specimens of the severe ulcerative stomatitis usually yield only nonspecific changes of inflammation, but the perilesional oral epithelium should show suprabasilar acantholysis.

IgA Pemphigus

The characteristic histologic feature in IgA pemphigus is formation of an intraepidermal pustule or vesicle (Fig. 29.16). The contents of the pustules consist predominantly of neutrophils. Acantholysis is usually not seen. IgA pemphigus is divided into two subtypes depending on the

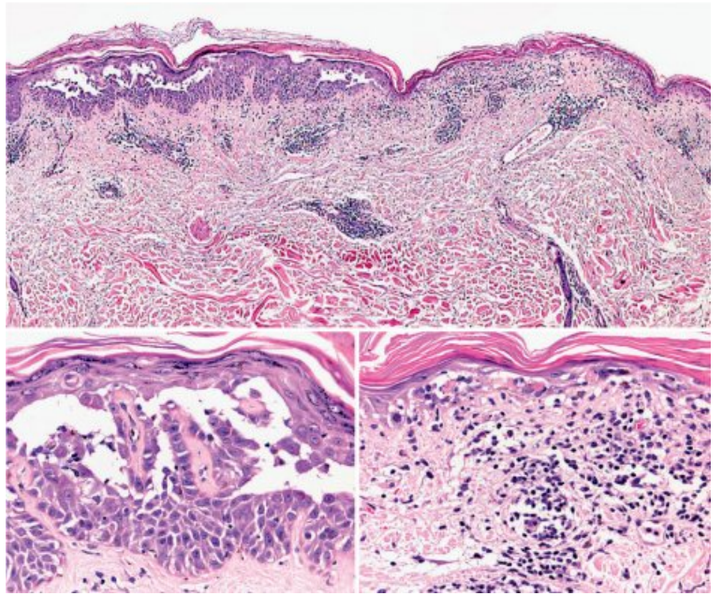


Fig. 29.15 Paraneoplastic pemphigus – histopathologic features. In the same biopsy specimen, there are areas of suprabasilar acantholysis (left inset) as well as an interface dermatitis with basal cell vacuolar change, necrotic keratinocytes, and lymphocytes within the epidermis (right inset). *Courtesy Lorenzo Cerroni, MD.*

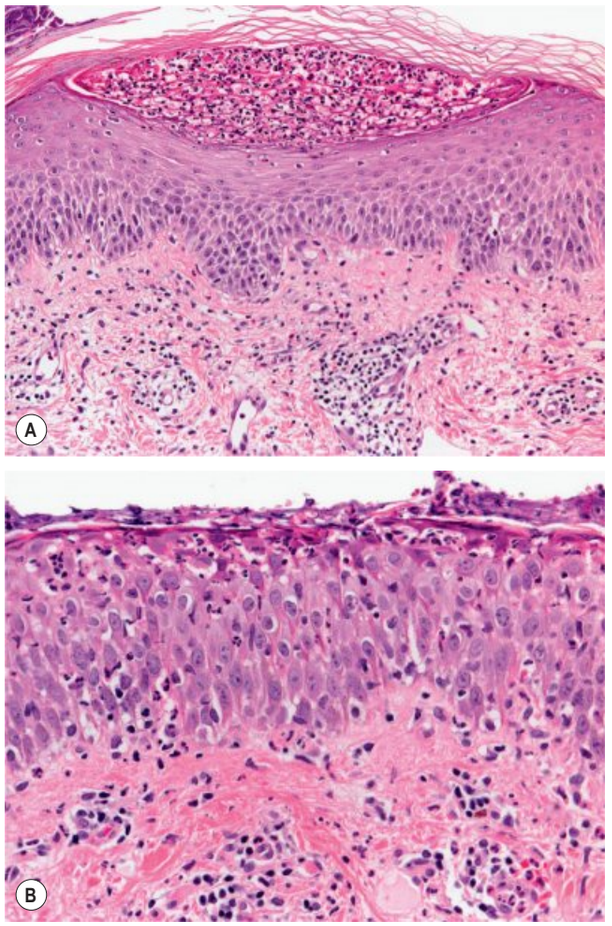


Fig. 29.16 IgA pemphigus – histopathologic features. Intraepidermal pustule with neutrophils present subcorneally in the subcorneal pustular dermatosis type (**A**), and within the entire epidermis in the intraepidermal neutrophilic type (**B**). *Courtesy Lorenzo Cerroni, MD.*

level of intraepidermal pustule; in the subcorneal pustular dermatosis type, pustules are located subcorneally in the upper epidermis, while in the intraepidermal neutrophilic type, suprabasilar pustules involving the lower or entire epidermis are present.

DIFFERENTIAL DIAGNOSIS

Demonstration of IgG (or IgA for IgA pemphigus) autoantibodies directed against the cell surface of keratinocytes is the gold standard for the diagnosis of pemphigus. By detection of these autoantibodies, pemphigus can be differentiated from other vesiculobullous or pustular diseases. Methods for demonstrating pemphigus autoantibodies include DIF, IIF, immunoprecipitation, immunoblotting, and enzyme-linked immunosorbent assay (ELISA).

DIF examines patients' skin or mucous membranes in order to demonstrate *in vivo* bound IgG deposition on the keratinocyte cell surfaces (Fig. 29.17A). The biopsy specimen should be taken from perilesional normal skin or mucous membrane (see Fig. 29.12). DIF is the most reliable and sensitive diagnostic test for all forms of pemphigus. However, on occasion, nonspecific cell surface staining may occur in other skin diseases, such as spongiotic dermatitis, burns, toxic epidermal necrolysis, systemic LE and lichen planus, or in patients with antibodies directed against blood groups A and B. If the DIF is negative, the diagnosis of pemphigus should be seriously questioned. IgG deposition is seen in up to 100% of patients with active pemphigus vulgaris and pemphigus foliaceus. IgM deposition is not found, but occasionally IgA deposition may also be seen. Complement (C3) deposition is not necessarily observed, probably because the dominant subclass of IgG is IgG4, which does not fix complement. The staining pattern of paraneoplastic pemphigus shows deposition of IgG and C3 on epidermal cell surfaces as well as variably along the basement membrane zone. In IgA pemphigus, IgA (but not IgG) deposition is detected on keratinocyte cell surfaces.

IIF examines patients' sera in order to demonstrate circulating IgG autoantibodies directed against epithelial cell surfaces (Fig. 29.17B). In order to optimize sensitivity, there are recommended substrates based upon the particular autoantibody (Table 29.5)[53]. Except for a few patients with early localized disease or those in remission, most patients with pemphigus have circulating anti-epithelial cell surface IgG as determined by IIF. Despite the different antigens involved in pemphigus vulgaris and foliaceus, the staining pattern obtained by DIF or IIF is similar, which makes it difficult to serologically distinguish the two diseases (compare Fig. 29.1B & C). Immunoprecipitation, immunoblotting, and ELISA can be used to demonstrate the target molecules of these autoantibodies.

Immunoprecipitation and immunoblotting detect the target antigens as protein bands of a particular molecular weight that have been separated by electrophoresis (see Ch. 30). Immunoblotting requires denaturation of the protein substrates, but immunoprecipitation does not. Therefore, immunoprecipitation is superior to immunoblotting in detecting antibodies that react with epitopes dependent on three-dimensional structure (conformational epitopes), while immunoblots detect antibodies that react with epitopes that are preserved even after denaturation (linear epitopes). However, an immunoblot is easier to perform because immunoprecipitation requires radioisotopes to label protein substrates.

ELISA is increasingly being used to detect antigen-specific autoantibodies for the diagnosis of pemphigus (Table 29.6)[21,22]. The patient's serum is tested on ELISA plates pre-coated with relevant recombinant proteins, e.g. Dsg1, Dsg3. Thus, specific antibodies directed against Dsg1 or Dsg3 can be detected. This assay has enabled investigators to serologically distinguish subtypes of pemphigus vulgaris and foliaceus. If a serum is positive against Dsg1 but negative against Dsg3, this suggests a diagnosis of pemphigus foliaceus. If negative against Dsg1 but positive against Dsg3, this suggests a diagnosis of the mucosal-dominant type of pemphigus vulgaris. If positive against both Dsg1 and Dsg3, this suggests a diagnosis of mucocutaneous type of pemphigus vulgaris (see Fig. 29.4). Furthermore, ELISA scores demonstrate parallel fluctuations with disease activity and are useful in monitoring disease activity, planning schedules for tapering corticosteroids, and predicting flares or relapses before there is clinical evidence. The *c*hemi*l*uminescent *e*nzyme *i*mmuno*a*ssay (CLEIA) is an even more sensitive and more rapid technique for detecting IgG autoantibodies in patients with pemphigus.

Differential Diagnosis of Pemphigus Vulgaris

Establishing the diagnosis in patients with only oral lesions is more difficult than in those with cutaneous blisters and erosions. The differential diagnosis of mucosal lesions of pemphigus vulgaris includes acute herpetic stomatitis, aphthous stomatitis, erythema multiforme major or Stevens–Johnson syndrome, lichen planus, systemic LE, and mucous membrane (cicatricial) pemphigoid. For cutaneous lesions of pemphigus vulgaris, the differential diagnosis includes other forms of pemphigus, bullous pemphigoid, linear IgA bullous dermatosis, erythema multiforme, Hailey–Hailey disease, and transient acantholytic dermatosis (Grover disease). The differential diagnosis of pemphigus vegetans is outlined in Table 29.7.

The demonstration of IgG autoantibodies against keratinocyte cell surfaces and anti-Dsg3 IgG, as mentioned above, will exclude these diseases (with the exception of drug-induced pemphigus vulgaris and paraneoplastic pemphigus). Fresh blisters of bullous pemphigoid are tense due to a subepidermal split. Hailey–Hailey disease has full-thickness acantholysis ("dilapidated brick wall") with epidermal hyperplasia and an impetiginized scale, and the acantholysis does not extend down follicles as it does in pemphigus. Transient acantholytic dermatosis exhibits only small foci of intraepidermal acantholysis in addition to dyskeratosis; the latter is not present in pemphigus.

Differential Diagnosis of Pemphigus Foliaceus

This differential includes other forms of pemphigus, bullous impetigo, subcorneal pustular dermatosis, subacute cutaneous LE, and seborrheic dermatitis. As discussed earlier for pemphigus vulgaris, the demonstration of IgG autoantibodies against epidermal cell surfaces is essential for separating these disorders from the pemphigus

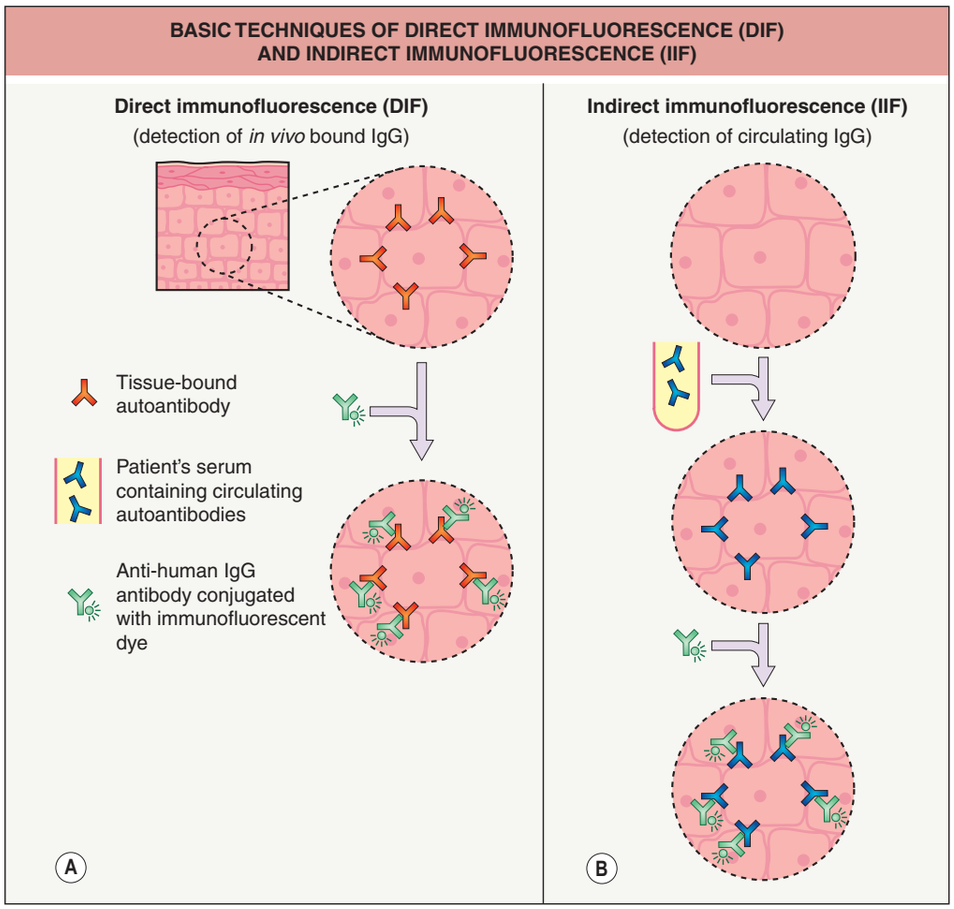


Fig. 29.17 Basic techniques of direct immunofluorescence (DIF) and indirect immunofluorescence (IIF). A DIF is performed on skin biopsy specimens in order to detect *in vivo* bound IgG. **B** IIF is performed utilizing patients' sera in order to detect circulating autoantibodies that bind epithelial antigens.

INDIRECT IMMUNOFLUORESCENCE (IIF) – RECOMMENDED SUBSTRATES	
Type of pemphigus	**Recommended substrates (autoantibodies)**
Pemphigus vulgaris	Monkey esophagus (anti-Dsg3)
Pemphigus foliaceus	Human skin or guinea pig esophagus (anti-Dsg1)
Paraneoplastic pemphigus	Monkey and guinea pig esophagus (anti-Dsg1, anti-Dsg3) Rat bladder (anti-plakin)
Bullous pemphigoid Linear IgA bullous dermatosis	Human skin, salt-split
Mucous membrane (cicatricial) pemphigoid	Human skin, salt-split; normal oral or genital mucosa or conjunctiva

Table 29.5 Indirect immunofluorescence (IIF) for pemphigus and bullous pemphigoid – recommended substrates.

ELISA TO DETECT IgG AUTOANTIBODIES IN AUTOIMMUNE BULLOUS DISEASES – AVAILABLE TARGET AUTOANTIGENS						
Target autoantigen	**Autoimmune bullous diseases**					
	PV	**PF**	**PNP**	**BP**	**MMP**	**EBA**
Dsg1	✓	✓	✓			
Dsg3	✓		✓			
BP180				✓	✓	
BP230			✓	✓	✓	
Laminin 332					✓	
Type VII collagen					✓	✓
Envoplakin			✓			
Periplakin			✓			

Table 29.6 ELISA to detect IgG autoantibodies in autoimmune bullous diseases – available target autoantigens. For BP180, the NC16A domain is utilized and for BP230, the N- and/or C-terminus. BP, bullous pemphigoid; EBA, epidermolysis bullosa acquisita; MMP, mucous membrane pemphigoid; PF, pemphigus foliaceus; PNP, paraneoplastic pemphigus; PV, pemphigus vulgaris.

family. A complete review of medications should be done to exclude the possibility of drug-induced pemphigus foliaceus. Because the lesions of pemphigus foliaceus may become secondarily infected, the finding of bacteria does not confirm a diagnosis of bullous impetigo. Likewise, a clinical flare or recalcitrant disease may represent a superimposed disorder, e.g. tinea corporis, especially in patients on systemic corticosteroids.

Differential Diagnosis of Paraneoplastic Pemphigus

This differential includes pemphigus vulgaris, mucous membrane pemphigoid, erythema multiforme or Stevens–Johnson syndrome, lichen planus, GVHD, persistent HSV infection, and other viral infections; stomatitis due to chemotherapy will be limited in duration (7–14 days) (Table 29.8). In two-thirds of patients with paraneoplastic pemphigus, it arises in the context of a known underlying neoplasm, usually a lymphoproliferative disorder, which may have been treated for years before the mucocutaneous lesions appear. In approximately one-third of patients, the underlying neoplasm is undiagnosed at the time the mucocutaneous disease develops. In these latter patients, examination for an occult neoplasm is required, and, given the most commonly associated ones (see earlier), a CT scan of the chest, abdomen, and pelvis should accompany a complete blood count, flow cytometry of peripheral blood, LDH, and serum protein and immunofixation electrophoreses. Severe intractable stomatitis that extends onto the vermilion lip is a key clinical feature in differentiating paraneoplastic pemphigus from

PEMPHIGUS VEGETANS – DIFFERENTIAL DIAGNOSIS	
Major entities	
Hailey–Hailey disease	Vegetative lesions also seen when Darier disease involves intertriginous zones; see Ch. 59
Pemphigoid vegetans	Especially in major body folds; see Fig. 30.6C
Blastomycosis-like pyoderma	Vegetating plaques due to inflammatory reaction to bacterial infection, most commonly *Staphylococcus aureus*; immunosuppression, systemic or local, a risk factor
Pyodermatitis–pyostomatitis vegetans	Form of pyoderma gangrenosum; see Ch. 25
Other entities	
Halogenoderma	
Infections Bacterial – granuloma inguinale, condylomata lata Fungal – dimorphic, chromomycosis Viral – condylomata acuminata, herpes simplex vegetans, chronic verrucous herpes zoster* Parasitic – amebic granuloma	
Buschke–Löwenstein tumors Extramammary Paget disease	
*Occurs in immunocompromised hosts.	

Table 29.7 Pemphigus vegetans – differential diagnosis.

DISORDERS WITH HEMORRHAGIC CRUSTS OF THE VERMILION LIPS	
• Herpes simplex • Herpes zoster	
• Erythema multiforme major • *Mycoplasma*-induced rash and mucositis (MIRM)* • Stevens–Johnson syndrome/toxic epidermal necrolysis spectrum	
• Pemphigus vulgaris • Paraneoplastic pemphigus	
• Contact cheilitis	
*Also referred to as reactive infectious mucocutaneous eruption (RIME).	

Table 29.8 Disorders with hemorrhagic crusts of the vermilion lips. *Photograph: Courtesy Jeffrey P. Callen, MD.*

THERAPEUTIC LADDER FOR PEMPHIGUS VULGARIS	
Standard treatment	
Oral prednisone	1 mg/kg/day as an initial dose (usually 60 mg/day) (1)
Rituximab	375 mg/m^2 once weekly for 4 weeks or 1 g initially then at two weeks; either regimen may need to be repeated every 3–6 months (1)
Aggressive treatment	
Immunosuppressive agents in combination with oral prednisone:	
Azathioprine	2–4 mg/kg/day (usually 100 to 300 mg/day) (1)
Mycophenolate mofetil	2–3 g/day (2)
Cyclophosphamide	1–3 mg/kg/day (usually 50 to 200 mg/day) (2)
Cyclosporine	3–5 mg/kg/day (2)*
Pulse methylprednisolone	1 g/day over a period of 2–3 hours for 3–5 consecutive days (2)
Methotrexate	7.5–20 mg/week (2)
Pulse cyclophosphamide	500–1000 mg/m^2 every 4 weeks (3)
Plasmapheresis	1–2 times per week, at the onset (2)
High-dose IVIg	400 mg/kg/day for 5 consecutive days (1); may need to be repeated monthly
Extracorporeal photopheresis	2 days per month (3)
Topical treatment	
• Topical corticosteroids (1), especially Class I to localized persistent sites	
• Topical antibiotics (2)	
• Topical immunomodulators (e.g. cyclosporine, tacrolimus) (3)	
Intralesional therapy	
• Corticosteroids (3)	
• Rituximab (5 mg/cm^2) (3)	
*In one trial, shown not to be of benefit when added to systemic corticosteroids.	

Table 29.9 Therapeutic ladder for pemphigus vulgaris. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

most cases of pemphigus vulgaris or mucous membrane pemphigoid. The gold standard for the diagnosis of paraneoplastic pemphigus is the demonstration of the characteristic combination of IgG autoantibodies – anti-plakin autoantibodies by immunoprecipitation, immunoblotting or ELISA and anti-desmoglein autoantibodies by ELISA (see Table 29.6).

Differential Diagnosis of IgA Pemphigus

The differential diagnosis includes subcorneal pustular dermatosis, pemphigus foliaceus, bullous impetigo, dermatitis herpetiformis, linear IgA bullous dermatosis, and pustular psoriasis. The clinical and histologic features of the SPD type of IgA pemphigus and classic subcorneal pustular dermatosis are indistinguishable. The demonstration of IgA autoantibodies is essential for separating these other disorders from IgA pemphigus.

TREATMENT

Pemphigus Vulgaris

Before the advent of systemic corticosteroids, pemphigus vulgaris was usually a fatal disease; most patients died within 2–5 years of the onset of the disease because large areas of the skin lost their epidermal barrier function, leading to the loss of body fluids or to secondary bacterial infections. Pemphigus foliaceus had a better prognosis, except for the occasional acute cases with generalized involvement. Because pemphigus is caused by pathogenic autoantibodies, therapy must be designed to reduce autoantibody production, not just to suppress local inflammation. The introduction of systemic corticosteroids and immunosuppressive agents has greatly improved the prognosis of pemphigus; however, the morbidity, and occasional mortality, is still significant due to complications of therapy. Systemic corticosteroids are the mainstay of therapy for pemphigus. Immunosuppressive agents are often used for their corticosteroid-sparing effect in order to reduce the side effects of the corticosteroids (Table 29.9), with the goal of therapy being to control the disease with the lowest possible dose of corticosteroids. High-dose IVIg, which is non-immunosuppressive, and anti-CD20 monoclonal antibodies have been recently added to the therapeutic armamentarium for pemphigus. Introduction of PDAI (pemphigus disease area index) and ABSIS (autoimmune bullous skin disorder intensity score) allow for more standardized assessment of disease extent and response to treatment[54].

Systemic corticosteroid therapy, usually in the form of oral prednisone, is standard treatment (see Ch. 125). Prednisone at 1 mg/kg/day (usually 60 mg/day) is a typical initial dosage. The therapeutic effects are clinically estimated by the number of new blisters per day and the rate of healing of new lesions, and the prednisone is then gradually tapered. Once clinical remission is obtained, changes in the titer of circulating autoantibodies, as determined by IIF or ELISA, are helpful in gauging the dose of prednisone[22]. If there is no response in 3–7 days, other options may be employed, as discussed below. Intravenous pulse therapy with 1 g/day methylprednisolone (over a period of 2–3 hours, with continuous cardiac monitoring) for 3–5 consecutive days is an alternative choice for severe cases.

In general, immunosuppressive agents, such as *azathioprine*, *mycophenolate mofetil* and *cyclophosphamide*, when combined with corticosteroids, may result in gaining early control of the disease and an increased percentage of clinical remissions[55–60]. For example, in patients with mild to moderate disease who received corticosteroids plus either placebo or mycophenolate mofetil in a prospective, randomized trial, the latter group showed faster and more durable responses[61]. Azathioprine is used at a dose of 2–4 mg/kg/day (usually 100–300 mg/day) and its major side effects are nausea and dose-dependent myelosuppression (see Ch. 130). Mycophenolate mofetil is used at a dose of 2–3 g/day and it has a similar action to azathioprine, with less myelosuppression but more gastrointestinal toxicity[58]. Cyclophosphamide is given at a dose of 1–3 mg/kg/day (usually 50–200 mg/day) orally or 500–1000 mg/m^2 every four weeks intravenously and its major side effects are hemorrhagic cystitis, sterility and leukopenia, with an increased risk of bladder carcinoma long-term; there is a movement away from lower doses of daily cyclophosphamide in an effort to possibly reduce the risk of bladder cancer. Chlorambucil, like cyclophosphamide, is an alkylating agent and although there is no bladder toxicity, side effects include myelosuppression and long-term an increased risk of developing leukemia.

If complete remission is achieved with the combined therapy, the dosage of the immunosuppressive drug is maintained while the prednisone is slowly tapered; when a dose of 5–10 mg/day is reached, careful taper then discontinuation of the immunosuppressive drug is attempted. In young patients, the potential increase in malignancies that might be associated with the use of these drugs must be taken into account. In some patients, especially those who are elderly with limited disease or those in whom corticosteroids are contraindicated, immunosuppressive agents alone may be used.

While *cyclosporine* (3–5 mg/kg/day) has been used as an immunosuppressive agent in some patients with pemphigus vulgaris, a randomized trial found that the addition of cyclosporine to corticosteroids did not offer a benefit. Also, *gold* is rarely utilized nowadays.

Plasmapheresis is useful for quickly reducing the titers of circulating autoantibodies and should be considered for severe pemphigus if the disease is unresponsive to a combination of prednisone and immunosuppressives[59]. Concomitant immunosuppression with corticosteroids and cyclophosphamide prevents a post-plasmapheresis rebound increase in the production of autoantibody.

High-dose IVIg is another option for resistant disease. IVIg is a blood product prepared from pooled plasma that has immunomodulatory effects when used in a high dose. It is thought to exert its effect via multiple modes of action, including modulation of expression and function of Fc receptors and the cytokine network; provision of anti-idiotypic antibodies; and modulation of dendritic cell, T cell, and B cell activation, differentiation, and effector functions[62]. A multicenter, randomized, placebo-controlled, double-blind trial demonstrated that high-dose IVIg is an effective and safe treatment for steroid-resistant pemphigus[63].

Rituximab is a potent B cell-depleting chimeric anti-CD20 monoclonal antibody that was first used to treat B cell malignancies, but increasingly is used for a variety of autoimmune diseases, including pemphigus. CD20 is a transmembrane glycoprotein specifically expressed on B cells (from the pre-B stage in the bone marrow to the activated and memory B stage in blood or secondary lymphoid organs), but its expression is lost upon plasma cell differentiation[64]. Rituximab seems not only to induce a depletion of CD20$^+$ B cells and a decline in IgG (including anti-desmoglein autoantibodies), but also decreases desmoglein-specific T cells[65]. When used as adjuvant therapy in non-randomized prospective studies, rituximab led to a complete remission in most of the patients with refractory pemphigus vulgaris and foliaceus[66–68]. A prospective, open-label, randomized trial demonstrated that as an adjuvant therapy rituximab led to a greater proportion of patients achieving complete remission off-therapy, compared with corticosteroid treatment alone[69]. The US FDA has approved rituximab for moderate-to-severe pemphigus and a consensus group has suggested that it be considered early in the course of disease rather than just for patients with recalcitrant disease[60]. The side effects of rituximab, including infusion reactions, reactivation of hepatitis B virus, and progressive multifocal leukoencephalopathy, are discussed in Chapter 128. Because rituximab is a chimeric biologic agent, patients may develop anti-drug antibodies and in theory a lower therapeutic response. As in primary cutaneous B cell lymphoma, there are reports of the use of intralesional injections of rituximab for refractory pemphigus vulgaris[70]. Humanized anti-CD20 antibodies, e.g. obinutuzumab, ofatumumab, may become alternative options for B cell depletion.

Desmoglein-specific immune suppression, via targeting T cells or B cells, would represent an ideal therapeutic strategy given that the target antigens and pathophysiological mechanisms of pemphigus have been well characterized. In 2020, the FDA granted DSG3-CAART, which targets Dsg3-specific B cells[71], orphan drug designation for the treatment of pemphigus vulgaris. Lastly, in a recent phase II trial, efgartigimod, an inhibitor of the neonatal Fc-receptor (FcRn) led to early disease control in 28 of 31 patients with either pemphigus vulgaris or pemphigus foliaceus[72].

Pemphigus Foliaceus

When pemphigus foliaceus is active and widespread, the treatment is, in general, similar to that for pemphigus vulgaris. In some patients, pemphigus foliaceus may be localized for many years; they do not necessarily have to be treated with systemic therapy, and superpotent topical corticosteroids may be sufficient to control the disease. Dapsone can also be used when neutrophils are dominant histologically.

Paraneoplastic Pemphigus

Patients with benign tumors, such as thymomas or localized Castleman disease, should have the tumor surgically excised. The majority of these patients will either improve substantially or clear completely. However, it may take 6–18 months to see complete resolution of lesions after excision of a benign neoplasm. In patients with malignant neoplasms, there is no consensus on a standard effective therapeutic regimen. Administration of tumor-specific chemotherapy or targeted therapy may result in complete resolution of the malignancy and a slow resolution of the skin lesions. Cutaneous lesions respond more rapidly to therapy, in contrast to the stomatitis, which is generally refractory to most forms of treatment. Overall, the prognosis of paraneoplastic pemphigus is poor due to its resistant nature to treatment.

IgA Pemphigus

Dapsone is the drug of choice for most patients with IgA pemphigus. A clinical response usually occurs within 24–48 hours. If dapsone is not well tolerated, sulfapyridine and acitretin are useful alternatives. Occasionally, those drugs are not effective, and low- to medium-dose prednisone may be considered, as well as photochemotherapy (PUVA) or colchicine.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 29.1 Pemphigus vulgaris. Flaccid blisters and an erosion due to rupture of a bulla.



eFig. 29.2 Pemphigus foliaceus. Multiple erosions as well as thick scale-crusts on the upper back.



eFig. 29.3 Pemphigus foliaceus of the scalp that may be misdiagnosed as sebopsoriasis. *Courtesy Jeffrey P. Callen, MD.*



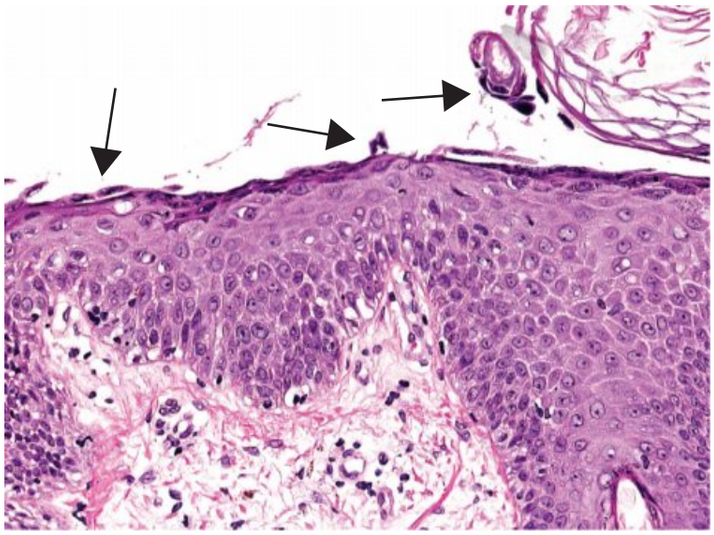
eFig. 29.4 Pemphigus foliaceus. Generalized erythema with large erosions and widespread scale-crusts. The latter are said to resemble corn flakes.



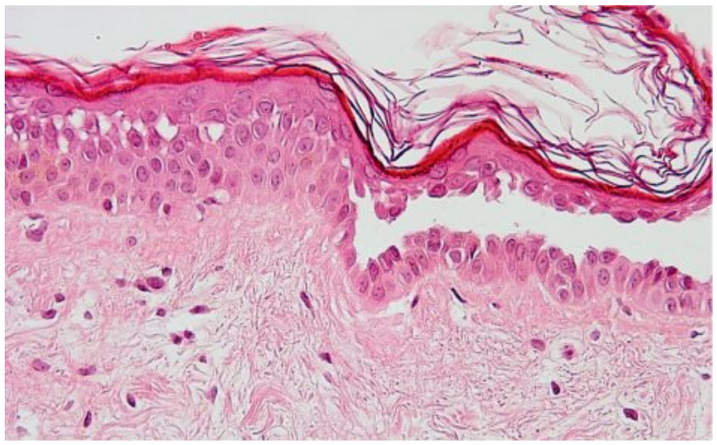
eFig. 29.5 Paraneoplastic pemphigus. Fragile vesicles and bullae on an inflammatory base. See Figure 29.10C for lichenoid lesions in the same patient. *Courtesy Jennie Clarke, MD.*



eFig. 29.6 IgA pemphigus. Intraepidermal neutrophilic (IEN) type. The characteristic sunflower-like configuration of pustules is seen.



eFig. 29.7 Pemphigus foliaceus – histopathological features. Cleavage within the granular layer results in detachment of the horny layer; note a few acantholytic keratinocytes as a clue (arrows). *Courtesy Lorenzo Cerroni, MD*.



eFig. 29.8 Pemphigus foliaceus – histopathological features. Clefting is seen in the upper spinous layer of the epidermis with several acantholytic cells detaching from the roof of the blister.

Pemphigoid Group 30

Luca Borradori and Michael Hertl

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BULLOUS PEMPHIGOID

Synonym: ■ Pemphigoid

Key features

- Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease, and its onset is often after 60 years of age
- It is usually a chronic disease, with spontaneous exacerbations and remissions, which may be accompanied by significant morbidity
- BP is associated with tissue-bound and circulating autoantibodies directed against BP antigen 180 (BP180, BPAG2, or type XVII collagen) and BP antigen 230 (BP230 or BPAG1e), components of junctional adhesion complexes called hemidesmosomes that promote dermal–epidermal cohesion
- The spectrum of clinical presentations is extremely broad. Characteristically, BP is an intensely pruritic eruption with widespread blister formation. In its early stages, or in variants of the disease, only eczematous or urticarial lesions (either localized or generalized) or just excoriations due to intense pruritus are present
- Diagnosis relies on immunopathologic examinations, particularly direct and indirect immunofluorescence (IF) microscopy as well as ELISA for anti-BP180/BP230 autoantibodies

Introduction

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease. It typically presents in older adults as a generalized pruritic bullous eruption and is often associated with significant morbidity. The clinical presentation is quite polymorphic, particularly during the early stages of the disease or in atypical variants, in which full-blown bullous lesions may be absent. In these cases, establishing the diagnosis of BP requires a high degree of suspicion. The antigens targeted by patients' autoantibodies represent two components of hemidesmosomes, the junctional adhesion complexes found in skin and adjacent mucosae (see Fig. 28.3A).

History

In 1953 Lever recognized BP as a disorder distinct from the various types of "true" pemphigus based upon specific clinical and histopathologic features[1]. A decade later, Jordon, Beutner, and colleagues[2] demonstrated that BP patients had tissue-bound and circulating autoantibodies directed against the cutaneous basement membrane zone (BMZ), an observation that suggested that subepidermal dysadhesion was due to autoantibodies directed against structural components of the skin[2]. Further milestones in our understanding of BP included the immunochemical characterization of targeted proteins, the cloning of their genes, and the development of animal models of the disease[3–5].

Epidemiology

BP is typically a disease of older adults, with a mean age of presentation between 65 and 85 years. The annual incidence has been estimated to range from 5 to 45 new cases per million population per year. The incidence rate of BP appears to have significantly increased over the past two decades, most likely reflecting an aging population, better recognition of atypical variants, and a rise in drug-induced BP[6]. A relative risk for patients over 90 years of age appears to be ~300-fold higher than for those 60 years of age or younger. The disease also occurs in children, but rarely. Certain HLA class II alleles are more prevalent in patients with BP than in the general population[7]. In Caucasians, a significant association with the allele DQB1*0301 has been noted, while an increased frequency of the alleles DRB1*04, DRB1*1101, and DQB1*0302 has been observed in Japanese patients.

Pathogenesis

BP is an example of an immune-mediated disease that is associated with a humoral and cellular response directed against two well-characterized self-antigens: BP antigen 180 (BP180, also known as BPAG2 or type XVII collagen) and BP antigen 230 (BP230, also referred to as the epithelial isoform of BPAG1 [BPAG1e]) (Table 30.1)[3,4]. While the former is a transmembrane protein with a large collagenous extracellular domain, the latter is a cytoplasmic protein belonging to the plakin family (see Ch. 28). These two antigens are components of the hemidesmosomes, which are adhesion complexes promoting epithelial–stromal adhesion in stratified and other complex epithelia.

In vitro studies and *in vivo* animal models have demonstrated the pathogenic role of autoantibodies in BP. Furthermore, in gestational pemphigoid, a disease closely related to BP, the transplacental transfer of anti-BP180 autoantibodies from the mother to the neonate can result in a transient bullous eruption (see Ch. 34).

Humoral and cellular responses

Almost all patients with BP have circulating IgG autoantibodies that bind to BP180. Specifically, it is the non-collagenous NC16A domain, a region of BP180 located extracellularly but close to the transmembrane domain, that constitutes the immunodominant region (see Fig. 31.9)[8,9]. However, additional antigenic sites exist within both the extracellular and intracellular domains of BP180, and they are recognized by up to 70% of BP sera[8,9]. Patients with BP also exhibit significant autoreactivity to BP230, and BP230-reactive autoantibodies bind predominantly to the COOH-terminal region of this autoantigen[4,8,9]. The presence of several antigenic sites throughout BP180 and BP230 most likely results from the phenomenon known as "epitope spreading" (see below)[9]. This phenomenon may also account for the finding that patients' sera rarely contain autoantibodies targeting additional components of the BMZ.

Patients with BP develop an autoreactive T cell response to BP180 and BP230. Likely related to a dysfunction of regulatory T cells, it is crucial for stimulating B cells to produce autoantibodies[10,11]. The responsiveness of anti-BP180 autoreactive T cells is restricted by certain HLA class II alleles (e.g. HLA-DQB1*0301), which are prevalent in BP patients. These T lymphocytes, whose major relevant epitopes seem to be harbored within the NC16 domain, have a $CD4^+$ phenotype and produce both Th1 (e.g. interferon-γ) and Th2 cytokines (e.g. interleukin [IL]-4, IL-5, IL-13; see Ch. 4)[10,11]. Th2 and Th17 cytokines, which are particularly relevant to the pathophysiology of BP, predominate within lesional tissue and in patients' sera[10–13].

Upon binding of autoantibodies to their target antigens, subepidermal blister formation results from a cascade of events in which Fc

MAJOR AUTOANTIGENS OF SUBEPIDERMAL AUTOIMMUNE-MEDIATED BLISTERING DISEASES			
Disease	**Target antigen(s)**	**Mol. wt. (kDa)**	**Morphologic structures**
Bullous pemphigoid (BP)	BP180/BPAG2/collagen XVII BP230/BPAG1e	180 230	Hemidesmosomal plaque/anchoring filaments Hemidesmosomal plaque
Gestational pemphigoid	BP180/BPAG2/collagen XVII BP230/BPAG1e	180 230	Hemidesmosomal plaque/anchoring filaments Hemidesmosomal plaque
Mucous membrane pemphigoid	BP180/BPAG2/collagen XVII BP230/BPAG1e† Laminin 332 (laminin 5; $\alpha_3\beta_3\gamma_2$; epiligrin) Laminin 311 (laminin 6; $\alpha_3\beta_1\gamma_1$)‡ Integrin β_4 subunit§ Integrin α_6 subunit§ LABD97, LAD-1 Type VII collagen†	180 230 165, 140, 105 165, 220, 200 200 120 97, 120 290/145	Hemidesmosomal plaque/anchoring filaments Hemidesmosomal plaque Anchoring filaments Anchoring filaments/extracellular matrix Hemidesmosomal plaque/anchoring filaments Anchoring filaments Anchoring fibrils
Linear IgA bullous dermatosis (LABD)	LABD97, LAD-1¶ BP180/BPAG2/collagen XVII BP230/BPAG1e† Type VII collagen†	97, 120 180 230 290/145	Anchoring filaments Hemidesmosomal plaque/anchoring filaments Hemidesmosomal plaque Anchoring fibrils
Epidermolysis bullosa acquisita	Type VII collagen	290/145	Anchoring fibrils
Anti-p200 pemphigoid (anti-laminin γ1 pemphigoid)	Laminin γ1 chain*	200	Extracellular matrix
Bullous systemic lupus erythematosus	Type VII collagen†	290/145	Anchoring fibrils
Lichen planus pemphigoides	BP180/BPAG2/collagen XVII BP230/BPAG1e†	180 230	Hemidesmosomal plaque/anchoring filaments Hemidesmosomal plaque

*Major target antigen; additional target antigens, which may be critical in the pathogenesis, have been identified in one-third of cases.
†Detectable in a subset of patients.
‡Binding to laminin 311 depends on the presence of cross-reactive autoantibodies directed against the α-chain of laminin 332 (laminin 5).
¶They constitute the most characteristic serologic marker for LABD. The 120 kDa LAD-1 antigen corresponds to the cleaved, shed extracellular domain of BP180/BPAG2. The 97 kDa LABD97 protein results from its further proteolytic degradation (see Fig. 31.9).
§Reactivity against the α_6 and β_4 subunits of the $\alpha_6\beta_4$ integrin have been described in subsets of patients with oral- and ocular-predominant MMP, respectively. The significance of these autoantibodies remains to be validated.

Table 30.1 Major autoantigens of subepidermal autoimmune-mediated blistering diseases. Not an exhaustive list. In the course of these diseases, it is possible to detect autoantibodies directed against additional antigens, the significance of which remains to be established. In certain cases, a so-called "intermolecular epitope spreading" phenomenon is thought to occur.

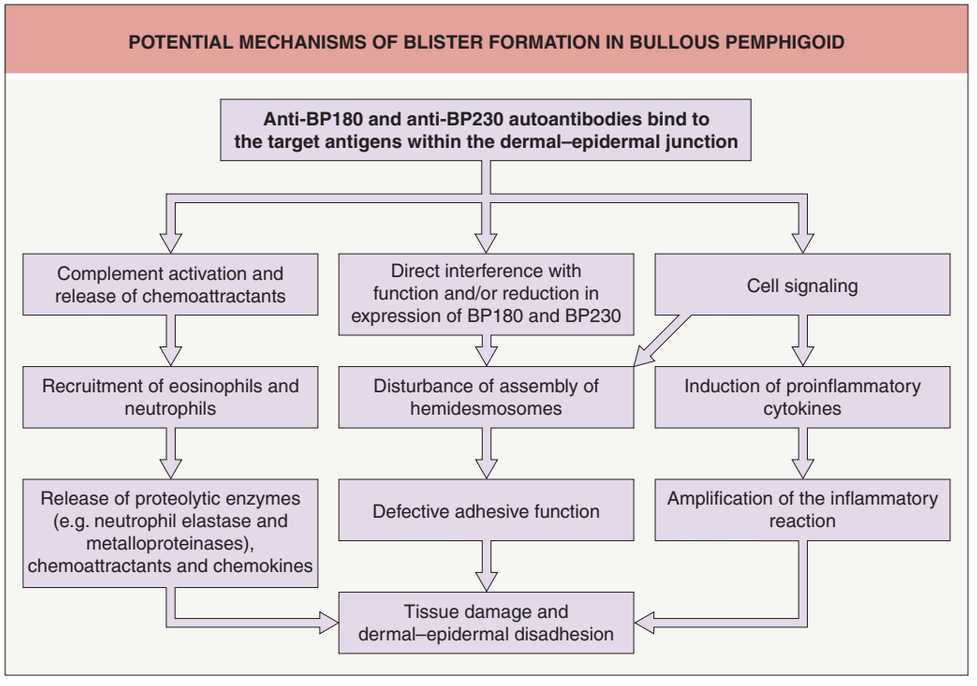


Fig. 30.1 Potential mechanisms of blister formation in bullous pemphigoid. IgG autoantibodies are classically involved in the pathogenesis, but more recently IgE autoantibodies have also been described. The latter may directly trigger the degranulation of FcεRI-expressing cells, such as eosinophils and mast cells.

receptor-mediated mechanisms are critical[5,11,14–18]. The latter involve activation of the complement cascade along with stimulation and recruitment of inflammatory cells including macrophages, neutrophils, mast cells, and eosinophils. These inflammatory cells contribute to tissue damage via liberation of various proteases (e.g. matrix metalloproteinase-9, neutrophil elastase, mast cell proteases), eosinophil toxic granules, and a variety of cytokines (e.g. IL-4, -5, -8, -13, -17, eotaxin). The latter serve to further amplify the inflammatory response[5,11–16] while the proteinases, together with reactive oxygen species, degrade various extracellular matrix proteins as well as BP180.[11–16] IgG anti-BP180 autoantibodies can also boost the inflammatory response by stimulating keratinocytes to express inflammatory cytokines (Fig. 30.1)[11]. Furthermore, IgG autoantibodies are able to directly impair dermal–epidermal adhesion without complement activation[11].

Finally, BP patients often have circulating IgE anti-BP180 autoantibodies which may bind to the epidermal BMZ. These IgE autoantibodies also seem able to form complexes with shed BP180 fragments, which are prominently detected in the dermis on the surface of mast cells and/or eosinophils expressing FcεRI. Hence, IgE autoantibodies most likely directly contribute to tissue damage by triggering the degranulation of these FcεRI-expressing cells[11,15,16].

Animal models have provided strong evidence that IgG autoantibodies against BP180 are pathogenic[5,11,14,17,18]. When passively transferred to neonatal mice (in which BP180 had been fully or partially humanized by genetic engineering), human autoantibodies against the NC16A domain were able to induce a blistering disorder that reproduced all the key features of BP[11,17]. In addition, passive transfer experiments in mice have indicated that IgE antibodies directed against BP180 contribute to skin inflammation[15]. The prevailing pathomechanism is that antibodies against the ectodomain of BP180 are critical for disease initiation, while the development of antibodies against BP230 represents a secondary event that contributes to tissue damage[9,11,18]. However, recent studies utilizing a mouse model demonstrated that anti-BP230 antibodies also had a direct pathogenic effect[19].

Clinical Features

Non-bullous pemphigoid

The cutaneous manifestations of BP can be extremely polymorphic (Figs. 30.2–30.6)[1,18,20–22]. In the prodromal, non-bullous phase of the disease, signs and symptoms are frequently nonspecific, but mild to severe intractable pruritus is a consistent feature. Clinical findings vary from excoriations to eczematous, papular, and/or urticarial lesions that have persisted for several weeks or months (see Figs. 30.3 to 30.5). Importantly, these nonspecific skin findings may remain as the only signs of the disease. At least 20% of patients have neither obvious blisters nor erosions due to ruptured bullae at the time of diagnosis[18,20,22].

Bullous phase

The bullous stage of BP is characterized by the development of vesicles and bullae on apparently normal or erythematous skin, together with urticarial and infiltrated papules and plaques that occasionally assume an annular or figurate pattern. The blisters are tense, up to 1–4 cm in diameter, contain a clear fluid, and may persist for several days, leaving eroded and crusted areas (see Fig. 30.2). Occasionally, the blister fluid becomes blood-tinged. The lesions frequently have a symmetric distribution pattern, and they predominate on the flexural aspects of the extremities and the lower trunk, including the abdomen. Within intertriginous zones, vegetating plaques may be observed (pemphigoid vegetans; see Fig. 30.6C). The extent and degree of disease activity can be assessed by employing the BP disease area index (BPDAI)[21] or a daily blister count.

Residual postinflammatory changes include hyper- and hypopigmentation and, less commonly, milia. Involvement of the oral cavity is observed in 10%–30% of patients, more often in those with moderate to severe disease. The mucosae of the eyes, nose, pharynx, esophagus, and anogenital region are more rarely affected. In ~50% of patients, a peripheral blood eosinophilia is noted.

Clinical variants

Several clinical forms of BP have been described and are outlined in Table 30.2[18,20,22]. *Gestational pemphigoid* (pemphigoid gestationis) is also a variant of BP, which typically occurs during pregnancy (see Ch. 27).

While the individual lesions of BP in infants and in older children (*infantile* and *childhood BP*) are similar to those observed in older adults, the sites of involvement can differ (Fig. 30.7). In infants, bullae often first appear in acral locations and then can generalize to other sites, including often the face. Involvement of the genital region (e.g. *vulvar childhood pemphigoid*) as well as other mucosal sites has been observed in children[18,20].

Associated Diseases

The association of internal malignancies with BP is probably related primarily to the older age of the patient. In case–control studies, the trend towards an increased risk of malignancy was marginal[18,20] while an English national record linkage study found no overall increased risk for concurrent or subsequent malignancies in BP patients[23]. Nonetheless, individuals with BP should be up to date with age-related cancer screening tests recommended for the general population.

Rarely, BP has been described in patients with inflammatory bowel disease or other autoimmune diseases including Hashimoto thyroiditis,

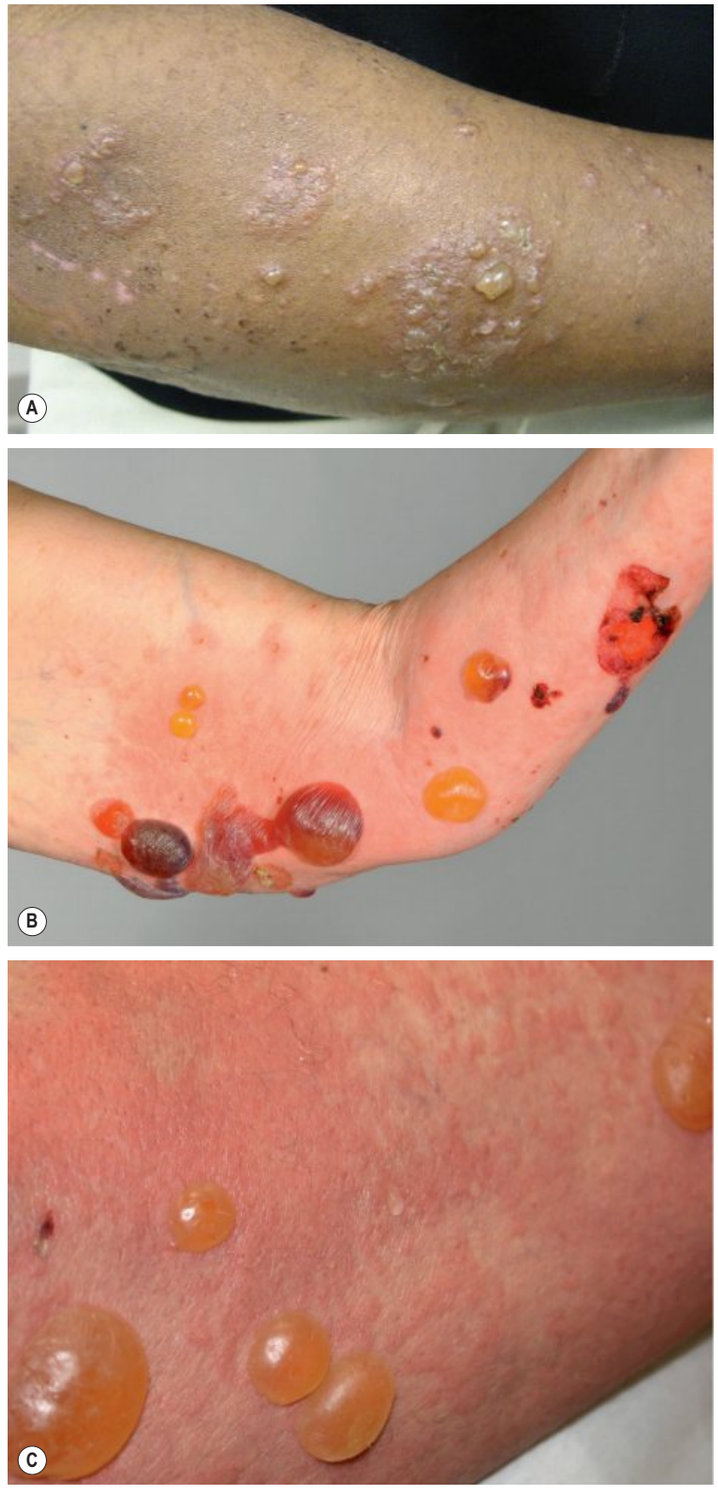


Fig. 30.2 Bullous pemphigoid – classic presentation. A–C Tense vesicles and bullae vary in size from a few mm to several cm in diameter and can arise within normal-appearing skin, areas of erythema, or urticarial plaques. The blister fluid may be serous or hemorrhagic. The flexor aspect of the extremities is a common site of involvement. As the bullae age, they become flaccid and rupture, leaving erosions and serous or hemorrhagic crusts. Biopsies of vesiculobullae for routine histology should be obtained from the edge of a fresh tense blister. *Jeffrey Callen, MD.*



Fig. 30.3 Bullous pemphigoid – urticarial presentation. Multiple, firm annular, arciform and polycyclic urticarial plaques. Note the absence of bullae.



Fig. 30.4 Bullous pemphigoid – eczematous presentation. Large pink eczematous plaques on the trunk and upper extremities.

rheumatoid arthritis, dermatomyositis, and lupus erythematosus (LE)[18,20,23,24]. These associations may be fortuitous or they could reflect a genetically determined susceptibility to develop autoimmune disorders. While one case–control study did not find an increased risk for autoimmune diseases[24], a sample analysis of US hospitalized patients with BP reported a slight risk for other autoimmune disorders[25].

In some patients, BP appears to be triggered by trauma, burns, radiotherapy or UV irradiation (including PUVA). BP has also been observed in association with certain dermatoses, in particular lichen planus and psoriasis (Fig. 30.8)[18,20]. In *lichen planus pemphigoides*, BP coexists with lichen planus (see Ch. 11). Theoretically, a dysfunction of T regulatory cells leads to both a lichenoid interface dermatitis and an autoantibody response to BP180 and BP230. In the setting of chronic inflammation at the dermal–epidermal junction, exposure of antigens to autoreactive T lymphocytes could result in a secondary immune response[26].

Finally, BP has been strongly associated with psychiatric and neurologic disorders; the latter include Parkinson disease, dementia, multiple sclerosis, and stroke[27]. It should be noted that a neuronal variant of BP230 is expressed in the central and peripheral nervous systems[19], while available data regarding the expression of BP180 are contradictory. Whether exposure to neuronal antigens, via a compromised blood–brain barrier, plays a role in the development of BP remains to be determined.



Fig. 30.5 Bullous pemphigoid – nonspecific lesions due to pruritus. Multiple excoriations and nonspecific lesions of prurigo simplex are present. Bullous pemphigoid is in the differential diagnosis of chronic pruritus associated with secondary excoriations.

Drug-induced bullous pemphigoid

In certain patients, systemic medications can lead to the development of BP (Fig. 30.9)[28,29]. There are multiple implicated drugs, in particular diuretics (e.g. furosemide), NSAIDs, antibiotics (e.g. amoxicillin, ciprofloxacin), ACE inhibitors, and TNF inhibitors. More recently, dipeptidyl peptidase-4 inhibitors (e.g. vildagliptin, linagliptin) and immune checkpoint inhibitors (e.g. nivolumab, pembrolizumab) have been strongly associated with BP. A meta-analysis suggested that exposure to aldosterone antagonists, dipeptidyl peptidase-4 inhibitors, anticholinergics, and dopaminergic medications were significantly associated with BP[28]. Therefore, a detailed history is essential. Discontinuation of the drug, or a drug holiday in the case of immune checkpoint inhibitors, may or may not lead to improvement[22,29a]. As a result, initiation of standard therapies may be required.

A number of hypotheses have been put forth to explain drug-induced BP – an underlying genetic predisposition, medication-related alteration of the antigenic properties of the BMZ[28,29], and a breakdown of immune tolerance in the case of immune checkpoint inhibitors. In dipeptidyl peptidase-4 inhibitor-induced BP, autoantibodies also recognize BP180 epitopes other than the NC16A domain.

Diagnosis

The diagnosis of BP is based upon the typical clinical presentation, compatible histologic features, and, most importantly, positive direct immunofluorescence (DIF) microscopy studies (see Fig. 29.17)[18,20–22]. Further support for the diagnosis of BP requires the detection of specific circulating IgG autoantibodies (anti-BP180, anti-BP230) via either indirect immunofluorescence (IIF) microscopy or ELISA. In the vast majority of patients, these tests allow for the correct classification of patients. However, in a minority of patients (~10%) in whom both IIF microscopy and ELISA are negative, additional immunopathological studies, e.g. n-serration *versus* u-serration pattern analysis (see below), can be employed to demonstrate indirectly an autoantibody response to BP180 and/or BP230 and thereby exclude other autoimmune bullous diseases (see Table 30.1)[12,20,22].

Light microscopy

In the non-bullous phase or in atypical variants of BP, routine histology may provide less specific information, since only eosinophilic spongiosis and/or dermal inflammatory infiltrates admixed with numerous eosinophils may be seen (Fig. 30.10)[18,20,22]. In biopsy specimens of an early bulla, a subepidermal blister accompanied by a dermal inflammatory infiltrate composed of eosinophils and mononuclear cells is typically observed. The infiltrate favors the uppermost dermis, and the cavity of the bulla contains a net of fibrin with a variable inflammatory



Fig. 30.6 Bullous pemphigoid – uncommon clinical variants. A, B In dyshidrosiform pemphigoid, clusters of vesicles and bullae appear on acral skin and can resemble dyshidrotic eczema or pompholyx. **C** In pemphigoid vegetans, vegetating plaques can develop in major body folds, including the inguinal crease. **D** Toxic epidermal necrolysis-like lesions with large erosions.

UNUSUAL CLINICAL VARIANTS OF BULLOUS PEMPHIGOID
• Dyshidrosiform pemphigoid – palmoplantar vesicles and bullae (Fig. 30.6A,B) • Pemphigoid vegetans – intertriginous vegetating plaques (Fig. 30.6C) • Pemphigoid nodularis – prurigo nodularis-like lesions • Vesicular pemphigoid – dermatitis herpetiformis-like presentation with small grouped vesicles • Large erosive TEN-like lesions (Fig. 30.6D) • Papular pemphigoid • Eczematous pemphigoid (Fig. 30.4) • Erythrodermic pemphigoid • Lichen planus pemphigoides (see Fig. 11.9C) • Acquired reactive perforating dermatosis-like

• *Localized forms:*
  • pretibial
  • vulvar
  • peristomal
  • umbilical
  • distal end of amputated limb*
  • paralyzed limb
  • sites of radiotherapy†
  • Brunsting–Perry form‡

*Also referred to as "stump" pemphigoid. †Radiotherapy can also provoke generalized form of pemphigoid. ‡Also variant of mucous membrane pemphigoid.

Table 30.2 Unusual clinical variants of bullous pemphigoid.

infiltrate (Fig. 30.11). Conventional electron microscopy studies have shown that subepidermal blister formation usually occurs at the level of the lamina lucida.

Direct immunofluorescence (DIF) microscopy

In almost all patients, DIF microscopy of *perilesional* skin, either normal-appearing or if inflamed 1–2 cm from a bulla, will characteristically demonstrate the presence of fine, linear, continuous deposits of IgG and/or C3 (and, more rarely, other Ig classes) along the epidermal basement membrane (see Fig. 1.9)[18,20,22]. IgG4 and IgG1 are the predominant IgG subclasses. Two additional studies are helpful in distinguishing BP from other autoimmune blistering disorders: (1) close analysis of the linear fluorescence pattern at the BMZ in order to determine if it is *n-serrated* (BP and linear IgA bullous dermatosis) versus *u-serrated* (epidermolysis bullosa acquisita)[30]; and (2) the salt-split skin assay in which perilesional skin is examined after treatment with 1 M NaCl (see Fig. 28.7)[18,20,22]. In BP, immune deposits are found in the epidermal side (roof) or in both the epidermal and dermal sides of the split. Although not routinely available, the computer-aided fluorescence overlay antigen mapping (FOAM) technique allows for more precise localization of the deposited immunoreactants.

Indirect immunofluorescence (IIF) microscopy

For IIF studies in subepidermal blistering diseases, salt-split normal human skin is the substrate of choice, rather than intact normal human skin or monkey esophagus (see Table 29.5). Circulating anti-basement membrane autoantibodies of the IgG class, and less frequently of the IgA and IgE classes, are detectable in 60%–80% of patients[18,20]. These autoantibodies typically bind to the epidermal side or, less frequently, to both the epidermal and dermal sides of saline-separated normal human skin (Fig. 30.12). In a single miniature incubation field, multiplex tests that combine IIF with BIOCHIP technology have been used to screen for autoantibodies against multiple target antigens[31].

ELISA

An increasing number of autoantibodies associated with autoimmune bullous diseases can be detected via ELISA (see Table 29.6). Target antigens include the NC16A domain of BP180 and the COOH-terminus (± the NH2-terminus) of BP230[8,9,18,20,22]. In the case of BP, these tests have been found to be fairly *specific* (≥90%); occasionally, low-titer, false-positive results are observed in healthy subjects and elderly patients with pruritic cutaneous eruptions[18]. When performed in unselected BP patients, the overall *sensitivity* of the BP180–NC16A ELISA is comparable to that of IIF (with salt-split human skin as a substrate)[9,18,20,31]. Combining the ELISA for BP230 with the BP180–NC16A ELISA increases the overall sensitivity by ~10% so the former

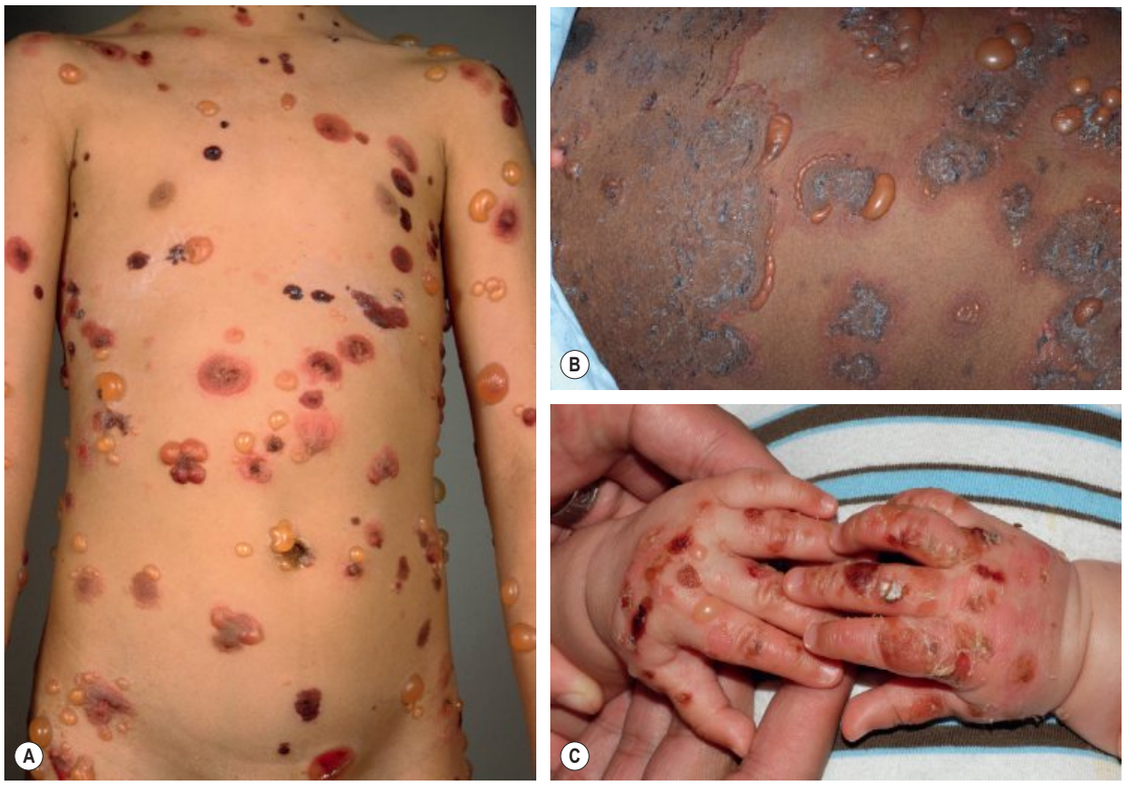


Fig. 30.7 Childhood bullous pemphigoid. A Generalized tense bullae and circular crusted erosions. **B** Tense vesicles and bullae in an annular or figurate array at the edge of expanding lesions, a presentation that might be diagnosed clinically as linear IgA bullous dermatosis. **C** A predominance of acral involvement is often seen in infants. *B, C, Courtesy Julie V. Schaffer, MD.*



Fig. 30.8 Bullous pemphigoid localized to a psoriatic plaque. No obvious trigger was detected, as the patient was not receiving phototherapy. *Courtesy Jean L. Bolognia, MD.*

is only recommended in the setting of a negative BP180 ELISA[32]. A multivariant ELISA that contains multiple autoantigens and utilizes BIOCHIP technology has recently been introduced[33].

Other immunopathological studies

In immunoblot and immunoprecipitation studies of keratinocyte extracts, which are not commercially available, 60%–100% of patients' sera contain IgG autoantibodies that bind to BP180 and BP230, respectively (Fig. 30.13A,B). Patients' sera also frequently contain specific IgA and IgE autoantibodies. In general, recombinant forms of BP180 and BP230 expressed in prokaryotic or eukaryotic systems are used for the detection of autoantibodies (Fig. 30.13C)[9,10,18,20].

Differential Diagnosis

Because the clinical findings in the non-bullous forms of BP may be nonspecific, they can resemble a variety of dermatoses, including drug reactions, contact dermatitis, prurigo (simplex and nodularis), urticarial dermatoses, arthropod reactions, and scabies[18,20,22]. These disorders are usually distinguished on the basis of the clinical history and setting, pathologic features, and the negative findings with IF microscopy. The presence of bullae raises the possibility of bullous arthropod bites and the eosinophilic dermatosis of hematologic malignancy, allergic contact dermatitis, bullous drug eruptions (see Ch. 33), dyshidrotic eczema, pseudoporphyria, or porphyria cutanea tarda. In children, bullous impetigo, inherited epidermolysis bullosa, and bullous mastocytosis must also be considered.

The pemphigus group, paraneoplastic pemphigus, and dermatitis herpetiformis can be differentiated on the basis of distinctive immunopathologic findings and clinical context. In patients with a subepidermal blistering disorder associated with linear deposits of IgG or C3 along the BMZ, the presence of the following clinical criteria point to the diagnosis of BP: (1) absence of skin atrophy; (2) absence of mucosal involvement; (3) absence of head and neck involvement; and (4) age greater than 70 years[18,20,22]. Nevertheless, the distinction of BP from the following disorders can sometimes prove challenging (see Table 30.1).

- **Epidermolysis bullosa acquisita (EBA)** has a wide spectrum of clinical presentations (see below). While the classic "non-inflammatory" form of EBA is sufficiently distinctive, the "inflammatory" form closely mimics BP. As in BP, mucosal involvement may be present[18,20].
- **Linear IgA bullous dermatosis (LABD)** represents a group of subepidermal blistering diseases rather than a single entity (see Ch. 31). While features of LABD are polymorphic in adults, during childhood the condition is frequently associated with annular and polycyclic lesions, often with peripheral blisters, as well as involvement of the genital and perioral region. However, identical features are also observed in childhood BP (see Fig. 30.7B)[18,20].
- **Anti-p200 pemphigoid (anti-laminin γ1 pemphigoid)**. Although patients often have features similar to BP, they tend to be younger and are more likely to have involvement of palmoplantar and cephalic regions as well as the oral mucosa. Neutrophils are usually the predominant cells within the inflammatory infiltrate. These patients have circulating autoantibodies that bind to: (1) the dermal side of salt-split human skin; and (2) a 200 kDa protein in immunoblots of human dermal extracts. The major target antigen, detected by ~90% of sera, is laminin γ1 (see Table 30.1); additional

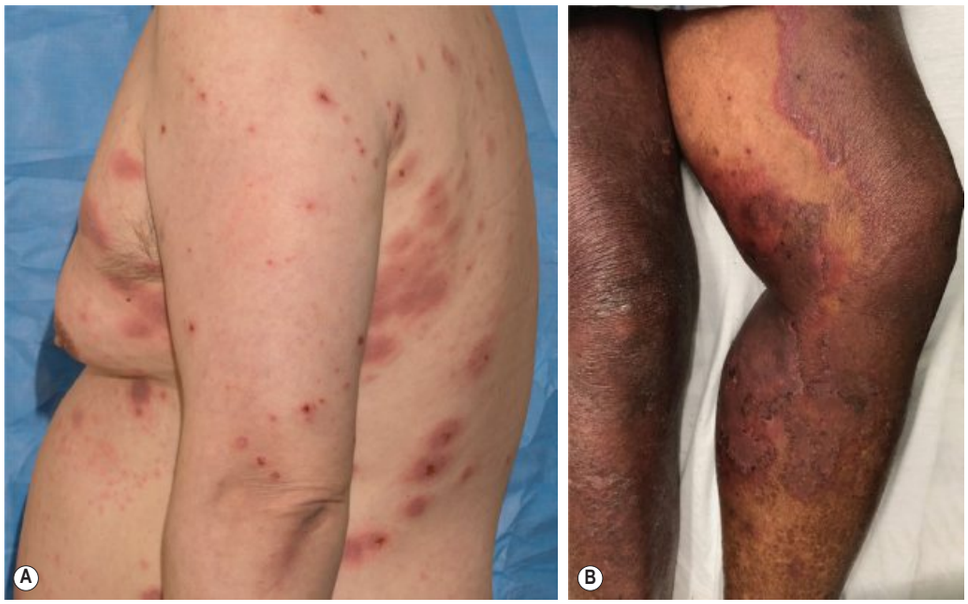


Fig. 30.9 Drug-induced bullous pemphigoid. **A** Scattered pruritic urticarial papules and plaques, some of which have a central hemorrhagic crust, in a patient receiving nivolumab, an anti-PD-1 antibody. **B** Dull violet-brown plaques with a thin inflammatory figurate border and crusting in a patient receiving furosemide. *A, Courtesy Edward Cowen, MD; B, Courtesy Jeff Gehlhausen, MD, PhD.*

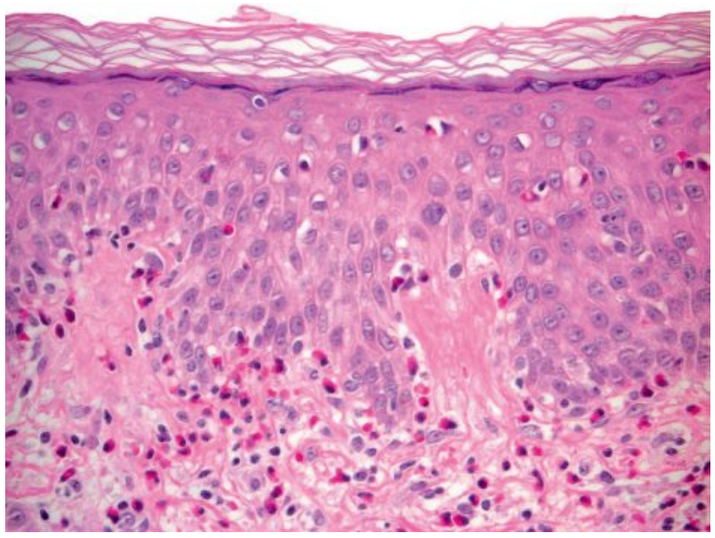


Fig. 30.10 Urticarial phase of bullous pemphigoid – histopathologic features. Eosinophils are present within the dermis as well as the epidermis (eosinophilic spongiosis). Some of the eosinophils have lined up at the dermal–epidermal junction, a typical finding in the urticarial stage of BP. *Courtesy Lorenzo Cerroni, MD.*

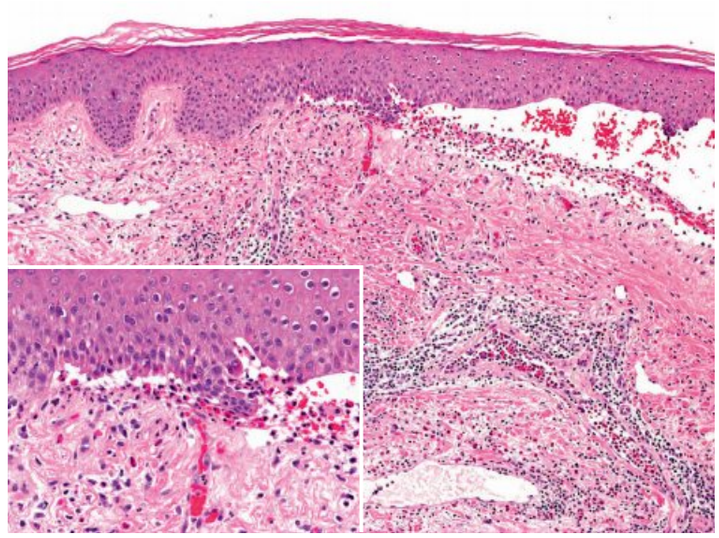


Fig. 30.11 Bullous pemphigoid – histopathologic features. Subepidermal blister which contains fibrin, eosinophils and mononuclear cells (see inset). *Courtesy Lorenzo Cerroni, MD.*

target antigens, which may be pathologically important, have also been identified[20,34]. Of note, anti-p200 pemphigoid and psoriasis often co-exist, especially in Japanese patients.

- **Mucous membrane pemphigoid (MMP)** is a heterogeneous group of diseases which have in common the predominant involvement of the mucosae, a chronic course, and a scarring tendency (see below)[20]. Skin lesions occur in up to 30% of patients and favor the head and upper trunk. When there is both mucosal and cutaneous involvement, distinction from BP may be difficult, but a predominance of mucosal lesions with a scarring tendency and limited skin involvement point to MMP.
- **Chronic pruritic dermatoses of the elderly and early-stage BP**. In the elderly, pruritus, alone or in combination with nonspecific skin lesions, is a common complaint. There are myriad underlying causes and a thorough assessment is often required (see Ch. 6). A dilemma arises when patients with pruritus have circulating autoantibodies to the epidermal BMZ and reactivity with BP180 and/or BP230, but routine DIF microscopy remains negative[18,35]. A small minority of these patients, with initially negative DIF microscopy findings, eventually develop BP[18]. With few exceptions, DIF remains a more definitive diagnostic test than either IIF or ELISA[22].

Prognosis

BP is a chronic disease characterized by spontaneous exacerbations. Approximately 30% of BP patients have a relapse during their first year of treatment, with extensive disease and associated dementia representing independent risk factors for relapse. Furthermore, after cessation of therapy, ~50% of patients experience a relapse, most often within the first 3 months[18,36].

Mortality is considerable among elderly patients. The estimated death rate during the first year varies between 10% and 40%, depending on the series[6,18,20,36]. Older age, dementia, history of a cerebrovascular accident (CVA), and low Karnofsky score have a negative impact on survival[6,36]. The use of systemic corticosteroids or immunosuppressive drugs is also likely to influence overall mortality. Impaired quality of life is obviously an issue for many patients given the associated symptoms[21,22].

Monitoring

The practicality of using the results of quantitative serologic tests, such as ELISA-BP180 or perhaps distinct inflammatory biomarkers[13], as a means of guiding treatment remains to be established. That said, serum

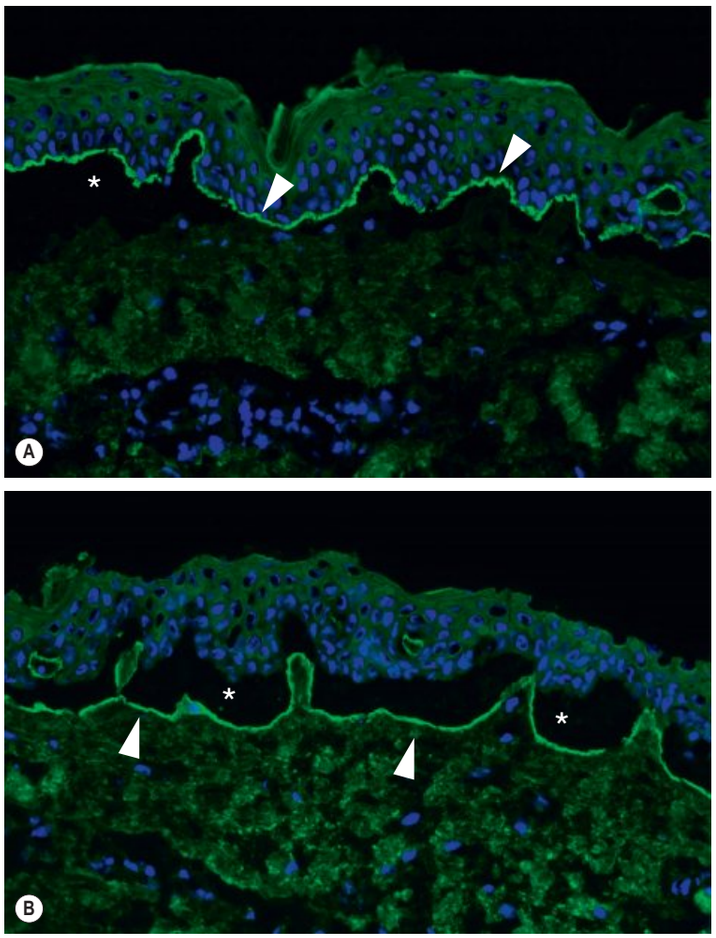


Fig. 30.12 Indirect immunofluorescence (IIF) microscopy utilizing salt-split human skin. A Circulating IgG autoantibodies from BP patients bind to the epidermal side (roof) of the salt-induced split (arrows); the artificial separation is indicated by an asterisk. **B** IgG autoantibodies from patients with EBA, anti-p200 pemphigoid (anti-laminin γ1 pemphigoid), and certain forms of mucous membrane pemphigoid (e.g. with antibodies against laminin 332) react with the dermal side (floor) of the blister (arrows). *Courtesy H. Pas, MD.*

levels of IgG autoantibodies to BP180 correlated with disease severity in several ELISA-based studies[8,9,20,36]. Furthermore, determination of anti-BP180 IgG antibody levels by ELISA at days 0, 60, and 150 appeared to help predict disease relapse – a small (<20%) decrease in serum autoantibody levels between days 0 and 60 was associated with relapse during the first year of therapy[35]. Finally, a high BP180–NC16A ELISA score (>27 U/ml) and, to a lesser degree, positive DIF findings at cessation of therapy are both good indicators of future relapse of BP.

As noted previously, the extent and degree of disease activity can be assessed by employing the BP disease area index (BPDAI)[21] or a daily blister count.

Treatment

The choice of treatment depends on the severity of the disease and comorbidities (Tables 30.3 and 30.4)[22,37–47]. For **extensive** disease, often defined as >10 new blisters/day or inflammatory lesions involving large areas or multiple body sites, either systemic or widespread ultrapotent corticosteroids are employed. *Oral prednisone* (0.5–0.75 mg/kg/day; 1 mg/kg may result in significant side effects and increased mortality) usually controls the disease within 1–2 weeks. If there are no new lesions or pruritus for at least 2 weeks[22,39], then the dosage is progressively tapered to a low dose over a period of 4–6 months, or occasionally longer. Low-dose prednisone is then continued for an additional 3–6 months[22]. Rarely, pulse therapy with methylprednisolone is required for rapid control of the disease. In controlled trials, *ultrapotent topical corticosteroids*, e.g. clobetasol propionate 0.05% cream, had the same efficacy as oral corticosteroids, with fewer systemic side effects and reduced mortality[22,41]. Two topical regimens have been described: standard and mild, in which the starting doses are clobetasol 40 g/day and clobetasol 10–30 g/day, respectively (see Table 30.3)[41]. While ultrapotent topical corticosteroids can be tried first, cost, compliance, and ease of application in the elderly may be limiting factors.

Immunosuppressive therapies can serve as *steroid-sparing agents* and are employed when corticosteroids alone fail to control the disease, there are contraindications to the use of systemic corticosteroids, and/or comorbidities exist that limit the dosage of corticosteroid (e.g. diabetes mellitus, osteoporosis, psychosis)[22]. The most frequently employed agents are azathioprine, mycophenolate mofetil (1.5–3 g/day), methotrexate (7.5–15 mg/week), and cyclophosphamide (see Table 30.4). The dosage of azathioprine (0.5–2.5 mg/kg/day) should be adjusted according to the level of thiopurine methyltransferase, in order to increase efficacy and reduce myelosuppression (see Ch. 130). In the elderly, the dose of methotrexate requires careful monitoring as renal function is often

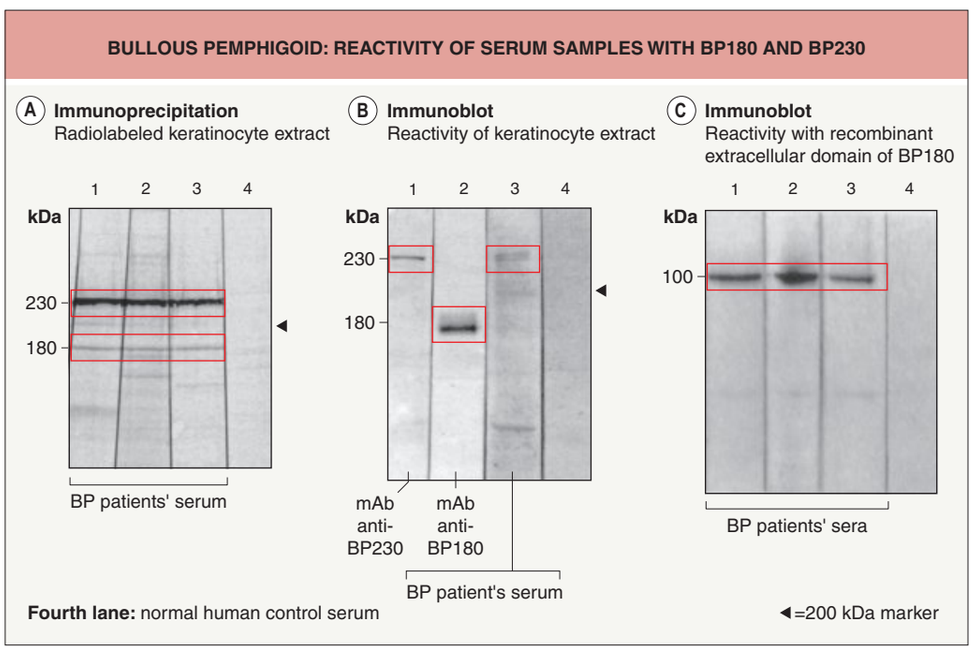


Fig. 30.13 Bullous pemphigoid (BP): reactivity of serum samples with BP180 and BP230. A Immunoprecipitation studies utilizing radiolabeled human keratinocyte extracts: lanes 1–3, serum samples from BP patients immunoprecipitate proteins of 230 kDa (BP230) and 180 kDa (BP180); lane 4, reactivity of normal human serum. **B** Immunoblot studies of keratinocyte extracts: lane 1, reactivity of monoclonal antibodies directed against BP230; lane 2, reactivity of monoclonal antibodies directed against BP180; lane 3, reactivity of a BP serum sample with a protein of approximately 230 kDa; lane 4, reactivity of normal human serum. **C** Reactivity with the extracellular domain of BP180, which was expressed by transfection of COS-7 cells: lanes 1–3, serum samples from BP patients; lane 4, normal human serum.

SURVEY OF SELECTED CONTROLLED TRIALS FOR THE TREATMENT OF PATIENTS WITH BULLOUS PEMPHIGOID						
Authors (year)	**Trial design**	**Intervention**		**Number of patients**	**Response**	**Remarks**
Guillaume et al.[37] (1993)	Randomized, multicenter	Group 1	Prednisolone (1 mg/kg/day) alone	98	At month 6, no significant difference in remission rate between group 1 (42%), group 2 (39%), and group 3 (29%)	More complications in group 2 No adjustment of doses of azathioprine based on TPMT levels
		Group 2	Prednisolone plus azathioprine (100–150 mg/day)			
		Group 3	Prednisolone plus 4 plasma exchanges			
Joly et al.[39] (2002)	Randomized, multicenter	Group 1	Topical clobetasol propionate	341	At week 3, control rates better in group 1	At year 1, topical therapy was associated with a significantly reduced mortality and complication rate
		Group 2	Prednisone (0.5–1 mg/kg/day)			
Beissert et al.[40] (2007)	Randomized, multicenter, prospective	Group 1	Methylprednisolone (0.5 mg/kg/day) plus azathioprine (2 mg/kg/day)	38	Disease control similar in the two groups	In group 1, higher incidence and severity of liver toxicity Trend for faster disease control and less total cumulative doses of corticosteroids in group 1 No adjustment of doses of azathioprine based on TPMT levels
		Group 2	Methylprednisolone (0.5 mg/kg/day) plus mycophenolate mofetil (2 g daily)	35		
Joly et al.[41] (2009)	Randomized, multicenter, prospective	Group 1	Topical clobetasol propionate *standard* regimen for 12 months (40 g daily as starting dose)	153	Time to achieve disease control similar in both groups At 1 year, trend for higher relapse rate in patients with moderate BP treated with *mild* regimen	In moderate BP treated with *mild* regimen, decrease in side effects and death Lower cumulative dose of clobetasol in *mild* regimen
		Group 2	Topical clobetasol propionate, *mild* regimen for 6 months (10–30 g daily as starting dose)	159		
Williams et al.[42] (2017)	"Pragmatic" parallel-group, randomized, multicenter, prospective	Group 1	Doxycycline (200 mg/day); localized adjuvant potent topical corticosteroids permitted during first three weeks After 6 weeks, possible switch to group 2	132	At week 6, proportion of participants with ≤3 blisters is lower in group 2 (adjusted difference favors prednisolone) At one year, severe and fatal events appear to be lower in group 1	Per authors, doxycycline noninferior for short-term blister control and better long-term safety profile Limitations include study design with possible switch in treatment and use of topical corticosteroids by some participants
		Group 2	Prednisolone (0.5 mg/kg per day) After 6 weeks, possible switch to the other therapy or adjustment of prednisolone dose	121		
Amagai[43] (2017)	Randomized, double-blind multicenter	Group 1	Add-on therapy with IVIg (2 g/kg/day) in patients with no improvement on prednisolone ≥0.4 mg/kg/day	29	Trend towards better responses in group 1 during the observation period (days 15 and 56 were time points)	Primary endpoint did not reach statistical significance (but *post-hoc* analysis of covariance demonstrated clinical significance) Compared to placebo, IVIg improved severe disease and increases in prednisolone dose not required
		Group 2	Placebo as add-on therapy in patients with no improvement on prednisolone ≥0.4 mg/kg/day	27		
Simon et al.[44] (2019)	Randomized, placebo-controlled, double-blind, single institution	Group 1	Mepolizumab (750 mg every 4 weeks for 12 weeks) in addition to standard of care: prednisolone (0.5 mg/kg/day) with discontinuation of prednisolone within 12 weeks	20	Group 1 regimen (i.e. add-on mepolizumab) did not significantly affect clinical outcome at weeks 16 and 36	For patients on prednisolone, mepolizumab did not significantly impact disease control or relapse rate compared to placebo Significantly lower number of circulating eosinophils in group 1, but no difference in tissue eosinophils Inclusion of few patients with severe disease could obscure effect of mepolizumab
		Group 2	Placebo every 4 weeks for 12 weeks in addition to standard of care with prednisolone (see group 1)	10		

Table 30.3 Survey of selected controlled trials for the treatment of patients with bullous pemphigoid. TPMT, thiopurine methyltransferase.

significantly reduced. The choice of a particular immunosuppressive drug depends on its side-effect profile, the patient's overall condition, and the experience of the physician.

For **localized** involvement or mild disease with a limited number of non-bullous inflammatory lesions, potent topical corticosteroids represent first-line therapy[21]. Tetracycline, doxycycline or minocycline, alone or in combination with nicotinamide (500–2000 mg/day), can lead to clinical improvement and may be considered as a therapeutic alternative when contraindications to corticosteroids exist[22,38]. A trial comparing doxycycline with prednisolone reported acceptable blister control and a better safety profile with doxycyline, but the latter often needed to be combined with corticosteroids during the course of the disease[42]. Unless there is glucose-6-phosphate dehydrogenase deficiency, the use of dapsone may also be warranted, particularly in the presence of mucosal involvement; topical immunomodulators (e.g. tacrolimus) are an additional option.

THERAPEUTIC LADDER FOR BULLOUS PEMPHIGOID Rx
Mild and/or localized disease
First-line
• Superpotent topical corticosteroids (1*) • Oral corticosteroids† (1) • Minocycline, doxycycline or tetracycline, alone or in combination with nicotinamide (1)
Second-line
• Topical immunomodulators (e.g. tacrolimus) (3) • Dapsone, sulfonamides (3) • Erythromycin, penicillins (3)
Extensive/persistent cutaneous disease
First-line, as primary treatment
• Superpotent topical corticosteroids (1*) • Oral corticosteroids† (1‡)
Second-line, or as adjunctive therapy
• Azathioprine (1) • Mycophenolate mofetil (1) • Methotrexate¶ (2) • Omalizumab (3) • Dupilumab (3) • IVIg (1) • Rituximab (3) • Cyclophosphamide (3) • Immunoadsorption (3)
Note: Superpotent topical corticosteroids should be considered in any patient and may be combined with a systemic therapy.
*Validated. †Prednisone doses of at least 0.5–0.75 mg/kg/day seem to be necessary to control extensive disease, with increased side effects and mortality at 1 mg/kg. For mild to moderate disease, 0.5 mg/kg/day is sufficient. ‡Validated for prednisone. ¶In elderly patients, low-dose regimen (2.5–10 mg/week) can be effective.

Table 30.4 Therapeutic ladder for bullous pemphigoid. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

In case series, both dupilumab and omalizumab have been used as monotherapy or as steroid-sparing agents with favorable responses and safety profiles (see Ch. 128)[45,46]. The pathogenic roles of IL-4 and IL-13 signaling pathways as well as IgE autoantibodies suggest that they are potential therapeutic targets in BP. In treatment-resistant cases, anti-CD20 immunotherapy (rituximab)[47] and IVIg can also be considered. Therapies under investigation include inhibitors of IL-17, IL-12/-23, IL-5Rα, eotaxin, and complement molecules (e.g. C5aR).

While the optimal duration of therapy has not been established, BP patients usually need to be treated for a range of 9–12 months, depending upon the severity of the disease and therapeutic response. The exception is steroid-resistant or steroid-dependent disease. This time period includes a maintenance phase in which low-dose oral prednisone (<10 mg/day) or topical clobetasol propionate (10 g/week) is continued for 1 to 6 months after cessation of clinically active disease[25]. Finally, in all patients with BP, it is important to minimize the complications of both the cutaneous lesions and the systemic treatment, including using osteoporosis prophylaxis and gastric protection (see Ch. 125).

MUCOUS MEMBRANE PEMPHIGOID

Synonyms (becoming historical): ■ Cicatricial pemphigoid ■ Benign mucous membrane pemphigoid

Subtypes/variants: ■ Anti-laminin 332 (mucous membrane) pemphigoid – anti-epiligrin cicatricial pemphigoid ■ Brunsting–Perry pemphigoid

Key features

- Mucous membrane pemphigoid is a chronic, autoimmune, subepithelial blistering disorder characterized by predominant involvement of the external mucosal surfaces and a tendency for scarring
- It is associated with tissue-bound and, less often, serum autoantibodies directed against distinct structural components of basement membranes in stratified and some complex epithelia: BP180, BP230, laminin 332 (laminin 5), type VII collagen, and likely integrin β_4 and α_6 subunits
- The condition should not be regarded as a clinical entity, but as a "disease phenotype" shared by a heterogeneous group of diseases with lesions that favor the mucosal surfaces and, less frequently, the skin
- As scarring frequently affects the conjunctivae, the disorder can be devastating and ultimately lead to blindness
- Diagnosis relies on immunopathologic examinations, especially DIF microscopy, and serological immunoassays

Introduction

Mucous membrane pemphigoid (MMP) is a rare autoimmune subepithelial blistering disorder characterized by predominant involvement of the mucosae, a chronic course, and a tendency towards scarring of the affected areas. The disorder should not be regarded as a clinical entity, but rather as a "disease phenotype" shared by a heterogeneous group of blistering diseases, with predilection for the mucosal surfaces[48]. The majority of patients have linear deposits of immunoglobulins and/or complement components along the epithelial BMZ of the skin and mucosae. Circulating anti-BMZ autoantibodies are detected in the serum of some patients (20%–30% by standard IIF), usually at a low titer or concentration. It is a chronic and progressive disease, which may result in serious mucosal complications. When postinflammatory atrophy or scarring affect the conjunctivae, the disorder can be devastating and ultimately lead to blindness.

History

In 1794, Wichmann first described a chronic blistering disease associated with involvement of the eyes. Civatte separated this disorder from pemphigus on the basis of peculiar histopathologic findings in 1949, and Lever later suggested the name "benign mucous membrane pemphigoid", a misnomer in view of the potentially severe complications of the disorder. During the latter part of the 20th century, the term "cicatricial pemphigoid" was used primarily. In 2012, based upon an international consensus conference, the term "mucous membrane pemphigoid" was proposed. Demonstration of immunoreactants deposited along the epithelial BMZ by IF microscopy pointed to an autoimmune origin.

Epidemiology

The annual incidence of MMP is ~1 to 2 cases per million population[49], with a calculated prevalence (in Germany) of 25 cases per million inhabitants. MMP typically occurs in the elderly, with a mean age at the time of diagnosis of between 60 and 80 years. However, isolated cases have been reported in children. Women are affected more frequently than men (estimated ratio 1.5–2:1). Although no geographic or racial predilection has been described, several studies have shown an association with specific immunogenetic HLA class II haplotypes, e.g. HLA-DQw7 (subtype HLA-DQB1*03:01), in both oral and ocular forms of the disease[50]. There is no overall association with malignancy, but in a distinct subtype associated with IgG autoantibodies directed against laminin 332 (also known as anti-epiligrin cicatricial pemphigoid), an increased relative risk for cancer has been suggested[48,51]. Although this is debated, a search of an associated solid tumor may be recommended in case of anti-laminin 332 reactivity.[48] For example, in a retrospective study of 154 patients, an association of anti-laminin 332 reactivity with malignant neoplasms was noted, with an adjusted odds ratio of 23[50a]. Recently, MMP has been observed in patients receiving immune checkpoint inhibitors.

Pathogenesis

Mucocutaneous lesions are thought to result from the binding of autoantibodies to the BMZ of stratified epithelia of mucosae and skin. These autoantibodies recognize distinct structural components of the hemidesmosomal adhesion complex. Specifically, they appear to bind predominantly to antigenic sites located extracellularly within the anchoring filament zone rather than within the hemidesmosomal plaque[52]. However, the pathogenicity of various IgG autoantibodies associated with this disease phenotype (see Table 30.1) has not yet been established unequivocally and other mechanisms may also be involved. In a minority of patients with MMP, BP180–NC16A domain-specific T cells are detectable. Increased expression of collagen-binding heat shock protein 47 (HSP47) and TGF-β1 by conjunctival fibroblasts may contribute to the conjunctival scarring seen in patients with ocular disease[53].

Based upon their autoantibody profile, patients with MMP can be divided into four distinct subgroups. The **first** subgroup includes those with autoantibodies directed against laminin 332. This subgroup was previously referred to as *anti-laminin 332 MMP* or anti-epiligrin cicatricial pemphigoid[54]. It is estimated that 18%–30% of patients with MMP belong to this subgroup[55]. Patients with anti-laminin 332 IgG autoantibodies frequently have multiple sites of mucosal involvement, including the pharynx, larynx, and trachea[48]. Their circulating IgG autoantibodies bind to the dermal side of salt-split skin and react with the α_3 chain (G domain) and, less frequently, the β_3 and/or γ_2 chain of laminin 332 ($\alpha_3\beta_3\gamma_2$) (see Fig. 28.5). Occasionally, antibody binding to the α_3 chain of laminin 311 (previously termed laminin 6 [a heterotrimer of $\alpha_3\beta_1\gamma_1$ chains]) is also observed because of the presence of cross-reacting autoantibodies. *In vitro* and *in vivo* studies have provided convincing evidence that autoantibodies to laminin 332 are pathogenic[55].

In the **second** group of patients, involvement is exclusively or predominantly ocular. IgG autoantibodies that bind to the β_4 subunit of $\alpha_6\beta_4$ integrin, a transmembrane hemidesmosomal component that interacts with laminin 332, have been described anecdotally. Some clinicians refer to this subset as *ocular MMP* (see Fig. 28.3A)[56].

A **third** subgroup of patients, who lack a specific clinical phenotype, have tissue-bound and circulating IgG antibodies that react with the same target antigens as in BP, especially BP180. These patients, who have been classified as having *anti-BP antigen MMP*, represent the largest subgroup. The antigenic regions targeted on BP180 are located within the NC16A domain and on its distal COOH-terminal portion. The latter appears to extend into the lamina densa region of the BMZ (see Fig. 28.3A)[52]. There is ample scientific evidence that anti-BP180 IgG antibodies are pathogenic[11].

The **fourth** group is rather heterogeneous. It includes patients who have variable involvement of the mucosae without involvement of the skin. While it is yet unclear whether injury occurs as a result of an autoantibody-mediated immune response against proteins of the BMZ, a few patients with an MMP phenotype have shown reactivity against type VII collagen. It has been reported that a small subset of patients with oral MMP have autoantibodies which bind to the α_6 subunit of $\alpha_6\beta_4$ integrin, but this needs to be validated[57].

Clinical Features

Mucous membranes

The two most frequently involved sites in patients with the "mucous membrane pemphigoid phenotype" are the oral and conjunctival mucosae. However, the disease may also start in, and affect, any mucosal site, including the nasopharyngeal, anogenital, laryngeal, or esophageal mucosa (in descending order of frequency)[48,58–60].

Approximately 90% of patients have oral involvement (often in the absence of skin lesions), and the oral cavity may be the only site of disease activity in up to 30% of patients. Lesions frequently involve the gingiva, buccal mucosa, and palate; the alveolar ridges, tongue, and lips are less commonly affected. A classic oral presentation is desquamative gingivitis accompanied by bleeding erosions and paresthesias (Fig. 30.14A); small intact blisters are rarely observed. Chronic inflammation may lead to periodontal ligament damage and the loss of teeth. In other areas of the mouth, transient vesicles give rise to chronic erosions, especially on the palate (Fig. 30.14B), with variable associated pain. Lesions on the tongue are usually localized to its lateral and ventral surfaces. Adhesions may develop in the area of the uvula and tonsillar fossae as well as between the tongue and the floor of the mouth. White, reticulated striations that resemble oral lichen planus may also be seen.

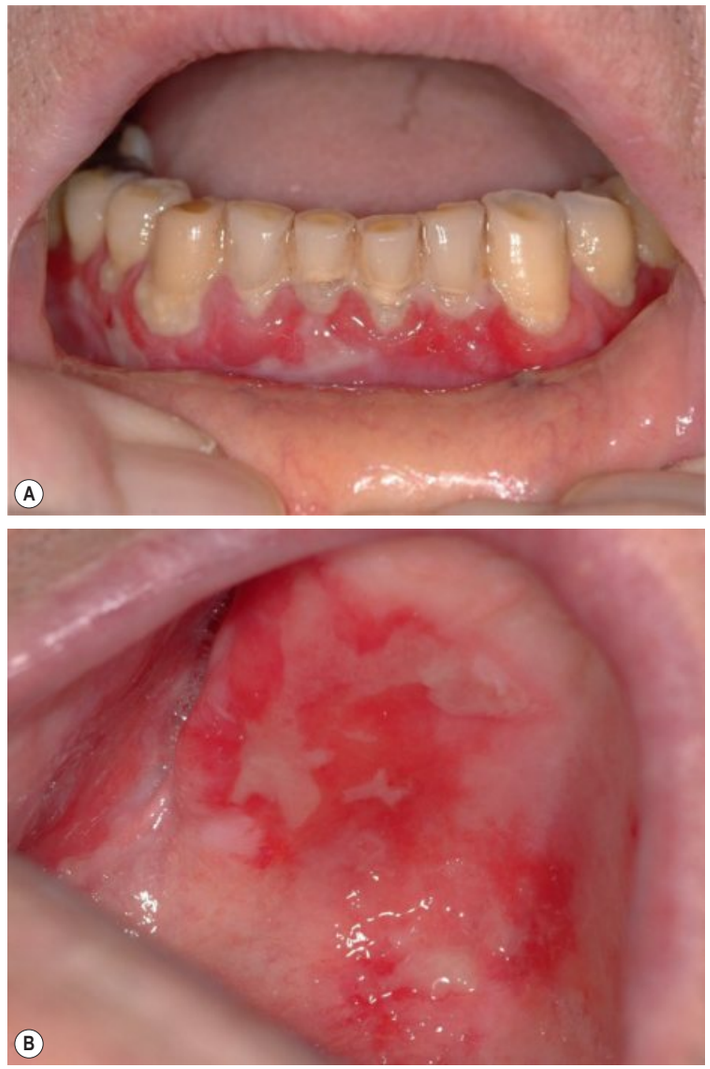


Fig. 30.14 Mucous membrane pemphigoid. A Desquamative gingivitis with erythema and erosions of the gingival margins. Note the sloughing of the mucosa with shaggy margins. **B** Chronic erosions on the hard palate with irregular borders. Sloughing of mucosa is seen superiorly.

Conjunctival involvement occurs in ~40% of patients[48,54] and can result in blindness[60]. The conjunctivae are frequently the only site affected. Although the disease may begin unilaterally, in the majority of patients, lesions appear in both eyes. Ocular involvement starts as a nonspecific chronic conjunctivitis and limbitis, with burning, soreness, foreign-body sensation, decreased vision, and/or mucus production. Periods of exacerbations and subsequent remissions are typical, with eventual progression to a scarring due to subepithelial conjunctival fibrosis (Fig. 30.15).

Conjunctival vesicles or blisters are rare on the tarsal conjunctiva. Chronic inflammation may result in progressive scar tissue formation, leading to a shortened inferior fornix and symblepharon (an adhesion between bulbar and palpebral conjunctival surfaces; Fig. 30.16) as well as ankyloblepharon. Conjunctival fibrosis can also result in trichiasis (inwardly angled eyelashes) and entropion[60]. In uncontrolled disease, trichiasis, entropion, and xerosis (due to scarring of the lacrimal ducts) eventuate in superficial corneal trauma, corneal neovascularization with subsequent corneal ulceration, and blindness[48].

Nasopharyngeal involvement occurs in a third of patients with MMP and is typically chronic and asymptomatic[48,59]. It results in crusted intranasal ulcerations, epistaxis, fibrous adhesions between adjacent mucosal surfaces, and airway obstruction. Pharyngeal involvement presents as ulcerations of the posterior or lateral pharynx and dysphagia. Laryngeal involvement is a potentially serious manifestation, presenting as hoarseness, loss of speech, and even life-threatening stenosis, which requires tracheostomy.

Although esophageal disease may be accompanied by dysphagia resulting from erosions of the esophageal mucosa, involvement can be

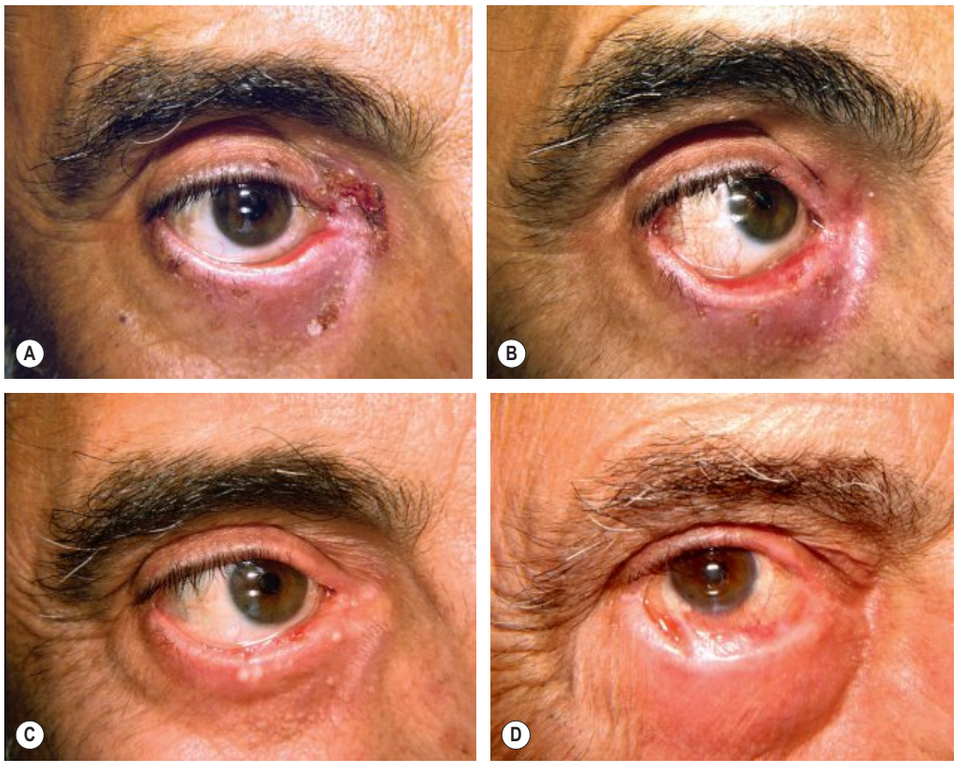


Fig. 30.15 Ocular involvement in mucous membrane pemphigoid. A Erosion and erythema of the lower medial eyelid margin plus scale-crust of the inner canthus and lower eyelid. **B** Three months later, ectropion and thickening of the lower eyelid in addition to erosions. **C** Six months later, smaller erosions but scarring and milia formation. **D** Seven years later, further scarring with significant shortening of the inferior fornix due to symblepharon. *Courtesy Louis A. Fragola, Jr, MD.*

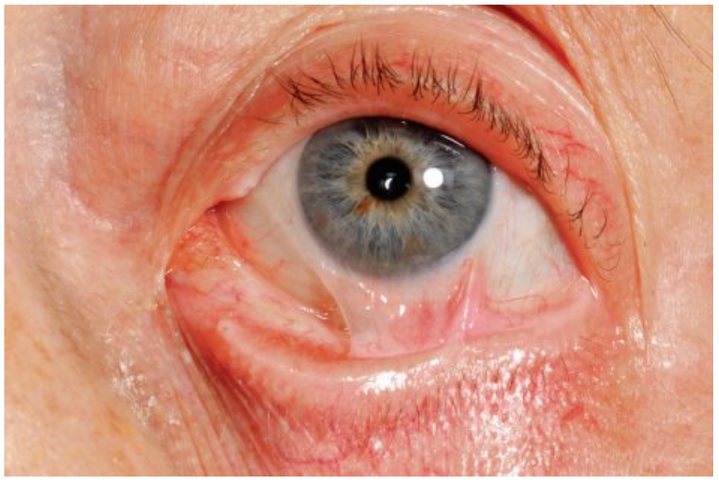


Fig. 30.16 Mucous membrane pemphigoid. Typical ocular involvement as manifested by fibrous tracts, representing partial or incomplete symblepharon.

entirely asymptomatic. Chronic inflammation can lead to strictures and stenosis, with associated dysphagia[48].

Involvement of genital and anal mucosae is relatively uncommon, but increasingly recognized. Early lesions consist of blisters and chronic erosions. In female patients, progressive disease leads to scarring and narrowing of the introitus. In male patients, adhesions can form between the prepuce and the glans penis. Anal involvement can also lead to scarring and, in severe cases, to stricture formation[48].

Cutaneous lesions

The skin is involved in 20%–35% of patients. The most frequently involved sites are the scalp, face, neck, and upper trunk. Lesions typically present as erythematous plaques, which become sites for recurrent blister formation and erosions, with subsequent scarring. Their extent and number are generally limited, but an individual patient can have a BP-like clinical presentation[48].

In the *Brunsting–Perry variant*, skin lesions are localized predominantly to the head and neck and upper trunk (Fig. 30.17A,B)[61]. Mucosal involvement is usually absent or minimal. On the scalp, significant scarring alopecia can result (Fig. 30.17C).

Diagnosis and Differential Diagnosis

The diagnosis of MMP has to be considered in all patients who have blistering or erosive lesions that predominantly involve mucous membranes and whose affected tissues show linear, continuous deposits of immunoreactants along the epithelial BMZ. Unfortunately, there is frequently a significant delay, often more than a year, before the diagnosis is established. As a result, moderate to severe scarring, especially ocular, may have already occurred.

Light microscopy and electron microscopy

The histopathologic features of MMP and BP are often similar. Examination of a fresh vesicle or bulla demonstrates subepithelial or subepidermal blister formation (without acantholysis). A mixed cellular infiltrate of variable intensity is present, with a predominance of neutrophils; the number of eosinophils is increased in older lesions, but they are still fewer than in BP. Older lesions also tend to have scarring in the submucosa or upper dermis. In oral lesions, the inflammatory infiltrate typically contains some plasma cells, a nonspecific finding related to the mouth being a mucosal site. The epithelium of affected conjunctivae is often invaded by inflammatory cells, including mononuclear cells and mast cells, while granulation tissue is found in the submucosa.

In most cases, electron microscopy studies of a fresh blister demonstrate that the dermal–epidermal cleavage occurs within the lamina lucida. In advanced conjunctival lesions with scarring, the lamina densa appears to be discontinuous, focally thickened, or duplicated.

Direct immunofluorescence (DIF) microscopy

By DIF microscopy, 80%–95% of patients with MMP have *in vivo* bound autoantibodies directed against the BMZ of mucosae and/or skin. The majority of patients exhibit continuous, fine, linear deposits of IgG, IgA, and/or C3 along the epithelial BMZ in perilesional biopsy specimens. It should be noted that DIF microscopy studies of mucosae are more frequently positive (50%–90%) than those of skin (20%–50%). IgG deposits belong primarily to the IgG4 and IgG1 subclasses; deposits of IgM and fibrin are less common. DIF microscopy of salt-split skin is of less diagnostic value. Although a combined pattern with staining of both the epidermal and dermal sides is frequently observed, reactivity with either the epidermal roof or the dermal floor of the separated skin is occasionally noted. If circulating autoantibodies are not detected, analysis of the

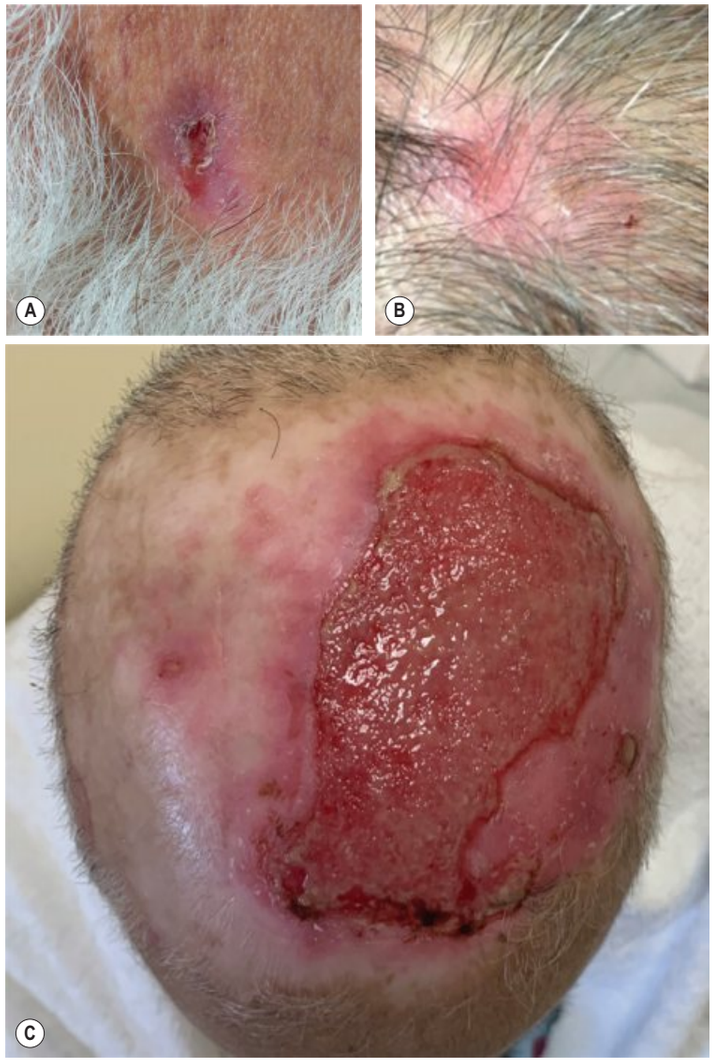


Fig. 30.17 Mucous membrane pemphigoid – Brunsting–Perry variant. A Crusted erosion on the lower cheek within an oval area of inflammation and scar. **B** Mild involvement of the scalp with scarring and atrophy resulting in limited alopecia. **C** Severe involvement of the scalp with an ulceration within a large area of scarring alopecia. *B, Courtesy Karynne O. Duncan, MD; C, Courtesy Michael Gowen, MD.*

linear fluorescence pattern of autoantibody deposits at the cutaneous BMZ (*n-serrated* [pemphigoid group] versus *u-serrated* [EBA]) or results of the FOAM technique (see above) may prove helpful. Of note, in mucosal specimens, the serration pattern cannot be assessed[48].

Immunoelectron microscopy

Although electron microscopy studies are not routinely available and are time-consuming, they may be particularly useful in establishing the diagnosis of MMP, especially in patients in whom standard DIF and IIF microscopic findings are negative. Direct immunoelectron microscopy studies in MMP have demonstrated immune deposits distributed either: (1) in the lower lamina lucida and above the lamina densa; or (2) on and around hemidesmosomes, with most of the labeling on the outside of basal keratinocytes below their plasma membranes[48,52].

Indirect immunofluorescence (IIF) microscopy

By standard IIF, anti-BMZ autoantibodies can be detected in serum samples from 20%–30% of patients with MMP. Antibodies are mainly of the IgG class, but circulating IgA or IgE may also be detected. Antibody concentrations are usually very low. Some authors have suggested that patients with high serum levels of IgG and IgA anti-BMZ autoantibodies have more severe disease[62]. The sensitivity of IIF can be increased either by the use of normal oral or genital mucosa and conjunctiva as substrates, or by utilizing salt-split skin. Using this latter technique, most patients with MMP have antibodies that bind to the epidermal roof, whereas MMP patients with anti-laminin 332 or anti-type VII collagen reactivity have IgG antibodies that bind to the dermal side (see Fig. 30.12). The use of salt-split oral mucosa does not improve the overall sensitivity. Distinguishing MMP with anti-laminin 332 autoantibodies from EBA may be possible by IIF microscopy using "knockout" skin substrates, i.e. substrates deficient in specific basement membrane proteins[63].

Immunochemical studies, including ELISA

Immunochemical techniques, including ELISA, immunoblots, and immunoprecipitation, have confirmed that the autoantigens targeted in patients with a MMP phenotype are heterogeneous[54,55,57,63–67]. Serum autoantibodies react with various proteins located within the epithelial BMZ, e.g. BP180, laminin 332, type VII collagen (see Table 30.1). Depending upon the patient population and specific assay, IgG anti-BP180 or anti-laminin 332 antibodies are detected in 30–70% or 15–30% of MMP patients, respectively. These targeted antigens appear to constitute serologic markers for different subgroups of MMP (see above).

Patients may have IgA autoantibodies directed against the ectodomain of BP180[6]. As a result, salivary IgG and IgA autoantibodies directed against BP180–NC16A may serve as diagnostic biomarkers. In some cases, these autoantibodies appear to preferentially bind to antigenic reactive sites present on the proteolytically cleaved and shed portion of the extracellular domain of BP180, i.e. the LABD antigen (LAD-1; see Ch. 31). Lastly, several unidentified target antigens of varying molecular weights have also been reported.

ELISAs that utilize recombinant proteins or affinity-purified native proteins (e.g. BP180, laminin 332, type VII collagen) can be useful in the search for circulating autoantibodies[31].

Differential diagnosis

Distinction from other subepidermal autoimmune bullous diseases (including BP, EBA, and LABD) may be difficult and often relies on the predominance of mucosal involvement and chronic course. In contrast, pemphigus vulgaris and non-autoimmune blistering diseases are more easily excluded via histology and IF microscopy.

If oral involvement, especially isolated desquamative gingivitis, is the sole manifestation of MMP, it can be difficult to differentiate clinically from pemphigus vulgaris or erosive lichen planus. End-stage, scarring conjunctival lesions may mimic severe chronic infectious conjunctivitis, ocular pseudopemphigoid due to ophthalmologic preparations (including pilocarpine, idoxuridine, guanethidine, β-blockers), or sequelae of Stevens–Johnson syndrome and toxic epidermal necrolysis. While the rare, generalized cutaneous form of MMP can be impossible to distinguish from BP, involvement of multiple mucosal sites favors the former.

Prognosis

MMP is a particularly chronic, potentially devastating, but rarely fatal disease. The most important complication is impairment of vision due to ocular involvement. It can also lead to weight loss as well as respiratory, sexual, or urinary complications. Even with localized involvement, this disease can have a major negative impact on quality of life. Life-threatening complications, due to severe laryngeal, tracheal or esophageal disease, are rare.

Treatment

Treatment can be difficult and at times frustrating, with therapeutic regimens based primarily on clinical experience[67].

Local therapy is crucial and, for limited involvement, it can be sufficient. Mild to moderate disease activity may be successfully treated with potent topical corticosteroids. Oral lesions can respond to topical corticosteroids (as mouthwashes or topical preparations in a gel or occlusive base supplemented by customized prosthetic devices to provide occlusion) in conjunction with tetracycline mouthwashes and professional dental hygiene. Corticosteroid sprays and inhalers may prove useful in nasal, pharyngeal, or esophageal disease. Recalcitrant lesions of both skin and mucous membranes may improve with intralesional injections of triamcinolone. Esophageal strictures may require dilatations to prevent dysphagia, while severe tracheal involvement may require a tracheostomy to prevent asphyxiation[68].

Systemic medications include dapsone (50–150 mg/day) as a first-line therapy for controlling oral and cutaneous lesions, and it may also

be used for mild ocular disease without rapid worsening. Dapsone can be particularly beneficial in patients with linear deposits of IgA at the BMZ. Cyclophosphamide (1–2 mg/kg/day) is considered the treatment of choice for rapidly progressive or severe ocular disease[60] – alone, in combination with oral corticosteroids, or as pulse therapy. Such regimens are effective in resolving severe conjunctival inflammation and preventing recurrences and secondary scarring. Azathioprine (2 mg/kg/day) and mycophenolate mofetil (2 g/day) have also been reported to be helpful in reducing the dose of corticosteroids required for control of ocular involvement and cutaneous lesions.

Systemic corticosteroids alone are generally insufficient therapy for patients with significant disease, and they are less effective for mucosal than for cutaneous disease. Patients with significant esophageal or laryngotracheal involvement should be treated aggressively with the combination of prednisone and cyclophosphamide or mycophenolate mofetil to prevent potentially life-threatening complications. Other therapies reported to be of potential value in the treatment of MMP include topical tacrolimus, a combination of tetracycline and niacinamide, minocycline, sulfapyridine, methotrexate, TNF inhibitors, IVIg, topical or systemic cyclosporine, thalidomide, and subconjunctival mitomycin[69–73]. Case series have also underscored the efficacy of rituximab in controlling progressive ocular involvement and severe extraocular complications[67,72]. When these manifestations fail to respond to cyclophosphamide plus corticosteroids or there is an intolerance or contraindication to this regimen, rituximab can be considered as second-line therapy[58].

Surgical therapy may occasionally be necessary for severe scarring involving the eye, larynx, esophagus, or genitalia. It should be performed when the disease is fully controlled by medical therapy. For ocular disease, surgical intervention includes corneal grafts, allograft limbal transplantation, amniotic membrane transplantation, and tarsorrhaphy.

EPIDERMOLYSIS BULLOSA ACQUISITA

Synonym: ■ Acquired epidermolysis bullosa; dermolytic pemphigoid

Key features

- Epidermolysis bullosa acquisita is a rare, acquired, subepidermal bullous disease associated with autoimmunity to type VII collagen, the major component of the anchoring fibrils of the dermal–epidermal BMZ
- Patients may present either with a mechanobullous disorder, mimicking dystrophic epidermolysis bullosa, or with clinical features that resemble BP or infrequently MMP, the Brunsting–Perry variant of MMP, or LABD
- Diagnosis relies on immunopathologic examinations, especially immunofluorescence microscopy, immunoserologic studies, and occasionally immunoelectron microscopy
- The disease is usually chronic and more refractory to treatment than BP

Introduction

Epidermolysis bullosa acquisita (EBA) is a rare, acquired, subepidermal bullous disease associated with autoimmunity to type VII collagen, the major component of the anchoring fibrils of the dermal–epidermal BMZ[74–77]. Patients may present with either a non-inflammatory variant, the features of which strikingly resemble those observed in patients with dystrophic epidermolysis bullosa (EB), or with an inflammatory variant that mimics BP. Infrequently, the clinical phenotype resembles MMP, the Brunsting–Perry variant of MMP, or LABD.

History

The first cases of an acquired bullous disease with clinical features mimicking hereditary dystrophic epidermolysis bullosa were described by Elliot in 1895. In the early 1970s, before the advent of cutaneous immunopathology, Roenigk and colleagues proposed the initial clinical criteria for EBA. A few years later, IF microscopy studies demonstrated that EBA patients have anti-BMZ antibodies, similar to BP patients. In the early 1980s, immunoelectron microscopy studies separated EBA from BP by demonstrating that IgG deposits in EBA were located in the sublamina densa region of the BMZ. In the 1990s it was shown that EBA autoantibodies bind to type VII collagen, the major component of anchoring fibrils[75].

Epidemiology

EBA has been reported in both children and adults and may occur at any age. It is one of the rarest subepidermal autoimmune bullous diseases in Western Europe, with an estimated annual incidence of ~0.25 per million people[49,77]. It may be more common in specific Asian populations (e.g. Koreans) as well as in African-Americans.

Pathogenesis

The pathogenic role of autoantibodies to type VII collagen is supported by several lines of evidence[76]. Patients with EBA have tissue-bound and circulating IgG autoantibodies against type VII collagen, the major component of anchoring fibrils (see Fig. 28.3A). In addition, titers of anti-type VII collagen antibodies parallel disease activity in EBA patients, and neonates of mothers with EBA can develop transient blisters due to diaplacental transfer of anti-type VII collagen IgG autoatibodies[74,77].

Type VII collagen is located within the lamina densa and sublamina densa region of the BMZ (see Fig. 28.2). It is composed of three identical α-chains, each of which consists of a central 145 kDa collagenous triple helical segment, flanked by a large 145 kDa non-collagenous NH2-terminal domain (NC1) and a short 30 kDa COOH-terminal region (NC2). Patients' autoantibodies target immunodominant epitopes within the NC1 domain of the protein. However, reactivity with either the central collagenous domain or the NC2 domain is also observed, albeit rarely. It is, as yet, unclear if binding activity to certain antigenic regions of the molecule correlates with a distinct clinical phenotype (see below).

In vitro, EBA autoantibodies, together with the complement system and neutrophil elastase and gelatinase B, are able to mediate leukocyte infiltration (via FcγRIV expression) and dermal–epidermal separation. In mice, studies involving passive transfer of antibodies or active immunization with autologous type VII collagen have shown that autoantibodies to type VII collagen are capable of inducing dermal–epidermal separation, i.e. are pathogenic[76,77].

EBA autoantibodies may also directly interfere with the association and assembly of type VII collagen molecules into anchoring fibrils and/or by critically affecting the interactions between type VII collagen and other matrix proteins such as laminin 332, fibronectin, or type IV collagen.

As in the case of other autoimmune diseases, certain HLA class II alleles appear to be more prevalent in EBA, e.g. DRB1*15:01 and DR5 in White individuals and African-Americans or DRB1*13 in Koreans. It is likely that the expression of distinct HLA alleles has a critical impact on the susceptibility to developing EBA. The observation that deficient expression of type VII collagen in patients with various forms of dystrophic EB causes skin fragility and dermal–epidermal separation demonstrates unequivocally the importance of this protein in maintaining the integrity of the epidermal BMZ[77].

Clinical Features

EBA usually occurs in adult patients, although pediatric cases have been reported. Cutaneous manifestations are heterogeneous and may mimic other bullous diseases[77,78].

The classic presentation is that of a *non-inflammatory mechanobullous disease* characterized by the development of acral blisters that heal with atrophic scarring, milia formation, and dyspigmentation[77]. Cutaneous blisters, which may become hemorrhagic, and evolving erosions appear within non-inflamed skin or on areas of scarring. They are localized to trauma-prone surfaces, especially the elbows, knees, and dorsal aspects of the hands, occiput, back, feet, and toes (Fig. 30.18). As in inherited dystrophic EB, acral involvement in EBA may be mutilating, leading to a "mitten" deformity of the digits, webbing between adjacent fingers or toes (pseudosyndactyly), nail dystrophy, and complete

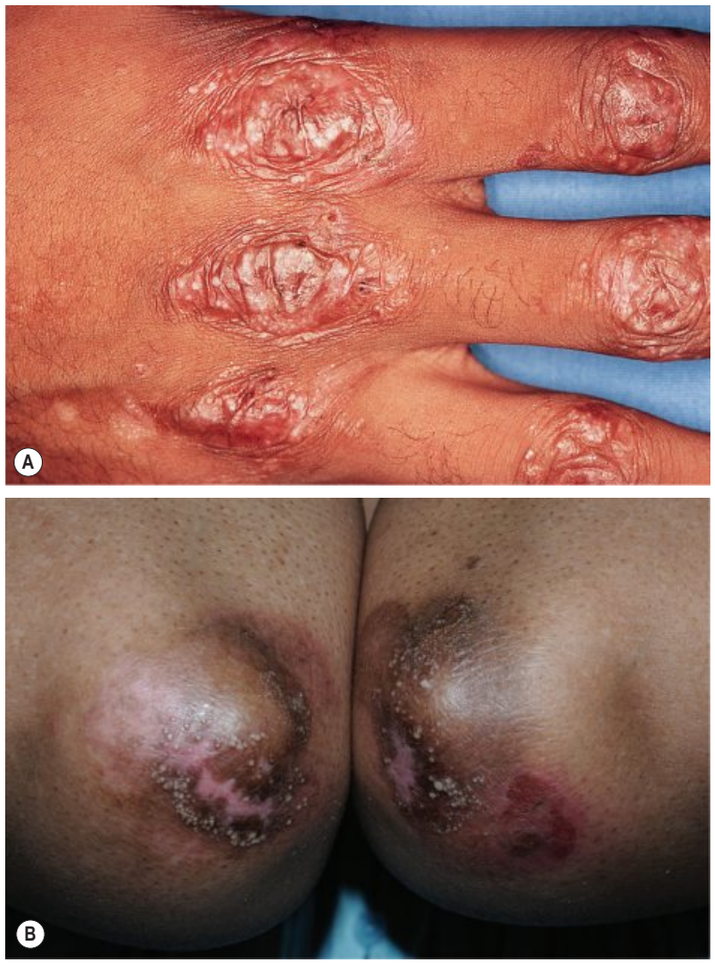


Fig. 30.18 Epidermolysis bullosa acquisita – mechanobullous presentation. **A** Milia and scarring that favor sites of trauma overlying joints, in association with skin fragility. Note the resemblance to dystrophic epidermolysis bullosa. **B** Postinflammatory hyperpigmentation, mild scarring, and milia in sites of trauma in a patient with systemic lupus erythematosus. Note the ruptured bulla on the left elbow. *B, Courtesy Kalman Watsky, MD.*



Fig. 30.19 Epidermolysis bullosa aquisita – inflammatory presentation. Widespread erythematous plaques, some of which have erosions and hemorrhagic crusts. Although there is accentuation on the elbows, the differential diagnosis would include bullous pemphigoid. *Courtesy Lorenzo Cerroni, MD.*



Fig. 30.20 Epidermolysis bullosa acquisita – oral involvement. Multiple erosions of the palate reminiscent of mucous membrane (cicatricial) pemphigoid. *Courtesy C. Prost, MD.*

nail loss. Scalp involvement occurs in up to 20% of patients, and, in isolated cases, extensive non-healing erosions with scarring alopecia have been described.

Several *inflammatory subtypes* of EBA have also been described, which may occur more frequently than the mechanobullous form[77,78]. The *BP-like presentation* is the most common inflammatory form of EBA[77–79]. It is characterized by widely distributed, pruritic vesicles and bullae on an erythematous base. Any cutaneous site may be involved, as well as the oral mucosa. Lesions heal without milia or atrophic scars (Fig. 30.19).

Other inflammatory subtypes of EBA are quite uncommon[77–79] and include those whose presentation resembles MMP, the Brunsting–Perry variant of MMP with scarring alopecia, and LABD with a polymorphous bullous eruption and a linear band of IgA deposits along the BMZ. Of note, during the course of the disease, the clinical features can convert from one variant to another or, alternatively, a mixture of inflammatory and non-inflammatory features may coexist.

Mucous membrane involvement occurs not only in MMP-like EBA, but is also observed in up to 50% of patients with the mechanobullous and BP-like presentations[77–79]. Erosions and intact vesicles may be seen in the mouth (Fig. 30.20), larynx and esophagus, and they may lead to dysphagia and laryngeal stenosis. Ocular involvement with severe cicatrizing conjunctivitis and blindness have been reported in the MMP-like phenotype[77,80]. Lastly, features of childhood EBA have substantial overlap with those observed in childhood BP and LABD.

In some reports, a number of systemic diseases have been described in association with EBA, particularly Crohn disease and ulcerative colitis (up to 30% of cases) and, more rarely, myeloma, systemic LE, rheumatoid arthritis, thyroiditis and diabetes mellitus[77].

Diagnosis and Differential Diagnosis

Light microscopy and electron microscopy

By light microscopy, biopsy specimens of bullae show a subepidermal cleavage. In the BP-like or MMP-like variants of EBA, there is a variable inflammatory infiltrate within the dermis, composed predominantly of neutrophils admixed with eosinophils and lymphocytes. In the mechanobullous non-inflammatory lesions, there is a minimal-to-absent cellular infiltrate.

Electron microscopy studies of fresh vesicles demonstrate that dermal–epidermal cleavage occurs within the sublamina densa zone. In addition, a reduction in the number of anchoring fibrils may be observed. However, in some cases, separation within the lamina lucida has been noted, most likely reflecting the formation of a subepidermal blister at the *locus minoris resistentiae*. The level of cleavage is, therefore, not always a reliable criterion for discriminating EBA from other subepidermal bullous disorders.

Direct immunofluorescence (DIF) microscopy

DIF microscopy studies of perilesional skin demonstrate IgG deposits distributed in a continuous, rather broad, linear pattern along the epidermal BMZ. Less commonly, linear deposits of C3, IgA, or IgM are found. In salt-split skin preparations of perilesional skin, the immune deposits are typically located on the dermal side of the cleavage. A u-serrated immune deposition pattern at the epidermal BMZ is very helpful in differentiating EBA from the other subepidermal bullous diseases, i.e. the "pemphigoids", which have an n-serrated pattern of immunoreactants

at the BMZ. Finally, the FOAM technique (see above), employing a confocal laser scanning microscope, localizes the immunoreactants to the level of the BMZ where type VII collagen is expressed[77].

Indirect immunofluorescence (IIF) microscopy

By standard IIF, circulating anti-BMZ antibodies can be detected in ~50% of patients with EBA. They are primarily of the IgG class, but serum IgA autoantibodies have also been reported. By IIF on salt-split skin, circulating IgG or IgA antibodies bind to the dermal side of the artificial blister[30,77,79,81]. Although not often available, testing of patients' sera either against a panel of skin substrate specimens lacking distinct basement membrane molecules (e.g. BP180, type VII collagen, laminin 332) or against HEK cells transfected with the recombinant NC1 domain of type VII collagen can prove helpful in characterizing the antigens targeted by circulating autoantibodies.

Immunoelectron microscopy

Immunoelectron microscopy has traditionally been considered the "gold standard" for diagnosing EBA, especially when circulating autoantibodies are absent and therefore cannot be characterized by IIF microscopy, immunoblot, or ELISA (see below)[77]. By immunogold techniques, which allow a more precise localization than peroxidase labeling, EBA autoantibodies specifically bind to the anchoring fibrils and the lamina densa where anchoring fibrils originate and terminate (see Fig. 28.3A).

Other immunochemical studies, including ELISA

In Western immunoblot analyses of dermal extracts, serum autoantibodies from patients with EBA were found to bind to proteins of ~290 kDa and, less frequently, 145 kDa. These proteins have been clearly shown to correspond to type VII collagen and its NH2-terminal NC1 subdomain, respectively[77,81]. Epitope mapping studies using recombinant forms of type VII collagen have demonstrated that immunodominant epitopes are located within the NC1 domain[81]. ELISAs are now available, utilizing either the recombinant NC1 domain of type VII collagen or a combination of recombinant NC1 and NC2 domains[82,83]; these assays exhibit high specificity (>96%) and are likely more sensitive than IIF microscopy studies utilizing salt-split skin[83]. Serum concentrations of collagen VII-specific IgG autoantibodies, as determined by ELISA, may correlate with disease severity[77].

Differential diagnosis

EBA may be confused with inherited dystrophic EB, BP, MMP, LABD, porphyria cutanea tarda, pseudoporphyria, or rare variants of porphyria (e.g. porphyria variegata). Clinically, the mechanobullous type of EBA most closely resembles mild dominant dystrophic EB, but the lack of a family history, late onset, and the positive DIF findings generally allow for distinction. However, some patients with inherited EB do develop autoantibodies against type VII collagen. The involvement of the hands may mimic porphyria cutanea tarda, but the latter can easily be excluded by porphyrin studies. Occasionally, patients with EBA on incriminating medications are misdiagnosed as having pseudoporphyria. The inflammatory type of EBA is clinically indistinguishable from BP, anti-p200 (anti-laminin γ1) pemphigoid, or MMP, including the Brunsting–Perry variant. These conditions may be distinguished by u-serrated versus n-serrated DIF pattern analysis, FOAM technique, ELISA, IIF with salt-split skin as a substrate, Western immunoblot analysis of both epidermal and dermal extracts, and direct immunoelectron microscopy studies[77,84].

Bullous systemic LE usually presents as a transient, widespread, inflammatory subepidermal blistering condition (see Ch. 41), and, less frequently, as a mechanobullous eruption with milia formation and scarring[75,77]. In a number of these cases, circulating autoantibodies show binding to type VII collagen and the possibility of systemic LE-associated EBA could be considered. In addition to differences in histology, adult EBA exhibits a poor response to treatment, while a significant improvement following initiation of dapsone or azathioprine therapy is generally seen in patients with bullous systemic LE[85].

Treatment

Treatment of EBA is difficult and often unsatisfactory. Because of the rarity of the condition, most data on treatment are based on anecdotal reports[67,74,77]. Systemic corticosteroids and immunosuppressive agents, such as azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide or, more recently, rituximab, are sometimes helpful in controlling the BP-like variant of EBA, which may eventually go into clinical remission. Colchicine, dapsone, and cyclosporine have also been reported to have some benefit. In patients with severe EBA unresponsive to conventional immunosuppressive therapy, IVIg ± rituximab may prove effective[77,85]. A combination of dapsone plus prednisolone has been recommended by some authors for the treatment of childhood EBA[74].

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 30.1 Bullous pemphigoid – bullous presentation. A Classic presentation with multiple tense bullae arising on normal and erythematous skin. Several of the bullae have ruptured, leaving circular erosions. **B** Multiple tense bullae that contain serous fluid arising whithin an area of erythema in addition to hemorrhagic crusts. *B, Courtesy Kalman Watsky, MD.*



eFig. 30.2 Bullous pemphigoid. Fresh blisters are tense while older ones have become flaccid or led to erosions. They are arising with large areas of erythema.



eFig. 30.3 Bullous pemphigoid – urticarial (and bullous) presentation. Firm annular urticarial plaques. There is also subtle crusting.



eFig. 30.4 Bullous pemphigoid – eczematous presentation. Large pink eczematous plaques on the trunk and upper extremities.



eFig. 30.5 Bullous pemphigoid – progression of disease. A Urticarial, infiltrated and annular erythematous plaques on the trunk and upper extremity. **B** Generalized eruption with blisters as well as numerous erosions and hemorrhagic crusts in the same patient later in the course of the disease.





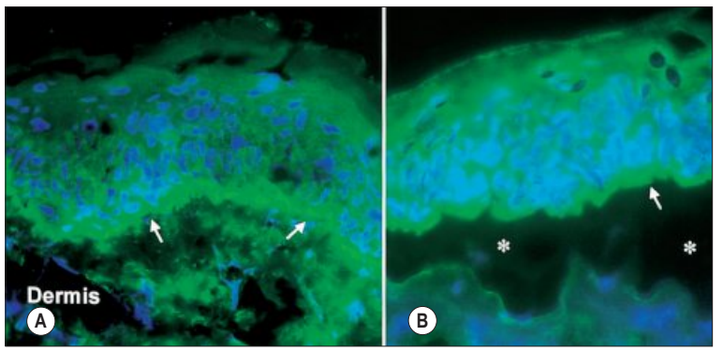
eFig. 30.6 Bullous pemphigoid. A Excoriated eczematous lesions on the upper extremity. **B** Confluent plaques with tense blisters in the inguinal area and inner aspect of the thighs in the same patient.



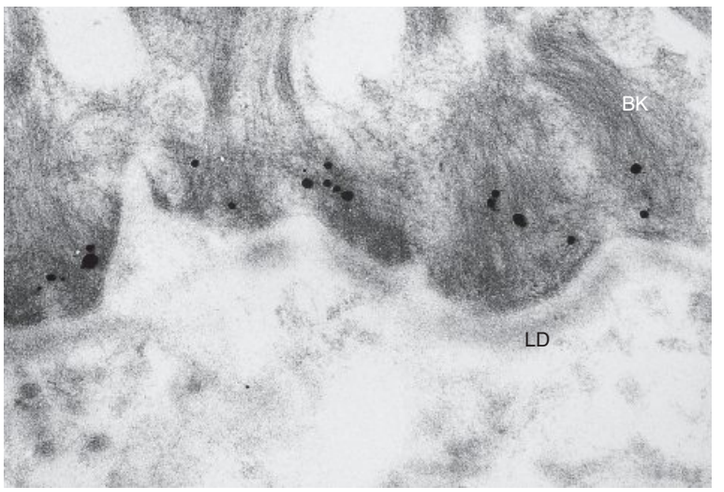
eFig. 30.7 Oral mucosal involvement (desquamative gingivitis) in a patient with bullous pemphigoid. *Courtesy Mark Bernstein, MD.*



eFig. 30.8 Childhood bullous pemphigoid. A predominance of acral involvement is often seen in infants. *Courtesy Julie V. Schaffer, MD.*



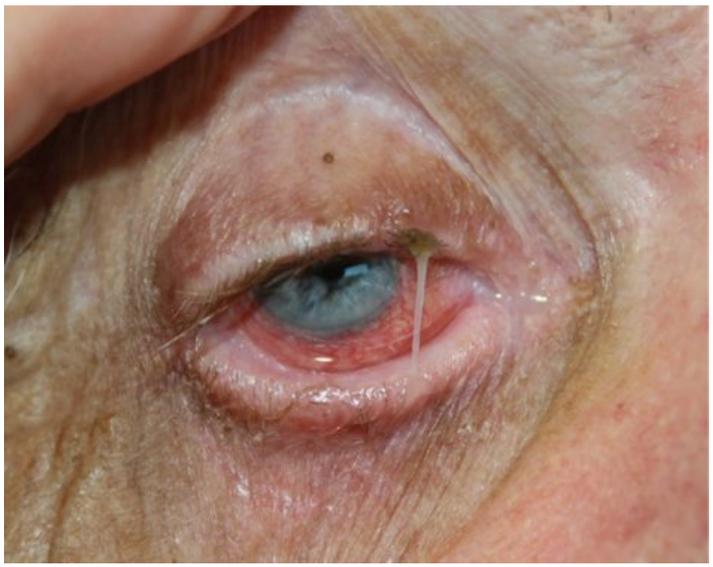
eFig. 30.9 Bullous pemphigoid – direct and indirect immunofluorescence microscopy. A Direct immunofluorescence microscopy studies of perilesional skin demonstrating linear continuous deposits of IgG along the epidermal basement membrane zone (arrows). The same pattern of labeling is observed in cicatricial pemphigoid and epidermolysis bullosa acquisita. **B** Indirect immunofluorescence microscopy study utilizing salt-split normal human skin as a substrate. IgG autoantibodies from the patient's serum are bound to the epidermal side (roof) of the split (arrow). The level of the artificial subepidermal separation is indicated by asterisks. The same pattern of labeling is observed in a subset of patients with cicatricial pemphigoid. Cell nuclei are stained blue.



eFig. 30.10 Bullous pemphigoid – indirect immunoelectron microscopy utilizing immunogold labeling. Autoantibodies directed against BP230 specifically label the hemidesmosomal plaque of the hemidesmosomal adhesion complex (gold labeling = black dots). BK, basal keratinocyte; LD, lamina densa. *Courtesy Professor H. Shimizu.*



eFig. 30.11 Mucous membrane pemphigoid. Typical ocular involvement as manifested by fibrous tracts, representing partial or incomplete symblepharon.



eFig. 30.12 Mucous membrane pemphigoid. Thickening of the lower eyelid with ectropion and exudative conjunctivitis. *Courtesy Jeffrey P. Callen, MD.*



eFig. 30.13 Mucous membrane pemphigoid. Desquamative gingivitis can be the presenting sign of the disease. *Courtesy Jeffrey P. Callen, MD.*



eFig. 30.14 Mucous membrane pemphigoid. Erythema and erosions of the gingival margins (desquamative or erosive gingivitis).



eFig. 30.15 Mucous membrane pemphigoid. Cutaneous involvement of the scalp with scarring and atrophy resulting in alopecia.



eFig. 30.16 Mucous membrane pemphigoid. Irregularly shaped ulceration within an area of scarring on the mid chest. Multiple sites of scarring point to chronicity. *Courtesy Michael Gowen, MD.*



eFig. 30.17 Epidermolysis bullosa acquisita in a patient with systemic lupus erythematosus. Postinflammatory hyperpigmentation, milia and scarring that favor sites of trauma overlying joints. Note the resemblance to dystrophic epidermolysis bullosa. *Courtesy Kalman Watsky, MD.*



eFig. 30.18 Epidermolysis bullosa acquisita – inflammatory bullous pemphigoid-like presentation. Bullae and circular erosions in a patient with multiple myeloma.

31 Dermatitis Herpetiformis and Linear IgA Bullous Dermatosis

Bridget E. Shields, Christopher M. Hull and John J. Zone

Key features

- Dermatitis herpetiformis (DH) is differentiated from linear IgA bullous dermatosis (LABD) on the basis of granular IgA versus linear IgA deposition at the basement membrane zone, as observed by direct immunofluorescence
- DH is a cutaneous manifestation of celiac disease (CD) and is associated with gluten sensitivity in virtually all cases
- DH and CD are genetic disorders strongly associated with HLA-DQ2 and DQ8 genotypes
- CD-associated IgA antibodies are directed against *tissue* transglutaminase (transglutaminase 2 [TG2]); IgA antibodies in the skin of DH patients are directed against *epidermal* transglutaminase (transglutaminase 3 [TG3])
- The intestinal and cutaneous disease in DH can be controlled by gluten restriction; both DH and LABD respond to sulfone therapy
- In adults, LABD is often drug-induced

DERMATITIS HERPETIFORMIS

Synonym: ■ Duhring disease

Introduction

Dermatitis herpetiformis (DH) is a cutaneous manifestation of gluten sensitivity. Although over 90% of DH patients have evidence of a gluten-sensitive enteropathy (GSE), only about 20% have intestinal symptoms of celiac disease (CD). Both the skin disease and the intestinal disease respond to gluten restriction and recur with institution of a gluten-containing diet.

Four findings support the diagnosis of DH:

- pruritic papulovesicles or excoriated papules on extensor surfaces
- neutrophilic infiltration of the dermal papillae with vesicle formation at the dermal–epidermal junction
- granular deposition of IgA and epidermal transglutaminase (TG3) within the dermal papillae of clinically normal-appearing skin adjacent to a lesion
- a response of the skin disease, but not the intestinal disease, to dapsone therapy.

Although DH is usually a lifelong condition, the course may wax and wane. A spontaneous remission may occur in up to 10% of patients, but most clinical remissions are related to dietary gluten restriction[1].

History

Dr Louis Duhring described DH at the University of Pennsylvania in 1884. It was the first skin disease described by an American dermatologist. The critical discoveries in our understanding of DH are listed in Table 31.1.

Epidemiology

DH occurs more commonly in people of northern European origin. It is uncommon in African-Americans and Asians. The annual incidence ranges from 0.4–3.5/100 000 and appears to be declining, likely secondary to better recognition of early celiac disease[2]. The mean age of onset is during the fourth decade, but it may first appear from age 2 to 90 years. Although adolescent and prepubescent children in the US and northern Europe are infrequently affected, this age group is more commonly affected in other countries such as Hungary and Italy. In most epidemiologic studies, DH occurs more frequently in men, in a ratio of 1.1 : 1 to 1.9 : 1[3]. From 1979 to 1996, the familial incidence of DH in Finland was studied prospectively. DH was diagnosed in 1018 patients and 10.5% of these patients had one or more affected first-degree relatives[4].

A study in Utah (1987) found a prevalence of 11.2 per 100 000. The annual incidence during the years 1978 to 1987 was 0.98 per 100 000. Mean age of onset for men was 40 years and for women was 36 years. The male-to-female ratio was 1.44 : 1[5].

Pathogenesis

Our knowledge of the pathogenesis of DH is based on a number of clinical and laboratory observations. The key observations that have been integrated into theories of pathogenesis are:

- a strong genetic association with HLA DQ2 haplotype and less often DQ8

DERMATITIS HERPETIFORMIS – HISTORIC LANDMARKS	
1884	Louis Adolphus Duhring of Philadelphia described in detail "dermatitis herpetiformis" (DH)
1888	Jean Louis Brocq of Paris renamed the condition "dermatite polymorphe prurigineuse"
1890	T Caspar Gilchrist outlined the histologic changes of DH, which were included in the 1897 edition of Duhring's textbook *Cutaneous Medicine: A Systemic Treatise on Diseases of the Skin*
1940	Sulfapyridine was reported to be an effective treatment for DH. The clinical response to sulfapyridine became a diagnostic test
1950	Dicke, a Dutch pediatrician, observed that patients with celiac disease (CD) improved during World War II when bread was in short supply, and their disease worsened when grain supplies were restored
1953	Diamino-diphenyl sulfone (dapsone), the parent compound of sulfapyridine, also proved to be effective in DH
1967	Independent accounts connected DH with CD
1969	JB van der Meer demonstrated IgA deposits in the papillae of uninvolved skin in DH
1972	Stephen Katz linked DH to the HLA-B8 antigen. This strengthened the association between CD and DH
1986	IgA class anti-endomysial antibodies discovered to be highly specific for DH and CD
1997	DH and CD found to have a common immunogenetic background with strict association with HLA alleles DQ A1*0501 and B1*02, which encode HLA-DQ2 heterodimers
2003	Sardy and colleagues identified epidermal transglutaminase as an autoantigen in DH
2012	Zone and colleagues demonstrated that transfer of DH sera or goat anti-human epidermal transglutaminase antibodies to human skin-grafted mice mimics DH immunopathology

Table 31.1 Dermatitis herpetiformis – historic landmarks.

- some degree of GSE on small bowel biopsy in virtually all patients, accompanied by a TG2-targeted immune response in the intestine in both CD and DH plus an additional anti-TG3 response in DH
- granular IgA deposition within the papillary dermis of the skin (this is essential for the diagnosis and occurs at the site of eventual inflammation)
- neutrophilic infiltration into the dermal papillae
- improvement of symptoms with dapsone therapy and worsening of symptoms with inorganic iodide ingestion.

Genetic predisposition

Specific HLA DQ2 or DQ8 genes, which encode molecules that interact with T cell receptors, are believed to provide the antigenic specificity that processes the gliadin antigen in genetically susceptible individuals. This HLA association is the same for patients with CD and DH. Genes encoding the DQ2 (A1*0501, B1*02) heterodimer are carried by 90% of CD and DH patients, while genes encoding the DQ8 (A1*03, B1*03) heterodimer are carried by the remaining DH patients[6]. Previous descriptions of associations with HLA-B8, as well as HLA-DR3 and HLA-DR5/DR7, represent class I and class II molecules that are in linkage disequilibrium with DQ2. However, it has been established that <50% of the genetic predisposition in CD and DH is due to specific HLA genes. However, genomic searches for non-HLA genes in patients with DH have to date been unsuccessful. Monozygotic twins, one with DH and the other with CD, have been reported, indicating that environmental as well as genetic factors play a role in the development of CD and/or its extraintestinal manifestation, DH[7].

Gluten-sensitive enteropathy (GSE)

In small bowel biopsies, more than 90% of DH patients have some degree of GSE. The bowel abnormality is caused by gliadin, the antigenic alcohol-soluble fraction of gluten. Gluten consists of a family of grain proteins found in: wheat, rye, barley, and hybrids of these grains (e.g. kamut, spelt, triticale). It is not found in rice, corn, sorghum, or most oats. The spectrum of intestinal involvement ranges from minimal infiltration of the lamina propria by lymphocytes (with normal villi), to minimal atrophy of the jejunum accompanied by intraepithelial lymphocytic infiltrates, to total villous atrophy of the small intestine. The enteropathy is often patchy and may require multiple small bowel samples for diagnosis. Symptomatic malabsorption occurs in ~20% of patients with DH.

The proposed pathogenesis of DH and CD is presented in Fig. 31.1. Following ingestion of gluten-containing grains (see above), one of the products of digestion is gliadin (see Fig. 31.1A). Once gliadin is absorbed via the lamina propria, glutamine residues within gliadin are deamidated by tissue transglutaminase (TG2) and covalent cross-links (isopeptidyl bonds) are formed between lysine residues in TG2 and glutamines in gliadin. Deamidation by TG2 is thought to be a critical step as it serves to optimize antigen presentation.

Deamidated gliadin peptides bind to the groove of the HLA-DQ2 molecule on dendritic antigen-presenting cells (see Fig. 31.1B), and the gliadin antigen is then presented to sensitized helper T cells in the context of HLA-DQ2 or DQ8 specificity. These helper T cells can stimulate B cells, with differentiated plasma cells producing IgA antibodies to multiple antigens, including gliadin, gliadin cross-linked to TG2, TG2, and epidermal transglutaminase (TG3). IgA anti-TG2 antibodies have become the serologic hallmark for CD.

In addition, stimulated natural killer (NK) lymphocytes cause crypt hyperplasia and villous atrophy. Elevated serum levels of interleukin (IL)-17 and IL-36 in patients with DH suggest a possible role for these cytokines in NK cell signaling and neutrophil activation[8]. The IL-31 pathway may also be involved in mediating the pruritus found in DH[9].

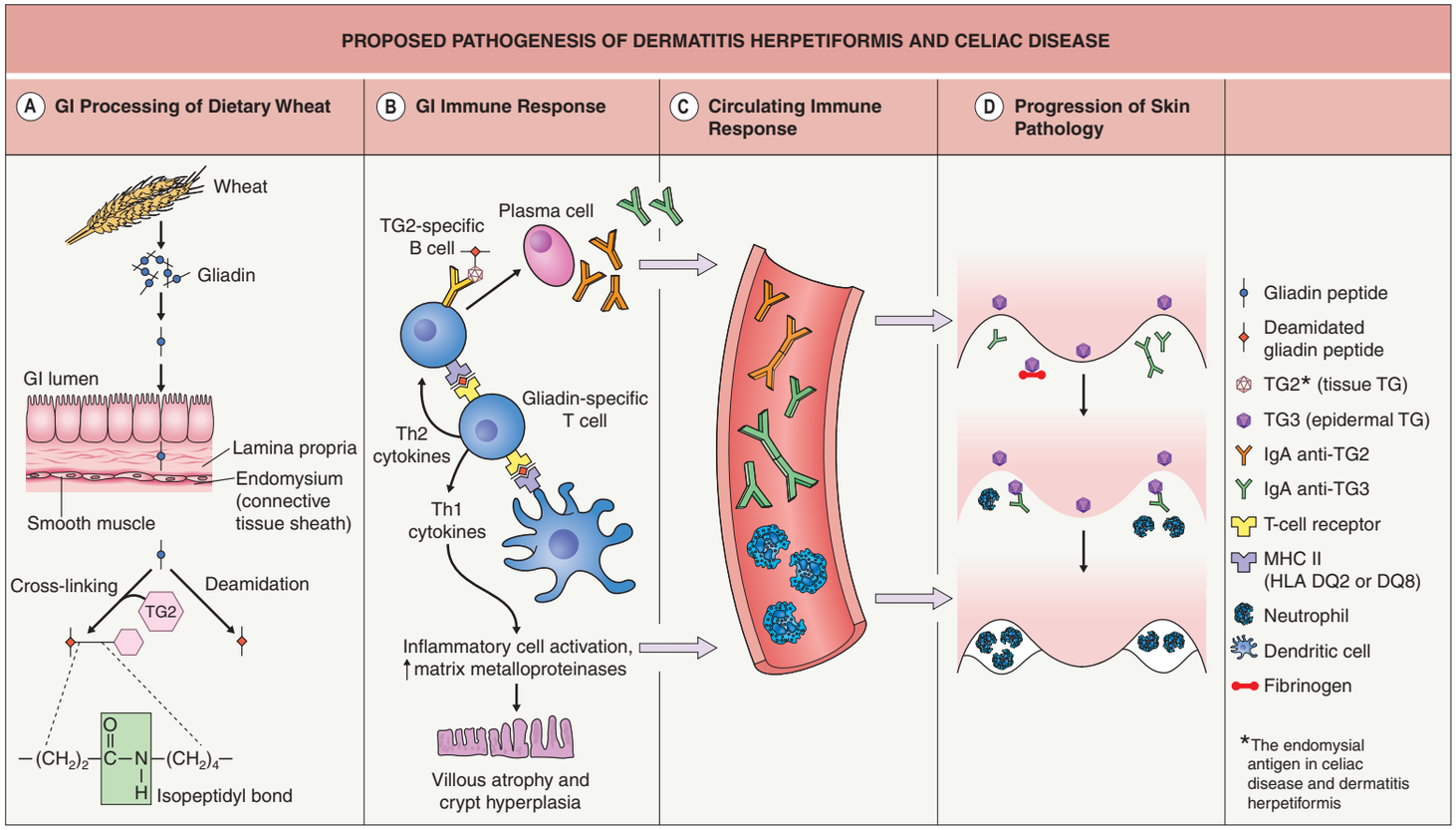


Fig. 31.1 Proposed pathogenesis of dermatitis herpetiformis and celiac disease. A Dietary wheat, barley, or rye is processed by digestive enzymes into antigenic gliadin peptides, which are transported intact across the mucosal epithelium. Within the lamina propria, tissue transglutaminase (TG2): (1) deamidates glutamine residues within gliadin peptides to glutamic acid; and (2) becomes covalently cross-linked to gliadin peptides via isopeptidyl bonds (formed between gliadin and TG2 lysine residues). **B** $CD4^+$ T cells in the lamina propria recognize deamidated gliadin peptides presented by HLA-DQ2 or -DQ8 molecules on antigen-presenting cells, resulting in the production of Th1 cytokines and matrix metalloproteinases that cause mucosal epithelial cell damage and tissue remodeling. In addition, TG2-specific B cells take up TG2–gliadin complexes and present gliadin peptides to gliadin-specific helper T cells, which stimulate the B cells to produce IgA anti-TG2. **C** Over time, IgA directed against TG3 (IgA anti-TG3) forms as a result of epitope spreading and both IgA anti-TG2 and IgA anti-TG3 circulate in the bloodstream. **D** When IgA anti-TG3 antibodies reach the dermis, they complex with TG3 antigens which have been produced by keratinocytes (epidermal TG) and then have diffused into the dermis. That is, IgA/TG3 immune complexes are formed *locally* within the papillary dermis. This leads to neutrophil chemotaxis (with formation of neutrophilic microabscesses), proteolytic cleavage of the lamina lucida, and subepidermal blister formation.

In the setting of continued exposure to gliadin, epitope spreading is thought to lead to development of IgA anti-TG3 antibodies in patients who already have IgA anti-TG2 antibodies. Patients with CD and DH have an immune response to TG2 within their intestinal mucosa, while those with DH have an additional response to TG3[10] (see Fig. 31.1B,D). Epitope spreading is a possible explanation for why DH tends to present at a later age than symptomatic CD (the latter often manifests in childhood) and why patients with CD alone tend to have more severe intestinal disease than patients with DH. Formation of IgA anti-TG3 antibodies is thought to require time and continued exposure to gluten and this would be more likely to occur in patients with less severe, relatively asymptomatic intestinal involvement. Findings in support of this theory include the presence of IgA anti-TG2 antibodies in most DH patients and a higher prevalence of IgA anti-TG3 antibodies in adults than in children with CD (i.e. developing later in the evolution of the disease). The declining incidence of DH, despite the rising incidence of CD, might further support this theory, with CD being diagnosed earlier before epitope spreading has the chance to occur[1].

The formation of IgA anti-TG3 antibodies also activates circulating neutrophils (see Fig. 31.1C). Deposition of these antibodies within the dermal papillae results in the infiltration of activated neutrophils from the circulation into the dermal papillae (see Fig. 31.1D). Degranulation of neutrophils releases proteases which disrupt the lamina lucida and produce a subepidermal blister.

Since both the skin disease and the intestinal disease resolve with dietary gluten restriction and recur with return to a regular diet, it is clear that the dietary protein gluten is central to the pathogenesis of the cutaneous eruption. In addition, it is the HLA class II antigen that acts as a gate through which gluten can reach the inflammatory cells and initiate the autoimmune process[11,12].

Circulating antibodies

The first serologic difference between DH and CD was described in 2002, with TG3 identified as the autoantigen in DH[13]. Additional studies have demonstrated that circulating IgA anti-TG3 antibodies are not only elevated in patients with DH, but can be assayed and may be helpful in monitoring response to a gluten-free diet[14,15]. TG3 was also found to co-localize with IgA in dermal papillae of DH patients and is enzymatically active in this site (see Fig. 31.5B)[13,16,17]. TG3 is expressed in many tissues of the body, including the epidermis. When IgA anti-TG3 antibodies reach the dermis, they complex with TG3 antigens which have been produced by keratinocytes (epidermal TG) and then have diffused into the dermis. In other words, IgA/TG3 immune complexes are formed *locally* within the papillary dermis (see Fig. 31.1D).

When goat anti-human TG3 antibodies (IgG) were passively transferred into SCID mice grafted with human skin, immune deposits were detected within the papillary dermis which reacted with rabbit anti-TG3 and DH sera. Transfer of sera from DH patients (who had high circulating levels of IgA anti-TG3 antibodies) led to similar granular IgA and TG3 dermal deposits[18]. In DH skin, IgA-bound deposits of TG3 are enzymatically active and therefore TG3 likely plays an important role in the covalent binding of IgA to connective tissue fibers. Enzymatically active TG3 also binds to soluble fibrinogen whose subsequent degradation may play a key pathogenic role[17]. In an animal model, evidence supported local formation of immune complexes in the papillary dermis, supplanting previous theories in which IgA complexes within DH skin were thought to represent deposits of circulating immune complexes.

Granular IgA deposition

Granular IgA deposition within dermal papillae is the hallmark of DH (see Fig. 31.5A). The deposits are composed of IgA1 antibodies directed against TG3. Circulating IgA antibodies to TG2 (an endomysial antigen) have been identified by indirect immunofluorescence (IIF) microscopy using a monkey esophagus substrate, and the presence of these antibodies correlates with the degree of GSE. IgA anti-TG3 antibodies, but not IgA anti-TG2 antibodies, are responsible for the IgA deposition in DH skin.

Iodide

Ingestion of iodide can lead to worsening of DH and topical application of iodide onto the normal skin of DH patients produces lesions that are histologically identical to spontaneous lesions. Even in normal subjects, topical iodides may produce follicular neutrophilic pustules. When potassium iodide is added to DH skin *in vitro*, the enzymatic activity of TG3 that is complexed to IgA dramatically increases[19]. It is therefore possible that the clinical worsening of DH after iodide application or ingestion is due to an iodide-induced increase in TG3 activity. In patients with refractory DH, a search for covert iodide ingestion should be undertaken as iodide can be found in medications, dietary supplements, and foods (e.g. eggs), in addition to radiographic contrast media[19a].

Associated Disorders and Malignancies

A strong association exists between DH and thyroid disease, particularly Hashimoto thyroiditis. In one study, the presence of some type of thyroid abnormality was found in 26 of 50 patients with DH[20]. Although the pathogenetic relationship between DH and thyroid disease is unknown, it may represent a coexistence of autoimmune disease[20]. The incidence of enteropathy-associated T cell lymphoma is also increased in patients with DH and warrants increased surveillance. Of note, adhering to a gluten-free diet protects against developing lymphoma, in particular after the patient has adhered to a gluten-free diet for five years. This further supports advising patients with DH to adhere to a strict gluten-free diet *ad infinitum*. Other autoimmune disorders reported to be associated with DH and CD are listed in Table 31.2.

Clinical Features

DH has a symmetric distribution and favors the elbows, knees, extensor forearms, back, and buttocks (Fig. 31.2 & 31.3). The primary lesions are pleomorphic, with urticarial plaques, papules, and vesicles. Grouped or "herpetiform" papulovesicles with an erythematous base are characteristic of this autoimmune disorder. Intense pruritus leads to secondary excoriation and crusting. Even if only hemorrhagic crusts or secondary changes from scratching are present, the diagnosis should be suspected on the basis of the distribution pattern. Less common presentations are isolated facial or scalp involvement, exclusively macular lesions, and hemorrhagic acral macules (usually palmoplantar; see Fig. 31.3C).

Pathology

For routine histology, it is optimal to capture a small, intact vesicle. If this is not available, an area of erythema should be biopsied. Areas of erythema will show dermal papillary edema and neutrophil infiltration associated with a superficial perivascular lymphocytic infiltrate. Dermal papillae filled with neutrophils, with relative sparing of the lowermost tips of the intervening rete ridges, is a characteristic finding. When an intact vesicle is biopsied, a subepidermal blister containing predominantly neutrophils is usually seen (Fig. 31.4). Sometimes only a lymphohistiocytic infiltrate or spongiosis is seen, emphasizing the important role of direct immunofluorescence (DIF) microscopy[15,21]. Also, as with other autoimmune bullous disorders, the presence of typical histologic features depends on the site and quality of the biopsy.

AUTOIMMUNE DISORDERS ASSOCIATED WITH DERMATITIS HERPETIFORMIS	
Common	
• Autoimmune thyroid disease (Hashimoto thyroiditis) • Insulin-dependent diabetes mellitus	
Uncommon	
• Pernicious anemia	
Rare	
• Addison disease • Autoimmune chronic active hepatitis • Alopecia areata • Myasthenia gravis • Sarcoidosis	• Systemic sclerosis (scleroderma) • Sjögren syndrome • Systemic lupus erythematosus • Vitiligo

Table 31.2 Autoimmune disorders associated with dermatitis herpetiformis.



Fig. 31.2 Dermatitis herpetiformis. A Pink papulovesicles, erosions, and hemorrhagic crusts on the elbow. **B** Multiple urticarial pink papules on the knee, in addition to a few erosions and small subtle intact vesicles (arrows and half-circles). **C** Pink plaques on the knee composed of grouped papules and papulovesicles, admixed with tiny hemorrhagic crusts. **D** Crusted papules as well as an intact vesicle on the elbow. *C, Courtesy Thomas Horn, MD.*

IgA Deposits

In patients with DH, dermal IgA deposits are not uniformly distributed throughout the skin. Notably, IgA deposits are present in greater amounts near active lesions. The optimal biopsy site for DIF microscopy is normal-appearing skin immediately adjacent to a lesion (see Fig. 29.12). A false-negative DIF can occur if lesional skin is biopsied, since the inflammatory infiltrate can destroy the epitopes on IgA[22]. A definitive diagnosis of DH depends upon the demonstration of dermal IgA deposits by DIF microscopy. Granular IgA deposits localized to the dermal papillae are found in 85% of cases of DH (Fig. 31.5), while continuous granular deposition of IgA along the basement membrane occurs in 5% to 10% of cases. A fibrillar pattern of IgA deposition occurs rarely although it is more commonly observed in Japanese patients[23]. Because DH represents a lifetime diagnosis with systemic and therapeutic implications, definitive immunopathologic confirmation is essential.

Although granular deposits of IgA in the skin along with serum IgA anti-TG3 antibodies is considered characteristic of DH, a recent study found that a subset of newly diagnosed CD patients without skin disease could have cutaneous IgA deposits and circulating IgA anti-TG3 antibodies[24]. It is possible that this subset of CD patients may go on to develop DH.

Laboratory evaluation

Anti-endomysial IgA antibodies are very specific for the GSE present in CD and DH. Their levels indicate the severity of GSE and reflect the degree of compliance with dietary gluten restriction. IgA anti-endomysial antibodies are found in ~80% of patients with DH and >95% of patients with active CD at the time of diagnosis. The endomysium is the connective tissue covering the smooth muscle layers of the esophagus, stomach, and small intestine (see Fig. 31.1A) and TG2 has been identified as the endomysial antigen.

Anti-TG2 and -TG3 antibodies play a key role in the pathogenesis of CD and DH (see above). The normal physiologic function of transglutaminase is to repair injured tissue by cross-linking extracellular matrix proteins in order to protect surrounding tissue from further damage. Transglutaminase facilitates the linkage of the carboxamide group of the amino acid glutamine, found in gliadin, to an ε-amino group of a lysine residue in transglutaminase located in the intestinal tract (see Fig. 31.1A). The glutamine in gliadin is especially vulnerable to cross-linkage with transglutaminase, and this linkage is perceived as a foreign antigen by the host immune system. As antibodies to transglutaminase are produced, the normal function of transglutaminase in repairing the damaged intestinal mucosa is impaired.



Fig. 31.3 Dermatitis herpetiformis. A Grouped pink papulovesicles on the upper back, neck, and scalp in a child. **B** Pruritic pink papules on the buttocks, some of which have central hemorrhagic crusts and are grouped. **C** Multiple hemorrhagic macules on the fingertips. *B, Courtesy Louis A. Fragola, Jr, MD; C, Courtesy Jeffrey Callen, MD.*

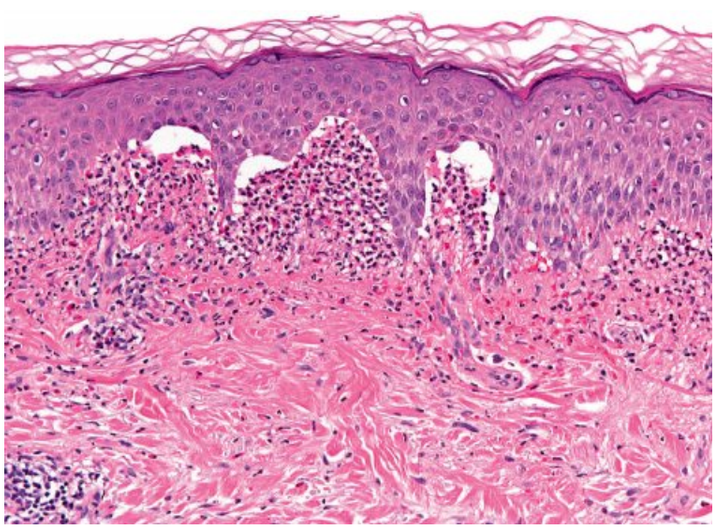


Fig. 31.4 Dermatitis herpetiformis – histopathologic features. Subepidermal clefts beneath which are collections of neutrophils within dermal papillae. Scattered eosinophils are also present. *Courtesy Lorenzo Cerroni, MD.*

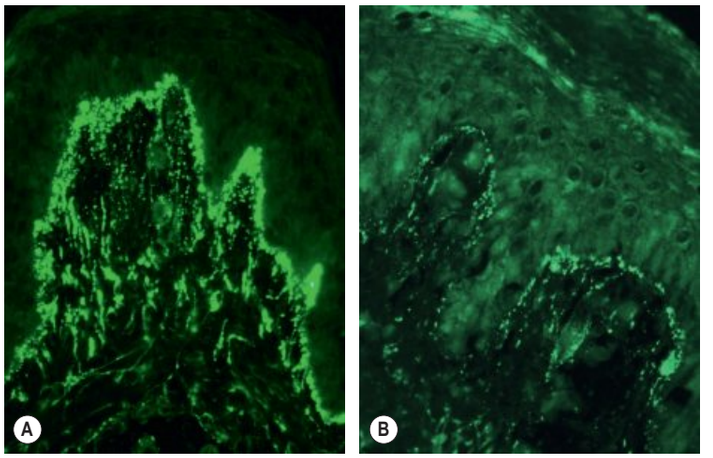


Fig. 31.5 Dermatitis herpetiformis – direct immunofluorescence. A Granular IgA deposition along the dermal–epidermal junction of normal-appearing skin adjacent to a lesion. **B** Granular deposition of epidermal transglutaminase (TG3) within the dermal papillae, which co-localizes with the IgA. *A, Courtesy Kristin Leiferman, MD.*

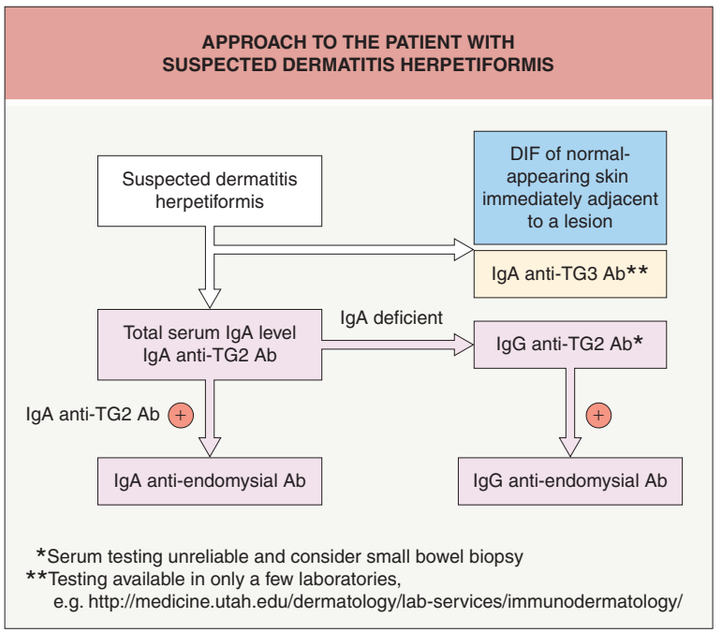


Fig. 31.6 Approach to the patient with suspected dermatitis herpetiformis. IgA anti-TG2 and anti-endomysial antibodies can be monitored over time to assess compliance with a gluten-free diet. Because the anti-endomysial antibody assay is based upon analysis of indirect immunofluorescence, it is more expensive than the IgA anti-TG2 antibody assay; thus, the recommendation that the latter assay be performed first. Anti-deamidated gliadin peptide IgG testing may have utility for individuals with IgA deficiency or weakly positive anti-TG2 IgA. Ab, antibody; DIF, direct immunofluorescence; TG, transglutaminase.

An approach to the laboratory evaluation of a patient with suspected DH is outlined in Fig. 31.6.

Differential Diagnosis

The differential diagnosis includes arthropod assault, scabies, and urticarial vasculitis, as well as erythema multiforme, bullous lupus erythematosus, linear IgA bullous dermatosis (LABD), and bullous pemphigoid. Table 31.3 outlines the clinical and histologic features that help differentiate DH from LABD and bullous pemphigoid. Erythema multiforme is characterized by target lesions that are often acral in distribution and show vacuolar degeneration and focal epidermal necrosis histologically as well as a lack of IgA deposition at the basement membrane zone (BMZ; see Ch. 20).

CHARACTERISTICS THAT DIFFERENTIATE DH, LABD, AND BP			
	DH	**LABD**	**BP**
Cutaneous lesion	Grouped papules and small vesicles, often excoriated	Small vesicles and/or large bullae	Large tense bullae
Distribution pattern	Extensor surfaces, symmetrical	Similar to DH or BP; may involve mucosae	Trunk, extremities, occasionally mucosae
Routine histology	Subepidermal bullae with neutrophilic infiltrate	Subepidermal bullae with neutrophilic infiltrate (sometimes eosinophils predominate)	Subepidermal bullae with eosinophilic infiltrate
Direct IF	Granular IgA in dermal papillae	Linear IgA at BMZ, possibly also IgG	Linear IgG and C3 at BMZ
Site to biopsy for direct IF	Adjacent normal-appearing skin	Perilesional	Perilesional
Routine indirect IF	Negative	Linear IgA at BMZ (70%)	Linear IgG at BMZ (70%)
Enteropathy	>90%	Rare	None
HLA-DQ2	>90%	30%	Normal (20%)
Dapsone responsiveness	Excellent	Good, may also require systemic corticosteroids	Minimal to moderate

Table 31.3 Characteristics that differentiate dermatitis herpetiformis (DH), linear IgA bullous dermatosis (LABD), and bullous pemphigoid (BP). BMZ, basement membrane zone; IF, immunofluorescence.

SIDE EFFECTS OF DAPSONE		
Red blood cell toxicity	• Hemolytic anemia • Methemoglobinemia*	
White blood cell toxicity	• Leukopenia • Agranulocytosis	
Dapsone hypersensitivity syndrome	• Fever, fatigue, anorexia, hepatitis, lymphadenopathy	
Cutaneous reactions	• Morbilliform eruption • Urticaria • Fixed drug eruption • Erythema nodosum • Exfoliative dermatitis	• SJS/TEN • Phototoxicity • Drug-induced cutaneous lupus erythematosus
Gastrointestinal manifestations†	• Anorexia, nausea • Hepatitis • Cholestatic jaundice • Severe hypoalbuminemia	
Neurologic associations†	• Headache, dizziness • Peripheral neuropathy • Blurred vision, tinnitus • Insomnia • Psychosis	
Miscellaneous	• Fever • Nephrotic syndrome	

*Patients should be warned that arterial desaturation may be noted by pulse oximetry, even with relatively low levels of methemoglobinemia.
†In decreasing order of frequency.

Table 31.4 Side effects of dapsone. SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Bullous lupus erythematosus presents with urticarial papules and vesicles on an erythematous base and a histologic picture similar to LABD and DH. However, the patients have clinical and serologic findings of systemic lupus erythematosus. DIF reveals multiple immunoglobulins (including IgA) in a granular or broad linear pattern along the BMZ, whereas in LABD there is a fine linear IgA deposition.

Crusted papules are also seen on the elbows and knees in patients with granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis, but histologic features of vasculitis are observed.

Treatment

The treatment of DH includes dapsone and a gluten-free diet, with the pruritus of DH relieved within 48–72 hours after instituting dapsone (4′,4′ diamino-diphenyl sulfone). Lesions abruptly recur within 24–48 hours of therapy discontinuation. However, dapsone has no effect on the intestinal pathology.

Dapsone is begun after screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency, with initial dosages of 25–50 mg in adults and 0.5 mg/kg in children. Initiation of therapy with higher doses may precipitate severe hemolysis and cardiac decompensation in susceptible individuals. The average maintenance dose in adults on a normal diet is 50–100 mg daily. The half-life ranges from 12 to 32 hours, so divided doses are seldom of benefit. The daily dose can be regulated on a weekly basis to optimize control. One to two new lesions per week should be expected on the optimal dose. Higher doses increase toxicity with little benefit.

Outbreaks of facial and scalp lesions while on otherwise adequate treatment can occur, but are not common. Facial disease may prove refractory to dapsone therapy. Breaking the vesicles followed by application of a potent corticosteroid gel may be helpful.

Although there are many side effects of dapsone (Table 31.4; see Ch. 130), the drug is well tolerated for years in more than 90% of patients. Hemolysis occurs in virtually every patient on dapsone therapy, since sulfones produce an oxidant stress on aging red blood cells. In patients with G6PD deficiency, dapsone may produce severe hemolysis. Although most patients have evidence of drug-induced hemolysis, a compensated *hemolytic anemia* develops. Drug-induced hemolysis can be confirmed and followed by a reticulocyte count, which should show increased erythropoiesis. Of note, dapsone is secreted in breast milk and may cause hemolytic anemia in breastfed infants. In the setting of a persistent severe anemia, a search for contributing causes, such as iron, vitamin B_{12} or folate deficiencies or hereditary spherocytosis, should be pursued.

Methemoglobin is present in the blood of most patients taking 100 mg or more of dapsone daily. Although the amount of methemoglobin usually does not exceed 5%, there are patients who have maintained levels between 10% and 15%. Methemoglobinemia in the absence of cardiopulmonary symptoms does not require alteration of dapsone dose. Patients should be warned that arterial desaturation may be noted by pulse oximetry, even with relatively low levels of methemoglobinemia.

Fatal *agranulocytosis* has developed in patients with DH treated with dapsone. This drug-induced agranulocytosis usually occurs after 2–12 weeks of continuous dapsone treatment. Re-administration of dapsone then causes leukopenia within hours. A simple measure is to warn the patient to discontinue the drug and report immediately if fever, a sore throat, or other signs of infection develop.

Dapsone hypersensitivity syndrome (see Ch. 21) is a rare, but potentially severe, reaction, characterized by fever, a cutaneous eruption, and internal organ involvement. It is usually seen 2–7 weeks after initiation of therapy. The cutaneous manifestations vary from a morbilliform eruption to exfoliative dermatitis, while the systemic manifestations include fever, pruritus, lymphadenopathy, hepatitis, an elevated ESR, leukocytosis, and, rarely, eosinophilia. Among patients with leprosy, HLA-B*13:01 has been associated with the development of the dapsone hypersensitivity syndrome. Reported population frequencies of HLA-B*13:01 are 2%–20% (Chinese), 1.5% (Japanese), 1%–12% (Indians), and 2%–4% (Southeast Asians); this allele is largely absent in Europeans and Africans[25]. Patients should be educated about this syndrome and instructed to discontinue therapy and notify their medical provider if any signs or symptoms of the dapsone hypersensitivity syndrome develop.

Peripheral neuropathy induced by dapsone may occur within the first few weeks of therapy. The neuropathy was initially reported as a pure motor neuropathy (involving primarily distal extremity muscles);

however, pure motor, pure sensory, and combined motor and sensory neuropathies have subsequently been reported. Relatively high daily doses of dapsone (200–500 mg) have been implicated.

If patients are intolerant to dapsone, therapy with **sulfapyridine** can be considered. The initial dose of sulfapyridine is usually 500 mg three times daily and it can be safely increased to 2 g three times a day; however, some patients may not respond to sulfapyridine at any dose. Adequate fluid intake and alkalinization of the urine minimizes the risk of nephrolithiasis. Because sulfapyridine is currently not commercially available in the US, sulfasalazine may be used as a second alternative. Sulfasalazine is metabolized to sulfapyridine and 5-aminosalicylate by intestinal bacteria, making dosing less predictable. In adults, a standard starting dose is 500 mg four times daily.

Dapsone monitoring includes a baseline complete blood count (CBC) and liver function tests, then weekly CBCs for the first month, twice monthly CBCs for the second month, then monthly CBCs for the next 4 months, and semiannual CBCs thereafter while the patient remains on therapy. Liver function tests should be repeated at 6 months and annually thereafter. Some clinicians measure baseline G6PD activity in all patients, while others focus on those of African, Asian, or southern Mediterranean ancestry. Sulfapyridine rarely produces hemolytic anemia, but the potential for agranulocytosis does exist. Consequently, similar monitoring is recommended for chronic sulfapyridine or sulfasalazine therapy.

Patients can also be treated with a **gluten-free diet** (which includes corn, rice, and most oats). Because several months on a gluten-free diet is typically needed for a response, concurrent suppression of symptoms with dapsone is usually necessary. Most patients with granular IgA deposits respond to a strict gluten-free diet such that they can either decrease or eliminate their need for dapsone. With a prolonged gluten-free diet, IgA in the skin decreases and eventually disappears, but with the reintroduction of gluten, IgA deposits and skin disease return in the vast majority of patients. Minor fluctuations in disease severity are most likely related to oral gluten intake. The gluten-free diet is inconvenient and unacceptable to some patients.

Patient Support

The Gluten Intolerance Group and the Celiac Disease Foundation (www.celiac.org) offer information on foods and additives that should be avoided. The former patient support group has a *Quick Start Gluten-Free Diet Guide* that may be useful for patients. Their website is www.gluten.org.

LINEAR IgA BULLOUS DERMATOSIS

Synonyms: Adults: ■ Linear IgA dermatosis (LAD) ■ Linear IgA disease of adults ■ Linear IgA disease ■ Linear IgA dermatitis herpetiformis ■ Linear dermatitis herpetiformis ■ Adult linear IgA disease ■ IgA bullous pemphigoid ■ Pemphigoid linear IgA

Children: ■ Chronic bullous disease of childhood ■ Benign chronic bullous dermatosis of childhood ■ Childhood linear IgA dermatitis herpetiformis ■ Linear IgA disease of childhood

Introduction

LABD is an immune-mediated, subepidermal, vesiculobullous eruption that occurs in both adults and children. It has been defined on the basis of a unique immunopathology consisting of linear deposition of IgA along the cutaneous BMZ. In adults, the clinical findings associated with this immunopathologic pattern may resemble those of DH or bullous pemphigoid (BP) (see Table 31.3), but in children, the cutaneous features may be clinically unique.

The childhood form is frequently termed "chronic bullous disease of childhood" (CBDC). It is a subepidermal vesiculobullous disease that was initially described on the basis of its clinical findings – annular erythema and blisters (often referred to as a "crown of jewels"), which developed predominantly in flexural areas, particularly the lower trunk, thighs and groin, in preschool children (Fig. 31.7). However, it is invariably characterized by the linear deposition of IgA along the BMZ

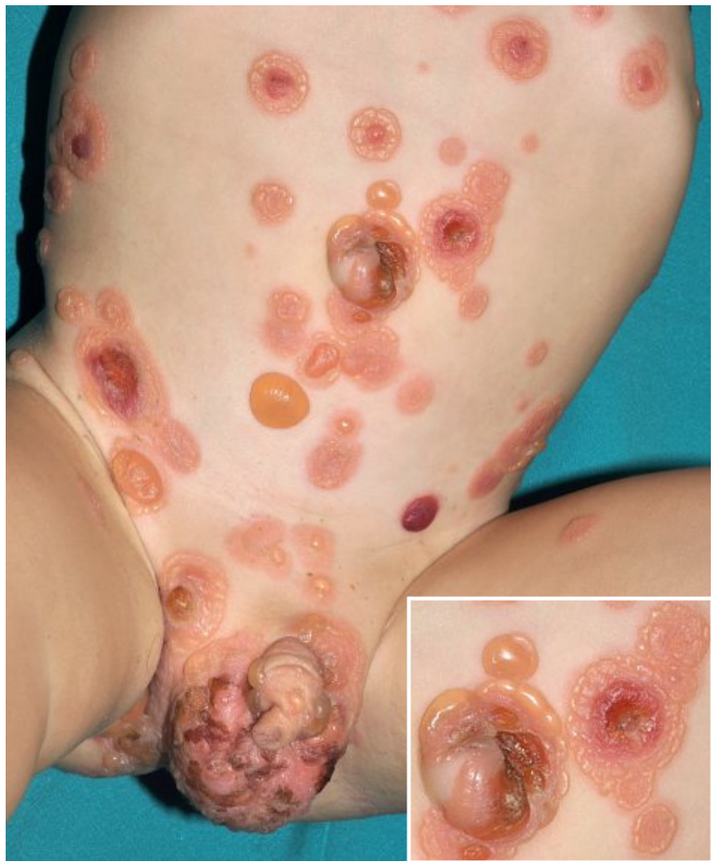


Fig. 31.7 Linear IgA bullous dermatosis. Characteristic findings in this child include the annular array of bullae (inset) and involvement of the genital region. There are also tense bullae arising on normal-appearing skin with either clear or hemorrhagic fluid and annular bullae with central crusting. *Courtesy Antonio Torello, MD.*

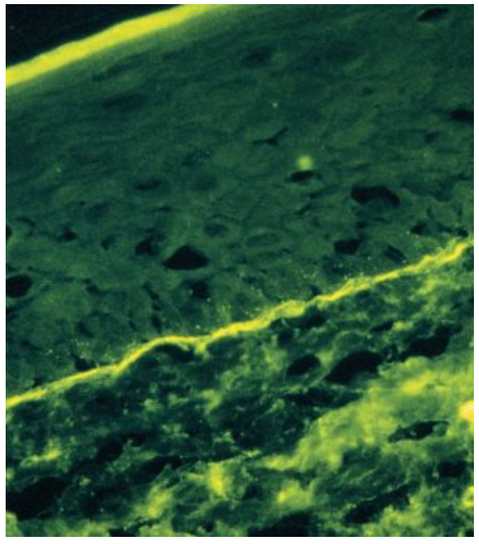


Fig. 31.8 Linear IgA bullous dermatosis – direct immunofluorescence. A linear pattern of IgA deposition is present within perilesional skin.

(Fig. 31.8) as well as circulating antibodies against the same BMZ antigens described in the adult form[26].

There are two distinct types of LABD based upon the site of IgA deposition as determined by immunoelectron microscopy: a lamina lucida type (majority) and a sublamina densa type. In adults, LABD is frequently drug-induced.

History

In 1969, it was noted that patients with vesiculobullous lesions and the histologic findings of DH could have linear rather than granular deposits

of IgA along the epidermal BMZ[27]. In 1975, Chorzelski and Jablonska[28] first suggested the term LABD and suggested that it was a separate entity based on its immunopathologic findings. Since then, there has been general agreement that LABD is a distinct disease entity from DH[29,30]. Nowadays, the term linear IgA disease (LAD) is often used as synonymous with LABD and perhaps is a preferred term, especially when there is mucosal involvement.

In 1970, Jordon et al.[31] first proposed the name "benign chronic bullous dermatosis of childhood". Subsequent investigators, using antisera specific for IgA, identified the characteristic linear IgA deposition along the epidermal BMZ in children with CBDC[32]. On a molecular basis, CBDC is the same disease as LABD in that the circulating IgA antibody found in the serum of patients with CBDC binds to the same 97 kDa proteolytic fragment of BP180 antigen described in adults with LABD[26].

Epidemiology

The annual incidence of LABD varies globally, ranging from 0.5 to 2.3 cases per million per year[33]. Incidence in the US has not been reported, but we have estimated the prevalence of LABD in Utah to be 0.6 per 100 000 adults. In adults, the average age of onset of LABD is over 60 years of age[33,34]. There appears to be a slight female preponderance, although this has not been observed in all series[33]. Childhood LABD occurs at a mean age of 4.5 years[34].

Pathogenesis

Both BP and the lamina lucida type of LABD have lamina lucida deposition of immunoglobulin and are associated with BMZ vesiculation. However, the antigenic specificity differs. In BP, the pathogenic IgG antibodies bind the MCW-1 region of the NC16 domain of BP antigen 2 (BPAG2; BP180), whereas the epitopes that have stimulated an IgA response in LABD are toward the carboxy terminus of the same molecule (Fig. 31.9)[35]. In adult and childhood LABD patients, this IgA antibody was initially found, on immunoblot, to react against a 97 kDa antigen in an epidermal extract[36]. Subsequently, there was definitive characterization of the antigenically active fragments of the physiologically cleaved BP180 ectodomain[37]. Sera from LABD patients preferentially react with two fragments that contain neoepitopes but not with intact BP180. These two fragments are LAD-1 (120 kD) and LABD97 (97 kD; see Fig. 31.9)[37]. Why BP antibodies should react predominantly with antigens near the transmembrane portion of BPAG2 and LABD antibodies react with cleaved epitopes within the collagenous domain is unclear.

IgA class antibodies from patients with the sublamina densa type of LABD have been reported to bind to type VII collagen within anchoring fibrils[38,39].

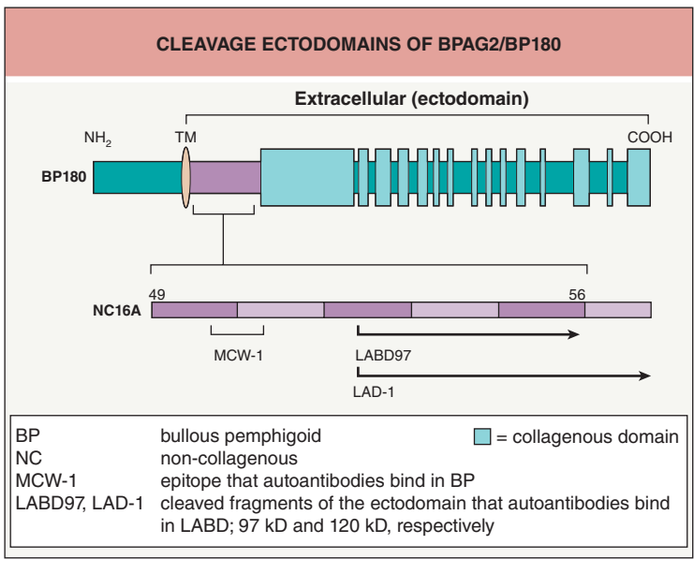


Fig. 31.9 Cleavage ectodomains of BPAG2/BP180. BP, bullous pemphigoid; COOH, carboxy terminus; LABD, linear IgA bullous dermatosis; NH_2, amino terminus; TM, transmembrane region.

There have been reports in the literature of the association of LABD with various disorders such as gastrointestinal diseases, autoimmune diseases, malignancies, and infections (see below). The significance of these associations is yet to be determined, but they may play a role in the initial stimulation of the IgA mucosal immune system.

The incidence of gluten-sensitive enteropathy in LABD has been reported in the literature to range from 0 to 24%[30,32,40]. In one case series, two of six patients with LABD had gluten-sensitive enteropathy, and two of six patients' skin lesions improved on a gluten-free diet; however, none of the patients completely cleared[40]. In contrast, a second series found no histologic evidence of gluten-sensitive enteropathy in the six patients they studied[30]. LABD clearly has a much lower prevalence of small bowel histologic abnormalities than does DH. Ulcerative colitis, Crohn disease, and gastric hypochlorhydria have also been described in association with LABD[29,41]. LABD associated with ulcerative colitis was reported to remit after colectomy[42].

Data on the association of autoimmune diseases with LABD are not sufficient to allow statistical analysis of prevalence. However, there are reports in the literature of the association of systemic lupus erythematosus and dermatomyositis with LABD, as well as thyrotoxicosis, autoimmune hemolytic anemia, rheumatoid arthritis, and glomerulonephritis[43,44].

An association between LABD and malignancy has also been described. Tumors that have been reported in patients with LABD include: B cell lymphoma, chronic lymphocytic leukemia, and carcinoma of the bladder, thyroid, colon and esophagus; single case reports of plasmacytoma, hydatidiform mole, renal cell carcinoma, and ocular melanoma have also been described[33,45–48]. In addition, LABD has been reported to be associated with several infections, including varicella zoster virus, antibiotic-treated tetanus, and upper respiratory infections. It has been postulated that the infectious agent may have triggered an immune response[49,50]. Lastly, there are reports of new-onset LABD developing after SARS-CoV-2 vaccination, but whether this represents a true association remains speculative.

There are multiple reports of drug-induced LABD; the drugs associated with LABD are listed in Table 31.5, with vancomycin being the most common inducer (Fig. 31.10)[51,52]. While IIF studies are generally

DRUG-INDUCED LINEAR IgA BULLOUS DERMATOSIS

Common

- Vancomycin*

Less common

- Penicillins
- Cephalosporins
- Captopril > other ACE inhibitors
- NSAIDs: diclofenac, naproxen, oxaprozin, piroxicam

Uncommon

- Phenytoin
- Sulfonamide antibiotics: sulfamethoxazole, sulfisoxazole

Rare

- Acetaminophen
- Allopurinol
- Amiodarone
- Amlodipine
- Angiotensin receptor blockers: candesartan, eprosartan
- Atorvastatin
- Buprenorphine
- Carbamazepine
- Cyclosporine
- Enoxaparin
- Furosemide
- Gemcitabine
- Glibenclamide
- Glyburide
- Granulocyte colony-stimulating factor
- Infliximab
- Influenza vaccination
- Interferon-α and interferon-γ
- Interleukin-2
- Lithium carbonate
- Metronidazole
- Minocycline
- Moxifloxacin
- PUVA
- Rifampin
- Somatostatin
- Tea tree oil
- Ustekinumab
- Verapamil
- Vigabatrin

*Unusual variants include toxic epidermal necrolysis-like and morbilliform.

Table 31.5 Drug-induced linear IgA bullous dermatosis. ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.



Fig. 31.10 Drug-induced linear IgA bullous dermatosis. Annular vesicopustules and central crusting are seen in this patient receiving vancomycin.



Fig. 31.12 Linear IgA bullous dermatosis. Annular and herpetiform vesicles arising on an inflammatory base. Annular pink plaques are also present. *Courtesy Jeffrey P. Callen, MD.*



Fig. 31.11 Linear IgA bullous dermatosis. Vesicles and bullae arising within normal-appearing skin as well as scattered annular lesions. The former can also be seen in bullous pemphigoid. *Courtesy Jeffrey P. Callen, MD.*



Fig. 31.13 Linear IgA bullous dermatosis. Striking annular vesiculobullous lesions on the thigh with central erosions and crusting. A figurate outline is seen in the area of coalescence.

negative in drug-induced LABD, addition of vancomycin to patients' sera can result in a positive IIF assay, with reactivity against the NC1 domain of type VII collagen. These novel findings suggest that vancomycin either mediates or enhances IgA autoreactivity to type VII collagen[53]. Drug-induced LABD usually remits within 2–6 weeks of cessation of the drug, although it can persist for months[52].

Clinical Features

Clinical manifestations of LABD are variable and patients can present with findings suggestive of DH as well as subepidermal tense bullae that are often indistinguishable from BP (Fig. 31.11). However, the vesiculobullous lesions often appear in a herpetiform arrangement on erythematous and/or normal-appearing skin (Fig. 31.12). Some patients present with expanding annular plaques (Fig. 31.13), while others have lesions that are scattered and asymmetric[29]. An isomorphic response, including lesions appearing at previous sites of adhesive tape, has been reported.

LABD may present as a variant of mucous membrane pemphigoid, with oral, nasal, pharyngeal, and esophageal lesions. Involvement of the tracheobronchial mucosa was reported in a severe case[54]. The ocular form of LABD is clinically indistinguishable from ocular mucous membrane pemphigoid[55].

LABD secondary to drugs, in particular vancomycin, may have a toxic epidermal necrolysis (TEN)-like or morbilliform presentation.

Pathology

LABD is a subepidermal vesicular dermatosis in which neutrophils predominate. In early urticarial papules or plaques, neutrophils are aligned along the BMZ, accompanied by vacuolar change and sometimes

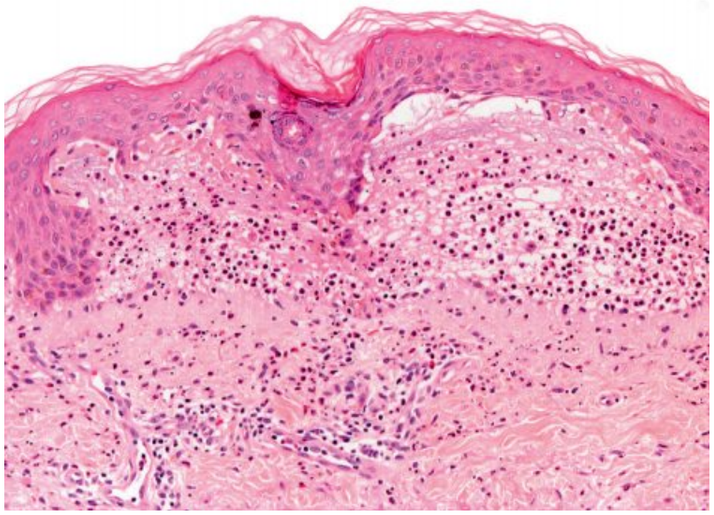


Fig. 31.14 Linear IgA bullous dermatosis – histopathologic features. Subepidermal blister filled with neutrophils. Neutrophils and a few eosinophils are also present within the underlying dermis. *Courtesy Lorenzo Cerroni, MD.*

by neutrophilic microabscesses in dermal papillae. These papillary dermal collections, if numerous enough, can resemble the picture seen in DH[29]. In fully developed lesions, there are subepidermal bullae in which neutrophils are present in the underlying dermis, either alone or with eosinophils (Fig. 31.14). Eosinophils can become more numerous over time, particularly in adults, thus mimicking the histopathologic picture of bullous pemphigoid. Although in most cases distinguishing between DH and LABD is impossible by light microscopy, a linear distribution of neutrophils along the BMZ and neutrophils at the very tips of dermal papillae favor LABD[56]. However, the latter cannot be considered a specific finding.

LABD can be subdivided on the basis of immunoelectron microscopy findings, with most patients having IgA deposits within the lamina lucida[30,57]. Less commonly, there is deposition of IgA in the sublamina densa, associated with anchoring fibrils[30]. In a few cases, deposits of IgA have been observed in both sites[58]. In one report, the deposition of IgA was initially in the lamina lucida, but later had a combined pattern[58].

Galactose-deficient IgA1 (Gd-IgA1) is implicated in the pathogenesis of IgA nephropathy and deposits of Gd-IgA1 have been detected in systemic and skin-limited forms of IgA vasculitis[59]. However, the role of Gd-IgA1 in DH and LABD remains unknown. A single case report has suggested the passive transfer of pathogenic IgA autoantibodies to a newborn from an asymptomatic mother via breast milk[59a].

Differential Diagnosis

LABD can be difficult to diagnose clinically, especially in adults, and is often confused with DH and BP. By definition, LABD is separated from DH and BP on the basis of findings by DIF (see Table 31.3). Linear IgA deposition along the BMZ in perilesional skin is characteristic of LABD (see Fig. 31.8), in contrast to either DH, which shows granular deposition of IgA in dermal papillary tips or in a continuous pattern along the basement membrane[28–30], or BP, which shows linear deposition of IgG along the epidermal BMZ. The classification of cases demonstrating both IgG and IgA along the BMZ is problematic. Some authorities include only those patients with IgA as the sole BMZ immunoglobulin under the term LABD and categorize all others as BP. Others categorize patients with both IgG and IgA along the BMZ based on the predominant immunoglobulin by DIF. Perhaps the most important point is that patients with IgA along the BMZ, alone or in combination with IgG, are more likely to respond to dapsone therapy. Distinguishing the sublamina densa form of LABD from epidermolysis bullosa acquisita is also made on the basis of the class of immunoreactant and classification can be problematic.

Circulating anti-BMZ antibodies of the IgA class can be demonstrated in 60%–70% of LABD sera. In contrast, patients with DH have not been shown to have circulating antibodies that bind to skin, and 60%–70% of patients with BP demonstrate circulating IgG class antibodies (see Table 31.3)[28]. Circulating IgA class anti-BMZ antibodies from the lamina lucida type of LABD have been shown to adhere to the epidermal side (roof) of salt-split skin, while patients with sublamina densa binding of IgA on direct immunoelectron microscopy have serum antibodies which bind to the dermal side of salt-split skin. Patients with both IgA and IgG at the BMZ demonstrate binding to the epidermal side of salt-split skin[60]. Whether or not such antibody titers correlate with disease activity has not yet been established.

For the morbilliform or TEN-like presentation of LABD due to drugs, in particular vancomycin, routine microscopy plus DIF aids in the diagnosis.

Treatment

The majority of patients with LABD respond to oral dapsone, sulfapyridine or sulfasalazine. These medications have been reviewed in detail in the section on the treatment of DH. Most patients with LABD have a clinical response within 48–72 hours. In occasional patients, it may be necessary to add oral prednisone in doses up to 40 mg daily to achieve complete control of the disease. However, the majority of our patients have been controlled by dapsone alone. It is our observation that patients in whom both IgG and IgA deposits are present in the BMZ represent those who are likely to require additional therapy with systemic corticosteroids. The average dose of dapsone required to control LABD in adults is 100 mg daily, but doses as high as 300 mg daily may be needed. If doses >200 mg per day are necessary, close monitoring should be undertaken. Children usually respond to a dose of 1–2 mg/kg daily.

Successful treatment of both adult and childhood LABD with antibiotics, including dicloxacillin, erythromycin, tetracycline (in those >9 years of age), and trimethoprim–sulfamethoxazole, has been reported. No specific microorganism was incriminated in these cases and therapeutic trials were empirical. A clinical trial of these relatively benign therapies may be undertaken, but no method of predicting a response has been identified. Mycophenolate mofetil, azathioprine, IVIg, and rituximab can be used as steroid-sparing agents in patients who do not respond to a combination of prednisone and dapsone or in patients with severe disease.

The natural course of the disease is characterized by persistence for several years with eventual spontaneous remission in many patients. Reported remission rates vary from 10%–60%, depending on the underlying trigger. There should be repeated attempts to taper systemic medications, on the chance that a spontaneous remission has occurred. Childhood LABD remits within 2–4 years.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 31.1 Dermatitis herpetiformis. Multiple pruritic papules, many of which have central hemorrhagic crusts. *Courtesy Noah Hornick, MD, PhD, and Nan Ring, MD.*



eFig. 31.2 Multiple hemorrhagic macules on the volar aspect of the thumb. Similar lesions were present on other fingers, but typical lesions were not found elsewhere. *Courtesy Edward Cowen, MD*



eFig. 31.3 Linear IgA bullous dermatosis. The circumferential and linear vesicles and bullae are typical of this disorder.



eFig. 31.4 Linear IgA bullous dermatosis. Annular and herpetiform vesiculobullae on the face of a child.



eFig. 31.5 Linear IgA bullous dermatosis. Annular vesiculobullous lesions on the hands with central erosions and crusting. A figurate outline is seen in the area of coalescence.





eFig. 31.6 Linear IgA bullous dermatosis. A, B Annular and polycyclic plaques of the trunk in two women with the disorder.

Epidermolysis Bullosa 32

Jo-David Fine and Jemima E. Mellerio

Synonyms: ■ All forms of EB: EB hereditaria ■ EB simplex: epidermolytic EB ■ Junctional EB: EB atrophicans, EB letalis ■ Dystrophic EB: EB dystrophica

Key features

- Epidermolysis bullosa (EB) encompasses multiple clinically distinctive disorders that share three major features: genetic transmission, mechanical fragility of the skin, and blister formation
- There are four major forms of inherited EB – EB simplex, junctional EB, dystrophic EB, and Kindler EB – which differ in the ultrastructural site within which cutaneous blisters form
- EB may be diagnosed by immunofluorescence antigenic mapping, transmission electron microscopy, or genetic analysis
- Any epithelial-lined or epithelial-covered organ is at potential risk for involvement in the more severe forms of inherited EB
- In the absence of specific therapy, management is primarily focused on prevention of blisters, wound care, and treatment of extracutaneous complications

INTRODUCTION

Inherited epidermolysis bullosa (EB), the prototypic mechanobullous disease, is characterized by the development of blisters following seemingly minor or insignificant trauma or traction to the skin[1,2]. The most recent classification includes four major forms of classic EB – EB simplex, junctional EB, dystrophic EB, and Kindler EB – and at least 30 distinctive clinical phenotypes[1] (Table 32.1). Inherited EB can result from mutations within the genes that encode at least 16 structural proteins: keratins 5 and 14; the subunits of laminin 332 (formerly laminin 5); types VII and XVII collagens; plectin; $\alpha_6\beta_4$ integrin; α_3 integrin subunit; bullous pemphigoid antigen 1; kindlin-1; exophilin 5; kelch-like protein 24; and CD151 (tetraspanin 24). The current EB classification also delineates other disorders associated with skin fragility in which blistering is a relatively minor feature, with at least 23 additional genes implicated in their pathogenesis[1]. These entities include several disorders that were previously classified as suprabasal forms of EB simplex, such as acral peeling skin syndrome (transglutaminase-5; see Table 57.8), skin fragility–ectodermal dysplasia syndrome (plakophilin-1), and acantholytic erosive disorder (desmoplakin or plakoglobin).

Although most forms of EB are rare, research into their underlying pathophysiologic bases has led to major advances in our understanding of the cell and molecular biology of keratins, other keratinocyte-associated structural proteins, collagens, and the cutaneous extracellular matrix (ECM). Study of EB has also helped to elucidate mechanisms of epithelial cell adhesion, migration, and differentiation and to highlight the role of the epidermal basement membrane in health and disease. The creation of *in vitro* and animal models of EB has facilitated the development of novel translational therapeutic approaches for the treatment of EB patients[2].

HISTORY

Epidermolysis bullosa was first described in 1870 by von Hebra under the name "erblichen pemphigus"[3]. Its current name, "epidermolysis bullosa hereditaria", was coined by Koebner in 1886. Hallopeau recognized the distinct clinical features of simplex and dystrophic forms of EB in 1898. Junctional EB was first identified in 1935 by Herlitz and termed "EB letalis". Precise characterization of these three major EB types via the use of transmission electron microscopy was first achieved by Pearson in 1962[4]. In the ensuing years, additional EB phenotypes were described. Monoclonal antibody studies provided the first suggestion that specific protein defects underlie individual types and subtypes of this disease[5–8]. In 1986, the National EB Registry was established in the US by the National Institutes of Health, facilitating epidemiologic, clinical, and laboratory characterization of each major EB type and subtype[9,10]. In 1991, Bonifas et al.[11] utilized linkage analysis to demonstrate the molecular basis for EB simplex. Subsequent work by others has established the precise molecular basis for most of the EB subtypes recognized to date.

EPIDEMIOLOGY

Based on National EB Registry data[12,13], the estimated overall prevalence and incidence of EB in the US are 11.1 per 1 million population and 19.6 per 1 million live births, respectively. Carrier frequencies have also been reported[14]. The approximate prevalences and incidences, respectively, of the major types of EB are as follows: EB simplex, 6.0 and 7.9; junctional EB, 0.5 and 2.7; dominant dystrophic EB, 1.5 and 2.1; and recessive dystrophic EB, 1.4 and 3.0.

PATHOGENESIS

EB is caused by mutations within genes that encode structural proteins that reside within the epidermis (EB simplex), dermal–epidermal junction (junctional EB), or uppermost papillary dermis (dystrophic EB). The site within which each of these proteins resides determines the ultrastructural location where the blisters arise (Fig. 32.1, see Table 32.1).

EB Simplex

The most common forms of EB simplex (EBS) are transmitted in an autosomal dominant manner and are associated with blistering at the level of the basal keratinocyte. EBS most often results from a dominant-negative mutation (see Ch. 54) within the keratin 5 (*KRT5*) or 14 (*KRT14*) genes, expression of which is primarily within the basal layer of the epidermis[15,16]. The clinical severity and other phenotypic features of EBS are closely associated with the genotype. For example, mutations in the helix initiation and termination motifs of *KRT5* and *KRT14* lead to the severe subtype of EBS (severe EBS, previously known as EBS-Dowling–Meara), whereas the specific phenotype of EBS with mottled pigmentation almost always arises from a particular missense mutation in the V1 domain of *KRT5*.

Dominant stabilizing mutations in the kelch-like protein 24 ubiquitin ligase gene (*KLHL24*) lead to EBS via increased ubiquitination and degradation of keratin 14[17]. An autosomal recessive form of EBS due to mutations in the gene encoding plectin (*PLEC*) is associated with muscular dystrophy, which is not surprising considering that plectin is expressed in skeletal muscle as well as in the hemidesmosomes of basilar keratinocytes. Other EBS patients with plectin or rarely $\alpha_6\beta_4$ integrin deficiencies present with pyloric atresia, while autosomal recessive variants of EBS caused by mutations in bullous pemphigoid antigen 1/dystonin (*DYS*) or exophilin 5 (*EXPH5*) genes have also been reported.

Junctional EB

Junctional EB (JEB) is almost always transmitted in an autosomal recessive manner (see Table 32.1). The severe subtype of JEB (severe JEB,

CLASSIC EPIDERMOLYSIS BULLOSA: SIMPLEX, JUNCTIONAL, DYSTROPHIC, AND KINDLER SUBTYPES		
Subtype	**Inheritance**	**Defective protein(s)**
Intraepidermal cleavage		
EBS, localized (formerly Weber–Cockayne)	AD	Keratins 5 and 14
EBS, severe (formerly Dowling–Meara)		
EBS, intermediate		
EBS with mottled pigmentation	AD	Keratin 5
EBS, migratory circinate		
EBS, intermediate or severe, AR	AR	Keratins 5 and 14
EBS, intermediate (formerly Ogna)	AD	Plectin
EBS, intermediate with muscular dystrophy	AR	Plectin
EBS, severe with pyloric atresia	AR	Plectin; $\alpha_6\beta_4$ integrin
EBS, intermediate with cardiomyopathy	AD	Kelch-like protein 24
EBS, localized or intermediate	AR	Bullous pemphigoid antigen 230 (BP230); exophilin 5
EBS, localized with nephropathy	AR	CD151 (tetraspanin 24)
Intra-lamina lucida cleavage		
JEB, severe (formerly Herlitz)	AR	Laminin 332
JEB, intermediate	AR*	Laminin 332; collagen XVII
JEB with pyloric atresia	AR	$\alpha_6\beta_4$ integrin
JEB, late onset	AR	Collagen XVII
JEB with interstitial lung disease and nephrotic syndrome	AR	α_3 integrin subunit
JEB, localized	AR	Laminin 332; collagen XVII; $\alpha_6\beta_4$ integrin; α_3 integrin subunit
JEB, inversa	AR	Laminin 332
JEB-laryngo-onycho-cutaneous syndrome	AR	Laminin α3 chain (a isoform)
Sublamina densa cleavage		
DDEB, intermediate	AD	Collagen VII
DDEB, localized†		
DDEB, pruriginosa		
DDEB, self-improving		
RDEB, severe (formerly Hallopeau–Siemens)	AR	
RDEB, intermediate		
RDEB, inversa		
RDEB, localized†		
RDEB, pruriginosa		
RDEB, self-improving		
Mixed cleavage planes		
Kindler EB	AR	Fermitin family homolog-1 kindlin-1

*One case with AD inheritance has been reported.
†Includes variants previously referred to as pretibial (DDEB & RDEB), acral (DDEB), and nails only (DDEB).

Table 32.1 Classic epidermolysis bullosa (EB): simplex, junctional, dystrophic subtypes, and Kindler EB. Entities in **bold** are the more common subtypes, and those with a darker background represent syndromic variants. AD, autosomal dominant; AR, autosomal recessive; EBS, epidermolysis bullosa simplex; DDEB, dominant dystrophic EB; RDEB, recessive dystrophic EB.

previously known as JEB-Herlitz) typically results from homozygous or compound heterozygous truncating mutations within a gene encoding one of the three subunits of laminin 332, a key component of the lamina lucida of the dermal–epidermal junction (see Ch. 28)[18]. In laryngo-onycho-cutaneous syndrome, the underlying mutations affect only the A isoform of the laminin α3 subunit. The milder intermediate form of JEB (intermediate JEB, previously known as JEB-non-Herlitz and generalized atrophic benign EB) results from mutations within the genes for either a subunit of laminin 332 or, less frequently, type XVII collagen/bullous pemphigoid antigen 2. JEB with pyloric atresia, which is much more common than EBS with pyloric atresia, is also caused by mutations within either of the two genes that encode the subunits of $\alpha_6\beta_4$ integrin. A form of JEB associated with respiratory and renal involvement results from mutations in the integrin α_3 chain.

Dystrophic EB

Dystrophic EB (DEB) is transmitted in either an autosomal dominant or autosomal recessive manner and is caused by mutations in the type VII collagen gene (*COL7A1*). Dominant DEB (DDEB) results from dominant-negative mutations, typically a missense mutation that leads to substitution of another amino acid for a glycine within the triple-helical domain of this collagen. Although the resultant protein is structurally abnormal, immunohistochemical staining for type VII collagen along the dermal–epidermal junction is usually indistinguishable from that of normal skin.

Recessive DEB (RDEB) is due to compound heterozygous or, less frequently, homozygous mutations within the type VII collagen gene[19–21]. Premature stop codons, which result in truncated proteins, are

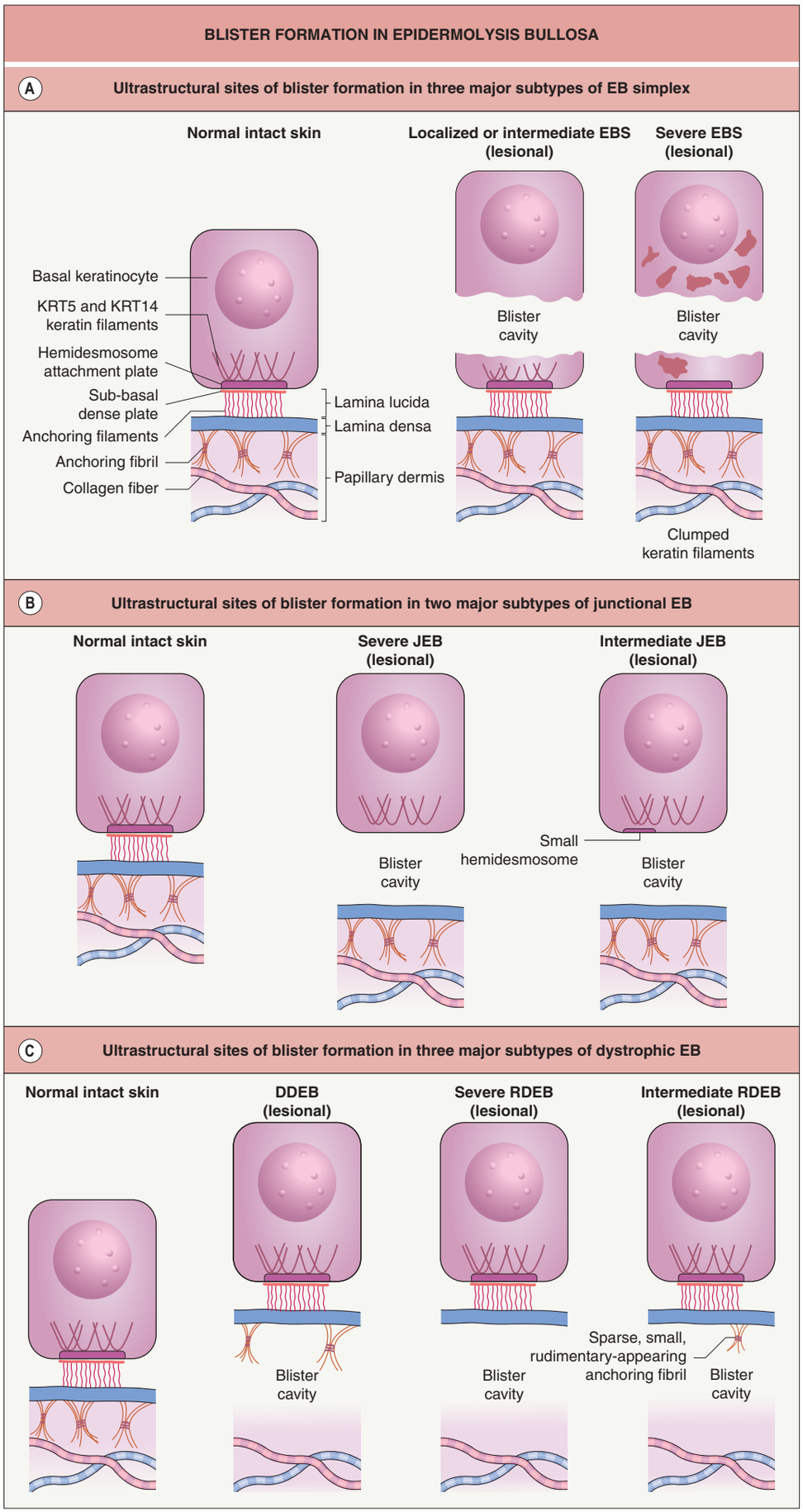


Fig. 32.1 Blister formation in epidermolysis bullosa (EB). A Ultrastructural sites of blister formation in three major subtypes of *EB simplex (EBS)*. The ultrastructure of normal intact skin is presented for comparison. In all three major subtypes of EBS – localized, intermediate, and severe – blisters arise within the lowermost intracytoplasmic portion of the basilar keratinocyte. In severe EBS, keratin filaments tend to coalesce into larger electron-dense clumps, especially in lesional skin. Keratin filaments are absent or reduced in the rare autosomal recessive form of EBS, and in EBS with muscular dystrophy there is lack of integration of keratin filaments into the underlying hemidesmosome. **B** Ultrastructural sites of blister formation in two major subtypes of *junctional EB (JEB)*. All forms of JEB are characterized by blister formation within the lamina lucida of the dermal–epidermal junction. As such, the lamina densa remains firmly attached to the dermis which forms the base of the blister cavity. Sub-basal dense plates and anchoring filaments are absent in generalized severe JEB and often attenuated in other subtypes of JEB. Hemidesmosomes are absent or extremely sparse and rudimentary in severe JEB, whereas they are normal or reduced in number and size in intermediate JEB. **C** Ultrastructural sites of blister formation in three major subtypes of *dystrophic EB (DEB)*. Blister formation occurs beneath the lamina densa in all forms of dystrophic EB. Anchoring fibrils appear normal in size and structure in dominant DEB (DDEB) skin, although they may be somewhat reduced in number. Consistent with the presence of sublamina densa cleavage, these anchoring fibrils remain attached to the blister roof, which is composed of intact epidermis and an attached basement membrane that includes the lamina densa. In contrast, anchoring fibrils are usually completely absent in lesional skin from patients with severe recessive DEB (RDEB). In intermediate RDEB, anchoring fibrils are reduced in number and rudimentary in appearance.

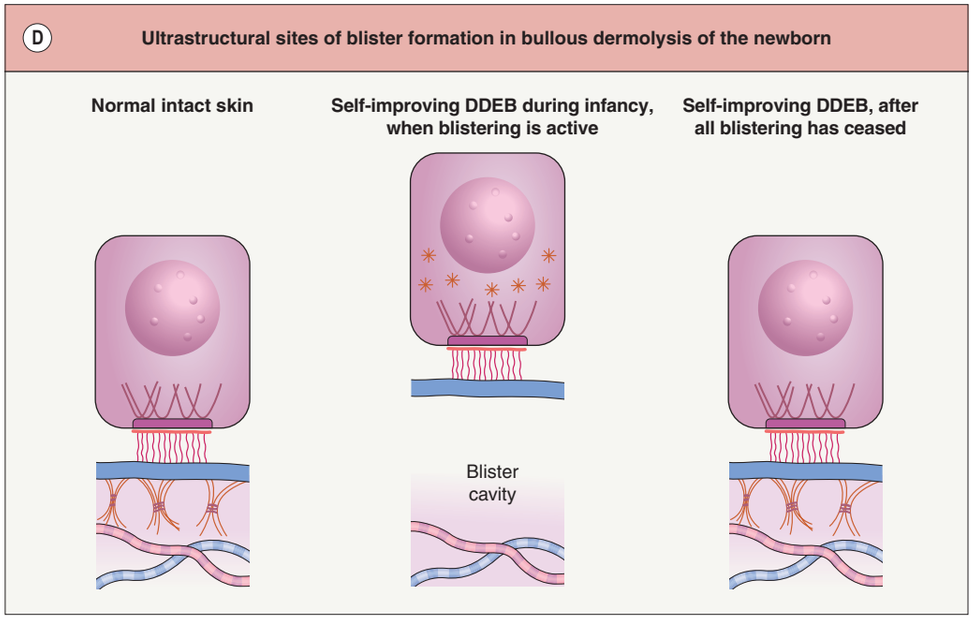


Fig. 32.1 Blister formation in epidermolysis bullosa (EB). (cont'd) D Ultrastructural site of blister formation in the form of DEB referred to as *self-improving DEB*. With age, there is improvement in the transport and deposition of type VII collagen from the keratinocyte cytoplasm to the anchoring fibrils of the basement membrane.

characteristic of the severe subtype (severe RDEB, previously known as RDEB-Hallopeau–Siemens). Consistent with the severity of these mutations, anchoring fibrils are undetectable or extremely sparse and poorly formed in skin biopsy specimens, and immunohistochemical staining with antibodies against the major epitopes of the type VII collagen molecule is absent or barely detectable. Milder forms of RDEB are associated with less severe biallelic mutations in the type VII collagen gene.

A single nucleotide polymorphism in the matrix metalloproteinase 1 gene promoter has been identified as a disease modifier in RDEB[22]. It is likely that additional modifying genes account for some of the inter- and intra-familial phenotypic variability observed in this and other forms of EB. There is also evidence for secondary effects from loss of protein expression in EB. For example, loss of collagen VII in RDEB fibroblasts leads to alterations in dermal matrix proteins, metalloproteinases, and transforming growth factor-β (TGF-β), which are thought to further influence keratinocyte adhesion, dermal–epidermal integrity, and dermal fibrosis[23,24].

Severe RDEB and (to a lesser extent) other forms of DEB, JEB, and Kindler EB are associated with an increased risk for the development of cutaneous SCCs. The pathogenesis of these tumors is multifactorial, and the cutaneous microenvironment plays a critical role in the initiation of carcinogenesis, tumor progression, and metastatic potential[2,25]. Increased dermal stiffness, bacterial colonization, chronic inflammation, and defects in the innate immune system contribute to the early development and aggressive nature of these tumors[23].

In self-improving DEB (previously known as bullous dermolysis of the newborn), inheritance is usually dominant and blistering is typically confined to the first 1–2 years of life[26–28]. Clinical expression coincides with a time during which type VII collagen is present primarily within basal keratinocytes in these patients' skin, rather than along the dermal–epidermal junction (see Fig. 32.1D). This suggests that there may be a temporary disruption in the transport of this protein from the keratinocyte cytoplasm to the underlying ECM.





Fig. 32.2 Localized epidermolysis bullosa simplex. A, B Bullae arising on the toes and plantar surfaces at sites of lateral or rotary traction. The majority of blisters occur in acral sites. *B, Courtesy Julie V. Schaffer, MD.*

CLINICAL FEATURES

Cutaneous Findings

All forms of inherited EB are characterized by mechanically fragile skin, erosions, and (with rare exceptions) macroscopic blisters (Figs. 32.2 & 32.3). Scarring is almost always atrophic and can occur in any subtype of EB (Fig. 32.4), including localized EBS. However, scarring is most frequent in the subtypes that are characterized clinically by generalized disease activity and ultrastructurally by disruption of the basement





Fig. 32.3 Intermediate epidermolysis bullosa simplex. Extensive blistering on the buttocks (**A**) and blistering in association with focal keratoderma on the soles (**B**) of a 2-year-old girl. *Courtesy Julie V. Schaffer, MD.*

membrane, particularly the lamina densa (Fig. 32.5). Whereas scarring is estimated to occur in only 15% of patients with localized EBS, it is present in essentially every patient with RDEB[29]. Other cutaneous findings that have similar variations in frequency across the major types and subtypes of EB include dystrophic or absent nails (see Fig. 32.4), milia, and scarring alopecia of the scalp.

Some cutaneous findings have diagnostic implications (Fig. 32.6)[13]. *Reticulated hyperpigmented macules* distinguish a rare subtype of EBS termed EBS with mottled pigmentation. *Grouped ("herpetiform") blisters*, often in an arcuate (Fig. 32.7) or polycyclic array, are highly characteristic of severe EBS, which is also associated with the gradual development of a diffuse palmoplantar *keratoderma* (Fig. 32.8). *Migratory circinate erythema* with vesiculation of the advancing edge has been described in patients with EBS caused by a frameshift mutation that leads to an elongated keratin 5 protein. *Excessive or exuberant granulation tissue*, usually in a symmetric distribution involving the perioricial areas, skin folds, upper back, nape of the neck, and periungual areas, is typical of severe JEB (Fig. 32.9). *Extremely pruritic papules* that can coalesce into a linear arrangement on the lower extremities, are characteristic of DEB pruriginosa (Fig. 32.10).

Distribution of skin disease activity is also useful in the subclassification of EB[29,30], although the pattern of involvement tends to be less distinctive in infants than in adults. Patients with the "inversa" subtypes of JEB and RDEB experience severe disease activity primarily in intertriginous areas such as the axillae and inguinal creases. In contrast, patients with localized JEB have involvement mainly in acral sites. Individuals with localized DEB may have lesions almost exclusively on the shins (previously referred to as pretibial DEB). A rare







Fig. 32.4 Dominant dystrophic epidermolysis bullosa. A, B Erosions, scarring and milia on the fingers. Note the partial (**A**) to almost complete (**B**) loss of the nails. **C** A discrete area of scarring on the elbow with blisters, crusting, and milia. *B, Courtesy Julie V. Schaffer, MD.*

subtype previously known as RDEB centripetalis initially features acral blistering, followed by slow progression of disease activity toward the trunk over the years.

Extracutaneous Findings

The molecular defects that affect the skin in patients with EB may also lead to manifestations in other tissues with an epithelial lining or surface, including the eye, oral cavity, and gastrointestinal, genitourinary, and respiratory tracts[31–36]. Major extracutaneous complications of EB are summarized in Table 32.2[31–33]. Although exceptions exist, extracutaneous involvement occurs most frequently in RDEB and JEB, and it can result in blisters, erosions, ulcers, and scarring. Rare subtypes of JEB and EBS present at birth with *pyloric atresia* as well as skin fragility and blistering[35]. In other forms of EB, extracutaneous disease may become apparent as early as the first few months of life. Repeated blistering of the *external eye* can result in neovascularization and blindness[34]. Chronic involvement of the *esophagus* leads to scarring, stricture formation and, rarely, even complete obstruction[35]. Involvement of the *small intestine* presents with chronic malabsorption, whereas disease activity within the *large intestine* tends to produce constipation and painful anal fissures or strictures. Recurrent *genitourinary tract* blistering may result in urethral or ureterovesical



Fig. 32.7 Severe epidermolysis bullosa simplex. Clustered vesicles in an arcuate array on the thigh of this child. *Courtesy Julie V. Schaffer, MD.*

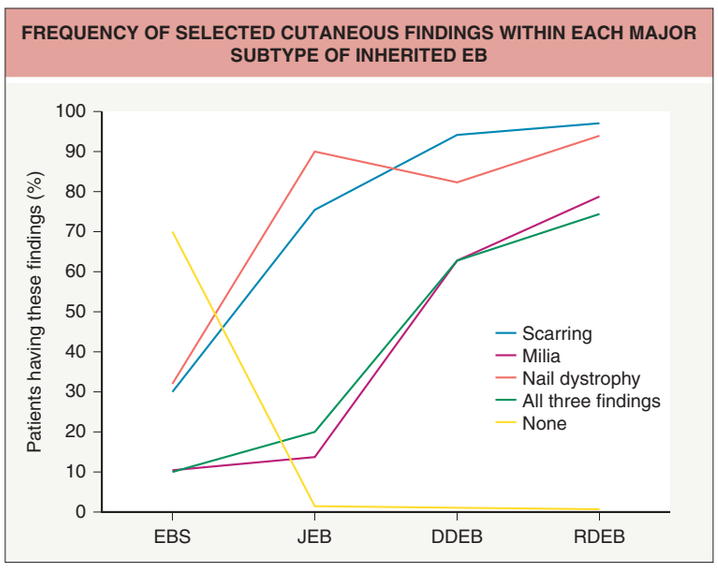


Fig. 32.5 Frequency of selected cutaneous findings within each major subtype of inherited epidermolysis bullosa (EB). Note the increasing frequency from localized EB simplex (EBS) to recessive dystrophic EB (RDEB). JEB, junctional EB; DDEB, dominant dystrophic EB.



Fig. 32.8 Severe epidermolysis bullosa simplex. Diffuse palmar keratoderma in an adult.

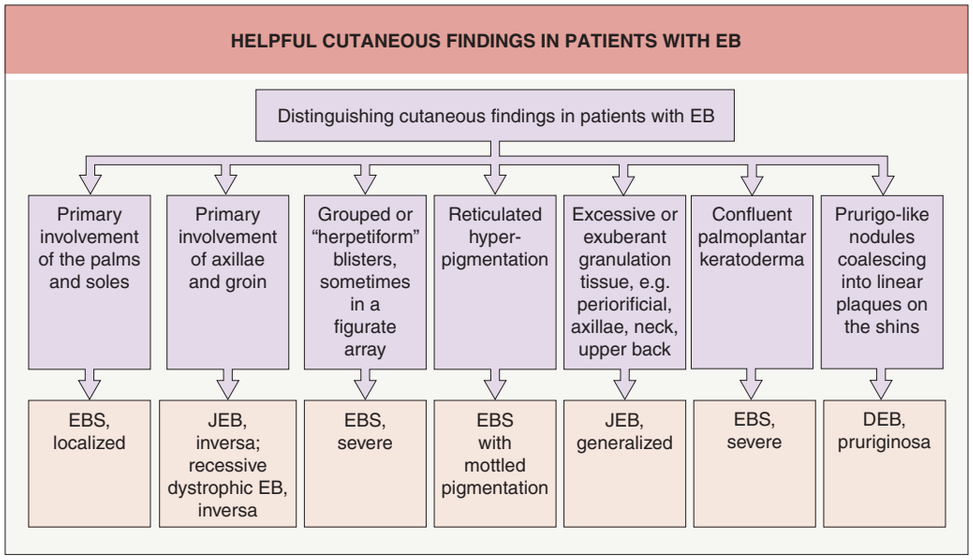


Fig. 32.6 Helpful cutaneous findings in patients with epidermolysis bullosa (EB). DEB, dystrophic EB; EBS, EB simplex; JEB, junctional EB.





Fig. 32.9 Severe junctional epidermolysis bullosa. A Blisters on the elbow and large areas of denuded skin; note the bright red color in the axilla and groin. **B** Blisters and large erosions on the abdomen of an infant. *B, Courtesy Julie V. Schaffer, MD.*



Fig. 32.10 Dystrophic epidermolysis bullosa pruriginosa. Prurigo-like papulonodules coalescing into linear plaques on the shin as a consequence of chronic scratching.

MAJOR EXTRACUTANEOUS COMPLICATIONS OF EPIDERMOLYSIS BULLOSA

Complication	EB subtype(s) most commonly affected	
	≥50% of patients	<50% of patients
Eyes		
Corneal blisters, ulcers and scarring	Sev-RDEB	Sev-JEB >intermed-RDEB, inv-RDEB, intermed-JEB
Ectropion formation		Sev-JEB; Kindler EB
Oral cavity and upper airway (excluding blisters)		
Microstomia	Sev-RDEB	Sev-JEB, inv-RDEB
Enamel hypoplasia	JEB (all subtypes)	
Excessive caries and premature loss of teeth	Sev-RDEB, sev-JEB	
Tracheolaryngeal stenosis	Sev-JEB	Intermed-JEB
Gastrointestinal tract		
Esophageal strictures	Sev-RDEB, inv-RDEB	Intermed-RDEB, Kindler EB > sev-JEB
Pyloric atresia	JEB-PA, EBS-PA	
Malnutrition/failure to thrive	Sev-RDEB, sev-JEB	Intermed-JEB
Severe constipation	Sev-RDEB	Sev-JEB, sev-EBS
GERD	RDEB	JEB, sev-EBS
Colitis		Kindler EB, sev-RDEB
Genitourinary tract		
Urethral meatal stenosis		Sev-RDEB, sev-JEB, Kindler EB
Chronic renal failure*		Sev-RDEB
Hydroureter and hydronephrosis		JEB-PA, sev-JEB
Nephrotic syndrome	JEB-ILD/ nephrotic	Sev-JEB
Heart		
Dilated cardiomyopathy		Sev-RDEB > JEB, intermed-RDEB
Musculoskeletal system		
Pseudosyndactyly	Sev-RDEB	Intermed-RDEB, Kindler EB
Osteoporosis or osteopenia	Sev-RDEB	Sev-RDEB, sev-JEB
Muscular dystrophy	EBS-MD	
Bone marrow		
Severe multifactorial anemia	Sev-RDEB, sev-JEB	

*Causes include renal amyloidosis and glomerulonephritis.

Table 32.2 Major extracutaneous complications of epidermolysis bullosa (EB). EBS, EB simplex; GERD, gastroesophageal reflux disease; intermed, intermediate; sev, severe; ILD, interstitial lung disease; inv, inversa; JEB, junctional EB; MD, muscular dystrophy; PA, pyloric atresia; RDEB, recessive dystrophic EB.

strictures; if persistent, the latter may eventuate in ureteric reflux and hydronephrosis. *Tracheolaryngeal* blistering and associated soft tissue edema, seen most often in infants and young children with severe JEB, may lead to potentially fatal acute airway obstruction[36]. JEB with respiratory and renal involvement is a rare subtype associated with severe interstitial lung disease.

Dental enamel hypoplasia, which occurs exclusively in JEB, is associated with pitting of the surfaces of primary and permanent teeth[37,38]. If untreated, affected individuals lose teeth during childhood due to excessive caries[39]. *Severe caries* and tooth loss also occur in severe RDEB, likely resulting from impaired clearance of food from the mouth and poor dental hygiene in the setting of intraoral injury and scarring, ankyloglossia, and microstomia.

Pseudosyndactyly ("mitten" deformities) of the hands and feet primarily affects patients with RDEB, especially severe RDEB, although it occasionally occurs to a lesser degree in DDEB and JEB[40] (Fig. 32.11B & C). Initially presenting as proximal web formation between adjacent digits, the digits may eventually become totally fused and



Fig. 32.11 Severe recessive dystrophic epidermolysis bullosa. A Area on the neck with chronic and recurrent wounds in a 7-year-old child. **B** Early proximal interdigital web formation together with atrophic scarring and loss of nails in a 5-year-old girl. **C** Partial "mitten" deformities of the hands in an older child. *A, B, Courtesy Julie V. Schaffer, MD.*

encased by scar tissue. Lack of mobility leads to progressive bone resorption and muscular atrophy, and hand function is severely compromised.

Osteoporosis, detectable by dual-emission X-ray absorptiometry (DEXA) scanning, is common in severe RDEB and severe JEB. Radiographs may demonstrate vertebral crush fractures in severe cases. EBS due to plectin deficiency is associated with mild to severe *muscular dystrophy*. Although the muscle disease presents during infancy in some patients, weakness often develops insidiously during later childhood or even early adulthood in those who are less severely affected.



Fig. 32.12 Squamous cell carcinoma. Large squamous cell carcinoma on the ankle of a 21-year-old man with severe recessive dystrophic epidermolysis bullosa. *Courtesy Julie V. Schaffer, MD.*

Chronic renal failure occasionally develops in patients with severe forms of EB, most notably severe RDEB, which is associated with a ~10% risk of death from renal failure by age 35 years[41]. Renal disease may result from untreated outflow obstruction, glomerulonephritis, secondary systemic amyloidosis, or IgA nephropathy. *Nephrotic syndrome* associated with altered expression of laminin isoforms in renal basement membranes has been reported in an infant with generalized JEB and it occurs congenitally as a result of integrin α_3 mutations in JEB with respiratory and renal involvement. A small subset of patients with severe forms of EB, especially RDEB, develop potentially fatal dilated *cardiomyopathy*[42]. Although as yet unproven, selenium or carnitine deficiency may be a contributing factor.

Although it was a common occurrence several decades ago, potentially lethal bacterial sepsis is now relatively rare in inherited EB[43], presumably due to improved wound care and the availability and judicious use of broad-spectrum antibiotics. When sepsis does occur in EB, it tends to affect infants with severe disease[44]. In contrast, failure to thrive is still common among infants with severe JEB and may lead to death.

Cutaneous Malignancies

A major complication, usually of RDEB, is the development of multiple cutaneous SCCs[45,46]. These tumors most often arise in chronic non-healing wounds or hyperkeratotic lesions (Fig. 32.12). Histologically, they are usually well differentiated. However, the borders of the lesions are often indistinct and they are difficult to completely excise, with a tendency to recur locally. In addition, SCCs in EB patients frequently metastasize and are strikingly unresponsive to chemotherapy or radiotherapy. Indeed, they represent the leading cause of death in EB at or after mid-adolescence, with death from an SCC of cutaneous origin occurring in most patients within 5 years of the diagnosis of their first SCC[44]. These tumors occur primarily in RDEB, especially when severe, although SCCs can also develop in adults with other forms of DEB, JEB, and Kindler EB. The cumulative risk of at least one SCC in patients with severe RDEB is 7.5% by age 20 years but rises to 68%, 80%, and 90% by ages 35, 45, and 55 years, respectively[33]. In contrast, the risk of SCC in other forms of RDEB is <25% by age 45 years[44].

Melanoma occurs in a small number of children with severe RDEB, with a cumulative risk of 2.5% by the age of 12 years[43]. Although this is a relatively infrequent complication, careful surveillance during childhood is indicated. Children with EB, in particular those with intermediate JEB, can develop large, irregularly shaped, darkly pigmented melanocytic nevi ("EB nevi") (Fig. 32.13) that clinically resemble melanoma, although they are histologically and biologically benign. A large size from the onset rather than a relatively slow horizontal expansion is a clue to the diagnosis of these EB-associated nevi.

APPROACH TO DIAGNOSIS

Patients with EB are classified on the basis of the clinical phenotype, mode of inheritance, ultrastructural level of blister formation, antigenic profile in the skin, and underlying genetic defect[2,29,47]. Although skin findings play an important role in determination of the EB phenotype, different subtypes of EB have considerable overlap in their cutaneous manifestations. In addition, the severity, distribution, and type of skin findings in an individual patient may change over time, such as evolution from generalized to localized blistering (or the opposite) or delayed development of sequelae such as exuberant granulation tissue, scarring, and nail dystrophy[1,29].



Fig. 32.13 Large acquired melanocytic nevus at a site of blistering in a teenage girl with junctional epidermolysis bullosa. *Courtesy Julie V. Schaffer, MD.*

Standard light microscopy has no role in the diagnosis of classic forms of inherited EB, since it may be difficult to distinguish between even lower intraepidermal and subepidermal blister formation, let alone between intra-lamina lucida (i.e. JEB) and sublamina densa (i.e. DEB) types, without more sophisticated staining techniques[47]. The diagnostic tests employed for EB include immunofluorescence antigen mapping (IFM), transmission electron microscopy (TEM), and increasingly genetic analysis[47]. TEM can define the ultrastructural level of blister formation and provide a quantitative and qualitative assessment of specific structures, such as basilar tonofilaments, hemidesmosomes, sub-basal dense plates, anchoring filaments, and anchoring fibrils[13,47]; however, currently it is routinely performed in only a few reference laboratories. A diagnostic algorithm is presented in Fig. 32.14.

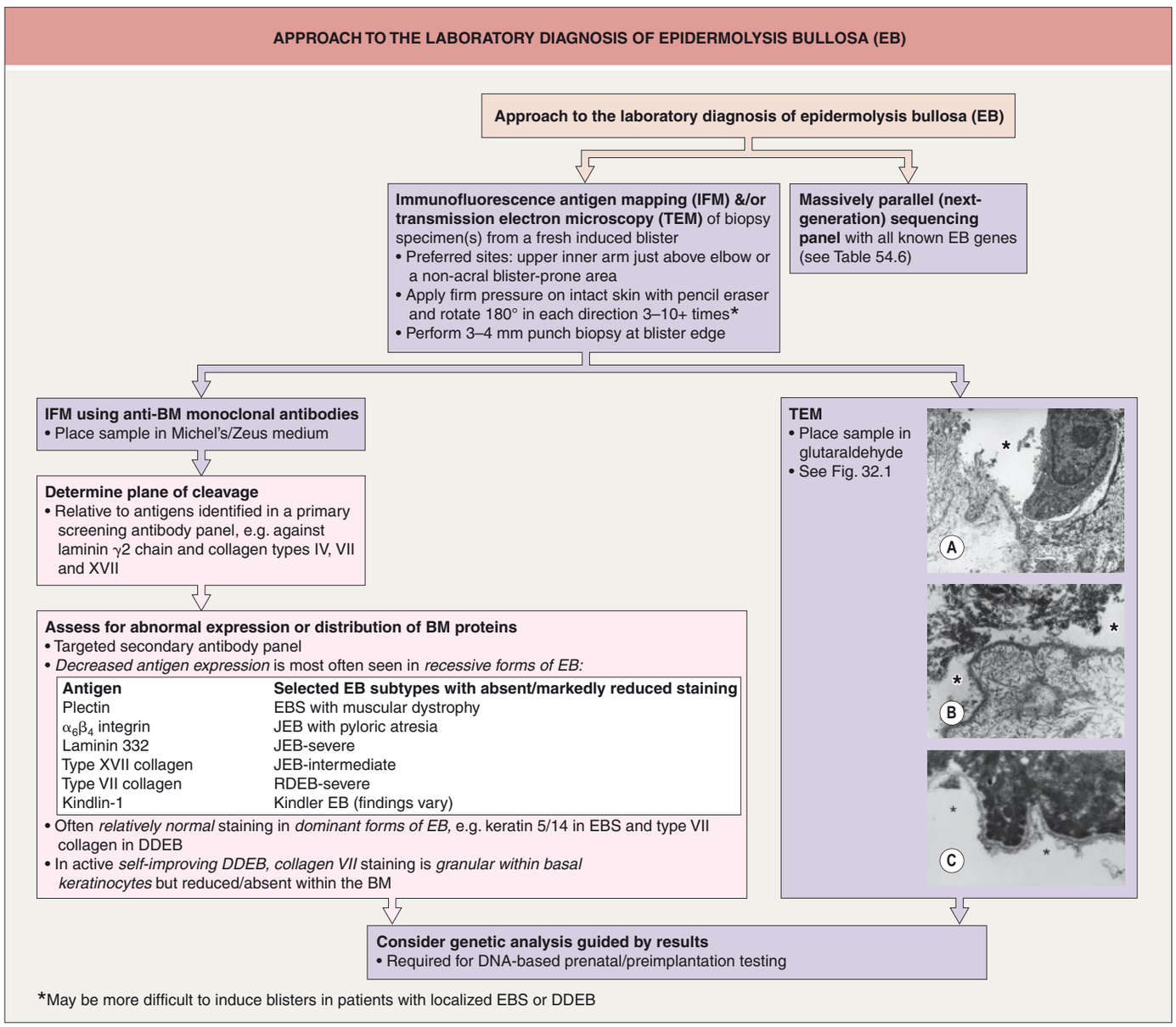


Fig. 32.14 Approach to the laboratory diagnosis of epidermolysis bullosa (EB). A Electron microscopy (EM) of an induced blister in localized EBS demonstrates skin cleavage (asterisk) within the inferior-most portion of the basilar keratinocyte. **B** EM of a spontaneous blister from a patient with the severe JEB reveals skin cleavage (asterisks) within the lamina lucida. Hemidesmosomes, sub-basal dense plates, and anchoring filaments are all absent. In contrast, anchoring fibrils are still present in normal amounts within the underlying dermis. **C** EM of the roof of a spontaneous blister from a patient with severe RDEB reveals cleavage (asterisks) beneath the level of the lamina densa. Anchoring fibrils are absent along the epidermal roof of the blister. BM, basement membrane; DDEB, dominant dystrophic EB; EBS, EB simplex; JEB, junctional EB; RDEB, recessive dystrophic EB.

Genetic analysis has become the first-line method for EB diagnosis and classification, with increasing availability and decreasing cost of massively parallel (next-generation) sequencing panels that include all known EB genes[47]. Molecular diagnosis allows more accurate genetic counseling and is required for DNA-based prenatal/preimplantation testing.

Differential Diagnosis

Although it is difficult to determine the subtype of inherited EB on the basis of clinical findings alone, the diagnosis of EB itself is usually straightforward, especially beyond early childhood. There is a limited differential diagnosis for a chronic mechanobullous disease with early onset and/or a positive family history[1,2]. Other genetic diseases that may present with blistering early in life include acantholytic erosive disorder and other skin fragility syndromes due to defects in desmosomal proteins as well as peeling skin syndromes and epidermolytic ichthyosis (see Ch. 57)[1] (Fig. 32.15A,B). Of note, the former disorders were previously categorized as forms of EBS. Genodermatoses that can be associated, at least transiently, with skin fragility or blisters and therefore potentially misdiagnosed as EB are outlined in Table 32.3. Less often, EB may be confused with acrodermatitis enteropathica, incontinentia pigmenti stage 1, pachyonychia congenita, or early lipoid proteinosis.

The differential diagnosis of blisters and erosions in neonates or young infants may also include infectious diseases (e.g. herpes simplex viral infection, staphylococcal scalded skin syndrome, bullous impetigo), sucking blisters, mastocytosis, autoimmune blistering diseases, and congenital erosive and vesicular dermatosis (see Ch. 34). Diagnostic considerations in patients with acral blistering, erosions, and ulcerations with progression to digital resorption may include congenital erythropoietic porphyria (see Table 32.3 and Ch. 49) and SAVI (*S*TING-*a*ssociated *v*asculopathy with onset in *i*nfancy [Fig. 32.15C]; see Ch. 45).

Congenital localized absence of skin (CLAS), also referred to as aplasia cutis congenita, can occur in any form of EB (see Ch. 64). In patients with EB, CLAS is distinguished by the associated skin fragility and blistering as well as its frequent location on the lower extremities (referred to as Bart syndrome), although involvement may be more widespread, especially in forms of EBS or JEB associated with pyloric atresia[48].

TREATMENT

Day-to-day management of EB revolves around the prevention of mechanical trauma, wound care, and avoidance of infection. Protective bandaging, padding over bony prominences, and soft/loose-fitting clothing can be helpful. Bathing or soaking with ~0.005% sodium hypochlorite (0.5 cup household bleach [6%–8.25% sodium hypochlorite] in a full standard bathtub) or 0.25% acetic acid (1 part white vinegar [5% acetic acid] to 19 parts water) may help to reduce bacterial colonization. Antibiotics should be used judiciously, with avoidance of chronic treatment with topical mupirocin or oral antibiotics. Problematic plantar hyperhidrosis in EBS patients may be reduced by the topical application of aluminum chloride hexahydrate, although its effect on blistering is less certain, and injection of botulinum toxin A can decrease plantar blistering and associated pain in some individuals with EBS[49].

A number of dressings are available for cutaneous wounds in EB patients (Table 32.4; see Ch. 145). As a general rule, only those that are non-adhesive or "low-tack" should be applied to EB skin. Soft silicone dressings, some of which incorporate an absorbent foam backing, are widely used. Silver-impregnated dressings may be helpful for heavily colonized or infected wounds, although long-term application should be avoided to prevent excessive systemic silver absorption and cutaneous argyria. Less expensive Vaseline®-impregnated gauze is another suitable dressing for non-infected wounds. Topical therapies under investigation include diacerein 1% cream, which downregulates production of interleukin-1β and keratin 14, thereby stabilizing the keratinocyte intermediate filament network and reducing blister formation in patients with EBS[50].

Systemic drugs that may be of benefit include tetracycline or erythromycin for EBS[51] and dupilumab, thalidomide, or cyclosporine for symptomatic relief in DEB pruriginosa[52,53]. There are few reports on the use of systemic retinoids in any form of EB, although these drugs appear to be tolerated, at least in low dosage, in patients with RDEB[54]. Whether long-term treatment with low-dose systemic retinoids would

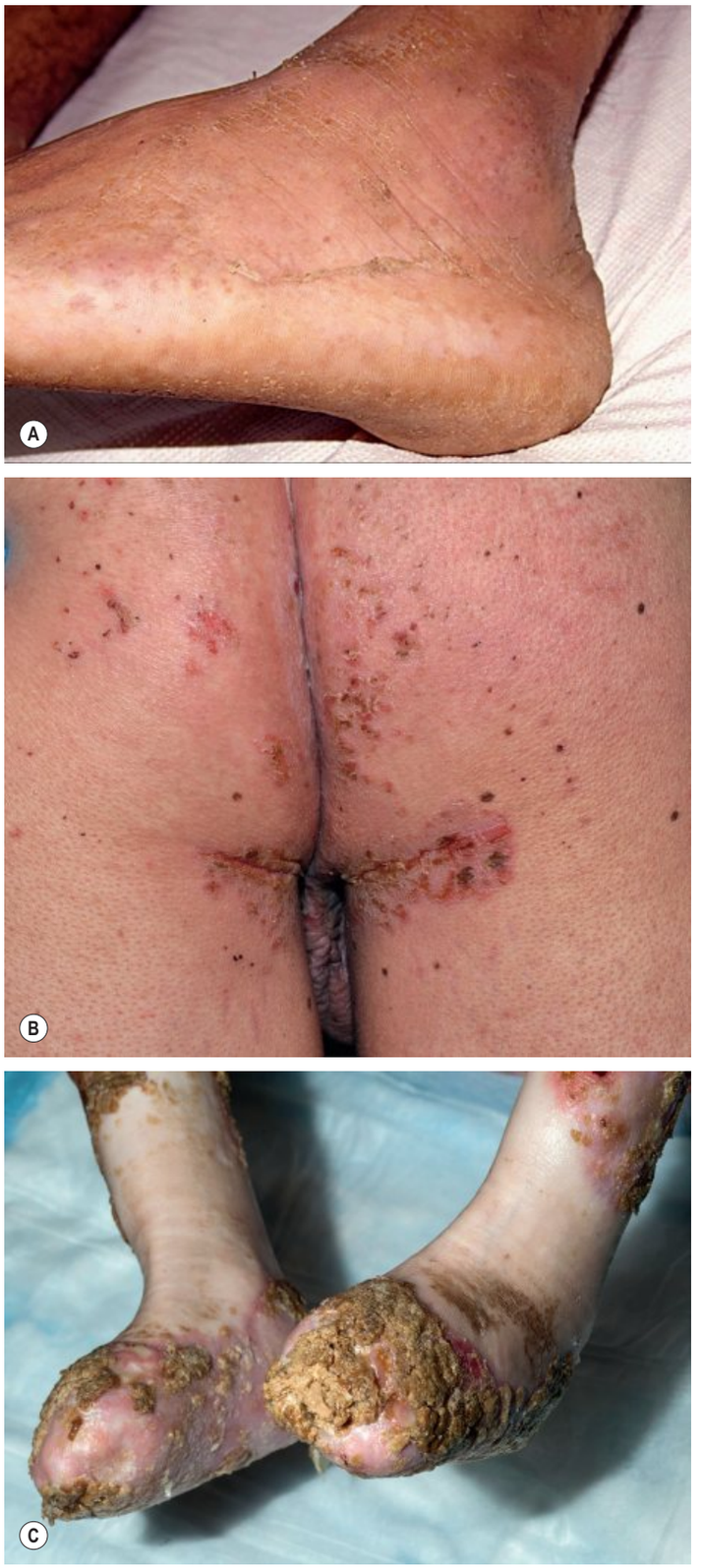


Fig. 32.15 Differential diagnosis of epidermolysis bullosa. A Acral peeling skin syndrome presenting with superficial peeling of the skin on the ankle and dorsal aspect of the foot. **B** Skin fragility–ectodermal dysplasia syndrome due to plakophilin 1 deficiency. Note the scattered erosions and crusts on the buttocks. **C** SAVI (*S*TING-*a*ssociated *v*asculopathy with onset in *i*nfancy) represents a vasculopathic genetic disorder that can result in digital resorption resembling that in recessive dystrophic epidermolysis bullosa. *A, Courtesy E. Sprecher, MD, PhD; B, Courtesy Antonio Torrelo, MD; C, Courtesy Edward Cowen, MD.*

ADDITIONAL GENODERMATOSES ASSOCIATED WITH SKIN FRAGILITY OR BLISTERS		
Disorder	**Defective protein/gene (inheritance)**	**Clinicopathologic features**
Erosive skin fragility disorders		
Skin fragility–woolly hair syndrome (DSP), skin fragility–ectodermal dysplasia syndrome (PKP1), and related conditions	Desmoplakin/*DSP*, plakophilin 1/*PKP1*, or plakoglobin/*JUP** (AR)	Erosions > blisters favor extremities (Fig. 32.15B), perioral and intertriginous fissures, focal PPK with fissures; sparse and/or woolly hair, nail dystrophy; acantholysis in skin biopsy specimens; **DSP:** follicular keratoses on extensor surfaces, variable cardiomyopathy and hoarseness; **JUP***: PPK, alopecia or curly hair, cardiomyopathy
Acantholytic erosive disorder (formerly acantholytic EBS)	Desmoplakin/*DSP* or plakoglobin/*JUP* (AR)	Generalized erosions at birth; universal alopecia; acantholysis in skin biopsy specimens; **DSP:** natal teeth, anonychia and variable cardiomyopathy; **JUP:** onycholysis and infections
Peeling skin fragility disorders		
Acral peeling skin syndrome	Transglutaminase 5 (AR)	Superficial peeling and erosions on hands and feet (see Fig. 32.15A)
EBS superficialis		
EBS superficialis	Unknown	Superficial erosions; postinflammatory hyperpigmentation; subcorneal cleavage
Hyperkeratotic skin fragility disorders		
Superficial epidermolytic ichthyosis	Keratin 2 (AD)	Mauserung phenomenon (desquamation); superficial intraepidermal blistering in skin biopsy specimens
Epidermolytic ichthyosis	Keratins 1 and 10 (AD)	Blistering primarily in the first few years of life; later, corrugated hyperkeratosis; epidermolytic hyperkeratosis in skin biopsy specimens; **keratin 1**: PPK
Connective tissue disorder with skin fragility		
Syndromic connective tissue disorder with skin fragility	Lysyl hydroxylase 3 (AR)	Predominantly acral blistering; scoliosis, joint contractures, pterygia, dysmorphic facies, ocular anomalies
Additional genodermatoses with erosions or blistering		
Congenital erythropoietic porphyria (Günther disease)	Uroporphyrinogen III synthetase (AR)	Severe photosensitivity leading to blistering, deep ulcerations and facial/digital mutilation; elevated uroporphyrin I and coproporphyrin I; red urine and teeth; hemolytic anemia
Mendes da Costa syndrome	Unknown (X-linked)	Spontaneous formation of bullae (unprovoked by trauma); atrichia; acrocyanosis; dyspigmentation; microcephaly; intellectual disability
AEC (ankyloblepharon–ectodermal dysplasia–clefting) syndrome	p63 (AD)	Ankyloblepharon; ectodermal dysplasia; cleft lip and palate; erythroderma; widespread erosions in neonates; chronic erosive scalp dermatitis; patchy alopecia

*Features overlap with those of Naxos disease (see Ch. 58).

Table 32.3 Additional genodermatoses associated with skin fragility or blisters in the differential diagnosis of epidermolysis bullosa. Additional diagnostic considerations may include other peeling skin syndromes (see Table 57.8) and pachyonychia congenita (see Chs. 58 & 71). Biallelic mutations in the genes encoding desmocollin 3 and desmoglein 3 have been implicated in hypotrichosis with recurrent skin vesicles and acantholytic oral/laryngeal blisters, respectively. AD, autosomal dominant; AR, autosomal recessive; EBS, epidermolysis bullosa simplex; PPK, palmoplantar keratoderma.

DRESSINGS FREQUENTLY USED IN PATIENTS WITH EPIDERMOLYSIS BULLOSA		
Dressing type	**Use**	**Examples®,™**
Soft silicone dressings ("low-tack")	• Suitable as primary or secondary dressings in many types of EB • May have a foam backing for mechanical protection or to wick exudate away from the wound	Mepitel, Mepilex, Mepilex Transfer, Mepilex Border
Non-adherent lipido-colloid dressings	• Suitable for primary contact	Urgotul
Hydrogel dressings	• Provide moisture to drier wounds to facilitate healing • May provide relief from pain or itch	Flexigel, Curagel, ActiForm Cool
Foam dressings	• Useful to absorb moderate amounts of wound exudate	Mepilex, Allevyn
Absorptive dressings	• Useful to absorb heavy amounts of wound exudate	Eclypse, Sorbion Sana
Silver-containing dressings	• Clinically infected or highly colonized wounds • Avoid prolonged use due to risk of silver absorption	Urgotul SSD, Mepilex AG
Other antimicrobial dressings	• Clinically infected or highly colonized wounds	PolyMem, Cutimed Sorbact, Activon Tulle, Suprasorb X + PHMB

Table 32.4 Dressings frequently used in patients with epidermolysis bullosa (EB).

help to prevent the development of SCCs in severe RDEB patients remains to be determined. The angiotensin receptor blocker losartan interferes with TGF-β signaling, which is upregulated in the skin of RDEB patients and may contribute to the risk of developing SCC. Losartan was shown to reduce cutaneous fibrosis and digital fusion in a mouse model of EB and is currently under investigation in RDEB patients[55].

Although not yet in mainstream clinical practice, translational therapeutic approaches for EB utilizing cell-, protein- and gene-based methods have been a focus of attention in recent years[2,56]. In clinical trials investigating the value of allogeneic bone marrow-derived stem cell transplantation in patients with RDEB, significant clinical responses were observed, with production of collagen VII at the dermal–epidermal junction and improved wound healing[57,58]. However, there was also

substantial associated morbidity and mortality, although ameliorated to some extent by using reduced-intensity conditioning regimens. An alternative approach has been to use intradermal[59] or intravenous[60,61] injections of allogeneic mesenchymal stem cells in patients with severe RDEB, which has led to improved wound healing as well as reduced inflammation and itch. Injections of allogeneic fibroblasts into RDEB wounds also improved wound healing in a small clinical trial[62]. In addition, intradermal and intravenous delivery of recombinant collagen VII has been explored in animal models of RDEB but not yet in human studies[63].

Gene therapy for EB is currently under investigation in several clinical trials. It was first successfully performed in a man with intermediate JEB, with *ex vivo* gene correction of autologous keratinocytes to restore laminin 332[64]. A skin equivalent was generated and grafted onto the patient's legs, with amelioration of blistering that persisted for years post-procedure. Similar approaches utilizing *ex vivo*-gene correction have subsequently been employed in a child with severe JEB, with graft coverage of ~80% of his body surface area, and patients with RDEB[65,66]. *In vivo* topical gene therapy with beremagene geperpavec (B-VEC), a non-replicating *COL7A1*-containing herpes simplex virus type 1 vector, was recently shown in a randomized placebo-controlled study to induce collagen VII expression and promote healing when applied to wounds in patients with RDEB[67]. Gene editing using technologies such as CRISPR/Cas9 and base editing to restore expression of functional proteins in EB has also been explored[68,69]. Another promising method is the use of drugs such as aminoglycoside antibiotics (e.g. topical or intravenous gentamicin) to induce read-through of nonsense mutations and improve wound healing in RDEB and JEB patients[70,71].

Revertant mosaicism in the skin of EB patients represents "natural gene therapy" that can restore wild-type function to a clone of cells, providing a model for potential gene manipulation strategies and possibly explaining the tendency for improvement with age in some subtypes of EB. Mitotic gene conversion, true back mutations, and second-site mutations that prevent a premature termination codon or restore the reading frame have been shown to reverse disease-causing type XVII collagen mutations in individuals with intermediate JEB, leading to decreased blistering in discrete areas of skin[72]. Second-site nonsense mutations have also been shown to abrogate blistering by silencing a dominant-negative keratin 14 allele in those with severe EBS, and revertant mosaicism has also been observed in RDEB patients. Furthermore, patients with intermediate JEB have had successful local treatment with autologous grafts harvested from areas of revertant skin[73].

Strategies for the medical and surgical management of long-term complications of EB are outlined in Table 32.5[33,74–76]. Multidisciplinary clinics can provide care and support for the wide range of needs that patients with EB and their families have. Families can also obtain helpful information from several support group websites, in particular www.debra.org and www.debra-international.org.

KINDLER EPIDERMOLYSIS BULLOSA

Synonyms: ■ Kindler syndrome ■ Kindler–Weary syndrome ■ Bullous acrokeratotic poikiloderma of Kindler and Weary ■ Hereditary acrokeratotic poikiloderma

Introduction

Kindler EB is a rare autosomal recessive genodermatosis that features skin fragility and photosensitivity during early life as well as progressive poikiloderma, cutaneous atrophy, and mucosal inflammation[2,77–79].

History

In 1954, Theresa Kindler described a patient with acral blistering and photosensitivity during infancy, followed later in life by progressive poikiloderma and atrophy. Twenty years later, Weary reported ten members of a single family with similar findings in addition to widespread atopic dermatitis during early childhood and keratotic papules over the joints of the arms and legs that appeared in childhood and persisted indefinitely. Oral involvement and other mucosal manifestations were subsequently emphasized[77–81].

Pathogenesis

Kindler EB is characterized ultrastructurally by basement membrane reduplication and mixed planes of cleavage that can be within basal keratinocytes, through the lamina lucida, and/or below the lamina densa[2,82]. It results from mutations in the FERM domain-containing kindlin-1 gene (*FERMT1*) which encodes kindlin-1, a component of focal adhesions that connect actin filaments in basal keratinocytes to the underlying ECM[81–84] (see Ch. 28). Through integrin-mediated signaling, kindlin-1 affects the shape, polarity, adhesion, proliferation, and motility of keratinocytes[78]. There is also evidence that kindlin-1 has a role in regulating cutaneous epithelial stem cell homeostasis, with loss of kindlin-1 leading to increased risk of skin cancer as well as cutaneous atrophy due to stem cell exhaustion and premature senescence of keratinocytes[84].

Clinical Features

Erosions are occasionally present at birth, most often on the forearms and shins, and blistering during infancy is most prominent on the hands and feet. In contrast to other forms of EB, skin fragility tends to decrease considerably during childhood. Photosensitivity manifesting as an increased susceptibility to sunburn also improves over time. Reticulated hyperpigmentation and telangiectasias begin to develop in sun-exposed areas during childhood, and after puberty these findings spread to sun-protected sites. A characteristic feature in adult patients with Kindler EB is poikiloderma (Fig. 32.16A), which persists throughout life. Tissue paper-like atrophy is frequently seen, particularly on the dorsal surfaces of the hands and feet (Fig. 32.16 B,C), and mild webbing of the digits (see Fig. 32.16C) and palmoplantar hyperkeratosis may also be evident. Eczematous dermatitis, typically beginning during infancy and resolving by early childhood, occurs in some patients.

Patients with Kindler EB often have erosive gingivitis and poor dentition. Mucosal involvement may result in intraoral and corneal scarring, ectropion, colitis, and strictures of the esophagus, urethra, vagina, and anus. Patients have an increased risk of SCC of the lip and oral mucosa as well as acral skin[81].

Pathology

In older patients, skin biopsy specimens show the typical changes of poikiloderma, including epidermal atrophy, vacuolization of the basal cell layer, variable epidermal melanin content, dermal melanophages, and capillary dilation. Immunostaining of skin biopsy specimens with anti-kindlin-1 antibodies often demonstrates a marked reduction or absence of this protein[82]. Ultrastructural findings are noted above.

Differential Diagnosis

The predominantly acral distribution of the blisters and associated atrophy and photosensitivity distinguish Kindler EB from other forms of EB, although a form of JEB characterized by progressive cutaneous atrophy similar to that in Kindler EB has been described[85]. As poikiloderma becomes apparent during early childhood, the differential diagnosis may include Rothmund–Thomson syndrome and other entities outlined in Table 63.9.

Treatment

Management is akin to other forms of EB, with the addition of sun protection and assiduous oral hygiene.

Additional figures available in our eBook (see inside front cover for access code).

MANAGEMENT OF LONG-TERM COMPLICATIONS OF EPIDERMOLYSIS BULLOSA		
Complication	**Prevention and monitoring/detection**	**Management**
Oral and gastrointestinal		
Excessive caries	• Diligent oral hygiene • Antiseptic and fluoride mouthwashes • Periodic evaluation and cleaning by a dentist	• Restorative dentistry
Microstomia		• Physical therapy • "Mouth expanding" devices
Oral ulceration		• Topical antiseptics, topical NSAIDs, barrier preparations (e.g. sucralfate suspension)
Esophageal strictures	• Evaluate dysphagia with contrast studies	• Dietary modification (soft foods/purées, caloric supplementation) • Fluoroscopically guided balloon dilatation; repeated procedures are often required • In severe and recalcitrant cases, surgical options include colonic interposition
Gastroesophageal reflux disease		• Proton pump inhibitors, H_2 blockers, prokinetic agents (e.g. metoclopramide, domperidone [not available in the US])
Constipation	• Ensure adequate fluid intake and dietary fiber	• Osmotic laxatives (e.g. containing polyethylene glycol), mineral oil • Avoid suppositories and enemas
Nutritional		
Growth retardation/inadequate intake to meet nutritional needs	• Monitor height, weight and body mass index • Periodically assess serum zinc, selenium, iron, vitamin D, and carnitine levels (e.g. yearly) • Oral supplements to optimize intake of calories, protein, vitamins, and minerals	• Consider gastrostomy feedings
Hematologic		
Anemia due to iron deficiency and chronic inflammation	• Monitor CBC and measures of iron stores	• Iron supplementation (oral or IV) • Consider erythropoietin or darbepoetin alpha • Consider blood transfusion if hemoglobin ≤7–8 g/dl and/or symptomatic
Genitourinary and renal		
Urinary outflow obstruction (e.g. urethral or ureteral strictures)	• Consider annual ultrasound of the urinary tract and urodynamic studies (especially for JEB)	• Dilatation procedures as needed to treat obstruction • Avoid unnecessary instrumentation
Renal disease (e.g. hydronephrosis, post-infectious glomerulonephritis, renal amyloidosis, IgA nephropathy)	• Blood urea nitrogen & serum electrolyte levels, urinalysis and blood pressure evaluation every 6 months in RDEB patients • Adequately treat streptococcal infections	• Hemodialysis or peritoneal dialysis if renal failure develops
Musculoskeletal		
Osteopenia and osteoporosis	• Annual DEXA scan and spinal radiographs beginning at age 5 years in RDEB and JEB patients • Calcium and vitamin D supplementation	• Consider IV bisphosphonate therapy
Pseudosyndactyly of hands/feet	• Cushioned splints on hands/forearms and individual wrapping of fingers in RDEB patients	• Surgery to release contractures and webbing
Oncologic		
Cutaneous squamous cell carcinoma	• Periodic total-body skin examinations; for RDEB patients, approximately every 3–6 months beginning at age 10 years and every 3 months after age 16 years • Biopsy or monitor non-healing ulcers (see Fig. 32.13) • Consider taking serial photographs	• Excision ± skin grafting (sometimes amputation); consider MRI to assess extent of local disease • Consider staging with CT, PET-CT, sentinel lymph node biopsy • Use of EGFR and immune checkpoint inhibitors for advanced disease has been reported
Ocular		
Chronic complications include corneal scarring, symblepharon, ectropion	• Periodic ophthalmologic evaluation for patients with eye involvement • Lubricating eye drops	• Surgical procedures, e.g. division of symblepharon, amniotic membrane transplantation
Cardiac		
Dilated cardiomyopathy	• Consider annual echocardiography beginning in late childhood for RDEB patients	• Medical management • Supplement selenium and carnitine if deficient
Psychological and psychiatric		
Disrupted family unit (e.g. via divorce)	• Consider family counseling, support groups	• Psychological/family counseling
Depression and suicidal ideation/attempts	• Consider psychological counseling, support groups	• Psychiatric evaluation, antidepressant therapy

Table 32.5 Management of long-term complications of epidermolysis bullosa (EB)[33,74,75]. CBC, complete blood count; CT, computed tomography; EGFR, epidermal growth factor receptor; JEB, junctional EB; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PET, positron emission tomography; RDEB, recessive dystrophic EB.

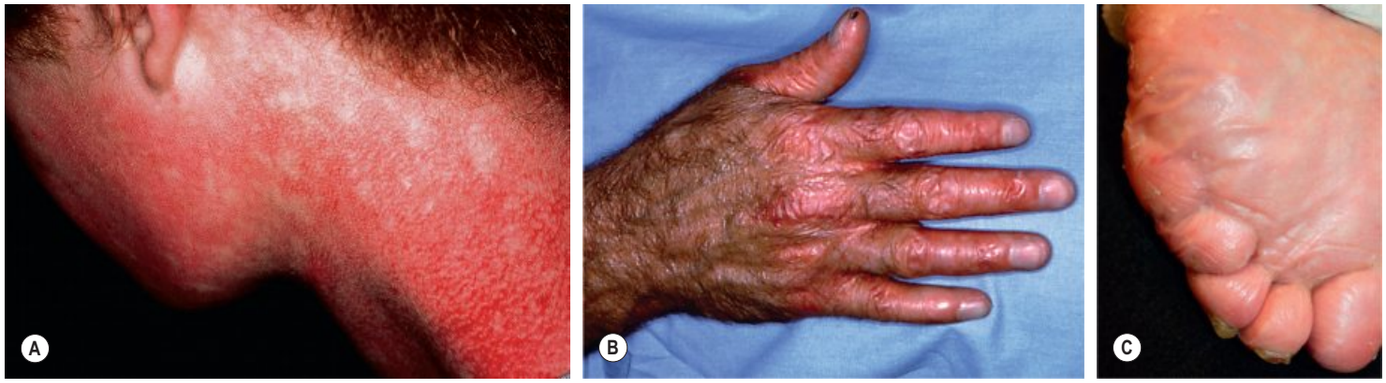


Fig. 32.16 Kindler epidermolysis bullosa. A Poikiloderma of the face and neck with "skip" areas. **B** Erythema and atrophy on the dorsal hand. **C** Progressive syndactyly of fourth and fifth toes in an adult. Note the near absence of dermatoglyphics. This patient also had ectropion and urethral strictures. *C, Courtesy Jean L. Bolognia MD.*

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eFig. 32.1 Epidermolysis bullosa simplex. Blistering and focal keratoderma on the soles of a 4-year-old boy. *Courtesy Julie V. Schaffer, MD*.



eFig. 32.2 Severe epidermolysis bullosa simplex. Clustered vesicles in an arcuate array on the arm of this child. *Courtesy Julie V. Schaffer, MD*.

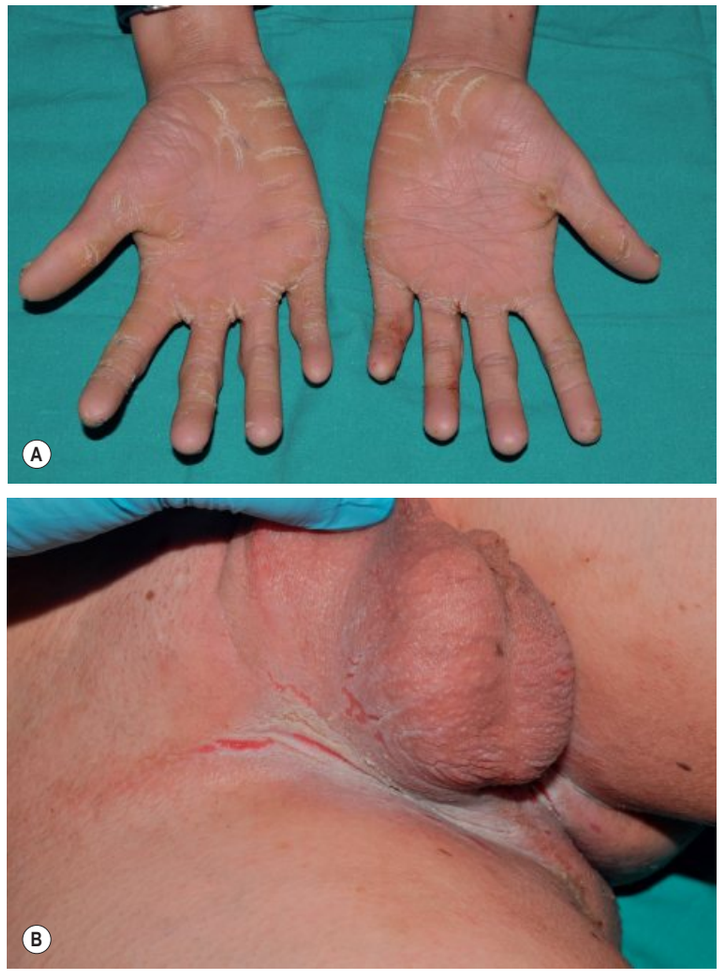




eFig. 32.3 Dominant dystrophic epidermolysis bullosa. A, B Erosions, scarring, and milia on the digits, as well as partial shedding of a toenail (**A**).



eFig. 32.4 Recessive dystrophic epidermolysis bullosa. Scarring with fusion of toes and ulcerations at sites of previous bullae. *Courtesy M. Joyce Rico, MD.*



eFig. 32.5 Skin fragility–ectodermal dysplasia syndrome due to plakophilin 1 deficiency. A Palmar keratoderma with accentuation in areas of friction and fissuring. **B** Erosions in intertriginous zones and multiple hemorrhagic crusts. *Courtesy Antonio Torrelo, MD.*



eFig. 32.6 Kindler epidermolysis bullosa. Wrinkling due to atrophy and fusion between the fourth and fifth toes. This patient also had ectropion and urethral strictures. *Courtesy Jean L. Bolognia, MD.*

33 Other Vesiculobullous Diseases

José M. Mascaró Jr

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Vesiculobullous diseases of the skin encompass a wide range of entities, including autoimmune bullous diseases and inherited blistering disorders (see Chs. 28–32). This chapter focuses on the remaining non-infectious disorders in which cutaneous bullae develop and represent the primary clinical manifestation.

BULLOSIS DIABETICORUM

Synonyms: ■ Diabetic bullae ■ Bullous eruption of diabetes mellitus ■ Bullous diabeticorum

Key features

- A rare condition associated with diabetes mellitus
- Tense blisters develop on normal-appearing skin in acral sites (feet, lower legs, hands); there is often an association with peripheral neuropathy
- Histologically, intraepidermal and/or subepidermal blisters are observed
- Spontaneous healing usually occurs in 2 to 6 weeks

History

Bullosis diabeticorum was first described by Kramer in 1930. In 1967, Cantwell & Martz[1] introduced the term "bullosis diabeticorum".

Epidemiology

The exact prevalence of bullosis diabeticorum is unknown. In a retrospective study of diabetic patients, the annual incidence was 0.16%[2]. The age of onset ranges from 15 to 85 years, with a mean age of 55 years. A 2:1 male-to-female ratio has been reported, and it occurs more frequently in the setting of longstanding diabetes and neuropathy.

Pathogenesis

Although bullosis diabeticorum has been related to trauma and the microangiopathy of diabetes, little is known about its cause. Diabetic patients can develop blisters after minimal trauma, and some authors have found a reduced threshold for inducing suction blisters in these patients[3,4]. There is no evidence of an infectious etiology.

Clinical Features

Bullosis diabeticorum is characterized by a sudden and spontaneous appearance of vesicles and bullae within normal-appearing, non-inflamed skin of the distal extremities of diabetics. The most frequent locations (in decreasing order) are the feet, distal legs, hands, and forearms. Bullae are rarely seen on the trunk. The lesions are usually asymptomatic, but occasionally there is a mild burning sensation. Blisters often develop "overnight" and in the absence of known trauma. The vesicles and bullae are tense and vary in diameter from 0.5 to several centimeters (Fig. 33.1). They contain a clear, sterile fluid that can be more viscous than that found in friction blisters.

Most patients have longstanding diabetes, but occasionally bullosis diabeticorum is a presenting sign of diabetes. It is associated with both insulin-dependent and non-insulin-dependent diabetes mellitus. Many patients have an associated polyneuropathy, retinopathy, or nephropathy.

Pathology

The histopathologic findings are heterogeneous. Initial reports described intraepidermal blisters, whereas more recent publications have usually described subepidermal bullae. It seems likely that the level of cleavage is subepidermal, and that intraepidermal blisters represent older lesions undergoing re-epithelialization. Direct immunofluorescence (DIF) examination is usually negative, although a few reports have described IgG or IgM and C3 deposits within dermal blood vessel walls. By electron microscopy, subepidermal blisters with a separation at the level of the lamina lucida or below the lamina densa have been described[5].

Differential Diagnosis

In porphyria cutanea tarda (PCT) and pseudoporphyria associated with dialysis and medications, the blisters are usually <1 cm in diameter and favor the hands rather than the feet and ankles. Complications of diabetes include both chronic renal failure and atherosclerotic cardiovascular disease and, as a result, patients may be receiving dialysis



Fig. 33.1 Bullosis diabeticorum. A large, tense bulla overlying the medial malleolus. Note the absence of erythema or edema in the surrounding skin.

and/or diuretics. The distal extremity is also a common site for fixed drug eruptions, but bullae develop on an inflammatory base. Localized bullous pemphigoid and epidermolysis bullosa acquisita (EBA) are differentiated by histologic examination and DIF, as well as by an accentuation of lesions at sites of friction in patients with EBA. If there is surrounding erythema, warmth, and tenderness, the possibility of bullous cellulitis must be considered.

Treatment

Most patients have spontaneous healing of their lesions within 2 to 6 weeks. To relieve pressure or improve appearance, the blisters can be cleansed with alcohol and then a small window is placed in the most dependent portion of the blister roof. The sites should be washed daily to prevent secondary infection followed by application of petrolatum. Occasionally, a secondary soft-tissue infection does develop, requiring systemic antibiotics or surgical intervention[2].

COMA BLISTERS

Synonyms: ■ Coma bullae ■ Drug-induced coma blisters ■ Barbiturate blisters ■ Neurologic blisters

Key features

- Associated with loss of consciousness, neurologic diseases, or prolonged immobilization
- Tense blisters develop on normal-appearing skin
- Histologically, intraepidermal or subepidermal blisters are observed, with a characteristic necrosis of sweat glands
- Spontaneous healing occurs within 1 to 2 weeks

Introduction

In some comatose patients, blisters, primarily within sites of pressure, will develop within 48–72 hours of loss of consciousness. Although historically associated with barbiturate overdose, they can be seen in the setting of coma due to other causes including medications (e.g. opioids), infections (e.g. viral encephalitis), metabolic disturbances (e.g. hypoglycemia), and neurologic dysfunction (e.g. cerebrovascular accidents).

History

Coma blisters were first described in 1806 by Dominique Larrey, Napoleon's surgeon, who noticed these lesions in soldiers who had been comatose from carbon monoxide intoxication.

Epidemiology

In 1952, Holten reported the appearance of coma blisters in 4% of a series of 501 patients with barbiturate poisonings[6]. In another study, blisters were found in 6.5% of barbiturate overdoses[7]. Although a number of reported cases have been associated with barbiturate overdose, blisters have also been observed in those whose comas were induced by overdosage of other medications, including opioids, benzodiazepines, hypnotics, tricyclic antidepressants and antipsychotics, as well as alcohol intoxication[8]. Similar lesions have also been described in patients with non-drug-induced coma due to carbon monoxide poisoning, head trauma, cerebrovascular accidents, viral encephalitis, hypoglycemia, diabetic ketoacidosis, or hepatic encephalopathy[9,10]. In addition, bullous lesions have been observed following surgical procedures requiring general anesthesia[11] and in non-comatose patients, in particular those with severe neurologic disease or prolonged immobilization (e.g. secondary to accidents)[12].

Pathogenesis

The pathogenesis is unclear. A direct toxic drug effect has been implicated, particularly because of the association with drug intoxication and the frequent finding of eccrine gland necrosis (many drugs are thought to be excreted by sweat glands). However, this would not explain the non-drug-induced cases. Therefore, pressure, friction, and local hypoxia have been implicated as etiologic factors. The pressure/ischemic hypothesis is currently favored and is supported by the observation that most (if not all) lesions appear at sites of pressure.

Clinical Features

Lesions develop at body sites exposed to maximum pressure during unconsciousness or immobilization. They first appear 24 hours after the onset of coma as blanchable erythematous patches or plaques that progress to violaceous plaques. Blisters or erosions then develop within 48–72 hours after the onset of coma at these sites (Fig. 33.2). If the patient survives, the erosions usually heal spontaneously over 1 to 2 weeks. In some individuals, residual scarring can result. Compression neuropathies and non-traumatic rhabdomyolysis are additional complications that may be seen in patients with coma bullae[8–10,12,13]. As mentioned previously, the same type of blisters can occur in patients with prolonged immobilization or neurologic diseases (Fig. 33.3).



Fig. 33.2 Coma bullae. Blisters developed in an area of pressure in a previously comatose patient.



Fig. 33.3 Neurologic blisters. Tense blisters on the dorsal aspect of the fingers on the hemiplegic side in a patient with a history of a cerebrovascular accident.

Pathology

The blisters are predominantly subepidermal. However, intraepidermal blisters are also observed as the result of re-epithelialization of older lesions or epidermal spongiosis. There is a variable degree of epidermal necrosis. Sweat gland necrosis is a characteristic finding (Fig. 33.4), and focal necrosis of the epithelium of the pilosebaceous units can also be seen. There is only a sparse inflammatory cell infiltrate. DIF is usually negative, but deposits of IgG, IgM, and/or C3 have been found within the walls of dermal blood vessels[8,9].

Differential Diagnosis

In most patients, the clinical setting alone is sufficient to make the diagnosis (Fig. 33.5). A cutaneous biopsy will allow differentiation from friction blisters. An intraepidermal blister cavity just below the granular layer is seen in friction blisters, whereas a subepidermal split with sweat gland/follicular necrosis is characteristic of coma bullae. Based upon the distribution pattern, clinical appearance, and histologic findings, multiple fixed drug eruption can be excluded.

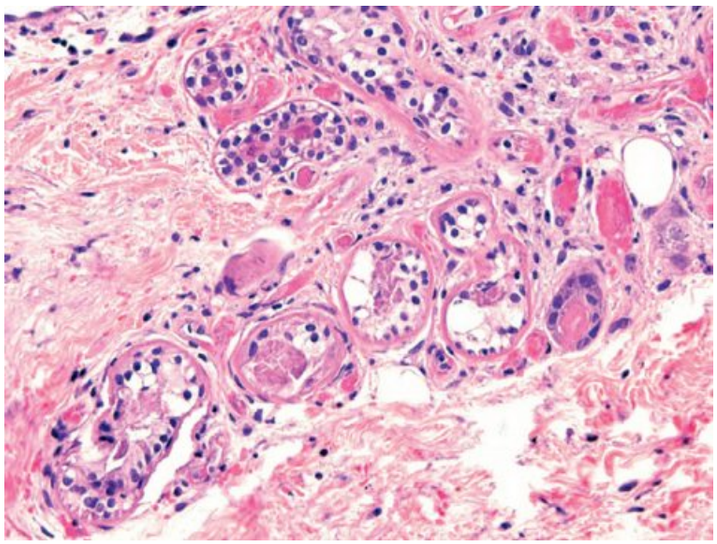


Fig. 33.4 Bulla due to prolonged immobilization ("coma blister") – histopathologic features. Following a fall and hip fracture, the patient remained immobilized on the floor for two days. Detection of the characteristic sweat gland necrosis aided in the diagnosis.

Treatment

Coma blisters heal spontaneously over 1 to 2 weeks. In non-comatose patients, frequent postural changes help to resolve and prevent the disorder.

FRICTION BLISTERS

Key features

- Friction blisters occur most commonly on the soles and heels
- They are the result of repeated friction, e.g. walking or running in ill-fitting shoes; they may also develop on the palms and fingers if a repetitive action is performed
- Histologically, blistering occurs just below the stratum granulosum

Epidemiology

Friction blisters are very common in the general population. Almost every person remembers developing such lesions when wearing a new pair of shoes. They are particularly common in young and active individuals, especially those engaged in the military and sports. In a military study at a Combat Support Hospital, the prevalence of foot friction blisters was 33% and they were more common in those who were unable to break in their boots[14].

Pathogenesis

Frictional shearing forces occur within the epidermis when the surface of an object rubs against the skin surface. Repetition of this rubbing action over a period of time can induce the appearance of blisters. Rubbing of moist skin produces higher frictional forces than with very dry or very wet skin[15]. Poorly fitting shoes, heat, and sweating are predisposing factors.

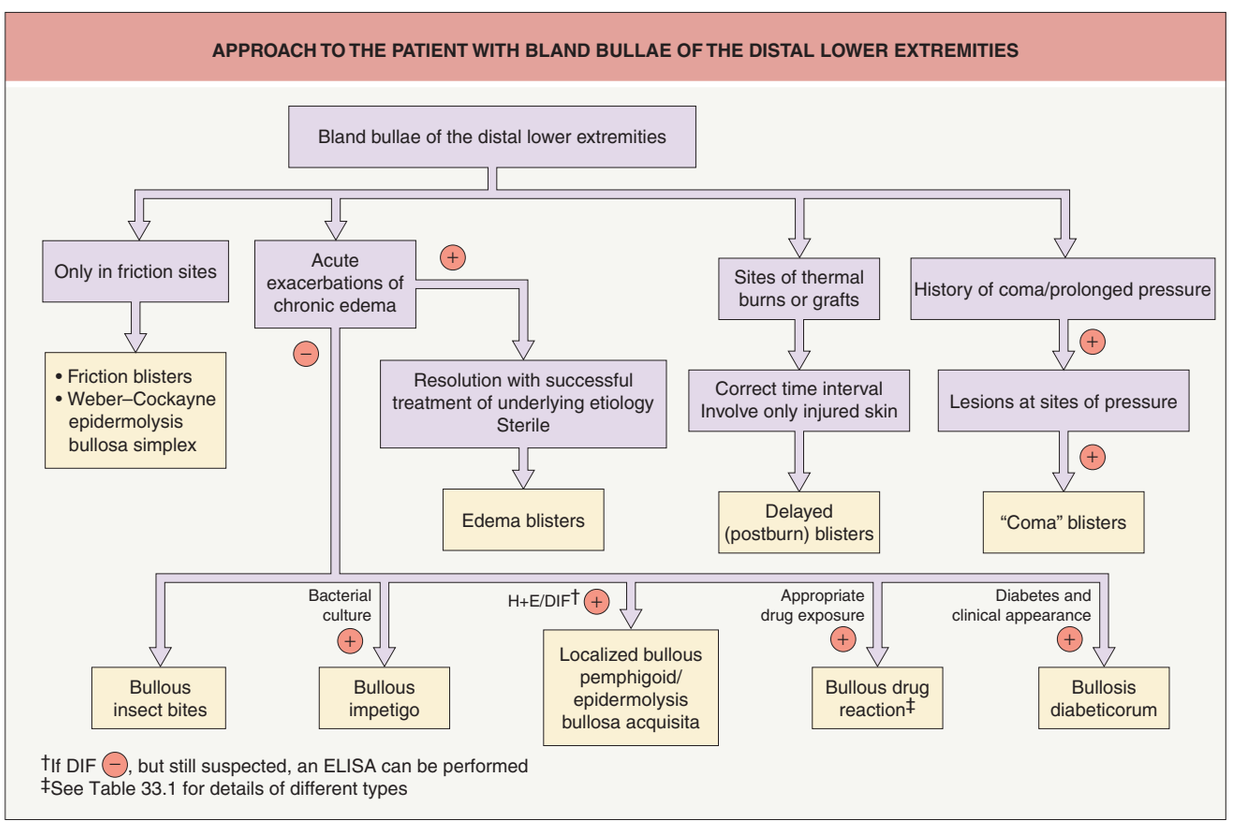


Fig. 33.5 Approach to the patient with bland bullae of the distal lower extremities.

Clinical Features

Friction blisters most frequently develop in areas with thick stratum corneum (soles, heels, palms, fingers). They are particularly common in sites where friction is intense and repeated (e.g. feet). The lesions initially begin as erythematous macules at sites of friction and later develop into blisters. The patients complain of an associated burning sensation or pain, and the blister fluid may be clear or blood-tinged.

Pathology

Friction blisters are intraepidermal blisters resulting from necrosis of keratinocytes. The level of the split is variable but usually in the stratum spinosum just below the stratum granulosum. The roof of the blister is formed by the stratum corneum, the stratum granulosum, and some cellular debris. Pale and degenerated keratinocytes that stain faintly are found within the upper portion of the floor of the blister cavity. The deeper layers of the epidermis are normal[16]. There is only a sparse perivascular inflammatory infiltrate in the superficial dermis.

Differential Diagnosis

In most patients, friction blisters can be easily diagnosed clinically. The localized variant of epidermolysis bullosa simplex (formerly Weber–Cockayne) is suspected when there is an exaggerated response to friction; histologic examination of a fresh or induced blister should show separation subepidermally or within the basal layer of the epidermis. EBA can also mimic friction blisters, but it is differentiated by histologic examination, DIF, and ELISA (see Fig. 33.5).

Treatment

Friction blisters can heal spontaneously without treatment. Drainage of blister contents via a small "window" in the blister roof relieves pressure and discomfort and prevents the accumulation of fluid; it also allows the blister roof to remain largely intact. Hydrocolloid or other dressings can also be utilized.

BULLOUS CUTANEOUS SMALL VESSEL VASCULITIS

Occasionally, patients with cutaneous small vessel vasculitis will develop superimposed vesicles and bullae, especially on the distal extremities (Fig. 33.6). These blisters are often hemorrhagic and can progress to ulceration. Edema of the lower extremities may also be present. In children, vesicles have been observed more frequently in IgA vasculitis (Henoch–Schönlein purpura) than in non-IgA vasculitis[17]. Histologically, a leukocytoclastic vasculitis is seen (in addition to a subepidermal blister with epidermal necrosis), which differentiates this entity from other blistering diseases. This may be a sign of more severe disease (see Ch. 24).



Fig. 33.6 Bullous variant of cutaneous small vessel vasculitis. *Courtesy Jeffrey P. Callen, MD.*

BULLOUS DRUG ERUPTIONS

Key features

- Some drug eruptions can present as blistering eruptions
- These eruptions can be localized or widespread
- Clinical, histologic, and immunofluorescence findings vary, depending on the type of drug eruption

Vesicles and bullae can develop in a variety of drug eruptions, which are outlined in Table 33.1 and discussed in detail in other chapters.

BULLOUS INSECT BITE REACTIONS

Synonyms (for exaggerated insect bite reactions in the setting of hematologic malignancies): ■ Eosinophilic dermatosis of hematologic malignancy ■ Eosinophilic dermatosis associated with hematological disorders

Key features

- Bullous insect bite reactions are fairly common, particularly in children, although patients often do not recall being bitten
- Severe insect bite reactions as well as insect bite-like reactions can occur in patients with hematologic malignancies, in particular chronic lymphocytic leukemia

Introduction

Although most insect bite reactions present as pruritic erythematous papules (see Ch. 85), vesiculobullous reactions are not uncommon.

History

An exaggerated reaction to insect bites in patients with chronic lymphocytic leukemia (CLL) was first described in 1965 by Robert Weed, and it has been increasingly recognized over the past two decades.

Epidemiology

There seems to be no difference in the incidence of insect bites based on sex, race, or age. Certain individuals may be bitten more frequently because of their body temperature, odor, use of perfumes, or carbon dioxide excretion. Children tend to have more severe reactions than adults because the latter tend to become desensitized by repeated exposures over time.

Patients with CLL, as well as other hematologic malignancies (e.g. non-Hodgkin lymphomas, acute leukemias, multiple myeloma), can develop both exaggerated reactions to insect bites and insect bite-like reactions[18,19]. The latter term is used to describe lesions that resemble insect bites clinically and histologically, but for which a clear link to insect bites cannot be established[20]. These exaggerated reactions can precede the diagnosis of the hematologic malignancy; in a large retrospective study of patients with CLL, the eruption preceded the diagnosis in 20% of patients[21]. Of note, no relationship to disease activity has been observed. More recently, these reactions have been referred to as "eosinophilic dermatosis associated with hematological disorders" or "eosinophilic dermatosis of hematologic malignancy"[22]; the term "eosinophilic dermatosis of myeloproliferative disease" is inaccurate, as CLL is not a myeloproliferative disorder (see Ch. 121).

BULLOUS DRUG ERUPTIONS		
Disease	**Characteristic features**	**Commonly implicated drugs**
Fixed drug eruption (see Ch. 21)	• Sharply circumscribed erythematous to dusky violaceous patches • Central blisters or erosions may appear • Often resolves with postinflammatory hyperpigmentation • Recurrence at same location(s) following drug re-exposure	Sulfonamides, NSAIDs, tetracyclines, barbiturates, aspirin, acetaminophen (paracetamol), metronidazole, phenolphthalein
Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (see Ch. 20)	• Prodrome of fever and painful skin • Areas of dusky erythema associated with epidermal detachment (varying from <10% [SJS] to >30% [TEN]) • Mucosal involvement	NSAIDs, antibiotics (sulfonamides and β-lactams), aromatic anticonvulsants, lamotrigine, allopurinol, immune checkpoint inhibitors
Drug-induced autoimmune blistering diseases (see Chs. 29–31)	• Primarily, linear IgA bullous dermatosis, bullous pemphigoid, pemphigus • Diagnosis based on histopathologic findings, immunofluorescence studies, and drug history	• Linear IgA bullous dermatosis: vancomycin > β-lactams, captopril, NSAIDs • Bullous pemphigoid: diuretics (especially furosemide), antibiotics, immune checkpoint inhibitors, gliptins • Pemphigus: captopril, β-lactams, penicillamine, gold
Drug-induced pseudoporphyria (see Ch. 49)	• Eruption resembles porphyria cutanea tarda • Porphyrins are within normal limits	NSAIDs (especially naproxen), nalidixic acid, thiazides, furosemide, tetracyclines, voriconazole
Acute generalized exanthematous pustulosis (see Ch. 21)	• Acute onset, usually occurring within 2 days of drug exposure • Areas of erythema studded with pustules; occasionally vesicles • Fever, malaise, leukocytosis	β-lactams, macrolides, pristinamycin, terbinafine, calcium channel blockers (diltiazem), hydroxychloroquine, carbamazepine, acetaminophen, metronidazole, immune checkpoint inhibitors
Phototoxic drug eruptions (see Ch. 87)	• Limited to sun-exposed areas • Resembles exaggerated sunburn	Tetracyclines (especially doxycycline), quinolones, psoralens, NSAIDs, diuretics, voriconazole, pirfenidone, BRAF inhibitors, EGFR inhibitors
Bromoderma and iododerma (see Ch. 21)	• Acneiform lesions, papulopustules, nodules, or even vegetating lesions simulating pemphigus vegetans • Clear or hemorrhagic blisters can develop (more common in iododerma)	Bromides, iodine-containing drugs (e.g. amiodarone), radiographic contrast media
Palmoplantar erythrodysesthesia (acral variant of toxic erythema of chemotherapy [TEC]; see Ch. 21)	• Painful erythema develops primarily on the palms, soles, and digits following chemotherapy administration • The skin becomes edematous, its color changes to dark red or violet, and blisters and erosions may develop • With severe TEC, bullae can be generalized	Cytarabine, doxorubicin, capecitabine, 5-fluorouracil (especially prolonged infusions), busulfan, multikinase inhibitors (e.g. sorafenib, sunitinib), taxanes, clofarabine, pralatrexate

Table 33.1 Bullous drug eruptions. Occasionally, eczematous drug reactions (e.g. secondary to warfarin, calcium channel blockers, angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers) and systemic contact dermatitis can be papulovesicular; patients with drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) and drug-induced Sweet syndrome can also develop vesicles. Coma blisters and bullous small vessel vasculitis are discussed in the text. EGFR, epidermal growth factor receptor; NSAIDs, nonsteroidal anti-inflammatory drugs.

Pathogenesis

Most lesions are the result of an individual's immune response to insect antigens introduced by the bite. Both humoral (IgE-mediated) and cell-mediated immunity (delayed hypersensitivity) are involved. Initial bites typically do not produce significant lesions, but sensitization occurs over a few weeks. Subsequent bites then induce a stronger reaction and even bullae formation. With time, repeated bites can result in desensitization. In the case of bullous bed bug reactions, cutaneous vasculitis may be playing a role[23].

In patients with NK/T cell lymphomas, severe hypersensitivity to mosquito bites has been well documented and a possible role for the EBV-induced clonal proliferation of NK cells has been raised[24]. For patients with ALK-positive anaplastic large cell lymphoma, the possibility has been raised that insect bite-associated antigens lead to an influx of T lymphocytes, some of which bear t(2;5). The release of cytokines then results in activation of these cells, expression of NPM-ALK (nucleophosmin–anaplastic lymphoma kinase) fusion protein, and subsequent uncontrolled proliferation[25]. In patients with B cell malignancies, an increased production of IL-4 and IL-5 may explain associated tissue eosinophilia[20].



Fig. 33.7 Bullous insect bite reactions. The serous blister fluid is sterile and the ankle is a common site. *Courtesy Luis Requena, MD.*

Clinical Features

Insect bites usually appear as intensely pruritic erythematous papules or nodules. They are usually grouped, and a linear arrangement is commonly seen. However, vesicular and bullous bite reactions are not uncommon, and blisters can develop centrally within papules or as bland vesiculobullae (Fig. 33.7). Flea bites are the most likely to cause blisters, especially on the legs, and bedbug bites can also be bullous. Some insects (e.g. fire ants) can produce pustular lesions. In patients with hematologic malignancies, the exaggerated reactions consist of persistent papulonodules, vesicles, bullae, and even necrotic lesions (Fig. 33.8).



Fig. 33.8 Exaggerated insect bite-like reactions in a patient with B cell chronic lymphocytic leukemia. Both bullae and erosions at sites of ruptured bullae are present. *Reprinted with permission from Cerroni L. Skin Lymphomas: The Illustrated Guide, 5ed. Oxford: Wiley-Blackwell, 2020.*

Pathology

The typical pattern is that of a superficial and deep perivascular and periadnexal lymphocytic infiltrate with abundant eosinophils. A wedge-shaped pattern is characteristic. During the initial phase, intraepidermal spongiotic vesicles may be present and they can be associated with eosinophilic spongiosis. Pronounced dermal edema leads to the formation of subepidermal blisters. Sometimes, epidermal necrosis develops. Flame figures (extruded eosinophilic granules aggregated onto collagen fibers that are classically associated with eosinophilic cellulitis) can be observed, particularly in the exaggerated reactions seen in patients with hematologic malignancies.

Differential Diagnosis

The presence of intense pruritus and lesion distribution usually suggests a bullous bite reaction. However, these reactions can mimic bullous pemphigoid, linear IgA bullous dermatosis, bullous erythema multiforme, bullous impetigo, allergic contact dermatitis, or even viral infections.

Treatment

Most patients with bullous insect bites can be managed with drainage of blisters plus topical corticosteroids and systemic antihistamines to relieve pruritus. In the most severe reactions, a short course of systemic corticosteroids may be necessary. Systemic corticosteroids can lead to improvement of eosinophilic dermatosis of hematologic malignancy, but lesions tend to recur when the dose is reduced. Dupilumab may represent a therapeutic option in these patients[26]. Protective clothing and insect repellants are important preventative measures (see Ch. 85).

DELAYED POSTBURN/POSTGRAFT BLISTERS

Key features

- Delayed postburn and postgraft blisters represent an under-reported condition
- Tense blisters develop weeks to months after the initial injury has healed
- Blistering can persist for several weeks or months

Introduction

Delayed blisters have been observed weeks to months after the initial healing of second-degree thermal burns, donor sites of split-thickness skin grafts, and recipient sites of split-thickness skin grafts[27,28].

History

The first report of this phenomenon is attributed to Barker and Cotterill in 1980.

Epidemiology

Delayed blisters have received little attention in the literature. However, it appears to occur to some degree in almost every patient with a thermal burn involving more than 30% of the body surface area[28]. Most descriptions refer to patients with thermal burns, where delayed blisters have been observed on the spontaneously healed skin, graft donor sites, and graft recipient sites[27]. They have also been seen after skin grafting for toxic epidermal necrolysis and within laser-resurfaced skin[29].

Pathogenesis

The exact pathogenesis is not known. The antigenic components of the normal dermal–epidermal junction appear sequentially during fetal life or wound healing. Therefore, it has been hypothesized that this phenomenon is due to the enhanced fragility of a newly synthesized, "immature" dermal–epidermal junction[27,28]. In fact, in conventional scars, a subepidermal cleft is not an unusual histopathologic finding.

Clinical Features

Tense vesicles or blisters develop several weeks after the injured skin (burned, donor site, recipient site) has completely healed. In one study, blisters appeared between 19 and 55 days after the patients had sustained their burns, with an average of 37 days[28]. Blisters do not develop within uninvolved skin. Although they heal spontaneously, there is a tendency for recurrences over a period of weeks to months.

Pathology

Histologically, subepidermal blisters with minimal inflammatory infiltrate are seen. Electron microscopy has shown that the blisters occur either in the dermis (below the dermal–epidermal junction) or intraepidermally through the basal keratinocytes. DIF studies have been negative. Immunofluorescence mapping has shown a diminished or variable expression of dermal–epidermal junction antigens, including type IV and type VII collagens, laminin, and bullous pemphigoid antigen[27].

Differential Diagnosis

Blistering associated with a healed injured site can also be due to herpetic infection, ischemia (in the case of graft recipient sites), or autoimmune bullous diseases. Herpetic infection can be excluded by a negative PCR, viral culture, Tzanck smear, direct fluorescent antibody test, and/or biopsy findings; ischemia is diagnosed on the basis of clinical findings; and autoimmune blistering diseases can be excluded by histologic features, DIF/IIF examination, and ELISA.

Treatment

These blisters heal spontaneously with simple care, topical antibiotics, wound dressings, and local compression.

EDEMA BLISTERS

Synonyms: ■ Edema bullae ■ Stasis blisters ■ Hydrostatic bullae



Fig. 33.9 Edema bullae on the thigh of an infant. The bullae are tense and are surrounded by edematous skin. Desquamation from a ruptured bulla is also seen.

Key features

- Edema blisters develop in patients with an acute exacerbation of chronic edema, particularly of the lower extremities, and in the setting of anasarca
- The tense bullae are usually non-inflammatory, but are surrounded by edematous skin
- Blisters resolve when the edema resolves

Epidemiology

This phenomenon has received little attention in the literature. These blisters are not infrequent and usually develop in elderly and immobile hospitalized patients as well as in the setting of anasarca. In a study of 13 patients, the mean age was 74 years[30].

Pathogenesis

The bullae usually develop on the legs in association with an acute exacerbation of chronic edema. Edema develops when the capillary filtration rate exceeds lymphatic drainage. This can be due to hypoalbuminemia, congestive heart failure, renal disease, hepatic cirrhosis, venous occlusion (thrombosis) or drugs, particularly calcium channel blockers. Cutaneous vesicles and bullae also occur with acute exacerbations of lymphedema.

Clinical Features

Due to gravitational effects and venous hypertension, most patients develop blisters on the distal lower extremities, particularly the dorsum of the foot and ankle. With acute exacerbations of chronic edema, blisters appear and enlarge slowly to reach a diameter of up to several centimeters. The bullae are tense and asymptomatic, and the surrounding skin is edematous. The sterile blister fluid is usually clear, but it can be serous or hemorrhagic. In patients with anasarca, there is a more widespread distribution (Fig. 33.9).

Pathology

Marked epidermal spongiosis is observed, with dilated dermal blood vessels and a mild inflammatory infiltrate. The dermis is markedly edematous with wide separation of collagen bundles. In some cases, a subepidermal blister is observed. DIF is negative.

Differential Diagnosis

Blistering in the setting of acute edema is usually not difficult to diagnose. However, the possibility of bullous pemphigoid, bullosis diabeticorum, or bullous drug eruption must also be considered. The correct diagnosis can usually be established via the clinical history and physical examination (see Fig. 33.5). If needed, bullous pemphigoid can be excluded by negative DIF/IIF examinations and ELISA.

ADDITIONAL VESICULOBULLOUS DISORDERS	
Disorder	**Characteristic features**
Fracture blisters	• Tense bullae that develop within edematous skin and overlie bony fractures (Fig. 33.10) • Most common sites: distal tibia, ankle, foot, elbow, wrist • Thought to be due to shearing forces related to the injury plus post-traumatic edema
Sucking blisters	• Seen in newborns in areas accessible to the infant's mouth, e.g. forearm (see Fig. 34.8A) • Develop *in utero*
Bullous dermatitis artefacta (self-inflicted injury)[31,32]	• Can be produced by a thermal, electrical, or chemical burn as well as application of a vesicant, coolant, or "salt and ice" (see Ch. 88) • Histologic features vary depending upon etiology, but the most common pattern is a subepidermal blister with epidermal necrosis +/– dermal damage
Jellyfish stings	• Intense pain followed shortly by a burning sensation or pruritus as well as erythema and edema • Linear vesiculobullae and occasionally necrosis may also appear • Flagellate distribution corresponds to sites of contact with the jellyfish tentacles
PUVA-induced acrobullous dermatosis	• Sudden appearance of sterile, tense blisters, usually on the distal extremities • Due to weakening of epidermal–dermal cohesion plus friction or trauma • DDx: phototoxicity (more widespread) and PUVA-induced bullous pemphigoid

Table 33.2 Additional vesiculobullous disorders. Sites of frostbite can also develop vesicles. DDx, differential diagnosis.



Fig. 33.10 Fracture blisters. Multiple blisters, containing serous or hemorrhagic fluid, developed on the lower extremity following blunt trauma to the thigh. The resultant hematoma and fracture was accompanied by edema of the affected limb.

Treatment

These blisters resolve rapidly when the cause of the edema is successfully treated. Diuretics, discontinuation of calcium channel blockers, leg elevation, and compressive bandages (followed by maintenance compression hose) may prove helpful.

ADDITIONAL VESICULOBULLOUS DISORDERS

These are summarized in Table 33.2.

Additional figures available in our eBook (see inside front cover for access code).

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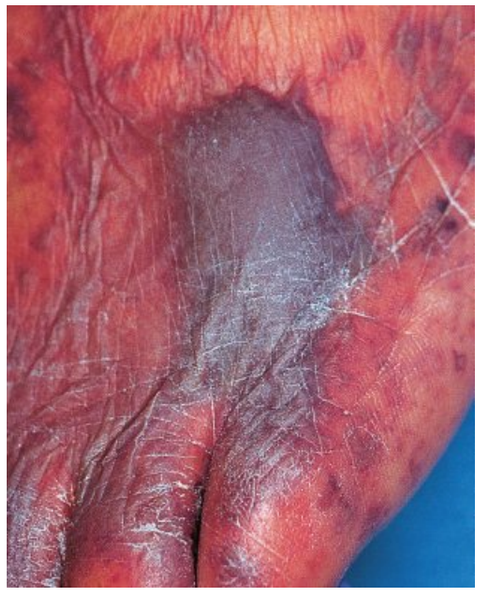
eFig. 33.1 Bullosis diabeticorum. A tense blister on the palm as well as desquamation at sites of previous bullae.



eFig. 33.2 Friction blisters. Tense blisters that developed on the shin of the author after continuous rubbing against a ski boot.



eFig. 33.3 Friction blisters. Erythema and a vesicle developed on the index finger after prolonged rubbing against a knife handle.



eFig. 33.4 Bullous variant of cutaneous small vessel vasculitis. The patient had chronic lower extremity edema. *Courtesy Jean L. Bolognia, MD.*



eFig. 33.5 Bullous variant of cutaneous small vessel vasculitis. Multiple vesicles within a purpuric plaque in a child with IgA vasculitis (Henoch–Schönlein purpura).



eFig. 33.6 Ofloxacin-induced linear IgA bullous dermatosis. This represents one form of bullous drug eruption. Although the initial clinical diagnosis was Stevens–Johnson syndrome or toxic epidermal necrolysis, the annular configuration and peripheral location of the bullae plus the histologic and DIF findings led to the diagnosis of linear IgA bullous dermatosis.



eFig. 33.7 Bullous insect bite reactions. This presentation can sometimes be misdiagnosed as localized bullous pemphigoid. *Courtesy Julie V. Schaffer, MD.*



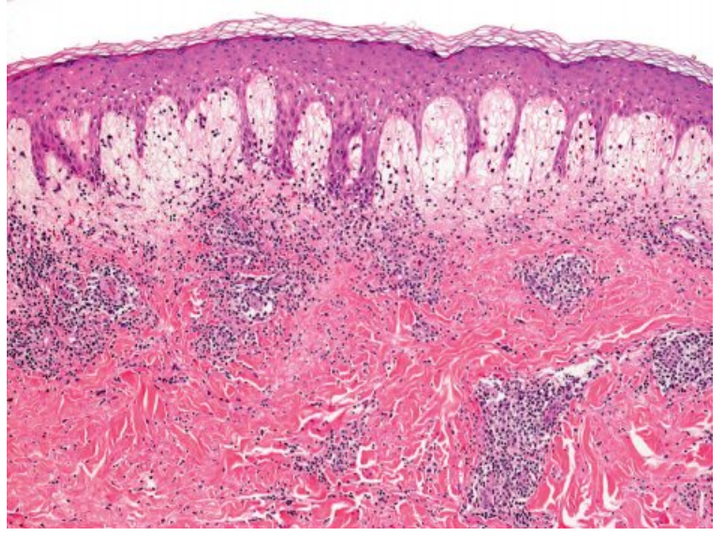
eFig. 33.8 Bullous insect bite reactions on the distal leg. Several tense bullae that may be misdiagnosed as localized bullous pemphigoid. *Courtesy Karynne O. Duncan, MD.*



eFig. 33.9 Bullous bedbug bite reactions. This patient presented with generalized papulovesicles, vesicles, and bullae and was initially misdiagnosed as bullous pemphigoid.



eFig. 33.10 Exaggerated insect bite-like reactions in a patient with chronic lymphocytic leukemia. There are multiple vesicles and hemorrhagic crusts on an inflammatory base.



eFig. 33.11 Bullous bug bite reaction – histopathologic features. In addition to intense papillary dermal edema, there is a prominent perivascular mononuclear cell infiltrate in the upper and mid dermis. Note the basket-weave pattern of the stratum corneum, suggesting an acute process. *Courtesy Lorenzo Cerroni, MD.*



eFig. 33.12 Edema bulla in the setting of an acute exacerbation of lower extremity edema. Given the size of the bulla and its sterility, the initial differential diagnosis would include bullosis diabeticorum. *Courtesy Dennis L. Cooper, MD.*



eFig. 33.13 Fracture blisters. Sterile bland bullae develop in areas of edema following bone fractures. *Courtesy Ian Odell, MD, PhD.*

34 Vesiculopustular and Erosive Disorders in Newborns and Infants

Nicole W. Kittler, Renee M. Howard and Ilona J. Frieden

A wide variety of conditions can cause vesicles, pustules, bullae, erosions, and ulcerations during the newborn period and infancy. Accurate and prompt diagnosis is important because some of the underlying disorders represent potentially life-threatening infections; conversely, many are benign and self-limited. Therefore, it is essential to develop a systematic approach to the evaluation and treatment of newborns and infants with these types of skin lesions. An algorithm outlining initial and subsequent investigations is presented in Fig. 34.1. This chapter highlights many causes of vesiculopustular and erosive eruptions during the first year of life, with more comprehensive lists provided in Tables 34.1 and 34.2. Most infectious etiologies are also covered in Chapters 74–82.

Key features

- Vesiculopustular eruption characterized by an eosinophilic infiltrate
- Affects nearly half of full-term neonates and resolves spontaneously over a few days
- Often involves the trunk as well as the face, proximal limbs, and buttocks
- Almost always spares the palms and soles
- Small wheals, inflammatory papules, pustules, and/or vesicles surrounded by blotchy erythema

COMMON CAUSES

Erythema Toxicum Neonatorum

Synonyms: ■ Erythema toxicum ■ Toxic erythema of the newborn

Erythema toxicum neonatorum (ETN) is a very common, benign condition. Originally described by Netlinger in 1472, it was known as "toxic erythema of the newborn" and was renamed erythema toxicum neonatorum by Leiner in 1912[1]. ETN occurs in approximately half of full-term neonates, possibly favoring those delivered vaginally, and is only rarely seen in premature infants or those weighing less than 2500 g[2,3].

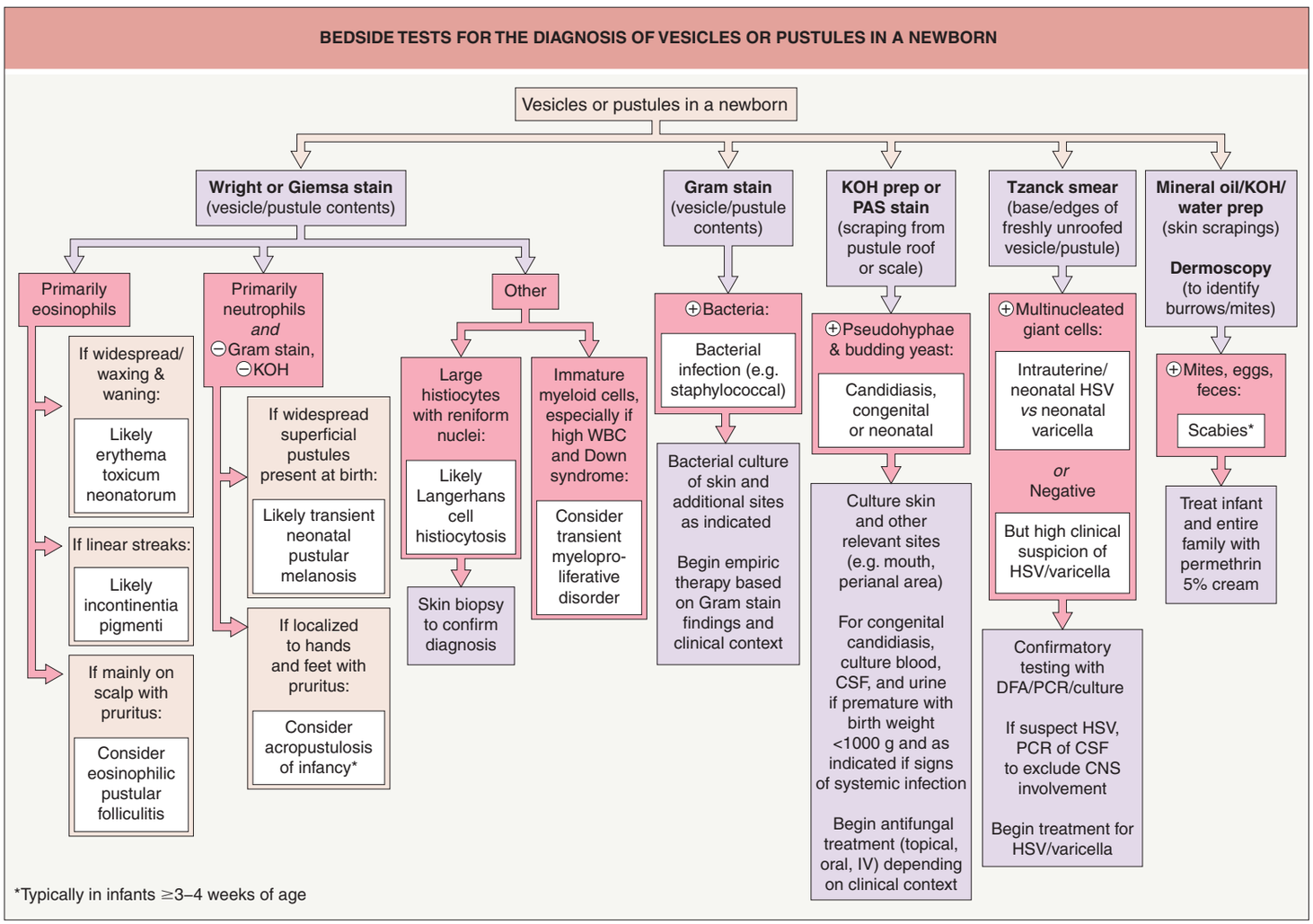


Fig. 34.1 Bedside tests for the diagnosis of vesicles or pustules in a newborn.

DIFFERENTIAL DIAGNOSIS OF VESICULOPUSTULAR DISEASES					
Disease	**Usual age of onset**	**Morphology**	**Distribution**	**Diagnostic studies (skin)**	**Comments**
Infectious diseases (more common conditions are in bold)					
Staphylococcal diseases: pyoderma and bullous impetigo (see Ch. 74) (Fig. 34.3A)	Few days to weeks or older	Pustules, bullae, occasionally vesicles; superficial erosions with collarettes of scale, crusts; furuncles	Favors diaper and periumbilical areas	Gram stain: Gram-positive cocci in clusters; bacterial culture	May occur in outbreaks
Group A streptococcal infection (see Ch. 74)	Few days to weeks or older	Isolated pustules, honey-colored crusts; moist, foul-smelling, fiery red intertriginous erythema	Any body region; may affect moist umbilical stump or skin folds	Gram stain: Gram-positive cocci in chains; rapid antigen test, bacterial culture	Occasionally cellulitis, meningitis, pneumonia
Group B streptococcal infection	Birth to first few days	Vesicles, bullae, erosions, pustules, honey-colored crusts	Any body region	Gram stain: Gram-positive cocci in chains; bacterial culture	Pneumonia, bacteremia, meningitis
Listeria monocytogenes infection (see Ch. 74)	Birth to first few hours	Hemorrhagic pustules and petechiae	Generalized, especially trunk and extremities	Gram stain: Gram-positive rods; bacterial culture	Sepsis, respiratory distress; history of maternal fever and premature labor
Haemophilus influenzae infection (see Ch. 74)	Birth to first few days	Vesicles, crusted papules	Any body region	Gram stain: Gram-negative bacilli, bacterial culture	Bacteremia, meningitis
Pseudomonas aeruginosa infection (see Ch. 74)	Days to weeks or older	Erythema, pustules, hemorrhagic bullae, necrotic ulcerations	Any region, especially anogenital area	Gram stain: Gram-negative rods; bacterial culture	Prematurity, low birth weight, immunodeficiency
Congenital candidiasis (Figs. 34.3B & 34.7)	Birth to first few days	Erythema, small papules and pustules, fine scaling; "burn-like" if extremely premature (see Table 34.2)	Any region; palms/soles often involved; nails may be affected	KOH: budding yeast; fungal culture; placental/umbilical cord lesions may be present	Prematurity, foreign body in cervix/uterus are risk factors; ascending *in utero* infection
Neonatal candidiasis	1–2 weeks of age	Beefy red patches with scale, satellite pustules and papules	Diaper area, other intertriginous zones, face	KOH: budding yeast, pseudohyphae; fungal culture	Usually otherwise healthy; acquisition during delivery or postnatally; oral thrush
Aspergillus infection (see Ch. 77)	Few days to weeks	Pustules (often clustered) rapidly evolve to necrotic ulcers	Any region, especially macerated skin in the diaper area and under adhesive tape/occlusive dressings	Skin biopsy: septate hyphae; tissue fungal culture	Extreme prematurity
Neonatal HSV infection (see Ch. 80) (Fig. 34.14)	Birth to 2 weeks, usually after 5 days	Vesicles, pustules, crusts, erosions	Any region, especially scalp, torso; may involve mucosa	Tzanck preparation, PCR, DFA or immunoperoxidase slide test, viral culture	Signs of sepsis, irritability, lethargy; must exclude herpes meningitis/encephalitis
Intrauterine HSV infection	Birth	Vesicles, pustules, widespread erosions, scars, areas of absent skin	Any body region	Tzanck preparation, PCR, DFA, or immunoperoxidase slide test, viral culture	Low birth weight, microcephaly, chorioretinitis; may mimic congenital erosive and vesicular dermatosis (see text)
Neonatal varicella (see Ch. 80)	Birth to 2 weeks	Vesicles on an erythematous base	Generalized distribution	Tzanck preparation, PCR, DFA, viral culture	Maternal primary varicella infection 7 days before to 2 days after delivery
Herpes zoster (see Ch. 80)	Typically 2 weeks or older	Vesicles on an erythematous base	Dermatomal pattern	Tzanck preparation, PCR, DFA, viral culture	Maternal primary varicella during pregnancy or up to a few days after delivery, or neonatal varicella
Scabies (see Ch. 84)	Typically 3–4 weeks or older	Papules, nodules, crusted areas, vesicles, pustules, burrows	Any region, including head and neck; especially axillae, groin, palms/soles, and wrists	Mineral oil preparation, dermoscopy	Family members may have pruritus and similar lesions

Table 34.1 Differential diagnosis of vesiculopustular diseases.

DIFFERENTIAL DIAGNOSIS OF VESICULOPUSTULAR DISEASES					
Disease	**Usual age of onset**	**Morphology**	**Distribution**	**Diagnostic studies (skin)**	**Comments**
Common transient conditions					
Erythema toxicum neonatorum (Fig. 34.2)	Typically 24–48 hours but can be birth to 2 weeks	Erythematous macules, papules, pustules > vesicles, wheals	Any region, except almost always spares palms/soles	Clinical; Wright's stain: eosinophils	Term infants >2500 g
Transient neonatal pustular melanosis (Fig. 34.4)	Birth	Pustules without erythema; collarettes of scale; hyperpigmented macules	Any region; most often forehead, neck, lower back, shins; may affect palms/soles	Clinical; Wright's stain: neutrophils, occasional eosinophils, cellular debris	Term infants; more common in infants of African descent
Miliaria crystallina (see Ch. 39) (Fig. 34.5A)	Birth to early infancy	Fragile vesicles without erythema	Forehead, upper trunk, arms most common	Clinical	Sometimes history of overheating or fever
Miliaria rubra (see Ch. 39) (Fig. 34.5B)	Typically ≥1 week	Erythematous papules with superimposed pustules	Forehead, neck, upper trunk; occluded areas most common	Clinical; Wright's stain: variable inflammatory cells but not prominent eosinophils	Sometimes history of overheating or fever
Neonatal cephalic pustulosis (neonatal "acne") (Fig. 34.6)	~5 days to 3 weeks	Papules and pustules on erythematous base	Cheeks, forehead, chin, eyelids; less commonly neck, upper chest, scalp	Clinical; Giemsa stain: yeast forms, neutrophils	Otherwise well
Uncommon and rare non-infectious diseases					
Acropustulosis of infancy (Fig. 34.10)	Typically 3–6 months, occasionally birth to weeks	Vesicles and pustules	Hands and feet; occasionally scalp, trunk	Clinical; assess for scabies infestation; skin biopsy: intraepidermal vesicle/pustule with neutrophils and occasionally eosinophils	Severe pruritus; lesions recur in crops; subset with prior scabies
Eosinophilic pustular folliculitis of infancy (Fig. 34.11)	Birth to 14 months, mean 6 months	Papules and pustules	Scalp > face > trunk, extremities	Skin biopsy: dense mixed infiltrate with eosinophils, often but not invariably centered on hair follicles	Pruritus; lesions recur in crops; often peripheral eosinophilia; *neonatal eosinophilic pustulosis* variant favors the face in premature boys
Congenital and neonatal Langerhans cell histiocytosis (see Ch. 91) (Fig. 34.12)	Birth to weeks	Vesicles, crusts, papules, nodules, petechiae	Any body region, especially flexural sites, palms/soles, scalp	Skin biopsy: $S100^{+}/CD1a^{+}$ histiocytes with reniform nuclei, focal invasion of epidermis	Occasional mucosal or extracutaneous involvement; pure cutaneous form often resolves spontaneously, but later cutaneous and systemic relapses possible
Incontinentia pigmenti (see Ch. 62) (Fig. 34.13)	Birth to weeks	Vesicles, hyperkeratotic papules along the lines of Blaschko	Vesicular lesions most common on the extremities	Skin biopsy: eosinophilic spongiosis with necrotic keratinocytes; genetic analysis (*IKBKG*/*NEMO*)	Ocular, CNS, and dental involvement common but often not evident at birth; X-linked dominant, patients usually female
Autosomal dominant hyper-IgE syndrome (see Ch. 60)	Birth to weeks	Single and grouped vesicles or papulopustules	Face, scalp, upper trunk, axillae, diaper area	Skin biopsy: intraepidermal vesicle with eosinophils, eosinophilic folliculitis; genetic analysis (*STAT3*)	Eosinophilia with variably elevated IgE levels, abscesses, pneumonias, and pneumatoceles often develop after neonatal period
Vesiculopustular eruption of transient myeloproliferative disorder in Down syndrome	Days to weeks	Vesicles and pustules	Face > trunk, extremities, sites of adhesive dressings, minor trauma	Intraepidermal spongiotic vesiculopustules, infiltrate containing immature myeloid cells	Trisomy 21 or mosaicism for trisomy 21, severe leukocytosis with immature myeloid cells, increased risk of myeloid leukemia
Erosive pustular dermatosis of the scalp	Weeks to months	Pustules, erythema with scale-crust, erosions; alopecia and scarring	"Halo scalp ring" pattern, vertex of scalp	Clinical, skin biopsy: alopecia, scarring, mixed dermal infiltrate	Prolonged labor and delivery, necrotic caput succedaneum at birth
Neonatal Behçet disease (see Ch. 26)	First week	Vesiculopustular, purpuric and necrotic skin lesions; oral and genital ulcers	Lesions favor hands and feet as well as oral and genital mucosae	Clinical	Maternal history of Behçet disease; diarrhea, vasculitis

Table 34.1 Differential diagnosis of vesiculopustular diseases.

Continued

DIFFERENTIAL DIAGNOSIS OF VESICULOPUSTULAR DISEASES					
Disease	**Usual age of onset**	**Morphology**	**Distribution**	**Diagnostic studies (skin)**	**Comments**
Pustular psoriasis, including deficiency of interleukin-36 receptor antagonist (DITRA; AR) and CARD14-mediated pustular psoriasis (CAMPS; AD) (see Chs. 8 & 45)	Weeks to months or older	Pustules and pustular lakes within areas of erythema	Often generalized with erythroderma; pustules in any body region, especially the palms/soles	Skin biopsy: spongiform pustules and micro-abscesses within the epidermis, parakeratosis, dilated dermal capillaries; genetic analysis (*IL36RN*, *CARD14*)	Occasional fever; often resistant to therapy, although DITRA often responds to IL-36 and IL-17 inhibitors
Deficiency of interleukin-1 receptor antagonist (DIRA; see Ch. 45)	Birth to weeks	Pustules within areas of erythema	Often generalized with erythroderma; oral lesions	Skin biopsy: neutrophilic microabscesses within acanthotic epidermis, parakeratosis, dilated dermal capillaries; genetic analysis (*IL1RN*)	Sterile osteolytic or hyperplastic bone lesions, neonatal distress, dramatic response to IL-1 antagonists
Perforating neutrophilic and granulomatous dermatitis associated with immunodeficiency	Birth to weeks	Papules evolve into vesicles, pustules, crusts, and ulcers	Varies: face, extremities, perineum	Skin biopsy: granulomas, neutrophilic infiltrate, transepidermal elimination of degenerated collagen and debris through hair follicles	Primary immunodeficiencies, including APLAID (autoinflammation and phospholipase C γ2-associated antibody deficiency and immune dysregulation)

Table 34.1 Differential diagnosis of vesiculopustular diseases. Additional etiologies include irritant contact dermatitis (see Table 34.2), dermatophyte infection, Sweet syndrome, and intrauterine coxsackievirus or Chikungunya virus infection. The vesicular eruption of lipoid proteinosis tends to develop after 1 year of age (see Ch. 48). AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; DFA, direct fluorescent antibody; HSV, herpes simplex virus; KOH, potassium hydroxide examination; MAPK, mitogen-activated protein kinase; PCR, polymerase chain reaction. *Adapted from Frieden IJ, Howard R. In: Eichenfield LF, Frieden IJ, Mathes EF, Zaenglein AL (eds). Neonatal and Infant Dermatology, 3rd edition. London: Elsevier, 2015:112–115.*

DIFFERENTIAL DIAGNOSIS OF BULLAE, EROSIONS AND ULCERATIONS					
Disease	**Usual age**	**Morphology**	**Distribution**	**Diagnostic studies (skin)**	**Comments**
Infectious diseases					
Staphylococcal scalded skin syndrome (see Ch. 74) (Fig. 34.17)	Few days to weeks; rarely congenital	Erythematous patches, fragile bullae, superficial erosions, peeling in sheets	Generalized with periorificial and intertriginous accentuation	Biopsy: epidermal separation at granular cell layer; culture positive only at primary site(s) of infection (toxin-mediated)	Irritability, temperature instability; high risk of secondary sepsis, fluid/electrolyte abnormalities
Group B streptococcal infection	(see Table 34.1)				
Pseudomonas aeruginosa infection	(see Table 34.1)				
Congenital syphilis (see Ch. 82)	Birth to first few days	Bullae or erosions; erythema and desquamation	Any region, especially perioral, palms/soles	Darkfield examination of serous exudates, DFA; serologic studies (treponemal and non-treponemal)	Snuffles, hepatosplenomegaly, periostitis with pseudoparalysis
"Invasive fungal dermatitis" due to candidiasis > other fungi (see text and below) in very-low-birth-weight premature newborns (Fig. 34.7)	Birth to 2 weeks	"Burn-like" erythema with desquamation and erosions; intertriginous maceration	Any region	KOH: budding yeast; fungal culture; placental/umbilical cord lesions may be present	Risk factors: birth weight <1000 g, vaginal delivery, systemic corticosteroid administration, prolonged hyperglycemia; high risk of disseminated systemic infection
Aspergillus infection	(see Table 34.1)				
Zygomycosis, trichosporonosis (see Ch. 77)	Days to weeks	Generalized peeling and skin breakdown; cellulitis evolving into necrotic ulcer	Any body region	Skin biopsy and tissue fungal culture	Extreme prematurity
Intrauterine HSV infection	(see Table 34.1)				
Congenital (fetal) varicella syndrome (see Ch. 80)	Birth	Erosions, ulcers, scarring, aplasia cutis congenita	Any region, especially extremities; may have dermatomal pattern	Variably positive Tzanck preparation, PCR, DFA, viral culture	Maternal varicella in the first or early second trimester; limb atrophy, CNS/eye abnormalities

Table 34.2 Differential diagnosis of bullae, erosions, and ulcerations.

DIFFERENTIAL DIAGNOSIS OF BULLAE, EROSIONS AND ULCERATIONS					
Disease	**Usual age**	**Morphology**	**Distribution**	**Diagnostic studies (skin)**	**Comments**
Conditions with exogenous causes					
Sucking blisters (Fig. 34.8)	Birth	Flaccid bulla or linear erosion, most often solitary	Radial forearm, wrist, hand, fingers, occasionally foot	Clinical	Due to sucking on affected areas *in utero*
Irritant contact dermatitis	First few days to weeks or older	Glazed erythema, vesiculation, punched-out erosions	Diaper area, especially on convex surfaces	Usually clinical	Severe form referred to as Jacquet erosive diaper dermatitis
Perinatal trauma/ iatrogenic injury	Birth or neonatal period	Erosions, ulcerations, scars, atrophic lesions	Depends on cause of trauma	Usually clinical	Perinatal history of fetal scalp electrode monitor, prolonged labor and/ or vacuum or forceps delivery, history of amniocentesis, etc.
Perinatal gangrene of the buttock	Days	Sudden-onset erythema and cyanosis, then gangrenous ulcers	Buttocks	Clinical	Umbilical artery catheterization in some cases
Associated with birthmarks and related conditions					
Erosions overlying large congenital melanocytic nevi (see Ch. 112)	Birth to first few days	Erosions, ulcerations	Superimposed on the congenital melanocytic nevus, most often on the back	Clinical, skin biopsy to exclude melanoma if persistent or other unusual features	Neurocutaneous melanosis present in subset of patients
Ulcerated infantile hemangioma (see Ch. 103)	Birth to first few weeks or months	Ulcer, often with a bright red or pale, vasoconstricted border	Any site, but diaper area and lip most common	Clinical	Cause often not clinically apparent until hemangioma begins to proliferate
Aplasia cutis congenita (see Ch. 64) (Fig. 34.9)	Birth	"Bullous" form: round/oval, sharply demarcated with overlying membrane; other types with raw, full-thickness ulcer; scar	Scalp (especially vertex) or face most common; other sites depending on etiology (e.g. shins in Bart syndrome)	Usually clinical; imaging studies to evaluate underlying bone, CNS	Possible associations: CNS defects, sagittal sinus thrombosis, trisomy 13, limb-reduction abnormalities
Linear porokeratosis, porokeratotic eccrine ostial and dermal duct nevus (PEODDN) (see Chs. 62, 109, & 111)	Birth or weeks to years later	Occasionally eroded at birth; usually erythema and keratotic border or (in PEODDN) spines	Often extremities, but any site possible	Skin biopsy: cornoid lamella (may not be evident in newborn period)	Risk of squamous cell carcinoma; mosaic *GJB2* mutations in PEODDN
Uncommon and rare non-infectious diseases					
Mastocytosis (see Ch. 118) (Fig. 34.18)	Birth to weeks or months	**Discrete lesions** ("maculopapular", mastocytoma): papules, plaques or nodules with intermittent superimposed wheals, bullae, erosions; often hyperpigmented **Diffuse**: blistering and erosions superimposed on infiltrated skin with *"peau d'orange"* appearance	Any body region	Positive Darier sign; skin biopsy: increased mast cells in dermis	Variably present: flushing, irritability, diarrhea, abdominal pain
Epidermolysis bullosa (see Ch. 32)	Birth to first few days or older	Mechanically induced blisters and erosions; depending on type: mucosal erosions, aplasia cutis congenita of anterior legs, scarring, milia, nail dystrophy	Widespread or limited, depending on type; most often extremities, especially hands/feet	Biopsy of induced blister for immunofluorescence antigen mapping ± electron microscopy; genetic analysis	Difficulty feeding, failure to thrive; occasionally ocular, respiratory tract or gastrointestinal (e.g. pyloric atresia) involvement; anemia
Kindler syndrome (see Ch. 32)	Birth to weeks or older	Trauma-induced blisters and erosions; progressive poikiloderma	Bullae most common in acral sites; poikiloderma is widespread with skip areas	Skin biopsy: immunostaining with anti-kindlin-1 antibody, genetic analysis (*FERMT1*)	Photosensitivity, gingivitis, colitis, mucosal stenoses (e.g. esophageal, urethral), acquired syndactyly (toes, proximal fingers); AR inheritance
Epidermolytic ichthyosis (see Ch. 57) (Fig. 34.16)	Birth	Erythroderma with blisters and erosions	Generalized	Skin biopsy: epidermolytic hyperkeratosis; genetic analysis (*KRT1*, *KRT10*)	Risk of sepsis, fluid and electrolyte imbalances; AD inheritance

Table 34.2 Differential diagnosis of bullae, erosions, and ulcerations.

Continued

DIFFERENTIAL DIAGNOSIS OF BULLAE, EROSIONS AND ULCERATIONS					
Disease	**Usual age**	**Morphology**	**Distribution**	**Diagnostic studies (skin)**	**Comments**
Maternal autoimmune bullous disease	Birth	Depends on type of maternal disease: tense or flaccid bullae, erosions	Variable, often widespread	Skin biopsy with DIF usually diagnostic	Maternal history of blistering disease, but occasionally inactive during pregnancy
Bullous pemphigoid (see Ch. 30)	Usually ≥2 months of age	Tense bullae	Favor hands and feet but may be generalized	Skin biopsy: subepidermal bullae with eosinophils; DIF: linear pattern IgG at DEJ	
Linear IgA bullous dermatosis (see Ch. 31)	Rarely at birth, usually later infancy or childhood	Tense blisters often form rosette or sausage shapes	Widespread but often concentrated in the girdle area; usually spares mucosa	Skin biopsy: subepidermal bullae with neutrophils, DIF: linear pattern IgA at DEJ	
Neonatal lupus (see Ch. 41)	Birth (~20%) to weeks or months	Congenital erosions/ulcers, crusting, rarely bullae as well as classic annular erythematous plaques; atrophy, scarring, background of livedo reticularis	Face favored, especially the periorbital area, but can be more widespread	Skin biopsy: epidermal atrophy, vacuolar interface dermatitis, variable mucin	Mother and infant with antibodies to SSA/Ro, SSB/La, and/or U1RNP; variable heart block, cardiomyopathy, hepatobiliary disease, cytopenias
Toxic epidermal necrolysis (TEN; see Ch. 20) or TEN-like GVHD (see Chs. 52 & 60)	Usually ≥6 weeks of age, except for intrauterine GVHD	Tender erythema, bullae, epidermal sloughing/erosions	Often widespread, evolving rapidly over hours to days; mucosal involvement	Skin biopsy: subepidermal blister with epidermal necrosis (usually full thickness)	Typically in setting of Gram-negative sepsis or due to maternofetal or transfusion-associated GVHD in infants with severe combined immunodeficiency
Intrauterine epidermal necrosis	Birth	Widespread erosions and ulcerations without vesicles or pustules	Generalized, spares mucous membranes	Skin biopsy: epidermal necrosis and calcification of pilosebaceous units	Prematurity, brain infarcts, cardiomegaly, renal tubular necrosis; rapid mortality
Congenital erosive and vesicular dermatosis (Fig. 34.15)	Birth	Erosions, vesicles, crusts, "scalded skin"	Generalized with relative sparing of face, palms/soles	Clinical diagnosis, often retrospective; skin biopsy (nonspecific): epidermal necrosis, neutrophils or mixed infiltrate; exclude HSV via PCR	Prematurity; heals with supple reticulated scarring; CNS/developmental abnormalities
Pyoderma gangrenosum (see Ch. 26)	Rare reports of congenital or neonatal onset	Sharply demarcated ulcerations with undermined borders	Any site, especially groin and buttocks	Clinical; exclusion of other etiologies; skin biopsy: infiltration of neutrophils without primary vasculitis or infection	Associations include inflammatory bowel disease, chronic recurrent multifocal osteomyelitis; consider immunodeficiency and autoinflammatory syndromes
Acrodermatitis enteropathica* (see Ch. 51)	Weeks to months	Sharply demarcated, eroded erythematous plaques with scale-crust; occasionally intact vesicles/bullae	Periorificial (i.e. around mouth, nose, eyes, anus, genitalia), neck folds, hands/feet	Low serum zinc and alkaline phosphatase levels	Irritability, diarrhea, failure to thrive; onset classically after weaning if breastfed; acquired zinc deficiency: low maternal breast milk zinc or prematurity; genetic form with AR inheritance (*SLC39A4*)
Methylmalonic acidemia, other organic acidemias/aminoacidopathies* (see Fig. 51.13)	Days to weeks	Erythema with or without erosions	Periorificial or more widespread	Urine organic acid analysis; plasma isoleucine level (if restricted diet); often included in newborn screening; genetic analysis	Lethargy, hypotonia, neutropenia, metabolic acidosis; skin findings may result from therapeutic restrictions of dietary amino acids
Restrictive dermopathy	Birth	Rigid tense skin with linear erosions, tears	Generalized; skin tears most common in flexural creases	Clinical; distinguish from Neu–Laxova syndrome (intrauterine growth retardation, microcephaly, abnormal brain development, edema, parchment-like or ichthyosiform skin), genetic analysis (*ZMPSTE24* > *LMNA*)	Joint contractures, micrognathia, fixed facial expression, restrictive pulmonary disease, early mortality

Table 34.2 Differential diagnosis of bullae, erosions, and ulcerations.

DIFFERENTIAL DIAGNOSIS OF BULLAE, EROSIONS AND ULCERATIONS					
Disease	**Usual age**	**Morphology**	**Distribution**	**Diagnostic studies (skin)**	**Comments**
Focal dermal hypoplasia (see Ch. 62)	Birth	Occasional blisters, but more often hypoplasia or aplasia of skin in linear and whorled pattern; also fat "herniation", telangiectasias	Any body region	Clinical; skin biopsy: dermal hypoplasia with fat abutting epidermis; genetic analysis (*PORCN*)	Skeletal, eye, and CNS abnormalities to varying degrees
Absent dermal ridges and congenital milia (Basan syndrome; see Ch. 64)	Birth	Bullae, absent dermal ridge patterns, multiple milia	Fingers, plantar surface of feet	Clinical; genetic analysis (*SMARCAD1*)	AD inheritance
Porphyrias (see Ch. 49)	Days to months	Photosensitive erythema, blistering, erosions, scarring	Sun-exposed areas or more generalized if phototherapy for hyperbilirubinemia	Transient form: elevated plasma porphyrins; heritable forms: elevated urine, fecal, and/or plasma porphyrins ± pink/fluorescent urine	Transient form usually related to hemolytic disease; heritable forms rarely present with blistering in infancy, e.g. congenital erythropoietic porphyria
Neonatal purpura fulminans	Days	Initially purpura or cellulitis-like areas evolving to necrotic bullae or ulcers	Buttocks, extremities, trunk, and scalp	Prolonged PT/PTT, low fibrinogen, elevated FDPs, low protein C or S levels	Related to sepsis or inherited protein C or S deficiency
Ankyloblepharon–ectodermal dysplasia–clefting (AEC) syndrome (see Ch. 63)	Birth	Erythroderma, peeling skin, superficial erosions	Generalized, with prominent scalp involvement	Clinical; genetic analysis (*TP63*)	Ankyloblepharon, ectodermal dysplasia, cleft lip/palate
*An acrodermatitis enteropathica-like eruption (periorificial or more widespread), often associated with edema and hypoalbuminemia, can occur in infants (typically 3–5 months of age) with cystic fibrosis as well as in those with organic acidemias/aminoacidopathies (see Ch. 51).					

Table 34.2 Differential diagnosis of bullae, erosions, and ulcerations. AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; CSF, cerebrospinal fluid; DEJ, dermal–epidermal junction; DFA, direct fluorescent antibody; DIF, direct immunofluorescence; FDP, fibrin degradation product; GVHD, graft-versus-host disease; PT, prothrombin time; PTT, partial thromboplastin time. Adapted from Frieden IJ, Howard R. In: Eichenfield LF, Frieden IJ, Mathes EF, Zaenglein AL (eds). Neonatal and Infant Dermatology, 3rd edition. London: Elsevier, 2015:112–115.

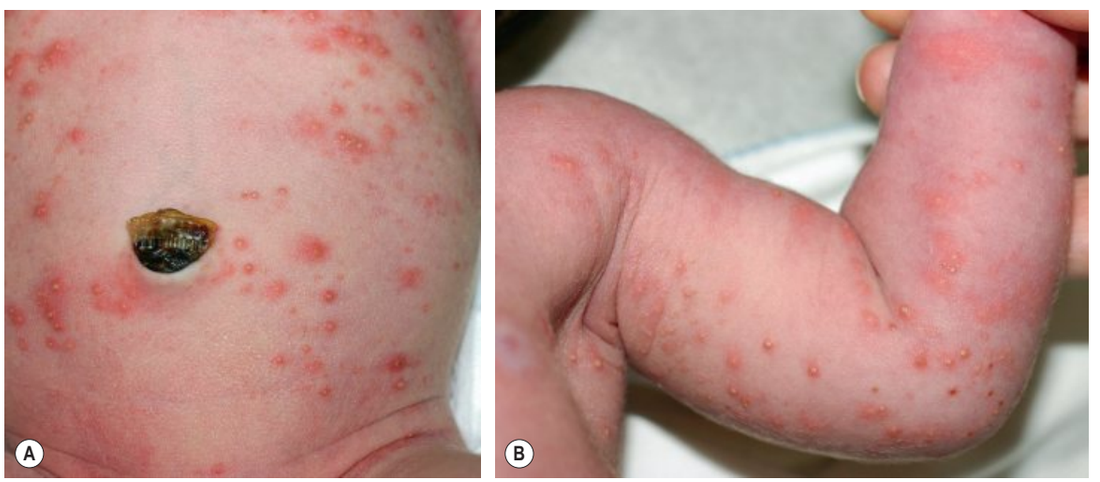


Fig. 34.2 Erythema toxicum neonatorum. Scattered papulovesicles and pustules with an erythematous flare on the abdomen (**A**) and upper extremity (**B**).

It is most commonly observed in infants with Fitzpatrick types I-II skin, although this may be related to the difficulty in perceiving erythema in infants with darker skin, and may be more prevalent in males[3,4].

Rarely presenting at birth, ETN usually begins 24 to 48 hours after delivery, followed by a waxing and waning course over the next few days. Although the onset may be as late as 1–2 weeks of age, additional diagnoses need to be considered in these cases. Five distinct components may be present in various combinations: erythematous macules, wheals, and small papules, vesicles and pustules, usually measuring 1–2 mm. The characteristic central papule with a surrounding erythematous flare is reminiscent of a flea bite (Fig. 34.2). Mechanical irritation may precipitate new lesions.

ETN most frequently affects the trunk but can also involve the face, buttocks, and proximal extremities; it almost always spares the palms and soles[2,3]. Individual lesions rarely persist for more than a day. The condition is asymptomatic and self-limited, requiring no therapy.

The diagnosis of ETN is usually made on clinical grounds. When necessary, the demonstration of numerous eosinophils via Wright stain of pustular contents can help to confirm the diagnosis. Peripheral eosinophilia is occasionally present. Histologically, pustules are intrafollicular, subcorneal, or intraepidermal and are composed of eosinophils and occasional neutrophils[5]. An eosinophilic infiltrate may also be present in the upper dermis. The pathogenesis of ETN is unknown, although an inflammatory response to microbial colonization of the follicle in the first days of life has been postulated[6].

The differential diagnosis includes other pustular disorders of the newborn, some of which may have important medical sequelae (see Table 34.1). Transient neonatal pustular melanosis (TNPM) is primarily neutrophilic, present at birth, usually affects infants with darkly pigmented skin, and resolves as pigmented macules that last weeks to months. However, overlap between ETN and TNPM has been observed (see below). Acropustulosis of infancy is an acral, rather than truncal, eruption that usually appears after the neonatal period. Eosinophilic pustular folliculitis of infancy favors the scalp and features lesions that often become crusted and recur in crops over a period of

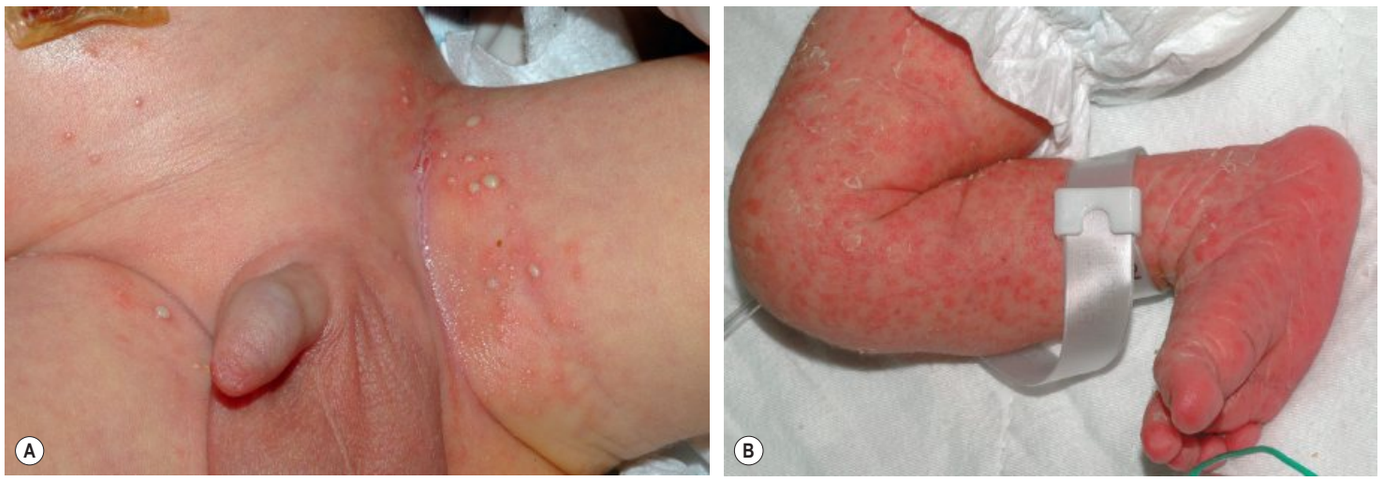


Fig. 34.3 Staphylococcal infection versus congenital candidiasis. A Multiple discrete superficial pustules with surrounding erythema in the diaper area of a 4-day-old boy due to infection with *Staphylococcus aureus*. **B** Numerous pink papules admixed with small superficial pustules and desquamation due to congenital candidiasis. Note the plantar involvement. *A, B, Courtesy Julie V. Schaffer, MD.*

months to years. Herpes simplex viral (HSV) infection presents with discrete vesicular lesions with progression to hemorrhagic crusting. *Staphylococcus aureus* infections manifest as more well-developed superficial pustules (Fig. 34.3A) or bullae that rapidly rupture, resulting in an erythematous base with a surrounding collarette. Congenital candidiasis presents with multiple tiny pustules and desquamation, with skin scrapings showing budding yeast and pseudohyphae on potassium hydroxide (KOH) examination (Fig. 34.3B). Both staphylococcal and candidal infections result in more persistent lesions that do not undergo the rapid spontaneous resolution characteristic of ETN. Miliaria rubra (prickly heat) is usually concentrated on the forehead and upper torso, with somewhat longer-lived lesions that lack a prominent erythematous flare or eosinophilic infiltrate[7].

Transient Neonatal Pustular Melanosis

Synonyms: ■ Transient neonatal pustulosis ■ Lentigines neonatorum

Key features

- Develops in ~5% of newborns with darkly pigmented skin
- Prominent superficial pustules without erythema that rupture, leaving a collarette of scale and hyperpigmentation that may last several months
- Sterile subcorneal neutrophilic infiltrate
- Favors the forehead, chin, neck, back, and shins but may be widespread

Originally described in 1961 as "lentigines neonatorum"[8], the full spectrum of TNPM was not recognized until 15 years later[9]. It occurs most commonly in infants with darker skin phototypes. There is no sexual predilection[4]. Lesions are virtually always present at birth and have three different morphologies that can coexist or occur sequentially. At delivery, superficial, 2–10 mm vesiculopustules (Fig. 34.4A) are present at sites such as the chin, forehead, nape of the neck, lower back, buttocks, and shins, and, less often, the remainder of the face, trunk, palms, and soles. These lesions may go undetected, as the fragile intra- and subcorneal pustules can be subtle or wiped away during the first bath. The second phase features slightly hyperpigmented macules with fine collarettes of scale at sites of ruptured and resolving pustules (Fig. 34.4B). Finally, residual brown macules may persist for several months. The name "lentigines" is a misnomer, as these lesions result from postinflammatory hyperpigmentation. Sometimes only the brown macules are noted at birth, suggesting that a previous pustular phase occurred *in utero*. Less commonly, infants with TNPM may present at a few weeks of age with extensive pigmented macules but no history of preceding pustules.

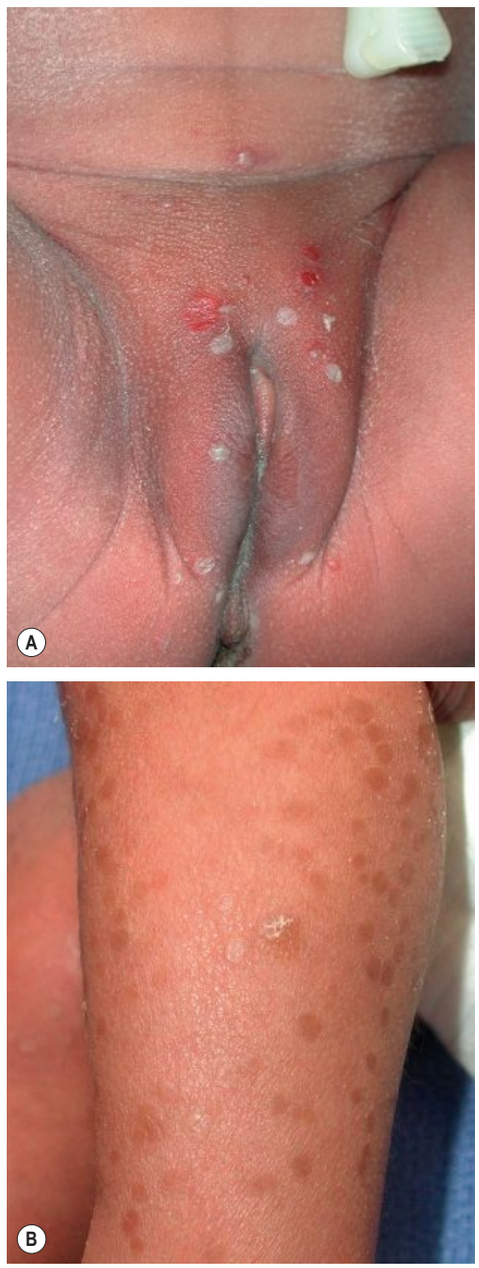


Fig. 34.4 Transient neonatal pustular melanosis in a Black neonate. A One hour after birth, flaccid vesiculopustules and superficial erosions with minimal surrounding erythema are present in the groin. **B** On the 8th day of life, hyperpigmented macules and a few collarettes of scale are evident on the lower leg.

Histologic examination is rarely necessary to make the diagnosis, but when performed on early lesions, it demonstrates intra- or subcorneal pustules containing primarily neutrophils and occasionally some eosinophils[5]. Pigmented macules show increased melanin within basal keratinocytes. The pathogenesis is unknown, and the differential diagnosis is similar to that discussed above for ETN. No treatment is necessary, and parents should be reassured of the benign and self-limited nature of the condition.

Sterile Transient Neonatal Pustulosis

It has been postulated that TNPM is simply a variant of ETN, based on their overlapping clinical and histologic features as well as reports of the two conditions coexisting in the same patient. The term *sterile transient neonatal pustulosis* has been proposed to encompass the ETN–TNPM spectrum[10]. However, most authors consider TNPM and ETN to represent separate entities.

Miliaria

Synonyms: ■ Heat rash ■ Miliaria crystallina – "dew drops" ■ Miliaria rubra – prickly heat

Key features

- Three variants: miliaria crystallina, miliaria rubra, and miliaria profunda (rare)
- Due to obstruction of eccrine sweat ducts, often in association with overheating, over-swaddling, or a fever
- Sites of predilection include the forehead, neck, upper trunk, and occluded areas
- Spontaneous resolution with cooling
- Prevention consists of avoidance of overheating and limiting excessive swaddling

Miliaria is a common condition that affects up to 15% of newborns, and it is seen more frequently in warm climates. Two types of miliaria (see Ch. 39) are typically observed in the newborn period. *Miliaria crystallina*, which is sometimes present at birth, is due to obstruction of the eccrine sweat duct as it courses through the stratum corneum. Sweat collects beneath the stratum corneum, causing clear, small, flaccid vesicles that are often likened to "dew drops" (Fig. 34.5A). *Miliaria rubra*, usually seen after the first week of life, is also caused by a blockage of the sweat ducts, but deeper within the spinous layer. The obstructed flow leads to leakage of fluid into the lower epidermis and upper dermis, resulting in an inflammatory response that produces small erythematous papules, papulovesicles, and pustules (Fig. 34.5B). *Miliaria profunda*, a variant caused by even deeper obstruction of the eccrine duct, is very rare in infants.

Both miliaria crystallina and miliaria rubra may be seen in relation to excessive warming inside an incubator, over-swaddling, fever, occlusive dressings, or a lack of air conditioning in warm climates. Lesions occur most commonly on the forehead, neck, and upper trunk as well as in areas of skin that have been occluded.

Miliaria crystallina features an intracorneal or subcorneal vesicle centered on the acrosyringium with relatively little inflammation. In miliaria rubra, intraepidermal spongiosis and vesicles are seen along with a chronic inflammatory infiltrate in the dermis[5] . An extracellular polysaccharide produced by *Staphylococcus epidermidis* present within the sweat duct may play a role[11], but this does not explain all cases, particularly congenital forms.

Miliaria resolves without treatment. Prevention is accomplished by avoidance of overheating and excessive swaddling when feasible.

Neonatal Cephalic Pustulosis

Synonym: ■ Neonatal acne





Fig. 34.5 Miliaria. A The tiny, superficial vesicles on the back and neck of this newborn are characteristic of miliaria crystallina. **B** Widespread miliaria rubra with numerous small papules and pustules. *A, From Eichenfield LF, Frieden IJ, Esterly NB, et al. (eds). Textbook of Neonatal Dermatology. © 2001 Saunders; B, Courtesy Antonio Torrelo, MD.*

Key features

- Onset usually within the first 2–3 weeks of life
- Inflammatory non-comedonal pustular eruption, most commonly observed on the cheeks, and less often on the forehead, chin, scalp, and chest
- *Malassezia* spp. have been implicated in its pathogenesis
- Spontaneous involution over weeks to months

Historically referred to as "neonatal acne", neonatal cephalic pustulosis lacks the comedones and more prolonged course that characterize infantile acne vulgaris (Table 34.3; see Ch. 36). Neonatal cephalic pustulosis develops within the first 2–3 weeks of life and resolves spontaneously by 3 months of age. Discrete papulopustules overlying variable background erythema are most commonly seen on the cheeks but may also develop on the forehead (Fig. 34.6), chin, eyelids, neck, upper chest, and scalp.

The results of some studies have suggested that an inflammatory response to *Malassezia (Pityrosporum)* spp. such as *M. furfur, M. sympodialis*, and *M. globosa* may be involved in the pathogenesis of neonatal cephalic pustulosis[12,13]. However, other studies have found no correlation between colonization of neonatal skin with *Malassezia* spp. and the presence or severity of neonatal cephalic pustulosis[14]. While these yeasts have been cultured from lesional skin in affected patients, they are part of the cutaneous microbiota in humans, and thus their exact role in the condition remains uncertain.

NEONATAL CEPHALIC PUSTULOSIS VERSUS INFANTILE ACNE		
	Neonatal cephalic pustulosis	**Infantile acne (see Ch. 36)**
Epidemiology	Common: >20%–50% of term infants Male : female = 1 : 1	Uncommon Males > females
Proposed pathogenic factors	Inflammatory reaction to *Malassezia* spp.	Androgen production
Typical age of onset	~5 days to 3 weeks	~6 weeks to 1 year
Typical duration	Weeks to 3 months	6 to 18 months
Morphology of lesions	Papules and pustules on an erythematous base	Open and closed comedones, papules, pustules, occasionally nodules
Distribution	Cheeks, forehead, eyelids, chin > neck, scalp, upper trunk	Primarily cheeks
Scarring	None	Occasionally
Treatment	Not usually necessary	More often necessary
	Topical imidazole or hydrocortisone	Topical retinoids, benzoyl peroxide, antibiotics; occasionally oral antibiotics or retinoids
Associated disease	Occasionally seborrheic dermatitis	Rarely an endocrine disorder, but need to consider when severe or other signs/symptoms (e.g. virilization, abnormal growth) Increased likelihood of severe adolescent acne

Table 34.3 Neonatal cephalic pustulosis versus infantile acne.



Fig. 34.6 Neonatal cephalic pustulosis. Papulopustules on the forehead and cheeks of a 3-week-old infant. *Courtesy Julie V. Schaffer, MD.*

A Giemsa-stained smear of pustular contents may demonstrate yeast forms, neutrophils, and other inflammatory cells; culture of *Malassezia* spp. requires specialized media[12]. The eruption can be treated with a topical imidazole or hydrocortisone, but this is not usually necessary[7].

Cutaneous Candidiasis

Key features

- *Neonatal* candidiasis is a common mucocutaneous infection acquired during delivery or postnatally, whereas *congenital* candidiasis is a relatively uncommon infection acquired *in utero*
- *Neonatal candidiasis* presents after the first week of life and is characterized by pink–red patches with satellite papules and pustules that favor the diaper area, other intertriginous sites, and face; oral thrush is often present
- When *congenital candidiasis* occurs in term neonates, it is characterized by a widespread vesiculopustular eruption, often involving the palms and soles
- In very-low-birth-weight premature newborns, cutaneous candidiasis may present as "burn-like" erythema with desquamation and erosions
- First-line therapy consists of topical anti-yeast medications (e.g. imidazoles), unless there is concern for systemic infection

Neonatal candidiasis is common and acquired during delivery or postnatally, whereas *congenital* candidiasis is uncommon and acquired *in utero*. In addition, premature newborns with a very low birth weight (often <1000 g) who develop cutaneous candidiasis prenatally or during the first two weeks of life can develop an "*invasive fungal dermatitis*" with a high risk of systemic involvement.

Neonatal candidiasis presents after the first week of life and involves primarily the diaper area and oral mucosa[7]. In some patients, other intertriginous areas and the face may be affected. Pink–red patches with satellite papules and pustules are the characteristic findings; pustules and scaling may also be present at the peripheral border.

In contrast, the relatively uncommon *congenital* candidiasis presents with a more widespread eruption, usually evident at birth but sometimes appearing as late as the 6th day of life. Congenital candidiasis is typically due to an ascent of yeast from the vagina into the uterine cavity. Risk factors include a foreign body in the uterus or cervix (e.g. retained intrauterine device, cervical cerclage), premature delivery, and a maternal history of vaginal candidiasis[15]. Skin lesions occur on the face, trunk, and extremities; the palms and soles are often involved, but the diaper area and oral mucosa are usually spared. Cutaneous findings vary and can include erythematous papules, vesiculopustules, diffuse erythema, and fine scaling[15,16]. Typically, erythematous papules appear first, followed by pustules and desquamation (see Fig. 34.3B). Nail dystrophy with yellowing and transverse ridging may be present and is occasionally the only manifestation[17].

"*Invasive fungal dermatitis*" in very-low-birth-weight newborns often presents as widespread "burn-like" erythema with desquamation and erosions (Fig. 34.7). Maceration in intertriginous areas may also be present. Additional risk factors include vaginal delivery (especially with instrumentation), invasive procedures, systemic corticosteroid administration, parenteral nutrition, and prolonged hyperglycemia. Although *Candida albicans* is the most frequent pathogen, infections with other *Candida* spp. and rarely *Trichosporon* or *Aspergillus* spp. can produce similar clinical findings.

In neonates, the differential diagnosis includes other infections (e.g. staphylococcal, streptococcal, listerial, HSV) as well as miliaria, ETN, and TNPM (see Table 34.1). Budding yeast and pseudohyphae in a KOH preparation that includes scale and/or the pustule and its roof points to the diagnosis, which can then be confirmed by culture. Cultures of blood, urine, and CSF (avoiding lumbar puncture if the skin overlying the spine is affected) should be performed in very-low-birth-weight premature infants with *congenital candidiasis* as well as in other neonates if there are signs of systemic infection (see below). When available, the placenta and/or umbilical cord should also be cultured and examined for characteristic yellow–white, bead-like papules.

For *neonatal candidiasis*, a topical anti-yeast medication (e.g. imidazole cream) is usually sufficient. Even if involvement is localized, premature neonates with very low birth weights (<1000 g) should be



Fig. 34.7 Congenital candidiasis in a neonate born at 24 weeks' gestation. This presentation is also referred to as "invasive fungal dermatitis" and has a high risk of systemic involvement. Note the "burn-like" appearance with erosions and desquamation. *Courtesy Julie V. Schaffer, MD.*

closely observed, with cultures of blood, urine, and CSF as indicated; treatment with parenteral antifungals should be considered if there are signs of worsening or systemic infection[7].

Treatment of *congenital candidiasis* is dependent on the gestational age and weight of the infant as well as the clinical presentation. Premature infants (<27 weeks' gestational age and <1000 g) are at high risk (~66%) for the development of disseminated systemic candidiasis and therefore should be treated with parenteral antifungal agents after appropriate cultures have been obtained (see above)[15,18]. Prompt initiation of a >14-day course of amphotericin B in such patients reduces the risk of disseminated infection and increases survival[18]. Infants of a more advanced gestational age with no evidence of systemic infection can be treated with topical therapy as discussed for *neonatal* candidiasis. However, regardless of gestational age, systemic antifungal therapy should be considered for infants with *congenital* candidiasis who have a "burn-like" presentation, respiratory distress, an elevated white blood cell count with a left shift, or other signs of systemic infection[15]. Oral fluconazole is an option for otherwise healthy full-term infants without evidence of disseminated candidiasis, while parenteral amphotericin B is indicated for those with high risk or signs of disseminated disease[18].

Sucking Blisters

Key features

- Caused by vigorous sucking of the affected region *in utero*
- Common locations include the radial forearm, wrist, hands, and fingers
- May present with an intact bulla, erosion, callus, or superficial ulceration on a non-inflamed base
- Usually an isolated finding without associated abnormalities
- Resolves over days to weeks and therapy is supportive

Sucking blisters are found in 1 of every 250 newborns, although they may be small and go unnoticed. They are an isolated finding caused by sucking *in utero* and are usually seen on the radial forearm, wrist, hand, or fingers (Fig. 34.8A). The flaccid bullae occur on a non-inflamed base and rupture easily, leading to linear or round erosions. Lesions are usually 5–15 mm in diameter and may be unilateral or bilateral.

The diagnosis of sucking blisters is usually straightforward and suggested by a non-inflammatory and, in most cases, solitary lesion in a typical location in a healthy infant. The lesions resolve in days to weeks without treatment.





Fig. 34.8 Physiologic skin findings in neonates. A Sucking blister on the dorsal hand. **B** Post-term desquamation is often most evident acrally. *A, Courtesy Ana Martín, MD; B, Courtesy Julie V. Schaffer, MD.*

Exogenous Causes of Erosions

Key features

- There are multiple exogenous causes for erosions, including friction from diapers and iatrogenic injury from monitors, adhesives, and procedures
- A typical location and known exposure to exogenous materials/procedures assist in diagnosis

Neonatal skin is more susceptible to erosions and ulcerations than is the skin of older infants or adults. Fragility is even more marked in preterm newborns. In full-term neonates, superficial erosions in the diaper area frequently occur within the first 2 weeks of life but then become less common. These erosions are primarily due to friction and irritation from the diaper, urine, and feces in the setting of transient neonatal skin fragility.

In neonates, iatrogenic causes of skin injury are numerous. A fetal scalp electrode monitor placed during delivery is a relatively common cause of superficial scalp erosions, but occasionally deeper lacerations or ulcers occur. Differentiation from aplasia cutis congenita (Fig. 34.9) is usually straightforward, but may be more difficult in severe cases. Pulse oximetry probes may lead to small blisters or erosions related to thermal burns or sustained pressure, especially if left in one place for more than 24 hours. Removal of adhesive materials such as tape over dressings and electrode leads can also cause erosions in fragile neonatal skin. These injuries may eventuate in anetoderma. Use of chlorhexidine-impregnated catheter-site dressings can result in irritant contact dermatitis, which may present with geometric erosions[19]. Puncture wounds from "heel sticks", a common method of phlebotomy utilized in the newborn nursery, are a potential cause of acral erosions; the medial or lateral (versus midline) location and procedural history are clues to the diagnosis[7]. Occasionally, heel-stick sites eventually develop calcinosis cutis (see Fig. 50.3).



Fig. 34.9 Aplasia cutis congenita (ACC) of the forearm. ACC in this location can be associated with underlying neurologic impairment, referred to as congenital Volkmann ischemic contracture, or bone abnormalities. The angulated borders help to distinguish it from intrauterine HSV or VZV infection. *Courtesy Julie V. Schaffer, MD.*



Fig. 34.10 Acropustulosis of infancy. Multiple vesiculopustules with an erythematous base on the medial ankle of an infant. *Courtesy Julie V. Schaffer, MD.*

UNCOMMON AND RARE CAUSES

Acropustulosis of Infancy

Synonym: ■ Infantile acropustulosis

Key features

- Onset usually between 3 and 6 months of age in the classic form
- A postscabetic variant also occurs
- Pruritic acral vesiculopustular eruption
- Recurs in crops, typically every 3–4 weeks, with decreased frequency and severity over time; the classic form usually resolves completely by ~3 years of age
- Symptomatic therapy with potent topical corticosteroids and oral antihistamines

Classic acropustulosis of infancy (AI) is an uncommon skin condition of unknown etiology that usually develops around 3–6 months of age but occasionally begins earlier. It affects all races but is more common in Black infants and boys. An association with atopy has also been observed[7]. More commonly, the same clinical findings occur in infants and children following scabies infestation. This is particularly frequent in international adoptees and has been referred to as "postscabetic acropustulosis" or, especially in younger patients, AI[20].

AI is characterized by outbreaks of pruritic vesicles and pustules in acral sites, in particular the palms, soles, dorsal aspects of the hands and feet, lateral fingers and toes, and, less often, wrists and ankles (Fig. 34.10). Occasionally, lesions are also found on the scalp, trunk, or proximal extremities. Vesiculopustules typically appear in crops that last 7–14 days and recur every 3–5 weeks. In both classic AI and the postscabetic variant, the flares decrease in frequency and severity over time. Spontaneous involution of classic AI usually occurs by 3 years of age.

A smear of pustular contents reveals numerous neutrophils, occasional eosinophils, and no bacteria or fungal elements. Histologic examination of lesional skin, while generally unnecessary, can help to confirm the diagnosis of AI. Histologic features include subcorneal pustules filled primarily with neutrophils; some mononuclear cells and eosinophils may be present[5].

The major challenge in the diagnosis of AI is distinguishing it from active scabies (see Ch. 84). Linear burrows are pathognomonic of active scabies; genital or more widespread lesions and pruritic eruptions in family members are also suggestive findings. Mineral oil examination of skin scrapings for mites, eggs, and scybala should be performed in all infants or toddlers with acral vesicles and pustules. Dermoscopy can also be used for *in vivo* visualization of mites and to increase the efficiency of skin scrapings. In uncertain cases, empiric treatment for scabies may be warranted. Other conditions with clinical overlap include dyshidrotic eczema and pustulosis palmaris et plantaris – both of which are rare in infancy. Congenital candidiasis is usually not limited to acral skin, and transient neonatal pustular melanosis is not pruritic, does not favor acral locations, and does not recur.

Symptoms can usually be controlled with intermittent application of potent or superpotent topical corticosteroids and administration of oral antihistamines[21].

Eosinophilic Pustular Folliculitis of Infancy

Synonyms: ■ Neonatal eosinophilic pustular folliculitis ■ Infantile eosinophilic pustular folliculitis ■ Eosinophilic pustular folliculitis in infancy ■ Eosinophilic pustulosis of infancy ■ Neonatal eosinophilic pustulosis

Key features

- Recurrent pruritic crops of follicular vesiculopustules
- Favors the scalp and face; occasionally involves the trunk and extremities
- Therapy is symptomatic; spontaneous resolution usually occurs by 3 years of age

Eosinophilic pustular folliculitis (EPF) of infancy is an uncommon entity with a mean age of onset at 6 months. It is occasionally present at birth and almost always develops before 15 months of age[22]. The male : female ratio is 4 : 1[22].

EPF of infancy is characterized by recurrent eruptions of sterile papules, pustules, and vesicles on an erythematous base. Lesions are located primarily on the scalp but can also occur on the face, especially in the brow region; the trunk and extremities are less commonly affected. Pruritic pustules often evolve into hemorrhagic crusts (Fig. 34.11) and occasionally result in scarring. The waxing and waning course persists for several months to years, usually with spontaneous resolution by three years of age. Because of its occasional acral involvement, cyclical recurrences, and self-limited nature, EPF of infancy has been thought to be related to AI; their coexistence has also been reported. Other



Fig. 34.11 Eosinophilic pustular folliculitis of infancy. Crusted papules and pustules of the scalp as well as larger areas of matted scale-crust in a one-year-old infant. The scalp hair has been shaved. *Courtesy Antonio Torrelo, MD*



Fig. 34.12 Congenital Langerhans cell histiocytosis. Numerous erosions with crusting on the face and trunk of a newborn.

authors have suggested that EPF of infancy represents a clinicopathologic reaction pattern with heterogeneous underlying causes rather than a distinctive inflammatory dermatosis[7].

A smear of the contents of the intraepidermal pustules demonstrates primarily eosinophils, without bacteria or yeast forms. Histologically, there is a dense eosinophilic infiltrate around follicles, within the outer root sheath, and/or in the dermal interstitium. Because not all biopsies show follicular involvement[22], some authors have suggested that the term "eosinophilic pustulosis of infancy" may be more appropriate. Peripheral blood eosinophilia is often present. The differential diagnosis may include ETN, TNPM, acropustulosis of infancy, bacterial folliculitis, tinea capitis, scabies, reactions to arthropod bites, and incontinentia pigmenti. Since the histologic findings of EPF are similar to those of the vesicular and papulopustular lesions seen in association with autosomal dominant hyper-IgE syndrome[23] (see below), this diagnosis should also be considered, especially in more severe cases.

Symptomatic therapy is similar to that for acropustulosis of infancy, with options including mid-potency topical corticosteroids, topical tacrolimus, and oral antihistamines[7,22]. Oral dapsone and other antibiotics are occasionally used as anti-inflammatory agents in patients with severe, recalcitrant EPF of infancy.

Congenital and Neonatal Langerhans Cell Histiocytosis

Synonym: ■ Classic terms for congenital self-limited variant: Hashimoto–Pritzker disease, congenital self-healing reticulohistiocytosis

Key features

- Crusted papules, vesiculopustules, erosions, or nodules; occasionally petechiae or purpura
- May be limited to the skin; less commonly associated with extracutaneous involvement
- Cutaneous infiltrates of $S100^+/CD1a^+$ Langerhans cells
- Purely cutaneous form often resolves spontaneously within weeks to months
- Both cutaneous and extracutaneous relapses may occur; patients require longitudinal evaluation

Langerhans cell histiocytosis (LCH) is a rare condition that can be evident at the time of birth or present during the neonatal period with crusted papules, pustules, papulovesicles, nodules, erosions, and ulcerations (Fig. 34.12; see Ch. 91). Hemangioma-like papules, petechiae, purpura, atrophy, milia, and mucosal erosions may also be seen. Lesions are often widespread but can be solitary, and they may continue to develop and evolve over the first days to weeks of life. LCH lesions can develop anywhere on the skin surface, including the palms and soles[7]. The differential diagnosis includes neonatal varicella or HSV infection, congenital candidiasis, congenital syphilis, intrauterine GVHD, and the early-onset form of AI.

Histologically, a proliferation of Langerhans cells – large, ovoid cells with "coffee bean" nuclei – is present in the superficial dermis and occasionally in the epidermis (epidermotropism). These cells exhibit positive staining with S100, CD1a, and CD207 (Langerin). Ultrastructurally, they contain characteristic Birbeck granules[24].

In an infant diagnosed with congenital or neonatal-onset cutaneous LCH, a prompt evaluation for systemic involvement is indicated, including a complete physical examination, chemistry panel including liver function tests, complete blood cell count with differential, urine osmolality, abdominal ultrasound, skeletal survey, and chest X-ray[25]. Referral to oncology with consideration of bone marrow aspiration or biopsy is recommended. Distinction between purely cutaneous and multisystem disease is not possible based solely on the skin findings. In fact, the histologic and immunohistochemical features of "congenital self-healing reticulohistiocytosis" and disseminated Langerhans cell histiocytosis are indistinguishable. These entities are now thought to represent different ends of the LCH clinical spectrum[26].

In patients whose disease is limited to the skin, lesions usually resolve spontaneously over a period of weeks to months and the prognosis is very good. However, relapses of cutaneous or extracutaneous disease (e.g. diabetes insipidus due to pituitary involvement) may occur months or years later, highlighting the importance of longitudinal evaluation of these patients. The prognosis of multisystem congenital LCH is less favorable, and systemic therapy is generally required[7]. In the majority of patients with LCH, lesional Langerhans cells harbor somatic activating mutations in *BRAF* V600E or genes that encode additional kinases in the RAS–MAP–kinase pathway (see Ch. 113). The *BRAF* V600E mutation is more frequent in younger children and has been associated with multisystem disease and a greater likelihood of relapse[27]. Although traditional therapy for multisystem LCH involves a combination of vinblastine and prednisone, there is an emerging role for targeted treatment with BRAF and MEK inhibitors[28,29].

Incontinentia Pigmenti

Synonym: ■ Bloch–Sulzberger syndrome

Key features

- X-linked dominant multisystem disease, usually lethal in male fetuses
- Cutaneous lesions are characterized by four phases: vesicular, verrucous, hyperpigmented, and hypopigmented/atrophic
- Extracutaneous manifestations are most commonly dental, ophthalmologic, and neurologic

Incontinentia pigmenti (IP) is an uncommon X-linked dominant multisystem disease that presents within the first 2 weeks of life in 90% of patients and is lethal in male fetuses unless they have X chromosome aneuploidy (e.g. Klinefelter syndrome) or genomic mosaicism (see Ch. 62). IP is caused by mutations in *IKBKG* (inhibitor of NF-κB kinase regulatory subunit γ), which is also known as *NEMO* (NF-κB essential modulator). Its protein product confers protection against apoptosis induced by the tumor necrosis factor family of cytokines (see Fig. 130.4).

Cutaneous lesions follow the lines of Blaschko and occur in four classic phases (see Fig. 62.5). The vesicular first phase usually lasts 1–2 weeks, with intermittent recurrences for up to a year and occasionally later in childhood in association with febrile illnesses. Streaks of vesicles most often develop on the extremities and scalp but can also appear on the trunk (Fig. 34.13A–C); the face is usually spared. The verrucous second phase of IP features hyperkeratotic linear plaques. The third phase, characterized by linear and whorled grayish-brown hyperpigmentation, occurs most often on the trunk and in some patients represents the only cutaneous feature (see Fig. 67.19). The first three phases typically resolve during infancy or childhood. The fourth phase, consisting of subtle atrophic, hypopigmented thin streaks favoring the calves, may persist indefinitely. Clinical stages of IP can overlap, occur *in utero*, or occasionally be skipped entirely. Additional cutaneous findings may include patchy scarring alopecia (typically at the vertex), areas of woolly hair, nail dystrophy, and anhidrosis within atrophic linear streaks. The most common extracutaneous manifestations are: (1) *dental* abnormalities such as hypodontia and conical teeth; (2) *CNS* involvement resulting in seizures, delayed psychomotor development, or spastic paralysis; and (3) *ocular* disease characterized by retinal vascular abnormalities with potential for blindness. During the vesicular phase, patients often have peripheral blood leukocytosis and eosinophilia.

Skin biopsy is often helpful in confirming the diagnosis. Histologically, lesions from the vesicular stage of IP demonstrate eosinophilic spongiosis with scattered or grouped necrotic keratinocytes (Fig. 34.13D). A dermal infiltrate composed predominantly of eosinophils is also present[5].

The cutaneous lesions generally do not require therapy. All affected infants should be referred for baseline and longitudinal ophthalmologic examinations and should have periodic neurodevelopmental and dental evaluations. Genetic testing is available.

Autosomal Dominant Hyperimmunoglobulin E (Hyper-IgE) Syndrome

Synonyms: ■ Job syndrome ■ STAT3 hyper-IgE syndrome



Fig. 34.13 Incontinentia pigmenti stage 1. A Admixture of erythematous streaks containing vesicles and yellow–brown streaks with scale on the lower extremity. **B, C** Vesicles and erythema in a linear and whorled configuration on the trunk, extremities, and ear of female neonates. **D** Histopathology showing eosinophilic spongiosis and dyskeratotic keratinocytes. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Luis Requena, MD; C, Courtesy Antonio Torrelo, MD and Luis Requena, MD; D, Courtesy Laura B. Pincus, MD.*

Key features

- Primary immunodeficiency syndrome with autosomal dominant inheritance due to *STAT3* mutations
- Characteristic neonatal papulopustular and vesicular eruption with crusting favoring the face, scalp, and neck as well as the axillae and diaper area
- During the first few weeks to months of life, serum IgE levels may not yet be elevated and other features such as "cold" abscesses, eczematous dermatitis, and recurrent infections are often absent

Autosomal dominant hyperimmunoglobulin E syndrome (AD-HIES) is a primary immunodeficiency caused by mutations in the *s*ignal *t*ransducer and *a*ctivator of *t*ranscription *3* gene (*STAT3*; see Ch. 60)[30]. Approximately 70%–80% of patients present with a papulopustular or vesicular eruption at birth or during the first month of life, with mean onset at 7 days of age[31]. The lesions are usually concentrated on the head and shoulders, but they can also affect the axillae and diaper area. AD-HIES is classically associated with high circulating levels of IgE (>2000 IU/ml) and peripheral eosinophilia. However, the IgE level may not yet be elevated in neonates and can fluctuate independently of skin disease severity. Histologic features of the vesicular and papulopustular lesions include intraepidermal vesicles containing eosinophils, perivascular infiltrates of eosinophils, and an eosinophilic folliculitis similar to that seen in eosinophilic pustular folliculitis[23].

Beyond the neonatal period, AD-HIES is associated with "cold" abscesses (see Fig. 60.8), pruritic chronic eczematous dermatitis, recurrent pneumonias with pneumatocele formation, osteopenia, and retention of deciduous teeth. Autosomal recessive variants of HIES have also been described, including dedicator of cytokinesis 8 (DOCK8) deficiency (see Ch. 60)[32]. The latter shares some features with HIES, including chronic eczematous dermatitis, recurrent sinopulmonary and staphylococcal skin infections, elevated serum IgE levels, and peripheral eosinophilia. However, DOCK8 deficiency is associated with severe viral skin infections and does not typically present with a neonatal vesiculopustular eruption[32].

VERY RARE DISORDERS

Neonatal Behçet Disease

Neonatal Behçet disease has been described in infants born to mothers with active Behçet disease during pregnancy (see Ch. 26), and it is thought to result from placental transfer of pathogenic maternal immunoglobulins. Cutaneous findings in these infants develop during the first week of life and resolve by 2–3 months of age. Manifestations include ulcerations of the oral and genital mucosae as well as vesiculopustular, purpuric, and necrotic skin lesions on the hands and feet; sites of trauma are favored, reflecting pathergy. Most infants have no additional symptoms, although there are isolated reports of colitis and other systemic involvement[7]. The differential diagnosis includes neonatal HSV infection (Fig. 34.14; see Table 34.1) and a monogenic autoinflammatory disease (see Ch. 45). A neonatal onset of pediatric Behçet disease has rarely been reported and is distinguished by the lack of a maternal history of Behçet disease, persistence beyond the neonatal period, and a higher likelihood of multisystem disease[33,34].

Vesiculopustular Eruption in Transient Myeloproliferative Disorder of Down Syndrome

There are a number of reports of a vesiculopustular eruption in neonates with trisomy 21 or mosaicism for trisomy 21. It begins during the first few days to weeks of life (rarely beyond 1 month) in the setting of transient myeloproliferative disorder, a congenital leukemoid reaction due to somatic *GATA1* mutations that affects ~10% of neonates with Down syndrome[35]. Vesicles and pustules develop initially and most prominently on the face but usually spread to involve the trunk and extremities[35]. As a consequence of pathergy, lesions have a predilection for sites of minor trauma or adhesive dressings[35]. Histologically, intraepidermal spongiotic vesiculopustules are present in association with a perivascular infiltrate. The infiltrate includes immature myeloid cells, which may be evident in a Tzanck smear of vesiculopustules and are usually also present in the peripheral blood[35,36].



Fig. 34.14 Neonatal HSV infection. Note the clustering of the vesicles on an erythematous base. *Courtesy Julie V. Schaffer, MD.*

Although the skin lesions tend to resolve spontaneously within weeks to months as the leukemoid reaction subsides, affected patients are at increased risk for the development of myeloid leukemia during the first few years of life and thus should be followed by a pediatric oncologist[35]. Considering that infants who are mosaic for trisomy 21 may not have phenotypic features of Down syndrome, an unexplained pustular eruption in a neonate accompanied by leukocytosis should prompt evaluation for transient myeloproliferative disorder and mosaic trisomy 21[37].

Congenital Erosive and Vesicular Dermatosis

Approximately 40 cases of "congenital erosive and vesicular dermatosis" (CEVD) have been reported since it was first described by Cohen and colleagues in 1985[38]. At birth, the neonates – almost all premature – have widespread erosions, vesicles, crusting and "scalded skin"-like erythematous areas affecting up to 75% of the body surface area (Fig. 34.15A). Reported associated findings include a collodion-like membrane, transparent areas of skin, livedo reticularis-like vascular patterns, and ulcerations. The face, palms, and soles are usually relatively spared. The lesions heal in 1 to 2 months with characteristic supple and reticulated scars that often cover large areas of the skin (Fig. 34.15B)[39]. Later on, scarring alopecia of the scalp and eyelashes, scarring of the tongue, absent or hypoplastic nails, and heat intolerance with hypohidrosis may be seen; mild ongoing blistering is occasionally observed[39]. Neurodevelopmental abnormalities, brain atrophy, hemiparesis, sensorineural hearing loss, and retinal scars have also been reported[39,40].

The cause of the condition remains unknown, but an intrauterine infection has been suspected. Although CEVD is diagnosed after exclusion of other etiologies, intrauterine HSV infection can mimic the findings of CEVD and likely accounted for a significant subset of reported cases, many of which predated widespread clinical use of HSV PCR[39,41]. The extracutaneous findings associated with CEVD overlap with those of congenital HSV infection, and recurrent HSV outbreaks during the first year of life were noted in 20% of reported CEVD cases[39,41].

Biopsy specimens from the acute phase have demonstrated epidermal necrosis, subepidermal vesiculation, or an eroded epidermis with a neutrophilic or mixed dermal infiltrate and no evidence of vasculitis or thrombosis[38,42]. Later in the course, biopsy specimens have shown scar formation with loss of eccrine structures[38,42].





Fig. 34.15 Congenital erosive and vesicular dermatosis. A Widespread bright red, irregularly shaped erosions on the back, buttocks, and extremities of a 2-week-old infant. Note the jagged outline of the healing lesion on the back. **B** Residual supple and reticulate scarring in a 9-month-old child. *A, Courtesy Anthony J. Mancini, MD; B, Courtesy Julie V. Schaffer, MD.*



Fig. 34.16 Epidermolytic ichthyosis. Diffuse scaling and a large erosion with scale-crust in a neonate. Histologically, epidermolytic hyperkeratosis was seen.

In addition to HSV infection (see above), which can be confirmed via PCR testing, the differential diagnosis includes other intrauterine infections, epidermolysis bullosa, epidermolytic ichthyosis (Fig. 34.16), acute intrauterine GVHD, and intrauterine epidermal necrosis (see Table 34.2). Infants with CEVD should be followed for evidence of diminished sweating and neurologic defects. Treatment is supportive with meticulous wound care, as no specific therapy is available.



Fig. 34.17 Staphylococcal scalded skin syndrome. Perioral and periorbital erythema and scale-crusts in a neonate (see Table 34.2). *Courtesy Julie V. Schaffer, MD.*



Fig. 34.18 Bullous mastocytosis. Tense bulla on the wrist and flaccid bullae on the dorsal hand as well as pink plaques on the trunk in a 1-month-old infant (see Table 34.2).

Pyoderma Gangrenosum

Rarely reported in infants and newborns, pyoderma gangrenosum in this age group most often involves the perineum, possibly because of pathergy. Otherwise, the clinical features of the ulcer, including an undermined violaceous border, are similar to those seen in older children and adults[43,44]. Biopsy specimens show a sterile neutrophilic infiltrate, but the diagnosis is often one of exclusion after other causes of ulceration such as infection, immunodeficiency, thrombosis, and vasculitis are eliminated. In recent reviews, up to 45% of infants with PG have an underlying disorder[44] (see Ch. 25). Intralesional or systemic corticosteroids are usually first-line treatment; other systemic agents such as dapsone, cyclosporine, and TNF inhibitors have also been used[44,45].

Restrictive Dermopathy

Restrictive dermopathy is a rare disease characterized by rigid, tense skin with erosions and linear tears that occur most commonly in

flexural creases[46]. The disorder results in a fetal akinesia or hypokinesia deformation sequence characterized by multiple flexion joint contractures, dysmorphic facies with a fixed facial expression, and polyhydramnios with reduced fetal movements; the latter results in premature delivery, most often at 30–33 weeks' gestation. Other features include translucent skin with prominent vessels, micrognathia, sparse/absent eyelashes, natal teeth, large fontanelles, dysplasia of the clavicles, and poorly expanded lungs as a result of the restrictive skin changes. Most affected newborns die from restrictive pulmonary disease within the first week of life. Restrictive dermopathy represents a lethal neonatal laminopathy, typically caused by either dominant *de novo* mutations in *LMNA*, which encodes nuclear lamin A/C proteins, or, more commonly, recessive null mutations in *ZMPSTE24*, which encodes a zinc metallopeptidase essential for lamin A processing (see Ch. 63)[47].

Noma Neonatorum

Two forms of noma have been described in the newborn period. The first is a manifestation of infection, usually *Pseudomonas aeruginosa* septicemia, and has been reported almost exclusively in low-income countries[48]. Infants present with an abrupt onset of gangrenous ulcerations of the nose, lips, mouth, eyelids, anus, and scrotum. In severe cases, the ulcerations can destroy underlying bony structures and cause extensive deformity. Predisposing factors include premature birth, low birth weight, malnutrition, and previous illness, although infectious noma has been reported in previously healthy term infants[49]. Some authors suggest that this form of noma neonatorum may represent a variant of neonatal ecthyma gangrenosum[50].

The second form of noma has been seen in Native American infants who present with perineal and oral ulcerations in the setting of severe combined immunodeficiency[51]. The presence of oral and perineal ulcerations in newborns and infants should prompt an evaluation for infection and immunodeficiency. Of note, neonatal nasal ulcerations are a characteristic feature of *p*hospho*l*ipase Cγ2 (*PLCG2*)-associated *a*ntibody deficiency and *i*mmune *d*ysregulation (PLAID)[52].

Perinatal Gangrene of the Buttock

This rare condition is characterized by the sudden onset of erythema and cyanosis of the buttocks, followed by progressive development of gangrene and ulceration. Although some cases have been associated with umbilical artery catheterization, others were spontaneous[53]. Occlusion or spasm of the internal iliac artery has been postulated as a potential cause[54]. Considerations when evaluating a neonate with hemorrhagic bullae and gangrenous soft tissue infarction also include purpura fulminans due to congenital coagulopathies (e.g. protein C or S deficiency) or infection.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 34.1 Erythema toxicum neonatorum. Scattered papulovesicles with an erythematous flare. *Courtesy Kalman Watsky, MD.*



eFig. 34.2 Erythema toxicum neonatorum. Multiple papulovesicles and pustules with an erythematous flare. *Courtesy Julie V. Schaffer, MD.*



eFig. 34.3 Transient neonatal pustular melanosis. Pustules, hyperpigmented macules, and collarettes of scale are seen on the chin and neck of an African-American neonate.



eFig. 34.4 Bullous impetigo in an infant. Rupture of fragile blisters leads to circular erosions. This is a common site of involvement. *Courtesy Julie V. Schaffer, MD.*



eFig. 34.5 Miliaria rubrum in a newborn. Transient eruption of papulovesicles and pustules. The neck and upper trunk are common sites of involvement. *Courtesy Julie V. Schaffer, MD.*





eFig. 34.6 Congenital candidiasis in premature neonates with very low birth weights. A, B This presentation is also referred to as "invasive fungal dermatitis" and can have a "burn-like" appearance. It is associated with a high risk of systemic involvement. *Courtesy Julie V. Schaffer, MD.*



eFig. 34.7 Acropustulosis of infancy. Multiple vesiculopustules with an erythematous base on the dorsal fingers.



eFig. 34.8 Acropustulosis of infancy. Multiple vesiculopustules with an erythematous base on the plantar surface.



eFig. 34.9 Acropustulosis of infancy. Multiple vesiculopustules on the ankle. *Courtesy Julie V. Schaffer, MD.*



eFig 34.10 Eosinophilic pustular folliculitis of infancy. Crusted papules and pustules on the scalp of a 1-year-old boy.



eFig. 34.13 Congenital and erosive vesicular dermatosis. Widespread red, irregularly shaped erosions on the buttocks and thighs of a 2-week-old infant. *Courtesy Anthony J. Mancini, MD.*



eFig. 34.11 Incontinentia pigmenti stage 1. Multiple vesicles and bullae with an erythematous border on the lower extremity. *Courtesy Anthony J. Mancini, MD.*

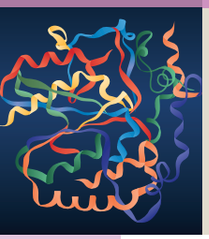


eFig. 34.14 Neonatal pemphigoid gestationis. Vesiculobullous lesions in a neonate whose mother had active pemphigoid gestationis. *Courtesy Jean L. Bolognia, MD.*





eFig. 34.12 Vesiculopustular eruption in transient myeloproliferative disorder of Down syndrome. A, B Numerous vesiculopustules, many of which have become eroded. The face is a common site of involvement. *Courtesy Silvia Moreno, MD.*



35 Structure and Function of Eccrine, Apocrine, and Sebaceous Glands

Martin Schaller and Gerd Plewig

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ECCRINE AND APOCRINE SWEAT GLANDS

Key features

- Eccrine sweat glands are widely distributed, with the highest density in palmoplantar skin; they are activated by emotional and thermal stimuli and are necessary for thermoregulation
- The eccrine secretory unit consists of a coiled secretory portion that drains into a long, thin duct whose apical portion (acrosyringium) opens to the skin surface
- Innervation of eccrine glands consists of postganglionic sympathetic fibers that have acetylcholine as their main neurotransmitter
- Apocrine glands are located primarily in the axillae, anogenital and periumbilical regions, and nipples; their apical portion (acrosyringium) drains into terminal hair follicles
- Apocrine glands continuously secrete a sterile, odorless, viscous fluid that is rich in precursors of odoriferous substances; they are androgen-dependent in their development and have an unclear function in humans

Introduction

Humans have both eccrine and apocrine sweat glands, which are distinct from one another structurally, developmentally, and functionally (Table 35.1, Fig. 35.1). Disorders of sweating are common and can be due to dysfunction of central sweat centers; sympathetic ganglia and their pre- and postganglionic fibers; or secretory glands and excretory ducts. Clinical manifestations include hyperhidrosis, hypohidrosis, and sweat retention (e.g. miliaria). Knowledge of the structure and function of sweat glands is important for proper diagnosis and treatment of sweating disorders (see Chs. 39 & 159).

ECCRINE SWEAT GLANDS

Structure

In the human body, there are ~1.5 to 4 million eccrine sweat glands and they are widely distributed, sparing only the skin of the external auditory canals, vermilion lips, clitoris, labia minora, and glans penis. The highest density is found on the palms and soles. The eccrine secretory unit consists of a proximal coiled secretory portion in the lower dermis and subcutaneous tissue. This drains into a long, thin duct with an apical portion (acrosyringium) that opens directly onto the skin surface (see Fig. 35.1)[1,2]. The secretory coils contain two cell types interspersed within a single cell layer: (1) large clear cells responsible for the gland's secretion of electrolytes and water; and (2) dark cells, of unknown function, with basophilic granules that are thought to produce sialomucin. Both cell types are surrounded by myoepithelial cells, which probably function to enhance the delivery of sweat to the skin surface. The ductal epithelium is composed of two or more layers of cuboidal cells without surrounding myoepithelium. The intraepidermal portion of the duct, the acrosyringium, is twisted like a corkscrew with similar coils in the stratum corneum[2]. Stem cell markers (e.g. prominin-1/CD133) are expressed in the secretory and ductal portions of eccrine glands[3].

The eccrine glands are innervated by postganglionic sympathetic fibers that have acetylcholine (not norepinephrine) as their primary terminal neurotransmitter (Table 35.2). These sympathetic fibers are controlled by the hypothalamic sweat center[2]. The sweat center responds to its own temperature (as a reflection of core body temperature) and to neural stimuli from the periphery.

Development

During embryogenesis, at 3 months' gestation, sweat glands begin to develop as cords of epithelial cells arising from the epidermal ridges on the palms and soles. By 5 months' gestation, similar structures have developed in the remainder of the body. Functional eccrine glands are present at birth and react to thermal and emotional stimuli. Unlike apocrine glands, they have no developmental relationship with the pilosebaceous follicle[2,4].

Function

Eccrine sweat is a sterile, dilute electrolyte solution that contains primarily sodium chloride (NaCl), potassium, and bicarbonate. Other components include antimicrobial peptides (e.g. dermcidin)[5], proteolytic enzymes, glucose, pyruvate, lactate, urea, ammonia, calcium, amino acids, epidermal growth factor, cytokines, and immunoglobulins. In addition, other organic compounds and heavy metals such as arsenic, cadmium, lead, and mercury are excreted in sweat[6]. One study demonstrated that sweat activates NF-κB, ERK, and JNK pathways in keratinocytes, resulting in the upregulation of interleukin (IL)-8 and IL-1β production[7]. Keratinocyte outgrowths from eccrine sweat glands also play a central role in re-epithelializing wounds[8].

The quantity and quality of eccrine sweat secretion varies widely in response to emotional and environmental stimuli. There are several methods for measuring sweat production, e.g. gravimetry, starch–iodine reaction (see Ch. 39). At maximal stimulation, the body can produce

CHARACTERISTICS OF SWEAT GLANDS		
	Eccrine	**Apocrine**
Localization	Entire body skin, highest density on palms and soles	Axillae, anogenital, periumbilical, nipples, and areolae
Morphology	Long, thin duct opens to skin surface	Short, thick duct opens into upper part of follicular canal
	Secretory coil with narrow lumen	Secretory coil with wide lumen
Cell types in secretory coil	Large secretory clear cells, dark cells, and myoepithelial cells	Epithelial (typically cuboidal) and myoepithelial cells
Main innervation/ neurotransmitter	Sympathetic fibers/ acetylcholine	Unclear/possible humoral effects of β-adrenergic receptor agonists
Development	Present at birth	Present at birth
	No relationship to pilosebaceous follicle	Associated with terminal hair follicle
Function/ pathogenesis	Thermoregulation/ dysfunction in hyperhidrosis, hypohidrosis, and miliaria	Possible role in olfactory communication/dysfunction in Fox–Fordyce disease

Table 35.1 Characteristics of sweat glands.

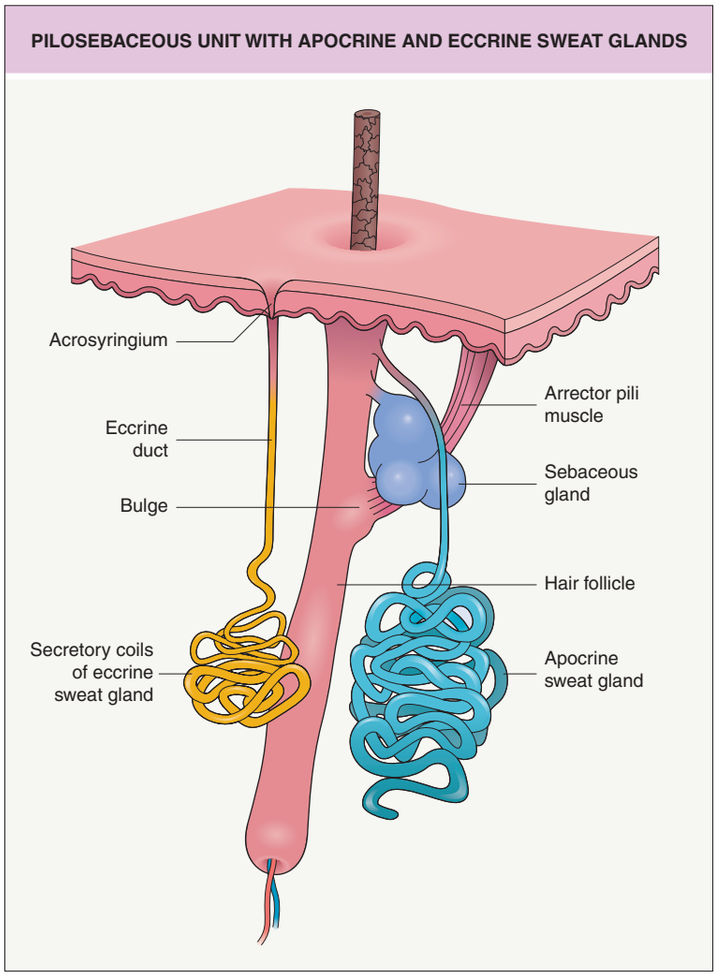


Fig. 35.1 Pilosebaceous unit with apocrine and eccrine sweat glands. Pilosebaceous unit with an associated apocrine sweat gland and a nearby eccrine sweat gland.

INNERVATION AND RECEPTOR PROFILES OF SWEAT GLANDS		
	Eccrine	**Apocrine**
Nerve fibers near gland	+	±
Cholinergic muscarinic (M_3) receptors	++	±
α_1-adrenergic receptors	+	–
β_2- > β_3-adrenergic receptors	+	+
Purinergic receptors	+	+

Table 35.2 Innervation and receptor profiles of sweat glands.

3 liters in 1 hour. Sweat is formed in two steps[9]: (1) release of nearly isotonic primary sweat by the secretory coil; and (2) partial reabsorption of NaCl by duct cells, resulting in the delivery of a hypotonic fluid to the skin surface. The final concentration of NaCl may be higher when sweat is produced at a more rapid rate. The neuropeptide galanin and its receptors regulate transepithelial ion transport and fluid secretion from human eccrine sweat glands[10].

Sweat secretion provides mechanisms for thermoregulation via evaporative heat loss, maintenance of electrolyte balance, and keeping the stratum corneum moist to ensure fine tactile skills and pliability of the palms and soles. The excretory function of the sweat gland can be instrumental in the delivery of systemically administered drugs to the stratum corneum (e.g., fluconazole, griseofulvin), and it provides an explanation for cutaneous side effects of certain chemotherapeutic drugs. Botulinum toxin can be used to treat eccrine hyperhidrosis. After dermal injection, botulinum toxin taken up by the nerve terminal interferes with proteins required to release acetylcholine at the neuroglandular junction (see Fig. 159.1).



Fig. 35.2 Toxic erythema of chemotherapy (palmar erythrodysesthesia). Erythema and blister formation, most notably on the distal portion of the first and second digits and the digital creases (arrows).

Pathophysiology

Disorders affecting eccrine function involve modifications of sweat quantity or quality; these can be localized (e.g. distribution of the auriculotemporal nerve in Frey syndrome [see Ch. 39]) or generalized (e.g. hypohidrotic ectodermal dysplasia). The sweat glands are also affected in cystic fibrosis (CF). Individuals with CF lose excessive amounts of salt (NaCl) when they sweat, and the most common screening test for CF measures the amount of Cl^- in the sweat.

Hyper- and Hypohidrosis

Increased activity of eccrine glands is typically due to enhanced cutaneous sympathetic outflow in response to mental and thermal stimuli. The secretory clear cells of eccrine glands represent the major source of sweat in hyperhidrosis[4]. In the emotional form of hyperhidrosis, excessive sweating primarily affects the palms, soles, and axillae[11]. Stimulation of eccrine sweat glands may also occur in association with menopause-related hypoestrogenemia and a number of neurologic, infectious, neoplastic (e.g. lymphomas), and endocrine diseases (see Ch. 39).

Increased sweating can lead to overhydration and even maceration of the skin. This may be accompanied by secondary bacterial and fungal infections (see Chs. 74 & 77). Proteolytic activity by resident and transient skin microbiota can lead to odor-producing substances (e.g. ammonia, short-chain fatty acids); this is referred to as eccrine bromhidrosis.

Hypohidrosis or anhidrosis may be congenital, e.g. due to a reduced number of eccrine glands in patients with hypohidrotic ectodermal dysplasia. It can also be acquired, e.g. due to poral occlusion in patients with ichthyosis or administration of medications with anticholinergic effects.

Drug-Related Eccrine Disorders

Drugs known to be secreted into eccrine sweat include chemotherapeutic agents (e.g. cyclophosphamide, cytarabine), antibiotics (e.g. ciprofloxacin, β-lactams) and antifungals. In patients receiving chemotherapy, excretion of toxic components into eccrine sweat is thought to play a role in the production of neutrophilic eccrine hidradenitis and other forms of toxic erythema of chemotherapy (Fig. 35.2). Toxic insult to the eccrine ductal cells from chemotherapy leads to the histologic finding of eccrine squamous syringometaplasia (see Ch. 21).

Disorders of Sweat Retention

Occlusion of the eccrine ducts can result from a parakeratotic plug of PAS-positive material, which then leads to sweat retention. Miliaria may be triggered by a high environmental or body temperature, excessive sweating (especially under occlusive clothing or dressings), and an increased density of resident bacteria (e.g. *Staphylococcus epidermidis*). Ductal plugs within the stratum corneum lead to superficial miliaria (miliaria crystallina), while intraepidermal and dermal duct occlusion induce miliaria rubra and profunda, respectively (see Ch. 39).

APOCRINE SWEAT GLANDS

Structure

Apocrine sweat glands are confined to certain anatomic sites (axillae, anogenital region, periumbilical area, areolae, nipples, vermilion border of the lip) and are larger than eccrine glands. Modified forms of apocrine glands are found in the external auditory canals (ceruminous glands) and on the eyelid margins (glands of Moll). Apocrine glands consist of a secretory portion located in the deep dermis and subcutaneous fat, and a stretched duct that opens into the upper portion of the follicular canal, i.e., the apocrine acrosyringium (see Fig. 35.1). The secretory unit is a convoluted tube with a single layer of epithelial cells (typically columnar) surrounded by myoepithelial cells. The duct consists of a double layer of cuboidal cells, as well as myoepithelial cells that support the movement of secretions to the skin surface.

Differentiating the *secretory* portion of apocrine glands from those of eccrine glands is relatively easy based simply upon morphologic (histopathologic) features, e.g. large lumina and "decapitation" secretion. However, the *excretory* ducts of the two types of sweat glands cannot be distinguished by either histopathologic features or immunohistochemistry; the only difference is that eccrine ducts end "free" in the epidermis, whereas apocrine ducts open into the upper portion of the follicular canal.

Apocrine gland secretion increases in response to local or systemic administration of catecholamines and cholinergic agonists, but the mechanisms controlling physiologic secretion are poorly understood. In a study of normal axillary skin, secretory coils of apocrine glands were found to have β-adrenergic and purinergic, but not cholinergic, receptors (see Table 35.2)[12]. Nerve fibers were found near eccrine glands but not apocrine glands, suggesting that catecholamines stimulate the latter through humoral mechanisms[12].

Development

Embryologically, apocrine sweat glands derive from the primary epithelial germ layer, which also gives rise to the sebaceous glands and hair follicles. In the embryo, apocrine sweat glands are present throughout the entire skin, but most of them subsequently disappear, resulting in the characteristic distribution found in adults. Enlargement of the glands occurs with the onset of puberty due to hormonal stimulation, primarily by androgens.

Function

Apocrine glands continuously secrete small quantities of an oily fluid. This sweat is sterile, odorless, and viscous, with a pH between 5.0 and 6.5. It is rich in precursors of odoriferous substances such as cholesterol, triglycerides, fatty acids, cholesterol esters, and squalene. It also contains androgens, carbohydrates, ammonia, and ferric iron. *Apocrine* or "decapitation" secretion refers to the "pinching off" and release of the luminal portion of secretory cells; apocrine glands also employ *merocrine* (exocytosis of vesicles) and *holocrine* (rupture of the plasma membrane) secretion.

In animals, apocrine glands are the source of pheromones, which act as chemical signals that instigate behavioral responses (e.g. sexual attraction) or mark territorial boundaries. In humans, apocrine glands do not have a clear function but may play a role in olfactory communication.

Pathophysiology

Although apocrine sweat is initially sterile and odorless, bacteria on the skin surface modify and degrade the secreted substances, resulting in rancid (*Corynebacterium* spp.) or sweaty (*Micrococcus* spp.) body odor, i.e. bromhidrosis. Insufficient body and textile hygiene will worsen the condition. Of note, some androgenic steroids have an odor similar to natural axillary odor.

Apocrine chromhidrosis refers to the secretion of pigmented (yellow, green, or black) sweat. It is a reflection of the rich lipofuscin content of apocrine sweat. Pseudo- or extrinsic apocrine chromhidrosis results from staining of the sweat by chromogenic bacteria, especially *Corynebacterium* spp., or colored garments. Hormonal factors are thought to play a role in the occlusion of apocrine ducts by a keratinous plug in Fox–Fordyce disease (see Ch. 39).

SEBACEOUS GLANDS

Key features

- Sebaceous glands produce sebum via holocrine secretion and have multiple biological functions, including hormonal (e.g. androgen synthesis) and immune modulation
- Except for ectopic or free sebaceous glands of the vermilion lips, orogenital mucosa, areolae, and eyelids, sebaceous glands are associated with hair follicles
- Sebum consists of free fatty acids, wax and sterol esters, triglycerides, and squalene
- Sebum production is a sensitive indicator of androgenic activity; it increases during puberty and decreases in later adulthood, particularly in postmenopausal women
- Sebaceous follicles are rich in microorganisms such as *Malassezia* spp., *Staphylococcus epidermidis*, and *Cutibacterium* spp.

Introduction

Except for the free sebaceous glands found on the vermilion lips and oral mucosa (Fordyce spots or granules), eyelids (meibomian glands), areolae (Montgomery tubercles), and labia minora and prepuce (Tyson glands), sebaceous glands are associated with hair follicles (Fig. 35.3). Sebaceous glands produce sebum, which is released into the infundibular portion of the hair follicle. Sebum production increases at the time of puberty and is a critical factor in the pathogenesis of acne vulgaris[13–15]. Sebaceous

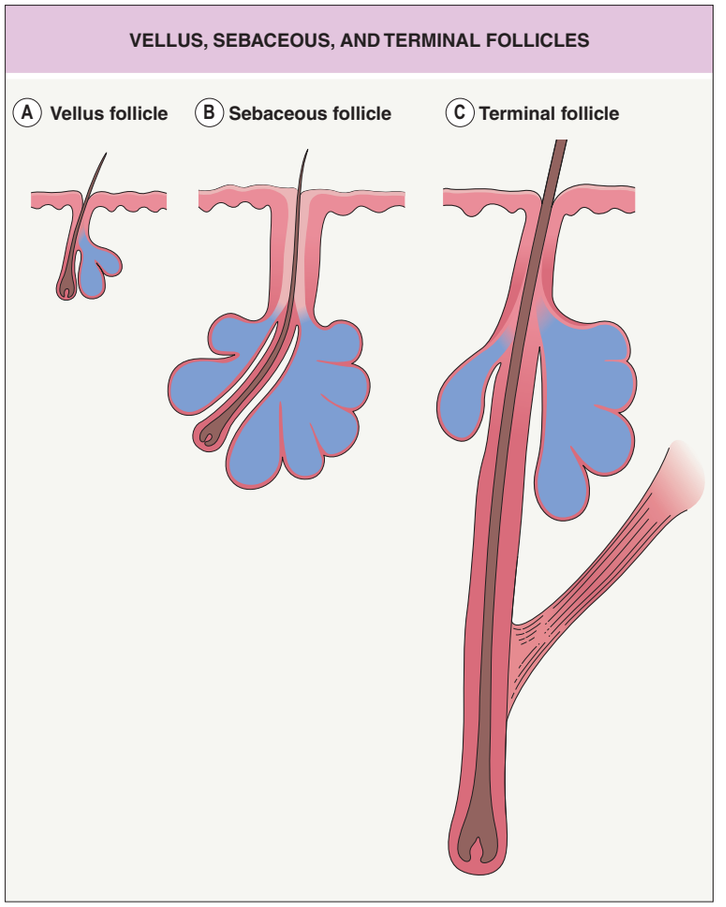


Fig. 35.3 Vellus, sebaceous, and terminal follicles. Three different types of pilosebaceous units. **A** Vellus follicle with a small sebaceous gland and short thin hair. **B** Sebaceous follicle with a large multilobular sebaceous gland and mid-sized hair. **C** Terminal follicle with a fairly large sebaceous gland and thicker hair. *Adapted from Plewig G, Melnik B, Chen W. Plewig and Kligman´s Acne and Rosacea, 4th ed. Berlin: Springer, 2019.*

glands also play an important role in cutaneous endocrine function, including the hypothalamic–pituitary–adrenal-like axis of the skin and androgen metabolism. As outlined in Table 35.3 and Fig. 35.4, the pathogenesis of acne involves interactions of the sebaceous gland with neuropeptides, androgens, and the innate immune system, including the production of antimicrobial peptides.

Structure

The distribution of sebaceous glands within the skin is variable. However, they are particularly well developed on the face, scalp, upper back, and chest. There are three different types of pilosebaceous units: vellus, sebaceous, and terminal (see Fig. 35.3).

A sebaceous follicle consists of four parts: the keratinized follicular infundibulum, the hair, the cauliflower-like convoluted sebaceous gland, and the sebaceous duct which connects the gland with the infundibulum (see Fig. 35.1). The infundibulum is divided into two parts. The distal portion (*acroinfundibulum*) has an epidermal keratinization pattern with a granular layer and corneocytes (squames) shedding into the lumen. In contrast, the lower part (*infrainfundibulum*) has a tricholemmal keratinization pattern with no granular layer.

The resident microbiota, i.e. normal flora, of sebaceous follicles is complex and includes both bacteria (e.g. *S. epidermidis*, *Cutibacterium* spp. such as *C. acnes*) and fungi (e.g. *Malassezia* spp.) (Fig. 35.5). These follicles also harbor *Demodex* mites, which increase in number in older adults and are rarely seen in prepubertal children.

Development

Sebaceous glands are derived from the epidermis as buds from developing hair follicle root sheaths and grow downward into the dermis. Sebaceous glands are present at birth, and sebum production is relatively high at this time. It soon declines and remains low until puberty, when it again increases. Androgens, in particular 5α-dihydrotestosterone (DHT), appear to be the major factor that controls gland development and sebum production. The level of sebum production at the end of puberty remains constant until mid-adulthood. Sebum production declines in women after menopause, and in men during the sixth to seventh decades of life.

Although stem cells in the hair follicle bulge can regenerate sebaceous glands following injury, under homeostatic conditions bulge cells do not appear to contribute to the formation of sebaceous glands[16].

ROLES OF THE SEBACEOUS GLAND IN PATHOGENESIS OF ACNE VULGARIS AND ROSACEA

Sebaceous gland component	Actions in sebaceous glands	Observations in sebaceous glands of patients with AV and R
A – Hypothalamic–pituitary–adrenal-like and other hormonal axes		
Corticotropin-releasing hormone (CRH)* and CRH receptors (CRH-Rs)	↑ lipid and androgen synthesis ↑ production of IL-6, IL-8 (CRH-R2)	↑ levels of CRH and (in sebaceous ducts) CRH-R1 in **AV**
α-Melanocyte stimulating hormone (MSH)* and melanocortin-1 & -5 receptors (MC1-R, MC5-R†)	↑ sebocyte differentiation and lipid synthesis (MC5-R)	↑ levels of MC1-R in **AV**
Growth hormone and insulin-like growth factor-1 (IGF-1) receptors	↑ sebocyte proliferation ↑ lipid and androgen synthesis	Association of high glycemic-load diets and intake of insulinotropic dairy products with **AV**
B – Other neuropeptides		
Substance P	↑ sebocyte proliferation/differentiation ↑ production of inflammatory cytokines	↑ substance P-containing nerves in **AV**
C – Androgens		
Testosterone* and dihydrotestosterone (DHT)*	↑ sebocyte proliferation/differentiation and lipid synthesis (especially DHT) May ↑ infundibular keratinization	↑ conversion of testosterone to DHT in **AV** Association of hyperandrogenic disorders with **AV**‡
D – Sebum components and derivatives		
Monounsaturated fatty acids (MUFAs), lipoperoxides (LPs), other proinflammatory lipids (e.g. generated via 5-lipoxygenase), linoleic acid (LA)	↑ infundibular keratinization (MUFAs, LPs, *deficient* LA) ↑ cytokine production, chemotaxis, and PPAR activation (MUFAs, LPs)	↑ overall sebum production, MUFAs, and LPs in **AV** ↑ 5-lipoxygenase in **AV** ↓ linoleic acid in **AV**
E – Innate immune system		
Toll-like receptors (TLRs, especially TLR2)	Upon stimulation (e.g. by *C. acnes*), ↑ production of IL-1, IL-8, IL-12, TNF (TLR2)	↑ expression of TLR2 and TLR4 in **AV** Possible ↑ expression of TLR2 in **R**
Defensins, cathelicidins, MUFAs (e.g. sapienic acid)	Antimicrobial properties ↑ cytokine production and chemotaxis	↑ levels of LL-37 via proteolysis of cathelicidin by kallikrein 5 in **R**, leading to proinflammatory and vasoactive effects
F – Organisms		
Cutibacterium (formerly *Propionibacterium*) *acnes*¶	↑ production of antimicrobial peptides & inflammatory cytokines/chemokines, especially IL-1β and IL-17, via stimulation of TLR2 and the NLRP3 inflammasome ↑ free fatty acids (e.g. via lipase activity) May ↑ infundibular keratinization	↑ *C. acnes* in **AV**
Demodex folliculorum	May stimulate or carry bacteria (e.g. *Bacillus oleronius*) that stimulate innate and adaptive immune reactions	↑ density of *D. folliculorum* and reactivity to *B. oleronius* in R

*Can be produced locally by the sebaceous gland as well as remotely.
†Marker of sebocyte differentiation.
‡Most AV patients have normal levels of circulating androgens.
¶Different phylogenetic clusters of *C. acnes* vary in their ability to induce immune responses.

Table 35.3 Roles of the sebaceous gland in pathogenesis of acne vulgaris (AV) and rosacea (R). IL, interleukin; PPAR, peroxisome proliferator-activated receptor; TNF, tumor necrosis factor.

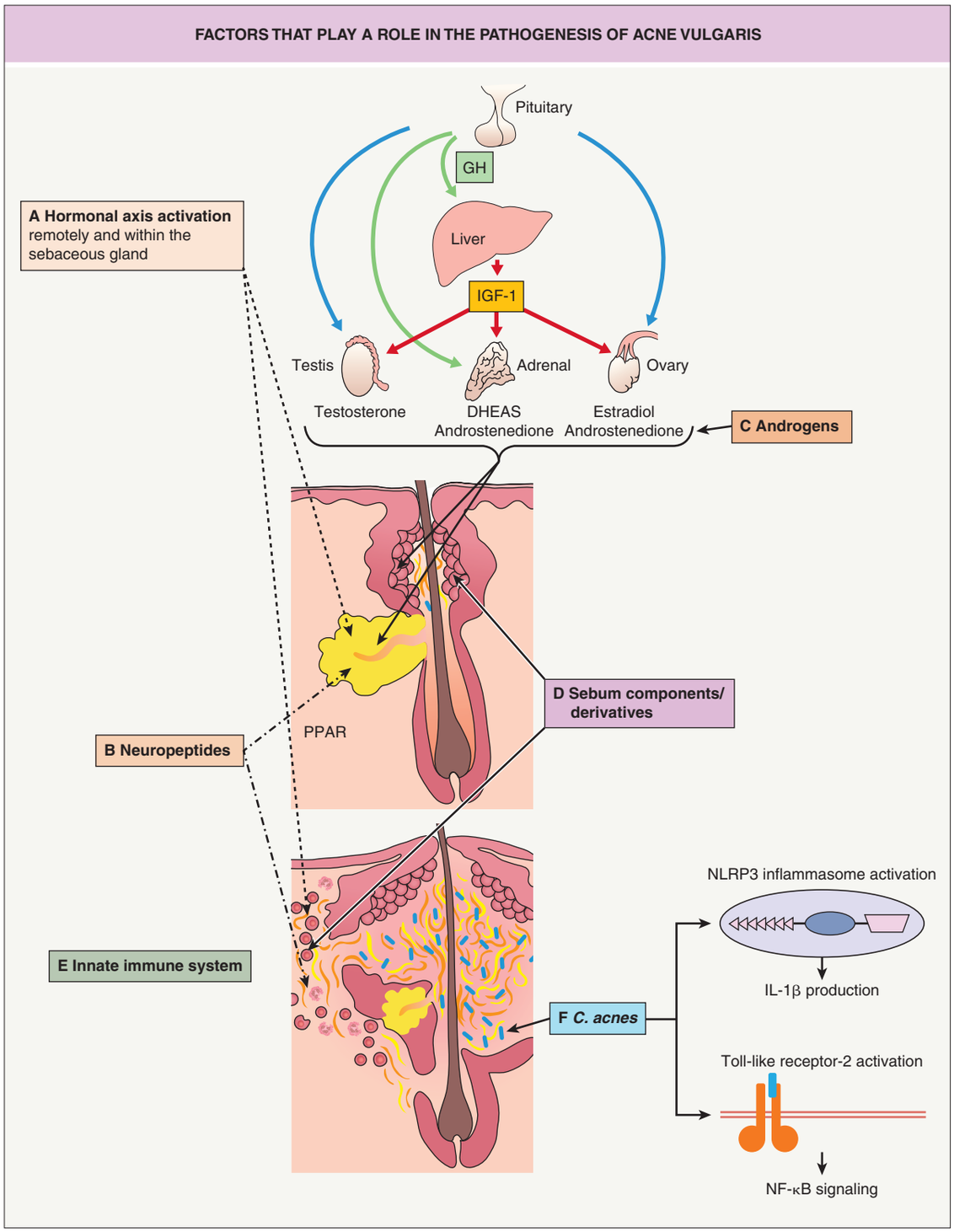


Fig. 35.4 Factors that play a role in the pathogenesis of acne vulgaris. **A–F** correspond to the sections of Table 35.3. DHEAS, dehydroepiandrosterone sulfate; GH, growth hormone; IGF-1, insulin-like growth factor-1; IL, interleukin; NLRP3, NOD-like receptor pyrin domain-containing protein 3; PPAR, peroxisome proliferator-activated receptor.

Immortalized cells derived from the human sebaceous gland can differentiate into both sebocytes and interfollicular epidermal cells, suggesting a bipotential stem cell function[17]. In cultured human sebocytes and an *in vivo* mouse model, overexpression of c-Myc stimulated *sebaceous* differentiation, whereas overexpression of β-catenin induced *epidermal* differentiation[17]. Expression of the stem cell marker keratin 15 has been observed in human basal sebocytes[16]. Blimp-1 (*B-l*ymphocyte-*i*nduced *m*aturation *p*rotein-1) was found to be a marker for sebocyte progenitor cells in mice, but in humans it is expressed by terminally differentiating cells of the sebaceous gland, hair follicle, and interfollicular epidermis[17].

Function

Sebum is a light yellow viscous fluid. It is composed of triglycerides, free fatty acids, squalene, wax and sterol esters, and free sterols. The admixture of ceramides, mostly derived from epidermal lipids, occurs in the acroinfundibulum before the sebum mixture reaches the skin surface. Secretion of sebum is holocrine, that is, the sebocytes disintegrate and thereby release their sebum as they migrate towards the central gland and sebaceous duct. Sebocyte turnover time is ~14 days, and the flow of sebum is relatively continuous. The amount of sebum produced varies among individuals and ethnic groups, but the average rate in adults is ~1 mg/10 cm^2 every 3 hours[18].

Sebaceous gland function is influenced by genetic factors and levels of circulating hormones. The cells within sebaceous glands contain androgen receptors that bind DHT and are then translocated to the nucleus[15,19]. They also express functional receptors for neuropeptides such as corticotropin-releasing hormone (CRH), melanocortins, and substance P[13,20]. These receptors contribute to proliferation and differentiation of cells in the sebaceous gland (sebocytes) and modulate

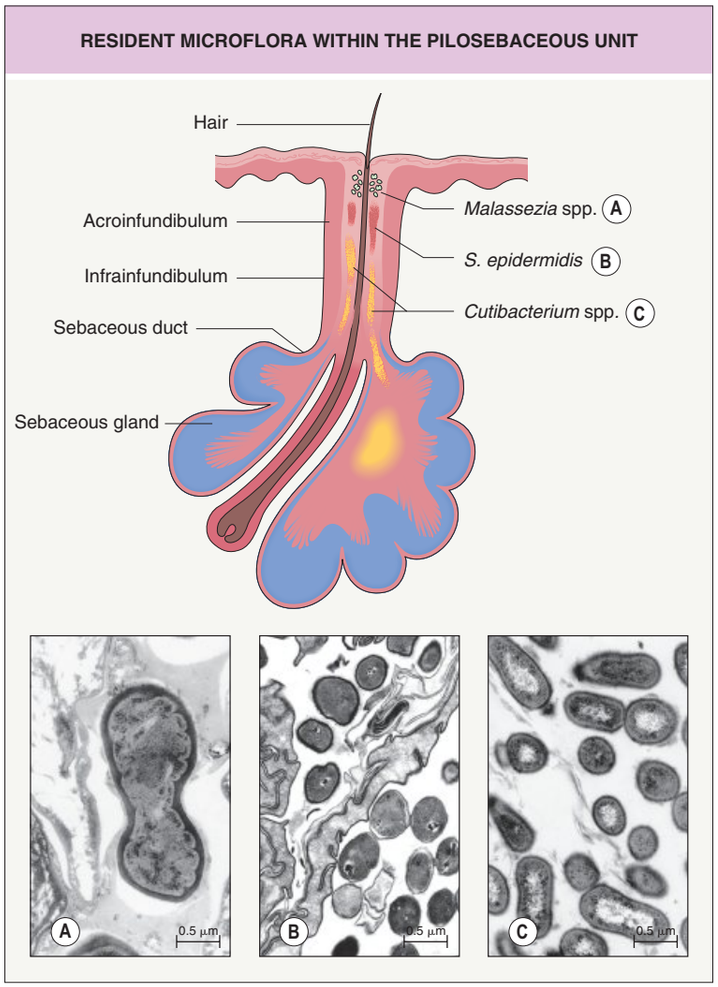


Fig. 35.5 Resident microflora within the pilosebaceous unit. Localization of resident microflora within the pilosebaceous unit and electron microscopic view of organisms: **A** *Malassezia* spp.; **B** *Staphylococcus epidermidis*; **C** *Cutibacterium* spp., including *C. acnes*, *C. granulosum*, and least often *C. parvum*.

their production of lipids, androgens, and cytokines in response to stimuli such as emotional stress (see Table 35.3). Sebaceous glands produce the majority of skin surface lipids, which not only promote barrier function but also possess both pro- and anti-inflammatory properties[15].

Pathophysiology

Sebum production of less than 0.5 mg/10 cm^2 every 3 hours is associated with *sebostasis* or dry skin, while 1.5–4.0 mg/10 cm^2 every 3 hours is considered excessive and is referred to as *seborrhea*. The presence of well-developed sebaceous follicles on the face and upper portions of the chest and back corresponds to the distribution of acne vulgaris. Clinically, these areas tend to be oilier than the rest of the body. In general, acne patients have larger sebaceous glands and produce more sebum than individuals without acne.

Growth of sebaceous glands and increased sebum production are both induced by androgens, particularly DHT. In men, DHT is mainly derived from testosterone, while in women, androstenedione is the main precursor. The conversion of testosterone to DHT is 30 times higher in skin affected by acne than in normal skin. Eunuchs, who lack testicular function, do not develop acne. However, increased sebum production alone is insufficient to cause acne vulgaris, as evidenced by the marked seborrhea but lack of acne in patients with Parkinson disease.

Sebaceous glands play several major roles in the pathogenesis of acne vulgaris and may also contribute to the pathogenesis of rosacea (see Table 35.3, Fig. 35.4, and Fig. 37.1)[19,21]. Sebum in sebaceous glands and ducts is sterile and contains no free fatty acids, but the microenvironment of the infundibulum favors the growth of *C. acnes* and *S. epidermidis*[22]. In patients with acne vulgaris, the resident microorganisms, especially *C. acnes*, are quantitatively increased in sebaceous follicles. Their lipases split di- and triglycerides, producing free fatty acids that alter the pattern of keratinization within the infundibulum. Abnormal keratinization is one of the first pathogenic steps in acne vulgaris, with increased proliferation and retention of corneocytes in the infundibulum resulting in a microcomedo. In addition, free fatty acids are chemotactic and attract neutrophils. Modulating the transcriptome of the skin microbiota can also promote acne, e.g. high-dose vitamin B_{12} supplementation was found to increase the production of inflammation-inducing porphyrins by *C. acnes*.

The infrainfundibulum of acne patients responds to a variety of physiologic and exogenous stimuli more readily than that in individuals without acne. For example, acne patients are more susceptible to the comedogenic effects of agents such as halogenated cyclic hydrocarbons, tar products, and some cosmetics[18]. Follicular acneiform eruptions also develop in patients receiving inhibitors of the *e*pidermal growth *f*actor *r*eceptor (EGFR), including antibodies that block interaction of EGF with its receptor (e.g. cetuximab) as well as inhibitors of EGFR tyrosine kinase activity (e.g. gefitinib; see Ch. 21). EGFR is highly expressed in keratinocytes and in cells of eccrine and apocrine glands. Inhibition of the EGFR disturbs the normal differentiation and morphogenesis of hair follicles, with induction of excessive follicular hyperkeratosis, follicular plugging, and growth of microorganisms in the dilated infundibula[23].

Additional table on Methods for evaluating sweat production, available in our eBook (see inside front cover for access code).

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METHODS FOR EVALUATING SWEAT PRODUCTION
• Visualization of sweat by the starch–iodine reaction (see Figs. 39.3, 39.4B, 39.6 & 39.7) or quinizarin method • Measurement of electric potential and resistance of the skin • Measurement of skin temperature (e.g. infrared thermography) • Gravimetry (e.g. weighing filter paper before and after application to the skin) • Measurement of evaporative water loss from the skin

eTable 35.1 Methods for evaluating sweat production.

36 Acne Vulgaris

Andrea L. Zaenglein, Amanda M. Nelson and Leah E.B. Lalor

Synonym: ■ Acne

Key features

- A multifactorial disorder of the pilosebaceous unit
- Significant psychological and ecownomic impact
- Clinically characterized by comedones, papules, pustules, and nodules
- Potential sequelae include persistent erythema and postinflammatory hyperpigmentation as well as scarring

INTRODUCTION

Acne vulgaris is a multifactorial disorder of the pilosebaceous unit. The clinical picture can vary significantly, from mild comedonal acne to fulminant systemic disease. Although all age groups may be affected by its many variants, the peak incidence is during adolescence. Acne has an undeniable psychosocial impact, and affected individuals have an increased likelihood of self-consciousness, social isolation, anxiety disorders, depression, and even suicidal ideation[1,2]. Insights into the pathogenesis of acne have aided significantly in further defining the subtypes of acne and establishing effective treatment regimens.

HISTORY

In the sixth century CE, the term "acne" was first used by the Emperor Justinian's physician, Aetius Amidenus. It was later translated from Greek into Latin, and through these translations confusion arose regarding its original meaning. The debate continues as to whether its origin is from the Greek *acme*, meaning peak, or whether acne was actually the original term. Its use became obsolete until the 1800s, when "acne" regained a place in medical dictionaries. In 1842, Erasmus Wilson separated acne simplex (acne vulgaris) from acne rosacea[3].

EPIDEMIOLOGY

Acne vulgaris affects ~40–50 million individuals each year in the US alone, leading to an estimated annual cost in the US of at least $2.5 billion. Globally, acne accounts for ~0.3% of the total and ~15% of the dermatologic disease burden[4]. With a peak incidence during adolescence, acne affects ~85% of young people between 12 and 24 years of age and is therefore a physiologic occurrence in this group. With the general trend over the past few decades for an earlier onset of puberty, preadolescent acne affecting children 7 to 11 years of age has also become more common[5,6]. While typically thought of as a disease of youth, acne often continues to be problematic well into adulthood. In a survey-based study in the US, 35% of women and 20% of men reported having acne in their 30s, while 26% of women and 12% of men were still affected in their 40s[7]. White boys and men have a tendency to have more severe nodulocystic disease than other groups.

Individuals at increased risk for the development of acne include those with an XYY karyotype or endocrine disorders such as polycystic ovarian syndrome, hyperandrogenism, hypercortisolism, and precocious puberty. Patients with these conditions tend to have more severe acne that is less responsive to standard therapy.

Genetic Factors

The precise role of genetic predisposition in the multifactorial pathogenesis of acne remains to be determined. The number, size, and activity of sebaceous glands is inherited. In addition, the concordance rate for the prevalence and severity of acne among identical twins is extremely high. It is widely believed that the tendency to have substantial acne (including the nodulocystic variant) runs in families, and an association between moderate-to-severe acne and a family history of acne has been observed in several studies[8]. Genes found to have a possible link to acne via genome-wide association studies (GWAS) and other methods include those encoding components of the tumor transforming growth factor-β (TGF-β) pathway, other inflammatory mediators, and regulators of androgen metabolism[6,9,10].

Dietary Factors

The relationship between diet and acne remains controversial. Several observational studies in different ethnic groups have found that the intake of milk, especially skim milk, is positively associated with acne prevalence and severity[11,12]. Exacerbation of acne with the use of whey protein supplements for bodybuilding has also been reported[13]. Vitamin B_{12} supplementation can potentially trigger the development of acne or an acneiform eruption by altering the transcriptome of skin microbiota, leading to increased production of proinflammatory porphyrins by *Cutibacterium acnes*.

PATHOGENESIS OF ACNE

The development of acne involves the complex interplay of four main factors: (1) follicular hyperkeratinization; (2) hormonal influences on sebum production and composition; (3) inflammation; and (4) *C. acnes* residing in the sebaceous follicle (Fig. 36.1). Appreciating the anatomy and physiology of the pilosebaceous unit is essential to understanding the pathogenesis of acne and designing effective treatment regimens. Genetics and exogenous factors such as diet, medications, and environmental exposures can also play a role in acne pathogenesis. The structure and function of sebaceous glands are reviewed in detail in Chapter 35, with summaries of their roles in acne in Table 35.3 and Fig. 35.4.

Follicular Hyperkeratinization

The *microcomedo* is thought to be the precursor of all clinically apparent acne lesions. It forms in the upper portion of the follicle within the lower portion of the infundibulum, the infrainfundibulum. Corneocytes, which are normally shed into the hair follicle lumen and extruded, accumulate due to increases in both follicular keratinocyte proliferation and corneocyte cohesiveness, leading to the development of a hyperkeratotic plug that acts as a bottleneck. In acne patients, non-invasive high-resolution imaging of facial skin has confirmed that follicular dilation and accumulation of a keratotic plug precede the appearance of an inflammatory papule[14]. The exact inciting event for microcomedo formation is unknown, but data support a putative role for interleukin-1α (IL-1α) and increases in skin pH[15].

Hormonal Influences on Sebum Production and Composition

The sebaceous gland expresses multiple receptors including androgen, estrogen, progesterone, retinoid, and peroxisome proliferator-activated receptors (PPARs; see Table 35.3)[16–18]. Sebum production is controlled primarily by androgens, with additional influences from other hormones and neuropeptides. Androgens are produced both outside the pilosebaceous unit, mainly by the gonads and adrenal glands, and locally within the sebaceous gland via the action of androgen-metabolizing

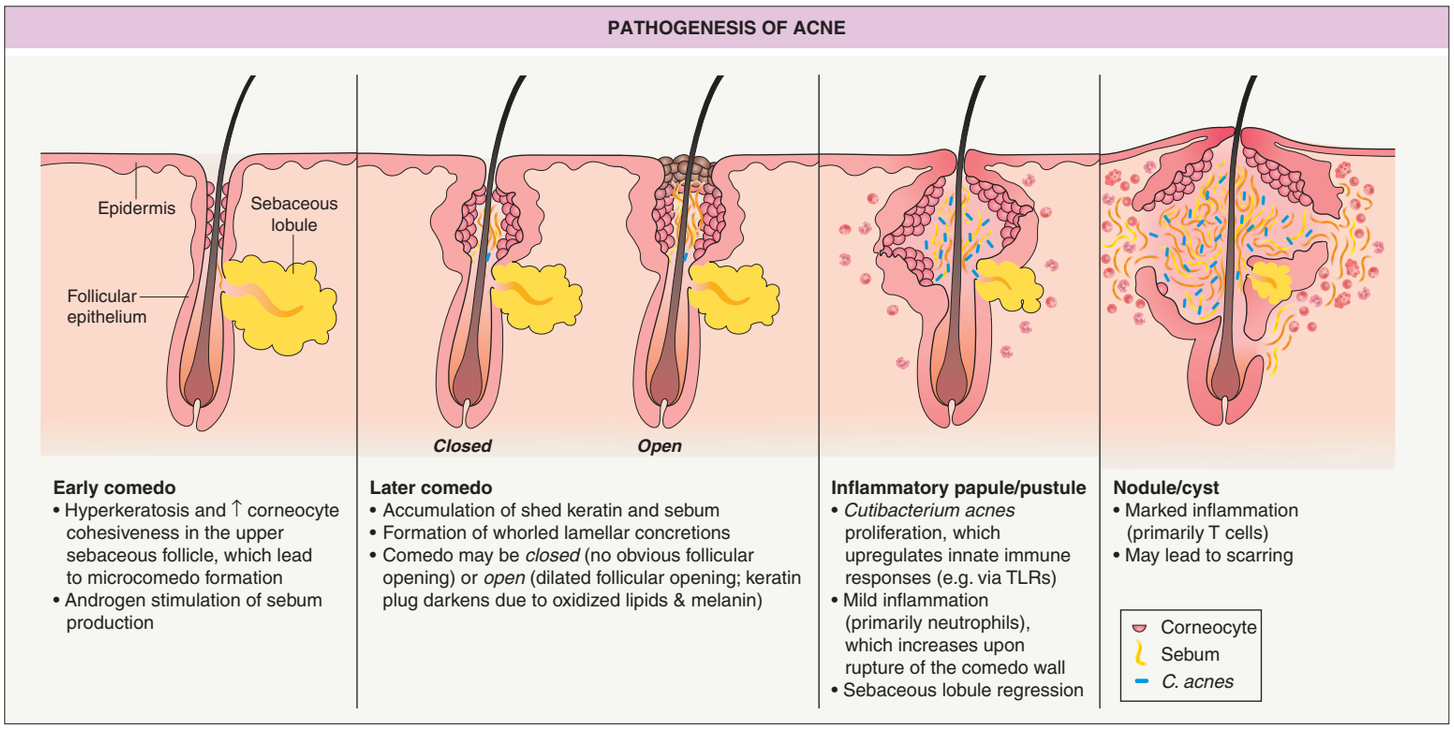


Fig. 36.1 Pathogenesis of acne.

enzymes such as 3β-hydroxysteroid dehydrogenase (HSD), 17β-HSD and 5α-reductase (see Fig. 70.16). Androgen receptors, found in the cells of the basal layer of the sebaceous gland and the outer root sheath of the hair follicle, are responsive to testosterone and 5α-dihydrotestosterone (DHT), the most potent androgens. DHT has a 5- to 10-fold greater affinity than testosterone for the androgen receptor and is the principal androgen mediating sebum production.

The impact of androgens on sebaceous gland activity begins during the neonatal period. From birth until approximately 6–12 months of age, infant boys have elevated levels of luteinizing hormone (LH), which stimulates testicular production of testosterone. In addition, both male and female infants exhibit increased levels of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) secondary to a large, androgen-producing "fetal zone" in the adrenal gland that involutes during the first year of life. Sebaceous gland activity in infants is not the result of persistent maternal hormonal stimulation, as was previously hypothesized. Both testicular and adrenal androgen production decrease substantially by 1 year of age and remain at a stable nadir until adrenarche.

With the onset of adrenarche, typically at 7–8 years of age, circulating levels of DHEAS begin to rise due to its production by the adrenal gland. This hormone serves as a precursor for the synthesis of more potent androgens within the sebaceous gland (see Fig. 70.16). The rise in DHEAS serum levels in prepubescent children is associated with increased sebum production and often the initial development of comedonal acne[19]. Although the overall composition of sebum is similar in adolescents irrespective of the presence or absence of acne, the sebum in those with acne tends to have higher levels of squalene monounsaturated fatty acids and less linoleic acid. In infants with facial acne, the skin surface lipid composition has also been shown to differ from those without acne[20].

The physiologic role of estrogens and progesterone in modulating sebum production is not fully understood. Estrogens, when administered systemically in sufficient amounts, decrease sebum production[21], although the dose needed is greater than the dose required to suppress ovulation and increases the risk of thromboembolic events. However, acne often responds to treatment with lower-dose oral contraceptives containing 20–50 mcg of ethinyl estradiol or its esters because suppression of ovulation itself inhibits ovarian androgen production. Postulated mechanisms for estrogen-mediated downregulation of sebogenesis include direct opposition of androgens within the sebaceous gland, a negative feedback loop that decreases androgen production via inhibition of pituitary gonadotropin release, and regulation of genes that affect sebaceous gland activity. Although the role of progesterone in human sebum production remains to be fully determined, it can increase sebum production in both male and female rats, likely via modulation of the androgen receptor[22].

Inflammation in Acne

Although tremendous progress has been made in our understanding of acne as an inflammatory process, several questions remain regarding inflammation during acne lesion development. It is clear that when a follicle involved with acne ruptures, it exudes keratin, sebum, *C. acnes*, and cellular debris into the surrounding dermis, thereby intensifying inflammation. However, inflammation is also seen early in acne lesion formation. For example, in acne-prone sites, the number of $CD4^+$ T cells and levels of IL-1 are increased perifollicularly prior to hyperkeratinization[23]. In addition, insulin-like growth factor-1 has been found to increase the expression of inflammatory markers and sebum production in cultured sebocytes. TREM2 macrophages induced by lipids such as squalene have been shown to promote inflammation in acne lesions and block oxidative killing of *C. acnes*[23a].

The type of inflammatory response determines the clinical lesion observed. If neutrophils predominate (typical of early lesions), suppuration occurs and a pustule is formed. Neutrophils also promote the inflammatory response by releasing lysosomal enzymes and generating reactive oxygen species; levels of the latter in the skin and plasma may correlate with acne severity[24]. An influx of lymphocytes (predominately T helper cells), foreign body-type giant cells, and neutrophils results in inflamed papules, nodules, and cysts. The type of inflammatory response also plays a role in the development of scarring. Early, nonspecific inflammation results in less scarring than does a delayed, specific inflammatory response[25].

Cutibacterium acnes colonization and activities

C. acnes (previously known as *Propionibacterium acnes*) is a Gram-positive, anaerobic/microaerophilic rod that is found on the skin surface and within the sebaceous follicle[26], often together with smaller numbers of *C. granulosum*. In adults, *C. acnes* is the predominant organism in the microbiome of facial and other sebaceous skin. *C. acnes* produces porphyrins (primarily coproporphyrin III) that fluoresce with Wood's lamp illumination.

C. acnes is considered a commensal organism of the skin rather than a pathogen *per se*[27]. Although studies have documented increased levels

of *C. acnes* on the facial skin of acne patients, the *C. acnes* density does not correlate with clinical severity[28]. In a comparison of the microbiome of facial skin in adults with and without acne, *C. acnes* ribotypes 4 and 5 were more frequently found in acne patients, suggesting that these strains are either more capable of inducing acne or better suited to survive in an acne environment[29]. In addition, acne-associated *C. acnes* phylotypes (IA-2, IB-1, IC) stimulated peripheral blood monocytes to produce the proinflammatory cytokines IL-17 and IFN-γ, whereas phylotypes found in healthy skin (II [RT6], III) preferentially induced monocytes to secrete the anti-inflammatory cytokine IL-10[30]. However, another study found that while isolated peripheral blood monocytes from patients with acne exhibited a more robust release of inflammatory cytokines in response to *C. acnes* stimulation than did monocytes from individuals without acne, no differences were observed when *C. acnes* strains isolated from acne lesions were compared to strains from the normal skin of unaffected adults[31].

The pathogenicity of *C. acnes* includes the direct release of lipases, chemotactic factors, and enzymes that contribute to comedo rupture, as well as stimulation of inflammatory cells and keratinocytes to produce proinflammatory mediators and reactive oxygen species. Interactions between the skin's *innate* immune system and *C. acnes* play an important role in acne pathogenesis. One mechanism is via Toll-like receptors (TLRs), a class of transmembrane receptors that mediates the recognition of microbial pathogens by immune cells (monocytes, macrophages, and neutrophils) as well as by keratinocytes (see Ch. 4). TLR2, which recognizes lipoproteins and peptidoglycans as well as CAMP factor 1 produced by inflammatory strains of *C. acnes*[32], is found on the surface of macrophages surrounding acne follicles[33]. *C. acnes* has also been shown to increase expression of TLR2 and TLR4 by keratinocytes. Through activation of the TLR2 pathway, *C. acnes* stimulates the release of proinflammatory mediators such as IL-1α, IL-8, IL-12, tumor necrosis factor (TNF), and matrix metalloproteinases[33–35]. IL-8 leads to neutrophil recruitment, the release of lysosomal enzymes, and subsequent disruption of the follicular epithelium, while IL-12 promotes Th1 responses (see Ch. 4).

C. acnes has been shown to activate NLRP3 inflammasomes in neutrophils and monocytes, resulting in the release of proinflammatory IL-1β[36]. As noted above, *C. acnes* also stimulates Th17 responses within acne lesions[37]. Lastly, *C. acnes* can induce monocytes to differentiate into two distinct innate immune cell subsets: (1) $CD209^+$ macrophages, which more effectively phagocytose and kill *C. acnes* and whose development is promoted by tretinoin; and (2) $CD1b^+$ dendritic cells that activate T cells and release proinflammatory cytokines[24].

CLINICAL FEATURES

Acne is typically found in sites with well-developed sebaceous glands, most often the face and upper trunk. Despite evidence that inflammation is present in even the earliest comedones, acne lesions are divided into non-inflammatory and inflammatory groups based upon their clinical appearance. Non-inflammatory acne is characterized by open and closed comedones (Fig. 36.2). The histologic features of these follicular-based lesions are reflected in their clinical appearance. Closed comedones (whiteheads) are generally small (~1 mm), skin-colored papules with no apparent follicular opening or associated erythema. These lesions may be subtle and better appreciated upon palpation, stretching, or side-lighting of the skin. In contrast, open comedones (blackheads) have a conspicuous dilated follicular opening that is filled with an inspissated core of shed keratin (see Fig. 36.4). Melanin deposition and lipid oxidation within the debris may be responsible for the black color. Larger macrocomedones are deep-seated and may be cystic.

Inflammatory acne is characterized by papules, pustules, and nodules of varying severity (Figs. 36.3–36.6). Erythematous papules typically range from 1 to 5 mm in diameter. Pustules tend to be approximately equal in size and are filled with white purulent material and normal microbiota, including *C. acnes*. As the severity of lesions progresses, nodules form and become markedly inflamed, indurated, and tender. The pseudocysts of acne are deeper and filled with a combination of pus and serosanguineous fluid. In patients with severe nodulocystic acne, these lesions frequently coalesce to form large, complex, inflamed plaques that can include sinus tracts.

Early treatment of acne is essential for the prevention of lasting cosmetic disfigurement due to scarring. Erythema and

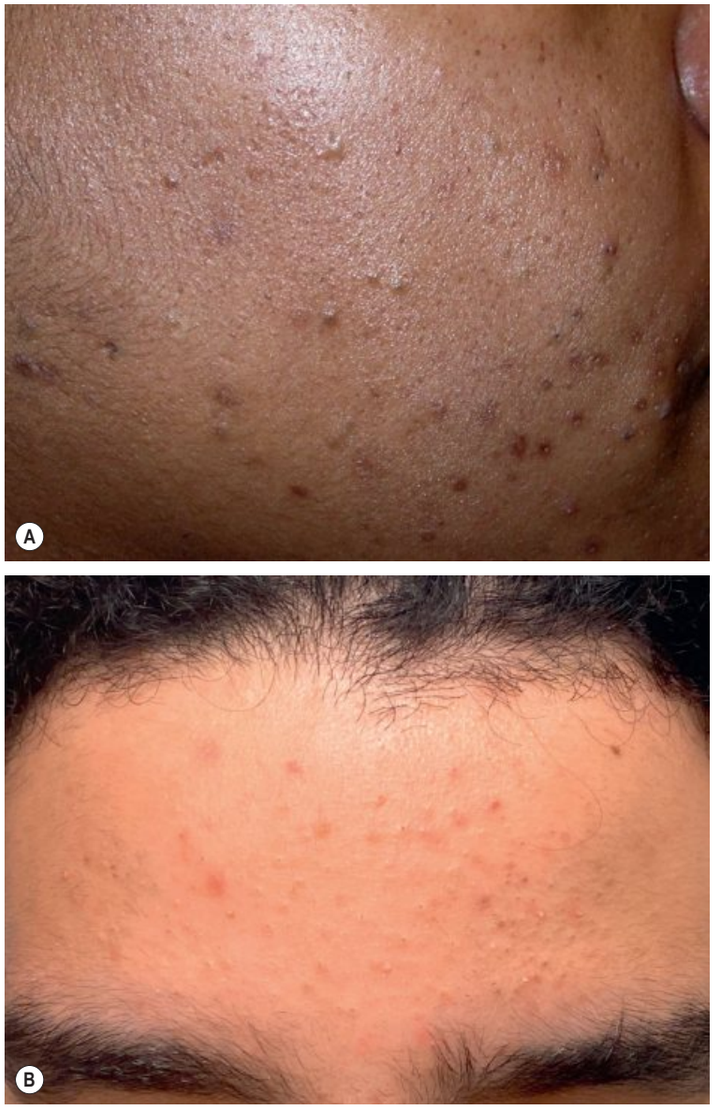


Fig. 36.2 Comedonal acne vulgaris. On the cheek (**A**) and forehead (**B**), there are open and closed comedones as well as postinflammatory hyperpigmentation (**A**) and inflammatory papules (**B**). *B, Courtesy Kalman Watsky, MD.*



Fig. 36.3 Moderate acne vulgaris. Scattered papulopustules and papulonodules are present on the cheek. *Courtesy Kalman Watsky, MD.*

postinflammatory hyperpigmentation (Fig. 36.7) often persist after resolution of inflammatory acne lesions. Although the pigmentary changes usually fade over many months if the acne is brought under control, occasionally they can be permanent. Unfortunately, pitted scars (Fig. 36.8A) or hypertrophic scars (most commonly on the trunk; Fig. 36.8B,C) are often sequelae of nodulocystic acne. Skin-colored, dome-shaped papules on the nose and chin with histopathologic features indistinguishable from angiofibromas represent an additional form of acne scarring that has a predilection for male patients with darkly pigmented skin (Fig. 36.9)[38].



Fig. 36.4 Moderate to severe acne vulgaris. Inflammatory papules and pustules as well as both open and closed comedones are evident on the cheek, forehead, and chin. Note the nodular lesion on the temple and open comedones in the concha of the ear. Scarring is present in the preauricular area.

Acne Variants

Post-adolescent acne in women

Inflammatory acne beyond 25 years of age is most common in women and may be associated with a high level of psychological stress[11]. The majority of affected women present with findings similar to those of adolescent acne, with a mixture of inflammatory and comedonal lesions involving various facial sites and sometimes the trunk[39]. Although the mandibular area is involved in ~80% of women with acne, a distinct smaller subset has inflammatory papules, pustules, and nodules exclusively in this location. Half of women report persistence of their acne since its onset, often during adolescence, while one-quarter describe periods of remission followed by recurrences. Premenstrual flares are common[40], but only ~20% of women with acne have irregular menses. Up to 30% of those in the latter group have other signs of hyperandrogenism, such as hirsutism and androgenetic alopecia (see below). A predominantly comedonal, adult-onset form of acne that is associated with smoking has also been described[41].

Acne fulminans

Acne fulminans is the most severe form of acne and is characterized by the abrupt development of nodular and suppurative acne lesions in association with systemic manifestations. This uncommon variant primarily affects boys 13–16 years of age. Patients typically have mild to moderate acne prior to the onset of acne fulminans, when numerous microcomedones suddenly erupt and become markedly inflamed. There is rapid coalescence into painful, oozing, friable plaques with hemorrhagic crusts (Fig. 36.10). The face, neck, trunk, and arms are all affected. Lesions tend to ulcerate and can lead to significant scarring.

Osteolytic bone lesions may accompany the cutaneous findings; the clavicle and sternum are most commonly affected, followed by the ankles, humerus, and iliosacral joints. Systemic manifestations include fever, arthralgias, myalgias, hepatosplenomegaly, and severe malaise. Erythema nodosum may also arise in association with acne fulminans. Laboratory abnormalities vary and include an elevated ESR, proteinuria, leukocytosis, and anemia. Laboratory studies are not required to establish the diagnosis, but their evolution may parallel the clinical course and response to therapy. The related *s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis, and *o*steitis (SAPHO) syndrome, which can accompany acne fulminans, is discussed in detail in Chapter 26. Acne fulminans has also been associated with late-onset congenital adrenal hyperplasia and anabolic steroid use, including therapeutic testosterone.

Recommended treatment of acne fulminans includes prednisone 0.5–1 mg/kg/day as monotherapy for at least 2–4 weeks, followed by initiation of low-dose isotretinoin (e.g. 0.1 mg/kg/day) after the acute inflammation subsides; after at least 4 weeks of this combination, the isotretinoin dose can be slowly increased and the prednisone tapered over a period of 1–2 months[42]. Paradoxically, an acne fulminans-like flare occasionally develops during the first few weeks of isotretinoin therapy



Fig. 36.5 Moderate to severe acne vulgaris. Multiple coalescing papules, papulopustules, and small nodules are present on the cheeks (**A,B**) and temple (**A**). Early scarring is evident laterally (**A**). *B, Courtesy Kalman Watsky, MD.*



Fig. 36.6 Severe to very severe nodular acne. **A** Numerous nodules. **B** Acne conglobata with coalescence of purulent nodules on the forehead, with associated eyelid edema. This form is best treated with prednisone and a low dose of isotretinoin initially. *B, Courtesy Julie V. Schaffer, MD.*



Fig. 36.7 Postinflammatory hyperpigmentation secondary to acne. Such pigmentary changes are common in patients with darker skin tones.

for acne[43]; this may be avoided by starting with a low dose of isotretinoin and concomitant administration of oral corticosteroids at the first sign of a flare or possibly preemptively in high-risk patients (see Ch. 126). Additional treatment options for acne fulminans include topical or intralesional corticosteroids, oral antibiotics (generally of limited efficacy), TNF inhibitors, IL-1 antagonists, and immunosuppressive agents (e.g. azathioprine, cyclosporine). Dapsone may be particularly beneficial in the treatment of acne fulminans associated with erythema nodosum[44].

Acne conglobata and associated conditions

Acne conglobata (see Fig. 36.6B) is a severe form of nodulocystic acne that may have an eruptive onset but without systemic manifestations. This recalcitrant acne variant is part of the follicular occlusion tetrad, along with dissecting cellulitis of the scalp, hidradenitis suppurativa, and pilonidal sinus (see Ch. 38).

The association of sterile *p*yogenic *a*rthritis, *p*yoderma gangrenosum, and *a*cne conglobata can occur in the context of an autosomal dominant autoinflammatory disorder referred to as PAPA syndrome, which can be caused by mutations in *PSTPIP1* which encodes *p*roline–serine–*t*hreonine *p*hosphatase *i*nteracting *p*rotein 1[45]. Dysfunction of PSTPIP1, which has a role in actin reorganization and interacts with the pyrin protein (defective in familial Mediterranean fever), compromises the physiologic signaling required for maintenance of a proper inflammatory response. *PSTPIP1* mutations have also been identified in some patients with *p*yogenic *a*rthritis, *p*yoderma gangrenosum, *a*cne, and *s*uppurative *h*idradenitis (PAPASH) and *p*yoderma gangrenosum, *a*cne, and *s*uppurative *h*idradenitis (PASH) syndromes[46,47]. Of note, a possible association between nodulocystic acne and inflammatory bowel disease may potentially confound links that have been observed between the latter disorder and acne therapies such as tetracyclines and isotretinoin[48].

Solid facial edema

An unusual and disfiguring complication of acne vulgaris is solid facial edema (Morbihan disease). Clinically, there is a distortion of the midline face and cheeks due to soft tissue swelling (Fig. 36.11). The woody induration may be accompanied by erythema. Impaired lymphatic drainage and fibrosis (potentially induced by mast cells) in the setting of chronic inflammation are thought to be involved in the pathogenesis of solid facial edema, and a report of its occurrence in identical twins with acne suggests that genetic factors may also have a role. Similar changes have been described in patients with rosacea (see Table 36.2). Although fluctuations in severity are common, solid facial edema does not usually resolve spontaneously. Treatment with isotretinoin (0.2–1 mg/kg/day) for 4–6 months has been reported to lead to improvement, although a more extended course of 9–24 months is often required[49]. Combination of isotretinoin with ketotifen 1–2 mg/day (not available in the US) or prednisone 10–30 mg/day may have additional benefit[50].

Neonatal cephalic pustulosis (neonatal acne)

Neonatal cephalic pustulosis occurs in more than 20% of healthy newborns (see Ch. 34). Lesions usually appear at about 2 weeks of age and generally resolve within the first 3 months of life. Small papulopustules, but not comedones, arise primarily on the cheeks, forehead, eyelids and chin, although the neck and upper trunk can also be involved (see Fig. 34.6).

An inflammatory response to *Malassezia* spp. (e.g. *sympodialis, furfur*) has been proposed as the etiology by some investigators. Additional support for this view comes from the clinical response to treatment with topical imidazoles (e.g. ketoconazole 2% cream). Active sebaceous glands in neonates and their relatively high sebum excretion rate (see Pathogenesis) are also thought to play a role. The substantial decline in sebum production after the first few months of life helps to explain the limited duration of neonatal cephalic pustulosis. Given the



Fig. 36.8 Scarring secondary to acne. A Pitted scars on the cheeks. **B, C** Mixture of atrophic and hypertrophic scars on the back. *B, Courtesy Julie V. Schaffer, MD.*



Fig. 36.9 Dome-shaped papular scars on the nose. This form of acne scarring has histologic features indistinguishable from angiofibromas and a predilection for male patients with darker skin phototypes.



Fig. 36.10 Acne fulminans. Eruptive, friable papulopustules with erosions, oozing, and formation of granulation tissue.



Fig. 36.11 Solid facial edema due to acne vulgaris. There is soft tissue swelling in the central portion of the face. *Courtesy Boni Elewski, MD.*

transient and benign nature of this eruption, parental reassurance alone is usually adequate. However, as noted previously, therapy with topical imidazoles can be effective.

Infantile acne

Infantile acne typically has its onset at 2–12 months of age[5]. In contrast to neonatal cephalic pustulosis, comedo formation is prominent and pitted scarring may develop in up to half of patients (Fig. 36.12)[51]. Deep, suppurative nodules are occasionally seen. Its pathogenesis reflects the androgen production intrinsic to this stage of development (see Pathogenesis), including elevated levels of LH that stimulate testicular production of testosterone in boys during the first 6–12 months of life and elevated levels of DHEA produced by the infantile adrenal gland in both boys and girls. These androgen levels normally decrease substantially by 12 months of age and remain at nadir levels until adrenarche. Patients with infantile acne should be assessed for signs of hyperandrogenism, precocious puberty, or abnormal growth; if these findings are present, endocrinologic evaluation including a hand/wrist X-ray to determine bone age and laboratory testing of hormone levels should be performed.

Infantile acne usually resolves within 6–18 months and remains quiescent until around puberty, with an increased risk of severe acne during adolescence having been observed[5]. Topical retinoids (e.g. tretinoin, adapalene) and benzoyl peroxide are first-line treatments for infantile acne. Oral antibiotics (e.g. erythromycin, azithromycin) can be helpful for patients with a more severe inflammatory component, and isotretinoin is occasionally required for recalcitrant or nodulocystic presentations[52].

Mid-childhood acne

Acne presenting between 1 and 6 or 7 years of age is categorized as "mid-childhood acne"[5]. Because this is an uncommon time for acne development due to quiescent androgen production, the possibility of an underlying hyperandrogenic condition such as premature adrenarche, congenital adrenal hyperplasia, or an androgen-secreting tumor should be considered. In addition to a thorough history and physical examination to assess for signs of hyperandrogenism (see below) and precocious puberty, the child's growth curve should be carefully reviewed and a hand/wrist bone age X-ray performed if there are signs of accelerated growth. A complete endocrine evaluation is required if any abnormalities are present[53]. Treatment strategies are the same as for infantile acne.

Preadolescent acne

It is common for acne to begin to develop with the onset of adrenarche, typically between 7 or 8 to 11 years of age, which is often prior to other signs of pubertal maturation[5]. Preadolescent acne tends to be primarily comedonal and favors the forehead and central face ("T-zone"). Polycystic ovary syndrome (PCOS) and other endocrinologic abnormalities should be considered when the acne is unusually severe or accompanied by



Fig. 36.12 Infantile acne. Presentations can range from numerous open comedones (**A**) to primarily papulopustules (**B**). *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Kalman Watsky, MD.*

signs of hyperandrogenism. Treatment is similar to that for adolescent acne, although tetracycline courses of >21 days should be avoided in children <8 years of age.

Acne excoriée

Acne excoriée occurs more often in young women, in whom it may be referred to as acne excoriée des jeunes filles. Typical comedones and inflammatory papules are systematically excoriated in a ritualistic manner, leaving crusted erosions that may scar (see Ch. 7). Linear erosions suggest self-manipulation, and an underlying psychiatric component should be considered. Individuals with an anxiety, obsessive–compulsive, or body dysmorphic disorder are particularly at risk, and antidepressants or psychotherapy may be helpful in these patients.

Acne associated with endocrinologic abnormalities

Although most patients with acne do not have overt endocrinologic abnormalities, hyperandrogenism should be suspected in women and late adolescent girls with irregular menstrual periods. Acne in such patients is often severe or more difficult to treat, and the onset can be fairly abrupt. Other signs and symptoms of hyperandrogenism in women and children include hirsutism (see Ch. 70), coarsening of the voice, a muscular habitus, androgenetic alopecia, clitoromegaly with variable posterior labial fusion, and increased libido. *I*nsulin *r*esistance and *a*canthosis *n*igricans can occur in association with *h*yper*a*ndrogenism in the HAIR-AN syndrome. These patients are at increased risk for accelerated cardiovascular disease and diabetes mellitus, and they should be followed by appropriate medical specialists.

The evaluation of patients suspected of having hyperandrogenism includes a thorough history and physical examination; the age of the patient and pubertal status are also important parameters. Prepubertal children, adolescent girls, and women with signs of hyperandrogenism should undergo appropriate evaluation, and laboratory studies should not be performed while the patient is taking oral contraceptives. Initial tests typically include serum levels of total and free testosterone, DHEAS, and 17-hydroxyprogesterone. Patients with clinical findings suggestive of hypercortisolism should also be initially assessed with either a late-night salivary cortisol level, 24-hour urine cortisol level, or low-dose dexamethasone suppression test[54]. In prepubertal children, growth charts should be assessed and X-rays of the hand and wrist performed to evaluate bone age (see Mid-childhood acne).

Understanding pathways of hormone production is essential in the evaluation of hyperandrogenic states (see Fig. 70.18). For example, an elevated serum DHEAS or 17-hydroxyprogesterone level indicates an adrenal source of excess androgen production. The degree to which levels of these hormones are increased is then useful in discerning an etiology. DHEAS values in the range of 4000–8000 ng/ml or 17-hydroxyprogesterone levels >3 ng/ml may be indicative of congenital adrenal hyperplasia. Defects in adrenal enzymes, most commonly 21-hydroxylase and less often 11-hydroxylase, lead to this condition. Patients with severe deficiencies of these enzymes become symptomatic during infancy, whereas those with partial deficiencies present in adolescence. If the serum DHEAS is >8000 ng/ml, with or without an elevated testosterone level, an adrenal tumor should be suspected.

If the testosterone levels (total and free) are elevated and the DHEAS level is relatively normal, an ovarian source is likely. Polycystic ovary syndrome (PCOS) is the most common condition associated with an elevated serum testosterone, with levels typically ranging from 100 to 200 ng/dl. An increased LH/FSH ratio (>2–3) is also commonly observed. Symptoms of PCOS include irregular menstrual periods, hirsutism, obesity, insulin resistance, and reduced fertility (see Fig. 70.14). When levels of serum testosterone exceed 200 ng/dl, an ovarian tumor should be considered.

Acne associated with genetic syndromes

Apert syndrome (acrocephalosyndactyly type I) is an autosomal dominant disorder that features disfiguring synostoses of the bones of the hands and feet, vertebral bodies, and cranium. Affected individuals have an increased incidence of severe, early-onset acne that tends to be nodulocystic and have a more widespread distribution than in classic acne, often involving the entire extensor aspects of the arms, buttocks, and thighs[55]. Acne in patients with Apert syndrome is typically resistant to therapy, although isotretinoin has been reported to be beneficial[56]. Other cutaneous findings in this disorder can include marked seborrhea, nail anomalies (e.g. a single nail for the second through fourth digits), and diffuse pigmentary dilution of the hair and skin. Of note, Apert syndrome results from activating mutations in *FGFR2*, which encodes fibroblast growth factor receptor 2; mosaicism for the same *FGFR2* mutations has been found to underlie the Munro acne nevus (see Ch. 62). FGFR2 signaling has been shown to have effects on follicular keratinocyte proliferation, sebaceous lipogenesis, and inflammatory cytokine production.

Frank–ter Haar syndrome (Borrone dermato-cardio-skeletal syndrome), an autosomal recessive disorder caused by *SH3PXD2B* mutations that affect epidermal growth factor signaling, is characterized by dysmorphic facies, thick skin, severe acne, vertebral abnormalities, and mitral valve prolapse[57]. Early-onset, severe acne and hidradenitis suppurativa have been reported in patients with Patau syndrome (trisomy 13). *PAPA syndrome* and related conditions are discussed in the section on acne conglobata.

Acneiform Eruptions

Drug-induced acne

Acne or acneiform eruptions (e.g. folliculitis) can be seen as a side effect of a number of medications (Table 36.1). An abrupt, monomorphous eruption of inflammatory papules and pustules is often observed in drug-induced acne (Fig. 36.13), in contrast to the heterogeneous morphology of lesions seen in acne vulgaris. When a history of prescription medication use is not elicited, a comprehensive review of all over-the-counter medications and supplements, as well as recent medical procedures, may reveal the responsible agent (see Table 36.1). Bodybuilders and athletes should be questioned about the use of anabolic steroids as well as protein supplements. It is important to

CAUSES OF DRUG-INDUCED ACNE	
Common	**Uncommon**
Anabolic steroids (e.g. danazol, testosterone)	Azathioprine
Bromides*	Checkpoint inhibitors (e.g. anti-PD-1; see Ch. 21)
Corticosteroids (see Fig. 36.13)	Cyclosporine
Corticotropin	Disulfiram
EGFR and EGFR/MEK inhibitors** (see Fig. 36.14 and Ch. 21)	Elexacaftor-tezacaftor-ivacaftor***
Iodides†	Ethosuximide
Isoniazid	Other kinase inhibitors (e.g. vemurafenib, ibrutinib)
JAK inhibitors (e.g. upadacitinib)	Phenobarbital
Lithium	Propylthiouracil
MEK inhibitors (e.g. trametinib; see Ch. 21)	Psoralen + ultraviolet A
mTOR inhibitors (e.g. sirolimus)	Quinidine
Phenytoin	Quetiapine
Progestins (see text)	TNF inhibitors
	Vedolizumab
	Vitamins B_6 and B_{12}

*Found in sedatives, analgesics, cold remedies, and ipratropium bromide inhalers.
**3rd generation EGFR inhibitors are less likely to induce an acneiform eruption.
***Used to treat cystic fibrosis; necrotizing infundibular crystalline folliculitis may be evident histologically.
†Found in contrast dyes, cold/asthma remedies, kelp, and combined vitamin–mineral supplements.

Table 36.1 Causes of drug-induced acne. EGFR, epidermal growth factor receptor.



Fig. 36.13 Acneiform eruption secondary to high-dose dexamethasone. Abrupt eruption of monomorphous follicular papules and pustules on the chest.

note that gender-affirming hormonal therapy (e.g. testosterone) can exacerbate acne in transgender patients[58]. In one study, a third of transgender patients receiving masculinizing hormonal therapy had acne[59].

High-dose intravenous or oral corticosteroids commonly induce characteristic acneiform eruptions with a concentration of lesions on the chest and back (see Fig. 36.13). Steroid-induced acne (and rosacea) can also result from the inappropriate use of topical corticosteroids on the face. Inflamed papules and pustules develop on a background of erythema that favors the distribution of corticosteroid application. Lesions eventually resolve following discontinuation of the corticosteroid, although "steroid dependency" can lead to prolonged and severe flares post-withdrawal (see Ch. 37).



Fig. 36.14 Acneiform eruptions due to epidermal growth factor receptor inhibitors. Numerous monomorphous follicular pustules on the face of an adolescent boy treated with erlotinib.

Epidermal growth factor receptor (EGFR) inhibitors, kinase inhibitors (e.g. MEK inhibitors), and immune checkpoint inhibitors (e.g. anti-PD-1, -PD-L1, -CTLA-4) can induce acneiform papulopustular eruptions[60] (Fig. 36.14; see Tables 21.16 & 21.18). Janus kinase (JAK) inhibitors (e.g. upadacitinib, tofacitinib) have also been associated with exacerbation of acne. Eruptions of comedo-like and cystic lesions similar to chloracne have been described in patients receiving the BRAF inhibitor vemurafenib[61].

Occupational acne, acne cosmetica, and pomade acne

Exposure to insoluble, follicle-occluding substances in the workplace is responsible for occupational acne (see Ch. 16). Offending agents include cutting oils, petroleum-based products, chlorinated aromatic hydrocarbons, and coal tar derivatives. Comedones dominate the clinical picture, with varying numbers of papules, pustules, and cystic lesions distributed in exposed as well as typically covered areas. Primarily comedonal facial acne, with a predominance of closed comedones, can also develop in sites chronically exposed to follicle-occluding cosmetics (*acne cosmetica*) or hair products. The latter, referred to as *pomade acne*, favors the forehead and temples. Face mask-induced acneiform eruptions ("maskne") became more common during the SARS-CoV-2 pandemic[62].

Chloracne (metabolizing acquired dioxin-induced skin hamartomas [MADISH])

Chloracne results from systemic exposure to halogenated aromatic hydrocarbons, which accelerate keratinization and convert sebocytes to keratinocytic differentiation via activation of the aryl hydrocarbon receptor and induction of cytochrome P450 1A1 expression. Chloracne typically develops several weeks after exposure, which can occur via percutaneous absorption, inhalation, or ingestion. The following agents, found in electrical conductors and insulators, insecticides, fungicides, herbicides and wood preservatives, have all been implicated: polychlorinated naphthalenes, biphenyls, dibenzofurans and dibenzodioxins; polybrominated naphthalenes and biphenyls; tetrachloroazobenzene; and tetrachloroazoxybenzene.

Comedo-like lesions and yellowish cysts with relatively little associated inflammation most commonly affect the malar and retroauricular areas of the head and neck (see Fig. 16.13), as well as the axillae and scrotum. The extremities, buttocks, and trunk are variably involved. Cystic lesions can heal with significant scarring, and the condition may persist for several years following cessation of exposure. Additional findings may include hypertrichosis and grayish discoloration of the skin.

Initial management is aimed at removal of the source of exposure. Topical or oral retinoids may be beneficial, but chloracne is often recalcitrant to therapy.

Acne mechanica

Acne mechanica is due to repeated mechanical and frictional obstruction of the pilosebaceous outlet. Comedo formation is the result. Mechanical factors include rubbing by helmets, chin straps, suspenders, and collars as well as friction between the inner thighs[63]. Orthopedic causes include acne mechanica in the axillae due to the use of crutches and on amputee stumps due to friction from prostheses[64]. A classic example of acne mechanica is fiddler's neck, where repetitive trauma from violin placement on the lateral neck results in a well-defined, lichenified, hyperpigmented plaque interspersed with comedones. Linear and geometrically distributed areas of involvement suggest acne mechanica. Treatment is aimed at eliminating the inciting forces.

Tropical acne

Tropical acne is a follicular acneiform eruption that results from exposure to heat and humidity. This can occur in tropical climates or secondary to scorching occupational environments, as in furnace workers. Historically, tropical acne caused significant morbidity among military troops. Markedly inflamed nodulocystic acne involving the trunk and buttocks is typically seen, and secondary staphylococcal infection is a frequent complication. Treatment is often of limited efficacy until the patient returns to a more moderate climate.

Radiation acne

Radiation acne is characterized by comedo-like papules occurring at sites of previous exposure to therapeutic ionizing radiation. The lesions begin to appear as the acute phase of radiation dermatitis starts to resolve. The ionizing rays induce epithelial metaplasia within the follicle, creating adherent hyperkeratotic plugs that are resistant to expression.

"Pseudoacne" of the nasal crease

The transverse nasal crease is a horizontal anatomical demarcation line found in the lower third of the nose, which corresponds to the separation point between the alar cartilage and the triangular cartilage. Milia, cysts, and comedones can line up along this fold (Fig. 36.15A)[65]. These acne-like lesions are not hormonally responsive and arise during early childhood prior to the onset of puberty. Treatment consists of mechanical expression or topical therapy with a retinoid or benzoyl peroxide as needed.

Idiopathic aseptic facial granuloma (idiopathic facial aseptic granuloma)

This painless nodule with an acneiform appearance typically develops on the cheeks of young children (mean age, ~3.5 years), although older children are occasionally affected[66]. Multiple lesions are uncommon. Histopathologic evaluation reveals a dermal lymphohistiocytic infiltrate with foreign body-type giant cells. In general, cultures are negative and the lesions do not respond to antibiotic therapy. Eventually, after an average of one year, the lesions resolve spontaneously[67]. It has been suggested that this entity represents a form of childhood rosacea as >40% of patients have at least two other clinical signs of rosacea including recurrent chalazions, facial flushing, telangiectasias, or papulopustules[67,68].



Fig. 36.15 Disorders in the differential diagnosis of acne vulgaris. A Pseudoacne of the transverse nasal crease in a young child. Note the milia and comedones located along this anatomical demarcation line. **B** Demodicosis presenting as pustules on the nose of a healthy child. An increased number of *Demodex* mites was observed in a scraping. **C** Acneiform follicular mucinosis on the cheek of a woman. **D** Follicular mycosis fungoides that presented as numerous lesions with a comedonal appearance on the chest, abdomen, and back. *A, B, D, Courtesy Julie V. Schaffer, MD; C, Courtesy Lorenzo Cerroni, MD.*

Childhood flexural comedones

This entity is characterized by discrete, double-orifice comedones localized to the axillae and, less commonly, the groin[69]. The majority of patients have a single lesion and the average age at diagnosis is 6 years, with boys and girls equally affected. Occasionally, the condition is familial. There is no association with hidradenitis suppurativa, acne vulgaris, or precocious puberty. In addition to hidradenitis suppurativa, the differential diagnosis includes comedones associated with resolving molluscum contagiosum or pseudoxanthoma elasticum.

PATHOLOGY

Histopathologic examination of acne lesions demonstrates the stages of acnegenesis that parallel the clinical findings (see Fig. 36.1). In early lesions, microcomedones are seen. A mildly distended follicle with a narrowed follicular opening is impacted by shed keratinocytes. The granular layer at this stage is prominent. In closed comedones, the degree of follicular distension is increased and a compact cystic structure forms. Within the cystic space, eosinophilic keratinaceous debris, hair, and numerous bacteria are present. Open comedones have broad, expanded follicular ostia and greater overall follicular distension. The sebaceous glands are typically atrophic or absent. A mild perivascular mononuclear cell infiltrate encircles the expanding follicle.

As the follicular epithelium distends, the cystic contents inevitably begin to rupture into the dermis (Fig. 36.16). The highly immunogenic cystic contents (keratin, hair, and bacteria) induce a marked inflammatory response. Neutrophils first appear, creating a pustule. As the lesion matures, foreign body granulomatous inflammation engulfs the follicle and end-stage scarring can result.

In acne fulminans, there is massive inflammation with varying degrees of overlying necrosis. Comedones are rarely observed. Severe scarring may be seen in resolving lesions.

DIFFERENTIAL DIAGNOSIS

Although classic acne vulgaris is usually easily recognized clinically, the differential diagnosis of acneiform eruptions is broad and depends upon the age of onset, lesional morphology, and location (Table 36.2; see Fig. 36.15). During the neonatal period, acne must be differentiated from other common dermatoses. Sebaceous hyperplasia occurs in the majority of healthy neonates, presenting as transient yellowish papules on the cheeks, nose, and forehead. Miliaria rubra is also very common during the neonatal period, when overheating and bundling can cause temporary eccrine duct obstruction that leads to the formation of small inflammatory papulopustules. Small, white milia are often apparent on the cheeks and nose of neonates, but they generally resolve within a few months.

Predominantly comedonal acne vulgaris needs to be differentiated from comedonal eruptions caused by follicular occlusion or friction, including acne mechanica, acne cosmetica, pomade acne, and occupational acne (see above); history as well as location can help to make the diagnosis of these forms of "contact acne". Sebaceous hyperplasia, a very common finding in adults, is relatively uncommon in adolescents. These yellowish, lobulated papules arise primarily on the forehead and cheeks.

A solitary enlarged comedo is better classified as a dilated pore of Winer; such lesions rarely represent a large-pore basal cell carcinoma. Multiple open comedones are clustered in the lateral malar region in Favre–Racouchot syndrome (see Ch. 87) or appear in a linear array in nevus comedonicus (see Chs. 62 & 109). If multiple vellus hairs arise from a dilated follicular orifice in association with keratinous debris, trichostasis spinulosa is the likely diagnosis. The most common location is the nose.

Angiofibromas and appendageal tumors of follicular origin, e.g. trichoepitheliomas, trichodiscomas and fibrofolliculomas, often present as multiple facial papules (see Ch. 111). They are typically non-inflammatory, and trichoepitheliomas are concentrated in the nasolabial folds. Non-inflammatory, closed cystic papules and nodules on the central chest and back characterize steatocystoma multiplex (see Ch. 110). This autosomal dominant disorder must be differentiated from a related entity, eruptive vellus hair cysts. These smaller cysts may become inflamed and, as the name implies, contain multiple vellus hairs that can be easily visualized microscopically.

The follicle-based inflammatory papules and pustules of acne vulgaris must be distinguished from the many forms of folliculitis, including staphylococcal, Gram-negative, and eosinophilic variants (see Fig. 38.1). In folliculitis, the lesions are relatively monomorphous and comedones are not present. Gram-negative folliculitis can complicate acne vulgaris treated with oral antibiotics for a prolonged period; the inflammatory lesions typically appear on the central face, including the upper lip, and cheeks. In contrast, *Pseudomonas* ("hot tub") folliculitis favors the lower trunk and other sites covered by a bathing suit. *Malassezia* (*Pityrosporum*) folliculitis, which may develop in acne patients receiving antibiotic therapy, presents with fine papules and pustules favoring the forehead and upper trunk[70]. Eosinophilic folliculitis usually occurs in the setting of immunosuppression (e.g. HIV infection) and is markedly pruritic.

Pseudofolliculitis barbae and acne keloidalis nuchae most often affect men with Afro-textured hair (see Ch. 38). The papular component of rosacea favors the malar region, chin, and forehead; the presence of telangiectasias, an absence of comedones, and a history of easy flushing can aid in diagnosis (see Ch. 37). Rosacea typically occurs at a later age than acne, but both can develop in a single individual. Prolonged use of topical corticosteroids on the face may lead to rosacea-like lesions or periorificial dermatitis, and patients treated with oral corticosteroids can develop an eruption of monomorphous papulopustules that favors the trunk ("steroid folliculitis"; see Fig. 36.13). This can occur at any age and resolves upon discontinuation of the corticosteroid. Lastly, psychogenic (neurotic) excoriations and factitial dermatitis concentrated on the face, chest, and back can mimic acne, particularly acne excoriée. Linearity and the lack of clinically detectable primary lesions are clues.

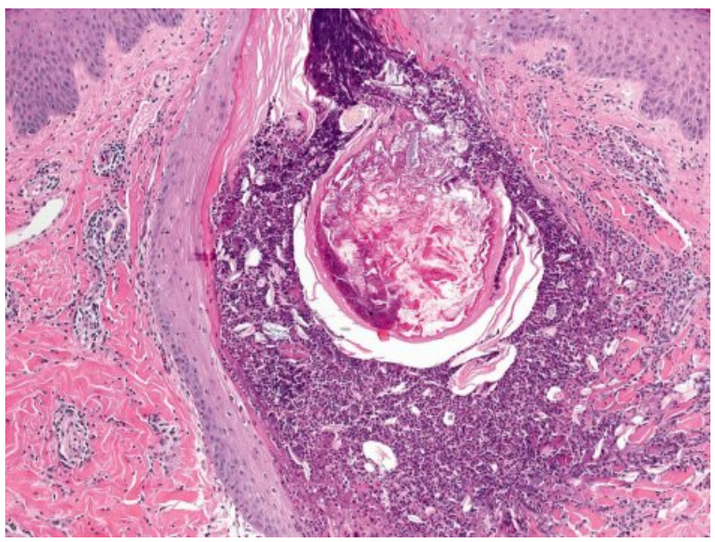


Fig. 36.16 Histology of an inflamed comedo. There is disruption of the pilosebaceous unit and secondary inflammation. *Courtesy Lorenzo Cerroni, MD.*

TREATMENT

A thorough history and physical examination are key to developing an appropriate and maximally effective treatment plan[71] (Table 36.3). The physician should review with the patient all prescription and over-the-counter medications used for acne or other conditions, noting the response to acne treatments. A review of cosmetics, sunscreens, cleansers, and moisturizers is also helpful. In female patients, a menstrual and oral contraceptive history is important in determining hormonal influences on acne. Some patients may report an improvement following sun exposure while others experience an exacerbation.

On physical examination, lesional morphology should be assessed, including the presence of comedones, inflammatory lesions, nodules, and cysts. Secondary changes such as scarring and postinflammatory pigmentary changes are also important clinical findings. The patient's skin color and type can influence the chosen formulation of a topical medication. For example, patients with oily skin tend to prefer the more drying gels and lotions, whereas those with drier skin types may prefer creams.

Table 36.4 provides an overview of the approach to acne therapy. Lack of adherence to the recommended acne treatment plan is a frequent



DIFFERENTIAL DIAGNOSIS OF ACNE	
Acne vulgaris – comedonal	
Closed	***Open***
• Milia • Osteoma cutis • Sebaceous hyperplasia • Pseudoacne of the nasal crease (see Fig. 36.15A) • Syringomas • Trichoepitheliomas* • Trichodiscomas, fibrofolliculomas • Eruptive vellus hair cysts†, steatocystoma multiplex† • Colloid milium • Acne exacerbated by systemic corticosteroids‡ or anabolic steroids • Contact acne (occupational, pomade, cosmetica, mechanica; chloracne) • Follicular keratosis of the chin/face • Follicular mucinosis (see Fig. 36.15C) • Follicular mycosis fungoides (see Fig. 36.15D) • Comedonal Darier disease	• Contact acne (see Closed) • Acne exacerbated by systemic corticosteroids‡ or anabolic steroids • Trichostasis spinulosa (see inset) • Favre–Racouchot syndrome • Pseudoacne of the nasal crease (see Fig. 36.16A) • Nevus comedonicus • Basaloid follicular hamartoma syndrome • Familial dyskeratotic comedones • Comedonal Darier disease • Dowling–Degos disease • Radiation-induced comedones • Molluscum-induced comedones • Childhood flexural comedones (often a single double-orifice lesion) • Dilated pore of Winer (single lesion) • Trichofolliculoma (usually a single lesion) • Follicular spines – in settings such as viral-associated trichodysplasia¶, type VI pityriasis rubra pilaris¶, multiple myeloma, demodicosis¶, follicular mucinosis, follicular porokeratosis, and drug-induced (e.g. BRAF inhibitors, cyclosporine¶, acitretin)
Acne vulgaris – inflammatory	
• Rosacea • Perioral/periorificial dermatitis • Demodicosis (adults > children¶; see Fig. 36.15B) • Folliculitis – culture-negative, staphylococcal, Gram-negative, eosinophilic¶, *Malassezia* • Acne/acneiform eruptions due to topical or systemic corticosteroids‡, anabolic steroids, or other medications (e.g. lithium, EGFR inhibitors; see Table 36.1) • Pseudofolliculitis barbae, acne keloidalis nuchae • Pseudoacne of the nasal crease • Furuncle/carbuncle • Idiopathic aseptic facial granuloma (in children) • Papulopustular eruption of Behçet disease • Neutrophilic dermatoses, neutrophilic eccrine hidradenitis, and neutrophilic sebaceous adenitis	• Keratosis pilaris • Follicular keratosis of the chin/face • Viral-associated trichodysplasia (trichodysplasia spinulosa)¶ • Lupus miliaris disseminatus faciei • Psychogenic (neurotic) excoriations, factitial lesions • Follicular mucinosis (see Fig. 36.15C) • Follicular mycosis fungoides (see Fig. 36.15D) • Tinea faciei • Molluscum contagiosum (especially inflamed lesions) • Angiofibromas • Angiofibroma-like papules of the nose and chin • Dowling–Degos disease (especially the Haber syndrome variant) • Follicular porokeratosis • Cutaneous Rosai–Dorfman disease • Granulomatosis with polyangiitis • Syndromes associated with acne, e.g. PAPA, (PA)PASH, SAPHO, Apert syndrome
Neonatal cephalic pustulosis (neonatal acne)	
• Sebaceous hyperplasia • Milia • Miliaria rubra (especially pustular variant)	• Candidal infection • Papulopustular eruption of hyper-IgE syndrome • Vesiculopustular eruption of transient myeloproliferative disorder
Solid facial edema secondary to acne vulgaris	
• Solid facial edema secondary to rosacea • Melkersson–Rosenthal syndrome, sarcoidosis (e.g. Heerfordt syndrome), lepromatous leprosy • Lymphoma (B or T cell), leukemia cutis, angiosarcoma • Scleromyxedema, myxedema, self-healing (juvenile) cutaneous mucinosis • Autoimmune connective tissue disease (e.g. dermatomyositis, lupus erythematosus, Still disease)	• Angioedema (lasts <24–72 hours), C1 esterase inhibitor deficiency (lasts 2–3 days), blepharochalasis/Ascher syndrome • Sweet syndrome or cellulitis – more abrupt onset • Superior vena caval obstruction • Lymphatic malformation • Pachydermoperiostosis and other genetic disorders with coarse facies • Other – trichinosis, primary systemic amyloidosis

*Early or small-sized.
†In the differential diagnosis of cystic lesions of the trunk.
‡Can also lead to rosacea-like picture (see Ch. 37).
¶Often in the setting of HIV infection or other immunocompromised states.

Table 36.2 Differential diagnosis of acne. EGFR, epidermal growth factor receptor; PAPA, *p*yogenic *a*rthritis, *p*yoderma gangrenosum, and *a*cne conglobata; (PA)PASH, (*p*yogenic *a*rthritis), *p*yoderma gangrenosum, *a*cne, and suppurative *h*idradenitis; SAPHO, *s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis, and *o*steitis.

reason for therapeutic failure. Some strategies to help improve outcomes are listed in Table 36.5.

Topical Treatments

Topical retinoids

The anti-acne activity of topical retinoids involves normalization of follicular keratinization and corneocyte cohesion, which aids in the expulsion of existing comedones and prevents the formation of new ones. Topical retinoids also have significant anti-inflammatory properties and therefore may be used as monotherapy for acne with both comedonal and mild inflammatory components. In addition, concurrent use of a topical retinoid can enhance the efficacy of benzoyl peroxide and topical antibiotics by increasing the penetration of the latter medications into the sebaceous follicle. Topical retinoids used for acne include tretinoin, adapalene, tazarotene, and trifarotene (see Ch. 126); topical products that combine tretinoin with clindamycin or benzoyl peroxide and adapalene with benzoyl peroxide are also available.

HISTORY AND PHYSICAL EXAMINATION OF THE ACNE PATIENT	
History	**Physical examination**

• Age
• Sex or gender identity
• Impact of acne on quality of life
• Motivation and goals for treatment
• Lifestyle, occupation, hobbies
• Current and previous treatments
• Use of cosmetics, sunscreens, cleansers, astringents, moisturizers, masks, scrubs, cleansing brushes
• Menstrual history
• Medications
  • Corticosteroids
  • Hormonal contraceptives, anabolic steroids, gender-affirming therapy
  • Other (e.g. lithium, EGFR inhibitors; see Table 36.1)
• Nutritional supplements
• Concomitant illnesses
• Family history (including severity of acne, polycystic ovary syndrome)
	• Skin type (e.g. oily versus dry)
	• Skin phototype
	• Distribution of acne
	  • Face (e.g. "T-zone", cheeks, jawline)
	  • Neck, chest, back, upper arms
	• Overall degree of involvement (mild, moderate or severe; see Table 36.4)
	• Lesion morphology
	  • Comedones
	  • Papules, pustules
	  • Nodules
	  • Cysts
	  • Scarring
	  • Atrophic, pitted
	  • Hypertrophic, keloidal
	  • Papular
	  • Sinus tracts
	  • Persistent erythema
	  • Postinflammatory hyperpigmentation

Table 36.3 History and physical examination of the acne patient. EGFR, epidermal growth factor receptor.

The most common side effect of topical retinoids is local irritation resulting in erythema, dryness, peeling, and scaling. This tends to peak after 2–4 weeks of treatment and improves with continued usage; transient application of a low-potency topical corticosteroid may be of benefit for patients with significant irritation[72]. Delivery systems have been developed to permit a greater concentration of retinoid while decreasing irritancy, primarily through controlled slow release, e.g. tretinoin impregnated into inert microspheres or incorporated within a polyolprepolymer. An acne flare may occur during the initial month of treatment with a topical retinoid, but resolves spontaneously with continued usage. Although not true photosensitizers, if a retinoid causes skin peeling or irritation, this may increase the user's susceptibility to sunburn. Appropriate use of sunscreens should therefore be advised.

Tretinoin (all-*trans*-retinoic acid), a naturally occurring metabolite of retinol, was the first topical comedolytic agent used for the treatment of acne. To decrease the potential for irritation, treatment is often started with a lower-concentration cream formulation of tretinoin and the strength later increased (see Table 126.5). Alternate-night to every-third-night application may be necessary initially, with increased frequency as tolerated. Because the standard generic tretinoin formulation is photolabile, night-time application is recommended to prevent early degradation; it is also inactivated by concomitant application of benzoyl peroxide, so the two medications should not be used at the same time. However, specialized microsphere formulations of tretinoin are not photolabile and can be applied together with benzoyl peroxide without degradation.

Although epidemiologic studies have not shown an increased risk of birth defects in infants of mothers using topical tretinoin during the first trimester, sporadic case reports of birth defects have been published[73,74]. Because of this and the fact that systemic retinoids are known teratogens, the use of topical tretinoin in pregnancy is discouraged. That said, dietary intake of vitamin A has been shown to have a greater influence on serum retinoid levels than facial application of tretinoin[75].

The third-generation synthetic retinoid *adapalene* is an aromatic naphthoic acid derivative (see Fig. 126.1). In the skin, it primarily binds the retinoic acid receptor γ (RARγ), whereas tretinoin binds to both RARα and RARγ. Unlike tretinoin, adapalene is light-stable and resistant to oxidation by benzoyl peroxide. Table 126.5 outlines the currently available formulations.

Tazarotene is a synthetic acetylenic retinoid that, once applied, is converted into its active metabolite, tazarotenic acid. Like adapalene, this metabolite selectively binds RARγ but not RARα or RXR (see Ch. 126). Both daily overnight application of tazarotene and short contact therapy regimens have been shown to be effective in the treatment of comedonal and inflammatory acne. Per the FDA, topical tazarotene is contraindicated during pregnancy (formerly FDA category X), so contraceptive counseling should be provided to women of childbearing age who are prescribed this medication. Like adapalene, it is light-stable and can be applied together with benzoyl peroxide.

Trifarotene is a fourth-generation topical retinoid that is selective for RARγ. A 0.005% cream formulation was recently approved for the treatment of moderate acne on the face and back in patients ≥9 years of age[76].

Antimicrobial agents

Benzoyl peroxide is a potent bactericidal agent that reduces *C. acnes* within the follicle. It also has mild comedolytic properties and is particularly effective when used in combination with other therapies. In contrast to topical antibiotics, microbial resistance to benzoyl peroxide has not been reported. Many preparations for all skin types are available in both over-the-counter and prescription formulations. These include bar soaps, washes, gels, lotions, creams, foams, and pads in concentrations ranging from 2.5% to 10% as well as products that combine benzoyl peroxide with clindamycin, erythromycin, adapalene, or tretinoin. Benzoyl peroxide's bactericidal properties are not concentration dependent, although irritation is more common with higher strengths. As benzoyl peroxide is a bleaching agent, whitening of clothing and bedding can occur. Development of allergic contact dermatitis to benzoyl peroxide and its metabolite benzoic acid is also possible, and this should be suspected in patients who develop marked erythema or vesiculation with its use.

Topical antibiotics are widely used for the treatment of acne and are available alone as well as in combination with benzoyl peroxide or a retinoid. Topical formulations of *clindamycin*, *erythromycin*, and *minocycline* utilized for acne include creams, gels, foams, solutions, and pledgets (see Ch. 127). Of note, *C. acnes* commonly develops resistance to clindamycin and erythromycin, with rates of >50% in some countries[77]; as a result, topical antibiotic monotherapy for acne is not generally recommended.

Azelaic acid is a naturally occurring dicarboxylic acid with both prescription (15%–20%) and over-the-counter (10%) formulations (see Table 127.2). By inhibiting the growth of *C. acnes*, azelaic acid reduces inflammatory acne. It also reverses altered follicular keratinization and thus demonstrates some comedolytic properties. In a randomized controlled study, azelaic acid 15% gel had non-inferior efficacy and greater tolerability than adapalene 0.1% gel in maintenance therapy for inflammatory acne in women[78]. In addition, azelaic acid can help to lighten postinflammatory hyperpigmentation[79].

Sodium sulfacetamide is a well-tolerated topical antibiotic that is thought to restrict the growth of *C. acnes* through competitive inhibition of the condensation of para-aminobenzoic acid with pteridine precursors (see Ch. 127). It is formulated as a lotion, suspension, foam, and cleanser, either alone or in combination with 5% sulfur. Tinted formulations are also available. When used together with benzoyl peroxide, sodium sulfacetamide can cause an orange discoloration of fabrics[80].

Topical *dapsone* 5% and 7.5% gels are FDA-approved for the treatment of acne vulgaris in patients ≥12 and ≥9 years of age, respectively[81]. In two randomized controlled trials (RCTs) (total n = 4340), 30% of patients ≥9 years of age with moderate acne treated with dapsone 7.5% gel once daily were clear to almost clear at week 12, compared to 21% for placebo ($p<.001$)[81]. Of note, a temporary yellow–orange staining of the skin and hair occasionally occurs with concomitant application of topical dapsone and benzoyl peroxide. Methemoglobinemia has been reported in cases of misuse or ingestion[82,83].

Clascoterone 1% cream is a topical androgen receptor inhibitor that was recently approved for treatment of acne in patients ≥12 years of age. However, in two RCTs (total n = 1440) in patients ≥9 years of age with moderate to severe acne, 18%–20% of patients treated with clascoterone 1% cream twice daily were clear or almost clear after 12 weeks versus 6%–9% with the vehicle control ($p<.001$)[84].

Other topical medications

Salicylic acid is a widely used comedolytic agent (see Ch. 153 and Table 129.7). Salicylic acid is available over the counter in concentrations of up to 2% in numerous delivery formulations, including gels,

TREATMENT OF ACNE VULGARIS		
Acne activity	**Treatment**	
	Initial	**Follow-up**
Mild: Several papules, pustules, and/or comedones; no nodules. 	**First-line** Topical retinoid or BPO ± topical antibiotic[†] or Topical retinoid + BPO ± topical antibiotic[†] **Alternative topicals** Dapsone Clascoterone Azelaic acid[*]	**For additional control:** Increase strength of topical retinoid or Change from wash to leave-on BPO or Add or replace with another topical agent
Moderate: Multiple papules and pustules; few scattered nodules; variable comedones 	**First-line** Topical retinoid + BPO ± topical antibiotic, oral antibiotic[‡], and/or oral hormonal therapy[¶] (female patients) **Alternative topicals** Dapsone Clascoterone Azelaic acid[*]	**For additional control:** See above for topical options Add oral antibiotic[‡] and/or hormonal therapy[¶] (female patients) or Change to isotretinoin
Severe: Numerous papules and pustules; multiple nodules; variable comedones 	**First-line** Topical retinoid + BPO + oral antibiotic[‡] ± hormonal therapy[¶] (female patients) or Isotretinoin **Consider alternative topical (see above)**	**For additional control:** Change to isotretinoin
Very severe: Numerous nodules with conglobate or hemorrhagic lesions; ± systemic symptoms (acne fulminans) 	Prednisone ± isotretinoin (low-dose initially)	Isotretinoin (slow dose escalation)

[*]Especially when postinflammatory hyperpigmentation is present.
[†]Topical antibiotics with level I evidence include clindamycin, minocycline, and erythromycin; sodium sulfacetamide represents another option.
[‡]Oral antibiotics with level I evidence include doxycycline, minocycline, sarecycline, and azithromycin.
[¶]Combined oral contraceptive and/or spironolactone.

Table 36.4 Treatment of acne vulgaris. Lack of response to therapy should prompt consideration of non-adherence, exacerbating factors (e.g. medications [see Table 36.1], endocrinologic abnormalities), or another diagnosis (e.g. Gram-negative or *Malassezia* folliculitis; see Table 36.2). In general, monotherapy with a topical or oral antibiotic should be avoided. There is currently level I evidence for topical retinoids, dapsone, clascoterone, azelaic acid, benzoyl peroxide, and antibiotics (the latter two especially in combination) as well as oral antibiotics, isotretinoin, spironolactone, and combined contraceptives; see footnotes for additional information. Procedural treatments include comedo extraction and (especially for nodular and cystic lesions) intralesional triamcinolone. Therapeutic options for pregnant women (in consultation with their obstetrician) include topical agents (azelaic acid, clindamycin, erythromycin), oral antibiotics (azithromycin, cephalexin), and intralesional triamcinolone. BPO, benzoyl peroxide.

TIPS FOR TOPICAL ACNE THERAPY
Educate on how to use medications, how they work, and treatment expectations
• Inform patients that it will take 6–8 weeks of treatment for substantial improvement • Address potential for postinflammatory hyperpigmentation and scarring • Explain that topical medications (especially retinoids) should be used to the entire acne-prone region rather than as "spot treatment" of individual lesions • Provide instructions on where to apply the medication and how much to use
Improve adherence – avoid compromise due to patients having busy schedules and quitting when the response is not rapid
• Ask about current skin care routine (e.g. when they shower and wash their face, if they moisturize, products used) • Simplify the regimen: once daily when possible; consider combination products (e.g. benzoyl peroxide + adapalene, tretinoin, or clindamycin; tretinoin + clindamycin) • Ask specifically about adherence: "Out of 7 nights, how many times do you apply the medication?"
Minimize irritation – most common in patients with atopic dermatitis and adults
• Note that using too much medication or applying it too frequently can increase irritation • Devise a gradual initial approach to improve tolerance in patients with sensitive skin; for example, a single agent may be used for the first 2–3 weeks (starting every other day for retinoids), followed by slow introduction of a second medication (e.g. transitioning from alternate days to daily) • Advise to avoid harsh scrubs and other irritating agents (e.g. toners, acne products that are not part of the regimen) • Suggest use of a non-comedogenic sensitive skin moisturizer if dryness occurs
Avoid exacerbation
• Review all skin care products and cosmetics; having patients bring everything that they apply to their face to a visit may help to determine the source of problems • Advise non-comedogenic products (e.g. moisturizers, sunscreens, make-up) and to avoid having oily hair or using pomades that may contribute to acne • Instruct patients not to pick or manipulate lesions
Reinforce the plan
• Recognize that patients often forget what is recommended and are bombarded by advertising and false information about acne (especially on social media platforms) • Provide a written handout with specific instructions https://pedsderm.net/site/assets/files/1028/1_spd_acne_short_web_final.pdf • Recommend additional reliable educational resources about acne and its treatment https://www.aad.org/public/diseases/acne www.webmd.com/skin-problems-and-treatments/acne/default.htm

Table 36.5 Tips for topical acne therapy.

creams, lotions, foams, solutions, and washes. Side effects of topical salicylic acid include erythema and scaling.

Niacinamide (nicotinamide) is a common ingredient in over-the-counter acne products. It can decrease sebum and increase ceramide production in the skin[85,86]. Although data on its efficacy for acne are limited, comparative studies have found nicotinamide 2% gel to be non-inferior to clindamycin 1% gel in the treatment of moderate acne[87].

Systemic Therapies

Antibiotics

First-line therapy for moderate to severe inflammatory acne includes use of oral tetracyclines, primarily doxycycline, minocycline, or sarecycline. Details regarding the mechanism of action, recommended dosages, and side effects of these antibiotics are reviewed in Chapter 127. Resistance of *C. acnes* to all the antibiotics used for acne has been documented and patterns vary significantly worldwide[88]. Acne management guidelines recommend that courses of oral antibiotics be limited to 3 to 4 months[71,77,89] and not be administered as monotherapy. In multiple clinical trials, combination of an oral antibiotic with a topical retinoid ± benzoyl peroxide resulted in greater improvement of acne than the antibiotic alone, and continuing these topicals after completion of the antibiotic course was found to be beneficial[71,90,91].

Tetracyclines suppress the growth of *C. acnes*, thereby reducing bacteria-mediated inflammation, and they have intrinsic anti-inflammatory properties via downregulation of proinflammatory cytokines (e.g. TNF, IL-1, IL-6)[92]. *Doxycycline* and *minocycline* are deemed equally effective in the treatment of the inflammatory component of moderate to severe acne[93]. Subantimicrobial doses of doxycycline (20 mg twice daily or 40 mg daily) have similar efficacy but fewer adverse effects than doxycycline 100 mg daily[94–96]. While doxycycline-related phototoxicity and gastrointestinal upset can be problematic, minocycline is associated with a higher incidence of serious adverse events, including a minocycline-induced hypersensitivity syndrome (see Ch. 21) and autoimmune reactions (hepatitis, lupus erythematosus-like syndrome, and cutaneous polyarteritis nodosa). As a result, some international guidelines recommend doxycycline over minocycline as the first-line oral antibiotic for acne[97–99]. *Sarecycline* has a narrower antimicrobial spectrum than other tetracycline derivatives and is approved for treatment of acne in patients ≥9 years of age[100].

Oral macrolide antibiotics, *erythromycin* and *azithromycin*, can be used for acne in patients who are unable to tolerate tetracyclines, pregnant, or <8 years of age. Although controlled studies have found that azithromycin has efficacy comparable to that of doxycycline[101], the high risk of bacterial resistance limits utilization of macrolides for acne. *Trimethoprim-sulfamethoxazole* may also be of benefit for acne, but its use is discouraged due to the greater risk of severe adverse reactions[71].

Hormonal therapy

Hormonal therapy can be an effective acne treatment for female patients, irrespective of their serum androgen levels. Combined oral contraceptive pills, which contain an estrogen (usually ethinyl estradiol) plus a progestin (variable), block both ovarian and adrenal production of androgens. A meta-analysis found that oral contraceptives, which are especially helpful for inflammatory acne, are equivalent to oral antibiotics in reducing the number of acne lesions after 6 months of therapy[102]. Most progestins have intrinsic androgenic activity, which is decreased in second-generation (e.g. ethynodiol diacetate, norethindrone, levonorgestrel) agents and even lower in third-generation agents (e.g. desogestrel, norgestimate, gestodene). Fourth-generation progestins (e.g. drospirenone, dienogest) and cyproterone acetate actually have *anti*androgenic properties.

Three oral contraceptives are currently FDA-approved for the treatment of acne, although others also have evidence of efficacy[103] (Table 36.6). Side effects from oral contraceptives include nausea, vomiting, abnormal menses, weight gain, and breast tenderness. Agents containing drospirenone have antimineralocorticoid properties (equivalent to ~25 mg of spironolactone) and can lead to elevations in serum potassium levels, but this is generally not clinically significant. While monitoring of serum potassium levels is not necessary in otherwise healthy individuals, it is recommended in patients with renal disease or those taking an angiotensin-converting enzyme (ACE) inhibitor, angiotensin-II receptor antagonist, potassium-sparing diuretic, potassium supplementation, heparin, aldosterone antagonist, or NSAID[104].

Rare but more serious complications from oral contraceptives include hypertension and thromboembolism (e.g. deep venous thrombosis, pulmonary embolism). The increase in risk of venous thromboembolism ranges from 2- to 4-fold with levonorgestrel or norethindrone to 3.5- to 7-fold with desogestrel, drospirenone, and cyproterone acetate; risk of thrombosis is greatest early on during treatment[105–107]. Overall the risk is highest for women over the age of 35 years, smokers, and those with other prothrombotic risk factors such as hereditary thrombophilia[108].

The antiandrogen *cyproterone acetate* is currently marketed in Europe and Canada but is not available in the US. Its anti-acne effects are mediated primarily through androgen receptor blockade. The standard contraceptive formulation combines cyproterone acetate (2 mg) with ethinyl estradiol (35 or 50 mcg). This preparation is widely used in Europe as the treatment of choice for sexually active women

ROLES OF COMMONLY USED CONTRACEPTIVES FOR ACNE	
Oral contraceptive®	**Estrogen mcg/progestin mcg**
FDA-approved as treatment for acne vulgaris	
Ortho Tri-Cyclen, Tri-Estarylla, Tri-Linyah, Tri-Sprintec, Tri-Previfem, Trinessa	Ethinyl estradiol 35/norgestimate 180, 215, 250
Estrostep, Tilia, Tri-Legest	Ethinyl estradiol 20, 30, 35/norethindrone 1000
Yaz, Gianvi, Jasmiel, Loryna, Lo-Zumandimine, Nikki, Vestura, Beyaz*	Ethinyl estradiol 20/drospirenone 3000
Clinical data to support use for acne (selected products)	
Alesse, Aubra, Aviane, Lutera, Orsythia, Vienva	Ethinyl estradiol 20/levonorgestrel 100
Diane-35†	Ethinyl estradiol 35/cyproterone acetate 2000
Yasmin, Ocella, Syeda, Zarah, Zumandimine, Safyral*	Ethinyl estradiol 30/drospirenone 3000
Natazia	Estradiol valerate 1000, 2000, 3000/dienogest 2000, 3000
May worsen acne	
Combined oral contraceptives containing more androgenic progestins (e.g. norgestrel, levonorgestrel)	
Progestin-only depot injections, subdermal implants, and progestin-containing intrauterine devices	

*Also contains levomefolate calcium for protection against neural tube defects.
†Not available in the US.

Table 36.6 Roles of commonly used contraceptives for acne.





Fig. 36.17 Cutaneous complications of isotretinoin therapy. **A** Impetigo in a patient treated with isotretinoin. Multiple serous crusts are evident. **B** Pyogenic granuloma-like healing on the chest of an adolescent boy on his third month of isotretinoin therapy. This is more likely to occur when isotretinoin therapy is started at a full dose rather than a lower initial dose, especially in teenage boys.

with hormonally responsive acne. Formulations of cyproterone acetate alone are also available. Approximately 75%–90% of patients treated with either the standard contraceptive formulation or higher doses of 50–100 mg daily (with or without ethinyl estradiol 50 mcg) show substantial improvement[109]. The most frequent side effects are breast tenderness, headache, nausea, and irregular menses; hepatotoxicity and thromboembolism represent uncommon complications.

Spironolactone functions as an androgen receptor blocker and, in doses of 50–100 mg twice daily, has been shown to reduce sebum production and improve acne[110,110a]. In two retrospective studies, 66% of women (261/395) and 23% of female adolescents (18/80) treated with spironolactone achieved ≥90% improvement in their acne[111,112]. Spironolactone side effects are dose-related and include irregular menstrual periods, breast tenderness, headache, and fatigue. These potential sequelae can be minimized if therapy is initiated at a low dose (25–50 mg/day). Hyperkalemia is rare and monitoring of potassium levels is not required in young healthy patients[113]. Although breast tumors have been reported in rodents given spironolactone, this drug has not been directly linked to the development of cancer in humans[114]. Because it is an antiandrogen, there is a risk of feminization of a male fetus if a pregnant woman takes this medication. As with other hormonal therapies, a clinical response may take 3–6 months. Effective maintenance doses range from 25 to 200 mg/day, and long-term use appears to be well-tolerated[115].

Flutamide, a nonsteroidal androgen receptor blocker approved by the FDA for the treatment of prostate cancer, may be of benefit for acne in women at doses of 62.5–500 mg/day. However, severe dose-related hepatotoxicity limits its use.

Isotretinoin

Since 1971, oral isotretinoin (13-*cis*-retinoic acid) has been available in Europe for the treatment of acne. In the US, it was FDA-approved in 1982 for patients with severe, nodulocystic acne refractory to treatment including oral antibiotics. Over time, other clinical forms of acne have also been shown to benefit greatly from the use of isotretinoin[116]. These include significant acne that is resistant to therapy (including oral antibiotics), relapses quickly, and/or results in scarring, as well as Gram-negative folliculitis, pyoderma faciale, and acne fulminans. The mechanism of action of isotretinoin, as well as dosing regimens, side effects and monitoring protocols, are discussed in detail in Chapter 126.

Isotretinoin is a highly effective acne therapy, with ≥95% of patients achieving a good clinical response after 20 weeks of treatment[117]. Standard isotretinoin dosing for acne is 0.5–1 mg/kg/day taken with a fatty meal to increase gastrointestinal absorption. One formulation, lidose–isotretinoin, can be taken without food[118]. Patients occasionally experience an initial acne flare, usually during the first month of treatment, with risk factors including macrocomedones and a higher starting dose[119,120]. Severe, isotretinoin-induced acne fulminans is a rare complication occurring more frequently in younger adolescent boys (Fig. 36.17; see above)[121]. Starting with a lower dose (≤0.5 mg/kg/day) during the first month of treatment reduces isotretinoin-induced flaring and allows the patient to adjust to dose-dependent side effects[122].

Reaching a cumulative isotretinoin dose of 120–150 mg/kg (e.g. 1 mg/kg/day × 4–5 months after an initial month of 0.5 mg/kg/day) has been shown to reduce the risk of acne relapse[123]. However, a 6-month course of lower-dose isotretinoin (e.g. 0.25–0.4 mg/kg/day [40–70 mg/kg cumulative]) can be effective in the treatment of moderate acne, with fewer side effects[124]. Some authors recommend treatment until 1–3 months after clearance of acne is achieved[124a]. Patients with PCOS and women with less severe acne are less likely to respond to isotretinoin, while male sex, young age, short treatment duration, and low

cumulative dose are associated with acne recurrence after isotretinoin therapy[123,125–127]. Maintenance with a topical retinoid ± benzoyl peroxide following completion of isotretinoin therapy may reduce the recurrence rate[127a]. Associated scarring and sinus tracts do not respond to isotretinoin but may improve with surgical modalities.

The most common adverse effects of isotretinoin involve the skin and mucous membranes and are dose-dependent. These include cheilitis, dryness of the oral and nasal mucosa, generalized xerosis, and skin fragility. Other cutaneous side effects such as excessive granulation tissue, paronychia, and cutaneous infections (in particular with *Staphylococcus aureus*) can also occur (see Fig. 36.17).

Teratogenicity is a serious potential complication (see Table 126.7), and female patients of childbearing potential must have at least one (two in the US) negative pregnancy test(s) before starting treatment and practice effective contraception for 1 month prior to, during, and for 1 month after completing therapy. In the US, prescription of isotretinoin requires physicians and patients to register with a pregnancy risk management program (iPLEDGE™), which mandates monthly office visits for all patients that include counseling not to share the medication as well as monthly pregnancy testing for patients with childbearing potential.

Isotretinoin therapy increases serum triglyceride and/or cholesterol levels in ~20%–50% of patients; however, severe elevations that require dose modification are rare and typically develop within the first two months of therapy[128,129]. Elevated serum creatine kinase levels and rhabdomyolysis have been reported in patients on isotretinoin and are more common in athletes[130]. Other potential side effects involve the musculoskeletal system (myalgias, low back pain), eyes, liver (occasional mild elevation in transaminases), and central nervous system (see Table 126.8 and Ch. 126). To date, no firmly established causal association with depression or suicide attempts has been demonstrated. Meta-analyses have not shown an association between isotretinoin treatment and increased risk of depression; instead, acne therapy led to a decreased prevalence of depression[131]. Current data do not support an association between isotretinoin and inflammatory bowel disease[132–134].

Surgical Treatment

Comedo extraction can improve the cosmetic appearance of acne and may aid in therapeutic responsiveness to topical comedolytic agents. The keratinous contents of open comedones can be expressed using a comedo extractor. The Schamberg, Unna, and Saalfield types of comedo expressers are most commonly used. Nicking the surface of a closed comedo with an 18-gauge needle or a #11 blade allows easier expression. Extraction is especially beneficial for deep, inspissated, and persistent comedones. This procedure should be used in conjunction with a topical retinoid or other comedolytic treatment for maximum benefit. Comedo extraction should not be performed on inflamed comedones or pustules because of the risk of scarring. Light electrocautery and electrofulguration (see Ch. 140) have also been reported as effective treatments for deep comedones. In selected patients, cryotherapy represents another surgical option for the treatment of comedonal acne (see Ch. 138).

Photodynamic therapy utilizing topical 5-aminolevulinic acid together with various light sources (e.g. blue, red, intense pulsed) or lasers (e.g. pulsed dye, 635 nm red diode) as well as methyl aminolevulinate plus red light have been successfully used to treat acne (see Ch. 135). In addition, blue or intense pulsed light alone and lasers such as the pulsed dye, the 1320 nm neodymium:YAG, and especially the 1450 nm diode may be of therapeutic benefit for inflammatory acne (see Ch. 137).

Intralesional injection of corticosteroid (triamcinolone acetonide 2 to 5 mg/ml, ~0.1 ml per lesion) can quickly improve the appearance and tenderness of deep, inflamed nodules and cysts. Larger cysts may require incision and drainage prior to injection. The risks of corticosteroid injections include hypopigmentation (particularly in darkly pigmented skin), atrophy, telangiectasias, and yellow–white dermal deposits of the medication.

Low-concentration chemical peels are also beneficial for the reduction of comedones. Common peeling agents include α-hydroxy acids (including glycolic acid), salicylic acid, and trichloroacetic acid. These lipid-soluble comedolytic agents act by decreasing corneocyte cohesion at the follicular opening and assist in comedo plug extrusion. Such agents are generally well tolerated by most skin colors and types, and they can be used by the patient at home or in the dermatologist's office. Higher-concentration glycolic acid peels (20%–70%, depending on the patient's skin type) and the less predictable phenol peel may also be performed in the office setting (see Ch. 154). Risks of chemical peels include irritation, pigmentary alteration, and scarring.

One of the most distressing consequences of acne vulgaris is scarring. Surgical treatments should be aimed at the type of scarring present. Laser resurfacing (fractionated as well as traditional), dermabrasion, and deeper chemical peels seek to reduce the variability of the skin surface and smooth out depressed scars that improve when the skin is stretched. For discrete depressed scars, soft tissue augmentation can be temporarily beneficial. Filler substances used include poly-L-lactic acid, calcium hydroxylapatite, and autologous fat (see Ch. 158). Surgical subcision is also used for management of acne scars and punch grafting is an option for patients with "ice-pick" scarring. For larger hypertrophic scars, aggregated pitted scars, and sinus tracts, full-thickness surgical excision may result in improved scar placement and a better cosmetic appearance.

Additional figures available in our eBook (see inside front cover for access code).

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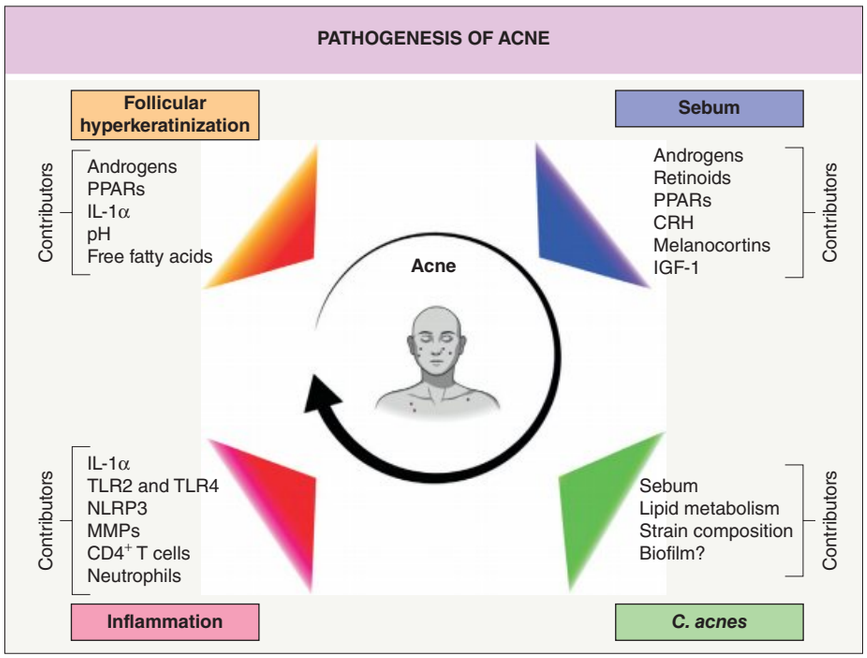
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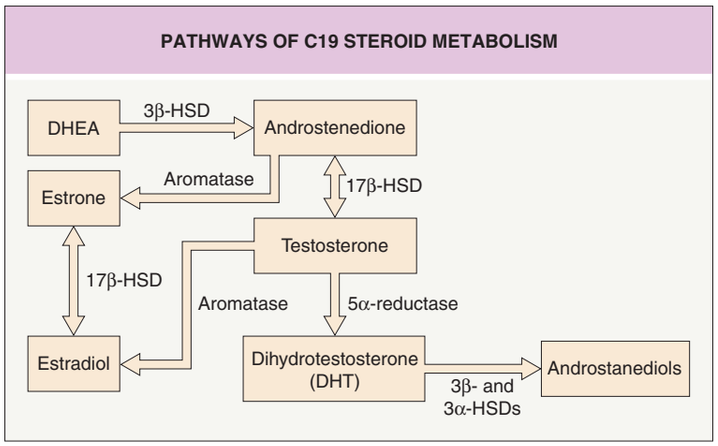
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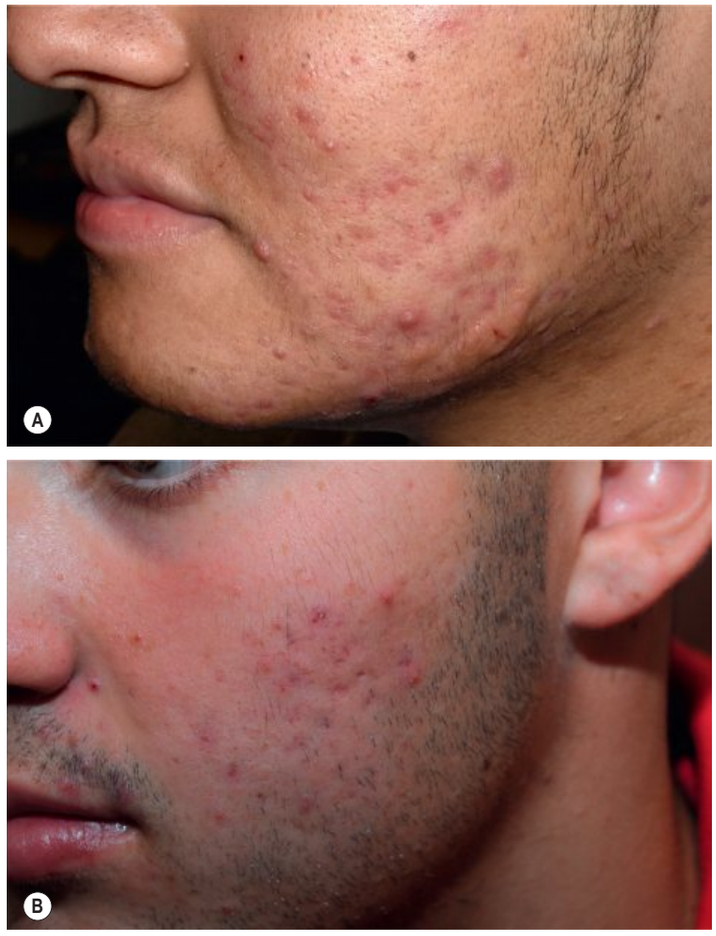
eFig. 36.1 Pathogenesis of acne.



eFig. 36.2 Pathways of C19 steroid metabolism. Dehydroepiandrosterone (DHEA) is a weak androgen that is converted to the more potent testosterone by 3β-hydroxysteroid dehydrogenase (HSD) and 17β-HSD. 5α-reductase then converts testosterone to dihydrotestosterone (DHT), the predominant hormonal effector on the sebaceous gland. Both DHEA and testosterone can be metabolized to estrogens by the enzyme aromatase. The sebaceous gland expresses each of these enzymes.



eFig. 36.3 Comedonal acne vulgaris. On the forehead, there are open and closed comedones and inflammatory papules. *Courtesy Kalman Watsky, MD.*



eFig. 36.4 Papulopustular acne vulgaris. A Postinflammatory erythema and scarring are also present. **B** Microcystic lesions are also present. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Kalman Watsky, MD.*



eFig. 36.5 Open comedones in a patient with scarring cystic acne.



eFig. 36.6 Nodulocystic acne vulgaris of the chest with erosions and ulcerations. There is also significant scarring. Initially, a low dose of isotretinoin was administered. *Courtesy Luis Requena, MD*.



eFig. 36.8 Infantile acne. Presentations can range from scattered papulopustules (**A**) to multiple coalescing papulonodules and inflammatory cysts (**B**). If the latter child failed to improve with a topical retinoid plus an oral antibiotic, consideration would be given to oral isotretinoin. *A, Courtesy Julie V. Schaffer, MD. B, Courtesy Kalman Watsky, MD*.





eFig. 36.7 Postinflammatory hyperpigmentation secondary to acne. A, B Such pigmentary changes are common in patients with darker skin tones.



eFig. 36.9
Drug-induced acne due to isoniazid. *Courtesy Kalman Watsky, MD.*



eFig. 36.10 Disorders in the differential diagnosis of comedonal acne vulgaris – trichostasis spinulosa. Multiple vellus hairs and keratinous debris are found within the dilated follicular orifices. *Courtesy Judit Stenn, MD.*

37 Rosacea and Related Disorders

Síona Ní Raghallaigh

INTRODUCTION

The term "*rosacea*" encompasses a constellation of clinical findings, with either fixed centrofacial erythema in a characteristic pattern that may periodically intensify or phymatous changes classified as diagnostic features[1,2]. Other common features are papules and pustules, flushing, telangiectasia, and ocular manifestations such as blepharitis and chalazia. Many patients report increased facial skin sensitivity and dryness, often identifying specific aggravating triggers. The progression of rosacea is variable and at times unpredictable, with sporadic periods of exacerbations and remissions. For some patients, the psychosocial impact of this disorder can be marked.

HISTORY AND EPIDEMIOLOGY

Robert Willan is credited with the earliest medical descriptions of "acne rosacea" in the early 1800s, focusing on the papulopustular presentation. Nonetheless, estimating the true prevalence of rosacea has been limited over the years by discrepancies in disease definition, diagnostic methods, and study populations. Although some epidemiologic studies have reported a prevalence of 10% or higher in White adults[2], a systematic review of 32 studies examining 41 populations found a global adult prevalence of 5.5%[3]. In previous studies, women were observed to be affected by rosacea more often than men[4], but this systematic review found that rosacea affected both sexes equally. Notably, phymatous rosacea is rare in women.

Rosacea occurs primarily in adults older than 30 years of age, with the highest prevalence in individuals aged 45–60 years. While rosacea is rare in children, rosacea-like conditions such as periorificial dermatitis and steroid-induced rosacea are relatively common. Although described as a disease that predominantly affects individuals of Northern European descent with skin phototypes I and II[5], rosacea is likely underdiagnosed in individuals with darker skin phototypes in whom flushing, telangiectasia, and erythema are less perceptible[6].

Systemic comorbidities that may be associated with rosacea include inflammatory bowel disease, neurologic disorders (e.g. migraine, Alzheimer disease), and autoimmune diseases (e.g. multiple sclerosis, rheumatoid arthritis)[7]. A possible explanation is shared genetic, environmental, and/or pathophysiologic factors but further investigations are needed.

PATHOGENESIS

Several different but interrelated pathomechanisms have been proposed for rosacea (Fig. 37.1), with predominant pathways reflecting clinical features.

Genetic Factors

Rosacea is more common in individuals of Northern European descent and concordance in monozygotic twins has been demonstrated. A genome-wide association study identified two single-nucleotide polymorphisms and three HLA alleles associated with rosacea[8].

Dysregulated Cutaneous Immunity

Dysregulation of the cutaneous innate immune system can lead to abnormal inflammatory responses to environmental stimuli and commensal microorganisms. Triggering this innate immune system leads to the release of antimicrobial peptides such as cathelicidin (LL-37). After LL-37 propeptide is secreted by keratinocytes and other epithelial cells, it is cleaved into its active form by proteases (e.g. kallikrein-5). Active cathelicidin peptides then induce both proinflammatory and angiogenic activity. In the facial skin of individuals with rosacea, there are abnormally high levels of LL-37 (see Fig. 37.1)[9]. Also, LL-37 has been shown to contribute to inflammation via activation of the NLRP3 inflammasome (see Fig. 4.2)[10].

Toll-like receptors (TLRs) are pathogen-associated molecular pattern sensors that are involved in cutaneous innate immunity (see Fig. 4.1). In rosacea, keratinocytes express elevated levels of TLR2, leading to increased expression and activity of kallikrein proteases and thus cathelicidins[11]. In addition, matrix metalloproteinases, which activate kallikrein 5, are up-regulated in patients with rosacea[12]. Mast cells, which also release cathelicidin, are increased in number within the dermis of rosacea patients[13]. Lastly, in addition to dysregulated innate immunity, an abnormal adaptive immune response has been observed in rosacea, with Th1/Th17 polarized inflammation and macrophage infiltration[14].

Neurogenic Inflammation

Patients with rosacea often report sensations of stinging or burning of their skin, with affected individuals exhibiting lower heat pain thresholds when compared to controls[15]. When cutaneous nerve endings expressing transient receptor potential vanilloid (TRPV) cation channels are stimulated by trigger factors (e.g. spicy food, heat, alcohol), this can lead to dysesthesia, flushing, and erythema[16]. Heightened TRPV activity has been detected in the skin of rosacea patients and it leads to neurogenic inflammation, i.e. an inflammatory response induced by sensory nerves in which neuromediators are released at the site of inflammation. These neuromediators can result in vasodilation, extravasation of plasma proteins, and recruitment of inflammatory cells (see Fig. 37.1).

Vascular Alterations

Several clinical features of rosacea, including transient erythema, persistent centrofacial erythema, telangiectasias and flushing, point to the role the vascular system plays in its pathogenesis. An increase in blood flow within skin lesions of rosacea has been demonstrated[17], and patients with rosacea flush more readily in response to heat. Histopathologic studies of lesional skin found an elevated expression of vascular endothelial growth factor (VEGF), CD31, and the lymphatic endothelial marker podoplanin (D2-40), implying increased stimulation of vascular and lymphatic endothelial cells[18].

Ultraviolet Radiation (UVR)

Exposure to UVB can induce angiogenesis and increase secretion of angiogenic factors (e.g. VEGF) from keratinocytes[19]. UVR also induces production of reactive oxygen species, which upregulate matrix metalloproteinases that lead to vascular and dermal matrix damage[20]. Although clinically the erythema and telangiectasias of rosacea can resemble telangiectatic photoaging, a case–control observational study provided evidence that they are distinct entities[21], but as expected can overlap.

Epidermal Barrier Dysfunction

Several clinical features of rosacea imply skin barrier dysfunction. Rosacea patients often report facial dryness, and studies have confirmed a lowered threshold for skin irritancy[22]. In rosacea skin, there is increased transepidermal water loss, a marker of epidermal barrier dysfunction. It has been suggested that disruption or abnormalities of the stratum corneum allow penetration of sensory irritants[23]. In addition, patients with papulopustular rosacea have an abnormal skin surface fatty acid

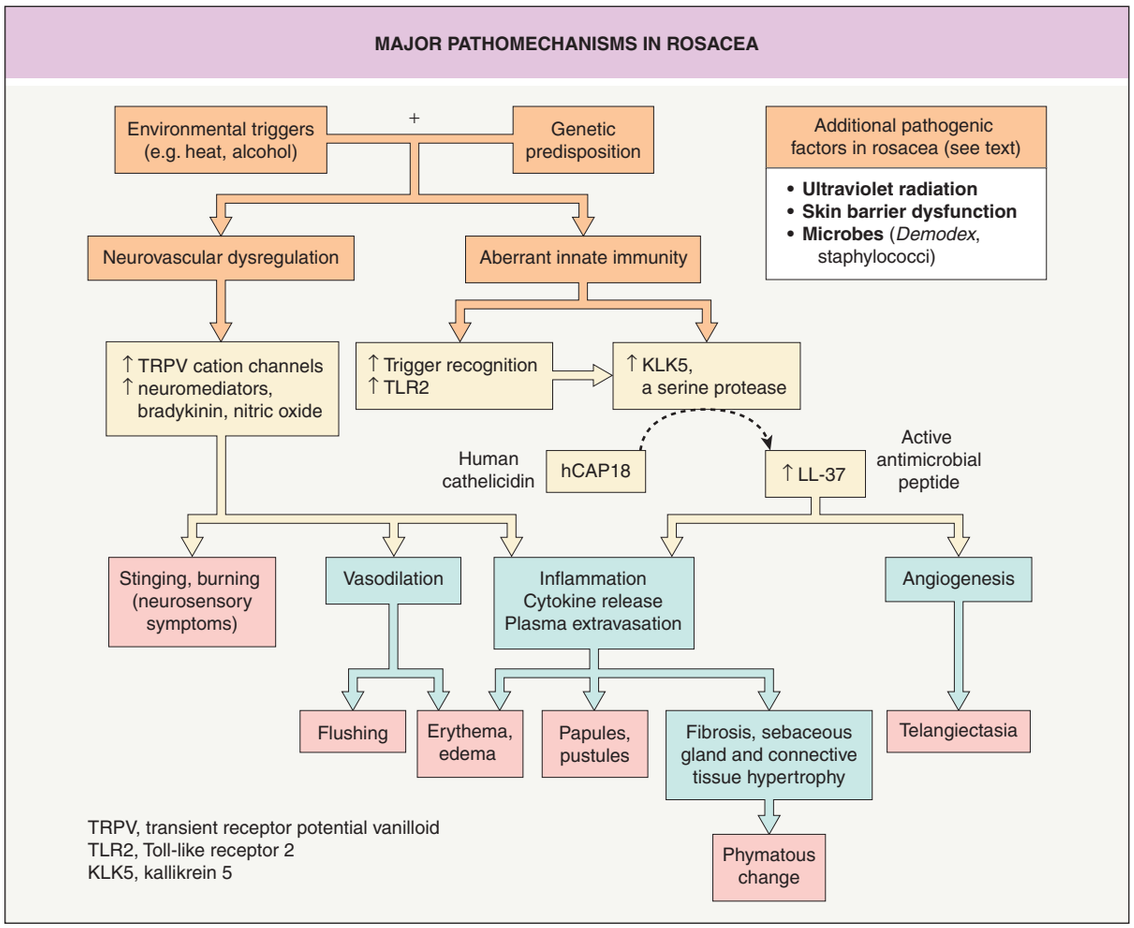


Fig. 37.1 Major pathomechanisms in rosacea. In genetically predisposed individuals (e.g. HLA-DRB1*03:01, HLA-DQA1*05:01, HLA-DQB1*02:01, SNP rs763035), environmental factors can trigger neurovascular dysregulation and an aberrant innate immune response, both of which can lead to cutaneous inflammation, including the clinical manifestations of rosacea. *Adapted from Steinhoff M, Buddenkotte J, Aubert J, et al. Clinical, cellular, and molecular aspects in the pathophysiology of rosacea. J Invest Dermatol Symp Proc. 2011;15:2–11.*

profile[24] as well as reduced epidermal hydration levels. The latter have been shown to improve following treatment with minocycline and resolution of inflammatory lesions[25].

Microorganisms

Demodex mites (*folliculorum* and *brevis*) are normally present on the face as commensal microbes, but in rosacea, greater numbers of these mites are detected by skin surface biopsy techniques[26,27]. In routine histologic sections, the mites often appear prominently within pilosebaceous follicles, and follicular infestation with multiple mites can be associated with an intense perifollicular infiltrate of predominantly CD4 T helper cells[28]. In addition, antigenic proteins from a bacterium (*Bacillus oleronius*) isolated from *Demodex* mites can stimulate inflammation in patients with papulopustular rosacea[29]. It has been suggested that *Demodex* mites and their associated bacteria upregulate local proteases, thereby potentiating dysregulation of the cutaneous innate immune response (see above)[30].

Study results differ as to whether *Helicobacter pylori* infection of the upper gastrointestinal tract plays a role in the pathogenesis of rosacea. A meta-analysis of 14 observational studies did not find statistically significant associations between either *H. pylori* infection and rosacea or *H. pylori* eradication therapy and symptomatic improvement of rosacea[31].

CLINICAL FEATURES

In 2002, a classification scheme divided rosacea into four main subtypes – erythematotelangiectatic, papulopustular, phymatous, and ocular – based upon the predominant lesion morphology[32]. However, it did not account for the frequent co-occurrence of more than one subtype nor the potential progression of one subtype to another. Recognizing these potential shortcomings, a revised classification of rosacea was recommended by the global ROSacea COnsensus (ROSCO) panel in 2016 and by the National Rosacea Society Expert Committee in 2017 (Table 37.1)[1,2].

PHENOTYPIC CLASSIFICATION OF ROSACEA (2017)
Diagnostic phenotypes
Fixed centrofacial erythema in a characteristic pattern that may periodically intensify
Phymatous changes
Major phenotypes
Papules and pustules
Flushing
Telangiectasia
Ocular manifestations*
Secondary signs and symptoms
Burning or stinging
Facial edema
Dry appearance of the skin
Ocular manifestations†
*Lid margin telangiectasia, interpalpebral conjunctival injection, spade-shaped infiltrates in the cornea, scleritis and sclerokeratitis. †Honey-crust and collarette accumulation at the base of the lashes, irregularity of the lid margin, evaporative tear dysfunction (rapid tear breakup time).

Table 37.1 Phenotypic classification of rosacea (2017). A diagnosis of rosacea may be considered in the presence of at least one diagnostic or two major phenotypes. Secondary signs and symptoms may appear concomitantly with one or more diagnostic or major phenotypes. *Adapted from Tan J, Almeida LM, Bewley A, et al. Updating the diagnosis, classification and assessment of rosacea: recommendations from the global ROSacea COnsensus (ROSCO) panel. Br J Dermatol. 2017;176:431–8; and Gallo RL, Granstein RD, Kang S, et al. Standard classification and pathophysiology of rosacea: the 2017 update by the National Rosacea Society Expert Committee. J Am Acad Dermatol 2018;78:148–55.*

Both groups agreed that either one of the following two phenotypes are diagnostic of rosacea: (1) fixed centrofacial erythema in a characteristic pattern that may periodically intensify; and (2) phymatous changes. They also concluded that in the absence of one of these two *diagnostic phenotypes*, the presence of two or more of the following four *major phenotypes* can be diagnostic: (1) papules and pustules; (2) flushing; (3) telangiectasia; and (4) ocular manifestations. Secondary signs and symptoms that may also occur in conjunction with one or more diagnostic or major phenotypes include burning and stinging, facial edema, dry appearance of the skin, and other ocular manifestations.

Diagnostic Phenotypes (Table 37.2)

Fixed centrofacial erythema in a characteristic pattern that may periodically intensify

Persistent erythema of the central face is the most common presentation of rosacea in patients with skin phototypes I–III (Fig. 37.2). Of note, it may be more difficult to appreciate in darker skin phototypes. In addition, it can be challenging to differentiate from telangiectatic photoaging, although there are relative differences (see Table 37.4)[21]. In addition, other entities that can cause persistent facial erythema should be considered, e.g. lupus erythematosus, seborrheic dermatitis.



Fig. 37.2 Fixed facial erythema due to rosacea. There was greater involvement of the medial cheek. *Courtesy Frank C. Powell, MD.*

CLINICAL FEATURES AND MANAGEMENT OF ROSACEA

Predominant phenotype	Predominant clinical features	Severity		Management
		Grade	Features	
Erythema and telangiectasia (formerly termed erythematotelangiectatic)	• Persistent centrofacial erythema • Flushing • Telangiectasia • Skin sensitivity	1	Occasional mild flushing; faint persistent centrofacial erythema; few telangiectasias	• General recommendations for facial skin care (see Table 37.5) • Reduce flushing • Minimize irritation • Topical treatments used in papulopustular rosacea may cause irritation • Laser therapy of prominent blood vessels in grades 2 and 3 disease
		2	Frequent troublesome flushing; moderate persistent centrofacial erythema; several distinct telangiectasias	
		3	Frequent severe flushing; pronounced persistent centrofacial erythema; many prominent telangiectasias; possible edema	
Papules and pustules (previously termed papulopustular)	• Persistent centrofacial erythema • Papules • Pustules/papulopustules • Overlap with other subtypes may occur	1	Few papules and/or papulopustules; mild persistent centrofacial erythema	• Topical or systemic medications for grades 1 and 2 disease • Systemic medications for grade 3 • May require repeated courses or gradual taper
		2	Several papules and/or papulopustules; moderate persistent centrofacial erythema	
		3	Extensive papules and/or papulopustules; pronounced persistent centrofacial erythema; inflammatory plaques or edema may be present	
Phymatous	• Thickened, nodular skin • Prominent pores • Can affect nose (rhinophyma), chin (gnathophyma), forehead (metophyma), ears (otophyma), eyelids (blepharophyma) • May be associated with other features of rosacea or occur in isolation	1	Puffiness; mildly patulous follicles; no clinically apparent hypertrophy of connective tissue or sebaceous glands; no change in contour	• Surgical or laser therapy for grades 2 and 3 rhinophyma • Other phymas are more difficult to treat but may improve with systemic treatments, if an inflammatory component is present
		2	Moderate swelling; moderately dilated patulous follicles; clinically, mild hypertrophy of the sebaceous glands or connective tissue; change in nasal contour without nodular component	
		3	Marked swelling; large dilated follicles; distortion of contour due to hypertrophy of the sebaceous glands and/or connective tissue, with a nodular component	
Ocular	• Dry, gritty sensation • Blepharitis • Conjunctivitis • Chalazia and hordeola • Keratitis, episcleritis, scleritis, iritis (rare)	1	Mild itch, dryness, or grittiness; fine scaling of eyelid margins; telangiectasia of eyelid margins; mild conjunctival injection	• Topical medications for grade 1 • Systemic medications for grade 2 • Refer to ophthalmologist for persistent grade 1 or 2 disease or suspected grade 3 disease
		2	Burning or stinging; crusting, irregularity, erythema and/or edema of eyelid margins; definite conjunctival injection; chalazion or hordeolum	
		3	Pain, photosensitivity, blurred vision; severe eyelid changes with loss of lashes, severe conjunctival inflammation; corneal changes, with potential loss of vision; episcleritis, scleritis; iritis	

Table 37.2 Clinical features and management of rosacea. *Adapted from Pelle MT, Crawford GH, James WD. Rosacea: II. Therapy. J Am Acad Dermatol 2004;51:499–512.*



Fig. 37.3 Rhinophyma. Hypertrophy of sebaceous glands and connective tissue as well as patulous follicles are seen. The changes are more prominent in the mid to lower nose. In addition, there is evidence of papulopustular rosacea. *Courtesy Kalman Watsky, MD.*



Fig. 37.4 Tortuous, telangiectatic vessels on the distal aspect of the nose contribute to its hyperemic appearance. This hyperemia may predispose to the subsequent hypertrophic changes of rhinophyma. Note the early sign of patulous follicles ("dilated pores"). *Courtesy Frank C. Powell, MD.*

TYPES OF PHYMATOUS ROSACEA	
Phyma	**Clinical features**
Rhinophyma	• Apparent initially as dilated patulous follicles at the distal end of the nose • When marked, can lead to debilitating nasal deformity
Gnathophyma	• Rare occurrence, with central chin typically involved • May give rise to asymmetrical swelling
Otophyma	• Usually affects the lower half of the helices and lobes of the ears
Metophyma	• Cushion-like, firm swelling of central forehead
Blepharophyma	• Swelling of the eyelids • Usually seen as a component of edematous rosacea but may accompany severe papulopustular or ocular rosacea

Table 37.3 Types of phymatous rosacea.



Fig. 37.5 Moderate papulopustular rosacea of the forehead. Note the superficial nature of the inflammatory lesions. *Courtesy Frank C. Powell, MD.*

Phymatous changes

These changes include sebaceous gland hypertrophy, patulous follicles, a bulbous appearance on the distal portion of the nose, and eventual fibrosis. Rhinophyma is by far the most common clinical presentation, occurring primarily in men (Fig. 37.3). Involvement of other anatomic sites has been reported, but it is rare (Table 37.3). Patients with rhinophyma may have other features of rosacea, usually mild to moderately severe papules and pustules. However, phymatous changes may arise *de novo* without any preceding skin changes and therefore should not be viewed as "end-stage rosacea"[33].

The earliest clinical sign of rhinophyma is the appearance of patulous follicles on the distal portions of the nose. It has been suggested that telangiectatic vessels in this same location may predispose to hypertrophic changes (Fig. 37.4). In severe cases of rhinophyma, the tissue hypertrophy leads to nasal distortion, with soft fleshy nodular growths resulting in significant disfigurement. Although basal cell carcinomas have been reported to arise in skin affected by rhinophyma, there is insufficient evidence to suggest that this condition predisposes to malignant change.

Major Phenotypes

Papules and pustules

Patients typically have a centrofacial eruption of multiple small (<3 mm), dome-shaped, erythematous papules and/or pustules that appear singly or in crops (Fig. 37.5 & 37.6). Individual lesions last about two weeks and are then replaced by blotchy postinflammatory erythema which gradually fades. Residual scarring is not a feature of papulopustular rosacea. A halo of erythema may surround larger inflammatory lesions and tiny telangiectatic vessels may be visible within this rim. Occasionally, when there is more severe disease, scaling or superficial crusting may be seen and this has been referred to as rosacea dermatitis (Fig. 37.7). Lastly, some patients will have some degree of persistent erythema of the cheeks that may represent a combination of postinflammatory erythema, telangiectasias, and vasodilation.

Flushing

Frequent flushing and blushing are common in patients with rosacea and occur in response to neurostimulation by various triggers (e.g. heat, alcohol consumption, certain social situations). Although quite noticeable in skin phototypes I–IV, flushing may be less visible in darker phototypes but rather experienced as a sensation of increasing warmth in the face. In addition, when patients complain of significant flushing, other causes of flushing should be considered as outlined in Tables 106.2 & 106.3.

Telangiectasia

Telangiectasias are common and involve primarily the central face, including the chin, in patients with lighter skin phototypes. They need to be distinguished from telangiectatic photoaging (see Table 37.4) and are less common as well as less perceptible in individuals with darker skin phototypes.



Fig. 37.6 Papulopustular rosacea – spectrum of severity in different skin phototypes. A Mild disease with scattered lesions on the cheek. **B** Moderate disease with increased number of lesions and areas of background erythema. **C** Severe disease with characteristic centrofacial distribution. Note the associated xerotic scale. *A, B, Courtesy Kalman Watsky, MD.*



Fig. 37.7 Rosacea dermatitis. When there is more severe disease, scaling and superficial crusting may be seen as on the cheek of this woman. *Courtesy Kalman Watsky, MD.*



Fig. 37.8 Inflammatory rosacea with edematous changes. An intensely erythematous plaque is present on the medial aspect of the cheek. This may improve once the underlying inflammation is treated appropriately. *Courtesy Frank C. Powell, MD.*

Ocular manifestations

Ocular manifestations of rosacea are discussed below.

Secondary Signs and Symptoms

Burning and stinging

Burning and stinging of the facial skin is a common complaint in patients with rosacea while pruritus is unusual. These sensations often occur within a background of erythema and sometimes scale. Patients also report significant sensitivity to and irritation from many products that are applied to the skin.

Facial edema

Facial edema may occur along with or result from prolonged erythema or flushing of the face and is thought to develop from post-capillary extravasation due to inflammation[2]. The soft edematous changes that are sometimes seen in patients with severe inflammatory rosacea (Fig. 37.8) should not be confused with phymatous rosacea. Such changes, unlike those of phymatous rosacea, often improve following successful management of the inflammatory lesions. Solid facial edema is discussed below.

Dry appearance

The centrofacial skin may sometimes appear dry and scaly, almost resembling a type of eczematous dermatitis. Such a presentation is often accompanied by burning and stinging sensations as well as significant sensitivity to topical products. When present, consideration should be given to the concomitant diagnosis of seborrheic dermatitis, which often coexists (see Table 37.4).

Other ocular manifestations

Ocular manifestations of rosacea are discussed below.

Other Clinical Rosacea Presentations

Ocular rosacea

This entity may or may not be accompanied by cutaneous changes of rosacea. Without cutaneous manifestations, the diagnosis of ocular



Fig. 37.9 Ocular rosacea. A Tiny concretions of keratin (conical dandruff) are visible at the bases of some of the eyelashes of the lower eyelid. There is also evidence of blepharitis of the lower eyelid and conjunctival injection. **B** Erythema of the mucosal portion of the lower eyelid and ectropion. **C** Marked injection of the conjunctivae, leading to the appearance of red eyes. Ectropion is also present. *A, Courtesy Frank C. Powell, MD.*

rosacea can be difficult to establish with certainty (Fig. 37.9). Symptoms are often nonspecific and include dryness, a gritty sensation, an inability to wear contact lenses, tearing, and sometimes pruritus. Patients usually do not associate these ocular symptoms with their rosacea and may not volunteer such information unless specifically asked.

Signs that strongly suggest a diagnosis of ocular rosacea include eyelid margin telangiectasias, interpalpebral conjunctival injection, and on slit lamp examination, corneal spade-shaped infiltrates, scleritis, and sclerokeratitis (see Table 37.1)[2]. Other common, but less specific, signs include honey crusting and mild scaling of the eyelid margin, tiny concretions at the bases of the lashes (conical dandruff; see Fig. 37.9A), and irregularity of the eyelid margin. When the disease is more active, there is evidence of blepharitis, often with eyelid swelling and conjunctival injection (see Fig. 37.9C). Cysts arising from the meibomian glands (chalazia) present as firm non-tender swellings of the cutaneous tarsal surface, while hordeola (styes) are often painful. Severe ocular disease (e.g. keratitis, corneal neovascularization, uveitis, scleritis, iritis) is rarely seen in patients with rosacea.

Granulomatous rosacea

In *granulomatous rosacea*, there are monomorphic, persistent, skin-colored to dull red–brown facial papules that are dome-shaped, favor the central face, and usually measure 1–3 mm in diameter (Fig. 37.10). This variant occurs in both children and adults and it may resolve spontaneously a few years after lesions first appear and not recur. Extrafacial lesions (e.g. on the scalp, neck, and upper trunk) are seen more often with the granulomatous variant. Histologically, non-caseating epithelioid granulomas are present within the dermis (see Pathology).

Some authors consider *lupus miliaris disseminatus faciei* (LMDF) to be a severe form of granulomatous rosacea[34], with a predilection for the periocular region (as well as the central face) and an "apple-jelly" appearance on diascopy. However, the dermal granulomas seen in biopsy specimens often have central caseation necrosis, thus explaining why this disorder was initially considered a tuberculid. More recently, *facial idiopathic granulomas with regressive evolution* (FIGURE) was proposed as an alternative term for LMDF. Unfortunately, significant facial scarring can be a permanent sequela. Occasionally, there is extrafacial involvement, which may be confused with other granulomatous



Fig. 37.10 Granulomatous rosacea, lupus miliaris disseminatus faciei variant. Monomorphous, discrete skin-colored to brown papules scattered on the face that are more persistent than the lesions of papulopustular rosacea. Histologically, granulomas with central caseation necrosis were observed, which led to the diagnosis of lupus miliaris disseminatus faciei.

diseases such as sarcoidosis, cutaneous tuberculosis, or the necrobiotic form of granuloma annulare.

Some authors consider both *rosacea conglobata*, which is characterized by an eruption of inflammatory cystic lesions that heal with scarring, and *rosacea fulminans* (pyoderma faciale) to be within the rosacea spectrum. In rosacea fulminans, an explosive onset of inflammatory papules and pustules is superimposed on a background of facial erythema, usually occurring in young women and sometimes during pregnancy[35].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for each of the diagnostic and major phenotypic subtypes of rosacea are outlined in Table 37.4.

PATHOLOGY

Histopathologic changes in erythematous and telangiectatic rosacea may be subtle and are often limited to vascular ectasia and mild edema (Fig. 37.11A). In the inflammatory papules and pustules, a more prominent perivascular and perifollicular lymphohistiocytic infiltrate appears (Fig. 37.11B). Sebaceous hyperplasia may be prominent in some patients. Comedo formation is notably lacking. In the granulomatous form of rosacea, non-caseating epithelioid granulomas are seen within the dermis (Fig. 37.11C). Phymatous rosacea shows dilated hair follicles, marked hyperplasia of sebaceous glands, and a variably dense lymphohistiocytic inflammatory infiltrate.

TREATMENT

General skin care recommendations for all rosacea patients are outlined in Table 37.5 and they represent an important component of the overall therapeutic regimen[36,37]. Currently available treatment options for the various subtypes of rosacea are listed in Table 37.6[38,39]. Grading the predominant features of rosacea into mild, moderate, and severe (grades 1–3) assists in guiding initial therapeutic interventions and in monitoring the clinical response (see Table 37.2)[40]. At the initial consultation, the patient should be made aware of the chronic relapsing nature of rosacea and the need for maintenance therapy even when in remission[5].

Transient and Persistent Erythema and Telangiectasia

A skin care regimen aimed at reducing skin sensitivity and improving epidermal barrier function is particularly important in these patients (see Table 37.5). In addition, strict photoprotection is advised, as UV exposure may potentiate dermal matrix and vascular damage. Topical application of vasoconstrictive adrenergic agonists, such as brimonidine (selective α_2) or oxymetazoline (selective α_{1A} and partial α_2), may help to diminish persistent erythema[41,42]. Patients should be instructed on the proper application of these agents and informed of side effects including rebound erythema, a burning sensation, and irritant contact dermatitis.

Topical antibiotics such as metronidazole may reduce erythema in a select group of patients, but they can cause irritation (see Table 37.6).

DIFFERENTIAL DIAGNOSIS OF ROSACEA	
Rosacea phenotype and differential diagnosis	**Distinguishing feature(s) from rosacea**
Erythema and telangiectasia (previously termed erythematotelangiectatic)	
Actinic damage (telangiectatic photoaging)	• Also characterized by facial telangiectasias and erythema, but the latter favors the lateral more than the central face • There tends to be less transient and non-transient erythema • Some patients have both disorders
Seborrheic dermatitis	• Erythema with greasy scale in the eyebrows, nasolabial folds, auditory meatus, retroauricular sulcus, and scalp • Involvement of eyelid creases • Patients often have both disorders
Keratosis pilaris rubra	• Onset usually during adolescence • Background erythema of the lateral cheeks with superimposed tiny follicular papules
Acute cutaneous lupus erythematosus	• Absence of inflammatory papulopustules and ocular changes • At least 75%–80% of patients have systemic signs/symptoms of SLE • Often more well-demarcated edematous plaques with sparing of the nasolabial fold
Dermatomyositis	• Violaceous erythema that favors the eyelids and central face, including the nasolabial folds • Eyelid edema can be pronounced
Flushing (idiopathic or secondary)	• Intermittent erythema and warmth • Flushing in patients with rosacea is usually limited to the face • Consider other common etiologies (e.g. menopause, anxiety disorder) or a tumor-related phenomenon (carcinoid syndrome, occult pheochromocytoma, mastocytosis) when additional anatomic sites are involved or there are associated symptoms such as tachycardia and sweating
Papules and pustules (previously termed papulopustular)	
Acne (vulgaris)	• Onset at a younger age • Comedones, both open and closed, and cysts • Greater involvement of the upper trunk
Periorificial dermatitis and steroid-induced rosacea	• See text
Demodicosis	• Spectrum includes *Demodex* folliculitis (see Ch. 38) and pityriasis folliculorum (see text) • Patients may be immunosuppressed (HIV infection, leukemia) • Involves face, especially the nose, and upper chest • Responds to topical ivermectin or permethrin ± oral ivermectin or metronidazole (see Table 38.1)
Tinea incognito, candidiasis	• Both can mimic rosacea, especially if topical corticosteroids have been used • KOH examination demonstrates hyphae or budding yeasts
Acneiform (papulopustular) eruptions due to EGFR inhibitors and other targeted therapies (e.g. MEK inhibitors, HER2 inhibitors)	• Occurs in up to 90% of patients on these drugs (see Fig. 37.15) • Abrupt onset • May also involve scalp, neck, and trunk
Follicular mucinosis	• Multiple papules but not pustules • Erythematous plaques and alopecia
Ocular rosacea	
Seborrheic dermatitis	• Involvement beyond the eyelid margin; may be accentuated in the eyelid creases
Drug-induced ocular rosacea	• Eyedrops used to treat other ocular disorders, e.g. glaucoma
Phymatous rosacea	
Lupus pernio (sarcoidosis)	• Violaceous indurated plaque of the distal nose
Discoid lupus erythematosus	• Erythema, scaling, follicular plugging, and tendency for scarring
Lupus vulgaris (cutaneous TB)	• See Table 75.7
Neoplasms	• Basal cell carcinoma, lymphoma, angiosarcoma, cutaneous metastases (“clown nose”)

Table 37.4 Differential diagnosis of rosacea. Occasionally, trichostasis spinulosa has associated erythema, but detection of multiple hairs within the follicular orifice by dermoscopy or microscopic examination of follicular contents establishes the diagnosis. EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MEK, mitogen-activated protein kinase kinase; SLE, systemic lupus erythematosus; TB, tuberculosis.

Use of nonselective β-blockers (e.g. propranolol, carvedilol) to treat rosacea-associated flushing can be beneficial in selected individuals. Laser therapy (e.g. pulsed dye, potassium titanyl phosphate) and intense pulsed light can be used to ameliorate telangiectasias and improve erythema (see Ch. 137).

Papules and Pustules

In general, patients with inflammatory papules and pustules are treated with topical and/or systemic antibiotics (see Table 37.6)[43]. Although many of the antibiotics used to treat these lesions are the same as those used for acne vulgaris, the treatment course for rosacea is usually shorter (4–8 weeks as opposed to 3–4 months) and subantimicrobial doses may be effective. Sometimes successful treatment of the papulopustules may unmask background telangiectasias which then need to be addressed. Following successful clearance of inflammatory lesions, maintenance therapy (usually topical) should be instituted to avoid a likely relapse. Many patients with moderate and severe (grades 2 and 3) disease require repeated courses of systemic antibiotic therapy, but subsequent courses can often be shorter in duration, i.e. 3 to 4 weeks.

Topical ivermectin, which has both anti-inflammatory and antiparasitic properties, has become an important first-line therapy, as are

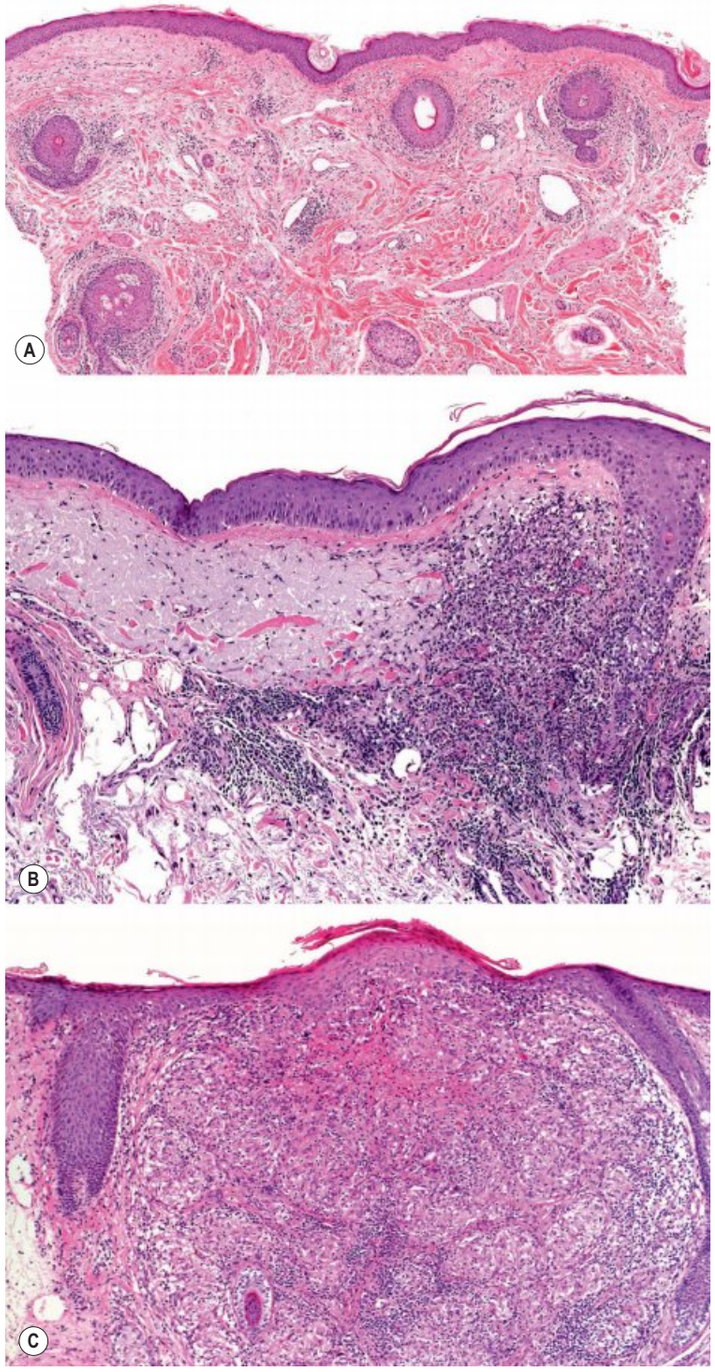


Fig. 37.11 Rosacea – range of histopathologic features. A *Erythema and telangiectasia* subtype with multiple dilated blood vessels as well as minimal perifollicular and perivascular lymphocytic infiltrates. **B** *Papules and pustules* subtype with a dense dermal infiltrate of lymphocytes, predominantly surrounding an involved hair follicle. There is also marked solar elastosis. **C** *Granulomatous variant* of rosacea with a nodular granulomatous infiltrate composed of histiocytes, histiocytic giant cells, and admixed lymphocytes filling the upper interfollicular dermis. *Courtesy Lorenzo Cerroni, MD.*

GENERAL RECOMMENDATIONS FOR FACIAL SKIN CARE AND EDUCATION IN PATIENTS WITH ROSACEA
Facial skin care
• Wash with lukewarm water and use soap-free cleansers or synthetic detergents (syndets) that are pH balanced • Cleansers are applied gently with fingertips • Use sunscreens with both UVA and UVB protection and an SPF ≥30 • Sunscreens containing the inorganic filters titanium dioxide and/or zinc oxide are usually well tolerated • Use cosmetics and sunscreens that contain protective silicones • Water-soluble facial powder containing inert green pigment helps to neutralize the perception of erythema • Moisturizers containing humectants (e.g. glycerin) and occlusives (e.g. petrolatum) help to repair the epidermal barrier • Avoid astringents, toners, and abrasive exfoliators • Avoid cosmetics that contain alcohol, menthols, camphor, witch hazel, fragrance, peppermint, and eucalyptus oil • Avoid waterproof cosmetics and heavy foundations that are difficult to remove without irritating solvents or physical scrubbing • Avoid procedures such as glycolic peels or dermabrasion
Patient education
• Reassure the patient about the benign nature of the disorder and the rarity of rhinophyma, particularly in women • Emphasize the chronicity of the disease and the likelihood of exacerbations • Direct patients to information websites such as those of the National Rosacea Society (www.rosacea.org) or the American Academy of Dermatology (www.aad.org) • Advise avoidance of recognized triggers • Explain the importance of compliance with topical regimens • Educate on the importance of sun avoidance

Table 37.5 General recommendations for facial skin care and education in patients with rosacea.

topical metronidazole and azelaic acid[44]. Other topical agents include sodium sulfacetamide +/− sulfur, minocycline[45], clindamycin, benzoyl peroxide[46], retinoids, and permethrin. Low-dose isotretinoin[47] and photodynamic therapy[48] are treatment options in patients whose lesions prove resistant to first-line therapies.

Other Forms of Rosacea

Rhinophyma is the type of phymatous rosacea most amenable to treatment (see Table 37.6). Mild disease may be responsive to low-dose isotretinoin, although conclusive evidence of efficacy is lacking. More severe (grades 2 and 3) disease responds best to physical modalities such as CO_2 laser therapy, electrosurgery, or surgical excision (see Fig. 140.7). Longitudinal evaluation of patients treated with CO_2 laser therapy suggests that improvement persists long-term[49]. Other sites of phymatous rosacea are very rare and there are no established therapeutic interventions.

Ocular rosacea is a common entity that is frequently underdiagnosed[50]. Patients with mild ocular rosacea (grade 1 disease) often respond to washing of the eyelid margins with gauze soaked with dilute, tear-free baby shampoo. This is combined with an oily tear replacement. Burning or stinging with crusting of the eyelid margins or the formation of a chalazion or hordeolum are manifestations of moderate (grade 2) disease and treatment consists of topical and/or systemic antibiotics (see Table 37.6). Pain, photophobia, and visual disturbances are features of severe (grade 3) disease. Such symptoms require prompt referral to an ophthalmologist.

Granulomatous rosacea is difficult to treat, and no consensus exists regarding first-line therapies. Anecdotally, options include dapsone, minocycline, isotretinoin, hydroxychloroquine, and the 1450-nm diode laser. Anecdotally, apremilast has been reported to improve LMDF.

While some authors consider *rosacea fulminans* (pyoderma faciale; Fig. 37.12) and *rosacea conglobata* to be within the rosacea spectrum, others view them as variants of acne vulgaris. Nonetheless, systemic corticosteroids are required to control the aggressive inflammation observed in both disorders, followed by the use of oral isotretinoin. Scarring can be a sequela despite these interventions.

ROSACEA-LIKE DISORDERS

- *Periorificial dermatitis*, originally termed perioral dermatitis, bears a superficial resemblance to rosacea, but the distribution pattern (perioral, perinasal, and/or periocular rather than centrofacial) and lesional morphology differ. In periorificial dermatitis, there are monomorphous superficial pinpoint pustules and/or pink papules as well as patches and thin plaques, some of which have fine scale (Fig. 37.13). A history of topical or inhaled corticosteroid use may be elicited. Overuse of cosmetics and moisturizers has also been

MEDICAL AND SURGICAL THERAPIES FOR ROSACEA	
Treatment	**Comments and/or doses**
Erythema and telangiectasia (previously termed erythematotelangiectatic)	
Facial skin care recommendations (see Table 37.5)	Particularly useful as this subtype is prone to skin irritation and "sensitivity"
Photoprotection	UVR may potentiate dermal matrix damage
Topical agents, e.g. azelaic acid, metronidazole	May reduce erythema, but their use is often limited by their irritant effects
Topical brimonidine tartrate (0.33% gel)*,†	Selective α_2-adrenergic agonist that improves erythema; effects are temporary and possible rebound erythema
Topical oxymetazoline HCl (1% cream)*	Selective α_{1A}-adrenergic agonist and partial α_2-adrenergic agonist that improves erythema; temporary effects are temporary and possible rebound
Laser therapy†	Use of vascular lasers (e.g. pulsed dye, potassium titanyl phosphate) as well as intense pulsed light may improve grades 2 and 3 (see Ch. 137)
Papules and pustules (previously termed papulopustular)	
Topical	
Ivermectin (1% cream)*,† once daily	More effective than placebo and slightly more effective than topical metronidazole in randomized controlled trials
Metronidazole (0.75% gel, cream, or lotion; 1% gel or cream)*,† once or twice daily	Can be used as initial treatment to clear inflammatory lesions or as indefinite maintenance therapy
Azelaic acid (15% gel and foam)*,† twice daily	Appears to be more effective than topical metronidazole but with more side effects, e.g. irritation Azelaic acid (20% cream twice daily) is a non-FDA-approved alternative dose
Sodium sulfacetamide (10%) ± sulfur (5%) lotion* or both in a cream*, gel*, foam*, or cleanser (wash, pads)* once or twice daily	Gel and cleanser formulations may include 10% urea
Minocycline (1.5% foam)* once daily	More effective than vehicle foam in reduction of inflammatory lesion count at 12 weeks[45]; well tolerated
Erythromycin (2% gel and solution) twice daily	Alcohol in gel and solution may reduce tolerance
Clindamycin (1% lotion) once daily	
Benzoyl peroxide 5% cream	Microencapsulated formulations* may be better tolerated[46]
Benzoyl peroxide 2.5%–5% plus clindamycin 1%–1.2% daily	May cause skin irritation
Tretinoin (0.025% cream; 0.05% cream; 0.01% gel) daily	Alters epidermal keratinization and may improve photodamage Poorly tolerated by some patients
Permethrin (5% cream) daily–weekly	As effective as topical metronidazole for the treatment of papules and erythema
Pimecrolimus (1% cream) or tacrolimus (0.03%, 0.1% ointment) twice daily	Some studies have shown improvement in erythema, but there have been reports of exacerbations and induction of rosaceiform dermatitis
Systemic	
Doxycycline (low-dose)	40 mg daily (30 mg immediate release and 10 mg delayed release)*,† for 4–8 weeks; as effective as the 100 mg dose but with fewer adverse effects 20 mg twice daily for 4–8 weeks may be more cost-effective
Doxycycline	50–100 mg once or twice daily for 4–8 weeks
Minocycline	50–100 mg twice daily or sustained action formula (1 mg/kg) daily for 4–8 weeks‡
Tetracycline†	250–500 mg twice daily for 4–8 weeks
Erythromycin	250–500 mg once or twice daily for 4–8 weeks
Azithromycin	250–500 mg (5–10 mg/kg) thrice weekly for 4–8 weeks
Metronidazole	200 mg once or twice daily for 4–8 weeks
Isotretinoin†	10–20 mg daily for 4–6 months
Phymatous	
Isotretinoin	May reduce nasal volume and halt the progression of rhinophyma
Electrosurgery	Can effectively debulk and resculpt the nose
CO_2 laser	
Surgical excision	
Ocular	
Eyelid hygiene and artificial tears	Frequently used to treat mild disease Useful for maintaining remission following treatment of grades 2 and 3 disease with systemic antibiotics
Topical antibiotics (metronidazole 0.75% gel, erythromycin 0.5% ophthalmic ointment, azithromycin 1% ophthalmic solution)	
Cyclosporine 0.5% ophthalmic emulsion†	More effective than artificial tears
Systemic antibiotics (see above section)	For grade 2–3 disease

*FDA-approved treatments for rosacea (evidence-based support = 1).
†In a Cochrane review of randomized controlled trials conducted for moderate to severe rosacea, these were the treatments shown to be effective[38].
‡In a 16-week trial, minocycline 100 mg daily was non-inferior to doxycycline 40 mg daily[54].

Table 37.6 Medical and surgical therapies for rosacea. If moderate to severe flushing persists despite avoidance of triggers, beta-blockers (e.g. carvedilol, nadolol) can be tried (see Ch. 106). Ophthalmic corticosteroids (e.g. dexamethasone, fluocinolone) can be used short-term to treat severe eyelid inflammation. UVR, ultraviolet radiation.

implicated in exacerbating periorificial dermatitis, and intolerance of sunlight and hot water are common symptoms.

A 4- to 8-week course of oral antibiotics (e.g. doxycycline, erythromycin, tetracycline, minocycline, often at subantimicrobial doses) is usually effective in clearing the skin; azithromycin 500 mg three times weekly for 4–8 weeks represents an alternative therapy (see Table 37.6). If topical corticosteroids are implicated in causing perioral dermatitis, they should be discontinued. However, a reduction in the strength and frequency of application of the topical corticosteroid, as opposed to an abrupt discontinuation, may help to avoid a significant rebound flare of the disease. Clearance is usually not followed by a subsequent relapse unless the patient is re-exposed to the inciting trigger. A variant seen in children is referred to as chronic granulomatous periorificial disease of children.



Fig. 37.12 Rosacea fulminans (pyoderma faciale). Sudden onset of tender plaques on the chin studded with pustules. The patient was pregnant and had no history of rosacea or acne vulgaris.

- *Steroid-induced "rosacea"* is a facial eruption in which erythema, papules, and pustules, and in some patients atrophic changes such as telangiectasias, develop from the repeated application of moderate to high potency topical corticosteroids (Fig. 37.14). As with periorificial dermatitis, reducing the strength of the topical corticosteroid as well as the frequency of application (rather than an abrupt discontinuation) is advisable to reduce a rebound flare. Systemic doxycycline, tetracycline, minocycline, azithromycin or erythromycin may also be required for 4 to 8 weeks. Although they have been reported to induce rosaceiform dermatitis, topical calcineurin inhibitors can also be used to reduce inflammation.
- *Rosaceiform dermatitis* is a term usually employed to describe a cutaneous reaction to a drug that clinically resembles rosacea. It is due primarily to topical or systemic corticosteroids and topical calcineurin inhibitors[51], and it is characterized by facial erythema plus small papules and numerous pustules. The distribution on the face is usually widespread, although there are exceptions. Abundant *Demodex* mites have been found on the facial skin of some of these patients, possibly the result of the immunomodulating effects of the inciting medications. This term is also used by some clinicians to describe patients with features of both rosacea and facial dermatitis.
- *Acneiform papulopustular eruption due to epidermal growth factor receptor (EGFR) inhibitors and other targeted therapies* – see Table 37.4 and Fig. 37.15.
- *Idiopathic facial aseptic granuloma* (IFAG) usually presents with a single erythematous nodule on the cheek of a child which persists for several months then spontaneously resolves. One theory is that it represents a form of childhood granulomatous rosacea.



Fig. 37.13 Periorificial dermatitis (often referred to as perioral dermatitis). A–C Pink papules, patches, and thin plaques as well as pinpoint superficial pustules around orifices, i.e. in a perioral, perinasal, and/or periorbital distribution pattern. In contrast to papulopustular rosacea, the papules are classically at the same stage of evolution. **D** Close-up of the characteristic pinpoint pustules (arrows). **E** Granulomatous periorificial disease in a child with monomorphous pink papules that have become confluent around the mouth. The eruption, which had previously worsened upon treatment with topical and oral corticosteroids, resolved with a 6-week course of azithromycin. *A, Courtesy Frank C. Powell, MD; B–D, Courtesy Kalman Watsky, MD; E, Courtesy Julie V. Schaffer, MD.*

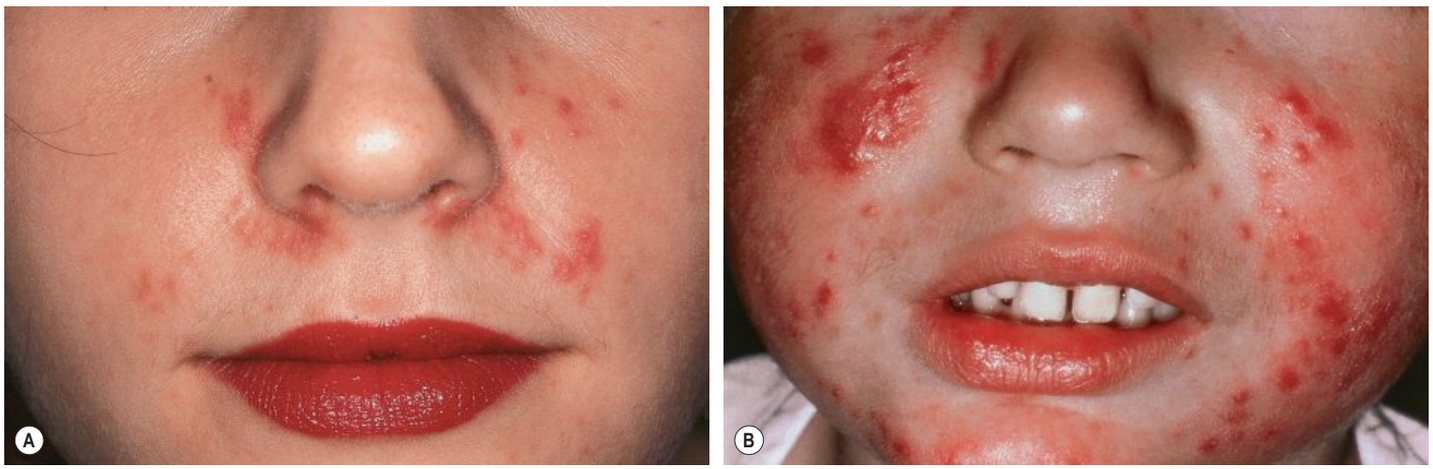


Fig. 37.14 Steroid rosacea. A Milder disease in an adult with scattered erythematous papules and papulopustules of the central face. **B** Severe disease in a child with confluence of erythematous papulopustules. *A, Courtesy Kalman Watsky, MD.*



Fig. 37.15 Papulopustular eruption due to an epidermal growth factor receptor (EGFR) inhibitor. There is a resemblance to rosacea but the onset is more abrupt. *Courtesy Frank C. Powell, MD.*



Fig. 37.16 Morbihan disease. Erythematous, firm, non-pitting, asymptomatic swelling of the upper midface. Areas of greatest involvement can acquire a "peau d'orange" appearance. *Courtesy Frank C. Powell, MD.*

- *Demodicosis* encompasses *Demodex* folliculitis (see Ch. 38) and pityriasis folliculorum. The latter is a poorly recognized disorder that primarily affects women in the 20- to 40-year age group who rarely allow water to contact their face and who instead often apply moisturizing and cleansing creams as well as cosmetic preparations. There is a roughened, whitish scaling skin surface on a background of faint erythema, along with some scattered fine papules and pustules that are not limited to the central face. The patient usually complains of increased skin sensitivity. KOH examination of skin scrapings demonstrates multiple dead and some live *Demodex* mites. Nightly application of topical ivermectin for 4 to 6 weeks is usually effective when combined with a facial washing routine.
- *Morbihan disease* (solid facial edema) is a rare facial disorder characterized by a progressive and persistent, asymptomatic, firm non-pitting swelling of the central upper face that is associated with fixed facial erythema (Fig. 37.16). Lymphedema in this location can result from a number of initiating factors, from injuries to contact allergy[52] to acne vulgaris. While rosacea has also been associated with Morbihan disease[53], there are patients with no history of a facial dermatosis. Histologically, it may be indistinguishable from other forms of rosacea, including presenting with granulomatous features. Lymphedema can also be seen. There is no consistently effective therapy, but prolonged courses of antihistamines and low-dose oral isotretinoin have been reported as helpful in individual patients.
- Patients with *Haber syndrome*, currently viewed as a subtype of Dowling–Degos disease with comedones of the trunk and pitted scars, can also have early-onset, rosacea-like facial erythema.

Acknowledgment

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Additional figures available in our eBook (see inside front cover for access code).

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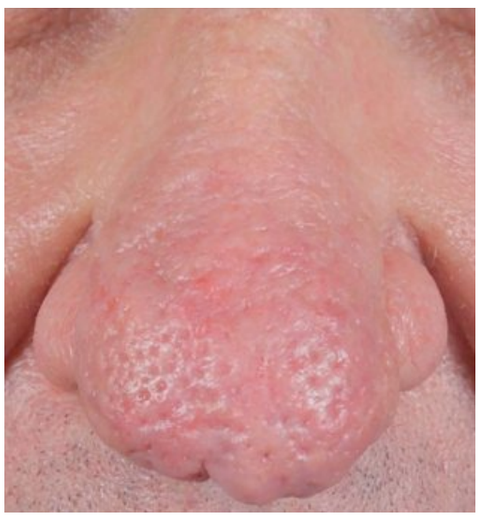
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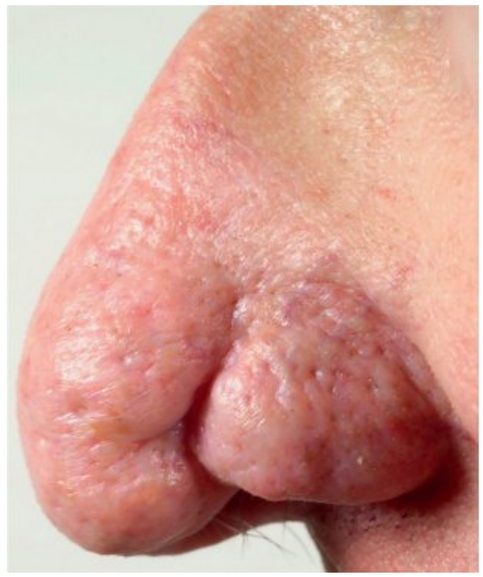
eFig. 37.1 Moderate to severe papulopustular rosacea. There is a typical centrofacial distribution of erythema, telangiectasias, papules, and pustules. In addition, the skin has a scaly, crusty surface and this is often a sign of more severe disease. *Courtesy Frank C. Powell, MD.*



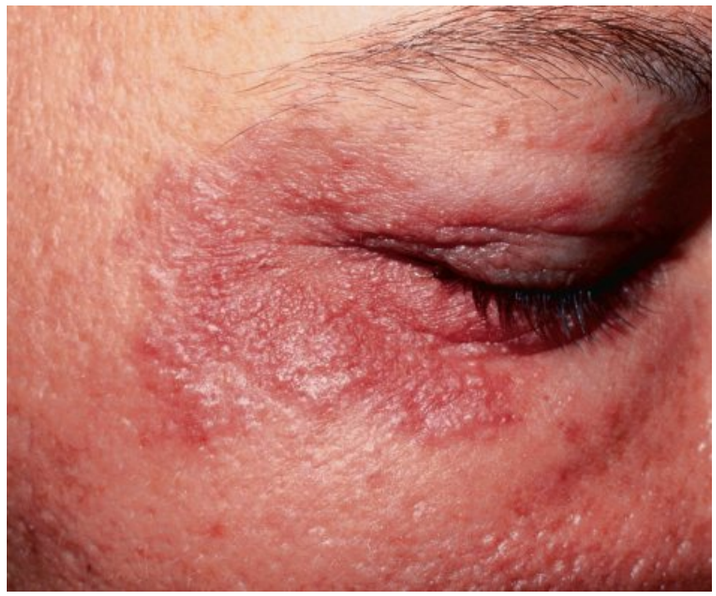
eFig. 37.2 Rosacea fulminans (pyoderma faciale). Striking plaque on the cheek studded with pustules.



eFig. 37.3 Earlier stage of rhinophyma with prominent follicular openings (patulous follicles) and evidence of the early nodular swelling. *Courtesy Frank C. Powell, MD.*



eFig. 37.4 Rhinophyma with distortion of nasal tissue due to nodular hypertrophy of sebaceous glands. Electrosurgery or laser therapy can be used to debulk and resculpt this nose. *Courtesy Frank C. Powell, MD.*



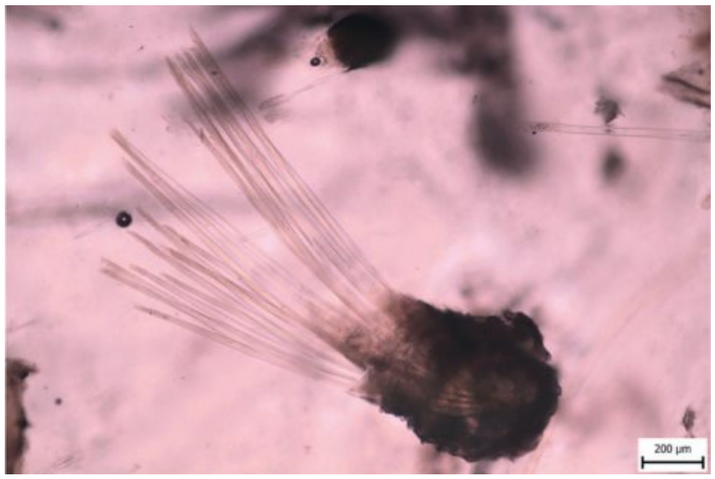
eFig. 37.5 Periocular dermatitis with multiple fine papules and pustules superimposed on a pink plaque. *Courtesy Ronald P. Rapini, MD.*



eFig. 37.6 Periocular (periorificial) dermatitis in a 17-year-old male patient. Note the clustered pinpoint pustules within an erythematous plaque. *Courtesy Kalman Watsky, MD.*



eFig. 37.7 Periocular (periorificial) dermatitis involving the forehead and eyelid. *Courtesy Kalman Watsky, MD.*



eFig. 37.10 Trichostasis spinulosa – microscopic examination of follicular contents. Tuft of multiple vellus hairs. *Courtesy Frank C. Powell, MD.*



eFig. 37.8 Severe steroid rosacea. The patient had been applying clobetasol, a class I corticosteroid, to the face. *Courtesy Kalman Watsky, MD.*



eFig. 37.9 Trichostasis spinulosa presenting with nasal erythema and prominence of the follicular orifices. *Courtesy Frank C. Powell, MD.*

38 Folliculitis, Follicular Occlusion Tetrad, and Other Follicular Disorders

Jennifer L. Hsiao, Vivian Y. Shi and Kieron S. Leslie

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INTRODUCTION

This chapter reviews both superficial and deep forms of folliculitis as well as disorders of follicular keratinization. Examples of superficial folliculitis include those due to *Staphylococcus aureus* or *Pseudomonas aeruginosa* infections, whereas acne keloidalis and pseudofolliculitis barbae are examples of deep forms. Hidradenitis suppurativa, a major entity within the follicular occlusion tetrad, is increasingly being recognized as a systemic inflammatory disorder. The disorders of follicular keratinization represent a varied group of dermatoses that have in common prominent keratotic follicular plugs. Some of these disorders are reviewed in other chapters, e.g. lichen planopilaris, pityriasis rubra pilaris (PRP) and keratosis pilaris, while others are discussed here, e.g. lichen spinulosus and erythromelanosis follicularis faciei.

SUPERFICIAL FOLLICULITIS

Synonym: ▪ Impetigo of Bockhart

Key features

- Folliculocentric papules and pustules, often arising on an erythematous base
- Favors areas with terminal hairs and a greater density of sebaceous glands, such as the scalp, beard, and upper trunk, as well as the buttocks and lower extremities
- Bacterial culture of pustular contents most commonly reveals normal flora, followed by *Staphylococcus aureus*
- Treatment depends on the particular type of folliculitis

Introduction

Folliculitis is a very common disorder characterized by follicular papules and pustules with varying degrees of inflammation. It occurs most commonly in adolescents and adults. Folliculitis can be secondary to a wide range of infectious agents, or be induced by irritants or drugs (Fig. 38.1). While potential pathogens include bacteria, fungi, viruses, and parasites, culture of pustular contents most commonly reveals normal flora ("culture-negative"), followed by *Staphylococcus aureus*.

Clinical features

Follicular pustules are usually accompanied by an erythematous rim (Fig. 38.2). If no pustules are present, follicular-based erythematous papules or a superimposed collarette of scale serve as clues to the diagnosis. Comedones are not typically seen unless the patient also has acne vulgaris. Lesions may be pruritic or even tender or painful. Generalized pruritus can accompany more widespread disease.

Folliculitis occurs most commonly in the head and neck region (especially the scalp and beard area), upper trunk, buttocks, and legs, as well as in the axillae and groin (Fig. 38.3). It favors areas that are occluded and/or have a greater density of terminal hairs. In addition, shaving can predispose to folliculitis.

Pathology

The early inflammatory infiltrate consists primarily of perifollicular neutrophils with extension into the follicular epithelium and follicular ostium. This is soon followed by an admixture with lymphocytes and macrophages. Late-stage changes include follicular rupture and a granulomatous response. Deeper inflammatory reactions may lead to scarring alopecia.

Tissue Gram stain may reveal pathogenic organisms. Occasionally, cytopathic changes due to herpes simplex or zoster viral infections are seen within the follicular epithelium (see Ch. 80). In dermatophyte infections, hyphae can be seen within hair shafts or in the follicular ostium (see Fig. 77.13G). The presence of *Demodex* organisms (see Fig. 38.5H) or yeast forms requires clinicopathologic correlation as they are commensal organisms.

Differential diagnosis

In addition to the various forms of folliculitis listed in Table 38.1, the differential diagnosis also includes acne vulgaris, pseudofolliculitis barbae, and occasionally, rosacea. Dermoscopy can assist in confirming that the papules are folliculocentric, allowing distinction from other disorders such as Grover disease. Microscopic examination of follicular contents may provide a clue to the type of folliculitis as can microbial cultures and histologic examination. In patients who are confined to bed, folliculitis may develop predominantly on the posterior trunk and thus needs to be distinguished from other disorders exacerbated by occlusion including Grover disease, miliaria rubra, and cutaneous candidiasis.

Treatment

Superficial folliculitis may be self-limited, especially if exacerbating factors are addressed. The treatment chosen depends upon the culture results and severity (see Chs. 74 & 127). For patients whose cultures fail to demonstrate a pathogenic microbe, the treatments, as in acne, include topical benzoyl peroxide, topical antibiotics, and oral antibiotics (e.g. doxycycline), with the anti-inflammatory properties of these antibiotics likely playing a role. This should be combined with measures to reduce overhydration of the skin, occlusion, and irritation.

Malassezia (*Pityrosporum*) Folliculitis

Malassezia (*Pityrosporum*) folliculitis is most commonly associated with *M. globosa*, *M. furfur*, and *M. sympodialis* (see Ch. 77). These commensal yeasts favor sebaceous-rich skin and typically become pathogenic under certain favorable conditions – a warm, humid climate, excessive sebum production or sweating, occlusion from emollients, use of systemic antibiotics, and immunosuppression. Yeast lipases can cleave sebaceous triglycerides, with the resultant free fatty acids serving as potential irritants and proinflammatory mediators.

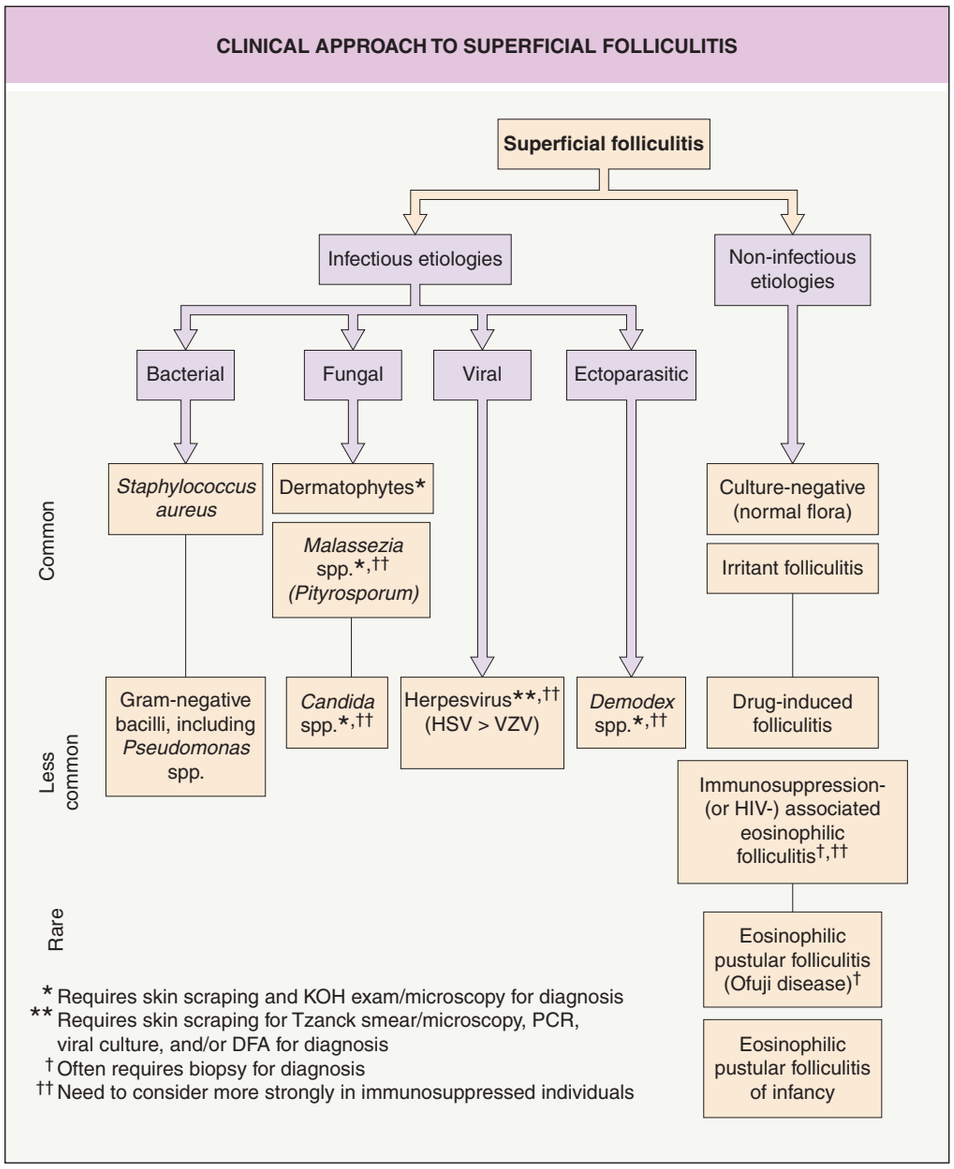


Fig. 38.1 Clinical approach to superficial folliculitis. Edematous lesions of folliculitis are most suggestive of eosinophilic folliculitis, *Demodex* folliculitis, and *Pseudomonas* "hot tub" folliculitis. See Table 38.1 for medications that can cause drug-induced folliculitis. *Courtesy Jean L. Bolognia, MD.*



Fig. 38.2 Folliculitis (culture-negative). Follicular pustules with an erythematous rim on the buttocks of a 3-year-old who wore "pull-ups" at night. *Courtesy Julie V. Schaffer, MD.*

Malassezia (Pityrosporum) folliculitis presents as multiple monomorphic, oftentimes pruritic, small follicular papules and occasionally pustules. A central keratin plug may be present. Lesions favor the upper trunk of teenagers and young adults (Fig. 38.5D), but may also appear on the shoulders, neck, and face (especially the forehead and anterior hairline). Diagnosis can be established via KOH examination of follicular contents, which demonstrates spherical yeast forms. In addition to addressing predisposing factors, treatment options include topical antifungal creams or lotions and selenium sulfide shampoo. For more widespread disease or topical therapy failure, oral fluconazole can be used, e.g. 150–300 mg once weekly for 1–2 months.

Eosinophilic Folliculitis

Three major forms of eosinophilic folliculitis have been described – eosinophilic pustular folliculitis (Ofuji disease), immunosuppression (or HIV)-associated eosinophilic pustular folliculitis, and eosinophilic pustular folliculitis of infancy.

Eosinophilic pustular folliculitis

Synonyms: ▪ Ofuji disease ▪ Eosinophilic folliculitis



Fig. 38.3 Folliculitis of the axilla and beard area due to *Staphylococcus aureus*. **A** Numerous follicular pustules with an erythematous rim emanating from the axillary vault. **B** Discrete papulopustules are seen posteriorly, while centrally there is deeper involvement with plaque formation (sycosis barbae). *A, Courtesy Kalman Watsky, MD.*

Key features

- Follicular papulopustules as well as erythematous patches and plaques with superimposed coalescent pustules; central clearing leads to figurate lesions
- Most commonly involves the face, followed by the upper extremities and trunk
- Often moderate to severe pruritus
- Recurrent crops of lesions typically involute over 7–10 days
- Peripheral blood eosinophilia also present
- Histologically, intrafollicular and perifollicular eosinophil-rich infiltrates

Introduction

Eosinophilic pustular folliculitis is characterized by recurrent episodes of eruptive, intensely pruritic, follicular papulopustules, often in association with peripheral blood eosinophilia. It typically affects "acne-prone" areas of the body such as the face, back, and extensor surface of the arms[1]. To date, this disorder has not been associated with systemic disease.

History

In 1965, Ise and Ofuji[2] were the first to report a patient who had repeated episodes of follicular pustules on the face and back along with peripheral blood eosinophilia. Of note, this disorder is not to be confused with papuloerythroderma of Ofuji (see Ch. 26).

Epidemiology

Eosinophilic pustular folliculitis is a relatively rare entity, with most of the cases reported from Japan. The majority of patients are Asian adults, with an average age of onset between 20 and 40 years. The ratio of men to women is ~5:1 amongst Japanese patients and ~1:1.6 in Singapore[3]. There have been occasional reports of eosinophilic pustular folliculitis in children, often with clinical features similar to the infantile form (see below).

Pathogenesis

The etiology of eosinophilic pustular folliculitis remains unclear. Proposed mechanisms include hypersensitivity reactions to various antigenic stimuli (e.g. infectious agents, medications), Th2 pathway skewing, and immune dysfunction[4]. The presence of $CD163^+$ M2 macrophages, which play a role in parasitic infections, as well as $pSTAT6^+$ and IL-10-producing cells within lesional skin point to Th2 polarization[5]. Via GATA3, STAT6 in concert with STAT5 induces Th2 cells to secrete IL-4, IL-5, and IL-13; these cytokines are known to play a key role in the recruitment of eosinophils. In addition, elevated serum levels of the chemokine TARC have been observed in eosinophilic pustular folliculitis[6], as in other disorders with peripheral eosinophilia such as drug reaction with eosinophilia and systemic symptoms (DRESS). Prostaglandin D2 may also play a role in the activation of pilosebaceous units and recruitment of eosinophils. This provides a possible explanation for the therapeutic response to indomethacin, a COX inhibitor that inhibits prostaglandin synthesis[7].

Clinical features

Recurrent crops of intensely pruritic, grouped, follicular pustules and papulopustules erupt in a rapid fashion. In addition, there may be erythematous patches and plaques with superimposed coalescent pustules; central clearing and centrifugal extension produce annular and figurate lesions. Typically, areas with "sebaceous" follicles, such as the face, back, and extensor surface of the arms, are affected. However, the digits, palms, and soles may be involved, proving that not all lesions are follicular. Lesions last 7–10 days and tend to relapse every 3–4 weeks. Because this disorder most commonly occurs in individuals with darker skin phototypes, postinflammatory hyperpigmentation is a common finding. The patients have no accompanying systemic symptoms.

Pathology

Involved follicles show spongiosis with exocytosis of eosinophils ("eosinophilic spongiosis"), admixed with variable numbers of lymphocytes and neutrophils. Micropustular aggregation develops, followed by the hallmark finding of infundibular eosinophilic pustules[8]. While these findings are particularly prominent in the infundibular region, they are accompanied by perifollicular inflammatory infiltrates with a similar cellular composition.

Differential diagnosis

Clinically, some of the lesions may resemble other forms of superficial folliculitis (see previous section), acneiform eruptions, and other figurate erythemas, in particular eosinophilic annular erythema, hydroxychloroquine-induced generalized pustular figurate erythema, and pustular psoriasis. However, the explosive crops, annular plaques with central clearing, intense pruritus, peripheral blood eosinophilia, and histologic findings typically enable differentiation from clinically similar entities. Rarely, early eosinophilic pustular folliculitis may have a symmetric, butterfly rash-like presentation that resembles acute cutaneous lupus erythematosus.

Treatment

Potent topical corticosteroids, tacrolimus ointment, topical indomethacin[9], and oral antihistamines can be prescribed for the associated pruritus as well as for mild localized disease. Oral indomethacin (50 mg/day) is recommended as first-line systemic therapy. Second-line therapies include UVB phototherapy, oral minocycline (100 mg twice daily), oral dapsone (100 to 200 mg/day for ≥2 weeks), systemic corticosteroids, and colchicine (0.6 mg twice daily). Oral cyclosporine or isotretinoin may be considered in patients with refractory disease.

LESS COMMON SPECIFIC FORMS OF FOLLICULITIS		
Etiology/risk factors	**Clinical features**	**Therapy**
Irritant folliculitis		
Usually occurs following the application of irritating topical medications (e.g. tar preparations), topical keratolytics, or chemical peels Exacerbated by application in a direction opposite that of hair growth	• Follicular papules and pustules in the sites of application or exposure to irritant • Favors areas with terminal hairs	• Discontinue inciting topical agent • Apply medications in the same direction as hair growth • Topical corticosteroids
Gram-negative folliculitis		
Due primarily to *Klebsiella, Escherichia coli, Enterobacter* and *Proteus* spp. Usually seen in patients with acne vulgaris receiving long-term antibiotic therapy Can occur in setting of primary immunodeficiency (e.g. HIV) or α-1-antitrypsin deficiency	• Papules and pustules in the facial T-zone and in a perinasal distribution • Adult men with oily skin • Organisms isolated from nares as well as cutaneous lesions	• Topical: gentamicin, benzoyl peroxide • Systemic: quinolones (e.g. ciprofloxacin), ampicillin or trimethoprim/sulfamethoxazole • If severe or recurrent: isotretinoin, 0.5–1 mg/kg/day for up to 16 weeks
Hot tub folliculitis, due primarily to *Pseudomonas aeruginosa* Follows exposure to contaminated water in hot tubs or whirlpools > swimming pools	• Typically appear 12–48 hours after exposure • Edematous, pink to red follicular papules and pustules, primarily on the trunk > extremities (Fig. 38.4) • Often pruritic and resolves spontaneously in immunocompetent patients • May lead to serious illness in immunocompromised patients (e.g. ecthyma gangrenosum)	• Generally self-limited; can use antibacterial soap • If severe or immunocompromised host: ciprofloxacin, 500 mg po twice daily for 7–14 days • Prevention: adequate chlorine levels, e.g. 2–4 mg/L for swimming pools, 3–5 mg/L for hot tubs, and pH of 7.2–7.4
Dermatophyte folliculitis		
Tinea barbae – usually due to zoophilic dermatophytes *Trichophyton mentagrophytes* or *T. verrucosum* Risk factors include occupational or recreational exposure to infected animals	• Inflammatory papules and pustules in the beard area more often than the mustache, with crusting • Loosened hairs can be removed without pain	• Topical antifungals (may be ineffective) • Terbinafine, 250 mg/day po for 2–4 weeks • Microsized or ultramicrosized griseofulvin, 500–1000 mg/day or 500–750 mg/day po, respectively, for 4–8 weeks • Fluconazole, 150 mg po once weekly for 2–4 weeks • Itraconazole, 200 mg po twice daily for 1 week per month, for 2 pulses
Majocchi granuloma – a follicular infection most commonly due to *T. rubrum* Can have perifollicular granulomatous inflammation Risk factors include shaving of legs, use of potent topical corticosteroids, occlusion, and immunosuppression	• Follicular pustules and follicular papules or nodules (Fig. 38.5A-C), most often located on the lower extremities • Often arises within expanding lesions of tinea corporis, cruris or pedis • Also arises in the setting of tinea incognito where scale is absent but KOH examination is floridly positive	• Oral antifungal medications recommended, with treatment regimens similar to tinea barbae (see above) • Immunosuppressed patients may need a longer course of therapy
***Candida* folliculitis**		
Most commonly caused by *Candida albicans* Predisposing factors include diabetes, obesity, immunosuppression, intravenous drug use, recent use of systemic corticosteroids or broad-spectrum antibiotics, occlusion, heat and humidity	• Pruritic satellite pustules surrounding areas of intertriginous candidiasis • Facial lesions may mimic tinea barbae or acne rosacea • KOH examination: budding yeasts and pseudohyphae	• Prevent skin-to-skin contact in intertriginous areas • If possible, discontinue antibiotics and/or corticosteroid therapy • Mild to moderate disease: topical antifungals • Recalcitrant or severe disease: fluconazole 150 mg po once weekly for 4 weeks, or 100 mg po daily for 1 week then every other day for 1 month
Herpetic folliculitis		
Herpetic sycosis is usually seen in men with a history of recurrent localized facial herpes simplex infection who shave with a blade razor Widespread or unusual presentations of herpes simplex folliculitis may be seen in HIV-infected or otherwise immunosuppressed individuals as well as in the setting of eczema herpeticum Often seen in herpes zoster	• Rapid development of individual and grouped follicular pustules and vesicles on an erythematous base • If due to herpes simplex, occurs most commonly on the face • When due to herpes zoster, can be associated with entities in Table 80.7 • A Tzanck smear or biopsy reveals multinucleated giant cells • Positive PCR or DFA	• Acyclovir 200 mg po 5 times per day for 5–10 days • Famciclovir 250–500 mg po three times per day for 5–10 days • Valacyclovir 500 mg po three times per day for 5–10 days • IV acyclovir 5–10 mg/kg every 8 hours can be used for extensive disease, especially in the context of immunosuppression
***Demodex* folliculitis (demodicosis)**		
Most commonly caused by *Demodex folliculorum* and *D. brevis* May be associated with immunosuppression	• Erythematous follicular papules and pustules on the face, especially the nose, and neck; may have a background of diffuse erythema (Fig. 38.5E,F) • Less common presentations include blepharitis, madarosis, and demodectic frost of the ear • Skin scrapings reveal numerous *Demodex* mites (Fig. 38.5G)	• Topical: ivermectin 1% cream, metronidazole 1% cream, permethrin 1% or 5% cream, sodium sulfacetamide 10%/sulfur 5% lotion, crotamiton 10% cream or lotion, benzyl benzoate 10% lotion • Systemic: ivermectin 200 mcg/kg po once weekly for 1–2 weeks, metronidazole 250 mg po TID for 7–14 days, ornidazole*, isotretinoin

Table 38.1 Less common specific forms of folliculitis.

LESS COMMON SPECIFIC FORMS OF FOLLICULITIS		
Etiology/risk factors	**Clinical features**	**Therapy**
Drug-induced folliculitis (acneiform eruption)		
Most common in acne-prone patients and age groups Corticosteroids, androgenic hormones, inhibitors of EGFR, BRAF, MEK and HER2, anticonvulsants, bromides, iodides, isoniazid, lithium, sirolimus, vitamin B_{12} supplementation Can develop within 2 weeks of starting the offending agent, but the risk is often proportional to the dose and duration of therapy	• Acute eruption of monomorphic erythematous follicular papules and pustules on the face, trunk, shoulders, and upper arms (see Figs. 21.21B & 36.13) • Multiple papulopustules of the face and scalp, sometimes admixed with scale-crust (see Figs. 21.21C & 36.15) • Unlike acne vulgaris, comedones are rarely present (with the exception of androgens)	• Discontinue or lower the dose of the offending drug, if possible • Topical: benzoyl peroxide, clindamycin, erythromycin, retinoids; corticosteroids (EGFR-induced eruptions; see Ch. 21) • Systemic: tetracycline, doxycycline, minocycline; if secondarily infected, antibiotic based upon culture; isotretinoin
Necrotizing infundibular crystalline folliculitis		
Yeasts (e.g. *Malassezia* spp.) and Gram-positive bacteria (e.g. *Cutibacterium acnes*) in affected follicles	• Waxy folliculocentric papules with predilection for the forehead, neck, and back • Birefringent, filamentous, crystalline deposits within follicular ostia • Thought to be microbial-induced crystallization of sebum	• Topical or systemic antimycotics • Topical or systemic antibiotics
Actinic folliculitis		
Seasonal, possibly caused by ultraviolet A radiation and local heat Follows initial summer sun exposure	• Monomorphic follicular papules and pustules in sun-exposed sites – face, neck, upper trunk, and arms • Arises 4–30 hours after sunlight exposure	• Sun avoidance as sunscreens will not prevent lesion formation • Usually resolution within 5–10 days after discontinuation of sunlight exposure • Topical mid-potency corticosteroids or retinoids • Isotretinoin 0.35–0.5 mg/kg/day for 3–6 months if severe
*Not an FDA-approved drug.		

Table 38.1 Less common specific forms of folliculitis. DFA, direct immunofluorescence assay; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; MEK, mitogen-activated protein kinase kinase (MAPK); mTOR, mechanistic target of rapamycin; PCR, polymerase chain reaction.

Immunosuppression-associated eosinophilic pustular folliculitis

Synonyms: ■ AIDS-associated eosinophilic folliculitis ■ HIV-associated eosinophilic folliculitis ■ Immunosuppression-associated eosinophilic folliculitis

Key features

- Markedly pruritic follicular papules, urticarial and/or pustular, that favor the face, scalp, and upper trunk
- Occurs in the setting of immunosuppression, including from HIV infection or systemic medications and following allogeneic hematopoietic stem cell transplantation
- In HIV-infected patients, the CD4 count is usually <200 cells/mm^3; it may also be a manifestation of IRIS (immune reconstitution inflammatory syndrome)
- Histopathologic findings, consisting of spongiosis and exocytosis of eosinophils and lymphocytes into the follicular epithelium, are similar to those in other types of eosinophilic pustular folliculitis

Introduction and history

A pruritic papular eruption with histologic features similar to eosinophilic pustular folliculitis (Ofuji disease) was originally described in HIV-infected patients, many of whom fulfilled the criteria for AIDS. Eosinophilic folliculitis has subsequently been observed in patients with myeloproliferative disorders, as well as in those who have undergone allogeneic hematopoietic stem cell transplantation; hence, the use of the term *immunosuppression-associated eosinophilic pustular folliculitis*. However, in contrast to Ofuji disease, coalescent pustules and figurate lesions would be unusual, and the individual lesions tend to be more persistent.



Fig. 38.4 *Pseudomonas* "hot tub" folliculitis. Edematous follicular papules of the flank that began to develop 2–3 days following the use of a hot tub. *Courtesy Kalman Watsky, MD.*

Epidemiology

Although the early descriptions of HIV-associated eosinophilic folliculitis were in men, it can also occur in women[10]. The majority of these patients are 20–50 years of age, while there is a wide range of ages in non-HIV-related cases, reflecting the age of onset of associated hematologic malignancies. Development of HIV-associated eosinophilic folliculitis correlates with a low CD4 count (in particular <200/mm^3 or CD4:CD8 ratio <0.5) and clinical improvement has been observed as the CD4 count rises due to antiretroviral therapy (ART). However, there are instances where eosinophilic folliculitis develops within 3 to 6 months of initiating ART, implying an association with the immune reconstitution inflammatory syndrome (IRIS; see Ch. 78).

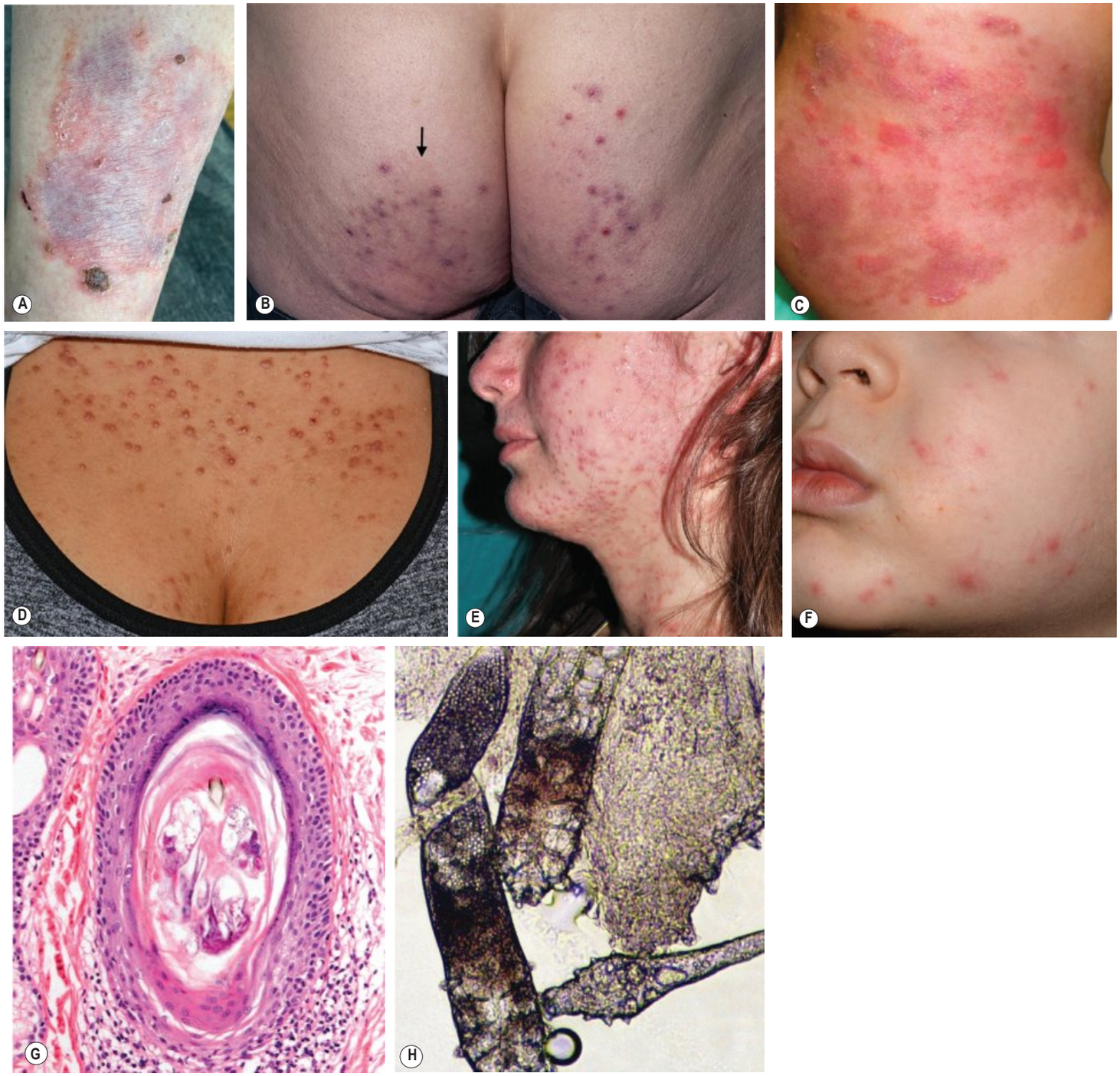


Fig. 38.5 Folliculitis – fungal and ectoparasitic. A Dermatophyte folliculitis of the shin within a lesion of tinea corporis; the lower leg is a common location. **B** Dermatophyte folliculitis on the buttocks arising within subtle tinea corporis (arrow). A few papulopustules admixed with both erythematous papules that have a collarette of scale and healed lesions. **C** Dermatophyte folliculitis with firm follicular papules in the setting of extensive tinea corporis. **D** *Malassezia* (*Pityrosporum*) folliculitis of the chest with multiple pruritic, monomorphic follicular papules; KOH examination of the follicular contents showed abundant yeast. **E** Numerous papules and papulopustules of *Demodex* folliculitis on the face and neck; note the edematous nature of several of the lesions. **F** Facial papules and papulopustules of *Demodex* folliculitis in a child with acute lymphocytic leukemia. **G** Histopathologic features of *Demodex* folliculitis with several organisms within the follicular ostium. **H** Microscopic findings of follicular contents obtained via scraping of *Demodex* folliculitis. *A, Courtesy Karynne O. Duncan, MD; B, Courtesy Edward Cowen, MD; D,F, Courtesy Julie V. Schaffer, MD; E, Courtesy Angela Hernández-Martin; G, Courtesy Lorenzo Cerroni, MD.*

Pathogenesis

Little is known about the exact pathogenesis of immunosuppression-associated eosinophilic folliculitis. However, as in other eosinophilic diseases, a Th2 immune response has been implicated. In patients with AIDS, elevated levels of interleukin (IL)-4, IL-5, RANTES (CCL5), and eotaxin (CCL11) mRNA were detected within lesional skin (see Ch. 26)[11]. Elevated serum levels of three additional chemokines, CCL17, CCL26 (eotaxin-3) and CCL27, have also been observed in patients with HIV-associated eosinophilic folliculitis[12].

Clinical features

Immunosuppression-associated eosinophilic folliculitis is characterized by recurrent, intensely pruritic papules and pustules in acne-prone areas, i.e. the face, scalp, and upper trunk (Fig. 38.6A). The papules are





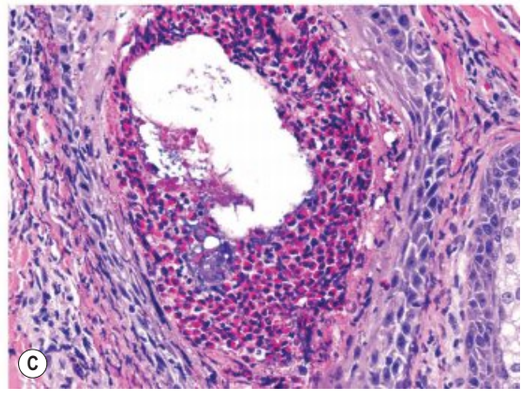


Fig. 38.6 Immunosuppression-associated eosinophilic folliculitis. **A** Multiple follicular papules on the anterior trunk in a patient who had received an allogeneic hematopoietic stem cell transplant. Note the edematous nature of some of the lesions. Very few pustules were present. **B** In some patients, multiple follicular pustules are seen. **C** A dilated hair follicle with an intrafollicular collection of eosinophils; a few eosinophils are also present within the follicular epithelium. *A, Courtesy Dennis Cooper, MD; B,C, Courtesy Luis Requena, MD.*

often slightly edematous and pustules may or may not be present (Fig. 38.6B). The associated pruritus is often intense. Some patients may also have lymphopenia.

Pathology
The histologic features are similar to those of Ofuji disease (see above; Fig. 38.6C)

Differential diagnosis
The differential diagnosis includes more common causes of folliculitis (see above) as well as the entities outlined in Table 38.1, especially *Demodex* folliculitis. Microscopic examination of follicular contents as well as performance of a biopsy may be necessary to establish the diagnosis (see Fig. 38.1). Additional disorders to consider, especially when there are no pustules and it is uncertain if lesions are follicular-based, are HIV-associated pruritic papular eruption[13], papular dermatitis, or arthropod bites and other causes of a "dermal hypersensitivity reaction".

Treatment
Although HIV-associated eosinophilic folliculitis can be refractory to treatment, institution of ART often leads to improvement; however, a flare may be seen in the setting of IRIS. In the latter patients, ART should be continued as the IRIS-related disease activity gradually subsides. Temporary interruption of ART is not required if eosinophilic folliculitis is the primary manifestation of IRIS.

For all patients, oral and topical antipruritics in combination with topical corticosteroids can be tried. Additional therapies include topical tacrolimus, topical permethrin, oral itraconazole (200–400 mg daily), oral metronidazole (250 mg three times daily), other oral antibiotics, and isotretinoin (0.5–1 mg/kg/day)[14]. UVB phototherapy may be tried when the folliculitis is extensive or recalcitrant.

Eosinophilic pustular folliculitis of infancy

Synonyms: ▪ Eosinophilic pustular folliculitis in infancy ▪ Infantile eosinophilic pustular folliculitis ▪ Neonatal eosinophilic pustular folliculitis ▪ Eosinophilic pustular folliculitis in childhood ▪ Eosinophilic pustulosis (of the scalp) in childhood

Eosinophilic pustular folliculitis of infancy is a rare, self-limiting disorder (see Ch. 34). It presents as pruritic, follicular-based pustules and vesiculopustules with an erythematous rim. The scalp is the most common site of involvement; less often lesions are seen on the face and neck, followed in frequency by the upper trunk and extremities. A cyclical course, with recurrences at intervals ranging from 1 to 12 weeks, is characteristic. Disease onset is nearly always prior to age 15 months, with a male-to-female ratio of 4:1. It differs from eosinophilic folliculitis in adults by primarily involving the scalp, frequently developing secondary crusting, and the lack of an annular configuration. Although there can be some clinical overlap, the hands and feet are the primary sites of involvement in infantile acropustulosis.

This disorder is currently viewed as a reaction pattern to a variety of triggers such as arthropod bites. Histologically, there is eosinophilic spongiosis as well as clusters of eosinophils and neutrophils within the hair follicle, especially its infundibular region. A perifollicular mixed inflammatory infiltrate can also be seen. The disease is benign and self-limited, with the majority of children experiencing resolution by 3 years of age. Topical corticosteroids can be used for relief of pruritus.

Disseminate and Recurrent Infundibulofolliculitis

Synonyms: ▪ Hitch and Lund disease ▪ Recurrent disseminated infundibulofolliculitis

Key features
- Seen primarily in young adults with darkly pigmented skin
- Numerous uniform, skin-colored papules that have been likened to "goose bumps"
- Favored sites of involvement are the trunk, neck, and upper extremities
- May last for months to years and can be pruritic
- Histologically, there is perifollicular edema and a mild inflammatory infiltration of lymphocytes within the follicular infundibulum

Disseminate and recurrent infundibulofolliculitis (DRIF) was first described by Hitch and Lund in 1968[15]. Most affected individuals have skin phototypes V or VI. DRIF is characterized by numerous 1–2 mm, pruritic, skin-colored, folliculocentric papules. Parallel rows of lesions correspond to the distribution pattern of hair follicles. The trunk is involved most often, followed by the neck, buttocks, and arms. The lesions may last for weeks, months, or years.

DRIF most closely resembles papular eczema, which also favors darker skin phototypes. Other diseases in the differential diagnosis include lichen nitidus and folliculitis (see above), but the follicular pattern and the lack of erythema or pustules exclude these two entities, respectively. The lack of keratotic plugs or spines within the hair follicles distinguishes this disorder from keratosis pilaris, pityriasis rubra pilaris (PRP), lichen planopilaris, and the disorders discussed in the next section (e.g. phrynoderma).

Although low serum vitamin A levels have been reported[16], the etiology remains unclear. Histologically, the principal findings are in the infundibular portion of the hair follicle. There is perifollicular edema and a slight infiltration of lymphocytes with occasional neutrophils[17]. Spongiosis of the follicular epithelium is usually absent or minimal.

Topical corticosteroids may provide symptomatic relief and lactic acid preparations (12%) or 20% urea may be helpful. If topical medications prove unsuccessful, doxycycline, vitamin A (50 000 IU twice daily), isotretinoin (0.5 mg/kg/day for 16 weeks), and PUVA (with twice monthly maintenance) have also been tried with mixed results.

DISORDERS OF FOLLICULAR KERATINIZATION

Although this group of dermatoses has a wide spectrum of clinical presentations, all are characterized by a prominent plug of keratin within the follicular orifice. For most of these entities, the cause of the abnormal keratinization is unknown. The dermatoses are usually distinguished on the basis of the size, extent, and distribution of the keratotic lesions, as well as the presence or absence of perifollicular erythema and associated scarring. Disorders in this group that are discussed in other chapters include keratosis pilaris (Ch. 12), PRP (Ch. 9), and lichen planopilaris (Ch. 11).

Erythromelanosis Follicularis Faciei

Synonym: ▪ Erythromelanosis follicularis faciei et colli

Key features

- An uncommon disorder that involves the lateral cheeks and sometimes the neck
- Multiple tiny follicular papules are superimposed on a red–brown patch; the papules often appear relatively hypopigmented
- May be accompanied by keratosis pilaris

Introduction

Erythromelanosis follicularis faciei was first described in 1960 by Kitamura and associates in Japanese men. It can begin during the second decade of life and is characterized by background erythema and hyperpigmentation as well as tiny follicular papules.

Epidemiology and Pathogenesis

Although the disorder was initially reported in Japanese men, it is now known to affect all races and both sexes[18]. However, the literature suggests it favors people of Asian ancestry. The pathogenesis is unknown.

Clinical features

Erythromelanosis follicularis faciei typically involves the lateral cheeks, including the preauricular area, with extension onto the neck. Involvement of the eyebrows, chin, submandibular region, and pinnae has also been described[18]. Numerous pinhead-sized follicular papules, which appear relatively hypopigmented, are superimposed on reddish-brown patches. The latter are due to a combination of vasodilation and hyperpigmentation, and by dermoscopy blue–gray peppering is seen with a reddish-brown background, along with an appreciation of keratotic follicular plugs[19]. In skin type I patients, there may be only erythema, leading to significant overlap with keratosis pilaris rubra. Patients may also have keratosis pilaris of the upper outer arms (see Ch. 12).

Pathology

There is slight follicular hyperkeratosis with increased epidermal pigmentation. Diameters of the hair shafts and outer root sheaths are decreased, as is the thickness of the inner root sheath. The adnexa are often surrounded by a lymphocytic infiltrate. Both the thickness and the compactness of the horny layer are usually increased. By quantitative histopathology, an increase in the percent area of superficial blood vessels was observed which correlated with visual grading of the associated erythema[20].

Differential diagnosis

The differential diagnosis of erythromelanosis follicularis faciei includes keratosis pilaris rubra as well as a combination of melasma plus telangiectatic erythema from photodamage (poikiloderma of Civatte). However, the former lacks hyperpigmentation and favors children, and while the telangiectasias in poikiloderma spare the perifollicular skin thus creating "hypopigmented" follicular papules, follicular hyperkeratosis is absent.

Less often, two disorders within the spectrum of keratosis pilaris atrophicans, ulerythema ophryogenes and atrophoderma vermiculatum, may be considered (Table 38.2). Although ulerythema ophryogenes is characterized by small follicular papules, they are erythematous, usually appear during early childhood, and favor the eyebrows. In addition, there is associated follicular atrophy and scarring alopecia of the lateral eyebrows. Atrophoderma vermiculatum affects the cheeks but presents with honeycomb scarring or a worm-eaten appearance (see Ch. 99).

Treatment

Various topical keratolytic agents have been tried, including urea cream (10%–20%), ammonium lactate lotion (6%–12%), tretinoin cream (0.025%–0.1%), adapalene (0.1%–0.3%), and an ammonium lactate plus hydroquinone (4%) cream combination. In a series of 11 patients, topical tacalcitol ointment (daily for 12 weeks) reduced roughness and scaling, but had a limited effect on facial erythema[21]. Both salicylic acid peels (20%–30%) and glycolic acid peels have been employed. When severe, limited courses of isotretinoin (0.1–1 mg/kg/day) have been tried. Laser treatment of the background erythema and/or hyperpigmentation may be attempted, but it requires multiple sessions. In a split-face study (n = 12), >50% improvement in the treated side was observed in five patients following five treatments with 585 nm PDL plus 1064 nm Nd:YAG lasers[22].

Keratosis Pilaris Atrophicans

Keratosis pilaris atrophicans encompasses a group of disorders in which the abnormality in follicular keratinization is accompanied by atrophy and scarring alopecia. The key features of ulerythema ophryogenes, atrophoderma vermiculatum, keratosis follicularis spinulosa decalvans, and folliculitis spinulosa decalvans are outlined in Table 38.2. Treatment with keratolytics, topical retinoids, topical or intralesional corticosteroids, oral antibiotics, and phototherapy has limited efficacy, but combination therapy may benefit individual patients and, anecdotally, oral retinoids, pulsed dye laser, and intense pulsed light have been reported to lead to improvement. In later stages, laser resurfacing, dermabrasion, and/or dermal fillers may help to improve the appearance of atrophic scarring.

Lichen Spinulosus

Synonyms: ▪ Keratosis spinulosa ▪ Keratosis follicularis spinosa (of Unna)

Key features

- Clusters of multiple follicular papules, each with a central keratotic spine
- Texture likened to that of a nutmeg grater
- Usually asymptomatic, arises suddenly, and enlarges over a week
- Appears most often in children and adolescents; favors the neck, extensor arms, abdomen, and buttocks
- Can persist indefinitely

THE SPECTRUM OF KERATOSIS PILARIS ATROPHICANS							
Disorder	**Mode of inheritance**	**Gene/ genetic locus**	**Age at onset**	**Distribution**	**Cutaneous features**	**KP***	**Other occasional features and associations**
Keratosis pilaris atrophicans faciei (ulerythema ophryogenes)	AD ≫ AR	18p11.2 (AD) *LRP1* (AR)	Infancy	Eyebrows, particularly the lateral third > temples, cheeks, forehead (Fig. 38.7)	• Skin-colored to erythematous follicular papules with central keratotic plugs, eventuating in follicular atrophy • Scarring alopecia of the lateral eyebrows	+	• Associated with Noonan syndrome, cardio-facio-cutaneous syndrome, monosomy 18p, woolly hair, and Swyer and Cornelia de Lange syndromes
Atrophoderma vermiculatum (see Ch. 99)	?AD	?	Childhood (usually between 5 and 12 years)	Cheeks (see Fig. 99.8) upper lip, forehead, ears	• Pitted, atrophic depressions in a vermiculate pattern ("worm-eaten" or "honeycomb" appearance)†	–	• Associated with Loeys–Dietz, Rombo, and Nicolau–Balus syndromes • Unilateral form has been associated with ipsilateral congenital cataract
Keratosis follicularis spinulosa decalvans, X-linked (KFSDX)	XLR	*MBTPS2*‡	Childhood (inflammation often remits at puberty)	Scalp, face, limbs, trunk	• Erythematous follicular papules with central keratotic plugs, eventuating in follicular atrophy • Scarring alopecia of the scalp, eyebrows, and eyelashes • Facial erythema • Palmoplantar keratoderma • Nail dystrophy (e.g. thickening, crumbling)	++	• Keratitis, blepharitis, corneal dystrophy, photophobia
Keratosis follicularis spinulosa decalvans (folliculitis spinulosa decalvans)	AD	?	Childhood; exacerbation after puberty	Scalp, face > trunk, extremities	• Compared to KFSDX: facial erythema and nail dystrophy more common; more severe scalp inflammation with pustules • Otherwise, features similar to KFSDX	++	• Blepharitis, conjunctivitis

*Associated keratosis pilaris (KP) on the extremities and trunk.
†May be preceded by erythematous keratotic follicular papules.
‡MBTPS2 (membrane-bound transcription factor peptidase, site 2) is a zinc metalloprotease required for cleavage of sterol regulatory element-binding proteins (SREBPs) and is essential for cholesterol homeostasis and the endoplasmic reticulum stress response; mutations in *MBTPS2* also underlie XLR IFAP syndrome (see Table 38.3).

Table 38.2 The spectrum of keratosis pilaris atrophicans. AD, autosomal dominant; AR, autosomal recessive; LRP1, low-density lipoprotein (LDL) receptor-related protein 1; XLR, X-linked recessive; +, mild to moderate; ++, severe.



Fig. 38.7 Ulerythema ophryogenes. Numerous skin-colored follicular papules of the lateral cheek arising within a background of erythema, along with alopecia of the eyebrows. Some of the lesions have become confluent. *Courtesy Alex Glazer, MD.*

History and epidemiology

First described by Crocker in 1883, lichen spinulosus is characterized by grouped, skin-colored, keratotic follicular papules. In one series, the average age at onset was 16 years[23].

Pathogenesis

Although several factors, such as atopy, infections and heredity, have been proposed as playing a role in lichen spinulosus, the exact etiology is unknown and most patients do not have associated systemic abnormalities. There are reports of lichen spinulosus-like lesions arising in the setting of HIV infection[24]. The terms *HIV-associated follicular syndrome* and *type VI PRP* have been proposed to encompass the constellation of HIV infection, nodulocystic acne, and lesions with follicular spines, including PRP and lichen spinulosus. Additional (likely coincidental) associations reported in the literature include seborrheic dermatitis, a drug reaction (omeprazole), Hodgkin lymphoma, Crohn disease, syphilis, and an id reaction to fungal infections.

Clinical features

Typical lesions measure 2–6 cm in diameter (Fig. 38.8) and are composed of grouped skin-colored, keratotic follicular papules, each of which has a central horny spine. Lichen spinulosus favors the neck, shoulders, and extensor surfaces of the arms, as well as the abdomen, buttocks, and popliteal fossae, and the distribution pattern may be symmetric. The hands and feet are usually spared. Lesions often arise suddenly in crops, enlarge over a week, and then remain stationary. Idiopathic lichen spinulosus usually appears during childhood and adolescence and is sometimes pruritic. Spinulosis of the face (tiny follicular keratotic spicules of the cheeks) may be a manifestation of lichen spinulosus.

Pathology

Histologically, lichen spinulosus most resembles keratosis pilaris, with follicular plugging of the infundibulum and a mild perivascular and perifollicular lymphocytic infiltrate in the upper dermis.

Differential diagnosis

The differential diagnosis of lichen spinulosus includes phrynoderma, keratosis circumscripta, follicular ichthyosis, and juvenile pityriasis

rubra pilaris (Table 38.3), in addition to folliculotropic mycosis fungoides[29]. Facial spines can also be seen in the setting of HIV-associated follicular syndrome (see above), viral-associated trichodysplasia, demodicosis, follicular mucinosis, and in patients with multiple myeloma. Lastly, widespread follicular plugging has been reported as a side effect of BRAF inhibitors and systemic lithium therapy.

Treatment

Topical therapies such as lactic acid, urea, and salicylic acid may improve the texture. There are case reports of successful treatment with adapalene gel, tacalcitol cream[30], glycolic acid peels, and tretinoin gel plus hydroactive adhesive applications[31].

Phrynoderma

Phrynoderma, which means "toad skin", is rarely seen in developed countries, except in settings such as intestinal malabsorption due to bariatric surgery and malnutrition from anorexia nervosa or fad diets (see Ch. 51). Phrynoderma is seen most often in association with vitamin A deficiency, but some patients may have measurable deficiencies in other vitamins and/or proven malnutrition[32]. Skin-colored to hyperpigmented acuminate follicular papules with central keratotic plugs favor the extensor surfaces of the extremities (see Fig. 51.7). Lesions of the face, hands, or feet would be unusual to rare[33]. Associated systemic findings (e.g. ocular, CNS), histologic features, diagnosis via measurement of serum vitamin A levels, and treatment are discussed in Chapter 51.



Fig. 38.8 Lichen spinulosus. Grouped, skin-colored follicular papules on the extensor surface of the arm. Central keratotic plugs can be seen.

TRICHOSTASIS SPINULOSA

Trichostasis spinulosa is a common, but often underdiagnosed, follicular disorder of unknown etiology. Comedo-like lesions that contain keratin and multiple vellus hairs are seen, primarily on the mid to lower central portion of the face, including the nose (see Table 36.2). Lesions can develop on the trunk, most commonly the interscapular region, and less often the axillae and scalp, including within an isolated collagenoma[34] and after application of minoxidil[35]. The differential diagnosis is outlined in Table 36.2. Histologically, within a dilated hair follicle, there are multiple, small vellus hairs and keratinous debris; a perifollicular, mild mixed inflammatory infiltrate may be present. Therapeutic options include keratolytics, topical tretinoin, depilatories, adhesive strips, and lasers (e.g. long-pulsed alexandrite, short-pulsed alexandrite, pulsed diode).

VIRAL-ASSOCIATED TRICHODYSPLASIA SPINULOSA

Synonyms: ■ Viral-associated trichodysplasia ■ Viral-associated trichodysplasia of immunosuppression ■ Trichodysplasia spinulosa

Viral-associated trichodysplasia (see Ch. 81) is associated with drug-induced immunosuppression, most often in organ transplant recipients, and it reflects infection with the *t*richodysplasia *s*pinulosa-associated *p*oly*o*ma*v*irus (TSPyV)[36] (see Ch. 81). The virus' small T antigen may play a role in disrupting the cycling of follicular keratinocytes[37]. Skin-colored to

DIFFERENTIAL DIAGNOSIS OF LICHEN SPINULOSUS	
Keratosis circumscripta[25–27] (psoriasis circumscripta with palmoplantar keratosis)	• Age at onset usually 3–5 years and described primarily in Africans • Well-circumscribed lesions consisting of grouped folliculocentric papules, with or without palmoplantar hyperkeratosis • Lesions favor the elbows and knees, neck, hips, sacrum, and posterior axillary folds • Some authors argue that this is a variant of psoriasis as the histologic findings are similar to those of plaque-type psoriasis
Follicular ichthyosis[28]	• Onset during early childhood • Keratotic papules with follicular plugging and prominent follicular ostia • Favors the head and neck region, but may also involve the extensor surfaces of the extremities, especially the fingers, elbows, and knees
Ichthyosis follicularis with atrichia and photophobia (IFAP) syndrome (Ch. 57)	• XLR (*MBTPS2* mutations, allelic with keratosis follicularis spinulosa decalvans; see Table 38.2) or AD (*SREBF1* mutations) • In female carriers, linear streaks consisting of follicular keratoses, scaling, and/or hypotrichosis • In affected males, generalized congenital non-scarring alopecia, photophobia, follicular keratoses, and psoriasiform plaques (see Fig. 55.11)
Hereditary mucoepithelial dysplasia	• AD with more widespread follicular keratoses and non-scarring alopecia (similar to IFAP; also *MBTPS2* mutations) • Severe keratitis, erythema of the oral mucosa (paucity of desmosomes and dyskeratotic cells histologically), and psoriasiform plaques that favor intertriginous zones, especially the perineal area
Juvenile pityriasis rubra pilaris (Ch. 9)	• Especially type IV (circumscribed), in which lesions favor the elbows and knees
Keratosis pilaris (Ch. 12)	• Perifollicular erythema in addition to follicular plugging • Favors the upper outer arms and the thighs, but lacks discrete clusters • May be more widespread in keratosis pilaris-like drug eruptions (e.g. sorafenib)
Lichen planopilaris (Ch. 11)	• Follicular keratotic plugs are surrounded by a narrow violaceous rim • Scarring alopecia of the scalp most common presentation but follicular lesions may be disseminated
Folliculotropic mycosis fungoides (Ch. 120)	• Acneiform lesions may be seen, including comedones (see Fig. 36.16B,C); they may be clustered
Phrynoderma (vitamin A deficiency; Ch. 51)	• Follicular papules with a central keratotic plug favor the extensor surfaces of the extremities and buttocks • Generalized xerosis, sparse fragile hair, night blindness, xerophthalmia

Table 38.3 Differential diagnosis of lichen spinulosus. Viral-associated trichodysplasia is discussed in the text and Chapter 81. The differential diagnosis also includes the spinous variant of lichen nitidus and follicular keratosis (of the chin). AD, autosomal dominant.

pink follicular papules and follicular spines favor the central face (see Fig. 81.16) and may be accompanied by loss of the eyebrows and eyelashes; extrafacial lesions with associated alopecia may also develop. Histologically, enlarged and distended anagen-type follicles have a high number of inner root sheath cells with excessive amounts of trichohyaline granules. If immunosuppressive therapy cannot be reduced, topical cidofovir or tazarotene gel or oral valganciclovir (900 mg once or twice daily) may be helpful.

DEEP FOLLICULITIS

The major forms of deep folliculitis are furuncles (see Ch. 74), sycosis (barbae [see Fig. 38.3B], lupoid, mycotic [Fig. 38.9]; Table 38.4), pseudofolliculitis barbae, acne keloidalis, and hidradenitis suppurativa. The lesions are firm, tender, erythematous papules or nodules. Deep lesions should never be manipulated (i.e. squeezed) by the patient, because this may cause bacteremia or seeding of the heart valves (endocarditis), brain (abscess), or bones (osteomyelitis).



Fig. 38.9 Mycotic sycosis. Firm plaque of the upper cutaneous lip studded with multiple pustules due to a zoophilic dermatophyte. *Courtesy Kalman Watsky, MD.*

FORMS OF SYCOSIS	
Type	**Characteristics**
Barbae	• Bacterial folliculitis of the beard and/or mustache areas, usually caused by *Staphylococcus aureus* • Deep-seated, edematous, perifollicular papules and pustules that may coalesce to form crusted plaques studded with pustules (see Fig. 38.3B) • Subacute to chronic course with frequent relapses
Lupoid	• Scarring form of deep folliculitis, typically affects the beard area; may be caused by *S. aureus* (although cultures often fail to reveal pathogenic organisms) • Peripheral extension of perifollicular papules and pustules with central scarring alopecia; appearance can be reminiscent of lupus vulgaris • Chronic course, refractory to treatment
Mycotic	• Dermatophyte folliculitis of the beard area, usually caused by zoophilic organisms • Inflammatory perifollicular papules and pustules coalesce to form nodules and plaques with crusts, purulent discharge from patulous follicles, and loose hairs that can be painlessly removed (Fig. 38.9)
Herpetic	• See Table 38.1

Table 38.4 Forms of sycosis. Sycosis is defined as chronic inflammation of hair follicles, especially of the beard.

Pseudofolliculitis Barbae

Synonyms: ■ Shave bumps ■ Razor bumps ■ Barber's itch ■ Folliculitis barbae traumatica ■ Scarring pseudofolliculitis of the beard ■ Chronic sycosis barbae ■ Ingrown hairs

Key features

- A common chronic disorder occurring most often in the beard area of men who shave
- It favors Black men with tightly curled hair
- Distal tips of hairs curve back into the skin after having been shaved
- Lesions range from inflammatory papules and pustules to firm papules and keloidal scars
- Although the only reliable way to cure the disease is to stop shaving, shaving techniques can be optimized and laser therapy can significantly reduce severity

Introduction

Pseudofolliculitis barbae is a common chronic inflammatory disorder of terminal hair-bearing sites, occurring most often in the beard area of men who shave and have tightly curled hair.

Epidemiology

Although pseudofolliculitis barbae can occur in any racial group, it primarily affects Black men. The incidence in African-American men varies from 45%–85%, depending upon the particular study. Pseudofolliculitis barbae is less common and is usually milder in those with straight hair. Women may also develop pseudofolliculitis following shaving or plucking of hairs in the groin, axillae, or a hirsute face.

Pathogenesis

The disorder is thought to be caused by re-entry of the distal portion of tightly curled hairs into the skin. In individuals with tightly curled hair, the hair follicles sit at an oblique angle and when shaved, a sharp tip is created at the distal end of the hair. Fig. 38.10 illustrates extrafollicular and transfollicular forms of hair penetration. Once the hair penetrates the dermis, an inflammatory reaction ensues.

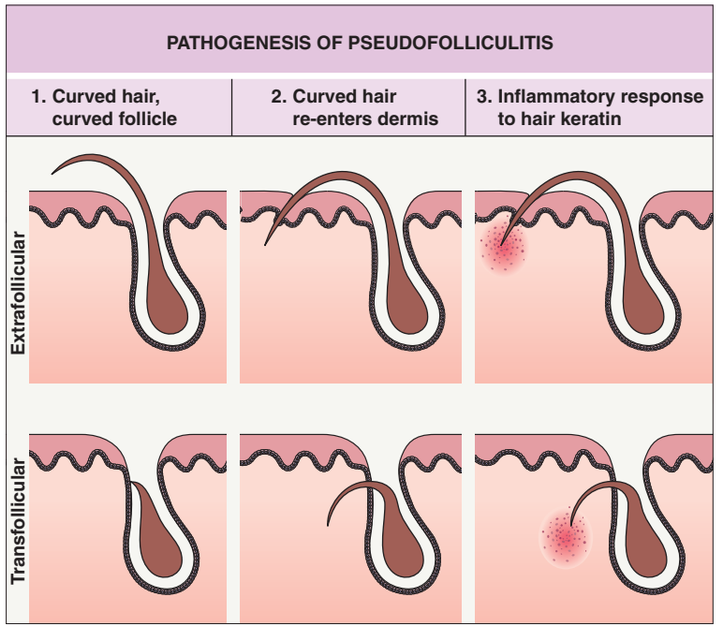


Fig. 38.10 Pathogenesis of pseudofolliculitis. In individuals with tightly curled hair, the hair follicles sit at an oblique angle and when shaved, a sharp tip is created at the distal end of the hair. There are two proposed mechanisms for hair penetration: (1) *extrafollicular* – the cut hair grows normally from the follicular orifice but then curves downward and penetrates the skin surface 1–2 mm distally from where the hair exits; and (2) *transfollicular* – the distal tip of the cut hair shaft pierces the follicular epithelium and penetrates the dermis instead of normally exiting the follicular orifice. *Courtesy M. A. Abdallah, MD.*

The presence of a single nucleotide polymorphism in the 1 A α-helical subdomain of the hair follicle companion layer-specific keratin K6hf (KRT75) has been reported to be an additional genetic risk factor for pseudofolliculitis barbae[38]. In women, hyperandrogenism may be a contributing factor[39].

Clinical features

Skin-colored to red-brown papules or pustules develop in hair-bearing sites that have been shaved (Fig. 38.11). These lesions are most commonly observed within the beard area. Postinflammatory hyperpigmentation and scarring, including keloid formation, are potential sequelae. Chronic lesions may cause the hair to create grooves in the skin; the anterior neck and submandibular areas are particularly prone to this complication. Once the grooves have formed, shaving becomes extremely difficult.

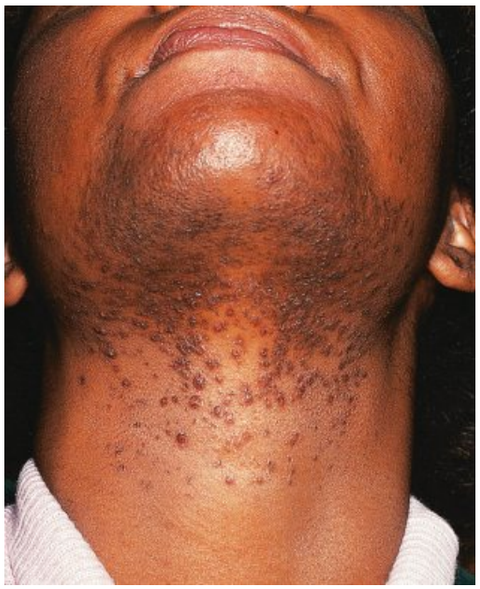


Fig. 38.11 Pseudofolliculitis barbae. Multiple firm hyperpigmented papules on the lower face and neck (beard distribution). *Courtesy Paul Kelly, MD.*

Pathology

The sharp cut end of the hair initially causes an invagination in the epidermis, which is accompanied by inflammation and frequently by an intralesional microabscess. As the hair penetrates the epidermis, a heavy mixed inflammatory cell infiltrate develops as a reaction to the downgrowth of the epidermis in an attempt to ensheathe the hair[40]. This is accompanied by abscess formation within the pseudofollicle and a foreign body giant cell reaction at the tip of the invading hair. Naked hair shafts surrounded by acute and chronic inflammation or a primarily fibrotic dermis are commonly observed.

Differential diagnosis

Facial acne vulgaris is similar in appearance, but differs by having open or closed comedones and a distribution beyond the beard region. In sycosis barbae, which also commonly occurs in the beard region, the lesions tend to be more confluent rather than discrete. Histologically, the foreign body reaction needs to be differentiated from cutaneous sarcoidosis.

Treatment

Before therapy is initiated, the patient should be given a candid explanation regarding the cause of pseudofolliculitis barbae. It should be stressed that the only reliable way to cure the disease is to stop shaving, but there are several treatments that may control the process, including laser therapy. In those with severe disease, a hiatus of several months without shaving is recommended. When patients resume shaving once the inflammatory lesions have completely cleared, they need to be given advice on shaving methods (Table 38.5).

Except for very mild cases, pseudofolliculitis barbae requires medical intervention during its acute phase, when it is often painful and/or pruritic.

THERAPEUTIC APPROACH TO PSEUDOFOLLICULITIS BARBAE	
Advice on shaving methods	
Important points	
• Do not pull the skin taut • Use a sharp razor each time (single-edged with protective foil preferred*) or an electric razor • Take short light strokes and do not shave over the same areas more than twice • For severe disease: discontinue shaving until all inflammatory lesions have cleared and all "ingrown hairs" are released; during this period, the patient can trim beard to a minimum length of 5 mm using scissors or electric clippers	
Method	
• Remove pre-existing hairs with electric clippers, leaving approximately 1–2 mm of stubble (only step if this length is acceptable to the patient) • Wash area with warm water, non-abrasive soap, and a soft brush or sponge • Rinse area with warm water or apply warm compress • Using shaving cream, massage moderate amount of lather on area to be shaved 5–10 minutes prior (do not allow lather to dry; if it does, reapply it) • Use a sharp blade* and shave the hair using short even strokes with minimal tension (and no more than twice over one area) • Traditionally, patients were advised to shave in the direction of hair growth ("with the grain"), but shaving against the grain may not worsen the disease[41] • After shaving, rinse with tap water and then apply a soothing aftershave preparation. If significant burning or itching ensues, apply a topical corticosteroid cream or lotion (1%–2.5% hydrocortisone)	
Treatment recommendations	
Compresses	• Warm tap water, saline, or Burow's solution (aluminum acetate) compresses for 10 minutes three times daily to soothe lesions, remove any crusts, reduce drainage secondary to inflammation and/or excoriations, and soften the epidermis to allow easier release of "ingrown hairs"
Topical and intralesional therapy	• Low-potency topical corticosteroid lotion, topical antibiotics (e.g. clindamycin), and/or topical retinoids should be applied after compresses and freeing of embedded hairs • Topical glycolic acid 8% lotion • Intralesional triamcinolone acetonide injections (5–10 mg/ml)
Secondary bacterial infection	• Appropriate systemic antibiotic should be prescribed, based upon bacterial cultures
Recalcitrant disease	• Topical eflornithine cream twice daily may be helpful† • Laser hair removal (utilizing appropriate laser for skin color) with goal of permanent hair reduction (see Ch. 137)
Postinflammatory hyperpigmentation	• Hydroquinone ± topical retinoids and corticosteroids, azelaic acid, kojic acid • Chemical peels (see Ch. 154)
*However, in one study, there was no difference in disease activity between single- versus multi-blade razors[72]. †Based upon case series.	

Table 38.5 Therapeutic approach to pseudofolliculitis barbae. *Courtesy A. Paul Kelly, MD.*

Although antibiotics, topical or systemic, are not particularly beneficial (unless secondary infection is present), they may provide some anti-inflammatory effect. The recommended therapeutic approach is outlined in Table 38.5. Adjunct treatments such as topical keratolytics (e.g. retinoids, α-hydroxy acids) and benzoyl peroxide washes may be used in patients with mild to moderate pseudofolliculitis barbae. However, those with severe and chronic disease usually have only slight improvement with these therapies.

Laser hair removal can lead to a significant reduction in disease severity. For example, the 1064 nm Nd:YAG laser can be used with a long pulse duration and continuous contact cooling, even in patients with skin types V or VI, as can a modified 810 nm super-long-pulsed diode laser. Treatment is given at 3- to 4-week intervals for two to three sessions. Care must be taken when selecting the laser fluence, especially in patients with darkly pigmented skin[42]. Additional therapeutic options are chemical depilatories and eflornithine cream; application of eflornithine cream twice daily between laser hair removal sessions led to better outcomes when compared with laser alone[43]. Prior to application of chemical depilatories, the beard should be trimmed and, to avoid irritation, treatments should be limited to twice weekly.

Acne Keloidalis

Synonyms: ■ Acne keloidalis nuchae ■ Folliculitis keloidis nuchae ■ Nuchal keloid acne ■ Folliculitis keloidalis ■ Dermatitis papillaris capillitii (historical)

Key features

- Begins as inflamed follicular papules or pustules on the posterior neck and occipital scalp
- With time, keloidal papules and plaques develop
- Vast majority of affected individuals are Black men

Introduction

Acne keloidalis refers to the presence of keloid-like papules and plaques on the occipital scalp and posterior neck. This disorder occurs primarily in Black men. The patients usually develop a chronic folliculitis and perifolliculitis of the posterior scalp and neck, which then heals with keloid-like papules. Over time, these papules may coalesce to form one or several large plaques, which gradually enlarge over a period of years. The lesions are usually pruritic and may also be painful and cosmetically disfiguring. Early intervention may prevent progression to disfiguring disease.

History

The disorder was first described by Hebra in 1860 as "sycosis framboesiformis". In 1869, Kaposi termed it "dermatitis papillaris capillitii". Three years after Kaposi's publication (1872), Bazin named the condition "acne keloidalis".

Epidemiology

In the US, acne keloidalis occurs most often in African-American men. Acne keloidalis may also occur in women, but the male:female ratio is at least 20:1. Development prior to puberty or after the age of 55 years is rare. An association with metabolic syndrome[44] and hidradenitis suppurativa has been observed in population-based studies.

Pathogenesis

The cause of acne keloidalis is unknown, and no specific genetic factor has been identified. Histologically, fragments of naked hair shafts, surrounded by microabscesses and/or granulomatous inflammation, can be seen within a fibrotic dermis[45]. A possible explanation is skin injury. In one study, the mast cell density of the neck/occipital scalp was increased compared with the anterior scalp; these mast cells may prompt rubbing and other physical manipulation of the skin, thereby predisposing this location to the development of acne keloidalis. Chronic irritation from high-collared shirts or helmets could also play a role. Perhaps acne keloidalis represents a primary form of scarring alopecia triggered by an aberrant cutaneous immune reaction[45].

Clinical features

Acne keloidalis often begins as a posterior scalp and/or neck folliculitis, followed by the development of 2–4 mm, dome-shaped, firm follicular papules that may or may not be pruritic (Fig. 38.12). Pustules may also be present within the same area but are usually short-lived because they are traumatized when the hair is combed or brushed or are easily ruptured by scratching. In contrast to acne vulgaris, comedones are not present.

As the disease progresses, more hard papules develop and slowly enlarge. Some coalesce and form keloid-like plaques, which are often arranged in a band-like distribution near the posterior hairline (Fig. 38.13). The plaques are usually only a few centimeters in diameter but may grow to more than 10 cm. Even when only papules are present, a large portion of the posterior scalp may be involved.

When the area of involvement is significant, there is usually associated patchy alopecia or complete hair loss. Occasionally, the scarring process may extend onto the vertex and/or parietal scalp. The upper borders of large lesions are often fringed with tufted hairs that resemble the hair on a doll's head, as seen in other scarring alopecias such as folliculitis decalvans (see Ch. 69). As in dissecting cellulitis, subcutaneous abscesses with draining sinuses may occasionally be present, and they may emit a malodorous discharge.



Fig. 38.12 Acne keloidalis. An admixture of follicular pustules, crusted papules and firm fibrotic hyperpigmented papules on the posterior neck and occipital scalp. There is associated alopecia.

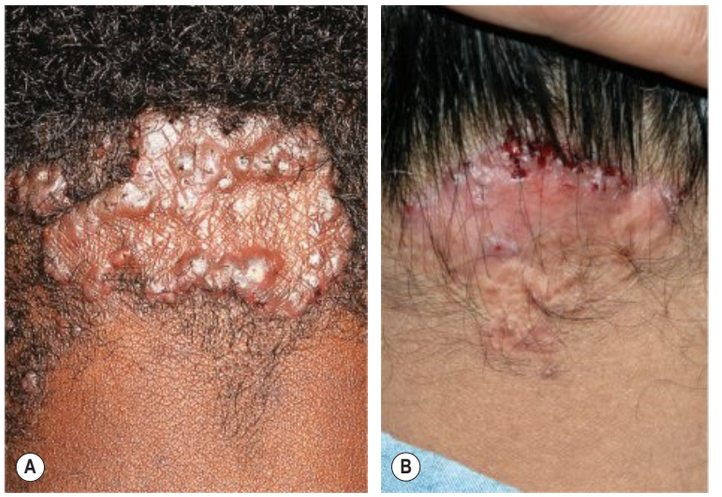


Fig. 38.13 Acne keloidalis. A Keloidal papulonodules and a large plaque of the occipital scalp, associated with scarring alopecia. Note the tufts of hair at the superior border of the scar. **B** Although the disorder is seen less often in Hispanic patients, the clinical findings are similar. *A, Courtesy Paul Kelly, MD; B, Courtesy Luis Requena, MD.*

Pathology
Inflammation begins in the upper one-third of the hair follicle. Descriptions of the initial infiltrate vary from it being composed of neutrophils and lymphocytes to predominantly plasma cells[46]. In more advanced lesions, hair follicles are disrupted, and fragments of naked hair shafts surrounded by microabscesses and/or granulomatous inflammation may be noted (Fig. 38.14). Dermal fibrosis is also present at this stage, and the collagen fibers resemble those seen in scar tissue rather than those seen in keloids. The lower portion of the follicle, including the matrix, is usually spared until later in the disease process. There is complete disappearance of sebaceous glands in late stages of the disease.

Differential diagnosis
Clinically, the initial lesions may resemble culture-negative or staphylococcal folliculitis (see above), while later-stage lesions may be mistaken for keloids or hypertrophic scars secondary to trauma. On the neck there may be overlap with pseudofolliculitis barbae, and when there is more extensive or severe scalp involvement, folliculitis decalvans and dissecting cellulitis may enter the differential diagnosis.

Treatment
Avoidance of exacerbating factors is the first line of defense. Those who have acne keloidalis should not wear any kind of head-dress or head gear that causes mechanical irritation of the posterior hairline. In addition, they should avoid wearing shirts or sweaters that irritate the posterior scalp and neck.

The sooner therapy is initiated, the less likely the patient is to develop large lesions and scarring. Twice-daily application of topical tretinoin and a mid- to high-potency corticosteroid may be sufficient to improve inflammatory papules and help flatten non-inflamed lesions. Topical or systemic antibiotics, as for acne vulgaris, may clear pustules but do not soften or clear the secondary keloidal lesions. A bacterial culture should be obtained from any site with oozing or drainage, followed by the appropriate systemic antibiotic. Triamcinolone acetonide (5–20 mg/ml) can be injected into persistent inflammatory or keloidal papules, taking into account hypopigmentation and atrophy as potential side effects.

If keloidal papules persist, they often need to be removed by a punch excision with a hair transplant trephine followed by either a primary closure or healing by second intention. The punch must extend below the level of the hair follicle to be successful. In addition, a 50:50 mixture of 2% lidocaine with epinephrine (adrenaline) and triamcinolone acetonide (40 mg/ml) may be employed for local anesthesia in order to help prevent recurrence. Excisions can be closed with silk rather than rigid sutures to prevent suture ends from piercing the surrounding skin.

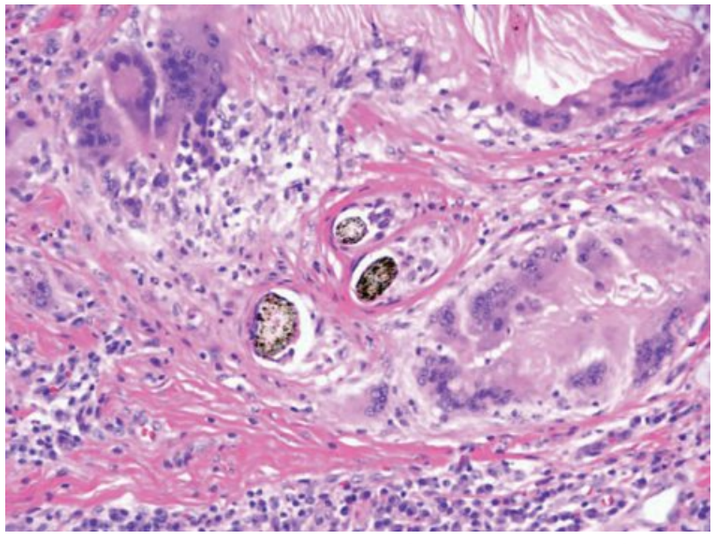


Fig. 38.14 Acne keloidalis – histopathologic features. Naked hair shafts in the dermis with perifollicular fibrosis and surrounding granulomatous inflammation with multinucleated giant cells.

For plaques 1.0–1.5 cm in vertical diameter, excision with primary closure is the treatment of choice, with the depth extending below the base of the hair follicles to reduce recurrence risk. Lesions >1.5 cm in vertical diameter should not be closed primarily because the postoperative scar usually spreads to the width of the excisional defect, producing a hairless flat scar. For these lesions, the area of acne keloidalis should be excised to the level of the fascia or deep subcutaneous tissue and left to heal by second intention. The horizontal surgical ellipse must include the posterior hairline[47], and it normally takes 8–12 weeks for the defect to close. During this healing phase, injection of corticosteroids may interfere with wound contracture. Excision with a CO_2 laser is another option and for large lesions, a staged excision.

The long pulsed Nd:YAG and diode lasers have been reported to be effective, particularly in decreasing the number of papular lesions[48]. Targeted UVB therapy was shown to decrease mean lesion count in a split-scalp comparison study of 11 patients[49]. Cryotherapy is also sometimes used, but in individuals with darkly pigmented skin, it may cause hypopigmentation. Based on case reports, a course of oral isotretinoin may prove helpful in severe recalcitrant inflammatory cases of acne keloidalis.

FOLLICULAR OCCLUSION TETRAD

In 1956, Pillsbury, Shelley and Kligman coined the term "follicular occlusion triad" for the association of acne conglobata (see Ch. 36), hidradenitis suppurativa, and dissecting cellulitis of the scalp (see Ch. 69). They proposed that the pathologic event unique to each disease was follicular hyperkeratinization[50]. In 1975, a fourth component, pilonidal sinus, was added, creating the follicular tetrad. Most commonly located within the superior portion of the natal cleft, a pilonidal sinus contains keratinous debris and often multiple hairs. There can be associated granulomatous inflammation, pustular discharge, and even abscess formation. It is also referred to as a pilonidal cyst or sacrococcygeal fistula and treatment involves surgical excision.

Hidradenitis Suppurativa

Synonyms: ■ Acne inversa ■ Verneuil disease ■ Velpeau disease ■ Apocrine acne
Advanced disease: ■ Fox-den disease ■ Pyoderma fistulans sinifica

Key features
- An inflammatory keratinization disorder characterized by follicular occlusion
- Associated with systemic inflammation, metabolic and polycystic ovary syndromes, and autoinflammatory disorders
- Predilection for intertriginous zones, especially the axillary, anogenital, and inframammary regions
- Recurrent painful inflamed nodules and abscesses; with increasing severity, formation of chronic draining tunnels, scars, and potentially squamous cell carcinoma
- Histologically, follicular dilatation and hyperkeratinization, with concomitant inflammation of the sweat glands in a minority of cases

Introduction
Hidradenitis suppurativa (HS) is a chronic cutaneous disorder that preferentially affects intertriginous skin, in particular the axillae and anogenital regions. It is characterized by recurrent inflammatory nodules and abscesses that may progress to form draining sinus tracts and scars.

History
In the 1830s, Velpeau and Verneuil conceptualized HS as a specific disease. Although apocrine gland dysfunction was initially considered to be the underlying cause, it is now believed that occlusion of the follicular

infundibula followed by follicular rupture is the inciting event, and apocrine gland involvement is secondary.

Epidemiology

In the US, the female : male ratio is 3 : 1 and African-Americans are 3–7 times more likely to be diagnosed with HS[51]. However, these statistics can vary, e.g. in South Korea the female : male ratio is 1 : 2[51]. Up to 25% of patients present prior to age 18 years ("early-onset" HS) and most commonly they are teenage girls 15–17 years of age. A prepubertal onset raises the possibility of an endocrine disorder, e.g. precocious puberty.

Pathogenesis

HS is a multifactorial inflammatory disease that is a consequence of follicular occlusion and immune dysregulation and is influenced by genetics/epigenetics, the cutaneous microbiome, and hormones.

The term *follicular occlusion* encompasses the predilection of HS for major skin folds, i.e. sites prone to friction and occlusion, as well as the follicular dilatation and hyperkeratinization that occurs microscopically. The latter is thought to be an inciting event, but actually may be a consequence of subclinical inflammation[52]. Follicular rupture, with release of keratin and bacteria into the dermis, follows comedone formation. An exuberant inflammatory response with abscess formation then ensues.

Immune dysregulation involves a host of cytokines and chemokines, including TNF, IL-1 α/β, IL-6, G-CSF, and various isoforms of IL-17[53,54]. Recruited neutrophils produce tissue damage via reactive oxygen species, proteases, and neutrophil extracellular traps (NETs); they also recruit macrophages, which produce additional proinflammatory cytokines, and activate complement (e.g. C3a, C5a). Degrading enzymes such as matrix metalloproteinases contribute to the thinning, fragility, and subsequent rupture of the follicular epithelium with generation of epithelial strands and tunnels.

Historically, a role for *genetics* was supported by up to 40%–50% of HS patients having a family history of HS[55] as well as an increased incidence of HS in patients with genetic disorders such as Dowling–Degos disease and the PASH (*p*yoderma gangrenosum, *a*cne, and suppurative *h*idradenitis) autoinflammatory disorder. More recently, mutations in one of three genes – *NCSTN, PSEN1*, or *PSENEN* – were shown to underlie inherited nonsyndromic ("pure") HS (Table 38.6)[56]. These genes encode three of the four components of the γ-secretase complex which cleaves proteins such as amyloid precursor protein and Notch. Of note, mice deficient in Notch 1 and 2 phenotypically mimic mice deficient in γ-secretase, with cyst formation and both epidermal and follicular defects, pointing to a role for the Notch cell signaling pathway in HS[57]. Additional possible candidate genes are outlined in Table 38.6[58].

Epigenetic changes include: (1) decreased expression of DNA hydroxymethylation regulators (e.g. TET1) in HS lesional skin; (2) inflammatory stage-dependent changes in expression of different microRNA (miRNA), which are involved in gene silencing via repression of mRNA translation (see Fig. 3.14); and (3) differential expression of RNA-induced silencing complex (RISC) components[58].

Regarding the *cutaneous microbiome*[59], a decreased relative abundance of skin commensal bacteria (specifically *Cutibacterium)* and an increased relative abundance of mixed anaerobic bacteria (e.g. *Prevotella, Porphyromonas*, *Peptoniphilus* spp.) have been observed in lesional skin when compared to either non-lesional or healthy control skin. Increased bacterial diversity and relative abundance of anaerobic bacteria both positively correlate with HS severity. When compared to healthy control skin, unaffected HS skin folds were also found to have an increased relative abundance of anaerobic bacteria. *Staphylococcus aureus* abundance in non-lesional skin positively correlates with overall HS clinical severity.



Fig. 38.15 Hidradenitis suppurativa. A Papulopustules, nodules, sinus tracts and scarring in the axilla (Hurley stage II). **B** Multiple tunnels and scarring in the axillary region. **C** Nodules, draining sinus tracts, and marked scarring (Hurley stage III). **D** Double-ended comedones that serve as a clue to the diagnosis, even in the absence of active disease. **E** Multiple interconnecting sinus tracts, one of which has developed granulation tissue (Hurley stage III). **F** Severe disease with inflammatory nodules, hypertrophic scarring, draining fistulae and sinus tract formation of the perianal region, buttocks, and upper thighs. This is the type of patient who is at risk for the development of squamous cell carcinoma and secondary amyloidosis. **G** Cribiform and atrophic scarring due to severe facial disease. *A, Courtesy Kalman Watsky, MD; C, Courtesy Marco Romanelli, MD; F, Courtesy A. Paul Kelly, MD.*

NONSYNDROMIC HIDRADENITIS SUPPURATIVA – ASSOCIATED GENES		
Gene	**Protein product**	**Proposed function related to HS**
Familial acne inversa (ACNINV) -1, -2, -3		
NCSTN	Nicastrin (γ-secretase complex)	Regulation of epidermal and follicular keratinocyte differentiation
*PSENEN**	Presenilin enhancer-2 (γ-secretase complex)	
PSEN1	Presenilin 1 (γ-secretase complex)	
Other genes implicated in HS pathogenesis		
TNF	Tumor necrosis factor	Promotion of inflammation
BCL2	Anti-apoptotic regulatory protein	Maintenance of homeostasis in outer root sheath cells of hair follicles
IL12Rβ1	Subunit of the IL-12 and IL-23 receptors (see Fig. 128.9D)	Regulation of T cell subset differentiation

*Allelic with Dowling–Degos disease and patients may have features of both disorders.

Table 38.6 Nonsyndromic hidradenitis suppurativa (HS) – associated genes. The fourth protein in the γ-secretase complex is anterior pharynx-defective 1. Additional implicated genes include DEFB (encodes β-defensin), *MYD88*, and *ABCC11* (affects apocrine sweat gland secretion).

COMORBIDITIES IN PATIENTS WITH HIDRADENITIS SUPPURATIVA	
Organ system	**Comorbidity**
Articular	Spondyloarthritis
Cardiovascular	Hypertension Myocardial infarction Cerebrovascular accident
Cutaneous	Acne vulgaris and acne conglobata* Dissecting cellulitis of the scalp* Pilonidal disease* Pyoderma gangrenosum
Gastrointestinal	Crohn disease Ulcerative colitis
Metabolic/endocrine	Metabolic syndrome (includes dyslipidemia, hypertension, insulin resistance; see Table 53.5) Obesity Diabetes mellitus Thyroid disease
Psychiatric	Depression Generalized anxiety disorder Suicidal ideation Substance use disorder
Reproductive	Polycystic ovarian syndrome Sexual dysfunction
Other	Smoking

*Components of follicular occlusion tetrad.

Table 38.7 Comorbidities in patients with hidradenitis suppurativa (HS).

Biofilm formation has been shown to play a role in the development of acute lesions, as well as the maintenance of chronic tunnels. The gut microbiome alterations in HS are less well characterized[60], but in smaller series findings were similar to those in patients with inflammatory bowel disease and metabolic syndrome, e.g. more abundant *Bilophila* and *Holdemania* genera and less abundant *Lachnobacterium* and *Veillonella* genera.

With regard to *hormonal factors*, there is a temporal relationship between HS onset and the rise in sex hormones during puberty. In addition, HS patients have an increased incidence of metabolic syndrome and polycystic ovary syndrome. The effect of pregnancy on HS disease activity is mixed, with women reporting improvement, no change, or exacerbation[61]. Of note, HS has been found to be a risk factor for adverse pregnancy and maternal outcomes[61a].

Clinical features

Typical lesions include comedones (including double-ended comedones; Fig. 38.15D), inflammatory papules and nodules, abscesses, tunnels (both sinus tracts and skin fistulae), and scars. Less often pyogenic granuloma-like lesions and ulcers are seen. Lesions favor major body folds including the axillae, groin, buttocks, and inframammary areas (Fig. 38.15A–C). Occasionally, the face (Fig. 38.15G), post-auricular region, neck, and trunk are involved. Initially, patients have recurrent inflammatory papulonodules and abscesses that are tender and extremely painful. Over time, tunnels (Fig. 38.15E) and scars (Fig. 38.15C,F) may develop. This can be accompanied by chronic, malodorous drainage, leading to a marked degree of frustration, embarrassment, and self-consciousness. The discharged fluid is often a mixture of serous exudate, blood and pus, in varying proportions. Of note, patients may also experience pruritus[62].

Complications include soft tissue infections, lymphedema, and scarring so severe as to lead to strictures of the urethra, anus, and rectum as well as limb contractures[63]. Rarely, squamous cell carcinoma (SCC) arises within chronic HS lesions, primarily in gluteal, perianal and perineal areas, and it has a high risk of morbidity and mortality[64]. Systemic complications include anemia, spondyloarthritis, SAPHO syndrome (see Table 25.18) and secondary AA amyloidosis with nephrotic syndrome. Depression, anxiety, sexual dysfunction, social isolation, and a limited ability, or complete inability, to work or participate in daily activities are additional psychosocial issues. Comorbidities identified in patients with HS are outlined in Table 38.7[65].

As noted previously, HS is associated with a variety of uncommon genetic and autoinflammatory disorders including Dowling–Degos disease, Down syndrome[66], KID syndrome, or PASH and its variants.

Staging and outcome measures

The three major clinical grading systems are listed in Table 38.8. While some of the scoring systems are useful for measuring outcomes, others (e.g. Hurley staging system) are less adept at capturing treatment-related changes. The Hidradenitis Suppurativa Clinical Response (HiSCR) represents a dynamic measure of the percent reduction in lesional count compared to baseline[69].

HS-associated pain can be measured using an 11-point Visual Analog Scale that ranges from 0 (no pain) to 10 (worst pain). Patient-reported outcome measurement tools[70] include: (1) Hidradenitis Suppurativa Impact Assessment (HSIA) for assessing a range of daily activities; (2) Hidradenitis Suppurativa Symptom Assessment (HSSA) tool for evaluating the burden of 9 physical symptoms, e.g. pain, drainage, tenderness, warmth, odor, pruritus; and (3) Hidradenitis Suppurativa Quality of Life (HiSQOL) scale.

Pathology

A mixed inflammatory infiltrate is present within the dermis and sometimes subcutaneous tissue along with dilated, often ruptured hair follicles and sinus tracts. Abscesses are observed in active cases[71]. Granulation tissue with inflammatory cells and occasional foreign body giant cells may be present. The sinus tracts contain inflammatory cells and keratinous debris (Fig. 38.16). In chronic disease, there is extensive fibrosis and scarring with destruction of pilosebaceous follicles and sweat glands.

Differential diagnosis

Early nodular lesions of HS may resemble acne cysts, but involvement of the face is unusual in HS as are double-ended comedones in acne; epidermoid cysts when only a few lesions are present; *staphylococcal* furunculosis; and a Bartholin cyst. Later on, a combination of inflammatory nodules, sinus tracts, and scars may resemble cutaneous infections (e.g. due to mycobacteria, *Nocardia*, *Klebsiella granulomatis*) and inflammatory disorders (e.g. cutaneous Crohn disease). Lymphedema secondary to HS should be differentiated from other causes (see Ch. 105).

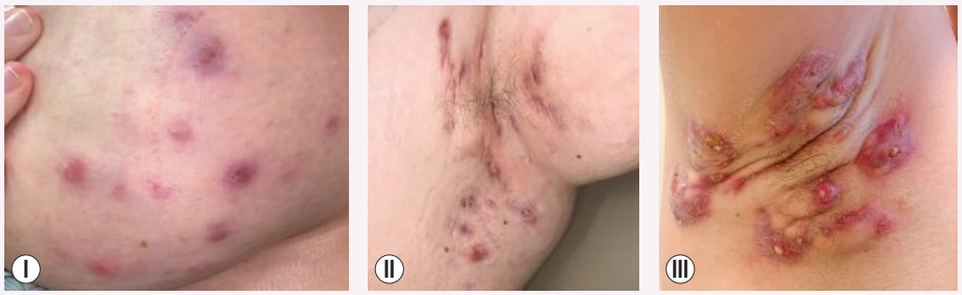
THREE MAJOR GRADING SYSTEMS FOR HIDRADENITIS SUPPURATIVA
Hurley staging system

• Stage I – one or more abscesses with no sinus tract or scar formation • Stage II – one or more widely separated recurrent abscesses, with sinus tract and scar formation • Stage III – multiple interconnected sinus tracts and abscesses throughout an affected region; more extensive scarring
Sartorius grading system[67]
• Anatomical regions involved: axilla (left/right), groin (left/right), gluteal (left/right) or other region (e.g. inframammary): 3 points per region involved • Number and scores of lesions for each region: nodules = 1; fistulae = 6 • The longest distance between two relevant lesions*, i.e. nodules and fistulae, in each region: <5 cm = 1; 5–10 cm = 3; >10 cm = 9 • Are all lesions clearly separated by normal skin? In each region – yes 0/no (Hurley III) 9
International Hidradenitis Suppurativa Severity Score System (IHS4)[68]
IHS4 (points) = number of nodules × 1 + number of abscesses × 2 + number of draining tunnels × 4 Mild HS: ≤3 points Moderate HS: 4–10 points Severe HS: ≥11 points
*Or size if only one lesion.

Table 38.8 Three major grading systems for hidradenitis suppurativa (HS). A refinement of the Hurley staging system in which stages I and II are subdivided into A, B, C subtypes is also utilized. In the Revuz modification of the Sartorius grading system, five regions (axilla, breast, inguino-femoral, perianal, perineal) are scored, with additional modifications including the addition of abscesses to fistulae. The Hidradenitis Suppurativa Physician Global Assessment (HS-PGA) is a 6-point scale with scores from 0 (clear) to 5 (very severe) based upon counts of inflammatory nodules, abscesses, and draining fistulae.

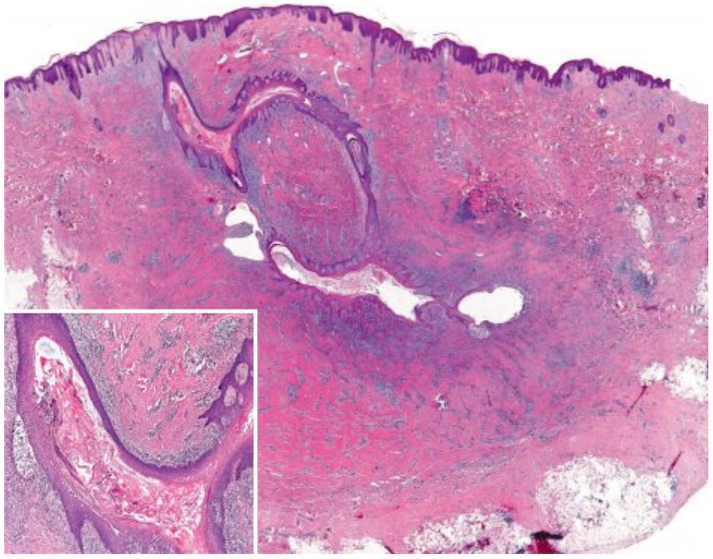


Fig. 38.16 Hidradenitis suppurativa – histopathologic features. A keratin-filled sinus tract (inset) is seen within the dermis, extending into the subcutaneous fat. It is surrounded by marked fibrosis and mixed inflammatory infiltrates. *Courtesy Lorenzo Cerroni, MD.*

Treatment

A multidisciplinary approach that addresses psychosocial issues as well as comorbidities is recommended[72–74]. A therapeutic approach to HS, based on disease severity, is outlined in Table 38.9. Individualized care is also required, e.g. a woman with pre-menstrual flares of HS may benefit from spironolactone, whereas a systemic immunomodulator may be optimal for the patient with concomitant moderate to severe HS and psoriasis (e.g. adalimumab).

Acknowledgment

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Additional figures and tables on Therapeutic interventions on acne keloidalis, and Syndromic hidradenitis suppurativa and genetic disorders in which hidradenitis can be an associated finding, available in our eBook (see inside front cover for access code).

HIDRADENITIS SUPPURATIVA THERAPEUTIC LADDER	
Indication	**Therapeutic interventions**
General measures	• Discuss pain management, smoking cessation, and a healthy diet • If obese or overweight, weight reduction is recommended and may require enrollment in a weight loss program or if morbidly obese, bariatric surgery • Assess patient's mental health and refer to specialist if needed • Recommend wearing soft, breathable fabrics and loose undergarments to reduce friction and moisture • Recommend antiseptic soaps, e.g. benzoyl peroxide or chlorhexidine washes • Provide and educate patient on wound care • Consider laser hair reduction
Mild disease (Hurley stage I) (see Table 38.8)	• Intralesional triamcinolone (5–10 mg/ml) injections into inflamed lesions • Topical therapies: resorcinol, clindamycin, dapsone • Oral antibiotics*: tetracyclines (doxycycline, minocycline), clindamycin, rifampin, trimethoprim-sulfamethoxazole, metronidazole, moxifloxacin • Hormonal therapies: spironolactone, oral contraceptive pills with antiandrogenic or low androgenic progestins, metformin, finasteride • Oral retinoids (especially if patient also has cystic acne): acitretin, isotretinoin • Complementary and alternative medicine: oral zinc • Surgical treatments†; deroofing, limited local excisions

Moderate disease (Hurley stage II) (see Table 38.8)	• Medical therapies for mild disease, alone or in combination with the following:
	  • Systemic immunomodulators ("biologics"): TNF inhibitors (adalimumab‡, infliximab), ustekinumab, IL-17 inhibitors[75,76,76a], IL-23 inhibitors[77,78], anakinra
	  • Other systemic immunomodulators/immunosuppressants: apremilast[79], colchicine (in combination with minocycline), cyclosporine, corticosteroids¶
	• Surgical treatments†; deroofing, local excisions, Nd:YAG laser, CO_2 laser ablation

Severe disease (Hurley stage III) (see Table 38.8)	• Medical treatments outlined for mild and moderate disease, alone or in combination with the following: • Intravenous antibiotics: ertapenem¶ • Surgical treatments†; deroofing, wide surgical excision of involved areas, CO_2 laser excision

*Combinations of oral antibiotics shown to be helpful: clindamycin + rifampin (for disease that is at least mild-to-moderate in severity) and rifampin + moxifloxacin + metronidazole (for moderate-to-severe disease); in a prospective international cohort study comparing oral tetracyclines versus clindamycin + rifampin, there was no significant difference in efficacy[74a].
†Incision and drainage is recommended only to provide acute relief for larger abscesses; it is not a definitive treatment measure given high rate of recurrence.
‡FDA-approved adult dosing regimen: 160 mg on Day 1 -or- 80 mg daily on Days 1 and 2, followed by 80 mg on Day 15 then 40 mg weekly -or- 80 mg every 2 weeks beginning on day 29. There is a weight-tiered dosing regimen for adolescents (12 years and older, weighing at least 30 kg).
¶Systemic corticosteroids may be considered for short-term rescue therapy during a severe flare, and systemic corticosteroids or intravenous ertapenem may be used as bridge therapy to a long-term therapeutic option.

Table 38.9 Hidradenitis suppurativa (HS) therapeutic ladder. Additional reported therapies include bermekimab[80], botulinum toxin A and B injections[81], JAK inhibitors[81a,81b], photodynamic therapy[82], and cryoinsufflation[83].

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eFig. 38.1 Folliculitis of the leg due to *Staphylococcus aureus*. *Courtesy Luis Requena, MD.*



eFig. 38.2 Folliculitis due to *Staphylococcus aureus*. Lesions of furunculosis can also be seen. *Courtesy Kalman Watsky, MD.*



eFig. 38.3 Folliculitis of the back due to methicillin-resistant *Staphylococcus aureus*. The patient had atopic dermatitis. *Courtesy Karynne O. Duncan, MD.*



eFig. 38.4 *Pseudomonas* "hot tub" folliculitis. Edematous follicular papules on the flank that begin to develop 2–3 days following the use of a hot tub. The number and size can vary. *Courtesy Kalman Watsky, MD.*



eFig. 38.5 *Pseudomonas* "hot tub" folliculitis. Edematous follicular papules on the flank that began to develop 2–3 days following the use of a hot tub. The number and size can vary. *Courtesy Kalman Watsky, MD.*



eFig. 38.6 Dermatophyte folliculitis (Majocchi granuloma). Firm follicular papules and nodule studded with pustules within a figurate lesion of tinea. *Courtesy Joseph Chao, MD.*



eFig. 38.7 Herpetic folliculitis. The monomorphous lesions have central hemorrhagic crusts. *Courtesy Julia Pettersen, MD.*



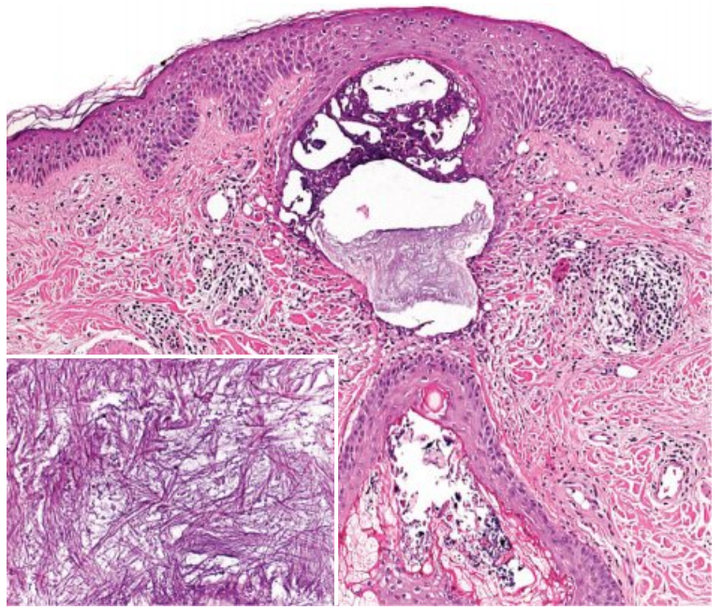
eFig. 38.8 Herpetic folliculitis. Follicular herpes simplex viral infection in an immunocompromised host. *Courtesy Karynne O. Duncan, MD.*



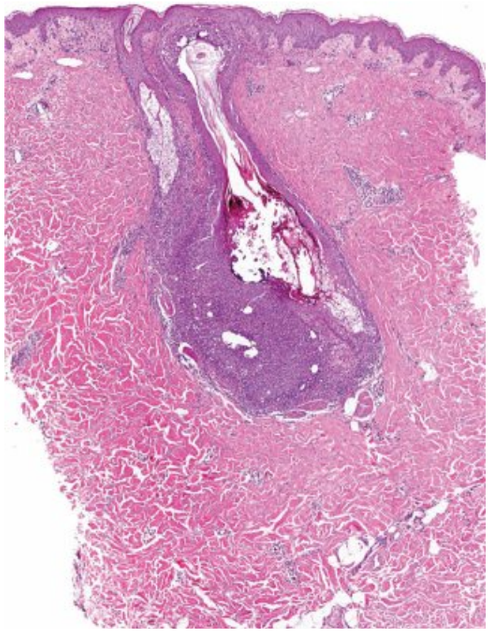
eFig. 38.9 *Demodex* folliculitis. Edematous papules superimposed upon the characteristic background erythema. *Courtesy Kalman Watsky, MD.*



eFig. 38.10 Microscopic findings of follicular contents obtained via scraping of *Demodex* folliculitis. *Courtesy Joseph Chao, MD.*



eFig. 38.12 Histopathologic features of necrotizing infundibular crystalline folliculitis. Dilated ostium of the hair follicle filled with keratin masses that show "needle-like" ("crystalline") structures. *Courtesy Lorenzo Cerroni, MD.*



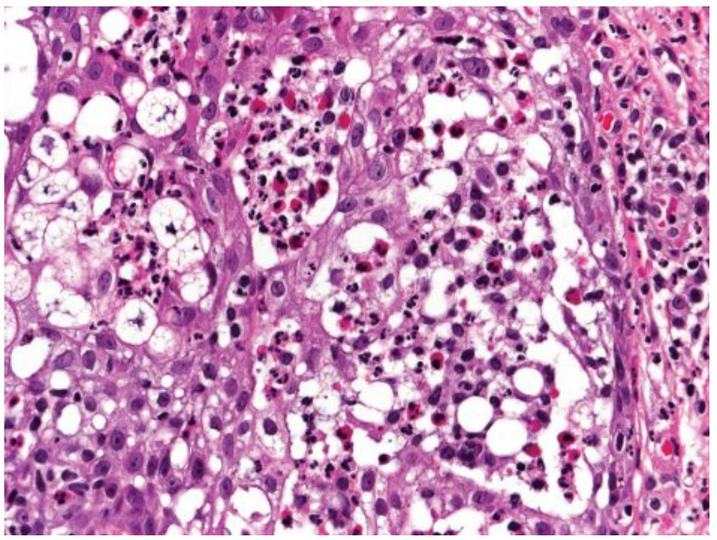
eFig. 38.11 Histopathologic features of folliculitis. Follicular and perifollicular abscess composed predominantly of neutrophils. The hair follicle is dilated and focally ruptured. *Courtesy Lorenzo Cerroni, MD.*



eFig. 38.13 *Malassezia (Pityrosporum)* folliculitis. Multiple follicular papules, some with a central pustule and others with central scale. *Courtesy Jean L. Bolognia, MD.*



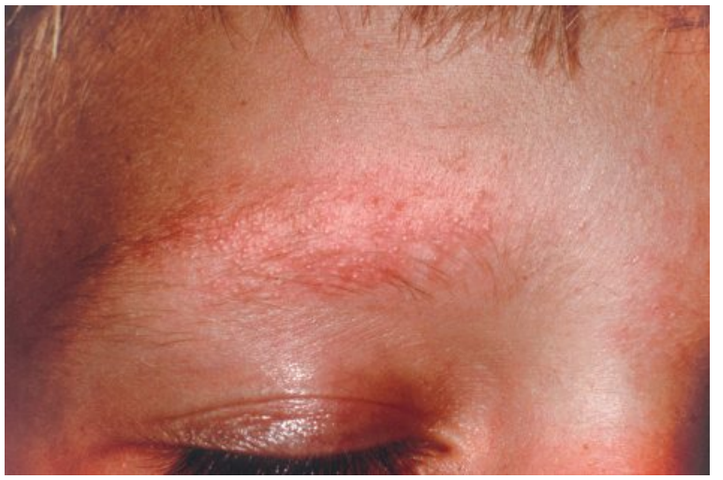
eFig. 38.14 Immunosuppression-associated eosinophilic pustular folliculitis. Multiple papulopustules developed on the forehead. *Courtesy Jean L. Bolognia, MD.*



eFig. 38.15 Histopathologic features of immunosuppression-associated eosinophilic folliculitis in a patient who was HIV-positive. This hair follicle has degenerative changes and many intrafollicular eosinophils, admixed with neutrophils and lymphocytes. *Courtesy Lorenzo Cerroni, MD.*



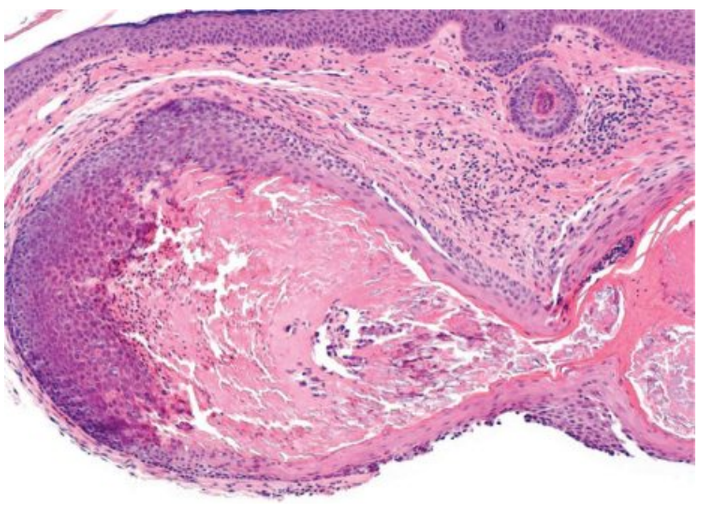
eFig. 38.16 Disseminate and recurrent infundibulofolliculitis (of Hitch and Lund). Numerous monotonous follicular papules on the chest. *Courtesy Jean L. Bolognia, MD.*



eFig. 38.17 Ulerythema ophryogenes. Alopecia of the eyebrow admixed with tiny follicular papules. *Courtesy Jean L. Bolognia, MD.*



eFig. 38.18 Ulerythema ophryogenes. Alopecia of the eyebrows on a background of erythema. *Courtesy Alex Glazer, MD.*



eFig. 38.19 Viral-associated trichodysplasia – histopathologic features. Dilatation and keratotic plugging of the follicle with basophilic germinative cells showing trichohyaline granules and numerous apoptotic cells. *Courtesy Leslie Robinson-Bostom, MD.*



eFig. 38.20 Pseudofolliculitis barbae. Hyperpigmented follicular papules on the neck in a woman.



eFig. 38.21 Pilonidal sinus and abscess formation at the superior portion of the intergluteal cleft. *Courtesy Kalman Watsky, MD.*

THERAPEUTIC INTERVENTIONS FOR ACNE KELOIDALIS	
Indication	**Therapeutic interventions**
Mild to moderately inflamed papules	Topical potent corticosteroid ± topical tretinoin twice daily
Inflamed lesions with pustules	Topical antibiotic (e.g. clindamycin solution) Consider bacterial culture and appropriate systemic antibiotic
	If severely inflamed, consider course of oral isotretinoin
Small keloidal papules	Topical potent corticosteroid and/or topical tretinoin twice daily
	Intralesional triamcinolone acetonide (5–20 mg/ml)
	Punch excision to a depth below the level of the hair follicles followed by either primary closure or second intention healing
	Laser hair removal for permanent hair reduction
Plaques ≤1.5 cm in vertical diameter	Excise and close primarily
Larger plaques and nodules (>1.5 cm in vertical diameter)	Excise with horizontal ellipse (include the posterior hairline)
	Extend excision to level of fascia or deep subcutaneous tissue
	Allow to heal by second intention
	Do not inject corticosteroids into postoperative site
	Laser excision is an alternative to scalpel excision

eTable 38.1 Therapeutic interventions for acne keloidalis. *Courtesy A. Paul Kelly, MD.*

SYNDROMIC HIDRADENITIS SUPPURATIVA AND GENETIC DISORDERS IN WHICH HIDRADENITIS SUPPURATIVA CAN BE AN ASSOCIATED FINDING	
Genes/chromosomes	**Encoded protein**
Syndromic hidradenitis suppurativa **– to date, genes are only implicated in pathogenesis**	
PASH and PAPASH, including variants PASS and PsAPASH	
Inflammasone activity (see Fig. 4.2)	
PSTPIP1	Proline-serine-threonine phosphatase-interacting protein 1
NLRP3	Cryopyrin
IL1RN	IL-1 receptor antagonist
MEFV	Pyrin
NFκB signaling pathway	
NOD2	Nucleotide-binding oligomerization domain-containing protein 2; plays a role in Crohn disease
Regulation of keratinocyte differentiation	
NCSTN	Nicastrin (γ-secretase complex)
Immunoproteosome component	
PSMB8	Proteosome 20 S subunit beta 8
Genetic disorders in which HS can be an associated finding	
Dowling–Degos disease	
PSENEN	Presenilin enhancer-2 (γ-secretase complex)
POFUT1	Protein O-Fucosyltransferase 1
Down syndrome	
Trisomy 21	Amyloid precursor protein – competitive substrate for γ-secretase complex, along with Notch
Pachyonychia congenita (primarily steatocystomas)	
KRT6A	Keratin 6a
KRT17	Keratin 17
Familial Mediterranean fever	
MEFV	Pyrin – regulates inflammasome activity
Darier disease	
ATP2A2	Sarco/endoplasmic reticulum calcium ATPase (SERCA) 2b isoform influences folding of Notch1 receptor within SER
Keratitis–ichthyosis–deafness (KID) syndrome	
GJB2 (G12R missense mutation)	Connexin 26

eTable 38.2 Syndromic hidradenitis suppurativa and genetic disorders in which hidradenitis suppurativa can be an associated finding. HS-like lesions can develop within a nevus comedonicus. PAPASH, pyogenic arthritis, acne, pyoderma gangrenosum, suppurative hidradenitis; PASH, pyoderma gangrenosum, acne, suppurative hidradenitis; PASS, pyoderma gangrenosum, acne, suppurative hidradenitis, ankylosing spondylitis; PsAPASH, psoriatic arthritis, pyoderma gangrenosum, acne, suppurative hidradenitis.

Diseases of the Eccrine and Apocrine Sweat Glands

39

Jami L. Miller

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SWEAT GLANDS

Eccrine Sweat Glands

Key features

- 2–5 million eccrine glands are unevenly distributed over the skin surface
- In healthy individuals, eccrine sweat is 99% water
- Sweating is a reflex sympathetic autonomic function mediated by cholinergic neurons

In humans, sweating is essential for thermoregulatory homeostasis. There are two main mechanisms for cooling the body: radiative cooling via cutaneous vasodilation and evaporative cooling via sweat. Sweat, primarily produced by the eccrine sweat glands, leads to dissipation of heat through evaporation. Few mammals except humans and horses produce sweat in sufficient quantities to affect thermoregulation. For the purposes of this discussion, the term "sweat" applies to eccrine glands and their secretory products unless otherwise specified.

Although there are 2–5 million eccrine glands distributed within the skin, none are found on the clitoris, glans penis, labia minora, external auditory canal, or lips. Eccrine glands are separate from the apocrine–pilosebaceous apparatus, and by dermoscopy, eccrine ductal orifices can be seen along the dermatoglyphic ridges of the palms and soles. The average healthy adult can produce over 0.5 liters of sweat per hour, 99% of which is water. Athletes or those acclimatized to hot environments can produce up to 3–4 liters per hour[1]. Compared to other individuals, physically fit or acclimatized persons initiate sweating earlier and conserve sodium, chloride, and other electrolytes more efficiently. Thermoregulatory control is similar in men and women and diminishes only slightly with age[2].

Sweating is a reflex function controlled primarily by the sympathetic nervous system. These nerves are anatomically sympathetic but functionally cholinergic, i.e. acetylcholine, rather than norepinephrine, is the principal terminal neurotransmitter. Neural impulses for sweating (sudomotor impulses) travel from the anterior hypothalamus via the reticulospinal tracts to the appropriate level in the spinal cord, out through the rami communicantes to autonomic ganglia, and then within sympathetic cholinergic neurons to the secretory cells of the eccrine glands. Adrenergic innervation of eccrine glands has also been demonstrated, but is not believed to be physiologically important[3]. In addition, the sweat glands, via a direct effect on the secretory cells, respond to certain drugs (e.g. cholinergic agonists) as well as to the local application of heat.

Apocrine Sweat Glands

In humans, apocrine sweat glands are confined to the eyelids (Moll's glands), external auditory meatus, axillae, areola and nipple, periumbilical region, and anogenital region, in particular the mons pubis, labia minora, prepuce, scrotum, and perianal area. At five months' gestation, apocrine glands are distributed all over the body, whereas in a full-term neonate they are limited to the above sites. In non-primate mammals, apocrine sweat glands are widely distributed but they also open into the pilosebaceous unit.

Apocrine secretion is a slow, usually continuous process analogous to milk formation in the mammary gland. The secretory product is an oily fluid composed of lipids, proteins, and sex hormones. At or near the skin surface, it mixes with sebum derived from the sebaceous gland that empties into the same pilosebaceous unit.

HYPERHIDROSIS

Key features

- Excessive sweating
- Primary hyperhidrosis is the most common type, typically affecting the palms, soles, and/or axillae
- Secondary hyperhidrosis is due to an underlying condition (e.g. infection, tumor, genetic syndrome) or medication and may be localized or generalized

Hyperhidrosis is estimated to affect 3% of the US population[4]. The most widely used classification system divides it into primary (idiopathic) and secondary types. Other classification systems separate hyperhidrosis into categories based on the source of the neural impulses that drive it: cortical (emotional), hypothalamic (thermoregulatory), medullary (gustatory), spinal cord, and local axon reflexes.

Primary Hyperhidrosis

Synonym: ■ Primary focal hyperhidrosis

Key features

- Main sites are volar (palms, soles) and axillary skin; the face may also be involved
- Hyperhidrosis arises from increased cortical stimulation and occurs *only* during waking hours (diurnal)
- Patients are otherwise healthy
- Up to 80% of affected individuals have a family history of hyperhidrosis

Primary hyperhidrosis, the most common type of hyperhidrosis, is defined as excessive sweating in localized areas (usually the palms, soles, and/or axillae) and is not associated with a systemic disorder.

Men and women of all races are equally affected. Table 39.1 lists the diagnostic criteria[5]. Between 60% and 80% of patients with primary hyperhidrosis have a family history[6], with a pattern of inheritance suggesting autosomal dominant transmission with incomplete penetrance. A locus for primary palmar hyperhidrosis was mapped to chromosome 14q in three Japanese families[7].

Intense emotion or stress can elicit sweating in anyone. It occurs most often on the palms, soles, or axillae and can also affect the face (Fig. 39.1), especially the forehead and the cutaneous upper lip. The post-orgasmic sweating observed with sexual activity may also derive from emotional stimulation[8].

Clinically significant primary hyperhidrosis occurs in two major patterns: volar (palmoplantar) and axillary, which can coexist[1], but usually one of the two sites predominates. The onset of volar hyperhidrosis is often during childhood, whereas axillary hyperhidrosis typically develops at or soon after puberty. Primary hyperhidrosis is seen in both cold and warm environments. A chronic and unremitting course is characteristic, with little or no variation in association with age, disease, or hormonal status.

Volar hyperhidrosis is the most common form of primary hyperhidrosis (Fig. 39.2), affecting ~50%–60% of patients[3,4]. The entire palm and sole, as well as the lateral aspects, tips and distal dorsal skin of the fingers, display sweating. It can clearly have an impact on quality of life.

Axillary hyperhidrosis is the second most common form of primary hyperhidrosis, affecting 30%–50% of patients[4]. The right axilla usually produces more sweat than the left (60:40). Exceptionally, one axilla may be hyperhidrotic while the opposite axilla is hypohidrotic or virtually anhidrotic. Odor (axillary bromhidrosis) is usually absent; the excessive quantities of eccrine sweat presumably rinse away or dilute odorogenic apocrine sweat droplets and bacteria.

CRITERIA FOR THE DIAGNOSIS OF PRIMARY HYPERHIDROSIS
1. Focal, visible excess sweating
2. Present for at least 6 months
3. No apparent secondary causes
4. At least two of the following:
• Bilateral and symmetric
• Impairs activities of daily life
• At least one episode per week
• Age of onset <25 years
• Positive family history
• Stops during sleep

Table 39.1 Criteria for the diagnosis of primary hyperhidrosis. *Adapted from Hornberger J, Grimees K, Naumann M, et al. Recognition, diagnosis and treatment of primary focal hyperhidrosis. J Am Acad Dermatol 2004;51:274–86.*



Fig. 39.1 Primary cortical (emotional) hyperhidrosis involving the face. Sweat droplets are evident on the upper cutaneous lip, jawline, and chin. *Reproduced from Hurley HJ. Hyperhidrosis. Curr Opin Dermatol 1997;4:105–14. Philadelphia: Rapid Science Publishers.*

Secondary Hyperhidrosis

Secondary hyperhidrosis is caused by or associated with another systemic disorder. It may be localized or generalized. There are many causes, which can be divided into categories based on the source of the neural impulse driving the response: cortical, hypothalamic, medullary, spinal cord, or local. A number of medications may also be associated with hyperhidrosis (Table 39.2).

Disorders associated with cortical (emotional) hyperhidrosis

Key features

- Several disorders of cornification and other genodermatoses affecting palmoplantar skin are associated with volar hyperhidrosis
- Patients with hereditary autonomic neuropathies can also exhibit cortical hyperhidrosis

Isolated sweating of the palms and soles is primarily due to cortical excitation by emotional or sensory stimuli. Excessive volar sweating associated with certain inherited palmoplantar keratodermas is assumed to be cortical in nature, although the pathogenic relationship between the abnormal keratinization and hyperhidrosis has not been precisely delineated. Many palmoplantar keratodermas are malodorous, likely related to sweat-induced maceration of the thickened stratum corneum and bacterial degradation of keratin. Other genodermatoses affecting the volar skin, such as epidermolysis bullosa simplex, can also have associated palmoplantar hyperhidrosis. Additional causes of cortical hyperhidrosis are listed in Table 39.3.



Fig. 39.2 Volar hyperhidrosis (primary cortical). A, B The plantar skin is moist and glistening with eccrine sweat. There are also sweat droplets. *Courtesy Jean L. Bolognia, MD.*

DRUGS THAT CAN STIMULATE ECCRINE SWEATING	
Direct-acting cholinomimetic agents	
• Acetylcholine	• Anti-xerostomia drugs (see Table 45.5)
Cholinesterase inhibitors	
• Anti-Alzheimer drugs* • Anticholinergic antidote	• Antimyasthenics
Adrenomimetic agents	
• Dopamine • Epinephrine (adrenaline) • Isoproterenol	• Norepinephrine (noradrenaline) • Phenylpropanolamine
Antidiabetic (hypoglycemic) agents	
• Insulins	• Sulfonylureas
• Biguanides	
CNS stimulants	
• Amphetamines • Caffeine	• Theophylline
Antidepressants	
• MAOIs† • SSRIs†	• Tricyclics†
Antipsychotics	
Antipyretics	
Opioids	
Other drugs	
• ACE inhibitors • Amlodipine • Atomoxetine • Dextromethorphan*,† • Ipecac • Pentoxifylline	• Phosphodiesterase inhibitors (e.g. sildenafil) • Sibutramine† • Sumatriptan† • Tramadol† • Yohimbine

*Increased sweating is infrequently observed at pharmacologic doses but represents a sign of overdose.
†Combination of MAOIs (which include linezolid as well as antidepressants) with drugs such as tricyclics, SSRIs, certain opioids, and tryptophan can result in the serotonin syndrome; the latter is characterized by mental status changes, autonomic hyperactivity (including hyperhidrosis), and neuromuscular abnormalities.

Table 39.2 Drugs that can stimulate eccrine sweating. Selective estrogen receptor modulators (e.g. tamoxifen, raloxifene) and aromatase inhibitors (e.g. anastrozole) can lead to menopausal symptoms including hot flashes with sweating. ACE, angiotensin-converting enzyme; CNS, central nervous system; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor.

CAUSES OF CORTICAL (STRESS/EMOTIONAL) HYPERHIDROSIS
Primary hyperhidrosis (see Table 39.1)
Secondary hyperhidrosis
Disorders of cornification
• Palmoplantar keratodermas • Pachyonychia congenita • Congenital ichthyosiform erythroderma and epidermolytic ichthyosis
Other genodermatoses
• Epidermolysis bullosa: simplex > junctional • Dermatopathia pigmentosa reticularis • Dyskeratosis congenita • Pachydermoperiostosis (digital clubbing and thick, furrowed skin on the face and scalp) • Apert syndrome (craniosynostosis, digital anomalies, severe acne; *FGFR2* mutations) • Nail–patella syndrome
Hereditary sensory and autonomic neuropathies (HSANs)*
• Familial dysautonomia (Riley–Day syndrome; HSAN type III; blotchy erythema accompanies episodic hyperhidrosis of the face and trunk, decreased lacrimation, postural hypotension, and dysautonomic crises [vomiting, hypertension]) • Congenital autonomic dysfunction with universal pain loss • Congenital sensory neuropathy (HSAN type II)
*Hypothalamic (thermal) hyperhidrosis can also occur.

Table 39.3 Causes of cortical (stress/emotional) hyperhidrosis. *Adapted from Moschella S, Hurley HV. Dermatology. Philadelphia: WB Saunders, 1992.*

Hypothalamic (thermoregulatory) hyperhidrosis

Key features

- Due to elevated body temperature (e.g. acute febrile illness, lymphoma, chronic infection) or direct hypothalamic stimuli (e.g. pheochromocytoma, medications, toxins)
- May be nocturnal (night sweats) or diurnal

The hypothalamus is responsible for many autonomic activities, including thermoregulation. Elevation of the temperature of the blood by 0.5°F (0.3°C) or more excites the hypothalamic nuclei and results in vascular dilation and generalized sweating responses aimed at dissipating body heat[3].

Febrile illnesses are among the most common pathologic states that cause hypothalamic sweating. At the height of the fever, notably with temperatures of 39–40°C (102–104°F) or above, sweating is absent, the apparent result of inhibition of the hypothalamic center for sweating. With defervescence, sweating characteristically ensues. Lymphomas and chronic infections (e.g. tuberculosis) can present with episodic thermoregulatory sweating, which may be described as "night sweats" (that actually follow unperceived mild febrile pulses).

Generalized sweating of hypothalamic origin can also be seen in a number of metabolic and endocrine disorders (Table 39.4). Patients with diabetes mellitus may exhibit hypohidrosis as well as various forms of hyperhidrosis. For example, hyperhidrosis is a characteristic sign of insulin-induced hypoglycemia (but not diabetic ketoacidosis), and compensatory hyperhidrosis of the trunk can develop in the setting of diabetic neuropathy affecting the extremities (see below). In addition, diabetics may exhibit gustatory hyperhidrosis, primarily of the face and neck. Troublesome sweating of the scalp can also be seen in poorly controlled diabetics, and, with regulation of the hyperglycemia, it often improves.

Disorders with vasomotor instability, such as Raynaud phenomenon, autoimmune connective tissue diseases, frostbite and other cold injuries, and complex regional pain syndrome, may be associated with excessive sweating because of disturbed autonomic function[9]. A synchronous discharge of vasoconstrictor and sudomotor impulses evokes a "cold sweat", usually of the hands and feet, producing macerated, soggy wet, violaceous skin known as symmetrical lividity.

Cerebral cortex lesions, such as a tumor, abscess or cerebrovascular accident, may be associated with a contralateral hyperhidrosis due to an impairment of the inhibitory cortical influence that normally regulates hypothalamic sudomotor activity[10]. Hypothalamic sweating is also observed in Parkinson disease and occurs as the "sweating sickness" following encephalitis. Harlequin syndrome, characterized by unilateral flushing and hyperhidrosis in association with contralateral anhidrosis, may be due to peripheral or central nervous system (CNS) abnormalities[11].

Episodic release of catecholamines from pheochromocytomas directly stimulates the hypothalamus and may elicit sweating[12]. Exposures to toxins and medications can also lead to hypothalamic hyperhidrosis, and a number of drugs that act on the CNS have increased sweating as a potential side effect (see Table 39.2). Additional causes of hypothalamic hyperhidrosis are presented in Table 39.4.

Pressure and postural hyperhidrosis may be due to hypothalamic or possibly cortical stimulation. With changes in posture or the application of pressure to one side of a supine individual, a variety of sweating patterns have been described, such as lateral hyperhidrosis, horizontal hemihidrosis, and crossed hemihidrosis. Idiopathic localized unilateral hyperhidrosis of the face and neck or forearm has been reported as an episodic disorder triggered by heat, emotional, or gustatory stimuli[13].

CAUSES OF HYPOTHALAMIC HYPERHIDROSIS						
Infection	**Tumors**	**Endocrine/ metabolic**	**Vasomotor**	**Neurologic**	**Drugs/ toxins**	**Miscellaneous**
• Acute febrile illnesses (defervescence) • Tuberculosis • Brucellosis • Malaria • Subacute bacterial endocarditis • Other	• Lymphoma • Pheochromocytoma* • Carcinoid*	• Menopause • Hypoglycemia • Obesity • Hyperthyroidism • Acromegaly • Pregnancy • Porphyria (acute intermittent) • Phenylketonuria • Gout	• Congestive heart failure† • Myocardial ischemia • Raynaud phenomenon • Acrocyanosis • Cold injury • Symmetrical lividity of the palms and soles‡ • Complex regional pain syndrome • Autoimmune connective tissue disease (e.g. rheumatoid arthritis, SLE)	• CNS tumors • Cerebrovascular accidents • Parkinson disease • Postencephalitic • Episodic spontaneous hypothermia with hyperhidrosis§ • Cold-induced sweating syndrome‖ • Familial dysautonomia‡	• Alcoholism • Alcohol or opioid withdrawal • SERMs and aromatase inhibitors • Mercury toxicity (acrodynia) • Chronic arsenic toxicity • See Table 39.2	• Compensatory hyperhidrosis (e.g. in association with miliaria, diabetic neuropathy, sympathectomy)¶ • Localized unilateral hyperhidrosis (face and neck, forearm)‡ • POEMS syndrome • Speckled lentiginous nevus syndrome • Mitochondrial disorders • Pressure and postural hyperhidrosis‡

*Via release of catecholamines (pheochromocytoma) or serotonin (carcinoid tumors, usually metastatic; see Ch. 106).
†Patients have sympathetic activation, with impaired vasodilatory responses to heating but preserved sweating.
‡Also associated with cortical hyperhidrosis.
¶Compensatory hyperhidrosis is also a feature of Ross syndrome (segmental anhidrosis, generalized areflexia and tonic pupils).
§Referred to as Hines–Bannick syndrome or, when associated with agenesis of the corpus callosum, Shapiro syndrome.
‖Autosomal recessive condition caused by mutations in the genes encoding cytokine receptor-like factor-1 and cardiotrophin-like cytokine factor-1; additional features include facial dysmorphism, flexion deformities (elbows, fingers), and scoliosis.

Table 39.4 Causes of hypothalamic hyperhidrosis. SERMs, selective estrogen receptor modulators; SLE, systemic lupus erythematosus. *Adapted from Moschella S, Hurley HV. Dermatology. Philadelphia: WB Saunders, 1992.*

Medullary (gustatory) hyperhidrosis

Key features

- Taste receptors in the mouth are the source of the afferent impulses that stimulate sweating
- *Physiologic* medullary hyperhidrosis is most commonly triggered by spicy foods, alcohol, and citrus fruits
- *Pathologic* medullary hyperhidrosis occurs when disrupted nerves for sweat aberrantly connect with nerves for salivation; this can be caused by local injury to, or disease of, the parotid gland (Frey syndrome), trauma to the sympathetic trunk, and CNS disorders (e.g. encephalitis, syringomyelia)

Physiologic medullary hyperhidrosis

Any food or drink that stimulates the taste buds may induce sweating in normal individuals, particularly of the face. This is thought to occur via a variant reflex arc in which afferent impulses from taste bud receptors travel via the glossopharyngeal nerve to nuclei within the medulla oblongata (hence the term "medullary" hyperhidrosis), but lead to provocation of sweating rather than (or in addition to) the usual response of salivation. A few minutes after ingestion of a stimulating food or beverage, sweating and erythema are seen most commonly on the upper cutaneous lip or cheeks. It may be unilateral or bilateral and may be brief or persist as long as the stimulating food or beverage is ingested. Associated vasodilation localized to the areas of sweating causes the erythema, which may be faint. Spicy or sharp-tasting foods and beverages, such as citrus fruits, alcohol and condiments, may elicit the reaction. It is most common in children and young adults and in warmer environments. A familial tendency has been described[14]. There are no other concurrent local or systemic signs or symptoms. A variant of gustatory hyperhidrosis can occur on the face in diabetics. Unusual types of gustatory hyperhidrosis involving the scalp and the knee have also been described and support the concept of a central medullary mechanism for these sweating responses[15].

Pathologic medullary hyperhidrosis

This disorder arises after disruption of nerves. During healing, nerve fibers mediating sweating aberrantly connect to nerves that mediate salivation. Impulses in parasympathetic fibers normally supplying the salivary glands are now misdirected to the sweat glands. As a result, salivary stimulation elicits sweating. Of note, thermal sweating in the areas of affected skin is reduced.

The parotid form appears weeks to months following a surgical procedure, trauma, or other disorder (e.g. abscess, herpes zoster) affecting the parotid gland. These patients experience vasodilation and sweating on the cheek and adjacent neck when salivary stimulation is induced by eating, drinking, or even chewing (Fig. 39.3). Sweating most often occurs in the distribution of the auriculotemporal nerve; at times there is also unilateral localized pain[16].

Auriculotemporal syndrome (Frey syndrome) is common after parotid surgery, developing in 40% or more of patients, although many



Fig. 39.3 Gustatory sweating in the auriculotemporal (Frey) syndrome, as a consequence of parotid surgery. The blue–black area represents sweating (starch–iodine technique). Salivary stimulation induced this sweating response. *Reproduced from Hurley HJ. Hyperhidrosis. Curr Opin Dermatol 1997;4:105–14. Philadelphia: Rapid Science Publishers.*

are not aware of it. It can also occur during infancy, frequently as a consequence of trauma to the parotid region in a forceps-assisted delivery. The infant presents with gustatory flushing, but usually no obvious sweating, and this is often erroneously attributed to food allergy. Another variant of gustatory hyperhidrosis is the chorda tympani syndrome in which salivary stimuli to the submandibular gland induce sweating on the chin and lower jaw line.

Patients with cluster headaches can have sympathetic deficits that result in impaired thermoregulatory sweating on the affected side of the forehead. In addition, ipsilateral hyperhidrosis and flushing may occur, together with excessive lacrimation, during headache attacks. This is due to misdirection of parasympathetic fibers, which normally supply the lacrimal glands, to sweat glands and blood vessels. Patients with Raeder syndrome (Horner syndrome [ptosis, meiosis ± anhidrosis] plus unilateral temporofrontal headaches and pain) may also have excessive supraorbital sweating, also referred to as lacrimal sweating.

Any condition that injures the vagus nerve and sympathetic trunk, as they lie close together in the thorax, may cause pathologic medullary hyperhidrosis (Table 39.5). Cholinergic fibers from the vagus nerve sprout into the adjacent sympathetic trunk during the healing process and can result in a gustatory hyperhidrosis with sweating on the face, neck, and portions of the trunk and upper extremities.

In patients with syringomyelia or encephalitis, gustatory hyperhidrosis is occasionally seen on the face and upper trunk. It involves the glossopharyngeal and vagus nerves. Disturbances in the brainstem apparently lead to transposition of the central medullary nuclei for salivation and sweating. There is no peripheral crossing of sympathetic and parasympathetic nerve fibers as is seen in other forms of pathologic gustatory hyperhidrosis.

Spinal (cord transection) sweating

Key features

- Spinal disorders may result in a lack of thermal sweating below the injury as well as unusual patterns of hyperhidrosis
- Mass reflex sweating may occur around the injured level

Any injury or disease process that severs or interferes with the reticulospinal tracts of the cord can disrupt the sweating reflex (see Table 39.5). Lack of a sweat response to thermal stimulation usually occurs below the level of the injury. Abnormal patterns of segmental sweating may occur in conjunction with other autonomic, sensory, and motor alterations. Onset and duration are unpredictable. Sweating can be excessive, drenching the patient in the regions involved. Bouts of "mass reflex sweating" are initiated in the skin below the level of the cord interruption. It is most intense in skin segments close to the level of the transection. Mass reflex sweating does not occur in transections below T8–T10.

Autonomic dysreflexia

Key features

- Direct stimulation (e.g. electrical, physical, or drug-induced) of a sympathetic axon can cause sweating
- May be seen with inflammatory skin diseases

Autonomic dysreflexia is a syndrome that may occur with spinal injuries at or above T6[17]. Massive episodic sympathetic discharge results in sweating above the level of the transection accompanied by headache, hypertension, facial flushing, bradycardia or tachycardia, piloerection, and paresthesias.

Direct stimulation of a cutaneous sympathetic axon with electrical and physical impulses or injections of drugs with nicotine-like effects on autonomic ganglia can induce sweating in an area ~4 cm in diameter[3]. Mediators from inflammatory skin conditions (e.g. psoriasis, dermatitis) can also elicit localized hyperhidrosis. Substance P and a number of other mediators, including kinins, dopamine, prostaglandins, angiotensin and adenine, may be involved[18].

Compensatory hyperhidrosis

Key features

- Anhidrosis in one area may cause hyperhidrosis in another
- Miliaria, diabetic neuropathy, and sympathectomy are well-known causes

The coordinated functioning of the body's eccrine sweat glands is illustrated by the phenomenon of compensatory hyperhidrosis, in which the sweat glands of one area become hyperactive in an effort to compensate for hypo- or anhidrosis in another. Apparently, a threshold number of sweat glands must be non-functional in order for the compensatory response to occur. The nature or type of the underlying process that produces the anhidrosis also appears to be important. For example, compensatory hyperhidrosis does not seem to develop secondary to the anhidrosis produced by lymphomas.

The best-known clinical forms of compensatory hyperhidrosis occur in the following three situations:

- *Miliaria*: longstanding or recurrent miliaria rubra or profunda typically results in numerous non-functional sweat glands within large areas of the trunk. This induces compensatory hyperhidrosis of the face (Fig. 39.4A), especially in response to ambient heat or exercise.
- In *diabetes mellitus*, disturbance of the autonomic nervous system due to peripheral neuropathy and microangiopathy often causes anhidrosis or hypohidrosis of the affected skin, particularly the legs. With the loss of sweating on the lower extremities, these patients may develop compensatory increases in thermal sweating on the trunk, especially the back. A second type of compensatory

OTHER CAUSES OF SECONDARY HYPERHIDROSIS			
Medullary (gustatory)	**Spinal cord**	**Axon reflex**	**Abnormal blood vessels or eccrine glands (non-neural)**
• Physiologic gustatory sweating • Frey syndrome • Chorda tympani syndrome • Cluster headaches • Sympathectomy • Sympathetic trunk and vagus nerve injury (e.g. by lung carcinoma, mesothelioma, thyroidectomy, subclavian aneurysm) • Encephalitis • Syringomyelia	• Spinal injury • Syringomyelia • Tabes dorsalis	• Inflammatory skin diseases • Drugs (see Table 39.2)	• Aquagenic palmoplantar keratoderma (see Fig. 58.19) • Eccrine nevi • Eccrine angiomatous hamartoma (see Fig. 39.5) • Maffucci syndrome • Arteriovenous fistula • Klippel–Trenaunay syndrome • Glomuvenous malformation • Blue rubber bleb nevus syndrome • Cold erythema • Granulosis rubra nasi • Pretibial myxedema

Table 39.5 Other causes of secondary hyperhidrosis. Gustatory lacrimation ("crocodile tears" syndrome) is due to transposition of autonomic fibers for lacrimation and salivation after facial nerve injury. *Adapted from Moschella S, Hurley HV. Dermatology. Philadelphia: WB Saunders, 1992.*

hyperhidrosis, gustatory in character and usually on the face and neck (Fig. 39.4B), may also be seen in diabetic patients with peripheral neuropathy of the lower extremities.

- *Post-sympathectomy*: with the loss of sweating that results from cervicothoracic sympathectomies, a thermal hyperhidrosis, usually on the trunk, is common. Sympathectomized patients may also experience gustatory hyperhidrosis.

Non-neural hyperhidrosis

Key features

- Direct stimulation of eccrine glands can cause sweating
- Triggers include local heat, drugs, and vascular tumors

Direct stimulation of eccrine sweat glands by heat or sudomimetic drugs can lead to localized sweating. Even denervated skin sweats when heat is applied[3]. Table 39.5 outlines additional non-neural causes of localized hyperhidrosis (Fig. 39.5). The rare disorder "cold erythema" affects the skin and gastrointestinal tract – exposure to cold produces local cutaneous erythema and intense pain along with a central area of hyperhidrosis. As with other entities in which local pain is a clinical feature (e.g. glomuvenous malformations), increased blood flow or an axon reflex (secondary to the pain) may be the causal mechanism for this sweating.

Diagnosis of Hyperhidrosis

Key features

- Differentiation between primary and secondary hyperhidrosis is important
- Hyperhidrosis can be documented by colorimetric and gravimetric methods

The first step is to differentiate between primary and secondary hyperhidrosis. History will elicit location, duration, and specific triggers. Other medical disorders and medications (including over-the-counter products) need to be ascertained. An extensive review of systems should point to any secondary causes.

Patients who do not fit the classic pattern of primary hyperhidrosis (see Table 39.1) should undergo further evaluation, focusing on possible etiologies (see Tables 39.2–39.5) during a complete history and physical examination. Laboratory testing and radiographic studies may be needed (Table 39.6).

Measurement of sweat can be performed. A grading scale for volar disease lists "low" as a moist palm or sole without visible sweat droplets. "Moderate" disease is characterized by sweating toward the fingertips. "Severe" cases drip sweat. Axillary involvement can be measured by the sweat stains on clothing: <5 cm is considered normal; 5–10 cm, mild; 10–20 cm, moderate; and >20 cm, severe.

Colorimetric techniques such as the starch–iodine or quinizarin methods demonstrate the sweating pattern and reveal the location of the most active sweat glands in a given area[19]. In the starch–iodine technique, iodine solution (e.g. 3.5% in alcohol) is applied to clean, shaved skin and allowed to dry. Starch powder (e.g. cornstarch) is then brushed onto the area. Sites with sweating turn blue–black (Fig. 39.6). A combination of iodine and paper impregnated with starch can also be utilized (Fig. 39.7).

Additional quantitative assessment methods are available. In order to document amounts of sweat produced, gravimetric (via weighing filter paper before and after application to the skin) and evaporative (via a device that assesses water vapor loss from the skin) measurements can be made in volar or axillary sites[19]. Infrared thermography and skin conductance measurements represent other methods of evaluating sweat gland function, allowing comparison between anatomic areas and even individual glands.

Treatment of Hyperhidrosis

Key feature

- Treatment options for hyperhidrosis include topical sweat duct blockers, topical glycopyrronium, sweat-reducing oral medications, botulinum toxin, iontophoresis, biofeedback therapy, microwave thermolysis, and surgical procedures

Treatment options available for hyperhidrosis are outlined in Table 39.7. Over-the-counter products include antiperspirants and deodorants; the latter contain antimicrobial agents while both contain odor-masking fragrances. The major active ingredient in topical antiperspirants is

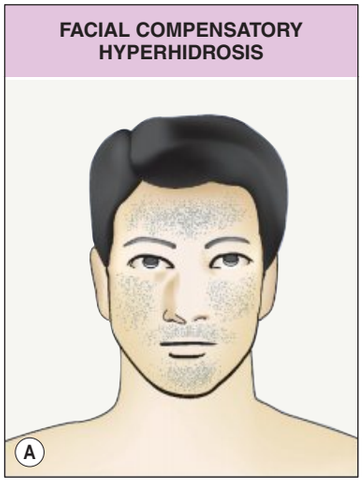




Fig. 39.4 Compensatory hyperhidrosis of the face. A Outline of the sites of facial compensatory hyperhidrosis in patients with extensive miliaria. **B** Facial compensatory hyperhidrosis (upper lip and chin) in a patient with diabetes mellitus (starch–iodine technique). *Courtesy Harry Hurley, MD.*



Fig. 39.5 Eccrine angiomatous hamartoma. Cluster of painful pink–violet papules and plaques on the thigh and knee that had been present since one year of age. There was associated hyperhidrosis, but not hypertrichosis. Histologically, an increased number of both eccrine glands and small blood vessels is seen. *Courtesy Julie V. Schaffer, MD.*

INITIAL PATIENT EVALUATION FOR SECONDARY HYPERHIDROSIS	
Laboratory test	**Disease**
Serum electrolytes, BUN, creatinine	Renal disease (rare)
Fasting blood glucose level and/or HbA1c	Diabetes mellitus
Thyroid function tests	Hyperthyroidism
Skin and/or blood tests for tuberculosis (e.g. PPD, QFTB-G)	Tuberculosis
Chest X-ray	Tuberculosis, neoplasm (e.g. lymphoma)
Complete blood count	Infection
Sedimentation rate/C-reactive protein test	Infection, neoplasm, inflammatory disease
Antinuclear antibodies	Autoimmune connective tissue disease
Urinary catecholamines*	Pheochromocytoma
*If suggestive signs or symptoms (see Ch. 106).	

Table 39.6 Initial patient evaluation for secondary hyperhidrosis. Further evaluation depends upon results and consideration of entities in Table 39.4. BUN, blood urea nitrogen; PPD, (tuberculin) purified protein derivative; QFTB-G, QuantiFERON-TB Gold.



Fig. 39.6 Delineation of area for injections of botulinum toxin A for axillary hyperhidrosis (starch–iodine technique). The blue–black area represents foci of sweating (reflected in black dots). In the case of onabotulinumtoxinA, a total of 50–100 U is injected within this area, utilizing 10 to 15 injection sites. *Courtesy Alastair Carruthers, MD, and Jean Carruthers, MD.*

metal (usually aluminum) salts which deposit within and temporarily block the sweat duct. Prescription antiperspirants contain higher concentrations of these salts. They should be applied to dry surfaces at night, when sweating is diminished. Occlusion enhances penetration of the salts. Application is recommended for three to five consecutive nights, then one to two times a week as needed to control sweating. Treated skin can be washed the following morning. Burning and irritant contact dermatitis are common side effects, particularly in women who shave their axillae and with higher salt concentrations.

Some patients who sweat significantly at night require a preliminary dose of an anticholinergic drug 1 hour before application for the first few applications (see below). This reduces sweating enough to prevent the topical solution from being rinsed away. Topical aldehyde agents such as formaldehyde and glutaraldehyde are effective, but allergic sensitization may develop that can result in cross-reactions with aldehydes in the environment (lotions, soaps, shoes).

Daily topical application of glycopyrronium tosylate via a cloth towelette is FDA-approved for the treatment of primary axillary hyperhidrosis in individuals nine years of age or older. After four weeks, 60% of treated

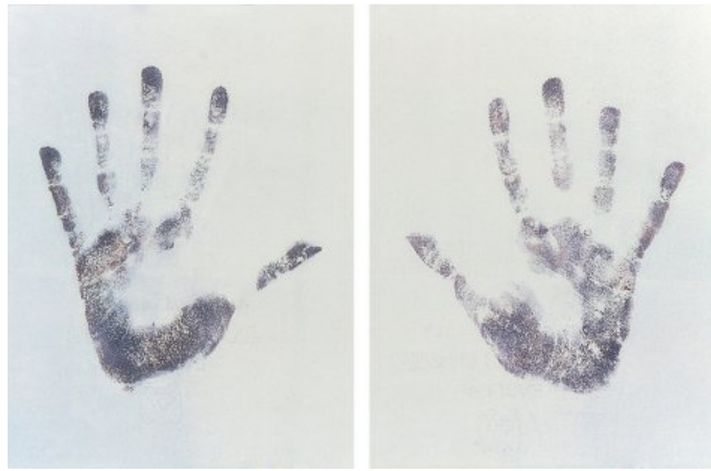


Fig. 39.7 Palmar hyperhidrosis as assessed by the semiquantitative starch paper–iodine technique. Sweating can also be demonstrated directly on palmar skin by the starch–iodine technique, as shown in Fig. 39.6 for axillary hyperhidrosis. *Courtesy Harry Hurley, MD.*

patients reported a significant reduction in sweat severity compared to 28% of those who applied the alcohol-based vehicle[20]. Botulinum liposomal cream and topical oxybutinin gel have also shown efficacy but currently are not commercially available. Table 39.7 outlines anticholinergic-related side effects. Patients with diseases that can be exacerbated by anticholinergics (e.g. glaucoma, myasthenia gravis, Sjögren syndrome, severe ulcerative colitis) should avoid their use.

Tap water iontophoresis over 20 minutes two to three times a week may be helpful. The mechanism of action is unknown but is thought to lead to blockage of the sweat duct in the stratum corneum. Side effects are minimal and include tingling of the skin during treatment. Introduction of anticholinergic medications via iontophoresis is not advised due to potential systemic absorption.

Oral anticholinergics will decrease sweating in most patients. The most commonly used agents are oxybutynin[21] and glycopyrrolate[22] (see Table 39.7 for recommended regimens). When higher doses are required to control the hyperhidrosis, unacceptable side effects can often develop, including dry eyes and mouth, insomnia, mental status changes (e.g. confusion, hallucinations), palpitations, seizures, blurred vision, bowel disturbances, urinary retention, and hypertension. More recently, a link between the long-term use of oral anticholinergic medications and development of dementia has been reported. As a result, limiting the duration of exposure to these medications has been recommended[23], and the use of calcium channel blockers as an alternative has increased.

Clonidine (an α_2-adrenergic agonist that decreases central sympathetic outflow) and phenoxybenzamine (an α-adrenergic blocker) have been used with some success in anecdotal reports[24,25]. Potential side effects include hypotension, rebound hypertension, sedation, constipation, weakness, and headache. Propranolol, a β-adrenergic blocker, is commonly used for the treatment of performance anxiety and it may improve hyperhidrosis temporarily. However, long-term use may induce hyperhidrosis.

OnabotulinumtoxinA (BTA) has been approved by the FDA for the treatment of severe axillary hyperhidrosis (see Fig. 39.6); it is also effective for volar disease. Botulinum toxins prevent the release of acetylcholine from cholinergic neurons (see Ch. 159). Injection into hyperhidrotic skin will produce near anhidrosis for 4 to 6 months (see Video 159.7). Side effects, if any, are short-lived. Muscle weakness, especially of the intrinsic muscles of the hands or feet, has been reported and resolves spontaneously over 2 to 5 weeks. Compensatory hyperhidrosis has not been observed[26]. Botulinum toxin injections should be avoided in patients who have pre-existing muscle weakness due to disorders such as myasthenia gravis and amyotrophic lateral sclerosis. To date, other botulinum toxins have not been FDA-approved for hyperhidrosis (see Table 159.1).

Surgical treatment may be offered if other therapeutic modalities have failed. Destruction of sweat glands by lasers[26], fractional microneedle radiofrequency, or microwave thermolysis can be performed[27]. Surgical dissection[28], curettage, or liposuction represent additional treatment options[29]. Excision of the sweat glands is often effective for axillary disease, but resection of the entire axillary skin causes significant scarring. However, compensatory hyperhidrosis is not seen with this form of local surgery.

TREATMENT OF HYPERHIDROSIS					
	Therapy	**Frequency & recommended dose**	**Side effects**	**Duration**	**Comments**
First-line	Topicals Aluminum chloride hexahydrate – 6.25% to 20% Aluminum chloride – 12% to 20% Aluminum sesquichlorohydrate – 15% Aluminum zirconium salts	Use nightly for 3–5 nights, then every few days as needed	Burning Irritant contact dermatitis	Days	Blocks sweat ducts Aluminum zirconium salts may be effective in axillae, but not volar surfaces
	Glycopyrronium cloth, 2.4%	At bedtime, one cloth applied to both axillae that are clean and dry	Local: erythema, burning, pruritus Systemic: dry mouth > mydriasis > urinary hesitation, blurred vision	Hours	Anticholinergic* Washing hands immediately after application avoids inadvertent eye exposure
	5% sofpironium gel	Daily			
Second-line	*Acetylcholine release inhibitors, i.e. botulinum toxins*	Every 4–6 months	Discomfort during injection Weakness of underlying muscles	Months	Prevents release of acetylcholine from neurons
	Iontophoresis	2–3 times a week	Discomfort during procedure	Days	Blocks sweat ducts
	Oral therapy†	As needed		Hours	
	Oxybutynin‡	1.25–5 mg daily - BID (IR) 5–15 mg daily (ER)	Dry mouth and urinary retention most common; also confusion and decreased mental status		Anticholinergic*
	Glycopyrrolate‡	1–2 mg BID - TID			Anticholinergic*
	Nifedipine XL	30 mg once daily with escalation to 90 mg once daily	Headache, flushing, ankle edema, hypotension		Calcium channel blocker
	Clonidine	0.1–0.3 mg BID	Hypotension, rebound hypertension		α_2-Adrenergic agonist
	Propranolol	10–40 mg BID	Hypotension, bradycardia, hyperhidrosis with long-term use		β-Adrenergic blocker
	Clonazepam	0.25–0.5 mg BID	Sedation		Anxiolytic
	Thermal ablation Nd:YAG laser Microwave thermolysis	Multiple	Expensive	Years	
Third-line	*Liposuction*	Once to more than once¶	Expensive	Semipermanent to permanent	
	Local excision	Once	Scarring	Permanent	Last resort
	Sympathectomy	Once	Compensatory hyperhidrosis Horner syndrome	Usually permanent	

*Contraindications to topical and oral anticholinergics include glaucoma, urinary retention, paralytic ileus or toxic megacolon, and myasthenia gravis.
†Combined with topical therapy.
‡A link between long-term use of oral anticholinergic medications and development of dementia has been reported.
¶May need to be performed more than once to treat glands that have regenerated or were missed.

Table 39.7 Treatment of hyperhidrosis. Examples of topical commercial products are Xerac® AC, Drysol®, and Driclor® (6.25%, 20%, and 20% aluminum chloride [AlCl] hexahydrate, respectively), Certain-Dri® (12% AlCl), and Carpe® lotion (aluminum sesquichlorohydrate 15%). Lumē is an aluminum-free product that can be used anywhere on the body. Ingredients in alternative aluminum-free products include baking soda, corn starch, tapioca starch, kaolin clay, candelilla wax, zinc oxide, and fragrances. BID, twice daily; ER, extended release; IR, immediate release; TID, three times daily.

Sympathectomy is the last resort for patients with volar hyperhidrosis. Advances in endoscopic surgery have decreased the morbidity associated with this procedure. Sympathectomy at the T2–T3 level for palmar disease and the lumbar area for plantar disease is effective. Risks of the procedure include Horner syndrome, hypotension, and pneumothorax. Compensatory hyperhidrosis of the trunk or gustatory facial sweating may occur[26] and the hyperhidrosis may gradually recur.

HYPOHIDROSIS AND ANHIDROSIS

Key features

- An inability to sweat can be life-threatening due to the development of heat-related illnesses
- Causes of hypo- and anhidrosis include central or neuropathic disruption of neural impulses, sweat gland abnormalities, and medications

Three major categories of disorders are recognized causes of anhidrosis: (1) central and neuropathic diseases or medications that disrupt neural impulses from the anterior hypothalamus to the eccrine gland; (2) peripheral (non-neural) alterations in the gland itself; and (3) idiopathic.

Central and Neuropathic Hypohidrosis

Disturbance or interruption of innervation at any level, from the sweating centers in the brain down through the descending neural tracts to the sweat glands, can result in decreased or absent sweating. Causes are listed in Table 39.8. Pontine or medullary lesions lead to unilateral facial anhidrosis on the ipsilateral side of the face and neck. Fiber tracts carrying sudomotor neurons to lower levels in the spinal cord are both crossed and uncrossed and the resultant anhidrosis of the skin may be ipsi- or contralateral.

Both peripheral neuropathies and degenerative neurologic disorders can cause anhidrosis. Chronic orthostatic (postural) hypotension may be associated with decreased sympathetic innervation of the sweat glands, and syncopal episodes in these patients are not accompanied by sweating.

CAUSES OF CENTRAL AND NEUROPATHIC HYPOHIDROSIS AND ANHIDROSIS

• Tumors, infarctions, and other lesions of the hypothalamus, pons, or medulla
• Spinal cord tumors and injuries
• Horner syndrome
• Degenerative syndromes
  • Pure autonomic failure
  • Multiple system atrophy (Shy–Drager syndrome)*
  • Ross syndrome (see text)
• Autoimmune autonomic neuropathy
• Congenital insensitivity to pain with anhidrosis
• Peripheral neuropathy due to:
  • Diabetes
  • Alcoholism
  • Leprosy
  • Amyloidosis (immunoglobulin light chain and transthyretin types)
• Drugs (see Table 39.9)

*Progressive autonomic dysfunction, parkinsonism, and ataxia.

Table 39.8 Causes of central and neuropathic hypohidrosis and anhidrosis.

DRUGS THAT CAUSE HYPOHIDROSIS AND ANHIDROSIS	
Blockade of neurotransmission	
Nicotinic acetylcholine receptor antagonists (ganglion-blocking agents)	
• Hexamethonium • Mecamylamine	• Tetraethylammonium • Trimethaphan
Muscarinic acetylcholine receptor antagonists*	
• Atropine • Glycopyrrolate	• Oxybutynin • Scopolamine
Calcium channel blockers	
α-Adrenergic blockers • Phenoxybenzamine (hypohidrosis occasionally observed) • Phentolamine†	
α_2-Adrenergic agonists‡ • Clonidine	
Dysfunction or destruction of the eccrine gland¶	
• Aldehydes (topical) • Aluminum salts (topical) • 5-Fluorouracil • Quinacrine	• Topiramate§ • Zirconium salts (topical) • Zonisamide§
*Antipsychotic drugs (e.g. phenothiazines), tricyclic antidepressants, and some antihistamines can also have anticholinergic effects, especially when administered in combination and at high doses. †Thought to suppress eccrine sweating by inhibiting ganglionic transmission. ‡Decrease sympathetic outflow from the CNS. ¶Eccrine gland necrosis is also a feature of coma bullae, which are classically associated with barbiturate overdose but can also be observed in comas induced by other drugs (see Ch. 33); syringosquamous metaplasia may result from the toxic effects of chemotherapeutic agents (e.g. cytarabine, doxorubicin) on the eccrine glands. §Decreased sweating has been attributed to inhibition of carbonic anhydrase isoenzymes in the eccrine glands.	

Table 39.9 Drugs that cause hypohidrosis and anhidrosis. Refers to systemic administration unless otherwise indicated.

This is in contrast to the sweating, pallor, and nausea seen in common vasodepressor fainting.

Ross syndrome, which consists of Adie syndrome (myotonic pupils and absent deep tendon reflexes) plus segmental anhidrosis that is typically associated with compensatory hyperhidrosis, also falls into this group. Congenital insensitivity to pain with anhidrosis (hereditary sensory and autonomic neuropathy type IV) is a rare autosomal recessive disorder which presents with recurrent fevers due to anhidrosis, self-mutilation due to insensitivity to pain, and intellectual disability. Mutations in *NTRK1*, which encodes the tyrosine kinase receptor for nerve growth factor, have been detected in these patients. Skin biopsy specimens reveal a lack of innervation of eccrine sweat glands.

Disruption of the superior cervical ganglion results in Horner syndrome, and chemical blockade of selected sympathetic ganglia will result in regional anhidrosis. Any drug that interrupts synaptic transmission in autonomic ganglia will suppress sweating (Table 39.9).

Peripheral Anhidrosis

Congenital and acquired alterations or disturbances of the sweat glands result in an absence or significant reduction in sweating (Table 39.10). Hypo- or anhidrosis is one of the clinical findings in several types of ectodermal dysplasia[30]. In patients with ichthyoses, obstruction of sweat ducts can lead to hypohidrosis.

The skin of elderly individuals may show some atrophy of the sweat glands, but overall they are preserved and continue to function with advancing age. Toxic and thermal insults to the skin and a variety of inflammatory and neoplastic disorders can destroy or produce atrophy of the sweat glands (see Table 39.10).

Diagnosis of Anhidrosis

Heat intolerance may be due to a number of underlying disorders. New symptoms such as drowsiness, fatigue, or inability to concentrate in hot environments in association with a decrease in the patient's "normal sweating" point to acquired hypo- or anhidrosis. A careful history will yield clues to the diagnosis, with special attention to new medications, recent medical events (e.g. a cerebrovascular accident), the presence of diabetes or other chronic conditions, and family history (see Tables 39.8–39.10).

Examination of the patient's skin may not reveal the presence or extent of anhidrosis. A hot environment or exercise may be required but excessive overheating must be avoided. Colorimetric or gravimetric testing (see above) and infrared thermography will demonstrate diminished or absent sweating. Local intradermal injection of cholinergic drugs to stimulate sweating in small areas can also be utilized, but the risk of side effects generally precludes their injection into large areas. Testing for axon reflex sweating with intradermal nicotine sulfate or picrate in appropriate doses (e.g. 0.001 mg) or administration of acetylcholine via iontophoresis may be performed in patients in whom peripheral neuropathies are suspected.

PERIPHERAL CAUSES OF HYPOHIDROSIS AND ANHIDROSIS DUE TO SWEAT GLAND ABNORMALITIES
Genetic disorders

• Ectodermal dysplasias
  • Hypohidrotic ectodermal dysplasia
  • Hypohidrotic ectodermal dysplasia with immune deficiency
  • Rapp–Hodgkin syndrome
  • Naegeli–Franceschetti–Jadassohn syndrome
• Incontinentia pigmenti
• Bazex–Dupré–Christol syndrome
• Fabry disease*

Destruction
• Tumors (e.g. lymphoma) • Burns • Radiation therapy, including electron beam therapy • Systemic sclerosis (scleroderma) and morphea • Sjögren syndrome† • Graft-versus-host disease • Acrodermatitis chronica atrophicans
Obstruction
• Miliaria • Ichthyoses (e.g. lamellar ichthyosis) • Psoriasis • Eczematous dermatoses • Bullous diseases (e.g. epidermolysis bullosa [inherited or acquired]) • Porokeratosis
*Hyperhidrosis (related to autonomic dysfunction) can also occur. †Hypohidrosis can also result from peripheral neuropathy.

Table 39.10 Peripheral causes of hypohidrosis and anhidrosis due to sweat gland abnormalities.

Finally, a biopsy specimen from an affected area of skin should be obtained in virtually all patients with anhidrosis to identify sweat gland abnormalities. When possible underlying etiologies have been excluded (see Tables 39.8–39.10), acquired idiopathic generalized anhidrosis should be considered (Table 39.11)[31,32].

Treatment of Anhidrosis

Treatment options for anhidrosis are limited. Offending medications should be discontinued. Keeping the patient in a cool environment is essential. For disorders due to clogged sweat ducts, gentle exfoliation may be helpful. Disorders of cornification (e.g. lamellar ichthyosis) associated with overheating should be treated aggressively. Use of water-containing spray bottles can prove useful.

ABNORMALITIES AND ALTERATIONS OF ECCRINE AND APOCRINE SWEAT COMPOSITION

Key features

- Some disorders (e.g. cystic fibrosis) lead to abnormal chemical composition of sweat
- Eccrine bromhidrosis is most commonly caused by maceration of the stratum corneum and bacterial degradation of keratin
- Apocrine bromhidrosis is related to bacterial degradation of apocrine sweat
- Eccrine chromhidrosis is due to *exogenous* chemicals that color the sweat
- Apocrine chromhidrosis is usually due to *intrinsic* causes

Abnormalities of eccrine sweat composition, as evidenced by altered electrolyte content or the presence of other anomalous substances, are recognized as disorders of eccrine function. Some of these glandular disturbances are not accompanied by clinically distinctive signs or symptoms, whereas others result in well-defined clinical entities.

ACQUIRED IDIOPATHIC GENERALIZED ANHIDROSIS
Rare disorder of unknown etiology Acquired, broadly distributed reduction in sweat production
Reported primarily in Asian populations, especially Japanese Male predominance (~80%) Most commonly presents during the 2nd to 4th decade When widespread, heat intolerance or stroke may occur
Three subtypes: • Sudomotor neuropathy • Idiopathic pure sudomotor failure (most common form) • Sweat gland failure
Diagnostic features: • By thermoregulatory sweat testing (starch–iodine test), hypohidrosis or anhidrosis involves >25% BSA and is usually symmetric • Sweating is preserved on the face, palms, and soles and in the axillae • Exclusion of other causes (e.g. medications, neurologic disorders, cutaneous diseases, Sjögren syndrome; see Tables 39.8–39.10)
Additional findings in affected areas: • Decreased sweating following local injection of acetylcholine • No induction of sweating by QSART, which assesses sweating due to the axon reflex • Marked variation in histologic findings, from normal-appearing eccrine glands to eccrine gland atrophy or absence, occlusion of proximal ducts, and periglandular inflammatory infiltrates
Treatment: • Lifestyle guidance, i.e. avoid heat if possible • Oral medications: pulse corticosteroids, cyclosporine, antihistamines

Table 39.11 Acquired idiopathic generalized anhidrosis. BSA, body surface area; QSART, quantitative sudomotor axon reflex test (acetylcholine is administered to the skin via iontophoresis and then sweating is measured). See refs. 31 and 32.

Notable among this group of disorders are those in which there is altered electrolyte concentration in sweat (Table 39.12). Cystic fibrosis, an autosomal recessive disorder caused by mutations in the *c*ystic *fi*brosis *t*ransmembrane conductance *r*egulator (*CFTR*) gene, is an important example in which all of the exocrine glands in the body are affected, leading to dysfunction of multiple organs, including the lungs, exocrine pancreas, intestines, and liver. Cystic fibrosis patients demonstrate decreased electrolyte reabsorption by the eccrine duct, which results in increased loss of sodium, chloride, and (to a lesser extent) potassium in sweat. Increased Cl^- concentration in sweat (>60 mEq/L on two separate occasions) remains the most widely used diagnostic assay for this disease; it is referred to as the sweat chloride test. Cystic fibrosis patients still produce sweat in response to heat and most pharmacologic stimuli, but the increased loss of electrolytes poses a systemic risk for them in hot environments. An absent or markedly diminished response of the eccrine glands and other exocrine glands to β-adrenergic agonists is another marker for this disorder, since the CFTR protein is a Cl^- channel activated via β-adrenergic stimulation.

Excretion of calcium in eccrine sweat has been demonstrated in patients with widespread idiopathic calcinosis cutis. In uremia, high levels of urea can produce a "uremic frost" on the skin of these seriously ill patients[33]; however, readily available dialysis has made this a rare finding. Decreased size of the sweat glands, the significance of which is unknown, has also been described in patients with uremia[34]. Many drugs, including opiates, amphetamines, anticonvulsants, antimicrobials (e.g. azole antifungals, griseofulvin), and chemotherapeutic agents, as well as metals such as copper and mercury have been shown to be secreted in sweat[35,36].

In healthy individuals, both eccrine sweat and apocrine sweat are odorless when they are secreted. Eccrine bromhidrosis can develop secondary to maceration of the stratum corneum with bacterial degradation of keratin; the odor emanates primarily from the feet and intertriginous zones, especially the inguinal region. In apocrine bromhidrosis, the odor reflects bacterial degradation of apocrine sweat into ammonia, volatile fatty acids, and thioalcohols. The types of bromhidrosis are listed in Table 39.13.

Malodorous sweat can also be caused by abnormal secretion of amino acids and their analogues or breakdown products. This occurs in several heritable metabolic disorders[37] (see Table 39.13). In addition, some foods such as garlic and asparagus can cause eccrine bromhidrosis.

Colored eccrine sweating (*eccrine* chromhidrosis) can result from hyperbilirubinemia (green), ingestion of certain foods (e.g. red due to cranberry juice), and dyes in drugs (e.g. yellow from tartrazine). Pseudochromhidrosis results from contamination of colorless eccrine sweat by pigment from microorganisms, including *Corynebacterium* spp. (blue, brown/black), *Serratia marcescens* (red/pink), *Pseudomonas*

SYSTEMIC DISORDERS THAT AFFECT THE LEVELS OF ELECTROLYTES IN SWEAT
Increased levels of electrolytes in sweat*

• Cystic fibrosis
• Endocrine disorders
  • Adrenal insufficiency (e.g. due to Addison disease or congenital adrenal hyperplasia)
  • Myxedema
  • Nephrogenic diabetes insipidus
• Familial intrahepatic cholestasis
• Malnutrition
• Metabolic disorders
  • Fucosidosis
  • Glycogen storage disease type I
• Unacclimatized individuals exposed to heat

Decreased levels of electrolytes in sweat

• Endocrine disorders
  • Aldosteronism
  • Cushing syndrome
  • Thyrotoxicosis
• Hypoproteinemic edema (e.g. due to cirrhosis or nephrotic syndrome)

*Elevated sweat electrolytes (which may result in a false-positive chloride sweat test) can also be observed in patients with skin conditions such as widespread atopic dermatitis, ichthyosiform erythroderma, or ectodermal dysplasia.

Table 39.12 Systemic disorders that affect the levels of electrolytes in sweat.

TYPES OF BROMHIDROSIS
Apocrine
• Axillary (formation of thioalcohols by *Staphylococcus hominis* a major component)
Eccrine

• Keratinogenic
  • Plantar
  • Intertriginous
• Metabolic
  • Phenylketonuria (musty or "mousy" odor)
  • Maple syrup urine disease (sweet odor)
  • Methionine adenosyltransferase deficiency ("boiled cabbage" odor)
  • Methionine malabsorption syndrome (oasthouse syndrome; "beer-like" odor)
  • Trimethylaminuria ("fishy" odor)*
  • Dimethylglycine dehydrogenase deficiency ("fishy" odor)
  • Isovaleric acidemia ("sweaty feet" odor)
• Exogenous
  • Foods, e.g. garlic, asparagus, curry
  • Drugs, e.g. penicillins, bromides
  • Chemicals, e.g. dimethyl sulfoxide (DMSO)

*Exacerbated by eating marine fish, eggs, kidney, or liver.

Table 39.13 Types of bromhidrosis.

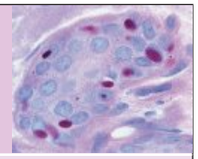
aeruginosa (blue-green), *Bacillus* spp. (blue), and *Malassezia furfur* (blue). Miners or workers in the copper industry often exhibit blue or blue–green sweat due to external deposits of copper salts. Sunless-tanning products can result in brown sweat. Hematidrosis (bloody sweat) has been reported periodically and appears to be associated with psychiatric disease. Red sweat has been described in patients receiving clofazimine and rifampin.

In contrast, *apocrine* chromhidrosis is usually intrinsic in origin and blue or black in color, resulting from the excretion in apocrine sweat of lipofuscin in large amounts or in a highly oxidized state. Chromhidrosis, primarily axillary in location and presumably of apocrine origin, can be seen in alkaptonuria and may be a presenting sign of the disease as the excreted pigment stains the undershirts of these patients.

DIAGNOSTIC MICROSCOPIC CHANGES IN ECCRINE SWEAT GLANDS

A variety of disorders display diagnostic microscopic findings within the eccrine sweat glands, ranging from intracellular inclusions and degenerative alterations to changes in the size of the glands or their components. Table 39.14 summarizes these distinctive histopathologic features, which may be overlooked in the diagnostic evaluation of patients. Most of the findings listed can be visualized by light microscopy. By electron microscopy, viral particles from Ebola virus and severe acute respiratory syndrome (SARS) have been found in eccrine sweat ducts[38]. Although there have been reports of SARS-CoV-2 being present in the sweat of infected individuals, more recent studies have failed to detect its secretion in sweat, with no evidence that sweat can serve as a source of transmission[39].

DIAGNOSTIC MICROSCOPIC CHANGES IN ECCRINE GLANDS



Disorder	Microscopic changes
Exposures/metabolic	
Argyria	Granules in eccrine basement membrane (darkfield)
Chemotherapy (traditional)	Vacuolar degeneration of secretory cells and/or ducts; dense eccrinotropic infiltrate of neutrophils (may be sparse or lymphocytic in neutropenic patients)
Coma bullae	Necrosis of secretory cells and duct cells
Hypothyroidism	PAS-positive, diastase-resistant granules in secretory cells
Uremia	Reduced size of sweat glands
Tumors	
Mycosis fungoides, syringotropic	Dense infiltrate of atypical lymphocytes within and around eccrine glands, often with squamous syringometaplasia
Genetic disorders	
Acid maltase deficiency Adrenoleukodystrophy Mucopolysaccharidoses (e.g. Hurler, Hunter, Sanfilippo) and mucolipidoses	Membrane-bound vacuoles in secretory cells
Lafora disease	PAS-positive granules in outer layer of duct cells (inset)
Neuronal ceroid lipofuscinoses	Cytoplasmic inclusions in secretory cells
Sphingolipidoses (e.g. Fabry, Niemann–Pick, Sandhoff)	Lipid inclusions in secretory cells
Trisomy 13, 18 or 21	Differences in duct: secretory coil length
Viral infections	
Ebola hemorrhagic fever Severe acute respiratory syndrome (SARS)	Viral particles in lumen of sweat gland tubule

Table 39.14 Diagnostic microscopic changes in eccrine glands. (Inset: Lafora disease.)

INFLUENCE OF SWEAT ON SKIN DISEASES

Key features

- Wet skin is more permeable than dry skin
- Wet skin is more likely to develop contact allergies than dry skin
- Several cutaneous diseases are aggravated by sweat

That wet skin is more permeable than dry skin has been clearly established, and skin wetted by perspiration is more likely to be sensitized to contact allergens. Damp skin is also more susceptible to absorption of toxic chemicals. The macerative effect of sweat is an essential early step in the pathogenesis of sweat retention syndromes, such as miliaria. Sweat-saturated keratin, upon bacterial degradation, gives rise to plantar bromhidrosis and pitted keratolysis. Softening of the skin by sweat facilitates the entry and growth of microbes, leading to flexural candidiasis, bacterial folliculitis, bullous impetigo, superficial dermatophyte infections, tinea versicolor, verrucae, and molluscum contagiosum. Grover disease, Darier disease, and Hailey–Hailey disease are clearly aggravated by sweating. Some systemic drugs, such as antifungal agents, are excreted in eccrine sweat and diffuse from the sweat ducts to the surrounding stratum corneum, exerting inhibitory effects on microorganisms.

ADDITIONAL DISORDERS OF THE ECCRINE SWEAT GLAND

Miliaria

Key features

- Sweat retention can be caused by obstruction of the eccrine duct at various levels
- Miliaria crystallina or sudamina (superficial ductal occlusion) – clear vesicles
- Miliaria rubra or prickly heat (intermediate ductal occlusion) – erythematous papules or pustules
- Miliaria profunda or mammillaria (deeper ductal occlusion) – white papules
- Common in neonates (whose eccrine sweat ducts are not fully developed) and adults living in hot, humid climates
- Resolves with relocation to a cool environment

THREE TYPES OF MILIARIA				
Type	**Location of obstruction**	**Cutaneous lesions**	**Patient population(s)**	**Most common locations**
Crystallina	Stratum corneum	Non-pruritic, clear, fragile, 1 mm vesicles	Neonates <2 weeks of age Children and adults in hot climates	Face and trunk (Fig. 39.8)
Rubra	Mid-epidermis	Pruritic, erythematous, 1–3 mm papules; may have pustules (miliaria pustulosa)	Neonates 1–3 weeks of age Children and adults in hot climates	Neck and upper trunk (Fig. 39.9)
Profunda	Dermal–epidermal junction	Non-pruritic, white, 1–3 mm papules	Adults in hot climates; often with multiple bouts of miliaria rubra	Trunk and proximal extremities

Table 39.15 Three types of miliaria.



Fig. 39.8 Miliaria crystallina. Multiple small superficial vesicles with clear fluid.

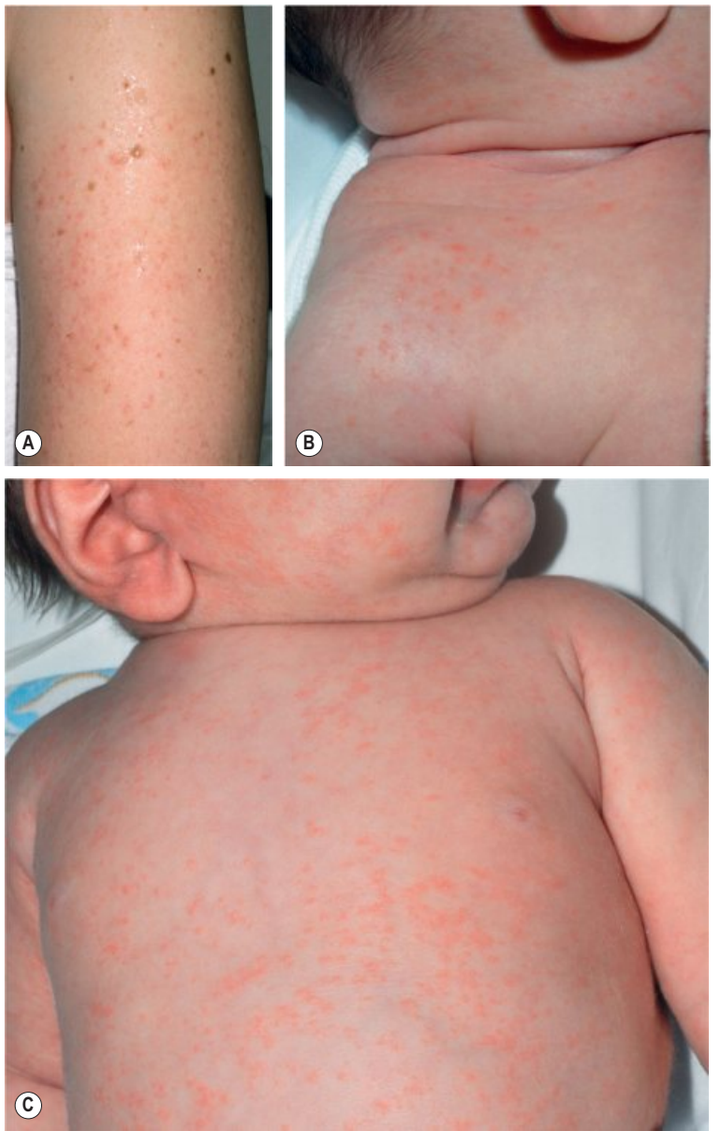


Fig. 39.9 Miliaria rubra. Multiple erythematous non-follicular papules and papulovesicles on the arm of an adult woman (**A**), on the upper trunk and neck of a neonate (**B**), and in a widespread distribution in an infant (**C**). In addition to obvious sweating, the woman also has a sunburn from recent sun exposure. Note that several of the lesions in the neonate have become pustular. *A, Courtesy Jennifer Powers, MD; B, Courtesy Julie V. Schaffer, MD; C, Courtesy Antonio Torrelo, MD.*

Miliaria encompasses a family of eccrine disorders all of which feature obstruction of the eccrine sweat duct. Three types are recognized, with each reflecting obstruction of sweat ducts at a different level, from the stratum corneum to the dermal–epidermal junction (Table 39.15). Blockage results in retention of sweat within the duct, causing a sweat retention vesicle to form.

Epidemiology and pathogenesis

Miliaria is most common in children, particularly neonates whose eccrine ducts are not fully developed. Congenital miliaria crystallina has even been described. Miliaria is also common in adults who live or work in very hot, humid environments. There is no racial or sex predisposition and it can occur in the elderly. Miliaria has not been associated with any specific underlying systemic disease.

Excessive sweating, particularly under occlusive clothing, can lead to maceration of the stratum corneum which is sufficient to cause blockage of the eccrine duct[30]. Keratinous plugs form, causing obstruction.

Clinical features

Each type of miliaria is clinically distinctive (see Table 39.15). *Miliaria crystallina* presents as small, clear superficial vesicles (Fig. 39.8) that rupture easily. It poses no systemic risk for the patient.

The most common form is *miliaria rubra*, which is characterized by small, non-follicular, erythematous macules and papules topped by a punctate vesicle (Fig. 39.9A,C). Lesions are usually pruritic and occasionally burn. Onset is within days to weeks of exposure to hot environments. Miliaria rubra may become pustular (Fig. 39.9B), especially in chronic, extensive cases. *Miliaria pustulosa*, as this variant is known, is sterile, although secondary bacterial infection may occur. Extensive cases of miliaria rubra can lead to hyperpyrexia.

When miliaria rubra is chronic or recurrent, occlusion may extend to a deeper level and produce *miliaria profunda*. Because of their deeper location, the sweat retention vesicles of miliaria profunda appear clinically as white papules, 1 to 3 mm in diameter. They start within minutes of initiation of sweating and subside within 1 to 2 hours after the sweating ceases. Lesions of miliaria profunda are asymptomatic. Only in those patients with concomitant miliaria rubra can pruritus or burning develop. When large numbers of sweat glands are occluded and essentially non-functional, these individuals are at risk for significant thermoregulatory problems and a compensatory hyperhidrosis of

the face is routinely observed (see Fig. 39.4A). Axillary and inguinal lymphadenopathy can also be seen, with resolution upon clearing of the miliaria. The term "tropical anhidrotic asthenia" has been applied to these patients.

Pathology

Biopsy specimens demonstrate ductal blockage. Keratinous obstruction of sweat ducts at the level appropriate for each type of miliaria may be seen, but several deeper sections may be required: in the stratum corneum for miliaria crystallina; the mid-epidermis for miliaria rubra; and at the dermal–epidermal junction for miliaria profunda. Sweat retention vesicles are seen underlying the respective sites of occlusion. Spongiosis in the vicinity of the epidermal sweat duct is common in miliaria rubra and miliaria profunda. Dermal inflammation is absent in miliaria crystallina, whereas perivascular lymphocytic infiltrates and vasodilation are evident in miliaria rubra. An eosinophilic cast can be seen occluding sweat ducts at the dermal–epidermal junction or intraepidermally in miliaria profunda. Periductal infiltration of lymphocytes is also seen along with mild focal spongiosis of the adjacent epidermis.

Differential diagnosis

The diagnosis is usually clinically apparent, but a simple diagnostic test consists of the puncture of a miliaria vesicle with a fine needle, resulting in release of the trapped clear sweat. In neonates, the differential diagnosis includes erythema toxicum neonatorum, neonatal cephalic pustulosis (which can involve the upper trunk as well as the face), candidiasis, and in atypical cases, other vesiculopustular diseases of the newborn (see Table 34.1). In adults, the differential diagnosis for miliaria rubra includes other conditions with a predilection for sites of occlusion and excessive sweating, such as folliculitis (with normal flora or *Staphylococcus aureus*), candidiasis, and Grover disease. The regression of miliaria profunda within hours of ceasing physical exertion and/or exposure to high temperatures distinguishes it from other papular eruptions.

Treatment

Management of all types of miliaria requires placement of the patient in a cool environment, in which sweating stops, for several days to weeks. Gradually, the obstructed sweat ducts shed their occluding keratinous plugs and normal sweating is restored. Topical anhydrous lanolin may dissolve the plugs in miliaria profunda. Anecdotally, other topicals (including corticosteroids and antibiotics) as well as oral antibiotics, retinoids, and vitamins A and C have been advocated as therapeutic options.

Multiple Sweat Gland Abscesses

Synonym: ▪ Periporitis staphylogenes

Key features

- Rare neonatal disorder
- Miliaria lesions become infected and form abscesses
- Most common on the neck, back, and buttocks
- May be associated with systemic symptoms

Multiple sweat gland abscesses represent a rare disorder of newborn infants that is likely due to a secondary staphylococcal infection of miliaria lesions. Malnourished or debilitated neonates are preferentially affected.

Clinically, erythematous papules and nodules are distributed on the occiput, neck, back, and buttocks. They are typically round or oval erythematous swellings that measure 1 to 2 cm in diameter and do not exhibit warmth, tenderness, or fluctuance. Lymphangitis and constitutional signs and symptoms such as fever and lassitude may occur with larger or more numerous lesions. Bacterial smears and cultures reveal *S. aureus*. Microscopically, abscess formation involving the sweat glands is seen.

The differential diagnosis includes furuncles or carbuncles and subcutaneous fat necrosis of the newborn. Although to date this disorder has not been associated with an immunodeficiency, primary immunodeficiencies (e.g. chronic granulomatous disease, hyper-IgE syndrome) should be considered in affected infants with recurrent cutaneous or extracutaneous infections. Systemic antibiotics, correction of the child's nutritional state, and elimination of factors encouraging the development of miliaria should be undertaken in the management of this condition.

Neutrophilic Eccrine Hidradenitis

Synonyms: ▪ Chemotherapy-associated eccrine hidradenitis ▪ Drug-associated eccrine hidradenitis

Key features

- Typically occurs following administration of chemotherapy
- Both children and adults can be affected
- Painful erythematous papules and plaques are classically found on the trunk
- Usually resolves within a few days to weeks

Epidemiology and pathogenesis

Neutrophilic eccrine hidradenitis (NEH) is a disorder of the eccrine sweat glands that occurs in both children and adults, but there may be a slight male predominance[40]. It was initially described in patients with acute myelogenous leukemia who had received cytarabine plus an anthracycline and this remains one of the most common clinical scenarios. NEH usually develops 7–14 days after initiating chemotherapy and can follow the administration of other chemotherapeutic agents including bleomycin, decitabine, and cyclophosphamide. It is generally regarded as a cytotoxic process directed at the sweat glands, e.g. via a direct toxic effect of chemotherapeutic drugs that are excreted in the sweat.

In addition, NEH has been reported after zidovudine treatment in HIV patients and following administration of granulocyte colony-stimulating factor, carbamazepine, TNF inhibitors, and targeted anti-cancer therapies including inhibitors of the epidermal growth factor receptor, KIT receptor, and BRAF[41]. In a small number of patients, NEH preceded and was believed to herald a new malignancy (usually acute myelogenous leukemia) or its relapse. An infectious form of NEH has also been described; most of the patients were immunocompromised, and the pathogenic organism (e.g. *Serratia, Enterobacter, S. aureus, Nocardia*) was often identified in tissue culture but not via light microscopy plus special stains of lesional specimens. Lastly, NEH has been observed in otherwise healthy persons.

Clinical features

Clinically, erythematous papules and plaques occur on the trunk and may also affect the extremities and face (Fig. 39.10). Polymorphic lesions, e.g. linear, annular, erythema multiforme-like, of varying sizes



Fig. 39.10 Neutrophilic eccrine hidradenitis. Erythematous plaques on the dorsal hand. *Courtesy Jeffrey P. Callen, MD.*

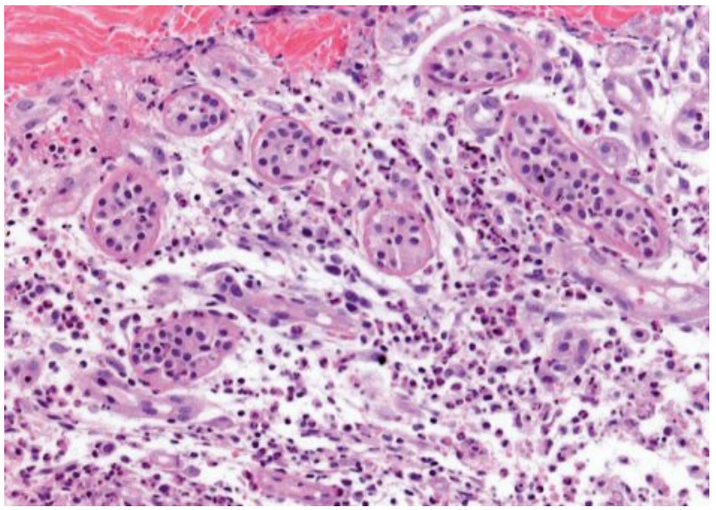


Fig. 39.11 Neutrophilic eccrine hidradenitis – histopathologic features. Neutrophils surround and infiltrate the eccrine glands and coils. There are degenerative changes of primarily secretory cells. *Courtesy Lorenzo Cerroni, MD.*

have been described, some of which were purpuric (typically in association with thrombocytopenia) or pustular. Patients are often febrile and neutropenic in the setting of chemotherapy-associated NEH.

Pathology

Histopathologic evaluation reveals eccrine sweat glands with degenerative vacuolar changes or even necrosis within secretory and (to a lesser degree) ductal cells; the process usually spares the acrosyringium. A neutrophilic inflammatory infiltrate classically accompanies these changes (Fig. 39.11). However, the infiltrate may be sparse or lymphocytic in the setting of chemotherapy-induced neutropenia. Squamous metaplasia of the cuboidal epithelial cells of the eccrine ducts, i.e. eccrine squamous syringometaplasia, is occasionally observed.

Differential diagnosis

The clinical differential diagnosis includes Sweet syndrome and infection, e.g. cellulitis, bacterial or fungal emboli. The histopathologic features of both NEH and eccrine squamous syringometaplasia can be seen in a number of chemotherapy-related entities including acral erythrodysesthesia and intertriginous eruption associated with chemotherapy. Toxic erythema of chemotherapy has been proposed as an overarching term for this spectrum of disorders[42] (see Ch. 21).

Treatment

The eruption of NEH is usually self-limited and resolves several days to weeks after cessation of chemotherapy, but may recur with subsequent cycles[34]. Because NEH usually arises in the setting of fever and neutropenia, empiric antimicrobial therapy is frequently administered until the possibility of infection is excluded. Corticosteroids seem to shorten the duration of the lesions and relieve the pain in some patients. Dapsone can be beneficial in treating NEH and preventing recurrences[42].

Idiopathic Palmoplantar Hidradenitis

Synonyms: ■ Palmoplantar eccrine hidradenitis ■ Recurrent palmoplantar hidradenitis

Key features

- Occurs primarily in otherwise healthy children
- Sudden onset of painful nodules on the palms and/or soles
- Resolves spontaneously within a few days to weeks, but may be recurrent



Fig. 39.12 Idiopathic palmoplantar hidradenitis. Erythematous papulonodules on the plantar surface. *Courtesy Michael L. Smith, MD.*

Idiopathic palmoplantar hidradenitis is primarily a disease of children and is not associated with any underlying medical conditions or medications[43]. Its onset is often preceded by vigorous physical activity. The proposed pathomechanism involves eccrine gland rupture due to mechanical and thermal trauma.

This disorder is characterized by the sudden onset of multiple, tender, erythematous nodules on the soles and less often the palms (Fig. 39.12). Neutrophilic infiltration of the secretory and ductal components of the coiled portion of the sweat glands is seen in biopsy specimens. This infiltrate is distinctly nodular, and neutrophilic abscesses may be observed. Eccrine squamous syringometaplasia is usually absent. The differential diagnosis includes the "pseudomonas hot-foot syndrome", panniculitis (e.g. erythema nodosum), pernio, and vasculitis (e.g. polyarteritis nodosa). Some have suggested that the entity "traumatic plantar urticaria" belongs within the spectrum of idiopathic palmoplantar hidradenitis.

Spontaneous resolution in a matter of days to weeks is the rule, although recurrent attacks occur in as many as half of affected children.

Granulosis Rubra Nasi

Key features

- Hyperhidrosis of the nose is followed by macular erythema; papules and vesicles can also develop
- The process may extend to the cheeks, lips, and upper chin
- Onset is during the first decade of life and usually resolves by puberty
- Autosomal dominant transmission

Granulosis rubra nasi is a rare inherited condition. It generally appears during childhood (peak incidence between ages 7 and 12 years), but adolescent or adult onset is possible. The etiology and pathogenesis of this disorder have not been elucidated. An autosomal dominant inheritance pattern has been described.

Hyperhidrosis of the tip of the nose may be present for years before the characteristic erythema develops on the nose; the latter can extend to the cheeks, chin, and upper lip. The entire area of erythema displays excessive sweating. Papules, sweat droplets, and vesicles may form at the orifices of the eccrine ducts. Cystic lesions can also develop and the nose may be cold. It may itch but is not painful. Primary hyperhidrosis of the palms and soles is a common concomitant finding, as is poor peripheral circulation with pernio or acrocyanosis. Granulosis rubra nasi usually resolves at puberty but may continue into adulthood.

Histopathologically, dilation of dermal blood and lymphatic vessels with mild inflammation around and within dilated sweat ducts (at times simulating a hidrocystoma) are seen. The epidermis, connective tissue, and pilosebaceous apparatus are otherwise normal and no heterotopic apocrine glands are found. No associated systemic disease or abnormal laboratory findings have been described.

The differential diagnosis includes rosacea, acne vulgaris, periorificial dermatitis, lupus pernio, and lupus erythematosus. Treatment can be disappointing and is limited to drying lotions, perhaps botulinum toxin injections or topical tacrolimus, and reassurance that the disorder typically resolves spontaneously at puberty.



Fig. 39.13 Keratolysis exfoliativa. Small annular collarettes of scale on the palm. *Courtesy Jean L. Bolognia, MD.*

Keratolysis Exfoliativa

Synonyms: ▪ Lamellar dyshidrosis ▪ Recurrent focal palmar peeling ▪ Dyshidrosis lamellosa sicca

Key features

- Superficial desquamation of the palms and occasionally the soles
- Non-inflammatory
- Treat with keratolytics

Keratolysis exfoliativa is a common, asymptomatic, superficial desquamative process of palmar and less often plantar skin; it usually worsens in warm weather and is occasionally associated with hyperhidrosis. Keratolysis exfoliativa is seen in healthy adults and possibly reflects low-grade damage to the thick stratum corneum of volar skin. Concurrent irritant dermatitis may also be present, and some cases may resemble or merge with pompholyx. Maceration may also be a pathogenic influence, although hyperhidrosis is not a regular feature.

Clinically, it appears as an irregular annular or circinate pattern of scaling, 2 to 15 mm in diameter (Fig. 39.13). There are no antecedent or concurrent vesicles or papules, and no fungi are recoverable from the lesions. Treatment is disappointing. Humectant and keratolytic topical products containing urea, ammonium lactate, or salicylic acid (5%–6%) may be helpful. Topical corticosteroids are not useful unless there is associated dermatitis.

Grover Disease (see Ch. 87).

DISORDERS OF THE APOCRINE SWEAT GLAND

Fox–Fordyce Disease

Synonym: ▪ Apocrine miliaria

Key features

- Caused by plugging of the apocrine sweat glands
- Occurs primarily in women 15–35 years of age
- Skin-colored follicular papules develop in the axillary, anogenital, and periareolar areas
- May be intensely pruritic

Epidemiology and pathogenesis

Fox–Fordyce disease is a chronic, pruritic disorder of the apocrine glands. It most commonly affects women between the ages of 15 and 35 years and usually remits after menopause.



Fig. 39.14 Fox–Fordyce disease. **A** Monomorphic skin-colored papules in the axillary vault, many of which are dome-shaped (inset). **B** Monomorphic hyperpigmented follicular papules with a central keratotic plug in the axillary vault. *A, Courtesy Jean L. Bolognia, MD; B, Courtesy Kalman Watsky, MD.*

The etiology of Fox–Fordyce disease is unknown, but hormonal factors are thought to play a role. Emotional and physical stimuli may also have a role in the disease course. It has occurred following the trauma of laser hair removal[44].

Clinical features

Fox–Fordyce disease presents as dome-shaped, skin-colored, discrete perifollicular papules within the axillary (Fig. 39.14), anogenital, and periareolar skin. Less common locations include the medial thighs, periumbilical area and sternal region. Loss of hair in affected areas is frequently observed. The condition is often intensely pruritic. Pregnancy and oral contraception may ameliorate the itching, while heat and emotional stress can aggravate symptoms.

Pathology

Early histologic findings of Fox–Fordyce disease include a keratin plug in the follicular infundibulum, which obstructs the entrance of the apocrine duct. This blockage leads to apocrine sweat retention and subsequent rupture of the duct at the level of the epidermis. Epidermal spongiosis and vesiculation are seen. Associated findings include a perifollicular and periadnexal mixed inflammatory infiltrate as well as perifollicular foam cells with PAS-positive cytoplasm, representing apocrine secretion material.

Treatment

Treatment of Fox–Fordyce disease is difficult. Topical and intralesional corticosteroids are often a first-line therapy, although their use may be limited by the risk of cutaneous atrophy. Topical calcineurin inhibitors may reduce pruritus and improve the appearance of skin lesions. Topical tretinoin has been shown to reduce pruritus, but has little effect on the clinical appearance of the disease and may produce irritation. Twice-daily clindamycin lotion may also be useful in minimizing symptoms. Some women respond to oral contraceptives, while other patients receive temporary relief from oral isotretinoin. Physical interventions that may be beneficial include phototherapy, electrocautery, and excision of periareolar skin.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 39.1 Sweating pattern in axillary hyperhidrosis. Blue–black areas represent foci of sweating, as demonstrated by the starch–iodine technique: iodine solution (e.g. 3.5% in alcohol) is applied to clean, shaved skin and allowed to dry, then starch powder (e.g. cornstarch) is brushed onto the area. *Courtesy Harry Hurley, MD*.



eFig. 39.2 Miliaria rubra. Multiple erythematous non-follicular papules and papulovesicles on the back.



eFig. 39.3 Severe keratolysis exfoliativa. Annular and figurate collarettes of scale of varying size on the plantar surface. *Courtesy Kalman Watsky, MD*.

Autoantibodies Encountered in Patients with Autoimmune Connective Tissue Diseases

40

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Key features

- Autoantibodies can play an important role in the diagnosis, management, and prognosis of autoimmune connective tissue diseases (AI-CTDs)
- The classic anti-nuclear antibody (ANA) assay remains the entrée into the world of AI-CTD serology, and understanding its limitations is critical for clinical decision-making
- While many autoantibodies are not disease-specific, certain autoantibodies have significant disease specificity and therefore are of diagnostic value
- Anti-dsDNA and anti-Smith (Sm) antibodies have high specificity for systemic lupus erythematosus (SLE)
- Anti-Mi-2, -TIF1-γ, -MDA5, -NXP-2, and -SAE antibodies are associated with different forms of dermatomyositis
- Anti-Jo-1 antibodies can be detected in antisynthetase syndrome
- Anti-topoisomerase-1 (Scl-70), -RNA polymerase III, and -centromere antibodies are associated with different clinical forms of systemic sclerosis
- Cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) are often detected in granulomatosis with polyangiitis

INTRODUCTION

Autoimmune connective tissue diseases (AI-CTDs) represent polygenic clinical disorders with heterogeneous and overlapping clinical features. AI-CTDs are characterized by an immune dysregulation that includes the production of antibodies to self-antigens, termed autoantibodies (aAb). When considering the diagnosis of an AI-CTD, the most commonly requested laboratory test is the measurement of anti-nuclear antibodies (ANA). ANA are defined as aAb that target primarily nuclear components, including DNA or small nuclear ribonucleoproteins (snRNP). Elevated ANA titers are seen in multiple AI-CTDs and they reflect inflammatory processes within tissue but rarely have pathogenic potential.

Clinical laboratory testing for ANA is essential in the diagnosis and management of AI-CTD patients[1]. Each AI-CTD has aAb that are quite specific to the particular disorder as well as aAb that are shared with other diseases. Although AI-CTDs are usually distinct clinical entities, some patients may have overlapping features of two or more AI-CTDs and, as a result, an overlap in their pattern of aAb production (Fig. 40.1). Familiarity with the actual serologic tests and the disease associations of the various aAb allows one to maximize the clinical utility of aAb testing.

This chapter discusses aAb associated with AI-CTDs that have cutaneous manifestations in addition to historical and technical aspects of ANA assays. Tables 40.1–40.4 summarize the molecular identity of the various autoantigens and their clinical associations. The prevalence of the aAb in these tables represents the estimated median values reported from different cross-sectional studies using conventional clinical laboratory testing procedures. However, the results of such studies can vary widely. In addition, there can be complex relationships between the presence and relative amounts of aAb, disease diagnosis, and prognosis. Because understanding the basic principles of aAb laboratory tests such as sensitivity and specificity assists in interpreting assay results, they are also reviewed. Chapters 4, 23, and 24 discuss the related subjects of circulating immune complexes and cryoglobulins while Chapters 41–45 contain an in-depth discussion of the various AI-CTDs.

HISTORICAL PERSPECTIVE

One can better appreciate the evolution of thought in this area by considering the changes in methodologies used to identify aAb that have occurred over time[2]. In 1948, the bone marrow from a patient with SLE was noted to contain polymorphonuclear neutrophils that had phagocytosed nuclear material from degenerated cells. The presence of these cells became an indicator of SLE (SLE cell phenomenon)[3] and occurred in the presence of antibodies to DNA.

Approximately 10 years later, indirect immunofluorescence techniques were used to detect ANA, with the fluorescent anti-nuclear antibody (FANA) test providing a more sensitive assay for SLE. Another decade later, the Ouchterlony double immunodiffusion (DID) technique was used to identify and define precipitating serum aAb that reacted with saline extractable nuclear antigens (ENA) such as nuclear ribonucleoprotein (nRNP), Sm, SSA/Ro, and SSB/La[4].

In 1979, the molecularly and genetically defined ANA era began as the result of work by Lerner and Steitz, who employed immunodiffusion and Western blotting to define the molecular identities of the nRNP and Ro/La families of ribonucleoprotein autoantigens. These observations generated the notion that aAb might be more efficiently and cost-effectively assayed by using purified or recombinant forms of the different autoantigens in solid-phase immunoassays. An example of the latter is the *e*nzyme-*l*inked *i*mmuno*s*orbent *a*ssay (ELISA). While less expensive and more convenient, there are some drawbacks to employing ELISA and related immunoassay techniques to detect ANA, e.g. increased sensitivity and decreased specificity for aAb such as anti-SSA/Ro and anti-dsDNA antibodies. Newer multiplex techniques (e.g. solid-phase multiplex bead assays, proteome microarrays, Luminex® xMAP® technology) are now widely used and allow the simultaneous profiling of all relevant aAb in a patient. The principles of these assays are shown in Fig. 40.2, and their limitations are discussed in a recent review[5].

THE FLUORESCENT ANTI-NUCLEAR ANTIBODY (FANA) TEST

Although there is debate about its role in the diagnosis and management of AI-CTD, the classic fluorescent ANA assay (i.e. FANA test) is still the most clinically efficient screening test for systemic autoimmune disorders[6]. The ANA assay identifies antibodies present in serum that bind to autoantigens present in the nuclei (or cytoplasm) of mammalian cells. Both the pattern, which reflects the localization of the autoantigen, and the titer are reported. The reported titer represents the last dilution at which the ANA pattern is detectable and a titer of ≥1 : 40 is considered "positive". For the FANA test, almost all clinical laboratories currently employ a human tumor cell line such as HEp-2 for the nucleated cell substrate. aAb are detected with fluorochrome-conjugated antibodies that bind human immunoglobulin (the aAb) bound to nuclei in the HEp-2 cells (see Fig. 40.2A).

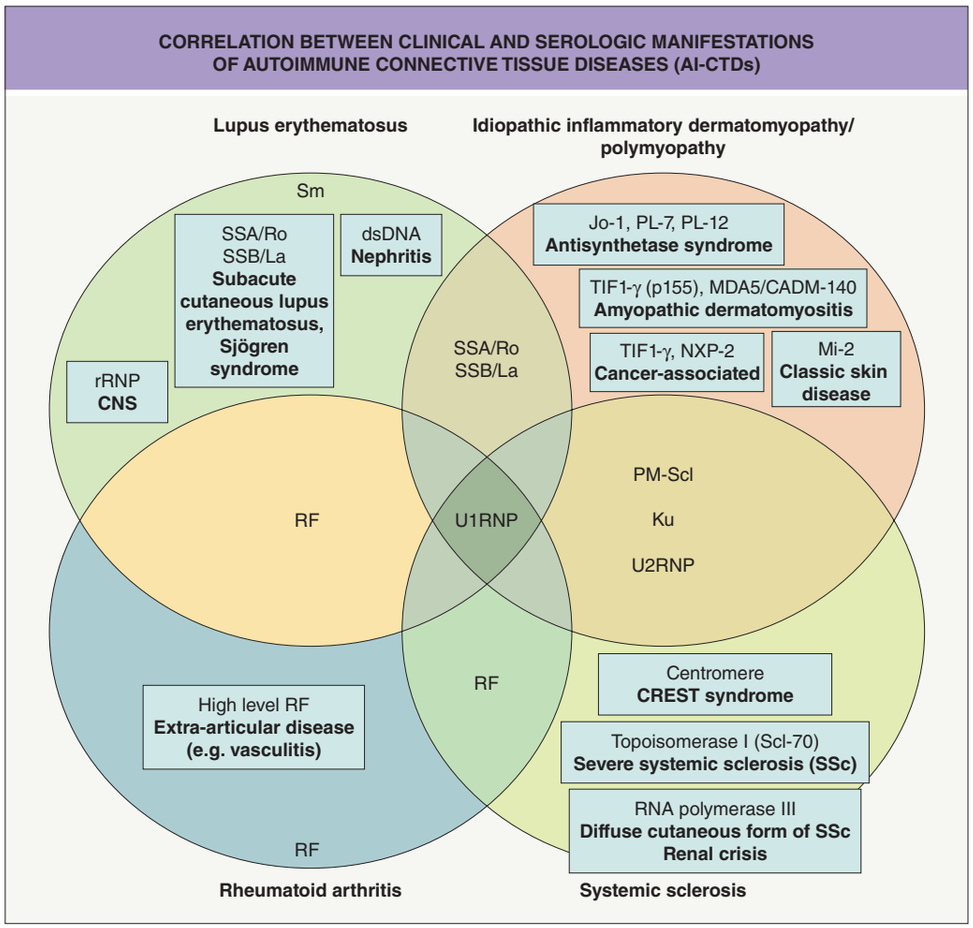


Fig. 40.1 Correlation between clinical and serologic manifestations of autoimmune connective tissue diseases (AI-CTDs). Venn diagram representation of major clinico-serologic correlations in the primary AI-CTDs that impact the skin. Some targets of autoantibodies are specific (boxed with clinical associations) while others are seen in the context of overlapping clinical features. High levels of U1RNP autoantibody with overlapping features of all four of these AI-CTDs defines the concept of mixed connective tissue disease. CADM, clinically amyopathic dermatomyositis; MDA5, melanoma differentiation-associated protein 5; p155, a 155 kDa polypeptide; RF, rheumatoid factor; RNP, ribonucleoprotein, TIF1-γ, transcriptional intermediary factor 1-gamma.

Earlier versions of the ANA assay utilized rodent cell lines that lack some of the autoantigens present in human cell nuclei (e.g. SSA/Ro). Thus, sera from SLE patients could be negative when assayed on rodent cells, especially if the predominant aAb were anti-SSA/Ro (i.e. "ANA-negative SLE"). In the past, this occurred in up to 15% of SLE patients, particularly those enriched in anti-SSA/Ro aAb-associated disorders such as subacute cutaneous LE (SCLE) and Sjögren syndrome (SjS). With the use of human HEp-2 cells, only ~1%–2% of SLE patients are ANA-negative, and "ANA-negative SLE" has almost become a historical phenomenon.

An important caveat is that the *titer* (which reflects the serial serum dilutions necessary for fluorescence to disappear) depends upon subjective interpretation by a laboratory technician. Consequently, a single serum specimen can have an ANA titer result that varies within a two-tube dilution range. In other words, a serum sample reported as having an ANA titer of 1:320 might be read as 1:160 or 1:640 upon repeat testing in the same laboratory. Although the World Health Organization tried to standardize reporting of ANA results with an international unit system (e.g. 1 IU rather than a titer of 1:160), many laboratories continue to report ANA results using a titer system. Of note, while an ANA titer of ≥1:40 is considered "positive", the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria require a titer of ≥1:80 for the diagnosis of SLE (see Table 41.5).

Automated Immunoassays – Solid Phase and Bead-Based Multiplex

Automated systems have been introduced to decrease variability and increase cost-effectiveness (see Fig. 40.2B,C); however, pattern reporting remains an issue[7]. In addition, concerns exist that the results from the FANA assay may not be comparable to those of ELISA- or multiplex bead-based assays. While the FANA test has a consistently high sensitivity, this can be more variable amongst different ELISA or bead-based assays, likely due in part to the requirement of the latter to have predefined antigen combinations for ANA identification. Use of such predetermined antigen combinations is not a component of the FANA test.

Compared to the quantitative ELISA, multiplex bead-based assays have reduced labor requirements and increased throughput, but require specialized equipment. The FANA assay has the drawback of requiring significant experience for proper interpretation as well as the need for subsequent tests for antigen identification and quantitation.

"Normal" Versus "Abnormal" ANA Titers

The ANA titer may vary significantly, depending upon how the assay is performed and interpreted (see above). Major commercial laboratories typically report three ANA categories: (1) negative (titer <1:40); (2) equivocal (1:40 to 1:80); and (3) positive (>1:80). However, some laboratories will record an ANA titer of 1:40 as abnormal, presumably because accepting such low levels of ANA as being abnormal retains a high degree of *sensitivity* in detecting systemic AI-CTD. However, using such low ANA titer cut-offs can lead to positive, but clinically insignificant, ANA test results; i.e., it reduces specificity. Several studies that have compared ANA results in SLE populations with those in normal control populations have indicated that a titer of <1:160 has little clinical utility. For example, in one report based upon 15 international laboratories, the ANA positivity rate in a population of healthy individuals (ages 20–60 years) was 13% at 1:80, 5% at 1:160, and 3% at 1:320[8]. Elevated ANA titers can be observed in the elderly, relatives of those with SLE, and patients with other autoimmune disorders (e.g., autoimmune thyroid disease), as well as in healthy individuals. Potential pitfalls when interpreting the results of ANA assays are summarized in Table 40.5.

Immunofluorescence Patterns

Various patterns of nuclear immunofluorescence can be observed in the FANA test (Fig. 40.3): homogeneous (syn. diffuse), peripheral (syn. rim), speckled (syn. particulate), nucleolar, and centromeric (syn. discrete speckled). Except for the centromeric pattern, these patterns

AUTOANTIBODIES ASSOCIATED WITH LUPUS ERYTHEMATOSUS			
Target	**Median prevalence***	**Molecular specificity**	**Clinical associations**
High specificity for SLE			
dsDNA	60%–90%	Double-stranded (native) DNA	LE nephritis and monitoring activity of nephritis
Sm	10%–30% of White population 30%–40% of Asians and African-Americans	Spliceosome RNP – RNP particles involved in splicing pre-mRNA	Renal, neurologic, and hematologic involvement
rRNP	7%–15% 40% of Asians	Ribosomal P proteins – involved in ribosome function	Neuropsychiatric LE
Low specificity for SLE			
ANA (most common IF patterns: homogeneous, peripheral)	99%		
ssDNA	70%–95%	Denatured DNA	Possible risk for SLE in DLE patients; also seen in RA, DM/PM, MCTD, SSc, SjS, morphea
Histones	30%–70%	Histones	Drug-induced SLE; also occur in SLE, RA, and SSc with pulmonary fibrosis (in conjunction with other aAb)
C1q	20%–50% Nearly 100% of patients with active lupus nephritis	C1q component of complement	LE nephritis, severe SLE, hypocomplementemic urticarial vasculitis syndrome
U1RNP	30%–50%	Spliceosome RNP	Overlapping features with other AI-CTDs; MCTD (100%)
SSA/Ro	30%–50%†	Ro60 (60 kDa protein): hYRNP – quality control function for misfolded RNA molecules Ro52 (52 kDa protein): also known as TRIM21 – interferon-inducible protein with ubiquitin modifying function	SCLE (75%–90%), neonatal LE/congenital heart block (99%), SCLE–SjS overlap, primary SjS (70%); in SjS associated with vasculitis
SSB/La	10%–20%	hYRNP	SCLE (30%–40%), SCLE–SjS overlap, primary SjS (40%); occurs in conjunction with SSA/Ro
Cardiolipin	IgM: 20%–75% IgG: 15%–30%‡	Cardiolipin – a negatively charged phospholipid	Recurrent spontaneous abortions, thrombocytopenia, and hypercoagulable state in SLE (cutaneous manifestations include livedo reticularis, leg ulcers, acral infarction/ulceration, hemorrhagic cutaneous necrosis); similar associations in primary antiphospholipid antibody syndrome (APS); clinical manifestations have strongest association with IgG class of anti-cardiolipin aAb
β2 glycoprotein I	IgM: 10%–35% IgG: 8%–25%‡	An important cofactor for cardiolipin in cardiolipin aAb assays	Relatively high risk of thrombosis in SLE and primary APS
"Non-criteria" phospholipids	Phosphatidylserine IgG: 20% of SLE patients with thrombosis Phosphatidylinositol IgG: 20% of SLE patients with thrombosis Phosphatidylcholine: rare Phosphatidylethanolamine: rare Annexin V: rare	Negatively charged phospholipids	Clinical significance remains under investigation; not currently included in SLE or APS clinical criteria
Rheumatoid factor	25%	Fc portion of IgG	Nonspecific
Ku	10%	DNA end-binding repair protein complex	Overlap with other AI-CTDs such as DM/PM, SSc
Alpha-fodrin	10%	An actin-binding protein found at the periphery of chromaffin cells that may be involved in secretion	SjS

*Based on most common assay techniques currently employed in clinical immunology laboratories.
†Refers to SSA/Ro antigen detection as a whole and not Ro52 or Ro60 subsets; see text for specific Ro52 and Ro60 associations.
‡Range depending on 99th or 90th percentile assay cut-off.

Table 40.1 Autoantibodies associated with lupus erythematosus. aAb, autoantibody; AI-CTDs, autoimmune connective tissue diseases; ANA, anti-nuclear antibodies; DLE, discoid lupus erythematosus; DM/PM, dermatomyositis/polymyositis; IF, immunofluorescence; LE, lupus erythematosus; MCTD, mixed connective tissue disease; PCNA, proliferating cell nuclear antigen; RA, rheumatoid arthritis; RNP, ribonucleoprotein; SCLE, subacute cutaneous lupus erythematosus; SjS, Sjögren syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis. Adapted from references 2, 16, 51–53.

AUTOANTIBODIES ENCOUNTERED IN THE IDIOPATHIC INFLAMMATORY DERMATOMYOPATHIES			
Target	**Median prevalence***	**Molecular specificity**	**Clinical associations**
High specificity for DM/PM			
Mi-2	Classic DM: 10%–35% Juvenile DM: 4%–10%	Helicase nuclear protein	• Gottron papules/sign, shawl sign, cuticular telangiectasias, cuticular overgrowth/dystrophy • Favorable response to therapy and better prognosis
TIF1-γ (p155)	Classic DM: 10%–30% Clinically amyopathic: 20%–45% Classic DM in Japanese adults: 50% Juvenile DM: 20%–35%	p155: transcriptional intermediary factor 1 gamma (TIF1-γ) p140: TIF1-α	• Clinically amyopathic DM • In adult-onset classic DM, increased risk of malignancy • Extensive photosensitive cutaneous disease • Mucocutaneous findings include palatal erythema ("ovoid patches"), psoriasiform lesions, and hypopigmented and telangiectatic ("red on white") patches • In juvenile DM, associated with treatment-refractory disease, ulcerations, and chronic course
MDA5/CADM-140	Classic DM: 10%–15% In adult Japanese: • classic: 10%–45% • clinically amyopathic: 70%–85% • Juvenile DM: 5%–10%	Melanoma differentiation-associated protein 5 (MDA5)/clinically amyopathic DM-140 kDa molecule/IFN-induced with helicase C domain protein 1 (IFIH1)	• Clinically amyopathic DM • Rapidly progressive interstitial lung disease • Cutaneous ulcerations with associated vasculopathy, tender palmar papules, oral pain and ulceration • In juvenile DM, milder muscle disease, mucocutaneous ulcerations, and interstitial lung disease
ARS	Jo-1: 15%–30% PL-7: ≤5% PL-12: ≤5% OJ, EJ, KS, ZO, YRS: rare	Aminoacyl tRNA synthetases (ARS), e.g. Jo-1 targets histidyl tRNA synthetase	• Antisynthetase syndrome with fever, myositis, polyarthritis, Raynaud phenomenon, interstitial lung disease
NXP-2 (p140)	Adult DM: 5%–25% (varies by ethnicity, most common in White population) Juvenile DM: 20%–25%	Nuclear matrix protein 2 (MORC family CW-type zinc finger 3 [MORC3])	• In adult DM, associated with malignancy, subcutaneous edema, and calcinosis • In juvenile DM, more severe muscle disease and calcinosis
SAE	1%–8%	SUMO activation enzyme – posttranslational modification of proteins that are critical for subcellular localization	• Severe cutaneous disease, progressive muscle disease, dysphagia
SRP	1%–8%	Signal recognition particle – intracytoplasmic protein translocation	• Fulminant DM/PM • Cardiac involvement
Low specificity for DM/PM			
ANA (most common IF patterns: speckled, nucleolar)	40%		• Clinically amyopathic DM (65%)
ssDNA	40%	Single-stranded DNA	• SLE, SSc, morphea
PM-Scl (PM-1)	10%	Ribosomal RNA processing enzyme	• Overlap with SSc
SSA/Ro (especially Ro52)	15%	hYRNP	• Overlap with SjS, SCLE, neonatal LE/CHB, SLE
U1RNP	10%	Spliceosome RNP	• Overlap with other AI-CTDs
Ku	3%	DNA end-binding repair protein complex	• Overlap with SSc
U2RNP	1%	Spliceosome RNP	• Overlap with SSc
*Using current assay techniques.			

Table 40.2 Autoantibodies encountered in the idiopathic inflammatory dermatomyopathies (DM/PM). Rarely, patients develop specific aAb targeting Fer (elongation factor 1-α) and Mas (small RNA). ANA, anti-nuclear antibodies; ARS, aminoacyl tRNA synthetase; CADM, clinically amyopathic DM; CHB, congenital heart block; DM/PM, dermatomyositis/polymyositis; IF, immunofluorescence; IFN, interferon; LE, lupus erythematosus; RNP, ribonucleoprotein; SCLE, subacute cutaneous lupus erythematosus; SjS, Sjögren syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis. Adapted from references 2, 32, 36, 54–57.

have little disease specificity and are of little value in the management of patients. The centromeric pattern reflects the binding of aAb to the polypeptide components of chromosomal centromeres (e.g. CENP-B) and is associated primarily with the limited form of SSc (see Table 40.3). A peripheral pattern can be suggestive of aAb to DNA, including dsDNA. The nucleolar pattern is due to aAb binding to ribosomal RNA processing molecules such as fibrillarin and can be indicative of SSc. A speckled pattern is due to various antibodies, including those that recognize Sm, RNP, SSA/Ro, SSB/La, Sc1-70, and RNA polymerases (RNAP). Nowadays, commercial laboratories often report primarily homogeneous and speckled staining patterns because they commonly occur in healthy and older individuals. As a result, a higher threshold (e.g. ≥1 : 160) may need to be considered for determining whether a titer is clinically relevant. In general, ANA patterns have been replaced by specific tests for nuclear and cytoplasmic antigens.

Clinical Utility of the ANA Assay

Key concepts in laboratory testing – sensitivity, specificity, positive predictive value, and negative predictive value – are presented in Fig. 40.4[9]. These concepts should be kept in mind when considering the cost–benefit ratio of laboratory testing for AI-CTD. The ANA test is used most often for the diagnosis of SLE. In SLE patients, its sensitivity and specificity are 98% and 90%, respectively[10], but in unselected patients, the positive predictive value for SLE detection is 30%–40%, while the negative predictive value is 99%. Thus, about

AUTOANTIBODIES ASSOCIATED WITH SYSTEMIC SCLEROSIS (SSc)				
Target	**SSc, all***	**SSc with diffuse cutaneous scleroderma***	**SSc with limited cutaneous scleroderma (CREST syndrome)***	**Clinical features**
High specificity for SSc				
Centromere (CENP-B)	20%–40%	30%	80%	Better prognosis; pulmonary arterial hypertension
DNA topoisomerase I (formerly Scl-70; DNA-unwinding enzyme)	15%–40%	60%	15%	Worse prognosis; pulmonary fibrosis
RNA polymerase III	5%–30%	45%	6%	Worse prognosis; aAb levels correlate with extent of skin involvement and renal disease; malignancy association, especially breast cancer
Th/To RNP (mitochondrial enzyme)	1%–15%	10%	20%	Worse prognosis; limited pulmonary fibrosis
Fibrillarin (U3RNP, spliceosome RNP)	5%–10%			Worse prognosis; cardiac, renal involvement
RNPC-3 (U11/U12RNP, spliceosome RNP)	3%			Worse prognosis; pulmonary fibrosis, GI involvement, Raynaud phenomenon, malignancy association
Low specificity for SSc				
ANA	95%*			
Angiotensin type 1/Endothelin-1 type A receptors	80%			
PDGFR (expressed on fibroblasts)†	30%–100%			
Endothelial cells (activation and apoptosis)	45%–85%			
MMP-1 and 3 (degrade ECM proteins; aAb prevents degradation)	50%	70%	33%	
HMG (non-histone nucleosomal protein)		30%	40%	
Fibrillin-1 (component of ECM)	>50%			
Histones	40%			
ssDNA	10%–30%			
Rheumatoid factor	25%			
PM-Scl	5%–10%		More commonly associated with limited SSc	Better prognosis; overlap with DM/PM
U1RNP (spliceosome RNP)	2%–15%		More commonly associated with limited SSc	Better prognosis; overlap with MCTD

*Median prevalence using current assay techniques.
†Results vary, depending upon study; evidence that aAb do not activate the receptor; seen in up to 20% of controls.

Table 40.3 Autoantibodies associated with systemic sclerosis (SSc). The hallmark aAb of SSc are shaded in orange. ANA, anti-nuclear antibodies; ECM, extracellular matrix; HMG, high mobility group; IF, immunofluorescence; MCTD, mixed connective tissue disease; PDGFR, platelet-derived growth factor receptor; RNP, ribonucleoprotein; RNPC-3, RNA binding region (RNP1, RRM) containing 3. Adapted from references 2, 49, 50, and 58.

two-thirds of the positive ANA levels observed in a general medical population will be associated with disorders other than SLE, and only very rarely will a person with a negative ANA have SLE. Positive ANA tests are also seen in a large percentage of patients with other AI-CTDs: SSc – 90%; SjS – 70%; and idiopathic inflammatory dermatomyopathies – 40%–65%. There are numerous clinical associations for a positive ANA test[11], and it is noteworthy that clinically silent systemic autoimmune diseases (e.g. autoimmune thyroiditis, pernicious anemia, Addison disease) can contribute to a positive ANA in patients with autoimmune dermatologic disorders such as vitiligo and alopecia areata.

Clinical Value of aAb in Diagnosis, Prognosis, and Disease Activity Monitoring

In everyday practice, these laboratory tests can be used to: (1) establish the diagnosis of an AI-CTD; (2) provide prognostic information; and (3) in specific instances, monitor the level of activity of an AI-CTD[10]. For example, the Sm aAb is highly specific for SLE and thus has considerable diagnostic value. However, the absolute amounts of anti-Sm aAb present in a patient at different time points do not correlate strongly enough with SLE disease activity to have practical clinical value in patient management. Likewise, there is not much value in serial determinations of ANA titers when monitoring disease activity in SLE. However, a few aAb can be used for establishing the diagnosis and monitoring systemic activity, e.g. anti-dsDNA in LE nephritis and cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) in granulomatosis with polyangiitis. Some aAb can even provide prognostic information, e.g. anti-RNAP aAb are a risk factor for developing renal crisis in patients with systemic sclerosis.

"Sontheimer's Corollary" to Greenwald's Law of Lupus

Robert A. Greenwald formulated a law stating that if a patient is diagnosed as having SLE, everything that happens to that patient afterward, rightly or wrongly, is attributed to SLE. Richard D. Sontheimer formulated a corollary to Greenwald's law, stating that anything happening to a patient with a positive ANA that is not immediately otherwise explicable will automatically be blamed on SLE[12]. This is especially true in patients presenting with non-lupus photosensitive facial eruptions (e.g. rosacea, polymorphic light eruption, photoallergic contact dermatitis) who might also have a positive ANA test for reasons other than SLE[13].

AUTOANTIBODIES ASSOCIATED WITH OTHER RHEUMATIC DISEASES HAVING CUTANEOUS MANIFESTATIONS			
Autoantibody	**Median prevalence***	**Molecular specificity**	**Clinical associations**
Rheumatoid arthritis			
Rheumatoid factor	80%	Fc portion of IgG	*Low levels*: very nonspecific (healthy elderly individuals, SLE, SSc, MCTD, neoplasia, chronic infections, chronic inflammatory lung diseases, chronic liver disease, sarcoidosis, systemic vasculitides) *High levels*: associated with erosive, crippling RA (25%–90%) and extra-articular manifestations of RA, e.g. systemic vasculitis (i.e. peripheral neuropathy, cutaneous vasculitis); mixed cryoglobulinemia secondary to hepatitis C infection (types II, III; 40%–100%); SjS
Anti-cyclic citrullinated protein (CCP) antibodies	70%	Citrullinated proteins in the skin (e.g., filaggrin) and joints	Increased severity of RA, including radiologic progression of erosive arthritic changes; predictor for the development of RA
Sjögren syndrome			
Alpha-fodrin	70%	An actin-binding protein found at the periphery of chromaffin cells that may be involved in secretion	More specific for SjS than anti-SSA/Ro aAb; also seen in SLE
SSA/Ro	60%	hYRNP	SLE, SCLE, neonatal LE/CHB
SSB/La	20%	hYRNP	SLE, SCLE, neonatal LE/CHB
Mixed connective tissue disease (MCTD, Sharp syndrome)			
U1RNP†	100%‡	Spliceosome RNP	Raynaud phenomenon, swollen hands with sausage-like swelling of digits, polyarthritis, myositis, inverse association with nephritis

*Using current assay techniques.
†In MCTD, associated with high-titer ANA and lack of other aAb.
‡By definition at time of diagnosis.

Table 40.4 Autoantibodies associated with other rheumatic diseases having cutaneous manifestations. More in-depth information concerning clinico-serologic associations can be found elsewhere[8,10,16,59]. aAb, autoantibodies; CHB, congenital heart block; LE, lupus erythematosus; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; RNP, ribonucleoprotein; SCLE, subacute cutaneous lupus erythematosus; SjS, Sjögren syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Phototherapy and ANA

The question of ANA and anti-SSA/Ro antibody testing often arises in patients being considered for phototherapy, especially if there is any concern about an underlying photosensitive state. However, when screening patients for a multisystem autoimmune disease such as SLE, it is a good rule to remember that patients having any degree of clinically significant SLE are virtually never asymptomatic. Symptoms such as easy fatigability, malaise, and arthralgias are almost always present. In addition, studies have shown that phototherapy protocols such as PUVA or NB-UVB do not significantly induce the appearance of ANA and other aAb[14]. Consequently, while a thorough history, review of systems, and physical examination are indicated in all patients prior to phototherapy, ANA testing is not, unless there is a consistent history or suggestive physical findings.

How Does One Evaluate a Positive ANA Result in a Patient Suspected of Having SLE?

This question would likely be answered differently depending upon the specialist. Dermatologists usually see a highly selected population of LE patients by virtue of their having some form of cutaneous involvement that at times can be the only significant clinical manifestation of the autoimmune disease process (e.g. chronic or subacute cutaneous LE). Therefore, compared to rheumatologists evaluating a patient with suspected SLE, a more focused approach can be undertaken by dermatologists evaluating a positive ANA in a patient who has or is suspected of having cutaneous LE (Fig. 40.5).

AUTOANTIBODIES IN LUPUS ERYTHEMATOSUS

Over 180 LE-associated aAb have been described[15]. Table 40.1 summarizes aAb that are highly specific for SLE as well as less specific aAb that occur in both SLE and other AI-CTD[16]. For example, aAb to dsDNA and Sm are quite specific and the presence of either one represents six points in the EULAR/ACR classification criteria for SLE (see Table 41.5)[17]. The 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification also includes both of these aAb in their immunologic criteria for SLE (see Table 41.4)[18]. Both the EULAR/ACR and SLICC classifications include antiphospholipid antibodies as a criterion, but these are not specific for SLE.

Anti-dsDNA Antibodies

Rising levels of anti-dsDNA aAb correlate positively with SLE disease activity, especially when associated with falling complement values. High levels can reflect an increased risk for LE nephritis. Unfortunately, the clinical value of anti-dsDNA aAb measurements is somewhat diluted by the characteristics of modern assay techniques. The popular ELISA assays preferentially detect *low-avidity* anti-dsDNA aAb that are also seen in patients who do not have SLE. It is recommended that all positive anti-dsDNA aAb ELISA results be confirmed by a second assay technique that detects *high-avidity* anti-dsDNA aAb, such as the Farr radioimmunoassay or the *Crithidia luciliae* indirect immunofluorescence test (CLIFT)[19,20].

Anti-SSA/Ro and Anti-SSB/La Antibodies

Anti-SSA/Ro and anti-SSB/La aAb were originally thought to react exclusively with cytoplasmic ribonucleoproteins (RNP) and were thus designated as cytoplasmic aAb. However, subsequent studies demonstrated that these aAb react with proteins present in human cytoplasmic RNP (hYRNP) that are found in both the cytoplasm and nucleus. Further investigations detected 52 kDa and 60 kDa Ro antigens (termed Ro52 and Ro60); Ro52 is localized within the cytoplasm, while Ro60 is in the nucleus. $Ro52^{-}Ro60^{+}$ serology has been associated with SLE, $Ro52^{+}Ro60^{+}$ with primary SjS, and $Ro52^{+}Ro60^{-}$ with several autoimmune diseases including inflammatory myositis[21]. Because the Ro and La antigens are present on the same RNP particles, an autoimmune response that develops against one of these autoantigens often spreads to the other. This explains the observation that when one aAb is present in an individual, the other is frequently present as well. However, while anti-SSA/Ro aAb can occur alone, this is extremely rare for anti-SSB/La aAb.

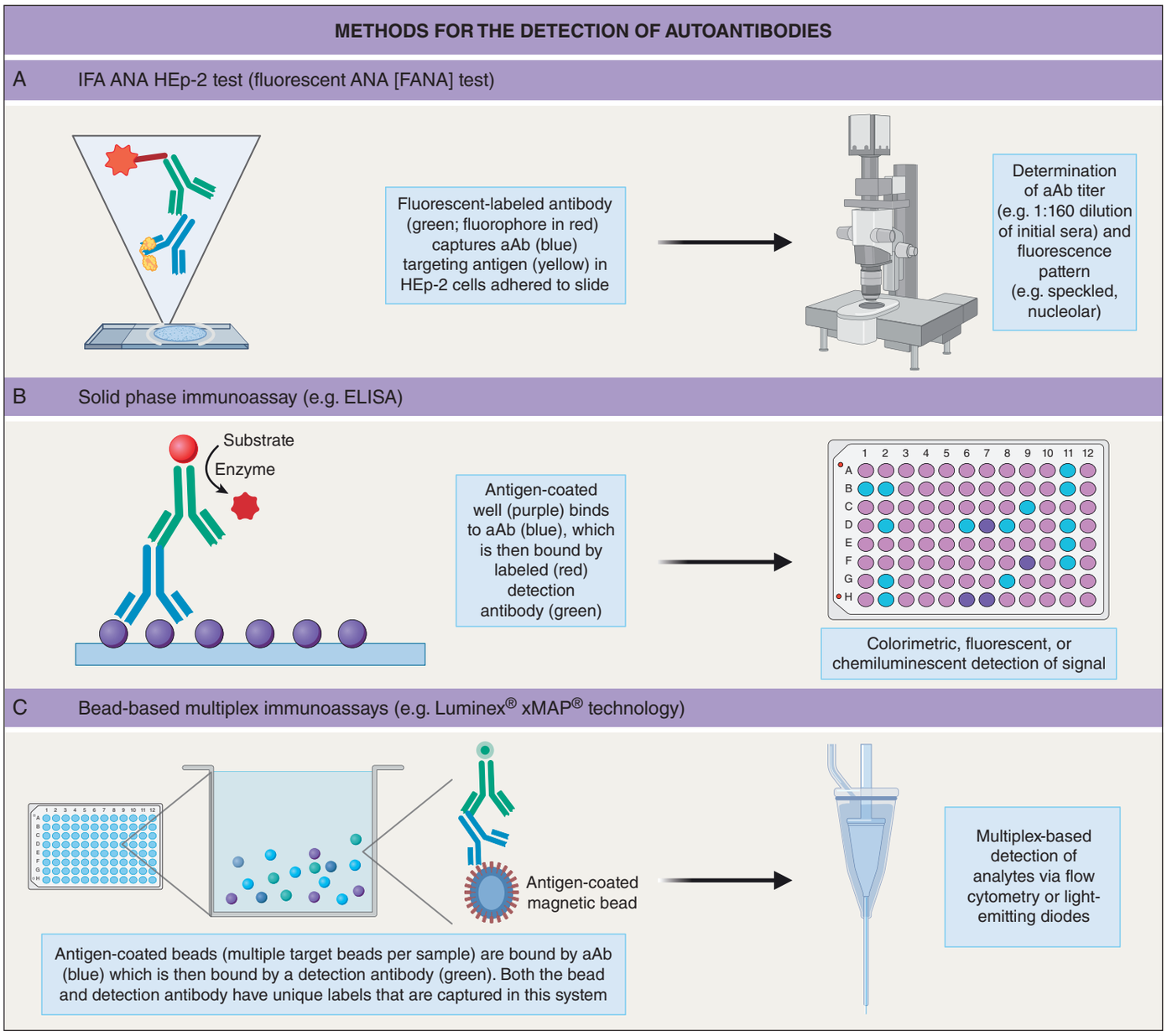


Fig. 40.2 Methods for the detection of ANA. A In the fluorescent ANA (FANA) test, serum samples are usually incubated on a slide with adherent HEp-2 cells. ANA that bind to autoantigens in HEp-2 cells are detected by fluorophore-labeled anti-immunoglobulin (detection) antibodies and visualized with a fluorescence microscope. **B** In a solid-phase immunoassay, a surface (e.g. polystyrene, nitrocellulose) is coated with autoantigens. Following binding of aAb to the autoantigens, they are detected by anti-immunoglobulin (detection) antibodies. By linking the detection antibody to an enzyme that produces one of the following – a colorimetric signal (enzyme-linked immunosorbent assay [ELISA]), a fluorescent signal (fluorometric enzyme-linked immunoassay [FEIA]), or a chemiluminescent signal (chemiluminescence immunoassay [CIA]) – the concentration of aAb is determined. **C** In bead-based multiplex immunoassays, autoantigens are coupled to beads. After the beads are incubated with the patient's serum, bound aAb are detected by fluorophore-labeled detection antibodies in a flow cytometry-based system using two lasers or light-emitting diodes. Both the beads and the detection antibodies have unique fluorescence signals, allowing simultaneous detection of multiple aAb.

MAJOR ISSUES RELATED TO THE INTERPRETATION OF RESULTS OF ANTI-NUCLEAR ANTIBODY (ANA) ASSAYS
• Methods of detecting and reporting ANA (e.g. use of a human tumor cell line substrate leads to increased sensitivity but decreased specificity)
• Subjective nature of FANA assay endpoint
• Requirement for predefined antigen combinations in ELISA or multiplex bead-based assays
• "Normal" versus "abnormal" ANA levels
• Patient age
• Drug-induced ANA
• ANA can be seen in disorders other than AI-CTDs
• Sontheimer's corollary to Greenwald's law of lupus

Table 40.5 Major issues related to the interpretation of results of anti-nuclear antibody (ANA) assays. AI-CTD, autoimmune connective tissue disease; ELISA, enzyme-linked immunosorbent assay.

As with anti-dsDNA aAb assays, it is important to understand certain technical considerations relating to anti-RNP aAb assays, such as those used to measure anti-SSA/Ro, anti-SSB/La, anti-U1RNP, and anti-Sm aAb (i.e. ENA). Nowadays, anti-RNP aAb are usually detected via solid-phase immunoassays such as ELISA (see Fig. 40.2B), which are more sensitive but less specific than the older double immunodiffusion (DID) assays. As a result, some of the original clinical correlations for anti-SSA/Ro, anti-SSB/La, anti-Sm, and anti-U1RNP aAb that were based upon the results of DID assays do not hold with regard to the results of modern ELISA. For example, Lee and colleagues[22] compared the sensitivity of DID assays and ELISA for the detection of aAb to SSA/Ro in patients with SCLE and discoid LE (DLE). High-titer anti-SSA/Ro aAb in the ELISA correlated with positive results in DID assays and the clinical diagnosis of SCLE. Low-titer anti-SSA/Ro aAb in the ELISA were observed in approximately two-thirds of DLE sera tested and correlated with negative results in DID assays. In conclusion, low

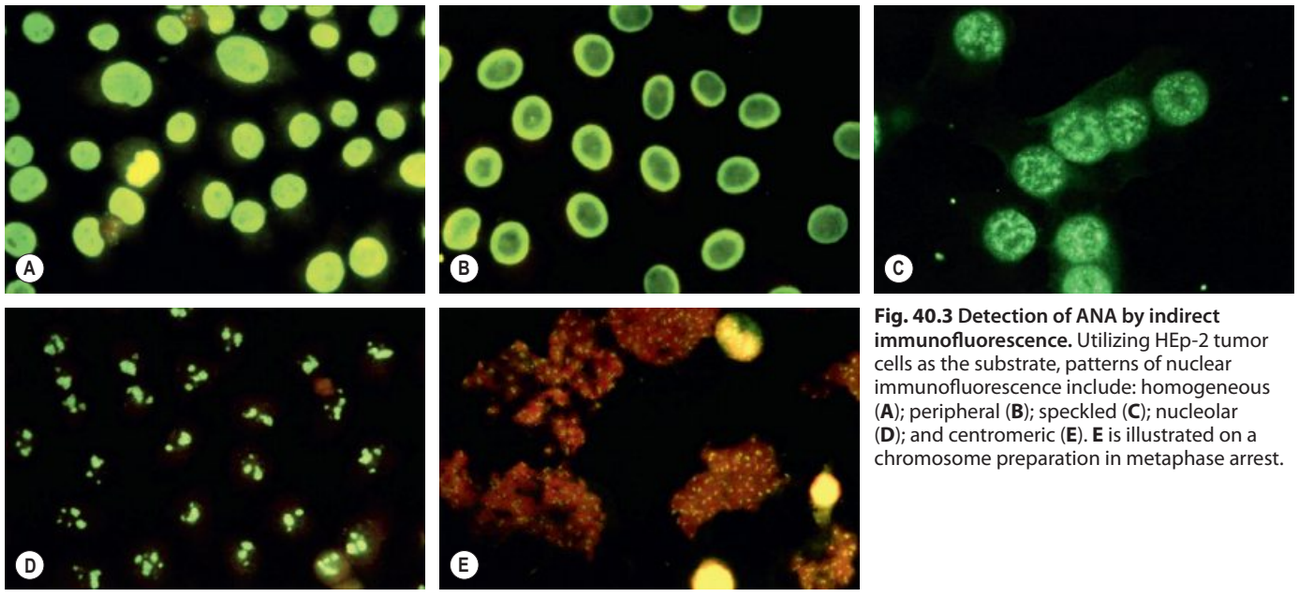


Fig. 40.3 Detection of ANA by indirect immunofluorescence. Utilizing HEp-2 tumor cells as the substrate, patterns of nuclear immunofluorescence include: homogeneous (**A**); peripheral (**B**); speckled (**C**); nucleolar (**D**); and centromeric (**E**). **E** is illustrated on a chromosome preparation in metaphase arrest.

CONCEPT OF CLINICAL UTILITY IN LABORATORY TESTING

	Disease present	Disease absent
Positive result	True positive (TP)	False positive (FP)
Negative result	False negative (FN)	True negative (TN)

Sensitivity=TP/(TP+FN)
Specificity=TN/(TN+FP)
Positive predictive value=TP/(TP+FP)
Negative predictive value=TN/(TN+FN)

Fig. 40.4 Concept of clinical utility in laboratory testing. *With permission from Ward MM. Laboratory testing for systemic rheumatic diseases. Postgrad Med 1998;103:93–100.*

anti-SSA/Ro titers are of uncertain clinical significance, may be found in normal sera, and should not be used as evidence to support diagnoses classically associated with anti-SSA/Ro aAb.

Drug-Induced ANA/SLE

Several drugs can trigger ANA or a drug-induced SLE syndrome, including minocycline, procainamide, hydralazine, isoniazid, chlorpromazine, phenytoin, quinidine, and methyldopa. The predominant clinical manifestations of drug-induced SLE are musculoskeletal symptoms (arthritis, arthralgia, myalgia) and serositis (pleuritis, pericarditis). Skin involvement is uncommon. In a comprehensive review[23], only 25% of hydralazine-induced SLE patients had "skin involvement", and fewer than 5% of procainamide-induced SLE patients experienced "skin changes", whereas 71% of idiopathic SLE patients had some type of skin change. Anti-histone aAb represent also a serologic marker of drug-induced ANA and drug-induced SLE (present in 95%), but can also be present in patients with idiopathic SLE.

A different set of drugs, including hydrochlorothiazide, terbinafine, proton pump inhibitors, griseofulvin, diltiazem and taxanes, can trigger anti-SSA/Ro aAb production and the cutaneous lesions of SCLE[24]. Anti-histone aAb are not a characteristic finding in drug-induced SCLE. Finally, SCLE, DLE, and SLE have occasionally been observed in patients receiving immune checkpoint inhibitors such as nivolumab and pembrolizumab[25].

Induction of ANA and anti-dsDNA antibodies by tumor necrosis factor inhibitors

Tumor necrosis factor (TNF) blockade by recombinant proteins is a common therapeutic intervention (see Ch. 128) and is associated with the induction of aAb, especially ANA and anti-dsDNA antibodies. However, the clinical significance of these aAb is not well defined and the incidence of clinically detectable autoimmune disease is low. In a study of 125 psoriasis patients treated with a TNF inhibitor, newly positive ANA titers developed after a mean of 8–20 months in ~20% of those who received etanercept (9/45) or adalimumab (9/47), compared with 48% of those who received infliximab (16/33); anti-dsDNA aAb developed in 6% of patients in each group (8/125 overall)[26]. However, clinical manifestations of LE were not evident in any of these patients. In a series of 22 patients who developed a lupus-like syndrome during therapy with either infliximab or etanercept, cutaneous features included: a butterfly rash (ACLE), SCLE, DLE, small vessel vasculitis, and chilblains[27]. Additional findings were arthritis, phlebitis (with anti-cardiolipin antibodies), leukopenia, thrombocytopenia, serositis, and general manifestations (e.g. fever, weight loss, asthenia); renal involvement was rare[28].

Notably, all the TNF inhibitors have the propensity to induce ANA and anti-dsDNA aAb as well as cutaneous LE, SLE, or a lupus-like syndrome. When a French pharmacovigilance database was analyzed for TNF inhibitor-induced LE or lupus-like syndrome, the estimated reporting odds ratios were 9–10 for infliximab and adalimumab, and 4 for etanercept[29]. Interestingly, in patients with rheumatoid arthritis and psoriasis, the production of lupus-associated antibodies was linked to both the formation of anti-drug antibodies (resulting in decreased therapeutic efficacy) and type 1 interferon production[30]. However, when over 1000 patients with rheumatoid arthritis underwent serial measurements of ANA and anti-dsDNA aAb, the serologic results failed to predict the onset of lupus or vasculitis[31].

In summary, although the development of aAb is relatively common during TNF inhibitor administration, they are only occasionally of clinical significance. In the absence of clinical signs or symptoms, we do not recommend screening for ANA prior to initiation of TNF inhibitors.

AUTOANTIBODIES IN IDIOPATHIC INFLAMMATORY DERMATOMYOPATHIES

The term "idiopathic inflammatory *dermato*myopathies" (syn. dermatomyositis [DM]/polymyositis [PM], idiopathic inflammatory myopathies; see Ch. 42) has been coined to include cutaneous-only or cutaneous-predominant subsets of DM, such as clinically amyopathic DM (i.e. amyopathic DM and hypomyopathic DM). Patients with adult-onset, clinically amyopathic DM (CADM) appear to have a somewhat higher prevalence of ANA (65%) than patients with classic DM and PM. Compared to LE, there are more highly specific aAb, and titers of some of these specific aAb are associated with disease severity[32]. Table 40.2

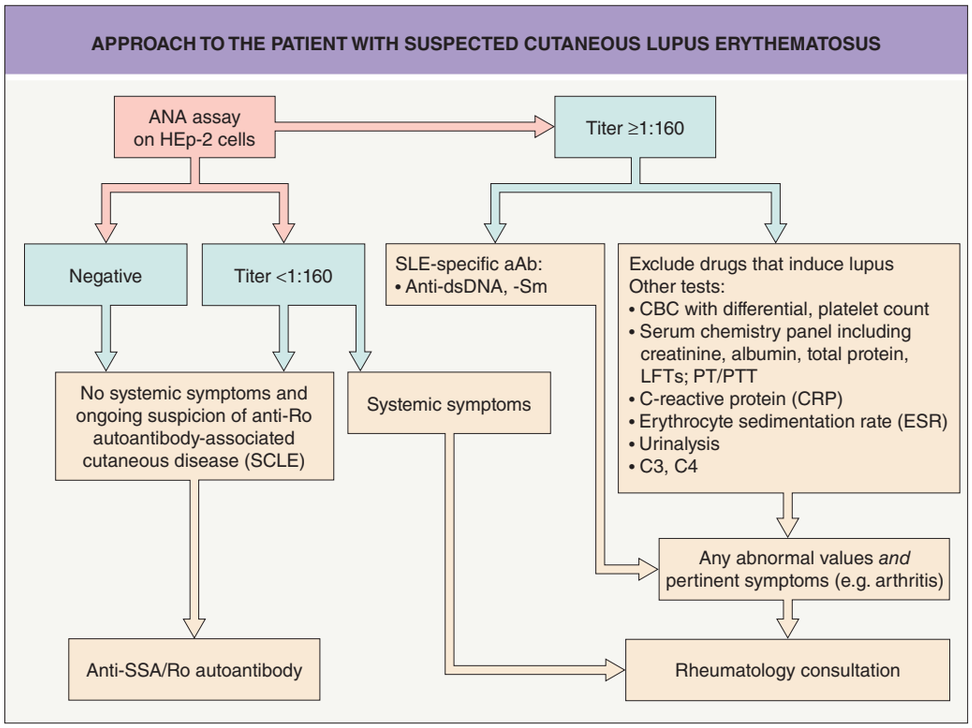


Fig. 40.5 Approach to the patient with suspected cutaneous lupus erythematosus. It should be noted that these recommendations are most relevant within the context of a dermatology practice setting. CBC, complete blood count; LFTs, liver function tests; PT, prothrombin time; PTT, partial thromboplastin time; SCLE, subacute cutaneous lupus erythematosus.

summarizes the aAb in patients with idiopathic inflammatory dermatomyopathies. Both high specificity and low specificity aAb are included, with the latter also seen in other AI-CTD.

Anti-TIF1-γ (p155), -TIF1-α (p140) Antibodies

aAb to a 155 kDa polypeptide was initially reported in 20%–30% of patients with the classic form of juvenile-onset or adult-onset DM[33] and was subsequently noted to bind to transcriptional intermediary factor 1 gamma (TIF1-γ). aAb to TIF1-α can also be observed in DM and are associated with TIF1-γ antibodies (see Table 40.2). In patients with adult-onset classic DM, the presence of anti-TIF1-γ aAb has been associated with an increased risk of internal malignancy[34]. Individuals with anti-TIF1-γ aAb often have diffuse erythema in a photodistribution, extensive inflammatory skin disease, and relatively mild muscle disease; calcinosis is uncommon[32]. They also have palatal erythema, a finding termed "ovoid patch"[35], in addition to keratotic palmar papules, psoriasiform lesions, and hypopigmented and telangiectatic ("red on white") patches[36].

Anti-MDA5/CADM-140 Antibodies

In adult Japanese patients with clinically amyopathic DM (CADM) and interstitial lung disease, aAb to a 140 kDa molecule (CADM-140) were first noted[37]. Subsequently these aAb were found to bind the interferon-induced with helicase C domain protein 1 (IFIH1), which is also known as melanoma differentiation-associated protein 5 (MDA5)[38]. In a retrospective series, plasma samples from 77 patients with DM were screened for anti-MDA5 aAb[39]. The ten patients (13%) with this aAb had a rather distinct clinical phenotype with cutaneous ulcerations that can overlie Gottron papules, tender palmar papules, oral pain and ulceration, arthritis/arthralgia, and diffuse hair loss. Recognition of this subset of patients is clinically important because of the association of anti-MDA5 aAb with rapidly progressive interstitial lung disease; the latter occurs more frequently in Asians[32]. The titer of anti-MDA5 aAb is used to monitor the associated interstitial lung disease and the risk of its relapse following therapy[40].

Anti-Jo-1 Antibodies

The anti-Jo-1 antibody is one of several myositis-specific aAb directed against the aminoacyl transfer RNA synthetases (ARS) that deliver amino acids to ribosomes during protein translation. The presence of one or more of these anti-ARS aAb correlates positively with a subset of mostly PM and some DM patients who have an increased risk of erosive arthritis, Raynaud phenomenon, and interstitial lung disease; this clinico-serologic constellation has been referred to as the "antisynthetase syndrome"[41]. The mechanic's hand skin lesion was originally described in these patients, but has subsequently been observed in other DM subsets, including CADM[42].

Anti-Mi-2, -SRP, -NXP-2, and –SAE Antibodies

Anti-Mi-2 aAb are found in patients with the hallmark skin lesions of DM (Gottron papules, Gottron sign, shawl sign). aAb to the signal recognition particle (SRP) are uncommon, but when present, they signal a risk for fulminant DM/PM with cardiac involvement and a high mortality rate. Anti-nuclear matrix protein 2 (NXP-2) aAb are associated with more severe muscle disease and calcinosis in children[32]; in adults, they are associated with subcutaneous edema, increased risk of cancer, and calcinosis[43,44]. aAb to SAE (SUMO activation enzyme) have been described in a rare subset of DM patients with severe cutaneous disease, progressive muscle involvement, and dysphagia[32].

AUTOANTIBODIES IN SYSTEMIC SCLEROSIS (SSc; SCLERODERMA) AND MORPHEA (LOCALIZED SCLERODERMA)

Table 40.3 summarizes aAb associated with SSc (see Ch. 43)[1,45,46]. The current classification criteria for SSc incorporate the following aAb: anti-centromere (CENP-B); anti-topoisomerase I (formerly Scl-70); and anti-RNA polymerases (RNAP), in particular anti-RNA polymerase III[47]. Anti-centromere aAb correlate with the limited cutaneous form of SSc (CREST syndrome), while aAb against DNA topoisomerase I and RNAP are seen more commonly in the diffuse cutaneous form of SSc. aAb that recognize RNAP are also associated with an increased risk of developing SSc-associated renal disease[48]. Anti-RNA polymerase III aAb have been associated with an increased risk of internal malignancies and may be indicative of paraneoplastic SSc[49,50], with triggering of cellular immunity by the malignancy also promoting sclerosis[50]. However, these aAb are not subset- or disease-specific; e.g. anti-CENP-B aAb can also be detected in ~10% of patients with diffuse cutaneous SSc as well as in disorders such as primary biliary cholangitis. Lastly, as with other AI-CTDs, some aAb encountered in SSc patients are nonspecific (e.g. anti-histone, anti-ssDNA, anti-PM/Scl).

While there is little clinical overlap between SSc and morphea (see Ch. 44), some degree of serologic overlap has been described (e.g.

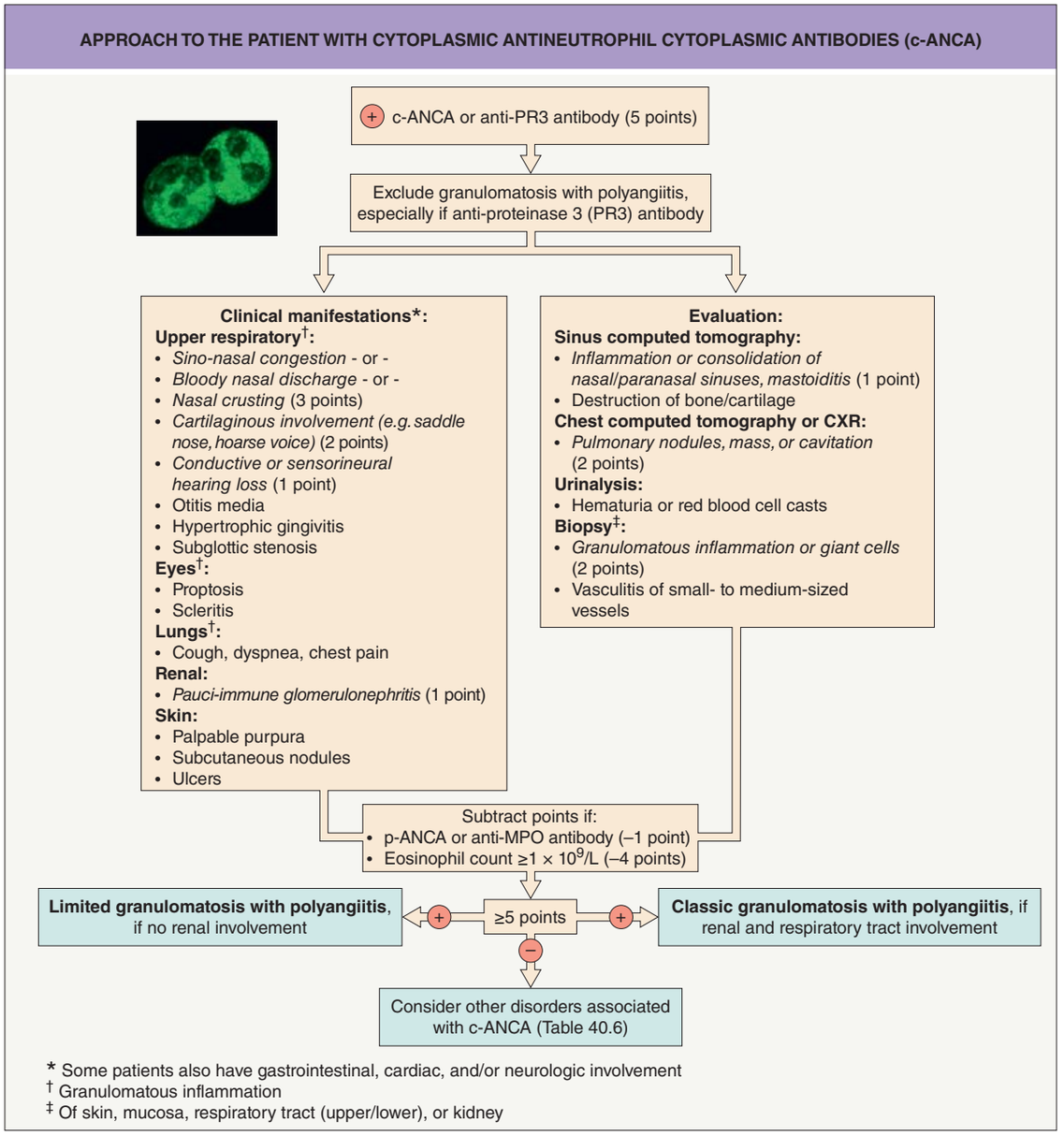


Fig. 40.6 Approach to the patient with cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA). The presence of ≥5 points yields a sensitivity of 93% and specificity of 94% for GPA per the ACR/EULAR 2022 classification criteria. *Photomicrograph from Wiik AS, Fritzler MJ. Laboratory tests in rheumatic disorders. In: Hochberg MC, Silman AJ, Smolen JS, et al. (eds). Rheumatology, 4th edn. London: Mosby Elsevier; 2008.*

anti-fibrillin-1 aAb). aAb to fibrillin-1 (as distinguished from fibrillarin [U3RNP]), histones, and ssDNA occur in 30%–50% of patients with morphea. As with classic ANA, these antibodies have been observed more often in patients with more widespread forms of morphea such as linear or generalized morphea. To date, morphea-specific aAb have not been identified nor have aAb that reflect disease activity or prognosis.

AUTOANTIBODIES IN OTHER RHEUMATIC DISORDERS AFFECTING THE SKIN

Table 40.4 summarizes aAb seen in patients with other rheumatic disorders that can have cutaneous manifestations (see Ch. 45)[1]. Anti-neutrophil cytoplasmic antibodies (ANCA) are a subgroup of neutrophil-specific aAb that are characteristic of systemic vasculitides (see Ch. 24). Figs. 40.6 and 40.7 present a clinical approach to patients with either cytoplasmic ANCA (c-ANCA) or perinuclear ANCA (p-ANCA) and Table 40.6 summarizes other disorders associated with ANCA.

Acknowledgment

The editors wish to thank Dr. Jan P. Dutz for his valuable contribution to this chapter in previous editions.

Additional figure available in our eBook (see inside front cover for access code).

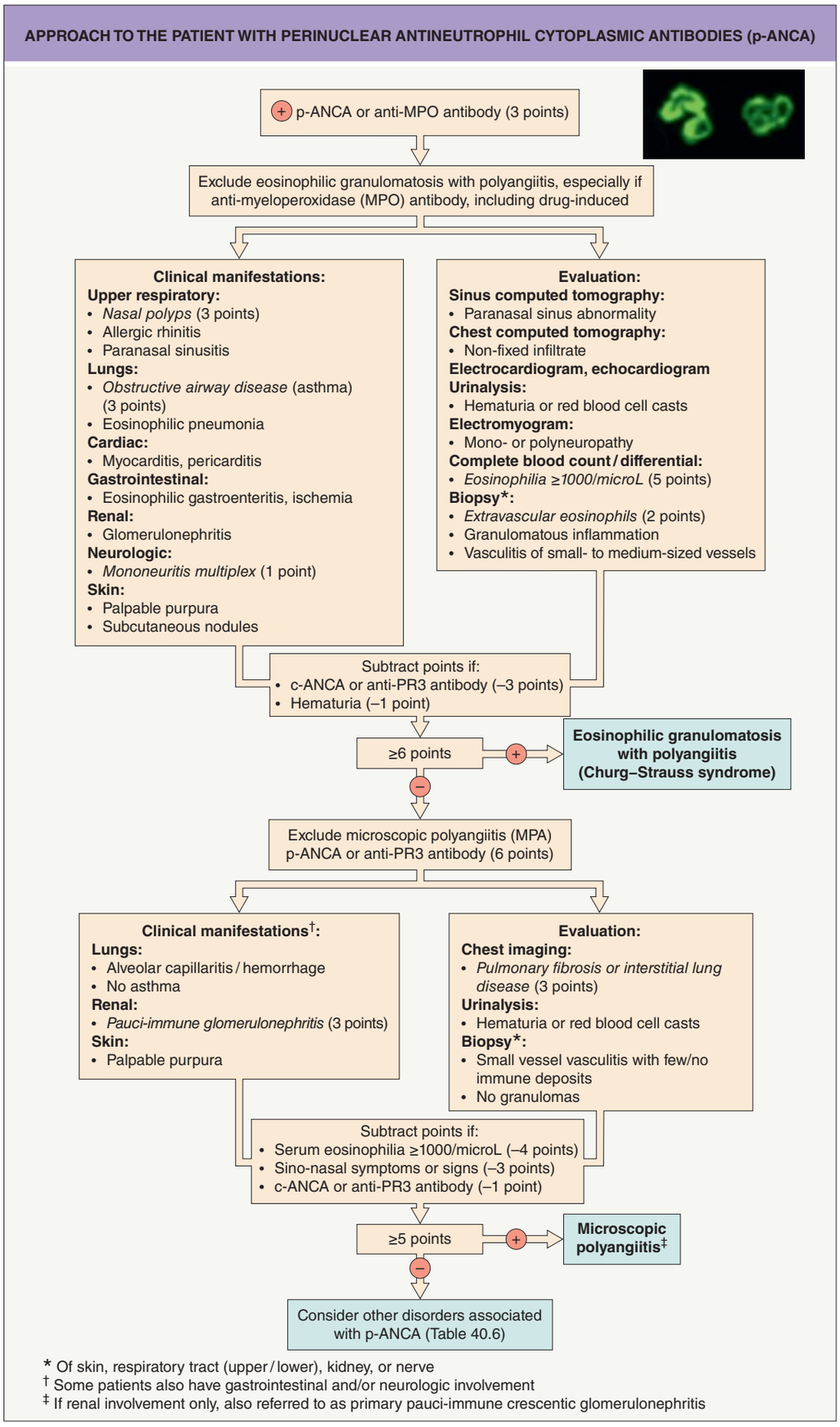


Fig. 40.7 Approach to the patient with perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA). Use of leukotriene inhibitors (see Ch. 130) has been associated with the onset of eosinophilic granulomatosis with polyangiitis (EGPA; Churg–Strauss syndrome). Whether this represents unmasking of previously undiagnosed EGPA is a subject of ongoing debate. The presence of ≥6 points yields a sensitivity of 85% and a specificity of 99% for EGPA while >5 points yields a sensitivity of 91% and a specificity of 94% for microscopic polyangiitis per the ACR/EULAR 2022 classification criteria. *Photomicrograph from Wiik AS, Fritzler MJ. Laboratory tests in rheumatic disorders. In: Hochberg MC, Silman AJ, Smolen JS, et al. (eds). Rheumatology, 4th edn. London: Mosby Elsevier; 2008.*

OTHER DISORDERS ASSOCIATED WITH ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA)			
	Type of ANCA*	**Major antigen(s)†**	**Evaluation**
Inflammatory bowel disease			
Ulcerative colitis (50%–70%) > Crohn disease (20%–40%)	p > c	Catalase, BPI, α-enolase, LF, CG, HMG1/2 > MPO, PR3	Colonoscopy
Autoimmune liver disease			
Autoimmune hepatitis (type 1; 80%), primary sclerosing cholangitis (70%) > primary biliary cirrhosis (30%)	p > c	Actin, HMG1/2	LFTs; ANA; anti-smooth muscle Ab; antimitochondrial Ab
Autoimmune connective tissue disease			
Systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis (20%–30%) > Sjögren syndrome, dermatomyositis, reactive arthritis, relapsing polychondritis, antiphospholipid syndrome	p > c	MPO, PR3, BPI, CG, LF, lysozyme, HMGI/2	ANA panel; RF; anti-cardiolipin and anti-β_2 glycoprotein I Ab
Drug-induced vasculitis/lupus/hepatitis			
Propylthiouracil (20%), minocycline, methimazole, carbimazole > levamisole, sulfasalazine	p > c	MPO > PR3, elastase	Skin biopsy; ANA panel; LFTs; discontinue drug
Hydralazine, penicillamine > allopurinol‡	p	MPO, elastase	
TNF inhibitors	p, c	MPO, PR3	
High-dose intravenous immunoglobulin	c	–	
Other cutaneous or systemic vasculitides¶			
Mixed cryoglobulinemia, Behçet disease, paraneoplastic	p > c	Variable	Skin biopsy; cryoglobulins; hepatitis B, C panels; exclude malignancy
Henoch–Schönlein purpura, Buerger disease	p	Variable	
Other glomerulonephritides			
Anti-GBM Ab-associated (30%) > immune complex (15%) > poststreptococcal	p	MPO	UA; BUN/creatinine; ASO; renal biopsy
Infections/Vaccines			
Respiratory tract infections (bacterial/mycobacterial/ fungal), enteritis, periodontitis, HIV, parvovirus B19, malaria, leprosy, SARS-CoV-2 infection, and SARS-CoV-2 mRNA vaccine	p, c	MPO, others	Cultures; serologies; echocardiogram
Onchocerciasis	p	Defensin	
Hepatitis C virus infection	p, c	CG, BPI, MPO	Serologies
Subacute bacterial endocarditis, chromomycosis, invasive amebiasis	c	PR3	
Miscellaneous			
Cystic fibrosis (80%)	c > p	BPI	Sweat test
Hypergammaglobulinemia	p, c	–	Serum protein electrophoresis

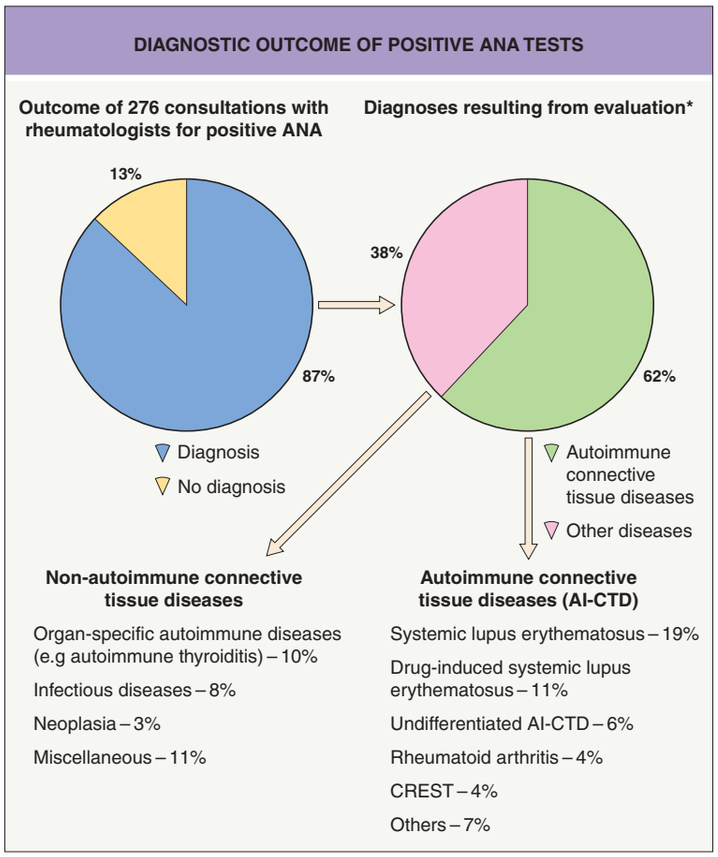
*c-ANCA are often atypical; in addition, immunofluorescence testing in some laboratories may not distinguish c-ANCA (atypical) from atypical ANCA.
†p-ANCA often have antigen specificity other than MPO, e.g., LF, elastase, CG, lysozyme, BPI, HMG1/2, α-enolase, catalase, actin, defensin; c-ANCA (atypical) have antigen specificity other than proteinase 3, e.g. BPI, lysozyme or multiple antigens.
‡Other drugs associated with p-ANCA in scattered case reports include cimetidine, cefotaxime, phenytoin, isotretinoin, clozapine, atorvastatin, indomethacin, isoniazid, and thioridazine.
¶Although primarily associated with c-ANCA, 5%–50% of patients with granulomatosis with polyangiitis have p-ANCA; likewise, although primarily associated with p-ANCA, 5%–30% of patients with eosinophilic granulomatosis with polyangiitis and ~25%–30% of those with microscopic polyangiitis have c-ANCA; ANCA have also been reported in leukocytoclastic vasculitis of unknown etiology and unclassified vasculitis.

Table 40.6 Other disorders associated with anti-neutrophil cytoplasmic antibodies (ANCA). Ab, antibodies; ANA, anti-nuclear antibodies; ASO, antistreptolysin O; BPI, bactericidal/permeability-increasing protein; c, cytoplasmic [c-ANCA or c-ANCA (atypical)]; CG, cathepsin G; GBM, glomerular basement membrane; HMG1/2, high mobility group non-histone chromosomal proteins; LF, lactoferrin; LFTs, liver function tests; MPO, myeloperoxidase; p, perinuclear (p-ANCA); RF, rheumatoid factor; UA, urinalysis. *Courtesy Julie V. Schaffer, MD.*

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eFig. 40.1 Diagnostic outcome of positive ANA tests. Outcome of rheumatology evaluations of patients referred for consultations for positive ANA of undetermined clinical significance. *Total number of patients = 276, but number of diagnoses = 284, because 8 patients had more than one diagnosis. *Adapted from data presented by Tan EM, et al. Arthritis Rheum 1997;40:1601–11.*

41 Lupus Erythematosus

Lela A. Lee and Victoria P. Werth

Synonyms/variants: ■ Discoid lupus erythematosus: a subset of chronic cutaneous lupus erythematosus ■ Lupus profundus: a variant of lupus panniculitis ■ Lupus erythematosus tumidus: tumid lupus

Key features

- There are several variants of cutaneous lupus, defined in part by the location and depth of the inflammatory infiltrate
- Acute cutaneous lupus involves primarily the epidermis and upper dermis and is usually associated with active systemic disease
- Subacute cutaneous lupus involves primarily the epidermis and upper dermis and most patients demonstrate or report photosensitivity and have anti-SSA/Ro autoantibodies sometime during the course of their disease; the majority do not have serious systemic involvement (renal, CNS, or cardiopulmonary)
- Discoid lesions of lupus involve the epidermis, upper and lower dermis, and adnexal structures, and they can develop atrophy and/or scarring; the majority of patients do not have clinically significant systemic disease
- Lupus erythematosus tumidus involves the dermis and adnexal structures, with sparing of the epidermis, and has a prominent infiltration of mucin; lesions are often photo-inducible
- Lupus panniculitis involves the subcutaneous tissue and may result in disfiguring depressed areas due to lipoatrophy

INTRODUCTION

Lupus erythematosus is a multisystem disorder that often affects the skin. Cutaneous lesions can be a source of disability and, on many occasions, indicate and correlate with internal disease.

HISTORY

The term "lupus erythemateaux" was first used by Cazenave in the mid-1800s[1]. Cazenave and others helped to articulate the difference between lupus erythematosus (LE) and lupus vulgaris, a clinical variant of cutaneous tuberculosis. Due in part to observations of Hutchinson, Osler, and Jadassohn, it was recognized that cutaneous lesions of LE may be associated with significant internal abnormalities, including arthritis, nephritis, serositis, cytopenias, and neurologic disease. In 1964 and during the following years, Dubois developed the concept of lupus as a spectrum of disease, ranging from isolated cutaneous lesions to life-threatening, multi-organ disease. Gilliam also developed the concept of a spectrum of cutaneous disease, and, in 1979, along with Sontheimer and Thomas, clearly separated and named the entity now known as subacute cutaneous lupus erythematosus (SCLE)[2]. The description was virtually identical to that of "ANA-negative" lupus, reported by Maddison, Provost, and Reichlin in 1981[3].

Important diagnostic advances included: discovery of the LE cell phenomenon by Hargraves, Richmond, and Morton in 1948; identification of ANA by Friou in 1957; description of the lupus band test by Burnham, Neblett, and Fine in 1963; and the association of specific clinical manifestations of lupus with specific autoantibodies by a variety of investigators[4–6]. With regard to skin disease, the associations of anti-Ro (also known as anti-SSA) autoantibodies with neonatal lupus by Weston et al.[7] in 1981 and with subacute cutaneous LE (SCLE) by Sontheimer et al.[8] in 1982 are noteworthy milestones.

Antimalarial therapy in the form of quinine was used for cutaneous lupus by Payne in 1894. By the late 1950s, synthetic antimalarials had become a mainstay of therapy. Systemic corticosteroids and other immunosuppressive agents came into use during the mid-twentieth century.

EPIDEMIOLOGY

Systemic lupus erythematosus (SLE) is a common disease with significant morbidity and mortality. The strongest factor affecting risk for lupus is *sex*: women with SLE outnumber men by at least 9 : 1[9]. Since SLE occurs most commonly in women during their childbearing years, it is likely that hormonal factors influence susceptibility. Consistent with the importance of sex steroids in the expression of disease, lupus is rare in prepubertal children. Those patients with "only" cutaneous lesions appear to have a somewhat lower female-to-male ratio (perhaps 3 : 1), but there is still a female predominance.

Ethnicity is also a major risk factor, and its effect in some populations is almost as strong as that of sex. In the US, the prevalence of SLE is fourfold higher in African-American women as compared to White women (211 in 100 000 versus 64 in 100 000)[9]. Additionally, African-Americans tend to develop disease at an earlier age and have a higher mortality rate. A long-term study of a multi-ethnic cohort of 587 SLE patients from Texas, Alabama, and Puerto Rico found that African-Americans and Hispanics from Texas had more severe disease than Whites or Hispanics from Puerto Rico[10]. It is likely that Asians, Latin Americans, and White populations in Europe have a similar prevalence of lupus as do White populations living in the US[9].

Highlighting the importance of skin disease in LE, population-based studies indicate that there are approximately as many patients who have cutaneous LE without concurrent SLE as there are patients who have SLE[11,12].

PATHOGENESIS

The pathogenesis of cutaneous LE is complex, and it involves an interaction between genetic and environmental factors. The latter include ultraviolet radiation (UVR), medications, cigarette smoking, and possibly viruses. This interplay triggers a complex inflammatory cascade of cytokine, chemokine, and inflammatory cell responses that include cells residing within as well as recruited to the skin. Overall, the lichenoid tissue reaction, defined as epidermal basal cell damage and a band-like lymphocytic infiltrate in the upper dermis, characterizes most subsets of cutaneous LE. It involves activation of keratinocytes, endothelial cells, and skin dendritic cells plus the production of type I interferons (IFNs), followed by the recruitment and activation of $CD4^+$ and $CD8^+$ cytotoxic T cells. The end result is cytotoxic keratinocyte damage.

Genes that can affect overall immunoreactivity include those whose protein products are involved in B and T cell function, innate immunity, immune complex clearance, apoptosis, ubiquitination, DNA methylation, or cellular adhesion[13]. Examples from all these gene classes, in addition to genes with unknown function, have been implicated in some way in human or animal models of SLE (Table 41.1; see Ch. 4).

Both genetic background based upon ancestry and mutations in specific genes contribute to the clinical heterogeneity in cutaneous LE. For example, the incidences of photosensitivity and discoid LE (DLE) differ in those of northern versus southern European ancestry[14], and SCLE is associated with the HLA-B8-DR3 extended haplotype (including *TNF2*), as well as C2 and C4 deficiencies (see Table 60.9)[15]. Genes previously associated with SLE, e.g. *TYK2*, *IRF5*, *CTLA4*, also confer

GENES ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS	
B and T cell function	***HLA-DR*** – major histocompatibility complex, class II
	BLK – B lymphoid tyrosine kinase
	BANK1 – B cell scaffold protein (with ankyrin repeats) 1
	CTLA4 – cytotoxic T lymphocyte antigen-4
	FCGR2B – Fc fragment of IgG receptor IIb (low affinity; CD32)
	LYN v-yes-1 – Yamaguchi sarcoma viral related oncogene homolog
	IKZF1 – Ikaros family zinc finger 1
	PTPN22 – protein tyrosine phosphatase, non-receptor type 22 (lymphoid)
	STAT4 – signal transducer and activator of transcription 4
	PDCD1 – programmed cell death 1
	IRAK1 – interleukin-1 receptor-associated kinase 1
	ETS1 – v-ets erythroblastosis virus E26 oncogene homolog 1
	TNFSF4 – tumor necrosis factor (ligand) superfamily member 4
	IL21 – interleukin-21
Innate immunity	***IRF5*** – interferon regulatory factor 5
	TNFAIP3 – tumor necrosis factor, alpha-induced protein 3
	SPP1 – secreted phosphoprotein 1 (osteopontin)
	TREX1 – three prime repair exonuclease 1 (see text)
	TYK2 – tyrosine kinase 2
	TLR7 – Toll-like receptor 7
	IRAK1 – see above
	STAT4 – see above
	RASGRP3 – RAS guanyl releasing protein 3
	SLC15A4 – solute carrier family 15 member 4
Immune complex clearance	*FCGR3A* – Fc fragment of IgG, low affinity IIIa, receptor (CD16a)
	FCGR3B – Fc fragment of IgG, low affinity IIIb, receptor (CD16b)
	CRP – C-reactive protein, pentraxin-related
	ITGAM – integrin, alpha M (complement component 3 receptor 3 subunit; CD11b)
	C4A – complement component 4A
	C4B – complement component 4B
	C2 – complement component 2
	C1Q – complement component 1, Q subcomponent
Apoptosis	*ATG5* – autophagy related 5 homolog
	STAT4 – see above
Ubiquitination	*UBE2L3* – ubiquitin-conjugating enzyme E2L3
	TNFAIP3 – tumor necrosis factor, alpha-induced protein 3
	TNIP1 – TNFAIP3 interacting protein 1
DNA methylation	*MECP2* – methyl CpG binding protein 2 (Rett syndrome)
Cellular adhesion	*ITGAM* – see above
Other/unknown	*PXK* – PX domain containing serine/threonine kinase
	ICA1 – islet cell autoantigen 1
	SCUBE1 – signal peptide, CUB domain, EGF-like 1
	NMNAT2 – nicotinamide nucleotide adenylyltransferase 2
	XKR6 – XK, Kell blood group complex subunit-related family, member 6
	KIAA1542

Table 41.1 Genes associated with systemic lupus erythematosus. For detailed information on the function of these protein products, see www.genecards.org. The most strongly associated genes are in bold. *Adapted from Moser KL, Kelly JA, Lessard CJ, et al. Recent insights into the genetic basis of systemic lupus erythematosus. Genes Immun 2009;10:373–9.*

an increased risk for developing DLE and SCLE[16], while mutations in *TREX1*, which encodes a DNA exonuclease, are associated with familial chilblain lupus[17]. In the latter patients, dysfunction of the exonuclease leads to an accumulation of IFN-stimulatory nucleic acids.

Autoantibodies clearly play a role in SCLE and neonatal lupus, where anti-SSA/Ro (more specifically, anti-SSA/Ro60 and anti-SSA/Ro52) and anti-La autoantibodies are frequently observed (see Ch. 40); in the case of neonatal lupus, these antibodies are transmitted transplacentally. Blocking the function of either SSA/Ro60 or SSA/Ro52 presumably predisposes one to these diseases. Of note, SSA/Ro60 plays an important role in cell survival following UVR, possibly via binding to misfolded non-coding RNAs and targeting them for degradation, and mice which lack SSA/Ro60 develop a lupus-like syndrome[18]. SSA/Ro52 has a known regulatory role in inflammation, targeting both

interferon regulatory factor 3 (IRF3) and IRF8 for degradation[19]; thus, antibodies to SSA/Ro52 may be proinflammatory. Alternatively, or in addition, these autoantibodies could lead to disease via activation of proteins and cells of the immune system, following immune complex formation.

Both ultraviolet B (UVB) and ultraviolet A radiation have been implicated in exacerbation of cutaneous LE, although UVB is a more efficient cause of photo-induced changes in the skin[20]. UVR induces apoptosis, which leads to translocation of cellular and nuclear antigens[21], and there may also be a reduction in the clearance of apoptotic cells. In addition, UVR increases keratinocyte production of SSA/Ro52[22] and type I IFNs[23].

A number of proinflammatory cytokines, including tumor necrosis factor (TNF), interleukin (IL)-1, IFN-γ, HMGB1 (high-mobility group box 1), and IL-18 are induced by UVR[24,25]. There is also upregulation of antimicrobial peptides within the skin as well as a release of *e*xtracellular *t*raps (ETs) by dying *n*eutrophils (NETosis); these traps are composed of a lattice of DNA, histones, and cytoplasmic proteins (Fig. 41.1)[26,27]. Following UV irradiation of keratinocytes, a complex array of chemokines, including chemokine (C-C motif) ligand 5 (CCL5), CCL20, CCL22, and chemokine (C-X-C motif) ligand 8 (CXCL8), is produced (see Table 11.3). Of note, there is an increase in these chemokines within lesions of cutaneous LE, likely leading to leukocyte recruitment to the skin[28]. These effects require adhesion molecules, with activation of endothelial cells (increased expression of ICAM-1, VCAM-1, and E-selectin) and induction of ICAM-1 on basal keratinocytes[29,30].

IFN is another cytokine that plays a role in the pathogenesis of cutaneous LE. Increased secretion of IFN can result from: binding of apoptotic cells to Fcγ receptors on macrophages; binding of viral pathogens, DNA, RNA, or immune complexes to Toll-like receptors on plasmacytoid dendritic cells; and single nucleotide polymorphisms (SNPs) in genes that encode proteins in the IFN pathway[31]. Notably, an increase in proteins upregulated by IFN, including the chemokines CXCL9 and CXCL10, has been observed in the skin of patients with

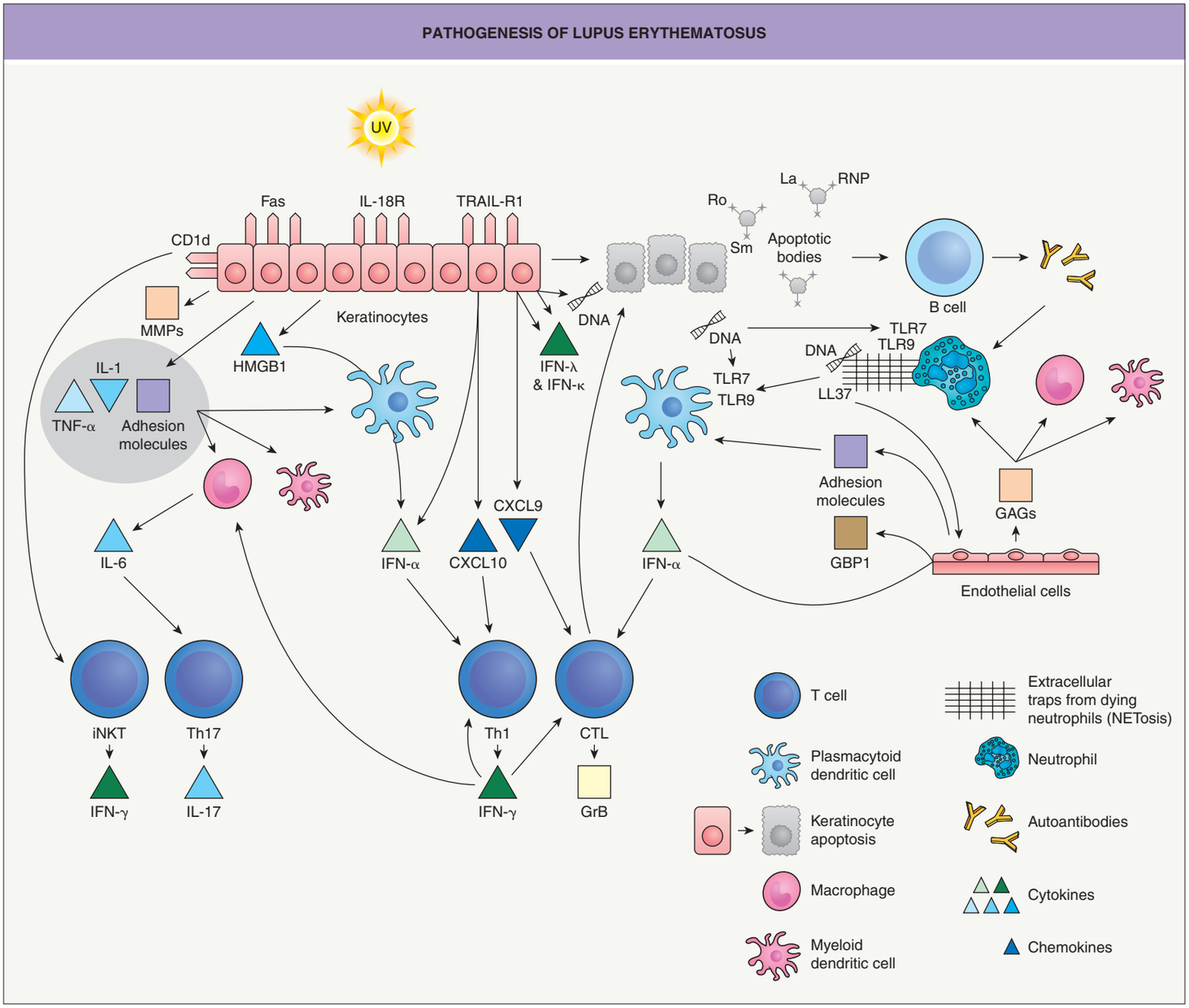


Fig. 41.1 Pathogenesis of lupus erythematosus. In photosensitive cutaneous LE, ultraviolet radiation triggers cytokine and chemokine production, innate immune proteins, NETosis of neutrophils, and apoptosis of cells leading to release of DNA. A lichenoid tissue reaction is the endpoint of a complex cascade that includes activation of dendritic cells, in part due to activation of the TLR7/MyD88 pathway, release of interferon (IFN), production of chemokines, and activation of T cells. CTL, cytotoxic T lymphocyte; CXCL, chemokine (C-X-C motif) ligand; GAGs, glycosaminoglycans; GBP1, guanylate binding protein-1; GrB, granzyme B; HMGB1, high-mobility group box 1; IL, interleukin; iNKT cells, invariant natural killer T cells; LL-37, cathelicidin; MMPs, matrix metalloproteinases; RNP, ribonucleoprotein; Th, T helper cell; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRAIL-R1, tumor necrosis factor-related apoptosis-inducing ligand-receptor 1. *Adapted from Achtman JC, Werth VP. Pathophysiology of cutaneous lupus erythematosus. Arthritis Res Ther 2015;17:182.*

cutaneous LE (see Fig. 41.1)[28,32]. IFN-α further drives the differentiation of monocytes to plasmacytoid dendritic cells, which are potent producers of IFN-α/β, thus forming an amplification loop[33]. Increased numbers of plasmacytoid ($CD123^+$) and myeloid dendritic cells have been found within cutaneous LE lesions[32,34]. Epidermal and dermal dendritic cells can acquire keratinocyte-derived antigens and prime $CD8^+$ T cells to these antigens within the skin-draining lymph nodes[35]. Corroborating evidence for the role of IFN-α is provided by the induction of cutaneous LE in patients receiving IFN-α for other medical conditions. The increased IFN signature seen in SLE has also been detected in peripheral blood mononuclear cells from patients with DLE and SCLE, but not those with LE tumidus[36].

The IFN-upregulated chemokines can recruit CXCR3-positive $CD4^+$ and $CD8^+$ T cells to the skin, as well as immature plasmacytoid dendritic cells, contributing to the characteristic interface infiltrate of cutaneous LE[28,37]. In addition, via the production of IFN-α, plasmacytoid dendritic cells drive the activation and expansion of T cells. There is also evidence for the presence of granzyme B and TIA1 (poly(A)-binding protein), two cytotoxic granule-associated proteins involved in apoptosis, in the skin of all subsets of cutaneous LE, although somewhat less so in SCLE, suggesting that there are fewer $CD8^+$ T cells in SCLE[37]. In patients with disseminated, scarring DLE, high numbers of circulating $CCR4^+$ cytotoxic T cells were detected[38]. One study found *decreased* numbers of $Foxp3^+CD4^+CD25^+$ T regulatory cells in the skin, but not the blood, of cutaneous LE patients, and Treg cells are known to downregulate the immune response[39].

A scenario that integrates current theories regarding the pathogenesis of several subsets of cutaneous LE is shown in Fig. 41.1. In the proposed model, a response to UVR triggers cytokine, chemokine, and antimicrobial peptide production by keratinocytes as well as endothelial cell activation, thereby initiating the immune response. In the context of genetic and environmental risk factors, a complex cascade ensues that includes activation of dendritic cells, release of IFN, activation of T cells, and production of chemokines; a positive feedback loop ultimately results in a lichenoid tissue reaction. In some patients with hydroxychloroquine-refractory disease, myeloid dendritic cells play a role and are associated with a TNF signature[34].

CLINICAL FEATURES

Cutaneous Lupus – Three Major Forms

Classification

The most commonly used classification of cutaneous lesions in LE is that of Dr. James Gilliam[40]. He segregated skin lesions into those that are specific for cutaneous LE and those that are not specific based upon whether the histopathology demonstrated an interface dermatitis or not, respectively. Within the category of specific cutaneous lesions, he subdivided these into acute cutaneous LE, subacute cutaneous LE, and chronic cutaneous LE (Fig. 41.2). This choice of terms was based upon the observation that three distinct types of cutaneous LE are commonly seen: the often transient lesions of acute cutaneous LE (ACLE) typified by malar erythema; the frequently long-lived, intensely inflammatory discoid LE (DLE) lesions which can lead to permanent disfiguring scars; and a photosensitive eruption characteristically more long-lasting than ACLE but without the potential for atrophy or scarring, for which the term subacute cutaneous LE (SCLE) was coined. Typically grouped within the chronic cutaneous LE category are the less common disorders LE tumidus, lupus panniculitis, and chilblain lupus (see Fig. 41.2), despite the observation that characteristic lesions frequently lack an interface dermatitis, especially LE tumidus.

Formal studies have not been done comparing duration of disease activity for the various types of cutaneous LE, and there is a considerable range in the duration of activity within each subtype. Patients with SCLE lesions may have a chronic, relapsing course, while DLE or LE tumidus lesions may have a relatively short duration due to resolution or effective disease control. In fact, some authorities have proposed that LE tumidus should be removed from the chronic category and be given its own category, intermittent cutaneous LE[41]. These controversies aside, Gilliam's classification schema has proven utility in the organization of the various types of cutaneous LE and it is the basis for the classification herein, accompanied by a focus on the morphology and histopathology of lesions (Fig. 41.3). The three major forms of cutaneous LE will be discussed first, followed by the remaining entities outlined in Fig. 41.2.

Discoid lupus erythematosus (DLE)

Discoid lesions represent one of the most common skin manifestations of lupus and they are most frequently found on the face, scalp, and ears (Fig. 41.4), but may be present in a more widespread distribution (Fig. 41.5). It is unusual for discoid lesions to be present below the neck without lesions also being present above the neck[41a]. Occasionally, discoid lesions develop on mucosal surfaces, including the lips, nasal mucosa, conjunctivae, and genital mucosa.

Some patients with discoid lesions exhibit a photodistribution, and sun exposure appears to have a role in lesional development. However, many patients have discoid lesions on sun-protected skin, and there is no clear association between sun exposure and their development.

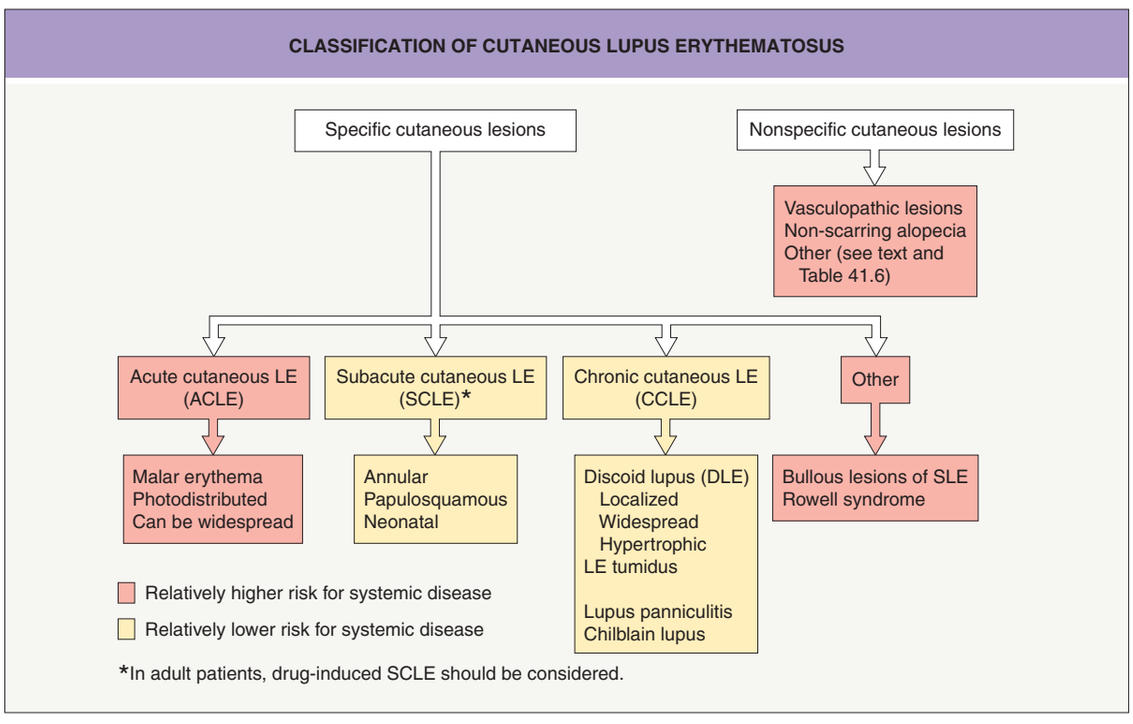


Fig. 41.2 Classification of cutaneous lupus erythematosus (LE). Based upon the classification system originally proposed by Gilliam and Sontheimer[40].

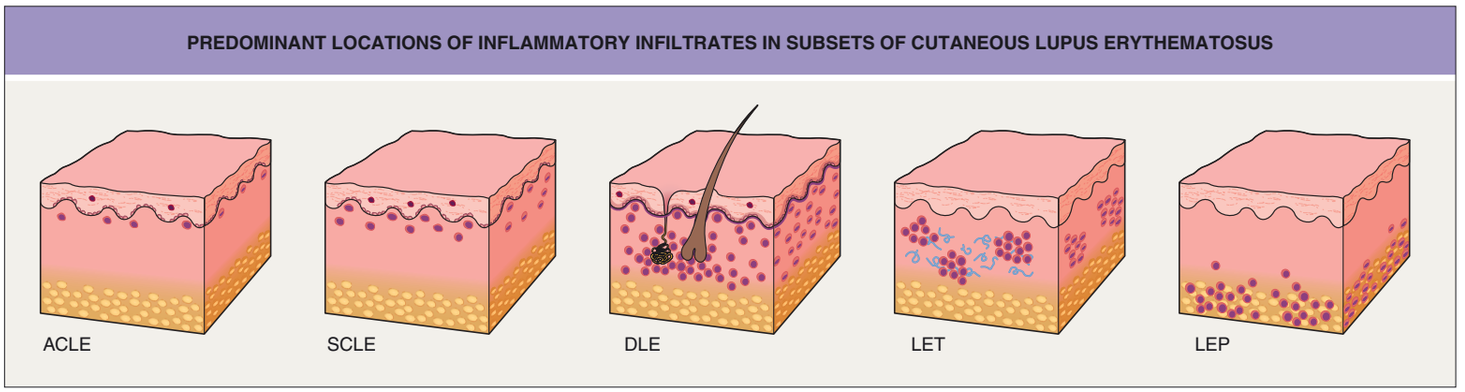


Fig. 41.3 Predominant locations of inflammatory infiltrates in subsets of cutaneous lupus erythematosus. The types of cutaneous lupus erythematosus are: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), discoid lupus erythematosus (DLE), lupus erythematosus tumidus (LET), and lupus panniculitis (LEP); the latter three are forms of chronic cutaneous lupus erythematosus (see Fig. 41.2). The primary locations of the infiltrates are as follows: superficial dermis, ACLE and SCLE; superficial and deep dermis perivascular and periadnexal, DLE; superficial and deep dermis perivascular and periadnexal, LET; and subcutaneous fat, LEP. The final diagnosis requires clinicopathologic correlation.

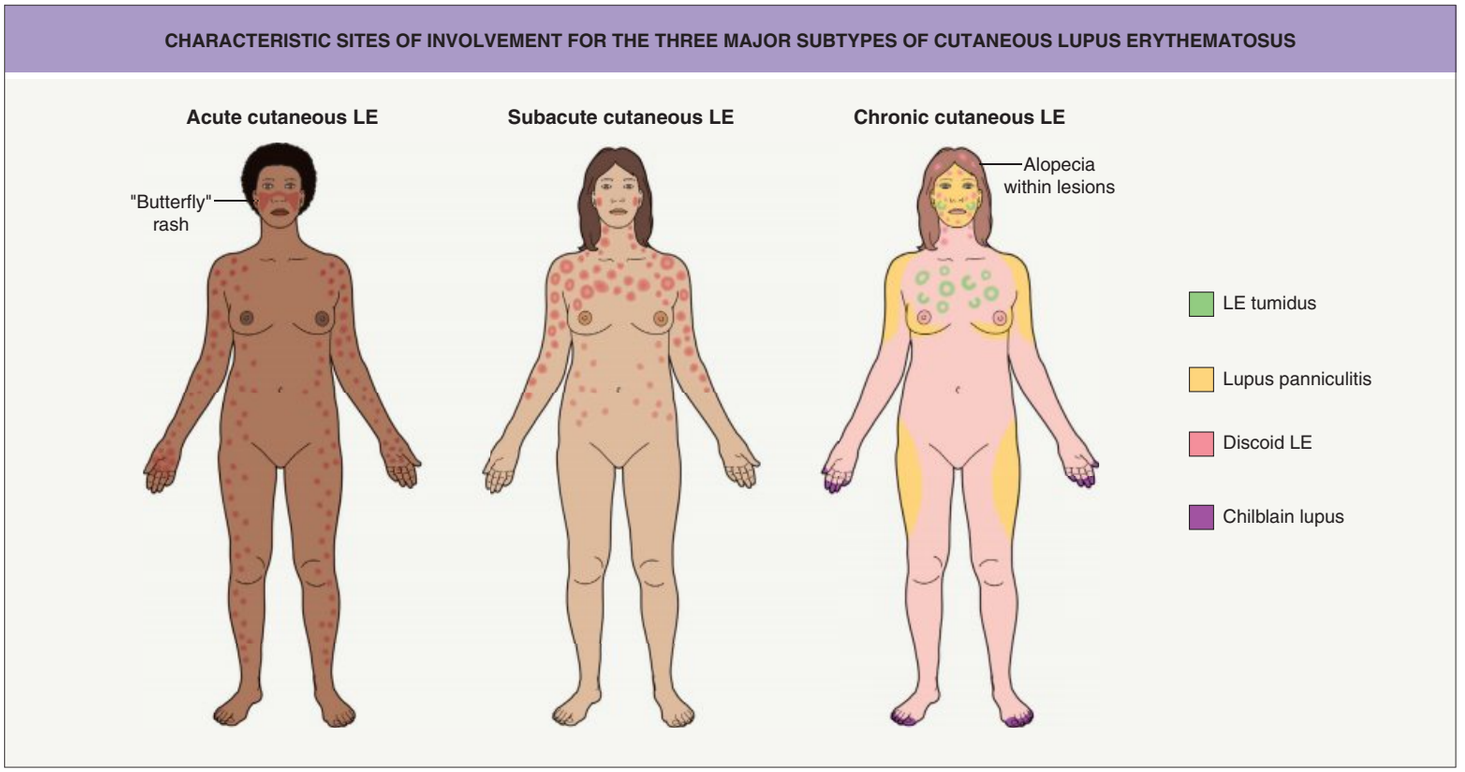


Fig. 41.4 Characteristic sites of involvement for the three major forms of cutaneous lupus erythematosus (LE).

Discoid lesions have the potential for scarring, and, over time, a substantial proportion of patients develop disfiguring scarring. Active lesions are intensely inflammatory, with a pronounced superficial and deep dermal inflammatory infiltrate. As a result, on palpation, active lesions typically feel thicker and firmer than surrounding uninvolved skin. The adnexa are prominently involved, with follicular plugging and scarring alopecia commonly observed. Dyspigmentation is a common sequela noted in longstanding lesions, typically with hypopigmentation in the central area and hyperpigmentation at the periphery (Fig. 41.6), but sometimes with vitiligo-like depigmentation. Rarely, squamous cell carcinoma develops in a longstanding discoid lesion.

Patients who present with discoid lesions may have associated arthralgias, but, over time, only ~10%–20% of these patients eventually meet the classification criteria for SLE (see below)[12,42–44]. Many of these patients meet criteria based primarily upon mucocutaneous disease and/or mild hematologic abnormalities (e.g. leukopenia) rather than serious internal disease[44], and the majority of those who progress do so within five years. The risk may be higher in patients with widespread (disseminated) discoid lesions, defined as having lesions below the neck[42,43], and in children[45].

An unusual variant of DLE is hypertrophic (verrucous) DLE, characterized by thick scaling overlying the discoid lesion or occurring at the periphery of the discoid lesion. The intensely hyperkeratotic lesions are often prominent on the extensor surface of the arms (see Fig. 41.5J), but the face and upper trunk may also be involved. Frequently, there are characteristic lesions of discoid LE present in other locations.

Subacute cutaneous lupus erythematosus (SCLE)

Patients with SCLE typically report photosensitivity and lesions of SCLE most frequently occur on sun-exposed skin. It is notable that the midface is usually spared, while the sides of the face, upper trunk, and extensor aspects of the upper extremities are commonly involved (Fig. 41.7; see Fig. 41.4)[46]. In some patients, the disease may be mild, with only a few small scaly patches appearing after sun exposure.

Lesions of SCLE may have an annular configuration, with raised pink–red borders and central clearing (Fig. 41.8), or a papulosquamous presentation with a chronic psoriasiform or eczematous appearance. SCLE



Fig. 41.5 Various presentations of discoid lesions of lupus erythematosus. A–C Lesions, which favor the head and neck region, may show erythema, scaling, atrophy, and dyspigmentation in addition to scarring (and alopecia). **D** Note the patulous follicular openings in addition to hyperpigmentation and scale. **E–G** The plaques are well-demarcated and both hypopigmentation and scarring can be seen in a range of skin phototypes. **H, I** Less common sites include the palms and soles, where lesions can be keratotic or ulcerative as in lichen planus. The patient with plantar involvement had systemic lupus erythematosus and responded well to isotretinoin. **J** Occasionally, hypertrophic lesions develop with significant hyperkeratosis. **K** The scarring process may be destructive. *C, Courtesy Kalman Watsky, MD; E–G, Courtesy Luis Requena, MD; J, Courtesy Julie V. Schaffer, MD.*

lesions characteristically have a relatively sparse, superficial inflammatory infiltrate, and, consequently, they are minimally palpable. Lesions often result in dyspigmentation, particularly hypopigmentation or even depigmentation, but rarely develop scarring or dermal atrophy as sequelae.

In about a third of patients with SCLE, the disease is linked to medications, either at its onset or as a drug-induced exacerbation of previously well-controlled disease (Table 41.2). The first drug associated with the development of SCLE was hydrochlorothiazide, but at least 100 agents have been reported subsequently to induce or exacerbate SCLE[47]. A population-based study from Sweden identified (in decreasing order) terbinafine, TNF inhibitors, anti-epileptics, and proton pump inhibitors as the most frequently associated medications[48]. More recently, immune checkpoint inhibitors, in particular pembrolizumab and nivolumab, have been linked to the development or exacerbation of SCLE[49,50]. The cutaneous lesions may or may not clear once the medication is discontinued.



Fig. 41.6 Discoid lupus erythematosus (DLE) lesions with dyspigmentation and scarring alopecia. Hypopigmentation often develops centrally with areas of hyperpigmentation at the periphery. Note the plugging of follicular openings at 12 o'clock. By trichoscopy, follicular red dots can be seen in addition to follicular keratotic plugs (see Ch. 69). *Courtesy Kalman Watsky, MD.*



Fig. 41.7 Subacute cutaneous lupus erythematosus (SCLE). Numerous erythematous annular plaques on the back, some of which have associated white scale. Note the photodistribution. *Courtesy Kathryn Schwarzenberger, MD.*



Fig. 41.8 Subacute cutaneous lupus erythematosus (SCLE). Lesions are most commonly seen on the upper trunk and sun-exposed aspects of the upper extremities. The margins of the annular lesions may have scale-crust (**A**) or be composed of multiple papules (**B**). **C** Note the peripheral scale and relative sparing of the proximal interphalangeal joints. **D** Numerous annular lesions with scale-crust in the inner borders in a patient with terbinafine-induced SCLE. *C, Courtesy Lorenzo Cerroni, MD; D, Courtesy Luis Requena, MD.*



Fig. 41.9 Acute cutaneous lupus erythematosus (ACLE). The facial erythema, often referred to as a "butterfly rash" may be variable (**A**), edematous (**B**), or have associated scale (**C**). The presence of small erosions can aid in the clinical differential diagnosis. *A, Courtesy Kalman Watsky, MD.*

MEDICATIONS ASSOCIATED WITH DRUG-INDUCED SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS
More common/higher risk*
Terbinafine
Thiazide diuretics (e.g. hydrochlorothiazide)
TNF inhibitors (e.g. adalimumab, etanercept, golimumab, infliximab)
Proton pump inhibitors (e.g. lansoprazole, pantoprazole, omeprazole)
Calcium channel blockers (e.g. diltiazem, nifedipine, nitrendipine, verapamil)
Anti-epileptics (e.g. carbamazepine, phenytoin)
Chemotherapy (e.g. taxanes, capecitabine, gemcitabine > doxorubicin, 5-fluorouracil)
Immune checkpoint inhibitors (e.g. nivolumab, pembrolizumab, atezolizumab)
ACE inhibitors (e.g. enalapril, lisinopril)
Less common*
β-blockers
Imiquimod (topical)
Interferon-α and -β
Other immunomodulators (e.g. abatacept, leflunomide, secukinumab, ustekinumab)
Palbociclib, abemaciclib
Ranitidine
HMG-CoA reductase inhibitors ("statins")
Tamoxifen
Thrombocyte inhibitors (e.g. ticlopidine)
VEGF/VEGFR inhibitors (e.g. bevacizumab, pazopanib)
*Medications are classified as being more common or having a higher risk if there were >10 cases reported in the literature as of 2023 or the relative risk in reference 48 was ≥2.0. Medications are classified as being less common if there have been 3–10 cases reported and the relative risk was <2.0.

Table 41.2 Medications associated with drug-induced subacute cutaneous lupus erythematosus (SCLE). ACE, angiotensin converting enzyme; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Approximately half of patients presenting with SCLE fulfill classification criteria for SLE[51]. However, most do so on the basis of laboratory and mucocutaneous findings. In a study of 85 SCLE patients, only six had renal and three had neurologic disease[51]. Since anti-SSA/Ro autoantibodies are associated with Sjögren syndrome as well as SCLE, it is not surprising that some patients have features of both conditions, and some may have serious internal manifestations of Sjögren syndrome such as pulmonary or neurologic disease.

An important feature of SCLE, from the standpoint of understanding the pathogenesis of lupus, is its regular association with anti-SSA/Ro autoantibodies (see Ch. 40). Although investigators differ in their opinions as to the prevalence of anti-SSA/Ro autoantibodies in SCLE, it is likely that a substantial majority of patients with this condition (~70% in a large series, reported range of 60%–100%) have anti-SSA/Ro antibodies[46,52].

Acute cutaneous lupus erythematosus (ACLE)

The lesions of ACLE are exemplified by the development of bilateral malar erythema ("butterfly rash"; Fig. 41.9). These lesions tend to be transient, follow sun exposure, and resolve without scarring (but sometimes with dyspigmentation). An association with anti-dsDNA antibodies and lupus nephritis has been proposed and is plausible, although some patients with a malar rash have neither anti-dsDNA antibodies nor lupus nephritis. Patients presenting with this type of eruption must be evaluated carefully for evidence of internal disease.



Fig. 41.10 Acute cutaneous lupus erythematosus (ACLE). This patient had ACLE lesions on the arms as well as the face.

The morphology of the lesions ranges from mild erythema to intense edema. The presence of telangiectasias, erosions, dyspigmentation and epidermal atrophy (i.e. poikiloderma) may help to distinguish the malar erythema of ACLE from that of common facial eruptions such as seborrheic dermatitis and the erythematotelangiectatic type of rosacea. Occasionally, there is a papular component, and occasionally lesions develop scaling (see Fig. 41.9C). The duration may range from a few hours to several weeks. The face, particularly the malar area, is most commonly affected, and there is often sparing of the nasolabial fold; sometimes lesions may be more widespread in distribution (Fig. 41.10; see Fig. 41.4). When lesions occur on the hands, the knuckles are typically spared. It is not unusual for patients with ACLE to also have oral ulcerations.

The presence of erythema multiforme-like lesions in lupus patients has been termed Rowell syndrome[53]. Rarely, patients develop an acute eruption clinically similar to toxic epidermal necrolysis or erythema multiforme major (see below). These lesions may represent a severe variant of ACLE or, in some cases, SCLE.

The three major types of cutaneous LE are not mutually exclusive. In a given patient, more than one type of cutaneous lesion may occur.

Cutaneous Lupus – Additional Variants (See Fig. 41.2)

Lupus erythematosus tumidus

Lesions are typically firm erythematous plaques that lack scale or follicular plugging. Although the epidermis appears to be uninvolved in the disease process, there is an intense perivascular and periadnexal inflammatory infiltrate within the dermis, as well as mucin deposition. LE tumidus lesions may be the same as the "urticarial plaques" described in lupus patients. However, these fixed plaques should not be confused with urticarial vasculitis (see Ch. 24). Some authors state that the lesions most commonly occur on the face, but they are often

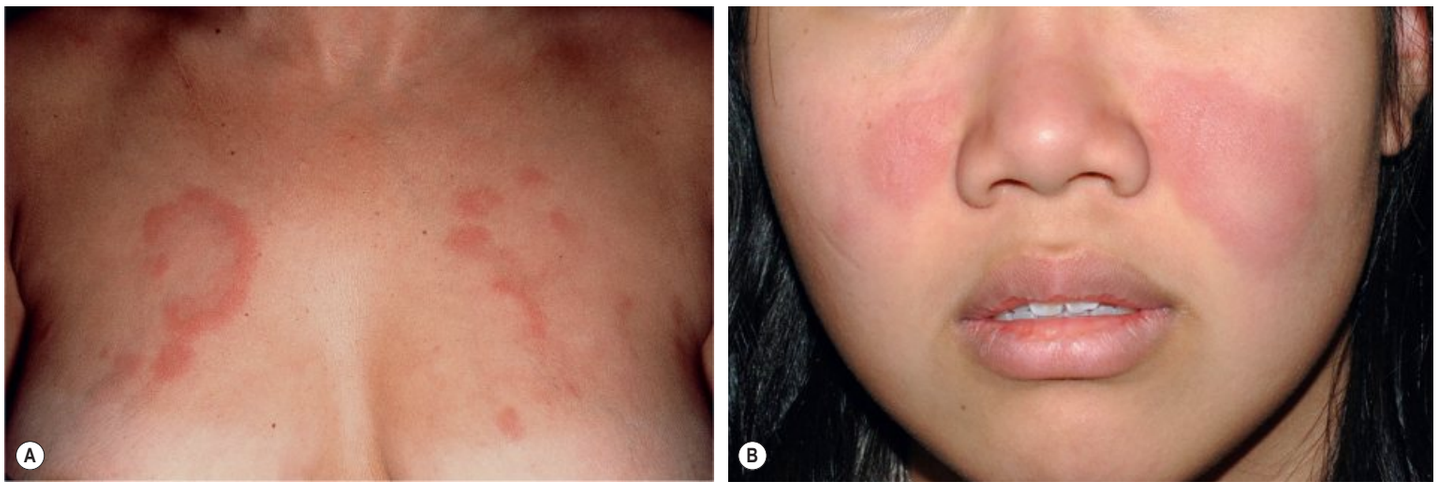


Fig. 41.11 Lupus erythematosus tumidus. Annular pink plaques on the chest (**A**) and pink–violet plaques on the face (**B**). None of the lesions have epidermal change. *B, Courtesy Julie V. Schaffer, MD.*



Fig. 41.12 Lupus panniculitis. Erythematous plaque on the upper arm. The lesions may resolve with lipoatrophy.



Fig. 41.13 Chilblain lupus. Violaceous plaques, some with scale, on toes. If there is a family history of this disorder, the possibility of mutations in *TREX1*, which encodes a DNA exonuclease, or *SAMHD1*, which encodes a host restriction nuclease that plays a role in the innate immune response, can be considered.

observed on the trunk as well (Fig. 41.11). Morphologically, the lesions are similar to those of lymphocytic infiltrate of Jessner and may have central clearing (see Ch. 121); some clinicians believe that lymphocytic infiltrate of Jessner and LE tumidus are either very closely related or exist along the same disease spectrum[54].

In patients reported to have LE tumidus, the very low prevalence of SLE, the relative lack of serologic abnormalities, and the very low prevalence of immunoglobulin deposition within the cutaneous lesions have made it difficult to determine whether LE tumidus is actually a variant of LE or an independent entity. However, the presence of LE tumidus lesions in patients with other specific types of cutaneous LE is evidence in favor of its being classified as a form of cutaneous LE. In the majority of patients, LE tumidus has been reported to be reproducible by phototesting[55]. The lesions tend to resolve without scarring, atrophy, or dyspigmentation.

Lupus panniculitis

Intense inflammation in the fat leads to indurated plaques that can evolve into disfiguring, depressed areas. Lesions of lupus panniculitis have a distinctive distribution, occurring predominantly on the upper arms (Fig. 41.12), face, scalp, upper trunk, thighs, buttocks, and breasts (see Fig. 41.4)[56]. Some patients may have discoid lesions overlying the panniculitis, and, in those cases, the condition is sometimes referred to as lupus profundus. For further discussion of lupus panniculitis, see Chapter 100.

Chilblain lupus

Chilblain lupus (SLE pernio; Fig. 41.13) consists of red or dusky purple papules and plaques on the toes, fingers, and sometimes the nose, elbows, knees, and lower legs. The lesions are brought on or exacerbated by cold, particularly moist cold climates. These lesions may represent the concurrence of ordinary chilblains in a patient with LE (see Ch. 88), although, with time, the lesions may develop a gross and microscopic appearance consistent with that of a discoid lesion.

Heterozygous mutations in *TREX1* (see above) or *SAMHD1* can lead to a familial form of chilblain lupus with an onset during childhood[57]. Affected individuals may have arthralgias and a positive ANA, but otherwise do not develop internal disease. Mutations in these same genes, as well as *ADAR1*, *IFIH1*, and *RNASEH2A/B/C*, can result in the Aicardi–Goutières syndrome, a primarily autosomal recessive autoinflammatory disorder characterized by recurrent sterile fevers, progressive developmental delay, and chilblains (see Table 45.7, Type I interferonopathies). Mutations in these seven genes lead to an accumulation of nucleic acids, e.g. dsDNA, RNA:DNA duplexes.

Discoid lupus erythematosus/lichen planus overlap syndrome

A discoid lupus erythematosus/lichen planus overlap syndrome has been described, in which lesions with features of both conditions are present (see Ch. 11).

Neonatal lupus erythematosus (NLE)

A neonatal form of SCLE may occur in infants whose mothers have anti-SSA/Ro autoantibodies. In babies who have neonatal lupus erythematosus (NLE), the SCLE-like lesions are histologically identical to



Fig. 41.14 Neonatal lupus erythematosus. Annular erythematous plaques on the forehead and scalp. Note the resemblance to the annular form of subacute cutaneous lupus erythematosus. *Courtesy Julie V. Schaffer, MD.*

SYSTEMIC EVALUATION OF AN INFANT WITH CUTANEOUS NEONATAL LUPUS ERYTHEMATOSUS
Initial and serial evaluations until 6–9 months of age
History, review of systems & physical examination: examination includes monitoring of growth and head circumference*; frequency depends upon degree of systemic involvement
Laboratory studies: electrocardiogram +/− echocardiogram, CBC with differential and platelet count, liver function tests; if tests are initially normal and infant without signs or symptoms, then tests repeated every 2–3 months × 2–3 (otherwise more frequently)
Family counseling and care coordination: risk for NLE in subsequent pregnancies, risk for development of AI-CTD in mother and, possibly, child
Preemptive treatment: for mothers of infants with cardiac NLE, consider hydroxychloroquine during subsequent pregnancies
Long-term considerations
History and physical examination: periodically per pediatrician
Laboratory studies: if normal or return to normal and the child remains healthy, further testing is not required
Risk of AI-CTD as adolescent/adult
*Macrocephaly/hydrocephalus and chondrodysplasia punctata (stippled epiphyses) have been reported as possible manifestations of NLE.

Table 41.3 Systemic evaluation of an infant with cutaneous neonatal lupus erythematosus (NLE). In the setting of characteristic skin lesions, the diagnosis is established via autoantibody testing in the mother (anti-SSA/Ro autoantibodies) +/− in the infant (anti-SSA/Ro, -RNP); if skin lesions are atypical, histologic examination may be required. AI-CTD, autoimmune connective tissue disease; CBC, complete blood count.

those of SCLE in adults, and there is a strong association with anti-SSA/Ro antibodies. Indeed, almost 100% of babies with NLE have anti-SSA/Ro antibodies[58], and less frequently anti-U_1RNP autoantibodies are present. Unlike SCLE in adults, lesions have a predilection for the face, especially the periorbital region and scalp (Fig. 41.14).

Photosensitivity is very common in NLE, but sun exposure is not required for lesions to form, as it is possible for lesions to be present at birth. Neonatal lupus skin lesions typically resolve completely, although perhaps one-fourth to one-third of children have cutaneous residua of telangiectasias, dyspigmentation, and/or atrophic scarring[59,60]. Atrophic scarring may be more likely in infants whose lesions began *in utero*[60].

Infants who have the cutaneous lesions of NLE may also exhibit internal manifestations. The major extracutaneous findings are congenital heart block (with or without cardiomyopathy), hepatobiliary disease, and cytopenias, in particular thrombocytopenia. The heart block is almost always present by birth, but on rare occasions has developed after birth. Clinically significant cardiomyopathy occurs concurrently in a small percentage of babies who have heart block. Usually, the cardiomyopathy is apparent during the neonatal period, but it is possible for it to become apparent only after several months have elapsed. Cardiac NLE has a mortality rate of approximately 20%, and approximately two-thirds of children require pacemakers[61].

Hepatobiliary disease and cytopenias, especially thrombocytopenia, may be present at birth, or they may develop within the first few months of life[62]. Hepatobiliary disease can vary in severity and may present as liver failure during gestation or in the neonatal period, conjugated hyperbilirubinemia during the first few weeks of life, or mild elevations of aminotransferases at 2–3 months of life. There are also reports of hydrocephalus, microangiopathic hemolysis, and disseminated intravascular coagulation.

Although most children with cutaneous NLE do not have significant internal involvement, a systemic evaluation and counseling is recommended (Table 41.3). Mothers who have had a baby with cutaneous NLE have an increased likelihood of having a subsequent pregnancy complicated by NLE, including cardiac involvement. When pregnant, these women should be cared for by a perinatologist who has specialized training in high-risk prenatal care.

Bullous lesions

In the clinical setting of lupus, bullous lesions may appear for several reasons. On occasion, bullous or crusted lesions occur simply as a result of the intensity of the basal cell damage in lesions of ACLE or SCLE (see Fig. 41.8A) or, possibly, DLE. Rarely, a dramatic, acute eruption similar to erythema multiforme major or toxic epidermal necrolysis (TEN) may occur in patients with preexisting ACLE or SCLE, or it may appear *de novo* (Fig. 41.15). Blisters occurring within ACLE and SCLE lesions and erythema multiforme-like and TEN-like cutaneous lupus fit within the category of lupus-specific skin lesions.



Fig. 41.15 Toxic epidermal necrolysis-like eruption of acute lupus erythematosus. This presentation has also been referred to as a form of *a*cute *s*yndrome of *a*poptotic *p*an-epidermolysis (ASAP).

The term bullous eruption of SLE, or bullous SLE, has been used to describe an acquired blistering eruption in patients who fulfill the criteria for SLE. It consists of vesicles and bullae whose histopathology often resembles dermatitis herpetiformis, with a primarily neutrophilic infiltrate and microabscesses within the dermal papillae (Fig. 41.16)[63]. In some patients, the clinical and histopathologic features may resemble neutrophil-rich bullous pemphigoid or epidermolysis bullosa acquisita. Immunoreactants are often found at the basement membrane zone and antibodies to type VII collagen have been detected in several patients[64]. This eruption may represent the concurrence of lupus with an autoimmune blistering disease due to autoantibodies to a component of the basement membrane zone. There are also a number of case reports of other autoimmune bullous diseases appearing in patients with lupus (reviewed in reference 65).



Fig. 41.16 Bullous eruption of systemic lupus erythematosus. A Vesicles and bullae due to autoantibodies against type VII collagen can develop in patients with systemic disease. **B** Multiple vesicles and bullae as well as erosions and hypopigmentation at sites of previous lesions in a woman with SLE. *B, Courtesy Edward Cowen, MD.*

Systemic Lupus Erythematosus

Lupus erythematosus is potentially a multi-organ disease, although in individual patients often only one or a few organs are significantly involved. Organ systems most commonly affected are joints, skin, hematologic, renal, and CNS as well as pleural and pericardial serosal surfaces. Nonspecific signs and symptoms such as fever, weight loss, fatigue, myalgias, and lymphadenopathy are also common in SLE. Additional less common manifestations are quite varied and include sensorineural hearing loss and vision loss. Although ACLE is the cutaneous phenotype with the strongest association with systemic disease, patients with any type of cutaneous LE may develop internal involvement.

Since SLE is complex and variable, classification criteria have been developed to ensure that patients in clinical studies have SLE rather than other conditions that may mimic it. Historically, the American College of Rheumatology (ACR) criteria, developed in 1982 and modified in 1997, have been most commonly used. In 2012, a new set of criteria from the Systemic Lupus International Collaborating Clinics (SLICC) aimed to improve the sensitivity of the ACR criteria[66] (Table 41.4). In 2019, the ACR, in concert with the European League Against Rheumatism (EULAR), released a new classification system[67] (Table 41.5). Some of its notable features are as follows:

1. Presence of ANA (titer ≥1 : 80) is an entry criterion. Patients with persistently negative ANA tests are excluded.
2. Individual criteria have different weights and need not occur simultaneously.
3. Within a particular domain (e.g. renal), only the highest weighted criterion counts.
4. A criterion is counted only if SLE is the most likely explanation for the finding.

Nonspecific Cutaneous Lesions

Vascular lesions are common in patients with LE, particularly in those who have systemic disease (Table 41.6). These lesions include Raynaud phenomenon (see Ch. 43), livedo reticularis, palmar erythema, and nail-fold telangiectasia. Purpura, urticarial papules, or ulcerations due to vasculitis may occur, as well as cutaneous infarctions resembling Degos disease or atrophie blanche. Patients with cutaneous LE who have any of these findings should be evaluated for systemic disease. Livedo reticularis, thromboses, ulcerations, and lesions resembling Degos disease have each been associated with antiphospholipid antibodies[68] (see Ch. 23). The association of livedo reticularis with ischemic CNS disease has been called Sneddon syndrome (see Ch. 23), and the phenotype of the antiphospholipid syndrome has been called Hughes syndrome[69].

Alopecia often occurs as a result of scarring discoid lesions. However, non-scarring diffuse alopecia can appear in patients with systemic disease. It has been reported that patients with lupus have an increased likelihood of alopecia areata compared with the general population.

Sclerodactyly, calcinosis, and rheumatoid nodules, findings more consistent with systemic sclerosis or rheumatoid arthritis, have been observed in some patients with lupus, although many of the patients with these findings may have overlap syndromes rather than classic lupus. Other skin findings reported to occur in patients who have lupus include erythromelalgia, papulonodular mucinosis (of Gold; see Ch. 46), and anetoderma (see Ch. 99). Of note, ~75% of the patients with papulonodular mucinosis have SLE. Rarely, significant periorbital edema can develop secondary to dermal mucin. A Sweet syndrome-like presentation can also be seen in patients with SLE and this has been given several names including neutrophilic dermatosis in conjunction with LE and non-bullous neutrophilic LE as well as simply Sweet syndrome in association with SLE.

Patients with SLE have more subtle nail-fold capillary abnormalities than do patients with systemic sclerosis or dermatomyositis. Prominent large, tortuous capillaries and areas of marked avascularity are not characteristic of SLE.

PATHOLOGY

Histopathology

Histologic findings in cutaneous LE depend in large part on the subtype (Fig. 41.17; see Fig. 41.3). Characteristic findings in ACLE, SCLE, discoid lesions, LE tumidus, and lupus panniculitis are outlined in Table 41.7. However, in practice, an overlap in histologic findings occurs among the various clinical phenotypes, particularly ACLE, SCLE, and discoid lesions. Some of the more distinctive histologic features of cutaneous LE are basal cell damage (also referred to as vacuolar degeneration, hydropic change, or interface dermatitis), lymphohistiocytic inflammatory infiltrates admixed with $CD123^+$ plasmacytoid dendritic cells, and, primarily in discoid lesions, periadnexal inflammation, follicular plugging, and scarring. In lesions of ACLE, dermal changes can be relatively subtle although basal cell damage may be pronounced. In SCLE, epidermal changes and a superficial lymphocytic infiltrate are common. In contrast to discoid lesions, SCLE lesions tend to have little or no hyperkeratosis, basement membrane thickening, periadnexal infiltrate, follicular plugging, deep dermal infiltrate, or scarring[70,71]. LE tumidus has prominent dermal mucin deposition and dermal perivascular and periadnexal lymphocytic infiltrates with a lack of epidermal change. While changes of lupus panniculitis are most prominent in the subcutis, there may be overlying changes of DLE[72]. Occasionally, cutaneous LE presents with a neutrophil-rich infiltrate mimicking that of a neutrophilic dermatosis.

The inflammatory infiltrates of cutaneous lupus typically contain plasmacytoid dendritic cells that produce interferons and may play a role in the induction of lesions. Immunohistochemical staining for CD123, a marker for plasmacytoid dendritic cells, has been explored as a means to distinguish cutaneous lupus from other inflammatory diseases (e.g. lichen planopilaris, polymorphous light eruption) and from cutaneous lymphoma. Although positive CD123-staining is not specific for lupus and its sensitivity and specificity remain to be definitively established[73], the pattern and intensity of staining may help to distinguish lupus from other conditions.

THE SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS (SLICC) CLASSIFICATION SYSTEM – CLINICAL AND IMMUNOLOGIC CRITERIA
Clinical criteria
1. Acute cutaneous lupus, including: • Lupus malar rash (do not count if malar discoid) • Toxic epidermal necrolysis variant of SLE • Photosensitive lupus rash in the absence of dermatomyositis • Bullous lupus • Maculopapular lupus rash *OR* Subacute cutaneous lupus (non-indurated psoriasiform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
2. Chronic cutaneous lupus, including: • Classic discoid rash – Localized (above the neck) – Generalized (above and below the neck) • Hypertrophic (verrucous) lupus • Mucosal lupus • Lupus panniculitis (profundus) • Lupus erythematosus tumidus • Chilblain lupus • Discoid lupus erythematosus/lichen planus overlap
3. Oral ulcers*: palate, buccal, tongue, *or* nasal ulcers*
4. Non-scarring alopecia†
5. Synovitis involving 2 or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and at least 30 minutes of morning stiffness
6. Serositis • Typical pleurisy for more than 1 day *OR* pleural effusions *OR* pleural rub • Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day *OR* pericardial effusion *OR* pericardial rub *OR* pericarditis by electrocardiography‡
7. Renal Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours *OR* red blood cell casts
8. Neurologic • Seizures • Psychosis • Mononeuritis multiplex¶ • Myelitis • Peripheral or cranial neuropathy§ • Acute confusional state‖
9. Hemolytic anemia
10. Leukopenia (<4000/mm^3 at least once)# OR lymphopenia (<1000/mm^3 at least once)^
11. Thrombocytopenia (<100 000/mm^3 at least once)**
Immunologic criteria
1. ANA level above laboratory reference range
2. Anti-dsDNA antibody level above laboratory reference range (or >2-fold the reference range if tested by ELISA)
3. Anti-Sm: presence of antibody to Sm nuclear antigen
4. Antiphospholipid antibody positivity as determined by any of the following: • Positive test result for lupus anticoagulant • False-positive test result for rapid plasma reagin • Medium- or high-titer anti-cardiolipin antibody level (IgA, IgG, or IgM) • Positive test result for anti-β2-glycoprotein I (IgA, IgG, or IgM)
5. Low complement: low C3, low C4, low CH50
6. Direct Coombs test in the absence of hemolytic anemia
*In the absence of other causes, such as vasculitis, Behçet disease, infection (herpesvirus), inflammatory bowel disease, reactive arthritis, and acidic foods. †Diffuse thinning or hair fragility with visible broken hairs in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia. ‡In the absence of other causes, such as infection, uremia, and Dressler pericarditis. ¶In the absence of other known causes such as primary vasculitis. §In the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus. ‖In the absence of other causes, including toxic/metabolic, uremia, drugs. #In the absence of other known causes, such as Felty syndrome, drugs, and portal hypertension. ^In the absence of other known causes, such as corticosteroids, drugs, and infection. **In the absence of other known causes, such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura.

Table 41.4 The Systemic Lupus International Collaborating Clinics (SLICC) classification system – clinical and immunologic criteria[66]. Criteria are cumulative and need not be present concurrently. The diagnosis of systemic lupus is based upon having at least 4 of 17 criteria, including at least 1 clinical criterion and 1 immunologic criterion OR biopsy-proven lupus nephritis in the presence of ANAs or anti-dsDNA antibodies. anti-dsDNA, anti-double-stranded DNA; ANA, anti-nuclear antibody; ELISA, enzyme-linked immunosorbent assay; SLE, systemic lupus erythematosus.

Antibody Deposits in Lesional Skin

Examination of the skin for deposits of immunoreactants is called direct immunofluorescence (DIF). DIF of lesional skin does not replace routine histologic staining as the method of choice for establishing a diagnosis of cutaneous LE. However, in those cases where the routine histopathology is equivocal, DIF can be a valuable asset in establishing a diagnosis.

The most characteristic DIF finding in cutaneous LE is antibody deposition at the dermal–epidermal junction and around hair follicles. These deposits are typically granular, and they are composed primarily of IgG and/or IgM (Fig. 41.18), although IgA can also occasionally be seen. In addition, deposits of complement proteins are to be expected. Some investigators have reported that in SCLE, granular deposits of IgG and IgM are observed primarily within the epidermis rather than at the dermal–epidermal junction[71]. There is evidence that the epidermal deposits are due to anti-SSA/Ro autoantibodies depositing directly within the skin[74].

In active lesions of ACLE, SCLE, and DLE, DIF of lesional skin is positive in the majority of cases. In general, a positive DIF supports

EULAR/ACR classification for SLE

Entry criterion
Anti-nuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

If absent, do not classify as SLE; if present, apply additive criteria

Additive criteria
- Do not count a criterion if there is a more likely explanation than SLE
- Occurrence of a criterion on at least one occasion is sufficient
- SLE classification requires at least one clinical criterion and ≥10 points
- Criteria need not occur simultaneously
- Within each domain, only the highest weighted criterion is counted toward the total score*

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		**Antiphospholipid antibodies**	
Fever (>38.3°C)	2	Anti-cardiolipin antibodies† *OR*	
Hematologic		Anti-β2GP1 antibodies *OR*	
Leukopenia (WBC <4.0 x 10^9/L)	3	Lupus anticoagulant	2
Thrombocytopenia (plts <100 x 10^9/L)	4	**Complement proteins**	
Autoimmune hemolysis	4	Low C3 *OR* low C4	3
Neuropsychiatric		Low C3 *AND* low C4	4
Delirium	2	**SLE-specific antibodies**	
Psychosis	3	Anti-dsDNA antibody‡ *OR*	
Seizure	5	Anti-Sm antibody	6
Mucocutaneous¶			
Non-scarring alopecia§	2		
Oral ulcers§	2		
Subacute cutaneous§ *OR* discoid lupus§	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria (>0.5 g/24 h)	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

Classify as systemic lupus erythematosus with a score of 10 or more if entry criterion fulfilled

*Additional criteria items within the same domain will not be counted.
†Anti-cardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 units or >99th percentile).
‡In an assay with at least 90% specificity against relevant disease controls.
¶If skin biopsy is performed, typical changes must be present.
§Observed by a clinician on physical examination or via a photograph.

Table 41.5 The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for systemic lupus erythematosus (SLE)[67]. plts, platelets. *Modified from Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol 2019;71:1400–12.*

CUTANEOUS FINDINGS (NONSPECIFIC) THAT SUGGEST THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS
Diffuse non-scarring alopecia
Raynaud phenomenon
Nail-fold (periungual) telangiectasias and erythema
Vasculitis
• Urticarial vasculitis
• Small vessel vasculitis (e.g. palpable purpura)
• Polyarteritis nodosa-like lesions
• Ulcerations
Cutaneous signs of antiphospholipid syndrome
• Livedo reticularis
• Ulcerations
• Acrocyanosis
• Atrophie blanche-like lesions
• Degos-like lesions
• Livedoid vasculopathy
Palmar erythema
Papular and nodular mucinosis
Sweet syndrome-like neutrophilic dermatosis and neutrophilic urticarial dermatosis

Table 41.6 Cutaneous findings (nonspecific) that suggest the diagnosis of systemic lupus erythematosus. These are in addition to skin signs of other autoimmune connective tissue diseases, which raise the possibility of an overlap syndrome.

the diagnosis of cutaneous LE, but a negative DIF does not exclude the diagnosis. It has been noted that DIF is most likely to be positive in well-established, active lesions. DIF is often negative or nonspecific in LE tumidus. In lupus panniculitis, DIF may show immunoreactants around dermal vessels, but granular deposits at the dermal–epidermal junction are not uniformly present.

Antibody Deposits Within Normal-Appearing Skin

In normal-appearing skin, the presence of antibody deposits at the dermal–epidermal junction correlates reasonably well with systemic disease. The antibody deposits are typically granular and are sometimes referred to as a "lupus band", with examination for the deposits referred to as the "lupus band test". The terminology is confusing, because some authors use the term "lupus band" to apply to the antibody deposits at the dermal–epidermal junction, whether the skin tested is normal-appearing or lesional, while other authors reserve the term "lupus band" to describe antibody deposits in normal-appearing skin. It has been proposed that, if this terminology is used, the investigator should modify the term "lupus band" by a preceding adjective of "lesional" or "non-lesional", so that the subject of discussion is clearly identified.

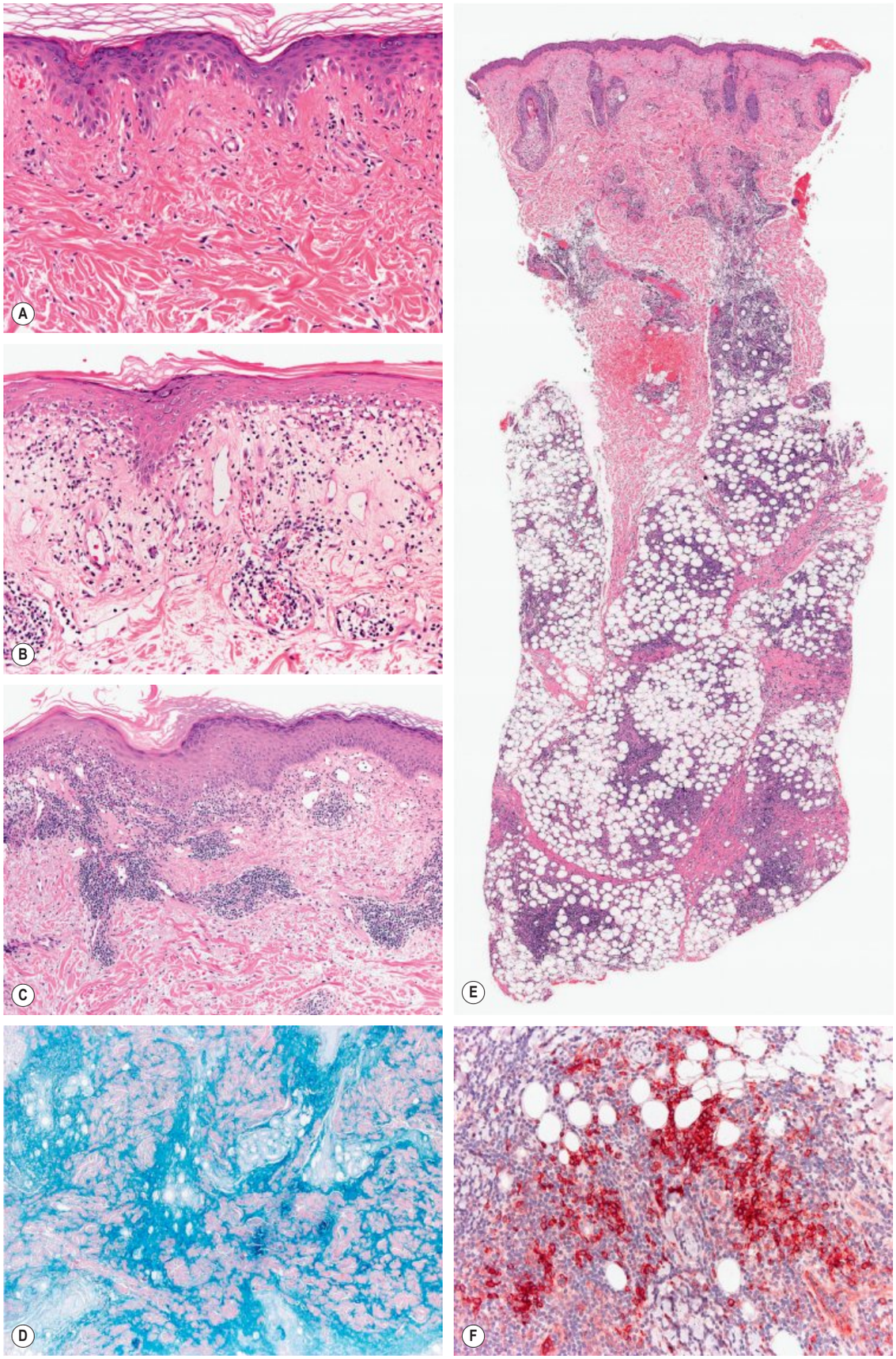


Fig. 41.17 Histopathologic features of cutaneous lupus erythematosus (LE). A Acute cutaneous LE showing mild interface dermatitis with vacuolization of basal keratinocytes and sparse superficial lymphoid infiltrates. **B** Subacute cutaneous LE with more obvious interface dermatitis and perivascular inflammation. **C** Discoid LE showing focal interface dermatitis and dense perivascular lymphoid infiltrates throughout the dermis. **D** Mucin deposition within the dermis highlighted by a colloidal iron stain. **E** Lupus panniculitis with prominent inflammatory infiltrates within the lobules of the subcutaneous fat. Perivascular and periadnexal lymphocytic infiltrates are also present in the dermis. **F** The pattern and intensity of immunohistochemical staining for CD123 (plasmacytoid dendritic cells) may help to distinguish cutaneous lupus, including lupus panniculitis, from other disorders. *Courtesy Lorenzo Cerroni, MD.*

Weak, discontinuous deposits may be seen in persons who do not have LE, including healthy adults, particularly when chronically sun-exposed skin is examined. For this reason, many investigators do not consider a non-lesional lupus band test to be positive unless the deposition of immunoreactants is strong and continuous. A true positive non-lesional lupus band test occurs in three-quarters or more of patients with SLE if sun-exposed skin is examined, and in about one-half of patients with SLE if sun-protected skin is examined[75]. A positive non-lesional lupus band test is unlikely to occur in patients who do not have SLE, but there are instances where the non-lesional lupus band test has been positive in patients with other autoimmune diseases.

CHARACTERISTIC HISTOLOGIC FINDINGS IN CUTANEOUS LUPUS ERYTHEMATOSUS (LE)					
Histologic finding	**Acute cutaneous LE**	**Subacute cutaneous LE**	**Discoid lesions of LE**	**LE tumidus**	**Lupus panniculitis***
Vacuolar alteration of basal layer	++	++	+	–	+/–
Apoptotic keratinocytes	+	++	+	–	+/–
Hyperkeratosis	–	–/+	+	–	–
Epidermal atrophy	+	++	+/–	–	+/–
Pilosebaceous atrophy	–	–	+	–	–
Follicular plugging	–	+	++	–	–
Basement membrane zone thickening	+/–	+	++	–	–
Lymphocytic infiltrate in the upper dermis	+	+	++	++	+/–
Lymphocytic infiltrate in the lower dermis	–	–	++	++	+
Lymphocytic infiltrate in the subcutis	–	–	+/–	+/–	++
Lymphocytic infiltrate, periadnexal	–	+/–	++	+	+/–
Dermal mucin	+	+	+	+	+/–
Dermal fibrosis	–	–	+/–	–	–

*May have overlying findings of discoid LE.

Table 41.7 Characteristic histologic findings in cutaneous lupus erythematosus (LE). The table is intended as a broad overview only. Not every feature will be present in every lesion, some features may be present that are not indicated as characteristic, and overlap exists amongst subtypes. [–], not a defining feature; [+/–], a feature that may be present in some lesions; [+], a feature that is typically present; [++], a defining feature that may be prominent.

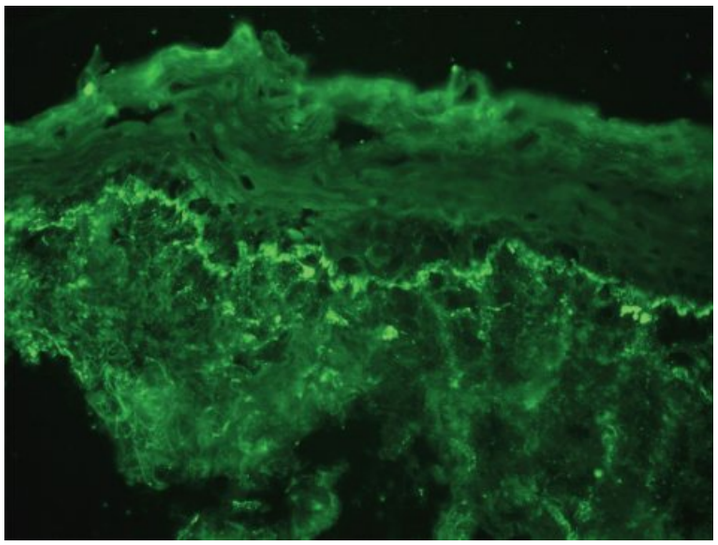


Fig. 41.18 Direct immunofluorescence of cutaneous lupus. Granular deposits of IgM are present at the dermal–epidermal junction within lesional skin. Antibody deposits at the dermal–epidermal junction are the most characteristic immunohistologic finding in lesions of cutaneous lupus and normal skin of patients with systemic lupus erythematosus. *Courtesy Janet Fairley, MD.*

In most cases, clinical evaluation and serologic testing for specific autoantibodies provide the required information, and the non-lesional lupus band test is superfluous. In cases where the clinical presentation or laboratory findings are atypical, the non-lesional lupus band test may have diagnostic value.

DIFFERENTIAL DIAGNOSIS AND EVALUATION

The differential diagnosis varies considerably with the subtype of cutaneous LE under consideration. Some of the major entities in each of the differential diagnoses are outlined in Table 41.8.

In evaluating a patient with cutaneous lesions, lesional biopsy for H&E is, in general, the most valuable diagnostic test. An approach to the diagnosis of cutaneous LE is shown in Fig. 41.19. In an occasional situation, such as that of a patient with known SLE who has transient facial lesions that appear to be ACLE, the clinician may forego a biopsy because of the high likelihood of obtaining nonspecific findings and the cosmetic sequela of a scar on the face. Thus, the diagnostic tree presented is not intended to be followed strictly for each situation, but

DIFFERENTIAL DIAGNOSES OF CUTANEOUS LUPUS SUBTYPES
Acute cutaneous lupus/malar rash
• Rosacea (including corticosteroid-induced) • Seborrheic dermatitis (especially photosensitive form) • Sunburn • Drug-induced photosensitivity (phototoxic and photoallergic) • Dermatomyositis • Erysipelas • Pemphigus erythematosus and foliaceus • Dermatitis – atopic, contact, and photocontact
Subacute cutaneous lupus
• Psoriasis • Dermatophytosis, including tinea incognito • Photolichenoid drug eruption • Polymorphous light eruption • Granuloma annulare • Figurate erythemas (e.g. erythema annulare centrifugum) • Dermatitis – atopic, contact and photocontact • Pemphigus foliaceus
Discoid lesions
• Facial discoid dermatosis • Tinea faciei, capitis or corporis, pityriasis (tinea) versicolor • Lichen planus and lichen planopilaris • Sarcoidosis • Granuloma faciale • Dimorphic fungal infections, lupus vulgaris • Follicular mucinosis (alopecia mucinosa) • When single lesion, non-melanoma skin cancer
Tumid lupus lesions
• Lymphocytic infiltrate of Jessner* • Polymorphous light eruption • Cutaneous lymphoid hyperplasia (pseudolymphoma of the skin) • Reticular erythematous mucinosis†
Lupus panniculitis
• Other panniculitides, in particular subcutaneous panniculitis-like T cell lymphoma (see Ch. 100)
*Some authorities believe that lymphocytic infiltrate of Jessner and LE tumidus are the same condition or along the same disease spectrum. †Some authorities believe that reticular erythematous mucinosis and LE tumidus are the same condition or along the same disease spectrum.

Table 41.8 Differential diagnoses of cutaneous lupus subtypes. Mothers of boys with X-linked chronic granulomatous disease and patients with Sjögren syndrome have an annular erythema similar to annular SCLE; patients with GVHD can develop SCLE-like lesions.

rather is meant as a general overview that is to be individualized for each patient.

In evaluating a patient with cutaneous lesions for the presence of systemic disease, the dermatologist can take a directed history, perform a cutaneous examination looking for signs of possible systemic disease (such as vasculitic lesions), and perform blood and urine testing for evidence of hematologic or renal disease, ANA, and SLE-specific autoantibodies (Table 41.9; see Fig. 40.5). Many clinicians also obtain an ESR and complement levels. Autoantibodies to dsDNA and Sm are relatively specific for SLE, and are, therefore, helpful indicators of a high likelihood of systemic disease (see Ch. 40). Autoantibodies to SSA/Ro, SSB/La, U1RNP, histones, and ssDNA are common in patients with SLE, but they are not disease-specific. An ANA test is helpful if negative, as it is quite unusual for patients with SLE to have a negative ANA test, particularly if the assay employed is the indirect immunofluorescent test. It is common for the ANA test to be positive in patients with cutaneous lesions, but a positive ANA is neither an indicator of systemic disease nor of LE. ANAs may be found in patients with many other diseases (see Ch. 40) and even in apparently normal individuals. Approximately a third of apparently normal individuals have a positive ANA at a dilution of 1:40, 13% at a dilution of 1:80, and 5% at a dilution of 1:160[76].

Clinical evaluation should also include consideration of drug-induced systemic or cutaneous lupus (Table 41.10). Drug-induced SLE typically presents as a systemic illness with arthralgias, myalgias, pleuritis, and fever, but lacking nephritis and CNS disease. SCLE is the most common form of drug-induced cutaneous LE and is clinically and serologically indistinguishable from the classic form; however, patients tend to be older.

In many cases, the decision to make a diagnosis of SLE is done on the basis of whether or not the patient's findings fulfill classification criteria (see Tables 41.4 & 41.5). However, there are limitations to making a diagnosis on the basis of criteria, which were developed primarily to improve reproducibility of research studies and clinical trials. Meeting criteria does not necessarily imply the presence or development of major organ involvement, nor does lack of meeting criteria ensure that an individual patient does not have SLE.

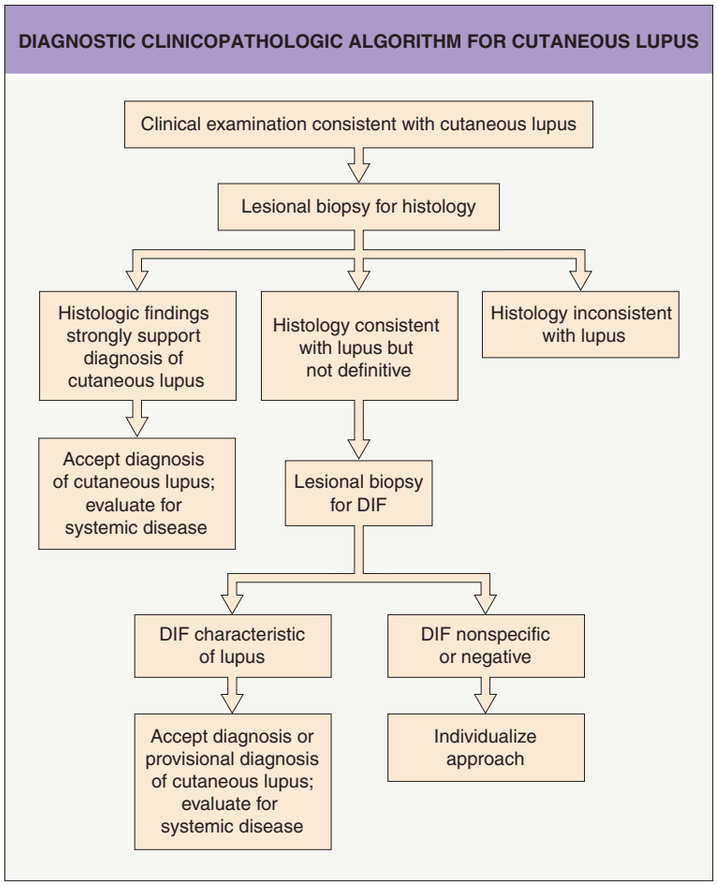


Fig. 41.19 Diagnostic clinicopathologic algorithm for cutaneous lupus. This algorithm is intended as a guide to diagnosis and should be individualized for each situation. For example, lesional biopsy for direct immunofluorescence (DIF) may be performed at the same time as a lesional biopsy for routine histology. Less definitive histologic findings might sometimes be acceptable if the patient is already known to have SLE. Whether a diagnosis is clear-cut or provisional may be, on occasion, a subjective determination.

TREATMENT

Topical Therapy

Topical or intralesional corticosteroids are a mainstay of therapy (Table 41.11). They offer a high degree of safety as well as the potential for a relatively rapid response. The systemic side effects of

EVALUATION FOR SYSTEMIC LUPUS ERYTHEMATOSUS
History and review of systems
Physical examination
• Specific cutaneous lesions (see Tables 41.4 and 41.5) • Nonspecific cutaneous lesions (see Table 41.6) • Lymphadenopathy, arthritis
Laboratory tests
• ANA with profile (anti-dsDNA, -Sm) • Urinalysis • CBC with differential, platelet count • Chemistries (BUN, creatinine) • ESR, CRP • Complement levels (C3, C4) • Antiphospholipid antibodies, PT/PTT

Table 41.9 Evaluation for systemic lupus erythematosus. ANA, anti-nuclear antibodies; BUN, blood urea nitrogen; CBC, complete blood count; CRP, C-reactive protein; ds, double-stranded; ESR, erythrocyte sedimentation rate; PT, prothrombin time; PTT, partial thromboplastin time; Sm, Smith.

CLASSIC DISTINCTIONS BETWEEN DRUG-INDUCED SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS (DI-SCLE) AND DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS (DI-SLE)				
Disease	**Most commonly associated medications**	**Cutaneous findings**	**Systemic findings**	**Associated autoantibodies**
DI-SCLE	See Table 41.2	SCLE	• Usually none • Sometimes arthralgias	Anti-SSA/Ro
DI-SLE	Hydralazine, procainamide, isoniazid, quinidine, methyldopa, chlorpromazine, minocycline, TNF inhibitors*	Usually absent May have malar or photodistributed erythema	• Serositis (arthralgia, pleuritis, pericarditis) • Fever, weight loss, myalgia • Nephritis and CNS disease usually absent	Anti-histone† Anti-dsDNA (reported with TNF inhibitors)
*TNF inhibitors have been associated with DI-SCLE and DI-SLE (as well as drug-induced discoid lupus erythematosus). †Anti-histone antibodies are not specific for DI-SLE as they are commonly found in patients with classic SLE, as well as in other autoimmune connective tissue diseases.				

Table 41.10 Classic distinctions between drug-induced subacute cutaneous lupus erythematosus (DI-SCLE) and drug-induced systemic lupus erythematosus (DI-SLE). CNS, central nervous system.

THERAPY OF CUTANEOUS LUPUS ERYTHEMATOSUS Rx
Local therapy
Sun protection (2)
Topical and intralesional corticosteroids (2)
Topical calcineurin inhibitors (2)
Topical retinoids (3)
Topical tofacitinib (3)
Systemic antimalarial therapy
Hydroxychloroquine (200 mg po daily–BID in adults; up to 6.5 mg/kg ideal body weight/day) (1)*
Chloroquine (125–250 po daily in adults; up to 3.5–4 mg/kg ideal body weight/day) (2)*
Quinacrine (100 mg po daily) (2)
Combination of hydroxychloroquine or chloroquine and quinacrine (2)
Systemic therapy for antimalarial-resistant cutaneous disease
Retinoids (e.g. acitretin, isotretinoin) (1,2)
Thalidomide (50–100 mg po daily for clearing and, if necessary, 25–50 mg po daily–twice weekly for maintenance)† (2)
Lenalidomide (5–10 mg po daily)† (2)
Dapsone (50–150 mg/day, primarily for bullous eruption of SLE) (2)
Methotrexate (10–25 mg/week, orally, IM, SC) (1)
Mycophenolate mofetil (1000–3000 mg/day) (2)
Azathioprine (100–150 mg/day) (3)
Anifrolumab (1, systemic; 2, cutaneous)
Litifilimab (1)
Daxdilimab (1)
JAK inhibitors (3)
Sulfasalazine (2)
Systemic corticosteroids (3)‡
IVIg (2 g/kg every 4–8 weeks, depending on response) (2)
Rituximab (3)
Belimumab (3)
*In 2016, the American Academy of Ophthalmology recommended a maximum dose of ≤5 mg/kg real weight/day of hydroxychloroquine and ≤2.3 mg/kg real weight/day for chloroquine[78]. In a patient weighing 140 pounds (63.6 kg), the dose would be 300 mg daily which could be administered as 200 mg tablets BID alternating with 200 mg daily versus 1.5 tablets daily.
†Concurrently with antimalarials as latter may reduce thrombosis risk.
‡Usually reserved for severe inflammatory cutaneous disease (e.g. Rowell syndrome).

Table 41.11 Therapy of cutaneous lupus erythematosus. General measures for all patients include avoiding photosensitizing medications and smoking cessation. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. BID, twice daily; IM, intramuscular; SC, subcutaneous.

corticosteroids are largely avoided, although the cutaneous side effects are not. It is frequently the case that topical corticosteroids need to be of high potency in order for a response to occur, and discoid lesions are one of the few instances where it may be appropriate to use high-potency corticosteroids on the face. Patients should be instructed about the risks and benefits of therapy, the need to limit the application to affected areas, and the need for monitoring for cutaneous side effects. Particularly in active discoid lesions and LE tumidus lesions, intralesional triamcinolone, often given in a concentration of 2.5–5 mg/ml, depending upon anatomic location, can be very effective. The injections may be repeated monthly while the lesions are active. There are also reports of the successful use of topical immunomodulators (e.g. tacrolimus, pimecrolimus) for cutaneous lesions.

Systemic Therapy

Antimalarial therapy has been used for more than a half-century for cutaneous LE, and it remains the gold standard for systemic therapy. Hydroxychloroquine sulfate is the most commonly chosen antimalarial, as it is usually well tolerated. Chloroquine and quinacrine (mepacrine) are alternatives, but quinacrine is currently not readily available in many parts of the world. In patients who are not responsive to hydroxychloroquine sulfate, quinacrine may be added to the regimen[77]. Quinacrine can turn the skin yellow, although it does not invariably do so. The dose of hydroxychloroquine sulfate chosen is usually 200 mg once or twice per day. It has been reported that if the dose does not exceed 5 mg/kg *actual body weight*/day, eye toxicity is quite unlikely[78]. For chloroquine, the usual dose is 125–250 mg/day, with the eye toxicity-minimizing dose being no more than 2.3 mg/kg *actual body weight*/day[78]. Quinacrine is thought by most not to cause eye toxicity. For patients on hydroxychloroquine sulfate or chloroquine, periodic eye examinations should be done by a physician knowledgeable in antimalarial eye toxicity.

The response to antimalarials is relatively slow. It may take 2 or 3 months for efficacy to be appreciated, and sometimes several more months to achieve maximal efficacy. Consequently, for patients who are beginning therapy for cutaneous LE, topical or intralesional therapy should usually be given along with antimalarial therapy. However, some patients do not respond either to single antimalarial therapy or to the combination of quinacrine with either hydroxychloroquine sulfate or chloroquine[78a].

Disease that is refractory to antimalarials is often refractory to other therapies as well. Nonetheless, it is reasonable to seek a therapy that will work well, if the risks of therapy are deemed to be worth the potential benefits. For antimalarial-resistant patients, therapeutic options include oral retinoids, dapsone, immunosuppressive agents such as mycophenolate mofetil, azathioprine or methotrexate, sulfasalazine, thalidomide or lenalidomide, and systemic corticosteroids[79]. Dapsone is used occasionally for cutaneous LE prior to advancing to immunosuppressive therapy, but it is most often employed for the rare bullous eruption of SLE[80]. Both retinoids and thalidomide are potent teratogens, making them difficult choices in women of childbearing potential. Thalidomide also frequently causes a peripheral neuropathy. For that reason, some clinicians have advocated giving thalidomide in low or intermittent dosing in an attempt to minimize toxicity. Lenalidomide, a second-generation thalidomide derivative, has led to improvement of refractory cutaneous LE and there may be a lower risk of developing peripheral neuropathy.

Responses to both belimumab and rituximab have been disappointing for patients with DLE and mixed for patients with SCLE, suggesting that the underlying pathogenesis, at least for DLE, is not dependent on B cells or that depletion of regulatory B cells by rituximab might be deleterious[81,82]. Of note, rituximab may be helpful for refractory bullous LE. In the future, other immune response modifiers such as anifrolumab (anti-IFN-α receptor antibody)[83], drugs that inactivate or deplete plasmacytoid dendritic cells (e.g. litifilimab, daxdilimab), iberdomide (promotes degradation of transcription factors Ikaros and Aiolos which regulate lymphocyte differentiation), anti-IL-33 antibody, or Janus kinase (JAK) inhibitors may play a role in the treatment of cutaneous LE.

In patients with systemic LE but no major organ involvement (i.e. potentially life-threatening involvement of visceral organs), treatment for mild disease includes NSAIDs, while corticosteroids and immunosuppressives (e.g. mycophenolate mofetil, azathioprine, methotrexate, leflunomide) are usually prescribed for moderate to severe disease. When there is a mild degree of major organ involvement, corticosteroids are the primary treatment, but for moderate to severe involvement, pulse cyclophosphamide or mycophenolate mofetil +/− pulse corticosteroids are often recommended. For a comprehensive review of future biologic therapies for refractory disease, see reference 79.

Adjunctive Therapy

Sun protection is a vital part of therapy for many patients because the sun exacerbates or initiates their skin lesions. For others, sun protection is important for cancer prevention, particularly in hypopigmented skin or in chronic discoid lesions, where the risk of skin cancer development may be higher. Cancer prevention is also essential for patients who are on immunosuppressive therapy. Lastly, it has been reported that sun exposure can exacerbate systemic disease in patients who have SLE. Therefore, there are a variety of reasons why sun protection should be emphasized, even in persons whose skin lesions are not induced or exacerbated by sun exposure.

Sunscreens should be applied to exposed skin daily, and more often if sun sensitivity is great or sun exposure is intense or prolonged. Broad-spectrum, high-SPF sunscreens are preferred (see Ch. 132). In some cases, the addition of a physical sunblock such as titanium dioxide or zinc oxide is useful. Protective clothing is important to emphasize, as the proper protective clothing is often significantly more effective

than sunscreens. Sun avoidance is even more effective than protective chemicals and clothing. Midday sun is particularly high in UVB, a spectrum of UV radiation to which many patients are susceptible. It is more difficult to minimize UVA exposure, as UVA is present in substantial quantities throughout the day and can penetrate some types of window glass. Education on the optimal use of sunscreens and protective clothing and effective approaches to sun avoidance is important for most patients with lupus. Careful attention should be given to vitamin D and calcium intake.

For some patients, cosmetic cover-up is the most helpful therapeutic intervention (see Ch. 153). Particularly in situations where the disease activity has subsided but dyspigmentation remains, cosmetic camouflage of the hyper- or hypopigmentation may be the best approach.

It has been observed that a larger-than-expected percentage of cigarette smokers are represented amongst patients who present with cutaneous lupus and that smokers may have more extensive cutaneous disease and may be more refractory to therapy. Thus, smoking cessation represents a useful adjunctive therapy in some individuals.

Additional figures and table, 1997 Update of the 1982 American College of Rheumatology revised criteria for classification of systemic lupus erythematosus, available in our eBook (see inside front cover for access code).

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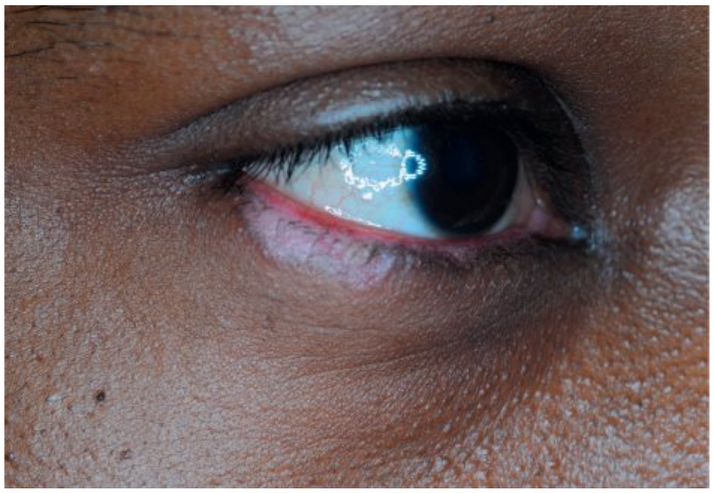
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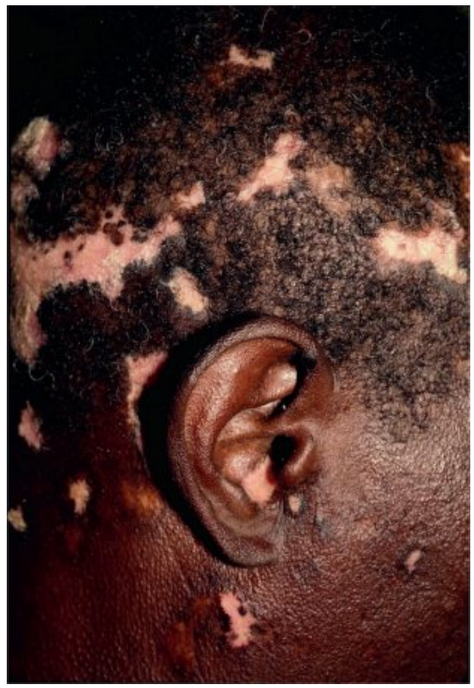
eFig. 41.1 Discoid lupus erythematosus of the lower eyelid. *Courtesy Kalman Watsky, MD.*



eFig. 41.2 Discoid lupus erythematosus. Pink plaque with adherent scale in the conchal bowl. *Courtesy Jeffrey P. Callen, MD.*



eFig. 41.3 Discoid lupus erythematosus. Erythema, hypopigmentation, and scarring. *Courtesy Luis Requena, MD.*



eFig. 41.4 Scarring alopecia due to discoid lupus erythematosus. Note involvement of the conchal bowl. There is not typically conductive hearing loss associated with this finding. *Courtesy M. Joyce Rico, MD.*



eFig. 41.5 Disseminated lesions of discoid lupus erythematosus. Hypopigmented plaques with scarring surrounded by postinflammatory hyperpigmentation. *Courtesy Luis Requena, MD.*



eFig. 41.6 Subacute cutaneous lupus erythematosus. Note the photodistribution of the erythematous papules and plaques with scale-crust. *Courtesy Luis Requena, MD.*



eFig. 41.7 Subacute cutaneous lupus erythematosus. A, B Multiple annular plaques that can resemble the deep form of erythema annulare centrifugum. *Courtesy Luis Requena, MD.*





eFig. 41.8 Subacute cutaneous lupus erythematosus. A, B Plaques can develop hemorrhagic crusts as well as scale and resemble lesions of dermatomyositis and pemphigus foliaceus. *Courtesy Luis Requena, MD.*



eFig. 41.9 Subacute cutaneous lupus erythematosus (SCLE). There are non-scarring, erythematous, slightly scaly plaques on the upper trunk (V-shaped pattern) and sun-exposed sites of the arms.



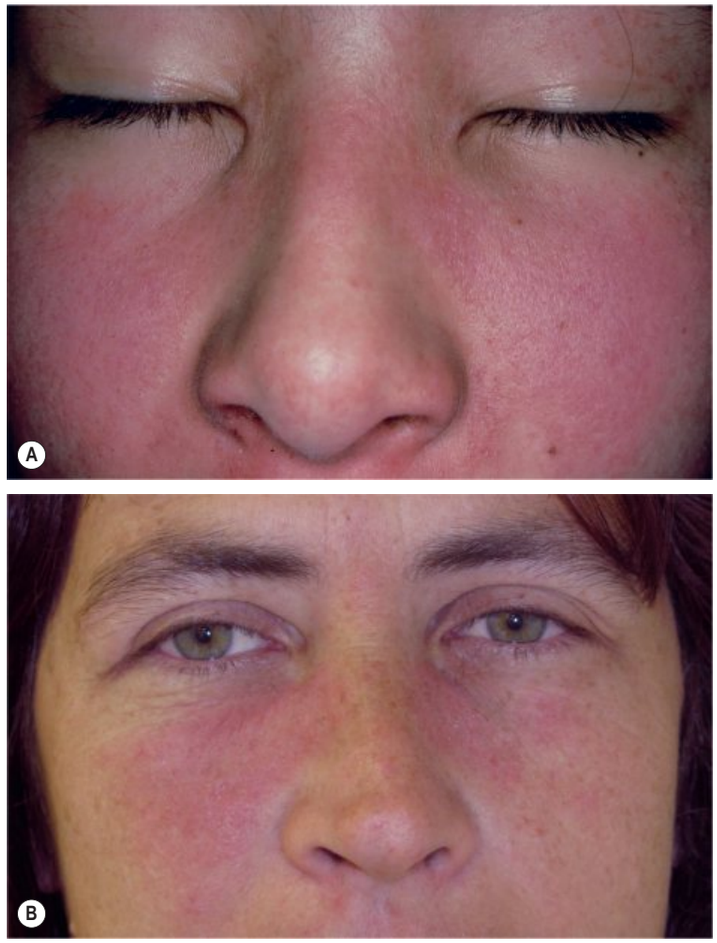
eFig. 41.10 Subacute cutaneous lupus erythematosus (SCLE). Lesions are often seen on the sun-exposed aspects of the upper extremities. The margins of the annular lesions may have scale-crust. *Courtesy Jean L. Bolognia, MD.*



eFig. 41.11 Subacute cutaneous lupus erythematosus induced by terbinafine. Multiple annular plaques of the upper trunk and proximal upper extremities. *Courtesy Jeffrey P. Callen, MD.*



eFig. 41.12 Subacute cutaneous lupus erythematosus. This was possibly exacerbated by a proton pump inhibitor. *Courtesy Jeffrey P. Callen, MD.*



eFig. 41.13 Acute cutaneous lupus erythematosus. A Erythema of the central face with relative sparing of the lower nose and melolabial (nasolabial) folds. **B** Asymmetric pink plaques of the central cheeks with sparing of the melolabial (nasolabial) folds. *A, Courtesy Peter W. Heald, MD; B, Courtesy Luis Requena, MD.*



eFig. 41.14 Acute cutaneous lupus erythematosus. Pink plaques, some of which are erosive, involve the interphalangeal skin as well as that overlying several joints. *Courtesy Luis Requena, MD.*



eFig. 41.15 Periungual infarcts in a patient with systemic lupus erythematosus. *Courtesy Kalman Watsky, MD.*



eFig. 41.16 Ulcerations of the fingertips in a patient with systemic lupus erythematosus. The patient had lupus nephritis and high-titer ANA. *Courtesy Luis Requena, MD.*



eFig. 41.17 Neonatal lupus erythematosus. Annular erythematous plaques on the forehead and scalp. Note the resemblance to the annular form of subacute cutaneous lupus erythematosus. *Courtesy Julie V. Schaffer, MD.*



eFig. 41.18 Neonatal lupus erythematosus. Widespread lesions, some of which are annular. *Courtesy Luis Requena, MD.*



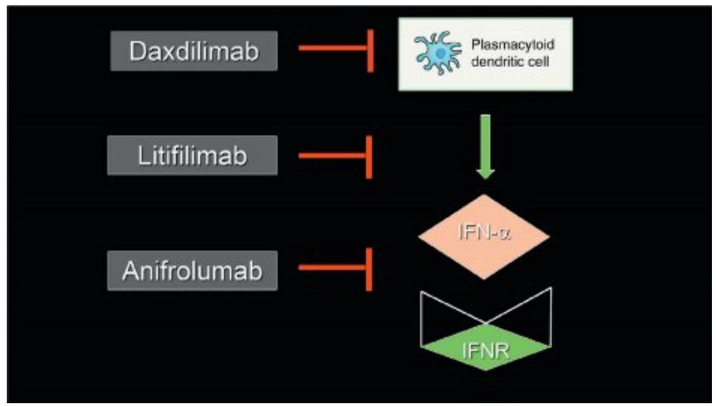
eFig. 41.19 Neonatal lupus erythematosus. Pink annular plaques with central hyperpigmentation on the chest. *Courtesy Julie V. Schaffer, MD.*



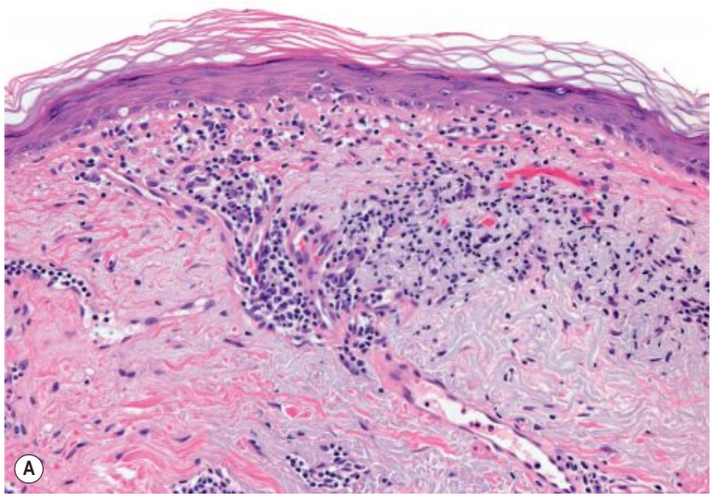
eFig. 41.20 Lupus erythematosus tumidus. Edematous papules and plaques, some of which are annular. No scale or central hypopigmentation is present. *Courtesy Kalman Watsky, MD.*

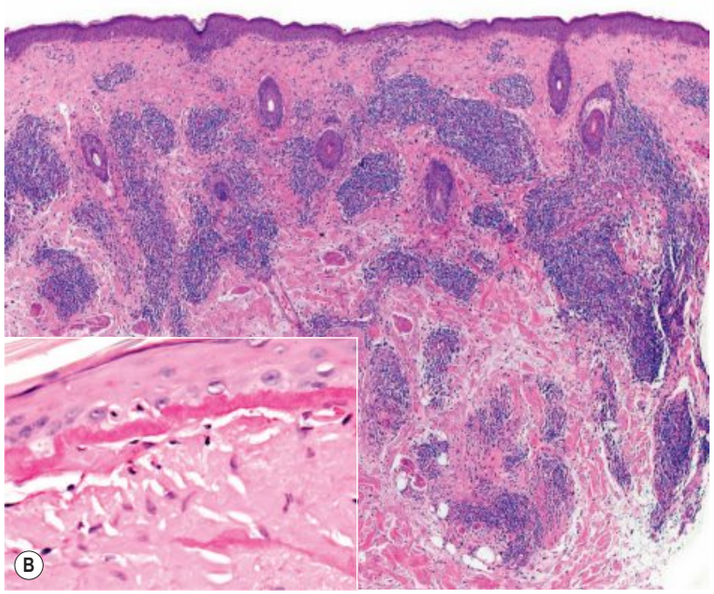


eFig. 41.21 Chilblain lupus. Erythematous plaques with desquamation. *Courtesy Luis Requena, MD.*



eFig. 41.23 Mechanisms of action of newer monoclonal antibodies. Daxdilimab binds to the ILT7 protein on plasmacytoid dendritic cells (pDCs), resulting in recruitment of effector cells that are cytotoxic to pDCs. Litifilimab binds to the blood dendritic cell antigen 2 (BDCA2) protein on pDCs, resulting in downregulation of type 1 interferons and inflammatory cytokines. Anifrolumab binds to subunit 1 of the type I interferon receptor, blocking the activity of type 1 interferons. As of July 2023, anifrolumab is FDA for systemic lupus erythematosus while daxdilimab and litifilimab are investigational drugs in phase 2 clinical trials in the US.





eFig. 41.22 Histologic features of cutaneous lupus erythematosus (LE). **A** Acute cutaneous LE showing interface dermatitis with vacuolization of basal keratinocytes and sparse superficial lymphoid infiltrates. **B** Chronic discoid LE showing focal interface dermatitis and dense perivascular and periadnexal lymphoid infiltrates throughout the entire dermis. A thickened basement membrane is a characteristic finding and can be highlighted by PAS staining (inset). *Courtesy Lorenzo Cerroni, MD.*

1997 UPDATE OF THE 1982 AMERICAN COLLEGE OF RHEUMATOLOGY REVISED CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS*	
Criterion	**Definition**
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) **Pleuritis** – convincing history of pleuritic pain, rubbing heard by a physician, or evidence of pleural effusion
	OR
	b) **Pericarditis** – documented by ECG, rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent **proteinuria** greater than 0.5 g/day or greater than 3+ if quantitation not performed
	OR
	b) **Cellular casts** – may be red cell, hemoglobin, granular, tubular or mixed
8. Neurologic disorder	a) **Seizures** – in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance
	OR
	b) **Psychosis** – in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a) **Hemolytic anemia** with reticulocytosis
	OR
	b) **Leukopenia** – less than 4000/mm^3 total WBC on two or more occasions
	OR
	c) **Lymphopenia** – less than 1500/mm^3 on two or more occasions
	OR
	d) **Thrombocytopenia** – less than 100 000/mm^3 in the absence of offending drugs
10. Immunologic disorder	a) **Anti-DNA antibody to native DNA** in abnormal titer
	OR
	b) **Anti-Sm** – presence of antibody to Sm nuclear antigen
	OR
	c) Positive finding of **antiphospholipid antibodies** based on: (1) an abnormal serum level of IgG or IgM anti-cardiolipin antibodies; (2) a positive test result for lupus anticoagulant using standard methods; or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test (FTA-ABS)
11. Anti-nuclear antibody	An abnormal titer of anti-nuclear antibody by immunofluorescence (or an equivalent assay) at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome
*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.	

eTable 41.1 1997 Update of the 1982 American College of Rheumatology revised criteria for classification of systemic lupus erythematosus. ECG, electrocardiogram; Sm, Smith; WBC, white blood cell. *Courtesy American College of Rheumatology, https://assets.contentstack.io/v3/assets/bltee37abb6b278ab2c/bltf92eb727fa57db8f/systemic-lupus-erythematosus-classification-criteria-revised-update-1997.pdf.*

42 Dermatomyositis

Ruth Ann Vleugels and Joseph L. Jorizzo

Synonyms: ■ Dermatomyositis ■ Idiopathic inflammatory myopathies ■ Idiopathic inflammatory dermatomyopathies

Key features

- Autoimmune connective tissue disease of uncertain etiology with both juvenile and adult forms
- Clinical and laboratory signs of proximal extensor inflammatory myopathy
- Distinctive, photodistributed, pink–violet poikiloderma favoring the scalp, periocular region, and extensor surfaces, in addition to distinctive nail-fold changes and pink–violet papules overlying the knuckles
- Histopathologic evidence of interface dermatitis plus mucin deposition in skin biopsy specimens and lymphocytic myositis in biopsy specimens from affected muscle
- When myositis is present, therapy includes systemic corticosteroids and steroid-sparing immunosuppressive and immunomodulatory drugs, with the prognosis being very good, except for those individuals with refractory myositis, systemic involvement, or an associated advanced malignancy
- Management of cutaneous dermatomyositis via skin-directed therapies can be challenging and is directed by disease severity

INTRODUCTION

Along with polymyositis and inclusion body myositis, dermatomyositis is classified as one of the idiopathic inflammatory myopathies. Dermatomyositis is a disease of presumed autoimmune pathogenesis that presents with a symmetric, proximal, extensor inflammatory myopathy and a characteristic cutaneous eruption. Previously, polymyositis was thought to represent the same disease process but limited to the muscles; however, there is robust evidence that the pathogenetic mechanisms of polymyositis and dermatomyositis differ significantly. In polymyositis, clonally expanded, autoreactive $CD8^+$ T cells invade myocytes expressing MHC class I antigens and cause necrosis via the perforin pathway. In contrast, there are data to support the theory that autoantigens activate a humoral immune process in dermatomyositis, in which complement is deposited in capillaries causing capillary necrosis and ischemia[1]. Because an appreciation of these pathogenetic differences occurred relatively recently, previous studies often pooled cases of dermatomyositis and polymyositis, making interpretation of their data challenging.

Dermatomyositis is characterized by a bimodal age distribution, with both adult and juvenile forms, and up to one-quarter of patients in the adult group having an associated malignancy. Patients with juvenile dermatomyositis do not have an increased risk of malignancy, but do have an increased incidence of calcinosis cutis and associated small vessel vasculitis. There is a subset of patients in whom the cutaneous manifestations of dermatomyositis exist without objective evidence of muscle inflammation, referred to as amyopathic dermatomyositis, and formerly known as dermatomyositis sine myositis. For dermatologists, establishing the diagnosis of dermatomyositis is important because it is a serious, treatable, multisystem disease that has a different prognosis and treatment approach from lupus erythematosus (LE). The malignancy association in adults provides the dermatologist with an opportunity to assist medical colleagues in detecting the tumor at an early stage because the skin disease often precedes the onset of symptoms related to the malignancy.

HISTORY

Dermatomyositis has been recognized as a clinical entity for more than 100 years. Although the first adult patients with dermatomyositis and malignancy were described early in the twentieth century, a causal association was not suggested until the 1940s. A major step forward in the understanding of this disorder occurred in 1975, when Bohan and Peter proposed generally accepted clinical diagnostic criteria[2,3]. Over the past two decades, it has become more widely accepted that a subset of patients has skin-limited disease (i.e. amyopathic dermatomyositis). For this reason, Sontheimer[4] proposed a revised classification of the idiopathic inflammatory myopathies that includes amyopathic forms of dermatomyositis, with muscle involvement no longer required for a definitive diagnosis (Table 42.1)[5]. Based upon epidemiologic studies, an estimated 20% of dermatomyositis patients have clinically amyopathic disease[6].

EPIDEMIOLOGY

Dermatomyositis is a relatively rare disease that occurs throughout the world. In adults, dermatomyositis affects women two to three times more often than men. The incidence of dermatomyositis ranges from 2 to 9 per million amongst various populations[6–8] and seems to be increasing, although this may simply be a result of increased detection, as well as better diagnosis and reporting. Table 42.2 summarizes the demographic findings from five series of patients with dermatomyositis[6,9–11,11a].

PATHOGENESIS

Dermatomyositis is believed to result from an immune-mediated process triggered by "outside" factors (e.g. malignancy, drugs, infectious agents)

REVISED CLASSIFICATION SYSTEM FOR THE IDIOPATHIC INFLAMMATORY DERMATOMYOPATHIES
Dermatomyositis (DM)
Adult-onset
Classic DM
Classic DM with malignancy
Classic DM as part of an overlapping connective tissue disorder
Clinically amyopathic DM*
Amyopathic DM
Hypomyopathic DM
Juvenile-onset
Classic DM
Clinically amyopathic DM*
Amyopathic DM
Hypomyopathic DM
Polymyositis
Isolated polymyositis
Polymyositis as part of an overlapping connective tissue disorder
Inclusion body myositis
*Both adult-onset and juvenile-onset amyopathic DM and hypomyopathic DM can be further subcategorized as "provisional" and "confirmed" when patients have biopsy-confirmed hallmark cutaneous manifestations of DM without muscle weakness and with normal muscle enzymes for ≥6 months (provisional) or 24 months (confirmed).

Table 42.1 Revised classification system for the idiopathic inflammatory dermatomyopathies. This classification scheme recognizes, with equal weighting, the cutaneous and muscle manifestations of this group of disorders. *Adapted from Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? J Am Acad Dermatol 2002;46:626–36.*

CLINICAL SUBTYPES OF DERMATOMYOSITIS – DEMOGRAPHICS AND ASSOCIATED FINDINGS						
	Clinical subtype					
	Adult-onset classic dermatomyositis[6,11a]		Adult-onset clinically amyopathic dermatomyositis[9,11a]		Juvenile-onset classic dermatomyositis[10]	Juvenile-onset clinically amyopathic dermatomyositis[11]
No. of patients	20	142	291	59	120	38
Mean age (years)	51.9	51	50	53	7.7	10.5
Malignancy detected	6/20 (30%)	14/142 (9.9%)	41/291 (14%)	1/59 (1.7%)	0/120 (0%)	0/38 (0%)
Sex ratio (F:M)	3:1	4.9:1	3:1	28.5:1	2.2:1	3:2

Table 42.2 Clinical subtypes of dermatomyositis – demographics and associated findings.

in genetically predisposed individuals. Table 42.3 illustrates some of the evidence that supports this theory[12–37]. Serum anti-nuclear autoantibodies are often present, as are other myositis-specific or myositis-associated autoantibodies, as summarized in Table 42.4[29,37–39]. The anti-synthetase antibodies are directed against cytoplasmic antigens; therefore the anti-nuclear antibody test may be negative. Patients with anti-synthetase antibodies often have overlap syndromes. The term anti-synthetase syndrome has been coined to refer to patients with these autoantibodies, fever, erosive polyarthritis, "mechanic's hands", Raynaud phenomenon, and interstitial lung disease[43].

CLINICAL FEATURES

Cutaneous Disease

The features that are classically considered pathognomonic for dermatomyositis include the heliotrope sign and Gottron papules (Fig. 42.1). The former is characterized by a pink–violet color, primarily of the eyelids and periorbital skin, which may have associated edema (Fig. 42.2). The heliotrope sign can be quite subtle, with only mild erythema of the eyelid margins, and it may wax and wane in intensity. Some patients will have more widespread facial erythema (see Fig. 42.2B,C) or midfacial erythema that tends to involve the nasolabial folds (Fig. 42.3).

The cutaneous lesions of dermatomyositis are accentuated on extensor surfaces, including the elbows, knees, metacarpophalangeal joints, and both the proximal and distal interphalangeal joints (knuckles; Fig. 42.4A). When papules on the knuckles develop a secondary lichenoid quality, they are termed *Gottron papules* (Fig. 42.4B,C); involvement of the elbows and/or knees is known as *Gottron sign* (Fig. 42.5).

A critical diagnostic feature of the cutaneous eruption of dermatomyositis is poikiloderma. This feature may occur both in patients with dermatomyositis, where it is frequently characterized by a pink–violet color, and in patients with lupus erythematosus, where the poikiloderma is typically more red in color. However, in patients with skin phototypes I and II, the hue of the poikiloderma of dermatomyositis may be pink–red rather than truly violet (Fig. 42.6A). Photodistributed poikiloderma is very characteristic of dermatomyositis, often involving the upper chest (*V-neck sign*) and the upper back (*shawl sign*). Poikiloderma can also affect photoprotected areas, such as the lateral thigh, referred to as the *holster sign* (Fig. 42.6B,C). If the clinician misses the poikiloderma, the eruption of dermatomyositis may occasionally be misdiagnosed as psoriasis, especially when there are well-defined plaques on the elbows and knees with fine silvery scale.

The cutaneous lesions of dermatomyositis are often intensely pruritic (Fig. 42.7), and this can significantly affect patients' quality of life[44]. IL-31 may play a role as it does in other pruritic disorders. Of note, pruritus is a feature that can occasionally help to distinguish dermatomyositis from LE.

An additional clinical clue to the diagnosis of dermatomyositis is nail-fold changes. Cuticular dystrophy (i.e. "ragged" cuticles and cuticular hypertrophy) is quite characteristic, as are nail-fold telangiectasias in which dilated capillary loops alternate with capillary dropout (Fig. 42.8). If the photodistribution and nail-fold changes are missed, the eruption may be misdiagnosed as other conditions characterized by poikiloderma, such as cutaneous T cell lymphoma. Often, the dermatologist correctly notices the photodistribution but considers the diagnosis of photodrug eruption or lupus erythematosus rather than dermatomyositis.

Calcinosis cutis is more prevalent in juvenile dermatomyositis, affecting 25%–70% of pediatric patients[7,45], and it is usually associated

PATHOGENESIS OF DERMATOMYOSITIS
Genetics[12–14]

• Monozygotic twins affected
• Associated human leukocyte antigens (HLA)
  • HLA-DR3 and -B8 (juvenile dermatomyositis)
  • HLA-DR52 (patients with anti-Jo-1 antibodies)
  • HLA-DR7 and -DRw53 (patients with anti-Mi-2 antibodies)
  • HLA-B14 and -B40 (adults with dermatomyositis overlap)
  • HLA-DRB1*15021 (Japanese with juvenile dermatomyositis)
• TNF-α 308 A allele polymorphism

Cellular immunity/apoptosis[15–21]
• Histopathologic findings in skin and muscle ($CD8^+$ lymphocytes) • Lymphocyte-mediated experimental myositis in mice • Increased Ki-67 and p53 expression in keratinocytes after UVB irradiation • Increased CD40 expression on muscle cells • Decreased circulating CD54 (ICAM-1)-positive lymphocytes • Dysregulaion of type 1 interferons • Fas ligand on T cells and Fas receptor on muscle cells • MHC class I overexpressed in affected muscle tissues • Elevated expression of COX-1, COX-2, and 5-LOX mRNA in affected muscle tissues
Humoral immunity[22,24,31,34]
• Association with autoimmune diseases (Hashimoto thyroiditis, Graves disease, myasthenia gravis, type I diabetes mellitus, primary biliary cirrhosis, dermatitis herpetiformis, vitiligo, and other autoimmune connective tissue diseases) • Myositis-specific autoantibodies (see Table 42.4) • Upregulation of interferon pathway and complement activation • Endomysial deposition of activated complement fragments (C5b–C9)
Infectious precipitants[23,24]
• Seasonal variation • Picornavirus substrate for aminoacyl-tRNA synthetases • *Escherichia coli*, muscle protein, and a capsid protein of a picornavirus that induces mouse myositis all have some homology in amino acid sequences with Jo-1 • Echovirus infection in patients with hypogammaglobulinemia • Coxsackievirus-9 myositis
Drug and vaccine precipitants[25,26,35–37]
• Hydroxyurea, lipid-lowering drugs (statins > gemfibrozil), TNF inhibitors, checkpoint inhibitors (e.g. nivolumab, ipilimumab), nonsteroidal anti-inflammatory drugs, immunostimulatory herbal supplements (e.g. *Spirulina*, IsaLean®), MAP kinase inhibitors, trastuzumab, taxanes, capecitabine, cyclophosphamide, BCG and SARS-CoV-2 vaccines, D-penicillamine; to date single case reports of alfuzosin (α-antagonist for BPH), articaine, etoposide, interferon-α-2b, ipecac (repeated exposures), omeprazole, phenytoin, sulfacetamide sodium ophthalmic drops, tegafur, terbinafine, zoledronic acid
Malignancy association (adults)[27–30]
• Anti-transcription intermediary factor 1-γ (TIF1-γ) antibodies, e.g. risk ratio = 5 in Chinese • Anti-nuclear matrix protein (NXP-2) antibodies, particularly in men • In one study, at least 80% of patients with cancer-associated dermatomyositis had antibodies against either TIF1-γ or NXP-2

Table 42.3 Pathogenesis of dermatomyositis. Other environmental triggers such as ultraviolet radiation may play a role (e.g. correlation between rate of dermatomyositis with anti-Mi-2 antibodies and proximity to the equator). BCG, Bacillus Calmette–Guérin; BPH, benign prostatic hyperplasia; ICAM, intercellular adhesion molecule; MAP, mitogen-activated protein; TNF, tumor necrosis factor.

SERUM AUTOANTIBODIES IN ADULT AND JUVENILE DERMATOMYOSITIS				
Autoantibodies	**Target antigen function**	**Clinical phenotype**	**Autoantibody frequency, %**	
			Adult DM	**Juvenile DM**
Anti-aminoacyl-tRNA synthetases (e.g. anti-Jo-1 [histidyl], anti-PL-7 [threonyl]; see Ch. 40)	Intracytoplasmic protein synthesis	Anti-synthetase syndrome (myositis, mechanic's hands, erosive polyarthritis, fever, Raynaud phenomenon, high frequency of interstitial lung disease)	up to 20	1–3
Anti-SRP	Protein translocation	Acute-onset necrotizing myopathy (severe weakness, high CK); may be refractory to treatment	5	<1
Anti-Mi-2	Helicase – transcription	Adult DM and juvenile DM (hallmark is cutaneous disease, milder muscle disease with good response to treatment)	15	<10
Anti-TIF1-γ (p155)	Cell proliferation, apoptosis, innate immunity	Cancer-associated myositis in adult DM; extensive cutaneous disease in adult DM and juvenile DM; palmar hyperkeratotic papules, psoriasiform lesions, red-on-white telangiectatic patches, ovoid palatal patch	20–40	~25
Anti-NXP-2 (p140)	Nuclear transcription, RNA metabolism	Cancer-associated myositis in adult DM (particularly in men); adult and juvenile DM with calcinosis; prominent muscle involvement with myalgias, peripheral edema, dysphagia, mild skin disease	10–20	~25
Anti-SAE	Post-translational modification	Adult DM; may present with clinically amyopathic DM	5	NA
Anti-MDA5 (CADM-140)	Innate immunity	Cutaneous ulcerations – periungual region and overlying Gottron papules and/or Gottron sign, tender palmar macules and papules that favor palmar and fingertip creases, oral ulcerations, prominent non-scarring alopecia, arthritis; clinically amyopathic DM; interstitial lung disease including a rapidly progressive form (often considered a dermato-pulmonary syndrome)	5–20	NA

Table 42.4 Serum autoantibodies in adult and juvenile dermatomyositis (DM). The autoantigen CADM-140 was subsequently found to be identical to two previously identified gene products, interferon induced with helicase C domain protein 1 (IFIH1) and melanoma differentiation-associated gene 5 (MDA5). amyo, amyopathic; CADM-140, clinically amyopathic dermatomyositis antibody, 140 kD; CK, creatine kinase; NA, not applicable; NXP-2, nuclear matrix protein-2; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle; TIF1-γ (transcription intermediary factor 1-γ). Note: Autoantibody frequencies vary depending on the ethnicity/population in which the study was conducted. Adapted from references 29, 39–42.

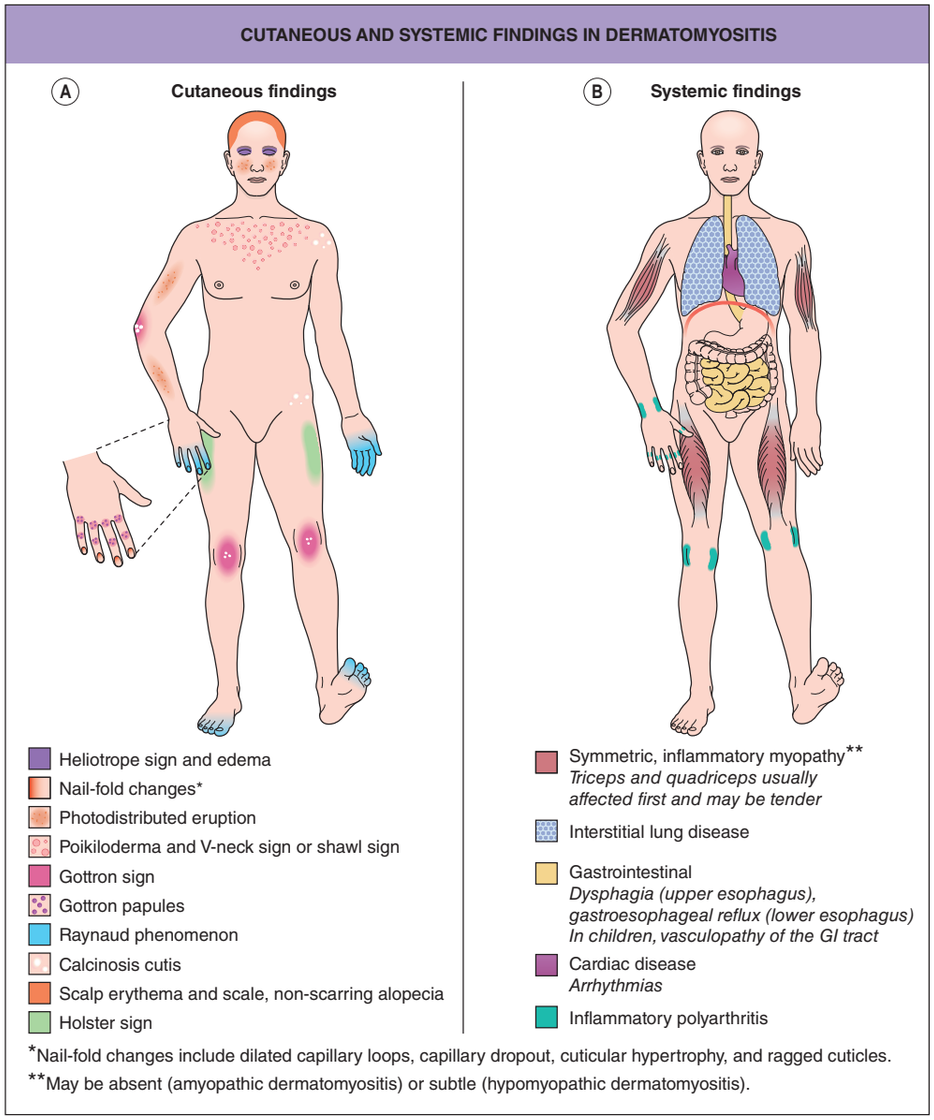


Fig. 42.1 Cutaneous and systemic findings in dermatomyositis. A Cutaneous. **B** Systemic.



Fig. 42.2 Dermatomyositis – eyelid edema and heliotrope sign. **A** Inflammation of the upper eyelid can be more subtle in darkly pigmented skin; note involvement of the lateral nasal root and the cheeks. The eyebrow alopecia is due to chemotherapy. **B** The characteristic pink–violet color is seen with involvement of the hairline, lower forehead, upper eyelids, and cheeks; the edema is striking, especially of the upper eyelids and nasal root. **C** Heliotrope with marked lower eyelid edema. *B, Courtesy Jean L. Bolognia, MD; C, Courtesy Kalman Watsky, MD.*



Fig. 42.3 Dermatomyositis – marked facial involvement. Note the violaceous hue. Misdiagnoses include psoriasis, contact dermatitis, and if there is significant facial involvement as in this patient, acute cutaneous lupus erythematosus.

with a delay in diagnosis, a delay in the institution of systemic corticosteroids, and/or advanced, therapy-resistant disease. In addition to the skin, calcium deposits may develop within the deep fascia and intramuscular connective tissue. Calcinosis cutis presents as hard, irregular papules, plaques, or nodules that occasionally drain a chalky material (Fig. 42.9A). Lesions favor sites of trauma, such as the elbows and knees (Fig. 42.9B), but can occur anywhere and may be painful and interfere with function.

Additional cutaneous manifestations range from poikiloderma and scaling of the scalp (often accompanied by non-scarring alopecia) to centripetal flagellate erythema (Fig. 42.10A) to erosions and ulcerations (Fig. 42.10B; Table 42.5)[46–48]. "Mechanic's hands" can also be seen, more commonly in patients with anti-synthetase syndrome (Fig. 42.10C). Occasionally, especially in the setting of more severe disease, there can be edema of the extremities or even anasarca. Wong-type dermatomyositis is a variant that occurs more commonly in Asians in which the cutaneous findings mimic pityriasis rubra pilaris[49]. Lastly, because of the frequency of overlap syndromes, it is important to look for the skin signs of other autoimmune connective tissue diseases in patients with dermatomyositis.

Patients may present with the classic cutaneous manifestations of dermatomyositis but no muscle disease. Upon careful patient evaluation and longitudinal assessment, some of these patients will be found to have skin disease alone (amyopathic dermatomyositis) while others eventually evolve into classic dermatomyositis (with muscle disease) or develop hypomyopathic dermatomyositis, i.e. no muscle weakness clinically but characteristic laboratory or radiographic abnormalities[50]. The clinical characteristics of patients with classic and amyopathic dermatomyositis have been compared[9], including an examination of differences in malignancy risk. Although it was generally thought that the malignancy risk was greater in the setting of classic dermatomyositis, there have been multiple studies that have observed associated malignancies in patients with amyopathic dermatomyositis. Fulminant lung disease has also been reported in patients with amyopathic dermatomyositis. Therefore, both malignancy screening and evaluation for pulmonary involvement are recommended, irrespective of muscle involvement.

Systemic Disease

In dermatomyositis, the dermatologic manifestations frequently precede the onset of *objective* muscle disease; however, when present, the muscle disease is clinically indistinguishable from that seen in polymyositis. The myopathy affects proximal muscle groups, especially the extensor groups (triceps and quadriceps), in a symmetric fashion. In advanced disease, all muscle groups can be affected. Patients may be unable to complete simple tasks such as combing their hair or rising to their feet from a sitting position. Muscle involvement is often accompanied by malaise and fatigue.

Muscle strength should be graded on sequential visits by muscle groups (e.g. right and left triceps 3/5, right and left quadriceps 4/5,



Fig. 42.4 Dermatomyositis – Gottron papules. A Only a few Gottron papules are present, but there is definite accentuation of the pink–violet inflammation over the metacarpophalangeal (MCP) joints and proximal and distal interphalangeal (PIP, DIP) joints as well as the proximal nail folds. Note the ragged cuticles. **B** The flat-topped (lichenoid) papules overlying the DIP, PIP, and MCP joints (knuckles) are subtle and were misdiagnosed as verrucae vulgares in this child. **C** More obvious disease in which the multiple pink–violet lichenoid papules are coalescing and there is some involvement of the interphalangeal skin. *A, Courtesy Kalman Watsky, MD; B, Courtesy Julie V. Schaffer, MD.*

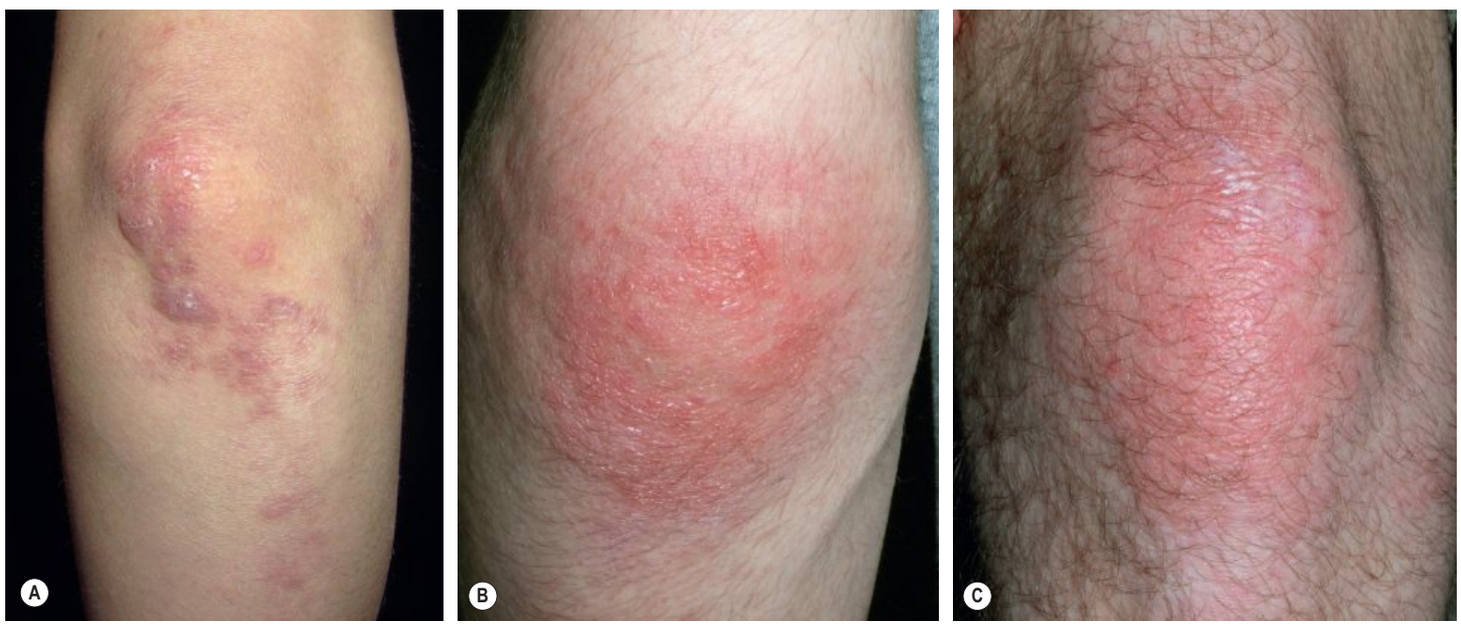


Fig. 42.5 Dermatomyositis – Gottron sign. Pink–violet papules (**A**) and thin pink plaques (**B**) of the elbows and knee (**C**). Some of the papules on the elbow are flat-topped (lichenoid) and others have white scale. The presence of plaques on the elbows and knees can lead to the misdiagnosis of psoriasis. *B,C, Courtesy Julie V. Schaffer, MD.*

etc.), although other more formal methods of quantification have been described. Assessment of neck flexor weakness can also be used to gauge muscle involvement. Symptoms of dysphagia should prompt investigation for overlap with systemic sclerosis, although patients with advanced muscle disease can have cricopharyngeal muscle dysfunction and consequently difficulty initiating swallowing. Distal esophageal involvement can present as gastroesophageal reflux disease.

Pulmonary disease occurs in ~15%–30% of patients with dermatomyositis, and generally presents as a diffuse interstitial fibrosis that is similar to that seen in patients with rheumatoid arthritis or systemic sclerosis[51]. Symptoms include a dry cough and progressive breathlessness. In one US-based study, there was no significant difference in the prevalence of interstitial lung disease when amyopathic dermatomyositis was compared to the classic form[52]. All adult patients should have screening pulmonary function tests (PFTs) that include diffusion capacity for carbon monoxide (DLCO)[52]. In those who have reduced DLCO, a high-resolution chest CT should then be performed. Patients with a high-risk phenotype for pulmonary involvement (e.g. anti-MDA5 dermatomyositis) often have a high-resolution chest CT performed at baseline as well as PFTs with DLCO.

In Eastern Asian populations, patients with anti-MDA5 (CADM) antibodies have a high risk of rapidly progressive lung disease and a poor prognosis despite a lack of muscle disease (see Table 42.4)[53,54]. Furthermore, a novel MDA5 antibody-associated dermato-pulmonary syndrome has been reported in non-Asian populations[55] in which patients develop tender palmar papules and cutaneous ulcerations, primarily on the elbows, dorsal hands, and periungual region (Fig. 42.11)[56]. Additional characteristic features of anti-MDA5 dermatomyositis include arthritis, oral ulcerations, and severe non-scarring alopecia. Recognition of this constellation of cutaneous findings alerts the clinician to the increased risk of associated and potentially fatal pulmonary disease.

Pulmonary involvement is also a notable feature of the antisynthetase syndrome[43]. For example, if anti-Jo-1 antibodies are present, there is a 70% likelihood that the patient will develop pulmonary disease. Because pulmonary disease associated with dermatomyositis is resistant to corticosteroid therapy, it follows a course independent from that of the muscle disease and can adversely affect prognosis.

Cardiac disease is usually not symptomatic. When it is, it commonly presents as arrhythmias or as conduction defects[57]. Patients with







Fig. 42.6 Dermatomyositis – poikiloderma and holster sign. A Photodistributed poikiloderma is very characteristic of dermatomyositis and often involves the upper chest (*V-neck sign*). In this patient with skin phototype I, the color is pink–red. **B** Broken-up pink–violet plaque on the upper lateral thigh (holster sign). **C** Holster sign with a pink–brown color in a patient with more darkly pigmented skin. *A, Courtesy Edward Cowen, MD; B, Courtesy Jonathan Leventhal, MD; C, Courtesy Sara Perkins, MD.*



Fig. 42.7 Dermatomyositis – involvement of the upper back. The pink–violet plaques, some with associated scale, were very pruritic, as evidenced by multiple excoriations. Linear streaks of erythema are also seen. *Courtesy Jean L. Bolognia, MD.*



Fig. 42.8 Dermatomyositis – cuticular dystrophy and nail-fold telangiectasias. The cuticles are "ragged" and within the proximal nail fold, dilated capillary loops alternate with vessel dropout (inset). Atrophy, telangiectasias, and hypopigmentation are present on the fingers. *Courtesy Julie V. Schaffer, MD.*

dermatomyositis are often not thoroughly evaluated for possible cardiac disease, and prompt treatment of the muscle disease may mask the true frequency of cardiac involvement. In one retrospective review, cardiac involvement was shown to be the major prognostic factor for death in patients with dermatomyositis, in the absence of an underlying malignancy[58]. Additional reported indicators of poor prognosis (other than malignancy) include older age, progressive disease, initiation of therapy after 24 months of muscle weakness, longer duration of symptoms before diagnosis, pulmonary disease, dysphagia, and extensive cutaneous involvement of the trunk[59].

For the patient with dermatomyositis, a thorough review of systems should include a discussion of arthritis, gastrointestinal disease, pulmonary disease, cardiac disease, and other manifestations such as Raynaud phenomenon. The presence of additional clinical findings and/or systemic symptoms may signify an overlap with other connective tissue diseases – in particular, systemic LE, rheumatoid arthritis, and systemic sclerosis. One dermatology-based case series observed a 19% overlap rate in adult patients with dermatomyositis[60].

Malignancy

The reported frequency of an internal malignancy in adults with dermatomyositis varies from <10% to >50%; however, the best data point to a probable risk of 15%–25%. The malignancy association occurs with adult dermatomyositis (both classic and amyopathic), but not with the juvenile form or with polymyositis. Genitourinary



Fig. 42.9 Calcinosis cutis. A Rock-hard hyperpigmented plaques on the buttocks with multiple sites of drainage in an adult with longstanding dermatomyositis. **B** In this patient with juvenile dermatomyositis, the nodules favored the extensor surface of the knees and resulted in a decrease in joint mobility. *A, Courtesy Edward Cowen, MD.*



Fig. 42.10 Dermatomyositis – less common presentations. A Flagellate erythema of the posterior trunk. **B** Cutaneous erosions and ulcerations can also occur. **C** Hyperkeratosis and mild erythema of the lateral and palmar surfaces of the fingers in a patient with "mechanic's hands".

malignancies, especially ovarian cancer, and colon cancer may be overrepresented[61,62]; in some Southeast-Asian populations, nasopharyngeal carcinoma is overrepresented[63]. Other commonly detected malignancies include breast, lung, gastric, pancreatic, and lymphomas (including non-Hodgkin)[62]. The risk of malignancy may return to a relative baseline after 3 years[28,62,64].

Callen has suggested that the best approach to patient management in this setting is ongoing vigilance with frequent and thorough medical histories, repeated review of systems, complete physical examinations, and screening laboratory tests[65]. He has also advocated for additional cancer-screening investigations, including CT of the chest, abdomen, and pelvis as well as transvaginal pelvic ultrasound in women (Table 42.6)[64]. Patients should be up-to-date with regard to recommended screenings such as colonoscopy and mammography.

Several myositis-associated autoantibodies have been described (see Table 42.4), and presence of the anti-TIF1-γ (p155) autoantibody in particular has been associated with an increased risk of malignancy[30]. Indeed, in one study, at least 80% of patients with cancer-associated dermatomyositis had antibodies against either TIF1-γ (transcription intermediary factor 1-γ) or nuclear matrix protein NXP-2[29]. In a recent systematic review and meta-analysis, older age, male sex, dysphagia, cutaneous ulceration, anti-TIF1-γ antibodies, and classic dermatomyositis (i.e. without anti-synthetase syndrome or clinically amyopathic dermatomyositis) were associated with a significantly higher risk of an underlying malignancy[66]. This study also concluded that CT

MUCOCUTANEOUS MANIFESTATIONS OF DERMATOMYOSITIS	
Common	**Uncommon**
Heliotrope sign (Fig. 42.2) Eyelid edema (Fig. 42.2) Gottron papules (Fig. 42.4) Gottron sign (Fig. 42.5) Photodistributed poikiloderma (includes facial erythema, shawl sign, V-neck sign) (Figs. 42.3, 42.6A & 42.7) Scalp poikiloderma and scaling Non-scarring alopecia Nail-fold changes (includes ragged cuticles, cuticular hypertrophy, nail-fold telangiectasias*) (Fig. 42.8) Holster sign (poikiloderma of the lateral thighs) (Fig. 42.6B,C) Psoriasiform lesions Calcinosis cutis (especially in juvenile dermatomyositis) (Fig. 42.9)	Cutaneous erosions or ulcerations (Figs. 42.10B & 42.11A,B) Flagellate erythema (Fig. 42.10A) Tender palmar macules and papules (Fig. 42.11C) Hyperkeratotic palmar papules "Mechanic's hands" (Fig. 42.10C) Exfoliative erythroderma Cutaneous eruption that mimics PRP (Wong variant) Vesiculobullous lesions Oral ulcers† Ovoid palatal patch Gingival erythema & telangiectasias Panniculitis Lipoatrophy (especially in juvenile dermatomyositis) Small vessel vasculitis (especially in juvenile dermatomyositis)
*Dilated capillary loops alternating with vessel dropout. †Additional intraoral findings include xerostomia and lichen planus-like changes.	

Table 42.5 Mucocutaneous manifestations of dermatomyositis. See Fig. 42.1. Rarely, patients have associated erythromelalgia. PRP, pityriasis rubra pilaris.

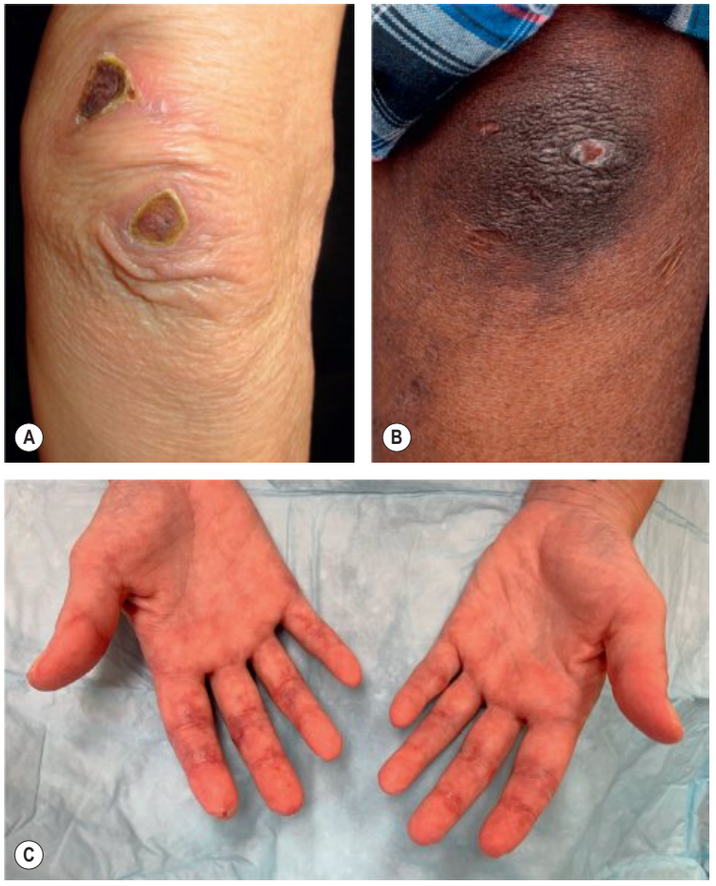


Fig. 42.11 Three patients with anti-MDA5 dermatomyositis. A, B Vasculopathic ulcerations favor the elbows, dorsal hands, and periungual region; they can be associated with Gottron sign and Gottron papules. **C** Painful violaceous macules and papules with an irregular outline that favor the digital creases.

EVALUATION OF THE PATIENT WITH DERMATOMYOSITIS	
History and physical examination	
• History, including potential triggers (see Table 42.3) and previous malignancies, and a review of systems • Physical examination – skin, muscle, and complete general examination, including, in adults, breast and pelvic (women), testicular and prostate (men), and rectal (both sexes) examinations; in Southeast-Asian patients, consider full ENT examination	
Laboratory evaluation	
Cutaneous	• Skin biopsy(ies)
Muscle	• Serum creatine kinase, serum aldolase, occasionally LDH (particularly in juvenile dermatomyositis) or urine creatine* • Electromyography (EMG); muscle biopsy; MRI or U/S (increasingly, MRI is being done in lieu of EMG and muscle biopsy if classic cutaneous findings are present)
Pulmonary	• Pulmonary function tests (PFTs) with CO diffusion • If PFTs abnormal, high-resolution chest CT; in patients with high-risk phenotypes (e.g. anti-MDA5 dermatomyositis), high-resolution chest CT performed at baseline as well as PFTs with DLCO
Cardiac	• Electrocardiogram (EKG) • If symptomatic, echocardiogram and/or Holter monitor
Esophageal	• If muscle involvement and symptoms, barium swallow or manometry
General	• Complete blood count, comprehensive metabolic panel with fasting levels of glucose and lipids†, comprehensive myositis antibody panel (in laboratories with reliable testing, e.g. Oklahoma Medical Research Foundation)
Malignancy screen (adults)‡,¶	• Urinalysis, stool occult blood testing • Serum prostate-specific antigen (PSA) [men] • Serum CA125 [women] • Serum CA19-9 [men and women] • Mammogram, Papanicolaou smear, and transvaginal pelvic U/S [women] • CT of chest, abdomen, and pelvis • Colonoscopy, if age-appropriate, iron deficiency anemia, occult blood in stool, or symptoms • Upper endoscopy – if colonoscopy negative in the setting of iron deficiency anemia, occult blood in stool, or symptoms
If planning chronic systemic corticosteroids	• DEXA bone density scan (see Ch. 125)
*Aspartate transaminase (AST), alanine transaminase (ALT), and lactic dehydrogenase (LDH) may also be elevated due to myositis; in children, serial examination of LDH is considered important. †Fasting levels of glucose and lipids are important in children. ‡Malignancy screening should be performed at the time of diagnosis and annually for a minimum of 3 years from disease onset; history and physical examination can be performed more frequently. ¶Can also consider serum protein and immunofixation electrophoreses.	

Table 42.6 Evaluation of the patient with dermatomyositis. CA125 screens primarily for ovarian carcinoma and CA19-9 for pancreatic and biliary tract carcinoma. Microscopic colitis can be seen in patients with chronic diarrhea. CO, carbon monoxide; CT, computed tomography; DEXA, dual energy X-ray absorptiometry; DLCO, diffusion capacity for carbon monoxide; ENT, ear, nose and throat; LDH, lactic dehydrogenase; MRI, magnetic resonance imaging; U/S, ultrasound.

of the chest, abdomen, and pelvis appeared to be effective in identifying otherwise asymptomatic malignancies, further supporting this screening strategy.

With regard to long-term survival, as expected, patients with cancer-associated dermatomyositis have an inferior survival curve when compared to patients with juvenile or non-cancer-associated adult myopathies[58].

PATHOLOGY

The characteristic changes seen in skin biopsy specimens from patients with dermatomyositis can be very subtle (Fig. 42.12) and include epidermal atrophy, signs of interface dermatitis with vacuolar alteration of basal keratinocytes and pigment incontinence, and dermal changes consisting of interstitial mucin deposition and a sparse lymphocytic infiltrate. In some cases, a colloidal iron stain may help to highlight

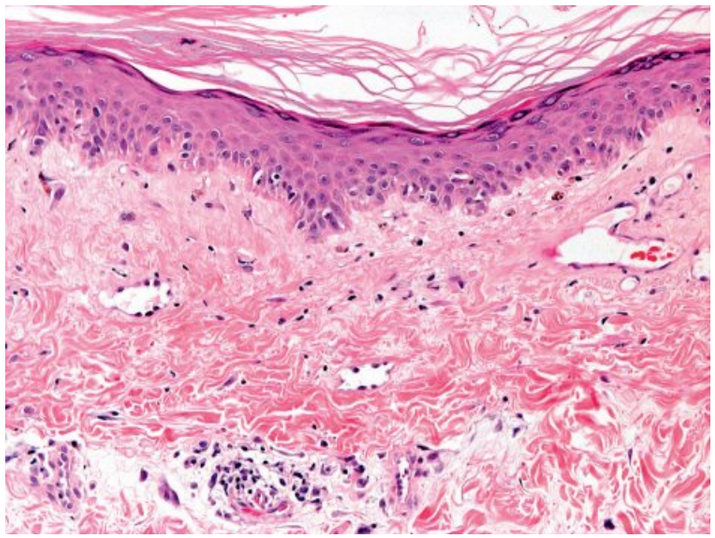


Fig. 42.12 Dermatomyositis – histopathologic features. The vacuolar changes within the basal layer can be subtle. In the dermis, dilated blood vessels and a sparse lymphocytic infiltrate are seen (poikilodermatous changes). *Courtesy Lorenzo Cerroni, MD.*

the presence of mucin. The histopathologic changes may be indistinguishable from those of cutaneous LE, in particular acute and subacute. Gottron papules show an interface dermatitis but have acanthosis and hyperkeratosis rather than epidermal atrophy[67]. A lobular panniculitis can also occur in patients with dermatomyositis and can resemble lupus panniculitis.

Muscle biopsy specimens also show characteristic changes. The combination of type II muscle fiber atrophy, necrosis, regeneration, and hypertrophy with centralized sarcolemmal nuclei, plus lymphocytes in both a perifascicular and a perivascular distribution, is classic[68]. It is best for the clinician to request that the surgeon sample triceps muscle rather than the usually biopsied deltoid muscle because the latter is often spared until late in the disease. Another option, especially for patients with mild involvement, is to choose the biopsy site based upon MRI findings (see below).

DIFFERENTIAL DIAGNOSIS AND EVALUATION

A detailed differential diagnosis of the patient who presents with proximal muscle weakness in the absence of skin lesions, i.e. the differential diagnosis of polymyositis, is beyond the scope of this dermatologic review. The patient with a characteristic cutaneous eruption should have a skin biopsy performed to confirm the clinical impression of dermatomyositis, keeping in mind that cutaneous LE can have similar histologic findings (Fig. 42.13). Table 42.7 summarizes the differential diagnosis of the dermatologic findings in dermatomyositis. Two validated instruments, the Dermatomyositis Skin Severity Index (DSSI) and the updated Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), can be used to determine the severity of cutaneous disease. These indices are helpful in assessing therapeutic responses in clinical trials[69,70].

Once the presumed diagnosis is confirmed histopathologically, a search for muscle and/or associated systemic disease must be undertaken (see Table 42.6), because it is their presence or absence that dictates therapeutic decisions. The evaluation for myositis can include: strength testing of proximal extensor muscles and other muscles including the neck flexors, serum levels of muscle enzymes, an electromyogram, and/or triceps muscle biopsy. However, increasingly, an MRI (Fig. 42.14) or ultrasound (Fig. 42.15) of proximal muscles is obtained prior to, or in lieu of, a muscle biopsy, especially in patients with classic cutaneous lesions. Individuals with normal muscle enzyme levels should be followed at regular intervals because these patients can have occult muscle disease, evolve into classic dermatomyositis, or remain as amyopathic dermatomyositis (see Fig. 42.13)[50].

Additional baseline investigations for pulmonary disease (predicted in part by autoantibody profile; see above and Table 42.4), for cardiac

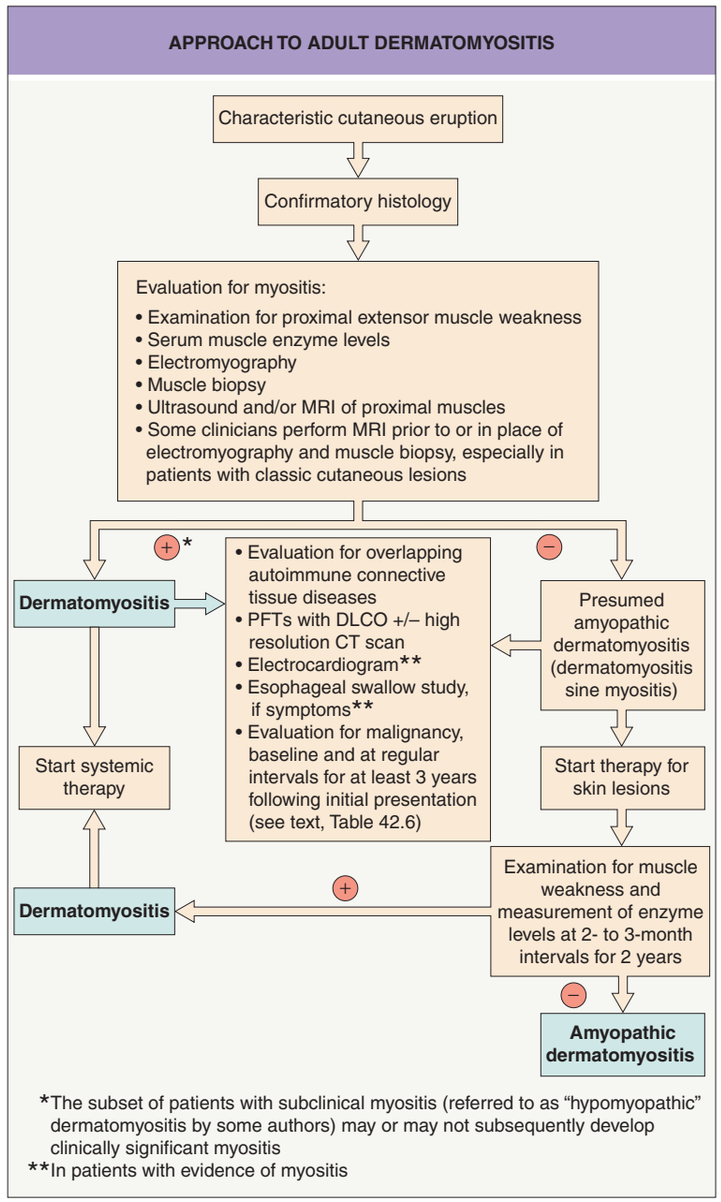


Fig. 42.13 Approach to adult dermatomyositis. The approach for children is similar but without the malignancy evaluation; in addition, pulmonary testing is not performed in children in the absence of symptoms given the low risk of interstitial lung disease. Table 42.1 outlines the definitions of "provisional" and "confirmed" amyopathic dermatomyositis but patients in the former group rarely go on to develop muscle disease. PFTs, pulmonary function tests.

disease, for symptomatic esophageal disease (barium swallow or manometry), and for features of overlap autoimmune connective tissue disease should be performed at this stage, prior to the institution of systemic therapy unless immediate therapy is warranted to halt rapidly progressive disease. Adult patients should have screening for malignancy annually for at least 3 years from disease onset (see Table 42.6), or more frequently based upon symptoms. A detailed history, review of symptoms, and complete physical examination should be performed at regular intervals of 4–6 months. Adult patients with amyopathic dermatomyositis should have similar evaluations for malignancy and associated pulmonary disease.

The classic muscle enzymes that should be assessed at baseline and at regular intervals throughout the treatment period are creatine kinase (CK) and aldolase. Aspartate and alanine transaminases and lactate dehydrogenase are often elevated as well, since they also are released from damaged muscle tissue. It has been estimated that 95% of patients with classic dermatomyositis have an elevated CK at some point during their illness[8]. Urine creatine is elevated in some patients who have a normal serum CK, but this test is not routinely performed.

DIFFERENTIAL DIAGNOSIS OF DERMATOMYOSITIS
Systemic lupus erythematosus*
Physician might notice nail-fold erythema and photodistributed poikiloderma but miss the muscle weakness, heliotrope, extensor distribution, pruritus, and the violaceous hue (Fig. 42.3) The malar rash of SLE classically spares the nasolabial folds, whereas the midfacial erythema of dermatomyositis involves the nasolabial folds Most commonly an issue when patient has amyopathic dermatomyositis and presents with a photosensitive eruption and no muscle weakness
Psoriasis
Involvement of elbows and knees with papulosquamous lesions can lead to misdiagnosis In addition, Gottron papules, extensor surfaces, and scalp can have psoriasiform scaling
Airborne or allergic contact dermatitis
Eyelid edema and lichenification secondary to pruritus can be marked in dermatomyositis; look for additional sites of contact dermatitis or dermatomyositis
Photodrug eruption
Photodistribution
Cutaneous T cell lymphoma
The poikiloderma often begins in intertriginous zones rather than on the scalp, face, and extensor surfaces
Atopic dermatitis
Usually in children, where the physician focuses on the pruritus and secondary lichenification
Systemic sclerosis*
The nail-fold telangiectasias may be similar in appearance, but the dyspigmentation is quite different; edema of the hands ("puffy hand sign") is an early sign of systemic sclerosis
Trichinosis
Patients have painful muscles and periorbital edema, but not other features
Photodistributed form of multicentric reticulohistiocytosis (MRH)
Firm papules have distinct histologic features and may occur along the nail fold Patients with MRH do not have the following nail-fold changes: dilated capillary loops, capillary dropout, cuticular hypertrophy, and ragged cuticles
Still disease
Persistent plaques may be linear Rarely, adults develop erythematous eyelid edema and flagellate erythema
*If the patient has an overlap syndrome, true lupus erythematosus or systemic sclerosis might be present.

Table 42.7 Differential diagnosis of dermatomyositis. SLE, systemic lupus erythematosus.

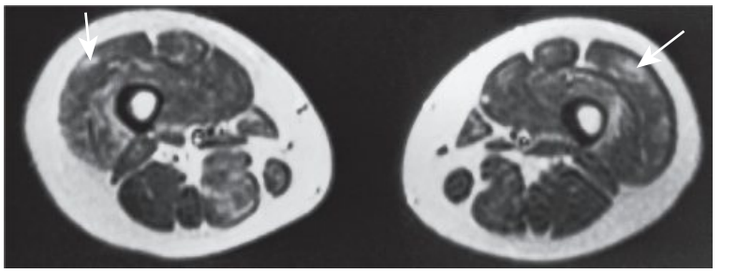


Fig. 42.14 T2-weighted MR images of the proximal thigh in a patient with dermatomyositis. Note the increased signal intensity, primarily in the extensor muscles (white color, arrows). The increased signal correlates with inflammation.

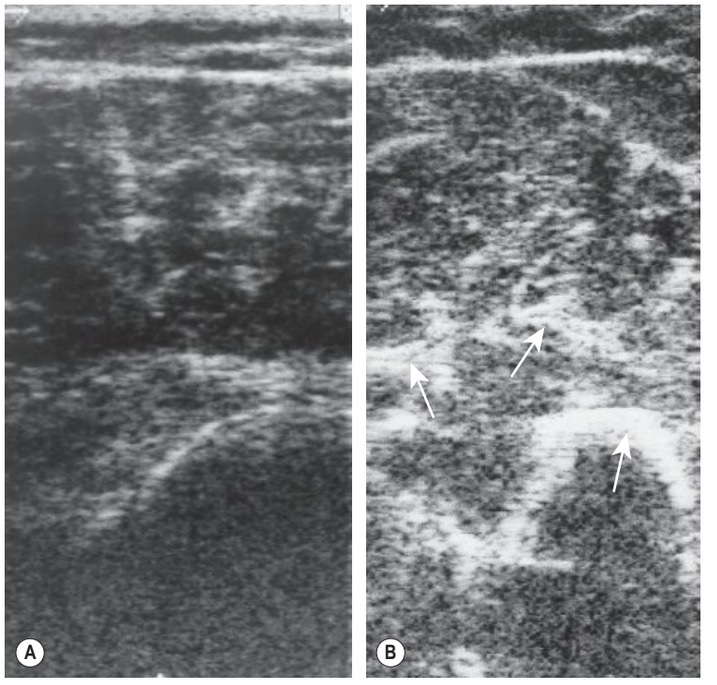


Fig. 42.15 Ultrasound images of the triceps muscle. A Cross-sectional ultrasound image from normal (control) triceps muscle. **B** Ultrasound image from affected triceps muscle in a patient with dermatomyositis. An increase in interstitial echoes is seen (arrows). This image highlights the triceps muscle, which is a higher yield biopsy site in dermatomyositis given that the deltoid muscle is often relatively spared until late in the disease.

Electromyography (EMG) is a sensitive but nonspecific test in patients with dermatomyositis. Over 90% of patients with classic dermatomyositis have abnormal EMG results. In the absence of classic cutaneous lesions, the muscle biopsy is a very important test for confirming the diagnosis and excluding other inflammatory myopathies. Surgeons will usually biopsy the deltoid muscle for convenience, but this muscle is relatively spared until late in the disease; therefore, the surgeon should be directed to perform a triceps muscle biopsy.

MRI (see Fig. 42.14) and ultrasound (see Fig. 42.15) of muscles are sensitive tests that can add greatly to patient evaluation. Both can be used to determine the appropriate site for a muscle biopsy[50]. Ultrasound is less expensive and easier to perform sequentially. MRI may be the most sensitive test for muscle disease, but it is more expensive[50,71]. In children with juvenile dermatomyositis, bilateral thigh MRI utilizing a myositis protocol is considered standard of care in many medical centers. MRI may also be useful in evaluating children for soft tissue changes that might precede calcinosis cutis[71].

TREATMENT

A therapeutic ladder for the treatment of patients with dermatomyositis is summarized in Table 42.8. As with many rare dermatologic diseases, there are few double-blind, placebo-controlled trials. However, a dermatology-based case series supported the belief that a number of patients (75%–85%) can become muscle disease-free, off treatment, after a period of 24–48 months, utilizing a slow corticosteroid taper[60]. Long-term follow-up of pediatric patients also confirmed this conclusion[45,72]. There is a clear discordance between response of the muscle disease to therapy and response of the skin disease[60]. Available therapy for the skin disease is clearly inadequate, with many patients experiencing persistent cutaneous disease and pruritus, especially of the scalp, which can become major complaints once the muscle disease is under control. Aggressive topical therapy and systemic therapy (e.g. antimalarials and/or weekly methotrexate) added specifically for the skin disease often do not provide adequate relief. However, it is clear that, except in adult patients with an advanced malignancy, the prognosis for corticosteroid-treated dermatomyositis in children and adults is excellent, especially when compared with a mortality rate of up to 50% in the pre-corticosteroid era[45].

The treatment of dermatomyositis must take into account the discordance between the response of the muscle disease and that of the dermatologic disease to systemic therapy. If *muscle disease* is confirmed, then

THERAPEUTIC LADDER FOR DERMATOMYOSITIS Rx
Systemic therapy
Oral prednisone: 1 mg/kg/day tapered to 50% over 6 months and to zero over 2–3 years (1)
Option to use pulse, split-dose, or alternate-day (2)
Methotrexate: 5–25 mg weekly po, sc, IM (2)
Azathioprine: 2–3 mg/kg/day po (1)
Others:
IVIg (2 g/kg/month) (1)
Mycophenolate mofetil (1–1.5 g po twice daily) (2)
Rituximab (375 mg/m^2 IV weekly × 4) (1)
Pulse cyclophosphamide (0.5–1.0 g/m^2 IV monthly) (2)
Cyclosporine (3–5 mg/kg/day po) (2)
Tacrolimus (0.12 mg/kg/day po) (3)
Sirolimus (5 mg/day × 2 weeks, 2 mg/day × 2 weeks, then 1 mg/day po) (3)
TNF inhibitors (e.g. infliximab, etanercept) (3)*
Fludarabine (3)
Hematopoietic stem cell transplantation (3)
Plasmapheresis (3)†
Cutaneous lesions
Photoprotection including sunscreens (high SPF including protection against UVA) and clothing (3)
Topical corticosteroids (3)
Topical tacrolimus (3)
Hydroxychloroquine (5 mg/kg divided over two doses daily [up to 200 mg po twice daily]; increased frequency of drug eruptions in patients with dermatomyositis) or chloroquine (250 mg po daily) (2)
Hydroxychloroquine (200 mg twice daily) or chloroquine (250 mg po daily) *plus* quinacrine (100 mg po daily) (3)
Low-dose weekly methotrexate (5–25 mg weekly po, sc, IM) (2)
Mycophenolate mofetil (3)
IVIg (2 g/kg/month) (1)
Lenabasum (cannabinoid receptor type 2 agonist) (1)
Tofacitinib (5–10 mg daily or 11 mg extended-release daily) (2)
Rituximab (750 mg/m^2 up to 1 g IV weekly × 2 – *or* – 1 g IV every other week × 2 doses – *or* – 375 mg/m^2 IV weekly × 4) (1)
Oral tacrolimus (3)
Retinoids (3)
Apremilast (3)
Dapsone (3)
Thalidomide (3)
Leflunomide (3)
Antiestrogens (e.g. tamoxifen, anastrazole) (3)
TNF inhibitors (e.g. infliximab, etanercept) (3)*
Low-dose naltrexone (4.5 mg nightly maximum dose) (3)
*Reported to cause drug-induced dermatomyositis and to induce disease flares in patients with pre-existing dermatomyositis; hence, most experts recommend avoiding these agents in patients with dermatomyositis.
†Double-blind trial showed no benefit.

Table 42.8 Therapeutic ladder for dermatomyositis. Dazukibart, which targets interferon beta 1, led to a reduction in cutaneous lesions in a phase II placebo-controlled trial. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. IM, intramuscular; IV, intravenous; IVIg, intravenous immunoglobulin; po, oral; sc, subcutaneous; SPF, sun protection factor.

systemic corticosteroid therapy is initiated in doses aimed at control of the myositis (i.e. generally prednisone 1 mg/kg/day). Patients with dermatologic manifestations alone can be treated as described below, with repeated clinical muscle examination and enzyme screening (generally CK and aldolase) at 2- to 3-month intervals.

If CK and aldolase serum levels are minimally elevated and corticosteroid therapy is initiated early, the disease generally comes under control rapidly over 2–4 weeks, with a taper to half the starting dose by 6 months. If the disease is advanced and enzyme levels are high (e.g. CK >1000 U/L), the disease can be much more difficult to control and often requires intravenous pulse corticosteroids plus early initiation of a steroid-sparing agent such as low-dose weekly methotrexate. Again, an attempt is made to taper the prednisone to 0.5 mg/kg/day in a single morning dose by 6–8 months.

Attention to general health maintenance principles and osteoporosis prevention is a key element of patient management (see Ch. 125). This can be accomplished by joint longitudinal care with an internist or pediatrician. Adults also need frequent (e.g. every 4–6 months for at least 3 years) complete physical examinations for malignancy.

Children with juvenile dermatomyositis should be followed at least twice yearly by a pediatrician comfortable with monitoring their developmental milestones while on immunosuppressive therapy. In addition, lipodystrophy and metabolic abnormalities, including hypertriglyceridemia and insulin resistance, have become increasingly recognized as potential complications of juvenile dermatomyositis[73,74].

When muscle disease is present, there is support for steroid-sparing therapies (especially in the setting of severe or recalcitrant disease), including IVIg[75–77], methotrexate[78], azathioprine[79], mycophenolate mofetil[80,81], rituximab[82,83], pulse cyclophosphamide[84,85], and cyclosporine (also for lung disease)[86]. Less often tacrolimus[87,88], sirolimus[89], infliximab[90], fludarabine[91], and hematopoietic stem cell transplantation[92] are used. Caution should be exercised if TNF inhibitors are being considered as cases of drug-induced and drug-exacerbated dermatomyositis have been reported. Consequently, many experts recommend avoiding these agents in patients with dermatomyositis.

Of the limited number of randomized, controlled trials performed to date, two assessed IVIg, with both demonstrating benefit in both muscle and skin disease[76,77], and one examined rituximab. The rituximab trial failed to reach its primary and secondary endpoints for muscle disease, but this was potentially related to study design – muscle disease improved in 83% of patients and a steroid-sparing effect was noted[83]. In this trial, none of the core measures of disease activity were skin-specific and no validated skin score was used; however, follow-up analysis utilizing a cutaneous visual analog scale demonstrated improvement of skin disease in both adult and juvenile dermatomyositis[93]. In contrast, a pilot trial of rituximab that used a validated skin score found no improvement in cutaneous disease activity[94]. A small, randomized pilot study that investigated abatacept for muscle disease in both dermatomyositis and polymyositis observed a reduction in disease activity in nearly 50% of treated patients[95]. Notably, a placebo-controlled study showed no benefit from plasmapheresis or leukapheresis in dermatomyositis[96]. In children with severe or refractory disease, IVIg is often administered[97].

Adjunctive physical therapy is also very important in improving muscle strength and endurance[98]. Benefits of exercise and rehabilitation have been demonstrated, even in the course of active disease, without inducing flares of the myositis[99].

Dermatologic disease can be particularly challenging therapeutically, and not all patients clear their cutaneous manifestations when their muscle disease remits. Patients with dermatologic disease without active muscle disease are generally not treated with systemic corticosteroids as a mainstay of their therapy, and they often present a unique therapeutic challenge. As a result, the treatment of amyopathic dermatomyositis often differs significantly from the treatment of classic dermatomyositis in that systemic corticosteroids are not traditionally utilized.

For cutaneous disease, anecdotal reports, case series, retrospective reviews, and limited prospective data support the use of topical corticosteroids, topical tacrolimus[100], antimalarial therapy[101,102] (either as monotherapy or in combination but with a less dramatic effect than in cutaneous LE), low-dose weekly methotrexate, mycophenolate mofetil[103], IVIg[76,104,105], dapsone[106], tofacitinib[107–109], and thalidomide[110], as well as additional agents listed in Table 42.8. Of note, there is an increased risk of a cutaneous drug reaction to hydroxychloroquine in patients with dermatomyositis as compared to those with LE[111]. This medication is still frequently used as first-line therapy, but a pre-treatment warning is recommended. Some patients who develop a cutaneous reaction to hydroxychloroquine may tolerate chloroquine[111].

Clinical studies to support a specific treatment algorithm for cutaneous dermatomyositis are lacking. A common therapeutic approach includes a trial of antimalarials for mild cutaneous disease, whereas patients with moderate to severe skin disease are often treated with methotrexate, mycophenolate mofetil, and/or IVIg[112]. As noted previously, antimalarials are considered less effective for cutaneous dermatomyositis as compared to cutaneous LE. In fact, one study

demonstrated that only 11% of patients with clinically amyopathic dermatomyositis achieved adequate control of their skin disease with antimalarial therapy[113].

Calcinosis cutis may respond to diltiazem and/or surgical excision[114]; other therapies include low-dose warfarin, bisphosphonates, probenecid, colchicine, TNF inhibitors, aluminum hydroxide, sodium thiosulfate, and electric shock wave lithotripsy (ESWL). Early and aggressive therapy of juvenile dermatomyositis does seem to reduce the risk of calcinosis cutis, which is often extremely challenging to treat[45].

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 42.1 Dermatomyositis. Gottron sign with violaceous poikiloderma over the knuckles.



eFig. 42.2 Dermatomyositis. Gottron papules, with the knuckle lesions showing a papular lichenoid quality.



eFig. 42.3 Dermatomyositis in a patient with renal cell carcinoma. More subtle presentation with a few Gottron papules and thin pink plaques overlying primarily the second and third metacarpophalangeal joints. *Courtesy Kalman Watsky, MD.*



eFig. 42.4 Dermatomyositis. Gottron papules overlying the small joints of the hand as well as a pink poikilodermatous plaque of the dorsal hand and wrist. *Courtesy Sara Perkins, MD.*



eFig. 42.5 Dermatomyositis. Pink–violet papules and plaques overlying the small joints and the extensor tendons of the hands as well as erythema of the proximal nail folds. Note that the lesions overlying the distal interphalangeal joints are flat-topped. *Courtesy Jeffrey P. Callen, MD.*



eFig. 42.6 Dermatomyositis. Pink plaques with scale that favor the skin overlying the small joints of the hands. This could be misdiagnosed as psoriasis. *Courtesy Jeffrey P. Callen, MD.*



eFig. 42.7 Dermatomyositis. Pink–violet plaques with scale that favor the skin overlying the small joints of the hands. Note the extension of metacarpophalangeal plaques onto the extensor tendons of the hands. *Courtesy Jeffrey M. Cohen, MD.*



eFig. 42.8 Dermatomyositis – holster sign. Slightly scaly, erythematous papular eruption on the left lateral thigh (the right thigh was similarly affected). *Courtesy Jeffrey P. Callen, MD.*



eFig. 42.9 Dermatomyositis – subtle holster sign.



eFig. 42.10 Dermatomyositis. Erythematous papules on the sun-exposed portion of the chest. *Courtesy Jeffrey P. Callen, MD.*



eFig. 42.11 Dermatomyositis. Pink–violet plaques in sun-exposed sites of the face and neck in a patient with multiple myeloma.



eFig. 42.12 Dermatomyositis – localized, intensely red poikilodermatous changes on the lateral arm. *Courtesy Edward Cowen, MD.*



eFig. 42.13 Dermatomyositis. Pink papules and poikiloderma of the outer upper arm.



eFig. 42.14 Anti-MDA5 dermatomyositis. Ulceration within one of the Gottron papules. Ragged cuticles are also present.



eFig. 42.15 Dermatomyositis. Ragged cuticles, cuticular hypertrophy, and nail-fold telangiectasias and hemorrhage.



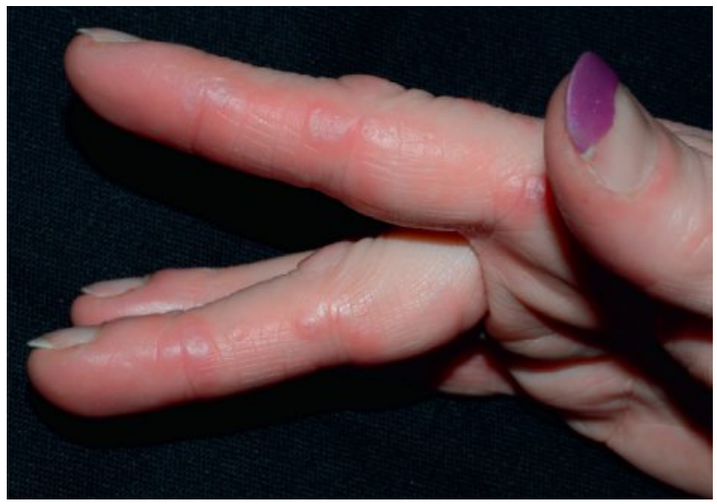
eFig. 42.16 Telangiectasias of the proximal nail fold in a patient with dermatomyositis. Nail capillaroscopy shows multiple dilated capillary loops. *Courtesy Edward Cowen, MD.*



eFig. 42.17 Calcinosis cutis of the shoulder in a patient with dermatomyositis. *Courtesy Jeffrey P. Callen, MD.*



eFig. 42.18 T2-weighted MR images of the pelvic region. A In a normal control patient. **B** In a patient with dermatomyositis. This shows increased signal intensity (white color; arrow) diffusely in multiple muscle groups. The increased signal correlates with inflammation.



eFig. 42.19 Dermatomyositis. Flat-topped pink papules with scale in a less common location. The patient also had interstitial lung disease. *Courtesy Sonya K. Burton, MD.*

43 Systemic Sclerosis (Scleroderma) and Related Disorders

Gideon P. Smith, Anna K. Haemel and M. Kari Connolly

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SYSTEMIC SCLEROSIS

Synonyms: Systemic sclerosis: ■ Scleroderma ■ Progressive systemic sclerosis
Subtypes of cutaneous involvement: ■ Diffuse ■ Limited (includes CREST syndrome)

Key features

- An uncommon autoimmune connective tissue disease of unknown etiology
- Characterized by symmetric hardening of the skin of the fingers, hands, and face that may generalize
- Raynaud phenomenon is common, and digital ulcers may develop
- Internal organ involvement is frequent and affects the lungs, gastrointestinal tract, heart, and kidneys
- Important to monitor for lung involvement because pulmonary disease is the leading cause of death
- Treatment focuses on internal organ manifestations; effective therapy for cutaneous sclerosis remains inadequate

Introduction

Systemic sclerosis (SSc, scleroderma) is an autoimmune connective tissue disease (AI-CTD) of unknown etiology that affects the skin, blood vessels, and internal organs[1]. The name *systemic sclerosis* is meant to convey the systemic nature of the disease, which has two major clinical subtypes: *limited cutaneous SSc* (lcSSc) and *diffuse cutaneous SSc* (dcSSc). LcSSc is characterized by cutaneous sclerosis that is limited to the fingers, hands, and face. In dcSSc, generalized cutaneous sclerosis is seen that usually begins in the fingers and hands but eventually extends to the forearms, arms, face, trunk, and lower extremities. Other entities that can lead to symmetric and widespread cutaneous induration include generalized morphea, eosinophilic fasciitis, scleromyxedema, nephrogenic systemic fibrosis, scleredema, and chronic GVHD (Table 43.1).

History

The first reported case of SSc in 1754 was a young Italian woman who developed progressive skin induration[1]. From the clinical description, it is impossible to determine whether she had true SSc or another sclerodermoid disorder such as scleredema.

Epidemiology

SSc has a worldwide distribution and affects all races. The annual incidence and prevalence rates in the US are approximately 20 and 275 cases per million, respectively[2]. Women are affected three to four times as often as men. Although SSc can occur in children and the elderly, onset is typically between the ages of 35 and 50 years. Black individuals have an earlier mean age of onset and a higher likelihood of diffuse disease[2]. Approximately 1.5% of SSc patients have one or more affected first-degree relatives, representing a 10- to 15-fold higher risk of SSc in family members than in the general population[1]. SSc is associated with significant mortality, with an overall 10-year survival of ~70%[1]. Clinical features predicting a worse prognosis include male sex, older age at diagnosis, being African-American, internal organ involvement (especially pulmonary) at the time of diagnosis, cutaneous sclerosis affecting the trunk, and elevated ESR[1].

Pathogenesis

The pathogenesis of SSc is unknown. Key pathogenic abnormalities in the skin and internal organs are vascular dysfunction, immune activation with autoantibody production, and tissue sclerosis characterized by deposition of collagen and other extracellular matrix proteins (Fig. 43.1)[2a–5].

Vascular dysregulation

Impaired angiogenesis is an early event in the pathogenesis of SSc[5]. The blood vessels affected range from the smallest capillaries within the proximal nail fold to the large pulmonary arteries. Endothelial cell injury occurs early (before sclerosis is evident), based on changes seen by electron microscopy, such as perivascular leak and edema[6]. Endothelial cell activation leads to increased expression of adhesion molecules and binding of circulating inflammatory cells. Vascular endothelial growth factor (VEGF) and its receptors (VEGFR) are elevated in the dermis in SSc[5].

Surrounding smooth muscle cells are also affected and have altered production of and responsiveness to vasoconstrictive (e.g. cold, endothelin) and vasodilatory (e.g. nitric oxide) factors. Structural abnormalities such as intimal proliferation lead to luminal occlusion and hypoxia which then induces synthesis of profibrotic cytokines, fibroblast activation, and collagen production[7]. Raynaud phenomenon and digital ulcers are caused by reversible vasospasm as well as irreversible arterial damage with intimal proliferation and luminal obstruction. Scleroderma renal crisis and pulmonary artery hypertension are manifestations of large vessel dysregulation.

Immune dysregulation

Autoantibodies unique to SSc, in particular anti-centromere, anti-topoisomerase I, and anti-RNA polymerase III, are useful for diagnostic and prognostic purposes (see Ch. 40)[1,8]. These three autoantibodies bind tissues of interest in SSc, as do anti-U3RNP (antifibrillarin), anti-Th/To, anti-U1RNP, anti-PM-Scl, and anti-Ku autoantibodies[5,8]. The latter are rather rare and play a role in overlap syndromes.

Evidence of a direct pathogenic role for these autoantibodies includes complexes containing topoisomerase I autoantibody that, when bound to the surface of fibroblasts, have been found to stimulate monocyte adhesion and activation. In addition, anti-endothelial cell antibodies from SSc patient sera can trigger endothelial cell apoptosis. One group described stimulatory autoantibodies against the platelet-derived growth factor (PDGF) receptor in SSc sera, which induced reactive oxygen species and expression of type I collagen by normal human fibroblasts[9]. However, two subsequent studies were unable to confirm these findings[10].

Lymphocytic infiltrates, composed of both T and B cells, have been observed in the skin and lungs of SSc patients before the development of fibrosis. Oligoclonal T cell expansion has been identified in lesional skin, indicating an antigen-driven response, and T cells demonstrate

MAJOR CLINICAL AND LABORATORY MANIFESTATIONS OF SYSTEMIC SCLEROSIS AND OTHER SELECTED CONDITIONS CHARACTERIZED BY CUTANEOUS INDURATION							
	Systemic sclerosis	**Morphea**	**Eosinophilic fasciitis**	**Scleredema**	**Scleromyxedema**	**NSF**	**Chronic GVHD**
Major clinical variants	• Limited • Diffuse	• Plaque-type (circumscribed) morphea • Linear morphea • Generalized morphea		• Post-infectious (type I) • Monoclonal gammopathy-associated (type II) • Diabetes mellitus-associated (type III)			• Lichen sclerosis-like • Morphea-like • Scleroderma-like • Fasciitis
Raynaud phenomenon	++	–	–	–	–	–	–
Symmetric induration	++*	– plaque-type and linear ± generalized	++*	++	++	+	+
Sclerodactyly	++	–	–	–	–	–	–
Facial involvement	+	– plaque-type and generalized + linear (en coup de sabre)	–	± types I and II – type III	+	–	±
Systemic involvement	++	– for plaque-type but ± for linear involving head (ocular, CNS)	+	–	++	+	+
Anti-nuclear antibodies	++	± generalized and linear – plaque-type	–	–	–	–	±
Anti-centromere antibodies	+ limited	–	–	–	–	–	–
Anti-topoisomerase I (Scl-70) antibodies	+ diffuse	–	–	–	–	–	–
Anti-RNA polymerase III	+ diffuse	–	–	–	–	–	–
Monoclonal gammopathy	–	–	±	+ type II	++	–	–
Spontaneous remission	–	++ plaque-type + generalized ± linear	++	++ type I ± types II and III	–	±†	–

*May be preceded by edematous phase.
†With improved renal function.

Table 43.1 Major clinical and laboratory manifestations of systemic sclerosis and other selected conditions characterized by cutaneous induration. NSF, nephrogenic systemic fibrosis; ++, almost always; +, common; ±, sometimes; –, rare or unusual. *Courtesy Vincent Falanga, MD.*

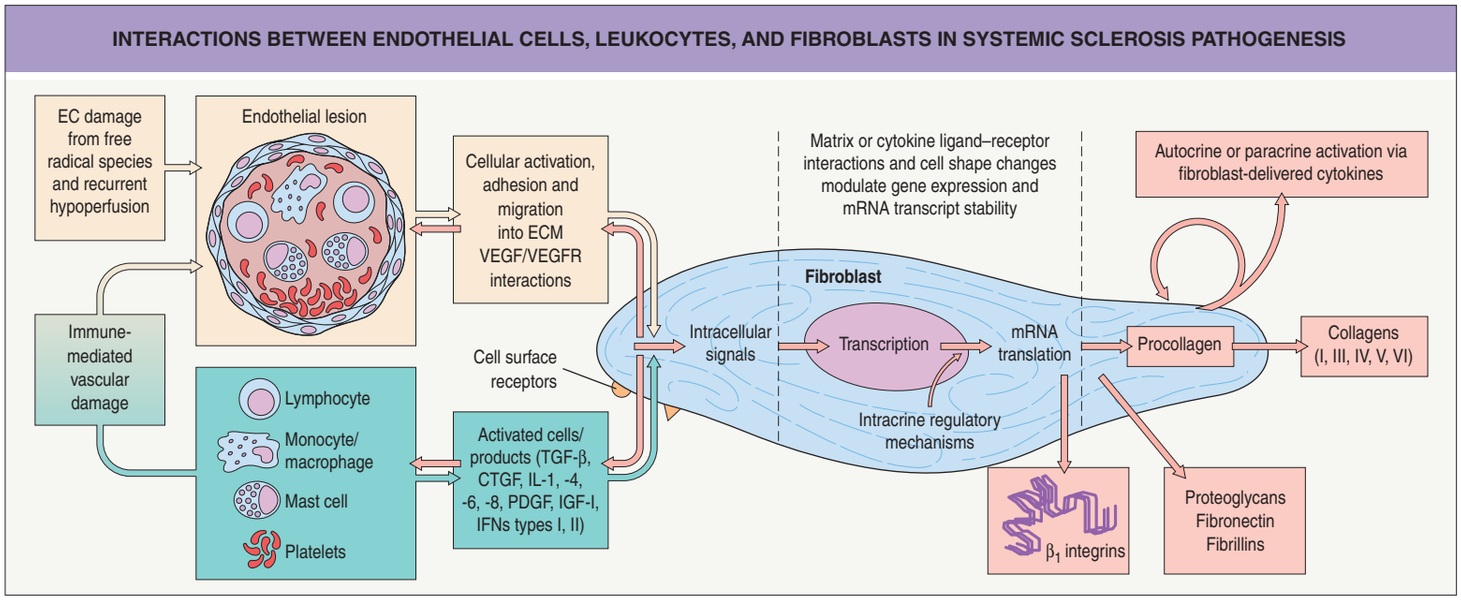


Fig. 43.1 Interactions between endothelial cells, leukocytes, and fibroblasts in systemic sclerosis pathogenesis. In patients with systemic sclerosis, variants in genes involved in innate immunity (e.g. *IRF5*), T cell activation (e.g. *STAT4*), and the TNF pathway (e.g. *TNFAIP3*) have been identified. Mutations in the gene that encodes fibrillin-1 (*FBN1*) lead to stiff skin syndrome. CTGF, connective tissue growth factor; EC, endothelial cell; ECM, extracellular matrix; IFN, interferon; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor. *Adapted from Hochberg MC, Silman AJ, Smolen JS, et al (eds). Rheumatology, 3rd edn. Edinburgh: Mosby, 2003.*

a Th2-predominant profile with up-regulation of profibrotic cytokines such as interleukin (IL)-4 and IL-13. SSc patients also have expansion of naive B cells and chronic activation, but a decreased number, of memory B cells.

More recently, Th17 cells and IL-17 have been implicated in SSc, as have the *innate* immune system and types I (α,β) and II (γ) interferons. For example, elevated numbers of plasmacytoid dendritic cells have been observed in the blood and skin of SSc patients[11]. In a proteome-wide analysis of five large cohorts, circulating levels of the chemokine CXCL4 were found to be significantly elevated (compared to controls), and the CXCL4 levels correlated with the presence and progression of pulmonary disease[11]. Prospective studies have shown changes in CXCL4 at 12 months predicted future progression[12].

Extracellular matrix dysregulation

Sclerosis represents the final common pathway for tissue damage in SSc. There is excessive deposition of collagens, proteoglycans, fibronectin, fibrillins, and adhesion molecules (e.g. β_1-integrins), which sequester cytokines and growth factors (see Fig. 43.1). Attention has focused on transforming growth factor β (TGF-β) and connective tissue growth factor (CTGF). The latter is induced by TGF-β and may be responsible for maintenance of collagen synthesis.

Given the complex extracellular matrix changes seen in SSc[13], both the fibroblast and the myofibroblast have been a focus of investigation. There is evidence suggesting an inherent defect, an autocrine loop, or a hypersensitivity to growth factors in SSc fibroblasts. Alternatively, SSc fibroblasts may have a normal phenotype but instead find themselves in an abnormal microenvironment with enhanced growth factors or ischemic mediators. The accumulation of collagen in SSc seems to be primarily the result of increased synthesis, rather than decreased degradation.

Clinical Features

Classification and diagnostic criteria

The American College of Rheumatology (ACR) updated the classification criteria for SSc in 2013 (Table 43.2)[14]. These classification criteria ensure the patient population being studied is well-defined and homogeneous, which is particularly important in rheumatic diseases where nonspecific and overlapping symptoms may lead to misclassification. As a result, *classification* criteria are stricter than the *diagnostic* criteria used for an individual patient. Nonetheless, for our purposes, they will be used interchangeably.

In the 2013 classification scheme for SSc, the sole major criterion – skin thickening of the fingers on both hands extending proximal to the metacarpophalangeal (MCP) joints – leads to a diagnosis of *definite* SSc (9 points)[14]. If the patient does not meet this criterion, seven other minor criteria may be used to reach a diagnosis of SSc (see Table 43.2). These 2013 criteria have greater sensitivity (91%) and specificity (92%) compared to older criteria[14].

Based upon the degree of skin involvement, there are two major clinical subtypes (Fig. 43.2): lcSSc and dcSSc[1]. When the skin disease involves the distal and proximal portions of the extremities, trunk and face, it is considered dcSSc, but when the induration is limited to the distal extremities and face, it is considered lcSSc[1]. Although both can have systemic manifestations, there are variable patterns and severity of internal organ involvement (Table 43.3). Typically, dcSSc is associated with early internal organ involvement (within 5 years of disease onset) and a worse prognosis[1], whereas patients with lcSSc tend to develop internal involvement later in the disease and have a better prognosis.

The acronym CREST describes clinical features in a subset of patients with lcSSc: *c*alcinosis, *R*aynaud phenomenon, *e*sophageal involvement, *s*clerodactyly and *t*elangiectasia. However, because not every patient has all five features, the term lcSSc is favored. Rarely, patients present with characteristic internal organ involvement, Raynaud phenomenon, abnormal nail-fold capillaries, and positive serologies, but no cutaneous sclerosis. This clinical presentation is referred to as *systemic sclerosis sine scleroderma* (ssSSc), and it behaves similarly to lcSSc.

Cutaneous features

Many patients with SSc experience an early edematous phase, which often features pitting edema of the digits (Fig. 43.3). Digital pits are also a characteristic finding (Fig. 43.4). The skin subsequently hardens and develops a taut, shiny appearance (indurated phase). Eventually,

ACR/EULAR CRITERIA FOR THE CLASSIFICATION OF SYSTEMIC SCLEROSIS

Item	Sub-item	Weight/score
Skin thickening of the fingers of both hands extending proximal to the MCP joints (*sufficient criterion*)	–	9
Skin thickening of the fingers	Puffy fingers - *or* - Sclerodactyly	2 4
Fingertip lesion	Digital tip ulcers - *or* - Pitting scars	2 3
Telangiectasias	–	2
Abnormal nail-fold capillaries	–	2
Pulmonary arterial hypertension - *or* - Interstitial lung disease		2 2
Raynaud phenomenon	–	3
SSc-related autoantibodies	Anti-centromere Anti-topoisomerase I Anti-RNA polymerase III	3

Table 43.2 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for the classification of systemic sclerosis (SSc). The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having *definite* SSc. *From Van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis. Arthritis Rheum. 2013;65:2737–47.*

COMPARISON OF CLINICAL AND LABORATORY FEATURES OF DIFFUSE AND LIMITED SYSTEMIC SCLEROSIS

Clinical feature	Diffuse SSc (%)	Limited SSc (%)
Raynaud phenomenon	90	99
Finger swelling	95	90
Tendon friction rubs	70	5
Arthralgia	98	80
Proximal weakness	80	60
Calcinosis	20	40
Mat telangiectasias*	60	90
Esophageal dysmotility	80	90
Small bowel involvement	40	60
Interstitial lung disease	70	35
Pulmonary arterial hypertension	10	30
Cardiomyopathy	15	10
Renal crisis	20†	1
Sicca syndrome	15	35
Anti-nuclear antibodies	90	90
Anti-centromere antibody	5-10	30-70
Anti-topoisomerase I (Scl-70) antibody	30-70	5-15
Anti-RNA polymerase III antibody	5-25	1-5
Cumulative survival (5 years)	80	90
(10 years)	70	80

*In addition, nail-fold capillary abnormalities are observed in >90% of SSc patients.
†Has decreased with the use of angiotensin-converting enzyme (ACE) inhibitors.

Table 43.3 Comparison of clinical and laboratory features of diffuse and limited systemic sclerosis (SSc). *Adapted from Pauling JD, McHugh N. The clinical aspects on autoantibodies. In: Varga J, Denton CP, Wigley FM (eds). Scleroderma: from pathogenesis to comprehensive management. New York: Springer Science+Business Media LLC 2012:209–25.*

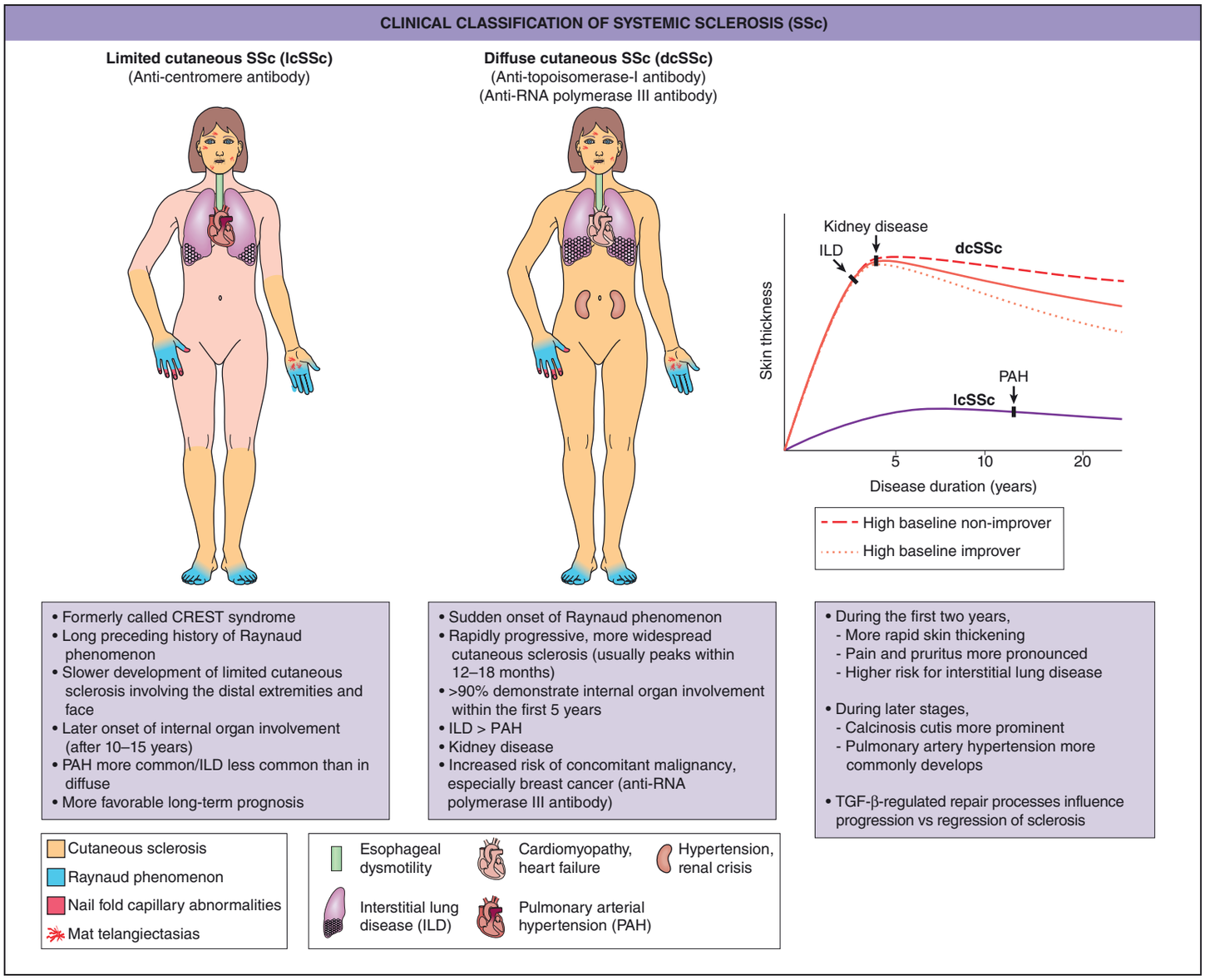


Fig. 43.2 Clinical classification of systemic sclerosis (SSc). *Courtesy Karynne O. Duncan, MD.*

there may be gradual thinning of the skin (late atrophic phase). The fingers can develop flexion contractures and ulcers (Fig. 43.5) while involvement of the face can lead to a beaked nose, microstomia, and a more youthful appearance.

There are a number of cutaneous changes other than sclerosis in patients with SSc. **Dyspigmentation** in areas of sclerosis is commonly observed. Some patients develop diffuse hyperpigmentation, with accentuation in sun-exposed areas and sites of pressure. The "leukoderma of scleroderma" is characterized by localized areas of depigmentation with sparing of the perifollicular skin; this helpful diagnostic finding is sometimes referred to as the "salt and pepper" sign (Fig. 43.6). Pigment may also be retained in the skin overlying superficial veins. This leukoderma favors the upper trunk and central face and may overlie uninvolved or sclerotic skin.

Telangiectasias are more common in patients with lcSSc but also occur in patients with dcSSc (see Table 43.3). The telangiectasias most often involve the face, lips, and palms. These telangiectatic macules are matted or squared-off (Fig. 43.7). Capillary abnormalities in the proximal nail fold are present in more than 90% of SSc patients and can be useful in supporting the diagnosis[15]. Use of magnification may enhance appreciation of these findings. In SSc, capillary loss ("drop out") alternating with dilated loops is characteristic, and density changes have been shown to have prognostic value for fingertip ulceration and lung disease progression.

Calcinosis cutis most commonly develops on the extremities, usually near joints and in distal locations (Fig. 43.8). In addition, the skin is often



Fig. 43.3 Early, edematous phase of systemic sclerosis. Note the demonstration of pitting edema on two of the digits. *Courtesy Jean L. Bolognia, MD.*

dry due to decreased sweating, and pruritus can be quite marked. Sclerotic skin may show diminished hair growth, but this is variable; hypertrichosis can also occur, particularly during the recovery phase. Overall, the cutaneous changes are extremely troublesome to patients with SSc. In a questionnaire-based study involving 300 patients with SSc, facial involvement and microstomia were the patients' greatest concerns[16].

Raynaud phenomenon is characterized by episodic vasospasm of the digital arteries resulting in white, blue, and red discoloration of the fingers secondary to cold exposure[17]. Raynaud phenomenon occurs in two settings (Table 43.4). *Primary Raynaud phenomenon* (Raynaud disease) typically develops in adolescent girls and young women and is not associated with any underlying medical problems[18]. Primary Raynaud phenomenon is common and estimated to affect 3% to 5% of the population. In contrast, *secondary Raynaud phenomenon* is uncommon and is associated with an underlying medical disorder, including SSc (Fig. 43.9; Table 43.5). An approach to differentiating primary from secondary Raynaud phenomenon is presented in Figure 43.10.

Cutaneous ulcers are common in patients with SSc (Fig. 43.11). Whereas ulcers on the tips of the digits are probably due to ischemia, those on the interphalangeal joints are more likely to persist because of continued trauma (see Fig. 43.5). They may also overlie sites of calcinosis cutis. Ulcers can lead to osteomyelitis and even amputation (autoamputation or surgical).

Extracutaneous features

The majority of SSc patients have internal organ involvement (Table 43.6), which is the major cause of morbidity and mortality in this disease[1,19]. Occasionally, a patient with SSc will present with internal organ involvement before skin involvement is evident. The most commonly affected organs are the gastrointestinal tract, lungs, heart, and kidneys. Of note, pulmonary disease has replaced renal crisis as the leading cause of death in SSc. There are two major forms of pulmonary involvement in SSc[1,19]: (1) interstitial lung disease (ILD); and (2) pulmonary arterial hypertension (PAH). Screening tests for both disorders are outlined in Table 43.6. Recently, a rare subtype of ILD referred to as pleuroparenchymal fibroelastosis (PPFE) was described. It is characterized by fibrotic thickening of the visceral pleura as well as the subadjacent parenchymal areas of the lungs' upper lobes. PPFE portends a poor prognosis and requires close monitoring with serial determinations of DLCO (*d*iffusing capacity of the *l*ungs for *c*arbon *m*onoxide) and high-resolution computed tomography scans.

Autoantibodies

Autoantibody testing is useful in confirming the diagnosis of SSc (see Ch. 40). Most SSc patients have elevated titers of anti-nuclear antibodies (ANA)[1,8], with the nucleolar or discrete speckled (centromere) patterns being relatively specific for SSc. Patients with anti-centromere antibodies are more likely to have lcSSc, digital gangrene, and PAH[1]. Patients with antibodies to topoisomerase I (Scl-70) are more likely to have dcSSc with an increased risk of ILD leading to pulmonary fibrosis[1]. Lastly, the subset of patients with anti-RNA polymerase III antibodies is more likely to have rapidly progressive, diffuse skin disease, and renal involvement[1]. This subset may also have an increased risk of an associated malignancy, most commonly breast cancer[20].

Pathology

Histologically, areas of cutaneous induration are characterized by compact or hyalinized collagen, excessive deposition of collagen, atrophic eccrine and pilosebaceous glands, "miniaturization" or loss of subcutaneous fat, and a sparse lymphocytic infiltrate in the dermis and subcutis (Fig. 43.12). Plasma cells may be present. Adnexal structures, especially eccrine glands, appear "trapped" by the excessive deposition of collagen. In some cases, there may be a



Fig. 43.4 Pitted scars of the digital pulp in a patient with systemic sclerosis. *Courtesy Kalman Watsky, MD.*



Fig. 43.5 Late-stage disease in a patient with diffuse cutaneous systemic sclerosis. Note the fixed flexion contractures, sclerodactyly, and the digital ulceration overlying the third proximal interphalangeal joint.



Fig. 43.6 The "salt and pepper" sign. Leukoderma with retention of perifollicular pigmentation in a patient with systemic sclerosis. *Courtesy Joyce Rico, MD.*

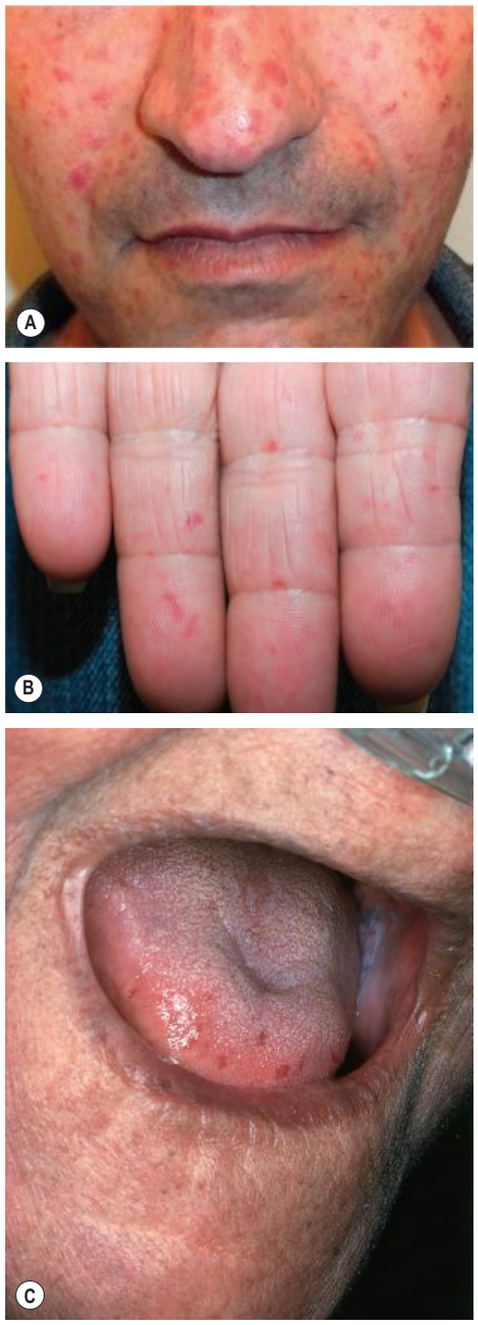


Fig. 43.7 Mat (squared-off) telangiectasias in systemic sclerosis (SSc). **A, B** Two patients with limited cutaneous SSc; the face and palms are two of the most common sites for mat telangiectasias. **C** This patient presented with diffuse hyperpigmentation and interstitial lung disease and the presence of mat telangiectasias pointed to the diagnosis. *B, Courtesy Kalman Watsky, MD; C, Courtesy Jean L. Bolognia, MD.*



Fig. 43.9 Raynaud phenomenon in a patient with early systemic sclerosis. There is obvious blanching of two fingers as well as a violaceous hue of the forefinger. *Courtesy Jeffrey P. Callen, MD.*

CLINICAL AND LABORATORY FEATURES OF PRIMARY AND SECONDARY RAYNAUD PHENOMENON

Feature	Primary	Secondary
Sex	F:M 20:1	F:M 4:1
Age at onset	Puberty	>25 years
Frequency of attacks	Usually <5 per day	5–10+ per day
Precipitants	Cold, emotional stress	Cold
Ischemic injury	Absent	Present
Abnormal capillaroscopy	Absent	>95%
Other vasomotor phenomena	Yes	Yes
Anti-nuclear antibodies	Absent/low titer	90–95%
Anti-centromere antibody	Absent	30–40%
Anti-topoisomerase I (Scl-70) antibody	Absent	20–30%
Anti-RNA polymerase III antibody	Absent	10–20%
In vivo platelet activation	Absent	>75%

Table 43.4 Clinical and laboratory features of primary and secondary Raynaud phenomenon. *Adapted from Pauling JD, McHugh N. The clinical aspects on autoantibodies. In: Varga J, Denton CP, Wigley FM (eds). Scleroderma: from pathogenesis to comprehensive management. New York: Springer Science+Business Media LLC 2012:209–25.*



Fig. 43.8 Calcinosis cutis of the finger in a patient with systemic sclerosis.

perineural arrangement of the inflammatory infiltrate within the deep dermis. Of note, the different subsets of SSc cannot be distinguished histologically.

Direct immunofluorescence studies are usually negative in patients with SSc. While endothelial damage can occur in cutaneous blood vessels, this finding is only seen at the ultrastructural level[6]; reduplication of the basement membrane is also observed. It should be noted that, in its end stage, areas of sclerosis may be indistinguishable histologically from other diseases characterized by collagen deposition, such as morphea (which tends to have a more robust inflammatory infiltrate than SSc in its earlier stages).

Differential Diagnosis

The primary differential diagnosis of SSc is outlined in Table 43.1 while additional entities that may have a sclerodermoid presentation are

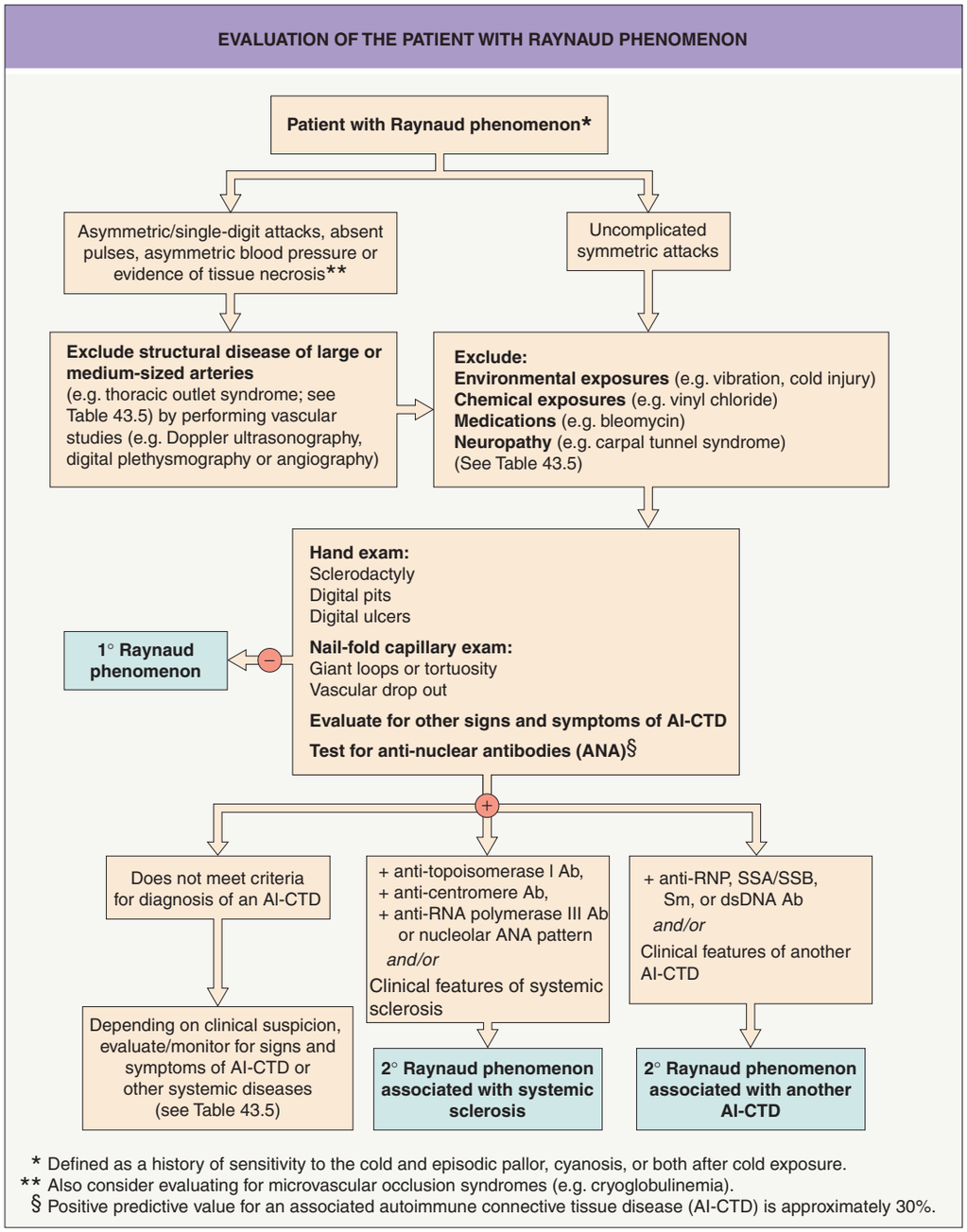


Fig. 43.10 Evaluation of the patient with Raynaud phenomenon. ds, double-stranded; RNP, ribonucleoprotein; Sm, Smith.

listed in Table 43.7[21]. Of note, chronic GVHD can have both pulmonary (e.g. bronchiolitis obliterans) and gastrointestinal manifestations. Some patients with SSc also have features of another AI-CTD, i.e. an overlap syndrome. Localized forms of scleroderma (morphea) are discussed in Chapter 44 as are morpheaform disorders.

Treatment

SSc is a challenging disease to treat[21a,21b]. Therapeutic interventions focus primarily on internal organ involvement (see Table 43.6), but unfortunately most of these treatments have minimal effect on cutaneous sclerosis and the other cutaneous manifestations (Table 43.8)[1,22].

Raynaud phenomenon

First-line therapy for Raynaud phenomenon is behavioral and involves educating patients to keep warm and avoid smoking to minimize the frequency and severity of attacks[23].

Second-line therapy is pharmacologic, starting with vasodilators[18]. Calcium channel blockers (e.g. nifedipine, amlodipine) have been the most widely used medications (see Table 43.8). Angiotensin II receptor blockers (e.g. losartan) may also be effective, and combination therapy can be tried. More recently, phosphodiesterase type 5 inhibitors (e.g. sildenafil, tadalafil) that target the nitric oxide-mediated vasodilation pathway have been employed[24]. Care must be taken so that the vasodilators do not excessively lower systemic blood pressure. In addition, calcium channel blockers may exacerbate gastroesophageal reflux disease and lead to peripheral edema. In patients who cannot tolerate these medications because of hypotension, a selective serotonin reuptake inhibitor (e.g. fluoxetine) may be an option[23]. Injections of botulinum toxin type A into the base of digits have also been reported as successful and their use has increased [24a], although outcomes in a prospective trial were disappointing[25].

Oral antiplatelet agents (e.g. low-dose aspirin, clopidogrel) and/or pentoxifylline may theoretically provide additional blood flow to compromised distal sites. Biofeedback can also be helpful. Use of HMG-CoA reductase inhibitors ("statins") as a vasoprotective treatment is under investigation and appears to be safe and well tolerated[26].

Cutaneous ulcers

Digital ulcers on the fingers are difficult to treat and a source of great morbidity. Management includes the treatments for Raynaud phenomenon outlined above. Detailed occupational and recreational histories are important to identify risk factors and sources of injury

DIFFERENTIAL DIAGNOSIS OF RAYNAUD PHENOMENON
Structural vasculopathies
Large and medium-sized arteries
Thoracic outlet syndrome
Brachiocephalic trunk disease (atherosclerosis, Takayasu arteritis)
Buerger disease (thromboangiitis obliterans)*
Crutch pressure
Small arteries and arterioles
Systemic sclerosis
Systemic lupus erythematosus
Dermatomyositis
Overlap syndromes
Cold injury
Vibration disease (hand–arm vibration syndrome, hypothenar hammer syndrome)
Chemotherapy (bleomycin, vinca alkaloids, cisplatin, carboplatin)
Vinyl chloride disease
Arsenic poisoning
Normal blood vessels – abnormal blood elements
Cryoglobulinemia (monoclonal or mixed)
Cryofibrinogenemia
Cold agglutinin disease
Myeloproliferative disorders (e.g. essential thrombocythemia)
Normal blood vessels – abnormal vasomotion
Primary (idiopathic) Raynaud phenomenon
Drug-induced (ergot alkaloids, bromocriptine, interferon, estrogen, cyclosporine, sympathomimetic agents, clonidine, cocaine, nicotine, calcitonin gene-related peptide (CGRP)-targeting drugs)
Carpal tunnel syndrome
Pheochromocytoma
Carcinoid syndrome
Complex regional pain syndrome
Other vasospastic disorders (migraine, Prinzmetal)
*Can also affect small arteries.

Table 43.5 Differential diagnosis of Raynaud phenomenon. Paraneoplastic acral vascular syndrome, which can present with Raynaud phenomenon as well as acrocyanosis and gangrene, has been observed in patients with various solid tumors (e.g. lung or ovarian carcinoma). In acute idiopathic blue finger (Achenbach syndrome), the digital blue discoloration represents ecchymosis.
Adapted from Hochberg MC, Silman AJ, Smolen JS, et al (eds). Rheumatology, 3rd edn. Edinburgh: Mosby, 2003. © Elsevier 2003.

and cold exposure. Based upon two randomized controlled trials, bosentan, an oral endothelin receptor antagonist, has been approved in Europe, but not the US, for the prevention of new digital ulcers in SSc patients[27]. While disappointing results were observed in a double-blind randomized trial of *oral* iloprost (a prostacyclin analogue)[28], when administered *intravenously*, it resulted in a reduction in digital ulcers and improved healing[29]. More limited studies of the subcutaneous prostacyclin analogue treprostinil suggest that it may also be effective. In refractory cases, nerve blocks and sympathectomies may be considered.

In patients with SSc, autolytic debridement of ulcers via occlusive dressings is thought to be safer than mechanical debridement. In general, moist hydrocolloid dressings provide a better wound healing environment than dry or wet-to-dry dressings. Skin equivalents or grafts can also be used to stimulate the wound bed and decrease wound pain. Topical vasodilators such as nitroglycerin are attractive because of ease of application and minimal systemic side effects; however, evidence-based data on their effectiveness are lacking[23].

Cutaneous sclerosis

In the early stage of SSc, cutaneous and subcutaneous edema develops rapidly, but during the indurated and atrophic stages, the cutaneous involvement progresses more slowly and tends to gradually improve, independent of treatment. Unfortunately, objective, quantitative measurements of cutaneous sclerosis that are sensitive to change over short periods of time are currently lacking for SSc. The traditional instrument for measuring skin involvement in SSc is the modified



Fig. 43.11 Cutaneous ulcerations in systemic sclerosis. Ulcers favor the digits (**A**) and sites of trauma such as the elbow (**B**). Note the calcinosis cutis at the base of the forefinger and the pterygium inversum unguis of the third finger.
A, Courtesy Kalman Watsky, MD; B, Courtesy Joyce Rico, MD.

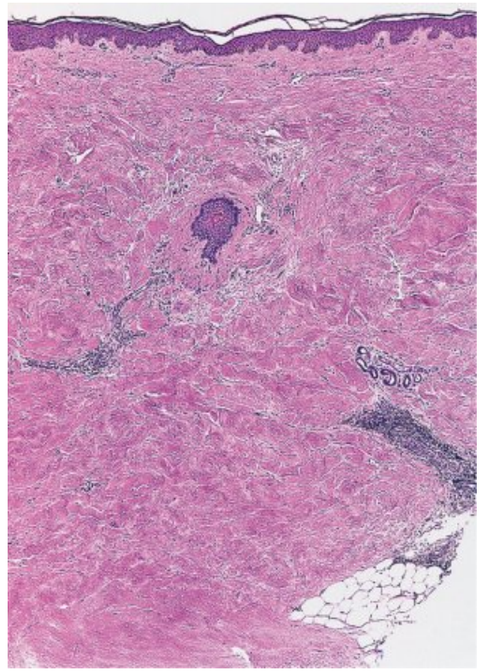


Fig. 43.12 Systemic sclerosis – histopathologic features. There is a dense sclerosis of the dermis with decreased adnexal structures and "trapping" of remaining adnexal structures that are encased by collagen. Sparse perivascular infiltrates of lymphocytes are present. *Courtesy Ronald P. Rapini, MD.*

INTERNAL ORGAN INVOLVEMENT IN SYSTEMIC SCLEROSIS – SCREENING AND TREATMENT OPTIONS		
Internal organ	**Screening tools***	**Treatment options**
Lung*		
• Interstitial lung disease (ILD)	• **PFTs (DLCO, spirometry, and lung volumes)** • **High-resolution CT (HRCT)** • Bronchoalveolar lavage and lung biopsy	• Immunosuppression (e.g. mycophenolate mofetil, cyclophosphamide, rituximab) • Nintedanib†, tocilizumab† • Lung transplantation • Autologous HSCT in selected patients with rapidly progressive ILD
• Pulmonary arterial hypertension (PAH)	• **Transthoracic echocardiography** • **Serum *N*-Tpro-BNP level** • Right heart catheterization	• Oxygen • Anticoagulation • Endothelin receptor antagonists (e.g. bosentan) • Phosphodiesterase type 5 inhibitors (e.g. tadalafil) • Prostacyclin analogues (e.g. treprostinil) • Prostacyclin receptor agonists (e.g. selexipag) • Soluble guanylate cyclase stimulant (e.g. riociguat) • Lung transplantation
Kidney		
• Renal crisis • Hypertension	• **Close monitoring of blood pressure** • **BUN/Cr** • **Urinalysis**	• ACE inhibitors instituted early for treatment but not helpful for prevention
Heart		
• Fibrosis/restrictive cardiomyopathy • Heart failure secondary to PAH	• Echocardiography	• ACE inhibitors
Gastrointestinal tract		
• Esophageal dysmotility • Small bowel involvement	• Barium swallow with small bowel follow through • Manometry • Endoscopy	• Proton pump inhibitors • Promotility agents (e.g. ondansetron)

*Patients are typically asymptomatic during the early stages of ILD and PAH, which is when the diagnosis should be made and treatment instituted; cough, dyspnea on exertion, and shortness of breath are typical later-onset symptoms.
†FDA-approved for SSc-ILD.

Table 43.6 Internal organ involvement in systemic sclerosis – screening and treatment options. Initial screening tests for all patients are in **bold**. ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen; Cr, creatinine; CT, computed tomography scan; DLCO, diffusing capacity of the lung for carbon monoxide; HSCT, hematopoietic stem cell transplant; *N*-Tpro-BNP, *N*-terminal pro b-type natriuretic peptide; PFTs, pulmonary function tests.

DIFFERENTIAL DIAGNOSIS OF SCLERODERMOID CONDITIONS	
Disorder	**Clinical features**
Mucinoses	
• Scleredema	Induration of the upper back, neck and face; occasional internal involvement (see Ch. 46)
• Scleromyxedema	Waxy papules (often in a linear array); diffuse induration favoring the face, upper trunk, arms, and thighs; monoclonal gammopathy; neurologic, gastrointestinal, and pulmonary involvement (see Ch. 46)
Immunologic	
• Sclerotic chronic GVHD*	Variable sclerosis that often resembles plaque-type or deep morphea initially and then may become generalized; eosinophilic fasciitis (see Ch. 52)
• Eosinophilic fasciitis	Symmetric induration with a “pseudo-cellulite” appearance on the extremities (sparing hands and feet) (see text)
• Generalized morphea*	Expansion and coalescence of morphea plaques to involve a large portion of the trunk and extremities (see Ch. 44)
• Fibroblastic rheumatism	Sclerodactyly; fibrotic nodules on the hands
• Overlap syndromes	Sclerodactyly; myositis; arthritis
Paraneoplastic	
• POEMS syndrome	Sclerotic skin on the extremities (see Ch. 114)
• Amyloidosis (primary systemic)†	Diffuse induration favoring the face, distal extremities, and trunk (see Ch. 47)
• Carcinoid syndrome	Sclerotic skin on the legs (see Table 53.2)
• Paraneoplastic scleroderma-like syndrome	Similar to systemic sclerosis, but older age at onset; seen in association with a monoclonal gammopathy, hairy cell leukemia, and solid tumors (e.g. breast, lung)
Neoplastic	
• Carcinoma *en cuirasse**	Sclerodermoid encasement of the chest by metastatic carcinoma (usually breast cancer) (see Ch. 122)

Table 43.7 Differential diagnosis of sclerodermoid conditions.

DIFFERENTIAL DIAGNOSIS OF SCLERODERMOID CONDITIONS	
Disorder	**Clinical features**
Metabolic	
• Diabetic cheiroarthropathy	Thickened skin and limited mobility of the hands (see Fig. 53.18)
• Porphyria cutanea tarda*,‡	Morpheaform plaques in sun-exposed areas (see Ch. 49)
Neurologic	
• Complex regional pain syndrome*	Painful, cold, swollen extremity eventually develops cutaneous sclerosis (see Ch. 6)
• Spinal cord injury	Sclerotic skin in affected areas
Toxin-mediated	
• Nephrogenic systemic fibrosis*	Associated with exposure to gadolinium-based contrast agents (new cases becoming rare) (see text)
• Eosinophilia–myalgia syndrome	Associated with L-tryptophan ingestion (US, 1989) (see text)
• Toxic oil syndrome*	Associated with toxic oil ingestion (Spain, 1981) (see text)
• Silicosis	Associated with occupations such as mining (see text)
Drug- or chemical-induced (see text)	
• Bleomycin*	Acrosclerosis; Raynaud phenomenon; pulmonary fibrosis (more common, usually no concurrent skin fibrosis)
• Taxanes*	Edema followed by sclerosis of the lower extremities; acrosclerosis; rarely, pulmonary fibrosis
• Vinyl chloride, chlorinated hydrocarbons*	Acrosclerosis; acral fibrotic papulonodules; Raynaud phenomenon; acro-osteolysis; pulmonary fibrosis
Venous insufficiency	
• Lipodermatosclerosis*	Woody induration and red–brown discoloration of the lower legs in the chronic phase; may also involve the pannus (see Ch. 100)
Genetic disorders	
• Restrictive dermopathy¶	Tight, thin skin over the entire body; joint contractures; *LMNA* or *ZMPSTE24* mutations
• Hutchinson–Gilford progeria syndrome	Sclerotic skin on the lower trunk, buttocks and thighs; *LMNA* mutations (see Ch. 63)
• Werner syndrome	Tight, sclerotic skin on the distal extremities; *WRN*/*RECQL2* mutations (see Ch. 63)
• Stiff skin syndrome*	Fibrosis of the skin/fascia of the buttocks and thighs with hip contractures; *FBN1* mutations (see text)
• Phenylketonuria	Sclerotic skin on the thighs and buttocks with hip contractures; *PAH* mutations (see Ch. 63)
• MONA (multicentric osteolysis, nodulosis, and arthropathy)	Areas of skin thickening with overlying hyperpigmentation and hypertrichosis; subcutaneous nodules favoring hands/feet; digital swelling; *MMP2* mutations
• Weill–Marchesani syndrome 2	Sclerosis of the back and extensor surfaces of the extremities, with sparing of the face; also referred to as GEMSS (glaucoma, lens ectopia, microspherophakia, stiffness of the joints, and shortness) syndrome; *FBN1* mutations
• Primary hypertrophic osteoarthropathy (pachydermoperiostosis)	Thickening of the skin of the distal extremities and face, with furrowing of the forehead; seborrhea; digital clubbing; *HPGD* and *SLCO2A1* mutations (see Ch. 98)
• Ataxia–telangiectasia	Tight, sclerotic facial skin; *ATM* mutations (see Ch. 60)
• Huriez syndrome	Congenital scleroatrophy of distal extremities, palmoplantar keratoderma, hypoplastic nails & development of aggressive SCC in affected areas; haploinsufficiency of *SMARCAD1* which encodes a DNA helicase (see Ch. 58)
• Geleophysic dysplasia	Thick skin, short stature, a "happy" face, and joint contractures; mutations in *ADAMTSL2*, *FBN1*, and *LTBP3*
• H syndrome (histiocytosis–lymphadenopathy plus syndrome)	*H*ypertrichosis in association with areas of *h*yperpigmentation and induration (primarily lower trunk and lower extremities), sensorineural *h*earing loss, short *h*eight, *h*eart anomalies, *h*epatosplenomegaly, scrotal masses, hypergonadotropic *h*ypogonadism, antibody-negative insulin-dependent diabetes mellitus, facial telangiectasias (see Fig. 55.2); mutations in *SLC29A3* which encodes nucleoside transporter hENT3

*Can overlap with morpheaform disorders, which are listed in Table 44.1.
†Primary cutaneous amyloidosis can also occur in patients with systemic sclerosis and generalized morphea.
‡May also be observed in patients with congenital erythropoietic porphyria and hepatoerythropoietic porphyria.
¶Sclerodermoid changes are typically present at birth.

Table 43.7 Differential diagnosis of sclerodermoid conditions. Disorders with a clinical presentation similar to systemic sclerosis are referred to as *sclerodermoid*, while those reminiscent of morphea are referred to as *morpheaform* (see Ch. 44).

Rodnan skin score (mRSS)[1]. Although this is a validated outcome measure, it is not ideal and is relatively insensitive to small changes over short periods of time. An adapted engineering tool, the durometer, may be more suitable for assessing cutaneous induration and hardness in patients with SSc[30]. Ultrasound and lasers have also been used to measure skin sclerosis.

In general, topical therapies and phototherapeutic regimens are those utilized for morphea (see Ch. 44)[31] and may help some SSc patients. With regard to systemic medications, in a trial of D-penicillamine for dcSSc, there was no difference between the low-dose and the high-dose treatment groups, and this drug is now rarely used[32]. Although minocycline looked promising in a pilot study, a larger follow-up study failed to show a benefit[33]. Methotrexate (MTX) can be helpful in SSc patients with overlapping myositis and inflammatory arthritis. However, in a randomized, placebo-controlled trial (involving 71 patients with early SSc) in which MTX was administered for 1 year, there was a trend in favor of MTX, but it did not reach statistical significance[34]. Nonetheless, based upon its usefulness in morphea[31], a 3- to 6-month trial of MTX is reasonable in patients *without* ILD (see Table 43.8).

Mycophenolate mofetil (MMF) is routinely used for SSc-ILD (see below) and in some patients, it may be of benefit for early cutaneous sclerosis[35]. However, there is no consensus regarding a 6- to 12-month empiric

CUTANEOUS FEATURES OF SYSTEMIC SCLEROSIS – POSSIBLE TREATMENTS	
Cutaneous feature	**Possible treatment options**
Cutaneous sclerosis	• Topical therapies (see Ch. 44) • UV phototherapy (see Ch. 44) • Mycophenolate mofetil • D-penicillamine* • Methotrexate (if no ILD)‡,¶ • IVIg • Rituxumab
Raynaud phenomenon (Figs. 43.9 and 43.10)	**First-line** • Cold avoidance • Hand and feet warming packets • Discontinue all tobacco products **Second-line** • Calcium channel blockers (for normotensive patients, starting doses: nifedipine SR 30 mg daily, increasing to BID after 2 weeks if tolerated; amlodipine 2.5 mg daily, with increments of 2.5 mg every 2 weeks as tolerated, up to 10 mg daily) **Third-line** (especially when accompanied by ulceration) • Phosphodiesterase type 5 inhibitors (sildenafil: initial dose as low as 5 mg PO TID, but most patients tolerate and require 50 mg PO BID; tadalafil: initially 20 mg PO every other day, then increased every 3–5 days as tolerated up to 40 mg PO daily) • α-Adrenergic blockers (e.g. prazosin) • Angiotensin II receptor blockers (e.g. losartan) • Endothelin receptor antagonists (e.g. bosentan) **Fourth-line** • Serotonin reuptake inhibitors (e.g. fluoxetine) • Botulinum toxin type A injections into base of digits
Cutaneous ulcers (Fig. 43.11)	• Avoid excessive debridement • Moist, non-adherent dressings • Therapies listed above for Raynaud phenomenon • Low-dose aspirin or clopidogrel • IV prostanoid (e.g. epoprostenol) • Surgical excision (recalcitrant and severe cases)
Calcinosis cutis (Fig. 43.8)	• Bisphosphonates • Calcium channel blockers (e.g. diltiazem) • Sodium thiosulfate (see Ch. 50)
Mat telangiectasias (Fig. 43.7)	• Lasers appropriate for vascular lesions

*Nowadays used infrequently.
‡Methotrexate-induced pneumonitis may complicate SSc-ILD picture.
¶Concern that concomitant administration of systemic corticosteroids may increase risk of developing renal crisis; low-dose corticosteroids (e.g. prednisone <10 mg daily) may be safe.

Table 43.8 Cutaneous features of systemic sclerosis – possible treatments. Therapeutic agents under investigation include romilkimab, a humanized antibody that neutralizes IL-4/IL-13, and in preclinical models, dersimelagon, an oral agonist of the melanocortin I receptor. BID, twice a day; ILD, interstitial lung disease; IV, intravenous; PO, per os (oral administration); SR, slow release; TID, three times a day; UV, ultraviolet.

trial of MMF (2–3 g daily) for early dcSSc. As expected, the dosage may need to be adjusted based upon side effects, in particular cytopenias and gastrointestinal symptoms (see Ch. 130). MMF may be used in junction with MTX for severe, rapidly progressive cutaneous sclerosis, but close monitoring is required. Sirolimus is an mTOR inhibitor that has been used for renal transplant rejection and may also be a candidate drug for SSc. It has an anti-fibrotic effect and has been used in GVHD. Some data exist to support the use of IVIg, even in recalcitrant cutaneous disease, but larger studies are needed[36]. In a phase II trial, the autotaxin inhibitor ziritaxestat led to an improvement in cutaneous sclerosis based upon mRSS.

A number of other systemic agents have been tried in SSc, but ultimately most have been shown to be ineffective[37]. A small study that examined anti-TGF-β1 antibodies did not show a benefit[1]. Histologically, a decrease in skin thickness was observed in dcSSc following 12 months of imatinib[38].

Other cutaneous complications

Calcinosis cutis represents a serious problem for which no effective medical therapy exists. While low-dose warfarin may decrease the inflammatory reaction associated with calcium deposits, it is no longer a recommended treatment[38a]. Although there were case reports of the effectiveness of calcium channel blockers for calcinosis, this was not observed in larger patient series. Topical and intralesional sodium thiosulfate has been used to treat calcinosis cutis[37], but the injections can be painful (see Table 50.2). In certain situations, surgical removal of the calcium deposits may be necessary. Treatment with extracorporeal shock wave lithotripsy has also been reported. Telangiectasias can be treated cosmetically with lasers appropriate for vascular lesions (e.g. pulsed dye).

Internal organ involvement

Treatment of specific internal organ involvement is outlined in Table 43.6. Detailed discussions of these therapeutic approaches are available in other texts[1,19]. Of note, the use of ACE inhibitors to treat scleroderma renal crisis represents a major therapeutic advance[1].

In a number of studies, treatment with either cyclophosphamide or MMF has been shown to benefit SSc-ILD[1]. For example, one prospective, randomized, controlled trial showed a modest benefit with oral cyclophosphamide (1 to 2 mg/kg/day for 1 year) compared to placebo[39]. However, there are significant potential side effects associated with cyclophosphamide, such as cytopenias, hemorrhagic cystitis, and an increased risk of bladder carcinoma (see Ch. 130). A large, multicenter, randomized, controlled trial showed that cyclophosphamide and MMF had an equivalent benefit on SSc-ILD, but MMF had a superior tolerability and safety profile[40].

Nintedanib blocks autophosphorylation-based activation of several growth factor receptors (GFRs) – fibroblast (FGFRs), platelet-derived (PDGFRs) and vascular endothelial (VEGFRs) – via binding to their intracellular ATP binding sites. It was FDA-approved for the treatment of SSc-ILD based upon less of a decline in forced vital capacity in a randomized, double-blind, controlled trial involving 576 patients[41]. The most common side effects include diarrhea, nausea, transaminitis, hypertension, and pneumonia. Tocilizumab, an interleukin 6 receptor inhibitor, is also FDA-approved for SSc-ILD but in a phase III randomized trial its effect on skin fibrosis did not differ from placebo[42].

Advances in the treatment of PAH have also occurred, in particular the use of oral vasoactive compounds, some of which are also used for Raynaud phenomenon and digital ulcers[1]. These include endothelin receptor antagonists (bosentan[43], ambrisentan, macitentan) and phosphodiesterase type 5 inhibitors (sildenafil, tadalafil). Prostacyclin analogues (iloprost [inhaled], epoprostenol [intravenous], treprostinil [inhaled, subcutaneous, or intravenous]) and the oral prostacyclin receptor agonist selexipag are approved for PAH in SSc patients but are no longer sole or first-line therapy[1]. Lung transplantation is an option, with survival rates as well as risks for developing acute rejection and bronchiolitis obliterans syndrome similar in SSc patients when compared to those without AI-CTDs[44].

A French nationwide cohort study found that IVIg led to an improvement in muscle and joint, but not skin, disease[45]. In a recent meta-analysis examining the efficacy of imatinib, cutaneous sclerosis improved based upon mRSS following a 6- to 12-month course, but there were insufficient data regarding its effect on lung involvement[46]. Rituximab has been investigated as a rescue therapy and in one trial was superior to cyclophosphamide for SSc-ILD[47].

Three randomized controlled trials comparing cyclophosphamide versus autologous hematopoietic stem cell transplantation (HSCT) demonstrated HSCT superiority, with greater improvement in lung and skin disease as well as quality-of-life[48]. Risks include transplant-related mortality and recurrence of disease. Therefore, autologous HSCT is considered for selected patients with rapidly progressive SSc at risk of organ failure or significant morbidity.

EOSINOPHILIC FASCIITIS

Synonyms: ■ Shulman syndrome ■ Diffuse fasciitis with eosinophilia

History

Eosinophilic fasciitis was first reported in 1975 by Shulman, who described a fibrosing disorder characterized by the rapid onset of woody induration of the extremities in association with peripheral eosinophilia[49].

Clinical Features

A history of strenuous physical activity precedes the clinical findings in about 30% of patients with eosinophilic fasciitis. Initial manifestations include edema and pain of the involved extremities, which quickly progress to sclerosis and a dimpled or "pseudo-cellulite" appearance (Fig. 43.13). The distribution is symmetric and usually spares the hands, feet and face. The "groove sign" refers to linear depressions where veins appear to be sunken within the indurated skin.

Laboratory findings include an elevated ESR, hypergammaglobulinemia, and peripheral eosinophilia[50]; the latter may not be present if the patient is already receiving corticosteroids. The ANA titer is typically not elevated, and complement levels are normal. Pancytopenia, anemia, thrombocytopenia, myeloproliferative disorders, and monoclonal gammopathy have been reported in association with this disease. Some authors have advocated that patients with eosinophilic fasciitis and unexplained anemia undergo bone marrow biopsy to evaluate for a hematologic malignancy. Patients with chronic GVHD can develop clinical manifestations resembling eosinophilic fasciitis (see Ch. 52), as can those receiving immune checkpoint inhibitors, in particular anti-PD-1 and -PD-L1 antibodies.

Pathology

Histologically, there is a thickening of the deep fascia, which may be 10 to 50 times the normal width (Fig. 43.14). Within the fascia and subfascial muscle, a patchy infiltrate composed of lymphocytes, plasma cells, and a variable number of eosinophils is seen. Dermal sclerosis is a feature in some cases[51].

Treatment

Once the diagnosis of eosinophilic fasciitis is established via fascial biopsy and/or MRI (see Fig. 52.9), prompt treatment is essential to preserve mobility and function and prevent joint contractures. Therapy is usually initiated with oral corticosteroids (e.g. prednisone 1–2 mg/kg daily). Response is typically noted within the first few weeks, and clinical improvement may be seen over several months. The dose of prednisone is tapered over 6–24 months as tolerated. Due to the need for a relatively prolonged course of corticosteroids, a concurrent immunosuppressive drug (e.g. methotrexate, MMF) is often administered[52]. If an inadequate response is observed, other options include pulse-dose corticosteroids, IVIg, hydroxychloroquine, JAK inhibitors, UVA-based phototherapy, and cyclosporine.

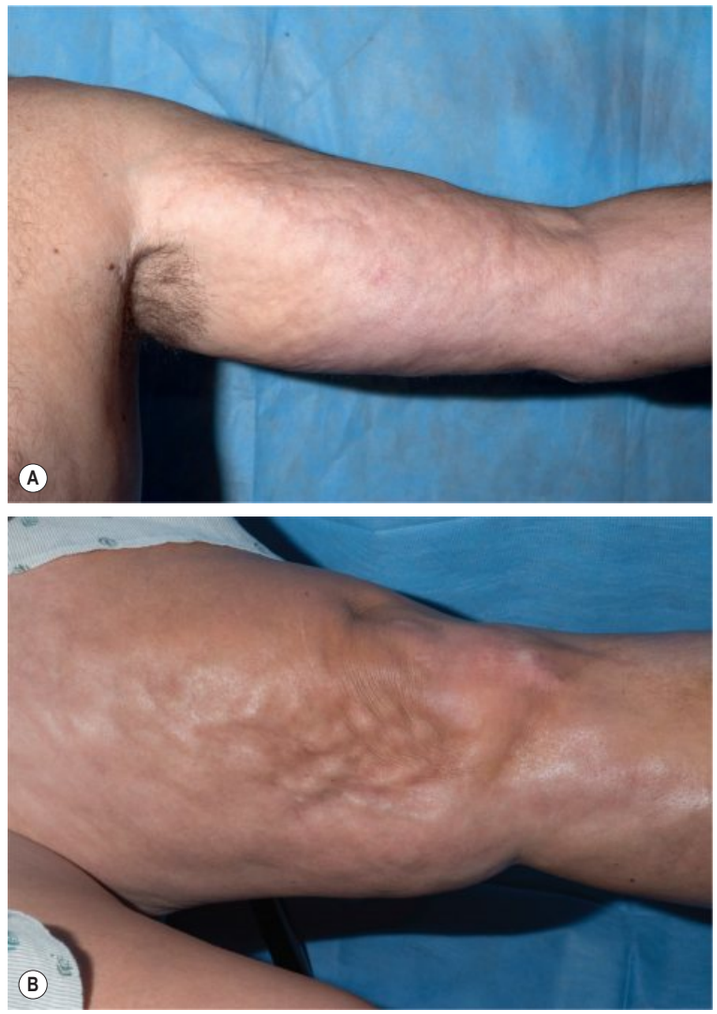


Fig. 43.13 Eosinophilic fasciitis – clinical features. A Induration of the arm with a dimpled or "pseudo-cellulite" appearance, also referred to as rippling or puckering. **B** Firm, irregular induration and nodularity of the medial thigh. The differential diagnosis includes deep morphea. *Courtesy Edward Cowen, MD.*

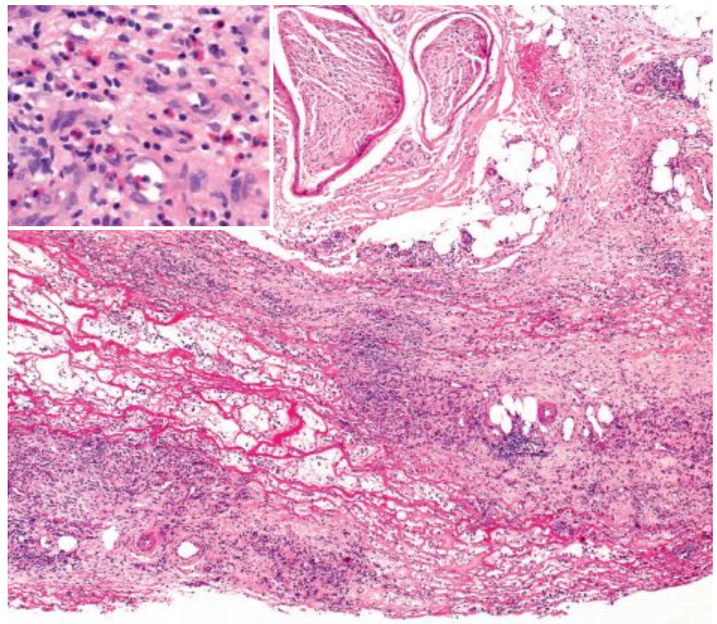


Fig. 43.14 Eosinophilic fasciitis – histopathologic features. Thickening of the deep fascia and septae of the subcutis with an inflammatory infiltrate comprised of lymphocytes, histiocytes, and eosinophils (inset). *Courtesy Luis Requena, MD.*

STIFF SKIN SYNDROME

Synonym: ■ Congenital fascial dystrophy

History

Stiff skin syndrome was first described by Esterly and McKusick in 1971[53].

Epidemiology

This condition may be congenital or develop during early childhood. Familial occurrences have been described.

Pathogenesis

Stiff skin syndrome is due to heterozygosity for a mutation in the gene that encodes fibrillin-1 (*FBN1*). The presence of giant "amianthoid-like" collagen fibrils in affected fascia had been postulated to reflect a disturbance in the organization of collagen and glycosaminoglycans within the extracellular matrix.

Clinical Features

Stiff skin syndrome is characterized by "rock hard" induration and thickening of the skin and subcutaneous tissues, which is most pronounced on the buttocks and thighs, with characteristic sparing of the inguinal folds[54]. The hands and feet are not involved. Mild hypertrichosis is often observed in affected areas. Restricted joint mobility leads to a characteristic posture of hip and knee flexion and prominent lumbar lordosis while standing, and patients may have short stature. The condition is stable or slowly progressive, and abnormalities of internal organs are not typically observed.

Patients with unilateral involvement have been reported, some with features that overlapped with scleredema, deep morphea, and linear melorheostotic scleroderma. In a patient with the segmental form of stiff skin syndrome, an interleukin(IL)-17C mutation was detected.

Pathology

Histopathologic examination demonstrates markedly thickened, hyalinized fascia without an associated inflammatory infiltrate. Thickened collagen bundles and mucin deposition may or may not be present in the overlying dermis.

Treatment

Stiff skin syndrome has a chronic course, and no effective treatments have been reported. Physical therapy can help to prevent progressive joint contractures. The segmental form with an associated IL-17 mutation (see above) was successfully treated with secukinumab.

SCLERODERMOID SYNDROMES INDUCED BY EXOGENOUS SUBSTANCES

Exposure to drugs, chemicals, and other exogenous substances can lead to cutaneous and extracutaneous sclerosis (see Table 43.7)[21].

Nephrogenic Systemic Fibrosis

Synonym: ▪ Nephrogenic fibrosing dermopathy

Fortunately, the incidence of nephrogenic systemic fibrosis (NSF) has steadily declined since nearly all patients had a history of exposure to gadolinium-based contrast agents with the vast majority having advanced chronic kidney disease or acute kidney injury at the time of exposure (see Table 43.1)[55–57]. Initial cases were described in the early 2000s and by 2010, the FDA had declared three gadolinium-based contrast agents (gadopentetate dimeglumine [Magnevist®], gadodiamide [Omniscan™], gadoversetamide [OptiMARK™]) as contraindicated in such patients.

NSF presents with thick, indurated plaques distributed symmetrically on the trunk and extremities, often resulting in joint contractures (Fig. 43.15). The plaques are erythematous to hyperpigmented and can have an irregular advancing edge with an "ameboid" appearance. In addition to yellow scleral plaques, fibrosis can develop within the heart, lungs, and skeletal muscle. Because the disease process typically extends along fibrous septa into the subcutis, a deep biopsy specimen is required for diagnosis. Histopathologic features include a haphazard arrangement of thickened collagen bundles and increased dermal fibroblast-like cells that stain positively for CD34 and procollagen I. Mucin deposition and osseous metaplasia may be seen and by energy dispersive spectroscopy, particles of gadolinium can be detected within involved tissue.



Fig. 43.15 Nephrogenic systemic fibrosis (NSF) – clinical features. Orange–brown indurated plaques. Note the "ameboid" outline of one of the plaques on the left foot. *Courtesy Edward Cowen, MD.*

NSF is generally refractory to treatment with corticosteroids and other immunosuppressive drugs; potential therapeutic options are outlined in Table 53.14. Improvement in renal function following renal transplantation has been reported to improve NSF.

Toxic Oil Syndrome

In 1981, the toxic oil syndrome affected more than 25 000 people in Spain; 600 died and ~300 remained permanently disabled. It resulted from the ingestion of aniline-degraded and reprocessed rapeseed oil, which led to a specific immune response in genetically susceptible individuals. In humans, toxic oil syndrome started with a morbilliform eruption and flu-like symptoms such as fever and headache; peripheral eosinophilia was observed in half of affected individuals. The inflammatory process subsequently affected the CNS, lungs, and salivary glands. Skin involvement either resolved, evolved into a lichen planus-like eruption, or progressed to a morpheaform or sclerodermoid picture.

Eosinophilia–Myalgia Syndrome

In 1989, a contaminated preparation of L-tryptophan led to an outbreak of "eosinophilia–myalgia syndrome", which affected more than 1500 people in the US and led to at least 30 fatalities. The acute phase of the condition was characterized by severe myalgias, fever, dyspnea, edema, a macular exanthem, and peripheral eosinophilia. Despite the discontinuation of L-tryptophan intake, approximately half of patients went on to a chronic phase that featured diffuse, deep sclerodermoid induration of the extremities (with acral sparing), progressive peripheral neuropathy, and myopathy.

Sclerodermoid Syndromes Induced by Other Chemicals

Exposure to certain organic chemicals can lead to a clinical picture that resembles SSc (see Table 43.7). In contrast to the acute onset of the toxic oil and eosinophilia–myalgia syndromes, exposure to vinyl chloride, organic solvents (e.g. trichloroethylene, trichloroethane, perchloroethylene), pesticides, or epoxy resins induces a slowly progressive process of sclerosis. It typically begins with insidious acrosclerosis and Raynaud phenomenon (especially with vinyl chloride exposure). Acral osteolysis, hepatic toxicity, and pulmonary involvement are often observed. In addition, patients experience fatigue, weight loss, arthralgias, and myalgias. Autoantibodies are absent, and cessation or reversal of the disease process follows removal of the exposure.

Silicosis

The incidence of SSc is approximately 20-fold higher in individuals with occupational exposure to silica, such as miners and foundry workers, than in the general population. In an epidemiologic study from Germany, three-quarters of men with typical SSc had been exposed to silica dust in the workplace. The mean duration of exposure was 14 years, with a mean delay in onset of the disease of 24 years from the first exposure. Once absorbed, silica cannot be removed from the body. Although silica has nonspecific proinflammatory and profibrotic effects, HLA and TNF allele associations suggest the need for a specific pre-existing immunophenotype for disease progression to occur. SSc associated with pulmonary silicosis is clinically, serologically, and immunologically indistinguishable from the idiopathic form of the disease.

Sclerodermoid Syndromes Induced by Drugs

Several drugs, particularly bleomycin and the taxanes (see Table 43.7), can induce cutaneous sclerosis and pulmonary fibrosis mimicking SSc. Additional medications that have been associated with sclerodermoid changes include other chemotherapeutic agents such as cisplatin, pemetrexed, carboplatin, topotecan, and gemcitabine (especially of the lower extremities) as well as ergot alkaloids, L-5-hydroxytryptophan +/− carbidopa, appetite suppressants, and cocaine.

Additional figures and table on Eosinophilic fasciitis - diagnostic criteria, available in our eBook (see inside front cover for access code).

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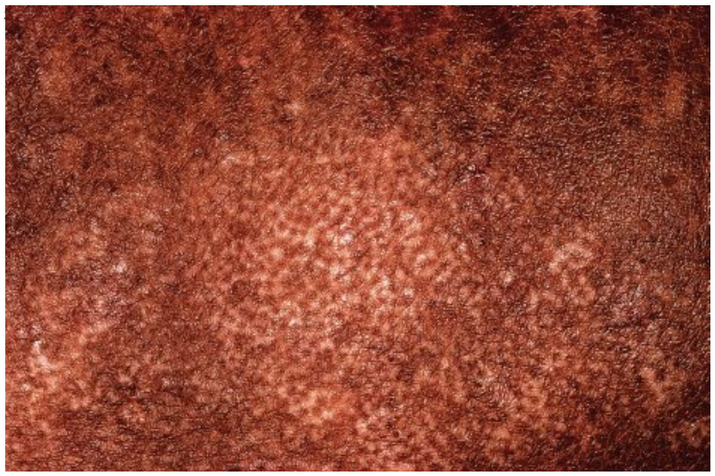
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eFig. 43.1 The "salt and pepper" sign. Leukoderma with retention of perifollicular pigmentation in a patient with systemic sclerosis.



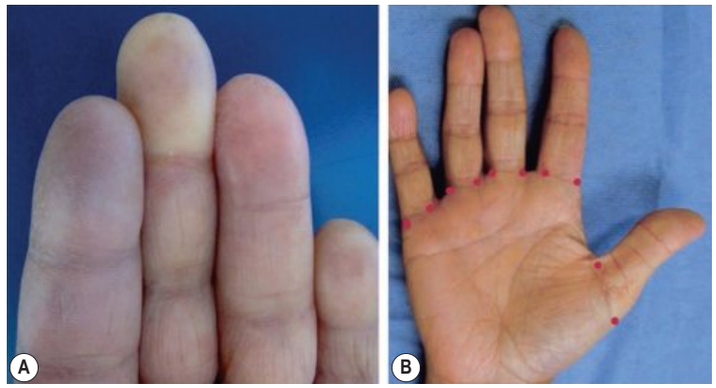
eFig. 43.2 Mat (squared-off) telangiectasias in systemic sclerosis. The palms are a common site for mat telangiectasias. *Courtesy Kalman Watsky, MD.*



eFig. 43.3 Pitted scars of the digital pulp in a patient with systemic sclerosis. *Courtesy Frank Samarin, MD.*



eFig. 43.4 Raynaud phenomenon in a patient with severe sclerotic chronic graft-versus-host disease. The fingers have a violaceous hue as well as areas of blanching (white) and digital ulceration. Oral sildenafil led to a significant improvement. *Courtesy Jean L. Bolognia, MD.*



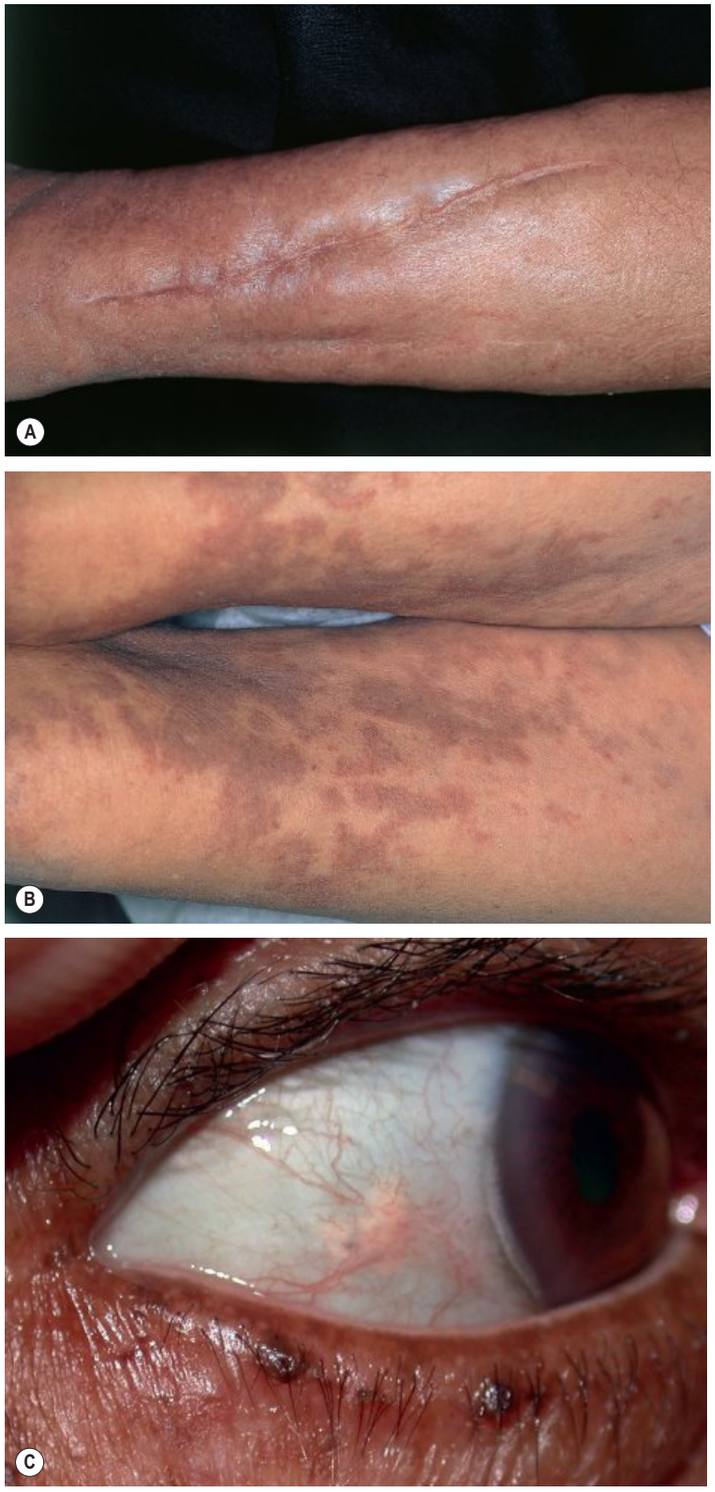
eFig. 43.5 Raynaud phenomenon. A Pallor of fingers due to vasoconstriction and interruption of regional vascular flow as well as blue-colored cyanosis corresponding to blood de-oxygenation. **B** Injection of botulinum toxin type A into the bases of the fingers restores normal circulation. Some clinicians avoid injecting the thumb unless there is significant symptomatic involvement. *Courtesy Alastair Carruthers, MD, and Jean Carruthers, MD.*



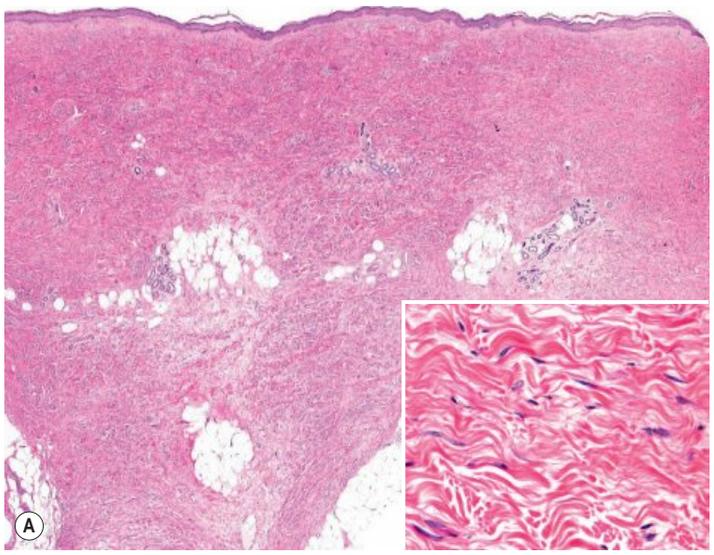
eFig. 43.6 Stiff skin syndrome. Rock-hard, irregular induration of the thighs with overlying hypertrichosis. The inguinal creases were spared. *Courtesy Julie V. Schaffer, MD.*

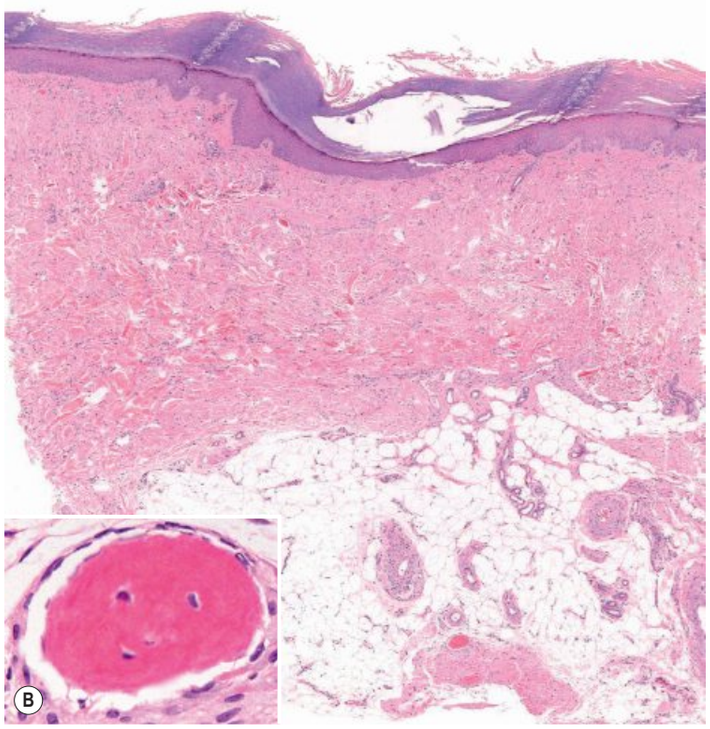


eFig. 43.7 Linear melorheostotic scleroderma. A Limb swelling accompanied by hyperostosis. **B** X-ray demonstrating the dripping candle wax-like changes of the cortical bone of the femur. *Courtesy Smita Jha, MD.*



eFig. 43.8 Nephrogenic systemic fibrosis (NSF) – clinical features. Thickening and induration of the skin can be obvious (**A**), or lesions may present as purple–brown plaques (**B**). Scleral plaques (**C**) in a patient less than 45 years of age is a minor criterion for NSF. *A, Courtesy Jean L. Bolognia, MD; B, Courtesy Kalman Watsky, MD.*





eFig. 43.9 Nephrogenic systemic fibrosis – histopathologic features. A, B There is an increase in the cellularity and amount of collagen in the dermis and within the septae of the panniculus. The spindle cells (inset, **A**) stain positively for CD34 and procollagen I. If present, osseous metaplasia ("osteoid bodies") is a useful clue to the diagnosis (inset, **B**). *Courtesy Lorenzo Cerroni, MD.*

EOSINOPHILIC FASCIITIS – DIAGNOSTIC CRITERIA
Major criterion
• Symmetric plate-like sclerotic lesions on four extremities*
Minor criteria
• Histopathology (biopsy specimen includes fascia) – fibrosis of subcutaneous connective tissue, with thickening of the fascia and inflammatory infiltrate of eosinophils and monocytes
• Diagnostic imaging, e.g. MRI – thickening of fascia
Definitive diagnosis: 1 major and 1 minor or 1 major and 2 minor criteria
*Absence of Raynaud phenomenon and systemic sclerosis excluded.

eTable 43.1 Eosinophilic fasciitis – diagnostic criteria.

Morphea and Lichen Sclerosus 44

Martin Röcken and Kamran Ghoreschi

Morphea and lichen sclerosus (LS) are inflammatory skin diseases that ultimately evolve into two distinct modes of cutaneous sclerosis. In morphea, there is inflammation of the dermis that may extend into subcutaneous structures. Lichen sclerosus is primarily a disease of the genital mucosa (and less often extragenital sites) that affects the epidermis and the dermis. Morphea may lead to joint contractures and atrophy of underlying muscle, but there is no involvement of internal organs. The exceptions are the ocular and neurologic symptoms seen in a small minority of patients with linear morphea of the head or Parry–Romberg syndrome, in which there is extension into underlying muscles, bones, and occasionally deeper structures. While some patients may develop both disorders simultaneously, they are addressed separately because of their distinct features and different but overlapping therapeutic approaches.

MORPHEA

Synonyms/subtypes: ■ Localized scleroderma ■ Circumscribed scleroderma ■ Plaque-type morphea ■ Linear morphea – linear scleroderma ■ Morphea *en coup de sabre* – scleroderma *en coup de sabre* ■ Deep morphea – morphea profunda

Key features

- Asymmetric sclerotic plaques, usually 2–15 cm in diameter
- Active lesions can have a lilac border with central hypo- or dyspigmentation, while inactive lesions often become hyperpigmented
- The sclerosis may extend deeply into the fat or underlying structures (e.g. fascia, muscle, bone), causing disability
- With the exception of ocular or neurologic symptoms in patients with linear morphea of the head, associated systemic disease is not observed
- Often progresses for several years, then regresses; the linear subtype is usually persistent

INTRODUCTION

Morphea is a clinically distinct inflammatory disease, primarily of the dermis and subcutaneous fat, which ultimately leads to a scar-like sclerosis. The small vessel changes, inflammatory infiltrate, and ultimate structural modifications are identical in morphea and systemic sclerosis (SSc), but the two diseases are distinct entities that can be distinguished clinically. In addition, their triggers presumably differ and coexistence of morphea and SSc is rare[1]. Morphea has an asymmetric patchy or linear distribution. In contrast, SSc begins either as symmetric tightening of the fingers and hands that extends progressively toward the forearms (*limited cutaneous* SSc [lcSSc]) or as symmetrically extending sclerosis of the trunk and proximal upper extremities (*diffuse cutaneous* SSc [dcSSc]). Rarely, generalized morphea may resemble early dcSSc. The presence of Raynaud phenomenon, digital sclerosis, and involvement of the gastrointestinal tract and the lung also allows differentiation of SSc from morphea. Distinguishing between deep morphea and eosinophilic fasciitis can prove more difficult – whether these two disorders represent distinct entities or simply the ends of a broad clinical spectrum remains debatable, e.g. eosinophils may be present at the inflammatory border of morphea[2].

Morphea can cause significant morbidity as a result of pain, skin tightness, and impaired joint mobility. In ~10% of patients with morphea, sclerosis leads to significant contractures, growth retardation, and even micromelia, resulting in long-term functional disability[3]. Disease activity correlates with reduced quality of life[4].

HISTORY

A disease with thickened skin was first mentioned by Hippocrates (400 BCE). The term "scleroderma" is derived from the Greek words *skleros* (hard or indurated) and *derma* (skin). The first description of a generalized "hardness" of the skin in a young woman was by an Italian physician, Carlo Curzio, in 1753; the French physician Gintrac coined the term "sclérodermie" in 1847. Thomas Addison has been credited with the first detailed description of morphea in 1854, which he referred to as Alibert's keloid syndrome. In 1924, Matsui described the typical histopathologic changes of scleroderma and in 1930 O'Leary and Nomland elaborated on the distinctive features of SSc versus morphea.

EPIDEMIOLOGY

Even though morphea has been long recognized as a well-defined entity, few population-based studies exist. A survey from Olmsted County, Minnesota attempted to register all patients with the disorder from 1960 to 1993[5]. During this period, the annual incidence rate was 27 per million. According to this study, 56% of patients had plaque-type, 20% linear, 13% generalized, and 11% deep morphea[5].

The prevalence of morphea increases with age, occurring in ~500 and 2200 per million at ages 18 and 80 years, respectively[3]. The disease is more prevalent in women than in men (2.6:1), with the exception of linear morphea, which has no sex preference. Data published on the incidence and prevalence of morphea probably reflect an underestimation, as they critically depend on clinical recognition and diagnosis.

Morphea is rarely life-threatening. In the Olmsted County study, the survival rate of patients with morphea was not significantly different from that of the general population[5]. However, in 11% of the patients, substantial disability occurred. This is of particular concern since disability occurs primarily with linear morphea, which has its onset before age 18 years in two-thirds of patients[3,4].

PATHOGENESIS

Autoantibodies are usually as prevalent in morphea as in the general population, with two exceptions: (1) an increased prevalence of anti-single strand DNA (ssDNA), -topoisomerase IIα, -phospholipid, -fibrillin-1, and -histone antibodies (AHA) in patients with morphea; and (2) high titers of anti-nuclear antibodies (ANA) in juvenile patients with linear morphea and individuals with generalized morphea. In patients with linear morphea, the presence of ssDNA antibodies or AHA seems to be associated with increased risk of functional impairment[6].

Neither histology nor immunohistology of a single lesion will distinguish between morphea and SSc. In most clinicopathologic reviews, it is assumed that the two diseases are triggered by distinct events. However, the development of sclerosis following the initiating event seems to follow a common pathway. It is therefore assumed that pathogenic steps leading to SSc also contribute to the development of morphea, so they will be included in this discussion.

Currently, sclerosis of the skin is thought to involve three major, closely connected components: vascular damage, activated T cells, and altered connective tissue production by fibroblasts (Fig. 44.1)[7].

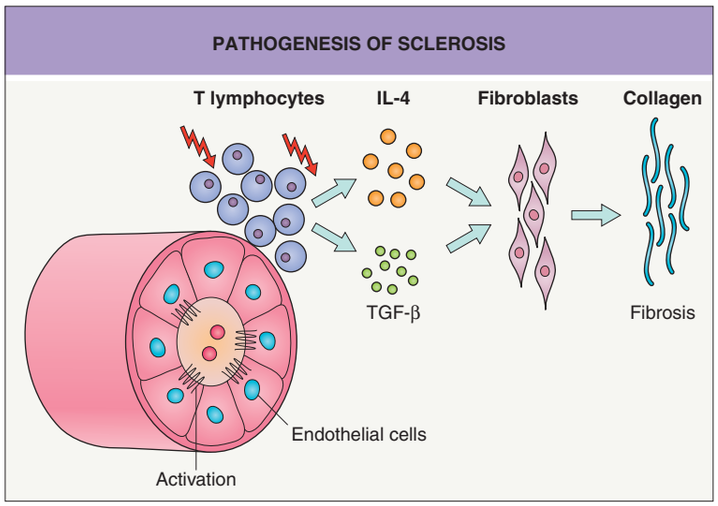


Fig. 44.1 Pathogenesis of sclerosis. Three components are involved during the formation of sclerosis: vascular damage, lymphocyte activation, and altered connective tissue production. IL, interleukin; TGF, transforming growth factor.

Vascular Changes

A prominent feature of advanced sclerosis is a reduction in the number of capillaries. Studies performed in SSc suggest that hypoxia resulting from microvascular injury is a very early, or even the primary, event. Endothelial cells respond to various stimuli, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β) (see Ch. 102). In the sera of patients with SSc, markers indicative of endothelial cell activation (e.g. soluble adhesion molecules, VEGF) are elevated. Morphologic changes principally affect capillaries and small arterioles, and the initial changes in SSc include expression of adhesion molecules and endothelial swelling, followed by thickening of the basement membrane and intimal hyperplasia. An extrapolation is that similar changes may occur early on in morphea.

Control of Fibroblast Function by T Cell-Derived Cytokines

Pioneering work by E. Carwile Leroy showed that *in vitro* cultured fibroblasts isolated from sclerotic tissue produce increased amounts of collagen (types I, II, and III) and other extracellular matrix proteins. These fibroblasts can maintain this phenotype for weeks over several passages. This raised the question as to whether SSc results from an inborn or acquired error in collagen metabolism within fibroblasts. Today, most data favor the concept that abnormal collagen production is directed by surrounding cells. T cells in particular have the capacity to modify collagen synthesis by fibroblasts, and T cells are regularly present, at least early on, in a perivascular location and especially at the leading edge of developing sclerosis (see Fig. 44.1).

Enhanced production of collagen and other extracellular matrix proteins is induced by T cell-derived cytokines, especially interleukin (IL)-4, IL-13, IL-17A, and TGF-β[8]. IL-4 is produced by $CD4^+$ T helper type 2 (Th2) lymphocytes (see Ch. 4) and can directly enhance TGF-β production[9]. Macrophages activated via the IL-4 receptor α (IL-4Rα) have been shown to influence collagen fibril assembly and promote fibrosis[10]. In contrast, production of collagen and other extracellular matrix proteins can be significantly suppressed by interferons that are associated with Th1 lymphocytes[9,10]. Th1 differentiation also implicates IL-12 signaling via the transcription factor STAT4. Of note, an association between *STAT4* polymorphisms (e.g. rs7574865) and susceptibility to SSc, especially the limited subtype, has been reported[11]. In a rare form of dominantly inherited pansclerotic morphea, gain-of-function variants in *STAT4* were detected, with JAK inhibition leading to reduction of the hyperinflammatory fibroblast phenotype *in vitro* and clinical improvement[11a]. Additional susceptibility loci associated with SSc include immune-related genes (e.g. *CD247*, *IRF5*, *HLA* region)[12] and the promoter region of the gene that encodes connective-tissue growth factor (CTGF)[13].

Circulating levels of the chemokine ligand CXCL4 (secreted by plasmacytoid dendritic cells) have been found to be significantly elevated in SSc[14]. Increased CXCL4 levels correlated with a higher prevalence of lung fibrosis and faster progression of skin fibrosis[14]. Interestingly, CXCL4 promotes the Th2 cytokines IL-4 and IL-13 and has anti-angiogenic properties.

IL-4 is the most potent force in driving differentiation of Th2 lymphocytes (see Fig. 4.9)[15]. Because IL-4 enhances pathologic collagen production by fibroblasts and induces recruitment of eosinophils, it is believed that immune responses dominated by IL-4- as well as IL-13- and TGF-β-producing cells are critical in the initiation of skin sclerosis[8,10]. This concept is supported by clinical and experimental data:

- *In situ* analysis of the advancing inflammatory margins of skin sclerosis revealed predominantly IL-4 expression.
- Th2-associated IL-13 and IL-33 have been shown to promote skin fibrosis in mice, and early treatment of scleroderma-developing mice with anti-IL-4 antibodies prevented scleroderma.
- Th2-like regulatory T (Treg) cells present in the skin of patients with SSc produce IL-4 and IL-13 and are responsive to IL-33[16].
- Systemic retinoids (which interact with TGF-β signaling) appear to reduce pathologic collagen synthesis by fibroblasts and may improve skin sclerosis in patients with chronic GVHD[17,18].
- Th2-promoting CXCL4 is so closely associated with SSc that it has been suggested as a biomarker for SSc[14].

One theoretical therapeutic approach for morphea would be to redirect Th2 responses into Th1 responses. Unfortunately, placebo-controlled clinical trials of the Th1-inducing cytokines IFN-γ or IFN-α in patients with morphea produced negative results[19]. The finding of elevated expression of IFN-related factors (e.g. CXCL9, CXCL10) in the skin and serum of cohorts with active morphea might provide an explanation[20], as it suggests that Th2 and Th1 cells may be activated simultaneously. Reports of the development of morphea and SSc during treatment with anti-PD-1 antibodies[21] also point to the importance of activated T cells in their pathogenesis. It remains to be determined whether highly effective, broader inhibitors of the Th2 cytokines IL-4 and IL-13 or other morphea-associated T cell responses could help prevent the inflammatory phase of morphea and attendant skin sclerosis. More recently, antibodies directed against type 1 IFN-triggered dendritic cell-derived epiregulin, which blocked activation of EGFR on fibroblasts and subsequent paracrine NOTCH activation, were shown to reverse fibrosis in skin explants[21a].

Lastly, when SSc fibroblasts are compared to control fibroblasts, there are differences in intracellular signaling proteins. Examples include activation of p38 mitogen-activated protein kinase and higher levels of Ha-Ras protein and reactive oxygen species. These findings plus data from animal studies demonstrating a link between skin fibrosis and pro-oxidative agents support hypoxia and oxidative stress as key factors in the pathogenesis of skin sclerosis.

Animal Model and Genetics

Currently, the best animal model for studying pathogenic events in SSc is the tight skin (TSK) mouse (Fig. 44.2). A partial duplication of the fibrillin-1 gene is thought to be responsible for the increased synthesis and accumulation of collagen in the skin and internal organs of TSK mice. TSK mice not only have increased collagen deposits, but also the collagen fibers are reduced in length and the quantity of hydroxyproline is increased in the dermis. Moreover, the mice have high antibody titers against topoisomerase I and fibrillin-1, similar to patients with SSc and morphea, respectively. One major difference is that blood vessels remain uninvolved in TSK mice, demonstrating that sclerosis of the skin can develop in the presence of apparently normal vessels[22]. The phenotype can be transferred from diseased animals to healthy syngeneic mice via bone marrow cells (see Fig. 44.2).

Fibroblasts from TSK mice have elevated IL-4Rα expression and back-crossing the TSK mice onto a genetic background that either cannot respond to IL-4 or is deficient in producing TGF-β prevents skin sclerosis. Moreover, this back-cross normalizes collagen length, skin thickness, and hydroxyproline content and prevents antibody formation to topoisomerase I (see Fig. 44.2)[22]. In this murine model of SSc, interventions that promoted Th1 responses or targeted PDGF receptor activity (e.g. imatinib) reduced dermal thickening and fibrosis[23]. More recent strategies for improving experimental skin fibrosis have focused on the role of platelet-derived serotonin[24], β-integrins, TGF-β[25], and

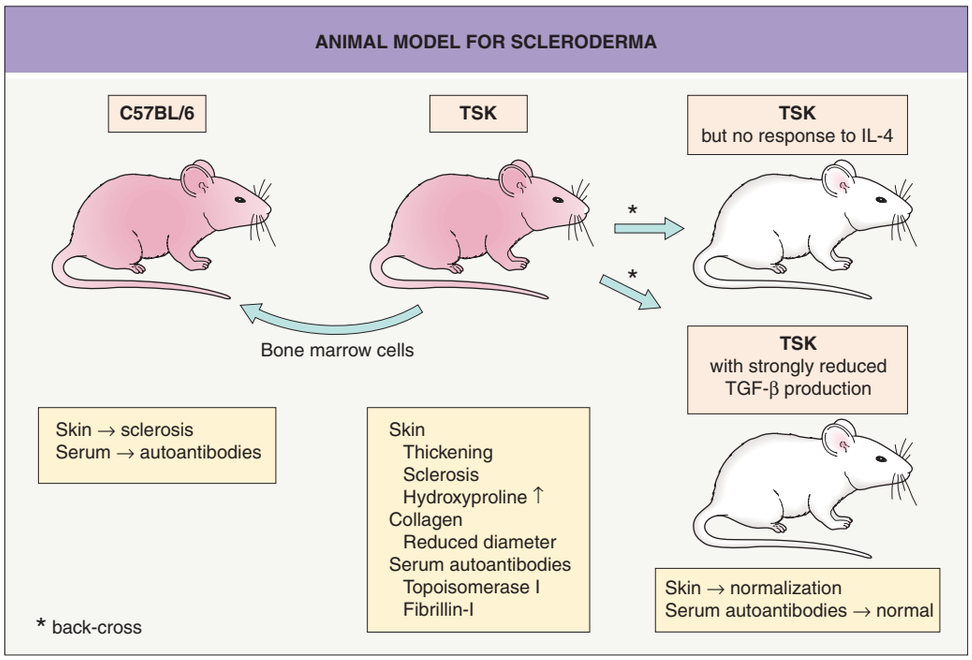


Fig. 44.2 Animal model for scleroderma. Transfer of scleroderma phenotype from diseased animals (TSK mice) to healthy syngeneic mice (C57BL/6) by bone marrow cells. Lack of tight skin and autoantibody production by back-crossing TSK mice with mice that cannot respond to IL-4 or mice that produce minimal amounts of TGF-β. IL, interleukin; TGF, transforming growth factor; TSK, tight skin strain of mice.

Janus kinases[26]. Of note, estrogen inhibition can exacerbate experimental dermal fibrosis driven by TGF-β[27].

In addition to the phenotypic similarities, the genetic locus associated with the TSK phenotype appears to be related to the risk of developing SSc. In humans, this susceptibility locus is on chromosome 15q in a region that contains the fibrillin-1 gene (*FBN1*); mutations in *FBN1* have been detected in patients with stiff skin syndrome (see Ch. 43)[28].

Triggering Events

Most immunologic and metabolic studies have been directed toward understanding SSc, and the question remains as to whether they can also explain focal, asymmetric inflammation and sclerosis of the skin. The major discriminating factor between morphea and SSc might be the triggering event, with morphea being caused by a local trigger within the skin and SSc initiated by a systemic insult. The putative local triggering events for morphea include mechanical trauma, injections, vaccinations[29], and X-irradiation.

These questions initiated the search for potential triggers and studies of diseases that share clinical features with morphea and SSc. One intensively investigated area was the potential role of infection with *Borrelia burgdorferi*. The isolation of *B. burgdorferi* from the skin of some selected patients with morphea originally supported this speculation. However, larger studies failed to confirm this initial observation[30]. Thus, this theory has been abandoned.

CLINICAL FEATURES

As outlined in Table 44.1, there are several classification schemes for morphea[31–34]. Major forms include plaque-type (circumscribed), linear, generalized, and other less common variants (e.g. nodular or keloidal). There are also inflammatory syndromes leading to superficial or deep sclerosis of the skin that resemble morphea (i.e. morpheaform; see below). Patients with morphea do not have Raynaud phenomenon or involvement of internal organs, except for underlying fascia, muscle, and bone in some patients with linear morphea and the occasional patient with linear morphea of the head who has ocular or neurologic symptoms. In rare patients with presumptive morphea, clinically insignificant fibrosis of the lung or slightly reduced esophageal motility has been detected radiographically or by scintigraphy. Clinically relevant involvement of internal organs is observed in certain types of pseudoscleroderma (see Ch. 43).

FOUR MORPHEA CLASSIFICATION SCHEMES

Peterson (1995)[31]	Padua (2006)[32]	European Dermatology Forum (2017)[33]	Dallas–Pittsburgh (proposed 2021)[34]
Subtypes	***Subtypes***	***Subtypes***	***Subtypes***
• Plaque	• Circumscribed	• Limited	• Circumscribed
• Plaque	• Superficial	• Plaque	• Linear
• Guttate	• Deep	• Guttate	• Generalized
• Superficial	• Linear	• Superficial	• Generalized
• Lichen sclerosus	• Trunk or limbs	• Generalized	• Panclerotic
• Generalized	• Head	• Generalized	• Mixed
• Bullous	• Generalized	• Panclerotic	***Modifiers***
• Linear	• Panclerotic	• Linear	• Superficial
• Extremities	• Mixed	• Extremities	• Deep
• *"En coup de sabre"*		• *"En coup de sabre"*	• Keloidal
• Parry–Romberg		• Parry–Romberg	• Bullous
• Deep		• Deep	
• Morphea profunda		• Mixed	
• Subcutaneous		• Eosinophilic fasciitis	
• Eosinophilic fasciitis			
• Panclerotic			

Table 44.1 Four morphea classification schemes. A recent cross-sectional study that included 944 adult and pediatric patients with morphea from two prospective cohorts compared three previously published morphea classification schemes. The Padua criteria performed best (95%) in classifying patients into groups with cohesive demographic and clinical features, compared with the Peterson (56%) and European Dermatology Forum (52%) criteria. Based on their findings, a modified morphea classification scheme was formulated[34].

Plaque-Type (Circumscribed) Morphea

Plaque-type (circumscribed) morphea, the most frequent variant, is characterized by the insidious onset of a slightly elevated, erythematous or violaceous, slightly edematous plaque that undergoes centrifugal expansion (Fig. 44.3). It is generally asymptomatic and therefore frequently goes unnoticed by the patient. The central portion of the progressing lesion starts to transform into sclerotic, scar-like tissue. Depending on the depth of the sclerosis, the skin becomes progressively indurated. Centrally, it can acquire a shiny white color and peripherally, a violaceous or "lilac" ring (Fig. 44.4A). Postinflammatory hyperpigmentation often dominates over the white sclerosis as the lesions mature (Fig. 44.4B).



Fig. 44.3 Early inflammatory plaque-type (circumscribed) morphea of the trunk. Early-stage lesion presenting as an erythematous edematous plaque.





Fig. 44.4 Plaque-type (circumscribed) morphea. A Sclerotic plaques with the characteristic lilac-colored rim. Histologic findings will differ depending upon whether the biopsy specimen is obtained from the inflammatory edge or the central area of sclerosis (see Fig. 44.12). **B** The predominant lesion is a large, well-demarcated, hyperpigmented plaque that is depressed centrally; the trunk is a common location for plaque-type morphea.

Skin structures such as hairs and sweat glands are frequently lost. Some patients complain of itch, perhaps due to associated xerosis. Once the "lilac" ring vanishes, the lesion's progression also halts. Although this inflammatory margin may be difficult to appreciate, especially in linear sclerosis, it is an important indicator of clinical activity.

The plaques of morphea most commonly develop on the trunk and in general are between 2 and 15 cm in diameter. They are usually multiple and asymmetric, but marked variation exists. Individual lesions may enlarge significantly or remain stable in size.

The course of morphea is also variable. In most patients, morphea progresses over 3–5 years, then arrests and eventually resolves spontaneously. However, residual atrophy and dyspigmentation are commonly observed. Patients rarely have relapsing disease for more than 5 years, but may have sequelae such as calcinosis cutis (see Fig. 50.2)[35].

Variants

Various manifestations of morphea have become associated with specific names. They do not really reflect unique entities, but rather different morphologic features, distribution patterns, or depth of involvement. In most patients, morphea seems to be randomly distributed. However, in some patients, the lesions are unilateral, and they may follow dermatomes or the lines of Blaschko.

- **Guttate morphea** presents primarily as multiple, rather superficial, nummular plaques. Even though relatively small, they may become deeply indurated.
- **Atrophoderma of Pasini and Pierini** is considered by some to be a very superficial variant of plaque-type morphea, while others consider it to be a separate entity in the differential diagnosis of "burnt-out" morphea (see Ch. 99). Hyperpigmented patches are seen most commonly on the posterior trunk; occasionally, lesions follow the lines of Blaschko (linear atrophoderma of Moulin).
- **Deep morphea** denotes inflammation and sclerosis that affects primarily the deep dermis and subcutaneous fat and may even involve underlying structures (e.g. the fascia) (Fig. 44.5A). Patients normally develop a small number of hard deep plaques that may impair motility of the skin; ultimately, lesions may calcify, leading to dystrophic calcinosis cutis. Because of the location of the sclerosis, individual lesions may resemble eosinophilic fasciitis (Fig. 44.5B and see Ch. 43).





Fig. 44.5 Comparison of deep morphea and eosinophilic fasciitis. A Note the "pseudo-cellulite" appearance of the involved skin of the thigh in deep morphea. **B** In eosinophilic fasciitis, the level of fibrosis is also deep, resulting in a similar rippled appearance. This patient had the eosinophilic fasciitis-like form of chronic GVHD, also referred to as chronic GVHD-related fasciitis. *B, Courtesy Edward Cowen, MD.*



Fig. 44.6 Nodular or keloidal morphea. Multiple firm, hyperpigmented nodules mimicking keloids in a 10-year-old girl. *Courtesy Julie V. Schaffer, MD.*



Fig. 44.7 Parry–Romberg syndrome. Unilateral sclerosis and loss of subcutaneous fat, leading to facial asymmetry. *Courtesy Lorenzo Cerroni, MD.*

- In **nodular or keloidal morphea**, inflammation within the dermis leads to thick, keloid-like nodules (Fig. 44.6) or bands. It can be clinically indistinguishable from indurated keloids.
- In rare patients, especially those where sclerosis of the skin is associated with diffuse, rapidly progressive edema, lymphoceles may result from stasis of lymphatic fluid. When the latter develop into bullae, this is referred to as **bullous morphea**. It is more frequently observed in generalized morphea and sclerodermoid or morpheaform GVHD and is rarely a feature of plaque-type morphea. Bullous morphea has to be distinguished from mechanical blisters that may occur centrally within plaques and are secondary to impaired mechanical stability of the dermal–epidermal junction.

Linear Morphea and Parry–Romberg Syndrome

Linear morphea is different from plaque-type morphea, with respect to age of onset, distribution, clinical outcome, and serologies. Morphea *en coup de sabre* (meaning stroke or blow with a single-edged sword) is a term used for linear morphea of the forehead and scalp. Hemifacial atrophy, or Parry–Romberg syndrome, is probably a very severe variant of linear morphea, but it may be a phenotype for more than one entity. There is a progressive loss of subcutaneous fat, but little or no sclerosis (Fig. 44.7). The entire distribution of the trigeminal nerve, including the eye and the tongue, may be affected.

Linear morphea may present initially as a linear, erythematous (inflammatory) streak, but more frequently begins as a harmless-appearing lesion of plaque-type morphea that extends longitudinally as a series of plaques that then join to form a scar-like band (Fig. 44.8). This band may severely impair the mobility of the affected limb. Linear morphea tends to involve the underlying fascia, muscle, and tendons. This leads not only to muscle weakness but also to shortening of the muscles and fascia which then impairs joint mobility. Linear morphea is especially problematic when it extends over joints, as this almost invariably results in a decrease in range of motion and functional impairment[36]. In some patients, involvement is circular rather than linear and results in progressive atrophy of the limb similar to the Parry–Romberg variant of facial morphea. The linear variant can have prolonged periods of quiescence followed by reactivation.

The *en coup de sabre* type of morphea represents linear morphea of the head (Fig. 44.9). It is typically unilateral and extends from the forehead into the frontal scalp. It may start either as a linear streak, which may initially mimic a port-wine birthmark, or as a row of small plaques that coalesce. A paramedian location is most common. Like plaque-type morphea, it may initially be surrounded by a discrete lilac ring that extends longitudinally and may reach the eyebrows, nose, and even the cheeks. As inflammation wanes, a linear, hairless crevice develops that in some patients is sclerotic, while in others appears more atrophic.



Fig. 44.8 Linear morphea of an extremity. A Linear sclerotic band of the arm with both hyper- and hypopigmentation. The majority of patients with linear morphea have unilateral involvement. **B** More inflammatory phase with ulceration in addition to induration. The differential diagnosis includes linear melorheostosis which is often associated with underlying candlewax-like linear hyperostosis. *A, Courtesy Julie V. Schaffer, MD.*

En coup de sabre morphea can also involve the underlying muscles and osseous structures. Rarely, the inflammation and sclerosis progress to involve the meninges and even the brain, creating a potential focus for seizures[37]. Ocular involvement has been reported in up to 15% of juvenile and 25% of adult patients.

Generalized Morphea

Generalized morphea normally begins insidiously on the trunk as plaque-type morphea. While individual lesions are indistinguishable in these two forms, in generalized morphea they do not stop expanding. Just as in the diffuse form of SSc, multiple plaques rapidly coalesce and can affect nearly the entire trunk, often only sparing the areolae and nipples (Fig. 44.10). The sclerosis may involve the extremities down to the hands (presenting initially as puffy edema). As the cutaneous sclerosis progresses, it may result in disabling constrictions that even cause difficulty in breathing due to impaired thorax mobility and inflammation of the intercostal muscles. Although an aggressive therapeutic approach is recommended, the disease is usually persistent given its often limited response to treatment.



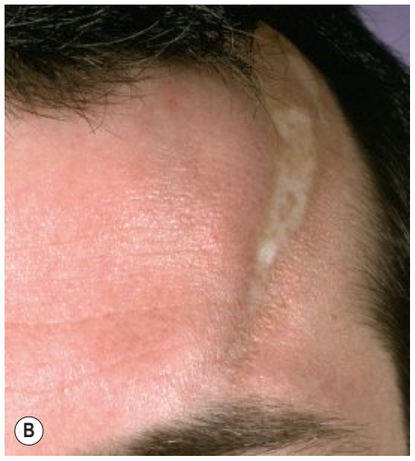






Fig. 44.9 Morphea *en coup de sabre*. On the forehead, the linear band(s) of sclerosis and atrophy are usually paramedian (rather than midline). **A** Both hyper- and hypopigmentation are present as well as subtle depression. **B** An obviously depressed, sclerotic, hypopigmented linear band. **C** Scarring alopecia develops when there is involvement of scalp; "lonely hairs" are also seen in other forms of scarring alopecia. **D** Note the prominent veins and loss of the medial eyebrow. Progression to Parry–Romberg syndrome would be a concern.





Fig. 44.10 Generalized morphea. A Multiple hyperpigmented plaques on the trunk that are becoming confluent. **B** Circumferential involvement with sparing of the central portion of the breast is a classic distribution pattern. *B, Courtesy Luis Requena, MD.*



Fig. 44.11 Extensive linear morphea of the right leg leading to hypoplasia. In addition to marked hypoplasia, there is induration and a flexion contracture of the knee.

Morphea in Childhood

Approximately 20% of individuals with morphea are children and teenagers. The female-to-male ratio for plaque-type morphea in this age group is about 2:1, with a mean age at disease onset of 7 years[38]. In two-thirds of patients with linear morphea, disease onset is prior to age 18 years, providing an explanation for the possibility of growth retardation of the affected limb. Thus, if left untreated, linear morphea may result not only in decreased range of motion of joints but also in permanent limb asymmetry from unilateral hypoplasia (Fig. 44.11).

Pansclerotic morphea, also referred to as disabling pansclerotic morphea of children, is similar to generalized morphea of the adult. It usually starts before 14 years of age and tends to cause lifelong severe disability due to persistent atrophy of the underlying muscles and contractures of the involved joints. The disease tends to extend from the trunk to the hands and feet. Periodontal atrophy may occur, but there is only slight involvement of the esophagus and lung. Distinction from SSc may prove challenging.

Importantly, in a large multicenter study of children with morphea, 22% had extracutaneous findings that were primarily articular (11%), neurologic (4%), and ocular (2%)[38]. The latter two findings were seen primarily in those with linear morphea of the head or Parry–Romberg syndrome, i.e., 85% of affected patients had these two variants.

LABORATORY FINDINGS

Laboratory abnormalities are not a prominent feature of morphea, except for generalized and linear morphea. The ESR and serum protein levels are usually normal, but eosinophilia may occur, especially during early active phases of the disease. High titers of ANA or antibodies to ssDNA and histones can be detected in 40%–80% of patients with linear and generalized morphea, but are uncommon in adults with plaque-type morphea (see above). Approximately 40% of children and adolescents with morphea have elevated ANA titers[38].

PATHOLOGY

The histopathology of morphea depends on two factors: the stage and area of the lesion sampled (inflammatory margin or central sclerosis) and the depth to which the disease extends. In most situations, morphologic changes are best seen at the border between the dermis and subcutaneous fat. Specimens for histopathology must include subcutaneous fat and it is important to note whether the biopsy specimen is taken from the inflammatory border or from the fibrotic center.

At the inflammatory border, vascular changes are relatively discrete by light microscopy. Vessel walls show endothelial swelling and edema. Capillaries and small arterioles are surrounded by an infiltrate that contains primarily $CD4^+$ T cells and sometimes eosinophils, plasma cells, and mast cells (Fig. 44.12A).

In later stages, the inflammatory infiltrate wanes and ultimately disappears completely, except in some areas of the subcutaneous fat. The epidermis is basically normal in appearance, but the rete ridges may be diminished, leaving a flattened dermal–epidermal junction. Edema is no longer visible in the dermis and upper subcutis. Capillaries and small vessels are significantly reduced in number, and homogeneous collagen bundles with decreased space between the bundles replace most structures. At this stage, collagen bundles in the reticular dermis appear densely packed, as evidenced by a more intense eosinophilic staining, and are aligned parallel to the dermal–epidermal junction (Fig. 44.12B). Eccrine glands appear atrophic and "trapped" within the thickened dermis. The underlying subcutis is homogenized and hyalinized.

Deep morphea affects primarily the deep subcutaneous tissue. Following the inflammatory phase, extensive sclerosis and hyalinization extend into the underlying fascia. Involvement of the underlying fascia is obligatory in deep morphea and is also frequently observed in linear and generalized types of morphea. In these patients, the fascia and even the underlying muscle (frequently vacuolated) are involved in the process of progressive sclerosis, characterized by replacement of the differentiated tissue by collagen bundles.

MORPHEAFORM (AND SCLERODERMOID) INFLAMMATORY SYNDROMES

Some disorders that are characterized by acrosclerosis and Raynaud phenomenon (e.g. sclerosis secondary to exposure to bleomycin, vinyl chloride, or epoxy resin) have a clinical presentation similar to lcSSc (i.e. sclerodermoid or pseudoscleroderma), while others present with circumscribed plaques similar to morphea (i.e. morpheaform). The former are discussed in Chapter 43 and the latter are discussed below and presented in Table 44.2. There are also clinical disorders that may have either type of clinical presentation, such as chronic GVHD.

While a variety of inflammatory diseases ultimately lead to superficial or deep sclerosis of the skin, their exact relationship to morphea is enigmatic. Some of these diseases are preceded by or associated with eosinophilia in blood or tissue. Infiltration by eosinophils may be of unknown etiology, as in eosinophilic fasciitis, or it may reflect an immune reaction to a defined toxic insult or antigenic stimulus, as in the L-tryptophan syndrome (eosinophilia–myalgia syndrome), toxic oil syndrome, or GVHD following hematopoietic stem cell transplantation (HSCT). Lastly, since certain exogenous drugs or chemicals, endogenous metabolites, or X-irradiation induce sclerosis at the site of tissue injury in only a subset of individuals, this suggests that unique metabolic events and innate or adaptive immune responses to these compounds determine the individual's susceptibility to develop sclerosis[2].

- **Lipodermatosclerosis**. Chronic venous insufficiency, along with chronic hypoxia, leads to sclerosis, most commonly on the lower extremities. This entity is discussed in Chapter 100.
- **Injections of vitamin K_1 (Texier disease)**. Rarely, injection of oil-soluble vitamin K_1 causes a strictly localized eosinophilic fasciitis that is indistinguishable from deep morphea. It may ultimately resolve with dermal and/or subcutaneous atrophy.
- **Vaccination-associated morphea**. Development of plaque-type or deep morphea has been described in children and adults at intramuscular vaccination sites. Given the limited number of case reports, it is uncertain whether the antigens, the adjuvants, or the injection trauma trigger the inflammatory fibrosis[39].
- **Paraffin and silicone injections or implants**. It is suspected that leakage of silicone implants and injection of silicone or liquid paraffin during reconstructive surgery and cosmetic soft tissue augmentation may cause chronic inflammation that results in localized morphea-like sclerosis. The belief that these substances

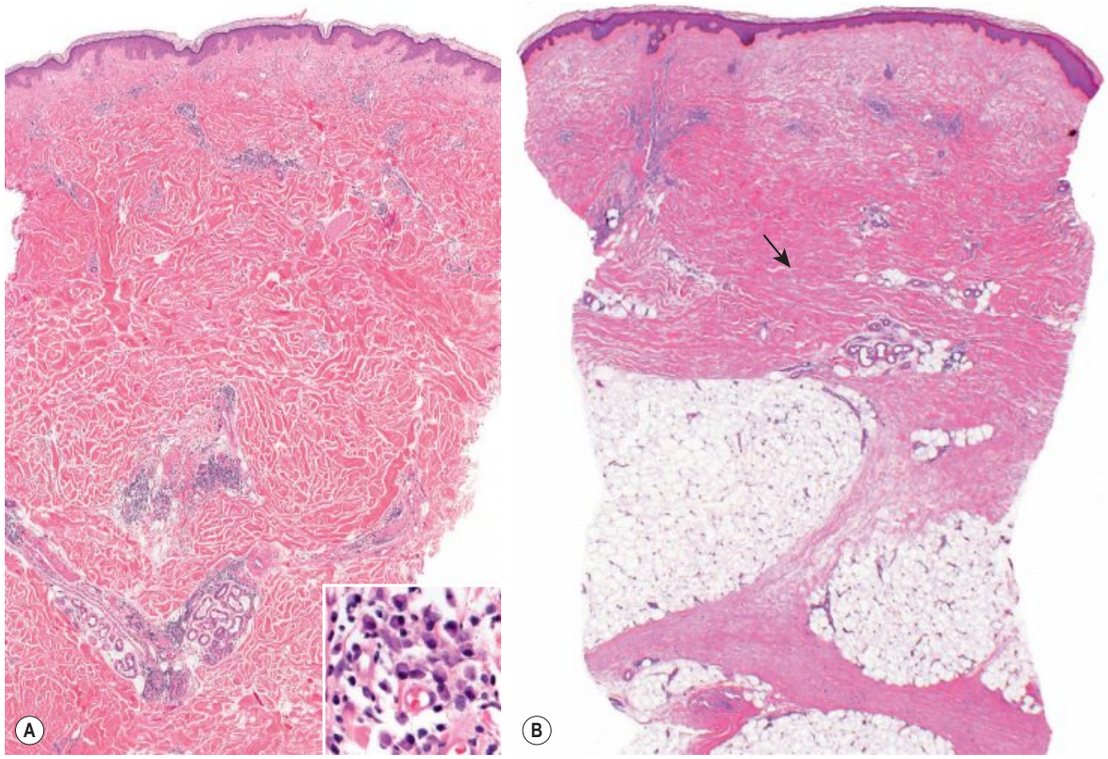


Fig. 44.12 Morphea – histopathologic features. A Overview with thickening of the dermis and perivascular and periecrine infiltrates of lymphocytes and plasma cells (inset). These changes can be seen in the inflammatory border. **B** Advanced sclerosis of the entire dermis extending into the fat with thickened collagen bundles and "trapped" eccrine glands (arrow). This corresponds to the areas of induration within the plaque. *A, Courtesy Lorenzo Cerroni, MD.*

can trigger systemic diseases such as SSc, eosinophilic fasciitis, or mixed connective tissue disease was not substantiated when meta-analyses were performed.

- **Porphyrias**. In adults, porphyria cutanea tarda can lead to morphea-like sclerosis in UV-exposed sites, such as the face, hairless scalp, dorsal aspects of the hands, and the upper chest. Histopathology and electron microscopy findings may resemble morphea except for the presence of PAS-positive deposits around dermal blood vessels. Other rare forms of porphyria can also lead to scarring in UV-exposed sites (see Ch. 49).
- **Radiation-induced morphea**. This disorder is characterized by marked sclerosis, erythema, and pigmentary changes occurring within the radiation field or even beyond it (Fig. 44.13). The incidence of radiation-induced morphea is about 1 in 500 patients and it is seen primarily in patients treated for breast carcinoma. Predictive risk factors for the development of radiation-induced morphea are unknown and it can present several years after radiation therapy. In addition to the changes of radiation dermatitis, histopathology demonstrates perivascular and subcutaneous inflammation together with dermal fibrosis and collagen deposition.
- **Nephrogenic systemic fibrosis**. This entity is discussed in detail in Chapter 43.
- **Chronic GVHD**. Patients with chronic GVHD may develop lesions that resemble morphea and lichen sclerosus as well as eosinophilic fasciitis (see Ch. 52).

DIFFERENTIAL DIAGNOSIS

In addition to the other morpheaform and sclerodermoid conditions discussed above, the most important entity in the differential diagnosis is SSc (see Ch. 43). Asymmetric skin involvement as well as the absence of Raynaud phenomenon and lung or esophageal involvement are characteristic features of morphea. The other common considerations are lichen sclerosus and keloids; however, the former can coexist with morphea. Dupuytren contracture and camptodactyly, a benign ulnar deviation of the fourth and fifth finger, can be clinically distinguished from linear morphea.

Scleredema leads to diffuse woody induration, primarily of the upper back and neck. Symmetric tightness and induration of acral skin can be seen in insulin-dependent diabetics with cheiroarthropathy, also referred to as waxy skin and stiff joints. In children, progeria and premature aging syndromes need to be distinguished from Parry–Romberg syndrome, but the latter is unilateral, as is silent sinus syndrome. Additional entities in the sclerodermoid differential diagnosis (e.g. scleromyxedema) are listed in Table 43.7.

TREATMENT

Various therapeutic modalities have been described for morphea, although quality evidence in support of many of these therapies has been limited[40]. In addition, there has been a lack of standardized outcome measures for assessing the efficacy of various therapies. However, the localized scleroderma cutaneous assessment tool (LoSCAT) is gaining recognition as a valid and reproducible index for disease activity and damage in morphea[41]. Radiologic imaging (e.g. ultrasound, MRI) may also provide useful information[41].

The major therapies for morphea include topical medications, phototherapy, systemic immunosuppressants, and physical/occupational therapy (Table 44.3). Several factors, including level of disease activity, subtype of morphea, depth of involvement, location and extent of disease, and degree of current or potential functional impairment or disfigurement, play a role in determining the most appropriate treatment.

Therapies are most effective when there is active disease (e.g. inflamed and expanding patches and plaques), whereas inactive disease (e.g. fixed sclerotic plaques) is less likely to respond. Plaque-type morphea

DIFFERENTIAL DIAGNOSIS OF MORPHEAFORM SKIN LESIONS
Morphea (plaque-type, linear, generalized* or deep*)
Chronic graft-versus-host disease*
Lichen sclerosus (may coexist with morphea)
Lipodermatosclerosis*
Sclerosis at injection sites
• Vitamin K_1 (Texier disease) or vitamin B_{12}
• Silicone or paraffin implants
• Interferon-β
• Glatiramer
• Enfuvirtide
• Bleomycin (intralesional therapy)
• Opioids (e.g. pentazocine, ketobemidone, methadone)
• Vaccinations
Medications and chemical/toxin exposures†
• Immune checkpoint inhibitors
• Aromatic/chlorinated hydrocarbons (e.g. benzene or toluene at sites of contact with skin)*
• Nephrogenic systemic fibrosis (induced by gadolinium-containing contrast media)*
• Toxic oil syndrome (historical)*
Radiation-induced morphea
Porphyria (porphyria cutanea tarda, hepatoerythropoietic porphyria, congenital erythropoietic porphyria)*
Muckle–Wells syndrome
Winchester syndrome*
Stiff skin syndrome*
Linear melorheostosis
Complex regional pain syndrome*
Morpheaform sarcoidosis
Sclerosing congenital melanocytic nevus
Paraneoplastic scleroderma-like syndrome*
Cutaneous metastases (e.g. carcinoma *en cuirasse*)
*Can overlap with sclerodermoid disorders, which are outlined in Table 43.7; in particular, deep morphea and eosinophilic fasciitis may have a similar appearance. †Systemic medications for which there have also been reports of an association with morpheaform lesions include bleomycin, taxanes (e.g. paclitaxel, docetaxel), bromocriptine, ethosuximide, valproic acid, appetite suppressants, and penicillamine.

Table 44.2 Differential diagnosis of morpheaform skin lesions.

APPROACH TO THE TREATMENT OF MORPHEA Rx	
Morphea variant	**Treatment**
Plaque–type (circumscribed)	*First-line** • Topical class I CS, daily–twice daily • Intradermal CS (e.g. triamcinolone acetonide 5–10 mg/mL) every 4–6 weeks into active rim • Tacrolimus 0.1% ointment, twice daily *Second-line* • Topical vitamin D analogue (calcipotriene [calcipotriol]) under occlusion ± class I topical CS • Lesion-limited phototherapy† *Third-line (or if lesions spreading, unstable)* • Generalized phototherapy† • Weekly methotrexate‡ • Topical crisaborole 2% ointment for steroid-refractory plaque *Refractory, rapidly progressive, or deep variant* • Weekly methotrexate‡ ± systemic CS¶ • CS-sparing agents (e.g. mycophenolate mofetil, JAK inhibitors [e.g. tofacitinib])
Linear	**Deep variant, facial involvement, crossing joints** *First-line** • Weekly methotrexate‡ ± systemic CS¶ *Second-line* • CS-sparing agents (e.g. mycophenolate mofetil, JAK inhibitors, tocalizumab) **Superficial variant, not involving face or crossing joints** • Phototherapy†
Generalized	*First-line** • Phototherapy† (if superficial and without joint contractures) • Weekly methotrexate‡ ± systemic CS¶ *Second-line* • CS-sparing agents (e.g. mycophenolate mofetil, JAK inhibitors [e.g. tofacitinib, baricitinib], tocalizumab)
Pansclerotic	See systemic therapies for generalized morphea
*If not improved after ~8 to 10 weeks, progress to next line of therapy. †Phototherapy choice based on local availability (UVA1, BB-UVA, PUVA), with preference for UVA1 if available; NB-UVB may be considered for limited, superficial plaque-type disease. ‡Weekly methotrexate doses, either orally or subcutaneously: adults, 15–25 mg/week; children, 0.3–0.5 mg/kg/week. ¶Especially for early/progressive lesions; pulsed dosing (e.g. intravenous methylprednisolone 1000 mg/day for three consecutive days per month, with a pediatric dose of 30 mg/kg/day in those ≤ 33 kg) favored over daily dosing (e.g. oral prednisone 1 mg/kg/day).	

Table 44.3 Approach to the treatment of morphea. Treatment is most effective in active, inflammatory lesions. Systemic therapy should be instituted if: (1) progression or risk of functional impairment (e.g. decreased range of motion of joints, involvement across joints) or significant disfigurement (e.g. linear facial morphea); (2) deep morphea (e.g. subcutaneous, fascia, muscles). Systemic retinoids (e.g. acitretin 10–50 mg/day), apremilast (30 mg twice daily), abatacept, and hydroxychloroquine (200–400 mg/day) are additional therapies. CS, corticosteroids.



Fig 44.13 Radiation-induced morphea. Erythema and induration of the left breast. *Courtesy Department of Dermatology, Medical University of Graz.*

with limited body surface area involvement can often be managed with topical therapies while generalized or extensive disease responds best to phototherapy or systemic medications. Active deep morphea with involvement of the subcutaneous tissue, fascia, or muscles as well as morphea with the potential for functional impairment (e.g. linear morphea overlying joints) or significant disfigurement (e.g. facial involvement) should be managed aggressively with systemic immunosuppressants. In addition, patients at risk for functional impairment (e.g. joint contractures, loss of mobility) should be referred to physical and occupational therapists before the onset of such complications.

If persistent contractures do develop, reconstructive surgery may be required. Surgical revision can be offered for inactive linear or *en coup de sabre* morphea. Autologous fat transplantation has been used successfully for Parry–Romberg syndrome and injection of hyaluronic acid fillers, with or without fractional laser ablation, to correct facial morphea has been reported[42]. Finally, patients with extracutaneous involvement may require additional evaluation and management, such as rheumatologic referral for arthritis or synovitis. Patients with

morphea that involves the head are at risk for ocular and/or neurologic complications and, when indicated, referred to ophthalmology and neurology, respectively.

Phototherapy

Phototherapy for morphea was first described in 1994[43], and since then, efficacy has been confirmed by more than 30 publications[44,45] and was recently supported by an open label controlled study[46]. Various phototherapy modalities have been used, including UVA1, broadband UVA (BB-UVA), PUVA, and narrowband UVB (NB-UVB). When available, UVA1 has become the phototherapy of choice, followed by BB-UVA and PUVA. NB-UVB, because of its shallower depth of penetration, may be beneficial for superficial morphea but is less effective for deeper morphea. Treatment can be lesion-directed when there is a limited number of plaques or administered to the majority of the skin surface. The efficacy of phototherapy is thought to be due to immunomodulatory effects as well as upregulation of matrix metalloproteinases that stimulate collagen breakdown. Patients may also benefit from phototherapy plus low-dose systemic retinoids as this combination has led to improvement of sclerodermoid GVHD and plaque-type morphea[18,47].

Due to the nature of phototherapy, placebo-controlled studies have not been performed. Nonetheless, little doubt exists as to the efficacy of this therapy, as untreated morphea normally progresses over 3–5 years and then regresses very slowly over several years. More rapid spontaneous improvement only occurs in a small minority of patients[3]. The clinical course is definitely different in patients receiving phototherapy. Following 30–36 treatments of bath PUVA therapy (at slightly suberythematous doses) or UVA1 (30–60 J/cm^2), morphea resolves or markedly improves in at least 60% of patients[48,49] (Fig. 44.14). Further advantages of phototherapy, and especially UVA1, include clinical improvement in all skin types[50] and sustained remissions. Recurrence of morphea plaques after successful phototherapy has been reported, but primarily in patients with a prolonged period of disease prior to initiation of phototherapy. The dose of UVA1 phototherapy (medium versus high) does not appear to correlate with risk of recurrence[51].

The ideal dose for UVA1 therapy has been debated. Most initial studies were performed with either low (20–30 J/cm^2) or medium doses (40–70 J/cm^2) of UVA1 and reported similar efficacy. A study that utilized 20 MHz ultrasound rather than clinical assessment of morphea lesions reported a better response with medium-dose (70 J/cm^2) than with low-dose (20 J/cm^2) UVA1[52]. In agreement with these reports, we have observed that 36 treatments with either 30 J/cm^2 or 50–60 J/cm^2 of UVA1 markedly improves morphea in the majority of patients[48]. Importantly, in responding patients, lesions of morphea continue to improve beyond the end of the therapy. Thus, therapy can be terminated after 36 treatments, even if the sclerosis has not yet completely resolved. The only exception appears to be linear morphea, which may require up to 60 treatments.

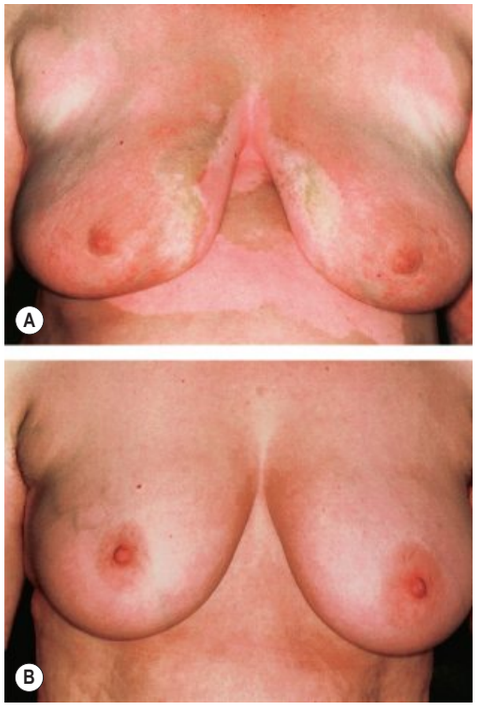


Fig. 44.14 Phototherapy for morphea. Disseminated morphea on the trunk, with sparing of the central portions of the breasts. Before (**A**) and after (**B**) PUVA bath photochemotherapy.

Systemic Therapies

Indications for systemic therapies are outlined above and in Table 44.3. For decades, methotrexate, either alone or in combination with systemic corticosteroids, has represented a first-line treatment[53–55]. Systemic corticosteroids are often added for severe involvement or when more rapid control of the disease is desired[56–58]. Typically, the methotrexate is continued for at least 12 months and tapering is not begun until at least 6–12 months after the disease is inactive. Tapering of systemic corticosteroids (over several months) usually occurs sooner, once the disease is no longer active.

Recent data from retrospective cohort and longitudinal studies suggest that mycophenolate mofetil (MMF) is also beneficial and well tolerated in patients with severe morphea, even in those with a history of previously ineffective treatments[59,60]. MMF is usually the next line of treatment should methotrexate +/– corticosteroids fail or be contraindicated. Efficacy data for other systemic agents are even more limited. In small case series, JAK inhibitors (e.g. tofacitinib, baricitinib) led to improvement in patients with recalcitrant morphea or eosinophilic fasciitis[61]. Additional reported therapies include hydroxychloroquine[62] and systemic retinoids (acitretin, isotretinoin)[17,18,63,64]. Of note, vitamin A derivatives have antifibrotic effects and can modulate collagen metabolism[65].

In case series and reports, improvement has been observed with tocilizumab, which blocks the IL-6R, including for pansclerotic morphea in children[66], as well as abatacept, a CTLA4 fusion protein that inhibits T cell activation[67]. A placebo-controlled, multi-center trial with dupilumab, which blocks the interaction of the profibrotic cytokines IL-4 and IL-13 with IL-4Rα, is currently underway. Lastly, a novel approach based upon genetically modified autologous fibroblasts that express metalloproteinase-1 (MMP-1) has not progressed beyond phase I/II trial status.

LICHEN SCLEROSUS

Synonyms/site-specific names: ■ Lichen sclerosus et atrophicus ■ Kraurosis vulvae ■ Balanitis xerotica obliterans (lichen sclerosus of the penis)

Key features

- Sclerotic, ivory-white, flat papules and plaques with epidermal atrophy and, in extramucosal sites, follicular plugging
- Most commonly affects female or male genitalia, less often extragenital skin
- May cause scarring of the vaginal introitus or phimosis
- Severe pruritus may occur
- No systemic manifestations

INTRODUCTION

Lichen sclerosus (LS) is a clinically distinct inflammatory disease, primarily of the superficial dermis or submucosa, that leads to ivory-white scar-like atrophy. Extragenital LS may itch and be cosmetically disturbing whereas genital LS causes both dryness and severe, persistent pruritus, and it often leads to progressive atrophy and functional impairment. Phimosis or scarring of the vaginal introitus are the most frequent complications. If left untreated, ~4% of patients with vulvar LS may develop differentiated vulvar intraepithelial neoplasia (VIN) or squamous cell carcinoma (SCC)[68].

HISTORY

François Henri Hallopeau's report on a "lichen plan atrophique" in 1887 is considered to be the first description of LS. The typical histopathologic changes of lichen sclerosus et atrophicus were published by Ferdinand Jean Darier in 1892. Unna, Westberg, von Zumbusch, and others elucidated the clinical features of LS in various case reports[69]. This contributed to the panoply of terms, such as white spot disease or lichen albus, an aspect that complicates any literature survey. Lichen sclerosus in the genital area was first described in women by August Breisky as kraurosis vulvae and 40 years later in men by Alfred Stühmer as balanitis xerotica obliterans. Today, lichen sclerosus, the term proposed by the International Society for the Study of Vulvar Disease, is used most frequently[70,71].

EPIDEMIOLOGY

Lichen sclerosus is relatively uncommon, although the exact prevalence is unknown. It occurs at all ages with a similar incidence in all races; the reported female-to-male ratio varies widely, depending upon the study, from 10:1 to 1:1[70,71]. In both sexes, the anogenital area is affected in ~85% of patients, but the best epidemiologic studies concentrate on vulvar disease.

Studies in adult patients suggest that LS is one of the most common causes of symptomatic vulvar disease. In two large series, LS was diagnosed in 13% to 19% of patients presenting with symptomatic vulvar disease. In women, the peak incidence is during the fifth and sixth decades, and a second peak occurs in girls between 8 and 13 years of age. Among prepubertal girls with vulvar disease, the relative frequency of LS is similar to that in adults. Extragenital LS is rare in children. In boys and men, LS frequently leads to phimosis (seen in 14 of 100 prepubertal boys undergoing circumcision for phimosis). Of 357 male patients attending a dermatology clinic because of genital skin disease, 14% had LS[72].

A recent retrospective analysis demonstrated a high prevalence of LS in patients with plaque-type morphea and generalized morphea[73]. This coexistence suggests either a common trigger or a common susceptibility factor for both diseases.

PATHOGENESIS

As in most inflammatory diseases, genetic predisposition contributes to the development of LS, as it may be found in monozygotic and fraternal twins. In addition, association with the MHC class II antigen HLA-DQ7 was observed in a relatively large study. The existence of a relevant susceptibility gene for sclerosis within this region of the MHC is underlined by the finding that the same region is associated with a greater risk of organ-specific autoimmune diseases. Even though inflammation seems essential for initiation and progression of LS, the mechanisms leading to subsequent sclerosis remain speculative. Increased production of IL-6, TNF, and collagen (types I, III, and V) is thought to promote the sclerosis[74].

Perhaps with the exception of autoantibodies against extracellular matrix protein 1 (ECM-1), no specific immunologic parameters have been identified in patients' sera that clearly correlate with either risk of disease or disease activity. IgG autoantibodies against ECM-1 are found in 80% of patients with LS[75]. Moreover, in female patients with LS, there is a higher prevalence of autoimmune diseases (especially autoimmune thyroid disease) and ANA positivity than in male patients with LS[76].

Oxidative stress may also play a role in the pathogenesis of LS, based upon analysis of lesional skin that showed lipid peroxidation of epidermal basal cell layers, oxidative DNA damage, and oxidative protein damage.

CLINICAL FEATURES

Lichen sclerosus most frequently affects the anogenital region, and less often extragenital skin. Lichen sclerosus of the oral cavity, palms, or soles is rare. Intraorally, bluish-white papules up to 5 mm in diameter may occur on the buccal mucosa or under the tongue. They can lead to superficial scar-like atrophy or erosions.

Extragenital LS normally does not cause symptoms except for dryness and associated pruritus. Lesions favor the trunk (Fig. 44.15) and the proximal extremities. More specific predilection sites include the neck, shoulders, flexor surfaces of the wrists, and sites of physical trauma or continuous pressure (e.g. the shoulder or hip). The periorbital area and scalp are rarely affected.

It is unusual to see extragenital disease during its early phases when single lesions begin as polygonal, bluish-white, shiny, slightly elevated, interfollicular papules. Over time, these papules often enlarge or coalesce into larger plaques. Most patients present with slightly sclerotic, scar-like papules and plaques that are usually ivory in color and have a shiny and/or wrinkled surface. Occasionally, lesions have a pink or light violet hue. At sites of continuous pressure, the surface may acquire a parchment-like appearance.

In more advanced stages, telangiectasias or follicular plugging can be seen (Fig. 44.16A). The flattened interface between the epidermis and dermis results in fragility of the dermal–epidermal junction. As a result, LS is occasionally complicated by the development of bullae that tend to become hemorrhagic (Fig. 44.16B).

In women, the vulva and the perianal region are commonly involved, often in a figure-of-eight configuration (see Ch. 73). Although the disease may be symptom-free, it frequently causes severe pruritus and soreness. These symptoms may be considerable and lead to dysuria, dyspareunia, or pain upon defecation (often manifesting as constipation in children). As a result, quality of life can be adversely affected, including in children and adolescents[77,78].

Vulvar LS often begins as a slightly elevated, sharply demarcated area of erythema, which can be slightly eroded. Over time, the involved skin becomes shiny, hypopigmented, and sclerotic, and fissures may develop, especially in the perineum (Fig. 44.17). When progressive, associated scarring can lead to burying of the clitoris and fusion of the

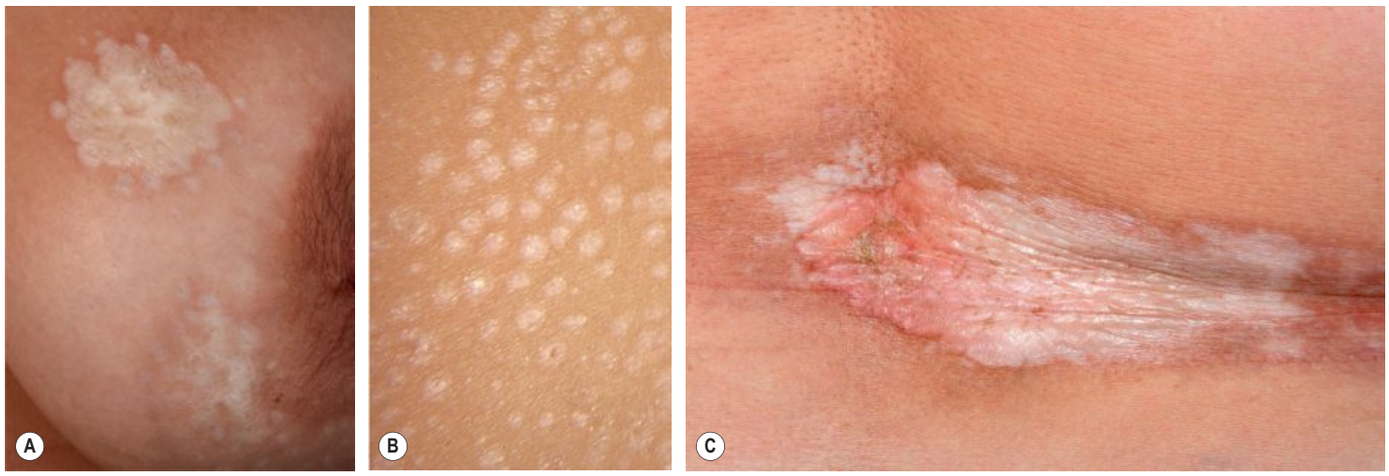


Fig. 44.15 Lichen sclerosus. A Shiny, ivory-colored plaques on the breast with several guttate satellite lesions. **B** In some patients, only guttate lesions are present. **C** Large ivory-colored, shiny plaque on the waistline, a site of persistent pressure. *B, Courtesy Louis A. Fragola, Jr, MD.*



Fig. 44.16 Lichen sclerosus. A Follicular plugging in a plaque of lichen sclerosus on the back of a patient with chronic GVHD. **B** Hemorrhagic bullae primarily at the periphery of a large plaque on the back. *A, Courtesy Jean L. Bolognia, MD; B, Courtesy Luis Requena, MD.*

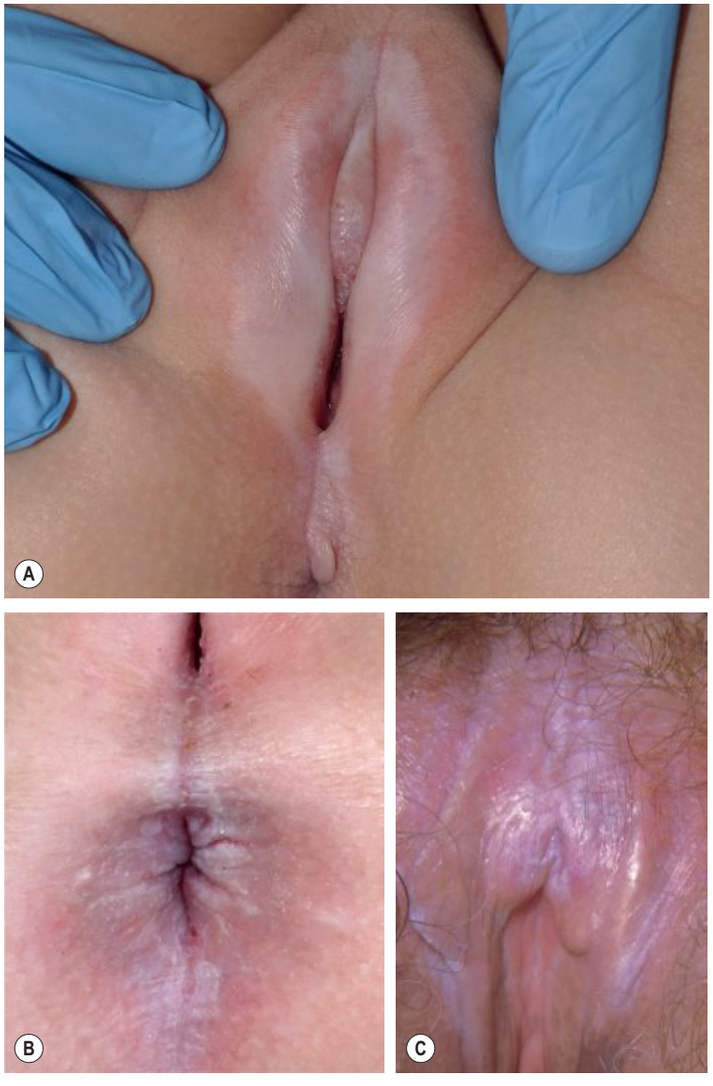


Fig. 44.17 Anogenital lichen sclerosus. A Characteristic vulvar, perineal, and perianal involvement in a child. Symmetric ivory-colored, shiny plaques with a thin pink peripheral rim are seen; a perianal pyramidal protrusion is also present. **B** Perianal lichen sclerosus in which the hypopigmented plaques are accompanied by a linear erosion (skin tear) at 6 o'clock and central fissuring of the perineum. **C** Involvement of the clitoral hood and clitoris as well as fusion of the left labia minora and labia majora. *A, Courtesy A. Hernández-Martín, MD; C, Courtesy Louis A. Fragola, Jr, MD.*



Fig. 44.18 Lichen sclerosus of the penis (balanitis xerotica obliterans). Note the ivory color, erosion, and scarring.

labia minora to the labia majora, and when untreated, an increased risk of malignancy[68]. With severe disease, loss of the labia minora and significant narrowing of the introitus can occur. Sexual intercourse may become impossible. In general, LS does not worsen during pregnancy and when treated successfully, vaginal delivery is possible without an increased incidence of perineal tears and episiotomies (compared with healthy control populations)[79].

Areas of purpura often develop within lesions of anogenital LS and can actually aid in the clinical diagnosis (see Fig. 73.3). However, the hemorrhage combined with erosions may be misdiagnosed as sexual abuse (see Ch. 90). A careful history and clinical examination, along with histologic confirmation when needed, can assist in establishing the diagnosis.

In boys and men, acquired phimosis or recurrent balanitis are the primary presenting features, and perianal involvement is rare. Itching and soreness are common. On the glans and the inner aspect of the foreskin, LS starts as sharply demarcated, sometimes slightly blue–red lesions, occasionally with erosions. This inflammation tends to evolve into an atrophic white sclerotic scar (Fig. 44.18). The constriction may cause pain on erection and, at advanced stages, dysuria and urinary obstruction. If the foreskin is affected in uncircumcised male patients, LS invariably leads to phimosis (difficulty in retracting the foreskin to uncover the glans), with the additional risk of paraphimosis (when a foreskin is retracted behind the glans and cannot be returned to its original position); the latter represents a urologic emergency. Many boys and men first present when the phimosis impairs repositioning of the foreskin;

in these situations, diagnosis depends on histology. With progression, poorly healing ulcers of the glans can develop. While circumcision is clearly a first-line therapy, LS may recur at the site of a circumcision.

A continuing debate is whether genital LS is a precancerous condition. Interpretation and comparison of the data are complicated by at least two factors: some of the patients reported as developing cancer had previously received X-ray therapy for the disease or had previous dysplasia due to human papillomavirus (HPV) infection. It is therefore very difficult to perform a useful meta-analysis based on existing data. Some data suggest that genital LS is not intrinsically precancerous, but a recent prospective cohort study of 507 women with vulvar LS noted the development of SCC or VIN in 5% of patients partially compliant with topical corticosteroid treatment and in none of the compliant patients, with a mean follow-up of 4.7 years[68,70,71,80]. Whether the microRNA signature will assist in identifying those patients at increased risk of SCC remains to be determined[80a].

Lentigines and melanocytic nevi can arise within areas of LS, primarily genital LS; histologically they may resemble persistent (recurrent) melanocytic nevi and therefore be confused with melanoma[81].

PATHOLOGY

Lichen sclerosus has a specific histologic pattern that is seen in all age groups[82]. Initially, superficial dermal edema is associated with a band-like lymphocytic infiltrate (Fig. 44.19A). The epidermis is thinned, with orthohyperkeratosis and vacuolar degeneration of the basal layer. Hyperkeratosis is especially pronounced at follicular openings and may lead to plugging. Vacuolar degeneration of the basal layer and flattening of the rete ridges predispose to the development of blisters, which may become hemorrhagic. The most important changes are found in the superficial dermis, where the pale staining reflects edema initially and then homogenized dermal collagen (Fig. 44.19B). Loss of elastic fibers is typical for LS and is not observed in morphea. Subepidermal clefting and hemorrhage within the homogenized papillary dermis is frequently observed.

During the early phases, the inflammatory infiltrate is especially pronounced along the zone of hyalinization and consists of lymphocytes ($CD3^+$, $CD4^+$, $CD8^+$), macrophages, and mast cells. In older lesions, the mononuclear infiltrate is reduced and sparse, and patchy islands of mononuclear cells are dispersed within the hyalinized dermis. Ultrastructural studies reveal shortened collagen fibers.

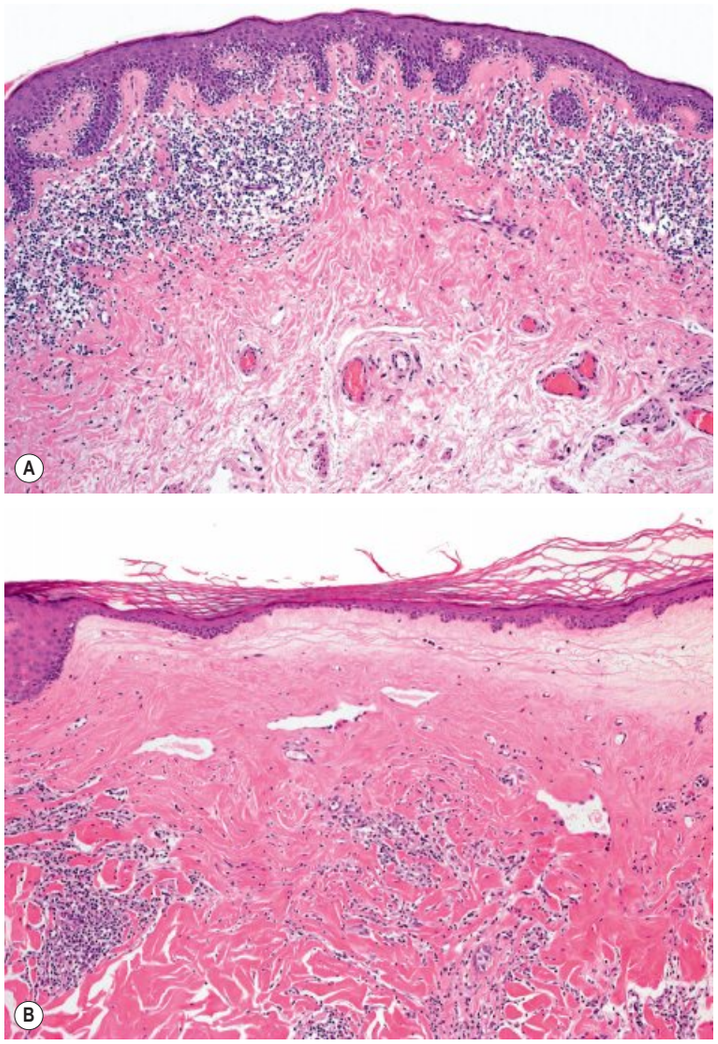


Fig. 44.19 Lichen sclerosus – histopathologic features. A Early lesion with band-like infiltrate of lymphocytes in the upper dermis and vacuolar change at the dermal–epidermal junction. Mild homogenization of the papillary dermis is present. **B** Late lesion with orthohyperkeratosis, thinning of the epidermis, and homogenization of the upper dermis. There is also hyalinization and sclerosis of the papillary dermis, telangiectasias, and an interstitial lymphocytic infiltrate. *Courtesy Lorenzo Cerroni, MD.*

DIFFERENTIAL DIAGNOSIS

The most important entity in the differential diagnosis of extragenital LS is morphea, and in the case of genital LS in girls and boys, sexual abuse. However, morphea and LS may coexist in the same patient. In adults, genital LS may mimic erosive lichen planus, mucous membrane pemphigoid, or erythroplasia of Queyrat (see Ch. 73). Distinction often requires histologic examination. Biopsies may also be needed to exclude associated differentiated VIN or invasive SCC. Histologically, LS-associated pseudoepitheliomatous hyperplasia has to be distinguished from SCC. A past history of allogeneic HSCT points to chronic GVHD that may be clinically and histologically indistinguishable from morphea or LS (see Fig. 44.16A).

TREATMENT

Genital Lichen Sclerosus

Identification, early treatment, and ongoing maintenance therapy of *genital* LS is recommended, with the goals of relieving symptoms (e.g. pruritus), reversing skin changes (e.g. hyperkeratosis), and preventing the development of scarring, adhesions, and SCC[68,83]. Table 73.1 outlines a detailed approach to anogenital LS.

Topical corticosteroids are the gold standard for treatment of genital LS in both adults and children and intralesional corticosteroids are also useful for treating areas of hyperkeratosis. Both retrospective and prospective studies have shown that ultrapotent topical corticosteroids (e.g. clobetasol propionate 0.05%) are highly effective in the treatment of *genital* LS[84–86]. In boys with genital LS, topical corticosteroids can avoid circumcision in one-third of patients[87].Topical calcineurin inhibitors, although less potent than the recommended class I corticosteroids, also have a role in topical therapy[84,85]. Ointments are preferred over creams because they are better tolerated, and frequent use of emollients (e.g. petrolatum) is also recommended. Topical JAK inhibitors (e.g. ruxolitinib 1.5% cream) are currently under investigation for anogenital LS.

Failure to respond to ultrapotent local corticosteroids should prompt evaluation for contributing factors, such as improper use of the corticosteroids, secondary infection (e.g. candidiasis), menopause-related vulvovaginal atrophy, and development of SCC. Second-line therapeutic options for *genital LS* have more limited efficacy data but include systemic agents (e.g. acitretin, abrocitinib)[88,89,89a].

Importantly, because symptoms often recur upon discontinuation of initial therapy and because of the long-term risk of malignancy (i.e. SCC), it is now recommended that patients follow a long-term maintenance regimen upon resolution of signs (e.g. hyperkeratosis, ecchymoses, fissures) and symptoms (e.g. pruritus) after ~6–12 weeks of induction therapy. Follow-up at regular intervals until a stable maintenance regimen is in place is advised, as is annual genital examination to exclude the development of malignancy.

Phototherapy

Phototherapy, primarily UVA1, has shown efficacy in some patients with genital LS and can be considered if topical/intralesional corticosteroids have failed. The long-term safety of UVA1 therapy in the genital region is unknown[90,91]. The successful use of photodynamic therapy (PDT) for vulvar LS has been reported in small case series and reports. Additional studies are needed to evaluate the role of PDT in treating genital LS.

Surgery

Circumcision is the treatment of choice for genital LS complicated by phimosis or paraphimosis. Excellent results have been reported[92]. Surgery in vulvar LS is indicated for the treatment of coexistent vulvar intraepithelial neoplasia, SCC, or fusion. LS will frequently recur around the scarring in females[93]. Lastly, fractional laser ablation has been used for treatment of hyperkeratotic LS plaques.

Extragenital Lichen Sclerosus

Fewer studies exist for the treatment of *extragenital* LS. Phototherapy and weekly methotrexate +/− systemic corticosteroids are potential treatment options for widespread disease, while potent topical corticosteroids and topical vitamin D analogues (e.g. calcipotriene [calcipotriol]) +/− under occlusion as well as topical calcineurin inhibitors are options for more limited disease[86,93]. When available, UVA1 phototherapy is preferred for widespread extragenital LS, followed by NB-UVB and then PUVA. The largest study to date of successful phototherapy for treating extragenital LS involved 10 patients who received 40 UVA1 sessions at a dose of 20 J/cm^2 four times/week[94]. Case reports exist for successful use of NB-UVB and PUVA[95–97].

Systemic immunosuppressive therapy is typically reserved for widespread cases that are refractory to phototherapy or in those patients who cannot undergo phototherapy. Weekly methotrexate alone (10–20 mg/week) or in combination with systemic corticosteroids (either pulsed [e.g. intravenous methylprednisolone 1000 mg/day for 3 consecutive days/month] or daily dosing [e.g. prednisone 1 mg/kg/day]) has shown efficacy in case reports and small case series[98–100]. In a case report, dupilumab led to improvement.

Additional figures available in our eBook (see inside front cover for access code).

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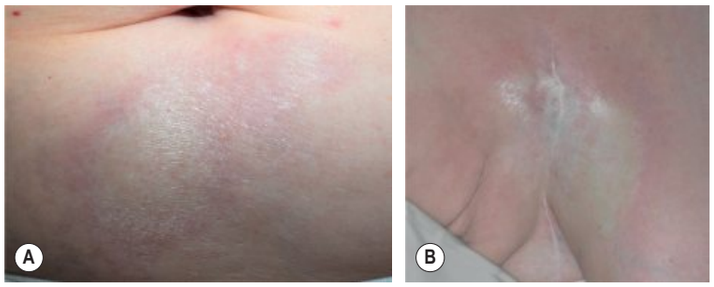
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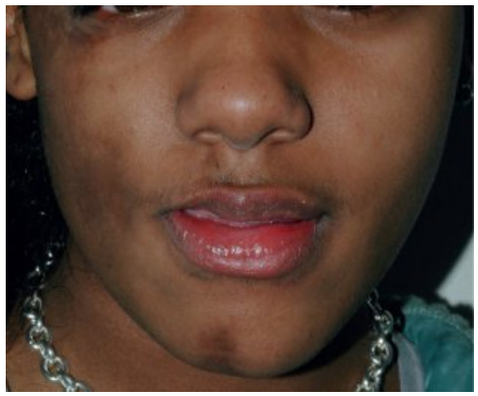
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eFig. 44.1 Plaque-type/circumscribed morphea. Shiny, ivory-colored plaques of the abdomen (**A**) and chest (**B**) surrounded by a lilac ring. Wrinkling is obvious within the abdominal plaque. *Courtesy Kalman Watsky, MD.*



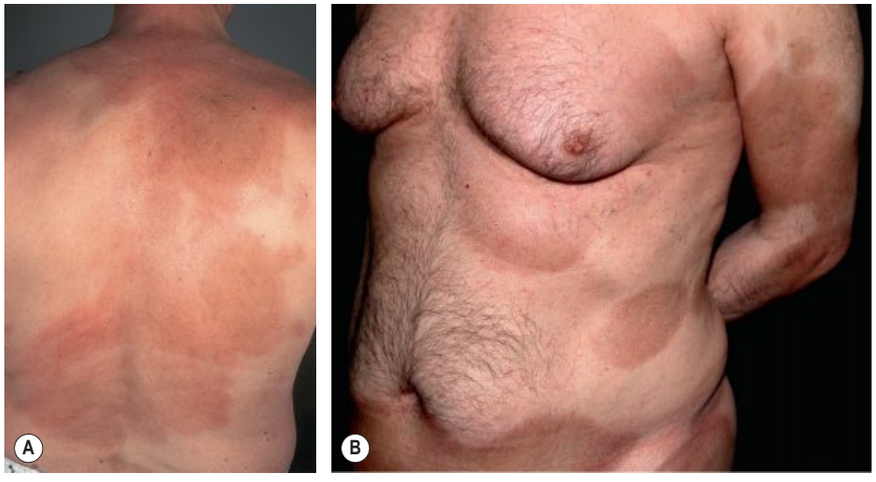
eFig. 44.3 Parry–Romberg syndrome. Hyperpigmentation and loss of subcutaneous fat, leading to facial asymmetry. *Courtesy Julie V. Schaffer, MD.*



eFig. 44.2 Nodular/keloidal morphea. Elevated, firm pink papulonodules arising within an area of hyperpigmented induration. *Courtesy Jean L. Bolognia, MD.*



eFig. 44.4 Morphea *en coup de sabre*. Linear depressions and sclerosis are more frequently paramedian (rather than midline) and can be thin. *Courtesy Julie V. Schaffer, MD.*



eFig. 44.5 Generalized morphea. Multiple, large hyperpigmented plaques, several of which have an inflammatory border, involving the posterior trunk (**A**) versus the anterior trunk and arm (**B**). *B, Courtesy Luis Requena, MD.*



eFig. 44.6 Radiation-induced morphea. Erythema and induration of the right neck. *Courtesy Kalman Watsky, MD.*



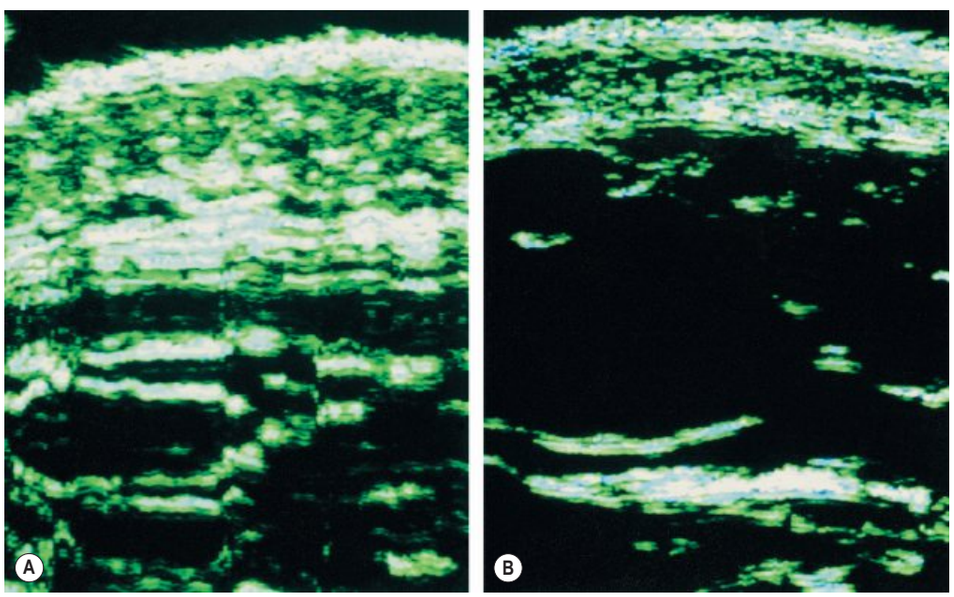
eFig. 44.9 Extragenital lichen sclerosus. White papules and small plaques on the neck.



eFig. 44.7 Linear morphea of the leg in an adolescent. Extensive induration of the left leg with hypoplasia and an obvious flexion contracture of the knee; there is also involvement of the right foot.



eFig. 44.10 Hemorrhagic bullae within extragenital lichen sclerosus. The explanation is fragility of the dermal–epidermal junction.



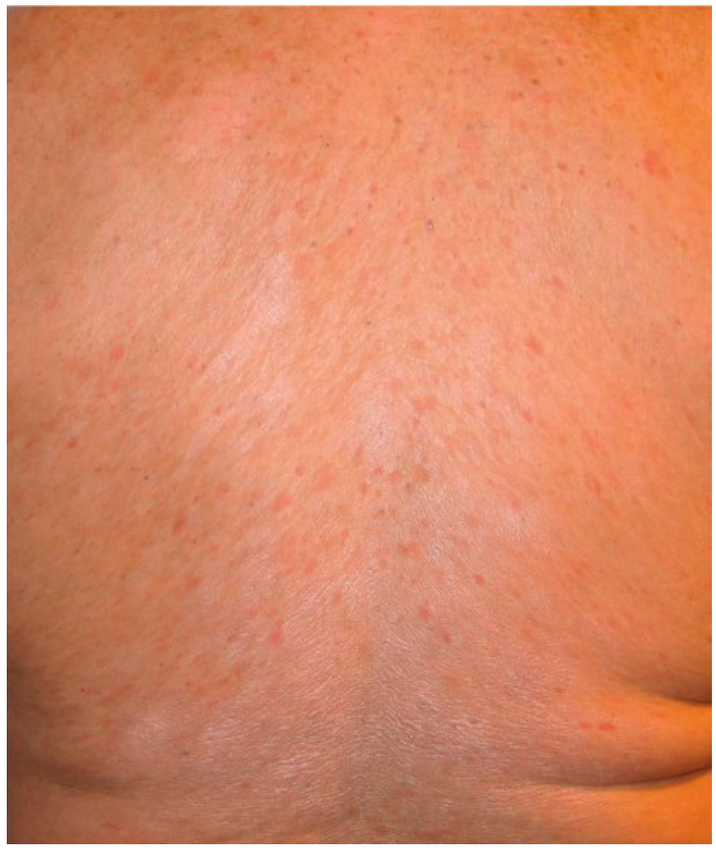
eFig. 44.8 High-frequency ultrasound (20 MHz) of a morphea plaque. Before (**A**) and after (**B**) PUVA bath photochemotherapy, showing reduction of dermis thickness and hyperechoic bands of connective tissue.



eFig. 44.11 Lichen sclerosus of the glans penis with extension onto the shaft. Note the hypopigmentation and purpura as well as scarring and ongoing inflammation. *Courtesy Kalman Watsky, MD.*



eFig. 44.12 Anogenital lichen sclerosus. The distribution pattern has a figure-of-eight configuration. The presence of purpura is also a clue to the diagnosis. *Courtesy Jeffrey P. Callen, MD.*



eFig. 44.13 Lichen sclerosus-like changes in a patient with chronic graft-versus-host disease. *Courtesy Dennis Cooper, MD.*



eFig. 44.14 Radiation-induced morphea and lichen sclerosus. The majority of indurated plaques are hyperpigmented but note the hypopigmented plaque at 3 o'clock. *Courtesy Jeffrey P. Callen, MD.*



eFig. 44.15 Ultrapotent topical corticosteroids in the treatment of lichen sclerosus. Before (**A**) and after (**B**) application of clobetasol propionate 0.05% cream daily for 5 months in this 12-year-old girl.

45 Other Rheumatologic Disorders and Autoinflammatory Diseases

Cédric Lenormand, Marco Gattorno and Dan Lipsker

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Although all the disorders in this chapter represent inflammatory systemic diseases, there are two major groups based upon underlying pathomechanisms. Disorders such as systemic-onset juvenile idiopathic arthritis (Still disease) and inherited autoinflammatory diseases are related to abnormalities in the innate immune system whereas other disorders, including rheumatoid arthritis and Sjögren syndrome, are characterized by autoimmune-mediated tissue damage via autoreactive antigen-specific T cells and the presence of characteristic autoantibodies.

SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS (STILL DISEASE)

Synonym: ■ Juvenile idiopathic arthritis: juvenile rheumatoid arthritis (JRA); juvenile chronic arthritis

Key features

- There are several types of juvenile idiopathic arthritis, including systemic-onset, polyarticular (either rheumatoid factor [RF]-positive or RF-negative), and oligoarticular
- Systemic-onset juvenile idiopathic arthritis, also known as Still disease, is characterized by high spiking fevers, lymphadenopathy, hepatosplenomegaly, and arthritis
- Most commonly, transient cutaneous eruptions of erythematous macules and papules, often accompanying the fevers and associated with Koebner phenomena, are seen; less often there are persistent, sometimes linear, plaques

Introduction

Juvenile idiopathic arthritis (JIA) is classified into seven major types (Table 45.1)[1], including systemic-onset, rheumatoid factor (RF)-positive polyarticular, RF-negative polyarticular, and oligoarticular. Systemic-onset JIA (sJIA), also known as Still disease, is characterized by an evanescent, erythematous eruption that typically accompanies spiking fevers. Cutaneous manifestations are less common in the other types, although the RF-positive subgroup of polyarticular JIA can present with rheumatoid nodules and other skin findings similar to those seen in adults with rheumatoid arthritis (see below), and nearly all patients with psoriatic arthritis have cutaneous and/or nail psoriasis (see Ch. 8).

History

In 1897, George Still, an English pediatrician, first described a chronic arthritis in children that was associated with fever, lymphadenopathy, and organomegaly.

Epidemiology

JIA is the most common rheumatic disease in childhood, and its overall prevalence is estimated to be 0.2–1 per 1000 children (≤16 years of age)[2]. sJIA comprises 15%–20% of all cases of JIA and can occur at any time from infancy through adolescence, with a mean age at onset of 6 years. Whereas most other types of JIA have a female predominance, sJIA affects both sexes equally. A monogenic autosomal recessive form of sJIA with an underlying mutation in *LACC1* has been described; its protein product regulates metabolism within macrophages[3].

Pathogenesis

More recent insight into the pathogenesis of sJIA suggests that it is better classified as an *autoinflammatory* rather than an autoimmune disease. The inflammation characteristic of this disease appears to result from activation of *innate* immune responses, in contrast to adaptive immune responses that are antigen-specific and lymphocyte-driven (see Ch. 4). Dysregulated production of interleukin (IL)-1 appears to play a critical role in the pathogenesis of sJIA, as exemplified by the ability of IL-1 antagonists (e.g. anakinra, rilonacept, canakinumab) to dramatically reduce disease activity in a subset of patients with sJIA (see below)[4]. The dysregulated IL-1 production may be due to inflammasome activation (see Fig. 4.2)[5] and/or dysregulation of the alternative secretory pathway downstream of caspase-1 that exerts proinflammatory effects on endothelial cells and leukocytes.

At the onset and during flares of sJIA, vascular endothelial cells express leukocyte adhesion molecules, leading to a perivascular infiltrate of neutrophils and activated monocytes that secrete proinflammatory cytokines including tumor necrosis factor (TNF), IL-1, and IL-6[6]. Many clinical features of sJIA can be explained by the effects of these cytokines. For example, IL-1 stimulates granulopoiesis in the bone marrow and activates thermoregulatory functions of the hypothalamus to cause fever. The chronic overexpression of IL-6 observed in sJIA increases osteoclastogenesis while reducing osteoblast activity and it stimulates hepatocytes to produce acute phase reactants such as C-reactive protein[7]. The association of polymorphisms in the genes that encode IL-6 and MIF with increased susceptibility to sJIA and the successful treatment of sJIA with anti-IL6R antibodies provide further support for the role of IL-6.

Clinical Features

Daily high fevers (usually above 38.9°C) that typically occur in the late afternoon or early evening are characteristic of sJIA. The arthritis is frequently polyarticular, and the joints most commonly affected are the wrists, knees, ankles and hips, followed by the small joints of the hands. A subgroup of patients may develop destructive joint disease similar to that seen in RF-positive polyarticular arthritis (see Table 45.1).

CLASSIFICATION OF JUVENILE IDIOPATHIC ARTHRITIS	
Systemic onset (15%–20%) (Still disease)	**Features required for diagnosis** • High episodic fevers – daily for ≥2 weeks and documented to be quotidian for ≥3 days • At least one of the following: *evanescent eruption*, generalized lymphadenopathy, hepatomegaly and/or splenomegaly, serositis • Symmetric polyarticular arthritis > oligoarticular arthritis (erosive in 20%)* ***Other features*** • Leukocytosis with neutrophilia, anemia (often severe), thrombocytosis, elevated ESR, elevated ferritin and C-reactive protein levels • Occasionally myocarditis, pneumonitis, anterior uveitis (<1%), CNS involvement, macrophage activation syndrome (~10%); rarely amyloidosis or interstitial lung disease due to pulmonary alveolar proteinosis and/or endogenous lipoid pneumonia (PAP/ELP) • RF- and ANA-negative in >95% of patients; absence of IBD or acute anterior uveitis
RF-negative polyarticular arthritis (15%)	• 3–9 years of age • ≥5 joints in the first 6 months • Small joints of the hands & feet > knees, wrists, ankles; erosive arthritis (15%) • RF-negative; ANA-negative
RF-positive polyarticular arthritis (5%)	• 10–16 years of age • ≥5 joints in the first 6 months • Small joints of the hands & feet > knees, wrists, ankles; erosive arthritis (>50%) • *Rheumatoid nodules*, low-grade fever, mild anemia, weight loss • RF-positive (100%): ≥2 tests at least 3 months apart during first 6 months; ANA-positive (70%)
Oligo/pauciarticular arthritis (50%): • type I – majority • type II – minority	• ≤4 joints in the first 6 months† • Knees > ankles, wrists; often asymmetric • Type I: 1–8 years of age; uveitis 30%–50%; ANA-positive 60%; RF-negative • Type II: 9–16 years of age; HLA-B27; RF-negative; ANA-negative
Enthesitis-related arthritis (5%–10%)	• Arthritis *and* enthesitis - or - • Arthritis *or* enthesitis plus ≥2 of the following: sacroiliac joint tenderness/inflammatory lumbosacral pain, HLA-B27, family history of HLA-B27-associated disease in first- or second-degree relative, acute anterior uveitis, onset of arthritis in a boy after age 6 years
Psoriatic arthritis (~5%)	• Arthritis and *psoriasis* - or - • Arthritis and ≥2 of the following: dactylitis, *nail pitting, onycholysis*, family history of psoriasis in ≥1 first-degree relative • Other features: anterior uveitis, ANA-negative
Other arthritis	• Children with arthritis of unknown cause persisting ≥6 weeks that does not fulfill criteria for any other categories or fulfills criteria for more than one category

*Onset may be delayed for months to years.
†The **persistent** oligoarticular arthritis subtype does not affect more than 4 joints, whereas the **extended** oligoarticular arthritis subtype affects a cumulative total of ≥5 joints after the first 6 months of disease.

Table 45.1 Classification of juvenile idiopathic arthritis. The previous term was juvenile rheumatoid arthritis. Enthesitis is inflammation at the site of insertion of muscles. For all the types, diagnosis requires onset before 16 years of age and duration of arthritis for ≥6 weeks in at least one joint. Reactive arthritis (formerly Reiter syndrome) should be excluded. ANA, anti-nuclear antibody; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; RF, rheumatoid factor.

An exanthem is present in up to 90% of patients with the acute febrile presentation of sJIA, and it is often preceded by or accompanied by arthralgias. Although arthritis usually develops during the first few months of the disease course, in approximately one-quarter of patients the exanthem begins prior to the onset of arthritis, occasionally by several years. The eruption is typically transient, non-pruritic, and erythematous, and it coincides with fevers (Fig. 45.1A). There is a predilection for the axillae and waist, and linear lesions secondary to the Koebner phenomenon are often observed. Other less common cutaneous features include persistent plaques, which also may be linear (Fig. 45.1B,C), and periorbital erythematous edema[8]. Rheumatoid nodule-like lesions that favor extensor surfaces have been described in the setting of methotrexate therapy for sJIA[9]. Additional systemic features are outlined in Table 45.1. Although there are no laboratory findings specific for sJIA, leukocytosis, granulocytosis, thrombocytosis, elevated hepatic enzymes, an elevated ESR, and a polyclonal gammopathy are commonly observed; ANA and RF are rarely present. Serum ferritin levels are elevated.

Up to 10% of children may develop a serious and potentially lethal complication, the macrophage activation syndrome (MAS), characterized by fever, cytopenias, liver dysfunction, coagulopathy, hypofibrinogenemia, hypertriglyceridemia, and very high serum levels of ferritin (see Table 91.1). Increased serum IL-18 levels and depressed NK cell cytolytic function are also observed in patients with sJIA who develop MAS. Another serious, albeit rare, complication is severe interstitial lung disease due to pulmonary alveolar proteinosis and/or endogenous lipoid pneumonia (PAP/ELP). Acute clubbing accompanied by digital erythema may be an early sign. Lymphopenia and elevated serum levels of ferritin are seen in children with PAP/ELP as is an increased incidence of drug hypersensitivity to IL-1 and IL-6 inhibitors[10].

Pathology

The evanescent exanthem is characterized by a perivascular and interstitial neutrophil-dominant mixed infiltrate, a reaction pattern also seen in autoinflammatory diseases (see below) and referred to as a "neutrophilic urticarial dermatosis"[11]. A variable number of dyskeratotic keratinocytes, located primarily in the upper epidermal layers, is also a typical finding, especially in linear and/or persistent lesions.



Fig. 45.1 Systemic-onset juvenile idiopathic arthritis (Still disease). **A** Evanescent pink papules and figurate plaques in a child. **B, C** Persistent linear plaques on the upper back that are pink-brown in lightly pigmented skin versus violet-brown in more darkly pigmented skin. *B,C, Courtesy Julie V. Schaffer, MD.*

Differential Diagnosis

The differential diagnosis of a transient exanthem associated with fever and arthritis/arthralgias includes rheumatic fever, hypocomplementemic urticarial vasculitis, serum sickness-like reaction, and hereditary periodic fever syndromes (Table 45.2). The characteristic cutaneous findings in rheumatic fever are erythema marginatum (see Ch. 19) and urticarial lesions; rheumatic fever nodules are unusual. Patients with urticarial vasculitis may have arthralgias and fever; however, the urticarial lesions persist >24 hours and often resolve with purpura or postinflammatory hyperpigmentation. Histologic examination of recent-onset lesions demonstrates leukocytoclastic vasculitis.

Additional disorders to consider include other autoimmune connective tissue diseases; leukemia (which may present with fevers and musculoskeletal complaints prior to the development of diagnostic abnormalities in the peripheral blood) as well as other malignancies (e.g. lymphoma); and infections such as parvovirus B19, malaria, chronic meningococcemia, and rat bite fever. In children with known cystic fibrosis, relapsing-remitting episodes of arthralgias plus evanescent, slightly pruritic, salmon-pink macules have been described, typically without fever or elevated inflammation markers (cystic fibrosis-associated episodic arthritis)[12].

Treatment

The course and prognosis of sJIA is variable. In ~40%–50% of patients, the arthritis resolves completely. However, approximately one-half of the children have a chronic course that includes persistent arthritis and systemic complications such as macrophage activation syndrome (see above), hepatitis, pericarditis, and rarely amyloidosis or PAP/ELP (see Table 45.1). Patients with symptoms that persist for longer than 6 months carry a worse prognosis.

Mild articular or extra-articular disease can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs). In the past, moderate or severe disease was often treated with systemic corticosteroids with or without adjuvant drugs such as methotrexate; however immunomodulators that target IL-1/IL-1R (e.g. anakinra, canakinumab) or IL-6R (e.g. tocilizumab) are increasingly employed as first-line therapy. This is due to superior effectiveness and more favorable side effect profiles, especially if used early during the course of the disease[13–18]. Inhibitors of TNF are less effective in patients with sJIA than in those with other

HEREDITARY PERIODIC FEVER SYNDROMES						
				Cryopyrin-associated periodic syndromes (CAPS)		
	FMF	HIDS	TRAPS*	MWS	FCAS† (1 and 2)	NOMID (CINCA)
Ethnicity	Sephardic Jewish, Arab, Turkish, Italian, Armenian	Predominantly Dutch, northern European	Any ethnic group	Any ethnic group	Any ethnic group	Any ethnic group
Inheritance	AR	AR	AD	AD	AD	AD
Gene	*MEFV*	*MVK*‡	*TNFRSF1A*	*NLRP3 (CIAS1)*	*NLRP3 (CIAS1); NLRP12*	*NLRP3 (CIAS1)*
Chromosome	16p13.3	12q24	12p13	1q44	1q44; 19q13	1q44
Protein	Pyrin	Mevalonate kinase	TNF receptor-1A	Cryopyrin	Cryopyrin; monarch-1	Cryopyrin
Attack length	1–3 days	3–7 days	Often >7 days	1–2 days	Minutes–3 days	Continuous + flares
Mucocutaneous lesions	Erysipeloid erythema and edema	Erythematous macules and edematous papules, which may become purpuric; occasional oral and vaginal ulcers	Erythematous patches and edematous plaques (often annular or serpiginous); later ecchymotic in appearance; rarely oral ulcers	Urticarial papules and plaques	Cold-induced urticarial papules and plaques	Urticarial papules and plaques; occasional oral ulcers

Table 45.2 Hereditary periodic fever syndromes.

HEREDITARY PERIODIC FEVER SYNDROMES						
				Cryopyrin-associated periodic syndromes (CAPS)		
	FMF	HIDS	TRAPS*	MWS	FCAS† (1 and 2)	NOMID (CINCA)
Distribution of skin lesions	Favor lower leg, foot	Widespread on face, trunk and extremities	Migrate distally on an extremity with underlying myalgia; may be more widespread	Widespread on face, trunk and extremities	Extremities > trunk, face	Widespread on face, trunk and extremities
Abdominal pain and serositis	Peritonitis > pleuritis > pericarditis	Abdominal pain, but rarely serositis	Peritonitis > pleuritis, pericarditis	Abdominal pain, but rarely serositis	Rare	Rare
Musculoskeletal findings	Monoarthritis > exercise-induced myalgia	Arthralgia > oligoarticular arthritis > myalgia	Migratory myalgia > arthralgia > monoarthritis	Myalgia ("lancinating limb pain"), arthralgia > large-joint oligoarticular arthritis	Arthralgia > myalgia	Epiphyseal and patellar overgrowth, arthritis, deforming arthropathy
Ocular findings	Uncommon	Uncommon	Periorbital edema, conjunctivitis, rarely uveitis	Conjunctivitis, episcleritis, optic disc edema	Conjunctivitis	Conjunctivitis, uveitis, optic disc edema, blindness
Neurologic findings	Rarely aseptic meningitis	Headache	Headache	Sensorineural hearing loss; headache	Headache	Sensorineural hearing loss; aseptic meningitis, seizures
Other clinical findings	Acute scrotal swelling; splenomegaly	Cervical LAN, HSM	Scrotal pain; splenomegaly, occasional LAN			LAN, HSM; dysmorphic facies – frontal bossing, protruding eyes
Amyloidosis	Most common in M694V homozygotes	Rare	~15% of cases	~25% of cases	Uncommon	Late complication
Dermal infiltrate in typical skin lesions	Neutrophils	Neutrophils and/or lymphocytes; mild vasculitis common	Lymphocytes, monocytes and a few neutrophils	Neutrophils and/or lymphocytes (sparse)	Neutrophils (perivascular)	Neutrophils (perivascular + periadnexal)
Cutaneous vasculitis	LCV/HSP (5%–10%), PAN (~1%)	LCV/HSP	Lymphocytic small vessel (rare)			
Laboratory abnormalities¶	Low C5a inhibitor in serosal fluids	High serum IgD§ (>100 IU/ml) and IgA1; mevalonate in urine during attacks; low lymphocyte mevalonate kinase	Low serum soluble TNF receptor-1 (<1 ng/ml between attacks)			
Treatment (Rx)	• Colchicine prophylaxis • If colchicine-resistant, IL-1/IL-1R antagonists: **canakinumab, anakinra, rilonacept** • 3rd line: TNF inhibitors, thalidomide, or tocilizumab	• For acute attacks, NSAIDs or corticosteroids, with anakinra as 2nd-line option • Canakinumab if prophylaxis required • 3rd line: TNF inhibitors (e.g. etanercept) or tocilizumab	• For acute attacks, corticosteroids • If frequent/severe recurrences, IL-1/IL-1R antagonists (see **FMF Rx**) • If failure of IL-1 blockade, etanercept (but *not* other TNF inhibitors) or tocilizumab	• Corticosteroids • IL-1/IL-1R antagonists (see **FMF Rx**)	• IL-1/IL-1R antagonists (see **FMF Rx**)	• IL-1/IL-1R antagonists (see **FMF Rx**)

*Includes familial Hibernian fever.
†Also referred to as familial cold urticaria.
‡Allelic with mevalonic aciduria, which is characterized by dysmorphology, psychomotor retardation, and progressive cerebellar ataxia as well as periodic fevers and other features of HIDS.
¶Genetic analysis can be performed to confirm the diagnosis.
§IgD levels are occasionally normal; elevated IgD may also be observed in FMF and TRAPS.

Table 45.2 Hereditary periodic fever syndromes. Patients with PLAID (see Table 45.7) can have findings that overlap with those of FCAS. AD, autosomal dominant; AR, autosomal recessive; CINCA, chronic infantile neurologic, cutaneous and articular syndrome; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D with periodic fever syndrome; HSM, hepatosplenomegaly; HSP, Henoch-Schönlein purpura; LAN, lymphadenopathy; LCV, leukocytoclastic vasculitis; MWS, Muckle–Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; NSAIDs, nonsteroidal anti-inflammatory drugs; PAN, polyarteritis nodosa; TNF, tumor necrosis factor; TRAPS, TNF receptor-associated periodic syndrome. *Courtesy Julie V. Schaffer, MD.*

types of JIA but they may play a role as a second-line therapy, especially for chronic polyarthritis or in combination with other steroid-sparing or immunomodulating agents (e.g. methotrexate, abatacept, azathioprine, leflunomide)[13]. Thalidomide is also a therapeutic option for children with sJIA if access to first-line therapies is limited. Hematopoietic stem cell transplantation has been successfully performed in children who have failed to respond to combinations of medications[13].

ADULT-ONSET STILL DISEASE

Synonyms: ■ Still disease in the adult ■ Adult Still disease

Key features

- A characteristic feature is recurrent episodes of high spiking fevers that often occur in the late afternoon
- An asymptomatic macular exanthem accompanies the fevers, is salmon-pink in color, and frequently demonstrates the Koebner phenomenon
- Arthritis with subsequent carpal ankylosis is a distinctive feature

Introduction

Adult-onset Still disease can be a severe debilitating systemic illness that is often difficult to diagnose. The vast majority of these patients have an exanthem, and this can be the most distinctive sign of the disorder.

Epidemiology

Adult-onset Still disease primarily affects young adults, with an onset before the age of 30 years in the majority of patients. Rarely, it occurs in individuals over the age of 60 years. Women are affected slightly more often than men.

Pathogenesis

Although the etiology of adult-onset Still disease is unknown, the underlying pathogenesis likely overlaps with that of sJIA (see above). The disease has been linked with a number of HLA antigens, suggesting a genetic component[19]; nonetheless, familial cases are uncommon. It has been hypothesized to occur in a susceptible individual as a reactive condition triggered by a variety of infectious agents, including a wide range of viruses, from enteroviruses to herpesviruses, as well as bacteria, in particular those that cause pneumonia and enterocolitis[19]. To date, however, no infectious agent has been implicated consistently.

Serum levels of IL-2, IL-6, IL-18, TNF, and IFN-γ are elevated in patients with the disease[19].

Clinical Features

The onset of the disease is frequently heralded by a sore throat and constitutional symptoms including arthralgias and myalgias. Fever is a prominent feature; it is usually above 39°C and has a spiking pattern, often occurring in the late afternoon or early evening and resolving within several hours. The skin eruption is asymptomatic and transient, occurring in association with the fever spikes. It is most often macular with a characteristic salmon-pink color (Fig. 45.2A), favors sites of pressure, and can exhibit the Koebner phenomenon. Although the trunk is most commonly involved, lesions can appear on the extremities, including the palms and soles.

Violaceous to reddish brown, scaly, persistent papules and plaques can also occur, and were observed in more than half of patients with adult-onset Still disease in a Taiwanese series[20]. Persistent erythematous eyelid edema and flagellate erythema are rare manifestations[21], both of which can mimic dermatomyositis. Persistent lesions, also categorized as "atypical", have been associated with a worse prognosis[22].



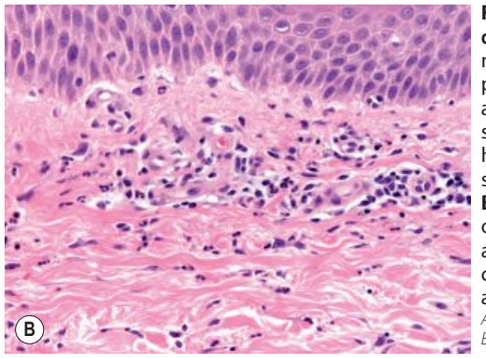


Fig. 45.2 Adult-onset Still disease. A Multiple pink macules and urticarial papules that were accompanied by a fever spike. The patient also had markedly elevated serum ferritin levels. **B** Histologic features of a mixed perivascular and interstitial infiltrate composed of neutrophils and lymphocytes. *A, Courtesy Diane Davidson, MD. B, Courtesy Lorenzo Cerroni, MD.*

Depending upon the series, arthritis occurs in 65%–100% of patients and most often affects the knees, wrists, and ankles, although other joints may also be involved. The pattern is usually symmetric, and most patients ultimately develop joint pain associated with the fever spikes. A distinctive feature of the arthritis of adult-onset Still disease is carpal ankylosis, which results in minimal pain but a limited range of motion in the carpal joints. Similar ankylosis may occur in the proximal and distal interphalangeal joints as well as the cervical spine. The metacarpophalangeal (MCP) joints are usually spared.

There may be hepatomegaly, but splenomegaly is less common. Involvement of the lungs (pleuritis, pleural effusions, pulmonary fibrosis, pulmonary arterial hypertension), heart (pericarditis, myocarditis, cardiac tamponade), and kidneys (nephritis) is rare.

Laboratory findings in adult-onset Still disease are similar to those of sJIA and include elevations in the C-reactive protein level, ESR, and platelet count. Leukocytosis and anemia are common, as are abnormalities in liver function tests. There are often significant elevations in serum ferritin levels, sometimes >4000 mg/ml, and ferritin levels may correlate with disease activity[19]; a low circulating level of glycosylated ferritin (fraction <20%) is characteristic. ANA and RF are either negative or, if present, low titer.

Pathology

Histopathologic changes of evanescent lesions are indistinguishable from those of the juvenile form of the disease (see above) and include an interstitial and perivascular neutrophil-dominant mixed infiltrate (Fig. 45.2B)[11]. Epidermal involvement is frequently seen in persistent lesions, including acanthosis, spongiosis, and/or necrotic keratinocytes within the spinous layer.

Differential Diagnosis

Adult-onset Still disease should always be considered in an adult with fever of unknown origin (defined as fever >101°F [38.3°C]

on several occasions over a period of at least 3 weeks or uncertain diagnosis after 1 week of hospitalization). The differential diagnosis is similar to that of sJIA (see above). Additionally, Schnitzler syndrome should be considered in an adult patient with recurrent fevers, arthralgia, and an urticarial eruption (see Ch. 18). In addition to non-pruritic urticaria, patients with Schnitzler syndrome have recurrent fevers, bone pain (lower extremity, iliac, and vertebral due to hyperostosis), and a monoclonal IgM gammopathy. Angioedema is observed in about 15% of these patients and lymphoplasmacytic malignancies in 10%–15%[23]. Histopathologic features are similar to those of adult-onset Still disease, i.e. a neutrophilic urticarial dermatosis[11], but the neutrophilic infiltrate may be more dense.

In patients with eyelid edema and/or persistent and linear lesions, dermatomyositis may be considered. Additional overlap occurs when there is involvement of the dorsal hands and face. Myositis, dermatomyositis-specific autoantibodies, and histopathologic features (e.g. interface dermatitis with vacuolar degeneration of the basal keratinocytes) are findings that point to the diagnosis of dermatomyositis.

Treatment

Although some patients respond to high-dose aspirin or NSAIDs, the majority require oral corticosteroids (e.g. 40–60 mg prednisone daily) to control acute systemic features. When corticosteroids cannot be tapered because of persistent arthritis, methotrexate is the most commonly employed second-line therapy. As in sJIA, biologic agents that inhibit IL-1/IL-1R (e.g. canakinumab) or IL-6R (e.g. tocilizumab) are increasingly utilized as first-line therapy for moderate to severe disease characterized by systemic inflammation without predominant joint disease[24,25]. A therapeutic response to TNF inhibitors has also been reported, especially in those patients with severe chronic polyarticular disease. Rituximab has been used effectively for refractory disease[26].

RELAPSING POLYCHONDRITIS

Synonyms: ■ Atrophic polychondritis ■ Systemic chondromalacia

Key features

- A prominent clinical feature is erythema, swelling and pain of the cartilaginous portion of the ear, followed by destruction of the cartilage
- Additional findings include nasal chondritis, which may result in a saddle nose deformity, as well as arthritis of the joints of the central chest
- The most serious complications result from ocular, renal, and respiratory tract involvement; some of the patients develop myelodysplastic syndrome

Introduction

Relapsing polychondritis is an uncommon inflammatory disorder with a suspected autoimmune origin that primarily affects cartilaginous structures. The diagnosis is usually established based upon the presence of: (1) histologically confirmed chondritis in *two* of the following three sites: auricular, nasal, or laryngotracheal cartilage; or (2) chondritis in *one* of the aforementioned sites plus at least *two* other features including: ocular inflammation, vestibular dysfunction, hearing loss, and seronegative inflammatory arthritis. Relapsing polychondritis has been associated with other autoimmune disorders (25%–30% of patients) as well as myelodysplastic syndromes, with the latter occurring primarily in the context of VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome (see Ch. 53). Dermatologic manifestations may be the initial presenting sign and early diagnosis and treatment can prevent later complications, e.g. ascending aortitis, glomerulonephritis.

History

The disease was first described in 1923 by Jaksch-Wartenhorst and was called "polychondropathia". It was later renamed "relapsing polychondritis" due to its episodic nature.

Epidemiology

Relapsing polychondritis is most common in the White population, but has been reported in other races. In 80% of cases, the onset is between the ages of 20 and 60 years. Men and women are equally affected.

Pathogenesis

Although the etiology of relapsing polychondritis is unknown, the pathogenesis appears to involve an immunologic reaction, both cellular and antibody-mediated, against various extracellular matrix components of cartilage[27]. Circulating antibodies against type II collagen are present in fewer than half of affected individuals, and antibodies against types IX and XI collagen or matrilin-1 have also been described[27]; however, their clinical usefulness is unclear. That said, transmission of relapsing polychondritis to a neonate from an affected mother has been reported (with subsequent recovery of the infant), lending support to an antibody-mediated pathogenesis. Additionally, there may be a positive association with HLA-DR4.

Clinical Features

The most prominent clinical feature is erythema, swelling, and pain of the cartilaginous portion of the *auricle*, sparing the earlobe (Fig. 45.3). Symptoms can persist for several days to weeks and may encroach on the external auditory meatus, compromising hearing. Chronic inflammation leads to destruction of the cartilage, leaving the ear unsupported and scarred. During the course of the disease, 90% of patients will develop auricular involvement, and in at least 25% it is a presenting sign.

Nasal chondritis eventually develops in up to 70% of patients and may result in a saddle nose deformity. Symptoms include pain, stuffiness, crusting, rhinorrhea, epistaxis, and compromise of olfaction. Nasal chondritis is typically less recurrent than the auricular chondritis, and the saddle nose deformity is more common in men[28].

Involvement of the cartilage of the *respiratory tract* (larynx, trachea, bronchi) and/or *costochondral joints* occurs in ~50% of patients and can be the most serious complication. Signs and symptoms include



Fig. 45.3 Relapsing polychondritis. Erythema and swelling of the ear with sparing of the earlobe. *Courtesy Kalman Watsky, MD.*

cough, hoarseness, choking, dyspnea, wheezing, or tenderness to palpation of the anterior neck in sites overlying the larynx or trachea. Complications include airway obstruction or collapse, flail chest, and secondary pulmonary infections.

Arthritis is common (50%–80% of patients) and it is the presenting symptom in one-third of patients. An episodic, migratory, asymmetric, non-erosive oligo- or polyarticular arthritis can affect any joint, although the knees and MCP and proximal interphalangeal joints are those most commonly affected. There may also be involvement of the sternoclavicular and sternomanubrial joints. *Ocular* inflammation develops in ~65% of patients. It can involve virtually any component of the eye, leading to conjunctivitis, scleritis, corneal ulcerations, uveitis, or optic neuritis[28].

A variety of reactive *cutaneous* lesions are seen in patients with relapsing polychondritis[29], including aphthae, small vessel vasculitis, annular urticarial plaques, Sweet syndrome (including the lymphocytic variant), erythema elevatum diutinum, livedo reticularis, superficial thrombophlebitis, and erythema nodosum. Although none is pathognomonic and some may be coincidental or due to a coexisting disease, the presence of Sweet syndrome or vasculitis, especially in an older man, points to the diagnosis of VEXAS syndrome. In addition to cutaneous small vessel vasculitis, the presence of aphthae have been reported to increase the likelihood of an associated myelodysplastic syndrome (see Ch. 24). Also an overlap between relapsing polychondritis and Behçet disease, termed *m*outh *a*nd *g*enital ulcers and *i*nflamed *c*artilage (MAGIC) syndrome, has been reported[30].

Less common systemic features include *audiovestibular* damage, *cardiovascular* disease (aortitis, valvular dysfunction, pericarditis, conduction system abnormalities, myocarditis), *renal* dysfunction (glomerulonephritis, glomerulosclerosis, tubulointerstitial disease), *neurologic* sequelae (cranial nerve palsies, vasculitis of the central or peripheral nervous system), and deep aseptic abscesses that are responsive to corticosteroids.

Pathology

Histologically, there is breakdown of the normal lacunar structure of the cartilage, with neutrophilic infiltrates initially, followed by lymphoplasmacytic infiltrates. In late stages, there is replacement of cartilage by granulation tissue and fibrosis.

Differential Diagnosis

During the early inflammatory phase, the erythema and pain may be misdiagnosed as erysipelas or cellulitis. Red ear syndrome is a rare disorder in which there are recurrent episodes of unilateral or bilateral erythema and pain of the ears. The attacks can last from seconds to hours and possible triggers include rubbing, heat, and cold; associated disorders include migraines, neuralgias, and cervical spine disease. In Europe and Asia, borrelial lymphocytoma involving the helix may also be considered, but this location is less common than the earlobe and there is no accompanying pain. Infectious or traumatic chondritis, granulomatosis with polyangiitis, small vessel vasculitis, and congenital syphilis may mimic the cartilage destruction seen in relapsing polychondritis (Table 45.3).

DIFFERENTIAL DIAGNOSIS OF NASAL DEFORMITY OR DESTRUCTION
Neoplastic disorders
Extranodal natural killer/T cell lymphoma, nasal-type*
Squamous cell and basal cell carcinomas
Olfactory neuroblastoma, salivary gland tumors
Rhabdomyosarcoma, chondrosarcoma, other sarcomas
Inflammatory disorders
Relapsing polychondritis, including VEXAS syndrome
Granulomatosis with polyangiitis
Sarcoidosis
SAVI (STING [*st*imulator of *in*terferon *g*enes]-associated vasculopathy with onset in infancy) (see Table 45.7)
PLAID (PLCG2-associated antibody deficiency and immune dysregulation) (see Table 45.7)
Infectious disorders
Bacterial
Rhinoscleroma
Glanders
Noma
Syphilis (late congenital and tertiary)
Yaws (gangosa)
Mycobacterial
Leprosy
Tuberculosis (lupus vulgaris)
Fungal
Paracoccidioidomycosis > other dimorphic fungal infections
Zygomycosis (mucormycosis and entomophthoramycosis)
Aspergillosis
Parasitic
Mucocutaneous leishmaniasis (espundia)
Amebiasis due to free-living organisms†
Rhinosporidiosis‡
Other etiologies
Substance abuse (e.g. cocaine)
Nasal myiasis
Factitious/traumatic, including trigeminal trophic syndrome
*Previously referred to as angiocentric T cell lymphoma and lethal midline granuloma.
†Include *Acanthamoeba* spp. and *Balamuthia mandrillaris*; granulomatous centrofacial skin lesions may lead to fatal amebic encephalitis.
‡Characterized by nasal polyps; recent molecular studies have classified the causative organism, *Rhinosporidium seeberi*, as an aquatic protistan parasite, phylogenetically at the animal–fungus boundary.

Table 45.3 Differential diagnosis of nasal deformity or destruction. VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic[31] (see Ch. 53).

Treatment

Although relapsing polychondritis has traditionally been associated with significant morbidity and mortality, it is a treatable disease, with a survival rate of ~95% at 8 years. A comprehensive evaluation for systemic involvement, including a PET scan, should be performed prior to initiation of therapy, as systemic disease requires more aggressive treatment. The most common causes of death are pneumonia, systemic vasculitis, airway collapse, and renal failure[28]. Patients who lack tracheobronchial involvement or associated myelodysplastic syndrome have a more favorable prognosis[32].

The initial treatment is with prednisone (0.5–1 mg/kg/day; higher range doses are given if there is visceral involvement), which improves acute flares and decreases the number and severity of recurrences. NSAIDs and colchicine may decrease fever, auricular chondritis, and arthralgias; dapsone (50–150 mg/day) can also be used. Hydroxychloroquine and immunosuppressive agents (e.g. methotrexate, cyclosporine, azathioprine, cyclophosphamide, mycophenolate mofetil) have been tried alone or in conjunction with corticosteroids, with variable responses. More recently, successful results were reported with anti-IL-6R antibodies (tocilizumab), TNF inhibitors (adalimumab, infliximab), and rituximab, while abatacept and the IL-1R antagonist anakinra were less effective[33]. Tocilizumab appears to be beneficial in patients with aortic involvement[34,35]. Surgery is sometimes performed to repair damage to cartilaginous structures after the inflammation has been controlled. Patients with myelodysplastic syndrome, often in the context of VEXAS syndrome, can be particularly treatment-resistant to therapies other than moderate- to high-dose corticosteroids[33].

SJÖGREN SYNDROME

Synonym: ■ Sicca syndrome

Key features

- This autoimmune disorder primarily affects secretory glands
- The most common features are xerostomia, xerophthalmia, and arthritis
- Cutaneous manifestations include xerosis, petechiae, purpura (palpable and non-palpable), urticarial vasculitis, and annular erythema
- Serious complications include B cell lymphomas, in particular extranodal marginal zone lymphomas of the MALT (mucosa-associated lymphoid tissue) type, peripheral neuropathy, interstitial pulmonary fibrosis, and systemic vasculitis
- Patients often have an additional autoimmune disorder, in particular rheumatoid arthritis and lupus erythematosus
- Factors associated with a poorer prognosis include vasculitis, hypocomplementemia, cryoglobulinemia, and/or parotid enlargement

Introduction

Sjögren syndrome (SjS) is an autoimmune disorder that affects secretory glands, in particular the lacrimal and salivary glands. In addition to exocrine gland dysfunction, patients may develop a range of systemic manifestations due to autoimmune-mediated insults to multiple organ systems. This disease can be difficult to diagnose due to its insidious onset and initially nonspecific symptomatology. Mucocutaneous manifestations are prominent and may be the initial presenting signs. SjS may exist as a primary disorder or in association with other autoimmune diseases (secondary SjS), including rheumatoid arthritis, systemic lupus erythematosus (LE), and systemic sclerosis.

History

The first description of SjS was by Hadden in 1888. However, it was not until 1933 that Henrik Sjögren described the triad of keratoconjunctivitis sicca, xerostomia, and arthritis. Over the past several decades, the diagnostic criteria for SjS have been debated and revised, and currently the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2016 Classification Criteria for Primary Sjögren's Syndrome are most often employed (Table 45.4)[36].

Epidemiology

Although SjS most commonly presents during the fourth and fifth decades, pediatric cases have been reported. The female:male ratio is 9:1 and men with this syndrome tend to have a less aggressive disease course with fewer extraglandular manifestations. SjS is one of the most common autoimmune disorders, affecting ~0.3%–0.6% of the total population[41]. The overall mortality rate in primary SjS is comparable to that in the normal population[41].

Pathogenesis

As in other autoimmune diseases, environmental factors likely trigger inflammatory events in a genetically susceptible host, resulting in the autoimmune phenomena characteristic of the disease. In SjS, it has been proposed that viral infection of the salivary glands (e.g. by EBV, HTLV-1, HCV) may stimulate the innate immune system, leading to autoimmune destruction of glandular cells due to molecular mimicry[42,43]. Upregulation of type I and II interferon gene expression, initiated by the viral infection and perpetuated by immune complexes such as anti-SSA/Ro or anti-SSB/La antibodies complexed with hYRNA, promotes activation of the adaptive immune system. The latter includes B cell activating factor (BAFF)-mediated B cell activation and proliferation as well as T cells with Th1 and Th17 phenotypes playing a leading role in glandular damage[44].

Patients with SjS frequently have hypergammaglobulinemia and autoantibodies that recognize SSA/Ro and/or SSB/La; presence of these autoantibodies increases the risk of developing subacute cutaneous lupus-like drug reactions and cutaneous small vessel vasculitis, both in patients with SjS and in those with systemic LE. Chronic antigen-driven B cell stimulation and clonal expansion may result in lymphomagenesis with development of marginal zone B cell lymphoma in salivary or lacrimal glands.

AMERICAN COLLEGE OF RHEUMATOLOGY (ACR)/EUROPEAN LEAGUE AGAINST RHEUMATISM (EULAR) 2016 CLASSIFICATION CRITERIA FOR PRIMARY SJÖGREN'S SYNDROME (SjS)

The classification of primary SjS applies to any individual who meets the inclusion criteria*, does not have any of the conditions listed as exclusion criteria†, and has a score of ≥4 when the weights from the five criteria items below are summed

Criterion	Weight/score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm²‡	3
Anti-SSA/Ro-positive	3
Ocular staining score ≥5 (or van Bijsterveld score ≥4) in at least one eye¶,§	1
Schirmer's test ≤5 mm/5 min in at least one eye¶	1
Unstimulated whole saliva flow rate ≤0.1 mL/min¶,¶¶	1

*Inclusion criteria apply to any patient with at least one symptom of ocular or oral dryness, defined as a positive response to at least 1 of the following questions: (1) Have you had daily, persistent, troublesome dry eyes for more than 3 months? (2) Do you have a recurrent sensation of sand or gravel in the eyes? (3) Do you use tear substitutes more than 3 times a day? (4) Have you had a daily feeling of dry mouth for more than 3 months? (5) Do you frequently drink liquids to aid in swallowing dry food? *or* in whom there is suspicion of SjS from the EULAR SjS Disease Activity Questionnaire (at least 1 domain with a positive item).
†Exclusion criteria include prior diagnosis of any of the following conditions: (1) history of head and neck radiation treatment; (2) active hepatitis C viral infection (with confirmation by PCR); (3) AIDS; (4) sarcoidosis; (5) amyloidosis; (6) GVHD; (7) IgG4-related disease.
‡Per Daniels et al. protocol[37] and performed by an experienced pathologist.
¶Patients taking anticholinergic drugs should be evaluated after a sufficient interval without these medications for tests to be valid.
§Per Witcher et al. scoring system[38] and van Bijsterveld scoring system[39].
¶¶Per Navazesh and Kumar protocol[40].

Table 45.4 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2016 classification criteria for primary Sjögren's syndrome. GVHD, graft-versus-host disease. *From Shiboski CH, Shiboski SC, Seror R, et al; International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis. 2017;76:9–16.*

Clinical Features

The most prominent feature of SjS is xerosis of the mucous membranes, particularly of the eyes, mouth, and vagina. Keratoconjunctivitis sicca occurs as a result of destruction of the lacrimal gland, and patients may experience ocular dryness, a foreign body sensation, pain, or photophobia. Objective tests to verify decreased tear production (e.g. Schirmer test) and to assess the integrity of the corneal surface (e.g. lissamine green stain, fluorescein stain, Rose Bengal dye) should be performed by an ophthalmologist (see Table 45.4)[42]. In the Schirmer test, a piece of Whatman paper wick is folded over the lower eyelid for 5 minutes. Tear film migration that is ≤5 mm is indicative of lacrimal gland dysfunction. Complications of xerophthalmia include keratitis, corneal thinning and ulceration, and recurrent infections[42].

Xerostomia due to destruction of the major and minor salivary glands may present as dryness, soreness, or burning of the mouth and lips. Patients may have difficulty swallowing or require frequent ingestion of fluids during conversations. On examination, the infralingual salivary pool may be absent and the saliva cloudy and stringy. Although the major salivary glands (parotid and submandibular) may become transiently enlarged (~20% of patients), persistent swelling of these salivary glands or lymphadenopathy should prompt an evaluation for lymphoma. Of note, patients with SjS have an incidence rate of lymphoma that is nearly 20× that of the general population[45]; these B cell lymphomas are often extranodal and can originate in salivary as well as lacrimal glands.

Xerostomia may be assessed functionally by salivary gland scintigraphy, sialometry, or parotid sialography, but these tests are not commonly

employed. On the other hand, salivary gland biopsy is a readily available procedure and represents an important component of the diagnosis of SjS (see Table 45.4). Perlèche or thrush can result from candidal overgrowth and should be suspected when patients report a sudden increase in pain. Dental caries are common, particularly along the gingival margin, and scrupulous dental hygiene with frequent dental examinations is crucial. Because saliva has an elevated pH that neutralizes gastric acid, patients with SjS may experience more severe gastroesophageal reflux disease or gastrotracheal reflux (which can mimic upper respiratory tract infections), and aggressive reflux treatment is warranted[42].

Vaginal xerosis is common, and since many patients are perimenopausal or postmenopausal, it may be multifactorial. Symptoms include dryness, burning, and/or dyspareunia. Candidal and bacterial overgrowth are common complications.

The most common skin finding is xerosis, usually presenting as pruritus. Other cutaneous manifestations include palpable and non-palpable purpura (Fig. 45.4), urticarial vasculitis, erythema nodosum, nodular amyloidosis, and Sweet syndrome. Lesions of annular erythema, clinically reminiscent of subacute cutaneous LE or LE tumidus, have been reported primarily in Japanese patients with SjS. Whether or not these patients have an LE/SjS overlap is a matter of debate. Raynaud phenomenon has been reported in 30% of patients with primary SjS and may precede sicca symptoms by years.

Vasculitis is the most important cutaneous finding in SjS and is associated with an increased risk of morbidity and mortality[46]. Patients with cutaneous small vessel vasculitis may present with palpable purpura or with urticarial lesions and may have hypo- or normocomplementemia (see Ch. 24). Some patients develop lesions of pigmented purpura (capillaritis) or macular hemorrhage, which can be identical to the lesions seen in patients with hypergammaglobulinemic purpura of Waldenström (see Ch. 22). Of note, many of the patients with the latter disorder have evidence of autoimmune connective tissue disease, including SjS. The presence of purpura should prompt an evaluation for cryoglobulinemia. Patients found to have vasculitis, cryoglobulinemia, and/or hypocomplementemia have an increased mortality rate and an increased risk of developing B cell lymphomas[45].

Extraglandular and extracutaneous involvement may present with a diverse array of symptoms due to involvement of a variety of tissues including the lungs (interstitial pneumonitis, often subclinical), kidneys (interstitial nephritis, tubular dysfunction), bone marrow, and peripheral and central nervous systems (peripheral neuropathy, short-term memory loss, depression, immune-mediated hearing loss, multiple sclerosis-like presentation)[42]. Arthritis is a common finding; it is usually polyarticular, non-erosive, chronic and progressive, and it can be asymmetric. The most frequently involved joints are the knees and ankles. This should be distinguished from fibromyalgia, which may develop in up to 40% of patients with SjS.

As discussed above, the risk of developing B cell lymphomas is increased in patients with SjS[45]. The lymphomas are often extranodal in origin (e.g. salivary glands, lacrimal glands) and usually marginal zone lymphomas of the MALT type[47].



Fig. 45.4 Cutaneous small vessel vasculitis in a patient with Sjögren syndrome. Patients can also develop lesions of pigmented purpura (capillaritis).
Courtesy Penn State Department of Dermatology.

Laboratory Findings

Primary SjS is associated with anti-SSA/Ro (~60%–80%), and anti-SSB/La (~40%–60%) autoantibodies. Patients with secondary SjS may have additional autoantibodies, depending upon the specific autoimmune connective tissue disease (see Ch. 40).

Other laboratory abnormalities often observed in patients with SjS include an elevated ESR, hypergammaglobulinemia, and a positive RF.

Pathology

In order to establish the diagnosis of SjS, a biopsy of the minor salivary glands is often performed. The presence of one or more foci of inflammatory cells (50 or more lymphocytes) in 4 mm^2 of salivary gland tissue fulfills one of the classification criteria for SjS (see Table 45.4). A mixture of B and T cells (with a normal CD4:CD8 ratio) is usually seen.

The typical histopathologic features of pigmented purpuric eruptions, cutaneous small vessel vasculitis, cryoglobulinemic vasculitis, and urticarial vasculitis are seen in the vasculopathies associated with SjS; however, none of the histologic findings is specific for SjS.

Differential Diagnosis

Sicca symptoms are common in the elderly in part due to age-related atrophy of secretory glands. Xerostomia is a common side effect of drugs with anticholinergic properties and it may also result from previous irradiation, salivary gland stones, and chronic viral infections. Xerophthalmia can be a symptom of ocular rosacea (see Ch. 37), infiltration of the lacrimal glands (e.g. sarcoidosis, amyloidosis), irradiation, and hypovitaminosis A. It may reflect impaired blinking (e.g. Parkinson disease) or herald the onset of mucous membrane (cicatricial) pemphigoid. In addition, patients with chronic GVHD can have both xerophthalmia and xerostomia.

Early in the disease course, it may be difficult to distinguish SjS from other autoimmune connective tissue diseases. Complaints such as arthralgias and myalgias are often nonspecific. Because 50% of the salivary glands must be destroyed before symptoms arise, sicca symptoms may not be a prominent complaint initially. Patients with SjS/LE overlap can pose a diagnostic challenge. They are often anti-Ro-positive and may have prominent cutaneous disease or they may be asymptomatic but give birth to a child with neonatal LE (anti-Ro antibodies are associated with subacute cutaneous LE as well as with neonatal LE; see Ch. 41).

Treatment

Therapy for most manifestations of SjS is symptomatic. Xerophthalmia may be treated with preservative-free artificial tears and lubricating ointments. The placement of punctal plugs that occlude the nasolacrimal ducts may increase accumulation of tear film. Home humidifiers may help relieve symptoms of xerophthalmia. Cyclosporine (0.05%) eye drops may prove helpful, but can cause eye irritation and take several months to achieve a therapeutic effect; autologous serum tears may be helpful. Treatment of xerostomia is outlined in Table 45.5.

Dryness of the skin can be treated with emollients. Vaginal dryness may be improved with artificial lubricants. Frequent monitoring for and treatment of candidal and bacterial overgrowth is recommended; prophylactic use of vaginal antifungal agents is an option. In postmenopausal women, intravaginal or systemic estrogen replacement therapy can reduce compounding of symptoms.

In general, immunosuppressive agents should be reserved for patients with cutaneous vasculitis or involvement of the nervous system and internal organs. Systemic corticosteroids, hydroxychloroquine, and steroid-sparing immunosuppressants (e.g. methotrexate, azathioprine,

XEROSTOMIA – PATIENT INSTRUCTIONS	
General measures	
Avoid smoking cigarettes, cigars	• Smoking exacerbates dryness
Reduce intake of salty, spicy and acidic foods	• These foods can exacerbate dryness and cause irritation
Limit carbohydrate intake, including sugars	• These foods or drinks increase risk of dental caries
Avoid acidic (low pH) drinks	• Examples: cola (pH 2.6), herbal tea (pH varies, but can be as low as 2.5–3), coffee (pH 5) • Acceptable drinks: black tea (pH 5.7–7), tap water (pH 7)
Reduce alcohol and caffeine consumption	• They can worsen dryness
Avoid excessive sipping	• Can reduce mucous film
Avoid OTC antihistamines and decongestants	• Further decrease saliva production
Use sodium bicarbonate mouth rinse* twice daily	• Analgesic effects via its buffer action • May improve taste disturbance • Can reduce tendency for oral candidiasis
Use a humidifier in bedroom overnight	• Adds moisture to the ambient air
Saliva substitutes (oral moisturizers)	
• Contain various combinations of xylitol, hydroxyethyl cellulose, glycerin, and sorbitol; should be alcohol-free and contain fluoride or calcium phosphate • Try different products as they vary in taste, viscosity, feel of lubrication, duration of efficacy; choice based upon patient preference	
Spray, e.g. Biotene® Moisturizing Mouth Spray, Oasis® Dry Mouth Moisturizing Spray	• Use prior to speaking and during the day to assist in talking
Solution, e.g. Salivart® Oral Moisturizer, Saliva Substitute™ (Roxane)	• Use prior to eating to assist in swallowing and to form food bolus
Gel, e.g. Biotene® Oral Balance Gel	• At bedtime
Lozenges, e.g. Xylimelts®, ACT® Dry Mouth Lozenges	• Use overnight
Saliva stimulants – sialagogues	
Local	
Sugar-free†, acid-free gum or candy that contains xylitol	• Should not contain lemon, orange or citric acid • Acceptable examples: Biotene® Dry Mouth Gum • Recaldent®-containing gum may also enhance remineralization, e.g. Trident Xtra Care®
Dried fruit slices	• Example: dried peaches
Systemic‡	
• Approximately 50% of patients respond • Judge response at 8–12 weeks; at that time point, dosage can be increased • Contraindicated in patients with pulmonary disease (e.g. asthma, bronchiolitis obliterans due to GVHD), narrow angle glaucoma	
Pilocarpine (Salagen®)	• 5 mg three times daily
Cevimeline (Evoxac®)	• 30 mg three times daily
Dental care	
Avoid toothpastes that contain detergent (e.g. SLS), whiteners, or flavorings if this causes burning	• Whitening toothpastes have abrasives that can be irritating • Acceptable toothpastes: Biotene® PBF Dry Mouth Fluoride Toothpaste
Avoid commercial mouthwashes that contain alcohol or peroxide	• Acceptable mouthwashes: Biotene® Dry Mouth Oral Rinse; supersaturated calcium phosphate rinses, e.g. NeutraSal®, Caphosol®
Avoid anti-bacterial mouthwashes that contain alcohol or phenol	• Acceptable anti-bacterial mouthwashes: alcohol-free chlorhexidine gluconate mouth rinse USP 0.12% (GUM®)
Professional dental cleaning	• 3 to 4 times per year
Topical fluorides	• Fluoride rinses, e.g. ACT® Total Care Dry Mouth Rinse • Brush-on fluoride gel (can also be applied in mouth tray 5 minutes/day), e.g. PreviDent® 5000
Remineralizing agents, e.g. Seal-Rite™	• Can be applied by dentist

*Half teaspoon of sodium bicarbonate in glass of tap water.
†Not sugarless, as these products may contain fructose.
‡Also helpful for xerophthalmia.

Table 45.5 Xerostomia – patient instructions. GVHD, graft-versus-host disease; OTC, over-the-counter; SLS, sodium lauryl sulfate. *Courtesy Alison Bruce, MD.*

mycophenolate mofetil) are used in patients with serious internal manifestations. Overall, therapy with TNF inhibitors has not proven to be very useful[42]. B cell depletion with rituximab has led to conflicting results[48], with no consistent effect on fatigue or xerostomia[49]. Rituximab is probably most useful in the treatment of symptoms related to cryoglobulinemic-associated vasculitis[50]. Belimumab (anti-BAFF antibody) may play a role as a rescue therapy in refractory cases[50].

MIXED CONNECTIVE TISSUE DISEASE

Synonyms: ■ Undifferentiated connective tissue disease ■ Sharp syndrome

Key features

- The existence of mixed connective tissue disease (MCTD) as a distinct entity is controversial, as patients often have overlapping clinical and serologic features of various combinations of systemic sclerosis, polymyositis, rheumatoid arthritis, and systemic LE
- Major disease features include: high-titer IgG anti-U1 ribonuclear protein (U1RNP) antibodies, Raynaud phenomenon, swollen hands or sclerodactyly, myositis, esophageal dysmotility, and arthritis
- Compared with systemic LE, there is a lower incidence of renal disease and a higher incidence of pulmonary disease
- Pulmonary hypertension is the most serious complication

Introduction

The designation of mixed connective tissue disease (MCTD) as a distinct disease entity continues to be debated. However, there is little argument that there exists a group of patients with a constellation of serologic and clinical manifestations for whom MCTD is a useful label. These patients have high titers of antibodies to U1RNP and certain clinical features observed in other autoimmune connective tissue diseases, including arthritis, pulmonary hypertension, esophageal dysmotility, myopathy, digital swelling, and constitutional symptoms. Over time, some patients with MCTD develop manifestations more consistent with the diagnosis of systemic LE or systemic sclerosis.

History

MCTD was first described by Sharp et al.[51] in 1972, including its clinical features and the presence of an antibody to an extractable nuclear antigen.

Epidemiology

MCTD is much more common in women than in men (9:1), with most patients presenting during the second or third decade of life. The exact incidence of MCTD is unclear, especially since some authors do not consider it to be a separate entity. It is believed that "classic" MCTD is the least common of the autoimmune connective tissue diseases. In the past, the prognosis of MCTD was thought to be better than that of systemic LE; however, long-term evaluation of patients with MCTD has found their prognosis to be poorer than that expected in patients with systemic LE. The majority of deaths in MCTD have been attributable to pulmonary hypertension[52,53].

Pathogenesis

Although the pathogenesis is not clear, there appears to be an immune response to U1RNP[54]. U1RNP plays an essential role in the splicing of pre-mRNA into mRNA. Although anti-U1RNP IgG antibodies may be seen in LE, systemic sclerosis and polymyositis, titers of anti-U1RNP tend to be higher in MCTD. Of note, antibodies to EBV and cytomegalovirus cross-react with components of U1RNP, suggesting that molecular mimicry related to prior exposure to these viruses may be involved in the development of anti-U1RNP autoimmunity. Genetic studies have demonstrated an association of HLA-DR4, -DR1 and -DR2 and MHC class I polypeptide-related sequence A (MICA) in patients with MCTD[55].

Clinical Features

MCTD often presents with prominent cutaneous symptoms, including Raynaud phenomenon and edematous erythematous digits. Raynaud phenomenon is often an early manifestation, and it eventually develops in almost all patients; "ice-pick" digital infarcts or even gangrenous digits can be observed. The patients often have nailfold telangiectasias with dropout areas, and the hands and fingers may feel sclerodermatous and tight due to increased dermal collagen deposition as well as edema. Calcinosis cutis can also occur.

Poikilodermatous areas on the upper trunk and proximal extremities are common, in addition to the sclerodermoid changes of the distal extremities. However, the diffuse involvement of the face, upper trunk or extremities observed in patients with systemic sclerosis is usually not seen. Photosensitivity and lesions indistinguishable clinically and histologically from acute systemic LE (e.g. malar rash) or subacute cutaneous LE may also occur. Cutaneous small vessel vasculitis and livedoid vasculopathy may develop as well[56]. Cutaneous mucinosis, rheumatoid nodules, and orogenital mucosal lesions such as buccal ulcers and nasal septal perforation have been described[56].

An inflammatory myopathy is common in patients with MCTD. However, dermatomyositis-specific findings such as Gottron papules, a periorbital heliotrope rash, and erythema and scaling of the scalp are not usually seen. Arthralgias or polyarticular arthritis occur in 50%–70% of patients with MCTD, often early in the disease course[56]. The arthritis ranges from mild to erosive.

Pulmonary hypertension is the most serious complication of MCTD (occurring in up to 25% of patients), and it may be associated with the presence of antiphospholipid antibodies and elevated serum levels of NT-proBNP (N-terminal pro-brain natriuretic peptide)[57]. Pulmonary fibrosis, often mild, may also occur and, like pulmonary hypertension, is frequently asymptomatic early during its course. Pleurisy and pericarditis occur in ~60% of patients[58]. Periodic pulmonary examinations, chest radiographs, high-resolution CT scans, echocardiography, and pulmonary function tests are warranted. Esophageal dysmotility is common, occurring in up to 85% of patients; it can be asymptomatic, but most commonly manifests as reflux esophagitis and dysphagia.

Pathology

There are no histopathologic features pathognomonic for MCTD. The histologic findings vary depending upon the type of skin lesion examined. In general, cutaneous manifestations clinically resembling acute or subacute cutaneous LE, leukocytoclastic vasculitis, or livedoid vasculopathy will have the histopathologic features characteristic of these entities.

Differential Diagnosis

The differential diagnosis of MCTD consists primarily of systemic sclerosis, systemic LE, dermatomyositis/polymyositis, and overlap syndromes. Some patients initially diagnosed with MCTD may over time develop a preponderance of clinical and serologic features of one of these diseases, requiring a change in diagnosis. The absence of hypocomplementemia or anti-dsDNA and anti-Sm antibodies helps to distinguish MCTD from systemic LE, while myositis and more severe arthritis help distinguish MCTD from systemic sclerosis. The inflammatory myopathies usually manifest with more severe myositis than is encountered in MCTD, and the former do not usually feature the lower esophageal dysmotility common in MCTD.

Treatment

The goal of therapy in MCTD is to control symptoms and maintain function. Therapy should be tailored to the specific organ involvement and disease severity. Patients with pulmonary hypertension require longitudinal care with a pulmonologist or rheumatologist experienced in managing pulmonary complications (see Ch. 43).

In general, manifestations of MCTD that often overlap with LE or polymyositis, such as serositis, cutaneous lesions, arthritis and myositis, usually respond to corticosteroids, while scleroderma-like features such as Raynaud phenomenon and pulmonary hypertension generally do not[59]. Topical corticosteroids and systemic antimalarials are often helpful for LE-like dermatoses. Raynaud phenomenon can be treated with vasodilators in addition to non-pharmacologic measures (avoidance of cold, gloves; see Ch. 43). For severe systemic disease, a variety of therapies have been evaluated, including immunosuppressive agents (e.g. methotrexate, cyclosporine, azathioprine, mycophenolate mofetil, cyclophosphamide), plasmapheresis, and autologous hematopoietic stem cell transplantation. It is difficult to evaluate the efficacy of these treatments since there are no prospective large-scale studies, and most are based on single cases or small case series.

EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Key features

- In addition to deforming arthritis, patients can develop rheumatoid nodules, pyoderma gangrenosum, and small and medium-sized vessel vasculitis
- Other cutaneous manifestations include rheumatoid neutrophilic dermatitis and palisaded neutrophilic and granulomatous dermatitis

Introduction

Rheumatoid arthritis (RA) is a systemic disease in which the primary manifestation is inflammatory arthritis, but there can be a variety of cutaneous manifestations (see Table 53.1). Several of these can serve as helpful diagnostic clues or, in the case of rheumatoid vasculitis, point to serious illness.

Epidemiology

RA is common, affecting 1%–3% of the adult population in the US. Women are affected two to three times more often than men, and although it may develop in any age group, the peak onset is between 30 and 55 years of age.

Pathogenesis

As with other autoimmune diseases, a complex interplay between innate and acquired immune responses appears to be involved. One hypothesis is that the preclinical stage, i.e. before joint symptoms develop, involves mucosal inflammation[60]. Initiating events in the joints include the binding of extracellular matrix constituents in the synovium to Toll-like receptors, leading to the subsequent induction of inflammatory responses (increased TNF, IL-6, chemokines, and angiogenic factors) and maturation of antigen-presenting cells. A gain-of-function polymorphism in *PTPN22*, which encodes a lymphoid-specific protein tyrosine phosphatase that serves as a negative regulator of T cell activation, confers susceptibility to RA and JIA as well as other autoimmune disorders (perhaps by impairing thymic negative selection or regulatory T cells). Of note, there is a reduction in the number of regulatory T cells in RA; Th17 lymphocytes are also thought to play a pathogenic role[61].

RA is also associated with HLA-DR1 and -DR4. The HLA-DRB1 shared epitope allele, a highly significant genetic risk factor for RA, contributes to its pathogenesis primarily by increasing the propensity to develop antibodies that target citrullinated proteins (which are found in the skin and joints). Such antibodies represent specific and predictive serologic markers for RA, and they have been shown to bind the synovium and enhance tissue injury in animal models of autoimmune arthritis. A variety of infectious agents, including particular proteins produced by EBV and *Escherichia coli*, have been thought to play a role due to molecular mimicry of the hypervariable domain of HLA-DRB1*0401 or induction of anti-citrullinated protein antibody production (detected by anti-cyclic citrullinated peptide [anti-CCP] antibody assays).

Clinical Features

Rheumatoid nodules

Rheumatoid nodules are present in 20% of patients with RA, and they occur in patients with moderate to high titers of RF (IgG, IgM, or IgA). Most, if not all, of the cases of seronegative RA with "rheumatoid nodule"-like lesions were proven to be subcutaneous granuloma annulare or other entities with palisading granulomas histologically (see Ch. 93). Rheumatoid nodules are firm, semi-mobile papulonodules that occur most commonly in periarticular locations over extensor surfaces (Fig. 45.5), and in areas subject to pressure or trauma. They range from several millimeters to as large as 5 cm in diameter and are typically asymptomatic. Occasionally the nodules are tender or painful, especially if there is associated trauma or ulceration. Rheumatoid nodules may also occur in visceral organs.

Accelerated rheumatoid nodulosis is characterized by the sudden appearance of multiple rheumatoid nodules (Fig. 45.6). Lesions usually appear following the initiation of methotrexate therapy, but rarely can occur after the initial administration of TNF inhibitors, leflunomide, or tocilizumab. In some of these patients, there had also been a tapering of systemic corticosteroids. Methotrexate can also induce a papular eruption whose histologic features overlap with those of interstitial granuloma annulare and reactive granulomatous dermatitis (see Ch. 93)[62].



Fig. 45.5 Rheumatoid arthritis and rheumatoid nodules. Note the periarticular location of the skin-colored nodules. *Courtesy Kalman Watsky, MD.*



Fig. 45.6 Methotrexate-induced nodulosis in a patient with rheumatoid arthritis. *Courtesy Jean L. Bolognia, MD.*

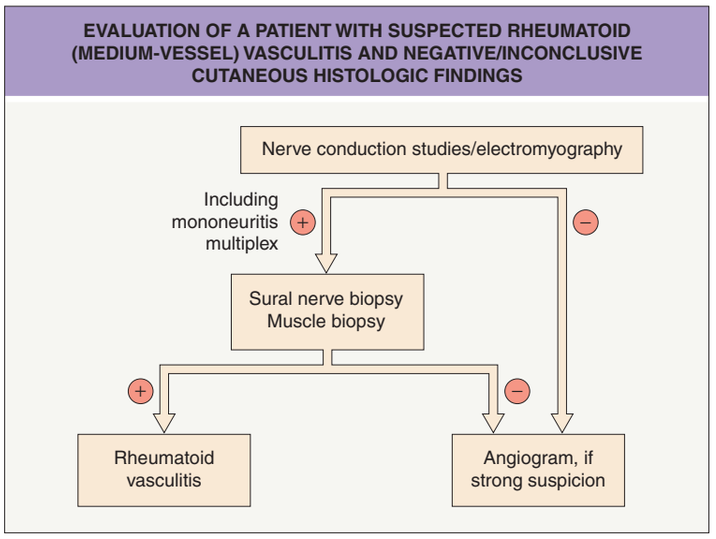


Fig. 45.7 Evaluation of a patient with suspected rheumatoid vasculitis (involving medium-sized vessels) in whom cutaneous histologic findings are negative or inconclusive.

Rheumatoid vasculitis

Rheumatoid vasculitis is a rare and typically late complication of RA. It is thought to occur in only 2%–5% of those with RA, but, at autopsy, vasculitis has been found in up to a third of patients. Rheumatoid vasculitis typically occurs in the context of high-titer RF, rheumatoid nodules, and a history of severe erosive arthritis. The vasculitis may affect vessels of any size, and the clinical presentations reflect this, with palpable and non-palpable purpura in small vessel disease versus nodules, ulcerations, necrotizing livedo reticularis, and/or digital infarcts in medium-sized vessel disease[63]. Systemic manifestations of rheumatoid vasculitis can include neuropathies, cerebral infarction, scleritis, alveolitis, carditis, intestinal ulcers, and proteinuria.

Clinicopathologic correlation and serologic assessment should be performed when rheumatoid vasculitis is suspected. For example, if an ulcer is biopsied, a wedge perpendicular to the edge of the ulcer which includes both surrounding non-ulcerated skin as well as the ulcer base should be obtained. In up to 40% of patients with RA and medium-sized vessel vasculitis, there is evidence of a peripheral neuropathy (subclinical or clinical) that often presents as mononeuritis multiplex. This incidence seems to be even higher in patients with extensive cutaneous disease. Therefore, if vasculitis cannot be identified after multiple deep skin biopsies but the diagnosis is still suspected, nerve conduction studies followed by sural nerve biopsy (or a muscle biopsy) can be performed (Fig. 45.7). Mortality may be as high as 40%[64], and, therefore, aggressive intervention is warranted.

Bywaters lesions

Bywaters lesions include nailfold thromboses and purpuric papules on the distal digits, especially the digital pulp (see Fig. 53.4). Histologically, there is a small vessel leukocytoclastic vasculitis. Typically these lesions are not associated with systemic vasculitis.

Felty syndrome

Felty syndrome represents an uncommon but severe subset of seropositive RA that is characterized by granulocytopenia, splenomegaly, and therapy-resistant leg ulcers (often pretibial). These patients are predisposed to cutaneous and systemic infections that can be refractory to standard treatment, and they are at increased risk of lymphomas and leukemias. The ulcers are likely multifactorial and may be secondary to pyoderma gangrenosum, medium-sized vessel vasculitis (although vasculitis is often not confirmed histologically), venous hypertension, immobilization (ankle ankyloses), neuropathy, or perhaps an ulcerating form of palisaded neutrophilic and granulomatous dermatitis (PNGD)[65].

Neutrophilic dermatoses

Sterile infiltration of the skin by neutrophils can occur in patients with RA. The primary disorders are pyoderma gangrenosum (PG), Sweet syndrome, and rheumatoid neutrophilic dermatitis (see Chs. 25 & 53), but there may be overlap and the term "neutrophilic dermatosis" is often used. Pyoderma gangrenosum occurs at a higher frequency in patients with RA than in the general population. Lesions can develop on the lower extremities (Fig. 45.8), as well as less common locations such as the abdomen and face.



Fig. 45.8 Pyoderma gangrenosum in a patient with rheumatoid arthritis. The chronic relapsing ulcerations involved the lower extremities.
Courtesy Carlos H. Nousari, MD.

Rheumatoid neutrophilic dermatitis (also referred to as rheumatoid neutrophilic dermatosis) resembles Sweet syndrome, both clinically and histologically. It occurs in patients with severe and usually seropositive RA, and it is characterized by erythematous urticarial papules and plaques that are persistent and asymptomatic, but occasionally ulcerate. Lesions are symmetrically distributed, most commonly on the extensor forearms and hands, but they can occur elsewhere.

Other

Patients with RA may also develop erythema elevatum diutinum (EED; see Ch. 24), PNGD (see Ch. 93), and intralymphatic histiocytosis (see Fig. 121.6) as well as a number of cutaneous side effects from medications used to treat the arthritis (see Table 53.1). In RA patients receiving methotrexate, EBV-associated lymphoproliferative disease may involve the skin.

Pathology

Rheumatoid nodules are typically located in the deep dermis or subcutis and are composed of a central zone of brightly eosinophilic fibrin surrounded by a palisaded layer of histiocytes and granulation tissue (Fig. 45.9). Acute or early lesions may show leukocytoclastic vasculitis and/or an interstitial neutrophilic infiltrate.

The histopathologic findings of PG, Sweet syndrome, and small, medium-sized and large vessel vasculitis are discussed in Chapters 24 and 25. When rheumatoid vasculitis affects medium-sized vessels, it can be histologically indistinguishable from polyarteritis nodosa. Direct immunofluorescence in rheumatoid vasculitis shows prominent deposition of IgM as well as C3 in small and medium-sized vessels, whereas in polyarteritis nodosa the IgM and C3 vascular deposits are weaker and sparse and limited to medium-sized vessels.

Differential Diagnosis

Although rheumatoid nodules share several histologic features with PNGD, in the latter the clinical lesions are more polymorphous, with papules and plaques rather than periarticular skin-colored nodules. Because both the clinical and histologic findings can be similar, subcutaneous granuloma annulare may be misdiagnosed as rheumatoid nodules. However, individuals with subcutaneous granuloma annulare are otherwise healthy and are usually children. Occasionally, gouty tophi, tuberous xanthomas, and late-stage EED may be mistaken clinically for rheumatoid nodules.

The differential diagnosis of cutaneous vasculitis is discussed in detail in Chapter 24. Specifically, rheumatoid vasculitis may be confused with mixed cryoglobulinemia given the presence of arthritis, RF, and complement activation in both entities. However, in the former the titer of RF is significantly higher and levels of both C3 and C4 are decreased,

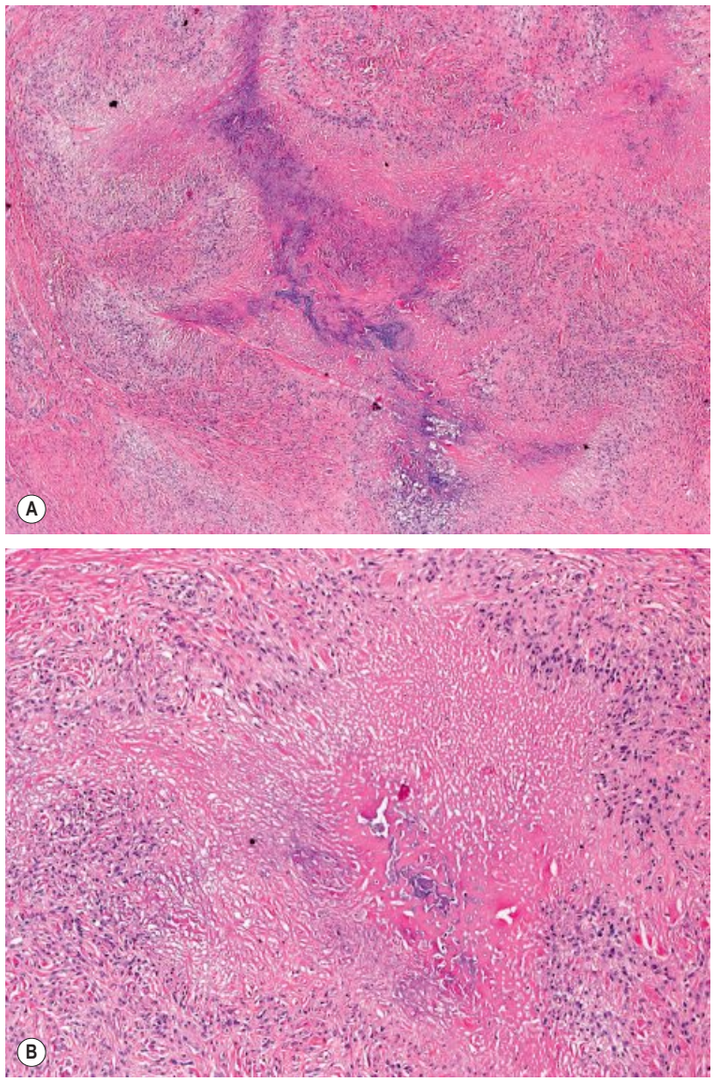


Fig. 45.9 Rheumatoid nodule – histopathologic features. A Large, irregular area of necrobiosis surrounded by a palisade of histiocytes. **B** Details of necrobiosis and palisade of histiocytes with elongated nuclei.
Courtesy Lorenzo Cerroni, MD.

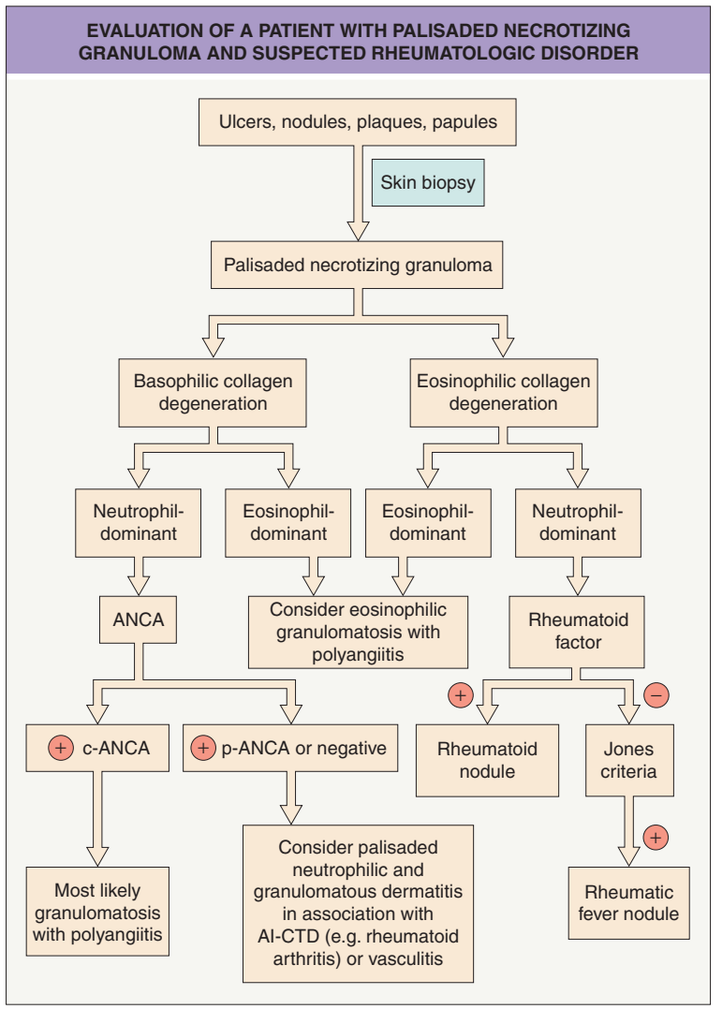


Fig. 45.10 Evaluation of a patient with palisaded necrotizing granuloma and suspected rheumatologic disorder. Jones criteria for rheumatic fever are reviewed in Chapter 19. AI-CTD, autoimmune connective tissue disease.

whereas in cryoglobulinemia C4 levels are low with relatively normal levels of C3. Bywaters lesions may resemble septic emboli, traumatic lesions and, less often, pernio.

As previously mentioned, rheumatoid neutrophilic dermatitis resembles Sweet syndrome, but could also be mistaken for urticaria or urticarial vasculitis. Ulcerations in RA and Felty syndrome may have a variety of causes, including PG, rheumatoid vasculitis, superficial ulcerating rheumatoid necrobiosis (see Fig. 53.3) and secondary antiphospholipid syndrome, as well as infections (especially in patients receiving immunosuppressives), lymphoma (particularly angiocentric variants), and thromboembolic disorders.

The evaluation of a patient with the histologic finding of palisaded necrotizing granulomas and a suspected rheumatologic disorder is outlined in Fig. 45.10.

Treatment

RA therapy is aimed at improving symptoms and preventing end-organ damage. Some of the cutaneous manifestations may improve with treatment of the joint disease, while others (e.g. rheumatoid nodules) often persist. Rheumatoid nodules can be excised, but recurrence is common. Intralesional corticosteroid injections may decrease the size of the nodules, but do not lead to complete resolution. Rheumatoid neutrophilic dermatitis is treated with oral corticosteroids or antineutrophilic agents such as dapsone or colchicine, while Felty syndrome may be treated with recombinant granulocyte colony-stimulating factor (G-CSF) and/or splenectomy.

Rheumatoid vasculitis involving medium-sized and large vessels requires aggressive treatment as it can be rapidly progressive and life-threatening. Intravenous methylprednisolone (500–1500 mg/day for 3 days) followed by prednisone (1 mg/kg/day) plus cyclophosphamide (daily or monthly) and plasmapheresis should be considered.

In less severe cases, including the small vessel variant of rheumatoid vasculitis, azathioprine and mycophenolate mofetil may be considered; methotrexate does not have a consistent effect in this complication of RA. Although there are reports of vasculitis developing in patients with RA after the initiation of TNF inhibitors, there are also multiple reports documenting their beneficial effects in the treatment of rheumatoid vasculitis[63,65]. Several reports have also documented improvement in rheumatoid vasculitis after rituximab therapy[63,65]. Recurrences of rheumatoid vasculitis are less likely to occur when a stable, long-term regimen re-establishes control of the underlying RA.

For the treatment of RA-associated PG, systemic corticosteroids and cyclosporine are highly effective. Excellent results have also been reported with TNF inhibitors. Additional treatments are reviewed in Chapter 25.

Treatment of the inflammatory arthritis consists of NSAIDs, low-dose systemic corticosteroids, disease-modifying antirheumatic drugs (e.g. hydroxychloroquine, leflunomide, methotrexate, sulfasalazine), biologic immunomodulators (e.g. TNF inhibitors, abatacept, tocilizumab, rituximab), and JAK inhibitors.

AUTOINFLAMMATORY DISEASES

RANGE OF CUTANEOUS FINDINGS IN INHERITED AUTOINFLAMMATORY DISEASES					
		Treatment*			
		Inhibition of:			
Cutaneous and histologic features	Inherited autoinflammatory disease(s)	IL-1	TNF	Other	Sporadic or complex disorders with similar findings
Evanescent maculopapular/urticarial eruption (often a neutrophilic infiltrate within the dermis [neutrophilic urticarial dermatosis])	Cryopyrin-associated periodic syndrome	√			• Schnitzler syndrome (Ch. 18) • *Adult-onset Still disease* • *Systemic-onset juvenile idiopathic arthritis (sJIA; Still disease)*
Ulcerations (a sterile neutrophilic infiltrate within the dermis† as in pyoderma gangrenosum)	PAPA spectrum disorders‡ PAAND	√	√		Pyoderma gangrenosum – idiopathic and in the setting of associated disorders (e.g. ulcerative colitis) (Ch. 25)
Pustules (sterile)	DIRA	√			• Generalized pustular psoriasis • Impetigo herpetiformis • SAPHO syndrome (Ch. 25) • Acne fulminans
	DITRA		√	√ [IL-17, IL-12/23 inhibitors]	
	PAPA syndrome‡	√	√		
	CAMPS			IL-12/-23 inhibitors	
Edematous papules, plaques, and nodules (a mainly neutrophilic infiltrate within the dermis and/or panniculus)	Majeed syndrome	√		√ [CS]	Sweet syndrome – idiopathic or occurring in the setting of associated disorders (e.g. acute myelogenous leukemia) (Ch. 25)
Also folliculitis and pathergy	Haploinsufficiency of A20	√	√	√ [colchicine]	• Behçet disease
	OTULIN-related autoinflammatory syndrome (ORAS)		√		
Livedo racemosa with nodules, digital necrosis (medium-sized vessel vasculitis or thrombotic vasculopathy)	ADA2 deficiency		√		• Sneddon syndrome • Sporadic polyarteritis nodosa
Periorificial violaceous erythema, lipodystrophy, and recurrent plaques that resemble cutaneous LE or dermatomyositis (atypical myeloid infiltrate)	Proteasome-associated autoinflammatory syndrome/ CANDLE syndrome/Nakajo–Nishimura syndrome			√ [JAK inhibitors]	• Lupus erythematosus • Dermatomyositis
Acral violaceous erythema with telangiectasia and sometimes ulcerations, often exacerbated by cold exposure (inflammatory and/or thrombotic microangiopathy)	STING-associated vasculopathy of infancy Aicardi– Goutières syndrome			√ [JAK inhibitors]	• Pernio • Lupus erythematosus • Dermatomyositis • Antiphospholipid syndrome
Small papules > plaques (granulomatous infiltrate)	Blau syndrome		√	√ [CS]	• Sarcoidosis • Crohn disease
Follicular papules and spines, coalescing keratosis (acanthosis and dyskeratosis)	*NLRP1*-associated autoinflammation with arthritis and dyskeratosis			√ [acitretin]	• Pityriasis rubra pilaris • Keratosis lichenoides chronica
Psoriasiform lesions	CAMPS (spectrum includes CAPE)			√ [IL-12/23 inhibitors]	• Psoriasis • Pityriasis rubra pilaris

*Given the rarity of many of the disorders, may be based on case reports or small series.
†Untreated lesion.
‡PAPA spectrum disorders are a group of diseases sharing two main clinical features, pyoderma gangrenosum (P) and propensity to severe acne (A), which may be associated with: pyogenic arthritis (PA) in PAPA syndrome; hidradenitis suppurativa (SH) in PASH syndrome; pyogenic arthritis and hidradenitis suppurativa in PAPASH syndrome; psoriatic arthritis (PsA) and hidradenitis suppurativa in PsAPASH syndrome; ankylosing spondylitis and hidradenitis suppurativa in PASS syndrome; ulcerative colitis (C) in PAC syndrome; or hepatosplenomegaly and pancytopenia in PSTPIP1-associated myeloid-related proteinemia inflammatory (PAMI) syndrome. Most of them have been linked to mutations in *PSTPIP1*, except for PsAPASH and PASS that still lack genetic characterization.

Table 45.6 Range of cutaneous findings in inherited autoinflammatory diseases. Disorders discussed in this chapter are in *italics*. Cutaneous vasculitis and neutrophilic dermatosis can also be seen in VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome[31], but the mutations in *UBA1* on the X chromosome are somatic (see Ch. 53). See Tables 45.2 and 45.7 for details of inherited autoinflammatory diseases. ADA, adenosine deaminase; CAMPS, CARD14-mediated psoriasis; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPE, CARD14-associated papulosquamous eruption; CS, corticosteroids; DIRA, deficiency of interleukin-1 receptor antagonist; DITRA, deficiency of interleukin-36 receptor antagonist; PAAND, pyrin-associated autoinflammation with neutrophilic dermatosis; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis.

Key features

- Monogenic diseases related to aberrant activation of the innate immune system that are characterized by recurrent fevers and flares of multi-organ inflammation; the skin is frequently involved as are the joints, eyes, and serosae
- This group includes the hereditary periodic fever syndromes, deficiency of the interleukin (IL)-1 receptor antagonist (DIRA), pustular psoriasis due to abnormal IL-36 signaling, and interferonopathies
- The cutaneous lesions reflect their pathomechanism and nosographic context:
  - aseptic neutrophilic dermatoses presenting as evanescent urticarial papules, sterile pustules, pyoderma gangrenosum, and Sweet syndrome
  - acne and hidradenitis suppurativa
  - cold-induced dermatoses presenting as pernio-like lesions and acral necrosis
  - panniculitis and lipoatrophy
  - vasculitis and livedo reticularis
  - granulomatous dermatoses and disorders of keratinization
- Increased production of IL-1 via inflammasomes can be seen and several of these entities respond to IL-1/IL-1R antagonists, e.g. anakinra, rilonacept, canakinumab
- Complex disorders such as Schnitzler syndrome, systemic-onset juvenile idiopathic arthritis (Still disease), and lupus erythematosus share mechanistic and clinical features

EXAMPLES OF INHERITED AUTOINFLAMMATORY DISEASES WITH CUTANEOUS MANIFESTATIONS

Disease	Proposed mechanism	Protein product of mutated gene (gene)	Mode of inheritance	Predominant ethnic group(s)	Age of onset	Clinical features	Treatment
Inflammasomopathies and other IL-1 family-related conditions (see Table 45.2 for additional entities)							
AIFEC (autoinflammation with infantile enterocolitis)*	NLRC4 activation	NLRC4 *(NLRC4)*	AD	Caucasian	Early infancy	Urticarial eruption with dermographism Enterocolitis Macrophage activation syndrome	IL-1 antagonists, e.g. anakinra, rilonacept, canakinumab IL-18 antagonists
DIRA (deficiency of interleukin-1 receptor antagonist)	Receptor antagonist deficiency	Interleukin [IL]-1 receptor antagonist *(IL1RN)*	AR	Puerto Rican, Brazilian, Lebanese, Newfoundlanders, Dutch	Neonatal	Pustules within areas of erythema – appearance similar to pustular psoriasis (Fig. 45.11A) Sterile osteolytic bone lesions Neonatal distress	IL-1 antagonists – often a dramatic response
DITRA (deficiency of IL-36 receptor antagonist)*	Receptor antagonist deficiency	Interleukin [IL]-36 receptor antagonist *(IL36RN)*	AR	Tunisian, Lebanese	Childhood to adulthood; can flare with pregnancy	Pustules within areas of erythema – resembles generalized pustular psoriasis (Fig. 45.11B)	Oral retinoids IL-1 antagonists – pustules may respond better than papulosquamous lesions IL-17 inhibitors IL-12/23 or IL-23 inhibitors
NAIAD (*NLRP1*-associated autoinflammation with arthritis and dyskeratosis)	NLRP1 activation	NLRP1 *(NLRP1)*	AD	Algerian Dutch	Early infancy	Follicular hyperkeratosis Arthritis Corneal and laryngeal dyskeratosis	IL-1 antagonists TNF inhibitors
PAAND (pyrin-associated autoinflammation with neutrophilic dermatosis)	Pyrin activation	Pyrin *(MEFV)*	AD	Spanish	Puberty	Recurrent pyoderma gangrenosum, severe pustular acne, neutrophilic panniculitis Arthritis	TNF inhibitors
PAPA spectrum disorders (see footnote Table 45.6)	Pyrin activation Cytoskeletal dysregulation	Proline-serine-threonine phosphatase-interacting protein 1 *(PSTPIP1)* To date, genetic bases unknown for PsAPASH and PASS	AD	Northern European	Childhood	See footnote Table 45.6; Fig. 45.11H	TNF inhibitors IL-1 antagonists Corticosteroids
NOCARH (neonatal onset cytopenias with dyshematopoiesis, autoinflammation, rash, and episodes of HLH)	Pyrin activation Cytoskeleton dysregulation	Cell divison cycle 42 *(CDC42)* Mutations in C-terminal domain	AD	Ethnically diverse	Neonatal	Urticarial plaques, some annular Fever, diarrhea, pancytopenia, death due to HLH	Corticosteroids Emapalumab IL-1 antagonists HSCT

Table 45.7 Examples of inherited autoinflammatory diseases with cutaneous manifestations. (cont'd)

EXAMPLES OF INHERITED AUTOINFLAMMATORY DISEASES WITH CUTANEOUS MANIFESTATIONS							
Disease	**Proposed mechanism**	**Protein product of mutated gene (gene)**	**Mode of inheritance**	**Predominant ethnic group(s)**	**Age of onset**	**Clinical features**	**Treatment**
Aberrant NF-κB and/or TNF activity							
ADA2 deficiency	Dysregulation of TNF	Adenosine deaminase 2 *(CECR1)*	AR	Georgian Jewish, German, Turkish	Infancy to adulthood	Childhood-onset polyarteritis nodosa Livedo racemosa (Fig. 45.11G) Early-onset strokes Hepatosplenomegaly Hypogammaglobulinemia, severe cytopenia	TNF inhibitors Allogeneic HSCT
ADAM17 deletion/ neonatal-onset inflammatory skin and bowel disease	Dysregulation of TNF	ADAM metallopeptidase domain 17 *(ADAM17)*	AR	Not known	Neonatal	Psoriasiform erythroderma and widespread pustules Short hair, wiry eyelashes & eyebrows Onychauxis, paronychia Diarrhea, often bloody; malabsorption	TNF inhibitors plus IL-12/23 inhibitors
Blau syndrome (familial juvenile systemic granulomatosis)	Dysregulation of NF-κB signalling	Nucleotide-binding oligomerization domain [NOD] containing 2 *(NOD2)*	AD	Not known	Childhood	Numerous tiny papules (Fig. 45.11C) Granulomatous infiltrate in dermis Uveitis Early-onset, symmetric, granulomatous polyarticular arthritis	Corticosteroids TNF inhibitors (e.g. infliximab) MTX, CSA IL-1 antagonists JAK inhibitors
Type I interferonopathies (increased IFN signaling)							
Aicardi–Goutières syndrome (AGS)/ familial chilblain lupus (FCL)	Nucleic acid processing and degradation	3′ repair exonuclease 1 (*TREX1*), SAM- and HD-domain containing protein 1 (*SAMHD1*) for AGS or FCL; adenosine deaminase, RNAspecific (*ADAR1*), interferon induced with helicase C domain 1 (*IFIH1*), and ribonuclease H2, subunits A, B or C (*RNASEH2A/B/C*) for AGS	AR >> AD (AGS) AD (FCL)	Ethnically diverse	Neonatal or infancy (AGS) to childhood (FCL)	Pernio-like lesions on hands, feet and ears (Fig. 45.11E) Arthritis (FCL) Encephalopathy with white matter changes and progressive developmental delay (AGS)	Difficult to treat JAK inhibitors
PRAAS (proteosome associated autoinflammatory syndrome)/ CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome/ Nakajo–Nishimura syndrome	Proteasome dysfunction disturbing intracellular protein homeostasis	Proteasome subunit, beta type, 8 (*PSMB8*), 4 (*PSMB4*), 9 (*PSMB9*) or 10 (*PSMB10*) Proteasome subunit, alpha type, 3 (*PSMA3*) Proteasome subunit, gamma type, 2 (*PSMG2*) Proteasome maturing protein (*POMP*)	AR (except for *POMP* mutations, AD) Can be digenic, e.g. *PSMB8* & *PSMA3*	Japanese, Spanish, Ashkenazi Jewish	Infancy	Violaceous plaques that can be annular, pernio-like lesions, eyelid edema and erythema Myeloid infiltrate in dermis – varies from immature to mature cells Partial lipomuscular atrophy, joint contractures Basal ganglia calcification (Fig. 45.11F)	JAK inhibitors Corticosteroids MTX

Table 45.7 Examples of inherited autoinflammatory diseases with cutaneous manifestations.

EXAMPLES OF INHERITED AUTOINFLAMMATORY DISEASES WITH CUTANEOUS MANIFESTATIONS							
Disease	Proposed mechanism	Protein product of mutated gene (gene)	Mode of inheritance	Predominant ethnic group(s)	Age of onset	Clinical features	Treatment
SAVI (STING [*st*imulator of *in*terferon *g*enes]-associated vasculopathy with onset in infancy)	Nucleic acid sensing	Stimulator of interferon genes (*STING1*)	AD (rarely, AR)	European, Turkish	Early infancy	Acral (digits, ears, nose) infarcts, ulcerations, and gangrene Bone resorption with loss of digits, including nails (Fig. 45.11D) Acral violaceous plaques Nasal septum perforation Interstitial lung disease	JAK inhibitors
Disorders of ubiquitination							
Haploinsufficieny of A20	Dysregulation of NF-κB signaling	NF-κB regulatory protein A20 (*TNFAIP3*)	AD	Ethnically diverse	Childhood	Recurrent oral and genital ulcers, pathergy, erythema nodosum-like lesions Scarring chorioretinitis Gastrointestinal ulcers Arthralgias/arthritis	JAK inhibitors IL-1 antagonists TNF inhibitors Colchicine
***OTULIN*-related autoinflammatory syndrome (ORAS)**	Dysregulation of NF-κB signaling	OTU deubiquitinase with linear linkage specificity (*OTULIN*)	AR	Consanguinity	Infancy	Panniculitis, lipodystrophy, large urticarial plaques Arthralgias	TNF inhibitors IL-1 antagonists
Other mechanisms							
APLAID (autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation)	Intracellular calcium signaling	Phospholipase C, γ2 (*PLCG2*)	AD	Caucasian	Early childhood	Variable presentation, from vesicles that resemble epidermolysis bullosa to erythematous plaques that resemble cellulitis, sometimes evolving to cutis laxa Ocular inflammation Interstitial pneumonitis Enterocolitis Mild to severe immunodeficiency	Not known
PLAID (PLCG2-associated antibody deficiency and immune dysregulation)	Intracellular calcium signalling	Phospholipase C, γ2 (*PLCG2*)	AD	Ethnically diverse	Childhood	Familial cold autoinflammatory syndrome (FCAS)-3 Cold air-induced/evaporative cooling-induced urticaria and angioedema, neonatal nasal ulcers Non-infectious cutaneous granulomas in a subset of patients Recurrent infections, antibody deficiency, autoimmunity	Protection from cooling H1 anti-histamines Antibiotic prophylaxis and/or IVIg based upon frequency of infections
IL-10/IL-10R deficiency	Cytokine dysregulation	Interleukin [IL]-10 (*IL10*) Interleukin [IL]-10 receptor α & β (*IL10RA*, *IL10RB*)	AR	Turkish, Lebanese	Neonatal	Folliculitis, primarily with IL-10R deficiency Severe infantile (very early-onset) enterocolitis	Allogeneic HSCT (case reports)

*Spectrum includes familial cold autoinflammatory syndrome-4 (FCAS4) which presents with fever, urticarial eruption, arthralgias, conjunctivitis, and panniculitis (adults).

Table 45.7 Examples of inherited autoinflammatory diseases with cutaneous manifestations. The classic hereditary periodic fever syndromes are outlined in Table 45.2. *Most of these disorders are also characterized by recurrent fevers and elevations in acute phase reactants.* AD, autosomal dominant; AR, autosomal recessive; CSA, cyclosporine; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplant; IFN, interferon; JAK, Janus kinase; MTX, methotrexate; NLRC4, NLR family CARD domain containing 4; NLRP1, NLR family pyrin domain containing 1; TNF, tumor necrosis factor.

Autoinflammatory diseases encompass the monogenic inflammatory diseases that reflect aberrant activation of the *innate* immune system[66], in contrast to autoimmune diseases where there is dysregulation of the adaptive immune system with formation of autoantibodies and T cell-mediated tissue damage. That said, some degree of autoimmunity or immune deficiency can be seen in autoinflammatory diseases[67].

As a group, autoinflammatory diseases are characterized by recurrent fevers and flares of multi-organ inflammation. These episodes are seemingly unprovoked and frequently involve the skin as well as the joints, eyes, and serosae. Oftentimes, these tissues contain sterile infiltrates of neutrophils. The cutaneous findings vary and include sterile pustules, transient urticarial papules, ulcerations, livedo reticularis, and pernio-like lesions (Table 45.6; see Table 45.2)[66]. It is important to appreciate the significant overlap these rare disorders have with more common polygenic disorders such as pustular psoriasis and chilblains. Their inclusion in the differential diagnosis, especially in early-onset or treatment-resistant disease, often allows for more specific therapy to be instituted.

Table 45.7 outlines the key features, in particular dermatologic, of several monogenic autoinflammatory diseases. The genetic basis of a number of these entities has only been described in the past several years so these diseases may not yet be that familiar to dermatologists. Of note, the pathophysiology of a significant percentage of the disorders in Table 45.6, as well as the cryopyrin-associated periodic syndromes (CAPS; see Table 45.2), involves interleukin (IL)-1 overactivity. There can be excessive production (e.g. CAPS) or defective inhibition (e.g. DIRA) of IL-1 (Fig. 45.12). This provides an explanation for the therapeutic efficacy of IL-1/IL-1R antagonists, including anakinra, rilonacept, and canakinumab (Fig. 45.13).

Histologically, the cutaneous infiltrates in patients can vary from granulomas within the dermis (Blau syndrome) to pustules within the epidermis (DIRA, CARD14-induced pustular psoriasis). A characteristic finding in patients with the hereditary periodic fever syndromes (see Table 45.2) has been termed "neutrophilic urticarial dermatosis"; biopsy specimens of transient urticarial papules demonstrate perivascular and interstitial infiltrates of neutrophils within the dermis[11].



Fig. 45.11 Cutaneous manifestations of inherited autoinflammatory disorders. A Annular erythematous plaques studded with pustules in an infant with deficiency of the interleukin-1 receptor antagonist (DIRA); note the similarity to pustular psoriasis. **B** Child with deficiency of interleukin-36 receptor antagonist (DITRA) – widespread psoriasiform plaques whose edges contain pustules. **C** Blau syndrome with numerous, small, pink-tan, flat papules in a generalized distribution in a 1-year-old boy; histologically, a granulomatous infiltrate is seen. **D** STING (*st*imulator of *in*terferon *g*enes)-associated vasculopathy with onset in infancy (SAVI) is characterized by acral violaceous plaques and resorption of digits and loss of nails; patients may be diagnosed as having Aicardi–Goutières syndrome, antiphospholipid antibody syndrome, or vasculitis. **E** Aicardi–Goutières syndrome with pernio-like lesions. **F** Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome with deforming arthritis (e.g. swan neck deformity) and thin pink plaques overlying the metacarpophalangeal joints that resemble dermatomyositis. **G** Livedo racemosa in a patient with adenosine deaminase 2 (ADA2) deficiency. **H** Cystic acne and extensive scarring in a pediatric patient with pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome. *A, Courtesy Gillian Clarke, MD. B, Courtesy Antonio Torrelo, MD. C,E, Courtesy Julie V. Schaffer, MD. D,F–H, Courtesy Edward Cowen, MD.*

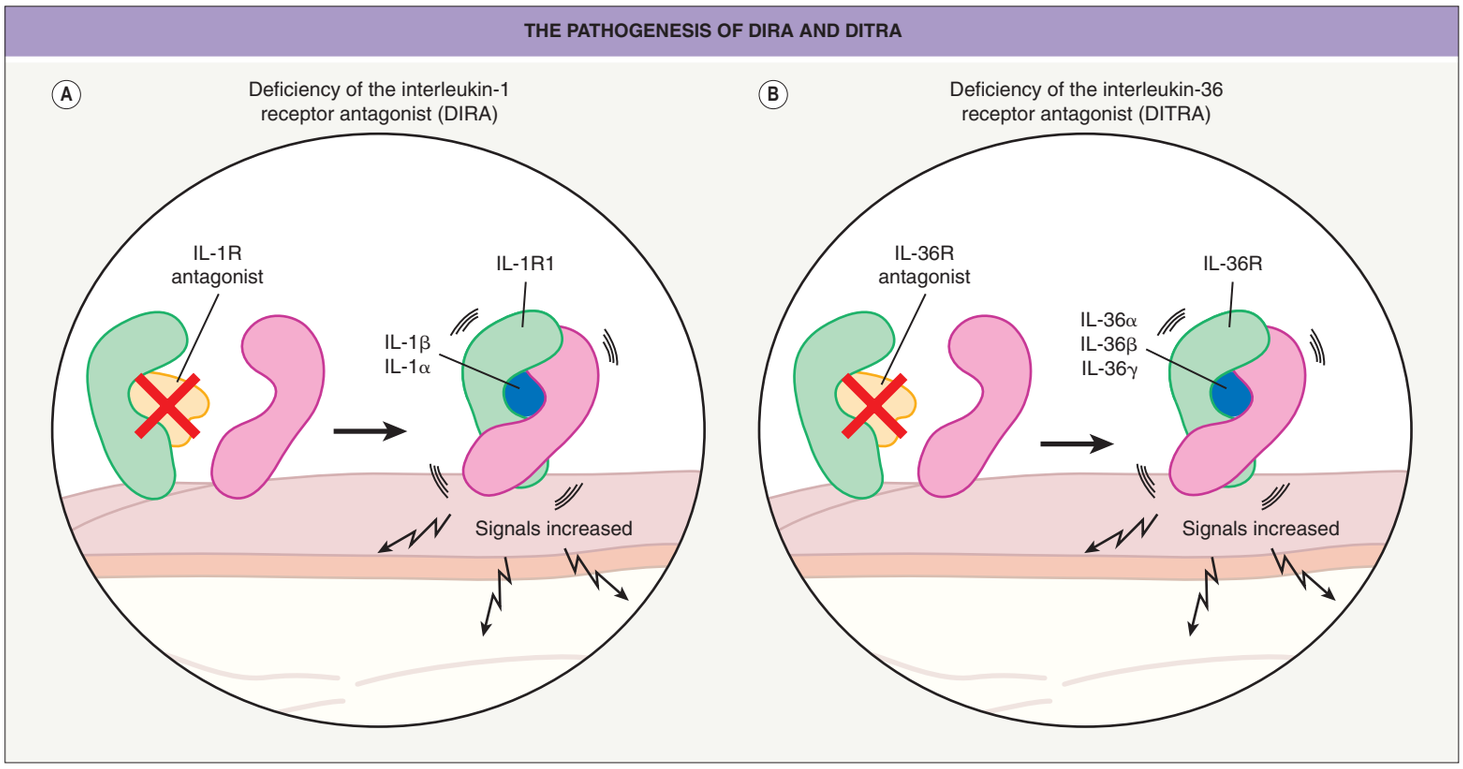


Fig. 45.12 The pathogenesis of DIRA (deficiency of interleukin-1 receptor [IL-1R] antagonist) and DITRA (deficiency of interleukin-36 receptor [IL-36R] antagonist). A Loss of the IL-1R antagonist leads to unopposed proinflammatory signaling by IL-1α and IL-1β in patients with DIRA. **B** In DITRA, loss of the IL-36R antagonist results in analogous unchecked signaling by IL-36α, IL-36β, and IL-36γ at the IL-36R. *Reproduced from Cowen EW, Goldbach-Mansky R. DIRA, DITRA, and new insights into pathways of skin inflammation. What's in a name? Arch Dermatol 2012;148:381–4.*

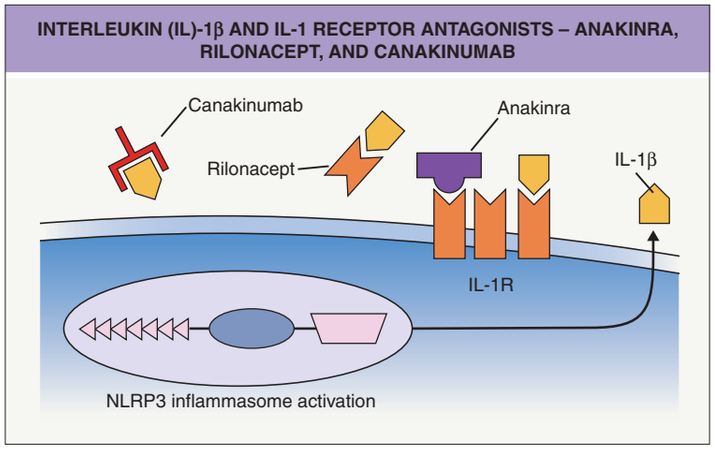


Fig. 45.13 Interleukin (IL)-1β and IL-1 receptor antagonists – anakinra, rilonacept, and canakinumab. Anakinra is an antagonist of the IL-1 receptor (IL-1R). Rilonacept is an IL-1 Trap. Canakinumab is an anti-IL-1β monoclonal antibody. See Fig. 4.2 for details of NLRP3 inflammasome. NLRP3, *NOD-like receptor pyrin* domain-containing protein 3.

Leukocytoclasia can be present, but not fibrinoid degeneration of vessel walls. As outlined in Table 45.6, neutrophilic urticarial dermatosis is also observed in patients with complex disorders such as Schnitzler syndrome (see Ch. 18), sJIA or adult-onset Still disease (see above), as well as some patients with SLE[68,69].

The group of autoinflammatory diseases continues to expand and some of the disorders classically categorized as neutrophilic dermatoses, e.g. Behçet disease, are beginning to be viewed as having a similar pathophysiology.

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Additional figures available in our eBook (see inside front cover for access code).

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eFig. 45.1 Systemic-onset juvenile idiopathic arthritis (Still disease). Evanescent pink papules and plaques in a child. Note the linear array of some of the lesions. *Courtesy Carlos H. Nousari, MD.*



eFig. 45.2 Hypergammaglobulinemic purpura in a patient with Sjögren syndrome. Purpuric macules and thin papules are admixed with hemosiderin deposition at previous sites of involvement. *Courtesy Julie V. Schaffer, MD.*



eFig. 45.3 Rheumatoid nodules in a patient with rheumatoid arthritis. Note the periarticular location of the nodules. *Courtesy Kalman Watsky, MD.*



eFig. 45.4 STING (*st*imulator of *in*terferon *g*enes)-associated vasculopathy with onset in infancy (SAVI). Resorption of distal digits with nail loss, telangiectasias, and scarring. *Courtesy Edward Cowen, MD.*



eFig. 45.5 Aicardi–Goutières syndrome with pernio-like lesions. *Courtesy Julie V. Schaffer, MD.*

46 Mucinoses

Franco Rongioletti

Key features

- The cutaneous mucinoses are a heterogeneous group of disorders in which an abnormal amount of mucin accumulates in the skin
- The etiopathogenesis of cutaneous mucinoses is unknown
- The cutaneous mucinoses are divided into two groups: (1) primary cutaneous mucinoses, in which the mucin deposition leads to clinically distinctive lesions and is the major histologic feature; and (2) secondary mucinoses, in which the mucin deposition is simply an associated finding
- Primary cutaneous mucinoses are further divided into degenerative–inflammatory forms (which may be dermal or follicular) and hamartomatous–neoplastic forms
- Associated disorders include paraproteinemia (scleromyxedema, scleredema), diabetes mellitus (scleredema), thyroid disease (pretibial myxedema, myxedema), and autoimmune connective tissue disease (lupus erythematosus, dermatomyositis)

INTRODUCTION

The cutaneous mucinoses are a heterogeneous group of disorders in which an abnormal amount of mucin accumulates in the skin, either diffusely or focally[1].

Mucin is a component of the dermal extracellular matrix and is normally produced in small amounts by fibroblasts. It is a jelly-like, amorphous mixture of acid glycosaminoglycans (formerly referred to as acid mucopolysaccharides), which are complex carbohydrates composed of multiple repeating polysaccharide units (see Ch. 95). The acid glycosaminoglycans may be attached to both sides of a protein core (proteoglycan monomer), as in the case of dermatan sulfate and chondroitin sulfate, or they may be free, as in the case of hyaluronic acid, which is the most important component of dermal mucin.

Mucin is capable of absorbing 1000 times its own weight in water, playing a major role in maintaining the salt and water balance of the dermis. In routinely stained sections, the presence of either a blue-staining material between separated collagen bundles or empty spaces within the dermis are good clues that there is mucin deposition. For confirmation, special stains can be used, such as Alcian blue, colloidal iron, or toluidine blue (Table 46.1). Furthermore, dermal mucin is PAS-negative and, if composed of hyaluronic acid, hyaluronidase-sensitive. Fixation of biopsy specimens in absolute alcohol, rather than formalin, may improve dermal mucin detection. In addition, monoclonal antibodies have been used to detect sulfated acid glycosaminoglycans[2]. An alternative approach is to utilize biotinylated hyaluronan (HA)-binding proteins coupled to an avidin–peroxidase reaction[3].

Why mucin abnormally accumulates within the skin of some individuals is unclear. Certain "serum factors", e.g. immunoglobulins and/or cytokines, could promote the upregulation of glycosaminoglycan synthesis[4]. For example, elevated serum immunoglobulin levels (monoclonal or polyclonal) and circulating autoantibodies can be found in association with cutaneous mucinoses such as scleromyxedema, Graves disease-associated pretibial myxedema, and papulonodular mucinosis of lupus erythematosus. However, the serum from these patients stimulates mucin production even *after* the elution of either the IgG paraprotein in those with scleromyxedema or the autoantibodies in those with Graves disease-associated pretibial myxedema. Circulating cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF), and TGF-β, which are known to stimulate glycosaminoglycan synthesis within the skin, could play a role in excess mucin deposition. A reduction in the normal catabolic degradation of mucin could also be a factor.

This chapter focuses on the disorders characterized by abnormal dermal deposits of mucin, composed primarily of hyaluronic acid (Fig. 46.1). The mucopolysaccharidoses, in which the predominant dermal mucin is dermatan sulfate or heparan sulfate (e.g. Hunter syndrome), are discussed in Chapter 48.

STAINING CHARACTERISTICS OF ACID GLYCOSAMINOGLYCANS (MUCOPOLYSACCHARIDES)

Histologic stain	Acid glycosaminoglycans (mucopolysaccharides)	
	Non-sulfated (hyaluronic acid*)	Sulfated (heparan sulfate, dermatan sulfate, chondroitin sulfate†)
Colloidal iron	+	+
Alcian blue		
pH 2.5	+	+
pH 0.5	–	+
Metachromasia with toluidine blue		
pH 4.0	+	+
pH <2.0	–	+
PAS‡	–	–
Hyaluronidase-sensitive	+	–

*Major GAG in the disorders discussed in this chapter; not bound to a protein core.
†Major GAGs in the mucopolysaccharidoses, e.g., Hunter syndrome, Hurler syndrome; bound to a protein core (proteoglycan).
‡Stains neutral mucopolysaccharides.

Table 46.1 Staining characteristics of acid glycosaminoglycans (mucopolysaccharides). GAG, glycosaminoglycan.

CLASSIFICATION

The cutaneous mucinoses may be classified as *primary*, in which mucin deposition is the major histologic feature resulting in clinically distinctive lesions (Table 46.2), or *secondary*, in which mucin simply represents an associated histologic finding (Table 46.3). Primary mucinoses can then be divided into *degenerative–inflammatory* forms and *hamartomatous–neoplastic* types. The former are further subdivided into dermal and follicular forms, based upon the location of the mucin (see Table 46.2).

PRIMARY DEGENERATIVE–INFLAMMATORY MUCINOSES

Dermal Mucinoses

Scleromyxedema

Synonyms: ■ Papular mucinosis ■ Diffuse/generalized and sclerodermoid lichen myxedematosus ■ Arndt–Gottron syndrome

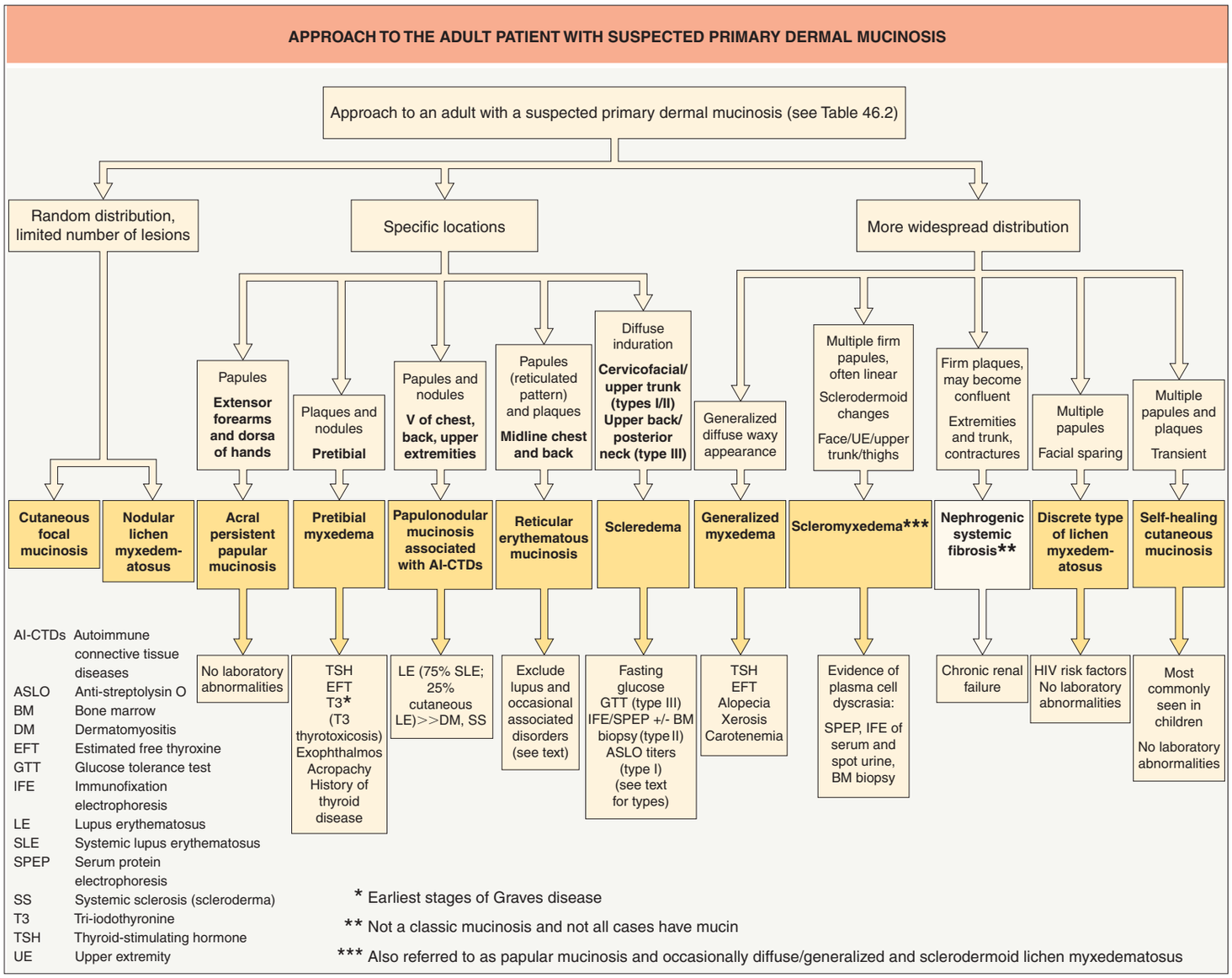


Fig. 46.1 Approach to the patient with suspected primary dermal mucinosis. Pretibial myxedema must be distinguished from obesity-associated lymphedematous mucinosis.

Introduction and definition

Scleromyxedema is a chronic idiopathic disorder characterized by numerous firm papules and areas of induration that are due to dermal mucin deposition in association with an increase in dermal collagen[4]. Nearly all patients also have a monoclonal gammopathy, and some may have systemic, even lethal, manifestations[5]. This entity must be distinguished from localized variants of lichen myxedematosus where the skin is the sole site of involvement (Table 46.4). There are, however, occasional patients who have an atypical constellation of findings and fall between scleromyxedema and localized lichen myxedematosus (see "atypical forms" below).

History

Although the first descriptions of scleromyxedema were attributed to Dubreuilh in 1906 and Reitman in 1908, it was not until the review of Montgomery and Underwood in 1953 that the disease was distinguished from scleroderma and generalized myxedema. A year later, Gottron and his colleagues gave the name "scleromyxedema" to the generalized and sclerotic form. The association of a monoclonal gammopathy with scleromyxedema was first described in 1963.

Epidemiology and pathogenesis

Scleromyxedema is a fairly uncommon disease, affecting middle-aged adults of both sexes equally. The pathogenesis of scleromyxedema is unknown. The role of the associated monoclonal gammopathy remains a matter of debate. While most patients have a plasma cell dyscrasia, paraprotein levels do not correlate with either the extent or the progression of the disease. In addition, sera from patients with scleromyxedema enhanced fibroblast proliferation *in vitro*, but an immunoglobulin purified from paraprotein-containing sera failed to do so, suggesting a pathogenetic role for circulating factors other than the paraprotein. Clinical remission of scleromyxedema, along with a reduction in the M-protein, that follows autologous hematopoietic stem cell transplantation (HSCT) points to the bone marrow as a source of these circulating factors.

In addition to circulating cytokines, such as IL-1 and TNF, which are known to stimulate glycosaminoglycan synthesis and fibroblast proliferation in the skin, analysis of RNA in involved skin tissue also confirmed a promoting role for TGF-β[6]. Abnormally high secretion of IL-4, a profibrotic cytokine, was recently detected in the serum of scleromyxedema patients, suggesting a chronic Th2-skewed response against an unknown target antigen[7]. Lastly, the development of scleromyxedema following a cutaneous granulomatous reaction to intradermal injections of hyaluronic gel or silicone breast implants suggests autoimmune phenomena[5].

Clinical features

In scleromyxedema, numerous, 2–3 mm, firm, waxy, closely aligned papules develop in a relatively widespread symmetrical pattern. The most common sites of involvement are the head and neck region, upper trunk,

CLASSIFICATION OF THE PRIMARY CUTANEOUS MUCINOSES
Degenerative–inflammatory mucinoses
Dermal
Scleromyxedema or papular mucinosis*
Lichen myxedematosus (localized variants)
• Discrete papular form†
• Acral persistent papular mucinosis
• Cutaneous mucinosis of infancy
• Nodular form
Self-healing cutaneous mucinosis
• Juvenile type
• Adult type
Scleredema
• Non-diabetic type (types I and II)
• Diabetic type (type III)
Mucinoses associated with altered thyroid function
• Localized (pretibial) myxedema
• Generalized myxedema
Reticular erythematous mucinosis
Papulonodular mucinosis associated with autoimmune connective tissue diseases (most commonly LE)
Cutaneous focal mucinosis
Digital mucous cyst (myxoid cyst)
Miscellaneous mucinoses
Follicular
Follicular mucinosis (Pinkus)
Urticaria-like follicular mucinosis
Hamartomatous–neoplastic mucinoses
Mucinous nevus
(Angio)myxoma
*Has been referred to as diffuse/generalized and sclerodermoid lichen myxedematosus. †Also seen in HIV-infected individuals.

Table 46.2 Classification of the primary cutaneous mucinoses. LE, lupus erythematosus.

MAJOR DISORDERS ASSOCIATED WITH HISTOLOGIC DEPOSITION OF MUCIN (SECONDARY MUCINOSES)
Epithelial mucinosis
• Basal cell carcinoma
• Rare – squamous cell carcinoma, keratoacanthoma, verruca, seborrheic keratosis, mycosis fungoides
Dermal mucinosis
• Granuloma annulare
• Lupus erythematosus, dermatomyositis > morphea, systemic sclerosis
• Obesity-associated lymphedema
• Rosacea, phymatous and granulomatous
• Mesenchymal tumors (e.g. myxosarcoma, myxoid lipoblastoma, DFSP)
• Neural tumors (e.g. neurofibroma, lobular neuromyxoma)
• Epithelial tumors (e.g. basal cell carcinoma, eccrine carcinoma)
• Other tumors (e.g. cutaneous metastases, mucinous carcinoma of the eyelid)
• Hypertrophic scar
• Rare – chronic GVHD, cutaneous reactions to interferon, herpes zoster, venous insufficiency, hereditary progressive mucinous histiocytosis
Follicular mucinosis
• Mycosis fungoides (rarely other T cell lymphomas)
• Eczematous dermatoses
• Rare – lupus erythematosus, insect bites (including so-called exaggerated insect bite-like reactions in the setting of CLL), rosacea, side effect of imatinib, familial reticuloendotheliosis

Table 46.3 Major disorders associated with histologic deposition of mucin (secondary mucinoses). A limited amount of dermal mucin can occasionally be observed in virtually all cutaneous disorders. CLL, chronic lymphocytic leukemia; DFSP, dermatofibrosarcoma protuberans; GVHD, graft-versus-host disease.

hands, forearms, and thighs (Fig. 46.2). Papules are often arranged in a strikingly linear array. The surrounding skin is shiny and indurated, i.e. sclerodermoid in appearance, and the glabella is typically involved with deep longitudinal furrowing. Severe involvement of the face can result in a leonine facies (Fig. 46.3A). Deep furrowing can also occur on the trunk and extremities and is referred to as the "Shar-Pei sign" (Fig. 46.3B).

Erythema, edema, and a brownish discoloration may also be seen in the involved areas, and pruritus is not uncommon. The mucous membranes and scalp are spared. As the condition progresses, erythematous and infiltrated plaques may appear with skin stiffening, sclerodactyly, and decreased motility of the mouth and joints. Overlying the proximal interphalangeal joints, a central depression surrounded by an elevated rim (due to skin thickening) can be seen and is referred to as

DIAGNOSTIC CRITERIA OF SCLEROMYXEDEMA VERSUS LOCALIZED VARIANTS OF LICHEN MYXEDEMATOSUS	
Scleromyxedema	**Localized variants of lichen myxedematosus**
Diffuse/generalized papular eruption and sclerodermoid features	Papular eruption (or nodules and/or plaques due to confluence of papules)
Microscopic triad (mucin deposition, fibroblast proliferation, fibrosis), or occasionally interstitial granulomatous pattern	Mucin deposition with variable fibroblast proliferation
Monoclonal gammopathy	Absence of monoclonal gammopathy
Absence of thyroid disorder	Absence of thyroid disorder

Table 46.4 Diagnostic criteria of scleromyxedema versus localized variants of lichen myxedematosus.



Fig. 46.2 Scleromyxedema. A, B Numerous monomorphic, firm, skin-colored to tan papules which can have a strikingly linear arrangement. This is most obvious on the posterior neck. **C** The skin can also become shiny and indurated, leading to a sclerodermoid appearance, but the small firm papules in a linear array are a clue to the diagnosis. *A, B, Courtesy Edward Cowen, MD; C, Courtesy Lorenzo Cerroni, MD.*

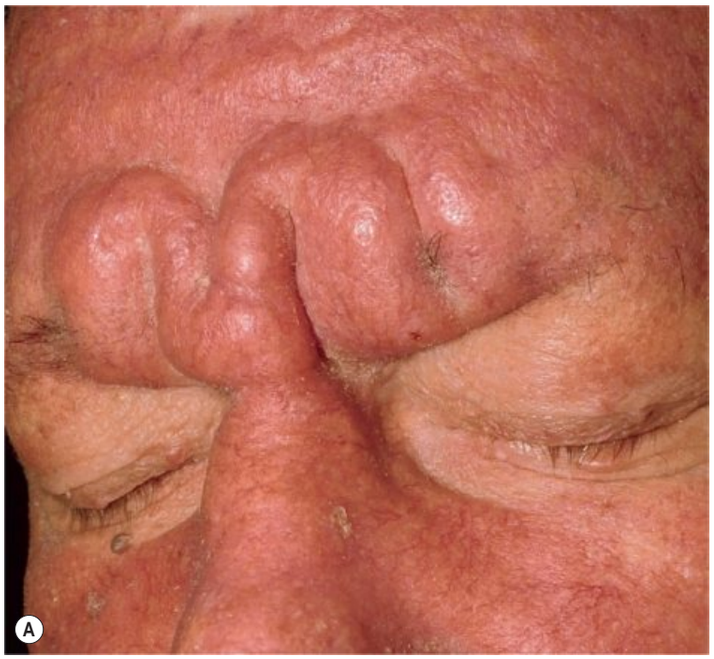




Fig. 46.3 Scleromyxedema. Thickening of the skin of the forehead (**A**) and trunk (**B**), leading to deep furrows and folds. Scleromyxedema is one of the causes of leonine facies. *A, Courtesy Joyce Rico, MD; B, Courtesy Lorenzo Cerroni, MD.*

the "doughnut sign". Mat and cuticular telangiectasias and calcinosis, as seen in systemic sclerosis, are absent.

Scleromyxedema is almost always associated with paraproteinemia. The monoclonal gammopathy is usually IgG and the light chains are more commonly lambda. Although a mild plasmacytosis may be observed in bone marrow biopsies, <10% of patients with scleromyxedema progress to symptomatic myeloma. Patients with scleromyxedema can have a number of internal manifestations, in particular muscular, neurologic, rheumatologic, pulmonary, renal, and cardiovascular. Dysphagia, proximal muscle weakness due to myositis, disturbances of the CNS leading to unexplained coma, peripheral neuropathy, arthropathies, carpal tunnel syndrome, restrictive or obstructive lung disease, and scleroderma-like renal disease may accompany or follow the cutaneous manifestations[5]. While the predominantly sensory peripheral neuropathy typically affects older men and has an insidious onset, the dermato-neuro syndrome is a potentially life-threatening encephalopathy. This syndrome begins abruptly with a worsening of skin lesions, a flu-like prodrome, fever, and seizures, and it can eventuate in an unexplained coma. Possible triggers include viral infections and vaccines (e.g. SARS-CoV-2)[7a].

Pathology

Scleromyxedema is characterized by a triad of microscopic features[8]:

- a diffuse deposit of mucin in the upper and mid reticular dermis
- an increase in collagen deposition
- a marked proliferation of irregularly arranged fibroblasts (Fig. 46.4).

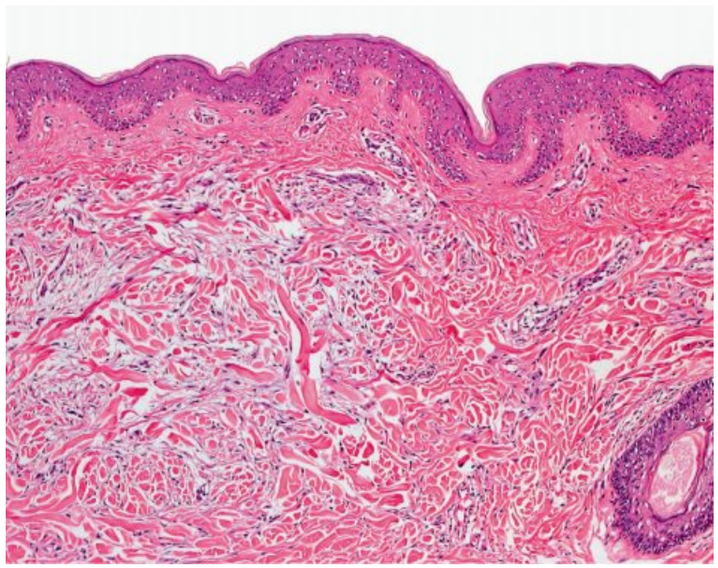


Fig. 46.4 Scleromyxedema – histopathologic features. Typical triad of fibrosis, an increased number of irregularly arranged fibroblasts, and interstitial deposits of mucin in the upper and mid reticular dermis. *Courtesy Lorenzo Cerroni, MD.*

The epidermis may be normal or thinned by the pressure of the underlying mucin and fibrosis; the hair follicles may be atrophic. A slight superficial, perivascular, lymphoplasmacytic infiltrate is often present. The elastic fibers are fragmented and decreased in number. More recently, an interstitial granuloma annulare-like pattern was described[9]. Mucin may fill the walls of myocardial blood vessels as well as the parenchyma of the kidney, pancreas, adrenal glands, nerves, and lymph nodes. In the dermato-neuro syndrome, autopsy findings have not proved helpful in elucidating an underlying pathogenesis.

Differential diagnosis

The primary differential diagnosis for scleromyxedema is systemic sclerosis (scleroderma) and scleredema. The presence of papules, especially in linear arrays, is a very helpful clinical sign in distinguishing scleromyxedema. In the occasional patient with systemic sclerosis who develops primary cutaneous amyloidosis (see Fig. 47.6), histologic findings allow distinction. Additional entities in the scleredermoid differential diagnosis should be excluded (see Ch. 43). For example, nephrogenic systemic fibrosis, which develops in individuals with renal impairment exposed to gadolinium-containing contrast media, may show mucin in biopsy specimens, but patients lack both facial involvement (commonly seen in scleromyxedema) and paraproteinemia. Criteria for diagnosing scleromyxedema versus localized variants of lichen myxedematosus are summarized in Table 46.4, and the dermatologic disorders in which leonine facies can develop are outlined in Table 46.5.

Treatment

Recommendations are still based on case reports and open-label small case series. In the past, monthly courses of melphalan were often the therapy of choice, targeting the plasma cell dyscrasia. However, while this alkylating agent can result in some clinical improvement, it has also been implicated in 30% of the deaths secondary to its induction of hematologic malignancies and septic complications[10]. Other chemotherapeutic agents (e.g. cyclophosphamide, methotrexate, chlorambucil, 2-chlorodeoxyadenosine) have been tried, but with no better results and the risk of significant side effects.

IVIg, alone or in combination with systemic medications (see below), has gained widespread acceptance as first-line therapy for both cutaneous involvement and associated systemic manifestations, including the dermato-neuro syndrome[11,12]. Although long-lasting remissions after cessation of IVIg therapy have been reported, the response is usually not permanent and maintenance infusions are required[5]. Either thalidomide or lenalidomide or a combination of lenalidomide, a proteasome inhibitor (e.g. bortezomib) and dexamethasone, standard therapy for multiple myeloma, is considered second-line treatment and is often

LEONINE FACIES – ASSOCIATED DERMATOLOGIC DISEASES
Scleromyxedema
Lepromatous leprosy
Leishmaniasis
Cutaneous lymphoma (T cell, rarely B cell)
Actinic reticuloid form of chronic actinic dermatitis
Leukemia cutis (specific cutaneous manifestation of B-CLL)
Phymatous rosacea
Viral-associated trichodysplasia
Systemic amyloidosis
Lipoid proteinosis
Mastocytosis (nodular)
Sarcoidosis
Multicentric reticulohistiocytosis
Progressive nodular histiocytosis
Other non-Langerhans cell histiocytoses (e.g. indeterminate cell histiocytosis)
Pachydermoperiostosis
Late-stage onchocerciasis
Trichoepitheliomas, cylindromas, and/or spiradenomas



Table 46.5 Leonine facies – associated dermatologic diseases. Leonine facies can also be seen in patients with Paget disease of the bone and rarely secondary syphilis. B-CLL, B cell chronic lymphocytic leukemia. *Inset, Courtesy Joyce Rico, MD.*

administered in combination with IVIg[11–13]. This multi-drug regimen may represent first-line therapy for individuals with severe disease including CNS or cardiac involvement[12]. Autologous HSCT represents third-line therapy, especially for individuals with disabling or potentially life-threatening disease[13]. Due to the excellent response observed in patients with myeloma, the anti-CD38 monoclonal antibodies daratumumab and isatuximab may represent future therapies.

Additional therapies, including PUVA, UVA1, systemic retinoids, cyclosporine, electron beam radiation, plasmapheresis, and extracorporeal photochemotherapy, have all produced variable results. Dysarthria and a flu-like illness may herald life-threatening coma, and the patient should be promptly admitted to the hospital for close observation and consideration of treatment with a multi-drug regimen (see above) plus IVIg and plasmapheresis[12].

Lichen myxedematosus (localized variants)

Introduction

In the localized variants of lichen myxedematosus, patients develop small, firm, waxy papules (or nodules and plaques produced by the confluence of papules) that are limited to only a few sites – usually the upper and lower extremities and/or trunk. The *skin is the only site of involvement* and these variants, in contrast to scleromyxedema, are not associated with sclerosis, paraproteinemia, or systemic involvement nor are they associated with thyroid disease (see Fig. 46.1)[4]. While most dermatologists equate lichen myxedematosus with localized, skin-limited disease, a source of potential confusion is the uncommon and more historical use of the term "diffuse/generalized and sclerodermoid lichen myxedematosus" to describe scleromyxedema.

The localized variants of lichen myxedematosus are subdivided into four subtypes:

- a discrete papular form
- acral persistent papular mucinosis
- cutaneous mucinosis of infancy
- a pure nodular form.

Localized variants of lichen myxedematosus may be observed in association with HIV infection, exposure to toxic oil or L-tryptophan (historical), and hepatitis C viral (HCV) infection.

Epidemiology

Exact incidence and prevalence rates for the localized variants of lichen myxedematosus are not known.

Clinical features

Discrete papular lichen myxedematosus is characterized by 2–5 mm papules, numbering from just a few to hundreds and involving the limbs and trunk in a symmetrical pattern[14] (Fig. 46.5). The affected skin is not indurated and the face is spared. Lesions progress slowly without systemic involvement. However, they rarely resolve spontaneously. To date, progression to scleromyxedema has never been definitively proven.



Fig. 46.5 Localized lichen myxedematosus – discrete papular type. Persistent whitish papules on the arms.



Fig. 46.6 Acral persistent papular mucinosis. Skin-colored papules on the dorsal aspect of the hands.

In **acral persistent papular mucinosis**, first described in 1986 by Rongioletti et al.[15], multiple ivory to skin-colored papules develop exclusively on the dorsal aspect of the hands and extensor surface of the distal forearms (Fig. 46.6). A female : male ratio of 3 : 1 has been noted. The lesions persist, but without systemic manifestations[16].

In **cutaneous mucinosis of infancy** (syn. papular mucinosis of infancy), first described by Lum in 1980, firm opalescent papules appear on the neck (Fig. 46.7), upper arms (especially the elbows), and trunk[17]. In contrast to self-healing mucinosis, neither systemic symptoms nor spontaneous resolution are observed. Of the handful of patients described to date, at least two have had a congenital linear variant, which might be better categorized as an example of a mucinous nevus[17].

Nodular lichen myxedematosus is characterized by multiple nodules on the limbs and trunk, with a mild or absent papular component. **Atypical tuberous myxedema** (Jadassohn–Dosseker) probably represents a pure nodular variant of lichen myxedematosus[1,17a].

Localized lichen myxedematosus in HIV-infected patients. The majority of patients developed either the discrete papular form or the nodular variant of lichen myxedematosus, with lesions on the limbs and trunk. All became infected with HIV before the onset of the lichen myxedematosus. Most had hypergammaglobulinemia, a well-recognized manifestation of HIV infection, and to date only two had paraproteinemia. Of note, up to 10% of HIV-infected individuals may have monoclonal gammopathy of undetermined significance (MGUS) and how this relates to the mucinosis remains to be determined. None of the patients had visceral involvement due to mucin deposition[18].

Localized lichen myxedematosus in "toxic" syndromes. Multiple papules due to mucin deposition with a clinical appearance similar to the discrete form of lichen myxedematosus have also been described



Fig. 46.7 Cutaneous mucinosis of infancy. Skin-colored papules on the back of the neck in a young girl.



Fig. 46.8 Self-healing cutaneous mucinosis. Pink to skin-colored dermal and subcutaneous nodules as well as periorbital swelling. *Courtesy Drs Hansgeorg Müller and Heinz Kofler.*

in the setting of toxic oil syndrome and L-tryptophan-associated eosinophilia–myalgia syndrome. Although unrelated epidemiologically and both of historical interest, toxic oil syndrome (due to the ingestion of adulterated rapeseed oil in Spain in the early 1980s) and L-tryptophan-associated eosinophilia–myalgia (related to a contaminant in L-tryptophan-containing products used as sedatives during the late 1980s) share several clinical features, including constitutional symptoms, peripheral eosinophilia, hyperpigmentation, and a sclerodermoid appearance[19], in addition to this mucinous papular eruption. Usually 1–5 months after the onset of the illness, 1–5 mm, white or skin-colored papules appeared, primarily on the limbs. The lesions resolved slowly after exposure to the toxic substance ceased.

Localized lichen myxedematosus and HCV infection. An association of lichen myxedematosus with chronic hepatitis due to HCV infection has been reported, especially from Japan[20], but this relationship needs to be confirmed by more extensive studies.

Cutaneous mucinosis consistent with **localized lichen myxedematosus** has been associated with several **medications** including targeted immunomodulators ("biologics"), inhibitors of CSF-1R (colony-stimulating factor-1 receptor), and interferons (including at injection sites) in addition to **trauma** (e.g. mechanical, following total knee replacement)[21].

Atypical forms of lichen myxedematosus. Occasionally patients with lichen myxedematosus have atypical features or features intermediate between scleromyxedema and localized lichen myxedematosus[22]. This group includes patients with scleromyxedema who lack a monoclonal gammopathy as well as individuals with localized forms of lichen myxedematosus who also have a monoclonal gammopathy and/or systemic symptoms. One possible explanation for the former group is performance of just a serum protein electrophoresis (SPEP), rather than an SPEP plus an immunofixation electrophoresis (IFE) of serum and urine, as IFE is a more sensitive assay.

Pathology

In the localized forms of lichen myxedematosus, the histologic changes are less characteristic than in scleromyxedema. Mucin accumulates in the upper and mid reticular dermis and fibroblast proliferation is variable; fibrosis is not marked and may even be absent. In acral persistent papular mucinosis, mucin accumulates focally in the upper reticular dermis (sparing a subepidermal zone) and fibroblasts are not increased in number. In cutaneous mucinosis of infancy, the mucin may be so superficial as to look as if it were "enclosed" by epidermis, although mucin may also deposit in the reticular dermis[17].

Differential diagnosis

Histologic examination of the skin helps to distinguish localized variants of lichen myxedematosus from several papular eruptions that can have a similar appearance, such as papular granuloma annulare, amyloidosis, colloid milium, molluscum contagiosum, papular elastorrhexis, and eruptive collagenomas. It is also important to differentiate these entities from scleromyxedema and the cutaneous mucinosis that can occur in the setting of autoimmune connective tissue diseases (see below).

Treatment

Localized lichen myxedematosus does not require therapy, and a wait-and-see approach is recommended. Topical application of corticosteroids, pimecrolimus, or tacrolimus may be of some benefit[14]. One patient with associated HIV infection had a complete remission after treatment with oral isotretinoin. Spontaneous resolution may occur, even in the setting of HIV infection[18].

Self-healing cutaneous mucinosis

Although previously considered a subtype of localized lichen myxedematosus, self-healing cutaneous mucinosis is best regarded as a distinct rare form of primary dermal mucinosis[23]. It was initially described in children, with ages of reported patients ranging from 1 to 15 years[17]. The same disorder was subsequently observed in a few adults, but in the author's opinion, some of the adult patients were actually examples of localized lichen myxedematosus with spontaneous resolution[24].

Self-healing cutaneous mucinosis is characterized by the following clinical presentations: (1) an acute eruption of multiple papules, sometimes coalescing into linear infiltrated plaques, on the face, neck, scalp, abdomen, and thighs; and (2) mucinous subcutaneous nodules in periarticular areas and on the face, with periorbital swelling (Fig. 46.8). In addition, systemic symptoms (e.g. fever, arthralgias, and muscle tenderness) may accompany the cutaneous lesions, but paraproteinemia, bone marrow plasmacytosis, and thyroid dysfunction are not observed. Spontaneous resolution over a period of 1–8 months is characteristic, hence the name. Histologically, papular lesions show dermal mucin deposition with mild inflammation and a small increase in the number of fibroblasts, whereas nodules have deep mucinous deposits associated with bands of fibrosis and a prominent proliferation of fibroblast-like cells and gangliocyte-like cells mimicking proliferative fasciitis[17,23]. While spontaneous complete regression is the expectation, longitudinal evaluation is recommended due to the possible development of dermato-rheumatologic disorders such as fibroblastic rheumatism[23].

Scleredema

Synonyms: ■ Scleredema adultorum of Buschke ■ Scleredema diabeticorum

Introduction

Scleredema is a symmetrical diffuse induration of the upper part of the body due to a thickened dermis and deposition of mucin.

History

Although Buschke has been credited with first describing scleredema, the original description dates back to Pitford in 1876. A relationship with diabetes mellitus was only established in 1970.

Epidemiology and pathogenesis

Scleredema is an unusual disease that affects all races. The form that is associated with diabetes mellitus is more prevalent in men, while other forms are seen more commonly in women. Irreversible glycosylation of collagen and resistance to degradation by collagenase may lead to an accumulation of collagen. Alternatively, enhanced stimulation by insulin, microvascular damage, and hypoxia may increase the synthesis of collagen and mucin. Streptococcal hypersensitivity (type I), injury to lymphatics, and paraproteinemia (type II) may also play a role.

Clinical features

Classically, there are three types of scleredema, although a simpler division into those with and those without diabetes has been suggested[25,26]. The *first type* affects primarily children and middle-aged women. It is preceded by fever, malaise, and an infection (usually streptococcal) of the upper or lower respiratory tract. The skin of the cervicofacial region suddenly hardens with extension to the trunk and proximal upper limbs. The face is expressionless and opening of the mouth and swallowing are difficult because of the involvement of the tongue and pharynx. This type usually resolves spontaneously.

The *second type* shares the same clinical features as the first but has a more subtle onset, without a preceding illness. It persists for years. This type is more frequently associated with a monoclonal gammopathy[25].

The *third type* occurs primarily in obese middle-aged men with insulin-dependent diabetes *(scleredema diabeticorum)*. The onset is subtle and the involvement persistent. Erythema and induration of the posterior neck and the back are commonly observed (Fig. 46.9), as is a *peau d'orange* appearance of the skin. In those patients who also have cheiroarthropathy, the skin of the distal extremities may appear waxy, presumably due to increased amounts of glycosylated collagen.

Occasionally, patients with limited site involvement (e.g. periorbital skin) have also been reported. In all three forms, systemic manifestations such as serositis, myositis, dysarthria, dysphagia, parotitis, and ocular and cardiac abnormalities (e.g. ophthalmoplegia, congestive heart failure) may occur, but are unusual. Scleredema may be idiopathic and anecdotal associations with autoimmune diseases (e.g. rheumatoid arthritis, Sjögren syndrome, primary biliary cholangitis, dermatomyositis, lichen sclerosus), internal neoplasms (malignant insulinoma, gallbladder carcinoma, carcinoid, pituitary–adrenocortical neoplasm), and HIV infection have been described[18,27]. Except for limitation of movement, scleredema usually causes little morbidity. While postinfectious scleredema may clear within 6–24 months, scleredema associated with diabetes or a monoclonal gammopathy has a chronic unremitting course. Rarely, death may occur when internal organs are involved.

Pathology

The principal alteration in scleredema is the thickening of the reticular dermis, with large collagen bundles separated from one another by clear spaces filled with mucin, resulting in fenestration of the dermis (Fig. 46.10). There is no increase in the number of fibroblasts, but the elastic fibers are reduced in number. At times, the mucin deposition can be so slight that multiple biopsies or staining of unfixed frozen sections are required to detect it. There is sometimes a sparse perivascular lymphocytic infiltrate. Direct immunofluorescence is usually negative, but deposits of IgG and C3 have been observed at the dermal–epidermal junction. Mucin also accumulates within skeletal muscle and the heart.

Differential diagnosis

Scleredema may be confused with systemic sclerosis, but the absence of Raynaud phenomenon and cuticular and mat telangiectasias points to scleredema. Histologically, mucin deposition may be observed in systemic sclerosis, but adnexal structures are atrophic or absent and the dermis is diffusely sclerotic, as opposed to the "fenestration" observed in scleredema. Patients with scleromyxedema also have firm papules (often in a linear array) in addition to dermal induration as well as a proliferation of fibroblasts histologically. The other types of cutaneous mucinoses are usually distinguished on the basis of clinical findings[26]. Additional entities in the sclerodermoid differential diagnosis should be excluded (see Ch. 43). Occasionally, because of associated erythema, diabetes-associated scleredema is sometimes misdiagnosed as cellulitis (usually by non-dermatologists).

Treatment

Therapy is unnecessary for scleredema associated with streptococcal infections because it is self-limited. Management of scleredema associated with diabetes or a monoclonal gammopathy is more difficult and no specific treatment is available. Phototherapy, in particular UVA1 and narrowband UVB, is considered first-line therapy as it can stimulate fibroblasts to synthesize collagenase, thereby enhancing degradation of sclerotic tissue[25,28]. For scleredema associated with a plasma cell dyscrasia, systemic medications used to treat myeloma (see above), may be effective. Some, but not all, patients with diabetes-associated scleredema improve with strict glycemic control.

Systemic and intralesional corticosteroids, intralesional hyaluronidase, antibiotics, methotrexate, cyclosporine, pulse therapy with cyclophosphamide plus oral corticosteroids, tamoxifen, and allopurinol have all been tried, with variable results. Electron beam radiotherapy, IVIg[29], and extracorporeal photopheresis are additional reported therapies. In patients with limited mobility or respiratory difficulty, ultrasonic massage and physical therapy can be employed. Aggressive therapies should be limited to individuals with disabling disease or systemic manifestations.



Fig. 46.9 Scleredema in association with diabetes mellitus. Diffuse induration of the upper part of the body with overlying erythema.

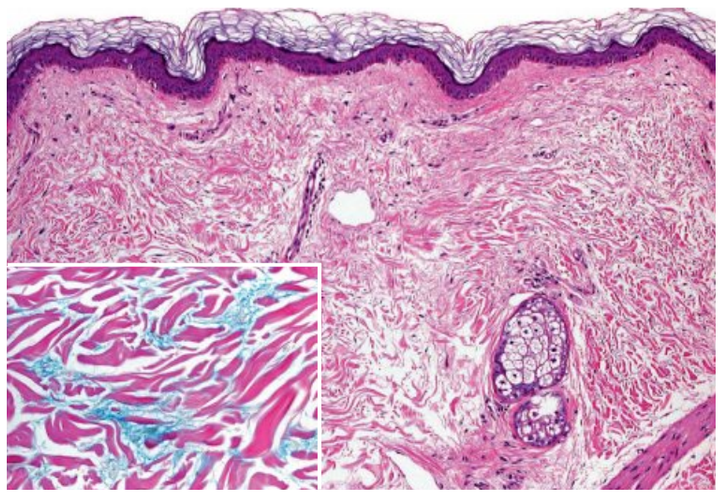


Fig. 46.10 Scleredema – histopathologic features. Slightly separated collagen bundles and normal dermal cellularity. Inset: Mucin deposits between collagen bundles. *Courtesy Lorenzo Cerroni, MD.*

Mucinoses associated with altered thyroid function

Localized (pretibial) myxedema

Definition

Localized or pretibial myxedema is characterized by cutaneous induration of the shins due to mucin deposition. It is often associated with hyperthyroidism (most commonly due to Graves disease), but may appear following treatment of the thyroid disease.

Epidemiology and pathogenesis

Graves disease is seven times more common in women than in men and onset is usually during the third or fourth decade. Pretibial myxedema is one sign of Graves disease, along with goiter, exophthalmos, thyroid acropachy, and thyroid-stimulating immunoglobulins that recognize the thyroid-stimulating hormone (TSH) receptor. Overall, pretibial myxedema is found in 1%–5% of patients with Graves disease, but in up to 25% of those with exophthalmos[30]. It can also appear in the setting of hypothyroidism following the treatment of Graves disease. Rarely, localized myxedema occurs in the setting of Hashimoto thyroiditis without thyrotoxicosis, and even in euthyroid patients.

A serum factor (unrelated to thyroid-stimulating immunoglobulins) may incite fibroblasts to produce mucin. Fibroblasts from the dermis of the lower extremities have been found to be more sensitive to such a factor than are fibroblasts from other areas of the body. An insulin-like growth factor, trauma, and lymphatic obstruction due to mucin may also play a role.

Clinical features

Localized myxedema presents as erythematous to skin-colored, but sometimes purple–brown or yellowish, waxy indurated nodules or plaques. A *peau d'orange* appearance is a characteristic finding (Fig. 46.11). The lesions are usually located on the anterolateral aspect of the lower legs or the feet. Localized myxedema can also present as a diffuse non-pitting edema of the shins or feet that evolves into elephantiasis. Even more rarely, localized myxedema affects the face, shoulders, upper extremities, lower abdomen, scars, or donor graft sites. Large plaques are often painful and pruritic. When present, hypertrichosis and hyperhidrosis are confined to pretibial myxedematous skin.

Apart from appearance and possible pain, associated morbidity is usually minimal. Entrapment of peroneal nerves by mucinous connective tissue may cause foot drop or faulty dorsiflexion.

Pathology

Large quantities of mucin are deposited within the reticular dermis, causing collagen bundles to separate and the dermis to thicken[6]. A subepidermal grenz zone of normal collagen is also observed. A perivascular and periadnexal lymphocytic infiltrate with mast cells is seen, as well as large stellate fibroblasts. Elastic fibers are reduced in number. There is often hyperkeratosis in addition to papillomatosis and hyperplasia of the epidermis.

Differential diagnosis

In addition to lichen simplex chronicus and hypertrophic lichen planus, pretibial myxedema should be distinguished from lymphedema, lipedema, and obesity-associated lymphedematous mucinosis[31]. In the latter disorder, semi-translucent papules, plaques with woody induration, and occasionally vesicles develop on the shins of euthyroid, morbidly obese individuals with significant lower extremity edema. Histologically, mucin deposition is found within the superficial papillary dermis and around vessels, in addition to epidermal atrophy (with effacement of the rete ridge pattern), vertically oriented capillaries, and deposits of hemosiderin[31].

Treatment

Corticosteroids, either applied under occlusive dressings or delivered by intralesional injection (e.g. triamcinolone 10–40 mg/cc), are considered first-line therapy[32]. Intralesional hyaluronidase, alone or in combination with intralesional corticosteroids, may also be tried[33]. More recently, teprotumumab, an IGF-1R inhibitor that is FDA-approved for the treatment of thyroid-associated ophthalmopathy, was reported to lead to improvement[33a]. For the severe elephantiasis form, medical treatments, including IVIg, rituximab, plasmapheresis and octreotide, have been of benefit and are sometimes combined with surgery[32,33]. Unfortunately, skin grafting is usually followed by recurrence. Compression stockings and gradient pneumatic compression are useful for the associated lymphedema. Addressing risk factors such as obesity and smoking is recommended. Therapy for hyperthyroidism does not improve the cutaneous lesions and, often, localized myxedema develops after treatment has been instituted or completed. Localized myxedema may clear spontaneously after an average of 3.5 years.

Generalized myxedema

Definition

Generalized myxedema is a manifestation of severe hypothyroidism in which mucin is deposited in the dermis, leading to waxiness of the skin.

Pathogenesis

Generalized myxedema is due to a quantitative or functional deficiency of thyroxine. Impaired degradation of mucin, rather than increased synthesis, has been suggested as the cause.

Clinical features

Hypothyroidism may be congenital, with sequelae formerly referred to as cretinism, or of juvenile or adult onset.

Congenital hypothyroidism affects 1 in 5000 neonates and may cause a distinctive syndrome of dwarfism, intellectual disability, and systemic and cutaneous findings. Somnolence, constipation, poor feeding, poor muscle tone, persistence of jaundice, and respiratory distress all suggest the diagnosis. However, more than a third of infants have no symptoms. Periorbital tissues and the tongue, lips, hands, and genitals are puffy. The skin is dry, cold, and pale. Nails and hairs are dry and brittle, and there can be patchy alopecia. The presence of a clavicular pad is diagnostic.



Fig. 46.11 Pretibial myxedema in patients with Graves disease. A Skin-colored to pink thick plaques on the shins. **B** Purple–brown nodules and plaques on the shins of a patient with a darker skin phototype. A *peau d'orange* appearance is present in both patients. **C, D** Induration and violaceous erythema of the legs with disfiguring soft tissue overgrowth of the dorsal feet and toes. *C, D, Courtesy Edward Cowen, MD.*

Juvenile hypothyroidism develops in a previously euthyroid child. Clinical features include short stature, abnormal physical and mental development, retardation of sexual maturity, and poor performance at school. Hypertrichosis may develop on the shoulders and upper back.

Adult hypothyroidism is the most common form of the disease. It is seen primarily in women 40–60 years of age, often as a result of autoimmune disease (usually Hashimoto thyroiditis), therapy of hyperthyroidism (usually Graves disease) or, rarely, pituitary or hypothalamic failure. Rarely, the ingestion of large quantities of foodstuffs that contain inhibitors of iodine uptake by the thyroid gland, e.g. raw bok choy, can lead to myxedema.

The initial symptoms are subtle and include mental and physical sluggishness, weight gain, constipation, leg cramps, loss of appetite, and cold intolerance. The face has a dull expression. The eyelids, lips, tongue, and hands are puffy, the nose is broad (Fig. 46.12), and the speech becomes hoarse and slurred. The skin is pale, cool, waxy, and dry; an absence of sweating can lead to acquired ichthyosis or eczema craquelé. A yellowish discoloration of the palms and soles due to carotenoderma may appear. Hair and nails are dry and brittle, and a diffuse non-scarring alopecia is common; alopecia of the lateral third of the eyebrows can also be seen. Purpura involving the extremities, blue telangiectatic fingertips, delayed wound healing, and xanthomas may be observed. Systemic manifestations include cardiomegaly, megacolon or bowel obstruction, psychiatric symptoms mimicking Alzheimer disease, serositis, carpal tunnel syndrome, and seventh nerve paralysis[34].

Pathology

Mucin deposits, mainly perivascular and perifollicular, splay collagen bundles and may extend into the subcutaneous fat and nerves. Fibroblasts are not increased in number, but elastic fibers are reduced. Mucin deposits in the brain probably cause the psychiatric symptoms.

Diagnosis and differential diagnosis

The diagnosis is suspected clinically. Low levels of circulating free T_4 confirm the diagnosis. Serum TSH level is high in primary hypothyroidism and low in secondary hypothyroidism. Myxedema does not seem to occur in secondary hypothyroidism.

Treatment

Early treatment is crucial for proper mental development of neonates with hypothyroidism, but it is also critical for the juvenile and adult forms. Measurement of serum levels of T_4 and/or TSH is performed between 2 and 4 days of age in newborn screening panels, and treatment should be initiated within the first 2 weeks of life. Usually, symptoms subside with thyroxine administration and recur if it is discontinued. Even areas of hair loss regrow with proper treatment. If untreated, patients can die as a result of "myxedema coma".



Fig. 46.12 Generalized myxedema in an adult with hypothyroidism. The face is puffy with a dull expression and the hair is dry.

Reticular erythematous mucinosis

Synonyms: ■ Plaque-like cutaneous mucinosis ■ Reticular erythematous mucinosis syndrome ■ Midline mucinosis

Introduction and definition

Reticular erythematous mucinosis (REM) is a disorder in which persistent, erythematous papules or plaques develop in the midline of the back or chest. The papules often have a reticular or net-like configuration. This disorder has some overlap with lupus erythematosus (LE) tumidus[35,36].

History

Steigleder and colleagues coined the term "reticular erythematous mucinosis" in 1974. However, in 1960, Perry and colleagues described three similar patients with plaque-like cutaneous mucinosis. Some authors regard these two entities as identical, while others view them as being on a continuum[36].

Epidemiology and pathogenesis

REM is a rare disorder that occurs most often in middle-aged women, although men and children are not spared. It is seen worldwide and can be provoked or exacerbated by a wide range of factors, from heat and perspiration to oral contraceptives and pregnancy to radiation therapy. There is debate as to whether REM is a photoaggravated disorder. Familial cases suggest a genetic predisposition.

Within endothelial cells and pericytes of lesional skin, tubuloreticular inclusions have been detected. Although these inclusions occur in viral infections, they can also be produced by high levels of interferon and are also found within endothelial cells in LE. Lastly, the fibroblasts of REM patients exhibit an abnormal overstimulation when exposed to exogenous IL-1.

Clinical features

Plaque-like cutaneous mucinosis and REM are probably different clinical presentations of the same rare syndrome. On the mid back or chest, pink to red macules and papules merge into reticulated and annular patterns (Fig. 46.13) or plaque-like lesions. They may be slightly pruritic and sometimes lesions spread to the abdomen. While sun exposure may worsen the eruption, it has also been reported to be beneficial. Provocative phototests (UVA and/or UVB) can sometimes reproduce REM lesions. In general, REM is not associated with systemic diseases or abnormal laboratory tests. However, there are reports of autoimmune diseases (e.g. SLE), hypothyroidism, and more common internal malignancies in patients with REM[35].



Fig. 46.13 Reticular erythematous mucinosis. Grouped pink papules and plaques on the chest. No surface changes are present and there is a reticulated configuration. *Courtesy Lorenzo Cerroni, MD.*

Pathology

The epidermis is normal. Interstitial deposits of small amounts of mucin are seen in the upper dermis, along with a perivascular and, at times, perifollicular T cell infiltrate[6]. Vascular dilation is present. Usually, direct immunofluorescence is negative, but, rarely, granular deposits of IgM, IgA, and C3 have been seen at the dermal–epidermal junction[36].

Differential diagnosis

In biopsy specimens of discoid lesions of LE there is involvement of the epidermis and deposits of IgG and C3 are found at the dermal–epidermal junction, and in lymphocytic infiltrate of Jessner, there is minimal, if any, dermal mucin. LE tumidus is very difficult to distinguish microscopically from REM. Both diseases have perivascular dermal infiltrates of T lymphocytes, primarily $CD4^+$, plus increased dermal mucin. In REM, the mucin and the lymphocytes tend to be more superficial and the lymphocytes more scattered. In LE tumidus, plasmacytoid dendritic cells were found to be clustered whereas in REM they were fewer in number and appeared as single cells[36]. These findings aside, some authors view REM and LE tumidus as variants of the same disease and along a continuum with cutaneous LE. It would be unusual for polymorphous light eruption to be restricted to the chest and histologically there is less abundant mucin and sometimes pronounced edema of the superficial dermis. Seborrheic dermatitis and tinea versicolor may involve the central chest, but they have associated scale and can be diagnosed clinically, as can confluent and reticulated papillomatosis.

Treatment

Hydroxychloroquine or chloroquine (+/− quinacrine) are usually effective in clearing the lesions within 4–8 weeks. Results from other treatments such as topical and systemic corticosteroids, topical calcineurin inhibitors, oral antihistamines, tetracyclines, cyclosporine, UVB irradiation, and pulsed dye laser are quite variable. Despite the potential for an exacerbation, improvement following UVA1 or UVB irradiation has been reported[35]. The lesions may clear spontaneously, even after 15 years.

Papulonodular mucinosis associated with autoimmune connective tissue diseases

Synonyms (when associated with LE): ■ Cutaneous lupus mucinosis ■ Papulonodular mucinosis in (systemic) lupus erythematosus ■ Papular and nodular mucinosis of Gold

Papules, nodules, and plaques secondary to mucin deposition may accompany or even antedate an autoimmune connective tissue disease, most commonly LE, and rarely dermatomyositis or systemic sclerosis. Cutaneous lupus mucinosis occurs in ~1%–2% of patients with LE[37]. Only in Japan has a male predominance been observed. The lesions present as asymptomatic, skin-colored, at times erythematous, 0.5–2 cm papules and nodules (Fig. 46.14); rarely, they merge into large plaques. Tangential illumination can be used to enhance detection of the lesions. A central depression and pigmentation may be additional features. The back, V of the chest, and the upper extremities are the most common sites of involvement. In only a few reported patients was there a flare of the papulonodules after sun exposure.



Fig. 46.14 Papulonodular mucinosis in a patient with lupus erythematosus. Skin-colored papules and nodules leading to a "lumpy" appearance of the chest.

Cutaneous lupus mucinosis can antedate LE or begin concurrently. The clinical course may correlate, in some patients, with underlying disease activity. Approximately 75% of patients with LE who develop papular and nodular mucinosis have systemic involvement, primarily renal and articular. The minority have only skin involvement, usually discoid or subacute cutaneous LE lesions.

Histologically, mucin abounds in the upper and mid dermis but may involve the subcutaneous fat as well. Sometimes, it is accompanied by a slight perivascular lymphocytic infiltrate. The epidermal changes of LE are absent, but linear or granular deposits of immunoglobulin and/or C3 are detected at the dermal–epidermal junction.

Cutaneous lesions of dermatomyositis often have dermal mucin histologically; rarely, patients develop erythematous nodules and plaques due to mucin deposition. The latter appear primarily on the trunk[38] and usually follow the myositis. Papular and nodular mucinosis can also occur in association with systemic sclerosis[39].

Treatment

Therapies for papular and nodular mucinosis are similar to those used for LE and dermatomyositis, i.e. sunscreens, topical corticosteroids, and oral antimalarials. For unresponsive cases, systemic corticosteroids can be prescribed. Intralesional corticosteroids may prove useful for reducing the size of large nodules and plaques.

Cutaneous focal mucinosis

Cutaneous focal mucinosis presents as an asymptomatic, skin-colored papule or nodule, <1 cm in diameter[40]. The lesion can occur anywhere on the body or in the oral cavity. Cutaneous focal mucinosis favors adults and only rarely has it been linked to thyroid disorders (without myxedema), REM, or scleromyxedema. Trauma can be an inciting factor[41]. The diagnosis is based upon histologic findings.

Histologically, mucin is dispersed throughout the upper and mid dermis, sparing the subcutaneous fat. Cleft-like spaces, but no cysts, are seen. Spindle-shaped or stellate, vimentin-positive fibroblasts are present[41]. There is also a minor population of dermal dendrocytes that are partially factor XIIIa-positive and partially CD34-positive. The elastic and reticulum fibers are absent, but capillaries are normal in number[40].

Cutaneous focal mucinosis results from a "muciparous" reaction of the connective tissue to nonspecific stimuli and should be distinguished from digital mucous cyst or from angiomyxoma, which represents a true neoplasm. Cutaneous focal mucinosis can be surgically excised, and relapses are uncommon.

Digital mucous cyst (myxoid cyst) is discussed in Chapter 110.

Primary Follicular Mucinoses

Mucin accumulates within the follicular epithelium in two distinctive primary disorders: Pinkus follicular mucinosis and urticaria-like follicular mucinosis. Otherwise, follicular mucinosis is considered a histologic epiphenomenon (i.e. secondary mucinosis), most often associated with cutaneous T cell lymphoma, in particular mycosis fungoides and Sézary syndrome, or other skin diseases (e.g. atopic dermatitis; see Table 46.3).

Follicular mucinosis

Synonyms: ■ Alopecia mucinosa ■ Mucinosis follicularis ■ Pinkus follicular mucinosis – benign primary form

History, epidemiology, and pathogenesis

This uncommon inflammatory disorder, described in 1957 by Pinkus, has a predilection for children and for adults in the third and fourth decades of life. It is unclear why dermal-type mucin is deposited selectively within an epithelial structure. Although follicular keratinocytes have been considered to be the source of the mucin, an etiologic role for cell-mediated immune mechanisms has been proposed[42], including a reaction to persistent antigens such as *Staphylococcus aureus*.

Clinical features

Primary follicular mucinosis is an idiopathic benign form of the disease, apparently not linked to lymphoma[42]. Clinically, it presents as an acute or

subacute eruption in children and young adults and is characterized by one or several pink plaques, often composed of grouped follicular papules. There may be associated scale, and lesions are limited to the face (Fig. 46.15A) and scalp and are associated with alopecia. Papulonodules (Fig. 46.15B), annular plaques, folliculitis, follicular spines, and acneiform eruptions have also been described[42,43]. A second type of follicular mucinosis, characterized by: (1) a more generalized distribution (extremities, trunk and face; Fig. 46.15C); (2) larger and more numerous plaques; (3) a chronic clinical course; and (4) occurrence in a slightly older age group[41], is probably best regarded as a secondary follicular mucinosis associated with atopic dermatitis or cutaneous T cell lymphoma, rather than a primary condition. Follicular mucinosis has occasionally been observed in patients with hematologic malignancies other than mycosis fungoides.

Pathology

Mucin accumulates within the follicular epithelium and sebaceous glands, causing keratinocytes to disconnect (Fig. 46.15D). In more advanced lesions, the follicles are converted into cystic spaces containing mucin, inflammatory cells, and altered keratinocytes. A perifollicular and intrafollicular infiltrate of lymphocytes, histiocytes, and eosinophils is seen[6].

Differential diagnosis

The differentiation between primary follicular mucinosis and mycosis fungoides-associated follicular mucinosis is very difficult[6], and there is no single reliable criterion. Although the existence of a primary form of follicular mucinosis has been questioned by some authors (who consider it as an "indolent" localized form of cutaneous T cell lymphoma[44]), features in favor of a primary form are the young age of the patient, a solitary plaque or limited number of lesions in the head and neck region, spontaneous resolution, and the absence histologically of epidermotropism and atypical lymphocytes. Detection of clonal T cell gene rearrangements does not seem to help differentiate the two types[42,42a].

Treatment

There is no specific treatment. A wait-and-see approach is recommended for primary follicular mucinosis as many cases resolve spontaneously within 2–24 months. Topical, intralesional, and systemic corticosteroids, antimalarials[44], phototherapy (PUVA, UVA1), minocycline, dapsone, indomethacin, oral isotretinoin, interferon-α-2b, and orthovoltage irradiation have been reported to be beneficial. For secondary forms, treatment of the underlying disease is indicated. Longitudinal evaluation and assessment for cutaneous T cell lymphoma is recommended for patients with presumed primary follicular mucinosis that is persistent or becomes more extensive.

Urticaria-like follicular mucinosis

Urticaria-like follicular mucinosis is a very rare disorder that occurs primarily in middle-aged men. Pruritic urticarial papules or plaques appear on the head and neck within an erythematous "seborrheic" background. As lesions resolve, red macules persist for a few weeks. Hair-bearing regions may be involved, but neither follicular plugging nor alopecia is seen. Urticaria-like follicular mucinosis waxes and wanes irregularly over a period that can vary from a few months to 15 years. There are no associated systemic diseases. Response to natural sunlight has been inconsistent, but it has been beneficial in a small number of cases.

As in primary follicular mucinosis, mucin-filled cystic spaces occupy hair follicles. In the upper dermis, lymphocytes and eosinophils are seen around blood vessels and hair follicles. In only a single patient to date were vascular C3 deposits seen by direct immunofluorescence. The prognosis is good, and based upon a limited number of case reports, antimalarials and dapsone were reportedly beneficial[45].

PRIMARY HAMARTOMATOUS–NEOPLASTIC MUCINOSES

Although stromal mucin deposition may be found in a variety of cutaneous tumors as an additional finding (e.g. basal cell carcinomas, neurofibromas), only in mucinous nevus and (angio)myxoma is the mucin deposition a distinctive feature.

Mucinous Nevus

A mucinous nevus (nevus mucinosus) is a benign hamartoma that can be congenital or acquired. It consists of a plaque that usually has a unilateral linear nevoid pattern[46]. Histologically, a diffuse deposit of mucin is seen in the upper dermis, and collagen and elastic fibers are absent within the mucinous area. The epidermis can be normal or it may be acanthotic with elongation of the rete ridges and hyperkeratosis, as in an epidermal nevus. The latter set of findings points to a combined hamartoma, in which features of an epidermal nevus are associated with those of a connective nevus of the proteoglycan type. The cellular component of a mucinous nevus consists of $CD34^+$ fibroblasts and scarce factor XIIIa-positive dendritic cells.

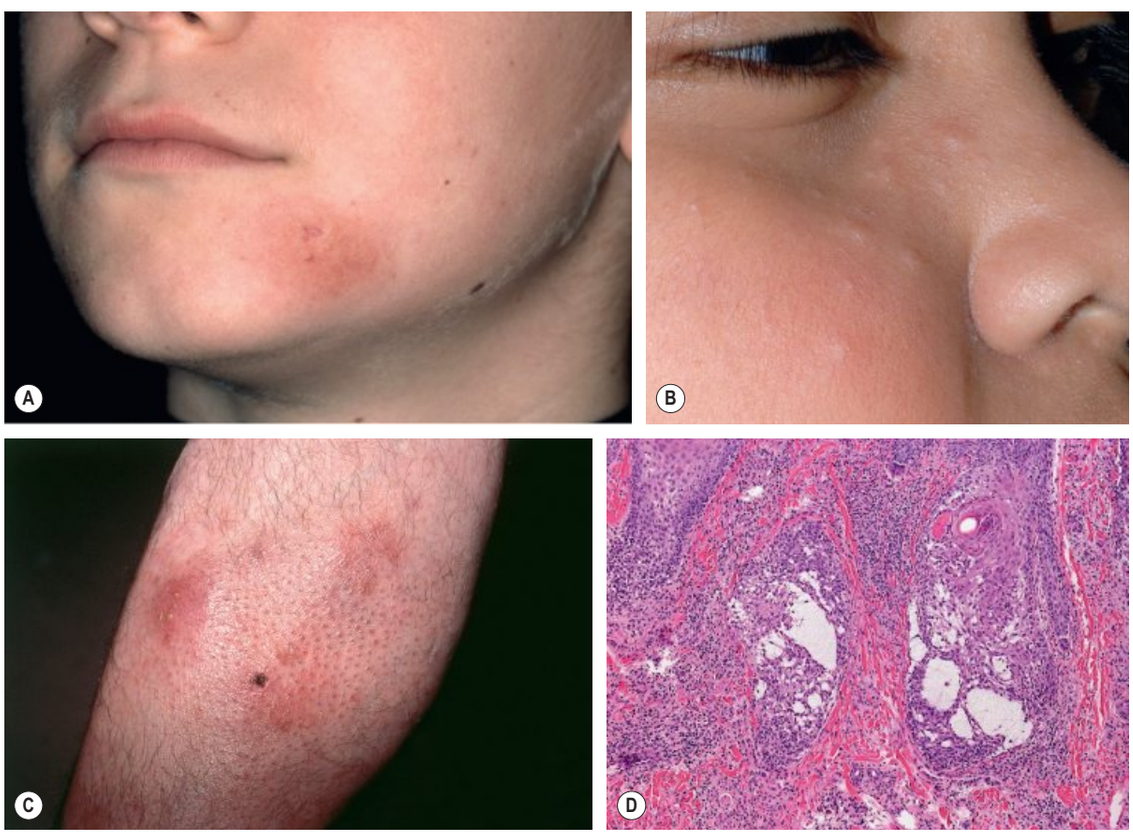


Fig. 46.15 Follicular mucinosis. **A** Pink plaque containing multiple follicular papules in a young boy. **B** Skin-colored papules on the cheek of a child. **C** Grouped follicular papules on the leg of an older adult in association with erythematous plaques. Note the associated alopecia. The hemorrhagic crust is the site of a previous biopsy. **D** Histology of follicular mucinosis (patient in **A**). Mucin deposition (wispy) within the follicular epithelia. *A, D, Courtesy Lorenzo Cerroni, MD; B, Courtesy Julie V. Schaffer, MD.*

Superficial (Angio)Myxoma

Superficial (angio)myxoma, also known as cutaneous myxoma, is an acquired benign neoplasm that is usually nodular and measures 1–5 cm in diameter. It favors the trunk, head and neck, and genital region; rarely, cutaneous myxomas have an acral location[47]. These tumors can be solitary, without any systemic abnormalities, or multiple. When multiple and involving the external ears, eyelids, or nipples, they may be a manifestation of Carney complex (cutaneous myxomas, cardiac myxomas, numerous lentigines, multiple blue nevi, endocrinopathies)[48].

Histologically, a cutaneous myxoma is a lobulated, well-defined lesion characterized by a mucinous matrix within the dermis and the subcutis, with variably shaped fibroblasts, mast cells, and a few collagen and reticulin fibers. Bizarre multinucleated cells and regular mitotic figures can be seen. The stromal cells are positive for vimentin and smooth muscle α-actin (SMA), with variable positivity for CD34, S-100, factor XIIIa, and CD68[47].

Myxomas must be distinguished from cutaneous focal mucinosis, a reactive lesion which is usually <1 cm and ill-defined histologically; the latter does not have an epithelial component and the mucin deposits are in the dermis but not the subcutis. This differentiation is important as (angio)myxomas are true neoplasms, although benign, which can recur after incomplete excision. When an (angio)myxoma is located in the genital region, it needs to be distinguished from an aggressive angiomyxoma, a rare neoplasm with potential for local recurrence and very rarely for distant metastases. Aggressive angiomyxomas usually stain positively for estrogen and progesterone receptors and are characterized by a different vascular component with variable thickness of vessel walls.

SECONDARY CUTANEOUS MUCINOSES

Secondary cutaneous mucinoses include all those diseases in which mucin deposition represents only an additional histologic finding and not the main feature[1]. As an epiphenomenon, a wide range of inflammatory disorders and neoplasms may have mucin deposition in the epidermis and/or dermis or within the follicular unit. Secondary mucinoses are outlined in Table 46.3.

Additional figures available in our eBook (see inside front cover for access code).

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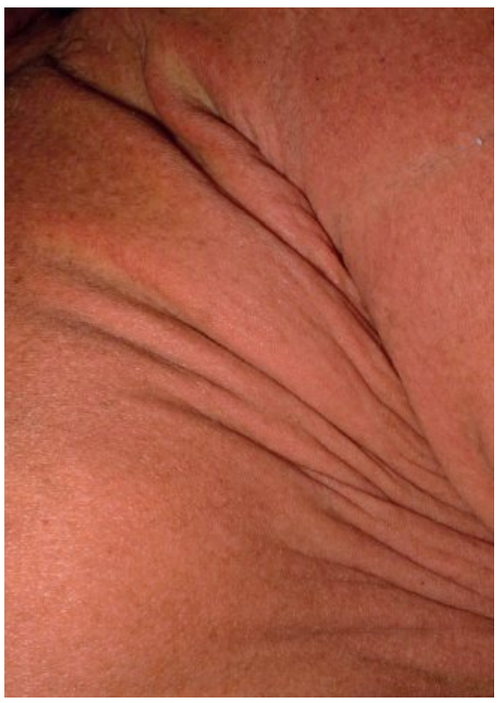
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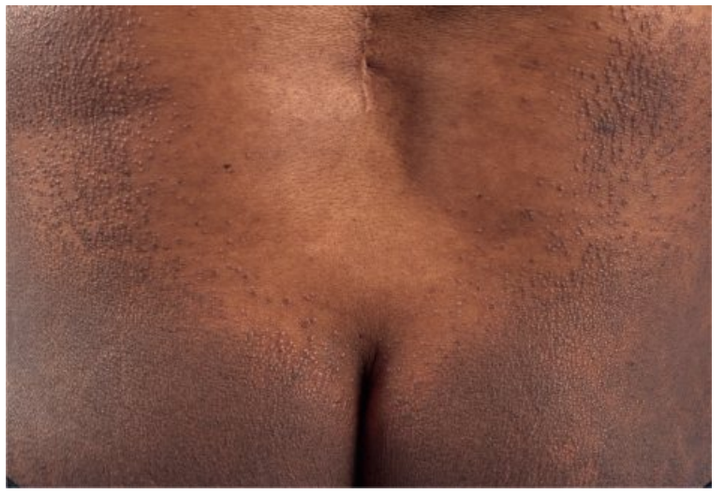




eFig. 46.1 Scleromyxedema. A, B Numerous monomorphic, firm, skin-colored to pink papules which can have a linear arrangement (most obvious on the left neck [**A**] and the upper back [**B**]).



eFig. 46.2 Scleromyxedema. Thickening of the skin of the trunk, leading to deep furrows and folds. The skin has been described as "elephant-like". *Courtesy Joyce Rico, MD.*



eFig. 46.3 Scleromyxedema. Numerous monomorphic, firm, skin-colored to hyperpigmented papules. Many of the papules have a linear arrangement. *Courtesy Edward Cowen, MD.*





eFig. 46.4 Pretibial myxedema and ophthalmopathy in a patient with Graves disease. A Induration and erythema of the legs with disfiguring soft tissue overgrowth of the dorsal feet and toes. **B** There is "scleral show", i.e. visible sclera between the eyelids and iris. *Courtesy Edward Cowen, MD.*



eFig. 46.5 Reticular erythematous mucinosis. Grouped pink papules on the central chest and upper abdomen. No surface changes are present and there is a reticulated configuration. *Courtesy Lorenzo Cerroni, MD.*



eFig. 46.6 Reticular erythematous mucinosis. Pink papules and plaques of the central chest. *Courtesy Judit Stenn, MD.*



eFig. 46.7 Reticular erythematous mucinosis. Grouped pink papules and plaques on the central chest with no surface changes; there is a subtle annular and reticulated configuration. Note the significant tan.



eFig. 46.8 Follicular mucinosis. Pink plaques with scale and an absence of hair. *Courtesy Eugene Mirrer, MD.*



eFig. 46.9 Follicular mucinosis. Several pink plaques on the face of a young girl.

Amyloidosis 47

Richard W. Groves

INTRODUCTION

Amyloidosis is not a single disease; rather, the term is used to refer to several diseases that share the common feature of abnormal extracellular deposition of amyloid, a fibrillar proteinaceous material, within tissues. Deposits of amyloid can be seen in a range of clinical disorders, from plasma cell dyscrasias and Alzheimer disease to familial polyneuropathies and primary cutaneous lichen amyloidosis.

Amyloid itself is not a single chemically distinct substance, and several types of amyloid have been described. However, regardless of the source, pathogenetic mechanisms, or underlying disease, amyloid material shares certain common tinctorial and physico-chemical properties, e.g. the cross-β-pleated sheet configuration[1].

The two clinical settings in which dermatologists are likely to encounter amyloidoses are: (1) the more common primary cutaneous forms of amyloidosis; and (2) the less common systemic amyloidosis with cutaneous manifestations (Fig. 47.1).

History

Virchow, in 1854, introduced the term "amyloid"[2]. He believed that the substance resembled starch or cellulose because, like starch, it turned blue when stained with iodine followed by dilute sulfuric acid. In 1928, Gutmann first described a patient with clinical features of lichen amyloidosis, while Freudenthal, in 1930, introduced the term "lichen amyloidosus"[3].

Epidemiology

The precise epidemiology of systemic amyloidosis is not known, as the disease is often underdiagnosed or misdiagnosed[4]. In the US, the incidence of primary systemic amyloidosis is estimated to be ~1300 to 3200 new cases per year[4]; an increase in detection will likely accompany more widespread use of the assay for serum free light chains. Since 1980, there has been a marked decline in the incidence of symptomatic rheumatoid arthritis-associated secondary systemic amyloidosis due to better control of the inflammatory response[5,6].

Primary cutaneous amyloidosis is commonly observed in Southeast Asian countries, including Singapore, Taiwan, and Thailand[7]. Lichen amyloidosis in particular appears to be more prevalent in those of Chinese descent. Macular amyloidosis is frequently seen in Central and South American countries, especially those close to the equator[8]. In general, macular and lichen amyloidosis occur more often in individuals with skin phototypes III and IV.

Classification

Amyloidosis can be classified clinically into systemic (generalized) forms, with involvement of several organ systems, and organ-limited (localized) forms, in which deposits are limited to a single organ such as the skin (Table 47.1). In the localized forms, amyloid deposition occurs at or near the site of synthesis, while in the systemic forms the precursors are secreted into the circulation, followed by amyloid deposition at distant sites[9]. Amyloidosis can also be classified according to its constituent precursor protein (Table 47.2; see next section).

Pathogenesis

The major component of amyloid is the fibril protein; the minor components are amyloid P component, glycosaminoglycans, and apoE lipoprotein. Amyloid P is a glycoprotein derived from serum amyloid P protein (SAP) and it has a specific calcium-dependent binding affinity for amyloid. Over 40 distinct forms of amyloid fibril proteins and their precursors have been identified[9a], including: AL (amyloid light chains), containing immunoglobulin light chains; AA (amyloid-associated), composed of an acute phase protein synthesized by the liver; Aβ amyloid, found in cerebral lesions of Alzheimer disease; and ATTR (transthyretin-associated), found in some forms of familial amyloidosis (mutated) and senile systemic amyloidosis (wild-type)[9]. Each condition is associated with a specific precursor protein (see Table 47.2)[10]; these amyloid precursors are initially soluble proteins that undergo changes leading to aggregation, polymerization, fibril formation, and, finally, extracellular tissue deposition as insoluble amyloid.

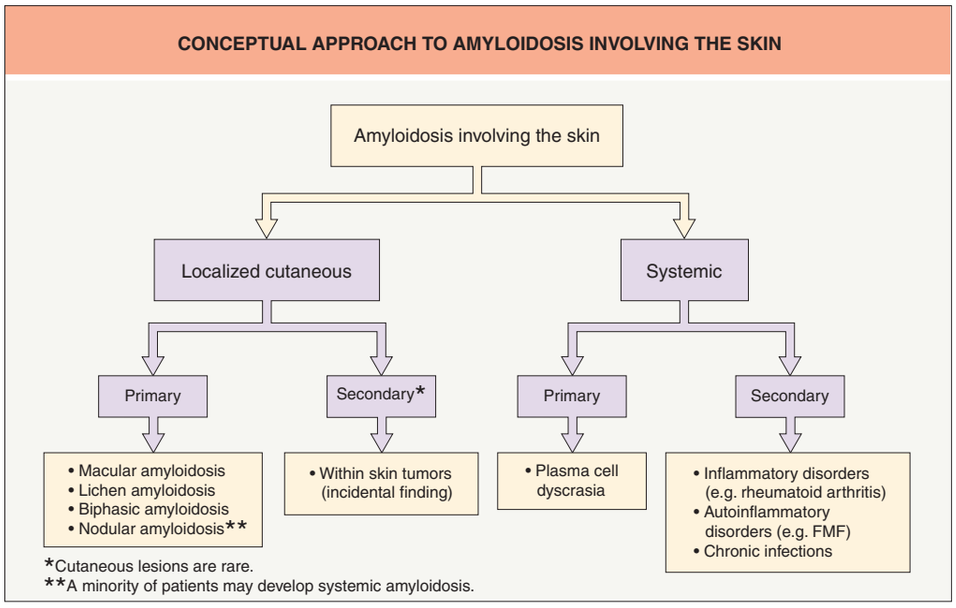


Fig. 47.1 Conceptual approach to amyloidosis involving the skin. FMF, familial Mediterranean fever.

CLINICAL CLASSIFICATION OF AMYLOIDOSIS
Organ-limited (localized) amyloidosis
Cutaneous • Primary: macular, lichen, biphasic, dyschromic, nodular • Secondary: incidental finding within various skin tumors (e.g. seborrheic keratoses, basal cell carcinomas, dermatofibromas, intradermal melanocytic nevi, adnexal tumors, Bowen disease, porokeratosis); following PUVA therapy Endocrine • Medullary carcinoma of the thyroid, insulinoma, type 2 diabetes Cerebral • Alzheimer disease
Systemic amyloidosis
Primary systemic amyloidosis (AL ≫ AH amyloid protein) • Plasma cell dyscrasias (more common) • Multiple myeloma-associated Secondary systemic amyloidosis (reactive; AA amyloid protein) • Chronic inflammation (e.g. rheumatoid arthritis, hidradenitis suppurativa) • Chronic infection (e.g. tuberculosis, Hansen disease [leprosy]) ATTR amyloidosis (transthyretin amyloid protein*) • Familial amyloid polyneuropathy (*TTR* mutations) • Familial amyloid cardiomyopathy/ATTR-CM (*TTR* mutations) • Wild-type ATTR amyloidosis (ATTRwt)/senile systemic amyloidosis/senile cardiac amyloidosis • ALect2 amyloidosis (leukocyte chemotactic factor 2) See Table 47.2 for additional forms
*Transthyretin is a serum transport protein for thyroxine and retinol-binding protein that is produced in the liver, choroid plexus and eye[9].

Table 47.1 Clinical classification of amyloidosis.

The process by which this transformation takes place differs amongst the various types of amyloidoses. In primary systemic amyloidosis, substitution of amino acids at specific positions within the variable region of the immunoglobulin light chain potentially destabilizes these chains thereby increasing the likelihood of their conversion to amyloid fibrils. Similarly, mutations in the transthyretin gene have been shown to alter the stability of the transthyretin protein and increase its baseline mild amyloidogenicity[1,4]. The accumulation of these relatively inert amyloid fibrils within vital organs leads to functional impairment.

The precise pathogenesis of primary cutaneous amyloidosis is not yet fully understood. Prolonged friction, genetic predisposition (e.g. *OSMR*, *IL31RA*), and environmental factors have all been implicated as possible etiologies. The precursor protein involved has not been fully characterized; however, for the macular and lichenoid variants of primary cutaneous amyloidosis it is thought to be keratinocyte-derived. This has been supported by ultrastructural studies demonstrating transitional forms between viable keratinocytes and amyloid, as well as by positive reactions with monoclonal antibodies directed against basal layer keratins[11]. The fibrillar theory proposes that keratinocyte tonofilaments undergo degeneration and pass into the dermis, where they are presumably modified by histiocytes and fibroblasts into amyloid material. An alternative theory suggests that the material is produced at the epidermo-dermal interface, with precursor proteins being secreted by basal keratinocytes. This hypothesis has been supported by ultrastructural findings and demonstration of basement membrane antigens such as type IV collagen and laminin within amyloid deposits[11]. Although these cutaneous amyloid deposits stain positively with anti-human antibodies directed against IgG, IgM and IgA, this staining is thought to be the result of nonspecific immunoglobulin absorption as opposed to an immunoglobulin being the putative precursor protein. Apolipoprotein E4, galectin-7, and actin have also been shown to be associated with primary cutaneous amyloid deposits and may be synthesized locally by keratinocytes[12,13]. Small fiber neuropathy has been observed in primary cutaneous amyloidosis and may be related to the associated pruritus[14].

In nodular amyloidosis there is no specific staining with antikeratin antibodies, but rather the amyloid deposits are composed of immunoglobulin light chains, suggesting plasma cell derivation akin to the cutaneous lesions of primary systemic amyloidosis. Thus, its origin is very different from that of either macular or lichen amyloidosis[11]. Presumably, there is local cutaneous production of light chains in nodular amyloidosis, whereas in primary systemic amyloidosis with skin involvement, the light chains are derived from the systemic circulation.

CHEMICAL CLASSIFICATION OF AMYLOIDOSES		
Precursor protein	**Amyloid protein**	**Clinical syndrome**
Aβ precursor protein (AβPP)	Aβ	Alzheimer disease, aging
(Apo) serum AA*	AA	Secondary systemic amyloidosis (see Table 47.1), autoinflammatory syndromes (e.g. familial Mediterranean fever, Muckle–Wells syndrome, TRAPS; see Table 45.2)
Apolipoprotein AI	AApoAI	Hereditary apolipoprotein AI-associated amyloidosis; distribution of organ involvement, including skin, related to location of mutation
Apolipoprotein AII	AApoAII	Familial renal amyloidosis
β_2-microglobulin	Aβ_2M	Chronic hemodialysis
Calcitonin	ACal	Medullary carcinoma of the thyroid
Cystatin C	ACys	Hereditary cystatin C amyloid angiopathy†
Gelsolin	AGel	Familial amyloidosis, Finnish type
Immunoglobulin heavy chain (very rare)‡	AH	Primary systemic amyloidosis
Keratin	AKer	Primary (localized) cutaneous amyloidosis
Immunoglobulin light chain	AL	Primary systemic amyloidosis (associated with plasma cell dyscrasia¶ ≫ multiple myeloma), primary cutaneous nodular amyloidosis
Medications: insulin enfurvitide anakinra GLP-1 receptor agonist	AIns AEnf AIL1RAP AGLP1	At sites of injections, firm nodules or in abdominal fat of normally appearing skin (AGLP1)
Leukocyte chemotactic factor 2	ALect2	Progressive renal insufficiency and hepatic involvement; favors Mexican-Americans
Transthyretin	ATTR	ATTR amyloidosis: (1) familial amyloid polyneuropathy (*TTR* mutations); (2) familial amyloid cardiomyopathy (*TTR* mutations); and (3) wild-type ATTR amyloidosis/senile systemic amyloidosis/senile cardiac amyloidosis
Corneodesmosin	ACor	Hypotrichosis simplex of the scalp

*Amyloid-associated protein synthesized by the liver.
†Detection of deposits within clinically normal skin allows diagnosis prior to clinical symptoms (cerebral hemorrhage).
‡More commonly, heavy chains produce a non-amyloid type deposit termed heavy chain deposition disease which is sometimes associated with acquired cutis laxa.
¶Monoclonal gammopathy; progression depends upon risk factors (e.g. non-IgG paraprotein).

Table 47.2 Chemical classification of amyloidoses. Except for Aβ, AApoAII, ACal and ALect2 (light shade), there are reports of amyloid deposits in involved or clinically uninvolved skin and/or oral mucosa. Although >40 types of amyloid have been characterized[9a], to date there are no reports of associated cutaneous lesions in types not listed in the table. GLP, glucagon-like peptide; IL1RAP, interleukin-1 receptor antagonist protein; TRAPS, TNF receptor-associated periodic syndrome. *Adapted from Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. Amyloid 2010;17:101–4.*

Amyloid Properties

In H&E-stained sections, amyloid appears as amorphous, eosinophilic fissured masses (Figs. 47.2, 47.3A & Table 47.3). With a Congo red stain, amyloid has an orange–red color on routine light microscopy, whereas under polarized light it exhibits green birefringence (Fig. 47.3B). Other special stains that can be used to detect amyloid deposits include crystal violet, methyl violet, periodic acid Schiff (PAS), Sirius red, pagoda red, Dylon stain, and Thioflavin T (Fig. 47.3C)[15]. AA (but not AL) amyloid loses its affinity for Congo red after exposure to potassium permanganate.

By electron microscopy, amyloid appears as 7 to 10 nm wide, non-branching, non-anastomosing fibrils (see Fig. 47.2). X-ray crystallography and infrared spectroscopy reveal a characteristic cross-β-pleated sheet conformation. These findings are identical in all types of amyloid, regardless of clinical setting or chemical composition[15]. The cross-β-pleated sheet structure of amyloid is believed to be responsible for its staining and birefringence with Congo red stain.

Immunohistochemical stains utilizing antibodies directed against the amyloid fibril proteins (e.g. immunoglobulin γ light chain, transthyretin, keratin, AA protein) can help to differentiate between the types of amyloid (Fig. 47.3D). However, these immunohistochemical stains have limitations. For precise protein identification, including AL, ATTR and Alect2, liquid chromatography–tandem mass spectrometry (LC-MS/MS) is performed on formalin-fixed, paraffin-embedded sections or subcutaneous fat fine needle aspirates (see Table 47.2)[16,17]. Laser capture technology can be used to obtain the sample for testing.

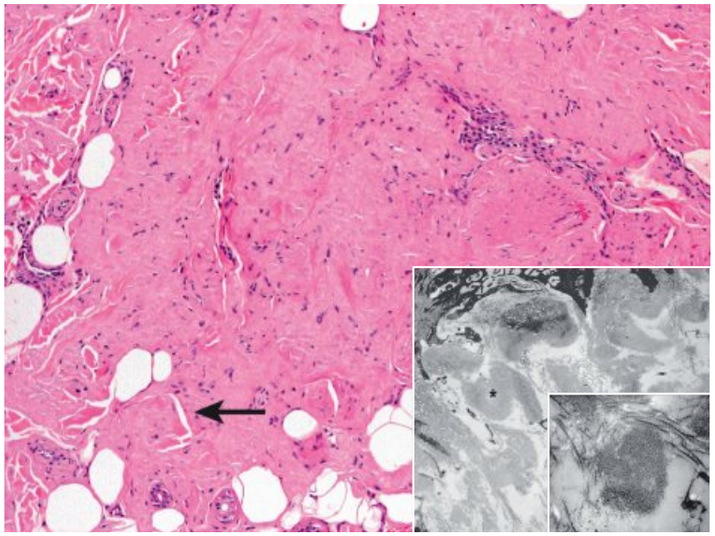


Fig. 47.2 Histologic features of amyloid deposits within the skin. In this example of nodular amyloidosis, the dermal deposits are eosinophilic, amorphous and contain fissures (arrow). By electron microscopy, there are clusters of filamentous deposits (*) and 7–10 nm non-branching fibrils (inset). *Courtesy Lorenzo Cerroni, MD and St John's Institute of Dermatology.*

HISTOPATHOLOGIC FEATURES OF AMYLOID DEPOSITS
• Homogeneous, hyaline, eosinophilic deposits in H&E-stained sections (Figs. 47.2 & 47.3A)
• Crystal violet metachromasia
• Positive staining with alkaline Congo red
• Apple-green birefringence under polarized light after Congo red staining; also dichroic (Fig. 47.3B)
• Fibrillar structure on electron microscopy (Fig. 47.2)
• Stains brightly by ultraviolet fluorescence microscopy after Thioflavin T staining (Fig. 47.3C)
• Staining with antibodies to amyloid P component
• Staining with antibodies directed against specific precursors (e.g. keratin [Fig. 47.3D])

Table 47.3 Histopathologic features of amyloid deposits[2].

PRIMARY LOCALIZED CUTANEOUS AMYLOIDOSIS

Primary cutaneous amyloidosis is associated with the deposition of amyloid in the skin but not internal organs (see Table 47.1). The most common variants are macular amyloidosis, lichen amyloidosis, and biphasic amyloidosis.

Clinical Features – Macular, Lichenoid, Biphasic, and Dyschromic Amyloidosis

Although primary cutaneous amyloidosis is classically divided into macular (macular amyloidosis), papular (lichen amyloidosis), and nodular (nodular amyloidosis) forms, the first two entities actually represent the ends of a clinical spectrum. In some patients and even some lesions both macular and papular forms can be present, termed "biphasic amyloidosis"[18,19]. Primary cutaneous amyloidosis can have a profound effect on quality of life due to the associated pruritus and visual appearance of the skin lesions[20].

Macular amyloidosis is often pruritic but it may be asymptomatic. The lesions of macular amyloidosis are hyperpigmented, either in a confluent or rippled pattern (Fig. 47.4A). The latter can be best appreciated by stretching the skin. The most common site of involvement is the upper back, especially over the scapular area, followed by the extensor surfaces of the extremities. A linear or even nevoid pattern may be seen (Fig. 47.4B). Macular amyloidosis usually presents in early adulthood, and women may be affected more often than men[15,21]. In biphasic amyloidosis, fine papular lesions are superimposed upon a background of hyperpigmentation.

The term "friction amyloidosis" has been used to describe a subgroup of patients in whom local friction from nylon brushes, towels, and other rough materials contributes to the production of macular and lichenoid lesions. There is also significant clinical overlap between macular amyloidosis and the pigmented form of notalgia paresthetica, where pruritus of the scapular areas leads to rubbing and scratching (see Ch. 6).

Lichen amyloidosis is the most common form of primary cutaneous amyloidosis and usually presents as persistent, pruritic plaques on the shins or other extensor surfaces, e.g. anterior thighs or forearms (Fig. 47.5)[10,18]. Initial lesions are discrete, firm, scaly, skin-colored or hyperpigmented papules, which later coalesce into plaques that often have a rippled or ridged pattern. At the onset, lesions are usually unilateral, but over time a bilateral symmetric distribution pattern can develop[18].

Primary cutaneous amyloidosis manifesting as pigmentation and lichenification of the anal and sacral regions has been described as an ano-sacral variant, but these patients often have lichen amyloidosis

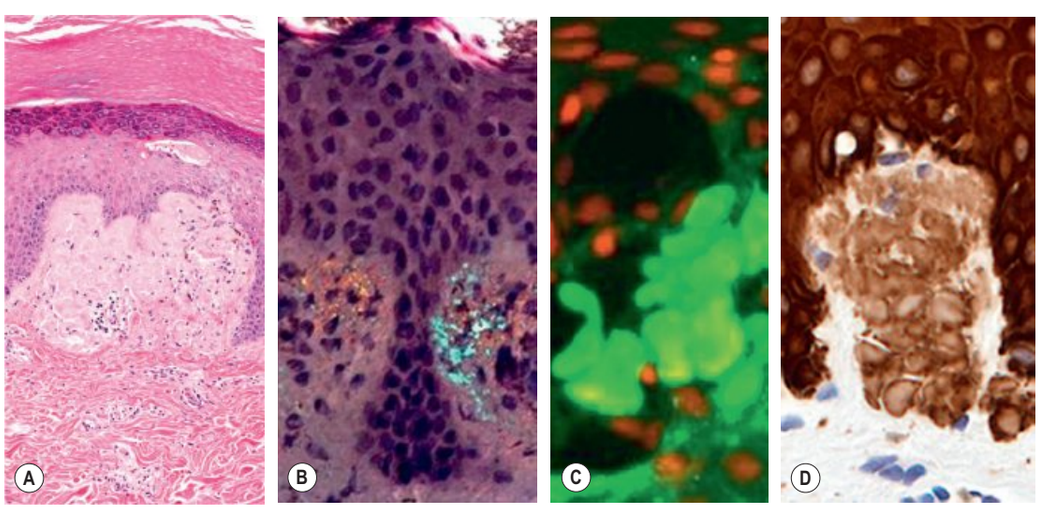


Fig. 47.3 Use of special stains to identify amyloid deposits within the papillary dermis in lichen amyloidosis. A In hematoxylin & eosin-stained sections, amyloid deposits, admixed with melanophages, are seen within the papillary dermis in addition to compact orthohyperkeratosis and acanthosis. **B** With Congo red stain, there is characteristic green birefringence with polarized light; the color can vary from yellow–green to blue–green. **C** With Thioflavin T stain, amyloid deposits stain brightly with ultraviolet fluorescence microscopy. **D** Positive immunohistochemical stain for keratin (MNF 116, broad-spectrum anti-keratin antibody). *A, Courtesy Lorenzo Cerroni, MD; B,C, Courtesy St John's Institute of Dermatology; D, Courtesy Jennifer McNiff, MD.*

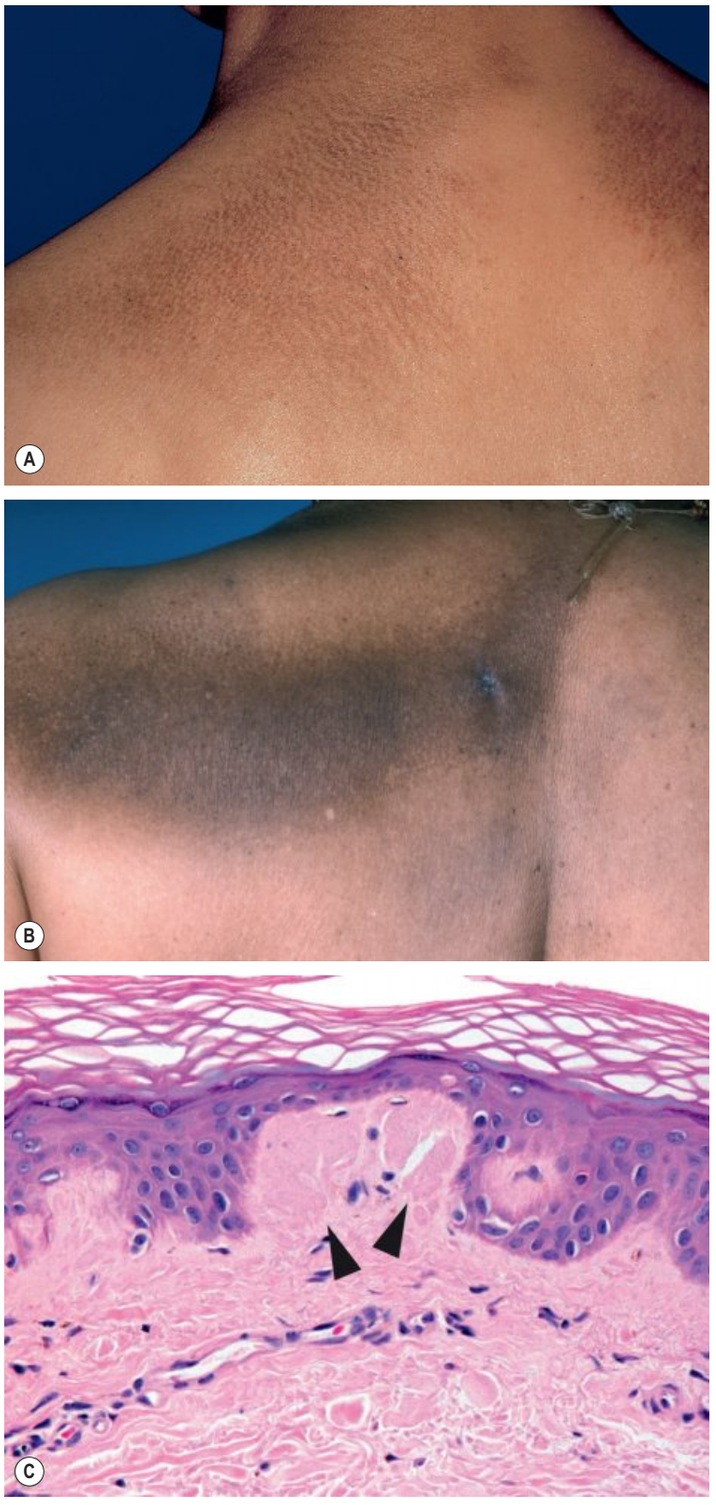


Fig. 47.4 Macular amyloidosis. A Characteristic rippled hyperpigmentation of macular amyloidosis. **B** Occasionally a linear accentuation is seen. Scattered papules can also be seen in both patients. **C** Histologically, deposits of amyloid within the dermal papillae (arrowheads) as well as melanophages within the papillary dermis; note the characteristic fissure in the amyloid deposit. These deposits may be subtle. *C, Courtesy Lorenzo Cerroni, MD.*



Fig. 47.5 Lichen amyloidosis. A Multiple monomorphous papules on the shin; the rippled appearance is most obvious laterally. **B** Numerous small monomorphous papules on the calves admixed with focal hemorrhagic crusts from scratching and hypopigmented scars. *B, Courtesy Lorenzo Cerroni, MD.*



Fig. 47.6 Primary cutaneous amyloidosis in a patient with systemic sclerosis. Note the numerous papules, some of which are in a grid-like array.

or biphasic amyloidosis elsewhere[18,19]. Bullous lesions have also been described in the setting of lichen amyloidosis, but they are more commonly associated with systemic amyloidosis.

Macular and/or lichen amyloidosis has also been described in association with autoimmune connective tissue disorders (e.g. systemic sclerosis [Fig. 47.6], systemic lupus erythematosus, dermatomyositis), and primary biliary cirrhosis[15]. One patient was observed to have sparing of lichen amyloidosis lesions in areas with higher cutaneous temperatures (such as along the course of large superficial veins), suggesting that amyloid fibril formation may be a temperature-dependent process *in vivo*[22].

Familial primary cutaneous amyloidosis syndromes

A number of genetic disorders have been identified that predispose to the development of primary localized cutaneous amyloidosis (PLCA).

IL-31 receptor-associated amyloidosis (PLCA1 and PLCA2)

Several families with primary localized cutaneous amyloidosis have been shown to have pathogenic variants in the genes that encode either the β subunit of the oncostatin M receptor (OSMR; PLCA1)[23] or the α subunit of the interleukin (IL)-31 receptor (IL-31RA; PLCA2)[24]. However, the protein product of *OSMR* serves as the β subunit of two receptors – not just OSMR but also IL-31R; this subunit then combines with IL-31RA to form the IL-31 receptor[25]. Of note, IL-31 has been shown to be of importance in pruritic skin conditions (e.g. dermatitis, prurigo nodularis), and nemolizumab, an anti-IL-31RA antibody, reduced pruritus in patients with atopic dermatitis[26]. In these families with primary localized cutaneous amyloidosis, IL-31 signalling may also be influenced by monocyte chemoattractant protein 1 (MCP-1)[27].

Dyschromic amyloidosis (PLCA3)

Dyschromic amyloidosis, also referred to as primary localized cutaneous amyloidosis 3 (PLCA3), is an unusual variant in which a guttate leukoderma is superimposed upon a background of hyperpigmentation and admixed with characteristic lesions of macular and lichen amyloidosis (see Fig. 67.27). Homozygous and compound heterozygous mutations in *GPNMB*, which encodes glycoprotein nonmetastatic melanoma protein b, have been detected in patients with dyschromic amyloidosis[28].

Sipple syndrome or multiple endocrine neoplasia (MEN) type 2A

Sipple syndrome is an autosomal dominant disorder with the triad of medullary carcinoma of the thyroid, pheochromocytomas, and hyperparathyroidism (see Ch. 63). Increased serum levels of calcitonin are a reflection of hyperplasia or carcinoma of the parafollicular calcitonin-producing C cells of the thyroid. Multiple endocrine neoplasia (MEN) type 2A is associated with pruritic areas of hyperpigmentation on the upper back. The lesions have been described as notalgia paresthetica, macular amyloidosis, and lichen amyloidosis. The unusual aspect is the early age of onset, often before the age of 10 years. Recognition of this skin sign of systemic disease can lead to prophylactic thyroidectomy once the diagnosis is established[29]. A study of 10 families with MEN 2A found an incidence of lichen amyloidosis of 36%; moreover, all those with cutaneous amyloidosis had a specific pathogenic variant in codon 634 of the *RET* proto-oncogene[30].

X-linked reticulate pigmentary disorder (Partington amyloidosis)

Partington and colleagues described a family with an X-linked disease in which adult women had linear streaks of hyperpigmentation and male patients manifested reticulated, mottled brown skin pigmentation, which on biopsy demonstrated dermal deposits of amyloid (in adults but not children). In women, involvement was limited to the skin, but in male patients, recurrent respiratory infections, corneal dystrophy, and photophobia were seen (see Ch. 67). As in macular amyloidosis, the amyloid deposits are keratin-positive and absent in other tissues[31].

Pathogenic variants in *POLA1* on chromosome Xp22, which encodes the catalytic subunit of DNA polymerase α1, have been detected in several families. This was associated with an activation of proinflammatory genes (e.g. NF-κB) and an increased type I interferon profile.

Other associated disorders

Primary cutaneous amyloidosis has also been reported in association with pachyonychia congenita, dyskeratosis congenita, and familial palmoplantar keratoderma[15]. At sites of injection of several medications, e.g. insulin, cutaneous amyloid deposits can develop (see Table 47.2)

Clinical Features – Nodular Amyloidosis

Nodular amyloidosis is rare, and presents as single or multiple waxy nodules or infiltrated plaques, most commonly on the trunk or extremities (Fig. 47.7A,B). Immunoglobulin γ light chains as well as β_2-microglobulin have been demonstrated within the deposits, and both are thought to be produced by plasma cells in the vicinity (Fig. 47.7D)[32]. In several patients with nodular amyloidosis, the cutaneous plasma cells had monoclonal restriction of their immunoglobulin light chains as determined by immunohistochemistry or *in situ* hybridization; examination of the bone marrow in one patient showed no evidence of a clonal plasma cell proliferation[33,34]. Of note, there may be an association between Sjögren syndrome and nodular amyloidosis of the skin or lung[35]. It has been suggested that at least some cases of cutaneous nodular amyloidosis could represent a variant of primary cutaneous marginal zone lymphoproliferative disorder (lymphoma) with unusual histopathologic features, but a similar excellent prognosis (see Ch. 119)[36,37].

There are reports of the nodular variant progressing to systemic involvement, hence longitudinal evaluation is appropriate. However, recent observations suggest that this risk is ~7%, much less than the previously quoted 50%. Although 40% of patients in this long-term study had a paraproteinemia at presentation, the gammopathy remained static during the follow-up period and progression to systemic involvement was

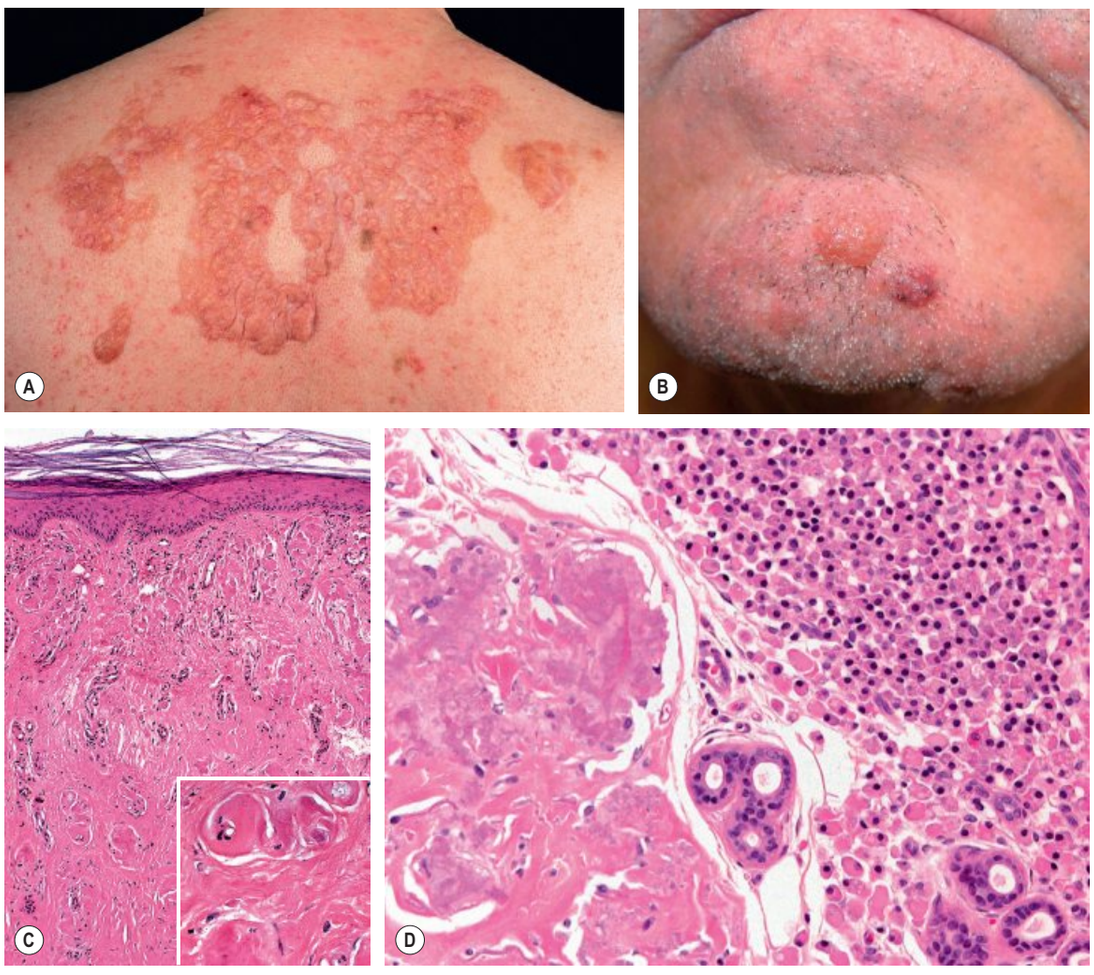


Fig. 47.7 Nodular amyloidosis. A, B Firm waxy plaques and nodules on the back and chin. The color can vary from skin-colored to pink–yellow to violaceous. **C** Histologically, there are extensive amyloid deposits within the dermis and around blood vessels. **D** An infiltrate of plasma cells can be seen in association with the amyloid deposits. *D, Courtesy Lorenzo Cerroni, MD.*

observed in only 1 of 15 patients, 23 years after the initial presentation[38]. A similar study of 16 patients with nodular amyloidosis found a near equal sex distribution, with a tendency for an acral distribution. There was one patient who subsequently died from systemic amyloidosis[34].

Pathology

In macular and lichen amyloidosis, amyloid deposits are restricted to the upper dermis, particularly the papillary dermis (Fig. 47.4C). In lichen amyloidosis, the deposits may expand the papillae and displace the elongated rete ridges laterally. The overlying epidermis often has features of chronic rubbing, e.g. acanthosis, compact orthohyperkeratosis (see Fig. 47.3A). Melanophages and a sparse perivascular lymphohistiocytic infiltrate can be seen in both forms. Although antikeratin antibodies (e.g. MNF 116) may be useful in confirming the keratin origin of the amyloid deposits in these two forms of primary cutaneous amyloidosis, they are seldom required (see Fig. 47.3D).

In contrast, in the nodular variant, the dermis, subcutis, and blood vessel walls are diffusely infiltrated with amyloid (Fig. 47.7C). A perivascular infiltrate of plasma cells is nearly universally present, but in most cases is inconspicuous (see Fig. 47.7D)[38]. Immunostaining for light chain deposition can aid in the diagnosis of nodular amyloidosis. As noted previously, these plasma cells are usually monoclonal, and it has been recently suggested that a number of cases of primary cutaneous nodular amyloidosis ("nodular amyloidoma") may represent a peculiar variant of cutaneous marginal zone lymphoproliferative disorder (lymphoma)[36,37].

Differential Diagnosis

The diagnosis of primary cutaneous amyloidosis is based on clinical morphology and histologic demonstration of amyloid deposits within the skin (see Table 47.3).

There is significant overlap in the appearance of *macular amyloidosis* and notalgia paresthetica. The latter is also seen on the upper back and can have rippled hyperpigmentation. Histologically, the early stages of notalgia paresthetica contain scattered necrotic keratinocytes and a few melanophages but no amyloid deposits. However, later on, even within the same lesion, deposits can appear. When macular amyloidosis is more diffuse or confluent, it must be distinguished from postinflammatory hyperpigmentation. Other entities in the differential diagnosis may include pityriasis versicolor, atrophic lichen planus (LP), erythema dyschromicum perstans (ashy dermatosis), and drug-induced pigmentation.

The primary differential diagnosis for *lichen amyloidosis* includes lichen simplex chronicus (LSC) and hypertrophic LP. Both are characterized by chronic pruritic plaques, often on the shins and, histologically, exhibit hyperkeratosis, acanthosis, and a mild to moderate lymphohistiocytic inflammatory infiltrate but no amyloid deposits. In LSC, lichenification is often prominent, while hypertrophic LP lesions may have a violaceous hue and, on histologic examination, a lichenoid infiltrate with vacuolar degeneration. Other entities that may be considered in the clinical differential diagnosis include papular mucinosis, pretibial myxedema, prurigo simplex/nodularis, pemphigoid nodularis, lichen ruber moniliformis, and epidermolysis bullosa pruriginosa.

Nodular amyloidosis may resemble the cutaneous lesions of primary systemic amyloidosis and the latter should be excluded. The clinical differential diagnosis also includes other nodular lesions (e.g. cutaneous lymphoid hyperplasia, sarcoidosis, colloid milium), all of which have rather distinctive histopathologic features and therefore can be easily differentiated.

Treatment

No treatment modalities described to date have proven to be curative or uniformly effective in patients with *macular or lichen amyloidosis* (Table 47.4)[39]. Treatment must be directed at breaking the itch–scratch–itch cycle usually present in these patients. Chronic friction, scratching, and rubbing can serve as possible precipitating or aggravating factors and patients should be advised of this. Potent topical corticosteroids are useful to some extent, especially in mild cases, and application under occlusion or in combination with a mild keratolytic agent such as salicylic acid (particularly in lichen amyloidosis) may have added benefit. The involved sites can be protected from scratching by applying occlusive dressings such as hydrocolloids or gauze wraps impregnated with zinc oxide for a period of weeks to months, but recurrence rates may be high. Based upon case reports, topical calcineurin inhibitors may play an adjunctive role, and more recently, dupilumab was observed to be an effective treatment for lichen amyloidosis[40]. Whether nemolizumab, the anti-IL-31RA antibody, will lead to improvement remains to be determined.

TREATMENT OF MACULAR AND LICHEN AMYLOIDOSIS
Potent topical corticosteroids, including under occlusion (2)
Topical calcineurin inhibitors (3)
Intralesional corticosteroids (3)
Occlusive dressings (e.g. hydrocolloid) or wraps (e.g. zinc oxide-impregnated) (3)
UVB phototherapy (2)
PUVA phototherapy (2)
Systemic retinoids (2)
Dermabrasion (2)
CO_2 laser therapy (2)
Low-dose cyclophosphamide (3)
Cyclosporin (3)
Dupilumab (3)
Thalidomide (3)

Table 47.4 Treatment of macular and lichen amyloidosis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. PUVA, psoralen plus UVA; UVB, ultraviolet B.

In a study that compared the efficacy of topical corticosteroids versus either UVB or topical PUVA phototherapy for the treatment of lichen amyloidosis, there was greater improvement in the pruritus and roughness scores on the sides treated with either form of phototherapy, with PUVA being marginally better in reducing pruritus[41]. Dermabrasion was shown to be beneficial in lichen amyloidosis involving the limbs with the effects lasting at least five years: the epidermis and part of the papillary dermis along with some of the amyloid was removed, permitting re-epithelialization to occur from the adnexal structures[42]. CO_2 or erbium:YAG laser therapy may also be of benefit in some patients with macular and lichen amyloidosis[43,44].

Retinoids including acitretin[45] and alitretinoin[46] have been reported to improve pruritus and result in flattening of lesions, with some clearance of the associated hyperpigmentation[45]. In a preliminary study, low-dose cyclophosphamide (50 mg daily) was effective in reducing pruritus and papules in lichen amyloidosis[47]. However, the side effects of these systemic medications (see Chs. 126 & 130) must be weighed against the possible benefits.

Surgical excision, cryotherapy, electrodesiccation, and CO_2 laser can be used to treat *nodular amyloidosis*, but local recurrences are common[42]. Rarely, the local recurrence lacks amyloid deposits and has the histopathologic features of a conventional primary cutaneous marginal zone lymphoma[36]. There are scattered reports of the use of cyclophosphamide (see above)[47].

SECONDARY CUTANEOUS AMYLOIDOSIS

Secondary cutaneous amyloidosis refers to amyloid deposits that are inapparent clinically but can be detected histopathologically within skin lesions, most commonly in seborrheic keratoses and basal cell carcinomas and occasionally in dermatofibromas, intradermal melanocytic nevi, pilomatricomas, trichoepitheliomas, sweat gland tumors, Bowen disease, and porokeratosis[15]. In these settings, the amyloid deposits represent a histologic epiphenomenon without obvious clinical implications. Secondary cutaneous amyloidosis has also been reported following PUVA therapy.

Hypotrichosis simplex of the scalp 1/hypotrichosis 2 (HYPT2) is an uncommon autosomal dominant disorder and is perhaps best regarded as a particular form of secondary cutaneous amyloidosis. Patients have normal hair at birth, but progressively lose most scalp hair by the third decade. Eyebrows, beard and axillary hair, nails, and teeth develop normally. Pathogenic variants in the gene that encodes corneodesmosin, a glycoprotein expressed in the epidermis and inner root sheath, lead to truncated corneodesmosin proteins. The latter accumulate as amorphous amyloid deposits around hair follicles and in the papillary dermis[48].

SYSTEMIC AMYLOIDOSIS

Primary Systemic Amyloidosis

Multiple forms of systemic amyloidosis have been identified, but skin involvement is variable[49]. The following discussion focuses on those in which the skin is a major target.

AL amyloidosis

AL amyloidosis is a life-threatening manifestation of an underlying plasma cell dyscrasia, although patients usually do not fulfill the criteria for multiple myeloma (e.g. hypercalcemia, osteolytic lesions; see Ch. 119). The fibrils are composed of AL protein, which consists of immunoglobulin light chains, usually λ-type (75%–80%).

Clinical features

AL amyloidosis is associated with a wide spectrum of organ involvement. The presenting symptoms are varied and nonspecific, such as fatigue, weight loss, paresthesias, dyspnea, and syncopal attacks due to orthostatic hypotension[4,50]. As a result, there is often difficulty and delay in diagnosis.

In the oral cavity, amyloid deposits appear as rubbery swellings or an infiltration of the mucosa (Fig. 47.8A). An associated hemorrhagic component is frequently seen. The tongue can be uniformly enlarged and firm (Fig. 47.8B), or it may have hemorrhagic papules, plaques, and blisters on its surface; the latter may vary from translucent to yellow–brown in color. Xerostomia can result from infiltration of the salivary glands.

Following minor trauma, petechiae, purpura, and ecchymoses are often observed, especially on the eyelids and neck and in the axillae and anogenital region (due to amyloid infiltration of vessel walls; Fig. 47.9). Characteristically, periorbital purpura (the "raccoon eyes" sign) may be precipitated by coughing, the Valsalva maneuver, or proctoscopy for a rectal biopsy, as well as after pinching or rubbing the skin (pinch purpura). Even removal of adhesive tape can lead to purpura.

Clinically evident skin involvement occurs in ~25% of individuals with AL amyloidosis. Skin infiltration by amyloid presents as waxy, translucent, or purpuric papules (Fig. 47.8D,E & 47.10), nodules, and plaques that resemble nodular amyloidosis. A smooth, erythematous, waxy infiltration with scattered superimposed papules can appear on the palms and volar aspect of the fingertips (Fig. 47.8C). Smooth, skin-colored papules, a few millimeters in diameter, may be seen on the face, neck, and scalp and in the anogenital region.

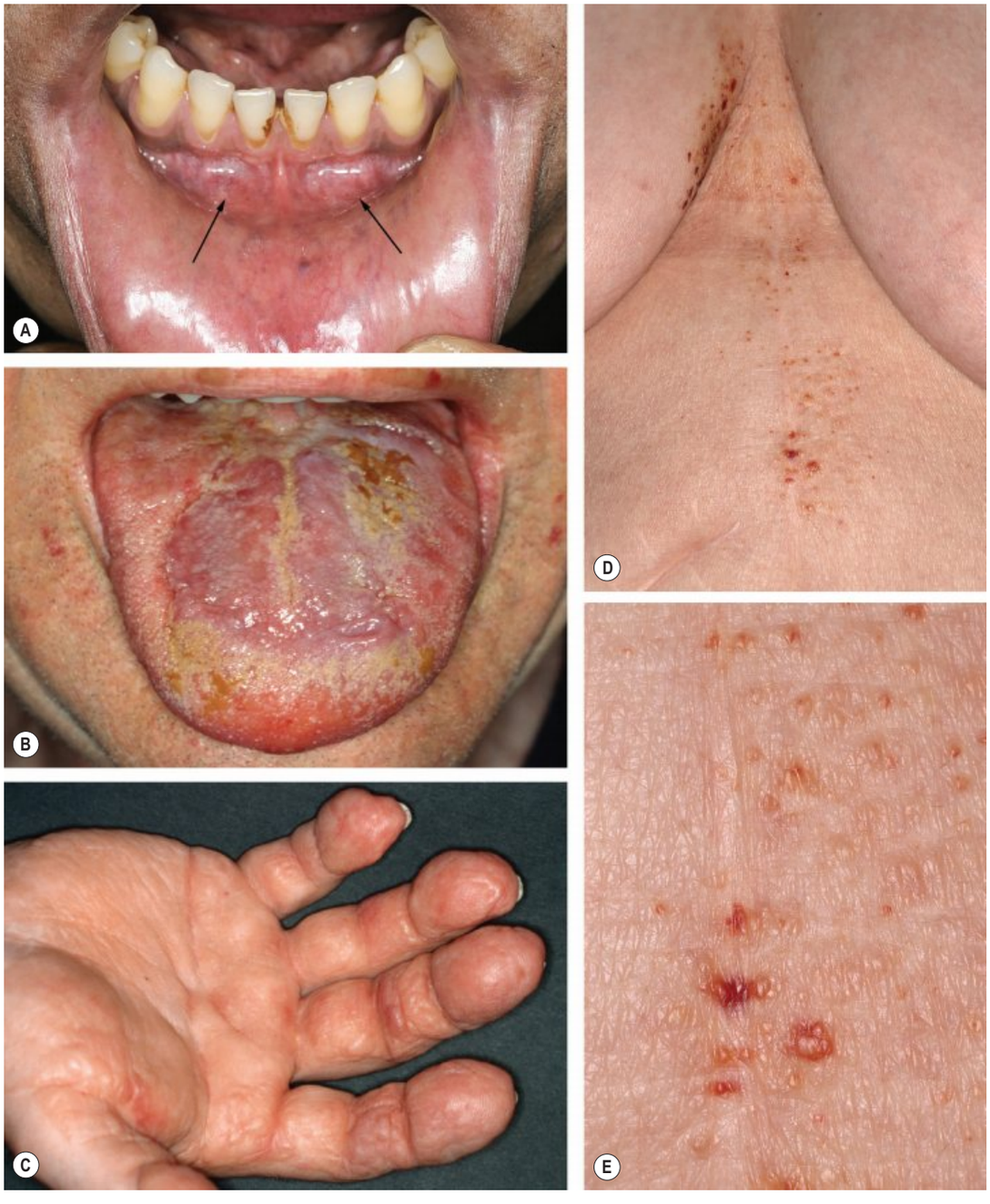


Fig. 47.8 Range of mucocutaneous findings in primary systemic AL amyloidosis. A Intraoral rubbery swellings (arrows). **B** Macroglossia with irregular thickening of the tongue. **C** Waxy infiltration of the palm and volar aspects of the fingers. **D, E** Multiple waxy, translucent papules on the breast, central chest, and upper abdomen; several of the lesions are purpuric. *Courtesy Lorenzo Cerroni, MD.*

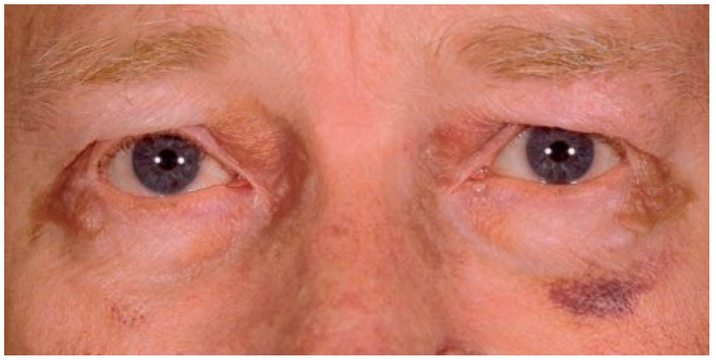


Fig. 47.9 Primary systemic AL amyloidosis. Purpura and yellow–brown plaques in a periorbital distribution. *Courtesy Joyce Rico, MD.*



Fig. 47.10 Primary systemic AL amyloidosis. A Numerous waxy translucent facial papules. Some have a yellow to yellow–brown color. **B** Some of the waxy papules have become purpuric, but this can be more difficult to appreciate because of the pigmentation of the skin (compare to Fig. 47.9). The periorbital region is a characteristic site of involvement. *A, Courtesy Jean L. Bolognia, MD; B, Courtesy Judit Stenn, MD.*

Less often, diffuse cutaneous infiltration can result in an infiltrated sclerodermoid appearance or cause the scalp skin to be thrown into folds resembling cutis verticis gyrata with associated alopecia. Bullous lesions, especially hemorrhagic blisters resembling those of porphyria cutanea tarda and epidermolysis bullosa acquisita, may be the initial sign of the disease. In addition, nail dystrophy can occur and may resemble lichen planus, with longitudinal ridging and thinning; histologically, amyloid deposits are found around blood vessels and in the dermis of the nail bed and matrix. Rarely, patients also have evidence of acquired acral cutis laxa. The presence of macroglossia together with carpal tunnel syndrome is a classic presentation and should trigger an investigation for amyloidosis.

Other signs and symptoms of AL amyloidosis depend upon the organs involved. Renal involvement manifests as proteinuria (albuminuria) which leads to hypoalbuminemia and edema, i.e. nephrotic syndrome. Cardiac involvement may eventually lead to a restrictive cardiomyopathy and congestive heart failure, but with a preserved ejection fraction. This results in dyspnea, hepatomegaly, and bilateral lower extremity as well as presacral edema. Autonomic and sensory neuropathies are common. Sensory involvement is usually bilateral and symmetrical, while autonomic involvement can result in postural hypotension, impotence, and disturbances in gastrointestinal motility (e.g. gastroparesis). Hepatomegaly due to amyloid infiltration or congestive heart failure may be present.

In up to 80%–90% of patients with AL amyloidosis, amyloid deposits can be demonstrated in random rectal mucosal biopsies or in abdominal subcutaneous fat aspirates; the latter is preferred because of the potential risk for bleeding with the former. Gingival or tongue biopsies may also be obtained to demonstrate the presence of amyloid, but in the absence of involvement clinically, they are less sensitive. In addition, bone marrow biopsies are examined for the presence of amyloid deposits. Based upon the finding that all of these amyloid deposits contain amyloid P (which is derived from serum amyloid protein [SAP]), SAP scintigraphy is also employed, primarily outside the US. It utilizes radioiodine-labeled SAP and is a sensitive, non-invasive method for locating amyloid deposits and monitoring disease. A more practical method for assessing response to therapy is measurement of serum free light chains.

The approach to a patient with suspected or confirmed AL amyloidosis is outlined in Fig. 47.11.

Pathology

In AL amyloidosis, cutaneous lesions are characterized by amyloid deposits in the dermis and subcutis. Amyloid is also often found around sweat glands and within blood vessel walls (Fig. 47.12). Rarely, an infiltrate of amyloid-producing monoclonal plasma cells can be found adjacent to the amyloid deposits. An unusual pattern of amyloid deposition around elastic fibers, in which the fibers appear coated with a thick mantle of amyloid-staining material, is occasionally seen and has been termed *amyloid elastosis*. The latter is rarely observed in primary cutaneous amyloidosis.

Differential diagnosis

The differential diagnosis of the waxy papules includes papular mucinosis, nodular amyloidosis, and lipoid proteinosis, and when the lesions are primarily on the face, they can be confused with adnexal tumors (see Ch. 111). Conditions in the sclerodermoid differential diagnosis (see Table 43.7) need to be considered when there is diffuse infiltration of the skin.

Treatment

Without therapy, the prognosis for AL amyloidosis is poor: median survival is ~13 months[50], especially if there is cardiac involvement. Treatment strategies have paralleled those for multiple myeloma, including melphalan and systemic corticosteroids[4,51,52]. The current FDA-approved treatment regimen for AL amyloidosis is the combination of cyclophosphamide, bortezomib, and dexamethasone (CyborD) plus daratumumab (anti-CD38 antibody). If the patient is younger and has minimal cardiac involvement, high-dose melphalan followed by autologous hematopoietic stem cell transplantation is a potentially curative therapeutic option. In one study with an 8-year follow-up period, a complete hematologic response was observed in 40% of transplanted patients and was associated with a prolonged survival. A survival benefit and clinical improvement in organ function was also seen in those who did not achieve a complete hematologic response[53].

Supportive measures are administered according to the organs affected and the consequent manifestations. Nephrotic syndrome and congestive heart failure require diuretic therapy and treatment of associated arrhythmias. Neuropathy and gastrointestinal involvement are treated symptomatically.

Secondary Systemic Amyloidosis (AA Amyloidosis)

Secondary systemic amyloidosis occurs as a complication of severe chronic inflammatory diseases of an infectious or non-infectious nature, such as tuberculosis, lepromatous leprosy, rheumatoid arthritis, and ankylosing spondylitis. It has also been observed in patients with hidradenitis suppurativa, dystrophic epidermolysis bullosa, generalized psoriasis, chronic pustular psoriasis, systemic sclerosis, dermatomyositis, autoinflammatory syndromes such as familial Mediterranean fever and Muckle–Wells syndrome, and systemic lupus erythematosus. Secondary systemic amyloidosis is characterized by the deposition of a distinctive non-immunoglobulin protein designated AA (amyloid A protein). The precursor is an acute phase protein which is synthesized by the liver and appears to have a regulatory function in lipoprotein metabolism during inflammation. AA amyloidosis usually affects the kidneys, liver, spleen, adrenals, and heart. Cutaneous lesions due to amyloid deposits are rarely seen in this type of amyloidosis, although amyloid can be detected within aspirates of subcutaneous fat[15].

Successful treatment of the underlying infectious or inflammatory disease may halt the progression of the reactive amyloidosis. For example, the use of systemic immunomodulators ("biologic agents") such as TNF inhibitors in patients with rheumatoid arthritis or ankylosing spondylitis and secondary amyloidosis has been shown to be clinically beneficial, resulting in a significant reduction in acute phase reactants and proteinuria[54]. A controlled clinical study found

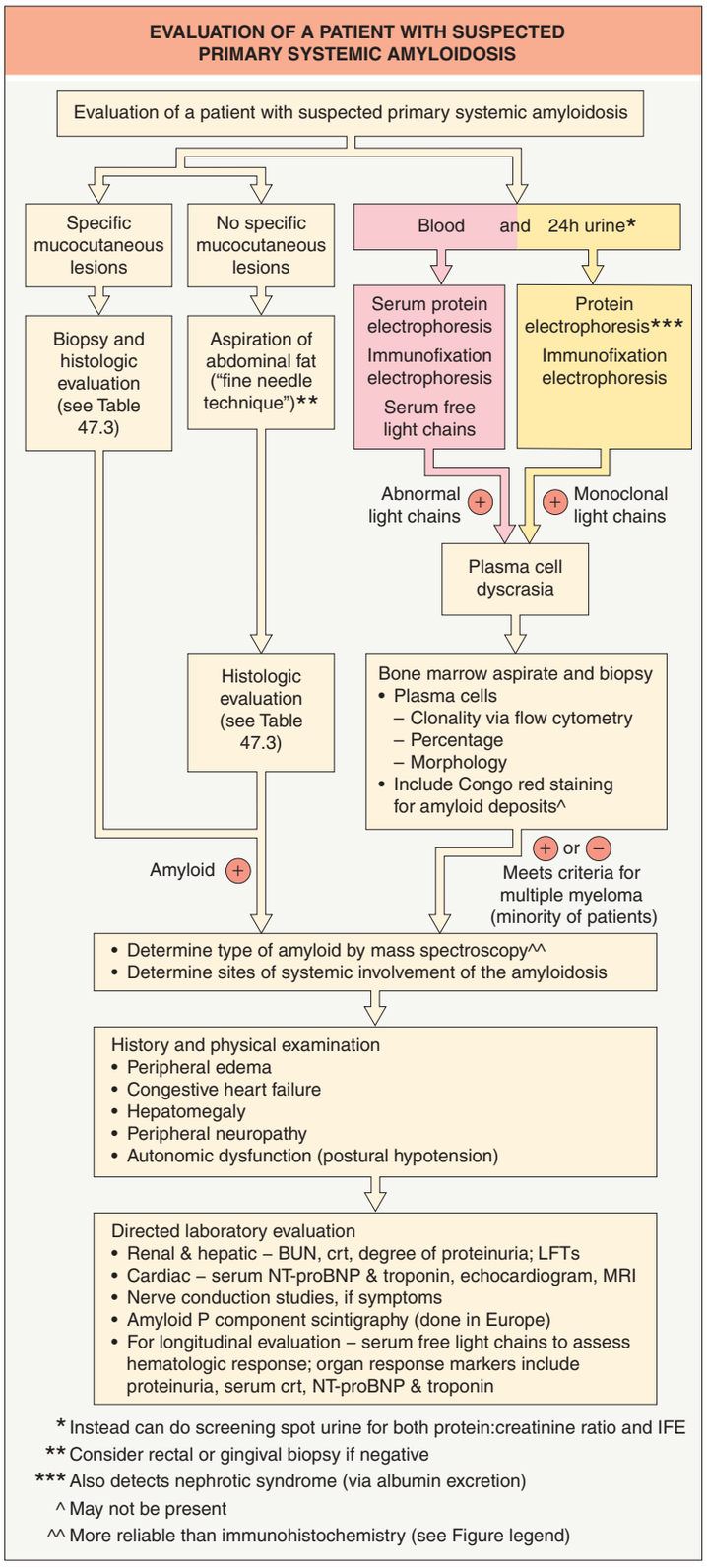


Fig. 47.11 Evaluation of a patient with suspected primary systemic AL amyloidosis. Because the amyloid is formed from immunoglobulin light chains, an abnormality of free light chains in the blood or urine (e.g. increased concentration or abnormal ratio in the blood, positive immunofixation electrophoresis [IFE] of the urine) is required for diagnosis. Mass spectroscopy has become more routine given the potential for misdiagnosis of older patients with wild-type ATTR deposits in the heart or ALect2 deposits in the kidney and liver in the setting of a monoclonal gammopathy of unknown significance. A positive cardiac pyrophosphate scan points to the diagnosis of ATTR amyloidosis. BUN, blood urea nitrogen; crt, creatinine; LFTs, liver function tests; NT-proBNP, N-terminal pro-brain natriuretic peptide.

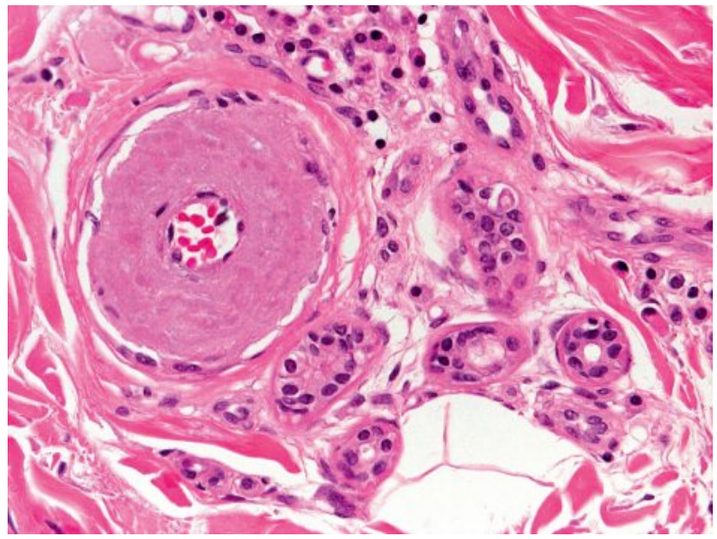


Fig. 47.12 Primary systemic AL amyloidosis – histopathologic features. Amyloid deposits are seen in a perivascular location. *Courtesy Lorenzo Cerroni, MD.*

that eprodisate may slow the loss of renal function in AA amyloidosis. Interestingly, this oral drug acts by changing the conformational configuration of the amyloid protein, rather than by affecting its production[55].

Hemodialysis-Associated Amyloidosis ($A\beta_2M$ Amyloidosis)

Hemodialysis-associated amyloidosis results from decreased excretion of β_2-microglobulin and is seen in patients receiving long-term hemodialysis for renal failure. Because β_2-microglobulin is not readily filtered through dialysis membranes, it is retained within the circulation and has a tendency to deposit in synovial membranes. Thus, the predominant manifestations are musculoskeletal, including carpal tunnel syndrome, bone cysts, and a destructive spondylo-arthropathy[4]. Occasionally, skin lesions have been observed, usually as subcutaneous nodules[56,57]. With improvement in dialysis membranes, the incidence has declined.

INHERITED AMYLOIDOSES

The genetic bases of primary localized cutaneous amyloidosis have been previously discussed (see above). Additional inherited forms of amyloidosis are listed in Tables 47.1 and 47.2, including those associated with autoinflammatory disorders (see Ch. 45).

Familial Amyloidosis, Finnish Type (AGel Amyloidosis)

Patients with the rare Finnish type of familial amyloidosis, which is due to variants in the gene that encodes gelsolin[58], present with a characteristic triad of corneal lattice dystrophy, cranial neuropathies, and skin findings including cutis laxa-like changes and skin fragility[59]. Interestingly, despite the multisystem nature of the condition, life expectancy does not seem to be affected[60].

Transthyretin Amyloidosis (ATTRwt/ATTRv Amyloidosis)

There are two forms of transthyretin amyloidosis: (1) ATTRwt which results from deposition of wild-type transthyretin in cardiac tissue and predominantly affects the elderly; and (2) ATTRv (variant transthyretin amyloidosis) that is due to mutations in the transthyretin gene and presents with either neurologic or cardiac dysfunction. The latter represents the commonest inherited form of systemic amyloidosis. The skin is only rarely involved[61], although cutaneous amyloid deposition occurs early in the disease and thus abdominal fat pad biopsy can be helpful in diagnosis.

Orthotopic liver transplantation represents a therapeutic option for hereditary ATTR amyloidosis[38] and tafamidis meglumine is FDA-approved for treatment of wild-type or hereditary ATTR cardiomyopathy[62]. Tafamidis binds selectively to transthyretin and slows monomer formation, misfolding, and amyloidogenesis. Patisiran, a small interfering RNA (siRNA), and inotersen, an antisense oligonucleotide, are approved therapies for hereditary ATTR polyneuropathy. A preliminary clinical trial utilized gene-editing CRISPR-Cas9 technology to target and significantly reduce production of misshapen transthyretin by the liver.

APPENDIX

Tandem mass spectrometry (TM/TM) for precise identification of an amyloid protein: Mayo Clinic Medical Laboratories, Rochester, MN, USA, and University of Tennessee Health Science Center, Knoxville, TN, USA.

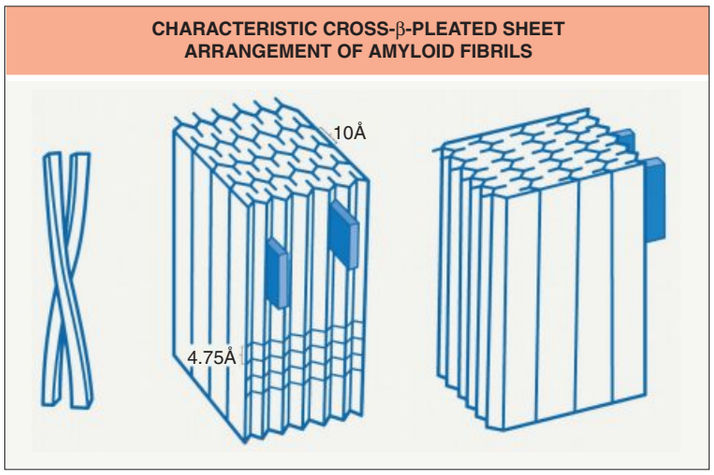
Additional figures available in our eBook (see inside front cover for access code).

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eFig. 47.1 Characteristic cross-β-pleated sheet arrangement of amyloid fibrils – schematic representation of findings seen by X-ray crystallography. There is an antiparallel configuration of paired filaments, and sites of binding of the planar Congo red dye are indicated by the solid blue blocks. *Adapted from Cooper JH. Selective amyloid staining as a function of amyloid composition and structure: histochemical analysis of the alkaline Congo red, standardized toluidine blue, and iodine methods. Lab Invest. 1974;31:232–8.*



eFig. 47.2 Lichen amyloidosis. Hyperpigmented thin papules in a parallel linear array. Note the admixed hemorrhagic crusts from scratching.



eFig. 47.3 Lichen amyloidosis. Keratotic hyperpigmented papules on the forearm, many of which are in a linear array. *Courtesy M. Joyce Rico, MD.*



eFig. 47.4 Lichen amyloidosis. Keratotic, hyperpigmented plaques on the legs. Inset: Closer view of individual keratotic papules. *Courtesy St John's Institute of Dermatology.*



eFig. 47.5 Lichen amyloidosis. Numerous small papules in linear arrays in addition to hyperpigmentation on the extensor surfaces of the arms. *Courtesy Jeffrey P. Callen, MD.*



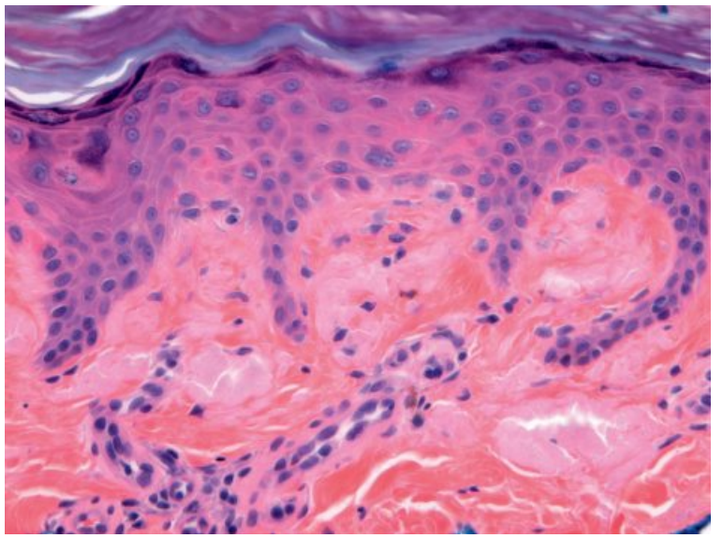
eFig. 47.6 Dyschromic amyloidosis cutis. An admixture of reticulated hyperpigmentation and guttate hypopigmentation is seen. *Courtesy Seth J. Orlow, MD.*



eFig. 47.7 Nodular amyloidosis. Firm plaques and nodules on the plantar surfaces.



eFig. 47.8 Nodular amyloidosis. Multiple firm papules on the plantar surface.



eFig. 47.9 Macular amyloidosis – histopathologic features. Deposits of amyloid within the dermal papillae and papillary dermis; note the characteristic fissure in the amyloid deposit. *Courtesy Jennifer McNiff, MD.*





eFig. 47.10 Primary systemic AL amyloidosis. A Macroglossia with dental impressions on the tongue. **B** Papulonodules of the tongue; some are purpuric while others are translucent with a yellowish hue. *B, Courtesy Dennis Cooper, MD.*



eFig. 47.11 Anakinra amyloidosis in a patient with NOMID (neonatal-onset multisystem inflammatory disease). A mass at the site of injection. *Courtesy Edward Cowen, MD.*

48 Deposition Diseases

Sven R. Quist, Jennifer E. Quist and Harald P. Gollnick

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INTRODUCTION

The cutaneous deposition disorders are a heterogeneous group of conditions characterized by the presence of primarily endogenous substances within the dermis or the subcutis. Deposition disorders can be associated with localized or generalized cutaneous findings, and skin involvement is sometimes the earliest sign of a deposition disease. Histologic examination of cutaneous lesions, along with the use of special stains including immunohistochemistry, is a very helpful diagnostic tool (Table 48.1). In addition, specific enzymatic assays or genetic mutational analysis can then be performed to establish the precise diagnosis.

This chapter will focus on gout, pseudogout, lipoid proteinosis, colloid milium, and the mucopolysaccharidoses. Additional deposition disorders such as mucinoses, amyloidosis, porphyria, and calcinosis cutis are reviewed in Chapters 46–50.

GOUT

Synonyms ■ Urate crystal arthropathy ■ Podagra (first MTP joint) ■ Urate deposition disease

Key features

- Gout is a metabolic disease in which the underlying abnormality is hyperuricemia
- Deposits of needle-like crystals of monosodium urate are found in several sites, most commonly the skin (as tophi) and the joints
- In fresh preparations of synovial fluid and expressed material from tophi, the crystals exhibit negative birefringence when examined by polarized light
- In routinely fixed histologic sections, amorphous deposits that contain needle-like clefts are seen in the dermis and subcutis

Introduction

Gout is a metabolic disease in which needle-like crystals of monosodium urate (the ionized form of uric acid) from supersaturated fluids are deposited within tissue. Clinical manifestations include gouty arthritis, accumulation of crystals in connective tissue (tophi), uric acid nephrolithiasis, and renal impairment[1,2].

Epidemiology

Gout is the most common form of crystal-induced arthritis, and its prevalence seems to have increased over the past several decades. Men 40–50 years of age are most commonly affected. The male-to-female ratio is 9:1, and most women with gout are postmenopausal. Gout is found in up to 4% of adults and ~20% of patients have a family history of gout[2,3].

Pathogenesis

Gout is a consequence of deposits of urate crystals that have precipitated from supersaturated body fluids. Uric acid is the end product of the catabolism of purines. When the body increases its production of uric acid or if the kidneys do not excrete sufficient amounts, the result is hyperuricemia (Table 48.2). Migration and activation of neutrophils that are attempting to phagocytize urate crystals lead to the generation of neutrophil extracellular traps (NETs). The latter activate the NLRP3 inflammasome (see Fig. 4.2) via RIPK3-MLKL signaling, with subsequent production of proinflammatory cytokines. RIPK3 and MLKL represent two core proteins of the necroptosis pathway. Of note, NETs can also promote auto-resolution of the inflammatory phase of gout[4].

Clinical Features

The typical patient with gout is a middle-aged or older man, who may have a family history of the disease. Risk factors include obesity, excessive alcohol intake, renal insufficiency, and certain medications, most commonly diuretics. The natural history of gout involves four clinical stages[1]: (1) asymptomatic hyperuricemia; (2) acute gouty arthritis; (3) intercritical gout (the intervals between attacks, which progressively become shorter in duration); and (4) chronic tophaceous gout.

Acute gouty arthritis

The most common symptom of gout is the development of severe joint pain over a period of 6–12 hours, accompanied by tenderness, erythema, warmth, and swelling. Initial attacks are often monoarticular, but in up to 40% of patients they may be polyarticular[5]. In 75% of patients, the first metatarsophalangeal joint is involved (referred to as podagra); additional sites include the knee, ankle, and foot, and less commonly, the hand, wrist, and elbow. Fever and systemic symptoms may accompany an acute attack of gout. As the swelling subsides, the skin acquires a violaceous hue often followed by desquamation as edema subsides.

Chronic tophaceous gout

Cutaneous deposits of monosodium urate, known as "tophi", usually appear an average of 10 years after the onset of gout. These tophi present as firm dermal or subcutaneous papules and nodules or as a fusiform swelling. Their contours may be smooth or multilobulated (Fig. 48.1) and they vary from skin-colored to white–yellow to red (Fig. 48.2). The surface may be ulcerated and there may be associated drainage of material, which varies from clear fluid with white flecks to a thick chalky material.

The most common locations for tophi are the skin overlying joints and the helix of the ear. Unusual sites include the eyes, nose, larynx, breast, and heart valves. However, tophi develop in fewer than 10% of patients with gout. Depending upon the size and location of the tophi, complete, partial, or minimal resolution can occur when the serum uric acid level is normalized[2,6].

Elevated levels of uric acid in the urine are associated with uric acid nephrolithiasis and may cause acute renal failure when uric acid precipitates in the renal tubules and collecting ducts. The most common setting for the latter is tumor lysis syndrome following chemotherapy for a rapidly dividing chemosensitive malignancy, e.g. leukemias, lymphomas.

The initial diagnosis of gout is usually made in the setting of acute arthritis, based upon the presence of urate crystals in an aspirate of joint fluid. Hyperuricemia is usually present, but alone it is insufficient for establishing a definitive diagnosis of gout. Additional laboratory abnormalities during an acute attack include elevated white blood cell count (in the joint fluid and blood) and ESR.

DISORDERS WITH DERMAL DEPOSITS – HISTOLOGIC FEATURES			
Disease	**Microscopic findings**	**Histochemical stains**	**Special processing**
Gout	In formalin-fixed specimens, dermal deposits of amorphous material with needle-like clefts surrounded by a granulomatous infiltrate with giant cells Polarizing light/fresh preparation – fine, needle-like crystals; negative birefringence	20% silver nitrate solution: urate crystals appear black and the surrounding tissue yellow De Galantha stain: crystals brown–black	Best fixative to preserve crystals: ethanol-based (Carnoy's fluid)
Lipoid proteinosis	Masses of amorphous or laminated hyalin-like material Also surrounds capillaries in the papillary dermis and appendages	Contains type IV collagen and laminin PAS-positive and diastase-resistant ⊕ Alcian blue, hyaluronidase-sensitive Sudan III (+/–) Congo red (usually –)	Direct immunofluorescence with anti-ECM1 antibodies to assess protein expression
Colloid milium (adult form)	Nodules of amorphous eosinophilic material Artifactual clefts Solar elastosis	Stains similarly to amyloid (especially in frozen sections): ⊕ Congo red ⊕ Thioflavin T ⊕ Crystal violet	
Mucopolysaccharidoses	Metachromatic granules within fibroblasts Large vacuolated cells in sweat glands and the external root sheath of hair follicles (gargoyle cells)	Granules within fibroblasts: ⊕ Metachromasia with toluidine blue and Giemsa ⊕ Alcian blue ⊕ Colloidal iron (see Table 46.1)	Fixation in absolute alcohol better than in formalin (consider when clinical diagnosis not supported by histologic findings)
Mucinoses, e.g. papular mucinosis, scleredema, pretibial myxedema (Ch. 46)	Mucin between collagen and variable fibroblast proliferation	⊕ Metachromasia with toluidine blue ⊕ Alcian blue ⊕ Colloidal iron (see Table 46.1)	Fixation in absolute alcohol better than in formalin
Amyloidosis (Ch. 47)	Fractured, amorphous, faintly eosinophilic material in dermis	⊕ Congo red ⊕ Thioflavin T ⊕ Crystal violet	In glutaraldehyde for electron microscopy
Ochronosis (Chs. 63 & 67)	Sausage- or banana-shaped brown/yellow/orange structures	Black staining with methylene blue or cresyl violet	
Calcinosis cutis (Ch. 50)	Irregular masses of deeply basophilic materialVariable granulomatous inflammation (may be absent)	⊕ von Kossa ⊕ Alizarin red (more specific)	May fracture microtome blade May need decalcification solution first
Porphyrias, in particular EPP (Ch. 49)	Perivascular rim of delicate eosinophilic fibrillar material In chronic lesions, also dense homogeneous deposits	PAS-positive and diastase-resistant Immunohistochemistry for BMZ components (type IV collagen)	

Table 48.1 Disorders with dermal deposits – histologic features. BMZ, basement membrane zone; ECM1, extracellular matrix protein 1; EPP, erythropoietic protoporphyria.

CLASSIFICATION OF HYPERURICEMIA	
Overproduction of uric acid	• Primary/idiopathic • Excessive dietary purine intake and obesity • Increased nucleotide turnover • High-grade lymphomas (e.g. Burkitt) and myeloma • Myeloproliferative disorders, esp. acute myelogenous leukemia • Tumor lysis syndrome • Hemolysis • Psoriasis (severe) • Accelerated ATP degradation • Alcohol abuse • Severe muscle exertion • Hypoxanthine–guanine phosphoribosyl transferase deficiency (Lesch–Nyhan syndrome) • Glucose-6-phosphatase deficiency (glycogen storage disease type 1; von Gierke disease) • Phosphoribosyl pyrophosphatase synthetase overactivity
Decreased excretion of uric acid	• Primary/idiopathic • Chronic kidney disease • Enhanced tubular urate reabsorption (e.g. diuretics, dehydration) • Drug ingestion (e.g. cyclosporine > tacrolimus, pyrazinamide, low-dose salicylates) • Toxins (e.g. lead-induced nephropathy) • Miscellaneous – lactic acidosis, ketoacidosis, hypertension, hyperparathyroidism, hypothyroidism

Table 48.2 Classification of hyperuricemia. ATP, adenosine triphosphate.



Fig. 48.1 Tophaceous gout of a digit. The deposits create a multilobulated appearance and there is evidence of transepidermal elimination. A small incision over the yellow–white papules followed by microscopic examination of the expressed material would allow for a bedside diagnosis. *Courtesy Lorenzo Cerroni, MD.*



Fig. 48.2 Tophaceous gout of the tragus. The erythema reflects surrounding inflammation.

When examined by polarized light microscopy, the needle-shaped urate crystals change color from yellow to blue based upon their alignment relative to the axis of the "red plate" compensator, i.e. they exhibit negative birefringence. In patients with recurrent attacks, radiographs of involved joints often show "punched-out" erosions with sclerotic "overhanging" margins, but no osteophytes. A 24-hour urine collection for uric acid allows the identification of patients at risk for nephrolithiasis (see Table 48.2).

Pathology

The key histologic feature of formalin-fixed gouty tophi is the presence of deposits of amorphous material within the dermis and subcutis, corresponding to sites of crystal deposition. These deposits contain needle-like clefts (which represent dissolved urate crystals) surrounded by a granulomatous infiltrate with multinucleated giant cells (Fig. 48.3). Secondary calcification or even ossification can occasionally be seen in older lesions.

In order to preserve the crystals, the biopsy specimen needs to be placed in an ethanol-based fixative, such as Carnoy's fluid. Then, under regular or polarized light, brightly refractile brown sheaths of fine needle-like crystals can be seen. Upon staining with 20% silver nitrate solution, the crystals appear black and the surrounding tissue yellow, whereas with the De Galantha stain, the crystals appear brown to black[7].

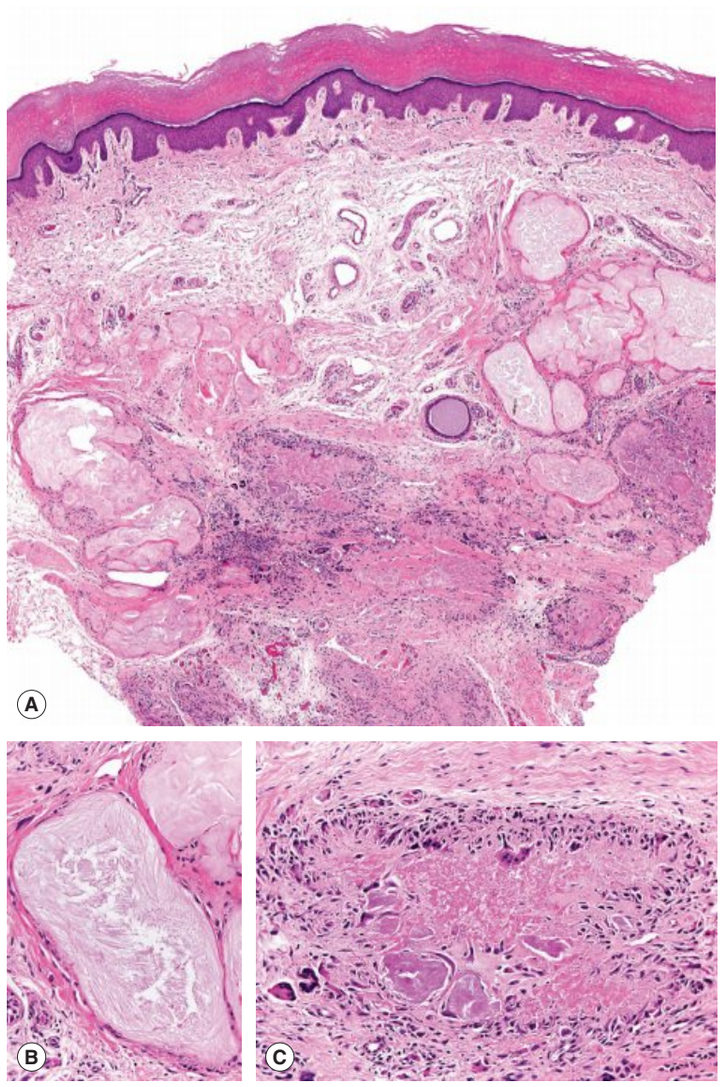


Fig. 48.3 Tophaceous gout – histopathologic features. A Within the dermis and subcutis, there are deposits of amorphous, acellular material. These deposits contain needle-like clefts (**B**). Histiocytes and multinucleated giant cells surround some of the deposits (**C**). *Courtesy Lorenzo Cerroni, MD.*

Differential Diagnosis

The differential diagnosis of acute gouty arthritis includes pseudogout (see below), osteoarthritis, psoriatic arthritis, reactive arthritis (previously referred to as Reiter disease), and septic arthritis. Given its destructive nature, septic arthritis needs to be considered even in patients in whom the diagnosis of gout has been previously established. The presence of needle-shaped crystals with negative birefringence in an aspirate of joint fluid is diagnostic of gout, while Gram stain and culture exclude septic arthritis. Occasionally, patients are misdiagnosed as having cellulitis.

The differential diagnosis of cutaneous gouty tophi includes xanthomas, rheumatoid nodules, and calcinosis cutis. Examination of expressed fluid or chalky material by polarized light can provide a "bedside" diagnosis. By ultrasonography, central clear spaces are seen within tophi whereas rheumatoid nodules contain central echodense areas[6].

Treatment

For acute gout, short-acting oral nonsteroidal anti-inflammatory drugs (NSAIDs) are taken within 24 hours of onset at the highest safe dosage as long as symptoms persist, e.g. indomethacin 50 mg three times daily for several days. Contraindications include peptic ulceration, renal insufficiency, and anticoagulation[6–8].

Colchicine, a derivative of the autumn crocus, inhibits the transport of phagocytized urate crystals to lysosomes within neutrophils via its binding to microtubules. Colchicine also interferes with leukocyte migration, chemotaxis, and adhesion. For patients with normal renal function who are not receiving strong CYP3A4 inhibitors, the recommended dosage for acute gout flares is 1.2 mg orally followed by 0.6 mg 1 hour later. Low-dose NSAIDs and colchicine (0.6 mg twice daily) are both utilized for prophylaxis. Outside of the US, colchicine tablets often contain 0.5 mg. Side effects of colchicine are outlined in Table 130.9. Intra-articular or systemic *corticosteroids* may be used for a period of 1–3 weeks if NSAIDs and colchicine are ineffective or contraindicated[6–8].

Urate-lowering therapy (ULT) consists of the xanthine oxidase inhibitors *allopurinol* and *febuxostat* which block uric acid production. Allopurinol is the preferred first-line ULT, but low starting doses (≤100 mg/day or lower if chronic kidney disease) are recommended[7]. ULT is indicated for patients with tophaceous gout, radiographic damage due to gout, or frequent gout flares. Concomitant anti-inflammatory prophylaxis therapy for 3–6 months is also recommended when initiating ULT[7].

Side effects of allopurinol include diarrhea, thrombocytopenia, hepatitis, and skin eruptions that can range from morbilliform to erythroderma to Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). HLA-B*58:01-positive individuals are at markedly increased risk of developing severe cutaneous adverse reactions, including both SJS/TEN and DRESS. Of note, this allele

is most common in those of Han Chinese, Korean, or Thai descent. Major side effects of febuxostat are liver enzyme elevations and cardiovascular thromboembolic events[9]. Drug–drug interactions, e.g. with azathioprine, can occur with both of these medications (see Fig. 130.5). Uricosuric agents such as oral *probenecid* can be added or used as second-line therapy for patients with normal renal function and no renal stones. Overall, maintenance of a serum uric acid level of ≤6 mg/dl is recommended. A newer agent, *lesinurad*, is a selective inhibitor of reabsorption of uric acid.

Some patients may benefit from a reduction in purine-rich foods (e.g. organ meats [liver, heart], fish), alcohol consumption, and body weight[6]. In the setting of potential tumor lysis syndrome, intravenous *rasburicase* can be administered, which rapidly converts uric acid to the more soluble allantoin. Bimonthly intravenous *pegloticase*, which has the same mechanism of action, can be used for patients with chronic gout refractory to conventional therapy. IL-1 blocking agents (e.g. *anakinra, canakinumab*) have been used for recurrent acute gout unresponsive to other therapies, but are not currently approved for this indication (see Fig. 45.13).

PSEUDOGOUT

Synonyms: ■ Chondrocalcinosis ■ Calcium pyrophosphate disease ■ Calcium gout

Key features

- Pseudogout is a form of arthritis that is due to deposits of calcium pyrophosphate dihydrate (CPPD) crystals within the joint
- It most commonly affects the knee and other large joints of older persons with osteoarthritis
- In aspirates of joint fluid, there are rhomboid CPPD crystals that exhibit weakly positive birefringence under polarized light

Pseudogout, which may be clinically indistinguishable from gout, was recognized as a distinct disease entity in 1962[10]. It results when CPPD crystals (produced by nucleoside triphosphate pyrophosphohydrolase, a catalytic enzyme found in osteoarthritic cartilage) form within joint fluid and then lead to lysis of neutrophils that have ingested the crystals. As in gout, the formation of NETs plays a role in the inflammatory cascade. Although pseudogout is most commonly related to osteoarthritis, it has also been associated with metabolic abnormalities such as hyperparathyroidism and hemochromatosis.

Symptoms of pseudogout include intermittent attacks of pain and swelling of affected joints, most commonly the knee, wrist, and shoulder. The onset of symptoms in pseudogout is usually more insidious than in gout. Occasionally, extra-articular CPPD deposition (tophaceous pseudogout) may present as a hard subcutaneous nodule overlying joints, primarily of the head (especially the temporomandibular joint), neck, or distal extremities[11].

Microscopically, CPPD crystals appear shorter than urate crystals and are often rhomboidal in shape. In tophaceous pseudogout, rhomboid crystals as well as foci of calcification can be seen within the dermis. Polarizing microscopy of sections stained with a non-aqueous alcoholic eosin stain (NAES) allows the demonstration of CPPD crystals with positive birefringence[12]. This is in contrast to the negative birefringence of urate crystals in gout and the lack of birefringence of calcium hydroxyapatite crystals in tumoral calcinosis. Treatment of the acute phase of pseudogout is identical to that of gout[11]. In patients with chronic renal failure, the anti-IL-1β antibody *canakinumab* may be considered (see Fig. 45.13)[13].

LIPOID PROTEINOSIS

Synonyms: ■ Hyalinosis cutis et mucosae ■ Urbach–Wiethe disease

Key features

- A rare autosomal recessive deposition disorder due to mutations in *ECM1*, which encodes extracellular matrix protein 1
- Hyalin-like material is deposited within multiple organs, including the skin, oral mucosa, larynx, and brain
- Papules and nodules favor the face, as do pitted scars; diffuse waxy thickening of the skin can be associated with verrucous changes, especially on the elbows, knees, and hands

History

Lipoid proteinosis was first described by Siebenmann in 1908. Twenty years later, it was established as a distinct entity by two Viennese physicians, Erich Urbach, a dermatologist, and Camillo Wiethe, an otorhinolaryngologist.

Epidemiology

Most patients are of European ancestry, including descendants of Dutch immigrants who settled in South Africa in the middle of the 17th century[14]. Not only do Afrikaners have the highest incidence of this genetic disease, they also exhibit a founder effect, i.e. the population shares a common mutation.

Pathogenesis

In 2002, lipoid proteinosis was shown to be due to loss-of-function mutations in *ECM1*, which encodes extracellular matrix protein 1[15]. ECM1 is a secretory glycoprotein that can act as a negative regulator of endochondral bone formation, a promoter of angiogenesis, and an inhibitor of matrix metalloproteinase 9. In addition, ECM1a (see below) is found within the basement membrane zone and can enhance the binding of collagen IV to laminin 332. It also interacts with components of the extracellular matrix such as fibronectin and glycosaminoglycans (e.g. hyaluronic acid, chondroitin sulfate)[16].

ECM1 has three major splice variants that result in different isoforms: (1) ECM1a, a protein of 540 amino acids encoded by a 10-exon gene; (2) ECM1b, a protein of 415 amino acids reflecting a lack of exon 7; and (3) ECM1c, a protein of 559 amino acids due to an additional exon 5a within intron 5. Patients with mutations in exon 7 still express the ECM1b isoform and tend to have milder disease as compared to those with mutations in exon 6, who tend to have more severe disease and reduced expression of all three isoforms. A majority of pathogenic mutations occur within exon 6 or 7[15]; occasionally, they occur in exon 2, 4, or 9[17]. The degree of dermal immunofluorescent staining (utilizing an anti-ECM1 antibody) points to the location; reduced staining suggests mutations in exon 7 and an absence of staining mutations in exon 6[16].

Clinical Features

The first clinical sign of lipoid proteinosis is often a weak cry or hoarseness due to infiltration of the laryngeal mucosa. Hoarseness remains throughout life. Cutaneous lesions usually appear during the first 2 years of life, in two overlapping stages. In the first stage, vesicles and hemorrhagic crusts develop within the mouth and on the skin of the face and extremities, often in association with trauma. The cutaneous lesions may resolve with scarring, including "ice-pick"-like scars.

During the second stage, there is an increase in the hyalin deposits within the dermis (Fig. 48.4). The skin becomes diffusely thickened and waxy and develops a yellow color. Papules, plaques, and nodules appear on the face (including the eyelid margin) as well as in the axillae and on the scrotum. Verrucous lesions may develop on the extensor surfaces, especially the elbows (see Fig. 48.4C), knees, and hands. Generalized scaling has also been observed as has alopecia of the eyebrows and eyelashes. Corneal ulcers may occur due to infiltration of the eyelids.



Fig. 48.4 Lipoid proteinosis – clinical features. A Beaded eyelid papules (moniliform blepharosis), hemorrhagic crusts, and confluent waxy papules of the glabella leading to an early leonine facies. **B** Skin-colored papulonodules of the elbow as well as irregular hypopigmented scars of the extensor forearm. **C** Characteristic verrucous changes of the elbow. **D** A firm tongue with numerous tiny papules on the dorsal surface. **E** Multiple, round hypopigmented and depressed scars on the shoulder. **F** Waxy, yellowish plaque on the back. *B, D, E, Courtesy Julie V. Schaffer, MD; C, Courtesy Judit Stenn, MD.*

In addition to involvement of the tongue (diffuse infiltration), the frenulum (restricted motion of the tongue), and the oropharynx, recurrent parotitis can occur due to occlusion of the salivary duct. Dental anomalies include hyperplasia or aplasia of the upper incisors, premolars or molars; patients usually lose their teeth at an early age. Neurologic manifestations are common and consist of behavioral and learning difficulties, seizures, and, less often, intracerebral hemorrhage. A pathognomonic radiographic finding is bilateral, intracranial, sickle-shaped calcification within the amygdalae[18]. More recently, an increased prevalence of renal cysts has been described.

In general, the disease has a stable or slowly progressive course that is compatible with a normal lifespan, except for the risk of respiratory obstruction in infancy. An elevated ESR may be seen due to increased α- or γ-globulins.

Pathology

The major clinical manifestations are related to the deposition of an amorphous or laminated material around blood vessels and within the connective tissues. The amorphous deposits consist primarily of non-collagen proteins, while the concentric layers of basement membrane-like material contain collagen (types II and IV) and laminin. In addition, the deposits are PAS-positive and diastase-resistant, indicating the presence of neutral glycosaminoglycans (GAGs; mucopolysaccharides).

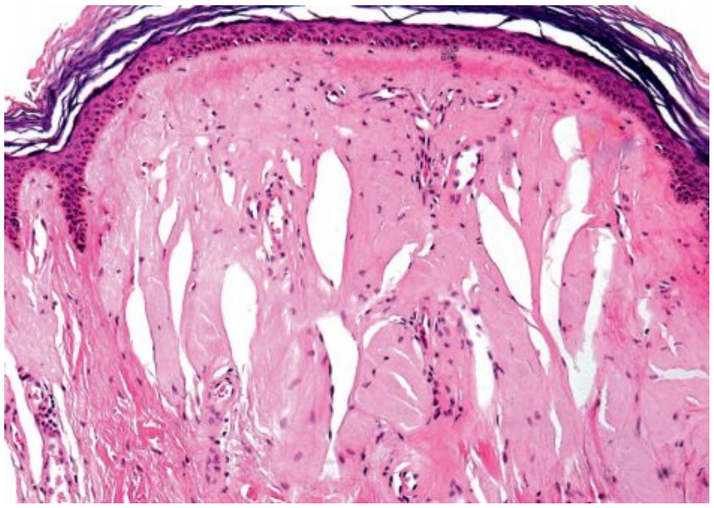


Fig. 48.5 Lipoid proteinosis – histopathologic features. Hyperkeratosis, a flattened epidermis, and vertically oriented eosinophilic deposits in the dermis. Note the cleft formation. *Courtesy Lorenzo Cerroni, MD.*

H&E-stained sections of early lesions reveal pink, hyalin-like deposits around the capillaries within the papillary dermis and at the periphery of eccrine sweat glands. Older lesions are characterized by hyperkeratosis, occasionally papillomatosis, and a thickened dermis in which bundles of pink hyalin deposits are found in a diffuse pattern (Fig. 48.5); the bundles are often oriented perpendicularly to the dermal–epidermal junction. There are smaller scattered deposits of hyalin in the lower dermis. Hyalin deposits also surround the hair follicles, sebaceous glands, and arrector pili muscles as well as the eccrine glands.

In addition to type IV collagen, laminin, and neutral GAGs, hyaluronic acid is present in the dermis, as demonstrated by Alcian blue and hyaluronidase staining (see Ch. 46). Fat stains (e.g. Sudan III) give inconsistent results when the tissue is formalin-fixed, and rarely the deposits stain with Congo red. Ultrastructurally, reduplication of the basement membrane of vessels and occasionally the dermal–epidermal junction is seen; the deposits appear to be composed of small granules and short filaments of low electron density that measure 3–5 nm in diameter.

There are few reports of the histopathologic features of the vesicular first phase and they vary from intraepidermal acantholysis to cell-poor subepidermal blisters.

Differential Diagnosis

The clinical differential diagnosis includes erythropoietic protoporphyria (EPP), amyloidosis, papular mucinosis (scleromyxedema), colloid milium, and non-Langerhans cell histiocytoses. During the initial phase, hydroa vacciniforme may be considered. In infants, the possibility of hyaline fibromatosis syndrome (juvenile hyaline fibromatosis and infantile systemic hyalinosis) needs to be considered, which is due to mutations in the gene that encodes capillary morphogenesis protein 2 (see Ch. 98). Histologically, the differential diagnosis includes EPP and colloid milium. In cutaneous lesions of EPP, colloid milium, and amyloidosis (see Table 48.1), the hyalinization is milder, more focal and superficial, and it rarely involves the eccrine glands. The deposits in colloid milium do not have the striking perivascular pattern seen in lipoid proteinosis.

Treatment

Currently, there is no known cure or effective treatment for lipoid proteinosis. Oral, intralesional (including submucosal), and topical corticosteroids have been used with some beneficial effect, as have humectants. Plastic surgery, dermabrasion, and laser resurfacing have been successfully performed[19], and there are limited reports of the use of systemic retinoids (e.g. acitretin 0.5 mg/kg/day for 6 months)[20], D-penicillamine, and oral dimethyl sulfoxide (DMSO)[21].

COLLOID MILIUM

Synonyms: ■ Colloid degeneration of the skin ■ Elastosis colloidalis conglomerata ■ Miliary colloidoma

Key features

- A rare disorder in which dome-shaped, translucent papules develop in sun-exposed skin
- Four variants are recognized: adult, juvenile, and pigmented colloid milium and nodular colloid degeneration
- Histologically, amorphous, eosinophilic, granular deposits are found within the superficial dermis

Introduction and Epidemiology

Adult colloid milium is the most common form of the disease. It usually occurs in middle-aged, fair-skinned individuals who have had significant cumulative sun exposure, with a male-to-female ratio of 4:1. The adult form has also been observed in outdoor oil refinery workers, suggesting an additional effect of petrochemicals. In general, *juvenile* colloid milium develops before puberty and both an autosomal recessive and an autosomal dominant inheritance pattern have been reported[22].

Pathogenesis

Although excessive sun exposure clearly plays a role in *adult* colloid milium, the precise pathogenesis is not known. Photoinduced damage to dermal elastic fibers, as in solar elastosis, has been suggested. In *juvenile* colloid milium, ultraviolet light-induced damage to epidermal keratinocytes has been observed and this may reflect an inherited susceptibility. *Pigmented* colloid milium is a variant of the adult form in which there is a combination of excessive sun exposure plus topical application of hydroquinone or phenols[23].

Clinical Features

In both the *adult and juvenile* forms, multiple, dome-shaped, translucent to yellow or yellow–brown papules are seen in areas of chronic sun exposure (Fig. 48.6), e.g. the face (especially periorbitally), ears, posterolateral neck, and the dorsal aspect of the hands and forearms. With minor trauma, lesions can become hemorrhagic. By dermoscopy, a diffuse orange background is seen along with linear-curved blurred telangiectasias and a few milia-like cysts. In *pigmented* colloid milium, grouped to confluent gray–brown papules are present on the face, whereas in *nodular colloid degeneration*, skin-colored to yellowish nodules or plaques develop, often on the face[22,23].

Pathology

In *adult* colloid milium, nodules composed of homogeneous eosinophilic colloid material are seen in the papillary dermis (Fig. 48.7). Within the nodules, there may be clefts and fissures. A grenz zone is often present, as is evidence of solar elastosis beneath the nodules. Although the colloid masses contain degenerated elastic fibers, they often exhibit a staining profile similar to amyloidosis, i.e. positive staining with crystal violet, Congo red, and thioflavin T stains; such staining is more consistent in frozen sections. In addition, PAS staining is positive. A negative pan-cytokeratin stain is helpful in distinguishing adult colloid milium from primary cutaneous amyloidosis (amyloid K).

In *juvenile* colloid milium, amorphous eosinophilic deposits are also found within the papillary dermis, but when compared to the adult form, there is less clefting and no grenz zone. As with colloid bodies (which are also keratinocyte-derived), nonspecific staining for immunoglobulins, complement, and fibrin is seen. Similar to primary cutaneous amyloidosis, staining for keratin is positive due to the presence of amyloid K.

In *pigmented* colloid milium, lightly pigmented islands of colloid material are found in the upper dermis. In *nodular colloid degeneration*,



Fig. 48.6 Juvenile and adult colloid milium. A Coalescing brown papules in sun-exposed sites of the face. Note the sparing of the philtrum. **B** Yellowish, translucent papules and multi-lobulated plaques are present on the nose, admixed with telangiectasias. *A, Courtesy Lorenzo Cerroni, MD, and Sergio Chimenti, MD; B, Courtesy Luis Requena, MD.*

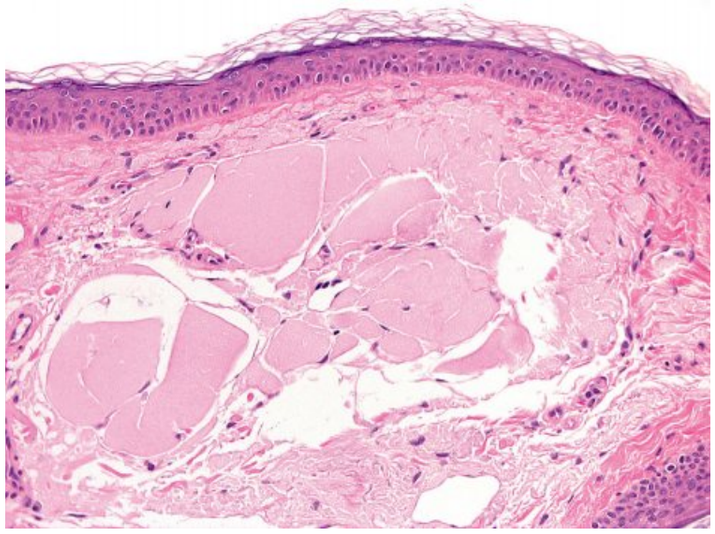


Fig. 48.7 Adult colloid milium – histopathologic features. Nodular mass of eosinophilic, homogeneous material within the upper dermis with a thin subepidermal grenz zone. Note fissures and clefts within the mass with a few fibroblasts along some of the clefts. *Courtesy Lorenzo Cerroni, MD.*

homogenized amorphous dermal collagen with small fissures and clefts is seen. Whether this entity is a variant of nodular amyloidosis is still under debate. Ultrastructurally, colloid milium is characterized by amorphous and granular material which lacks the straight, non-branching filaments seen in amyloidosis.

Differential Diagnosis

Clinically, the differential diagnosis of juvenile and adult forms of colloid milium includes erythropoietic protoporphyria (EPP), mucinoses (e.g. papular, self-healing), lipoid proteinosis, adnexal tumors, and primary systemic amyloidosis (adults). Pigmented colloid milium needs to be distinguished from exogenous ochronosis. Histologically, colloid milium must be distinguished from EPP, lipoid proteinosis, and primary cutaneous amyloidosis. In cutaneous lesions of EPP, there are hyalin deposits around and within the superficial blood vessel walls, whereas the dermal deposits of lipoid proteinosis are accentuated around the blood vessels. Primary cutaneous amyloidosis may be indistinguishable from the juvenile type of colloid milium, as both stain positively for keratin; some authors consider juvenile colloid milium to be a variant of lichen amyloidosis. Unlike lipoid proteinosis and lichen amyloidosis, the dermal deposits of adult colloid milium do not stain positively for laminin and type IV collagen or cytokeratin, respectively.

Treatment

Treatment modalities are limited and include laser therapy (e.g. long-pulsed Er:YAG, fractional photothermolysis), dermabrasion, intense pulsed light, photodynamic therapy, cryotherapy, and chemical peels[24].

MUCOPOLYSACCHARIDOSES

Key features

- A group of inherited disorders, primarily autosomal recessive, characterized by deficiencies of specific lysosomal enzymes involved in the catabolism of glycosaminoglycans (GAGs), also referred to as mucopolysaccharides
- Excessive amounts of the GAGs are found in various tissues and lead to coarse facies, intellectual disability, hepatosplenomegaly, skeletal abnormalities, and corneal clouding
- Hunter syndrome (X-linked recessive) has distinctive skin-colored to white papules over the scapulae (pebbling)
- Screening tests include examination of the urine, peripheral leukocytes, and dermal fibroblasts for the presence of excessive GAGs followed by genetic mutational analysis

Clinical Features and Pathology

The mucopolysaccharidoses are due to mutations in several genes that encode enzymes involved in the catabolism of glycosaminoglycans (GAGs)[25]. Examples of these GAGs include dermatan sulfate, heparan sulfate, and chondroitin sulfate. The storage of excessive amounts of GAGs in various tissues can lead to coarse facies, intellectual disability, hepatosplenomegaly, skeletal abnormalities (dysostosis multiplex), joint stiffness, cardiovascular disease, and corneal clouding (Table 48.3).

Cutaneous manifestations are nonspecific (e.g. hypertrichosis, thickening of the skin), except for the presence of skin-colored to white papules or nodules over the scapulae ("pebbling") in patients with Hunter syndrome[26], which is inherited in an X-linked recessive fashion. The lesions measure 1–10 mm in diameter and may become confluent; they can extend from the posterior axillary line to the midline. Less common sites are the arms, the lateral upper chest, and the buttocks. Extensive dermal melanocytosis (i.e. Mongolian spots) can occur on the trunk and extremities in patients with Hunter or Hurler syndrome.

Screening tests include examination of the urine for excessive amounts of GAGs and examination of circulating leukocytes or dermal fibroblasts for vacuoles or granules that can be demonstrated via special stains (see Table 46.1). The peripheral blood smear should be fixed in absolute methanol and fixation of the skin biopsy specimen in absolute alcohol is preferred. Specific enzyme assays or genetic mutational analysis can then be performed; prenatal diagnosis is possible.

THE MUCOPOLYSACCHARIDOSES				
Disorder	**Enzyme deficiency**	**Stored material**	**Clinical types (onset)**	**Inheritance**
MPS 1 H, Hurler	α-L-Iduronidase	Dermatan sulfate Heparan sulfate	Infancy	AR
MPS I H/S, Hurler/Scheie	α-L-Iduronidase	Dermatan sulfate Heparan sulfate	Childhood	AR
MPS I S, Scheie	α-L-Iduronidase	Dermatan sulfate Heparan sulfate	Late childhood/early adulthood	AR
MPS II, Hunter	Iduronate 2-sulfatase	Dermatan sulfate Heparan sulfate	Severe – infancy Mild – late childhood	X-linked recessive
MPS III A–D, Sanfilippo A–D	A: Heparan-*N*-sulfatase B: *N*-acetyl-α-glucosaminidase C: Acetyl-CoA: α-glucosaminide *N*-acetyltransferase D: *N*-acetyl-glucosamine-6-sulfatase	Heparan sulfate	Early childhood	AR
MPS IV A, Morquio A	*N*-acetylgalactosamine-6-sulfatase	Keratan sulfate Chondroitin-6 sulfate	Childhood	AR
MPS IV B, Morquio B	β-Galactosidase†	Keratan sulfate Chondroitin-6 sulfate	Childhood	AR
MPS VI, Maroteaux–Lamy	Arylsulfatase B (*N*-acetylgalactosamine-4-sulfatase)	Dermatan sulfate	Late infancy/childhood	AR
MPS VII, Sly	β-Glucuronidase	Dermatan sulfate Heparan sulfate Chondroitin-4 and -6 sulfate	Wide range Severe – neonatal Mild – adolescence	AR

*Persistent and extensive, often involving the anterior as well as posterior trunk; has also been described in patients with GM1 gangliosidosis (see Ch. 63).
†Allelic with GM1 gangliosidosis.

Table 48.3 The mucopolysaccharidoses. AR, autosomal recessive; MPS, mucopolysaccharidosis. *Adapted with permission from Hopkin RJ, Grabowski GA. Lysosomal storage diseases. In: Kasper DL, Fauci AS, Hauser SL, et al (eds). Harrison's Principles of Internal Medicine, 19th edn. New York: McGraw-Hill, 2015.*

In biopsy specimens from all types of mucopolysaccharidosis (MPS), metachromatic granules are seen within the cytoplasm of fibroblasts and in some cases in sweat glands, the external root sheath of hair follicles, and epidermal keratinocytes. The latter may have a pale distended cytoplasm which displaces the nucleus to one side. Biopsy specimens of diffusely thickened skin demonstrate fragmentation and hyalinization of collagen and increased mucin. Extracellular deposits of metachromatic material and mucin deposition are seen in the papulonodular lesions of Hunter syndrome[26]. By electron microscopy, fibrillogranular material is seen within lysosomes in all types of MPS.

Treatment

Although supportive interventions (e.g. home oxygen, physical therapy for joint stiffness, cardiac valve replacement) play an important role in the treatment of MPSs, additional therapeutic options – in particular, enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT) offer long-term hope for affected individuals[27,28]. Currently available ERT includes α-L-iduronidase (laronidase; Aldurazyme™) for MPS I, iduronate-2-sulfatase (idursulfase; Elaprase™) for MPS II, *N*-acetylgalactosamine 4-sulfatase (galsulfase; Naglazyme™) for MPS VI, and β-glucuronidase (vestronidase-α; Mepsevii™) for MPS VII. ERT is effective in controlling pulmonary insufficiency, decreased joint mobility and hepatosplenomegaly, but does not improve bone or valvular heart disease. Nor does it affect the intellectual disability, as the enzymes cannot pass the blood–brain barrier[27].

Allogeneic HSCT has been used successfully in patients with MPS I, II, IVA, VI, and VII[28]. Results vary depending upon the age of the patient and the disease stage at the time of the procedure, with better results when performed at an early age. Joint mobility, cardiopulmonary function, hearing, vision, and coarse facies can be improved with allogeneic HSCT, in addition to improvement of CNS impairment in MPS I, II, and VII[28]. Substrate reduction therapy and gene therapy represent future treatment options[25,29]. An example of the latter is administration of hematopoietic stem and progenitor cells transduced *ex vivo* with an α-L-iduronidase-encoding lentiviral vector after myeloablative conditioning[29a].

Additional figures available in our eBook (see inside front cover for access code).

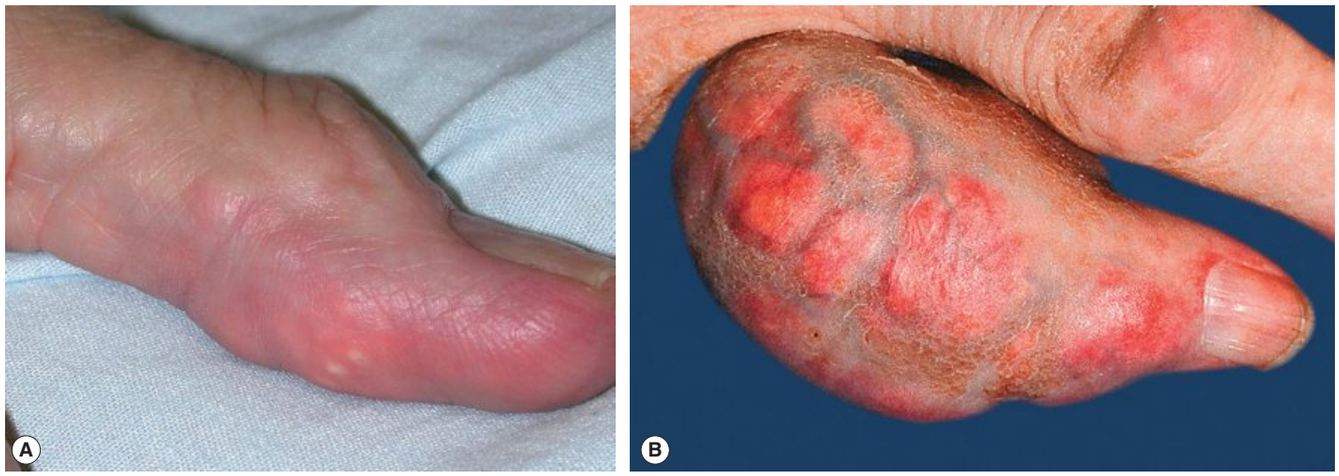
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THE MUCOPOLYSACCHARIDOSES					
Clinical features					
Neurologic	**Liver and/or spleen enlargement**	**Skeletal disease**	**Ophthalmologic**	**Hematologic**	**Other features**
Intellectual disability	+++	++++	Corneal clouding	Vacuolated lymphocytes	Coarse facies, cardiovascular involvement, respiratory compromise, joint stiffness, dermal melanocytosis*
Mild intellectual disability	++	++	Corneal clouding	Vacuolated lymphocytes	Severity intermediate between Hurler and Scheie
None	+	+	Corneal clouding	Vacuolated lymphocytes	Normal stature, valvular heart disease, joint stiffness, carpal tunnel syndrome
Intellectual disability, less in mild form	++ to +++	++ to ++++	Retinal degeneration, no corneal clouding	Granulated lymphocytes	Coarse facies, cardiovascular involvement, joint stiffness, distinctive pebbly skin lesions, dermal melanocytosis*
Severe intellectual disability, with deterioration during early childhood	+	+	None	Granulated lymphocytes	Mild coarse facies, usually normal stature, severe behavioral problems
None	+	++++	Corneal clouding	Granulated neutrophils	Distinctive skeletal deformity, odontoid hypoplasia, aortic valve disease
None	±	++++	Corneal clouding	Granulated neutrophils	See above, Morquio A
None	++	++++	Corneal clouding	Granulated neutrophils and lymphocytes (most prominent of all MPS)	Coarse facies, valvular heart disease, upper airway obstruction
Intellectual disability, absent in some adults	+ to +++	+ to +++	Corneal clouding	Granulated neutrophils	Coarse facies, cardiovascular involvement, hydrops fetalis in neonatal form

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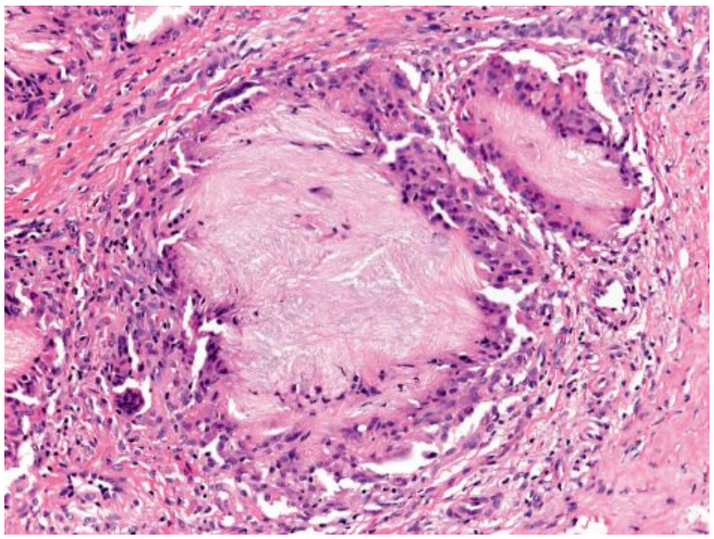
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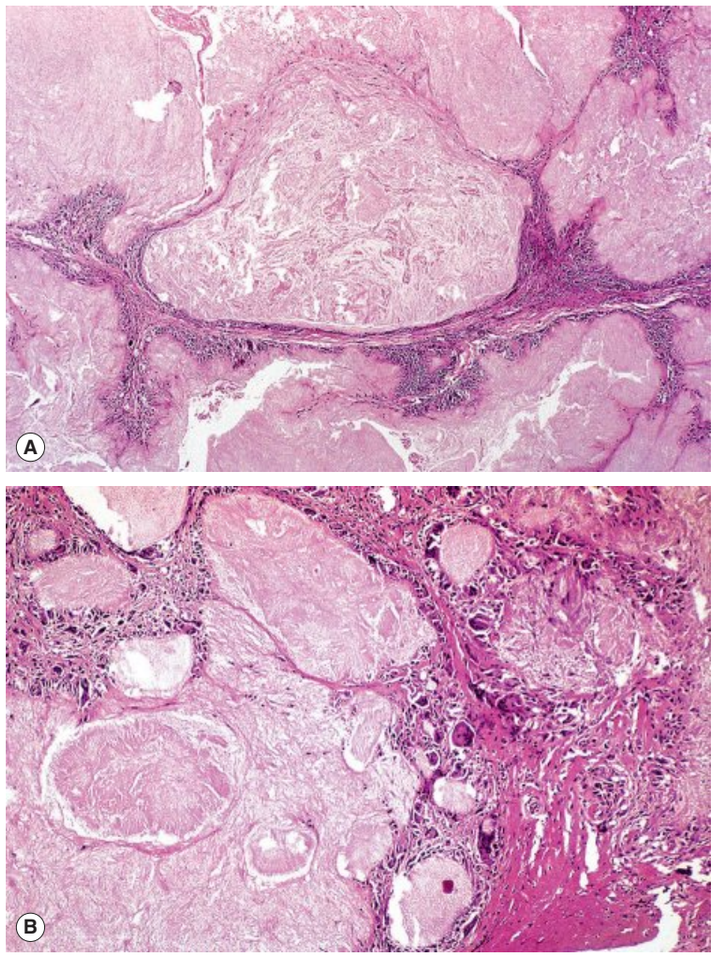
eFig. 48.1 Tophaceous gout. The deposits create a multilobulated appearance and can vary from localized (**A**) to extensive with fusiform swelling (**B**).



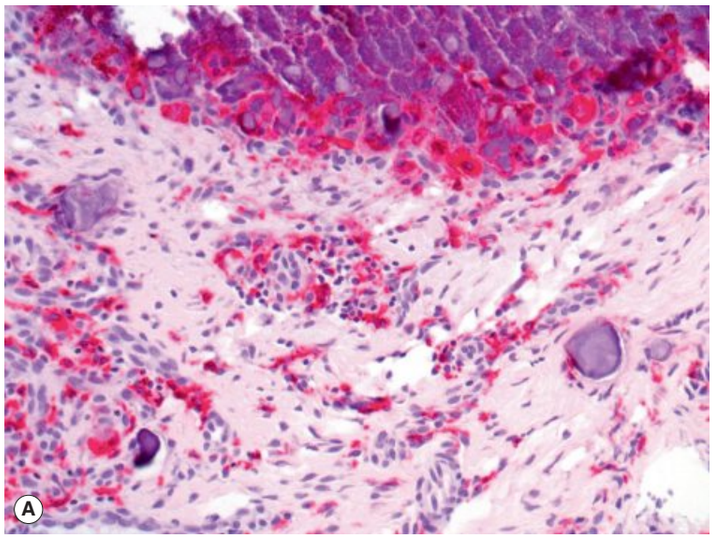
eFig. 48.2 Tophaceous gout involving the ear. A Small yellow papule on the helix. **B** Larger yellow nodule on the antihelix. The small yellow–white areas within the nodule represent deposits that can be expressed following a shallow incision, allowing for a bedside diagnosis. *A, Courtesy Jeffrey Cohen, MD; Courtesy Jonathan S. Leventhal, MD.*

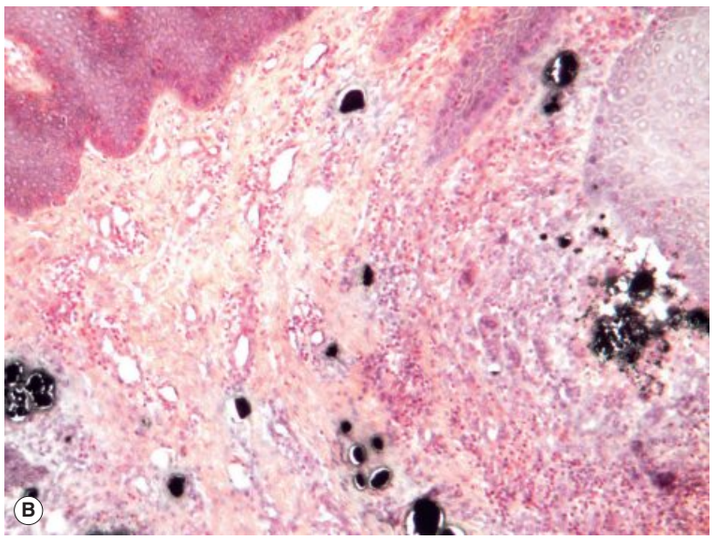


eFig. 48.3 Tophaceous gout – histopathologic features. Deposits of amorphous, acellular material within the dermis. Histiocytes and multinucleated giant cells surround the deposits. *Courtesy Lorenzo Cerroni, MD.*

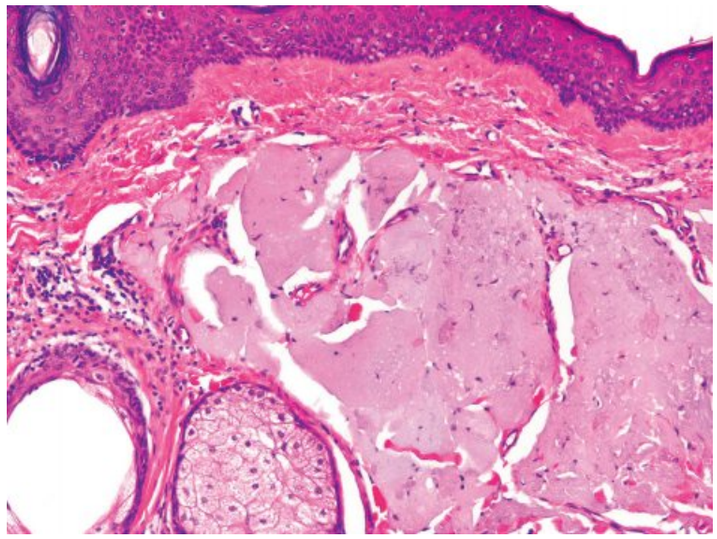


eFig. 48.4 Tophaceous gout – histopathologic features. A Deposits of amorphous, acellular material within the dermis. **B** Higher magnification. Needle-like spaces are present within the amorphous deposits, and histiocytes and multinucleated giant cells surround the deposits.





eFig. 48.5 Pseudogout – histopathologic features. A Calcium deposits in the upper dermis as well as rhomboid crystals. **B** Verhoeff–van Gieson staining demonstrates the foci of calcification.



eFig. 48.6 Adult colloid milium – histopathologic features. Nodular mass of homogeneous material within the upper dermis with a subepidermal grenz zone. Note fissures and clefts within the mass as well as scattered fibroblasts. *Courtesy Luis Requena, MD.*



eFig. 48.7 Extensive dermal melanocytosis (Mongolian spots) and hypertrichosis in a 4-month-old girl with Hunter syndrome.

49 Porphyria

Jorge Frank

Key features

- The porphyrias result from dysfunction of enzymes involved in heme biosynthesis
- The different types can be classified into either acute versus non-acute or cutaneous versus non-cutaneous forms
- Cutaneous symptoms exclusively involve sun-exposed areas of the body
- Life-threatening neurologic attacks can occur in the acute porphyrias
- Diagnosis of specific types of porphyria may at times be difficult because clinical symptoms are often nonspecific and biochemical findings can overlap
- The genetic bases of the porphyrias have been well characterized, facilitating accurate molecular diagnosis and genetic counseling

INTRODUCTION

The porphyrias are metabolic disorders, each arising from a predominantly hereditary deficiency of one of the eight enzymes of the porphyrin–heme biosynthetic pathway (Fig. 49.1)[1]. Traditionally, these disorders are subdivided into erythropoietic and hepatic forms, according to the major site of expression of the enzyme deficiency. From a dermatologist's perspective, the porphyrias can be classified into cutaneous and non-cutaneous forms (Table 49.1), whereas from a general clinician's point of view, it is more appropriate to classify the porphyrias into acute and non-acute forms, thereby emphasizing the presence or absence of potentially life-threatening acute neurologic attacks (Table 49.2)[2]. Therefore, we will adhere to the latter classification throughout this chapter.

The porphyrias are of particular dermatologic interest because most forms have characteristic cutaneous manifestations that often allow a presumptive diagnosis. Laboratory tests are then used to confirm the suspected diagnosis. The genetic defects underlying the porphyrias have been well characterized (Table 49.3), facilitating molecular diagnosis and genetic counseling for affected families.

HISTORY

In 1874, Schultz described a man with a history of cutaneous photosensitivity, accompanied by the excretion of wine-red urine[3]. Subsequently, Baumstark detected urinary pigments, which he named "urorubrohaematin" and "urofuscohaematin"[4]. Günther established the first classification of the porphyrias in 1911, recognizing them as hereditary metabolic disorders characterized by increased porphyrin excretion. He distinguished between two different forms: (1) haematoporphyria acuta, characterized by acute neurovisceral attacks without skin lesions; and (2) haematoporphyria congenita and chronica, both disorders having cutaneous findings in sun-exposed areas of the body[5]. In 1937, the terms "acute intermittent porphyria" and "porphyria cutanea tarda" were introduced. Over the next four decades, variegate porphyria (in 1953), hereditary coproporphyria (in 1955), erythropoietic protoporphyria (in 1961), hepatoerythropoietic porphyria (in 1969), and δ-aminolevulinic acid (ALA) dehydratase deficiency porphyria (in 1979) were described[6]. Most recently, X-linked dominant protoporphyria was recognized[7].

EPIDEMIOLOGY

The porphyrias are rare disorders, occurring in all races and both sexes. Whereas some forms appear during infancy, other variants usually do not present until puberty or adulthood. Prevalence rates vary from 0.1 to 10 per 100 000 individuals (see Table 49.2)[1,8]. However, the precise prevalence of the various porphyrias is not known, due primarily to geographic differences, the likelihood of underdiagnosis, and the incomplete penetrance of the dominantly inherited porphyrias.

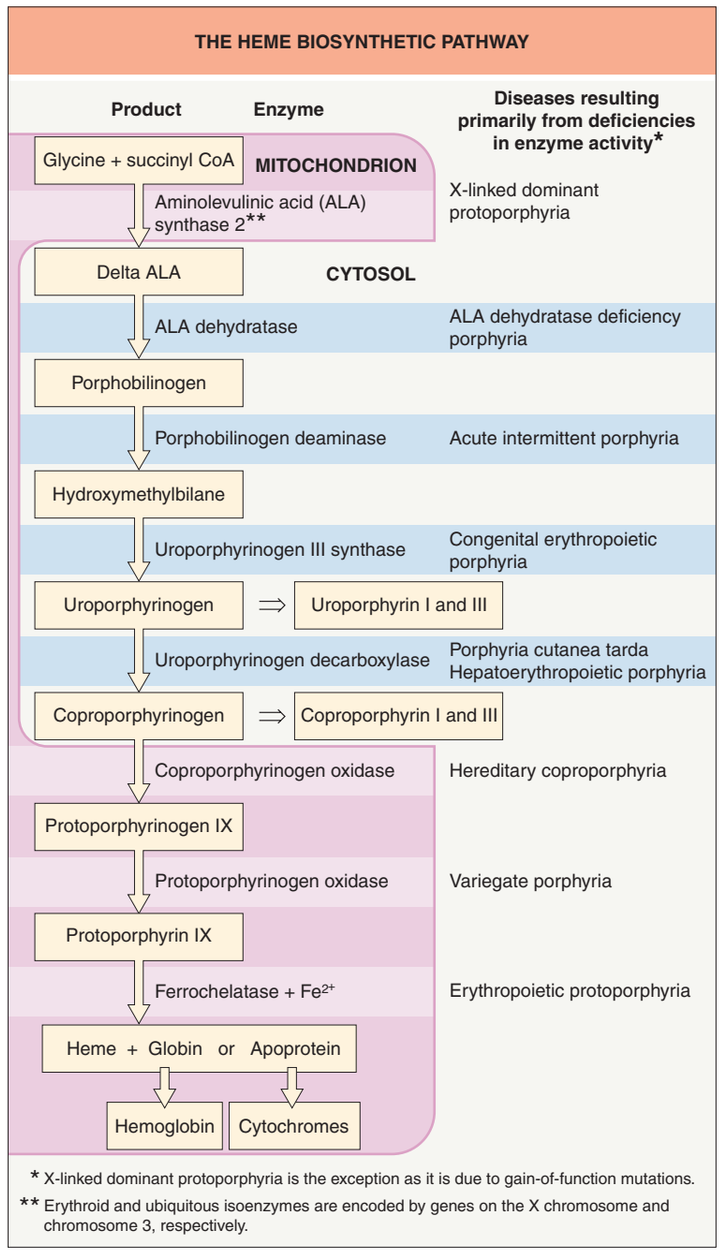


Fig. 49.1 The heme biosynthetic pathway. ALA, aminolevulinic acid, also referred to as δ-aminolevulinic acid or 5-aminolevulinic acid.

PATHOGENESIS

Mutations in any of the genes encoding the enzymes in the heme biosynthetic pathway can lead to a pathologic accumulation and excess excretion of porphyrins and/or porphyrin precursors, as a result of enzyme dysfunction[1]. Except for patients with acquired porphyria cutanea tarda, all forms of porphyria are inherited as monogenetic traits (see Table 49.3).

CLASSIFICATION OF THE PORPHYRIAS INTO CUTANEOUS AND NON-CUTANEOUS FORMS	
Cutaneous	**Non-cutaneous**
Porphyria cutanea tarda Erythropoietic protoporphyria Variegate porphyria Hereditary coproporphyria Congenital erythropoietic porphyria Hepatoerythropoietic porphyria X-linked dominant protoporphyria	Acute intermittent porphyria ALA dehydratase deficiency porphyria

Table 49.1 Classification of the porphyrias into cutaneous and non-cutaneous forms. ALA, aminolevulinic acid.

Cutaneous Findings

To date, no single factor can explain the various photosensitivity patterns evoked by porphyrins plus visible and UV radiation. Nonetheless, a number of cellular and soluble factors are thought to be involved, including reactive oxygen species, certain cell types (e.g. erythrocytes, mast cells, polymorphonuclear cells, fibroblasts), and soluble mediators (e.g. components of the complement system or factor XII-dependent pathways, eicosanoids), as well as matrix metalloproteinases[6]. Most likely, interactions between these factors contribute to the development of cutaneous lesions.

Within the Soret band (400 to 410 nm), porphyrins absorb light energy most efficiently and enter into an excited molecular state. There is also less prominent absorption of adjacent UV wavelengths and other minor visible bands. These light-excited porphyrins can then in turn transfer this absorbed energy to oxygen molecules thereby generating highly reactive oxygen species. Cellular and tissue damage induced by photoactivated porphyrins is believed to result primarily from the formation of reactive singlet oxygen and free radicals, with subsequent lipid peroxidation and protein cross-linking[9,10].

The type of cellular damage depends on the solubility and tissue distribution of the porphyrins. Accumulation of water-soluble uro- and coproporphyrins leads to blistering, as is seen in most of the cutaneous porphyrias (e.g. porphyria cutanea tarda, variegate porphyria). In contrast, accumulation of lipophilic protoporphyrins leads to an immediate cutaneous burning sensation after exposure to

CLASSIFICATION OF THE PORPHYRIAS INTO ACUTE AND NON-ACUTE FORMS			
Disorder	**Incidence**	**Age of onset**	**Important aspects**
Acute porphyrias			
Acute intermittent porphyria	0.5–1 per 100 000	Second to fourth decade of life; rarely before puberty	Most common acute porphyria worldwide; acute neurologic attacks but no photosensitivity/cutaneous manifestations
Variegate porphyria	~1 per 300 in South Africa; relatively rare elsewhere	Second to third decade of life; usually not before puberty	*Cutaneous manifestations similar to porphyria cutanea tarda*, and acute attacks similar to acute intermittent porphyria can occur (neurocutaneous porphyria); founder mutations identified in South Africa and Chile
Hereditary coproporphyria	Very rare (<75 cases reported)	Usually not before puberty	Acute attacks similar to acute intermittent porphyria; *cutaneous manifestations, including erythema and blistering in sun-exposed areas, can occur* (neurocutaneous porphyria)
ALA-D deficiency porphyria	Extremely rare (<10 cases reported)	Early and late onset have been described	Neurologic symptoms similar to acute intermittent porphyria can occur; no photosensitivity/cutaneous manifestations
Non-acute porphyrias (all can have cutaneous features)			
Porphyria cutanea tarda	Most common porphyria worldwide	Third to fourth decade of life; usually not before puberty	Acquired and hereditary variants exist; moderate to severe photosensitivity; cutaneous findings in sun-exposed areas include skin fragility, erosions, crusts, vesicles and bullae, milia, scarring, hyperpigmentation and hypertrichosis; indistinguishable from variegate porphyria
Erythropoietic protoporphyria	Second-highest incidence of the cutaneous porphyrias	Early childhood (1 to 4 years); late onset extremely rare	Cutaneous manifestations include erythema, edema, crusts, purpura, skin thickening, and waxy scars, primarily on the dorsal hands and face; usually no blistering; in ~5% of patients, severe liver disease can occur; cholelithiasis; palmar keratoderma in rare AR form; adult-onset form associated with underlying MPD or MDS
Congenital erythropoietic porphyria	Very rare (~170 cases reported)	Infancy/first decade of life	Very severe clinical course; in sun-exposed sites, vesicles and bullae, erosions, ulcerations, crusts, milia, scarring, hyperpigmentation, and hypertrichosis; mutilation; hemolytic anemia; hepatosplenomegaly; porphyrin deposition in bones and teeth (erythrodontia); pink, red, or violet staining of diapers
Hepatoerythropoietic porphyria	Extremely rare (~35 cases reported)	Early infancy	Homozygotic or compound heterozygotic variant of porphyria cutanea tarda; markedly increased photosensitivity and severe clinical course possible; in sun-exposed sites, vesicles and bullae, skin fragility, erosions, crusts, milia, scarring, and hypertrichosis; mutilation can occur; diapers stained by darkly colored urine
X-linked dominant protoporphyria	Very rare	Early childhood	Skin symptoms indistinguishable from erythropoietic protoporphyria; most recent type of porphyria to be recognized; liver disease appears to occur more frequently than in erythropoietic protoporphyria

Table 49.2 Classification of the porphyrias into acute and non-acute forms. Important clinical and epidemiological aspects are highlighted. ALA-D, aminolevulinic acid dehydratase; AR, autosomal recessive; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder.

GENETIC ASPECTS OF THE PORPHYRIAS			
Disorder	**Gene locus**	**Protein product and gene symbol**	**Mode of inheritance**
Acute porphyrias			
Acute intermittent porphyria	11q23.3	Porphobilinogen deaminase; *PBGD*	AD
Variegate porphyria	1q22–23	Protoporphyrinogen oxidase; *PPOX*	AD
Hereditary coproporphyria	3q12	Coproporphyrinogen oxidase; *CPO*	AD
ALA-D deficiency porphyria	9q34	δ-Aminolevulinic acid dehydratase; *ALAD*	AR
Non-acute porphyrias			
Porphyria cutanea tarda	1p34	Uroporphyrinogen decarboxylase; *UROD*	AD (up to 25% of cases); otherwise acquired
Erythropoietic protoporphyria	18q21.3	Ferrochelatase; *FECH*	AD*; rarely, AR
Congenital erythropoietic porphyria	10q25.2–q26.3	Uroporphyrinogen III synthase; *UROS*	AR
Hepatoerythropoietic porphyria	1p34	Uroporphyrinogen decarboxylase; *UROD*	AR
X-linked dominant protoporphyria	Xp11.21	δ-Aminolevulinic acid synthase 2; *ALAS2* (gain-of-function mutations)	XLD

*Actually semi-dominant inheritance with a mutation in one allele and a specific intronic polymorphism in the second allele ("hypomorphic" allele; see text).

Table 49.3 Genetic aspects of the porphyrias. ALA-D, aminolevulinic acid dehydratase; AD, autosomal dominant; AR, autosomal recessive; XLD, X-linked dominant.

the appropriate wavelengths of light, accompanied by erythema and edema, as seen in erythropoietic protoporphyria[10].

Acute Porphyric Attack

Two porphyria variants, ALA dehydratase deficiency porphyria and acute intermittent porphyria, are not associated with cutaneous findings (see Table 49.1). The dysfunctional enzymes in these two porphyrias are involved in early steps of heme biosynthesis, and their substrates, ALA and porphobilinogen (PBG), respectively, are non-phototoxic porphyrin precursors (see Fig. 49.1). However, both acute intermittent porphyria and ALA dehydratase deficiency porphyria can manifest with life-threatening acute neurologic attacks (see Table 49.2). It appears that ALA and PBG, which are excreted in massive amounts from the liver during an acute attack, are extremely neurotoxic. Lacking appropriate barrier protection, the autonomic and peripheral nervous systems are particularly susceptible to the toxic effects[11].

Of note, porphyrin abnormalities are also observed in the setting of lead poisoning, sideroblastic and hemolytic anemia, iron deficiency, renal failure, cholestasis, liver disease, and gastrointestinal hemorrhage. However, associated photosensitivity has only been documented in rare cases of sideroblastic anemia[6].

CLINICAL AND LABORATORY INVESTIGATION

In establishing the diagnosis of a specific type of porphyria, the medical evaluation involves up to four steps:

- a thorough clinical assessment that includes a family history and physical examination, with particular reference to sun-exposed sites
- biochemical measurement of porphyrins and porphyrin precursors in urine, feces, blood, and/or plasma (Table 49.4)
- determination of the activity of specific enzymes (specialized laboratories)
- DNA mutational analysis (specialized laboratories).

Difficulties in obtaining a definitive diagnosis are primarily a result of the different types of porphyria having overlapping clinical and/or biochemical features (Fig. 49.2). This is especially true of variegate porphyria and hereditary coproporphyria, which may present with cutaneous lesions similar to those observed in porphyria cutanea tarda and/or neurologic and visceral findings resembling those encountered in acute intermittent porphyria.

With regard to biochemical analyses, markedly elevated urinary levels of the porphyrin precursors ALA and PBG can be found during an acute attack. However, asymptomatic "carriers" (who harbor mutations) are rarely detected via measurement of urinary porphyrin precursors because the latter can exhibit significant variability and levels may be only slightly elevated or even normal during the intervals between acute attacks (see Table 49.4 [shaded areas]). In addition, diagnoses based upon measurements of enzymatic activity in fibroblasts or lymphocytes are not always conclusive. This is because an overlap exists between the values obtained in patients, asymptomatic carriers, and normal control individuals[12].

Therefore, the ability to detect specific genetic mutations has made a significant impact on the precise diagnosis of porphyrias and the ability to provide accurate genetic counseling[6,11].

THE NON-ACUTE PORPHYRIAS

The non-acute porphyrias consist of porphyria cutanea tarda (PCT), erythropoietic protoporphyria (EPP), congenital erythropoietic porphyria (CEP), hepatoerythropoietic porphyria (HEP), and X-linked dominant protoporphyria (XLDPP). All these porphyrias present primarily with cutaneous findings (see Tables 49.1 & 49.2)[1,6]. While histologic examination of involved skin is not required to confirm a presumptive diagnosis of any of the cutaneous porphyrias, a biopsy specimen may have been obtained to exclude other entities in the differential diagnosis. Occasionally, the pathologist may identify histologic features that support the diagnosis of cutaneous porphyria even though the clinician suspected another disorder, e.g. epidermolysis bullosa acquisita.

Porphyria Cutanea Tarda (PCT)

Worldwide, PCT is the most common type of porphyria. It results from decreased activity of uroporphyrinogen decarboxylase, the fifth enzyme in heme biosynthesis (see Fig. 49.1)[1,6].

At least two types of PCT can be distinguished: (1) a sporadic (acquired) variant, designated **type I PCT**, in which the dysfunctional enzyme is exclusively expressed in the *liver*; and (2) an autosomal dominant familial (hereditary) variant, designated **type II PCT**, in which the catalytic enzymatic defect is detected in *all tissues* (see Table 49.3). In most countries, the ratio of type I to type II PCT is currently estimated to be approximately 3 : 1 to 4 : 1[13]. Interestingly, Elder[14] reported several families with typical clinical and biochemical features of overt PCT but with normal uroporphyrinogen decarboxylase activity in their red blood cells. This variant of the disease has been designated **type III PCT**. Indeed, there is increasing evidence that some facets of the etiology of PCT have yet to be completely elucidated.

The cutaneous manifestations of PCT include increased photosensitivity and skin fragility as well as blistering, erosions, crusts, milia, and scars in sun-exposed sites (Fig. 49.3; see Table 49.2). Additionally, postinflammatory hyperpigmentation, hypertrichosis (Fig. 49.4), scarring alopecia, and morpheaform and sclerodermoid changes (Fig. 49.5) can be observed.

Histologic examination of vesiculobullae commonly reveals subepidermal cell-poor blisters with a characteristic festooning of dermal papillae; the latter is most likely due to the deposition of PAS-positive

CHARACTERISTIC BIOCHEMICAL FINDINGS IN THE PORPHYRIAS											
	Urine				Feces			Erythrocytes			
Type of porphyria	ALA	PBG	URO	COPRO	URO	COPRO	PROTO	URO	COPRO	PROTO	Plasma
Acute porphyrias											
Acute intermittent porphyria	++ to ++++	++ to ++++	+++	++	N to +	N to +	N to +	N	N	N	N
Variegate porphyria	++ to +++	++ to +++	+++	+++	N	+++	++++	N	N	N	624-626 nm*
Hereditary coproporphyria	N to ++	N to ++	++	++++	++	++++	N to +	N	N	N	619 nm*
ALA-D deficiency porphyrin	+++	N	+	++	N	+	+	N	N	++	ALA, COPRO & PROTO ↑
Non-acute porphyrias											
Porphyria cutanea tarda	N	N	++++	++	++	ISOCOPRO	+	N	N	N	URO ↑
Erythropoietic protoporphyria	N	N	N	N	N	++	++ to ++++	N	N to +	+++	PROTO ↑
Congenital erythropoietic porphyria	N	N	++++	++	+	+++	+	++++	+++	+++	URO & COPRO ↑
Hepatoerythropoietic porphyria	N	N	+++	ISOCOPRO	N	ISOCOPRO	N	N	+	+++	URO ↑
X-linked dominant protoporphyria	N	N	N	N	NA	NA	NA	NA	NA	++++†	PROTO ↑

*Peak fluorometric emission.
†Approximately 40% zinc protoporphyrin.

Table 49.4 Characteristic biochemical findings in the porphyrias. In patients with variegate porphyria or hereditary coproporphyria who have no symptoms (cutaneous or systemic), urine porphyrins may not be elevated (shaded areas). ALA, aminolevulinic acid; ALA-D, aminolevulinic acid dehydratase; COPRO, coproporphyrin; ISOCOPRO, isocoproporphyrin; PBG, porphobilinogen; PROTO, protoporphyrin; URO, uroporphyrin. N = normal; NA, not available; + = above normal range; ++ = slightly elevated; +++ = highly elevated; ++++ = very highly elevated; ↑ = increase.

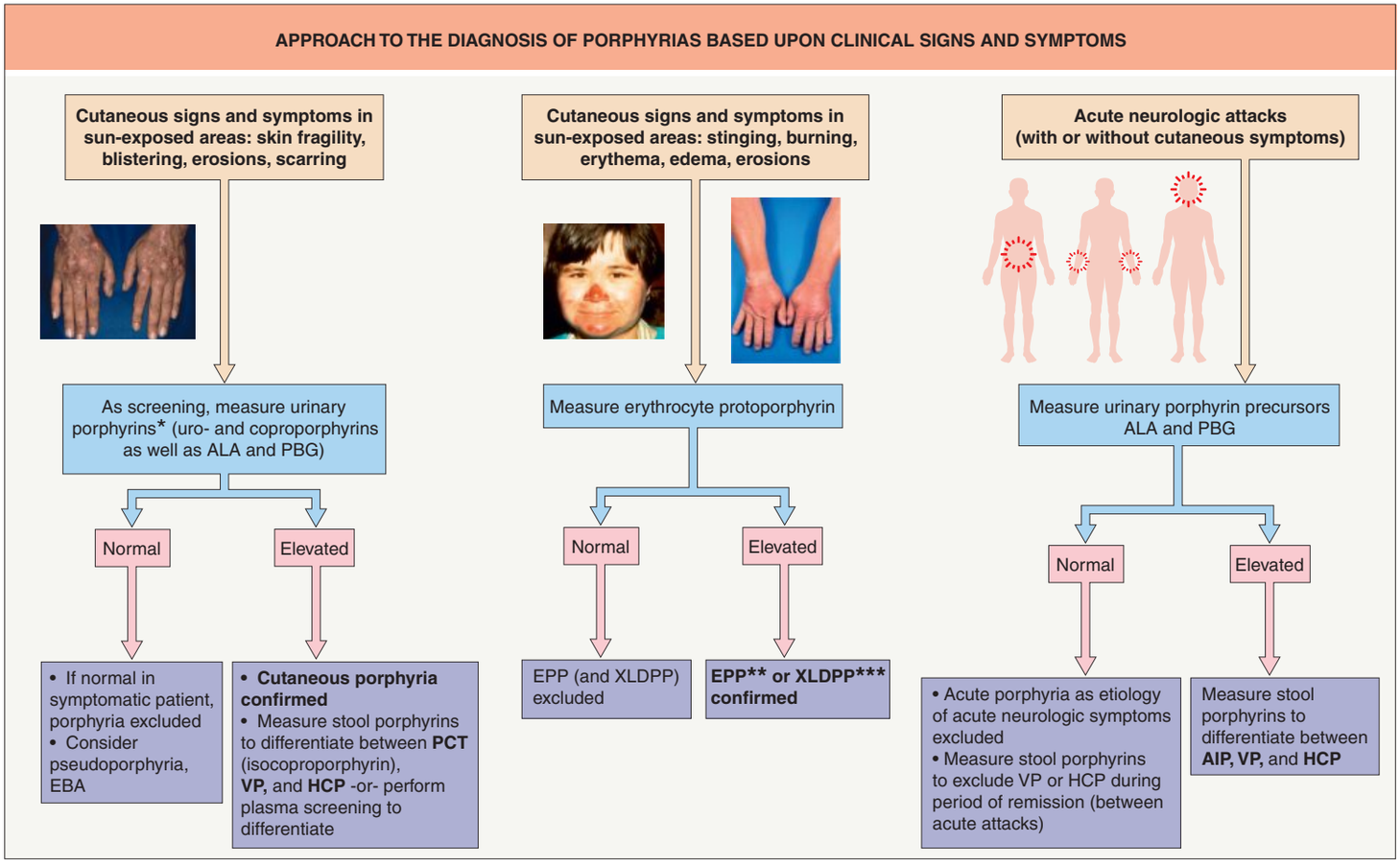


Fig. 49.2 Approach to the diagnosis of porphyrias based upon clinical signs and symptoms. Increased zinc protoporphyrin can be seen in iron deficiency anemia, heavy metal intoxication, and anemia of chronic disease. AIP, acute intermittent porphyria; ALA, aminolevulinic acid; EBA, epidermolysis bullosa acquisita; EPP, erythropoietic protoporphyria; HCP, hereditary coproporphyria; PBG, porphobilinogen; PCT, porphyria cutanea tarda; VP, variegate porphyria; XLDPP, X-linked dominant protoporphyria. *24-hour collection. **Increased free protoporphyrin. ***Increased free and zinc protoporphyrins; ~40% zinc protoporphyrin.



Fig. 49.3 Porphyria cutanea tarda. A Marked fragility with multiple hemorrhagic crusts, erosions, and milia as well as scars. **B** Flaccid hemorrhagic bulla and tense vesicle with clear fluid on the forefinger, accompanied by crusts and scars. **C** Extensive scarring of the bald scalp with multiple large hemorrhagic crusts in a patient with hepatitis C viral infection. *C, Courtesy Jeffrey P. Callen, MD.*

glycoproteins in and around the wall of vessels localized in the upper dermis (Fig. 49.6). Direct immunofluorescence microscopy often demonstrates immunoglobulins (mainly IgG; less commonly IgM), complement, and fibrinogen at the dermal–epidermal junction and around blood vessels of the papillary dermis. As opposed to autoimmune bullous diseases, these immunoglobulin deposits are presumed to be non-antigen-specific. In sclerotic lesions, there is dermal fibrosis as well as PAS-positive deposits around blood vessels.

Biochemically, increased urinary excretion of uroporphyrin (type I isomers > type III isomers), hepta-carboxylated porphyrins (type III isomers > type I isomers), and coproporphyrin can be detected, as well as increased excretion of isocoproporphyrin in the feces; the latter finding is exclusive to PCT and hepatoerythropoietic porphyria (see Table 49.4). Historically, a presumptive clinical diagnosis of PCT was followed by an examination of the patient's urine, both under Wood's lamp illumination (in the dark) and after exposure to natural light. Due to the excessive excretion of porphyrins, the urine of PCT patients turns red to brown after several hours of exposure to natural light and it has a pink to red fluorescence when exposed to a UVA light source. However, it has to be borne in mind that these bedside observations are neither sensitive nor specific diagnostic tests.

A wide variety of triggering factors (including hepatotoxins) have been reported to precipitate the clinical manifestations of PCT, among them alcohol (most common), estrogens, polychlorinated hydrocarbons, dialysis in patients with renal failure, iron, inheritance of specific mutations in *HFE* which underlie classic hemochromatosis, and viral infections such as hepatitis C and HIV. Interestingly, homozygosity for *HFE* mutation C282Y has been found to be associated with an earlier onset of disease in both sporadic and familial PCT, with the effect being more marked in familial PCT[15].

Erythropoietic Protoporphyria (EPP)

EPP is due to a semi-dominantly inherited deficiency of ferrochelatase, the last enzyme in the heme biosynthetic pathway (see Fig. 49.1)[1,6].

Clinically, EPP is characterized by cutaneous photosensitivity that typically manifests early in life, i.e. during early childhood. Acute photosensitivity episodes are characterized by intense burning,

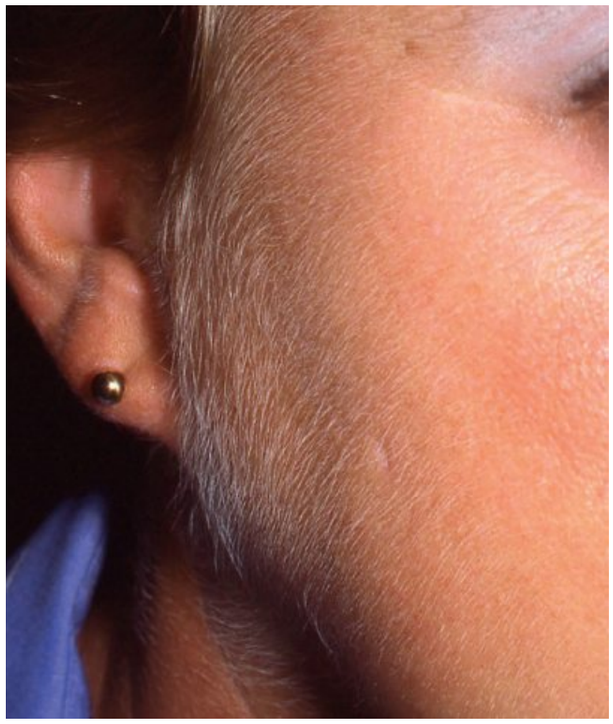


Fig. 49.4 Porphyria cutanea tarda. Hypertrichosis of the face. *Courtesy Jeffrey P. Callen, MD.*



Fig. 49.5 Porphyria cutanea tarda – sclerodermatous presentation. The patient had shiny, yellow–white to brown firm plaques on the neck and upper back.

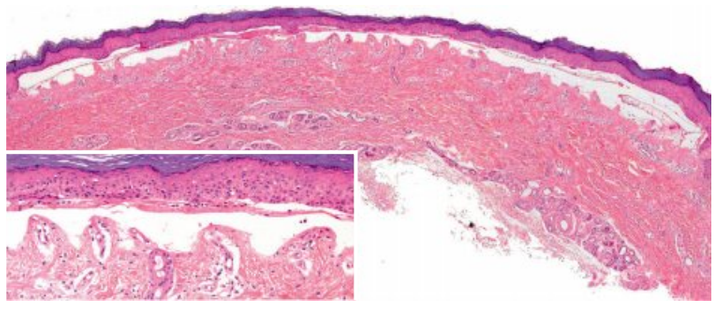


Fig. 49.6 Porphyria cutanea tarda – histologic features. Subepidermal blister of acral skin with a minimal ("cell-poor") dermal inflammatory infiltrate. Festooning of the dermal papillae is seen (inset). *Courtesy Lorenzo Cerroni, MD.*



Fig. 49.7 Erythropoietic protoporphyria. Erythema, edema, and hemorrhagic crusts on the nose as well as the fingers in a young girl.



Fig. 49.8 Erythropoietic protoporphyria. A Subtle scarring on the nose and linear scars on the upper cutaneous lip in a 6-year-old child. **B** Extensive scarring of the cheeks and linear scars on the upper cutaneous lip and chin in an adult. *A, Courtesy Gillian Murphy, MD; B, Courtesy Luis Requena, MD.*

stinging, and pruritus of sun-exposed skin, particularly on the nose, cheeks and dorsal hands, followed by erythema, edema, crusts, petechiae, and then wax-like scarring (Fig. 49.7 & 49.8; see Table 49.2); blistering usually does not occur. Skin symptoms can develop within minutes of sun exposure, often starting early in the springtime, continuing throughout the summer, and diminishing during fall and winter. Window glass does not protect the patient. Patients suffering from EPP often report that the only way to relieve the burning and stinging sensations is to cool the affected skin under cold water. In patients with EPP who have not had recent sun exposure, the only detectable cutaneous findings may be scars on the nose and lips (see Fig. 49.8). In rare patients with recessively inherited EPP, palmar keratoderma can be seen[16].

Adult-onset EPP, also referred to as late-onset EPP, is very unusual, and the atypical age of onset often delays the diagnosis. To date, all reported individuals with late-onset EPP have had a history of either a myeloproliferative disorder or myelodysplastic syndrome[17]. Interestingly, in these patients the hematologic disease is thought to possibly give rise to somatic hematopoietic mutations or clones that result in abnormal porphyrin metabolism and systemic protoporphyrin accumulation. Thus, this disorder should be considered in adults with new-onset, otherwise unexplained photosensitivity, especially if they have an underlying hematologic disorder.

Histologically, vacuolization of epidermal cells is seen in acute lesions. Intercellular edema may also be present, as well as vacuolization and

lysis of endothelial cells within superficial dermal blood vessels. In older lesions (e.g. areas of waxy scarring), eosinophilic PAS-positive deposits are observed around blood vessels (Fig. 49.9). There can be a resemblance to the amorphous protein depositions seen in lipoid proteinosis. Ultrastructurally, thickening and degeneration of capillary basement membranes is seen.

Biochemically, EPP is characterized by an increase in *free* protoporphyrin levels in erythrocytes, plasma, feces, and other tissues such as the liver (see Table 49.4)[1,6]. Historically, microscopic examination of a blood smear via UV illumination was performed to detect erythrocyte fluorescence. However, this test is not particularly sensitive or specific. The greatest concern in patients with EPP is a rapid accumulation of protoporphyrin within the liver and biliary system, with the development of cholestasis. This can lead to hepatic damage and progressive (even fatal) liver failure. Of note, liver function tests may remain normal until late in the course of the disease[18].

The genetic basis for the development of cutaneous symptoms in EPP has been elucidated. Only those individuals who inherit a heterozygous ferrochelatase gene mutation involving one parental allele (allele A) *and* a specific intronic polymorphism (IVS3–48 T/C) of the other parental allele (allele B) develop skin symptoms. This latter specific polymorphism *in trans* constitutes a "hypomorphic" allele and leads to abnormal modulation of splicing. As a result, the aberrantly spliced mRNA is degraded by a nonsense-mediated decay mechanism, producing a decreased steady-state level of mRNA. Combined, a mutation in allele A plus the polymorphism in allele B lead to a marked reduction in ferrochelatase activity that is ~15%–25% of normal[19].

Certainly, the identification of the molecular mechanisms underlying the photosensitivity observed in EPP has to be considered a milestone in porphyria research. Still, the development of protoporphyrin-induced hepatic disease and the molecular mechanisms underlying the phenotype associated with severe liver injury are not yet well understood.

X-linked Dominant Protoporphyria (XLDPP)

XLDPP is characterized by gain-of-function mutations in *ALAS2* on the X chromosome. This gene encodes the erythroid tissue-specific isoform of the first enzyme in the heme biosynthetic pathway, δ-aminolevulinic acid synthase 2. The resultant increase in synthetase activity eventually leads to an overproduction of protoporphyrin IX and a clinical phenotype that is indistinguishable from EPP. However, the percentage of patients at risk for potentially fatal liver disease appears to be higher than in classic EPP. Biochemical profiling demonstrates higher total protoporphyrin levels in erythrocytes (as compared to EPP due to ferrochelatase deficiency), with ~40% being zinc protoporphyrin[7].

Congenital Erythropoietic Porphyria (CEP)

Synonym: ■ Günther disease

With ~170 cases reported to date, CEP is a very rare, autosomal recessively inherited disorder that results from markedly decreased catalytic activity of uroporphyrinogen III synthase, the fourth enzyme in heme biosynthesis (see Fig. 49.1). CEP manifests shortly after birth with severe cutaneous photosensitivity, blistering, erosions, crusts, and ulcerations, followed by extensive scarring and deformation, primarily of the hands (Fig. 49.10A; see Table 49.2). On the face, a loss of eyebrows and eyelashes, as well as severe mutilation of cartilaginous structures (e.g. the nose), are frequently observed. Furthermore, erythrodontia (Fig. 49.10B), acro-osteolysis, and skeletal abnormalities (e.g. demineralization) are common clinical features. In addition, a variable degree of hematologic involvement, ranging from mild forms of hemolytic anemia to intrauterine hydrops fetalis and hepatosplenomegaly, can be observed. Pink, red, or violet staining of diapers can serve as an early clue to the diagnosis. Biochemically, there is increased urinary excretion of uroporphyrin I and coproporphyrin I plus elevated levels of coproporphyrin I in the stool (see Table 49.4)[20].

Hepatoerythropoietic Porphyria (HEP)

HEP, the homozygous (or compound heterozygous) variant of hereditary PCT, is an extremely rare disease that is due to a pronounced decrease in uroporphyrinogen decarboxylase activity (see Table 49.3). Clinically, HEP usually presents during early childhood, with dark urine in the diapers often the initial clinical finding. Subsequently, severe cutaneous photosensitivity develops, associated with blistering, pruritus, hypertrichosis, hyperpigmentation, and scleroderma-like scarring (Fig. 49.11; see Table 49.2). If the clinical course is severe, the symptoms closely resemble those observed in CEP. However, unlike the latter, HEP is not usually associated with hematologic abnormalities (e.g. severe anemia).

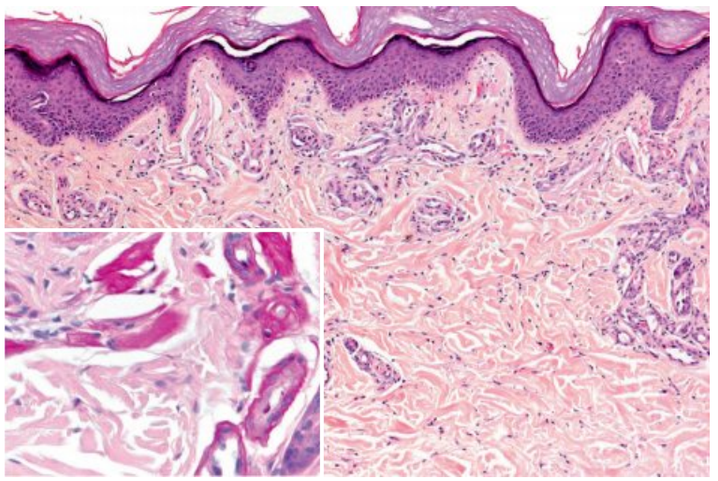


Fig. 49.9 Erythropoietic protoporphyria – histologic features. Eosinophilic deposits around blood vessels are more pronounced than in porphyria cutanea tarda. These deposits are highlighted by a PAS stain (inset). *Courtesy Lorenzo Cerroni, MD.*



Fig. 49.10 Congenital erythropoietic porphyria. A Severe mutilation of the hands due to scarring. **B** Erythrodontia due to massive protoporphyrin deposition in the teeth. *A, Courtesy José Mascaro, MD.*



Fig. 49.11 Hepatoerythropoietic porphyria. Hypertrichosis and severe scarring are seen, resulting in a clinical appearance similar to congenital erythropoietic porphyria. *Courtesy José Mascaro, MD.*



Fig. 49.12 Dialysis-associated pseudoporphyria. Vesicles formed on the dorsal aspects of the hands in this patient with chronic renal failure. *Courtesy Kalman Watsky, MD.*

DRUG-INDUCED PSEUDOPORPHYRIA	
NSAIDs*	
Naproxen (propionic acid derivative; NSAID most frequently implicated)	
Mefenamic acid	
Nabumetone	
Oxaprozin (propionic acid derivative)	
Ketoprofen (propionic acid derivative)	
Diflunisal	
Celecoxib	
Antibiotics	
Nalidixic acid	
Tetracycline, doxycycline	
Ciprofloxacin	
Ampicillin/sulbactam combined with cefepime	
Diuretics	
Furosemide	
Hydrochlorothiazide/triamterene	
Chlorthalidone	
Bumetanide	
Torsemide	
Retinoids	
Isotretinoin	
Acitretin	
Miscellaneous	
Amiodarone	**Imatinib**
Carisoprodol/aspirin – attributed to the carisoprodol	Leflunomide
Chlorophyll	Metformin
Cyclosporine	Olanzapine
Dapsone	Oral contraceptive pill (estrogens, progestins)
Finasteride	Pyridoxine (vitamin B_6)
5-Fluorouracil (intravenous)	Sunitinib
Flutamide	**Voriconazole**
*When caused by NSAIDs, consider prescribing indomethacin, meloxicam, or sulindac.	

Table 49.5 Drug-induced pseudoporphyria. The most common causes are in **bold**. In addition to discontinuation of the offending agent, antioxidants such as N-acetylcysteine have had a beneficial effect in some case series. NSAID, nonsteroidal anti-inflammatory drug. *Courtesy Misty Sharp, MD.*

Urinary levels of uroporphyrin and hepta-carboxylated porphyrins are elevated, as are fecal levels of coproporphyrin and isocoproporphyrin. Increased levels of zinc-chelated protoporphyrin within erythrocytes can also be seen (see Table 49.4)[1,21].

Pseudoporphyria

Pseudoporphyria (also referred to as pseudoporphyria cutanea tarda, bullous dermatosis of dialysis, or therapy-induced bullous photosensitivity) encompasses those conditions that clinically resemble PCT. However, in contrast to PCT, no biochemical abnormalities in porphyrin metabolism are detected (see Fig. 49.2). Skin fragility, erosions, blisters, and scarring have a predilection for the dorsal aspect of the hands (Fig. 49.12), the face, and the extensor surfaces of the legs. Pseudoporphyria is commonly encountered in patients suffering from stage 4 or 5 chronic kidney disease or in those undergoing renal dialysis (hemodialysis more often than peritoneal dialysis). It is also seen in association with the ingestion of specific drugs, including nonsteroidal anti-inflammatory drugs (e.g. naproxen, nabumetone, ketoprofen), furosemide, antibiotics (e.g. nalidixic acid, tetracycline), and retinoids (Table 49.5), and it can occur in association with the use of tanning beds. In the latter situation, vesicles may be seen on the palms.

Histologic findings are indistinguishable from those found in lesions of PCT. Patients who require renal dialysis may develop PCT or pseudoporphyria. Even if they are anuric, it is important to remember that the diagnosis of PCT can be established via plasma or stool studies (see Table 49.4). Treatment is easier for drug-induced pseudoporphyria, as the major recommendation is discontinuation of exposure to the suspected precipitant[22]. Sun protection is advised for all patients.

Differential Diagnosis

PCT must be distinguished from other types of cutaneous porphyria that manifest with blistering. These include mild variants of CEP and HEP and importantly (since they can be associated with life-threatening acute attacks), variegate porphyria (VP) and hereditary coproporphyria (HCP). Furthermore, pseudoporphyria (see above), epidermolysis bullosa acquisita, polymorphous light eruption, and phototoxic and bullous drug eruptions have to be excluded. These latter diseases can easily be differentiated from PCT by porphyrin analysis[1,6,15,23]. If no porphyrin abnormalities are detected, histologic examination of lesional skin (routine and immunofluorescence) can aid in establishing the diagnosis.

In ***EPP***, the differential diagnosis consists of solar urticaria, phototoxic or photoallergic contact dermatitis and drug reactions, polymorphous light eruption, hydroa vacciniforme, and lipoid proteinosis[1,6,16,23].

CEP has to be differentiated from HEP and the rare homozygous (or compound heterozygous) variants of VP and HCP as well as STING-associated vasculopathy with onset in infancy (SAVI; see Table 45.7). Mild variants can sometimes mimic PCT. Likewise, the most important entities in the differential diagnosis of ***HEP*** are CEP and the rare aforementioned homozygous or compound heterozygous variants of VP and HCP.

Treatment

A causal therapeutic strategy would consist of either specific enzyme replacement therapy or gene therapy. However, such therapeutic modalities are not currently available.

THERAPEUTIC APPROACHES TO THE ACUTE AND NON-ACUTE PORPHYRIAS	
Acute porphyrias	**Therapy strategies**
Acute intermittent porphyria; variegate porphyria; hereditary coproporphyria; ALA-dehydratase deficiency porphyria	**Acute attacks** 1. Identification and elimination of precipitating factors (porphyrinogenic drugs; alcohol; hormones) 2. Monitoring in intensive care unit and input from porphyria specialists 3. Adequate pain therapy, e.g. with opioid analgesics 4. Adequate therapy of nausea and vomiting, e.g. with ondansetron, promethazine 5. Intravenous administration of either: (1) heme arginate (Normosang®; Europe only), 3 mg/kg once daily for 4 consecutive days; or (2) hemin (Panhematin®; FDA-approved), usually 1–4 mg/kg/day (over 10–15 min) for 3–14 days *versus* 3–4 mg/kg once daily for 4 days with more extended treatment for severe cases 6. If necessary, until heme preparations become available, intravenous glucose infusions 7. Once monthly subcutaneous givosiran (Givlaari®), aminolevulinic acid synthase 1-directed small interfering RNAs (siRNAs) 8. Measurement of urinary porphyrin excretion during the acute attack (daily, if possible) **Cutaneous symptoms (variegate porphyria; hereditary coproporphyria)** 1. Photoprotection, e.g. broad-spectrum sunscreens*, protective clothing, window films 2. Avoidance of sunlight exposure and trauma
Non-acute porphyrias	**Therapy strategies**
Porphyria cutanea tarda	1. Photoprotection, e.g. broad-spectrum sunscreens*, protective clothing, window films 2. Avoidance of sunlight exposure and trauma 3. Cease alcohol ingestion; stop estrogen therapy 4. Phlebotomy: 400–500 ml every 2 weeks over ~3–6 months 5. *Low-dose* hydroxychloroquine: 100 mg twice weekly (e.g. on Monday and Thursday) over 6–12 months, until porphyrin excretion is within normal range 6. Measurement of urinary porphyrin excretion to monitor therapeutic outcome
Erythropoietic protoporphyria/ X-linked dominant protoporphyria	1. Photoprotection, e.g. broad-spectrum sunscreens*, protective clothing, window films 2. Avoidance of sunlight exposure (common window glass does not provide protection) 3. Oral β-carotene: 30–90 mg/day in children; 60–180 mg/day in adults. Desirable maximum plasma level: 600–800 mcg/dl. Administration during the spring, summer, and fall, with a hiatus during the winter in higher latitudes 4. Afamelanotide ([Nle^4, D-Phe^7]-α-MSH; 16 mg every 60 days as a resorbable implant) may increase tolerance to light exposure 5. Consider cholestyramine or charcoal to reduce enterohepatic recirculation of porphyrins and bile acids in order to enhance hepatic porphyrin excretion; results vary
Congenital erythropoietic porphyria	1. Photoprotection, e.g. broad-spectrum sunscreens*, protective clothing, window films 2. Strict avoidance of sunlight exposure 3. Change day–night rhythm 4. Splenectomy (reduces hemolysis and platelet consumption) 5. Bone marrow or hematopoietic stem cell transplantation
Hepatoerythropoietic porphyria	1. Photoprotection, e.g. broad-spectrum sunscreens*, protective clothing, window films 2. Strict avoidance of sunlight exposure and trauma 3. Change day–night rhythm 4. Of note, therapeutic approaches used in porphyria cutanea tarda (e.g. phlebotomy, antimalarials) are not effective
*Sunscreens that contain the physical blockers zinc oxide, titanium dioxide, and iron oxide are most effective.	

Table 49.6 Therapeutic approaches to the acute and non-acute porphyrias. While the therapeutic measures for an acute porphyric attack are the same for each of the acute porphyrias, different treatment strategies are recommended for each of the non-acute porphyrias, depending upon the prevailing manifestations and the respective form of porphyria. ALA, aminolevulinic acid; MSH, melanocyte stimulating hormone.

The avoidance of UV light exposure, sun-protective clothing, window films, and regular application of broad-spectrum sunscreens are crucial, both prophylactically and therapeutically. However, because the primary wavelengths that induce the porphyrias are in the visible 400–410 nm range, sunscreens are limited in their photoprotective efficacy, with the exception of titanium dioxide and zinc oxide (see Ch. 132). Tinted sunscreens containing iron oxide are also protective against visible light exposure.

Patients with ***PCT*** should be encouraged to eliminate triggering factors such as alcohol ingestion and estrogen therapy. In patients with iron overload, successful treatment can be achieved by repeated phlebotomy (venesection) of ~500 ml blood every 2 weeks, as tolerated by the patient; some authors recommend weekly venesections of 300 ml blood. When required, maintenance phlebotomy is performed at less frequent intervals.

Therapeutic phlebotomy reduces iron stores, thereby improving heme synthesis by reducing iron-induced inhibition of uroporphyrinogen decarboxylase activity. While the therapeutic goal is to reduce serum ferritin levels to the lower limit of the reference range, care should be taken to avoid inducing anemia. Phlebotomy usually leads to resolution of skin fragility and blistering within 2–4 months. However, normalization of urinary porphyrin concentrations will usually take longer (about 12 months).

Another therapeutic option is *low-dose* hydroxychloroquine. This antimalarial is thought to work by accelerating hepatic elimination and urinary excretion of porphyrins, and it may also inhibit porphyrin synthesis. Standard therapy consists of 100 mg of hydroxychloroquine *twice weekly*, and complete remission can be expected within 6–9 months (Table 49.6); scored tablets should be prescribed. Administration of higher doses (as are used in cutaneous lupus erythematosus) can lead to hepatotoxicity. Hydroxychloroquine can be combined with phlebotomy to induce a remission more rapidly[1,6,16]. The genetic background of PCT patients, with respect to the presence of *HFE* mutations, appears to play a critical role in the outcome of hydroxychloroquine treatment. Whereas heterozygosity for mutation *C282Y* and compound heterozygosity for *HFE* mutations did not compromise the therapeutic response, PCT patients homozygous for *C282Y* failed to respond to antimalarial therapy and retained high serum iron and ferritin levels as well as transferrin saturation[24].

In a pilot trial, deferasirox led to improvement of cutaneous findings in 8 of 10 patients with PCT who completed 6 months of treatment[25]. Treatment of underlying HCV infection with direct-acting antivirals also leads to improvement.

In some patients with ***EPP***, β-carotene minimizes burning, stinging, and photosensitivity reactions. Although β-carotene has no effect on the protoporphyrin levels in erythrocytes, it reduces photosensitivity

by quenching the formation of free radicals that occurs during the cutaneous photoreaction. The administered doses range from 30 to 90 mg/day in children and from 60 to 180 mg/day in adults, with desired maximum plasma levels of 600–800 mcg/dl. Afamelanotide, an analogue of melanocyte stimulating hormone ([Nle^4, D-Phe^7]-α-MSH), was FDA-approved for the prevention of EPP phototoxicity in 2019, and it received regulatory approval in Europe in 2016. In a multicenter, randomized, placebo-controlled trial involving 168 patients with EPP, those treated with afamelanotide (16 mg every 60 days as a resorbable implant) experienced increased tolerance to sun exposure and improved quality of life[26]. In a case series, narrowband UVB phototherapy, including home phototherapy, was shown to be of benefit after 15–20 treatments[27]. Cholestyramine or charcoal can be considered in order to reduce enterohepatic recirculation of porphyrins and bile acids. Overall, current therapeutic options for EPP are more limited than for PCT[1,6,10,11,16,28,29].

Patients with ***CEP*** require surveillance for anemia and skin infections. Frequent blood transfusions can suppress erythropoiesis, thereby decreasing porphyrin production and photosensitivity. Concomitant administration of deferoxamine or deferasirox can reduce the resulting iron overload. Bone marrow or hematopoietic stem cell transplantation leads to marked reduction of porphyrin levels and photosensitivity and has been reported to be curative[1,11,20].

No specific treatment options are currently available for patients with HEP and XLDPP. Careful patient education regarding sun protection is very important.

THE ACUTE PORPHYRIAS

The acute porphyrias consist of acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and δ-aminolevulinic acid dehydratase (ALA-D) deficiency porphyria (see Tables 49.1 & 49.2)[2,6].

Patients with acute porphyrias can present with a broad range of clinical findings, including persistent colicky abdominal pain, nausea and vomiting, obstipation, tachycardia, hypertension, seizures, paresthesias, para- and tetraplegia, and acute psychosis (Table 49.7). Unfortunately, this spectrum of fairly nonspecific symptoms can mimic a number of other diseases and the porphyrias are often not included in the differential diagnosis, especially if neurologic symptoms prevail[2,30]. Acute attacks can be precipitated by a variety of factors, including porphyrinogenic drugs (e.g. antimalarials, tetracyclines, sulfonamides), alcohol, hormonal changes, recurrent or chronic infections, and reduced caloric intake due to fasting or diets. The latter may be a result of enhanced expression of the transcriptional coactivator PGC-1α[31].

In addition to the manifestations outlined in Table 49.7, patients with VP and HCP may have cutaneous findings that are clinically indistinguishable from those of PCT. As a result, VP and HCP are also referred to as neurocutaneous porphyrias[1,2].

A consortium of porphyria specialists from several European porphyria centers has established the European Porphyria Network (EPNET). The goals of the EPNET are to set standards and provide guidelines for the diagnosis and treatment of porphyrias. On the EPNET (porphyria.eu) and the American Porphyria Foundation (porphyriafoundation.com) websites, important information is available for both patients and physicians.

POSSIBLE MANIFESTATIONS OF AN ACUTE PORPHYRIC ATTACK		
Gastrointestinal and metabolic	**Neurologic**	**Cardiac and pulmonary**
Colicky abdominal pain	**Paresthesias**	**Tachycardia**
Nausea and vomiting	**Motor and sensory peripheral neuropathy (para- and tetraplegia)**	Hypertension
Constipation	Seizures	Respiratory paralysis
Obstipation	Muscle pain, back pain	
Hyponatremia	Encephalopathy	
	Paralysis	
	Anxiety	
	Acute psychosis	
	Coma	

Table 49.7 Possible manifestations of an acute porphyric attack. The more prevalent symptoms are in **bold**.

Acute Intermittent Porphyria (AIP)

Worldwide, AIP is the most common type of acute porphyria. This autosomal dominantly inherited disorder is characterized by a deficiency of porphobilinogen deaminase, the third enzyme in heme biosynthesis (see Fig. 49.1).

AIP will not be discussed in detail here because patients do not have skin manifestations. It usually presents after puberty with acute porphyric attacks (see Table 49.7) that may be precipitated by the various trigger factors outlined above. Elevated urinary levels of the porphyrin precursors ALA and PBG can be detected during an acute attack: ALA levels range from 5 to 20 times normal and PBG levels are increased to as high as 20- to 50-fold normal[1,32].

Variegate Porphyria (VP)

Synonyms: ■ South African porphyria ■ Mixed porphyria

VP is characterized by an autosomal dominantly inherited deficiency of protoporphyrinogen oxidase, the seventh enzyme in the pathway of heme biosynthesis (see Fig. 49.1).

Cutaneous and neuropsychiatric symptoms can occur separately or simultaneously in affected individuals. Clinically, the skin findings in VP cannot be differentiated from those observed in PCT. Likewise, the acute attacks observed in VP are identical to those encountered in AIP.

During acute attacks, elevated urinary levels of ALA and PBG are encountered. However, during periods of remission, urinary ALA and PBG levels may be within normal range (see Table 49.4 [shaded areas]). Therefore, additional biochemical analyses of fecal porphyrins are mandatory in order to establish the diagnosis of VP. Elevated levels of stool protoporphyrin and coproporphyrin can be detected, with the concentration of protoporphyrin usually being higher than that of coproporphyrin. It is noteworthy that this abnormal biochemical stool profile can also be detected during periods of remission between attacks[1,33]. On the other hand, a plasma fluorescence emission peak of 624–626 nm is seen only in symptomatic patients, including those with cutaneous involvement.

Hereditary Coproporphyria (HCP)

HCP is a very rare autosomal dominantly inherited disease, characterized by a deficiency of coproporphyrinogen oxidase, the sixth enzyme in the porphyrin–heme biosynthetic pathway (see Fig. 49.1). The clinical symptoms are similar to those encountered in VP. However, in contrast to the latter, the concentrations of coproporphyrin in the stool are usually higher than those of protoporphyrin (see above)[1,34].

δ-Aminolevulinic Acid Dehydratase (ALA-D) Deficiency Porphyria

Synonyms: ■ Plumboporphyria ■ Doss porphyria

This autosomal recessively inherited porphyria variant is extremely rare. As fewer than 10 cases have been reported worldwide, ALA-D deficiency porphyria does not have an important clinical presence. The disease can present during early childhood (as well as in adulthood) with acute neurologic symptoms that resemble those encountered in AIP[1,7].

Differential Diagnosis

When patients with VP or HCP present with cutaneous manifestations, the differential diagnosis is identical to that of PCT (see above). If acute neurologic attacks prevail, a broad range of gastrointestinal, neurologic, and psychiatric diseases have to be excluded, including an "acute

abdomen", peripheral neuropathies, and viral infections[1,2,6]. A more detailed discussion can be found in textbooks of internal medicine.

Treatment

Cutaneous symptoms

Patients with VP or HCP must minimize outdoor light exposure by wearing sun-protective clothing and applying broad-spectrum sunscreens. In contrast to PCT, phlebotomy seems to be of no benefit as are chloroquine and hydroxychloroquine. Furthermore, the latter antimalarials belong to the group of drugs considered to be potential inducers of acute porphyric attacks. Thus, their use is not recommended.

Acute porphyric attack

An acute porphyric attack is a potentially life-threatening event associated with a significant mortality rate (up to 5%). It requires rapid therapeutic intervention to prevent complications such as paralysis, respiratory failure, and coma. Treatment should consist of the following consecutive measures (see Table 49.6)[2,29]:

1. Precipitating factors, e.g. porphyrinogenic drugs, must be identified and eliminated. If necessary, patients should be initially monitored in an intensive care unit.
2. Systemic symptoms such as abdominal pain, nausea, and vomiting should be treated symptomatically, e.g. by administration of opioid analgesics and ondansetron or promethazine, respectively.
3. The most important therapeutic step for a patient with an acute attack is prompt intravenous administration of heme preparations such as heme arginate (Normosang® [Orphan Europe/Recordati Rare Diseases]) or hemin (FDA-approved; Panhematin® [Recordati Rare Diseases])[35]. Heme arginate reduces the overproduction of porphyrin precursors via a negative feedback mechanism in which the increased activity of ALA synthase, the rate-limiting enzyme in heme biosynthesis, is repressed. Of note, heme preparations have the disadvantage of being unstable, and thrombophlebitis is a fairly common side effect[36–38].

Historically, acute attacks were treated primarily with glucose infusions. However, given the availability of effective heme preparations (see above), glucose should only be administered adjunctively or as a temporary measure if heme arginate or hematin are not immediately available.

In 2019 and 2020, the FDA and European Medicines Agency approved givosiran (Givlaari® [Alnylam Pharmaceuticals]) for the treatment of adults with acute (hepatic) porphyria. Givosiran is a solution of small interfering RNAs (siRNAs) that are injected subcutaneously once monthly. These siRNAs promote the degradation of aminolevulinic acid synthase 1 (ALAS1) mRNA within liver cells, thereby reducing circulating levels of neurotoxic metabolites[39]. The most common side effects are injection site reactions and nausea, and both liver function tests and serum creatinine need to be monitored. Givosiran can lead to severe hyperhomocysteinemia, probably due to inhibition of the heme-dependent enzyme cystathionine-β-synthase which is important for homocysteine metabolism, with subsequent protein-N-homocysteinylation[40].

APPENDIX

Laboratories that measure porphyrin level (serum, plasma, erythrocytes, urine and feces):

USA

- ARUP Laboratories (www.arupconsult.com)
- Mayo Medical Laboratories (www.mayocliniclabs.com) – also do enzyme assays and genetic analyses
- University of Texas Medical Branch – Porphyria Center (https://www.utmb.edu/internalmedicine/divisions/gastroenterology/research/research-programs/porphyria-program/porphyria-center)

Europe

- Porphyrin Laboratory, Free University of Brussels (frederic.cotton@lhub-ulb.be)
- Porphyria Research Centre Finland (raili.kauppinen@hus.fi)
- French Porphyria Center Paris (www.porphyrie.net)
- French Porphyria Center Bordeaux (emmanuel.richard@u-bordeaux.fr)
- European Porphyria Specialist Center, Düsseldorf (porphyriaspecialistcenter@med.uni-duesseldorf.de)
- German Competence Center for Porphyrias Karlsruhe (www.porphyrie.de)
- Porphyrin Specialist Center Dublin (vcrowley@stjames.ie)
- Porphyria Center Milano (maria.cappellini@unimi.it)
- Dutch Porphyria Center Rotterdam (stofwissselingsziekten@erasmusmc.nl)
- Norwegian Porphyria Center (NAPOS) (porfyri@helse-bergen.no)
- Porphyria Center Stockholm (porfyricentrum.karolinska@sll.se)
- Porphyria Center Barcelona (JTO@clinic.ub.es) (porphyria.eu/content/spain-barcelona)
- Porphyria Center Madrid (ddavola@unav.es)
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- Porphyria Center Wales, Cardiff (Mike.badminton@wales.nhs.uk)

Additional figures available in our eBook (see inside front cover for access code).

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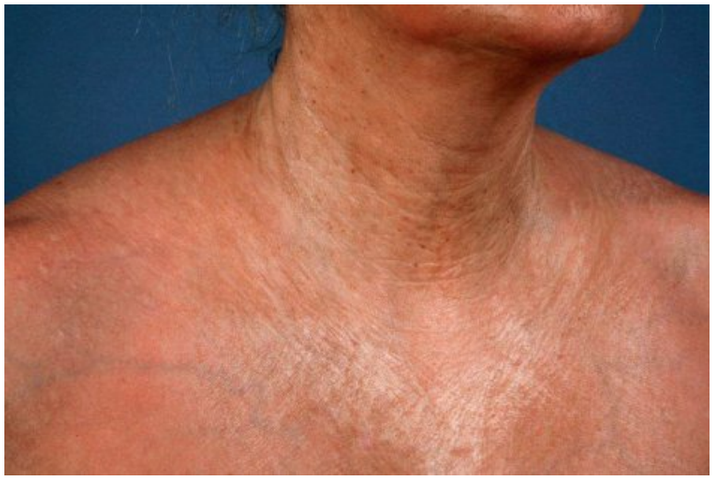
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eFig. 49.1 Porphyria cutanea tarda in a patient with hepatitis C viral infection. Fragility leading to multiple erosions with scale-crust on the dorsal hands and wrists. *Courtesy Jeffrey P. Callen, MD.*



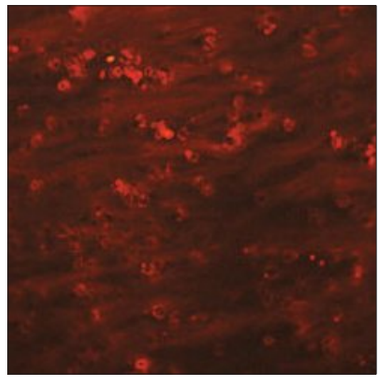
eFig. 49.2 Porphyria cutanea tarda. Hypertrichosis of the malar region of the cheek. *Courtesy Judit Stenn, MD.*



eFig. 49.3 Porphyria cutanea tarda presenting as yellow–brown morpheaform plaques. The plaques were in sun-exposed areas in this patient with a history of alcohol abuse.



eFig. 49.4 Porphyria cutanea tarda – sclerodermatous presentation. The patient had shiny, yellow–white to brown firm plaques on the neck and V of the chest.



eFig. 49.5 Fluorescence of circulating red blood cells. When exposed to UVA light, stable fluorescence is seen in congenital erythropoietic porphyria as opposed to transient fluorescence in erythropoietic protoporphyria (pictured), which is more difficult to photograph. *Courtesy José Mascaro MD.*

50 Calcifying and Ossifying Disorders of the Skin

Daniela Kroshinsky and Janet A. Fairley

Chapter Contents

Cutaneous Calcification 796
Cutaneous Ossification (Osteoma Cutis) 802
Laboratory Evaluation of Patients with Cutaneous Calcification and Ossification 804

Synonyms: ■ Calcinosis cutis: cutaneous calcification ■ Osteoma cutis: cutaneous ossification ■ Calciphylaxis: calcific uremic arteriolopathy; calcifying panniculitis; uremic gangrene syndrome ■ Subepidermal calcified nodule: solitary congenital nodular calcification; Winer's nodular calcinosis

Key features

- Calcium regulates several key physiologic events in the skin, including epidermal proliferation, differentiation, and cell–cell adhesion
- Disruption of normal calcium regulatory pathways can lead to calcification and/or ossification of the skin
- Five major types of cutaneous calcification are seen: *dystrophic*, in which pre-existing damage to the skin results in calcium deposits; *metastatic*, where systemic metabolic disorders lead to calcium deposits in the skin and often other tissues; *iatrogenic*, as a result of medical therapy or testing; *idiopathic*, in which no cause can be identified; and *mixed*, a combination of metastatic and dystrophic
- In cutaneous ossification, there is deposition of calcium and phosphorus as hydroxyapatite crystals within a protein matrix; it can occur in conjunction with calcification or primarily in a number of genetic syndromes
- Correct classification of calcifying disorders requires an evaluation of calcium-phosphate metabolism and examination for associated systemic abnormalities
- Treatment of calcifying disorders is difficult with removal of triggers and correction of any associated disorder, such as hyperparathyroidism, essential for preventing progression. Surgical excision may be useful in circumscribed disease that interferes with function while efficacy of agents that modify calcium metabolism is based primarily upon case series

INTRODUCTION

Calcium plays a vital role in regulating key physiologic events in many tissues, including the skin. In the epidermis, calcium assists in regulating major functions, including proliferation, differentiation, and cell–cell adhesion. Control of intra- and extracellular calcium concentrations and maintenance of gradients are essential for its regulatory role. When factors that regulate calcium in the skin are disrupted, either by local or systemic events, cutaneous calcification or ossification as well as acantholysis and dyskeratosis can develop.

Calcification arises from the deposition of amorphous, insoluble calcium salts, while ossification results from deposition of calcium and phosphorus in a proteinaceous matrix as hydroxyapatite crystals. Ossification may follow pre-existing calcification in the skin, but in most disorders one form of calcium deposition predominates. While each of the calcifying and ossifying disorders of the skin is rare, as an aggregate finding calcium deposition within the skin is not uncommon.

CUTANEOUS CALCIFICATION

Calcifying disorders of the skin are generally divided into five broad categories: dystrophic, metastatic, idiopathic, iatrogenic, and mixed calcification (Table 50.1)[1,2]. *Dystrophic* calcification occurs in the setting of localized tissue damage, without an underlying metabolic abnormality in calcium regulation. Theoretically, dystrophic calcification occurs because the underlying disease process damages cell membranes, allowing calcium influx and subsequent intracellular crystallization. Alternatively, the acidity that accompanies cell damage may disrupt normal processes that inhibit calcification. In contrast, *metastatic* calcification occurs in normal tissue when there is dysfunction of calcium regulatory systems. When no known local or systemic factors can be identified, the calcification is categorized as *idiopathic*, and that related to medical therapy or testing is *iatrogenic*. *Mixed* calcification arises when metastatic calcification due to an underlying metabolic abnormality acts as a trigger for dystrophic calcification.

Dystrophic Calcification

Autoimmune connective tissue disease

Dystrophic calcification may be seen in any of the autoimmune connective tissue diseases (AI-CTDs), but it is most common in childhood dermatomyositis and in the localized form of systemic sclerosis, also known as CREST (*c*alcification, *R*aynaud phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasia) syndrome. As a comparison, cutaneous calcification develops in 10%–20% of patients with adult dermatomyositis, whereas it occurs in up to 50% of children with the disease[3–5]. The presence of dermatomyositis-associated calcinosis correlates with longer disease duration, fingertip ulceration, and anti-NXP-2 autoantibodies, while a negative correlation exists with anti-transcriptional intermediary factor 1-γ antibodies[3]. Small deposits may occur in the skin or larger firm masses may begin in the muscle groups most severely affected by the disease. The most frequently involved sites are the elbows, knees, buttocks, and shoulders (see Fig. 42.9). Extrusion of calcium through the skin causes significant morbidity with pain and secondary infection.

In calcinosis universalis, the most severe form of dystrophic calcification, there is diffuse involvement with sheet-like masses of calcium. Calcification occurs along fascial planes, often leading to severe functional impairment. Aggressive treatment of dermatomyositis with immunosuppressive agents and/or IVIg may be warranted to try to limit this serious complication (see Ch. 42). However, once calcification has developed, the effectiveness of these therapies is quite variable.

The localized (CREST) variant of systemic sclerosis is the other AI-CTD in which cutaneous calcification is frequently seen. Calcification is usually less severe than in dermatomyositis and is usually restricted to the hands and upper extremities (Fig. 50.1); it is also seen over bony prominences and tendons. Extrusion of white chalky material is sometimes followed by localized ulceration, often at sites of trauma such as the digits. Calcinosis universalis can occur in systemic sclerosis, but much less frequently than in dermatomyositis.

Dystrophic calcification has occasionally been reported in chronic cutaneous, acute systemic, and subacute cutaneous lupus erythematosus as well as generalized morphea (Fig. 50.2)[6,7]. Calcification may also occur within lesions of lupus panniculitis. In systemic lupus erythematosus, calcification is most often an asymptomatic radiologic finding.

DISORDERS OF CUTANEOUS CALCIFICATION
Dystrophic
• Autoimmune connective tissue diseases, especially dermatomyositis, CREST • Panniculitis • Cutaneous tumors or cysts, e.g. pilomatricomas, pilar cysts • Infections, especially parasitic • Trauma, including "heel sticks" in neonates, injection sites, surgical scars • Chronic graft-versus-host disease • Genetic disorders, e.g. pseudoxanthoma elasticum, Ehlers–Danlos syndrome
Metastatic

• Advanced chronic kidney disease
  • Calciphylaxis*
  • Benign nodular calcification of renal disease
  • Tumoral calcinosis
• Hypervitaminosis D
• Milk–alkali syndrome
• Sarcoidosis
• Tumoral calcinosis (familial)
• Hyperparathyroidism
• Neoplasms (e.g. multiple myeloma, adult T cell leukemia/lymphoma, SCC of the lung or head and neck)

Idiopathic
• Idiopathic calcified nodules of the scrotum • Subepidermal calcified nodule • Tumoral calcinosis (sporadic) • Milia-like calcinosis
Iatrogenic
• Extravasation of intravenous solutions containing calcium or phosphate • Application of calcium-containing electrode paste for EMGs and EEGs • Application of calcium alginate dressings to denuded skin • Fibroblast growth factor receptor inhibitors† • Organ transplantation, especially liver • Gadolinium (nephrogenic systemic fibrosis)
*Can occasionally occur in the setting of severe primary hyperparathyroidism and, less often, in the absence of a clearly identifiable trigger. †Calcinosis cutis and calciphylaxis due to hyperphosphatemia.

Table 50.1 Disorders of cutaneous calcification. CREST, *c*alcification, *R*aynaud phenomenon, *e*sophageal dysmotility, *s*clerodactyly and *t*elangiectasia; EEG, electroencephalogram; EMG, electromyography; SCC, squamous cell carcinoma.



Fig. 50.1 Dystrophic calcification in a patient with the localized form of systemic sclerosis (CREST syndrome).



Fig. 50.2 Radiograph of calcinosis cutis in a patient with generalized morphea. Areas that were previously firm became rock-hard and lesions of perforating calcinosis cutis (transepidermal elimination) developed on both legs. *Courtesy Jean L. Bolognia, MD.*

Treatment of dystrophic calcification

The management of dystrophic calcification can be challenging. Therapies include a low calcium and phosphate diet, aluminum hydroxide, and bisphosphonates, as well as management of the underlying disorder, although no controlled trials have convincingly shown consistent clinical improvement. While long-term treatment with diltiazem has been reported to decrease the size of calcium deposits, presumably through its effect on calcium transport into cells, its efficacy is variable and months to years of treatment may be required for extensive calcification[8,9]. In case reports and series, minocycline, colchicine, probenecid, IVIg, and JAK inhibitors have demonstrated some efficacy. Application of topical sodium thiosulfate 250 mg/ml [12.5 gm/50 ml] compounded 1 : 1 with petrolatum applied daily) can lead to resolution, while larger lesions may variably respond to intralesional injections (Table 50.2)[10–13].

Surgical excision is appropriate in selected patients with localized masses that are painful or interfere with function, but recurrences can occur. Laser therapy and extracorporeal shock wave lithotripsy represent additional localized therapeutic options[13].

Panniculitis

Any lobular panniculitis may develop focal dystrophic calcification, including pancreatic panniculitis, lupus profundus, and subcutaneous fat necrosis of the newborn (see Ch. 100). In the latter, calcium deposits are small and are most easily noted radiologically; occasionally, more widespread deposits may be seen[14].

Genetic disorders

A number of genetic disorders may be accompanied by cutaneous calcification, including *pseudoxanthoma elasticum* (PXE; see Ch. 97). The coexistence of typical elastic fiber calcification along with small discrete foci of cutaneous calcification or ossification has been reported[15,16]. PXE most frequently results from inactivating mutations in *ABCC6* which encodes a membrane transporter system[17]. ABCC6 directly mediates the sinusoidal release of ATP from the liver, which is then converted to AMP and inorganic pyrophosphate (PPi) within the liver vasculature[18,19]. PPi normally prevents the matrix calcification that is thought to create the findings in PXE[19]. In addition, serum levels of fetuin-A, another major anti-mineralization protein, are significantly reduced in PXE patients[18,20]. These factors, combined with impaired carboxylation of the inhibitor matrix Gla protein, may allow for increased responsiveness to pro-calcifying stimuli and unchecked calcification of elastic fibers in affected tissues[20,21].

SODIUM THIOSULFATE – INTRALESIONAL AND INTRAVENOUS ADMINISTRATION	
Intralesional	
• 250 mg/ml solution • Interventions to address significant associated pain include: (1) premedication (e.g. acetaminophen, oxycodone, hydromorphone); (2) 1 : 1 dilution with 2% lidocaine without epinephrine (adrenaline); and (3) use of small gauge needles and low volume syringes • Inject solution into the skin surrounding the ulceration (not the ulcer) every 1 cm* not to exceed 25 g • Injected weekly until resolution of active erythema and purpura then as needed for new lesions	
Intravenous	
• If receiving hemodialysis, 12.5 g three times per week during the last hour of hemodialysis (first 3 doses) then can increase to 25 g three times per week as tolerated • If receiving peritoneal dialysis, 25 g weekly • If not receiving hemodialysis, can be dosed up to 25 g daily • Continue until resolution of active erythema and purpura	
Side effects†	
• Nausea, vomiting • Volume overload due to sodium load (intravenous)‡ • Hypotension • QT prolongation	• Anion gap metabolic acidosis (thiosulfuric acid) • Reduced bone density • Headache
*Injected in a manner similar to the injection of lidocaine for local anesthesia. †May be reduced by decreasing the dosage, increasing the interval (nonuremic patients), and/or changing the intravenous solution from saline-based to 5% dextrose in water. ‡Cardiology consultation for those with cardiovascular disease.	

Table 50.2 Sodium thiosulfate – intralesional and intravenous administration. The risk:benefit ratio must be considered before injecting lesions overlying bone. For injections into large dense calcium deposits, larger bore needles (e.g. 14g) are sometimes employed. g, gram. From references 37, 45, 55, 59, 62–65.

Ehlers–Danlos syndrome encompasses multiple disorders in which genetic mutations lead to abnormal collagen synthesis, metabolism, or function (see Ch. 95). Patients develop hard subcutaneous nodules known as spheroids or spherules over bony prominences, which are thought to represent herniated fat lobules that have calcified (see Ch. 97). It is also possible that minor trauma results in scar tissue which then becomes a focus for dystrophic calcification[22]. Of note, similar calcifications can occur within the breast in these patients and their detection by mammography may lead to false-positive radiographic findings for breast carcinoma.

Dystrophic calcification may also be seen in patients with *porphyria cutanea tarda* (PCT; see Ch. 49). It occurs most often in patients with longstanding disease who develop sclerodermoid changes and secondary calcification within these areas[23]. As with the other lesions of PCT, calcification appears most often in the head and neck region or on the dorsal surface of the hands. Ulceration has also been reported, although rarely, in association with these lesions.

Other rare genetic syndromes in which cutaneous calcification may be seen include *Werner syndrome* and *Rothmund–Thomson syndrome* (see Ch. 63). *Cerebral amyloid angiopathy*, an autosomal dominant condition due to mutations in the gene encoding the amyloid precursor protein, can present with dementia, patchy leukoencephalopathy, hemorrhagic stroke, external carotid artery dysplasia, and occipital calcifications[24]. Microcalcification of the dermal blood vessels may also be seen, and while the latter is asymptomatic, dermatologists might be called upon to biopsy the skin as a diagnostic measure.

Infections

Infections, particularly parasitic, can lead to dystrophic calcification. Calcified cysts form around larvae or worms, including *Onchocerca volvulus* and the tapeworm *Taenia solium*. Intrauterine herpes simplex viral infections may cause annular plaques of calcinosis cutis in newborns.

Neoplasms

Incidental calcification has been noted in a large number of benign and malignant tumors of the skin. Up to 75% of pilomatricomas develop calcification and in 15%–20% there is evidence of ossification. A chalky, calcium-containing material may drain from the surface of these tumors. Activating mutations in the β-catenin gene have been demonstrated in sporadic pilomatricomas[25]. Other calcifying adnexal tumors or cysts include basal cell carcinomas, pilar cysts, epidermoid cysts, and chondroid syringomas[26]. Rarely, melanocytic nevi, atypical fibroxanthomas, pyogenic granulomas, trichoepitheliomas, and seborrheic keratoses have been reported to calcify.



Fig. 50.3 Dystrophic calcification in an infant at the site of a previous "heel stick" for obtaining blood. *Courtesy Julie V. Schaffer, MD.*

Other

Trauma, "heel sticks" (for obtaining blood in neonates; Fig. 50.3), subcutaneous or intramuscular injection sites, surgical and burn scars, and keloids have also been reported as triggers of dystrophic calcification. Localized or widespread cutaneous calcification may also be seen in chronic graft-versus-host disease[27].

Metastatic Calcification

Renal disease

The most common cause of metastatic calcification is advanced chronic kidney disease (Fig. 50.4). In patients with renal failure, there is an impaired ability to clear phosphate and impaired activation of vitamin D_3, as 1-α hydroxylation occurs in the kidney. Impaired production of 1,25-dihydroxyvitamin D_3 leads to decreased absorption of calcium from the intestine and hypocalcemia. Hypocalcemia, in turn, induces increased secretion of parathyroid hormone (PTH) and subsequent mobilization of calcium and phosphate. The serum calcium concentration is normalized, but significant hyperphosphatemia may develop, leading to elevation of the calcium × phosphate solubility product and resultant metastatic calcification.

Benign nodular calcification usually develops in the setting of prolonged secondary hyperparathyroidism due to advanced chronic kidney disease. Clinically, there are large deposits of calcium in the skin and subcutaneous tissue, often in periarticular sites. The number and size correlate with the severity of the hyperphosphatemia. Lesions are usually asymptomatic except for pain from pressure placed on surrounding structures. Normalization of serum calcium and phosphate levels may result in resorption of the lesions; however, if larger deposits interfere with function, surgical removal is recommended.

In renal transplant recipients, deposition of calcium within the skin has been reported following subcutaneous administration of low-molecular-weight heparin (nadroparin). Nodules with secondary ulceration developed at the sites of the heparin injections, but the process was self-limited and resolved following discontinuation of the nadroparin. The calcium content of the heparin in combination with hyperphosphatemia due to renal dysfunction was hypothesized as the underlying pathogenic mechanism[28].

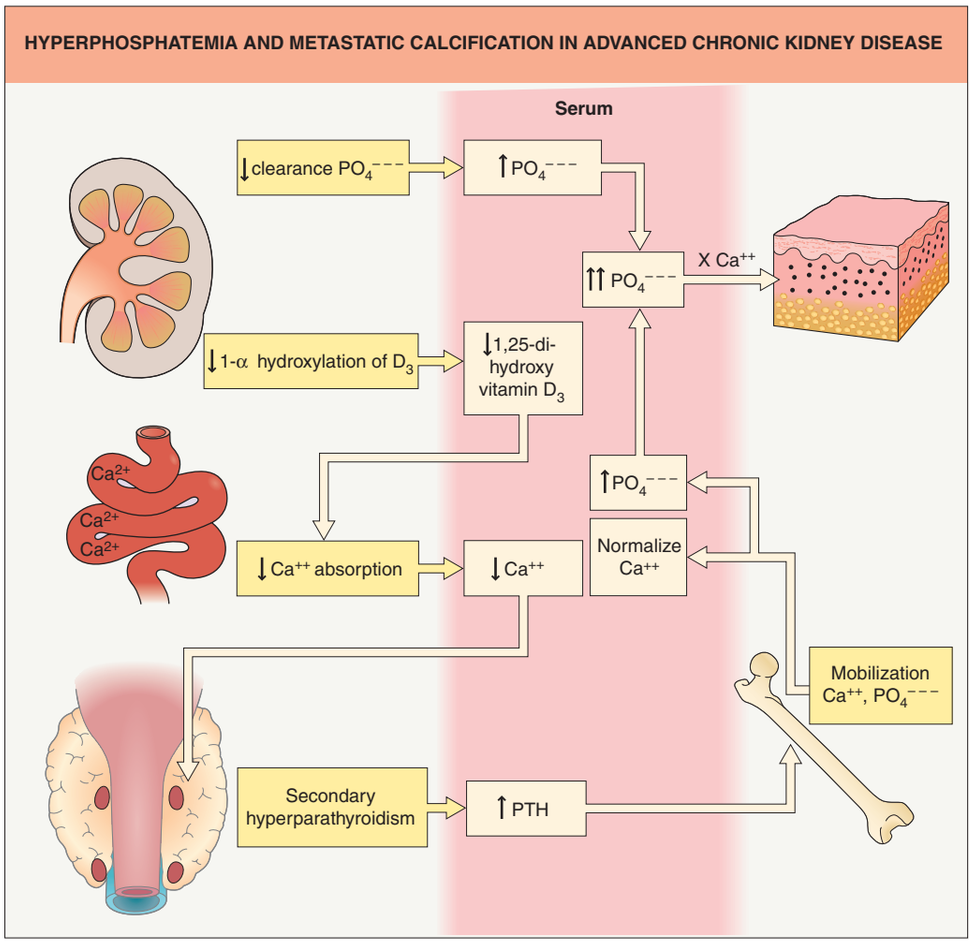


Fig. 50.4 Mechanisms of hyperphosphatemia and metastatic calcification in patients with advanced chronic kidney disease. PTH, parathyroid hormone.

Milk–alkali syndrome

Ingestion of excessive amounts of calcium-containing foods or antacids can lead to hypercalcemia and the milk–alkali syndrome. Patients with milk–alkali syndrome have acute manifestations including nephrocalcinosis, irreversible renal failure, and diffuse subcutaneous calcification.

Hypervitaminosis D

Chronic ingestion of supraphysiologic doses of vitamin D can lead to hypercalcemia and hypercalciuria. Clinical signs include weakness and lethargy, nausea, headache, and polyuria. Nephrolithiasis and calcinosis cutis may occur. Hypercalcemia is also seen in patients with sarcoidosis secondary to increased calcium absorption due to 1,25-dihydroxyvitamin D production by the granulomas. For other causes of metastatic cutaneous calcification, see Table 50.1.

Mixed Calcification

In mixed calcification, there is a combination of metastatic and dystrophic calcification, which is initiated by calcium dysregulation and then propagated by trauma.

Calciphylaxis

Calciphylaxis is a thrombotic vasculopathy that is characterized by microvascular deposition of calcium and subsequent thrombosis that results in ischemic necrosis of the skin and soft tissues[29,30]. While the majority of patients have severe or end-stage chronic kidney disease (CKD) requiring dialysis, nonuremic calciphylaxis can occur and has a better prognosis.

Early lesions usually present as poorly demarcated, often symmetric, extremely painful patches of erythema or livedo reticularis that progress to retiform purpura. Lesions favor areas with abundant adipose tissue such as the breasts and girdle area or sites of trauma, but they can also involve the distal extremities and penis (Fig. 50.5A,B)[29]. Bullae or a dusky gray color may then develop, signifying imminent tissue necrosis and the appearance of ulcerations with black, leathery eschars (Fig. 50.5C). Often, there is surrounding subcutaneous induration that extends beyond the margins of the visibly active lesions and may have a peau d'orange appearance; this can be helpful in distinguishing calciphylaxis from other forms of retiform purpura.

Early recognition and treatment is imperative because secondary infection and sepsis can develop as well as internal organ involvement. One-year mortality rates range from 30%–80%, with proximal lesion location and ulceration associated with a higher risk of death[29–32]. Nonuremic calciphylaxis is associated with lower one-year mortality rates which range from ~25% (all causes) to ~10% (when limited to calciphylaxis-related complications)[32].

The causes of calciphylaxis have not been fully elucidated. Selye, who coined the term calciphylaxis in 1961, suggested a "sensitizer plus challenger" model in which an underlying metabolic dysfunction involving serum levels of calcium and phosphate (e.g. secondary hyperparathyroidism) predisposed an individual to calciphylaxis. However, a second incident, or challenger, such as trauma or increased calcium load, ultimately resulted in calcium deposition and lesion formation[29,33,34]. In fact, new lesion formation has been reported following subcutaneous insulin or heparin injections and at sites of biopsies or aggressive debridement.

Additional contributing factors include thrombophilia (e.g. protein C or S deficiency, antiphospholipid antibodies) and alterations of vitamin K-dependent anti-calcification proteins such as fetuin-A and matrix Gla protein (see above)[35–38]. For vascular calcification to occur, an important step is the transdifferentiation of vascular smooth muscle cells into osteoblast-like cells. Phosphates, inflammatory mediators within the vessel wall, and bone morphogenic protein (BMP)-2 have all been proposed as potential stimuli for this conversion. In addition to matrix Gla protein and fetuin-A, BMP-7, osteoprotegerin, and phosphatonins are possible positive or negative regulators of this process[39]. Of note, patients who develop calciphylaxis have lower levels of anti-calcification proteins. Vitamin K is necessary to produce the active carboxylated forms of these proteins and a reduced level or inhibition of vitamin K is a known risk factor for calciphylaxis (see Ch. 23).



Fig. 50.5 Calciphylaxis in three patients with advanced chronic kidney disease. A Large reticulated violaceous plaques in an obese woman. Centrally, there is retiform purpura (inset) which precedes the ulcerations that are also present. **B** Irregular violaceous plaques on the leg with retiform purpura and hemorrhagic crusts overlying ulcerations. **C** Large ulceration with leathery black eschar. Retiform purpura and scarring are seen in the surrounding skin. *A, B, Courtesy Lorenzo Cerroni, MD.*

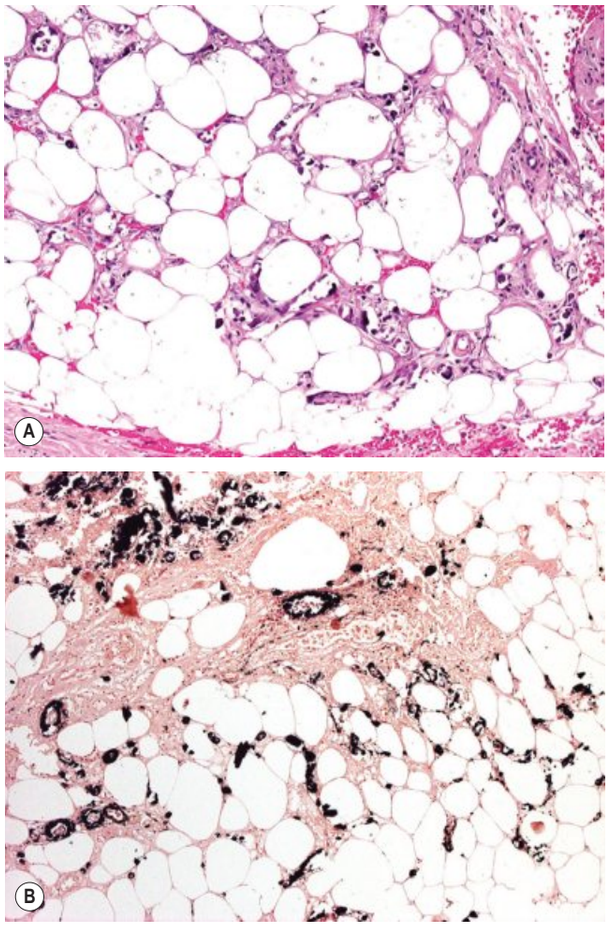


Fig. 50.6 Calciphylaxis – histopathologic features. A Perivascular deposition of calcium is seen within the walls of blood vessels in the subcutaneous fat. **B** Staining for calcium (von Kossa) highlights calcium deposition within blood vessel walls (black circular deposits) as well as focal, irregular calcification of connective tissue. Of note, even when the clinical lesions are impressive, the degree of calcification seen histologically may be subtle and clinical suspicion should remain high despite the absence of overt calcium deposits. *Courtesy Lorenzo Cerroni, MD.*

Additional risk factors include severe or end-stage CKD, dialysis, obesity, diabetes mellitus, AI-CTDs, and female sex as well as warfarin exposure, corticosteroids, and liver disease[29]. Hyperparathyroidism, calcium supplementation, and vitamin D intake are also risk factors, with the latter possibly related to stimulation from the conversion of vascular smooth muscle cells into osteoblast-like cells[40]. In nonuremic calciphylaxis, rapid weight loss, as seen in gastric bypass surgery, has emerged as a risk factor[41,42].

Diagnosis of calciphylaxis

Originally, calciphylaxis was thought to arise primarily in the setting of an elevated calcium × phosphate product. However, more recent studies have shown no statistical differences in the serum levels of calcium, phosphate, and PTH or the calcium × phosphate product in those with calciphylaxis compared to control dialysis patients at the time of presentation. The possible exception is elevations in time-averaged calcium × phosphate products or phosphate levels in affected individuals[43]. Nonetheless, initial evaluation should include a comprehensive metabolic panel, calcium, phosphorus, and PTH levels, and a complete coagulation profile.

While skin biopsy is currently considered the gold standard for diagnosing calciphylaxis, its role is controversial given the associated low sensitivity and specificity and risk of complications (e.g. ulceration). Classic findings are microvascular intimal calcium deposition and fibrin thrombi, often accompanied by ischemic changes and/or necrosis of the fat as well as the overlying epidermis and dermis. A calcifying lobular panniculitis is also a common finding (Fig. 50.6A). Because calcium

deposits may be subtle in H&E-stained sections, von Kossa and Alizarin red stains are used to increase detection (Fig. 50.6B)[44]. The presence of both media calcification and thrombosis increases the specificity of skin biopsies[45].

Clinicopathologic correlation is required as vascular calcium deposits +/− thrombosis can be seen in patients with and without CKD in the absence of calciphylaxis[45,46]. Some clinicians have therefore proposed that just clinical features, alone or aided by radiographic findings, be utilized to establish the diagnosis due to the potential shortcomings of histopathology[47,48]. That said, to increase sensitivity, biopsy specimens should be obtained from the most active margin rather than ulcerated or necrotic areas. In the authors' opinion, when biopsies are performed, "double-punch" or telescoping techniques with adequate fat sampling are preferred over thin wedge biopsies[45], but this is still debated. The key is obtaining an adequate depth. Image-guided biopsy (e.g. by xeroradiography or ultrasound) may increase diagnostic yield. When penile calciphylaxis is suspected, diagnostic imaging with Doppler ultrasonography and a CT scan is recommended rather than performing a biopsy[49,50].

The differential diagnosis of calciphylaxis is outlined in Table 50.3.

Treatment of calciphylaxis including wound care

A multimodal approach is essential for the management of calciphylaxis. Contributing factors (e.g. calcium and iron supplementation, vitamin D intake) should be identified and addressed. For patients with end-stage CKD, potential interventions include increased frequency or duration of dialysis, low calcium dialysate, low phosphate diet, and phosphate binders[33]. While the value of altering dialysis parameters or types requires additional investigation, at least temporary conversion from peritoneal dialysis to hemodialysis may allow for treatment optimization[47,51,52].

When possible, warfarin should be discontinued and can be replaced by direct factor Xa inhibitors as this has been associated with improved survival[32]. Given the thrombotic component of calciphylaxis, institution of direct-acting oral anticoagulants (DOACs) or low-molecular-weight heparin should be considered in general, especially in those with thrombophilic conditions[53,54]. Calcimimetics (e.g. cinacalcet, etelcalcetide) that reduce PTH secretion via activation of calcium-sensing receptors can be administered for hyperparathyroidism, with parathyroidectomy reserved for those who fail to respond to medical management[47,55,56].

There are multiple reports of the successful use of sodium thiosulfate, but larger controlled studies are needed[37,57–61]. The proposed mechanisms of action include reduction of reactive oxygen species, vasodilation via hydrogen sulfide and nitric oxide production, solubilization of calcium, inhibition of calcium deposition[37], and improvement in vascular endothelial function[37,55]. Table 50.2 outlines the dosing regimens and side effects for both intralesional and intravenous sodium thiosulfate. In some patients, there may be a role for topical sodium thiosulfate.

There are additional therapies that may be considered. Bisphosphonates such as pamidronate and etidronate may be helpful in patients who fail to improve with sodium thiosulfate[66–69]. Vitamin K supplementation may help restore the functionality of vitamin K-dependent anti-calcification proteins (see above)[70–72]. Renal transplantation may be curative but calciphylaxis has also been reported following transplantation and transplantation carries additional risks in patients with large, open wounds[73,74].

In patients with ulcerations, intensive wound care, including autolytic or chemical debridement (see Ch. 105) and appropriate dressings (see Ch. 145), is required to maximize healing and minimize infection and pain. While some analyses have shown that overall survival is improved by surgical debridement, patients were not controlled for extent of disease[75,76]. Given the concern for Koebner phenomena in patients with active calciphylaxis, i.e. trauma leading to new lesions or worsening of disease, it has been suggested that wounds with clean bases or non-infected dry eschars not undergo surgical debridement[59,77–80]. When debridement is indicated to remove deeply necrotic or infected tissue, conservative removal of devitalized tissue, often feasible at the bedside, is preferred over larger excisional surgical procedures[32,47,76,79].

Hyperbaric oxygen therapy may promote more rapid wound healing and has a precedent in other ischemic diseases. Via delivery of highly concentrated pressurized oxygen, there is stimulation of fibroblast proliferation, collagen production, angiogenesis, and phagocytosis as well as reduction in anaerobic colonization[81–83]. A multidisciplinary team approach that includes the pain service, nutritionists, and physical therapists can optimize recovery.

CALCIPHYLAXIS AND ITS DIFFERENTIAL DIAGNOSIS

Disorder	Most common locations for purpuric lesions* +/or ulcerations	Risk factors
Calciphylaxis	• Sites of greater adipose tissue, e.g. breasts, thighs, abdomen, buttocks • Sites of trauma, including lower extremities	• End-stage chronic kidney disease, dialysis, obesity, diabetes mellitus, AI-CTDs, female sex, thrombophilia/hypercoagulability, use of warfarin or corticosteroids, liver disease, hyperparathyroidism, excess calcium/vitamin D ingestion, rapid weight loss
Warfarin (Coumadin®) necrosis	• Sites of greater adipose tissue, e.g. breasts, thighs, abdomen, buttocks	• Starting warfarin with a large loading dose or without concomitant heparin; appears 2–5 days after initiating treatment • Female sex, age >50 years
Cholesterol emboli	• Lower extremities, especially distally	• Recent catheterization, introduction of anticoagulants 1–2 months prior
Infectious emboli	• Distal extremities or more widespread	• Immunosuppression, endocarditis (including prosthetic heart valves), intravenous drug use, implanted intravascular devices
Vasculitis of medium-sized blood vessels	• Primarily lower extremities†	See Ch. 24
Diffuse dermal angiomatosis (DDA)	• Lower extremities, including thighs • Breasts • Abdomen	• Peripheral artery disease, usually severe • Macromastia • Obesity • Changes of DDA can overlie calciphylaxis
Vasculopathy/vasculitis due to levamisole-adulterated cocaine	• Lower extremities, ears • Can be widespread	• Use of cocaine via smoking, snorting, or injection (see Ch. 89)
Thrombophilia (hypercoagulability)	• Depends on underlying cause, e.g. more widespread in DIC versus more acral in type I cryoglobulinemia	See Tables 22.5 and 105.9
Oxalosis	• Acral	See Ch. 23

*Macular, plaques
†Also subcutaneous nodules.

Table 50.3 Calciphylaxis and its differential diagnosis. Especially when on the lower extremities, additional causes of ulceration (e.g. venous ulcer, hypertensive ulcer, pyoderma gangrenosum) need to be excluded before establishing a definitive diagnosis of calciphylaxis (see Ch. 105). AI-CTDs, autoimmune connective tissue diseases; DIC, disseminated intravascular coagulation.

Idiopathic Calcification

Idiopathic calcified nodules of the scrotum

The term "idiopathic calcified nodules of the scrotum" is used to describe firm, skin-colored to yellow–white nodules that develop on the scrotum, typically in men 20 to 40 years of age[84]. Scrotal calcinosis occurs more often in individuals with darker skin phototypes. There can be multiple lesions and they may be asymptomatic, pruritic, or ulcerated. Histologically, a calcified epidermoid cyst or eccrine duct cyst may be seen; however, often only dermal calcinosis, with or without a surrounding granulomatous foreign-body type reaction, is present. This has led to a debate as to whether these nodules represent idiopathic or dystrophic calcification[85–87]. A female equivalent, idiopathic calcinosis of the vulva, has also been described[84,88]. Surgical excision is performed for symptomatic lesions and for cosmetic concerns. CO_2 laser has emerged as an alternative therapeutic option[89].

Subepidermal calcified nodule

Subepidermal calcified nodules are smooth to verrucous, firm, yellow–white to erythematous papules or nodules that can be solitary or multiple. They favor the head and neck region, but also occur on the extremities[90]. Subepidermal calcified nodules usually develop in children but have been observed in all age groups. Trauma, perhaps *in utero*, or calcification of a pre-existing milium, eccrine duct hamartoma, or hair follicle nevus has been hypothesized as the cause. Histologically, focal amorphous masses of calcium with a surrounding inflammatory infiltrate are seen. Epidermal ulceration and transepidermal elimination of the calcium deposits occur frequently. Surgical removal is recommended for symptomatic lesions that do not self-resolve.

Tumoral calcinosis

Tumoral calcinosis may be either sporadic or familial. In both forms, patients develop large, often painful, deposits of calcium phosphate in the dermis and subcutaneous tissues around large joints (Fig. 50.7). Ulceration of the overlying skin may occur in larger lesions. The *sporadic* form is most often associated with secondary hyperparathyroidism due to advanced CKD[91].

Familial tumoral calcinosis is inherited in an autosomal recessive pattern and has both hyperphosphatemic and normophosphatemic forms[92]. The hyperphosphatemic form is most commonly due to mutations in *GALNT3*, which encodes N-acetylgalactosaminyltransferase 3 (ppGalNAc-T3), an enzyme that initiates mucin-type O-glycosylation[93]. It is hypothesized that this glycosylation regulates "phosphatonins" that in turn modulate circulating phosphate levels. Hyperphosphatemic familial tumoral calcinosis can also be caused by loss-of-function mutations in either *FGF23* or *KL*; the former encodes fibroblastic growth factor 23, a phosphaturic protein that is glycosylated by ppGalNAc-T3, while the latter encodes Klotho, a co-receptor for FGF23. Homozygous mutations in *SAMD9* (*s*terile *a*lpha *m*otif *d*omain containing 9), which encodes a protein involved in the regulation of extraosseous calcification, has been found to underlie normophosphatemic familial tumoral calcinosis in families of Jewish Yemenite origin[94].

Dietary phosphate restriction and antacids that inhibit phosphate absorption may be of some benefit, but surgical excision of symptomatic lesions remains the treatment of choice.

Milia-like calcinosis

Idiopathic calcinosis may sometimes take the form of small, milia-like lesions that develop on the dorsal surface of the hands and the face. Most commonly, these lesions appear in the setting of Down syndrome, although rarely they have been reported in patients without other medical issues[95,96]. In some patients, the calcinosis appears to result from calcification of pre-existing syringomas, but usually no precursor lesions can be found.

Iatrogenic Calcification

Iatrogenic calcification is due to the rapid precipitation of calcium salts within the skin. When the tissue concentration of calcium rises and exceeds the solubility product, calcium precipitates within the tissue, resulting in firm nodules within the dermis and/or subcutaneous tissue. A secondary inflammatory response is elicited and, over a period of weeks to months, the calcium is either absorbed or is transepidermally eliminated, depending on the depth of the deposit.

Iatrogenic calcification most commonly occurs with extravasation of calcium gluconate, calcium chloride, or calcium phosphate-containing intravenous solutions[97]. In a rabbit model of iatrogenic calcification, intralesional injections of triamcinolone into sites of extravasation decreased inflammation and ulceration. This treatment appeared to be most helpful when given immediately after the initial extravasation. Iatrogenic calcification has also been reported following prolonged electroencephalograms, electromyography, and brainstem auditory evoked potential testing when a high-calcium electrode paste is employed[98]. Several patients were noted to develop calcification in split-thickness skin graft donor sites following the use of calcium alginate dressings[99].

Transient cutaneous calcifications have been observed in patients following liver or lung transplantation[100]. They are generally small deposits in the skin that appear shortly after the transplant. They are hypothesized to arise as a consequence of the large amounts of calcium and blood products containing citrate required during surgery, combined with metabolic abnormalities during the perioperative period[101].

CUTANEOUS OSSIFICATION (OSTEOMA CUTIS)

There are four genetic disorders that often have cutaneous or subcutaneous ossification: fibrodysplasia ossificans progressiva, progressive osseous heteroplasia, plate-like osteoma cutis, and Albright hereditary osteodystrophy (Fig. 50.8). Of these disorders, *fibrodysplasia ossificans progressiva* differs from the others in that the bone formation is endochondral and involvement of the skin and subcutaneous tissue

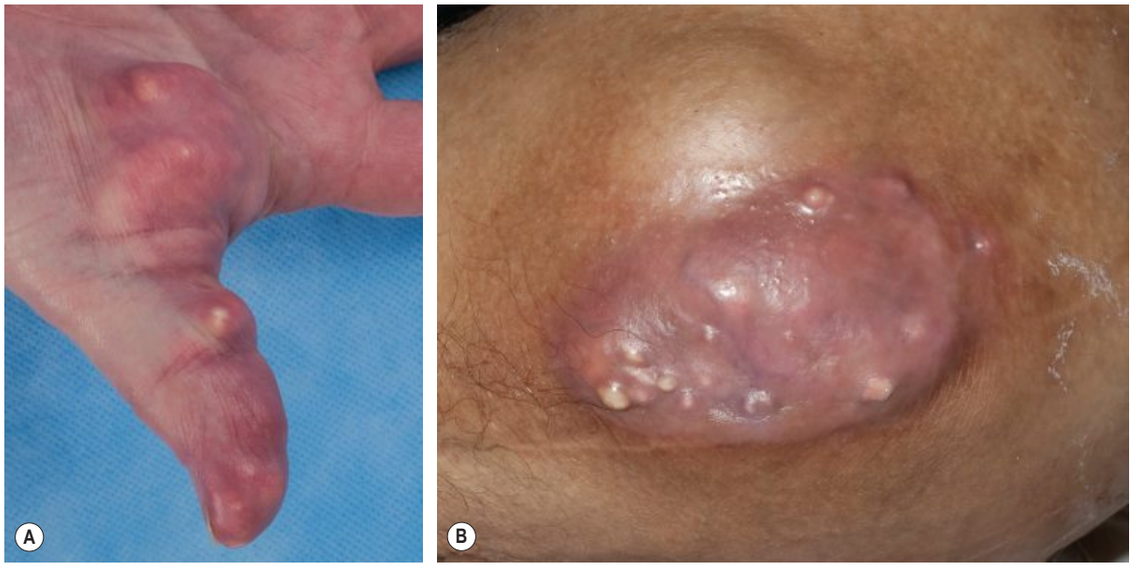


Fig. 50.7 Familial tumoral calcinosis. A, B There are large, frequently painful, deposits of calcium phosphate within the dermis and subcutaneous tissues, often around large joints. *Courtesy Edward Cowen, MD.*

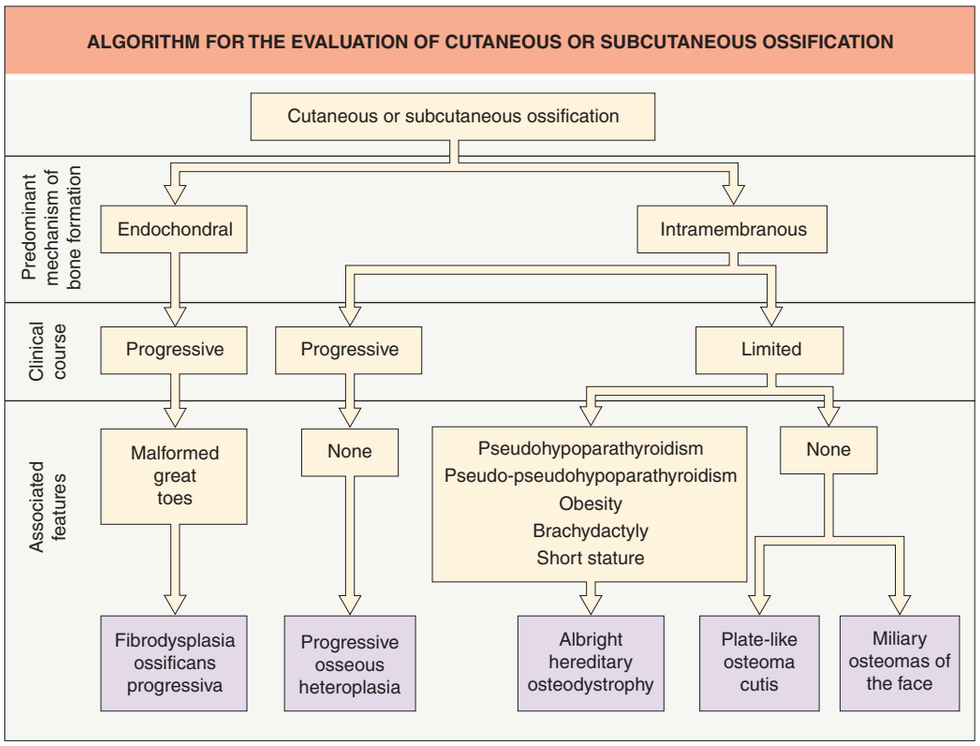


Fig. 50.8 Algorithm for the evaluation of cutaneous or subcutaneous ossification.

occurs only via extension from deeper tissues. These patients have extreme morbidity and often die at an early age due to restriction in movement of the chest. Fibrodysplasia ossificans progressiva is an autosomal dominant disorder with dysregulation of the bone morphogenic protein (BMP) signaling pathway. Heterozygosity for mutations in *ACVR1*, which encodes the activin A receptor (a BMP type I receptor), has been identified in both the inherited and sporadic forms of the disease. Of note, an arginine (R) to histidine (H) substitution at position 206 (R206H) was found not only in affected family members (i.e. the inherited form of the disease), but also in 30 of 32 *de novo* cases of fibrodysplasia ossificans progressiva, leading the authors to suggest that the R206H-associated mutation may represent one of the most specific codons in the human genome to be associated with a disease phenotype[102,103]. These patients are unlikely to present to a dermatologist due to their limited and late skin involvement.

Progressive osseous heteroplasia, plate-like osteoma cutis, and Albright hereditary osteodystrophy are all characterized by intramembranous ossification that begins in the dermis (Fig. 50.9). While distinctive features are seen in each of these entities, there is also considerable clinical overlap. The cutaneous lesions in *progressive osseous heteroplasia* are asymptomatic papules and nodules. Some are more plaque-like and studded with papules that give rise to a "rice-grain" texture. The lesions generally appear shortly after birth and may be rapidly progressive[104,105]. The location and extent of the ossification determines the associated morbidity; in general, there are no associated developmental or endocrine abnormalities. Unilateral involvement has also been described.

Plate-like osteoma cutis is considered to be a localized, non-progressive form of progressive osseous heteroplasia, with a single or limited number of sites of involvement[106]. *Albright hereditary osteodystrophy* is distinguished from these two entities by the presence of associated findings, including pseudohypoparathyroidism or pseudo-pseudohypoparathyroidism plus brachydactyly, obesity, short stature, and round facies. Fig. 50.8 demonstrates how clinical features may be used to classify these genetic disorders of cutaneous ossification.

Patients with progressive osseous heteroplasia, plate-like osteoma cutis, and Albright hereditary osteodystrophy all have mutations in the gene (*GNAS1*) that encodes the α-subunit of the stimulatory G protein which regulates adenyl cyclase activity[107,108]. The latter is believed to be a negative regulator of bone formation. Patients with progressive osseous heteroplasia have loss-of-function of the Gs-alpha isoform encoded by the **paternal** allele of *GNAS*, while those with Albright hereditary osteodystrophy have loss-of-function of the isoform encoded by the **maternal** allele of *GNAS*[109]. In other words, this locus is subject to imprinting (see Ch. 54), and different splice variants are expressed solely by maternal or paternal alleles[110].



Fig. 50.9 Osteoma cutis in Albright hereditary osteodystrophy. Hard pink–violet plaque studded with yellowish-white papules on the arm of an infant. *Courtesy Julie V. Schaffer, MD.*

Therapy for cutaneous ossification is difficult. Underlying abnormalities in calcium and/or phosphorus should be addressed; however, when complete ossification develops, the only therapeutic intervention is excision of neoformed bone. Even with surgical removal, recurrence of the bony deposits is common in this group of genetic disorders.

Miliary osteomas of the face is a fairly common entity characterized by multiple, scattered foci of cutaneous ossification. Small, firm papules appear on the face of adults and they can be skin-colored, white, or bluish (Fig. 50.10)[111]. Although these osteomas are often observed in the setting of chronic acne vulgaris, patients without a history of acne have also been reported. The unusual appearance of these osteomas on CT scan is shown in Fig. 50.10B. Histologically, islands of bone formation are seen in the dermis (Fig. 50.11).

Treatment of miliary osteoma cutis is primarily surgical. An incision over each lesion followed by gentle curettage of the bony



Fig. 50.10 Miliary osteoma cutis. A Multiple discrete white papules on the face of a patient with no previous history of acne. **B** The foci of ossification are readily apparent on the CT scan (arrow). **C, D** In contrast, many of the papules in these patients with a history of acne are skin-colored or blue.

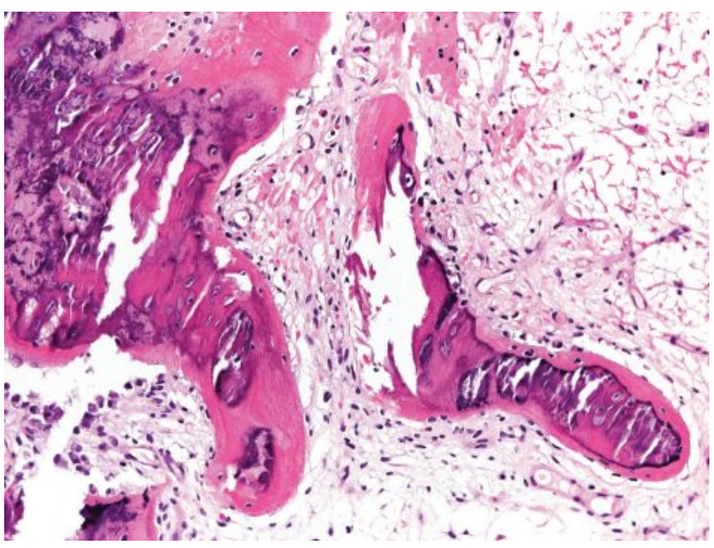


Fig. 50.11 Osteoma cutis – histologic features. Islands of bone formation are present within the dermis. Occasionally, osteoblasts and bone marrow elements can also be seen. *Courtesy Lorenzo Cerroni, MD.*

material with the edge of a surgical blade and then suture closure has been recommended. When lesions are numerous, however, this may not be practical. The use of lasers to expose osseous fragments has been reported[112,113]. Topical tretinoin gel may also be of some benefit[114].

"Secondary" Cutaneous Ossification

Ossification may develop as a secondary event. Most disorders in which calcification can be seen have also been reported to ossify. Ossification occurs as a result of inflammatory or neoplastic processes and is often preceded by calcification. Secondary ossification has been described in melanocytic nevi, pilomatricomas, pilar and epidermoid cysts, basal cell carcinomas, nephrogenic systemic fibrosis, and chronic calciphylaxis.

LABORATORY EVALUATION OF PATIENTS WITH CUTANEOUS CALCIFICATION/OSSIFICATION
Serum levels of: • Calcium • Phosphate • Parathyroid hormone (PTH) • Vitamin D_3
24-hour urinary calcium excretion
Protein C activity and function (if calciphylaxis suspected)
Genetic analysis (if hereditary disorder suspected)

Table 50.4 Laboratory evaluation of patients with cutaneous calcification/ossification.

LABORATORY EVALUATION OF PATIENTS WITH CUTANEOUS CALCIFICATION AND OSSIFICATION

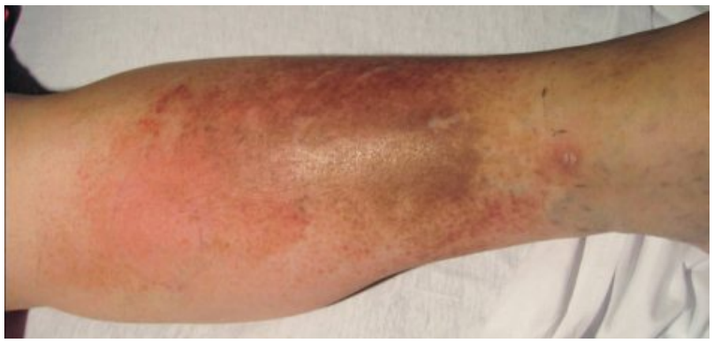
In addition to a thorough history and physical examination focusing on the associated features that have been described, selected laboratory investigations may be helpful in the evaluation of calcifying and ossifying disorders. A summary of this evaluation is outlined in Table 50.4. Abnormalities are expected most often in association with metastatic causes of calcification (see Table 50.1). Serum calcium and phosphate levels should be obtained in order to calculate the calcium × phosphate product. While this may give a general clue regarding the patient's metabolic status with regard to calcium and phosphate, a normal value does not necessarily exclude these disorders. There are rare reports of patients with calcinosis cutis and a normal serum calcium level, but abnormally low urinary excretion of calcium; thus, an assessment of the 24-hour urinary calcium excretion may be warranted in some patients.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 50.1 Early in the course of calciphylaxis, there is painful erythema that can mimic cellulitis. *Courtesy Anthony Cukras, MD, PhD.*



eFig. 50.2 Calciphylaxis in a patient with end-stage chronic kidney disease. Typical reticulated, violaceous plaques that usually precede ulceration. *Courtesy Kalman Watsky, MD.*



eFig. 50.3 Calciphylaxis in a patient with end-stage chronic kidney disease. Early lesion on the leg with retiform purpura but no ulceration.



eFig. 50.4 Calciphylaxis in a patient with end-stage chronic kidney disease. Lower extremity ulceration accompanied by retiform purpura.



eFig. 50.5 Calciphylaxis characterized by irregular purpuric plaques in the girdle area with an ulceration covered by a black eschar.



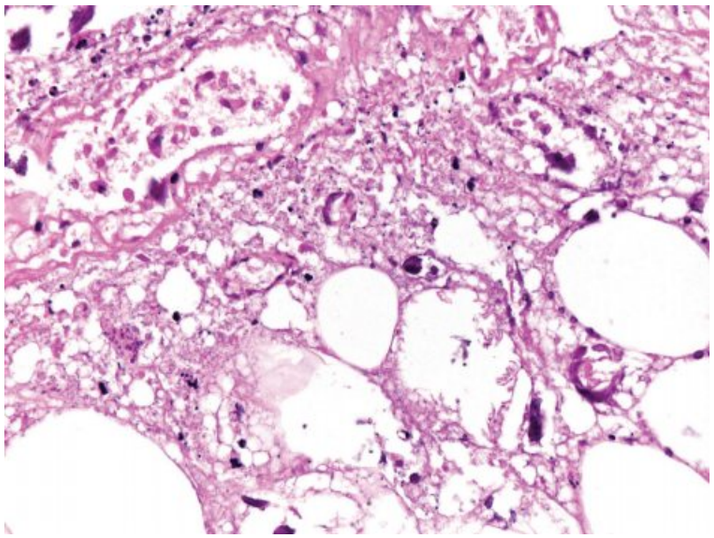
eFig. 50.6 Calciphylaxis. A thick black eschar overlies an ulceration.



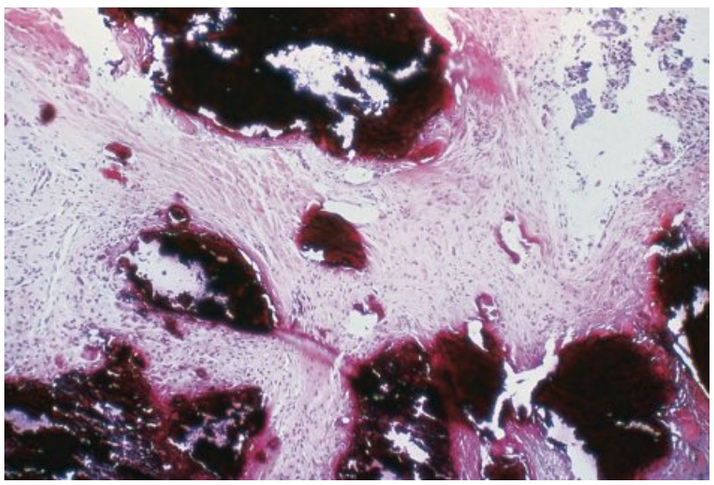
eFig. 50.7 Calciphylaxis in a patient with end-stage chronic kidney disease. Large ulceration on the leg with a black eschar and retiform purpura in surrounding skin.



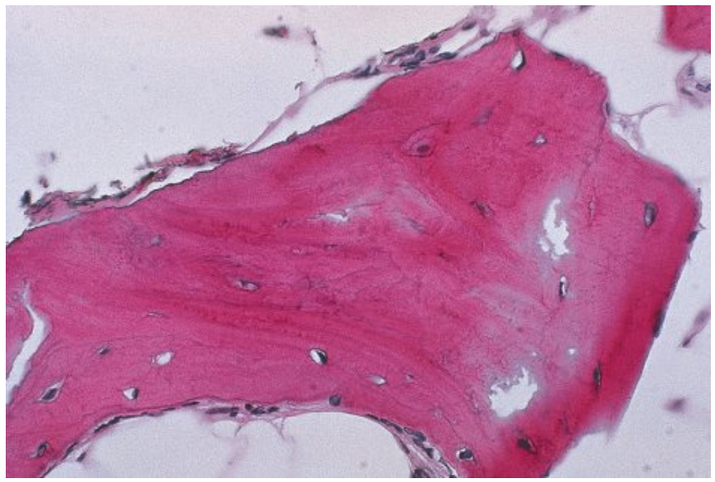
eFig. 50.8 Calciphylaxis in a patient with end-stage chronic kidney disease. Large ulceration on the leg with a fibrinous base and a black eschar superiorly.



eFig. 50.9 Calciphylaxis – histopathologic features. Deposition of calcium is seen within the walls of blood vessels in the subcutaneous fat, in addition to diffuse calcification within the connective tissue. *Courtesy Lorenzo Cerroni, MD*.



eFig. 50.10 Progressive osseous heteroplasia – histologic features. Deposits of calcium are seen more superficially, often with foci of cartilage and bone formation in the subcutaneous tissue.



eFig. 50.11 Osteoma cutis – histologic features. Islands of bone formation are present within the dermis. Occasionally, osteoblasts and bone marrow elements can also be seen.

Nutritional Diseases 51

Bernice Y. Kwong, Lucero Noguera-Morel, Stephanie Ann McLeish and Chad M. Hivnor

Key features

- Deficiencies in macronutrients (carbohydrates, fats, proteins) and micronutrients (vitamins, essential trace minerals) can affect any organ system, including the skin, which may provide clues to the diagnosis
- Severe acute malnutrition manifests as two classic protein–energy malnutrition syndromes: kwashiorkor and marasmus
- In addition to inadequate oral intake, there are secondary causes of nutritional deficiencies including intestinal malabsorption due to medical conditions, medications, and surgical procedures as well as increased nutritional demand due to severe illnesses (e.g. late-stage metastatic carcinoma, systemic infection)
- Vitamin and trace element deficiencies can lead to a wide range of mucocutaneous findings, from follicular keratoses to periorificial erosions to poor wound healing
- Obesity can be associated with high-calorie malnutrition and multiple skin changes ranging from acanthosis nigricans to lipodermatosclerosis

INTRODUCTION

Proper nutrition is fundamental to human life. From fetal development to adulthood, proper nutrition is essential for survival, physical growth, mental development, productivity, and overall health[1]. Deficiency of one isolated nutrient is rare, as individuals are usually deficient in multiple nutrients at the same time. In general, nutrients are categorized as macronutrients (carbohydrates, proteins, and fats) or micronutrients (vitamins and minerals). Most people who suffer from nutritional deficiencies live in low-income countries. However, there are certain conditions that predispose individuals from high-income countries to develop nutritional deficiencies, such as alcohol use disorder, intestinal malabsorption, anorexia nervosa or bulimia, restrictive diets, medications, and chronic or severe acute illnesses.

Nutrients require a process of ingestion, digestion, absorption, and circulation plus subsequent metabolism in order to be beneficial. When any one of these steps is disrupted, or if energy expenditure is increased, clinical manifestations may appear due to insufficient nutrition.

EPIDEMIOLOGY AND PATHOGENESIS

In low-income countries, malnutrition stems primarily from inadequate ingestion of all macronutrients as well as many micronutrients (Fig. 51.1). The World Health Organization (WHO) has estimated that worldwide, ~45% of deaths in children <5 years of age are due directly or indirectly to the multisystem ramifications of undernutrition. In industrialized regions of the world, malnutrition is directly linked to the per capita gross national product; if a country has a per capita income that is less than US$300 per year, endemic malnutrition is likely, especially in infants and young children.

At the same time, a global epidemic of obesity has emerged within industrialized countries, with increasing rates of death due to cardiovascular disease and diabetes mellitus[1]. Excessive consumption of foods high in calories but low in nutrients can lead to obese patients who lack essential vitamins and minerals. This is supported by a study in which 57% of morbidly obese patients undergoing preoperative assessment for bariatric surgery were found to have a deficiency in at least one micronutrient[2].

Restrictive diets, including those based upon real or perceived need (e.g. food allergies, weight loss, health benefit), psychiatric illness (e.g. anorexia nervosa) or mental impairment (e.g. substance use disorder), also disrupt the intake of appropriate nutrients and can result in malnutrition.

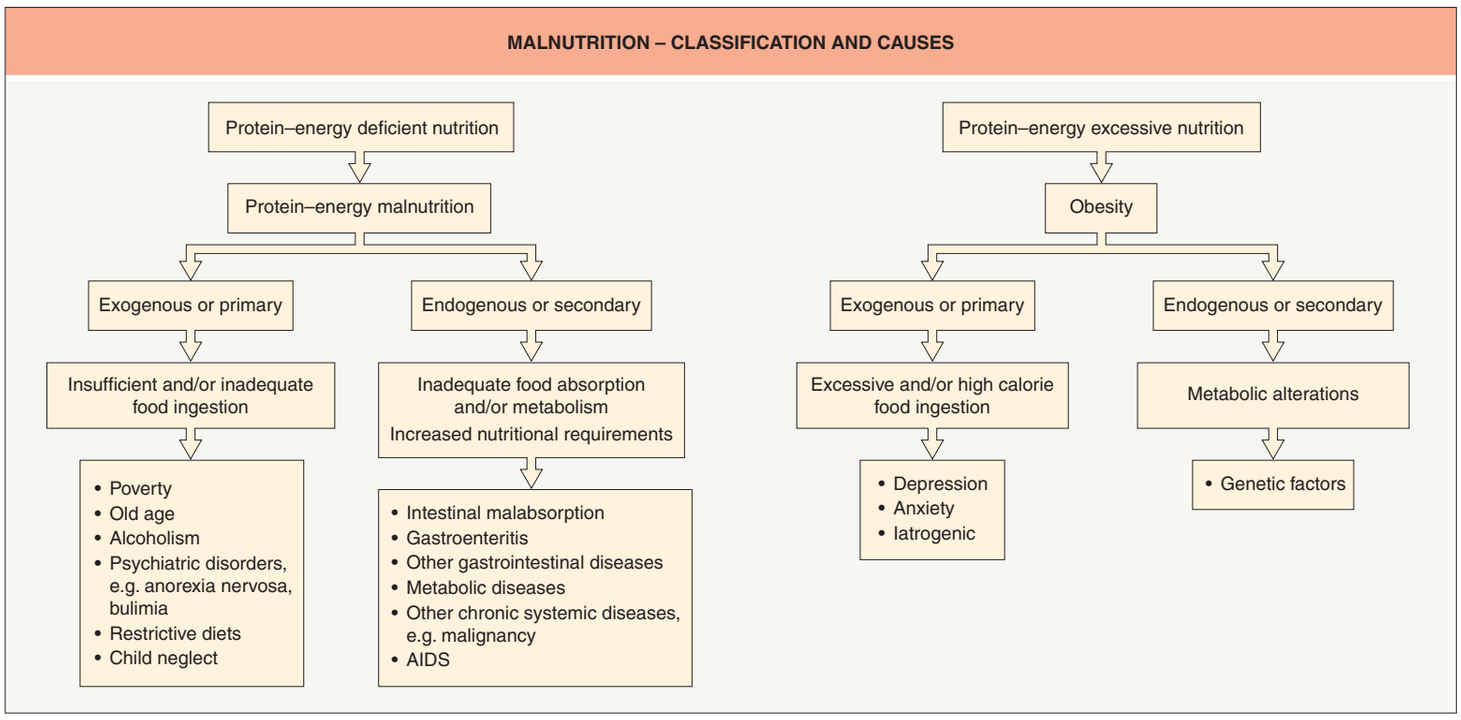


Fig. 51.1 Malnutrition – classification and causes. *Courtesy Ramón Ruiz-Maldonado, MD.*

In addition to a diet inadequate in the quantity and/or quality of macro- and micronutrients (i.e. primary causes), there are medical conditions that can lead to a functional malnutrition, i.e. secondary causes. The latter include an increase in metabolic requirements (e.g. severe infections, prolonged hospitalization) and/or a decrease in the transport and utilization of nutrients (e.g. intestinal malabsorption, bariatric surgery, medications). Malnutrition is also seen in individuals with late-stage internal malignancies and advanced AIDS as well as following allogeneic hematopoietic stem cell transplantation as a result of conditioning and/or gastrointestinal graft-versus-host disease (Table 51.1)[3].

CLINICAL FEATURES

Weight-for-height scores and height-for-age scores are utilized to evaluate malnutrition; scores are compared to the standard deviations (SD) from the median value for the reference population. An individual is considered to have moderate malnutrition if the scores are between the 2nd to 3rd (lower) SD and severe malnutrition if below the 3rd SD, with or without symmetrical edema[4]. Cutaneous manifestations in part reflect the fact that epidermal maturation (from basal cell layer to stratum corneum) occurs over a period of 10–14 days. Deficiencies,

CHARACTERISTICS OF SEVERE ACUTE MALNUTRITION (PROTEIN–ENERGY MALNUTRITION) AND ESSENTIAL FATTY ACID DEFICIENCY

	Severe acute malnutrition (protein–energy malnutrition)		
	Marasmus	**Kwashiorkor**	**Essential fatty acid deficiency[45,46]**
Causes	• Prolonged insufficient energy (caloric) intake • Develops over months to years • Primary causes: reduced caloric intake (poverty, alcoholism, substance use disorder, other psychiatric disorders, restrictive diets, child or elderly neglect/abuse) • Secondary causes: reduced absorption (intestinal malabsorption, chronic diarrhea), increased caloric demand (malignancies), chronic systemic diseases (e.g. hepatic failure, end-stage renal disease), AIDS*, metabolic disorders)	• Insufficient nutritional intake with adequate caloric intake during periods of stress lasting a few weeks or more • Diets consisting primarily of rice or rice-based beverages (e.g. "rice milk") for perceived milk intolerance, restrictive low-protein fad diets • Other causes: protein-losing enteropathies, malabsorption (e.g. cystic fibrosis), extensive gastrointestinal surgeries, HIV disease*, severe illnesses/prolonged hospitalizations	• Protein–energy malnutrition • Gastrointestinal disorders/surgeries causing severe fat malabsorption • Long-term parenteral nutrition without lipid supplementation • Diets extremely low in fat • Nephrotic syndrome • Inborn errors of metabolism, e.g. deficiency of fatty acid desaturase 2 (FADS2; also referred to as delta (6) desaturase)
Cutaneous features	• Dry, thin, pale, lax and wrinkled skin • Occasionally, fine scaling and hyperpigmentation (Fig. 51.3) • Follicular hyperkeratosis and folliculitis in adults • Ulcerations • Excess of lanugo-like hair • Thin hair that grows slowly and falls out readily • Impaired growth of nails and fissured nails • Purpura (Fig. 51.4)	• Dyschromia is a common finding • Pallor due to distention of the skin and loss of pigment • Hypopigmentation following abrasions; ulcerations and hyperpigmentation in areas subject to trauma • Superficial desquamation in mild cases ("enamel paint spots"), but in severe cases large areas of erosion ("flaky paint") (Fig. 51.6) • Other cutaneous signs include erythema, thinning, petechiae, ecchymoses, and purpura • Hair is sparse, dry, lusterless and brittle with a reddish tinge; bands of light and dark coloration ("flag sign") reflect intermittent periods of malnutrition; positive gentle hair pull test • Nails are soft and thin • Mucosal lesions: cheilitis, xerophthalmia, and vulvovaginitis	• Dry, scaly, and leathery skin with underlying erythema • Intertriginous erosions • Alopecia and more lightly pigmented hair • Increase in transepidermal water loss • Petechiae
Systemic features	• Starved appearance but alert • Reasonably preserved responsiveness to short-term stress • Bradycardia, hypotension, and hypothermia • Loss of subcutaneous fat and muscle (Fig. 51.3) • "Monkey facies" or an aged appearance (due to loss of buccal fat pads) • Suppression of growth	• Relatively well-nourished appearance • Edema or even anasarca (Fig. 51.5) • Apathy, anorexia, irritability • Failure to thrive (retardation of growth and mental development) • Superimposed bacterial and fungal (e.g. candidal) infections • Bilateral parotitis, hepatomegaly, diarrhea, loss of muscle mass	• Growth failure • Poor wound healing • Impaired reproduction • Abnormal liver and kidney function tests • Capillary fragility • Increased susceptibility to infections • Neurologic damage
Lab findings and diagnostic criteria	• Triceps skin-fold <3 mm • Mid-arm muscle circumference <15 cm • Creatinine–height index <60% of standard • Low plasma zinc levels • Epidermal acanthosis, confluent hyperkeratosis, pallor of upper layers of the epidermis (missing in later lesions) • Most hair bulbs are in the telogen phase • Abundant broken hairs	• At least one of the following: poor wound healing, decubitus ulcers, or skin breakdown • Anergy • Hypoalbuminemia (<2.5 g/dl) • Total iron-binding capacity <200 mcg/dl • Peripheral lymphocyte count <1500/mcl • Steatohepatitis • Decreased number of anagen hair follicles and increased number of telogen follicles • Structural abnormalities in anagen follicles – severe atrophy, shaft constriction, depletion of pigment • Exclude nephrotic syndrome	• Low plasma levels of linoleic and linolenic acids • Accumulation of 5,8,11-eicosatrienoic acid • Triene (eicosatrienoic acid) : tetraene (arachidonic acid) ratio >0.4 • Elevated levels of palmitoleic and oleic acids • Anemia, thrombocytopenia • Orthokeratotic hyperkeratosis, acanthosis with hypergranulosis, atrophic sebaceous glands, and papillary dermal vasodilation with a mixed cell infiltrate (in rat models) • Steatohepatitis

Table 51.1 Characteristics of severe acute malnutrition (protein–energy malnutrition) and essential fatty acid deficiency.

CHARACTERISTICS OF SEVERE ACUTE MALNUTRITION (PROTEIN–ENERGY MALNUTRITION) AND ESSENTIAL FATTY ACID DEFICIENCY			
	Severe acute malnutrition (protein–energy malnutrition)		
	Marasmus	**Kwashiorkor**	**Essential fatty acid deficiency**[45,46]
Treatment	• Treat or prevent hypothermia, dehydration, hypoglycemia, and electrolyte imbalances • Treat infections • *Slowly* replace proteins and calories, allowing for readaptation of metabolic and intestinal functions • Supplementation with linoleic acid and zinc • Monitor for hypophosphatemia and cardio-respiratory failure (associated with overly aggressive nutritional replacement) • Address underlying diseases, social issues	• Aggressive nutritional support is indicated to rapidly restore metabolic balance; correction of any electrolyte disturbances or hypoglycemia • Institute diet with adequate protein and caloric intake; supplementation with minerals and vitamins is required as patients often have multiple nutritional deficiencies • Identify and attempt to treat underlying cause(s), including bacterial and parasitic diseases • Topical moisturizers as needed	• Essential fatty acid replacement, depending upon severity • Correction of coexisting nutritional deficiencies
Prognosis	• 10% mortality, often secondary to diarrhea or pneumonia • Mortality rate related to underlying disease(s)	• Prognosis in adult patients is poor, even with aggressive nutritional support • In children, a lesser degree of stress is required to precipitate the disorder, so it is less foreboding • Severe, relapsing cases and those with coexistent HIV disease have a high mortality rate • Death usually occurs due to overwhelming infection despite antibiotic treatment	• Prognosis depends on the severity and coexistence of other nutritional deficiencies • Depends on awareness of this entity
*HIV disease is more often associated with marasmus than with kwashiorkor.			

Table 51.1 Characteristics of severe acute malnutrition (protein–energy malnutrition) and essential fatty acid deficiency. AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

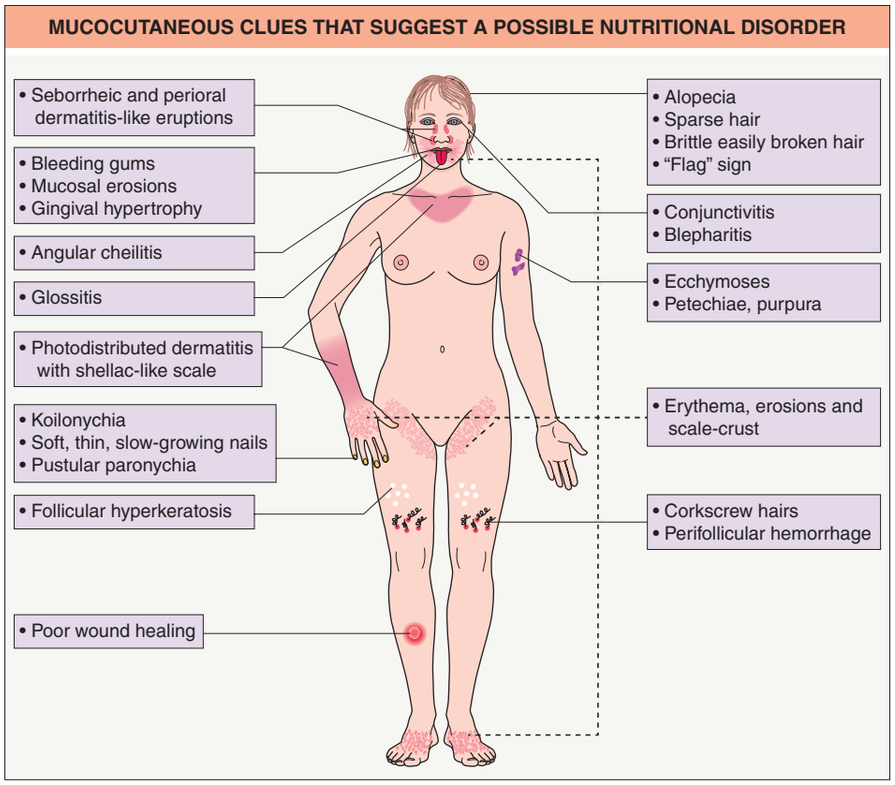


Fig. 51.2 Mucocutaneous clues that suggest a possible nutritional disorder. Risk factors are similar to those outlined for marasmus in Table 51.1. *Courtesy Karynne O. Duncan, MD.*

especially of macronutrients, can interfere with this process, resulting in skin that is dry and thin in appearance with associated epidermal atrophy. Prolonged deficiency can reduce both protein production, including that of dermal collagen and muscle, and the amount of subcutaneous fat. As a result, patients may develop dermal atrophy, muscle wasting, and/or lax skin.

Additional clinical findings of marasmus and kwashiorkor, such as dyschromia (hypo- and hyperpigmentation), desquamation, and erosions, are reviewed in Table 51.1. Patients may also have cutaneous manifestations from a deficiency in one or more micronutrients, and these are outlined in Table 51.2[5–10]. Mucocutaneous clues to the possibility of a nutritional deficiency are summarized in Fig. 51.2.

Protein–Energy Malnutrition

Worldwide, protein–energy malnutrition (or undernutrition) is the most prevalent nutritional deficiency. The two major forms of severe acute malnutrition (SAM) are: (1) marasmus, also referred to as wasting or malnutrition without edema (Figs. 51.3 & 51.4); and (2) kwashiorkor, also referred to as edematous malnutrition. Patients with marasmic kwashiorkor have features of both wasting and edema. According to the WHO, on a global basis, SAM affects almost 20 million young children (<5 years of age).

Marasmus (SAM *without* edema) can occur in individuals of all ages and results from a prolonged inadequate intake of total calories (energy).

These patients frequently develop recurrent infections due to their inability to mount a normal immune response.

Kwashiorkor (SAM *with* edema) is a more acute form of childhood and adult protein–energy malnutrition (see Table 51.1). A characteristic finding is peripheral edema or even anasarca in association with hypoalbuminemia (Fig. 51.5). One consequence of this edema is a body weight that is higher than is seen with marasmus, and it may be 60%–80% of expected weight (rather than <40%). Some patients will have overlapping features of both disorders and this is referred to as marasmic kwashiorkor[11]. In at-risk populations, kwashiorkor can develop after a child is weaned from breast milk and begins a diet rich in carbohydrates but deficient in protein. In addition to peripheral edema, patients with kwashiorkor also develop desquamation and erosions that have been likened to "enamel paint" and "flaky paint" (Fig. 51.6).

Based upon clinical observations, it was thought that kwashiorkor was due to a relative deficiency in protein *intake*. However, more recently, this proposed pathogenesis has been questioned based upon several findings. For example, protein intake was found to be similar in a group of children, irrespective of whether they had marasmus or kwashiorkor[12]. In addition, kwashiorkor can develop within just a few weeks of an acute, life-threatening illness. A current theory is that kwashiorkor is related to physiologic stresses secondary to an acute or chronic illness (including infections), with the stress leading to an increase in protein and energy requirements at a time when intake is frequently limited[13]. This would help to explain why kwashiorkor often occurs in the setting of an acute illness superimposed upon a chronic state of milder malnutrition. It is hypothesized that the stress of the acute illness blocks the protein-sparing response that is normally in effect during states of starvation. There is also increasing evidence for a relationship between the gut microbiome and the development of malnutrition, including kwashiorkor. A deficiency of anti-inflammatory taxa and an increase in inflammogenic bacteria were noted in the gut microbiome of affected children[14,15].

Both kwashiorkor and marasmus can have secondary causes such as "rice milk" diets or chronic diarrhea (see Table 51.1). The cutaneous and systemic abnormalities associated with primary protein–energy malnutrition are often reversible following nutritional therapy. However, if the malnutrition is prolonged, this may preclude normal physical and/or mental development[11].

Severe acute malnutrition is less common in adults, but can occur in the setting of critical illnesses requiring hospitalization, where catabolism exceeds anabolism. Protein loss and hypoalbuminemia may also develop in patients with exfoliative erythroderma (see Ch. 10). Delayed wound healing is one of the important consequences of protein deficiency.



Fig. 51.3 Marasmus. This child is emaciated and has obvious hyperpigmentation. Both erosions and desquamation are present on the scalp. *Courtesy Ramón Ruiz-Maldonado, MD.*

Essential Fatty Acid Deficiency

Essential fatty acids (EFAs) are unsaturated fatty acids that must be obtained from an exogenous source because they cannot be synthesized by the human body. Linoleic acid and alpha-linolenic acid, which



Fig. 51.5 Kwashiorkor. There is intense edema of the buttocks and lower extremities in addition to areas of erythema with erosions and desquamation. The edema is a reflection of hypoalbuminemia. *Courtesy Ramón Ruiz-Maldonado, MD.*



Fig. 51.4 Marasmus. Multiple sites of purpura are seen. *Courtesy Ramón Ruiz-Maldonado, MD.*



Fig. 51.6 Kwashiorkor. Edema, ulceration, and shellac-like scale that resembles peeling paint.

represent omega-6 and omega-3 fatty acids, respectively, are major types of EFAs. These fatty acids are present in plant oils (e.g. canola, flaxseed, soybean) and in fish oils. EFAs have multiple functions, both structural and synthetic, including prostaglandin formation, phospholipid membrane integrity, energy storage, and proper lamellar granule formation. Humans can convert linoleic acid into arachidonic acid. From 15% to 30% of the skin's fatty acids are EFAs and cutaneous as well as systemic manifestations of EFA deficiency are outlined in Table 51.1.

While an isolated deficiency of EFAs is uncommon, it may occur following parenteral nutrition without lipid supplementation and with overly aggressive low-fat diets. In most instances, however, EFA deficiency is associated with other nutritional deficiencies. The presence of decreased plasma levels of linoleic and linolenic acids plus increased levels of eicosatrienoic acid (normally undetectable) establishes the diagnosis of EFA deficiency (see Table 51.1).

Data from the American Heart Association suggest that obtaining 5%–10% of energy from omega-6 fatty acids (e.g. linoleic acid) reduces the risk of cardiovascular disease. However, there is still controversy regarding the recommended upper limit of consumption of EFAs, as epidemiologic studies suggest that an excess of linoleic acid may contribute to cardiovascular disease, cancer, and inflammation[16].

Vitamins and Trace Elements

Micronutrients represent a diverse array of dietary components that are necessary to sustain health. The physiologic roles of micronutrients are as varied as their composition. Several micronutrients function as cofactors for enzymes, while others act as biochemical substrates or hormones; in addition, there are some whose function has not been well defined[5]. Under normal circumstances, the recommended average daily dietary intake for each micronutrient is measured in milligrams or even smaller quantities. This distinguishes micronutrients from macronutrients (carbohydrates, fats, proteins) as well as the macrominerals (calcium, magnesium, phosphorus)[5].

Vitamins

Vitamins are required constituents of the human diet as they are essential for development and maintenance of bodily functions. However, they do not have a direct role as an energy source. Vitamins are categorized as either fat-soluble (A, D, E, K) or water-soluble (all others) (see Table 51.2). While none of the fat-soluble vitamins appear to serve as cofactors for enzymes, most of the water-soluble vitamins have this function[5]. In addition, symptomatic vitamin excess is more likely with fat-soluble vitamins (see below). Lastly, the use of vitamins

VITAMIN DEFICIENCIES IN ADULTS AND CHILDREN

Vitamin	Clinical manifestations			Reference values	Replacement therapy
	Mucocutaneous	Systemic	Other		
Fat-soluble vitamins – can easily accumulate and lead to toxicity if replaced in high doses for prolonged periods					
A (retinol)	• Phrynoderma – follicular papules with central keratotic plug; favors extensor surfaces of extremities (Fig. 51.7) & buttocks • Generalized xerosis • Sparse, fragile hair	• Night blindness • Xerophthalmia (dryness of the cornea & conjunctivae) • Bitot spots (gray–white patches on the conjunctivae) • Keratomalacia (softness of the cornea, sometimes with ulceration)[47] • Stunted growth	• Increase in measles-related mortality (see Ch. 81) • Increased susceptibility to and mortality from respiratory and diarrheal illnesses[47]	• Serum: LC–MS/MS for vitamin A levels • Reference values (fasting): 0–6 yrs: 11–65 mcg/dl 7–12 yrs: 13–80 mcg/dl 13–17 yrs: 14–98 mcg/dl ≥18 yrs: 32–78 mcg/dl • Supplementation recommended when <20 mcg/dl • Severe deficiency when <10 mcg/dl	• Based on severity of ophthalmologic impairment • Infants (<6 mos): 50 000 IU PO × 3 on days 1, 2, and at least 14 • Infants (6–12 mos): 100 000 IU PO × 3 doses (see above) • Children >1 yr, men, postmenopausal women: 200 000 IU PO × 3 doses (see above)* • Higher doses given if keratomalacia
D **D_2:** ergocalciferol **D_3:** cholecalciferol	None	• Muscle weakness • Rickets in children • Osteomalacia in adults	• Possible decrease in innate immunity (see Table 51.3) • Possible increase in internal malignancies (e.g. colon, prostate)	• Total serum or plasma 25(OH) vitamin D is measured (D_2 plus D_3) • Deficiency: <12 ng/ml (IU: <30 nmol/l) • Insufficiency: 12–20 ng/ml (IU: 30–50 nmol/l)[20]	• For deficiency, 50 000 IU of vitamin D_2 or D_3 (preferred) PO once weekly × 6–8 weeks • Maintenance dose is age-dependent (see text) • For insufficiency, vitamin D_3 800–1000 IU/day PO • Plus 1 g/day of oral calcium if deficient
E (tocopherol)	None	• Ophthalmoplegia, ptosis • Muscle weakness, ataxia, areflexia • Pigmentary retinopathy		• Serum: LC–MS/MS for vitamin E levels • Reference values (fasting): 0–17 yrs: 3.8–18.4 mg/l ≥18 yrs: 5.5–17.0 mg/l • Significant deficiency: <3.0 mg/l	• Children 200–300 mg/day PO • Adults 800–1000 mg/day PO
K **K_1:** phytonadione (source = diet) **K_2:** menaquinone (source = gut bacteria)	Petechiae, purpura, ecchymoses, mucosal bleeding	• If severe hypoprothrombinemia, extensive hemorrhage at any body site • Hemorrhagic disease of the newborn – infants not given vitamin K at birth plus inadequate diet or mother on medications which inhibit vitamin K function†,[47]		• Elevated prothrombin time & INR • Serum or plasma vitamin K_1 level is measured • ≥18 yrs: 0.10–2.20 ng/ml versus 0.2–3.2 ng/ml	• Newborns: 0.5–1 mg sc or IM • Children: 2 mg PO • Adults: 5–10 mg PO • IV or SC administration if emergency • Intravenously in emergencies (risk of anaphylaxis) • Fresh frozen plasma • Doses for K_1 and K_2 similar

Table 51.2 Vitamin deficiencies in adults and children.

Continued

VITAMIN DEFICIENCIES IN ADULTS AND CHILDREN					
Vitamin	**Clinical manifestations**			**Reference values**	**Replacement therapy**
	Mucocutaneous	**Systemic**	**Other**		
Water-soluble vitamins – less likely to accumulate & lead to toxicity, but in high doses can lead to side effects, e.g. nephrolithiasis (vitamin C), hepatitis (niacin)					
C (ascorbic acid)	• Spongy gingivae with bleeding & erosions • Petechiae, ecchymoses • Follicular hyperkeratosis, especially forearms, abdomen, & legs • Corkscrew hairs (flattened & curled) with perifollicular erythema or hemorrhage (Fig. 51.8) • Splinter hemorrhages • Poor wound healing	• Subperiosteal hemorrhage with "pseudoparalysis", especially in children • Arthralgias, joint swelling, edema • Loose teeth • Weakness, malaise, depression • Vasomotor instability[47] • In infants, hemorrhage into GI and GU tracts • Anemia • Impeded growth • Cerebral & femoral sheath hemorrhages	• Many of the signs of *scurvy* are related to impaired collagen synthesis • Fractures of cartilaginous matrix • Positive Rumpel–Leede capillary fragility test (>20 petechiae/inch^2)‡	• Plasma: HPLC for ascorbic acid levels • Conventional (fasting): 0.6–2.0 mg/dl • <0.2 mg/dl = scurvy • Absence of vitamin C in urine • Leukocyte vitamin C is more accurate, but less accessible, assay; 0 mg/dL = scurvy; up to 7 mg/dL = deficiency	• Adults: 200–1000 mg/day PO (in divided doses) • Children: 100–300 mg/day PO (in divided doses), then 100 mg PO once weekly • Higher dosage (1–2 g/day) may decrease symptom duration • IM or IV administration if required
B_1 (thiamin; thiamine)	• Peripheral edema with possible secondary skin breakdown in "wet" beriberi • Glossitis and glossodynia • Angular cheilitis	• Early – fatigue, apathy, irritability, depression, drowsiness, anorexia, nausea, abdominal pain • Late – peripheral neuropathy, weakness, cardiac failure, mental alterations, growth retardation • Prolonged deprivation – meningismus, coma	• *Beriberi* is divided into "wet" and "dry" forms¶ • Korsakoff syndrome – amnesia, confabulation & peripheral neuropathy • Wernicke encephalopathy – ophthalmoplegia, horizontal nystagmus, ataxia, confusion	• Whole blood thiamine diphosphate (TDP) level to assess active form of vitamin B_1 within erythrocytes • TDP reference values (fasting): 70–180 nmol/l • TDP level <70 nmol/l suggests deficiency	• 100 mg TID IV × several days, followed by 100 mg/day PO until complete recovery[41] • Infantile beriberi: 5–20 mg IV[41]
B_2 (riboflavin, lactoflavin)	• Angular cheilitis and dry fissured lips • Glossitis – pebbly appearance, then atrophic with irregular denudation of papillae • Pharyngitis • In periorificial sites (head & neck, anogenital region) – painless scaly papules, ulcers, indolent fissures & seborrheic dermatitis-like lesions • Conjunctivitis	• Superficial keratitis • Photophobia • Changes in iris (pigment clumping) • Anemia due to bone marrow hypoplasia • Intellectual disability in newborns	• In adults, *oro-oculo-genital syndrome* can occur, especially if there are additional B vitamin deficiencies	• Plasma: LC–MS/MS for riboflavin levels • Reference values (fasting): 1–19 mcg/l • Riboflavin level <1 mcg/l = deficiency; marginally low levels should also be corrected	• Riboflavin 3–10 mg/day PO • In refractory cases, 2 mg IM TID
B_3 (niacin, nicotinic acid)	• Photodistributed, well-demarcated erythema that becomes scarlet or hyperpigmented, with scale-crust; surface has shellac-like appearance (Fig. 51.9) • "Casal necklace" – well-demarcated band around the neck • Painful fissures of the palms & soles • Peri-anal & oral inflammation & erosions • Cheilitis and glossitis (atrophic, red) • Vaginitis with ulceration	• Peripheral neuropathy with dysesthesias, including burning • Esophagitis • Anorexia • Lassitude • Dizziness • Irritability, disorientation • Abdominal pain • Late – irritability, anxiety, apathy, diarrhea, nausea, dementia	• The classic triad of *pellagra* is dermatitis, diarrhea, and dementia, with the fourth "d" possibly death • Because of large tissue stores, symptoms develop after months of niacin or tryptophan deficiency • Other causes of pellagra include carcinoid syndrome, Hartnup disease, and medications, e.g. isoniazid	• Plasma; HPLC for niacin levels • Reference values (fasting; mcg/ml): Children <10 yrs 0.50–8.91 (normal) <0.50 (low) Adults & children >10 yrs: 0.50–8.45 (normal) <0.50 (low)	• Nicotinamide (niacinamide) is the amide/water-soluble form of niacin • Adults: nicotinamide 300 mg/day PO (in divided doses) × 3–4 weeks, then maintenance of niacin 15–20 mg/day PO • Children: 10–50 mg every 6 hours PO until resolution of all signs and symptoms, then maintenance of 15–20 mg/day of niacin • *For severe cases*, in adults: 50–100 mg five times/day IM or 25–100 mg twice daily IV (slow infusion); in children: up to 300 mg/day IV (slow infusion)

Table 51.2 Vitamin deficiencies in adults and children.

VITAMIN DEFICIENCIES IN ADULTS AND CHILDREN					
Vitamin	**Clinical manifestations**			**Reference values**	**Replacement therapy**
	Mucocutaneous	**Systemic**	**Other**		
B_5 (pantothenic acid)	• None	• Fatigue, headache & vomiting • Hypoglycemia • Paresthesias ("burning feet" syndrome)	• Rare	• Serum: microbiological assay • Reference values (mcg/l): ≤1 yr: 3.45–845 1–10 yrs: 3.45–229.2 >10 yrs: 37–147	Vitamin B_5 is ubiquitous in the food supply and deficiency rare
B_6 (pyridoxine, pyridoxamine, pyridoxal)	• Periorificial seborrheic dermatitis-like lesions • Angular cheilitis, stomatitis • Glossitis – atrophic with ulceration • Conjunctivitis • Intertrigo	• Anorexia, nausea, vomiting • Neurologic symptoms including peripheral neuropathy, somnolence, confusion, & seizures • Sideroblastic anemia, eosinophilia, lymphopenia		• LC–MS/MS for pyridoxal 5-phosphate levels • Reference value (fasting): 5–50 mcg/l	• Pyridoxine 50–100 mg/day PO to prevent neuropathy[41] • 100 mg/day IV in those with seizures[41]
B_7 (biotin)	• Alopecia • Seborrheic dermatitis of the scalp, face, and flexures • Periorificial dermatitis (ocular, nasal, oral, anal) • Cutaneous candidiasis • Nummular eczema[47] • Blepharitis, conjunctivitis • Brittle nails • Erythroderma in neonatal form • Juvenile form may resemble acrodermatitis enteropathica	• Depression, lassitude • Anorexia, nausea, & vomiting • Paresthesias & hyperesthesias • Hypotonia, muscle pain • Developmental delay, hearing loss • Seizures, ataxia • Both forms fatal if not treated	• Neonatal form – holocarboxylase synthetase deficiency (see Fig. 51.13) • Juvenile form – biotinidase deficiency • Two forms have overlap; both autosomal recessive • Metabolic acidosis, lactic acidosis, hyperammonemia	• White blood cells: levels of biotinylated carboxylases, e.g. 3-methylcrotonyl-CoA or propionyl-CoA carboxylases • Serum: microbiological assay • Reference values (pg/ml) for microbiologic assay: <12 yrs: 100–2460 ≥12 yrs: 221–3004 • Increased urinary excretion of organic acids (e.g. 3-hydroxy-isovaleric acid, 3-hydroxyisovalerylcarnitine) • Genetic analysis (see Fig. 51.13)	• Infants & children: 5–20 mg/day PO or IM • Adults: 10–40 mg/day PO or IM
B_9 (folic acid; folate)	• Cheilitis, glossitis, mucosal erosions and ulcerations • Diffuse hyperpigmentation, with accentuation in sun-exposed sites	• Megaloblastic anemia (macrocytosis plus hypersegmented neutrophils is pathognomonic)[47] • Weakness secondary to anemia • Neuropsychiatric symptoms due to impaired synthesis of myelin	• While folate can reverse the megaloblastic anemia of B_{12} deficiency, it cannot reverse the neurologic degeneration	• *Serum* folate levels: <4 mcg/l suggests folate deficiency • *RBC* folate levels: 140–628 ng/ml in packed RBCs • IU: 317–1422 nmol/l in packed RBCs	• Replace folate and exclude B_{12} deficiency • Folate 1 mg TID PO, followed by 1 mg/day • Folate 1–5 mg/day IV if acutely ill[41]
B_{12} (cyanocobalamin [CNCbl])	• Diffuse or patchy hyperpigmentation, including flexural areas, dorsal hands and feet, palmar creases, soles, nails, oral cavity • Glossitis with fissures of the oral mucosa (early sign prior to anemia)[48] • Painful, red, swollen tongue • Increased incidence of vitiligo, poliosis, and alopecia areata in patients with pernicious anemia	• Megaloblastic anemia due to altered folic acid metabolism • Peripheral neuropathy, ataxia	• Pernicious anemia – decrease in gastric intrinsic factor • Juvenile form – normal gastric acid secretion (in contrast to adult form) • Use of Schilling test has been supplanted by serologic testing for anti-parietal cell and anti-intrinsic factor antibodies • Associated autoimmune endocrinopathies	• Megaloblastic anemia with decreased serum B_{12} levels • Conventional: 200–835 pg/ml • IU: 148–616 pmol/l • More sensitive assay is serum levels of methylmalonic acid and homocysteine[§]	• Pernicious anemia: CNCbl 1000 mcg IM weekly × 4 weeks, then 1000 mcg PO, SL, or IM monthly • If neurologic symptoms or severe anemia: CNCbl 1000 mcg IM twice weekly × 2 weeks then weekly × 2 months then monthly[41]

*For women of reproductive age, 5000–10 000 IU/day × 4 weeks or 25 000 IU/week × 4 weeks unless severe keratomalacia.
†Medications that inhibit hepatic vitamin K epoxide reductase: warfarin, anticonvulsants, certain cephalosporins (containing side chains of N-methylthiotetrazole or methylthiadiazole), high-dose salicylates, and rifampin.
‡Following inflation of blood pressure cuff to a point between systolic and diastolic blood pressure for 5 minutes.
¶"Wet" beriberi derives its name from the edema that occurs secondary to cardiac failure, which can be high-output. In "dry" beriberi, neurologic manifestations predominate, e.g. peripheral neuropathy (sensory and motor), confusion, and nystagmus.
§Levels of both are increased early in vitamin B_{12} deficiency; in folate deficiency, homocysteine levels are elevated but methylmalonic acid levels are normal.

Table 51.2 Vitamin deficiencies in adults and children. HPLC, high performance liquid chromatography; IM, intramuscularly; INR, international normalized ratio; IV, intravenously; LC–MS/MS, liquid chromatography–tandem mass spectrometry; mos, months; PO, orally; SC, subcutaneously; SL, sublingual; TID, three times per day; yrs, years. Adapted in part from refs 5–10.

VITAMINS – SOURCES, FUNCTIONS AND RECOMMENDED PROPHYLACTIC DOSES				
Vitamin	**Natural sources**	**Functions**	**Underlying etiologies/risk factors**	**Recommended daily intake (RDA in bold and *AI in italics*)**
A (retinol)	• Dietary pro-vitamin A (e.g. beta-carotene) from plant sources: leafy green vegetables, sweet potatoes, carrots • Dietary preformed vitamin A (e.g. retinol) from animal sources: liver, milk, animal fats	• Normal vision • Embryogenic development • Physical growth • Immune function • Keratinocyte proliferation and differentiation • If deficiency, squamous metaplasia of sebaceous and eccrine glands	• Minimal, if any, animal fats in diet • Poverty • Alcohol use disorder • Anorexia nervosa • Fad diets • Fat malabsorption (e.g. gastric bypass, pancreatic insufficiency, inflammatory bowel disease, liver disease, cystic fibrosis)	• Measured in mcg of retinol activity equivalents (RAE)/day* • Infants & children: 0–12 mos: *400–500 mcg* 1–8 yrs: **300–400 mcg** 9–13 yrs: **600 mcg** • ≥14 yrs: **700–900 mcg** • Pregnant women: **750–770 mcg** • Lactating women: **1200–1300 mcg**
D **D_2:** ergocalciferol **D_3:** cholecalciferol	• Estimates of sources – 90% from UVB irradiation of the skin; 10% from food • Plant sources (D_2; e.g. spinach, mushrooms exposed to UVR) • Animal sources (e.g. cod liver oil, fatty fish such as salmon, herring, mackerel or tuna, fortified milk or yogurt)	• Induces antimicrobial peptide gene expression in keratinocytes, monocytes, NK cells, T cells, B cells, & neutrophils[17] • Induces cathelicidins via the vitamin D receptor • Helps absorption of ~85% of calcium and 40% of phosphorus via the gut • Decreases proliferation of malignant cells & induces terminal differentiation[17]	• Risk factors include: breastfed infants, individuals with highly pigmented skin or limited sun exposure, advanced age, BMI >30 (fat sequesters vitamin D), living at extreme degrees of latitude[17] • Generalized disorders of cornification • Impaired absorption (e.g. gastrointestinal disease, gastric bypass, medications including phenytoin, corticosteroids, and stimulant laxatives) • Organoid nevi	• Institute of Medicine recommendations: 0–12 mos: 400 IU 1–70 yrs: 600 IU >71 yrs: 800 IU • Many countries and institutions have their own recommendations regarding the appropriate dose of oral vitamin D per day
E (tocopherol)	• Ubiquitous in foods, so deficiency is rare	• Possible role in cellular homeostasis • Antioxidant • Interferes with vitamin K-dependent coagulation via unknown mechanism	• Long-term fat malabsorption (chronic cholestasis, small bowel resection, pancreatic insufficiency [absorption requires biliary and pancreatic secretions])[41] • Genetic disorders (e.g. *TTPA* [alpha tocopherol transfer protein] pathogenic variants)	• Infants & children: 0–12 mos: *4–5 mcg* 1–8 yrs: **6–7 mcg** 9–13 yrs: **11 mcg** • ≥14 yrs: **15 mcg** • Pregnant women: **15 mcg** • Lactating women: **19 mcg**
K **K_1:** phytonadione (source = diet) **K_2:** menaquinone (source = gut bacteria)	• K_1: green leafy vegetables & meat • K_2: fermented foods & grass-fed animals • Diet: ~50% • Bacteria within large bowel: ~50%	• K_1: hepatic synthesis of coagulation factors II, VII, IX & X and proteins C & S • K_2: regulates mineral localization (e.g. calcium)[49]	• Broad-spectrum antibiotics (reduce intestinal bacteria) • Malabsorption syndromes • Low-birthweight infants (inadequate intake, non-colonized colon, low hepatic stores, maternal medications†) • Liver diseases, biliary atresia, cystic fibrosis • Medications: cholestyramine, colestipol, colesevelam, orlistat, vitamin E, and inhibitors of vitamin K epoxide reductase† • Total parenteral nutrition (TPN)	• Infants & children: 0–12 mos: *2–2.5 mcg* 1–8 yrs: *30–55 mcg* 9–13 yrs: *60 mcg* 14–18 yrs: *75 mcg* • ≥19 yrs: *90–120 mcg* • Pregnant & lactating women: *75–90 mcg*
C (ascorbic acid)	• Fresh fruits & vegetables	• Collagen formation • Cofactor for several enzymes, e.g. lysyl hydroxylase • Antioxidant • Iron absorption • Folate metabolism (folic acid to active form folinic acid)	• Alcohol and substance use disorders • Fad diets • Deficient intake for as few as 3 months can lead to scurvy[47] • Increased requirements in the setting of febrile illnesses, malabsorption, iron deficiency, hemodialysis	• Infants & children: 0–12 mos: *40–50 mg* 1–8 yrs: **15–25 mg** 9–13 yrs: **45 mg** 14–18 yrs: **65–75 mg** • ≥19 yrs: **75–90 mg** • Pregnant women: **80–85 mg** • Lactating women: **115–120 mg**
B_1 (thiamine; thiamin)	• Yeast, cereals, liver, meat (pork), eggs, brown rice, vegetables including legumes	• Role in pyruvate metabolism (a source of energy generation) • Cofactor in metabolism of carbohydrates, lipids, branched-chain amino acids[41]	• Starvation, alcohol use disorder • Polished rice diet • Hyperemesis gravidarum • B_1-deficient diet (IV hyperalimentation or TPN) followed by high-carbohydrate diet exacerbates symptoms[41,‡] • Hemodialysis, leukemia, rapidly growing carcinoma • Urinary loss due to diuretics	• Infants & children: 0–12 mos: *0.2–0.3 mg* 1–8 yrs: **0.5–0.6 mg** 9–13 yrs: **0.9 mg** 14–18 yrs: **1–1.2 mg** • ≥19 yrs: **1.1–1.2 mg** • Pregnant & lactating women: **1.4 mg**

Table 51.3 Vitamins – sources, functions and recommended prophylactic doses.

VITAMINS – SOURCES, FUNCTIONS AND RECOMMENDED PROPHYLACTIC DOSES				
Vitamin	**Natural sources**	**Functions**	**Underlying etiologies/risk factors**	**Recommended daily intake (RDA in bold and *AI in italics*)**
B_2 (riboflavin; lactoflavin)	• Milk, cheese, eggs, fortified bread and cereals, yeast, lean meat, green vegetables	• Intracellular oxidation–reduction reactions	• Achlorhydria & GI malabsorption • Alcohol use disorder • Hypothyroidism • Neonatal phototherapy for hyperbilirubinemia • Low milk intake (e.g. due to lactose intolerance) • Medications: chlorpromazine, probenecid, tricyclic antidepressants • Exacerbated by respiratory infections	• Infants & children: 0–12 mos: *0.3–0.4 mg* 1–8 yrs: **0.5–0.6 mg** 9–13 yrs: **0.9 mg** 14–18 yrs: **1–1.3 mg** • ≥19 yrs: **1.1–1.3 mg** • Pregnant women: **1.4 mg** • Lactating women: **1.6 mg**
B_3 (niacin; nicotinic acid)	• Liver, lean pork, salmon, poultry, red meat, beans, milk, eggs • Humans are able to synthesize niacin from tryptophan (an essential amino acid)	• Vital oxidation–reduction reactions • Biosynthesis of epidermal lipids, e.g. ceramides	• Malnutrition • Intestinal malabsorption • Alcohol use disorder • Diet limited to tryptophan-deficient corn (maize)[¶] • Carcinoid syndrome[¶] • Hartnup disease[¶] • HIV infection, including those receiving isoniazid preventive therapy • Medications: isoniazid > 6-mercaptopurine, azathioprine, 5-fluorouracil and drugs that inhibit conversion from tryptophan (e.g. phenobarbital, ethionamide) • Deficiency of micronutrients (e.g. iron, riboflavin, pyridoxine) required for conversion from tryptophan	• Infants & children: 0–12 mos: *2–4 mg* 1–8 yrs: **6–8 mg** 9–13 yrs: **12 mg** • ≥14 yrs: **14–16 mg** • Pregnant women: **18 mg** • Lactating women: **17 mg**
B_5 (pantothenic acid)	• Synthesized in gut by bacterial flora	• Component of coenzyme A which plays major role in metabolism	• Protein–energy malnutrition	• Infants & children: 0–12 mos: *1.7–1.8 mg* 1–8 yrs: *2–3 mg* 9–13 yrs: *4 mg* • ≥14 yrs: *5 mg* • Pregnant women: *6 mg* • Lactating women: *7 mg*
B_6 (pyridoxine, pyridoxamine, pyridoxal)	• Widely distributed in nature • Pyridoxine in plant food • Pyridoxal and pyridoxamine in animal products • All forms convert to the active form pyridoxal phosphate	• Cofactor for multiple enzymes involved in amino acid metabolism and conversion of linoleic acid to arachidonic acid • Ceramide synthesis • Gluconeogenesis & heme biosynthesis[41]	• Other vitamin or trace element deficiencies (metabolism of B_6 is dependent on riboflavin, niacin, & zinc) • Medications: isoniazid, anticonvulsants, penicillamine, hydralazine, oral contraceptives, corticosteroids[41] • Inflammatory bowel disease, uremia, & cirrhosis	• Infants & children: 0–12 mos: *0.1–0.3 mg* 1–8 yrs: **0.5–0.6 mg** 9–13 yrs: **1 mg** 14–18 yrs: **1.2–1.3 mg** • ≥19 yrs: **1.3–1.7 mg** • Pregnant women: **1.9 mg** • Lactating women: **2 mg**
B_7 (biotin)	• Liver is best source • Other meats, egg yolks, yeast, soybeans, tomatoes • Probably synthesized in gut by bacterial flora	• Essential cofactor for several carboxylases involved in cellular metabolism, e.g. of fatty acids • Plays role in gluconeogenesis[47]	• Inborn error of metabolism (e.g. deficiencies of biotinidase or holocarboxylase synthetase) • Inadequate diet • Excessive raw egg white consumption[§] • Chronic anticonvulsant therapy • Pregnancy • Chronic alcohol use disorder	• Infants & children: 0–12 mos: *5–6 mcg* 1–8 yrs: *8–12 mcg* 9–13 yrs: *20 mcg* 14–18 yrs: *25 mcg* • ≥19 yrs: *25–30 mcg* • Pregnant women: *30 mcg* • Lactating women: *35 mcg*
B_9 (folate; folic acid)	• Liver, green leaves, meat, milk, yeast, fortified foods • Easily destroyed with cooking[47] • Body stores are limited, so anemia can result after 4–5 months of deficient intake	• DNA synthesis	• Deficient diets • *MTHFR* pathogenic variants • Alcohol use disorder • Intestinal malabsorption (inflammatory bowel disease, gastric bypass) • Medications (which interfere with folate metabolism): methotrexate, sulfasalazine, pyrimethamine, phenytoin, trimethoprim	• Measured in mcg of dietary folate equivalents (DFEs)[‖] • Infants & children: 0–12 mos: *65–80 mcg* 1–8 yrs: **150–200 mcg** 9–13 yrs: **300 mcg** • ≥14 yrs: **400 mcg** • Pregnant women: **600 mcg** • Lactating women: **500 mcg**

Table 51.3 Vitamins – sources, functions and recommended prophylactic doses.

Continued

VITAMINS – SOURCES, FUNCTIONS AND RECOMMENDED PROPHYLACTIC DOSES				
Vitamin	**Natural sources**	**Functions**	**Underlying etiologies/risk factors**	**Recommended daily intake (RDA in bold and *AI in italics*)**
B_{12} (cyanocobalamin)	• Fish, shellfish, meat, dairy products, fortified foods • Body stores are large, so development of deficiency requires 3–6 years of a deficient state	• DNA synthesis	• Strict vegetarianism/veganism • Decrease in gastric intrinsic factor (pernicious anemia) • Atrophic gastritis • Intestinal malabsorption (e.g. celiac disease, inflammatory bowel disease) • Gastrectomy, surgical resection of terminal ileum • Overgrowth of intestinal bacteria • Medications: metformin, H2 receptor antagonists, proton pump inhibitors, nitrous oxide • Alcohol use disorder	• Infants & children: 0–12 mos: 0.4–0.5 mcg 1–8 yrs: **0.9–1.2 mcg** 9–13 yrs: **1.8 mcg** • ≥14 yrs: **2.4 mcg** • Pregnant women: **2.6 mcg** • Lactating women: **2.8 mcg**

*1 IU retinol = 0.3 mcg RAE; 1 IU β-carotene (dietary supplements) = 0.15 mcg RAE; 1 IU β-carotene (food) = 0.05 mcg RAE; 1 IU α-carotene or β-cryptoxanthin = 0.025 mcg RAE.
†Medications which inhibit vitamin K epoxide reductase in the liver: warfarin, anticonvulsants, certain cephalosporins (containing side chains of N-methylthiotetrazole or methylthiadiazole), high-dose salicylates, isoniazid, and rifampin.
‡Pyruvate and lactate, which interfere with carbohydrate metabolism, accumulate in a B_1-deficient state. A high-carbohydrate diet accentuates the pre-existing vitamin-deficient state, often precipitating a Wernicke or Korsakoff syndrome.
¶Tryptophan (an essential fatty acid) is a precursor of niacin. Tryptophan is deficient in maize, and millet interferes with tryptophan metabolism as it is high in leucine. In carcinoid syndrome, tryptophan is preferentially converted to serotonin instead of niacin, and in Hartnup disease, niacin deficiency is due to decreased intestinal absorption of tryptophan.
§Excessive consumption of raw egg whites (>20 eggs/day) leads to high levels of the protein avidin, which binds to biotin, rendering it biologically unavailable. Avidin is deactivated by cooking, while biotin remains intact.
‖1 mcg DFE = 1 mcg food folate; 1 mcg DFE = 0.6 mcg folic acid from fortified foods or dietary supplements consumed with foods; 1 mcg DFE = 0.5 mcg from dietary supplements taken on an empty stomach.

Table 51.3 Vitamins – sources, functions and recommended prophylactic doses. Recommended Dietary Allowance (RDA) is the average daily dietary intake that is sufficient for 97%–98% of healthy individuals in a group while the Adequate Intake (AI) is an approximation when an RDA cannot be determined. mos, months; MTHFR, methylenetetrahydrofolate reductase; UVB, ultraviolet B radiation; UVR, ultraviolet irradiation; yrs, years. Adapted in part from refs 5–7,9,10.



Fig. 51.7 Phrynoderma of vitamin A deficiency. Multiple clusters of follicular papules with central keratotic plugs. Histologically, keratinous plugs within follicles, hyperkeratosis, and atrophy of sebaceous glands are seen. It must be differentiated from pityriasis rubra pilaris and keratosis pilaris.

as therapeutic interventions in dermatology includes topical vitamin D analogues for psoriasis[17] (see Ch. 129), oral nicotinamide for autoimmune blistering diseases and non-melanoma skin cancer prevention, oral or topical retinoids to treat acne and disorders of cornification (see Ch. 126), and topical vitamin C to try to reverse photodamage[18].

Tables 51.2 and 51.3 review the major fat- and water-soluble vitamins, including their functions and recommended daily dosages, as well as the risk factors for vitamin deficiencies and associated signs and symptoms[5–7,9,10].

Vitamin excess

Excessive ingestion of vitamins most commonly occurs in individuals seeking potential (and often unproven) "anti-aging" or antineoplastic effects. High doses of fat-soluble vitamins may lead to harmful side effects, including hepatic toxicity, nephrolithiasis, and peripheral neuropathy (Table 51.4)[5–7]. They may also have unanticipated effects at high doses in certain populations. For example, in the β-Carotene and Retinol Efficacy Trial (CARET), a large cancer prevention trial, patients at high risk for lung cancer were given supplements containing β-carotene and vitamin A. Not only did these supplements fail to prevent lung cancer, they were actually associated with increased rates

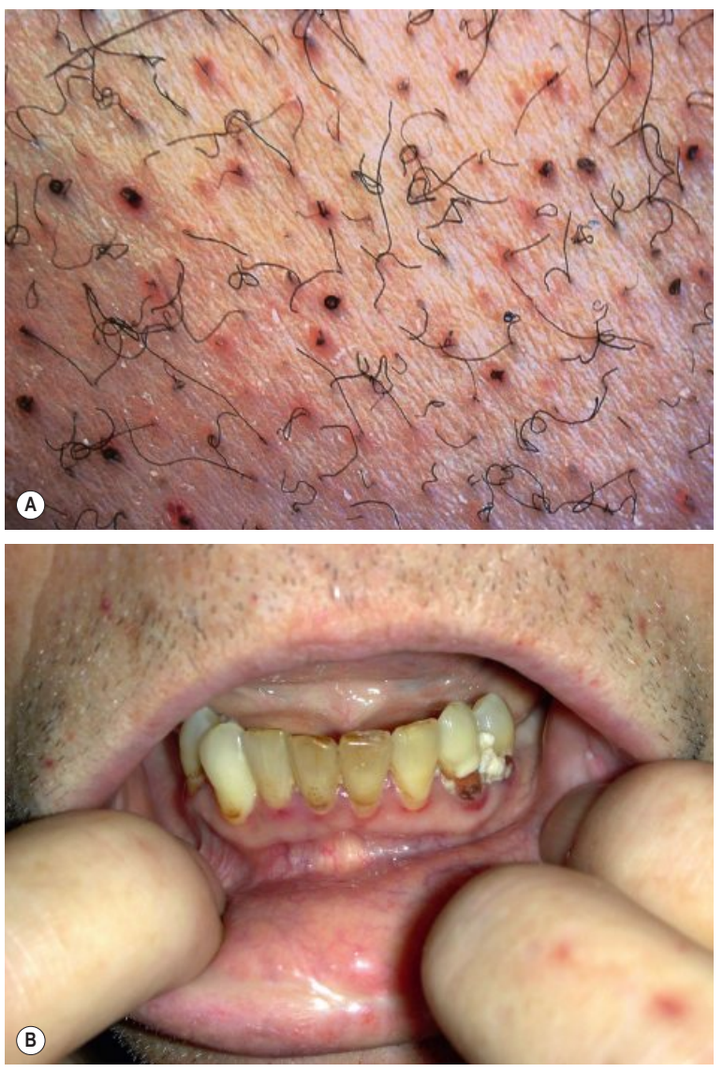


Fig. 51.8 Scurvy. A Corkscrew hairs and perifollicular hemorrhage on the lower extremities. **B** Gingivitis and gingival erosions. *B, Courtesy Jeffrey P. Callen, MD.*



Fig. 51.9 Pellagra. A Hyperpigmentation and desquamation of the dorsal aspects of the hands and forearms. The shellac-like scale is seen best on the forearms. **B** Striking hypopigmentation with peripheral desquamation of the sun-exposed area of the chest in a man from sub-Saharan Africa. *B, Courtesy Rosemarie Moser, MD.*

of lung cancer[19]. The reported association of oral isotretinoin and topical tretinoin with increased mortality in smokers remains controversial[20].

Toxicity due to high doses of water-soluble vitamins (i.e. B vitamins, vitamin C) is rarely seen, as these compounds are rapidly excreted via the urine. While not an excess issue, ingestion of biotin to possibly improve hair and nails can interfere with biotin-streptavidin-based cardiac troponin, β-hCG, parathyroid, and thyroid (TSH, T3, T4) immunoassays.

Vitamin D

Vitamin D plays a role in the absorption of calcium and phosphorus, helping to maintain normal serum levels of these minerals (Fig. 51.11). Vitamin D also functions as an antiproliferation and prodifferentiation hormone, but its exact role is not known[10]. Although a possible association of vitamin D deficiency with cutaneous disorders such as alopecia areata, atopic dermatitis, and psoriasis has been suggested, to date there are no known cutaneous signs of vitamin D deficiency. In addition, the Institute of Medicine (IOM) found no strong evidence to support a role for vitamin D supplementation for any medical condition other than bone health[21].

With the exception of individuals with sarcoidosis, the preferred method for assessing vitamin D status is measurement of total serum levels of 25-hydroxyvitamin D. While secondary hyperparathyroidism can influence the 1,25-dihydroxyvitamin D assay, this is not the case with the 25-hydroxyvitamin D assay. In addition, 25-hydroxyvitamin D has a longer half-life (2 weeks) and therefore is thought to better reflect body stores[18,22]. Currently, although a consensus is lacking, vitamin D *deficiency* is defined by most experts as a serum level of 25-hydroxyvitamin D that is <12 ng/ml (30 nmol/l), and vitamin D *insufficiency* as circulating levels of 12–20 ng/ml (30–50 nmol/l) (see Table 51.2).

Based upon these levels, it is estimated that one billion people worldwide have either deficient or insufficient levels of vitamin D[23]. Depending upon the study, ~50%–60% of nursing home residents, the elderly, and hospitalized patients in the US are deficient in vitamin D[23]. Decreased levels of 25-hydroxyvitamin D (<20 ng/ml) were also observed in half of US Hispanic or Black adolescents and White preadolescent girls[22]. In addition, ~50% of Black and 55% of White infants have vitamin D deficiency, while over 90% of infants in Iran, Turkey, and India have vitamin D deficiency.

While the IOM recommends a daily intake of vitamin D_3 of 400 IU/day (0–12 months of age), 600 IU/day (1–70 years of age), and 800 IU/day (>70 years of age), some experts have advocated 1000 IU/day for children or adolescents and 1500–2000 IU/day for adults (unless there are contraindications)[18,21,23]. All of these doses are below the age-dependent, tolerable, upper daily limits of 1000–4000 IU for infants and children (up to 18 years old) and 4000 IU for adults[23], with the range reflecting the current lack of a consensus regarding the upper daily limit. Vitamin D_3 (cholecalciferol; animal diet source) is viewed as nutritionally superior to vitamin D_2 (ergocalciferol; plant source) and therefore is regarded as the preferred form for supplementation and for fortifying foods. Although it is difficult to obtain enough vitamin D_3 from dietary sources alone, patients should be made aware of vitamin D-rich foods such as fatty fish, beef liver, cheese, egg yolks, mushrooms that have been exposed to ultraviolet light, and fortified foods[23].

An endogenous source of vitamin D production also exists, initiated with the conversion of 7-dehydrocholesterol to provitamin D_3 when skin is exposed to ultraviolet B radiation (see Fig. 51.11). It is thought that typically over 90% of vitamin D is produced via UVB exposure; however, the skin's ability to synthesize vitamin D diminishes with age and it is reduced in individuals with darker skin phototypes. The balance between sun protection (to prevent photodamage and cutaneous malignancies) and the risk of vitamin D deficiency has become a matter of debate. As effects of vitamin D, beyond calcium homeostasis and bone mineralization, have become increasingly recognized, the debate has intensified. For example, immunomodulatory effects via the innate immune system have been reported, as has an association between vitamin D deficiency and an increased risk of several internal malignancies[21]. While there are studies that refute the latter as well as no direct evidence linking sunscreen use with vitamin D deficiency[20,24], it is prudent to recommend that patients who are limiting sun exposure and/or have risk factors for the development of vitamin D deficiency ingest the daily recommended amount of vitamin D_3 (see Tables 51.2 & 51.3).

Trace elements

Trace elements and minerals constitute ~3% of body weight at birth and 4% in adults. Based upon animal studies, 15 trace elements have been identified as essential for health: *iron*, *zinc*, *copper*, *chromium*, *selenium*, *iodine*, *fluoride*, *manganese*, *molybdenum*, *cobalt*, nickel, tin, silicon, vanadium, and arsenic (in very small doses). There is compelling evidence that the first 10 (in italics) are essential nutrients in humans. They serve multiple cellular functions including as cofactors for enzymes and as prosthetic groups in metalloproteins. An example of the latter is the complexing of iron and protoporphyrin IX via ferrochelatase to form heme[4]. Deficiency syndromes related to essential trace elements, other than iron, zinc, copper, iodine or cobalt, were not recognized until more recently. Explanations include the exceedingly small requirements for these trace elements, their ubiquitous nature in foodstuffs[4], and the lack of routine laboratory assays. Only trace elements of dermatologic importance will be discussed in this chapter.

Zinc

Zinc is one of the most important trace elements in humans, playing a critical role in the function of more than 200 zinc-dependent metalloenzymes that regulate lipid, protein, and nucleic acid synthesis and degradation. Zinc can be found in human breast milk, animal-based foods, shellfish, legumes, and green leafy vegetables. There is evidence to suggest that zinc plays a role in enhancing wound healing as well as immune function[25] and this may explain the poor wound healing and

VITAMIN EXCESS IN ADULTS AND CHILDREN				
		Clinical manifestations		
Vitamin	**Mechanism of toxicity**	**Cutaneous**	**Systemic**	**Comments**
A	• Chronic intake of >25 000 IU vitamin A per day • Ingestion of polar bear liver • Coadministration with other retinoids	• Cheilitis • Xerosis with pruritus • Exfoliative dermatitis • Alopecia	• Painful swelling of the long bones in young children • Elevated hepatic enzymes • Skeletal hyperostosis • Calcification of extraspinal tendons and ligaments • Pseudotumor cerebri • Lethargy, anorexia	• Assessment by serum concentrations – unreliable • Similar side effects as oral retinoids (see Ch. 126) • Treatment – immediate discontinuation
Beta-carotene (natural provitamin of vitamin A)	• Carotenemia – high intake of carrots & yellow squash, including as baby food • Lycopenia – high intake of tomatoes, gac, papaya, pink guava, & other fruits • Inability to convert β-carotene to vitamin A (e.g. hypothyroidism, diabetes, anorexia nervosa)	• Yellow–orange discoloration (Fig. 51.10) due to deposition of carotenes/lycopenes in areas with: – the thickest layer of stratum corneum (palms & soles) – abundant sebaceous glands (nasolabial folds, forehead) • Carotenoderma usually appears when carotene levels are 3–4× normal	• None	• Skin discoloration slowly disappears after altering diet • Measurement of serum carotenoids (normal range: 0.4–1.5 mg/l) differentiates this disorder from jaundice, in which mucous membranes have a yellow color (most apparent in sclerae)
D	• >50 000 IU/day of oral supplementation	• None	• Nausea, vomiting • Poor appetite • Diarrhea, constipation • Weakness • Nephrolithiasis, nephrocalcinosis • Hypercalcemia, hypercalciuria, hyperphosphatemia	• NOT caused by excessive exposure to UVR (previtamin D_3 and vitamin D_3 inactivated by sustained exposure of skin to heat) • Tolerable upper limit for adults is 2000–4000 IU/day[6]
E	• High supplement doses	• Petechiae, ecchymoses	• May reduce platelet aggregation • Interferes with function of vitamin K	• Drug–drug interactions with warfarin (increased anticoagulant effect) and antiplatelet agents (enhanced effect) (see Ch. 133) • High doses of vitamin E (>400 IU/day) may reduce platelet aggregation
K	• None	• None	• None	• Side effects at sc injection sites: – early: erythematous plaque, often annular (see Ch. 21) – late: morpheaform plaque (Texier disease)
C	• Excessively high doses of oral supplements	• None	• GI upset • Osmotic diarrhea • Nephrolithiasis (oxalate renal calculi)	• Abrupt discontinuation of excessive vitamin C intake can also lead to scurvy
B_3 (niacin, nicotinic acid)	• Excessively high doses of oral supplements	• Flushing, pruritus, xerosis • Acanthosis nigricans	• Dyspepsia • Hepatic failure • Hyper- or hypoglycemia • Hyperuricemia • Hypothyroidism	
B_6	• Long-term oral doses of >200 mg/day	• Photosensitivity	• Loss of proprioception • Painful sensory neuropathy	
B_7 (biotin)				High levels of biotin may interfere with biotin-streptavidin-based cardiac troponin, β-hCG, parathyroid, and thyroid (TSH, T3, T4) immunoassays

Table 51.4 Vitamin excess in adults and children. GI, gastrointestinal; SC, subcutaneous; UVR, ultraviolet radiation. Adapted in part from refs 5–7.

increased susceptibility to cutaneous infections observed in patients with chronic zinc deficiency. Due to its antioxidant properties, zinc might protect the skin against UV-induced damage[26].

Patients with zinc deficiency can develop erythema, scale-crusts and erosions, especially periorally, acrally, and in the anogenital region (Fig. 51.12); occasionally, vesicles or bullae are seen as well as psoriasiform plaques. Zinc deficiency may also lead to alopecia, paronychia, onychodystrophy, blepharitis, conjunctivitis, stomatitis, and angular cheilitis. Diarrhea, depression (apathy), and dermatitis (erosive) are sometimes considered the triad of zinc deficiency, but the complete triad is seen in only 20% of patients. Superimposed cutaneous infections with *Candida* spp. and staphylococci are very common. Patients are typically irritable and sleep poorly; children with chronic zinc deficiency may experience growth retardation and/or develop hypogonadism. If treatment is not initiated, death may ensue.

Zinc deficiency can be either acquired or inherited as an autosomal recessive disorder, known as acrodermatitis enteropathica (AE). The latter is due to mutations in the gene that encodes the transmembrane



Fig. 51.10 Carotenoderma. The patient's legs are noticeably orange when compared to the photographer's hand.

zinc transporter SLC39A4 which is expressed in the intestine and kidney. Clinical manifestations usually appear within 1 to 2 weeks after weaning from breast milk, or at 4 to 10 weeks of age if bottle-fed. Of note, transient neonatal zinc deficiency can develop in breastfed babies when breast milk contains low levels of zinc due to dysfunction of SLC30A2, the zinc transporter in the breast (in the mother). In addition, infants and children with cystic fibrosis can develop zinc deficiency (Fig. 51.13). This deficiency should be considered in children who have treatment-resistant seborrheic dermatitis or anogenital dermatitis.

There are several risk factors for developing acquired zinc deficiency, including alcohol use disorder, anorexia nervosa, diets high in mineral-binding phytate (Middle Eastern diets), and vegan diets. Of note, vegan diets can also lead to low levels of long-chain n-3 (omega-3) fatty acids, calcium, vitamin D, and vitamin B_{12}[27]. Intestinal malabsorption often results in multiple deficiencies, including zinc. In addition, zinc deficiency can be seen in association with pregnancy, HIV disease, chronic renal failure, sickle cell disease, and drugs (e.g. penicillamine). Especially when combined with other risk factors, drugs such as diuretics and antacids can result in zinc deficiency while quinolones and tetracyclines can reduce absorption of zinc supplements.

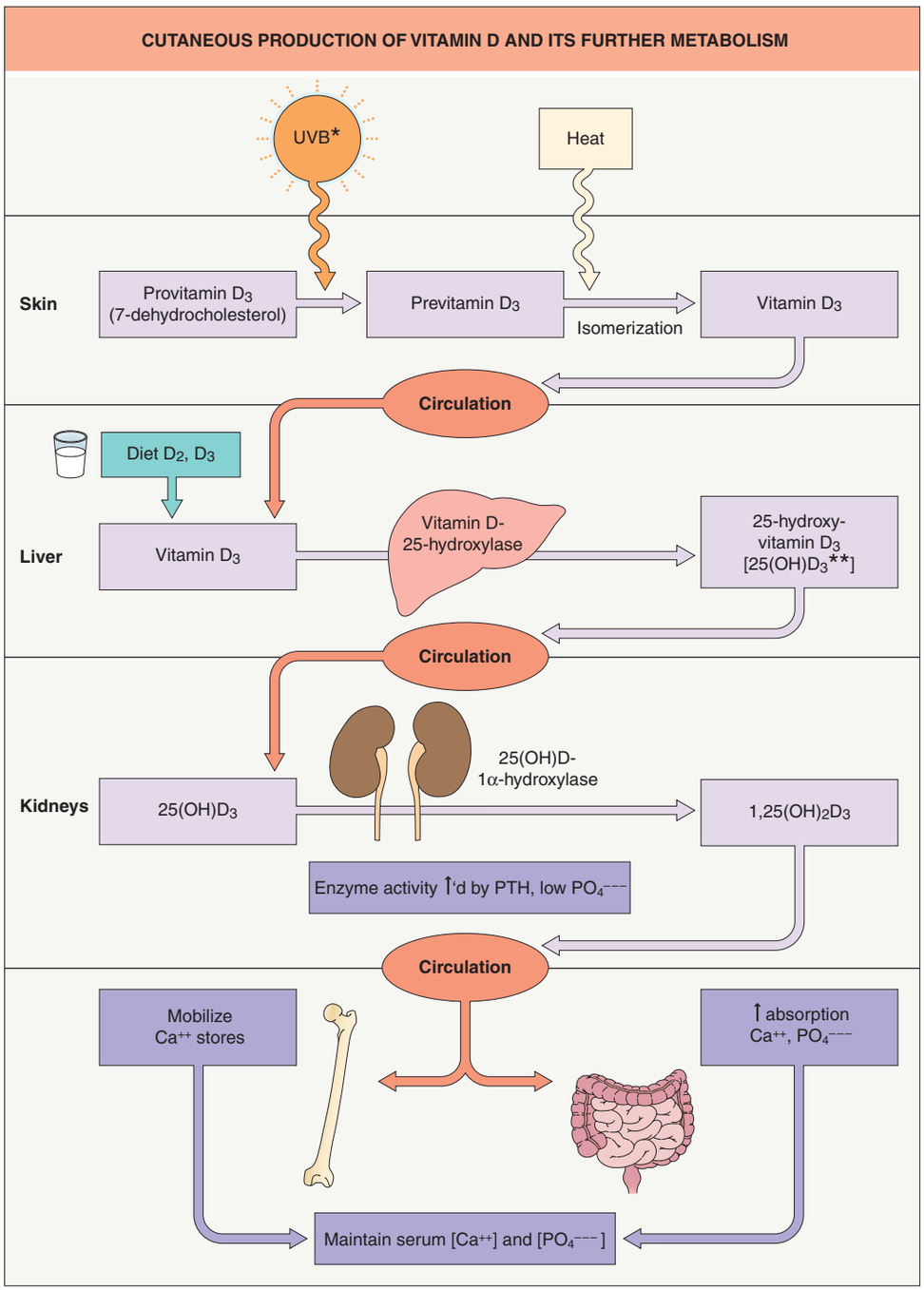


Fig. 51.11 Cutaneous production of vitamin D and its further metabolism. During exposure to ultraviolet B radiation, 7-dehydrocholesterol within the skin is converted to previtamin D_3, which is then immediately converted to vitamin D_3 in a heat-dependent process[22]. Of note, the heat from excessive sunlight exposure can degrade previtamin D_3 and vitamin D_3 into inactive photoproducts. Both forms of vitamin D (D_3 and D_2) are biologically inactive and they require activation in the liver and then the kidney. After binding to carrier proteins, vitamin D is transported to the liver, where it is enzymatically hydroxylated to 25-hydroxyvitamin D [25(OH)D], the major circulating form of vitamin D. 25-hydroxyvitamin D is then converted into its active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], within the kidney by the enzyme 1α-hydroxylase. Of interest, this final hydroxylation step can also occur in keratinocytes when the enzyme CYP27B1 is upregulated in response to wounding or by Toll-like receptor (TLR) activation from microbial-derived ligands[17]. Serum levels of phosphorus, calcium, and fibroblast growth factor 23 can either increase or decrease renal production of $1,25(OH)_2D$. $1,25(OH)_2D$ decreases its own synthesis via feedback inhibition and decreases the synthesis and secretion of parathyroid hormone by the parathyroid glands. $1,25(OH)_2D$ also enhances intestinal calcium absorption in the small intestine by interacting with the vitamin D receptor–retinoic acid X receptor complex (VDR-RXR) to enhance the expression of the epithelial calcium channel and calbindin-D 9 K, a calcium-binding protein. In addition, $1,25(OH)_2D$ is recognized by its receptor in osteoblasts, leading to a series of events that maintain calcium and phosphorus levels in the blood which in turn promotes mineralization of the skeleton. *Most effective wavelength = 300 ± 5 nm. **Measurement of this form most commonly done to assess vitamin D status.



Fig. 51.12 Zinc deficiency – inherited and acquired forms. Erythema with erosions and scale-crust that is often shellac-like favors the perioral (**A**), acral (**B–D**), and anogenital (**E**, **F**) regions. Pustular paronychia can also be seen (**B**). The degree of involvement can vary from subtle to striking and may mimic other types of "nutritional dermatitis" (see Fig. 51.13), necrolytic migratory erythema, and more common disorders such as seborrheic dermatitis and psoriasis. The superficial erosions are a reflection of necrosis of the upper portion of the epidermis (**G**). *A–C,F, Courtesy Julie V. Schaffer, MD; G, Courtesy Lorenzo Cerrroni, MD.*

The histologic finding of epidermal necrosis (see below) plus low serum alkaline phosphatase (a zinc-dependent enzyme) and zinc levels suggest zinc deficiency; the normal reference range for zinc is 70–150 mcg/dl (10.7–22.9 mcmol/l). Reduced zinc levels can occasionally lag behind cutaneous manifestations. Some patients with necrolytic acral erythema also have reduced zinc levels (and improve with zinc supplementation) while others have associated hepatitis C viral infections[28]. Likewise, zinc levels can be normal or reduced in patients with necrolytic migratory erythema (NME) as well as EGFR inhibitor-induced NME-like eruptions.

Cutaneous and systemic manifestations respond dramatically to supplementation with elemental zinc (1–2 mg/kg/day in the acquired forms and 3 mg/kg/day for AE). There are several forms of commercially available zinc supplements including zinc sulfate, zinc gluconate, and zinc acetate, and they contain variable amounts of elemental zinc, e.g. 220 mg zinc sulfate tablets contain 50 mg of elemental zinc. Patients with persistent malabsorption syndromes and AE require lifelong zinc supplementation, along with regular serum zinc determinations. Of note, ingestion of excessive amounts of zinc can decrease copper absorption and lead to copper deficiency.

Copper

Copper is an essential trace element that is required for the function of a number of enzymes, e.g. tyrosinase, lysyl oxidase. In the bloodstream, 90% of copper is associated with ceruloplasmin, and the remainder is bound to other plasma proteins, primarily albumin. Acquired copper deficiency is rare, but it has been reported in infants receiving milk low in copper, in protein–energy malnutrition, and as a consequence of excessive zinc intake. Symptoms include anemia, neutropenia, and failure to thrive. Cutaneous findings are limited to rare reports of pigmentary dilution of the skin and hair.

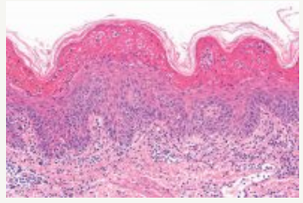
Menkes disease, also known as kinky hair disease, is an X-linked recessive condition characterized by defective copper absorption with low copper levels in the blood, liver, and hair. Affected infants may appear normal and develop normally until 2 to 3 months of age, when they gradually manifest failure to thrive, lethargy, hypothermia, and hypotonia. In addition to seizures and developmental delay, patients may also have anemia and bony abnormalities (similar to those in scurvy). Arteriography demonstrates tortuosity and elongation of arteries, a reflection of immature elastin[29]. Decreased activity of several enzymes, including cytochrome C oxidase (in the brain), lysyl oxidase (in connective tissues and blood vessels), and ascorbic acid oxidase (in bones), may account for the associated clinical findings.

Pudgy cheeks, a cupid's bow of the upper lip, and horizontal eyebrows comprise the typical facies in Menkes disease[30]. However, a more obvious and characteristic finding is alopecia with abnormal hair shafts. There are 180° twists of the hair (pili torti), segmental shaft narrowing (monilethrix), and brush-like swellings of the hair shaft (trichorrhexis nodosa). Hairs are light in color, sparse (Fig. 51.14), fragile, and kinky. Patients may also have diffuse cutaneous pigmentary dilution due to decreased activity of tyrosinase, a copper-dependent enzyme. In addition, obligate female carriers may have patches of swirled

DIFFERENTIAL DIAGNOSIS OF "NUTRITIONAL DERMATITIS"



Evaluation of the infant/child* with periorificial and acral erythema and erosions



Zinc deficiency	Essential fatty acid deficiency	Biotin deficiency	Organic acidurias**	Cystic fibrosis
Acrodermatitis enteropathica (genetic form): • Onset days to weeks after birth if bottle-fed, or after weaning if breastfed **Acquired forms:** • Low zinc level in maternal milk (transient neonatal) • Parenteral nutrition without zinc supplementation • Gastrointestinal disorders/ surgeries or high-fiber diets (high phytate content) causing poor absorption • HIV infection	• Parenteral nutrition without lipid supplementation • Gastrointestinal disorders/ surgeries causing severe fat malabsorption • Nephrotic syndrome	**Biotinidase deficiency:** onset age 3 months to 2 years (juvenile form) **Holocarboxylase synthetase deficiency:** onset days to months after birth (neonatal form) **Acquired forms:** • Parenteral nutrition without biotin supplementation • Gastrointestinal disorders/ surgeries causing severe malabsorption • Excessive intake of raw egg whites • Chronic anticonvulsant therapy (e.g. phenytoin, carbamazepine, valproic acid)	**Propionic acidemia** (propionyl CoA carboxylase deficiency) **Methylmalonic acidemia** (methylmalonyl CoA mutase deficiency or lack of vitamin B_{12} activity) **Maple syrup urine disease** (branched-chain α-ketoacid dehydrogenase deficiency) **Citrullinemia** (argininosuccinic acid synthetase deficiency)	Onset typically at age 3–5 months (precedes respiratory symptoms)
Signs: • Stomatitis, glossitis • Alopecia • Secondary infections (e.g. candidiasis) • Photophobia • Diarrhea • Irritability • Failure to thrive	**Signs:** • Diffusely xerotic skin • Alopecia and lightly pigmented hair • Failure to thrive • Thrombocytopenia	**Signs:** • Alopecia • Blepharitis, conjunctivitis • Secondary infections (e.g. candidiasis) • Vomiting • Metabolic acidosis • Hypotonia, lethargy, seizures, developmental delay • Optic atrophy, hearing loss, ataxia (with biotinidase deficiency)	**Signs:** • Alopecia • Secondary infections (e.g. candidiasis) • Vomiting • Metabolic acidosis • Hypotonia, lethargy, developmental delay • Failure to thrive • Pancytopenia	**Signs:** • Eruption often involves the trunk • +/– Alopecia • No mucous membrane involvement • Diarrhea • Edema • Irritability • Failure to thrive • Palmoplantar aquagenic wrinkling
Laboratory: • Plasma zinc level • Serum alkaline phosphatase level (low) • +/– Zinc level of maternal milk • Genetic analysis	**Laboratory:** • Plasma linoleic, arachidonic and eicosatrienoic acid levels; triene (eicosatrienoic acid): tetraene (arachidonic acid) ratio > 0.4	**Laboratory:** • Plasma ammonia and lactate levels • Urine organic acid analysis • Biotinidase activity in serum • Holocarboxylase synthetase activity in skin fibroblasts or peripheral blood lymphocytes • Genetic analysis	**Laboratory:** • Plasma ammonia and glycine levels • Urine organic acid analysis • Plasma isoleucine level (if on low branched-chain amino acid diet)	**Laboratory:** • Serum albumin level • Plasma zinc level • Sweat test • Genetic analysis

* In older patients, the differential diagnosis includes necrolytic migratory erythema (as seen in glucagonoma syndrome) and necrolytic acral erythema (in association with hepatitis C infection); periorificial (oral and perineal) erythema and erosions can also be seen in niacin (pellagra) and riboflavin deficiencies, with a characteristic photodistributed eruption found in the former; severe infantile seborrheic dermatitis typically involves other intertriginous sites such as the neck as well as the diaper area, scalp, and face

** Cutaneous eruptions may be associated with adherence to a therapeutic diet low in branched-chain amino acids (e.g. isoleucine deficiency)

Fig. 51.13 Differential diagnosis of "nutritional dermatitis" (in addition to exogenous protein–energy malnutrition). *Courtesy Julie V. Schaffer, MD; Photomicrograph Courtesy Luis Requena, MD.*

hypopigmentation or pili torti along the lines of Blaschko, as a result of lyonization.

The clinical features, low serum levels of copper and ceruloplasmin, and microscopic hair shaft findings establish the diagnosis. Infants with Menkes disease have a poor prognosis, with a life expectancy of 3 to 5 years and progressive deterioration leading to death. Treatment with copper histidine is unsuccessful in the majority of patients, but those with mutations leading to reduced, but not absent, copper transport may be more likely to respond to early intervention. Mutations in *ATP7A*, which encodes a copper-transporting ATPase, lead to Menkes



Fig. 51.14 Menkes disease. This child has the characteristic pale skin and sparse kinky hair. *Courtesy Ramón Ruiz-Maldonado, MD.*

disease (as well as occipital horn syndrome; see Ch. 97); therefore, prenatal diagnosis is possible.

Copper toxicity can be acquired or inherited. The acquired form usually results from the ingestion of excessive amounts of copper (e.g. milk boiled in eroded copper pots) and this leads to gastrointestinal symptoms and, occasionally (in predisposed individuals), childhood cirrhosis. The inherited form is Wilson disease, an autosomal recessive disorder characterized by an accumulation of copper within internal organs, in particular the liver, cornea, and brain. Affected individuals have mutations in *ATP7B* which also encodes a copper-transporting P-type ATPase. Dysfunction of this protein leads to an impairment of both intrahepatic trafficking and biliary excretion of copper[30].

Because daily copper intake exceeds the body's requirements, an effective means of excreting excess copper is crucial. This is accomplished by ATP7B, which mediates both copper secretion into plasma (coupled with ceruloplasmin synthesis) and its excretion into bile. When ATP7B is dysfunctional, the presence of excess copper within tissues induces free-radical reactions and lipid peroxidation. Resultant hepatic damage leads to steatosis, inflammation, cirrhosis, and eventually liver failure[31].

The diagnosis of Wilson disease is established by the detection of low serum ceruloplasmin, increased urinary copper excretion, increased hepatic copper content, and/or genetic testing. The clinical hallmarks of Wilson disease are hepatomegaly, cirrhosis, Kayser–Fleischer corneal rings, and neurologic symptoms (dysarthria, dyspraxia, ataxia, and parkinsonian-like extrapyramidal signs).

The chelating agents penicillamine and trientine, which facilitate excretion of copper, are approved for the treatment of Wilson disease. Oral zinc acetate can be prescribed for pre-symptomatic patients or as maintenance therapy, as it blocks intestinal absorption via induction of copper-binding metallothionein within enterocytes, thereby preventing serosal transfer.

Selenium

Selenium, in the form of selenocysteine, is an essential component of several enzymes, including those involved in thyroid hormone metabolism and protection against oxidative damage (e.g. glutathione peroxidase). Deficiency of selenium typically results in a cardiomyopathy as well as muscle pain and weakness due to muscle degeneration; there may also be signs and symptoms of hypothyroidism. Cutaneous manifestations include hypopigmentation of the skin and hair (considered early signs), leukonychia, and xerosis, all of which respond to selenium replacement[32]. There was also a report of erythematous scaly papules and plaques involving the cheeks, hips, thighs, and popliteal fossae, along with erosions in the diaper area[33]. Elevated serum levels of creatine kinase and transaminases are often present in selenium deficiency as well.

Selenium deficiency has been reported in patients receiving total parenteral nutrition and in those who live in areas where the soil content of selenium is poor[34]. Low serum levels of selenium and glutathione peroxidase activity are indicative of selenium deficiency. The recommended replacement dosage in selenium-deficient patients is a maximum of 100–200 mcg/day, and the Recommended Dietary Allowance (RDA) is 55 mcg/day for adults and 15 mcg/day for infants.

Although controversial, over-supplementation can occur due to reported beneficial cardiovascular and anticancer effects of selenium[35]. If supplements are taken, they should not exceed 200 mcg/day. Excessive selenium ingestion (e.g. supplements, Brazil nuts, selenium-enriched green tea) can produce selenosis in humans, leading to a peripheral neuropathy, dermatitis, facial flushing, alopecia, discolored or brittle nails, nausea and vomiting as well as a garlic-like breath odor. The use of selenium sulfide shampoo in large areas of eroded or ulcerated skin may lead to excessive absorption, with loss of appetite and tremor.

Anorexia Nervosa and Bulimia (Nervosa)

Anorexia nervosa and bulimia nervosa are eating disorders characterized by starvation, excessive exercise, self-induced vomiting, and/or abuse of medications (e.g. laxatives, diuretics). Both can result in primary and secondary nutritional deficiencies. Anorexia nervosa is a persistent unwillingness or inability to maintain adequate body weight, whereas patients with bulimia typically binge-eat then purge or fast. These disorders occur most commonly in adolescent girls and young adult women, but can affect both sexes and all age groups. Skin disorders, either real or perceived, are common in these patients and women in particular report a greater dissatisfaction with the appearance of their skin when compared to a similar cohort[36].

The dietary changes and starvation associated with anorexia nervosa and bulimia can lead to telogen effluvium, lanugo-like hair, xerosis, generalized pruritus, carotenoderma (see Fig. 51.10), and hyperpigmentation. In addition, patients can develop acrocyanosis, perniosis, and livedo reticularis. Signs of specific nutritional deficiencies (e.g. pellagra, scurvy) may be present, as well as poor wound healing, seborrheic dermatitis, and edema[37]. Additional clues to the diagnosis include petechiae, interdigital intertrigo, paronychia, and particularly calluses or scars on the knuckles or dorsal surface of the hand (Russell's sign) due to repeated self-induced vomiting over prolonged periods of time (Fig. 51.15). Patients with bulimia may also have enlarged salivary glands and erosion of their tooth enamel. Psychiatric and nutritional support must be instituted as severe malnutrition is common.

Obesity

Obesity, whether acquired or inherited, is defined as a body mass index (BMI; measured in kg/m^2), that is >30; the latter has been found to correlate with high levels of the adipokine leptin[38]. Genetic disorders such as Prader–Willi, Bardet–Biedl, Alström, and Wilson–Turner syndromes have been associated with childhood-onset obesity. In addition, endocrine disorders such as Cushing disease, Cushing syndrome, and insulin resistance include obesity amongst their clinical manifestations.

Acquired obesity is at epidemic proportions in both adults and children in industrialized nations. Although paradoxical, it is a functional malnutrition due to the consumption of high-caloric foods that are low in nutrients. Obesity is a systemic disease, as evidenced by an increased incidence of hypertension, hyperglycemia and hyperlipidemia, components of the metabolic syndrome (see Table 53.5), as well as atherosclerotic cardiovascular disease and premature death. Cutaneous manifestations are nonspecific, but some of the more common findings, such as acanthosis nigricans, appear to be related to insulin resistance (see Fig. 51.15)[39].

Bariatric Surgery and Gastrointestinal Malabsorption

The increase in acquired obesity has led to an increase in the number and types of bariatric surgery performed. Due to subsequent alterations in gastrointestinal absorption, post-bariatric surgery patients are at risk for developing nutritional deficiencies. Two of the more commonly performed surgeries are laparoscopic adjustable gastric banding and the Roux-en-Y gastric bypass. Because the normal absorptive surface is left intact with the former, nutrient deficiencies in these patients are rare. On the other hand, the Roux-en-Y gastric bypass procedure reduces stomach size and, as a result, there are lower levels of intrinsic factor, gastrin, hydrochloric acid, and pepsinogen, which lead to a reduction in protein digestion. The Roux-en-Y procedure also decreases the physical grinding of food that typically helps to release vitamins and minerals. Abnormally low levels of micronutrients, such as iron, zinc, copper, and vitamins A, E, B_9 (folate), and B_{12}, may be seen in these patients, and long-term monitoring is required, as it may take months or years for signs and symptoms to appear[40,41].

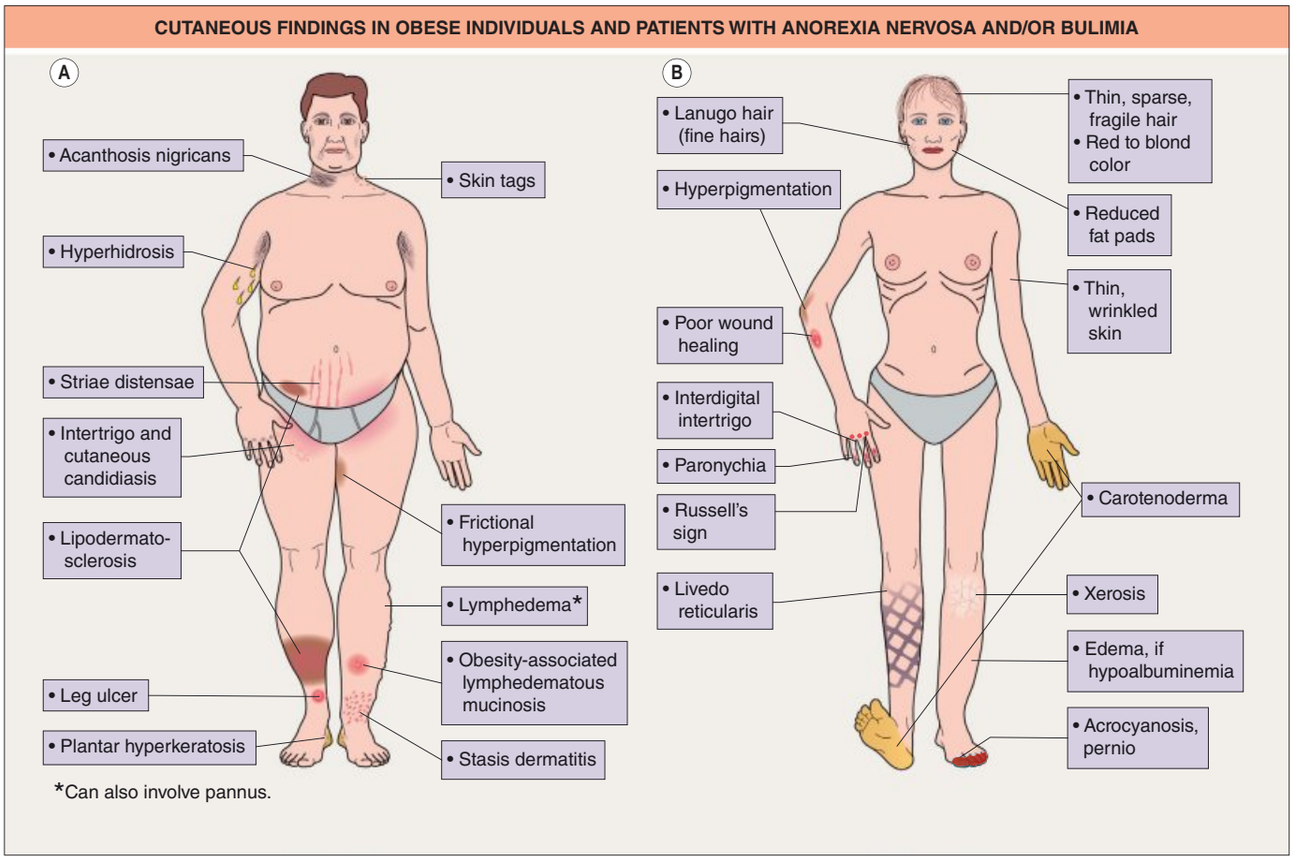


Fig. 51.15 Cutaneous findings in obese individuals (A) and patients with anorexia nervosa and/or bulimia (B). Russell's sign consists of calluses or scars on the knuckles or dorsal surface of the hand due to repeated self-induced vomiting over prolonged periods of time. See Fig. 51.2 for signs of nutritional deficiencies.

In disorders such as Crohn disease that are associated with gastrointestinal malabsorption, at least 50% of patients may have low plasma concentrations of vitamin C, copper, niacin, and zinc[42].

PATHOLOGY

Nutritional deficiencies generally occur in combination; therefore, the resultant pathologic changes are often very variable. Although nutritional diseases have been better studied biochemically than structurally, there are several helpful histologic clues, including necrosis of the upper one-third of the epidermis (see Fig. 51.12G). This distinctive reaction pattern has been reported in pellagra, acrodermatitis enteropathica, acquired zinc deficiency, and necrolytic migratory erythema. In the early stages, there is pallor and ballooning of the upper half of the epidermis. This stage is followed by the development of acanthosis, with confluent hyperkeratosis and degenerative features of the upper epidermal layers. In the late stages, the pallor of the upper epidermis is usually missing[43]. In protein–energy malnutrition, nonspecific histologic features are seen, such as epidermal atrophy and hyperkeratosis.

Hair is a superb model of growth and differentiation. In some patients, histologic study of the hair matrix and hair shaft may provide evidence of moderate to severe degrees of protein–energy malnutrition[44].

DIFFERENTIAL DIAGNOSIS

Nutritional dermatoses rarely result from the deficiency of a single nutrient, element, or vitamin as multiple deficiencies often coexist. A high index of suspicion is required in that clinical manifestations are often nonspecific and, in mild to moderate deficiencies, somewhat subtle. A few specific deficiencies do have characteristic mucocutaneous and systemic features that can be accurately recognized by the experienced clinician. Suspected deficiencies can usually be confirmed via laboratory analysis (see Table 51.2), and they readily respond to the administration of the deficient nutrient, element, and/or vitamin.

TREATMENT

The treatment of nutritional diseases must be individualized, taking into account the likelihood of multiple deficiencies of both macro- and micronutrients. The recommended treatment for specific nutritional diseases is reviewed in this chapter, but management frequently requires a multidisciplinary approach.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 51.1 Kwashiorkor. This child's arm has edema and superficial epidermal necrosis with a "flaky paint" appearance. *Courtesy Ramón Ruiz-Maldonado, MD.*



eFig. 51.2 Kwashiorkor. Edema, ulceration, and shellac-like scale that resembles peeling paint.



eFig. 51.3 Kwashiorkor. Edema and shellac-like scale in a child on a vegan diet. *Courtesy Jeff Gehlhausen, MD, PhD.*



eFig. 51.4 Vitamin A deficiency. Blindness due to vitamin A deficiency and corneal scarring. *Courtesy Peter Ehrnstrom, MD.*



eFig. 51.5 Pellagra. The photodistribution of erythema (**A**), erythema plus shiny desquamation (**B**), and erythema plus bullae (**C**) is apparent. Note the sparing under the watchband and shoes. *Courtesy Luis Requena, MD.*



eFig. 51.6 Pellagra. Hyperpigmented desquamation of the distal lower extremity. Note the shiny shellac-like appearance on the lateral ankle.



eFig. 51.8 Acrodermatitis enteropathica. A Erosive plaques of the buttocks and perianally. **B** Erosive plaques of the toes. *Courtesy Julie V. Schaffer, MD.*



eFig. 51.9 Acrodermatitis enteropathica. A Perioral and perinasal erosive plaques with desquamation and crusting in an infant. **B** Erythema with erosions and scale-crust that favors acral sites. *A, Courtesy A. Hernández-Martín, MD.*



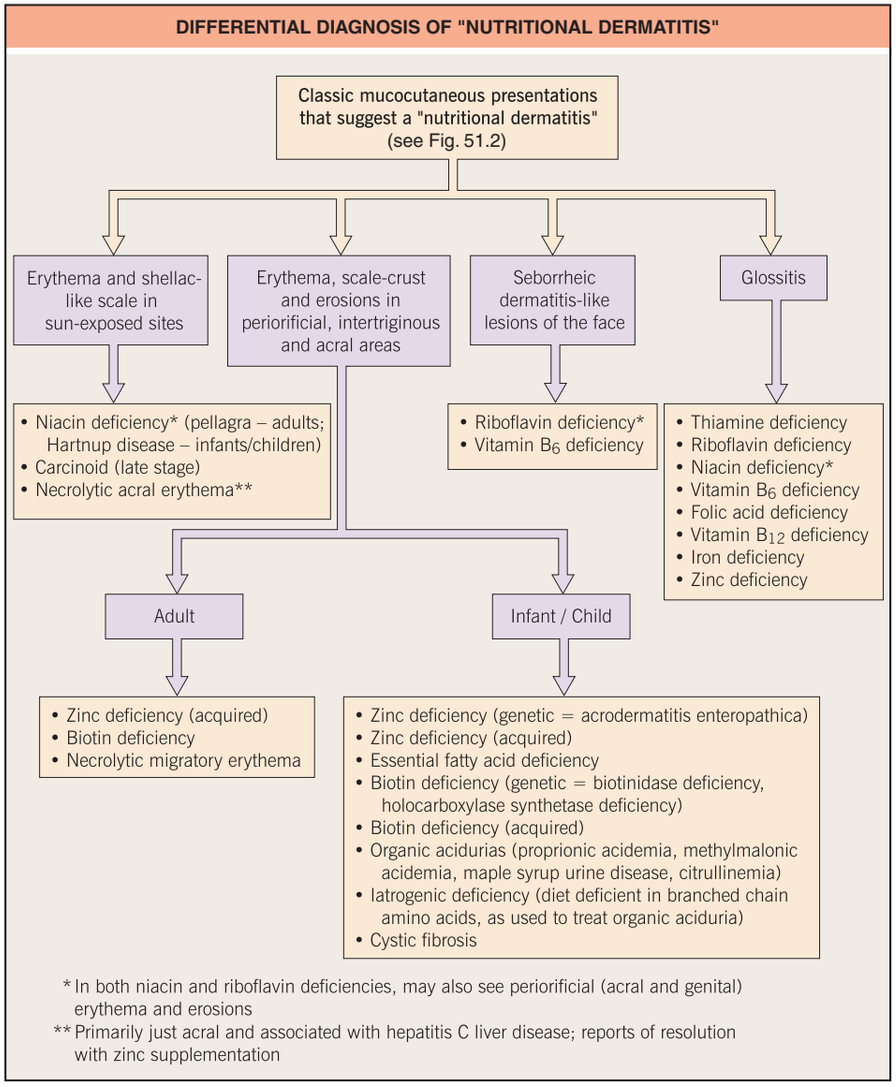
eFig. 51.7 Carotenoderma. Yellow–orange discoloration of the extensor elbows in an 8-year-old whose diet consisted primarily of pureed carrots due to numerous dental extractions. *Courtesy Edward Cowen, MD.*



eFig. 51.10 Acquired zinc deficiency. Erythematous plaques with scaling and a few erosions near one oral commissure in an adult. The latter are a clue that this is not simply seborrheic dermatitis. *Courtesy Luis Requena, MD.*



eFig. 51.11 Acquired zinc deficiency. A, B The findings within flexural areas are more subtle in this patient. **C** There is also nail dystrophy – thickening, yellow discoloration, loss of cuticle.



eFig. 51.12 Differential diagnosis of "nutritional dermatitis".

Graft-versus-Host Disease 52

Jennifer T. Huang and Edward W. Cowen

Key features

- Currently, over 35 000 allogeneic hematopoietic stem cell transplants (HSCTs) are performed worldwide each year
- An HLA-matched sibling donor is the ideal donor source
- Nowadays nearly all eligible patients can receive an allogeneic HSCT due to the increased use of alternative stem cell sources including matched unrelated donors, haploidentical donors, and umbilical cord blood
- Reduced intensity conditioning regimens allow older patients and those with comorbidities to receive allogeneic HSCTs
- Donor lymphocyte infusions as well as withdrawal of immunosuppression may impact the incidence, timing, and presentation of graft-versus-host disease (GVHD)
- Acute GVHD is a major complication of allogeneic HSCT; severe skin involvement, although uncommon, is associated with a high mortality rate
- Chronic cutaneous GVHD is a polymorphous condition with features that can resemble lichen planus, lichen sclerosus, morphea, and eosinophilic fasciitis
- Chronic cutaneous GVHD is difficult to treat and the aggressiveness of treatment must be balanced against the complications of chronic immunosuppression

INTRODUCTION

Graft-versus-host disease (GVHD) is a multi-organ disorder most commonly due to the transfer of foreign donor hematopoietic stem cells into a host recipient via an allogeneic hematopoietic stem cell transplant (HSCT). GVHD may also occur following transfusion of non-irradiated blood products (to immunocompromised hosts) or rarely in the setting of solid organ transplantation. Despite decades of experience with HSCT for a broadening array of disorders (Table 52.1), GVHD remains a significant cause of non-relapse-related morbidity and mortality.

HISTORY

The first successful allogeneic bone marrow transplant was performed in 1968. Subsequent advances in histocompatibility antigen testing increased safety, while establishment of bone marrow donor registries made HSCT accessible to thousands of patients each year who lacked a matched related donor. The introduction of alternative stem cell sources, including matched unrelated donors and especially haploidentical family donors, has led to a further increase in the number of transplants. In addition, when neither of these donor sources is available, umbilical cord stem cells represent a more universal option because a greater degree of mismatch is better tolerated. The evolution of reduced intensity conditioning regimens has permitted older patients and those with comorbidities to receive HSCTs. Post-transplant cyclophosphamide, initially introduced for haploidentical HSCTs, is increasingly being used for matched sibling and matched unrelated donor (MUD) HSCTs where it has significantly reduced the incidence and severity of acute and chronic GVHD.

EPIDEMIOLOGY

Currently, over 35 000 allogeneic HSCTs are performed worldwide each year. Although a variety of donor and recipient factors ultimately impact GVHD incidence (e.g. older age, T cell-replete graft), the most important predictor of GVHD remains HLA compatibility between donor and recipient. With traditional immunosuppression consisting of a calcineurin inhibitor plus either methotrexate or mycophenolate mofetil, ~40% of HLA-identical HSCT recipients and 60%–70% of HLA-mismatched HSCT recipients will develop GVHD. Of note, post-transplant cyclophosphamide (given on days +3 and +4) significantly reduces the incidence and severity of acute and chronic GVHD via enrichment of regulatory T cells. In addition, abatacept has recently been approved for prophylaxis against acute GVHD.

Because of ease of acquisition and more rapid engraftment, peripheral blood has surpassed bone marrow as the predominant source of stem cells. The one disadvantage is that peripheral blood has been associated with an increased risk of chronic GVHD (cGVHD)[1]. Cord blood stem cells are used primarily in children because of higher rates of non-engraftment in adults. The two major advantages of cord blood transplantation are: (1) decreased incidence of GVHD; and (2) nearly universal availability of donors for patients who lack matched related or unrelated donors.

Several other trends in HSCT are affecting the natural history of GVHD. Removal of donor T cells ("T cell depletion") prior to transplantation through *ex vivo* graft manipulation (e.g. cell separation), or *in vivo* treatment of the recipient (e.g. antithymocyte globulin, alemtuzumab), significantly decreases the risk of GVHD, but at the expense of increased infection rates. The advent of reduced intensity conditioning regimens has decreased conditioning-related toxicities (e.g. mucositis) and allowed for HSCT in older patients and those with comorbidities. While these regimens appear to decrease the risk of acute GVHD (aGVHD), they may also delay the appearance of "classic" aGVHD manifestations. The use of total body irradiation for conditioning (in place of or in conjunction with chemotherapy) may confer an increased risk for the later development of cGVHD[2]. Finally, donor lymphocyte infusions (DLI), administered to the recipient post-HSCT to augment the graft-versus-tumor effect or to attempt to reverse falling donor chimerism, can alter the traditional timing of both "acute" and "chronic" disease. For instance, DLI may induce classic aGVHD manifestations even when administered after the 100-day time period.

PRIMARY DISORDERS TREATED WITH ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION
• Leukemias (e.g. acute myelogenous, acute lymphoblastic > chronic myelogenous, chronic lymphocytic)
• Lymphomas (e.g. non-Hodgkin)
• Bone marrow failure (e.g. aplastic anemia, dyskeratosis congenita, Fanconi anemia)
• High-risk myelodysplasia
• Immunodeficiencies (e.g. severe combined immunodeficiency, Griscelli syndrome [type 2], Chédiak–Higashi syndrome, Wiskott–Aldrich syndrome, ataxia–telangiectasia syndrome, chronic granulomatous disease, DiGeorge syndrome, familial hemophagocytic lymphohistiocytosis, GATA2 deficiency, DOCK8 immunodeficiency syndrome)
• Other myeloproliferative disorders (e.g. myelofibrosis)
• Other hematologic disorders (e.g. plasma cell dyscrasias including myeloma, hypereosinophilic syndrome, paroxysmal nocturnal hemoglobinuria, sickle cell disease, thalassemia)
• Metabolic disorders (e.g. fucosidosis, Gaucher disease, mucopolysaccharidoses)
• Autoimmune diseases (e.g. ALPS, IPEX syndrome)
• Miscellaneous (e.g. congenital erythropoietic porphyria [Günther disease], histiocytoses, epidermolysis bullosa)

Table 52.1 Primary disorders treated with allogeneic hematopoietic stem cell transplantation. ALPS, autoimmune lymphoproliferative syndrome; IPEX, immune dysregulation, polyendocrinopathy, X-linked.

The skin is the most frequently affected organ in both aGVHD and cGVHD. Approximately 80% of patients who develop aGVHD have skin involvement at the time of diagnosis[3]. The incidence of skin involvement in patients with cGVHD ranges from 30%–40%[4]. In one institutional review of 270 consecutive patients following HLA-identical HSCT, only 7 (13%) of 53 patients with cGVHD manifested sclerotic features[5]. In contrast, in a cross-sectional cohort of 206 NIH cGVHD patients enriched for refractory disease, sclerotic features were detected in 109 (53%)[2].

PATHOGENESIS

The current model for aGVHD pathogenesis can be summarized in a three-step process. First, HSCT conditioning and consequent damage to host tissues leads to activation of *host* antigen-presenting cells (APCs). Second, *donor* T cells proliferate in response to contact with activated APCs. Finally, destruction of target tissues (skin, liver, gastrointestinal tract) occurs via cytotoxic T lymphocytes, natural killer cells, and soluble factors (TNF, IFN-γ, IL-1, nitric oxide)[6]. Recently, humanized mouse models have demonstrated that *donor* APC activation of *host* resident T cells can also elicit a graft-versus-host response. These two proposed mechanisms may not contradict, but rather complement, one another and suggests multiple pathways of disease pathogenesis.

A clear understanding of cGVHD is still lacking and available murine models recapitulate only select features of human disease (e.g. sclerotic skin involvement, autoantibodies). Alloreactive T cells are again thought to play a central role, but a number of other immune mediators have been increasingly implicated. Many cGVHD manifestations resemble autoimmune disease, suggesting a role for B cells in the disease process. Indeed, rituximab (anti-CD20 antibody) is a beneficial salvage therapy in some patients. B cells appear to prime T cells to minor histocompatibility antigens, and serum levels of *B* cell *a*ctivating *f*actor of the TNF *f*amily (BAFF), a marker of B cell activation, correlate with cGVHD. Multiple autoantibodies are often present in patients with cGVHD, including anti-nuclear, anti-dsDNA, and anti-smooth muscle antibodies, although, to date, they have not been shown to correlate with specific disease manifestations. Activating antibodies against the platelet-derived growth factor receptor (PDGFR) were observed in patients with cGVHD, suggesting that targeting this receptor and its profibrotic pathway with agents such as imatinib mesylate could improve cGVHD[7]. However, the functional significance of these antibodies remains uncertain[8].

HSCT recipients have also been shown to have a deficiency of regulatory T cells (Tregs) due to decreased thymic differentiation. Tregs are integral to the development and maintenance of self-tolerance, and impairment of Treg function is associated with autoimmunity. In mouse models of allogeneic HSCT, adoptive transfer of Tregs has been shown to ameliorate signs and symptoms of cGVHD[9]. A possible role for Th17 cells was suggested by elevated levels of IL-17 and -22 in tissue and plasma in patients and mouse models of cutaneous cGVHD[10,11] and IL-17 inhibitors have been investigated as treatment for cGVHD[12]. Of note, different mechanisms may underlie cGVHD based on duration and phenotype of disease[13].

CLINICAL FEATURES

Acute GVHD

Acute GVHD presents in the skin as a morbilliform exanthem (Fig. 52.1), with an initial predilection for acral areas (e.g. dorsal hands and feet, palms, soles, forearms, ears), as well as the upper trunk. Lesions most commonly appear 4–6 weeks following HSCT despite prophylactic immunosuppressive therapy. Pruritus is variable and a folliculocentric pattern may be observed. Patients may be thrombocytopenic, which can give the eruption a hemorrhagic appearance. The gastrointestinal tract (nausea, voluminous diarrhea, abdominal pain) and the liver (cholestasis > transaminitis) are the two other primary organ systems affected by aGVHD. Together with body surface area of skin involvement, these manifestations are used for staging and grading of disease severity (Table 52.2). Stage IV acute skin disease consists of generalized involvement with bullae formation which may lead to skin sloughing resembling toxic epidermal necrolysis and portends a very low likelihood of survival. Fortunately, this degree of severity is nowadays rarely seen.

Chronic GVHD

In contrast to aGVHD, cGVHD may manifest in nearly any organ system (Fig. 52.2). Skin and mucosal involvement are exceedingly common, but there is remarkable variability in both presentation and severity. Other common sites of involvement include the eyes (keratoconjunctivitis sicca, blepharitis, corneal erosions), salivary glands (sicca syndrome), and lungs (bronchiolitis obliterans); less commonly, the esophagus (strictures, webs), liver, and pancreas (exocrine insufficiency) are affected.



Fig. 52.1 Clinical spectrum of acute cutaneous graft-versus-host disease. A *Stage I* – discrete and coalescing small pink papules on the upper chest and neck of a woman 6 weeks following allogeneic bone marrow transplant. **B, C** *Stage II* – pink macules and papules on the dorsal aspect of the hands that are becoming confluent 4 weeks post allogeneic bone marrow transplant, and widespread pink–violet macules and papules on the abdomen in a liver transplant recipient. **D** *Stage III* – diffuse erythema with desquamation, but without bullae formation. **E** *Stage IV* – widespread bullae and epidermal necrosis in a patient who had received a donor lymphocyte infusion (DLI) following allogeneic bone marrow transplant; note the resemblance to toxic epidermal necrolysis. *C, Courtesy Julie V. Schaffer, MD.*

CLINICAL STAGING OF ACUTE GRAFT-VERSUS-HOST DISEASE (aGVHD)			
Stage	**Skin**	**Liver**	**Gut**
1	Erythematous macules and papules, <25% BSA	Bilirubin 2 to <3 mg/dl	Diarrhea, 500–1000 ml/day, or persistent nausea
2	Erythematous macules and papules, 25%–50% BSA	Bilirubin 3–6 mg/dl	Diarrhea, 1000–1500 ml/day
3	Erythematous macules and papules (>50% BSA) to generalized erythroderma	Bilirubin 6–15 mg/dl	Diarrhea, >1500 ml/day
4	Generalized erythroderma with bulla formation	Bilirubin >15 mg/dl	Severe abdominal pain with or without ileus

Table 52.2 Clinical staging of acute graft-versus-host disease (aGVHD). Grade I aGVHD represents stage 1 or 2 cutaneous aGVHD while grade II aGVHD represents stage 3 cutaneous aGVHD; neither grade I nor II have significant liver or gut involvement. Grades III and IV aGVHD require internal involvement. BSA, body surface area.

DIAGNOSTIC MUCOCUTANEOUS MANIFESTATIONS OF CHRONIC GRAFT-VERSUS-HOST DISEASE
Skin
Lichen planus-like (Fig. 52.3A)
Lichen sclerosus-like (Fig. 52.3B)
Morphea-like (Fig. 52.3C,D)
Scleroderma-like (Fig. 52.3F)
Fasciitis (Fig. 52.4)
Poikiloderma
Oral mucosa
Keratotic plaques
Lichen planus-like (Fig. 52.6B)
Restriction of oral opening from sclerosis
Genital mucosa
Lichen planus-like (Fig. 52.6A)
Vaginal scarring and/or stenosis

Table 52.3 Diagnostic mucocutaneous manifestations of chronic graft-versus-host disease (based on NIH Consensus Criteria[14]). For involvement of other organs, see Fig. 52.2.

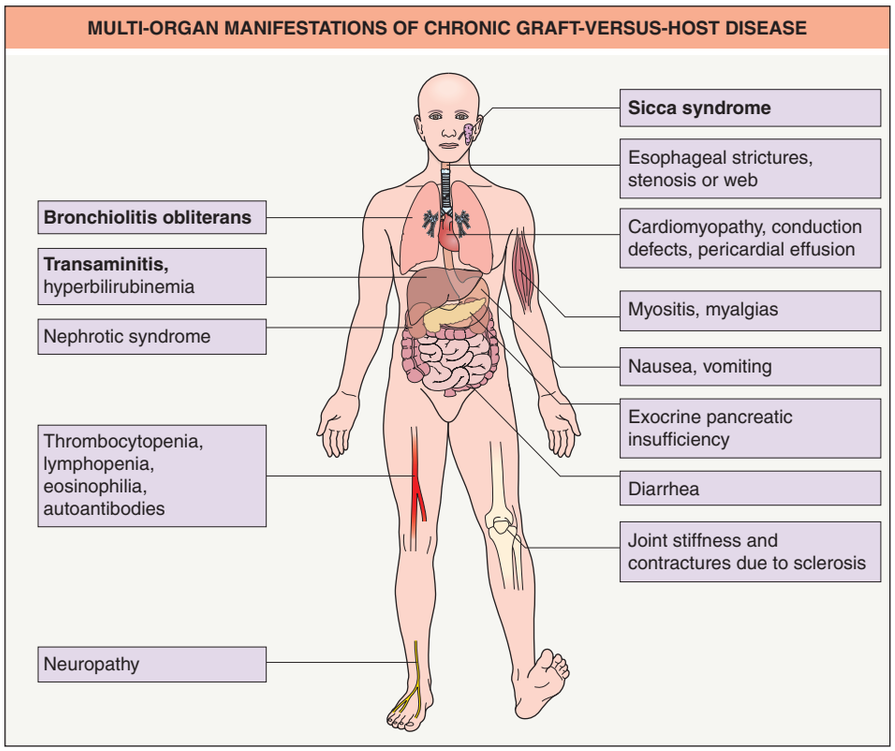


Fig. 52.2 Protean multi-organ manifestations of chronic graft-versus-host disease. The most common manifestations are in **bold**.

In the past, differentiation of aGVHD and cGVHD was linked to time of onset following HSCT (≤ or >100 days); however, this is a somewhat arbitrary distinction and newer HSCT regimens have altered the onset of classic aGVHD and cGVHD manifestations. As a result, acute features may first present after day 100 (delayed acute GVHD). In addition, features of aGVHD can be seen in patients who also meet the diagnostic criteria for cGVHD and is referred to as overlap cGVHD. The NIH Consensus Project proposed a classification of cGVHD using organ-specific criteria[14]. "Diagnostic" criteria, i.e. those skin manifestations sufficient to make a clinical diagnosis of cGVHD, are provided in Table 52.3. "Distinctive" cGVHD criteria (e.g. papulosquamous lesions, vitiligo, alopecia) require exclusion of other possible etiologies.

The most characteristic manifestation of epidermal cGVHD involvement is reticulate pink to violaceous papules and plaques with overlying scale, which in some patients resembles lichen planus (LP; Fig. 52.3A). Lesions often initially involve the dorsal aspects of the hands and feet, the forearms and trunk, but they can become widespread. In the past, the term "lichenoid" was used as a broad term which encompassed this presentation as well as all other non-sclerotic cGVHD skin eruptions. In light of the greater appreciation for the breadth of clinical presentations of cutaneous cGVHD and to utilize more precise diagnostic terminology, the term "lichenoid" should be reserved for histologic description rather than as designation of a GVHD phenotype. In addition to LP-like lesions, psoriasiform plaques, keratosis pilaris-like follicular erythema, a subacute cutaneous LE-like eruption, or poikiloderma may develop (Table 52.4). Epidermal cGVHD involvement often leaves a remarkable patterned hyperpigmentation which is often reticulated and resolves very slowly over several months.

Similar to the use of "lichenoid", the single designation "sclerodermoid" cGVHD is inadequate to describe the spectrum of sclerotic skin and subcutaneous tissue presentations. Sclerotic involvement includes superficial lichen sclerosus-like plaques, localized or widespread morphea-like involvement, and subcutaneous rippling of the skin with joint contractures resembling eosinophilic fasciitis[15]. Lichen sclerosus-like involvement commonly presents as shiny, wrinkled, gray–white plaques on the upper back (Fig. 52.3B); there may be associated follicular plugging. Morphea-like (morpheaform) areas of sclerosis may occur anywhere on the body, but frequently localize to sites of previous



Fig. 52.3 Clinical spectrum of chronic cutaneous graft-versus-host disease. A Lichen planus-like: thin pink–violet papules and plaques with scale, admixed with postinflammatory hyperpigmentation. **B** Lichen sclerosus-like: multiple gray–white thin plaques with obvious wrinkling are present on the mid back. **C, D** Morphea-like: shiny, hyperpigmented, sclerotic plaques extending from the breasts to the lateral torso and in the girdle area; the latter is a common site of involvement for this form of cGVHD. **E** Morphea-like: sclerotic hyperpigmented plaque on the upper arm, with shiny bound-down skin of the forearm and dorsal hand; note the joint contractures. **F** Scleroderma-like: the skin is shiny and bound-down with dyspigmentation, hair loss, multiple erosions and ulceration; angiomatous nodules and marked reduction in range of motion of the ankles are also present.

ADDITIONAL CUTANEOUS MANIFESTATIONS OF CHRONIC GRAFT-VERSUS-HOST DISEASE (cGVHD)
Skin lesions
• Psoriasiform, eczematous/dyshidrotic, SCLE-like, pityriasis rosea-like • Eczema craquelé, ichthyosis-like, keratosis pilaris-like follicular erythema • Hypo- or hyperpigmentation, vitiligo (Fig. 52.5A) • Angiomatous nodules (Fig. 52.3F) • Calcinosis cutis
Hair
• New-onset alopecia (patchy > diffuse; scarring or non-scarring; Fig. 52.5B), alopecia areata • Premature graying
Nails
• Ridging, thinning, splitting, brittleness, onycholysis, dorsal pterygium, anonychia (Fig. 52.5C)
Oral mucosa
• Gingivitis, mucositis, pseudomembranes, ulcers (Fig. 52.6B) • Xerostomia*, mucosal atrophy, mucocele
Genital mucosa
• Fissures, erosions, ulcers, balanitis, phimosis (Fig. 52.6C)
*For xerostomia treatment regimen, see Table 45.5.

Table 52.4 Additional cutaneous manifestations of chronic graft-versus-host disease (cGVHD). These clinical findings are considered non-diagnostic, i.e. insufficient to establish a diagnosis of chronic GVHD without further testing or evidence of other organ system involvement. SCLE, subacute cutaneous lupus erythematosus.



Fig. 52.4 Eosinophilic fasciitis-like presentation of chronic cutaneous graft-versus-host disease. A rippled appearance and irregular nodular texture to the skin is indicative of involvement of subcutaneous tissues. Especially in the earlier, edematous phase, the presence of hypereosinophilia may be a clue to the diagnosis.

skin injury (e.g. port placement sites) as well as areas of friction (e.g. the waistband) (Fig. 52.3C–E). In young children, the diaper area can be the initial area of involvement. In contrast to systemic sclerosis, cGVHD is rarely associated with sclerodactyly, pinched facies, or Raynaud phenomenon[15]. Deep-seated fibrosis of the subcutaneous tissue and fascia may present with insidious loss of joint range-of-motion or as nonspecific myalgias and cramping. Subtle rippling of the overlying skin may be present with a firm, nodular texture noted with deep palpation (Fig. 52.4). Linear depressions within sites of fascial involvement (groove sign) demarcate the path of vascular structures or fascial bundles. Longstanding fibrosis may result in skin ulceration, particularly of the legs and frictional surfaces, and the proliferation of benign angiomatous nodules[16] (Fig. 52.3F).

Vitiligo can develop within skin affected by cGVHD as well as uninvolved skin. It occurs in 1%–2% of patients who have had an HSCT and ~5% of patients with cGVHD[17,18]. The presence of vitiligo should alert the clinician to examine for additional evidence of cGVHD (Fig. 52.5A,B).

Mucosal surfaces are frequently affected by cGVHD (Fig. 52.6). Oral involvement resembles LP with lacy white plaques on the non-attached mucosa, ulceration, and gingivitis. Cheilitis is also a common manifestation (see Figs. 72.15 & 72.16F) and the development of mucoceles is an additional clinical finding. Genital involvement, ranging from



Fig. 52.5 Additional cutaneous findings in chronic graft-versus-host disease. **A** Vitiligo with patches of amelanosis; note the nail dystrophy. **B** Scarring alopecia and vitiligo in the setting of extensive sclerotic cGVHD. **C** Nail thinning, splitting, and dorsal pterygium formation.

erythema and fissuring to labial resorption and fusion, can occur in as many as 50% of female patients[19]. Symptoms of burning, pruritus, and dyspareunia are common. Scarring of the vagina may lead to shortening and narrowing of the vaginal canal and risk of hematocolpos in menstruating women. Male genital involvement is less common, but includes balanoposthitis and lichen planus-like lesions, and phimosis may develop in some patients.

Nail changes in cGVHD range from thin, brittle nails with distal splitting to dorsal pterygium and anonychia (Fig. 52.5C). In children, nail dystrophy, particularly dorsal pyterygium, has been associated with pulmonary cGVHD[20]. Additional cutaneous findings include facial milia, alopecia areata, angiomatous nodules, scarring alopecia, and calcinosis cutis. The latter three entities are seen in patients with sclerotic disease and calcinosis cutis may contribute to decreased range of motion[21].

PATHOLOGY

Histologically, aGVHD is characterized by widespread keratinocyte necrosis, basal layer hydropic degeneration, and a band-like lymphohistiocytic infiltrate in the upper dermis (Fig. 52.7). However, skin biopsies obtained shortly after disease onset may display more subtle findings, e.g. only focal vacuolar change of basal keratinocytes, and histologic features of aGVHD may be limited to the hair follicle. In addition, these histologic features overlap with those of viral exanthems and drug eruptions, making a definitive diagnosis difficult to render in some patients. With increasing severity of aGVHD, basilar vacuoles can fuse to form clefts and microvesicles and even complete separation of epidermis from dermis.

The histology of cGVHD reflects the variable skin manifestations of the condition[22]. cGVHD with epidermal involvement may resemble aGVHD, but with a more robust lichenoid infiltrate and additional features of epidermal orthohyperkeratosis, hypergranulosis, and variable (usually mild) acanthosis. The sclerotic subtypes of cGVHD may have concurrent epidermal features or may only demonstrate sclerosis of the dermis (Fig. 52.8), subcutaneous tissue, and/or fascia. Thickening of subcutaneous fat septae indicates a deep-seated sclerosis and magnetic resonance imaging may be helpful to identify fascial involvement (Fig. 52.9).

DIFFERENTIAL DIAGNOSIS

The primary differential diagnosis of aGVHD is morbilliform drug eruption, viral exanthem, and engraftment syndrome (Table 52.5). If there is prominent acral involvement, particularly involvement of the palms and soles, toxic erythema of chemotherapy should be considered, especially if there is flexural involvement and in men, scrotal burning and erythema. The possibility of a viral exanthem is more likely in children and is favored if conjunctivitis, rhinorrhea, or cough are present. Engraftment syndrome often presents with fever and fluid overload, including pulmonary edema, at the time of neutrophil engraftment (see Table 52.5).

Because of its clinical variability, the differential diagnosis of cGVHD is much broader, and includes lichenoid drug eruptions, autoimmune connective tissue diseases (lupus, dermatomyositis, morphea, systemic sclerosis), and papulosquamous disorders. Reports of transient acantholytic dermatosis[23] and voriconazole-associated photosensitivity[24] misdiagnosed as cGVHD emphasize the value of biopsy confirmation when non-diagnostic clinical features are encountered.

TREATMENT

Acute GVHD

Limited cutaneous aGVHD (without other organ involvement) may initially be managed with topical corticosteroids while patients with more extensive skin involvement or internal manifestations require systemic treatment. First-line therapy consists of adding oral prednisone or IV methylprednisolone (0.5–1 mg/kg twice daily) to ongoing prophylactic GVHD therapy (usually a systemic calcineurin inhibitor plus either methotrexate or mycophenolate mofetil). This treatment approach results in disease control in ~50% of patients. Recently, the JAK inhibitor ruxolitinib was FDA-approved for steroid-refractory aGVHD and represents the preferred second-line therapy[25]. Increasingly it is being used as a steroid-sparing agent earlier after the diagnosis of aGVHD. Third-line therapies include other immunomodulatory agents such as TNF antagonists, but they are associated with an increased risk of infections. Unfortunately, until the recent introduction of ruxolitinib, patients who did not respond well to corticosteroid therapy were at high risk of mortality.



Fig. 52.6 Orogenital involvement in chronic cutaneous graft-versus-host disease. A, B Lichen planus-like: flat-topped violet papules on the penis and several ulcers on the tongue with a lacy white pattern on the upper vermilion lip and the distal dorsal tongue. **C** Severe erosive disease of the vulva, with nearly total resorption of the labia minora and agglutination of the lips of the clitoral hood. The vulvar introitus is also markedly narrowed. *B, Courtesy Jean L. Bolognia, MD.*

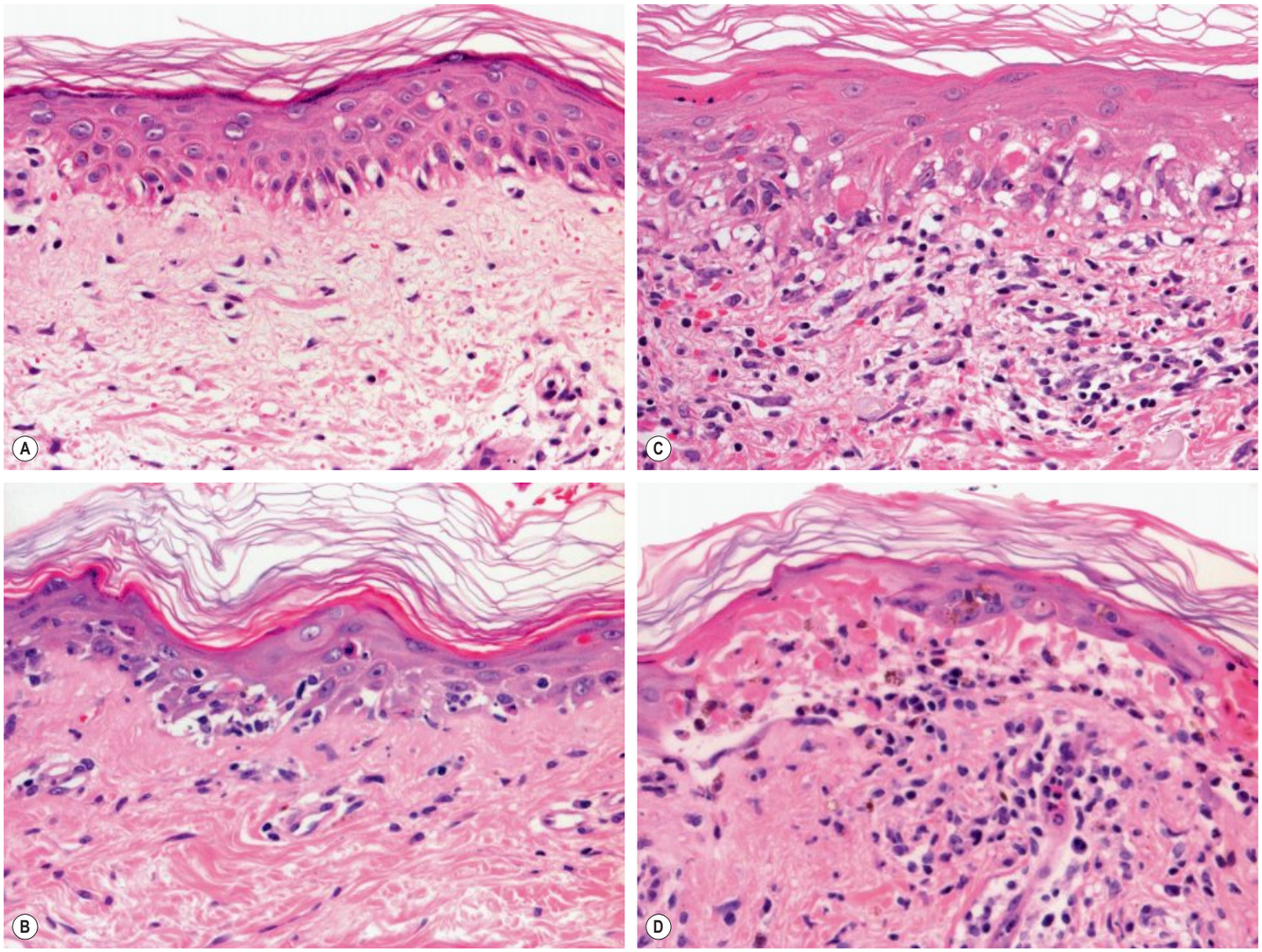


Fig. 52.7 Acute cutaneous graft-versus-host disease – histopathologic grades. A Grade I: focal vacuolar changes of the basal layer of the epidermis and sparse lymphocytic infiltrate. **B** Grade II: necrosis of keratinocytes and more obvious vacuolar degeneration of the basal layer. **C** Grade III: apoptosis of keratinocytes and blurring of the dermal–epidermal junction due to marked vacuolar degeneration and a lichenoid infiltrate of lymphocytes. **D** Grade IV: full-thickness necrosis of the epidermis with separation of the epidermis from the dermis. Of note, grade I changes are rather nonspecific and are also seen with autoimmune disorders showing the histopathologic pattern of an interface dermatitis (e.g. lupus erythematosus). *Courtesy Lorenzo Cerroni, MD.*

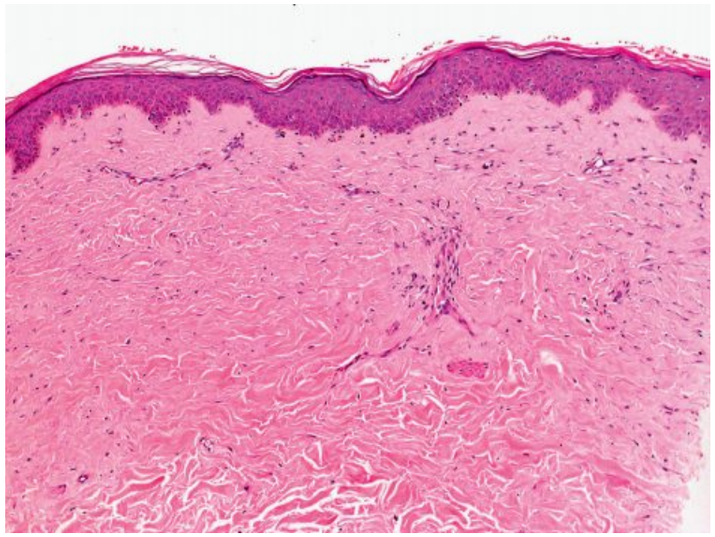


Fig. 52.8 Chronic cutaneous graft-versus-host disease (morphea-like) – histologic features. There is sclerosis of the dermis with thickening of collagen bundles. These same histologic features can be seen in morphea and systemic sclerosis (scleroderma). Pigmentary incontinence, with a few melanophages within the papillary dermis can also be seen in this form of chronic GVHD. *Courtesy Lorenzo Cerroni, MD.*

CLINICAL FEATURES OF ENGRAFTMENT SYNDROME VERSUS ACUTE GRAFT-VERSUS-HOST DISEASE (GVHD)

Clinical feature	Engraftment syndrome	Acute GVHD
Type of transplant	Autologous or allogeneic	Allogeneic
Exanthem	Yes	Yes
Pruritus	Variable	Variable
Fever	Yes	Uncommon
Peripheral eosinophilia	Variable	Variable
Diarrhea	No	Yes
Transaminitis/cholestasis	Uncommon	Yes
Pulmonary edema	Yes	No
Weight gain	Yes	No
Renal insufficiency	Variable	No
Encephalopathy	Uncommon	No
Rapid response to corticosteroids	Yes	Variable to yes
Timing post-transplant	~10–12 days (coinciding with myeloid recovery)	Peak incidence at 30–40 days

Table 52.5 Clinical features of engraftment syndrome versus acute graft-versus-host disease (GVHD).

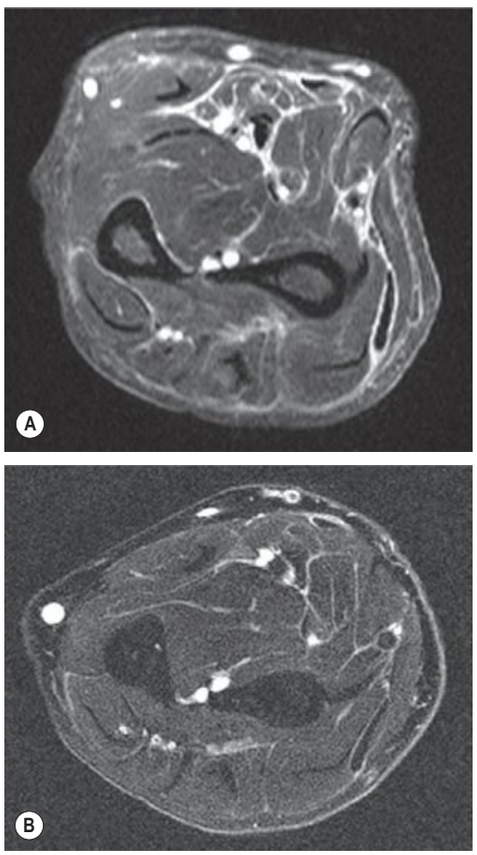


Fig. 52.9 Magnetic resonance imaging of the eosinophilic fasciitis-like presentation of chronic cutaneous graft-versus-host disease. A Prior to treatment (systemic corticosteroids), with a lace-like white pattern representing edema of the fascia. **B** After treatment, with marked diminution of edema. The round white circles represent blood vessels. *Courtesy Dennis Cooper, MD.*

Chronic GVHD

Chronic GVHD continues to be a major therapeutic challenge, but the consistent observation that post-transplant cyclophosphamide has reduced its incidence without an increase in relapse or opportunistic infections is encouraging. With respect to cutaneous cGVHD, skin-directed therapies can play an important adjunctive role. For an LP-like eruption or pruritus, medium- to high-potency topical corticosteroids and topical calcineurin inhibitors (pimecrolimus, tacrolimus) are effective. Of note, use of topical tacrolimus under occlusion may lead to toxic drug levels in patients on concurrent systemic tacrolimus[26]. Various forms of phototherapy have shown some benefit in small series, however controlled trial data are needed. The potential for increased skin cutaneous malignancies in the setting of concurrent immunosuppressive therapy or prophylactic voriconazole must also be weighed against the benefit of UV therapy.

As with aGVHD, first-line systemic therapy of cGVHD is systemic corticosteroids, but while the dose is less (maximum dose of prednisone is 1 mg/kg/day), the duration of treatment is often prolonged. This extended corticosteroid therapy is a major cause of non-relapse morbidity and mortality, especially from opportunistic infections. Approximately 50% of cGVHD patients will not respond adequately to corticosteroid therapy, and better treatment for this group remains a critical unmet need. Ibrutinib[27] is FDA-approved for steroid-refractory cGVHD, but since the approval of ruxolitinib[28] for the same indication, the use of ibrutinib has declined. For patients who have failed ≥2 lines of therapy, belumosudil, a well-tolerated oral inhibitor of rho-associated coil kinase 2 (ROCK2), has recently been FDA-approved given a response rate of >70%. There are also ongoing trials of the use of axatilimab, an anti-CSF-1R antibody, for cGVHD[28a]. Other options include extracorporeal photophoresis[29], sirolimus, imatinib mesylate[30], and rituxumab[31].

Patients with mucocutaneous cGVHD should undergo ocular, oral, and genital examinations. Site-specific therapies, including scleral contact lenses, oral rinses (e.g. dexamethasone elixir), and vaginal dilators can prove very helpful. Referral to physical therapy is strongly recommended in patients with sclerotic involvement to improve any decreased joint range-of-motion.

Long term, the importance of sun protection should be emphasized, as patients are typically prescribed one or more photosensitizing agents, including trimethoprim–sulfamethoxazole, levofloxacin, and voriconazole. In addition, the latter drug can increase the risk of developing cutaneous malignancies. Patients, especially those with significant photodamage and/or a previous history of cutaneous carcinomas, should be educated regarding skin cancer risk in the setting of immunosuppression, and they should receive regular surveillance for skin cancer. Ideally, patients with chronic mucocutaneous GVHD should be managed in a coordinated multidisciplinary manner by specialists in ophthalmology, gynecology, oral medicine, physiatry, and dermatology in order to optimize care.

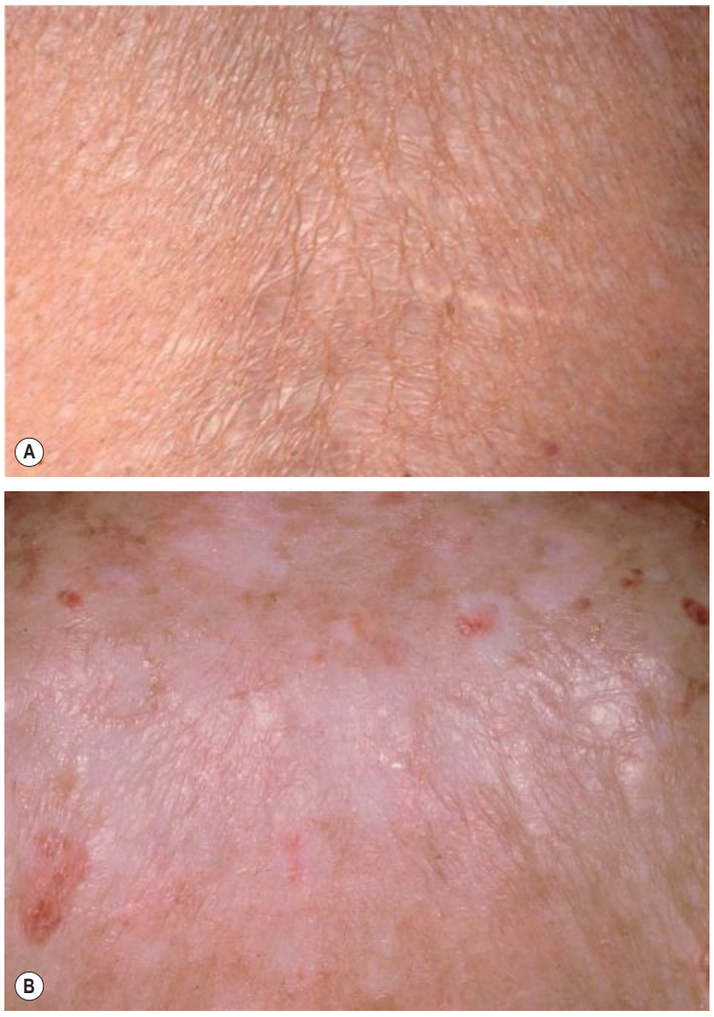
Additional figures and tables on Risk factors associated with the development of graft-versus-host disease, and Comparison of clinical and laboratory features of sclerotic-type chronic GVHD and systemic sclerosis, available in our eBook (see inside front cover for access code).

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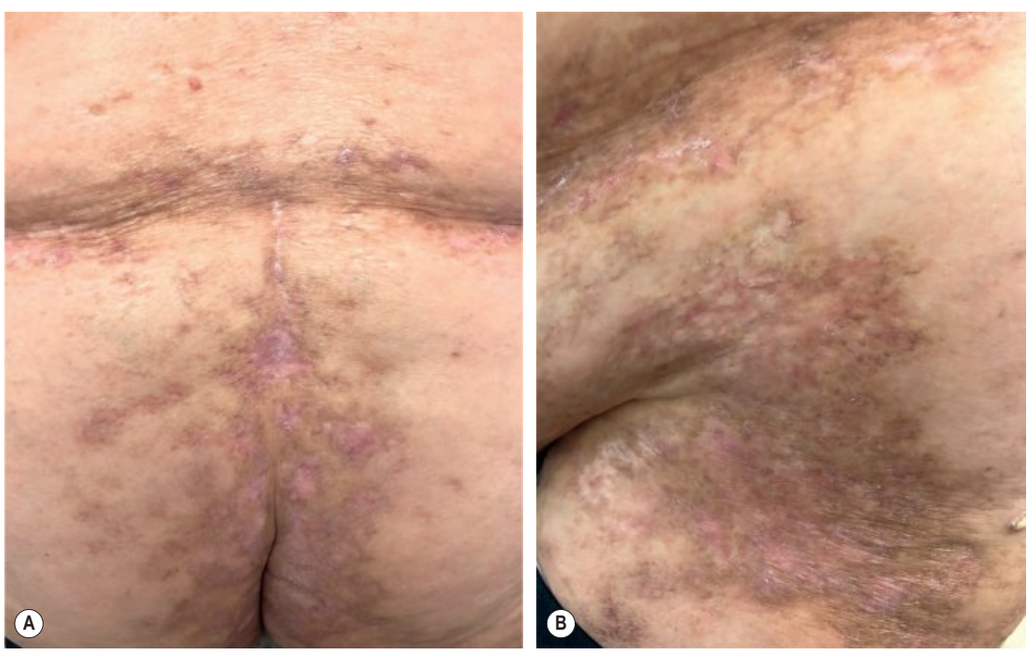
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eFig. 52.1 Chronic cutaneous graft-versus-host disease – lichen sclerosus type. A Subtle gray–white ovoid plaques on the back. **B** Shiny hypopigmented plaques of the upper back, a common location for this form of cGVHD. *B, Courtesy Joyce Rico, MD.*



eFig. 52.2 Chronic graft-versus-host disease – morpheaform type. A, B Symmetric sclerotic plaques with central inflammation and peripheral hyperpigmentation involving the major body folds and flanks. *Courtesy Jonathan S. Leventhal, MD.*



eFig. 52.3 Chronic graft-versus-host disease – morpheaform type. Sclerotic plaques in a "waistband" distribution in child who wears diapers.



eFig. 52.4 Chronic graft-versus-host disease – sclerotic type. Inflamed and hyperpigmented bound-down skin of the wrist and hand with joint contractures and superficial ulceration.



eFig. 52.5 Chronic graft-versus-host disease – sclero-derma-like (sclero-dermoid) type. The skin is shiny and bound-down. Additional findings include dyspigmentation, erosions, angiomatous papules, and a loss of the nail plates of the great toes.



eFig. 52.6 Chronic cutaneous graft-versus-host disease – eosinophilic fasciitis-like presentation. A rippled appearance and irregular nodular texture to the skin is indicative of involvement of subcutaneous tissues. Especially in the earlier, edematous phase, the presence of hypereosinophilia may be a clue to the diagnosis.



eFig. 52.7 Residual dyspigmentation from chronic cutaneous graft-versus-host disease (cGVHD). Extensive hyper- and hypopigmentation in an African-American child with a history of epidermal involvement of cGVHD.





eFig. 52.8 Chronic graft-versus-host disease. A Lacy white pattern on the mucosal surface of the lower lip in the lichen planus-like form. Note the Beau's lines of the fingernails reflecting the time of the transplant. **B** Morphea-like plaque with a healing ulceration on the shoulder.



eFig. 52.9 Chronic graft-versus-host disease. Well demarcated pink–violet plaques with scale favoring areas of pressure. *Courtesy Julie V. Schaffer, MD.*

RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF GRAFT-VERSUS-HOST DISEASE
Donor
HLA incompatibility with recipient Unrelated to recipient Female (especially multiparous) with male recipient
Recipient
Age (older-aged > middle-aged > pediatric)
Stem cell source
Peripheral blood > bone marrow > cord blood T cell-replete graft
Other
Myeloablative conditioning regimen*
*Associated with higher rate of acute GVHD compared with non-myeloablative HSCT, but does not affect incidence of chronic GVHD.

eTable 52.1 Risk factors associated with the development of graft-versus-host disease (GVHD). HSCT, hematopoietic stem cell transplant.

COMPARISON OF CLINICAL AND LABORATORY FEATURES OF SCLEROTIC-TYPE CHRONIC GVHD (cGVHD) AND SYSTEMIC SCLEROSIS		
	Sclerotic-type cGVHD	**Systemic sclerosis**
Autoantibodies	Variable, nonspecific	Yes, associated with specific clinical subtypes
Cardiac involvement	Rare	Yes, conduction system abnormalities
GI dysmotility/ strictures	Yes	Yes
Pulmonary hypertension	No	Yes
Pulmonary fibrosis	Yes*	Yes
Renal disease	Rare, nephrotic syndrome	Yes, scleroderma renal crises (in diffuse subtype)
Raynaud disease	Rare	Yes
Sclerodactyly	Rare	Yes
Skin manifestations		
Fibrosis	Dermis, subcutaneous tissue, and/or fascia	Dermis
Natural history	Patchy involvement, variable course	Symmetric, acral to proximal progression
Facial involvement	Rare, usually patchy involvement	Common, diffuse skin tightening (scleroderma facies)
*In setting of bronchiolitis obliterans.		

eTable 52.2 Comparison of clinical and laboratory features of sclerotic-type chronic GVHD (cGVHD) and systemic sclerosis.

PATIENT HANDOUT – GENERAL DERMATOLOGIC RECOMMENDATIONS FOR PATIENTS WITH CUTANEOUS GRAFT-VERSUS-HOST DISEASE (GVHD)
Dry skin and pruritus
Use soapless, fragrance-free cleansers
Apply emollients frequently, in particular ointments and thicker creams
Avoid tight-fitting or abrasive clothing; wear cool, breathable fabrics
Avoid antihistamines if there is dryness of the eyes or mouth (sicca syndrome)
Nail dystrophy
Keep nails trimmed or filed to prevent breakage and pain
A clear nail lacquer can be used as a nail hardener
Signs of skin sclerosis (hardening)
Early signs of skin sclerosis (hardening) include darkening or tightening of the skin at the waistband or bra line, rippling or dimpling of the skin, and decreased joint range-of-motion
Skin ulcers
Areas of skin breakdown serve as potential sites where bacteria can enter the body; these areas should be kept clean and covered
Recommendations regarding sun exposure and skin cancer
The risk of skin cancer is increased in patients with GVHD, especially those who are chronically immunosuppressed and/or receive phototherapy (e.g. UVB, PUVA)
Exposure to sunlight can trigger a flare of GVHD or photodrug eruption
Several frequently prescribed medications can increase sun sensitivity; they include trimethoprim–sulfamethoxazole (Septra®, Bactrim®) and voriconazole (Vfend®)
If possible, avoid outdoor activities during peak hours of UVR (10 am–4 pm)
Apply broad-spectrum sunblock on sun-exposed sites on a regular basis
Use a broad-brimmed hat and protective clothing; consider using a laundry additive that increases the UV protective factor of clothing (e.g. SunGuard™)
Perform skin self-examination on a regular basis

eTable 52.3 Patient handout – general dermatologic recommendations for patients with cutaneous graft-versus-host disease (GVHD).

Dermatologic Manifestations in Patients with Systemic Disease

53

Lauren M. Madigan, Kathryn Schwarzenberger and Jeffrey P. Callen

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Cutaneous Hematology and Oncology 835
Cutaneous Diseases in Patients with Endocrinologic and/or Metabolic Disorders 841
Cutaneous Gastroenterology 843
Other Systemic Diseases with Cutaneous Manifestations 848

Key features

- Because of the frequency of skin involvement in systemic diseases, cutaneous manifestations often prove helpful in establishing the correct diagnosis
- Skin signs of systemic disease can be specific, e.g. cutaneous lupus erythematosus, cutaneous sarcoidosis, in part because of associated histologic features, while others are best described as suggestive, e.g. pyoderma gangrenosum, acquired ichthyosis
- Cutaneous disease can serve as the initial manifestation of a systemic disorder, including an internal malignancy

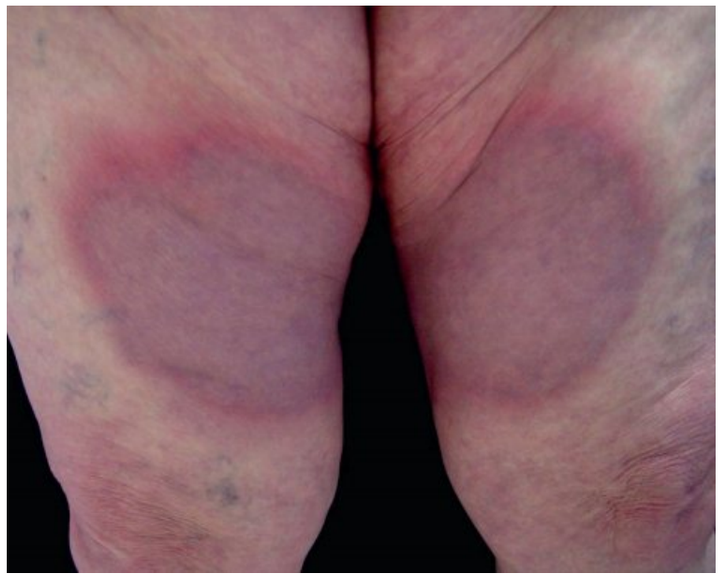


Fig. 53.1 Interstitial granulomatous dermatitis (IGD) – annular variant. This clinical presentation with annular plaques on the medial thighs is often seen in the setting of rheumatoid arthritis. Of note, IGD has also been implicated as a side effect of medications, including TNF inhibitors, HMG-CoA reductase inhibitors ("statins"), and calcium channel blockers.

Skin disease is often associated with internal manifestations[1], e.g. psoriatic arthritis, and there are many cutaneous disorders that are traditionally associated with systemic disease. For example, rheumatologic disorders frequently have skin manifestations, as do infectious diseases and endocrinopathies. When one examines many of the disorders that are discussed elsewhere in this text, it becomes clear that isolated dermatologic disease is relatively uncommon. A detailed review of all dermatologic signs of internal disease is beyond the scope of this chapter. Rather, representative disorders are discussed individually, while the remainder are reviewed via tables that contain information relevant to dermatologists. Disorders are grouped on the basis of affected organ systems.

CUTANEOUS RHEUMATOLOGY

The spectrum of disorders traditionally considered to be cutaneous rheumatology[2] includes: lupus erythematosus (Ch. 41); dermatomyositis (Ch. 42); systemic sclerosis (Ch. 43); Sjögren syndrome (see below and Ch. 45); vasculitides (Ch. 24); and miscellaneous disorders. Miscellaneous disorders usually include: rheumatoid arthritis (Ch. 45), reactive arthritis (formerly Reiter disease) (Ch. 8), psoriatic arthritis (Ch. 8), neutrophilic dermatoses including Behçet disease (Ch. 25), Kawasaki disease (Ch. 81), relapsing polychondritis (Ch. 45), and several of the autoinflammatory disorders (see Table 45.7).

Cutaneous conditions reported in patients with rheumatoid arthritis are summarized in Table 53.1 (Figs. 53.1–53.5)[3,4]. Dermatologists should be particularly careful in this group of patients to couple laboratory evaluation with a comprehensive cutaneous examination, including all mucosal surfaces, nails, nail folds, and hair. Clinical criteria are published for the diagnosis of many of these rheumatologic disorders; dermatologists should be familiar with the criteria and incorporate them into a focused, thorough history, which includes relevant negatives. It is very helpful to consider the clinicopathologic basis and pathogenesis of cutaneous lesions. For example, patients with systemic lupus erythematosus can have different types of photodistributed



Fig. 53.2 Rheumatoid papules. Multiple red–brown papules, some with scale-crust, on the lower extremity. This entity is within the spectrum of palisaded neutrophilic and granulomatous dermatitis (see Table 53.1).

CUTANEOUS MANIFESTATIONS OF RHEUMATOID ARTHRITIS	
Condition	**Features**
Palisading granulomas	
Rheumatoid nodules	• Seen in ~20% of RA patients, often associated with high-titer rheumatoid factor (RF) • Firm, semi-mobile papulonodules favoring periarticular locations (e.g. elbows; see Figs. 24.6B & 45.5) and other sites of repetitive trauma or pressure (e.g. the sacral region if bedridden) • Histologically, central zone of necrobiosis surrounded by palisaded histiocytes (see Fig. 45.9) • DDx: subcutaneous granuloma annulare, gouty tophi, synovial hyperplasia/cysts (softer, painful)
Reactive granulomatous dermatitis (includes interstitial granulomatous dermatitis [IGD] and palisaded neutrophilic & granulomatous dermatitis [PNGD])	• The clinical spectrum includes the annular variant of IGD (Fig. 53.1), rheumatoid papules (Fig. 53.2), and superficial ulcerating rheumatoid necrobiosis (Fig. 53.3) • See Ch. 93 for details
Neutrophilic dermatoses	
Rheumatoid neutrophilic dermatitis (rheumatoid neutrophilic dermatosis)	• Erythematous papules and plaques that may be vesiculated or crusted; favors extensor extremities • Unlike Sweet syndrome, usually not tender or associated with fevers and malaise
Sweet syndrome and pyoderma gangrenosum (PG)*	• See Chapter 25
Neutrophilic lobular panniculitis	• Tender red nodules favoring the lower legs; may ulcerate with purulent drainage • Overlap with subcutaneous Sweet syndrome; infectious etiologies need to be excluded
Vasculitis and vascular reactions	
Bywaters lesions	• Punctate purpuric papules on the distal digits due to cutaneous small vessel vasculitis (Fig. 53.4) • Often has a more benign course

Rheumatoid vasculitis	• Associated with long-standing (often "burnt out") joint disease, high-titer RF, and mononeuritis multiplex; may also affect the eyes and internal organs
	• Cutaneous involvement is usually the first manifestation
	  • *Small vessel vasculitis*: purpuric macules and papules (see Fig. 24.6B)
	  • *Medium-sized vessel vasculitis*: nodules, ulcers, digital gangrene, livedo reticularis, atrophie blanche-like scars
	• Systemic disease requires aggressive immunosuppressive therapy

Intralymphatic histiocytosis	• Erythema, induration, and plaques with a reticular pattern; co-localizes with involved joints or metallic orthopedic implants (see Fig. 121.6)
Erythema elevatum diutinum	• Firm, red to yellow–brown papulonodules and plaques, usually symmetrically distributed over joints and on extensor surfaces • Chronic cutaneous vasculitis occasionally associated with RA (exclude IgA monoclonal gammopathy)
Complications of therapy for RA	
NSAIDs	• Pseudoporphyria (particularly naproxen) (Fig. 53.5), phototoxicity, toxic epidermal necrolysis
Methotrexate	• EBV-associated lymphoproliferative disease that may involve the skin
Methotrexate >> TNF inhibitors, leflunomide, tocilizumab	• Accelerated rheumatoid nodulosis – sudden appearance of multiple papulonodules, especially on the hands (see Fig. 45.6)
TNF inhibitors	• Local injection site reactions, urticaria, urticarial eruptions; eczematous and psoriasiform eruptions, sometimes admixed, palmoplantar pustulosis; RGD, vasculitis, cutaneous LE, dermatomyositis (see Table 128.7)
IL-17 inhibitors	• Local injection site reactions, urticaria (see Table 128.7)
IL-12/23 & IL-23 inhibitors	• Local injection site reactions, urticaria (see Table 128.7)
*"PG-like" leg ulcers are a feature of Felty syndrome, which is characterized by the triad of neutropenia, splenomegaly, and RA; Felty syndrome is associated with a higher incidence of rheumatoid nodules and may be associated with T cell large granular lymphocyte leukemia.	

Table 53.1 Cutaneous manifestations of rheumatoid arthritis (RA). DDx, differential diagnosis; EBV, Epstein–Barr virus; LE, lupus erythematosus; RGD, reactive granulomatous dermatitis; TNF, tumor necrosis factor.



Fig. 53.3 Superficial ulcerating rheumatoid necrobiosis. Shiny, yellow plaques with red–brown edges and areas of ulceration that clinically resemble necrobiosis lipoidica. This patient had active rheumatoid vasculitis.



Fig. 53.4 Bywaters lesions. Tender, purpuric papules on the distal fingers in a patient with rheumatoid vasculitis. Histologically, leukocytoclastic vasculitis is seen.

lesions with an interface histopathology, e.g. discoid, subacute, poikilodermatous, and they have different implications with regard to systemic disease. Such lesions are also treated differently than those caused by vessel-based pathology, e.g. small or larger vessel vasculitis.

Sjögren syndrome is an autoimmune disorder characterized by keratoconjunctivitis sicca and xerostomia (see Table 45.4). In primary Sjögren syndrome, vascular inflammation within the skin (e.g. small vessel vasculitis, hypergammaglobulinemic purpura) can occur even before the clinical diagnosis has been established and may have prognostic implications. Some patients from the Far East, including Japan and the Philippines, have been described with "annular erythema of Sjögren syndrome". There is ongoing debate as to whether this disorder is unique to Sjögren syndrome or if it is, in fact, a form of subacute cutaneous lupus erythematosus[5]. Secondary Sjögren syndrome occurs in patients with other rheumatologic diseases, including rheumatoid arthritis, dermatomyositis, and systemic sclerosis. It is important to remember that the diagnosis of Sjögren syndrome is one of exclusion, and that other conditions can cause xerostomia/xerophthalmia, including chronic GVHD, sarcoidosis, primary systemic amyloidosis, hepatitis C viral infection, IgG4-related disease, and HIV disease.



Fig. 53.5 Pseudoporphyria in a patient with rheumatoid arthritis. The cause was a nonsteroidal anti-inflammatory drug. *Courtesy Kalman Watsky, MD.*

CUTANEOUS HEMATOLOGY AND ONCOLOGY

Disorders of mutual interest to the dermatologist and hematologist/oncologist are well covered in the following chapters of this textbook: metastatic disease (Ch. 122), leukemia/lymphoma (Chs. 119–121), dysproteinemias (Ch. 119), histiocytoses (Ch. 91), vascular neoplasms (Ch. 114), cutaneous T cell lymphoma (Ch. 120), melanoma (Ch. 113), and cutaneous reactions to chemotherapeutic agents, targeted therapies, and immune checkpoint inhibitors (Ch. 21). Skin signs of internal malignancy are summarized in Tables 53.2 and 53.3.

Both disease-specific and nonspecific skin lesions have been reported in association with *myelodysplastic syndrome* (MDS)[14]. The former include leukemia cutis and "cutaneous myelodysplasia"; the latter is characterized by an infiltrate of atypical myeloid cells in a patient who does not fulfill criteria for leukemia. Patients with MDS can also develop cutaneous small vessel vasculitis (CSVV; see Fig. 24.6), as well as Sweet syndrome, including the subcutaneous, histiocytoid, and lymphocytic variants[15–17]. The latter variant may portend a poorer prognosis[17]. In the VEXAS (*v*acuoles, *E*1 enzyme, *X*-linked, *a*utoinflammatory, *s*omatic) syndrome due to *somatic* mutations in *UBA1*, chondritis, Sweet syndrome, and vasculitis (CSVV > polyarteritis nodosa or giant cell arteritis) can accompany MDS; a clue to the diagnosis is vacuolated myeloid and erythroid precursors in the bone marrow[18].

PARANEOPLASTIC DERMATOSES		
Dermatoses	**Cutaneous findings**	**Comments**
Disorders that are associated with cancer in most or all cases		
Acquired hypertrichosis lanuginosa (malignant down)	Growth of fine lanugo hairs in a generalized distribution or localized to the face. With time, these hairs may become coarser (see Ch. 70)	Associated with a variety of internal malignancies, most often carcinoma of the lung, colon, or breast
AESOP syndrome	Large red to violet–brown patch	Patch overlies a plasmacytoma
Bazex syndrome (acrokeratosis paraneoplastica)	Acral psoriasiform plaques, typically with involvement of the nose and helices; often the lesions are violaceous (Fig. 53.6) Longitudinal and horizontal ridging of the nails occurs in 75% of patients	By definition, this condition is linked to malignancy, occurring most commonly in the upper aerodigestive tract (oropharynx, larynx, or esophagus)
Carcinoid syndrome	Rosacea-like flushing and erythema of the head and neck Pellagra-like dermatitis and sclerodermoid changes may develop in advanced disease	Flushing associated with ~10% of mid-gut tumors (small intestine, appendix, proximal colon) and liver metastases are required; type III gastric and bronchial carcinoid tumors are also associated with flushing (liver metastases are not required)
Ectopic adrenocorticotropic hormone (ACTH) syndrome	Generalized hyperpigmentation that may be accentuated in sun-exposed sites	Production of ACTH by a tumor (often a small cell carcinoma of the lung) may result in hyperpigmentation and features of Cushing syndrome
Erythema gyratum repens	Concentric erythematous lesions, often giving rise to a wood-grain appearance (Fig. 53.7; see Ch. 19)	Variable sites and types of malignancy
Glucagonoma syndrome	Necrolytic migratory erythema, angular cheilitis, glossitis	Due to a glucagon-secreting tumor of the pancreas and associated with weight loss and diabetes mellitus Patients often treated for intertrigo prior to diagnosis
Paraneoplastic pemphigus	Erosive disease of the mucous membranes and erythema multiforme-like, bullous pemphigoid-like or lichenoid skin lesions (see Fig. 29.10)	Most often associated with non-Hodgkin lymphoma, chronic lymphocytic leukemia or Castleman disease (with the latter accounting for the majority of cases in children and Asian populations) Castleman tumors have been shown to produce the autoantibodies responsible for paraneoplastic pemphigus, and their resection can lead to remission of mucocutaneous lesions Bronchiolitis obliterans is a common complication
Tripe palms	Ridged velvety lesions on the palms	May or may not be accompanied by acanthosis nigricans

Table 53.2 Paraneoplastic dermatoses[6–8].

Continued

PARANEOPLASTIC DERMATOSES		
Dermatoses	**Cutaneous findings**	**Comments**
Disorders that are strongly associated with cancer in a subset of cases		
Acanthosis nigricans	Rapid onset of hyperpigmented velvety changes in multiple flexural sites (e.g. neck, axillae, groin) May also involve extensor surfaces (e.g. elbows, knees, knuckles) and, in malignancy-associated cases, lips, oral mucosa, and palms (see above, tripe palms)	Association with adenocarcinomas (e.g. stomach, other sites within the GI or GU tracts) and often accompanied by weight loss More commonly associated with endocrinologic disorders, in particular insulin resistance (see Fig. 53.14); such patients are typically overweight, and the onset of the condition is usually insidious
Anti-laminin 332 mucous membrane pemphigoid/ anti-epiligrin cicatricial pemphigoid*	Oral ulcerations, conjunctival erosions, and scarring Tense blisters and erosions of the skin may also develop (see Ch. 30)	Roughly one-third of patients have or develop cancer within the first year following diagnosis Most often an adenocarcinoma and frequently diagnosed at an advanced stage
Dermatomyositis (adult)	Diffuse scaling and pruritus of the scalp, heliotrope, photodistributed poikiloderma, Gottron papules of the hands, thin plaques of the elbows, knees, lateral hips/thighs (holster sign) and upper back (shawl sign), nail-fold overgrowth with dilated capillary loops (see Ch. 42)	Population-based studies demonstrate an over-representation of ovarian, lung, colorectal, and pancreatic carcinomas and non-Hodgkin lymphoma in White individuals Nasopharyngeal carcinoma is over-represented in patients of Asian descent
Eosinophilic dermatosis of hematologic malignancy	Severe insect bite reactions and insect bite-like reactions with pruritic papulonodules and vesiculobullous lesions	Chronic lymphocytic leukemia, NK/T cell lymphoma, and ALK-positive anaplastic large cell lymphoma, in addition to other hematologic malignancies
Neutrophilic dermatoses	Sweet syndrome (Fig. 53.8) or pyoderma gangrenosum (particularly the atypical bullous form) (see Ch. 25)	~10%–20% of cases are associated with hematologic disorders such as acute myelogenous leukemia, myelodysplasia, or plasma cell dyscrasia (IgA) Underlying solid tumors are rare
Disorders associated with a monoclonal gammopathy†		
Acquired angioedema due to C1 esterase inhibitor dysfunction	Acquired angioedema without associated wheals (see Ch. 18)	Associated with B cell lymphoproliferative disorders, including lymphomas, as well as monoclonal gammopathy of undetermined significance (MGUS)
Amyloidosis, primary systemic	Waxy, translucent, or purpuric papules; periorbital and pinch purpura; macroglossia (see Ch. 47)	Monoclonal gammopathy due to plasma cell dyscrasia ≫ multiple myeloma; deposits composed of immunoglobulin light chain (AL)
Cryoglobulinemia, type I	Retiform purpura and necrosis that favors cooler acral sites; acral cyanosis; livedo reticularis (see Ch. 23)	Monoclonal gammopathy due to plasma cell dyscrasia or lymphoproliferative disorder
Necrobiotic xanthogranuloma	Indurated xanthomatous plaques with necrosis and ulceration, usually in a periorbital location (see Ch. 91)	Paraproteinemia (>80% of cases, most often IgG with κ light chains) due to plasma cell dyscrasia or lymphoproliferative disorder; multiple myeloma develops in a minority of patients
Normolipemic plane xanthoma	Yellowish patches and thin plaques that favor the skin folds, upper trunk, and periorbital area (see Ch. 92)	Paraproteinemia due to plasma cell dyscrasia or lymphoproliferative disorder
POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M*-protein and *s*kin changes)	Although the glomeruloid hemangioma (Fig. 53.10) is considered to be pathognomonic, it is present in a minority of patients Additional skin findings include cherry angiomas and other vascular tumors, hyperpigmentation, hypertrichosis, sclerodermoid induration, acrocyanosis, acquired facial lipoatrophy, hyperhidrosis, digital clubbing, plethora, and leukonychia	Monoclonal gammopathy due to plasma cell dyscrasia including multiple myeloma (osteosclerotic > osteolytic) and plasmacytomas or Castleman disease Patients may also have peripheral edema, ascites, pulmonary effusions, papilledema, thrombocytosis, polycythemia, and increased serum levels of VEGF
Schnitzler syndrome	Chronic urticarial lesions Histologically, a neutrophil-rich dermal infiltrate is often seen (see Ch. 18)	Associated with an IgM, usually κ, paraproteinemia, with lymphoma or multiple myeloma developing in ~15% of patients Additional manifestations include fevers, arthralgias, and bone pain[9] and treatment includes anti-IL-1 agents[10] (see Fig. 45.13)
Scleromyxedema	Sclerodermoid induration plus firm, waxy papules arranged in linear arrays (see Ch. 46)	Almost always associated with paraproteinemia (usually IgG with λ light chains); multiple myeloma develops in <10% of patients
Dermatoses that may be associated with cancer in a subset of patients		
Acquired ichthyosis	Resembles ichthyosis vulgaris; most often located on the legs	Most commonly associated with lymphoma, which typically predates the diagnosis of the ichthyosis
Cutaneous small vessel vasculitis	Palpable purpura; may be widespread and/or in unusual locations (see Ch. 24)	Less than 5% of patients with vasculitis have an associated malignancy, most commonly plasma cell dyscrasia, myelodysplasia, myeloproliferative or lymphoproliferative disorder, and hairy cell leukemia IgA vasculitis in adults may be associated with solid organ malignancies[10a]
Dermatitis herpetiformis (DH)	Pruritic blisters and erosions on extensor surfaces, scalp and/or buttocks (see Ch. 31)	Through the association of DH with gluten-sensitive enteropathy, enteropathy-associated T cell lymphoma can occur Possible association with B cell non-Hodgkin lymphoma[10b]

Table 53.2 Paraneoplastic dermatoses[6–8].

PARANEOPLASTIC DERMATOSES		
Dermatoses	**Cutaneous findings**	**Comments**
Eruptive disseminated porokeratosis	Abrupt onset of numerous, widespread, inflamed keratoses with histologic features of porokeratosis	In a literature review of 35 patients, ~30% of patients had an associated malignancy, most commonly involving the GI tract[11]
Exfoliative erythroderma	Widespread, diffuse, scaly erythematous skin (see Ch. 10)	May be associated with cutaneous T cell lymphoma or, occasionally, with a systemic lymphoma or leukemia
Juvenile xanthogranulomas (JXGs) in the setting of neurofibromatosis 1 (NF1)	Pink–yellow to red–brown, dome-shaped papules and nodules, most often located on the head and neck (see Ch. 91)	A triple association between JXGs, NF1, and juvenile myelomonocytic leukemia has been described
Multicentric reticulohistiocytosis	Papulonodular lesions, most often on the dorsal aspects of the hands, elbows, and face (Fig. 53.11)	Often accompanied by destructive arthritis Variety of associated malignancies reported, developing in ~25%–30% of adult patients[11a]
Mycosis fungoides	Patch, plaque, or nodular disease (see Ch. 120)	Increased risk of second malignancies: other lymphomas >> leukemia or solid organ malignancies
Pancreatic panniculitis	Subcutaneous nodules, most commonly on the legs, which may ulcerate and drain oily liquid (see Ch. 100)	Underlying pancreatic carcinoma or pancreatitis May herald metastatic disease Additional findings include polyarthritis (PPP syndrome), abdominal pain, and eosinophilia
Porphyria cutanea tarda (PCT)	Fragility, erosions, blisters, milia and scars on the dorsal aspect of the hands, facial hypertrichosis, sclerotic plaques (see Ch. 49)	Through its association with hepatitis C virus, PCT may also be associated with primary hepatocellular carcinoma (hepatoma)
Reactive granulomatous dermatitis (disseminated cutaneous granulomatosis)	Granulomatous papules and plaques, sometimes with an annular configuration Overlap with IGD, PNGD, & granuloma annulare	More commonly associated with myelodysplastic syndrome and lymphoproliferative disorders than with solid organ malignancies
Disorders whose association with cancer is controversial		
Sign of Leser–Trélat	Rapid appearance or growth of multiple seborrheic keratoses which may be inflamed	There is ongoing controversy as to whether this represents a paraneoplastic phenomenon, as many adults have numerous seborrheic keratoses and it can be difficult to determine if the keratoses are truly eruptive The rapid onset of numerous lesions, particularly if inflamed and associated with diffuse pruritus and/or acanthosis nigricans, may warrant evaluation Eruptive seborrheic keratoses can also develop in erythrodermic patients who do not have an underlying malignancy

*Evidence for this association is limited by the small number of affected individuals.
†Patients can also develop follicular spicules (Fig. 53.9); for complete list, see Table 119.5.

Table 53.2 Paraneoplastic dermatoses[6–8]. Other signs include pruritus (most commonly with lymphomas or carcinomas that lead to cholestasis) and pityriasis rotunda. AESOP, *a*denopathy, *e*xtensive *s*kin patch *o*verlying (a) *p*lasmacytoma; IGD, interstitial granulomatous dermatitis; GI, gastrointestinal; GU, genitourinary; PNGD, palisaded neutrophilic and granulomatous dermatitis; PPP, pancreatitis, polyarthritis, and panniculitis; VEGF, vascular endothelial growth factor.

INTERNAL MALIGNANCIES IN FAMILIAL CANCER SYNDROMES WITH CUTANEOUS MANIFESTATIONS
• Cowden disease (breast, thyroid and GU carcinomas), Muir–Torre syndrome (GI and GU carcinomas), Gardner syndrome (GI carcinoma), Peutz–Jeghers syndrome (various malignancies) – see Table 53.10
• Costello syndrome (rhabdomyosarcoma, neuroblastoma, bladder carcinoma), Werner syndrome (thyroid carcinoma, osteosarcoma) – see Table 53.12
• Birt–Hogg–Dubé syndrome, hereditary leiomyomatosis and renal cell cancer – see Tables 111.1 & 117.2
• Howel–Evans syndrome (esophageal carcinoma) – see Ch. 58
• Ataxia–telangiectasia (leukemia, lymphoma, breast cancer) – see Ch. 60
• Neurofibromatosis (malignant peripheral nerve sheath tumors, JMML, rhabdomyosarcoma, pheochromocytoma, carcinoid), tuberous sclerosis (renal cell carcinoma) – see Ch. 61 and Table 61.1
• Multiple endocrine neoplasia syndromes – see Table 63.2
• Dyskeratosis congenita (acute myelogenous leukemia, oral and anogenital SCC) – see Ch. 67
• Basal cell nevus syndrome (medulloblastoma, ovarian fibrosarcoma) – see Table 108.3
• Bloom syndrome (lymphoma, acute leukemias, GI malignancies), Rothmund–Thomson syndrome (osteosarcoma), xeroderma pigmentosum (brain tumors [e.g. medulloblastoma, glioblastoma], oral SCC [not just anterior tongue]) – see Table 87.4
• Familial melanoma (pancreatic carcinoma, neural tumors, renal cell carcinoma, and gliomas, when mutations in *CDKN2A* (p16), *CDKN2A* (p14), *MITF*, and *POT1*, respectively; uveal melanoma, mesothelioma, clear cell renal cell carcinoma, and cholangiocarcinoma with *BAP1* mutations)

Table 53.3 Internal malignancies in familial cancer syndromes with cutaneous manifestations[12,13]. GI, gastrointestinal; GU, genitourinary; JMML, juvenile myelomonocytic leukemia; SCC, squamous cell carcinoma.

Generalized granulomatous dermatitis, panniculitis, and a variety of autoimmune disorders including Behçet disease, and bullous pemphigoid have also been reported in patients with MDS. These cutaneous disorders may precede the diagnosis of MDS, serving as its harbinger. Recurrence of skin lesions, or their lack of response to therapy, may herald progression to leukemia.

An eczematous or psoriasiform plaque of the nipple and surrounding skin can be seen in *Paget disease* due to epidermal extension of an underlying ductal adenocarcinoma of the breast (Fig. 53.12). While extramammary Paget disease (EMPD) most commonly represents a primary intraepithelial or invasive adenocarcinoma (>75% of patients; Fig. 53.13), secondary EMPD can be due to an underlying visceral malignancy, e.g. colorectal, urothelial (see Fig. 73.16).

Acanthosis nigricans is characterized by velvety hyperpigmentation of intertriginous areas and, less often, extensor surfaces (Fig. 53.14 & 53.15). Although this disorder may be associated with an internal malignancy (e.g. gastric adenocarcinoma), it is most often associated with insulin resistance[19]. The sites most frequently affected are the neck and axillae, but can include any skin fold, including that of the lower lip and chin. Malignancy-associated acanthosis nigricans is usually rapid in onset and may be accompanied by skin tags, multiple seborrheic keratosis, tripe palms, or florid cutaneous papillomatosis. Verrucous changes of the lips may also develop, and weight loss is common. In contrast, acanthosis nigricans associated with endocrine dysfunction is more insidious in onset and less widespread, and the patients are often overweight or obese. In either instance, there are probably one or more circulating factors that stimulate the epidermal proliferation (i.e. papillomatosis) that is observed histopathologically. An approach to the patient with acanthosis nigricans in outlined in Fig. 53.16. Treatment of the underlying malignancy, or effective treatment of





Fig. 53.6 Bazex syndrome (acrokeratosis paraneoplastica). A Acral psoriasiform lesions that have a violaceous hue, accompanied by nail dystrophy. The patient had a squamous cell carcinoma (SCC) of the tonsillar pillar. **B** Thin hyperpigmented plaques of the helix and antihelix in a patient with SCC of the pharynx. *B, Courtesy Jean L. Bolognia, MD.*



Fig. 53.7 Erythema gyratum repens. This patient had cancer of the breast.



Fig. 53.8 Acute febrile neutrophilic dermatosis (Sweet syndrome). Vesicopustules with surrounding erythema on the dorsal hand in a patient with myelodysplastic syndrome.

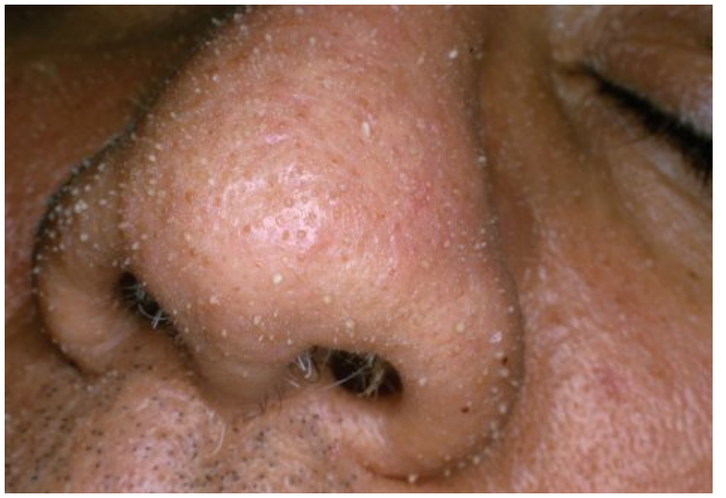


Fig. 53.9 Follicular spicules in a patient with multiple myeloma. *Courtesy Irwin Braverman, MD.*

the endocrinopathy, including weight loss and use of insulin sensitizers, may result in improvement or disappearance of the acanthosis nigricans. Recurrence of malignancy-associated acanthosis nigricans requires a search for recurrent cancer.

The glucagonoma syndrome is characterized by the development of *necrolytic migratory erythema* (NME), adult-onset diabetes mellitus, weight loss, and glossitis. These patients are also frequently anemic, and personality changes may occur. Skin lesions of NME are eroded, erythematous patches and plaques that characteristically involve the intertriginous areas, face (especially around the mouth), and distal extremities. Blisters may occur and lead to erythematous erosions. The eruption, which can be painful or pruritic, remits and recurs over the course of several weeks to months. It is frequently misdiagnosed as intertrigo or as seborrheic dermatitis. Histologically, pallor of the upper epidermis is highly suggestive of NME or a "nutritional" dermatosis (see Ch. 51). However, psoriasiform hyperplasia of the epidermis is often seen in NME and therefore clinicopathologic correlation is required.

Most, but not all, patients with NME have a glucagon-secreting tumor of the pancreas, and effective treatment of the tumor will result in a disappearance of the disease. Rarely, NME develops in the setting of severe liver disease or chronic pancreatitis. Similar skin lesions occur in patients with deficiencies of zinc, fatty acids or biotin (see Fig. 51.13) and replacement therapy leads to resolution of the cutaneous findings. The differential diagnosis of NME also includes necrolytic acral erythema (see below).



Fig. 53.10 POEMS syndrome. This patient had multiple angiomas on his trunk as well as his face and scalp. All the angiomas that were examined histologically were glomeruloid hemangiomas. In addition, he reported a recent 10 lb (4.5 kg) weight loss, impotence and fatigue, and was found to have a neuropathy, adult-onset diabetes, hypothyroidism, and peripheral edema. His underlying disorder was an osteosclerotic myeloma.

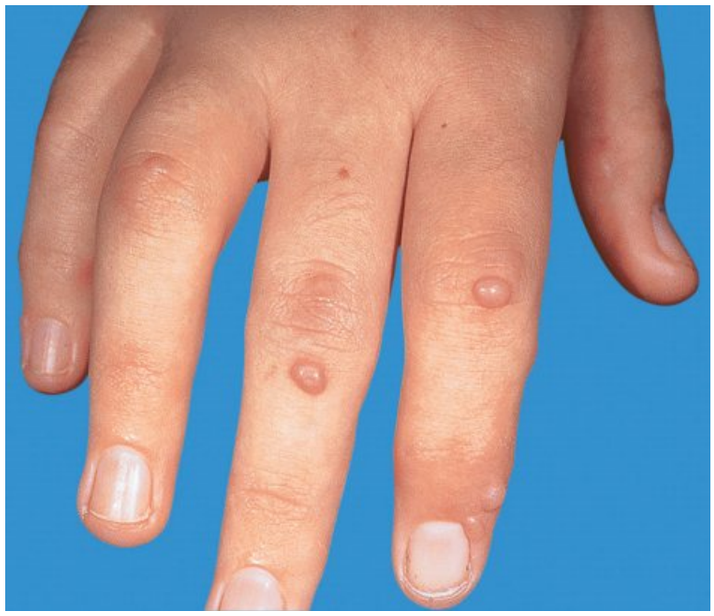


Fig. 53.11 Multicentric reticulohistiocytosis. Multiple nodules are present on the dorsal hands in this adolescent. This patient did not have a malignancy.

There is growing recognition of the role both inherited and acquired disorders of hypercoagulability or thrombophilia play in various skin disorders[20] (see Chs. 23 and 105). Some associations, such as those between protein C deficiency and neonatal purpura fulminans or prothrombin gene mutations and livedoid vasculopathy, are fairly well understood. However, there are other disorders in which cutaneous thromboses have been identified (e.g. calciphylaxis) where the precise role remains less well defined. Evaluation for hypercoagulability is warranted in patients with unexplained cutaneous thrombosis (see Table 105.9).



Fig. 53.12 Paget disease of the breast. A chronic, erythematous plaque surrounds the nipple. *Courtesy Robert Hartman, MD.*

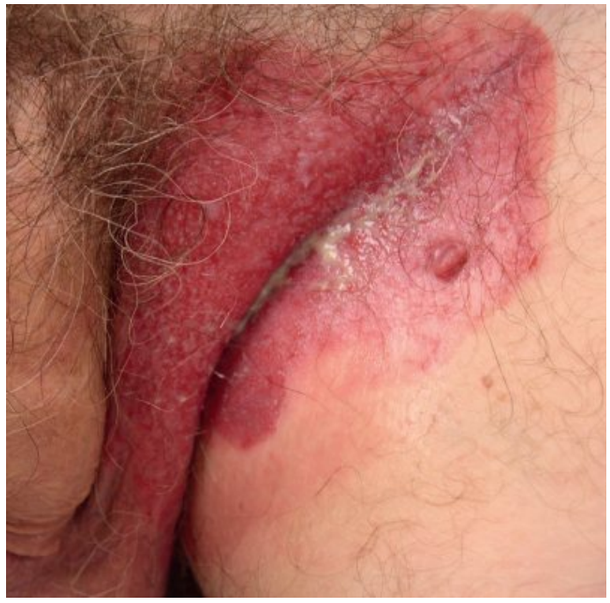


Fig. 53.13 Extramammary Paget disease. Eroded erythematous plaque with exudate, especially in the inguinal crease. The patient refused any further evaluation and had never undergone colonoscopy or cystoscopy.

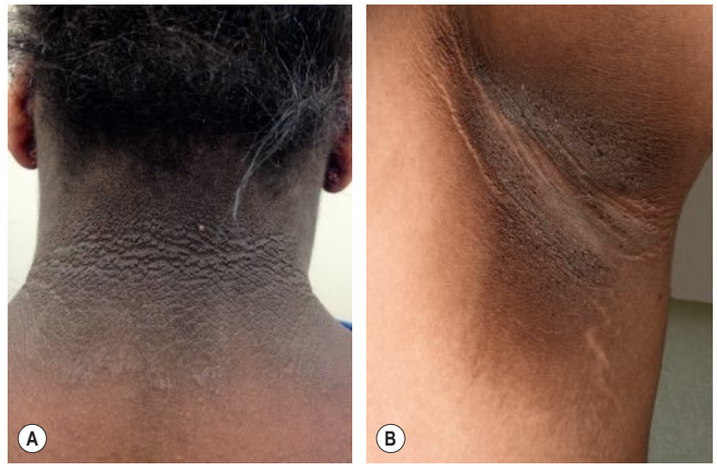


Fig. 53.14 Acanthosis nigricans. A Involvement of the posterior neck in a young woman with obesity and insulin resistance. There is also an acrochordon. **B** Axillary involvement in an obese 10-year-old Filipino boy with insulin resistance and a strong family history of type 2 diabetes mellitus. *B, Courtesy Julie V. Schaffer, MD.*



Fig. 53.15 Acanthosis nigricans (AN) of the hands. A Changes of AN overlie the knuckles in a patient with insulin resistance and obesity; acanthosis nigricans can involve extensor surfaces as well as flexural areas. **B** Diffuse involvement of the dorsal aspect of the fingers. Evaluation for an internal malignancy is recommended in patients with this type of clinical presentation. *A, Courtesy Jean L. Bolognia, MD; B, Courtesy Joyce Rico, MD.*

EVALUATION OF THE PATIENT WITH ACANTHOSIS NIGRICANS

Was AN apparent at birth or during early childhood and associated with skeletal abnormalities and/or short stature?	Consider autosomal dominant disorders due to FGFR defects, especially if AN is extensive: • Crouzon syndrome with AN (features craniosynostosis), SADDAN, and thanatophoric dysplasia (*FGFR3* mutations) • Beare–Stevenson cutis gyrata syndrome (features craniosynostosis; *FGFR2* mutations) Consider: • Costello syndrome (see Table 53.12) • Rabson–Mendenhall syndrome (features dental dysplasia, insulin-resistant diabetes mellitus; compound heterozygote for *INSR* mutation)
Was AN apparent during childhood or adolescence and associated with loss/absence of subcutaneous fat?	Consider generalized lipodystrophy (more extensive AN with congenital variant) or partial lipodystrophy (familial > acquired (see Ch. 101))
Was the onset sudden and accompanied by constitutional symptoms or weight loss?	Consider underlying malignancy, particularly if AN is extensive and involves sites such as the palms and soles. Restaging is required if AN recurs in a patient with a known malignancy
Is the patient overweight or obese?	Evaluate for associated insulin resistance states, especially diabetes mellitus. Consider evaluation for other underlying endocrinopathies, including thyroid disease
Does the patient have striae, hypertension, central obesity and/or a buffalo hump?	Evaluate for Cushing syndrome
If female, does the patient have acne, hirsutism and/or irregular menses?	Evaluate for polycystic ovary syndrome and HAIR-AN syndrome (see Fig. 70.17)
Is the patient on medications such as niacin, human growth hormone, oral contraceptives, corticosteroids or protease inhibitors?	AN may be drug-induced

Fig. 53.16 Evaluation of the patient with acanthosis nigricans (AN). Severe acanthosis nigricans may also be associated with epidermal growth factor receptor (EGFR) variants. FGFR, fibroblast growth factor receptor; HAIR-AN, hyperandrogenemia, insulin resistance, acanthosis nigricans; INSR, insulin receptor; SADDAN, severe achrondroplasia with developmental delay and AN.

CUTANEOUS DISEASES IN PATIENTS WITH ENDOCRINOLOGIC AND/OR METABOLIC DISORDERS

Cutaneous manifestations may provide important clues to the diagnosis of endocrine disorders, including diabetes mellitus[21]. Patients with endocrine diseases are especially susceptible to a number of associated mucocutaneous disorders.

Diabetes mellitus is a very common medical condition that affects almost every organ system. Table 53.4 summarizes cutaneous manifestations of diabetes mellitus (Figs. 53.17–53.22). Further details are available in reviews on the subject[19,21].

The primary characteristics of *metabolic syndrome* are central obesity, hypertension, dyslipidemia, and type 2 diabetes. Almost all patients have insulin resistance, and it is associated with a high risk of cardiovascular disease. Clinical criteria for the diagnosis of metabolic syndrome are outlined in Table 53.5. Women with polycystic ovary syndrome have a greater frequency of metabolic syndrome and often present with acanthosis nigricans, acne vulgaris, and hirsutism[22]. An association between psoriasis vulgaris and metabolic syndrome has also been identified, which may account for why patients with moderate to severe psoriasis have an increased risk of atherosclerotic cardiovascular disease[23].

Thyroid disease is also associated with a significant number of dermatologic disorders. Several reviews have highlighted these

SELECTED DERMATOLOGIC ASSOCIATIONS OF DIABETES MELLITUS

Dermatosis	Clinical description	Comments
Acanthosis nigricans (AN)	Velvety hyperpigmentation of the intertriginous/flexural areas (Fig. 53.14) and, less often, extensor surfaces (Fig. 53.15A)	Commonly associated with insulin resistance in both adults and children Most patients are obese More common in Hispanics and African-Americans
Acral dry gangrene	Necrosis of the toes > fingertips	Ischemia due to peripheral arterial disease
Acral erythema	Erysipelas-like erythema of the hands and/or feet	May be due to small vessel occlusive disease with compensatory hyperemia or autonomic dysfunction
Carotenoderma	Diffuse orange–yellow skin color	Related to an increase in serum carotene level
Charcot foot (neuropathic osteoarthropathy)	Erythema, warmth, swelling (early) Rocker bottom foot (later)	May be misdiagnosed as cellulitis, acute gout, or osteomyelitis
Diabetic bullae (bullous diabeticorum)	Tense non-inflammatory bullae on the lower extremities (Fig. 53.17)	Uncertain pathogenesis; microangiopathy possible contributor
Diabetic cheiroarthropathy	Thickened skin and limited joint mobility of the hands and fingers, leading to flexion contractures (starting with the fifth digit and progressing radially) and an inability to approximate the palmar surfaces of the hands and fingers (prayer sign; Fig. 53.18)	Postulated to result from increased glycosylation of collagen in the skin Associated with retinopathy, nephropathy, and duration (but not control) of the DM
Diabetic dermopathy	Brown atrophic macules and patches on the legs (Fig. 53.19)	Possibly due to trauma with altered healing due to microangiopathy
Disseminated granuloma annulare	Erythematous annular lesions composed of papules	There is controversy about the exact relationship of disseminated granuloma annulare and DM (see Ch. 93)
Eruptive xanthomas	Red–yellow papules that appear over a period of weeks to months (Fig. 53.20)	Associated with elevated serum triglycerides in patients with poorly controlled diabetes Control of the DM results in resolution of the xanthomas (see Ch. 92)
Hemochromatosis	Generalized bronzing of the skin due primarily to an increase in melanin	Excess iron stores associated with cirrhosis and cardiac dysfunction as well as DM Due to mutations in *HFE* (most commonly C282Y) and a risk factor for porphyria cutanea tarda
Necrobiosis lipoidica	Yellow atrophic patches, most often on the shins; a red–brown rim may indicate activity at the border (Fig. 53.21) Ulceration can occur and is often slow to heal	Develops in <1% of patients with DM (see Ch. 93) Not always associated with DM
Neuropathic ulcers	Non-painful ulcerations at sites of pressure, most commonly on the foot (Fig. 53.22) When the ulcer is on the plantar surface, a characteristic keratotic rim is seen	Associated with sensory neuropathy (see Ch. 105) Distinguish purely neuropathic ulcers from neuroischemic ulcers which also require vascular evaluation
Perforating disorders (e.g. acquired perforating dermatosis)	Keratotic papules, primarily on the extremities	Diabetic patients with chronic kidney disease on dialysis (see Ch. 96)
Rubeosis	Chronic, flushed appearance of the face, neck and upper extremities	Improves with dietary diabetic control and flares with vasodilator therapies
Scleredema (adultorum of Buschke)	Induration of the upper back and nape due to glycosaminoglycan deposition May have overlying erythema	No relationship to control of DM Also referred to as type III scleredema (see Ch. 46)

Table 53.4 Selected dermatologic associations of diabetes mellitus (DM). Additional cutaneous conditions associated with DM include hirsutism (e.g. related to polycystic ovary syndrome or HAIR-AN – *h*yperandrogenemia, *i*nsulin *r*esistance, *a*canthosis *n*igricans; see Ch. 70), necrolytic migratory erythema (in the setting of DM due to a glucagon-secreting pancreatic tumor; see Table 53.2), compensatory and gustatory hyperhidrosis (see Ch. 39), vitiligo, and infections such as mucocutaneous candidiasis, furuncles, abscesses, cellulitis, necrotizing fasciitis, malignant otitis externa, and erythrasma (especially the disciform variant). *Adapted from Jorizzo JL, Callen JP. Dermatologic manifestations of internal disease. In: Arndt KA, Robinson JK, LeBoit PE, et al (eds). Cutaneous Medicine and Surgery. Philadelphia: WB Saunders, 1996:1863–89.*



Fig. 53.17 Bullosis diabeticorum (diabetic bullae). Non-inflammatory bullae on the lower extremity in a patient with diabetes mellitus.



Fig. 53.19 Diabetic dermopathy. Note the brown macules and patches on the shins. *Courtesy Jean L. Bolognia, MD.*



Fig. 53.21 Necrobiosis lipoidica. This plaque on the shin has an inflammatory border and a yellow color with atrophy and telangiectasias centrally. Controversy exists about the exact risk of diabetes mellitus in such patients, but it is much more strongly associated with diabetes than is granuloma annulare.

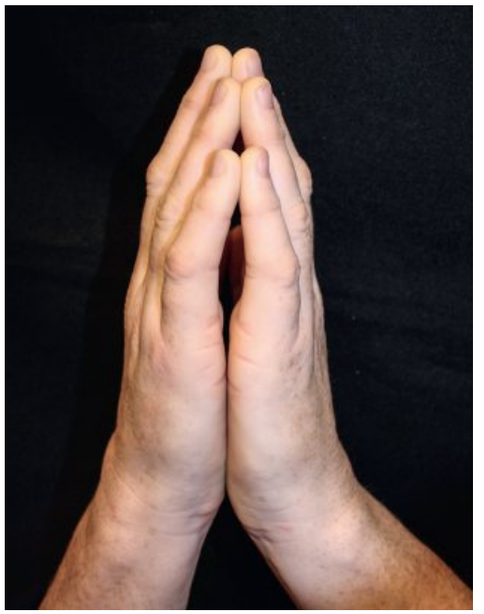


Fig. 53.18 Diabetic cheiroarthropathy (diabetic stiff hand syndrome). Because of limited joint mobility and thickening of the skin of the hand, the patient is unable to appose the palms ("prayer sign"). *Courtesy Jean L. Bolognia, MD.*



Fig. 53.20 Eruptive xanthomas in association with poorly controlled diabetes mellitus. This patient was first discovered to have diabetes following the appearance of these yellow–red papules.



Fig. 53.22 Neuropathic ulcers on the toes of a patient with diabetic sensory neuropathy.

CRITERIA FOR THE CLINICAL DIAGNOSIS OF METABOLIC SYNDROME
• Elevated waist circumference (population- and country-specific definitions)
• Elevated triglycerides (≥150 mg/dl)
• Reduced HDL (<40 mg/dl in males; <50 mg/dl in females)
• Elevated blood pressure (systolic ≥130 and/or diastolic ≥85 mm/Hg)
• Elevated fasting blood glucose (≥100 mg/dl)

Table 53.5 Criteria for the clinical diagnosis of metabolic syndrome. Metabolic syndrome is identified by the presence of three of these five criteria. Drug treatment for dyslipidemia, hypertension or hyperglycemia also fulfills the corresponding criterion. Most patients with type 2 diabetes mellitus meet criteria for metabolic syndrome. *Adapted from Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–5.*

DERMATOLOGIC MANIFESTATIONS OF THYROID DISEASE		
	Hyperthyroidism	**Hypothyroidism**
Cutaneous changes	Fine, velvety, smooth skin Warm and moist due to increased sweating Hyperpigmentation – localized or generalized Pruritus	Dry, rough, coarse skin Cold and pale Boggy and edematous skin (myxedema) Yellow discoloration as a result of carotenoderma Easy bruising (capillary fragility)
Cutaneous diseases	Pretibial myxedema*, thyroid acropachy (acral soft tissue swelling, periostitis, and clubbing of the digits) Urticaria, dermographism Increased incidence of vitiligo	Acquired ichthyosis and palmoplantar keratoderma Eruptive and/or tuberous xanthomas Increased incidence of vitiligo
Hair changes/ diseases	Fine, thin Mild, diffuse alopecia Increased incidence of alopecia areata	Dull, coarse, brittle Slow growth (increase in telogen hair phase) Alopecia of the lateral third of the eyebrows Increased incidence of alopecia areata
Nail changes	Onycholysis	Thin, brittle, striated
	Koilonychia	Slow growth
	Clubbing from thyroid acropachy	Onycholysis (rare)

*Can persist when patient is treated and becomes euthyroid or can be associated with euthyroid Graves disease.

Table 53.6 Dermatologic manifestations of thyroid disease. Serum thyroid-stimulating hormone (TSH) level is the most reliable test of thyroid function; it is usually markedly suppressed in patients with hyperthyroidism. Additional laboratory findings in hyperthyroid patients include elevated free T_3 and/or free T_4 levels. Patients with primary hypothyroidism have elevated TSH levels and decreased free T_4 levels. The detection of anti-thyroid peroxidase and/or anti-thyroglobulin antibodies suggests autoimmune thyroid disease (Hashimoto thyroiditis, Graves disease) while the presence of anti-TSH receptor antibodies points to Graves disease. Ascher syndrome consists of blepharochalasis, double lip, and goiter.

dermatologic manifestations and associations[24], and they are summarized in Table 53.6.

Adrenal disease classically manifests as excessive (Cushing syndrome) (Fig. 53.23 & 53. 24) or insufficient (Addison disease) corticosteroid activity (Fig. 53.25); this can include gluco- and mineralocorticoids. Excessive production of adrenal androgens may also occur (see Ch. 70). Features of these syndromes are outlined in Table 53.7 (see Ch. 125).



Fig. 53.23 "Buffalo hump" of Cushing syndrome due to fat redistribution. The patient also has evidence of hirsutism. *Courtesy Judit Stenn, MD.*



Fig. 53.24 Cushing syndrome with multiple striae. *Courtesy Judit Stenn, MD.*

CUTANEOUS GASTROENTEROLOGY

With the exception of Table 25.13, cutaneous aspects of gastroenterologic or hepatic disease are not specifically discussed elsewhere in this text[25–27]. Table 53.8 is a list of selected cutaneous associations of Crohn disease and ulcerative colitis (Figs. 53.26–53.28). Patients with ostomies, particularly those with an ileostomy, may develop peristomal dermatoses, the most common of which are listed in Table 53.9. Table 53.10 lists dermatologic conditions associated with gastrointestinal bleeding or hemorrhage (Figs. 53.29–53.32)[26].

Table 53.11 lists selected dermatologic aspects of liver disease[27]. Necrolytic acral erythema has been described in association with hepatitis C viral infection. This entity is histologically similar to necrolytic migratory erythema (see above), but is clinically distinct in that it primarily involves acral sites. The lesions present as painful or pruritic, pink to violet–brown plaques with hyperkeratosis (Fig. 53.33).



Fig. 53.25 Diffuse hyperpigmentation of Addison disease. The hyperpigmentation (shown in contrast to the physician's hand) is accentuated in sun-exposed skin and can also involve sites of trauma, skin creases, and mucosae.

DERMATOLOGIC MANIFESTATIONS OF ADRENAL DISORDERS	
Cushing disease*	**Addison disease**
Altered subcutaneous fat distribution • Rounded "moon" facies • Dorsal cervical fat deposition "buffalo hump" (Fig. 53.23) • Pelvic girdle fat deposition • Reduced fat in the arms and legs	Hyperpigmentation (MSH-like effect of ACTH) • Diffuse with accentuation in sun-exposed skin (Fig. 53.25) • Prominent at sites of trauma • Axillae, perineum, nipples • Palmar creases • Mucous membranes • Hair • Nails (longitudinal melanonychia) • Melanocytic nevi and lentigines
Skin atrophy • Multiple striae (Fig. 53.24) • Fragile skin • Prolonged wound healing • Purpura from minor trauma	Loss of androgen-stimulated (axillary, pubic) hair in postpubertal women
Cutaneous infections • Tinea (pityriasis) versicolor • Dermatophytosis and onychomycosis • Candidiasis	Fibrosis and calcification of cartilage, including ear (rare)
Acne	Vitiligo, alopecia areata, mucocutaneous candidiasis (in patients with APECED syndrome)
Hirsutism	
*Screening tests include urine free cortisol (24-hour), late-night salivary cortisol, 1-mg overnight low-dose dexamethasone suppression test (DST), and 8-mg overnight high-dose DST.	

Table 53.7 Dermatologic manifestations of adrenal disorders. Both over- and underproduction of adrenal hormones lead to characteristic skin findings. The plasma adrenocorticotropic hormone (ACTH) level is elevated in Cushing disease (pituitary overproduction) and ectopic ACTH syndrome, whereas it is suppressed in patients with adrenal tumors. Plasma ACTH levels are also elevated in patients with primary adrenocortical insufficiency (Addison disease) and suppressed in secondary adrenocortical insufficiency due to exogenous corticosteroid administration. When adrenal insufficiency is suspected, including in patients receiving a prolonged course of corticosteroids, an ACTH stimulation test can provide useful information. APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; MSH, melanocyte stimulating hormone.



Fig. 53.26 Pyoderma gangrenosum in a patient with ulcerative colitis and relapsing polychondritis. Central ulceration preceded by a violaceous bulla with an inflammatory border. *Courtesy Frank Samarin, MD.*



Fig. 53.27 Peristomal pyoderma gangrenosum in the setting of inflammatory bowel disease. Patients with ostomies, particularly ileostomies, are at risk for peristomal dermatoses, including pyoderma gangrenosum.

SKIN FINDINGS IN CROHN DISEASE AND ULCERATIVE COLITIS

• Erythema nodosum – often reflective of active bowel disease
• Urticaria
• Cutaneous small vessel vasculitis, cutaneous polyarteritis nodosa
• Thrombotic vasculopathy
• "Pustular" vasculitis or bowel-associated dermatosis–arthritis syndrome-like lesions
• Pyoderma gangrenosum – primarily the classic (typical) ulcerative form (Fig. 53.26) or peristomal lesions (Fig. 53.27); a vegetative pustular variant (pyoderma vegetans) occasionally occurs. These lesions may or may not reflect activity of the bowel disease
• Other neutrophilic dermatoses, ranging from acneiform lesions to Sweet syndrome to neutrophilic panniculitis
• Oral lesions (see Chs. 25 & 72)
  • Granulomatous infiltrates (with Crohn disease only)
  • Aphthosis
  • Angular cheilitis, including in children
  • Pyostomatitis vegetans (mucosal variant of pyoderma gangrenosum)
• Contiguous (anogenital) and noncontiguous ("metastatic") Crohn disease (Fig. 53.28)
• Fistulae (perianal and abdominal)
• Genital lymphedema
• Perianal skin tags
• Acquired acrodermatitis enteropathica-like lesions (patients with zinc deficiency and/or essential fatty acid deficiency)
• Epidermolysis bullosa acquisita
• Psoriasis
• Hidradenitis suppurativa

Table 53.8 Skin findings in Crohn disease and ulcerative colitis. See Ch. 93 for discussion of mucocutaneous manifestations of Crohn disease.



Fig. 53.28 "Metastatic" Crohn disease. Noncontiguous granulomatous inflammation of the skin is often manifested by deep inflammatory fissures in the inguinal folds. These have been described as "knife-like" fissures.



Fig. 53.29 Hereditary hemorrhagic telangiectasia. Several small red macules and papules on the lips. *Courtesy Irwin Braverman, MD.*



Fig. 53.30 Blue rubber bleb nevus syndrome. Several venous malformations are evident on this patient's tongue.

PERISTOMAL SKIN DISORDERS	
Skin disorder	**Comments**
Irritant contact dermatitis	Most common cause of peristomal dermatitis, especially in patients with an ileostomy Primarily attributed to exposure to feces or urine
Pre-existing skin disease (e.g. psoriasis, seborrheic dermatitis, atopic dermatitis)	May reflect Koebner phenomenon Exclude primary contact dermatitis or infection or superimposed contact dermatitis
Cutaneous infection (*Candida* spp., dermatophyte, herpes virus [primarily simplex], bacteria [especially *Staphylococcus aureus*])	Colonization with bacteria and/or yeast is common Recent treatment with antibiotics predisposes to candidiasis May initially improve then worsen if treated inappropriately with topical corticosteroids
Allergic contact dermatitis	Relatively uncommon; potential allergens include: adhesive pastes, adhesive ring or wafer of stoma bag, ostomy bag, epoxy resin, rubber, lanolin, and fragrances Patch test with both standardized allergens and patient's own products
Pyoderma gangrenosum	Infrequent cause of peristomal dermatitis Most common in patients with inflammatory bowel disease (Fig. 53.27)
Pseudoverrucous papules and nodules	Seen more commonly in association with urostomies; may be misdiagnosed as verrucae vulgares or condylomata acuminata
Bullous pemphigoid	Localized to stoma site but may precede generalized disease Exclude bullous contact dermatitis

Table 53.9 Peristomal skin disorders. Peristomal skin disorders are common and may limit use and efficacy of the stoma appliance. When the etiology **is uncertain, evaluation can include KOH examination, microbial cultures, patch testing, and histologic examination.** *Adapted from Lyon CC, Smith AJ, Griffiths CE, Back MH. The spectrum of skin disorders in abdominal stoma patients. Br J Dermatol 2000;143:1248–60.*

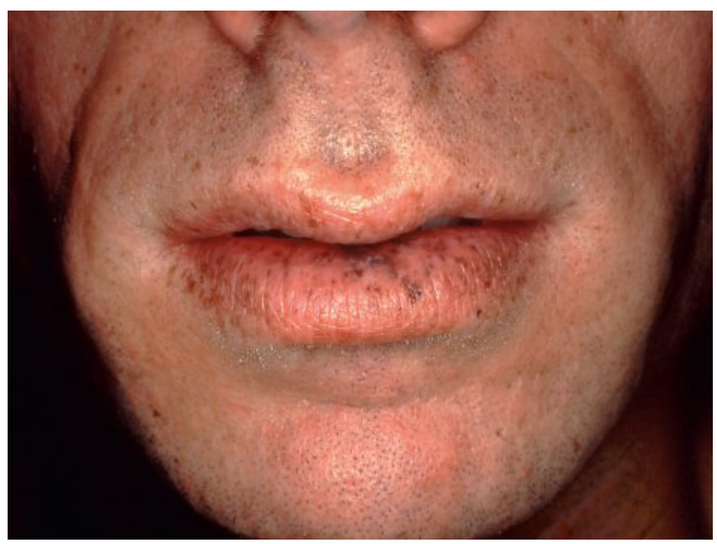


Fig. 53.31 Peutz–Jeghers syndrome. Multiple brown macules on the vermilion lips and a few on the lower cutaneous lip.

CUTANEOUS DISEASES ASSOCIATED WITH GASTROINTESTINAL BLEEDING OR HEMORRHAGE				
Disorder	**Cutaneous findings**	**Gastrointestinal features**	**Other pertinent findings**	**Treatment and comments**
Genetic (especially those associated with vascular malformations and GI polyps)				
Hereditary hemorrhagic telangiectasia (HHT)	Macular and papular telangiectasias on facial and acral skin as well as the oral mucosa (Fig. 53.29) Telangiectasias actually represent arteriovenous malformations (AVMs)	Recurrent hemorrhage in the upper GI tract due to AVMs Subset of patients have both juvenile GI polyposis and HHT, most commonly due to mutations in *SMAD4*; associated risk of early-onset colorectal cancer	Epistaxis is often the initial manifestation AVMs of the lungs, liver, and CNS	AD; ~80% of patients have mutations in *ENG* or *ACVRL1*, which encode endoglin and ALK1, both of which are TGF-β receptors Evaluation outlined in Table 104.6 Treatment consists of surgical resection, embolization or laser therapy of AVM causing hemorrhage
Blue rubber bleb nevus syndrome	Subcutaneous blue to purple venous malformations (Fig. 53.30)	GI vascular malformations	Possible vascular malformations in other organs (e.g. CNS, lungs, heart)	Mosaic due to double (cis) somatic *TEK* mutations in lesional tissue
Pseudoxanthoma elasticum	Yellow papules and plaques on neck and in intertriginous zones, redundant lax skin	Upper or lower GI hemorrhage	Angioid streaks in the eye, hypertension, premature atherosclerosis, uterine hemorrhage, vascular calcification	AR; due to mutations in *ABCC6*; PXE-like skin findings when mutations in *ENPP1* and *GGCX* Diet high in magnesium may be helpful
Ehlers–Danlos syndrome, vascular type	Translucent fragile skin with extensive bruising	GI hemorrhage due to arterial rupture or intestinal perforation	Minimal joint hyperextensibility (limited to digits), rupture of other arteries or the uterus, acrogeric facies	AD; deficiency of type III collagen
Gardner syndrome	Epidermoid cysts, pilomatricomas, lipomas, fibromas, and desmoid tumors	Hemorrhage from adenomatous colonic polyps Adenocarcinoma of the colon is universal if the colon is not removed	Mandibular and maxillary osteomas and cysts, *c*ongenital *h*ypertrophy of the *r*etinal *p*igment *e*pithelium (CHRPE)	AD; due to mutations in *APC* Colectomy must be appropriately timed
Peutz–Jeghers syndrome	Melanotic macules on mucosal surfaces (Fig. 53.31) and, less often, on acral or perioral skin	Hamartomatous polyps throughout the GI tract Intussusception or hemorrhage may occur	Increased incidence of breast, GI (colorectal, stomach, pancreatic, small intestine), lung, and GU (ovarian, uterine, cervical, testicular) carcinomas	AD; due to mutations in *STK11*, which encodes a serine/threonine kinase Screening includes upper endoscopy, video capsule endoscopy or MRE, and colonoscopy, beginning at age 8 years See www.cancer.net for additional screening recommendations
Cowden syndrome (PTEN hamartoma syndrome; multiple hamartoma syndrome)	Multiple facial or periorificial papules (tricholemmomas), perioral lentigines, cobblestoning of the oral mucosal surface (Fig. 53.32), acral keratotic papules, sclerotic fibromas, lipomas	Hamartomatous polyps throughout the GI tract Bleeding is rare as is colorectal carcinoma	Fibrocystic breast disease along with frequent cancers of the breast, often bilateral Thyroid tumors, including cancer GU carcinomas	AD; due to mutations in the *PTEN* tumor suppressor gene Screening recommendations are outlined in Table 63.3
Muir–Torre syndrome	Benign and malignant sebaceous neoplasms and multiple keratoacanthomas	Colorectal >> gastric carcinoma, carcinoma of the small bowel, hepatobiliary tract or pancreas	GU carcinomas (endometrial, ovarian, urinary tract) carcinomas second most common type after colorectal	AD; due to mutations in one of several mismatch repair genes, including *MSH2* (70%–90%), *MLH1* and *MSH6* Screening recommendations are outlined in Table 63.6
Inflammatory/autoimmune				
Cronkhite–Canada syndrome	Lentigines of buccal mucosa, face and hands/feet, alopecia, generalized nail thinning	Adenomatous GI polyps, diarrhea, abdominal pain	Weight loss due to malabsorption	Malignant degeneration is unusual, but 5-year mortality rate ~55%
Vasculitis	Palpable purpura, necrotizing livedo reticularis, nodules, or ulcers	Ulcerations secondary to vasculitis of the blood vessels in the bowel May be more common in IgA-associated vasculitis (Henoch–Schönlein purpura)	Arthritis and nephritis are two additional features of Henoch–Schönlein purpura	Corticosteroids and/or immunosuppressive agents may lead to improvement
Malignant atrophic papulosis (Degos disease)	Early lesions – pale red papules with central necrosis Late lesions – atrophic ivory scars	Small infarctions in the GI mucosa Hemorrhage and intestinal perforation may result in death	CNS involvement, pleuritis, pericarditis	No standard effective therapy Eculizumab and treprostinil may be beneficial in some patients Prognosis depends on systemic involvement

Table 53.10 Cutaneous diseases associated with gastrointestinal bleeding or hemorrhage.

CUTANEOUS DISEASES ASSOCIATED WITH GASTROINTESTINAL BLEEDING OR HEMORRHAGE				
Disorder	**Cutaneous findings**	**Gastrointestinal features**	**Other pertinent findings**	**Treatment and comments**
Ulcerative colitis	Erythema nodosum, vasculitis, pyoderma gangrenosum, aphthous stomatitis (see Table 53.8)	Uniform and continuous inflammation of the colon Rectal involvement is present in majority (>95%) of patients Toxic megacolon may develop	Colorectal carcinoma frequently occurs in uncontrolled, longstanding disease	Treatment options include 5-aminosalicylates, immunosuppressives (e.g. azathioprine, TNF inhibitors, vedolizumab), corticosteroids, and total colectomy
Crohn disease	Erythema nodosum, vasculitis, pyoderma gangrenosum, perianal fistulae, and noncontiguous Crohn disease (see Table 53.8)	Chronic inflammation, often granulomatous, of the bowel Skip areas occur	Aphthous stomatitis, arthritis, chronic blood loss	Treatment options include corticosteroids and other immunosuppressives, including azathioprine, TNF inhibitors, vedolizumab, ustekinumab, natalizumab
Nutritional				
Scurvy	Perifollicular purpura, corkscrew hairs	Collagen degeneration in the vasculature due to vitamin C deficiency GI blood loss results in anemia	Gingivitis with friable gums and easy bleeding, conjunctival hemorrhage, difficulty walking	Vitamin C replacement (see Table 51.2)
Neoplastic				
Kaposi sarcoma (KS)	Violaceous macules, papules, and nodules of the skin and oral mucosa	Similar tumors may occur in the GI tract Possible complications include ulceration, bleeding, perforation and ileus, which are more common in AIDS-related than in classic type	Includes AIDS-related (epidemic), African endemic, iatrogenic (immunosuppression-related), and classic subtypes (see Table 114.3) Caused by HHV-8 infection	Antiretroviral therapy or reduction of exogenous immunosuppression (if indicated), chemotherapy (e.g. liposomal anthracyclines, taxanes), and/or radiation therapy may be helpful for GI KS See Ch. 114 for treatment options for cutaneous KS
Adapted from refs 26 & 27.				

Table 53.10 Cutaneous diseases associated with gastrointestinal bleeding or hemorrhage. AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; GGCX, γ-glutamyl carboxylase; GI, gastrointestinal; GU, genitourinary; HHV, human herpesvirus; MRE, magnetic resonance enterography; SMAD, *s*mall (body size) plus *m*others *a*gainst *d*ecapentaplegic [involved in TGF-β signaling]; TGF, transforming growth factor.



Fig. 53.32 Gingival cobblestoning in Cowden disease. This patient also had trichilemmomas and a "Cowden nodule" or sclerotic fibroma on the neck.



Fig. 53.33 Necrolytic acral erythema. This is a manifestation of hepatitis C viral infection.

DERMATOLOGIC ASPECTS OF LIVER DISEASE		
Liver disease	**Dermatologic manifestations/associations**	**Other features, treatment, and comments**
Cirrhosis	• Spider angiomas and other telangiectasias • Palmar erythema • Dilated abdominal wall veins • Terry nails (white nail bed) • Muehrcke nails (transverse white bands) • Sparse axillary, pubic, and pectoral hair • Pruritus • Jaundice	• Gynecomastia • Parotid enlargement
Primary biliary cholangitis (PBC)	• Jaundice • Diffuse hyperpigmentation • Xanthomas – eruptive, planar and, occasionally, tuberous • Pruritus • May coexist with systemic sclerosis	Cholestyramine, rifampin, ursodiol, SSRIs, phototherapy, and opioid receptor antagonists may help to relieve pruritus (see Table 6.7) Treatment options for PBC include ursodiol, obeticholic acid, fibrates, colchicine, methotrexate, and liver transplantation
Hemochromatosis ("bronze diabetes")	• Generalized bronzing of the skin due primarily to an increase in melanin	See Table 53.4
Wilson disease (hepatolenticular degeneration)	• Kayser–Fleischer ring – golden brown or greenish circle of pigment in Descemet membrane at the periphery of the cornea • Blue lunulae • Pretibial hyperpigmentation	AR; due to mutations in *ATP7B* which encodes a copper-transporting ATPase Neuropsychiatric symptoms and jaundice are additional findings Treatment with copper-chelating drugs (trientine, penicillamine) or metallothionein-inducer drugs (zinc acetate); liver transplantation for hepatic failure
Hepatitis B and C viruses	• Cutaneous small vessel vasculitis (B,C) • Cryoglobulinemic vasculitis (C≫B) • Urticarial vasculitis (B,C) • Polyarteritis nodosa (classic – B, cutaneous – C) • Necrotizing livedo reticularis (C) • Urticaria (B,C) • Porphyria cutanea tarda (C>B) • Pruritus (B,C) • Lichen planus – particularly erosive oral disease (C) • Necrolytic acral erythema (Fig. 53.33) (C) • Gianotti–Crosti syndrome (B>C) • Erythema multiforme (B,C) • Erythema nodosum (B>C) • Sarcoidosis (following therapy with interferon and/or ribavirin) (C>B)	Treatment of hepatitis viral infections vary based on disease stage, patient comorbidities, and hepatitis C virus genotypes Hepatitis B Rx options include: entecavir, tenofovir, lamivudine, adefovir, telbivudine, and interferon Hepatitis C Rx options include: direct-acting antivirals (DAAs), which include hepatitis C protease and polymerase inhibitors (e.g. sofosbuvir + velpatasvir, glecaprevir + pibrentasvir); nowadays pegylated interferon + ribavirin is used less commonly

Table 53.11 Dermatologic aspects of liver disease. AR, autosomal recessive; Rx, treatment; SSRIs, selective serotonin reuptake inhibitors.

Blisters and erosions are common, and disease activity tends to wax and wane. Most reported cases have been associated with hepatitis C viral infection, and there has been variable success following treatment with oral zinc supplementation and/or treatment of the underlying hepatitis C viral infection. Occasionally, patients with hypothyroidism develop similar lesions[28].

OTHER SYSTEMIC DISEASES WITH CUTANEOUS MANIFESTATIONS

Sarcoidosis is an example of a multisystem disease with a range of cutaneous manifestations (see Ch. 93)[29]. Table 53.12 reviews the cardiac and dermatologic features of multisystem disorders (Fig. 53.34 & 53.35)[31,32]. Skin changes associated with pulmonary and renal disorders are summarized in Tables 53.13 and 53.14, respectively (Figs. 53.36–53.38)[33–38].

Pruritus is a feature of uremia, but can also occur in non-uremic patients on hemodialysis. It is still unclear why patients with chronic kidney disease on dialysis experience itching, and it may be localized or generalized (see Ch. 6).

Solid organ transplant recipients receive immunosuppressive agents, including cyclosporine, tacrolimus, sirolimus, azathioprine, and/or corticosteroids, in order to prevent rejection. The combination of these drugs predisposes the patient to two significant cutaneous problems: infection (e.g. HPV, CMV) and malignancy (e.g. squamous cell carcinoma, Kaposi sarcoma, Merkel cell carcinoma).

Pregnancy is an important physiologic state that is associated with its own specific dermatoses and with modification of other skin disorders (see Ch. 27)[39]. Mast cell disease is covered in Chapter 118. Internal diseases can have a range of effects on the nails, hair, and mucous membranes, and the reader is referred to the chapters that review these structures in detail. Leg ulcers are also potential clues to underlying disease and are discussed in Chapter 105.

Additional figures available in our eBook (see inside front cover for access code).

CARDIOCUTANEOUS ABNORMALITIES IN MULTISYSTEM DISORDERS			
Disease	**Cutaneous features**	**Cardiovascular findings**	**Comments**
Genetic			
Connective tissue disorders			
Cutis laxa	Lax redundant skin with reduced elasticity	Aortic dilation and rupture, pulmonary artery stenosis, right-sided heart failure	AD and AR forms due to mutations in several genes including those that encode elastin, EFEMP2/fibulin-4, fibulin-5, and V-type H^+ ATPase subunit (see Table 95.5); systemic involvement is more common in the AR form
Ehlers–Danlos syndrome (EDS)	Variable degree of skin hyperelasticity and fragility (e.g. "cigarette" paper scars, ecchymoses)	Classic and hypermobility types: aortic root dilation, mitral and tricuspid valve regurgitation or prolapse	Due to mutations in the genes encoding collagen V (classic type), tenascin X and adipocyte enhancer-binding protein 1 (classical-like types), collagen III (vascular type), and collagen I (cardiac valvular type)
		Vascular type: arterial aneurysms, dissection and rupture	
		Cardiac valvular type: valvular abnormalities	
Loeys–Dietz syndrome	Translucent skin, easy bruising, atrophic scarring, milia, atrophic scarring	Aortic aneurysms, arterial tortuosity; significant risk of aortic dissection and rupture, even at an early age	AD; mutations in the genes that encode TGF-β receptor 1 and 2, TGF-β 2 and 3, SMAD family member 2 and 3 Overlapping clinical features with Marfan syndrome and vascular type EDS, with variable craniofacial anomalies
Enzyme deficiencies			
Fabry disease	Angiokeratoma corporis diffusum, hypohidrosis	Hypertrophic cardiomyopathy, valvular abnormalities, conduction defects, progressive atherosclerotic disease of the coronary and cerebral arteries	α-Galactosidase A deficiency, X-linked recessive disorder Cardiac and cerebrovascular disease and renal failure are the usual causes of death
Homocystinuria	Livedo reticularis, malar rash, tissue-paper scars, diffuse pigmentary dilution	Atherosclerosis, arterial and venous thrombosis	AR; most commonly due to homozygous cystathionine β-synthase (CBS) deficiency; rarely due to deficiency of MTHFR or other enzymes listed in Table 97.1 Patients also exhibit marfanoid characteristics and ectopia lentis Hyperhomocysteinemia (due to homozygous MTHFR deficiency ≫ heterozygous CBS deficiency) also increases risk of arterial and venous thrombosis
Palmoplantar keratodermas			
Carvajal syndrome	Striate epidermolytic palmoplantar keratoderma, woolly scalp hair	Dilated left ventricular cardiomyopathy	AR; due to desmoplakin mutations
Naxos disease	Diffuse non-epidermolytic palmoplantar keratoderma, woolly scalp hair	Arrhythmogenic right ventricular cardiomyopathy	AR; due to mutations in the gene that encodes plakoglobin
Premature aging syndromes			
Hutchinson–Gilford progeria syndrome	Sclerodermoid changes, mottled hyperpigmentation, loss of subcutaneous fat, alopecia	Premature atherosclerosis	AD; premature aging syndrome due to mutations in the gene encoding lamins A and C
Werner syndrome	Premature graying, alopecia, sclerodermoid changes, loss of subcutaneous fat, ankle ulcerations	Premature atherosclerosis	Myocardial infarction is usually responsible for death by the fifth decade AR; due to mutations in *WRN*/*RECQL2*, which encodes a helicase Other features include cataracts and sarcomas
RASopathies (see NF1 below)			
Cardio-facio-cutaneous syndrome	Keratosis pilaris, keratosis pilaris atrophicans, focal palmoplantar keratoderma, numerous melanocytic nevi, café-au-lait macules, sparse curly hair, sparse or absent eyebrows and eyelashes	Pulmonic stenosis, atrial septal defects, hypertrophic cardiomyopathy	AD "RASopathy" due to mutations in four genes that encode proteins in the RAS/MAPK (mitogen-activated protein kinase) pathway (see Fig. 55.4): *BRAF* > *MAP2K1, MAP2K2* > *KRAS* Patients have characteristic facies, short stature, and developmental delay
Costello syndrome	Lax skin on the hands and feet, deep palmoplantar creases, periorificial papillomas, acanthosis nigricans, curly hair	Pulmonic stenosis, hypertrophic cardiomyopathy, arrhythmias	AD "RASopathy" due to mutations in two genes that encode proteins in the RAS/MAPK pathway: *HRAS* > *KRAS* Patients have mental and growth retardation and an increased risk of rhabdomyosarcoma and bladder carcinoma
Noonan syndrome with multiple lentigines/ LEOPARD syndrome	Multiple lentigines, café-au-lait and café-noir macules	ECG abnormalities, pulmonary artery stenosis	*L* – lentigines, *E* – ECG abnormality, *O* – ocular hypertelorism, *P* – pulmonary stenosis, *A* – abnormalities of the genitalia, *R* – retardation of growth, *D* – deafness AD "RASopathy" due to mutations in *PTPN11*, *RAF1*, and *BRAF* (see Fig. 55.4)

Table 53.12 Cardiocutaneous abnormalities in multisystem disorders.

Continued

CARDIOCUTANEOUS ABNORMALITIES IN MULTISYSTEM DISORDERS			
Disease	**Cutaneous features**	**Cardiovascular findings**	**Comments**
Tumor predisposition syndromes			
Carney complex (NAME and LAMB syndromes)	Cutaneous myxomas, blue nevi, lentigines, café-au-lait and café-noir macules	Atrial myxoma	Endocrine neoplasia of the adrenal glands, pituitary gland, and/or testes AD – due to mutations in *PRKAR1A*; 2nd genetic locus on chromosome 2p16
Multiple endocrine neoplasia (MEN) types 2A (Sipple syndrome) and 2B (multiple mucosal neuroma syndrome)	MEN 2A – notalgia paresthetica, macular or lichen amyloidosis, often with childhood onset MEN 2B – neuromas of the eyelids, lips, tongue and other mucosal sites	Hypertensive crises due to pheochromocytomas (often bilateral)	AD; due to mutations in the *RET* proto-oncogene Also manifest with medullary cell carcinoma of the thyroid (MEN 2A and 2B), parathyroid adenomas (MEN 2A), and a marfanoid habitus (MEN 2B)
Neurofibromatosis 1 (NF1)	Café-au-lait macules, neurofibromas, intertriginous freckling (lentigines)	Hypertension, essential or due to pheochromocytoma or renal artery stenosis	AD; due to mutations in *NF1*, which encodes neurofibromin; the latter interacts with the RAS/MAPK pathway (see Fig. 55.4)
Tuberous sclerosis complex (TSC)	Facial angiofibromas, ungual fibromas, ash leaf macules, shagreen patch	Cardiac rhabdomyomas, arrhythmias	Developmental delay, seizures, renal angiomyolipomas, CNS tumors, lymphangioleiomyomatosis (women) Due to mutations in *TSC1* or *TSC2*, which encode hamartin and tuberin, respectively
Other			
Hemochromatosis	Generalized bronzing of the skin due primarily to an increase in melanin	Congestive heart failure, supraventricular arrhythmias	See Table 53.4
Inflammatory/autoimmune			
Behçet disease	Oral and genital aphthae, pathergy, pustular vasculitis, pyoderma gangrenosum-like lesions, erythema nodosum-like lesions	Pericarditis, coronary arteritis, myocarditis, arrhythmias, valvular disease; vasculitis of the vasa vasorum, primarily of large blood vessels	Ocular and CNS involvement Inflammatory bowel disease should be excluded
Dermatomyositis	Gottron papules, heliotrope rash, photodistributed poikiloderma (see Table 53.2)	Usually asymptomatic; arrhythmias, conduction defects; pericarditis and congestive heart failure are rare	Cardiac involvement is a poor prognostic sign
DRESS/DIHS (drug hypersensitivity with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome)	Widespread morbilliform, urticarial or EM-like eruption and erythroderma; facial edema and lymphadenopathy often present	Myocarditis due to infiltrates of eosinophils Can occur during initial presentation or be delayed, including following corticosteroid taper Elevated cardiac enzymes, ECG changes, systolic dysfunction on echocardiography	Myocarditis associated with mortality rate up to 50%–55% Fever, hepatitis, and peripheral eosinophilia common (see Table 21.9) Treatment consists of discontinuation of offending drug and corticosteroids +/– other immunosuppressives Long-term consequences include persistent cardiac and thyroid dysfunction[30]
Kawasaki disease (mucocutaneous lymph node syndrome)	Glossitis, cheilitis, acral erythema, edema and desquamation, polymorphous eruption, conjunctival injection	Coronary arteritis, coronary artery aneurysms	High fever, lymphadenopathy Treatment with IVIg and aspirin significantly decreases risk of coronary artery disease
Neonatal lupus erythematosus (NLE)	Transient, non-scarring annular lesions of LE (SCLE-like) that favor the periorbital region	Congenital heart block (CHB)	Presumed to be due to transplacental passage of autoantibodies, most commonly anti-SSA/Ro, but anti-RNP also detected May have transient cytopenias and hepatitis Mothers may have a known AI-CTD (~50%) and in those without a known AI-CTD, a significant percentage will develop one over time; for mothers with anti-SSA/Ro antibodies, there is <1% chance of having a baby with NLE, but once have baby with NLE, chance in subsequent pregnancies is 25% Hydroxychloroquine may reduce recurrence rate
Systemic lupus erythematosus	Malar erythema, photosensitivity, range of lupus skin lesions Patients with antiphospholipid antibodies may have necrotizing livedo reticularis, leg ulcers or widespread cutaneous necrosis (Fig. 53.34)	Pericarditis, verrucous endocarditis (Libman–Sacks), coronary artery disease	Anti-cardiolipin antibody may play a role Treatment of LE with systemic corticosteroids may predispose to coronary artery disease
Multicentric reticulohistiocytosis	Erythematous nodules of the hands and, less often, the extremities and the face (Fig. 53.11)	Pericarditis, congestive heart failure, coronary artery disease, cardiomegaly	Deforming arthritis is frequent

Table 53.12 Cardiocutaneous abnormalities in multisystem disorders.

CARDIOCUTANEOUS ABNORMALITIES IN MULTISYSTEM DISORDERS			
Disease	**Cutaneous features**	**Cardiovascular findings**	**Comments**
Psoriasis	Well-demarcated, pink-to-red plaques with silvery scale on the elbows, knees and scalp, around the umbilicus, and in the gluteal cleft	Increased risk of cardiovascular disease, including cerebrovascular and peripheral artery disease In patients with moderate to severe psoriasis, possible increased risk of death from atherosclerotic cardiovascular disease	High incidence of metabolic syndrome in patients with moderate to severe psoriasis (see Table 53.5) Systemic therapy may reduce mortality from cardiovascular disease
Relapsing polychondritis	Beefy, red ears (sparing the lobes); inflammation in other tissues with cartilage (e.g. nose, larynx, trachea) Late findings include floppy ears and weakness in other areas where the cartilage was affected (Fig. 53.35)	Aortic and mitral regurgitation, aortic root dilation, aortic aneurysms (thoracic, abdominal) > heart block, pericarditis, coronary artery vasculitis	Arthritis, scleritis, eyelid edema and chemosis, tracheal collapse, MDS; for latter consider VEXAS syndrome Rx: dapsone, corticosteroids, and/or other immunosuppressive agents
Rheumatic fever	Erythema marginatum, subcutaneous nodules	Pancarditis in the acute phase Late manifestations include mitral and/or aortic valve dysfunction	Rare in US Follows pharyngitis due to group A β-hemolytic streptococcal infection Polyarthritis, chorea, fever
Sarcoidosis	Papules, nodules, plaques and/or lesions in scars (Fig. 53.36)	Conduction defects, congestive heart failure	Pulmonary disease, lymphadenopathy, hepatic involvement, hypercalcemia Cardiac involvement denotes a poor prognosis
Systemic sclerosis (scleroderma)	Cutaneous sclerosis, Raynaud phenomenon	Pulmonary artery hypertension, conduction defects, pericarditis, visceral Raynaud phenomenon	Cardiac involvement denotes a poor prognosis May also have interstitial lung disease
Vasculitis	Palpable purpura, nodules, livedo reticularis, ulcerations	Coronary artery vasculitis	Arthritis, GI colic, or bleeding Cardiac involvement is uncommon
Neoplastic			
Primary systemic amyloidosis (AL)	Pinch purpura, waxy skin, translucent papules, macroglossia	Restrictive cardiomyopathy, conduction disturbances	Proteinuria, urinary light chains, association with plasma cell dyscrasia ≫ multiple myeloma
Carcinoid syndrome	Flushing, telangiectasias, pellagra-like dermatitis, and occasionally sclerodermoid features	Endocardial plaques – tricuspid insufficiency, conduction defects	Flushing associated with ~10% of mid-gut tumors (small intestine, appendix, proximal colon) and liver metastases are required; type III gastric and bronchial carcinoid tumors are also associated with flushing (liver metastases are not required)
Infectious			
Endocarditis – bacterial or fungal	Purpura, nail-fold infarction, Janeway lesions, Osler's nodes In subacute bacterial endocarditis, vasculitis, digital clubbing	Vegetations and dysfunction of the valves	Fever often present
Metabolic/endocrine			
Diabetes mellitus	See Table 53.4	Coronary artery and peripheral artery disease	Occurs with both type 1 and type 2; insulin resistance may contribute
Hyperlipidemia	Xanthomas of multiple types	Coronary artery disease	See Ch. 92
Other			
Exfoliative erythroderma	Exfoliative dermatitis	High-output cardiac failure	The eruption may be idiopathic or due to a drug, primary skin disease (e.g. dermatitis, psoriasis), or neoplasm (e.g. cutaneous T cell lymphoma)
PHACE(S) syndrome	Segmental infantile hemangioma, most often of the face and neck	Coarctation of the aorta, atrial and ventricular septal defects, anomalous cervical and cerebral arteries	*P* – posterior fossa malformations, *H* – hemangioma, *A* – arterial anomalies, *C* – cardiac defects and coarctation of the aorta, *E* – eye anomalies, *S* – sternal defects and supraumbilical raphe

Table 53.12 Cardiocutaneous abnormalities in multisystem disorders. AD, autosomal dominant; AI-CTD, autoimmune connective tissue disease; AR, autosomal recessive; CNS, central nervous system; ECG, electrocardiogram; GI, gastrointestinal; EFEMP2, epidermal growth factor (EGF)-containing fibulin-like extracellular matrix protein 2; IVIg, intravenous immunoglobulin; LAMB, lentigines, atrial myxoma, mucocutaneous myxoma, blue nevi; LE, lupus erythematosus; MDS, myelodysplasia syndrome; MTHFR, methylenetetrahydrofolate reductase; NAME, nevi, atrial myxoma, myxoma of the skin, ephelides; TGF, transforming growth factor; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic. *Adapted from Jorizzo JL, Callen JP. Dermatologic manifestations of internal disease. In: Arndt KA, Robinson JK, LeBoit PE, et al (eds). Cutaneous Medicine and Surgery, Philadelphia: WB Saunders, 1996:1863–89.*



Fig. 53.34 Antiphospholipid antibody syndrome. In addition to bland thromboses, these patients may have cardiac valvular vegetations.

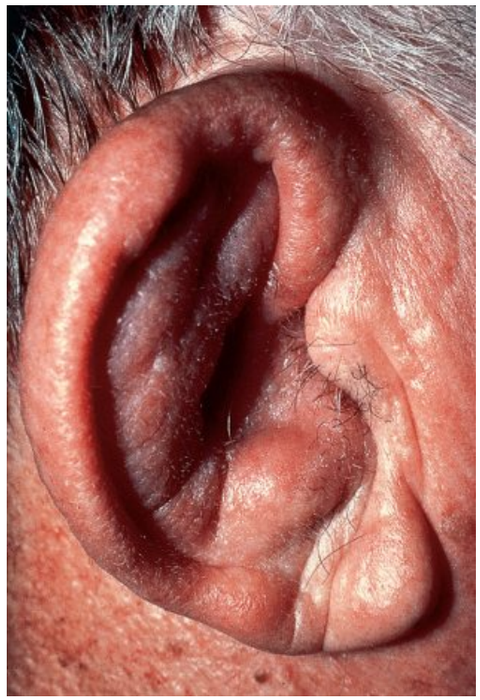


Fig. 53.35 Relapsing polychondritis. The inflammation spares the earlobes, which lack cartilage.

PULMONARY DISEASE AND THE SKIN				
Disorder	**Cutaneous findings**	**Pulmonary disease**	**Other features**	**Treatment and comments**
Genetic				
Birt–Hogg–Dubé syndrome	Classic triad of fibrofolliculomas, trichodiscomas and acrochordons	Lung cysts, spontaneous pneumothoraces	Increased risk of renal carcinoma Due to mutations in the gene encoding folliculin	High-resolution CT scan of the chest and renal MRI scan (preferred) or abdominal/pelvic CT scan* See Table 111.1 for recommendations regarding frequency of screening exams
Hereditary hemorrhagic telangiectasia	Macular and papular telangiectasias on facial and acral skin as well as the oral mucosa (Fig. 53.29) Telangiectasias represent AVMs	Pulmonary AVMs that can lead to hypoxia, hemorrhage, and paradoxical emboli	Epistaxis, recurrent GI bleeding, AVMs in other organs including the CNS	Transcatheter embolotherapy; antibiotic prophylaxis for procedures with risk of bacteremia and avoiding air bubbles during IV access (see Table 104.6)
Yellow nail syndrome	Thickened, slow-growing, excessively curved, yellow-to-green nails with onycholysis, transverse ridging, onychomadesis, and absent cuticles and lunulae	Pleural effusions, bronchiectasis, chronic bronchitis	Lymphedema, sinusitis	Complete triad of yellow nails, lymphedema and respiratory tract involvement seen in only one-third of patients; 2 of 3 findings needed for diagnosis Treatment options outlined in Ch. 71
Tuberous sclerosis complex	See Table 53.12	Lymphangioleiomyomatosis (women)	See Table 53.12	Outlined in Ch. 61
Inflammatory/autoimmune				
Sarcoidosis – chronic	Papules, nodules, plaques (Fig. 53.36), lupus pernio, lesions in scars and tattoos; acquired ichthyosis	Fibrosis secondary to granulomatous inflammation can lead to “honeycombing” of the lung parenchyma	Hypercalcemia, lymphadenopathy, hepatosplenomegaly, uveitis, CNS disease, bone cysts	Rx of skin lesions includes hydroxychloroquine, MTX, prednisone, other immunosuppressive agents (e.g. oral tacrolimus, TNF inhibitors, JAK inhibitors)
Sarcoidosis – acute	Erythema nodosum	Bilateral hilar lymphadenopathy	Arthritis, anterior uveitis	Self-limiting NSAIDs or potassium iodide may provide symptomatic relief

Table 53.13 Pulmonary disease and the skin.

PULMONARY DISEASE AND THE SKIN				
Disorder	**Cutaneous findings**	**Pulmonary disease**	**Other features**	**Treatment and comments**
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)	Vasculitic lesions (e.g. palpable purpura, nodules), crusted papules due to RGD, pyoderma gangrenosum-like ulcers (see Table 24.7)	Dyspnea, cough, hemoptysis, and/or pleuritis; irregular pulmonary infiltrates or nodules that may cavitate	Glomerulonephritis, upper respiratory tract inflammation, mucosal ulceration, friable hypertrophic gingiva ("strawberry gums")	Presence of antineutrophil cytoplasmic antibodies (ANCA) may aid in diagnosis Rx (usually combination): corticosteroids, rituximab, cyclophosphamide, methotrexate, sulfonamides
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)	Palpable purpura, urticarial plaques, nodules, crusted papules of the elbows due to RGD, ulcers (see Table 24.7)	Asthma, eosinophilic pneumonia	Paranasal sinusitis, allergic rhinitis, nasal polyps, peripheral eosinophilia, mononeuritis multiplex, systemic vasculitis	Presence of antineutrophil cytoplasmic antibodies (ANCA) may aid in diagnosis Rx: corticosteroids, cyclophosphamide, mepolizumab, and/or rituximab
Dermatomyositis	Diffuse scaling and pruritus of the scalp, heliotrope, Gottron papules and sign, photodistributed poikiloderma, nail-fold overgrowth with dilated capillary loops	Interstitial lung disease (ILD), aspiration pneumonitis, hypoventilation	Proximal, symmetric muscle weakness	If PFTs demonstrate reduced DLCO, high-resolution chest CT should be performed Higher risk with anti-MDA5 (CADM-140) antibodies and antisynthetase syndrome Rx: corticosteroids, immunosuppressive agents (e.g. MTX, mycophenolate mofetil, JAK inhibitors), and/or IVIg
Systemic sclerosis (scleroderma)	DcSSc: Raynaud disease (sudden onset), more widespread sclerosis LcSSc: Raynaud disease (preceding long duration), limited, acrofacial sclerosis	DcSSc: Interstitial lung disease (ILD) > pulmonary artery hypertension (PAH) LcSSc: PAH > ILD	Esophageal dysmotility, hypertension, renal crisis, cardiomyopathy	Evaluation of ILD: PFTs, high-resolution chest CT Evaluation of PAH: transthoracic echocardiography, serum N-Tpro-BNP level Rx: mycophenolate mofetil, cyclophosphamide for ILD; endothelin receptor antagonists, prostacyclin analogues, phosphodiesterase-5 inhibitors for PAH
Urticarial vasculitis	Urticarial papules and plaques, often with a subtle purpuric component, angioedema	Chronic obstructive pulmonary disease	Hypocomplementemic variant may involve the joints, GI tract, kidneys and eyes as well as the lungs; patients may have SLE or Sjögren syndrome	Oral corticosteroids, hydroxychloroquine, dapsone, colchicine (see Table 24.10)
Neoplastic/paraneoplastic				
Kaposi sarcoma	Red–violet to dark purple plaques and/or nodules of the skin and oral mucosa; in the classic form, most commonly seen on the lower extremities	Multifocal involvement can be asymptomatic or lead to dyspnea, cough, hemoptysis and/or chest pain (especially in AIDS-related type)	Lymphedema of the lower extremities Gastrointestinal involvement common	See Table 53.10 for systemic therapies
Lymphomatoid granulomatosis	Papulonodules, plaques, ulcers	Cough, dyspnea, and chest pain due to angiocentric, angiodestructive infiltrate of atypical lymphocytes	Fever, arthralgias, myalgias; associated with EBV infection and diffuse large B cell lymphoma	Multi-drug chemotherapy and/or rituximab. If present, reversal of exogenous immunosuppression
Paraneoplastic pemphigus	Erosive disease of the mucous membranes and erythema multiforme-like, bullous pemphigoid-like or lichenoid skin lesions	Bronchiolitis obliterans	Most often associated with non-Hodgkin lymphoma, chronic lymphocytic leukemia or Castleman disease	Abnormal PFTs Rx: rituximab, immunosuppressive/cytotoxic medications, and/or plasmapheresis, IVIg Resection of Castleman disease can lead to remission of mucocutaneous lesions
Infectious				
Tuberculosis	Lupus vulgaris, orificial, acute miliary, tuberculous gumma, scrofuloderma (see Table 75.7)	Apical infiltrates, cavitating infiltrates; non-productive or productive cough	Fever, weight loss	Multi-drug regimens based on patient and antibiotic sensitivities (see Ch. 75)
Blastomycosis†	Verrucous, ulcerated plaques or nodules; may be studded with pustules, especially at the periphery	Patchy infiltrates, nodules, interstitial or miliary disease Chest X-ray may be normal	Bone and GU involvement, including testes	Inhalation followed by dissemination, including to skin; treatment includes itraconazole, amphotericin B

Table 53.13 Pulmonary disease and the skin.

Continued

PULMONARY DISEASE AND THE SKIN				
Disorder	**Cutaneous findings**	**Pulmonary disease**	**Other features**	**Treatment and comments**
Cryptococcosis	Variable cutaneous findings, from papulonodules and plaques to molluscum contagiosum-like lesions and cellulitis	Varies from asymptomatic infection to severe pneumonia and acute respiratory distress syndrome	Meningeal involvement (needs to be excluded via lumbar puncture)	Severe infections favor immunocompromised hosts Depending upon severity, amphotericin B ± flucytosine and/or fluconazole
Aspergillosis	Angioinvasive *Primary* cutaneous lesions – violaceous or necrotic papules, plaques, or nodules *Secondary* cutaneous emboli – necrotic papules and plaques, often with ulceration and rapidly progressive	In those with disseminated cutaneous emboli, cavitating infiltrates and nodules	In immunocompromised hosts, can disseminate widely	Disseminated disease affects primarily patients who are neutropenic and immunosuppressed (e.g. chronic corticosteroids) Rx: voriconazole or posaconazole + echinocandin, voriconazole, posaconazole, isavuconazonium sulfate, or amphotericin B May require surgical debridement
Varicella	Lesions in various stages of development, including papules, papulovesicles, pustules, and hemorrhagic crusts; cephalocaudal progression	Pulmonary involvement correlates with severity of skin involvement Interstitial infiltrates or patchy airway disease leads to cough and dyspnea	Liver and CNS additional sites of infection Reye syndrome associated with use of aspirin	Adults, pregnant or postpartum women, and immunocompromised individuals at highest risk for pulmonary disease Systemic antiviral medications recommended (see Table 127.23)
Other				
Toxic epidermal necrolysis	Widespread necrosis and detachment	When there is involvement of bronchial epithelium Acute respiratory distress syndrome, secondary bacterial pneumonia Chronic sequelae	Erosions of the oropharyngeal, nasal, conjunctival, esophageal, and GU mucosa	Prompt discontinuation of all potential culprit drugs; treatment options include etanercept, cyclosporine, corticosteroids, and IVIg; management in intensive care or burn unit

*Renal surveillance begins at age 20 years.
†Primary pulmonary infection also occurs in other systemic mycoses due to dimorphic pathogens, including coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis.

Table 53.13 Pulmonary disease and the skin. Bronchiolitis obliterans can occur in the setting of graft-versus-host disease and thrombophilia with retiform purpura can be seen with severe SARS-CoV-2 infection. AVMs, arteriovenous malformations; CNS, central nervous system; CT, computed tomography; DcSSc, diffuse cutaneous systemic sclerosis; DLCO, diffusion of carbon monoxide; EBV, Epstein–Barr virus; GI, gastrointestinal; GU, genitourinary; HHV, human herpesvirus; IV, intravenous; IVIg, intravenous immunoglobulin; LcSSc, limited cutaneous systemic sclerosis; MRI, magnetic resonance imaging; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; *N*-Tpro-BNP, N-terminal pro b-type natriuretic peptide; PFTs, pulmonary function tests; RGD, reactive granulomatous dermatitis; Rx, treatment; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.

RENAL DISEASE AND THE SKIN				
Disorder	**Cutaneous findings**	**Renal abnormality**	**Other findings**	**Treatment and comments**
Genetic				
Tuberous sclerosis complex (TSC)	Facial angiofibromas, ash leaf macules, shagreen patch, ungual fibromas	Renal hamartomas (angiomyolipomas) Polycystic kidney disease may occur in a contiguous gene syndrome with TSC2	See Table 53.12	See Table 53.12
Fabry disease	Angiokeratoma corporis diffusum	Proteinuria, renal failure due to accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids	Acral pain and paresthesias, hypohidrosis, corneal and lenticular opacities Hypertrophic cardiomyopathy, coronary artery disease, CVAs	X-linked recessive disorder Replacement therapy with the deficient enzyme, α-galactosidase A, migalastat (oral chaperone), renal transplantation
Nail–patella syndrome	Hypoplasia of the nails, with greatest involvement of medial digits; triangular lunulae	Congenital nephrosis, glomerulonephritis	Absence or hypoplasia of the patella, iliac horns	AD; due to mutations in *LMX1B*
Birt–Hogg–Dubé syndrome	Classic triad of fibrofolliculomas, trichodiscomas and acrochordons	Renal tumors, in particular chromophobe, oncocytic, and/or hybrid	Spontaneous pneumothoraces, lung cysts	See Table 53.13 & Table 111.1
Hereditary leiomyomatosis and renal cell cancer (Reed syndrome)	Multiple cutaneous leiomyomas	Type 2 papillary renal cell carcinoma (early-onset, aggressive) > collecting duct renal cell carcinoma Benign cysts	Uterine leiomyomas	AD; due to mutations in the gene encoding fumarate hydratase. See Table 117.2 for screening recommendations
BAP1 tumor predisposition syndrome	Epithelioid atypical Spitz tumors, cutaneous melanoma	Clear cell renal cell carcinoma	Uveal melanoma, mesothelioma, cholangiocarcinoma	AD; due to mutations in *BAP1*

Table 53.14 Renal disease and the skin.

RENAL DISEASE AND THE SKIN				
Disorder	**Cutaneous findings**	**Renal abnormality**	**Other findings**	**Treatment and comments**
Inflammatory/autoimmune				
Systemic lupus erythematosus (SLE)	Malar erythema, cutaneous LE lesions, photosensitivity, diffuse alopecia, vasculitis	Glomerulonephritis – focal, membranous or proliferative	Arthritis, serositis, cytopenias, multiple autoantibodies, hypocomplementemia	Varies, depending upon the organ system involved and the severity or type of involvement
Systemic sclerosis (scleroderma)	Raynaud phenomenon, diffuse or limited cutaneous sclerosis, CREST syndrome	Hypertension, renal crisis	Esophageal dysmotility, arthritis, interstitial lung disease, pulmonary artery hypertension (see Table 53.13)	Angiotensin-converting enzyme inhibitors, avoidance of high-dose corticosteroids if possible to reduce risk of renal crisis, dialysis, renal transplantation
Henoch–Schönlein purpura	Palpable purpura	IgA-associated glomerulonephritis which may be chronic	Arthritis, GI vasculitis with abdominal pain, GI bleeding, and/or vomiting	Supportive care; systemic corticosteroids may be beneficial for nephritis
Systemic (classic) polyarteritis nodosa (PAN)	Palpable purpura, retiform purpura, livedo reticularis/racemosa, ulcers > subcutaneous nodules	Renal artery aneurysms, renovascular hypertension, renal failure	Arthritis, mononeuritis multiplex, abdominal pain, orchitis, fever	For systemic PAN, corticosteroids +/– cytotoxic agents (e.g. cyclophosphamide) If present, treat HBV infection
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)	Vasculitic lesions (e.g. palpable purpura, nodules), crusted papules due to PNGD, pyoderma gangrenosum-like ulcers (see Table 24.7)	Glomerulonephritis	See Table 53.13	See Table 53.13
Cutaneous small vessel vasculitis	Palpable purpura, urticarial lesions, hemorrhagic vesicles, and occasionally pustules or ulcerations	Glomerulonephritis may occur	Arthritis	Basic evaluation includes urinalysis Symptomatic therapy or corticosteroids, with or without immunosuppressive agents
Sarcoidosis	Papules, nodules, plaques (Fig. 53.36)	Hypercalciuria, nephrolithiasis	Lymphadenopathy, uveitis, pulmonary fibrosis, hepatosplenomegaly, CNS disease, hypercalcemia	Corticosteroids, immunosuppressive agents
Nephrogenic systemic fibrosis (NSF)	Woody indurated plaques on the extremities > trunk, often becoming confluent and limiting motion of the joints Peau d'orange appearance is common (Fig. 53.38)	Occurs primarily in patients with chronic renal failure on dialysis, but also described in renal transplant recipients and patients with acute renal failure	Systemic fibrosis (e.g. heart, lungs, skeletal muscle) has been observed Caused by gadolinium-containing contrast media Hypercoagulable state also a risk factor	Prevention via assessment of renal function pre-MRI Hemodialysis, renal transplantation, and, based upon case series, imatinib, rapamycin, UVA1 phototherapy, ECP
Neoplastic				
Primary systemic amyloidosis (AL)	Pinch purpura, hemorrhagic bullae, translucent papules, macroglossia	Proteinuria, including nephrotic syndrome, and renal insufficiency	Restrictive cardiomyopathy, paraproteinemia due to plasma cell dyscrasia	First line: daratumumab + dexamethasone + bortezomib + cyclophosphamide; lena-/pomalidomide, melphalan, isatuximab, hematopoietic stem cell transplant
Other				
Cutaneous changes of end-stage renal disease	1. Pale color, sallowness 2. Xerosis or acquired ichthyosis 3. Pruritus 4. Acquired perforating dermatosis 5. Pseudoporphyria 6. Calciphylaxis (Fig. 53.37) 7. Uremic frost	End-stage renal disease of various causes 1–6 are more common in dialysis patients; 7 is rarely observed	1. Anemia of chronic disease 2. – 3. Possible increase in tissue mast cells 4. Related to pruritus 5. Porphyrins may be borderline elevated or within normal limits 6. Risk factors include obesity, systemic corticosteroids, warfarin; calcium and phosphorus dysregulation, increased PTH level; calcification of the vessel walls and microthrombi lead to tissue necrosis	1. Erythropoietin, transplantation 2. Emollients, lactic acid or urea preparations 3. UV light 4. See Table 96.4 5. Erythropoietin, N-acetylcysteine 6. Dialysis optimization, phosphate binders (non-calcium), sodium thiosulfate, consider DOAC, wound care/hyperbaric oxygen; parathyroidectomy may be helpful 7. Dialysis
Cutaneous diseases associated with long-term immunosuppression	1. Infections – mycobacterial, viral, bacterial, fungal 2. Neoplasia – porokeratosis, squamous cell carcinoma, Kaposi sarcoma, Merkel cell carcinoma, melanoma	Transplant recipients with end-stage renal disease from various causes	–	Reduction in level of immune suppression Treat infections with appropriate antimicrobials Treat carcinomas with removal of lesions and reduce number with oral acitretin; consider sirolimus rather than calcineurin inhibitor

Table 53.14 Renal disease and the skin. AD, autosomal dominant; CNS, central nervous system; CREST, *c*alcinosis, *R*aynaud, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasias; CVA, cerebrovascular accident; DOAC, direct oral anticoagulant; ECP, extracorporeal photophoresis; GI, gastrointestinal; HBV, hepatitis B virus; MRI, magnetic resonance imaging; PTH, parathyroid hormone.



Fig. 53.36 Periorificial and facial papules of sarcoidosis. The presence of lesions on the nasal rim is often associated with granulomatous inflammation of the upper respiratory tract.



Fig. 53.37 Calciphylaxis. This patient presented with these necrotic skin lesions and was found to have severe end-stage renal disease due to renal amyloidosis.

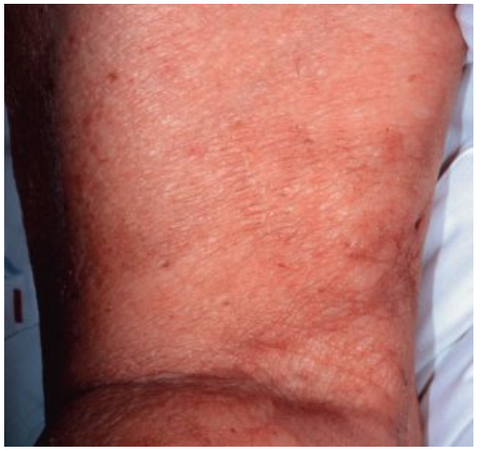


Fig. 53.38 Nephrogenic systemic fibrosis. This sclerosing disorder is seen almost exclusively in patients with renal failure who have received gadolinium-containing contrast media. In addition to the peau d'orange appearance of the skin, this patient had severe restriction of the movement of his hands, wrists, and feet.

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eFig. 53.1 Paraneoplastic pemphigus. Lesions that resemble bullous pemphigoid in a patient with immunopathologic confirmation of paraneoplastic pemphigus despite an underlying malignancy not having been detected.



eFig. 53.2 Paraneoplastic pemphigus. Oral lesions may resemble lichen planus.



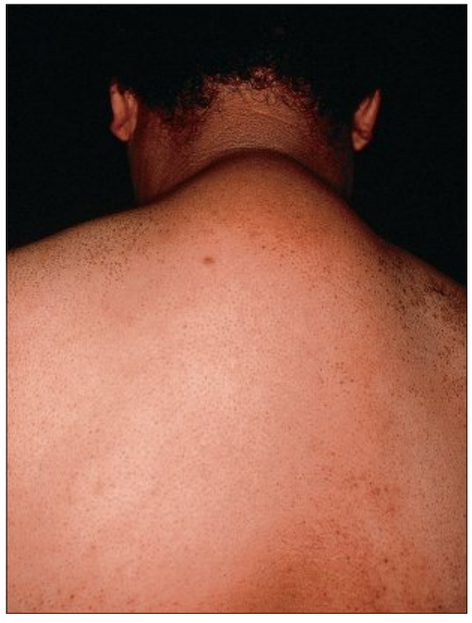
eFig. 53.3 Hypertrichosis lanuginosa. This patient had a pancreatic cancer. *Courtesy Joseph J. Chanda, MD.*



eFig. 53.4 Acanthosis nigricans and acrochordans. Insulin resistance is a common associated finding. *Courtesy Frank Samarin, MD.*



eFig. 53.5 Acanthosis nigricans. Circumferential hyperpigmented velvety plaques as well as numerous acrochordons on the neck of a girl with Rabson–Mendenhall syndrome. The latter is due to mutations in the gene that encodes the insulin receptor, resulting in severe insulin resistance. *Courtesy Edward Cowen, MD.*



eFig. 53.6 "Buffalo hump" of Cushing's disease due to fat redistribution.



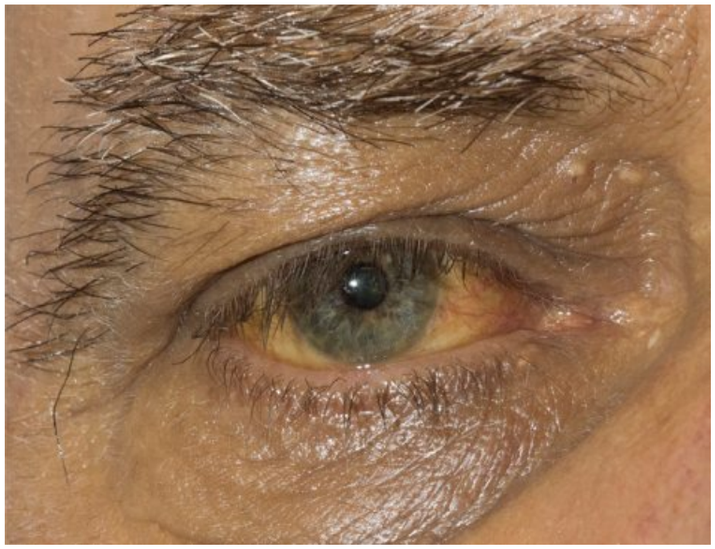
eFig. 53.7 Cushing's disease with multiple striae. This patient had a pituitary adenoma.



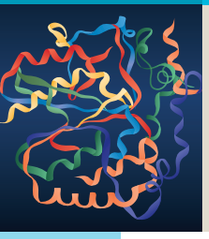
eFig. 53.9 Peutz–Jeghers syndrome. Multiple brown macules on the lips and oral mucosa.



eFig. 53.8 Hemochromatosis. There is diffuse hyperpigmentation (bronzing) of the skin.



eFig. 53.10 Conjunctival icterus in the setting of jaundice due to liver failure. *Courtesy Edward Cowen, MD.*



54 Basic Principles of Genetics

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INTRODUCTION

The complete sequencing of the human genome, with an estimated size of 3.2 gigabases (Gb) containing ~20 000–25 000 genes[1], represented a major scientific accomplishment. Detailed information on human sequence variation and advanced technologies for its detection continue to broaden our knowledge of the genetic basis of human disease. The pathogenesis of many disorders also involves epigenetics, which represent heritable changes in phenotype and/or gene expression that do not result from changes in the DNA sequence.

A wide variety of molecular biology techniques (see Ch. 3) and information-based tools provide direct access to clinically relevant genetic information. Consequently, it is important for physicians in general, and dermatologists in particular, to understand basic concepts of genetics (Table 54.1). Familiarity with new techniques and approaches to identifying disease-causing genes is essential in order to appropriately utilize and interpret the results of genetic studies in the patient care setting. The wealth of new information emphasizes the need to bridge the gap between the bench and the bedside, bringing together efforts from the clinical and research arms of dermatology.

Access to patients with genetic disorders and accurate clinical descriptions are essential for laboratory investigations aimed at the identification of disease-causing genes. Combined with functional studies and translational approaches, these findings can in turn provide benefits to affected individuals. Such insights have importance in genetic counseling and prenatal diagnosis, and they can also contribute to the identification of at-risk individuals/families, prediction of disease course and possible complications, determination of response to therapeutic interventions, and even the development of targeted treatments.

Since the early 1980s, the molecular bases of numerous cutaneous genetic disorders have been elucidated, including multiple forms of epidermolysis bullosa (EB; see Ch. 32), ectodermal dysplasia (ED; see Ch. 63), and ichthyosis (see Ch. 57). The gene-identification strategies employed for these relatively uncommon Mendelian (single-gene) disorders have provided a foundation for the study of common complex disorders such as atopic dermatitis, psoriasis, and alopecia areata. Advances in mapping and detecting human sequence variation have led to more sophisticated approaches, including genome-wide association studies (GWAS) and whole-exome or whole-genome sequencing. Functional genomic studies, e.g. comparison of the transcriptome (expressed genes) in samples from patients and unaffected individuals, have also helped to identify candidate genes for further investigation. The clinician plays a key role in enabling such research, which requires a well-characterized collection of patient samples.

GENETIC DISEASES

Key features

- Accurate information about phenotype and family history is essential in identifying the pattern of inheritance of a genetic disease
- Genetic diseases include Mendelian (monogenic) disorders caused by defects in one gene as well as polygenic disorders due to defects in more than one gene; complex (multifactorial) disorders result from the interaction of environmental and genetic factors
- The major Mendelian patterns of inheritance are autosomal recessive (e.g. oculocutaneous albinism), autosomal dominant (e.g. Darier disease), X-linked recessive (e.g. hypohidrotic ectodermal dysplasia), and X-linked dominant (e.g. incontinentia pigmenti)
- Factors modifying the basic Mendelian pattern of inheritance include incomplete penetrance, age-dependent penetrance, variable expression, *de novo* mutations, pseudodominant inheritance, genomic imprinting, and mitochondrial inheritance
- Chromosomal anomalies can consist of abnormalities in the number (e.g. polyploidy, aneuploidy) or structure (e.g. translocations, inversions) of the chromosomes
- Heterogeneity at the locus or allelic level can make identification of the genetic defects responsible for cutaneous disorders challenging

Genetic diseases can manifest in multiple members of a family. However, not every disease presenting in more than one family member is genetic. Pedigrees of families in which a genetic disease is transmitted (i.e. segregates or is inherited) can range from a single affected member to many affected members in several generations.

Mendelian (monogenic) diseases are caused by defects in one gene, while *polygenic* diseases result from defects in more than one gene and *complex (multifactorial)* diseases result from the interaction of environmental and genetic factors. In addition to mutations within particular genes, abnormalities in the structure, number, or parental contribution of chromosomes can cause disease.

In the following sections, we provide an overview of the different types of genetic diseases. While this chapter focuses on genodermatoses, the explanations of Mendelian and complex traits also apply to extracutaneous diseases.

MENDELIAN PATTERNS OF INHERITANCE

A key initial step in the assessment of reproductive risk for a particular inherited disease is determination of its mode of inheritance. For this purpose, it is essential to collect accurate information on the clinical phenotype and to examine as many family members as possible to classify their status – affected or unaffected. The family is usually ascertained through one affected family member, the *proband*, around whom the pedigree is built with information on the phenotypes and relationships between different individuals.

Even when a single-gene defect is enough to cause a disease phenotype (monogenic disorders), the clinical expression can be affected by variable expression and incomplete penetrance (see below). Genes are expressed on a particular genetic background, which is different in every individual, and genes and their products interact with other genes and proteins. One can therefore expect that monogenic disorders will show some degree of variability.

Allelic heterogeneity refers to mildly or even considerably different clinical entities due to different mutations in the same gene[2–11] (Table 54.2). In contrast, *locus (genetic) heterogeneity* refers to mutations in different genes that result in the same phenotype[12–18] (Table 54.3). Of note, there are some diseases, such as EB simplex, that display both allelic and locus heterogeneity. Thus, diagnosis based purely on either clinical signs/symptoms or the results of genetic testing can lead to misclassification, underscoring the importance of integrating clinical and molecular findings.

Once a phenotype and its range of clinical findings are defined, the trait can be followed within a pedigree. The transmission of the trait in the pedigree defines the pattern of inheritance of the disease. The genes responsible for monogenic traits can be located either on autosomes, resulting in an autosomal pattern of inheritance, or on the X chromosome in the case of an X-linked pattern of inheritance. Irrespective of the gene location, when a mutation in one of two alleles

BASIC CONCEPTS IN GENETICS	
Nuclear DNA	• Deoxyribonucleic acid (DNA) contained within nuclei of eukaryotic organisms • Packed into chromosomes during cell division • Selectively folded and unfolded to allow the expression of appropriate genes at different times and in different cell types • Each somatic cell contains approximately 2 meters of DNA
Chromosome	• Organized structures of DNA and proteins that are found within a eukaryotic nucleus • Each diploid organism (including humans) has two sets of chromosomes, one from its father and one from its mother • Each pair of chromosomes contains two homologous chromosomes, one from each parent • Humans normally have 23 pairs of chromosomes: 22 pairs of autosomes and one pair of sex chromosomes (XX in females and XY in males) • Chromosomes X and Y share only two small homologous regions, known as pseudoautosomal regions
Karyotype	• Describes the full chromosomal constitution of an individual (e.g. 46, XY or 46, XX)
Haploid cell	• Contains only one chromosome complement or "n" (for humans, n = 23) • Gametes (paternal and maternal) are haploid cells
Diploid cell	• Contains two chromosome complements or "2n" (for humans, 2n = 46) • Human cells (other than gametes) are diploid

Centromere	• A site of constriction in a chromosome that is essential for correct cell division
	• Depending on the position of the centromere, chromosomes can be:
	  • *Metacentric*: centromere near the middle, two "arms" of similar length
	  • *Submetacentric*: centromere between the center and end, two "arms" of somewhat different lengths
	  • *Acrocentric*: centromere near the end, two "arms" of very different lengths
	• Composed of a series of histone proteins and repetitive DNA sequences (several thousand kilobases)
	• Divides the chromosome into two arms: the short (petite) arm or ***p***, and the long arm or ***q***

Telomere	• A region of repetitive DNA (TTAGGG sequence) and proteins at the ends of each chromosome • Plays a key role in the maintenance of chromosomal integrity and ensuring correct replication
Meiosis	• The process of cell division by which a diploid cell from the germline gives rise to haploid gametes via segregation and random assortment of homologous chromosomes • Results in combinations of chromosomes in the daughter cells that are different than that in the parental cell
Mitosis	• The process of somatic cell division of proliferating cells by which the genetic material of a cell is duplicated and equally distributed between the two resulting daughter cells • To achieve this duplication of genetic material, the chromosome replicates itself and forms two *sister chromatids*, which will each become the chromosome of a daughter cell
Locus	• The location of a particular sequence of DNA (e.g. a gene or DNA fragment) on a chromosome • Since we have two copies of each chromosome, we also have two copies of each locus, which can be identical or different
Gene	• A segment of DNA that encodes a protein (or occasionally an RNA chain) that serves a function

Allele	• Alternative forms of a particular gene or DNA sequence at a given locus
	• An individual has two alleles at each autosomal locus (one from each parent), and the locus/individual is referred to as:
	  • *Homozygous* if the alleles are identical
	  • *Heterozygous* if the alleles are different
	• Since males have only one copy of the X and Y chromosomes, they are *hemizygous* for loci on these two chromosomes

Polymorphic locus	• Exhibits at least two alleles with a frequency in the general population of >1% • Can be located within or outside of a gene
Single nucleotide polymorphism (SNP)	• A single nucleotide in a particular location within the genome that has at least two different forms with a frequency of >1% in the general population • Occurs on average every 1000 nucleotides
Mutation	• A change in the DNA sequence • Refers to variation resulting in a disease phenotype • Although any change in the DNA is technically a mutation, the term is often used to refer to a pathogenic variant that results in a disease phenotype
Genotype	• The alleles present at a specific locus (or in the whole genome) of an individual
Phenotype	• The manifestation of a particular genotype (in the context of the environment in which it is expressed) • Different genotypes are not always recognizable as distinct phenotypes • A change in a phenotype can be caused by variant alleles that are present in the general population (normal variation) or by pathogenetic variation that leads to a disease

Table 54.1 Basic concepts in genetics.

is sufficient to produce the phenotype, the trait is considered *dominant*. In contrast, when both alleles of a gene (or one allele in hemizygotes) must be altered in order to produce the phenotype, the condition is considered *recessive*. Hence, Mendelian inheritance patterns include autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive (Table 54.4). There are also Y-linked genes that primarily affect male fertility[19], although their relevance in more general diseases is possible.

Autosomal Dominant Inheritance

In a pedigree of an autosomal dominant disease, each affected person other than the first affected family member, who has a *de novo* mutation, has an affected parent. Both sexes are equally affected and can transmit the trait, and there is vertical transmission from generation to generation (Fig. 54.1A)[20–22]. Since a single mutant allele is enough to produce the phenotype, each offspring of an affected individual has a 50% risk of inheriting the mutant allele and therefore the disorder. Examples of

EXAMPLES OF ALLELIC HETEROGENEITY IN GENODERMATOSES	
Mutated gene	**Phenotypes**
GJB3	Erythrokeratodermia variabilis et progressiva AR and AD nonsyndromic hearing impairment AD peripheral sensory neuropathy and hearing impairment
Desmoplakin (*DSP*)	Striate palmoplantar keratoderma Carvajal syndrome (dilated cardiomyopathy with woolly hair and keratoderma) Severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome Skin fragility–woolly hair syndrome Acantholytic erosive disorder Arrhythmogenic right ventricular cardiomyopathy
ABCA12	Harlequin ichthyosis Lamellar ichthyosis
Plectin (*PLEC*)	EBS and limb-girdle muscular dystrophy EBS of the Ogna type EBS with pyloric atresia

Table 54.2 Examples of allelic heterogeneity in genodermatoses[2–11]. *ABCA12*, ATP binding cassette, family 1 member 12 gene; AD, autosomal dominant; AR, autosomal recessive; *ATP7A*, ATPase, Cu^{2+}-transporting, α-polypeptide gene; EBS, epidermolysis bullosa simplex; *GJB3*, gap junction β3 gene (encodes connexin 31).

EXAMPLES OF GENODERMATOSES WITH LOCUS (GENETIC) HETEROGENEITY	
Phenotype	**Gene**
Striate palmoplantar keratoderma	*DSG1* *DSP* *KRT1*
Epidermolytic ichthyosis	*KRT1* *KRT10*
Epidermolysis bullosa simplex (localized and generalized variants)	*KRT5* *KRT14*
Hermansky–Pudlak syndrome (HPS)	*HPS1, HPS3, HPS4, HPS5, HPS6* *AP3B1, AP3D1* *DTNBP1, BLOC1S3, BLOC1S5, BLOC1S6*
Tuberous sclerosis complex (TSC)	*TSC1* *TSC2*
Hypohidrotic ectodermal dysplasia*	*EDA* (ectodysplasin A) *EDAR* (ectodysplasin A receptor) *EDARADD* (EDAR-associated death domain)

*Mutations in different genes result in X-linked recessive (EDA), autosomal recessive (EDAR, EDARADD), and autosomal dominant (EDAR, EDARADD) forms of the disorder (see Fig. 63.15).

Table 54.3 Examples of genodermatoses with locus (genetic) heterogeneity[12–18]. *AP3B1/D1*, adaptor related protein complex 3, β1/δ1 subunit gene; *BLOC1S3/5/6*, biogenesis of lysosome-related organelles complex-1, subunit 3/5/6 gene; *DSG1*, desmoglein 1 gene; *DSP*, desmoplakin gene; *DTNBP1*, dystrobrevin binding protein 1 gene; *KRT*, keratin gene.

PATTERNS OF INHERITANCE					
Pattern	**Parents affected**	**Sex affected**	**Transmission**	**Recurrence risk**	**Risk factors**
Autosomal recessive	No (carriers)	Both equally	Disease seen in siblings of proband, not in parents or offspring Usually only in one generation	1 in 4	Consanguinity, isolated population (e.g. geographically, linguistically)
Autosomal dominant	Yes*	Both equally	Disease seen in successive generations	1 in 2	*De novo* mutations
X-linked recessive	Mother a "carrier"*	Males have the "complete" disease Female "carriers" may have mild manifestations (e.g. in a mosaic pattern)†	No male-to-male transmission (but all daughters of an affected male are "carriers")	1 in 2 male children born to a female "carrier" will be affected (and 1 in 2 of her female children will be carriers)	*De novo* mutations
X-linked dominant	Yes*	Predominantly females if lethal in males during embryonic development; otherwise milder in females (often with a mosaic pattern of skin lesions) and more severe in males	Affected males have: (1) no affected sons; and (2) all daughters affected No male-to-male transmission	1 in 2 children born to affected female; may spontaneously abort male fetuses if "male-lethal" condition	*De novo* mutations

*Unless the proband has a *de novo* mutation and is therefore the first generation affected.
†Does not represent a "pure" X-linked recessive disorder if there are manifestations in female "carriers".

Table 54.4 Patterns of inheritance.

autosomal dominant genodermatoses include EB simplex, Darier and Hailey–Hailey diseases, and nail–patella syndrome.

A patient with an autosomal dominant disease is usually heterozygous for the disease-causing mutation. Homozygosity for autosomal dominant traits occasionally occurs, and this usually results in a more severe phenotype. For example, a mutation in the keratin 14 gene (*KRT14*) may give rise to localized EB simplex when heterozygous but generalized EB simplex when homozygous[23]. Exceptions to the expected autosomal dominant inheritance pattern may also be due to incomplete penetrance or variable expression (see below).

Dominant mutations can give rise to a phenotype by: (1) *haploinsufficiency*, in which the protein produced from one wild-type (non-mutant) allele is not sufficient to sustain normal function; or (2) a *dominant negative effect*, where the mutated proteins physically interfere with wild-type proteins and prevent them from functioning properly. The latter mechanism often occurs when the mutated protein forms dimers or polymers; examples include keratins (e.g. *KRT14* in EB simplex) and tyrosine kinase receptors (e.g. *KIT* in piebaldism).

Autosomal Recessive Inheritance

In a pedigree of an autosomal recessive disease, an affected individual has clinically unaffected parents, both sexes are equally affected, and there is no transmission from generation to generation (Fig. 54.1B). Both alleles of a given gene must be mutated for the disease to develop. When both parents are heterozygous carriers of a pathogenic allele, the chance of inheriting the disorder is 25% for each of their offspring. Oculocutaneous albinism type 1 and atrichia with papular lesions are examples of autosomal recessive genodermatoses.

There is often an increased frequency of *consanguinity* (sharing a common ancestor) in families with rare recessive conditions. Consanguineous matings (inbreeding) increase the probability that a mutated allele present in the common ancestor will become homozygous in the offspring (homozygosity by descent); these individuals are typically also homozygous for the region surrounding this mutated gene. When more than one affected family member with an autosomal recessive disease is present in a single pedigree, they are usually part

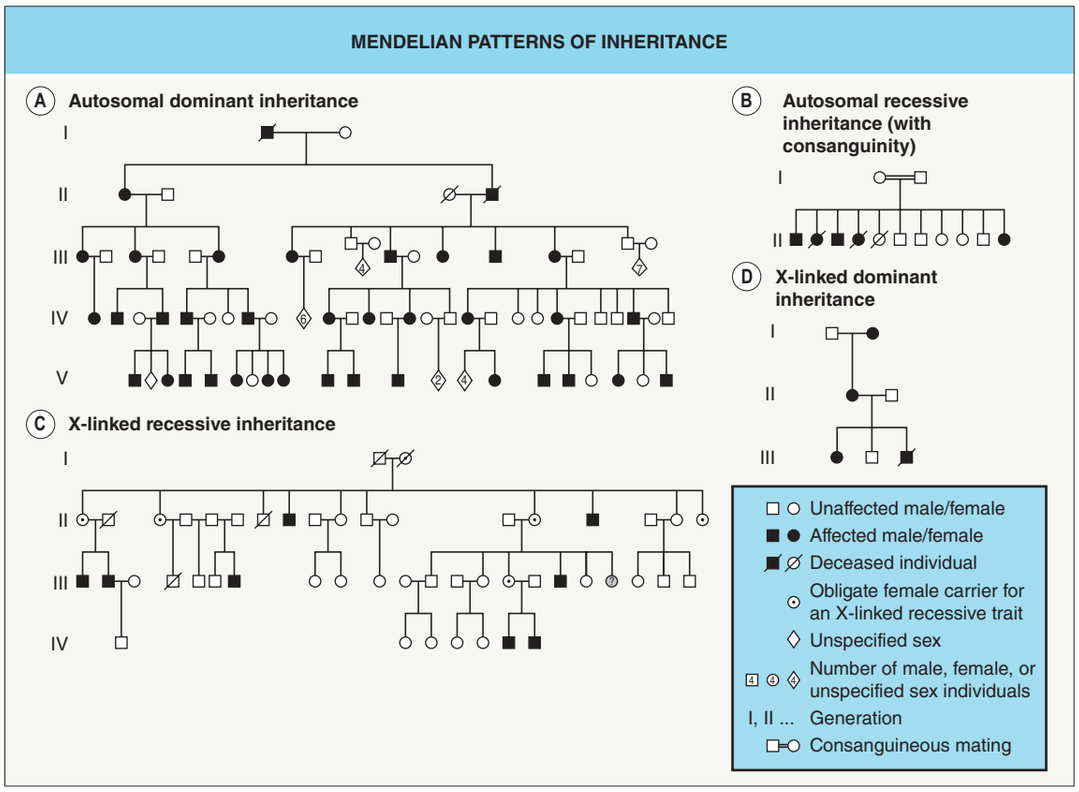


Fig. 54.1 Mendelian patterns of inheritance. A Autosomal dominant. Note the involvement of both sexes in multiple generations. **B** Autosomal recessive. **C** X-linked recessive. **D** X-linked dominant lethal, e.g incontinentia pigmenti.
A, Adapted from ref. 22; B, Adapted from ref. 21; C, Adapted from ref. 46; D, Adapted from ref. 20.

of the same generation. However, the presence of consanguinity can also explain some pedigrees in which an autosomal recessive trait is observed in more than one generation. For example, matings between unaffected carriers and affected patients can give rise to affected family members in two consecutive generations (pseudodominant inheritance; see below).

Patients with an autosomal recessive disease have two mutant alleles (biallelic mutations), while both of their parents are typically heterozygous carriers of one mutant allele and one wild-type allele. If both parents carry the same mutation, their affected offspring will be homozygous for the disease-causing mutation; this is the usual mechanism in consanguineous families. However, the parents may carry two different mutations in the same gene, and their affected offspring will be *compound heterozygous*.

X-Linked Recessive Inheritance

Patients with an X-linked recessive disease are typically male, and they classically have unaffected parents. However, in several X-linked "recessive" disorders, patients' mothers have some clinical evidence of the condition due to functional mosaicism (see Ch. 62). These mosaic manifestations in female "carriers" blur the distinction between recessive and dominant forms of X-linked inheritance, thereby removing such conditions from the "pure" X-linked recessive category. With variable skewing of X-inactivation (see below), the spectrum of disease in female "carriers" can range from absent to severe.

There is no male-to-male transmission, since an affected male will transmit his Y chromosome and not the mutated X chromosome to each son, and the complete (non-mosaic) trait does not appear in successive generations (Fig. 54.1C). However, one rare exception is the offspring of an affected male and a female carrier.

The inheritance risk for the offspring depends on the parent transmitting the disease allele. An affected father will transmit his mutated X chromosome (but not the complete disease) to all his daughters, but to none of his sons. Thus, his daughters become obligate carriers and will transmit the mutated allele to 50% of their children. As a result, the sons and daughters of a carrier mother will have a 50% chance of being affected or carriers, respectively.

Examples of recessive X-linked diseases in dermatology include hypohidrotic ectodermal dysplasia and X-linked recessive ichthyosis (steroid sulfatase [STS] deficiency; see Ch. 57). Because the *STS* gene is located on a region of the X chromosome that partially escapes inactivation, female carriers do not show any features of the disorder.

X-Linked Dominant Inheritance

In a pedigree of an X-linked dominant disease, affected individuals have an affected parent, with the exception of the first affected family member. Unless male-lethal, these disorders occur in both males and females. However, because females are heterozygous rather than hemizygous, they generally have a milder and/or mosaic phenotype (see below). There is no male-to-male transmission, and the trait appears in successive generations (Fig. 54.1D). The risk of the offspring inheriting the disease depends on the transmitting parent. An affected father will transmit the trait to all his daughters, but to none of his sons. An affected mother, on the other hand, will transmit the trait to 50% of her children, regardless of the sex of the offspring.

Some X-linked dominant diseases are lethal in males during early intrauterine development. In this situation, the disorder almost exclusively affects females, and when these women become pregnant they may have an increased frequency of spontaneous abortions. Occasional male patients can be explained by mosaicism, either functional in the setting of Klinefelter syndrome (47, XXY karyotype) or genomic due to mosaicism secondary to a *de novo* half-chromatid or postzygotic mutation (see Ch. 62).

Because female embryos undergo lyonization, i.e. the random epigenetic inactivation of one of the two X chromosomes in each cell, female patients with X-linked dominant skin diseases typically have a mosaic pattern of cutaneous lesions (see Ch. 62). Non-random patterns of X-inactivation in these patients may reflect preferential survival of cells expressing the normal X chromosome. Examples of X-linked dominant, male-lethal diseases in which girls present with a mosaic pattern of skin findings are focal dermal hypoplasia (Goltz syndrome)[24] and incontinentia pigmenti[25].

EXCEPTIONS TO BASIC MENDELIAN PATTERNS OF HERITANCE

Although the genotype at a single locus is responsible for the development of a Mendelian disease, other factors can affect the phenotypic manifestations and pattern of inheritance. Exceptions to basic Mendelian inheritance patterns are presented in Table 54.5 and Fig. 54.2.

EXCEPTIONS TO BASIC MENDELIAN INHERITANCE PATTERNS			
Type of exception	**Impact on phenotype and inheritance**	**Examples in dermatology**	**Impact on genetic counseling**
Variable expression	• Different degrees of phenotypic manifestation of a particular genotype, either between or within families • *Genetic anticipation* refers to the tendency of certain traits (primarily neuromuscular conditions) to increase in severity through successive generations	Broad ranges of severity in Darier disease and neurofibromatosis type 1	• Difficult to predict the severity of the phenotype
Incomplete/reduced penetrance	• Not all individuals with the disease genotype manifest with the condition • An AD trait may appear to skip a generation (see Fig. 54.2A)	Hereditary leiomyomatosis and renal cell cancer syndrome	• With incomplete penetrance, the phenotype may not correlate with the genotype
Age-dependent penetrance	• In *late-onset diseases*, some individuals are too young to exhibit manifestations	Late onset in Darier and Hailey–Hailey diseases	• Younger individuals in a pedigree may falsely appear to be unaffected
X-inactivation (lyonization; see Ch. 62)*	• The phenotype of an X-L condition in a female patient depends on the proportion of cells expressing the mutant allele in a particular tissue • Skewed/non-random X-inactivation can result from negative selection against cells with an active mutant allele • X-L skin disorders typically have a mosaic distribution	Skewed X-inactivation favoring the wild-type allele in the skin of girls with incontinentia pigmenti and the hematopoietic cells of female carriers of X-L dyskeratosis congenita	• In general, X-L dominant traits are milder in females than in males, and female "carriers" of X-L "recessive" conditions can exhibit some symptoms
De novo mutations	• A *de novo* (new) mutation (e.g. during meiosis) can produce an AD disease in a child who has no family history of that condition • *De novo* mutations account for a higher proportion of affected individuals in AD diseases that are severe or otherwise decrease reproductive fitness	*De novo* mutations account for ~30%–50% of patients with NF1 and >60% of those with tuberous sclerosis complex	• Future offspring of the unaffected parents of a child with an AD disease due to a *de novo* mutation are not at increased risk of the condition
Genomic mosaicism: somatic and gonadal (see Ch. 62)	• Genomic mosaicism results from a postzygotic alteration in the DNA sequence that gives rise to a genetically heterogeneous organism • The timing of the mutational event and the cell type(s) affected influence the extent, distribution, and type of clinical findings • Although a postzygotic mutation in somatic cells is not transmitted to the offspring, a mosaic mutation affecting the gonads may transmit *generalized* disease to the offspring	Transmission via gonadal mosaicism has been documented in NF1, dominant dystrophic EB, and epidermolytic ichthyosis (± an epidermolytic epidermal nevus reflecting somatic mosaicism in the parent)	• The proportion of gonadal cells that carry the dominant mutation determines the risk for generalized disease in the offspring; affected children are born to clinically unaffected or mosaic parents in the first generation, with an AD inheritance pattern in subsequent generations
Type 1 and 2 mosaicism/segmental manifestations in AD disorders (see Ch. 62)	• Cutaneous mosaicism can result in skin changes following the lines of Blaschko or in other segmental patterns (e.g. a block-like distribution) • In *type 1 mosaicism*, segmental affected skin is heterozygous for a dominant mutation, with a wild-type, unaffected background • In *type 2 mosaicism*, the genetic background is heterozygous for a mutation that causes an AD disorder, and a postzygotic mutation in the other allele ("second hit" resulting in loss of heterozygosity; see below) leads to a segmental region of skin with two mutations and often more severe disease	Type 1: epidermal nevi, linear Darier disease Type 2: linear porokeratosis superimposed on disseminated superficial actinic porokeratosis, segmental Hailey–Hailey disease in the setting of milder classic symmetric disease	• In patients with type 1 segmental skin disease, the potential presence of gonadal (in addition to somatic) mosaicism may result in some risk for generalized disease in offspring • In type 2 segmental diseases, the "background" condition has an AD inheritance pattern, with a 50% chance of the mutant allele being transmitted to each offspring
Loss of heterozygosity in AD tumor predisposition syndromes	• Affected individuals have a constitutional heterozygous loss-of-function mutation in a tumor suppressor gene that is involved in the regulation of cell growth • These individuals are at high risk of tumor formation, which can result from a single somatic mutation ("second hit") inactivating the second (normal) allele of the same gene; this process often involves *loss of heterozygosity (LOH)* resulting from deletion of the normal allele or gene conversion leading to two copies of the mutant allele	Skin tumors in hereditary leiomyomatosis and renal cell cancer and basal cell nevus (Gorlin) syndrome	• Affected individuals often develop multiple tumors
Revertant mosaicism† (see Ch. 62)	• A postzygotic mutation leads to partial or complete recovery of the wild-type phenotype in segment(s) of skin	Several types of EB, ichthyosis with confetti	• These somatic mutations are not transmitted to offspring
Consanguineous mating (inbreeding)	• In inbred populations, the probability that two carriers of a mutation originating from a common ancestor will mate and have a child with an AR disease is significantly higher than in the general population • Conversely, consanguinity is relatively common in families with AR diseases when the mutant alleles are rare within the general population	A founder effect due to ancestors (Dutch settlers) carrying a recessive mutation explains the high incidence of porphyria variegata in White South Africans	• When analyzing a pedigree, the possibility of consanguinity/over-representation of recessive mutations should be considered, especially for individuals in geographically, linguistically, and/or socially isolated populations where the probability of mating with related individuals is higher

Table 54.5 Exceptions to basic Mendelian inheritance patterns.

EXCEPTIONS TO BASIC MENDELIAN INHERITANCE PATTERNS			
Type of exception	**Impact on phenotype and inheritance**	**Examples in dermatology**	**Impact on genetic counseling**
Quasidominant (pseudodominant) inheritance	• Inheritance of an AR trait can mimic an AD pattern when an individual with an AR disorder mates with a carrier of a recessive mutation in the same gene (see Fig. 54.2C) • This parent-to-child transmission does not usually occur in successive generations	Consanguineous families with atrichia with papular lesions or pseudoxanthoma elasticum	• Mating between a homozygous affected individual and heterozygous carrier of an AR disorder produces a 50% risk of the disease in each offspring
Mitochondrial inheritance	• Inheritance of a mutation in the mitochondrial genome, with all (*homoplasmy*) or some (*heteroplasmy*) of the mitochondria affected • Women transmit the disease, but both male and female offspring may be affected • The phenotype depends on proportion of mutant versus normal mitochondria in a particular tissue	Mutation in the mitochondrial serine tRNA gene underlying palmoplantar keratoderma with or without associated sensorineural deafness	• Mitochondrial diseases have variable expression and incomplete penetrance
Phenocopy	• Clinical findings caused by environmental factors sometimes mimic the phenotype of a genetic disorder	A clinical presentation similar to porphyria cutanea tarda (PCT; an AD disorder) can result from exposure to certain hydrocarbons and pesticides	• Possible environmental as well as genetic etiologies for a condition should be considered
Imprinting and uniparental disomy (UPD)	• Imprinting is an epigenetic phenomenon in which the sex of the transmitting parent determines which allele of a given gene is expressed in the offspring (see Fig. 54.3A) • UPD represents inheritance of both homologous chromosomes from one parent due to errors in meiosis, either as *heterodisomy* with two different homologs from the same parent or *isodisomy* with a duplicated chromosome	Prader–Willi and Angelman syndromes (see Fig. 54.3B); uniparental isodisomy involving a recessive mutant allele has been reported in junctional EB, recessive dystrophic EB, and Harlequin ichthyosis	• Rare event with low risk for subsequent offspring • Prenatal screening can detect UPD by analysis of copy number variants and SNP/microsatellite markers

*For dosage compensation in females, one of the two X chromosomes in each cell is randomly inactivated via epigenetic mechanisms during embryonic development; this inactivation represents functional mosaicism that is passed on to all the "daughter" cells derived from each progenitor. However, genes in the pseudoautosomal region of the X chromosome escape inactivation.
†Genomic mechanisms include back mutations, mitotic recombination, gene conversion, and second-site mutations.

Table 54.5 Exceptions to basic Mendelian inheritance patterns. AD, autosomal dominant; AR, autosomal recessive, EB, epidermolysis bullosa; NF1, neurofibromatosis type 1; SNP, single nucleotide polymorphism; X-L, X-linked.

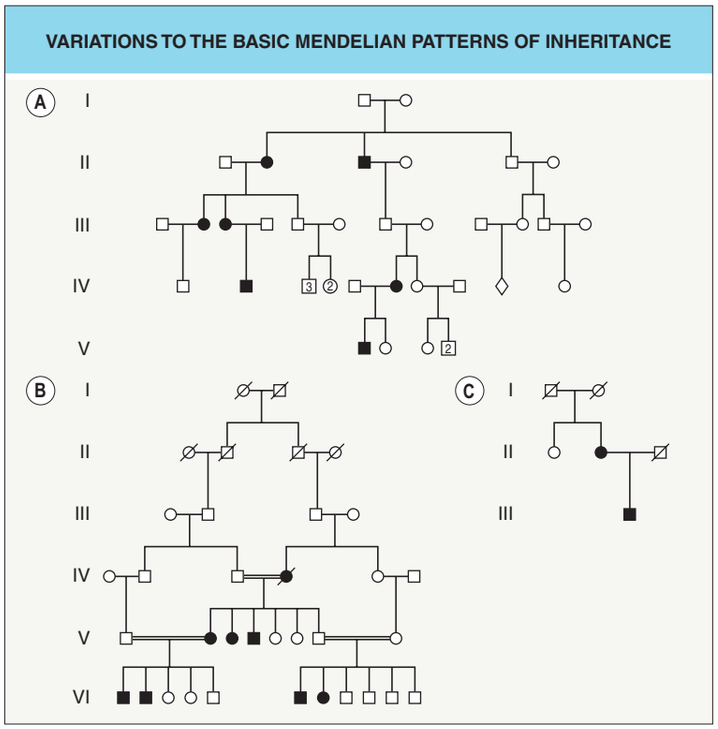


Fig. 54.2 Variations to the basic Mendelian patterns of inheritance. A Reduced penetrance in a pedigree with autosomal dominant retinitis pigmentosa. **B** High degree of consanguinity in a family with affected family members in several generations. **C** Pseudodominant inheritance in autosomal recessive disorder. The inheritance in this pedigree mimics an autosomal dominant resulting from the mating between a patient homozygous for the causative genetic mutation (II:2) and an unaffected carrier. The key for symbols commonly used for pedigree drawing is indicated at the bottom of Fig. 54.1. *A, Adapted from ref. 46; C, Adapted from ref. 47.*

EPIGENETICS AND IMPRINTING

Epigenetics refers to heritable changes affecting gene expression that do not result from alterations in the DNA sequence[26]. Epigenetic changes can involve DNA methylation or modification of histones (e.g. acetylation and deacetylation) and chromatin. RNA-dependent gene silencing can also occur under the influence of small and large RNA species, including small interfering RNAs (siRNAs)[27], microRNAs (miRNAs)[28], and large intervening non-coding RNAs (lincRNAs)[29].

Imprinting is an epigenetic phenomenon in which the sex of the transmitting parent determines whether particular genes are expressed in the offspring (Fig. 54.3A). For example, mating of a male lion with a female tiger results in the giant "liger" (due to inheritance of a growth gene from the lion father that is "turned on"), whereas a male tiger and female lion produce a considerably smaller "tigon" (due to inheritance of a growth gene from the lion mother that is "turned off").

The effect of imprinting is especially apparent in the case of *uniparental disomy (UPD)*, where both homologous chromosomes are derived from the same parent, instead of one from each parent. UPD can go undetected for some chromosomes, while it results in a disease phenotype for others. A classic example of the latter is UPD for chromosome 15 in Prader–Willi and Angelman syndromes (Fig. 54.3B). UPD that results in inheritance of a duplicated maternal or paternal recessive mutant allele can also produce various autosomal recessive disorders (see Table 54.5).

In addition to their roles in monogenic diseases, epigenetic changes are involved in cancer. Cancer is typically characterized by global hypomethylation and site-specific hypermethylation. The hypomethylation activates growth-promoting genes such as *HRAS*, cyclin D1 (*CCND1*), and those in the melanoma antigen family (*MAGE*)[26]. In contrast, hypermethylation silences tumor suppressor genes such as retinoblastoma 1 (*RB1*), von Hippel–Lindau (*VHL*), and adenomatosis polyposis coli (*APC*)[26]. Epigenetic alterations can also contribute to inflammatory disorders such as systemic lupus erythematosus.

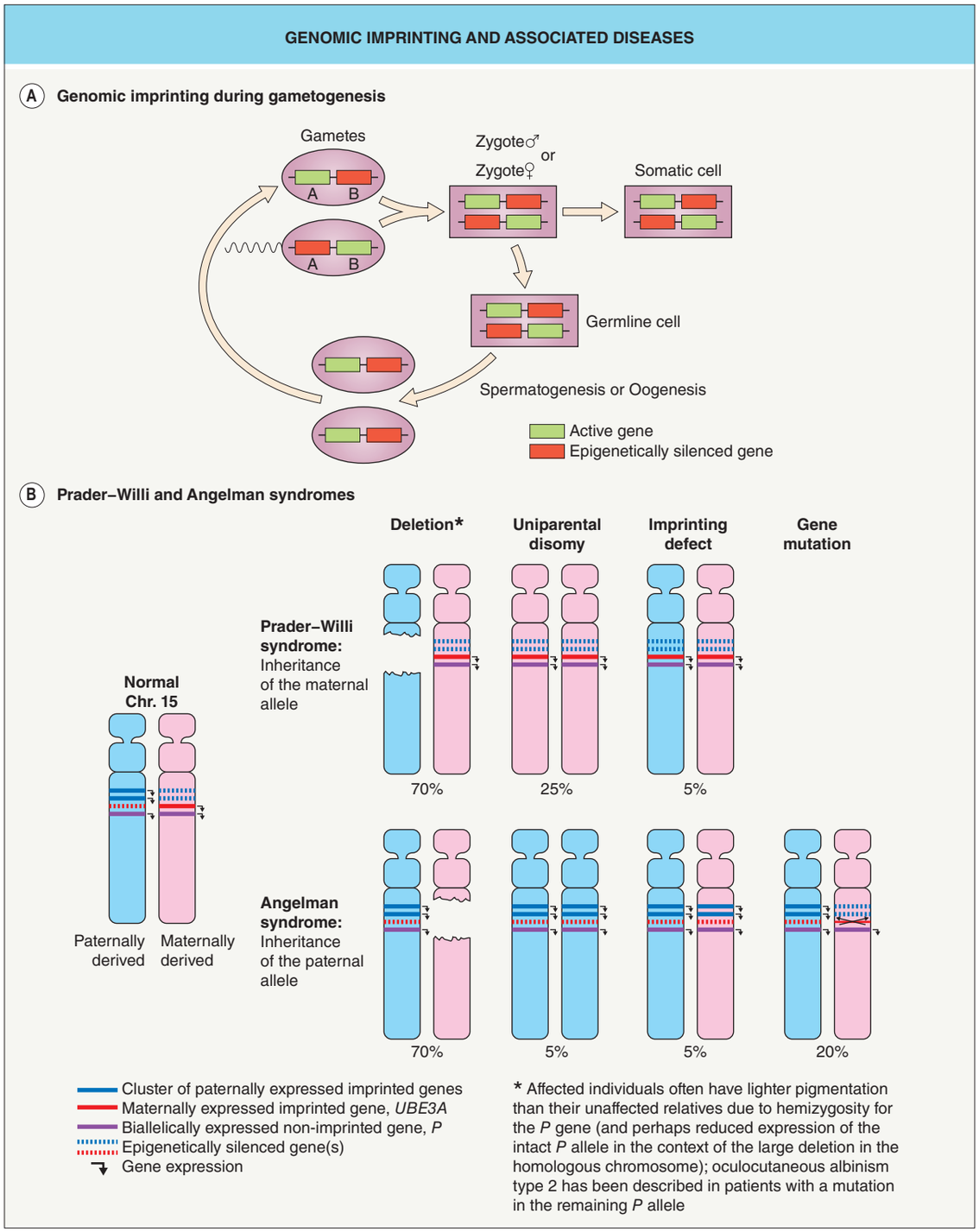


Fig. 54.3 Genomic imprinting and associated diseases. A Genomic imprinting occurs during gametogenesis. Genes A and B are epigenetically silenced in male and female gametes, respectively. Somatic cells in males and females maintain the imprinting pattern present in the gametes. In the germline, on the contrary, the imprinting is erased and the corresponding sex-specific imprint established. **B** Prader–Willi and Angelman syndromes represent diseases shaped by genomic imprinting.

CHROMOSOMAL DISORDERS

The above sections discussed disease-causing mutations that affect a single gene. However, other disorders can result from larger aberrations at the chromosomal level, and these anomalies may produce severe phenotypes due to the involvement of multiple genes and regulatory regions. For example, the majority of spontaneous abortuses exhibit chromosomal anomalies[30].

Chromosomal anomalies can affect the number or structure of chromosomal segments or the entire chromosome. Numeric chromosomal abnormalities may involve the whole genome (polyploidy) or just one pair of homologs (aneuploidy). The forms of *polyploidy* observed in humans are triploidy with three complete sets of chromosomes ($3n$), and tetraploidy with four chromosome complements ($4n$). However, unless mosaic, polyploidy results in a spontaneous abortion or death soon after birth. *Aneuploidy* refers to extra or missing chromosome(s), such as trisomies with three copies of a single chromosome or monosomies with only one copy. Trisomies for a whole chromosome that are compatible with extrauterine life (outside the setting of mosaicism) involve chromosomes 21 (Down syndrome), 18 (Edwards syndrome), 13 (Patau syndrome), and 23 (XXY, Klinefelter syndrome; XYY). Monosomy for the X chromosome (Turner syndrome) can also occur. Other trisomies and monosomies may be observed in mosaic or partial (e.g. due to translocations) forms.

Structural abnormalities involve breakage of chromosomes. They are *balanced* if there is no net gain or loss of genetic material, or *unbalanced* when they are accompanied by additional or missing genetic information. The stability of the resulting rearranged chromosome through cell division will depend on the presence of a centromere and two telomeres, the necessary elements for the correct segregation of chromosomes.

Balanced chromosomal abnormalities include some types of translocations and inversions. In a reciprocal translocation, two breaks in two non-homologous chromosomes occur and the chromosomal segments distal to the breaks are exchanged. The total number of chromosomes

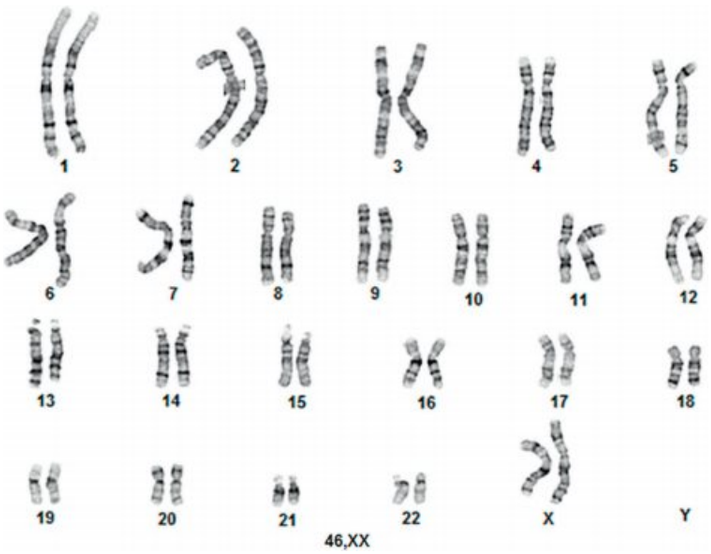


Fig. 54.4 Normal female karyotype. Metaphase chromosomes are photographed, cut out and placed in pairs from largest to smallest, including 22 autosomal pairs and 2 sex chromosomes.

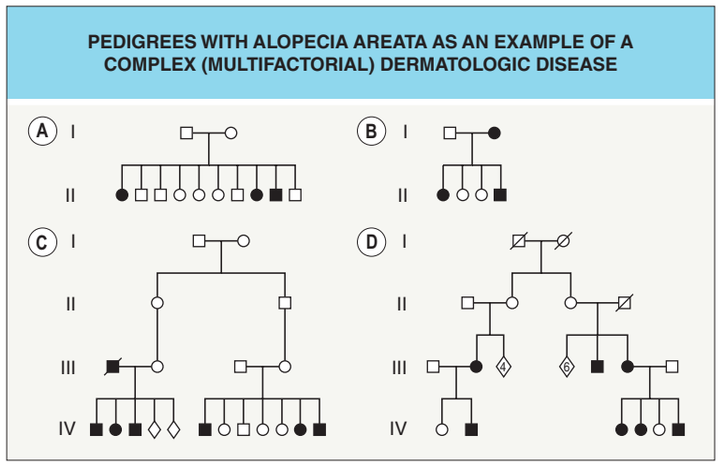


Fig. 54.5 Pedigrees with alopecia areata as an example of a complex (multifactorial) dermatologic disease. Although some of the pedigrees individually can mimic Mendelian patterns of inheritance (**A, B**), others show a more complex pattern (**C, D**). In some cases, the disease can be inherited through two unrelated branches of the family (**C**). A single mode of inheritance cannot be established for the disease as a group. The key for symbols commonly used for pedigree drawing is indicated at the bottom of Fig. 54.1.

remains the same. If the translocation breakpoint affects a gene or its regulatory sequence, or otherwise places a gene under the control of novel regulatory elements (e.g. the Philadelphia chromosome), it can result in an observable phenotype (e.g. chronic myelogenous leukemia). In addition, clinical manifestations related to reciprocal translocations can occur in the offspring of the carriers. Depending on the combination of parental chromosomes inherited, the offspring may have partial trisomy or monosomy for the chromosomal regions involved in the translocation, i.e. an *unbalanced* chromosomal anomaly.

Inversions are balanced rearrangements in which two breaks occur in the same chromosome and the intervening segment is inverted before the chromosome is reconstituted. In a *pericentric inversion*, the inverted segment includes the centromere, whereas in a *paracentric inversion*, the two breaks occur in the same chromosome arm, without involvement of the centromere.

Numerical and structural chromosomal aberrations can be detected using karyotypes, which allow visualization of banding patterns in stained metaphase chromosomes (Fig. 54.4). Fluorescence *in situ* hybridization (FISH) can identify much smaller changes in the chromosomal constitution that are not visible with conventional banding techniques but requires the use of preselected probes (see Table 3.5 and Fig. 3.8). More recently, advances in microarray technology have enabled the use of array-based comparative genomic hybridization (CGH) for detection of copy number variations (CNVs) at a considerably higher level of resolution than can be accomplished via karyotypes. Conventional CGH identifies chromosomal gains and losses and all CNVs in a single hybridization procedure[31]. While this method has improved resolution (5–10 Mb) compared to chromosomal banding, it still requires metaphase chromosomal preparations and is unable to identify balanced chromosomal rearrangements. However, array-based CGH (aCGH) that incorporates DNA microarray technologies has an improved resolution of ~100 Kb. Currently, single nucleotide polymorphism (SNP) oligonucleotide microarray analysis (SOMA), which combines SNP data with the detection of CNVs, yields the highest resolution (~6 Kb)[32] and detects both visible and submicroscopic imbalances, including cryptic insertions/deletions in apparently balanced chromosomes. It also provides SNP genotype information for additional studies, such as assessment of uniparental disomy (UPD) and zygosity.

Classic examples of skin conditions associated with chromosomal anomalies are linear nevoid hypo- or hyperpigmentation (including "hypomelanosis of Ito" and "linear and whorled nevoid hypomelanosis"), where streaks and swirls of hypo- or hyperpigmentation following the lines of Blaschko reflect mosaicism. In a subset of such patients, especially those with associated extracutaneous manifestations, a mosaic chromosomal anomaly can be identified in affected skin via culture of lesional fibroblasts[33]. Other genodermatoses are occasionally caused by chromosomal abnormalities. For example, hypohidrotic ectodermal dysplasia can result from X;autosome translocations or genomic deletions involving *EDA*[34].

COMPLEX GENETIC TRAITS

Classic Mendelian disorders represent only a small proportion of genetic diseases. Many common conditions develop as a consequence of multiple genetic factors that confer disease susceptibility, interacting with each other and the environment. Such complex (multifactorial) traits tend to cluster or aggregate in families (Fig. 54.5). In contrast to the predictable recurrence risks for Mendelian traits, the risks for complex traits are estimated based on epidemiologic data. Examples of complex traits in dermatology include atopic dermatitis, psoriasis, vitiligo, and alopecia areata.

Attempts to define the genetic basis of complex disorders have included twin studies, parametric linkage analysis, and genome-wide association studies (GWAS). The comparison of concordance rates in monozygotic (identical) and dizygotic (fraternal) twins represents a powerful technique for determining the genetic and epigenetic components of human diseases[35]. For psoriasis and alopecia areata, concordance rates of ~50%–70% in monozygotic twins compared to ~10%–20% in dizygotic twins demonstrate a strong genetic basis[36,37]. In investigations utilizing GWAS, several hundred thousand SNPs can be analyzed in thousands of individuals to help determine the genetic architecture of complex diseases.

Our understanding of the complex genetic and epigenetic architecture underlying polygenic diseases has been greatly facilitated by endeavors such as the Human Genome Project that mapped all human genes (completed in 2003), the Encyclopedia of DNA Elements (ENCODE) that catalogs all the functional regulatory elements in the human genome[38], and the Roadmap Epigenomics Project. The field of functional genomics is also playing a key role in the mission to decode the genetic architecture of complex traits. This progress will continue to elucidate disease mechanisms and facilitate the development of targeted therapies.

IDENTIFICATION OF DISEASE GENES

Key features

- Targeted multi-gene panels represent an efficient testing strategy for disorders with overlapping clinical features
- Whole-exome sequencing (WES) and whole-genome sequencing (WGS) are increasingly being utilized in clinical practice as a diagnostic tool
- Testing for somatic mutations and chromosomal aberrations in tumor tissue can help provide prognostic input and direct therapy
- Recognition of hereditary cancer syndromes caused by germline mutations is essential in order to facilitate appropriate evaluation and surveillance of patients and their families

INTERPRETATION OF SEQUENCE VARIANTS

A *mutation* is defined as a permanent change in the nucleotide sequence of DNA. There are several different types of mutations. Point mutations consist of the substitution of a single nucleotide position. This change can lead to an amino acid substitution (missense mutation), the generation of a termination codon (nonsense mutation), or no change in the protein sequence (silent mutation). There can also be small duplications, insertions, or deletions. If they affect a piece of the protein-coding sequence in a manner that is not a multiple of three nucleotides (a codon), this will lead to a frameshift in the protein sequence and often the generation of a premature termination codon. These types of mutations can affect both coding and non-coding sequences, e.g. the promoter region, consensus splicing signals, other key intronic positions. Large rearrangements, such as partial or complete deletions of the entire gene, can also occur.

It is important to recognize that some "mutations" as described above actually represent non-pathogenic variants present in the general population as "polymorphisms"; the latter are defined as having a population frequency of >1%. To avoid potential confusion regarding the consequences of a particular sequence variant, the American College of Medical Genetics and Genomics (ACMG) developed guidelines for the use of standard terminology in clinical genetic testing[39]. These guidelines recommend avoiding the terms "mutation" and "polymorphism" to describe genetic alterations relevant to Mendelian disease, and instead using "variant" with one of the following modifiers: pathogenic, likely pathogenic, uncertain significance, likely benign, or benign. However, the simple term "mutation" is embedded in the medical lexicon and appears in this textbook.

For the detection of mutations, traditional Sanger sequencing of genes, based upon the incorporation of fluorescent chain-terminating nucleotide analogues (see Ch. 3), can be performed; next-generation sequencing is described below. Additional methods that assess copy number and can detect larger deletions or duplications include multiplex ligation-dependent probe amplification (MLPA), quantitative PCR, targeted aCGH, and FISH (see above & Ch. 3).

Following the identification of genetic variants in both Mendelian and complex diseases, the next step is often determination of their downstream consequences, e.g. on gene expression and protein function. Methods to evaluate gene expression include microarray analysis, quantitative reverse transcription PCR, RNA sequencing, and immunohistochemical characterization of patient samples. Quantitative assays can be performed to determine whether the mutation leads to a loss or gain of protein function, and functional experiments may employ *in vitro* cell culture systems and mouse models.

NEXT-GENERATION (MASSIVELY PARALLEL) SEQUENCING

In recent years, high-throughput technology has revolutionized genetic testing via "next-generation" techniques that allow much faster and less expensive DNA and RNA sequencing than does the traditional Sanger method. Also referred to as massively parallel sequencing, this process involves amplification of fragmented sequences of DNA to produce thousands of copies, which are then sequenced as a group (see Table 3.2 and Fig. 3.5).

Multi-gene panels utilizing next-generation sequencing enable a large group of genes associated with a particular phenotype (e.g. epidermolysis bullosa, ichthyosis, vascular malformation) to be evaluated in a cost-effective manner. When testing of a single gene or panel of genes based on the clinical findings in a patient suspected of having a genetic disorder fails to provide an answer, WES or WGS can be the next step (Tables 54.6 and 54.7). For example, in a patient with sparse hair, hypohidrosis, and absent teeth, the initial step toward establishing a molecular diagnosis is targeted testing utilizing a panel of genes known to be associated with ectodermal dysplasia. An advantage of targeting specific genes is that coding regions and some non-coding regions can be analyzed in fine detail for both sequence aberrations and deletions or duplications. In contrast, WES uses an array to specifically capture the protein-coding (expressed) regions of the human genome, which account for only 1%–2% of genetic material but contain >85% of disease-causing mutations[40]. If a patient with ectodermal dysplasia has no pathogenic changes identified via targeted testing, WES enables examination of the coding regions of many additional genes. Currently, for identifying disease-causing mutations in both recessively and dominantly inherited conditions, WES followed by bioinformatics analysis of the data generated represents a more efficient and cost-effective approach than WGS (see Table 54.6)[41]. However, genetic technology is advancing rapidly, and further optimization of WGS is expected to lead to its increased use in the future.

COMPARISON OF NEXT-GENERATION SEQUENCING (NGS) OPTIONS

	Targeted testing (e.g. multi-gene panel)	WES	WGS
Optimized for genes/ mutations associated with a particular phenotype	Yes	No	No
Exons evaluated	Yes	Yes	Yes
Introns evaluated	Varies	No	Yes
Duplications evaluated	Better than WES & WGS	Larger errors may not be detected	Better than WES
Mitochondrial DNA evaluated	Varies	No	Yes
Mosaic mutation <20% in blood sample*	No	No	No
Cost	$	$$	$$$$

*NGS with deep sequence coverage can enhance sensitivity for lower-level mosaicism (e.g. <20%) that would be undetectable by conventional Sanger sequencing.

Table 54.6 Comparison of next-generation sequencing (NGS) options. All of these modalities can be performed on DNA extracted from a variety of sample types (e.g. blood, saliva, tissue), and none is able to completely exclude the possibility of a particular disorder. Whole-exome sequencing (WES) analyzes only expressed regions, which account for ~2% of the genome. Whole-genome sequencing (WGS) covers more non-coding regions, but at a lower depth of coverage compared to WES. For WES and WGS, samples from a parent–child trio can help to determine which variants are pathogenic and increase the diagnostic yield, and bioinformatics analysis is required to filter and prioritize variants identified based on function, zygosity, and population frequency.

GENETIC COUNSELING

Geneticists and genetic counselors can assist in educating patients and families about genetic diseases and testing, provide psychological support, and aid in decision-making processes. A typical visit includes a three-generation family history and drawn pedigree (see Fig. 54.1). Prior to proceeding with genetic analysis, its potential impact on the patient's diagnosis, prognosis, and medical care as well as implications for family members and reproductive planning are discussed. The limitations of genetic testing and possibility of equivocal or non-informative results are also reviewed. For example, a mutation in the protein kinase, cAMP-dependent, regulatory type Iα gene (*PRKAR1A*) that is known to cause Carney complex (myxoma, spotty pigmentation, and endocrine overactivity) is identifiable in ~70% of patients who meet clinical criteria for this condition. Possible explanations for false-negative findings include genetic alterations not detectable by the methods utilized, mosaicism (see Ch. 62), locus heterogeneity (see above), and laboratory error.

Other topics to address with patients and families undergoing genetic testing may include confidentiality, detection of non-paternity, and (for WES or WGS) incidental findings in a gene unrelated to the disease being investigated. In the US, the Genetic Information Nondiscrimination Act (GINA) of 2008 provides protection against access to genetic information and genetic discrimination in health insurance and employment settings. However, GINA does not include all possible forms of genetic discrimination (e.g. life or disability insurance). Many state governments require documentation of consent for performance of genetic testing and disclosure of genetic information.

GENETIC TESTING STRATEGIES		
Clinical findings	**Appropriate test**	**Example result**
Severe anomalies: e.g. recognizable trisomy with major neurologic abnormalities and aplasia cutis congenita	Karyotype	Trisomy 13 with associated aplasia cutis congenita
Multiple congenital anomalies: e.g. developmental delay, ichthyosis, anosmia	Chromosomal microarray	X-linked ichthyosis due to *STS* and contiguous gene deletion
Mendelian (single-gene) syndrome suspected: e.g. congenital erythroderma with erosions and epidermolytic hyperkeratosis histopathologically e.g. congenital ichthyosiform erythroderma without syndromic features	 Sequencing of most likely genes (*KRT1* & *KRT10*) Targeted panel of genes known to cause ichthyosis	 Epidermolytic ichthyosis with heterozygous *KRT1* pathogenic variant Autosomal recessive congenital ichthyosis due to biallelic *ALOX12B* pathogenic variants
If uninformative targeted testing results		
Unknown single gene disorder suspected: e.g. congenital ichthyosis, developmental delay, short stature, renal dysfunction	WES or WGS	Identification of a pathogenic variant in a novel gene expressed in the skin, brain, bones, and kidneys

Table 54.7 Genetic testing strategies. A genetic test should match the size of the error it is aiming to detect. A karyotype is a "big picture" genome-wide snapshot. Since approximately one-third of genes control brain function, errors seen by karyotype usually include cognitive deficits. Chromosomal microarray or "molecular karyotyping" has a finer resolution and detects errors too small to be seen at the chromosomal banding level. Multi-gene panels are useful for assessing related disorders with overlapping phenotypes and detect alterations as small as a single base pair. Finally, whole-exome sequencing (WES) and whole-genome sequencing (WGS) utilizing next-generation technology offer a broader, un-targeted approach. *ALOX12B*, arachidonate 12-lipoxygenase, 12 R type; *KRT1/10*, keratin 1/10; *STS*, steroid sulfatase.

TUMOR GENETICS FOR THE DERMATOLOGIST

Somatic Versus Germline Mutations

Analysis of the genetic alterations underlying cancer has revolutionized our understanding of the multiple intersecting signaling pathways involved in tumorigenesis (see Ch. 107) and provided tumor-specific therapeutic targets. *Somatic* mutations occur after conception and can result in mosaic skin conditions as well as cutaneous neoplasms. Mosaicism reflects a disease-causing somatic mutation that arises *in utero* (postzygotic) and presents with skin findings in developmental patterns (e.g. following the lines of Blaschko or segmental; see Ch. 62). The clinical manifestations of mosaic diseases depend upon the timing of the genetic change and cell type(s) affected, ranging from birthmarks such as congenital melanocytic and epidermal nevi to segmental forms of neurofibromatosis type 1 and Darier disease.

Examples of somatic mutations that commonly underlie cutaneous neoplasms include *BRAF* mutations in melanocytic nevi and melanomas, *PTCH1* (patched) mutations in basal cell carcinomas (BCCs), and UV-signature *TP53* mutations in BCCs and cutaneous squamous cell carcinomas (cSCCs) (see Chs. 107 and 113). Although somatic mutations typically result in focal lesions, exceptions with widespread skin involvement and systemic manifestations include maculopapular and diffuse cutaneous mastocytosis due to somatic activating *KIT* mutations and VEXAS (vacuoles, E1 ubiquitin activating enzyme, X-linked, autoinflammatory, somatic) syndrome due to somatic *UBA1* mutations.

Germline (constitutional) mutations can result in hereditary cancer predisposition syndromes that are associated with cutaneous malignancies (e.g. basal cell nevus syndrome) or benign cutaneous neoplasms (e.g. Cowden syndrome). These syndromes may be divided into three general categories: (1) defective "caretaker" genes involved in DNA repair and protection of genomic integrity (e.g. nucleotide excision repair genes in xeroderma pigmentosum; see Ch. 87); (2) defective tumor suppressor ("gatekeeper") genes (e.g. *PTEN* in Cowden syndrome; see Ch. 63); and (3) activated oncogenes (e.g. *RET* in multiple endocrine neoplasia 2 A/B; see Ch. 63). Increased risk of melanoma can result from germline mutations in high-penetrance genes such as *CDKN2A* (found in ~2% of melanoma patients overall and ~20%–40% of melanoma kindreds) as well as pigmentation genes such as *MC1R* responsible for the lightly pigmented skin that increases propensity for melanoma development (see Ch. 113).

Testing of Cutaneous Tumors for Somatic Mutations

In contrast to use of a blood or saliva sample to test for germline mutations, testing for somatic mutations typically requires lesional tissue. However, next-generation technology can potentially be employed to analyze circulating tumor DNA.

Carcinomas are characterized by a wide variety of mutations as well as other genetic abnormalities such as structural rearrangements, copy number aberrations, and gains and losses of partial or whole chromosomes (see Ch. 107). FISH utilizes fluorescent probes to target specific genes or chromosomes in order to assess DNA copy number changes (see Fig. 3.8). Array CGH uses different technology for a similar purpose, with applications such as helping to distinguish proliferating nodules from melanoma within congenital melanocytic nevi (see Ch. 112). The presence of a larger number of genetic errors is often (but not always) suggestive of a more malignant process. Various gene-expression profile assays are commercially available for pre-biopsy (via epidermal tape stripping) and post-biopsy assessment of pigmented lesions, but their use in clinical decision-making has limitations[42] (see Ch. 113).

Of note, evidence of certain somatic mutations in tumor tissue can raise the possibility of a hereditary cancer predisposition syndrome. Sebaceous neoplasms in the setting of Muir–Torre syndrome (MTS; a subset of Lynch syndrome) due to a heterozygous germline mutation in a mismatch repair gene represent an example relevant to dermatologists. Evidence of microsatellite instability and loss of expression of mismatch repair proteins (e.g. MLH1, MSH2, MSH6, and/or PMS2) via immunohistochemical staining are each more frequently present in MTS-associated than in sporadic sebaceous neoplasms[43]; testing for a germline mutation in mismatch repair genes should be considered in these patients, especially when there is clinical suspicion of MTS (see Table 63.5). Likewise, identification of BAP1-inactivated melanocytic tumors can prompt genetic testing to diagnose *BAP1* tumor predisposition syndrome due to a germline *BAP1* mutation[44].

The ability to test tumor tissue for somatic mutations enables molecularly targeted cancer therapy. For example, in advanced melanomas with an activating *BRAF* mutation, a marked tumor response is seen with the combination of a selective BRAF inhibitor plus a MEK inhibitor (see Ch. 113). Testing for other somatic mutations continues to evolve in an effort to better characterize tumors and direct therapy.

Testing for Hereditary Cancer Predisposition Syndromes

It is important for dermatologists to recognize the cutaneous manifestations of hereditary cancer syndromes in order to facilitate appropriate patient evaluation (see Table 55.5). General features that suggest the possibility of a cancer predisposition syndrome include younger age at cancer onset, multifocal tumors, multiple primary cancers (synchronous or asynchronous), certain characteristic tumor types (alone or in combination), multiple affected family members, and the absence of environmental risk factors. For example, pancreatic cancer and cutaneous

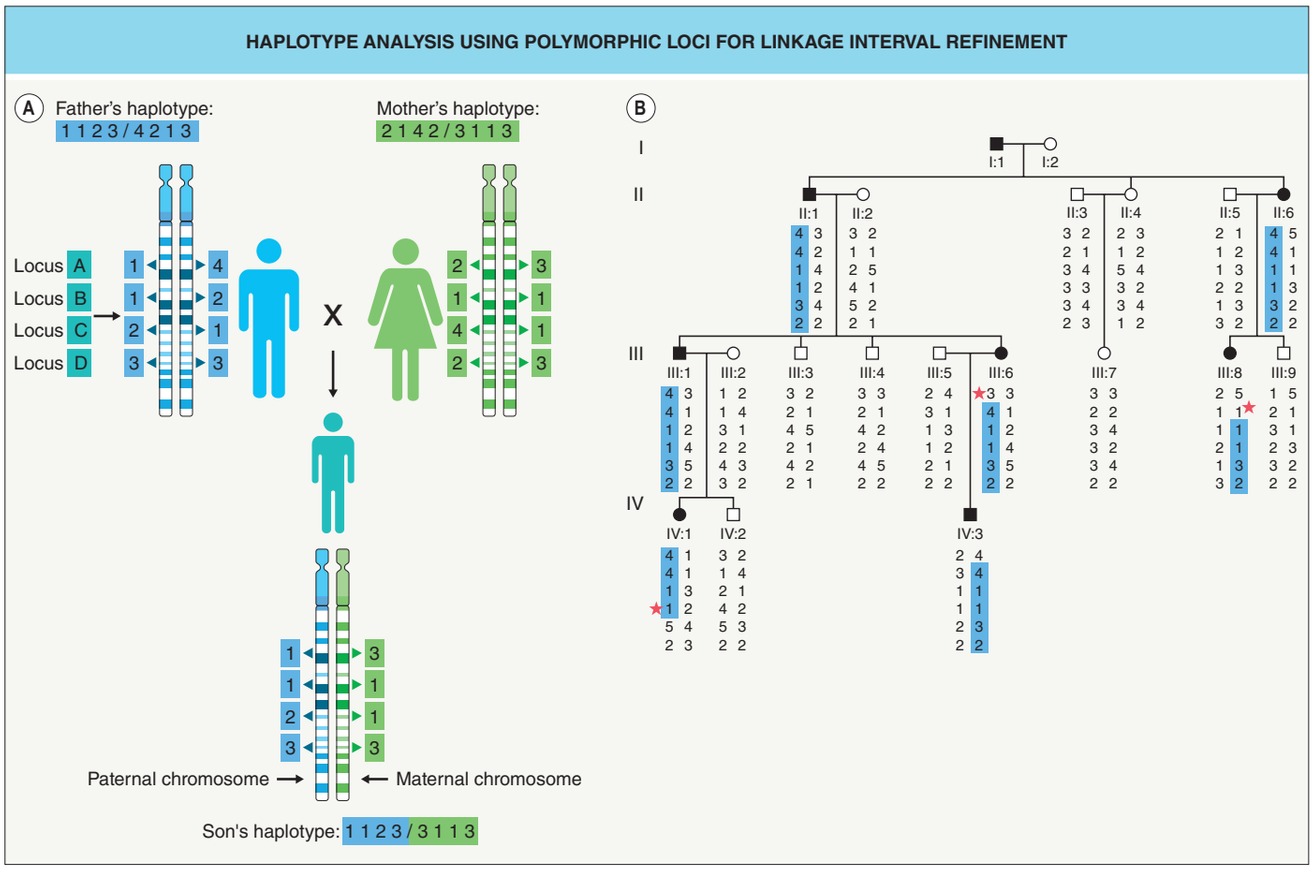
melanoma in the same individual raises suspicion for a *CDKN2A* mutation. Genetic testing should be considered in melanoma patients with risk factors such as ≥3 primary invasive melanomas or ≥2 first-degree relatives with a primary invasive melanoma and/or pancreatic cancer (see Table 113.4). Targeted multi-gene panels represent an efficient testing strategy when the features of different cancer predisposition syndromes overlap, and this represents the recommended approach when familial melanoma is suspected[45].

Of note, current technology does not confirm the molecular etiology in every patient with clinical findings suggestive of a genetic cancer predisposition syndrome. For example, in a patient strongly suspected to have hereditary leiomyomatosis and renal cell cancer (HLRCC [Reed syndrome]; see Table 117.2) based on clinical criteria, the fumarate hydratase (*FH*) pathogenic variant detection rate is ~70%–90%. It is recommended that individuals who meet clinical criteria but do not have an identifiable *FH* mutation still undergo annual surveillance for renal cancer. Conversely, it is important to recognize that many patients and families with multiple skin cancers have a multifactorial pathogenesis, with interactions between genetic susceptibility (e.g. pigmentary and nevus phenotypes) and environmental exposures (e.g. ultraviolet light, immunosuppression) (see Chs. 108 and 113).

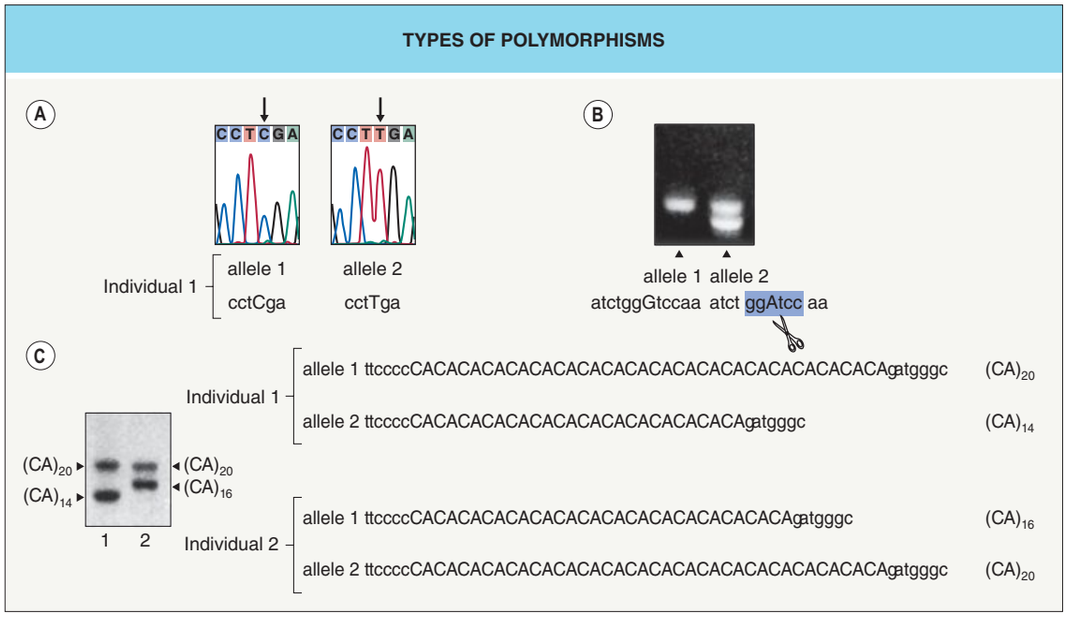
Additional figures available in our eBook (see inside front cover for access code).

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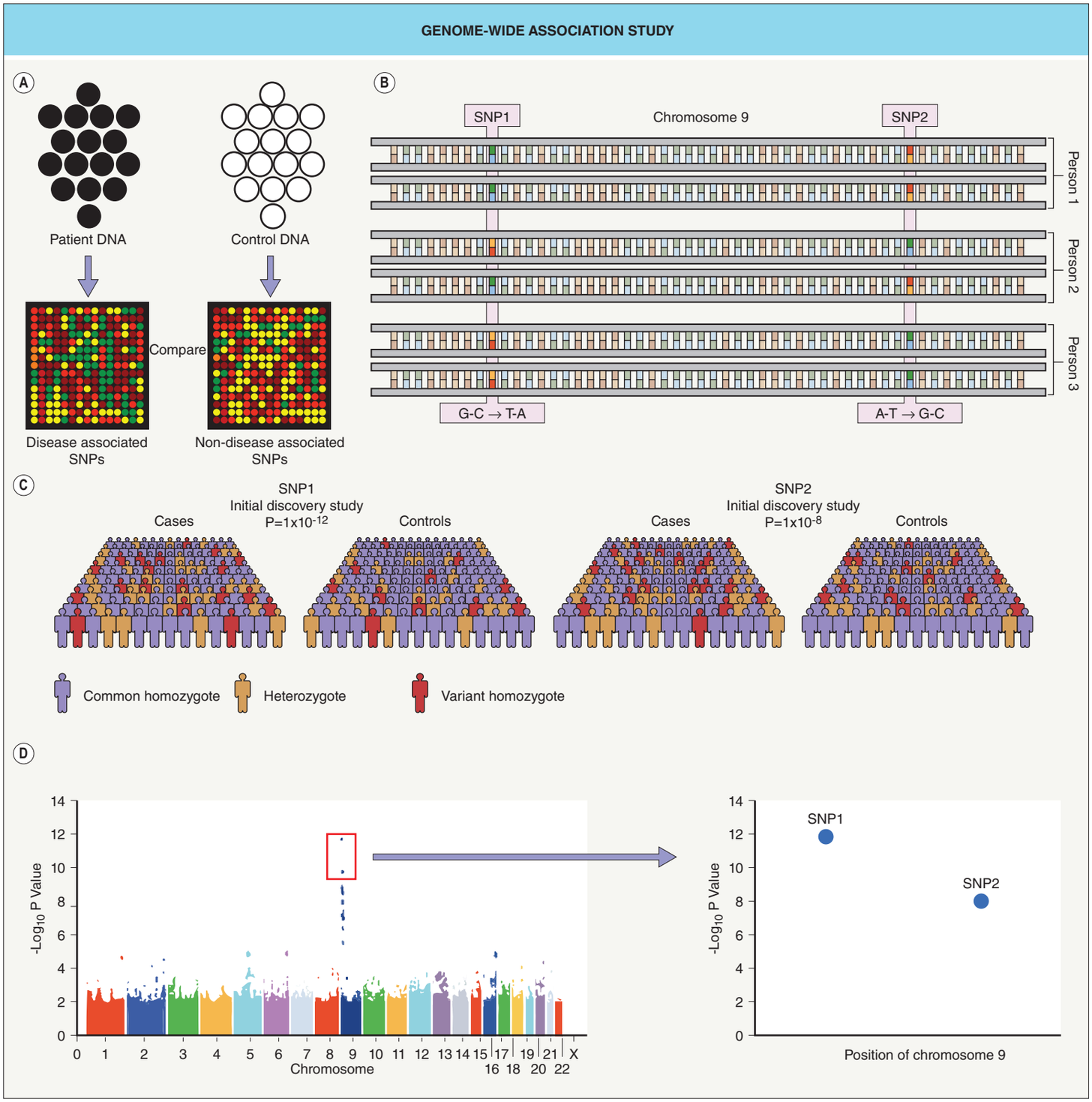
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eFig. 54.1 Haplotype analysis using polymorphic loci for linkage interval refinement. A Haplotypes for a chromosomal region containing four polymorphic loci, A, B, C and D. Loci very close together will rarely be separated by recombination. **B** Haplotype analysis for the refinement of a linkage interval. The disease-associated haplotype, 4 4 1 1 3 2 (shaded in blue), has been broken by genetic recombination in three family members (stars). The two key recombinant individuals, III:8 and IV:1, have allowed the narrowing of the disease interval. The key for symbols commonly used for pedigree drawing is indicated at the bottom of Fig. 54.1.



eFig. 54.2 Types of polymorphisms: single nucleotide polymorphisms (SNPs) and microsatellites. SNPs consist of single base substitutions and can be detected via DNA sequencing (**A**) and restriction enzyme cleavage (**B**). **A** Point substitution (arrows) replacing a cytosine (C) with a thymidine (T) identified by DNA sequencing. **B** The sequence *ggAtcc* is the target site for the restriction enzyme *BamH1*. In the presence of this particular sequence, the enzyme will cut the DNA into two fragments, detected as two bands in an agarose gel (allele 2). If this sequence is altered by a base substitution and, therefore, not recognized by the enzyme, no cleavage occurs (allele 1). A polymorphism that affects the recognition site for a restriction enzyme is referred to as an RFLP (restriction fragment length polymorphism). **C** Example of microsatellites. The repeat unit of the microsatellites shown here is the dinucleotide (CA). The number of tandem repeats of the (CA) unit can vary in each allele. The figure shows two individuals heterozygous for the number of repeats of this dinucleotide. The differences in length between these three alleles appear as bands of DNA of different sizes in a polyacrylamide gel.

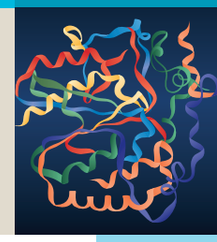


eFig. 54.3 Genome-wide association study (GWAS). A In a GWAS with a case–control design, single nucleotide polymorphisms (SNPs; markers of genetic variation) across the human genome are genotyped using DNA microarrays in a large group of individuals with a certain disease and compared to controls from the general population. **B** A small locus on chromosome 9 (representing a tiny fragment of the genome) containing two SNPs is depicted as an example. **C** The strength of the association between each SNP and the disease is calculated based on that SNP's prevalence in cases versus controls. Because of the large number of statistical tests that are performed and the resulting high false-positive rate, statistical significance is typically set a P value of 10^{-8}. In this example, SNPs 1 and 2 on chromosome 9 are associated with the disease, with P values of 10^{-12} and 10^{-8}, respectively. **D** For all genotyped SNPs that have survived a quality-control screen, the chromosomal location is plotted on the *x*-axis and the negative logarithm of the P value on the *y*-axis (a Manhattan plot). Each chromosome is shown in a different color. The results implicate a locus on chromosome 9, marked by SNPs 1 and 2, which are adjacent to each other (graph at right), and other neighboring SNPs. *Adapted with permission from Manolio TA. Genomewide association studies and assessment of the risk of disease. N Engl J Med 2010;363:166–76.*

Genetic Basis of Cutaneous Diseases

55

Vered Molho-Pessach and Julie V. Schaffer



Key features

- Advances in molecular technology have led to elucidation of the genetic bases of many single-gene inherited and mosaic skin disorders, greatly improving our understanding of these conditions
- McKusick's Online Mendelian Inheritance in Man (OMIM) database provides easily accessible, up-to-date information on human genes and genetic diseases; each gene or phenotype entry is assigned a specific six-digit MIM number
- Genotype–phenotype correlations in genodermatoses are often complex, with multiple examples of allelic heterogeneity (mutations in a single gene causing more than one disorder) and locus heterogeneity (mutations in different genes causing the same disorder)
- Molecular classification of genodermatoses into categories such as keratin defects and RASopathies complements traditional morphologic classification, highlighting pathomechanisms and relationships between conditions
- Certain syndromic associations actually represent contiguous gene syndromes caused by large deletions that affect two or more neighboring genes
- Types 1 and 2 mosaicism in autosomal dominant disorders have been confirmed on a molecular level, and functional X-chromosome mosaicism can lead to a mosaic distribution of skin lesions in female patients heterozygous for X-linked disorders
- Determining the molecular basis of monogenic skin disorders can enable the development of targeted therapies and provide insights into the pathogenesis of acquired skin diseases
- Molecular research has paved the way to the goal of gene therapy for severe inherited skin disorders such as epidermolysis bullosa

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; XR, X-linked recessive.

INTRODUCTION

In 1987, deletions in the steroid sulfatase gene were found to underlie X-linked recessive ichthyosis[1]. This heralded an era of tremendous progress in the elucidation of the genetic bases of inherited skin disorders, made possible by rapid advances in molecular technology (including the development of next-generation massively parallel sequencing; see Fig. 3.5), utilization of animal models, and sequencing of the human genome[2–4]. Better understanding of signaling pathways, molecules involved in cell–cell communication and adhesion, and mechanisms of cutaneous differentiation have also contributed to the momentum.

As a result of this explosion in research, more than 1000 genes were recognized to be responsible for a particular human phenotype by the year 2000, with approximately 300 of these conditions including cutaneous abnormalities[5]; by 2023, these numbers had increased to nearly 5000 and 1700, respectively[6–8]. Currently, the molecular genetic bases of the majority of single-gene inherited skin disorders have been established[9,10]. Multigene panels as well as whole-exome (the transcribed portion of the genome) and whole-genome sequencing utilizing next-generation technology are clinically available to assist in the identification of disease-causing genes[10].

In the past, diagnosis of genodermatoses was complicated by the existence of multiple complex classification systems based on various combinations of clinical, histologic, radiographic, and biochemical criteria. Inconsistent nomenclature laden with descriptive terms, eponyms, and synonyms added to the confusion and potential for misdiagnosis[11]. As the genetic bases of genodermatoses have been determined, integration of molecular and clinical data has helped to simplify disease categorization and eliminate redundant terminology. This has been successfully accomplished for disorders such as epidermolysis bullosa (EB) and ichthyoses, but it represents a work in progress, to be continually refined as additional genotype–phenotype correlations are established[12,13]. In addition, grouping hereditary skin disorders according to their molecular bases (Table 55.1) can supplement traditional morphologic classification, clarifying pathomechanisms and the relationships between conditions. Groups of monogenic conditions listed in tables elsewhere in the book are noted in Table 55.2.

As the "morbid anatomy of the dermatologic genome" continues to be established, new challenges will arise and additional questions will be answered[14]. Because of the rarity of many genodermatoses, their full clinical spectra have yet to be elucidated. However, with the increasing availability of genetic testing, dermatologists can establish the diagnosis in patients with mild or atypical presentations, thereby expanding the range of phenotypes. Continuing to decipher heritable skin disorders will require close interactions between basic scientists and clinicians[15]. Hopefully, such research will continue to lead to better understanding of cutaneous structure and function; insights into the pathogenesis of common multifactorial disorders; and effective therapies as well as diagnostic and prognostic information, improved genetic counseling, and DNA-based prenatal/preimplantation testing for patients with genodermatoses.

McKUSICK'S MENDELIAN INHERITANCE IN MAN

McKusick's Mendelian Inheritance in Man (MIM) database was first published in 1966 as "Catalogs of Autosomal Dominant, Autosomal Recessive and X-linked Phenotypes". In the 1994 edition, the subtitle was changed to "A Catalog of Human Genes and Genetic Disorders", reflecting the progress that had been made in the field. Online MIM (OMIM; https://omim.org/) has been widely available on the Internet for almost 40 years, providing immediate access to current information on human genes and genetic diseases[6,7]. This database is updated continuously and can be searched by entering a constellation of clinical features as well as the name of a gene or syndrome.

A particular six-digit number (MIM number) is assigned to each OMIM entry. The first digit of the MIM number indicates the mode of inheritance of the corresponding genetic defect: 1 for autosomal dominant (entries before May 1994); 2 for autosomal recessive (entries before May 1994); 3 for X-linked; 4 for Y-linked; 5 for mitochondrial; and 6 for autosomal dominant or recessive (entries after May 1994). *Phenotype entries* describe the clinical and biochemical features, inheritance, mapping, and molecular genetics of a given disease or trait; a "#" is used to designate those for which the molecular basis is known (e.g. #162200). *Gene entries* are marked by a "*" (e.g. *613113), while *gene plus phenotype* entries are indicated with a "+" (e.g. +107670); both are appended with important disease-causing allelic variants (each of which is given a four-digit extension, beginning with .0001).

GENOTYPE–PHENOTYPE CORRELATIONS

Genotype–phenotype correlations in genodermatoses are often complex. Mutations in a single gene can cause more than one clinical disorder, a phenomenon referred to as *allelic heterogeneity* (see Table 54.2). This usually results from different mutations in a particular gene. However, it occasionally reflects the same mutation

MOLECULAR CLASSIFICATION OF GENETIC SKIN DISORDERS	
Molecular defect	**Examples of skin disorders that result**
Keratin defects	See Table 56.4 and Fig. 56.5
Defects in structural proteins of the cornified cell envelope	Ichthyosis vulgaris, loricrin keratoderma (variant Vohwinkel syndrome)
Lipid metabolism defects	Various ichthyoses, including CHILD syndrome, Conradi–Hünermann–Happle syndrome, neutral lipid storage disease, lamellar ichthyosis/congenital ichthyosiform erythroderma spectrum (e.g. defective lipoxygenase 3 or 12R, cytochrome p450 4F22), self-healing collodion baby (defective lipoxygenase 3 or 12R), late-onset autosomal recessive congenital ichthyosis, Refsum disease, rhizomelic chondrodysplasia punctata, Sjögren–Larsson syndrome, X-linked recessive ichthyosis and ichthyosis, intellectual disability and spastic quadriplegia; various hyperlipidemias; Farber lipogranulomatosis, Gaucher disease type 2, hyperimmunoglobulinemia D syndrome, localized autosomal recessive hypotrichosis II/autosomal recessive woolly hair, Niemann–Pick disease, psoriasiform dermatitis–microcephaly–developmental delay syndrome
Transglutaminase defects	Congenital ichthyosiform erythroderma spectrum (transglutaminase 1), acral peeling skin syndrome
Protease/proteasome defects	Dermatosparaxis, familial hidradenitis suppurativa, hereditary angioedema (type III), Howel–Evans syndrome, ichthyosis–hypotrichosis syndrome, IFAP (*i*chthyosis *f*ollicularis–*a*trichia–*p*hotophobia) syndrome, KLICK (*k*eratosis *l*inearis–*i*chthyosis *c*ongenita–sclerosing *k*eratoderma) syndrome, Olmsted syndrome, Papillon–Lefèvre and Haim–Munk syndromes, prolidase deficiency, restrictive dermopathy (defective zinc metallopeptidase), hereditary thrombotic thrombocytopenic purpura, MONA (*m*ulticentric *o*steolysis, *n*odulosis, and *a*rthropathy), proteasome-associated autoinflammatory/CANDLE/Nakajo–Nishimura syndrome)
Protease inhibitor defects	Antithrombin III deficiency, autosomal recessive exfoliative ichthyosis, hereditary angioedema (types I & II), Netherton syndrome
Desmosomal defects (see Fig. 56.8)	Acantholytic erosive disorder, arrhythmogenic right ventricular dysplasia/cardiomyopathy + palmoplantar keratoderma + woolly hair; Carvajal syndrome, erythrokeratodermia–cardiomyopathy syndrome, generalized inflammatory peeling skin syndrome, hypotrichosis and skin lesions, hypotrichosis simplex of the scalp, localized autosomal recessive hypotrichosis, monilethrix (autosomal recessive), Naxos disease, SAM (severe dermatitis, *a*llergies, and *m*etabolic wasting), skin fragility–ectodermal dysplasia syndrome, skin fragility/woolly hair syndrome, striate palmoplantar keratoderma
Connexin defects (see Table 58.5)	Bart–Pumphrey syndrome, Clouston syndrome, erythrokeratodermia variabilis et progressiva, lymphatic malformation 3, ILVEN, keratoderma–hypotrichosis–leukonychia totalis, KID (*k*eratitis–*i*chthyosis–*d*eafness) syndrome, oculodentodigital dysplasia, palmoplantar keratoderma with deafness, porokeratotic adnexal ostial nevus, Vohwinkel syndrome (classic)
Other defects in cell-to-cell adhesion	Ichthyosis–hypotrichosis–sclerosing cholangitis syndrome, cleft lip/palate–ectodermal dysplasia syndrome, ectodermal dysplasia–syndactyly syndrome, ectodermal dysplasia–ectrodactyly–macular dystrophy, hypotrichosis with juvenile macular dystrophy, leukocyte adhesion deficiency type I
Defects in keratinocyte–extracellular matrix (ECM) adhesion	Various forms of epidermolysis bullosa (EB) simplex, junctional EB, and dystrophic EB (keratin–ECM linkage); Kindler EB (actin–ECM linkage)
ATP-binding cassette (ABC) transporter defects	Harlequin ichthyosis, lamellar ichthyosis/congenital ichthyosiform erythroderma spectrum (defective ABCA12), pseudoxanthoma elasticum, sitosterolemia, Tangier disease/familial hypoalphaproteinemia
Calcium pump defects	Darier disease, Hailey–Hailey disease
Copper transporter defects	Menkes disease, occipital horn syndrome, Wilson disease
Defects in other transporters	Acrodermatitis enteropathica (zinc transporter), arterial tortuosity syndrome (glucose transporter), autosomal dominant hemochromatosis (iron-regulated transporter), spondylodysplastic Ehlers–Danlos syndrome (zinc transporter), H syndrome (nucleoside transporter), Hartnup disease (neutral amino acid transporter), ichthyosis–prematurity syndrome (fatty acid transporter), oculocutaneous albinism (transporters on lysosome-related organelles)
Collagen defects	Various types of dystrophic EB, various types of Ehlers–Danlos syndrome, Ullrich muscular dystrophy, lysyl hydroxylase 3 deficiency
Defects in other ECM proteins	Autosomal dominant cutis laxa, autosomal recessive cutis laxa type I, cutis laxa with severe pulmonary/gastrointestinal/urinary abnormalities, classic-like and hypermobile Ehlers–Danlos syndrome, juvenile hyaline fibromatosis/infantile systemic hyalinosis, lipoid proteinosis, Marfan syndrome, stiff skin syndrome
Nuclear membrane defects (see Table 63.10)	Buschke–Ollendorff syndrome/melorheostosis, Néstor–Guillermo progeria syndrome, Hutchinson–Gilford progeria syndrome, mandibuloacral dysplasia, partial > generalized lipodystrophy (familial and "acquired" forms), restrictive dermopathy
Defects in pyrin/NOD-family members and related proteins (see Fig. 4.2)	Blau syndrome, Yao syndrome, NOMID syndrome, familial cold autoinflammatory syndrome, familial Mediterranean fever, Muckle–Wells syndrome, PAPA syndrome
Interferonopathies (see Ch. 45)	Aicardi–Goutières syndrome, familial chilblain lupus, proteasome-associated autoinflammatory/CANDLE/Nakajo–Nishimura syndrome, SAVI (*STING*-*a*ssociated *v*asculopathy with onset in *i*nfancy), X-linked reticulate pigmentary disorder
RecQ DNA helicase defects	Bloom syndrome, Rothmund–Thomson syndrome, Werner syndrome
Classic DNA repair defects	Various subtypes of xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome; Muir–Torre syndrome, constitutional mismatch repair deficiency syndrome
Cell cycle checkpoint defects	Ataxia telangiectasia, familial atypical mole and melanoma (FAMM) syndrome, multiple endocrine neoplasia (MEN) 4
Defects in telomere maintenance	Dyskeratosis congenita (see Table 67.8; 11 genes implicated to date)
RAS–MAPK pathway activation (RASopathies; see Fig. 55.4)	Capillary malformation–arteriovenous malformation, cerebral capillary malformations (familial), cardio-facio-cutaneous syndrome, congenital melanocytic nevi, Costello syndrome, Legius syndrome, neurofibromatosis type 1, Noonan syndrome (with multiple lentigines), Noonan-like disorder with loose anagen hair, verrucous epidermal nevi, nevus sebaceus, woolly hair nevi

Table 55.1 Molecular classification of genetic skin disorders.

MOLECULAR CLASSIFICATION OF GENETIC SKIN DISORDERS	
Molecular defect	**Examples of skin disorders that result**
Phosphatidylinositol 3-kinase (PI3K)/AKT pathway activation	Epidermal nevi, lymphatic malformations, PIK3CA-related overgrowth spectrum (see Table 104.5), Proteus syndrome, PTEN hamartoma tumor syndrome, tuberous sclerosis complex, venous malformations
G protein activation	Diffuse capillary malformation with overgrowth (some patients), extensive dermal melanocytosis, McCune–Albright syndrome (versus loss-of-function in Albright hereditary osteodystrophy), phakomatosis pigmentovascularis, port-wine birthmarks, Sturge–Weber syndrome
cAMP and AMP-activated protein kinase pathway defects (see Fig. 55.3)	Albright hereditary osteodystrophy, Carney complex, McCune–Albright syndrome, Peutz–Jeghers syndrome, tuberous sclerosis complex
Defects in WNT/β-catenin signaling (see Fig. 55.6)	Anonychia congenita, ectodermal dysplasia–neoplastic syndrome, Gardner syndrome, Goltz syndrome (focal dermal hypoplasia), hereditary hypotrichosis simplex, palmoplantar keratoderma with cutaneous SCC and sex reversal, WNT10A-related ectodermal dysplasias (including odonto-onycho-dermal dysplasia and Schöpf–Schulz–Passarge syndrome)
Defects in transforming growth factor (TGF)-β signaling	Buschke–Ollendorff syndrome/melorheostosis, Ferguson–Smith multiple self-healing squamous epitheliomas, hereditary hemorrhagic telangiectasia, Loeys–Dietz syndrome, Marfan syndrome, stiff skin syndrome
Defective vesicle assembly/ protein sorting to vesicles	ARC (*a*rthrogryposis–*r*enal *d*ysfunction–cholestasis) syndrome, Hermansky–Pudlak syndrome, MEDNIK (*m*ental disability, *e*nteropathy, *d*eafness, *n*europathy, *i*chthyosis, *k*eratodermia) syndrome
Defective vesicle trafficking or transport	Autosomal recessive cutis laxa type IIA, CEDNIK (*c*erebral *d*ysgenesis, *n*europathy, *i*chthyosis and *k*eratoderma) syndrome, Chédiak–Higashi syndrome, gerodermia osteodysplastica, Griscelli syndrome, ocular albinism type 1, wrinkly skin syndrome, MACS (*m*acrocephaly, *a*lopecia, *c*utis laxa and *s*coliosis) syndrome

Table 55.1 Molecular classification of genetic skin disorders. cAMP, cyclic adenosine monophosphate; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CHILD, congenital hemidysplasia with ichthyosiform nevus and limb defects; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NOD, nucleotide-binding oligomerization domain; NOMID, neonatal-onset multisystem inflammatory disease; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; SCC, squamous cell carcinoma; STAT, signal transduction and activation of transcription; STING, stimulator of interferon genes; WNT, wingless-type integration site.

in patients with different ages at presentation, e.g. Cowden syndrome and Bannayan–Riley–Ruvalcaba syndrome (*PTEN*), or the same *mosaic* mutation affecting different cell types, e.g. nevus spilus and nevus sebaceus (*HRAS*). Mutations that affect different domains of a protein can produce divergent phenotypes; for example, mutations in the sterile alpha motif (SAM) domain of the p63 protein typically cause AEC (*a*nkyloblepharon, *e*ctodermal dysplasia, and *c*left lip/palate) syndrome, while those in the DNA-binding domain give rise to EEC (*e*ctrodactyly, *e*ctodermal dysplasia, and *c*left lip/palate) syndrome. Different mutations in a gene can also lead to disorders with distinct modes of inheritance, such as X-linked dominant incontinentia pigmenti and X-linked recessive hypohidrotic ectodermal dysplasia with immunodeficiency due to a partial deletion and milder, "hypomorphic" mutations in *IKBKG* (inhibitor of nuclear factor κB kinase regulatory subunit γ; *NEMO*), respectively. Lastly, mutations with opposite effects on a gene can produce disorders with completely disparate phenotypes, such as Ferguson–Smith multiple self-healing squamous epithelioma and Loeys–Dietz syndrome due to loss-of-function versus gain-of-function mutations in *TGFBR1* (TGF-β receptor 1), respectively.

The type of mutation can also affect the severity of a genodermatosis. The oftentimes lethal severe form of junctional EB (JEB), an *autosomal recessive* disorder, is typically caused by *LAMB3* mutations that produce a premature termination codon and absence of the LAMB3 protein. In contrast, milder forms of JEB result from missense mutations that result in decreased LAMB3 function. Conversely, in *autosomal dominant* conditions such as piebaldism (*KIT*) where the mutated protein forms a dimer, *dominant negative* missense mutations often result in more severe disease (via abnormal proteins disrupting normal proteins) than do premature termination codons that produce *haploinsufficiency* (absence of half of the proteins).

In other instances, mutations in different genes produce the same clinical disorder. This *locus heterogeneity* typically occurs when the mutated proteins serve a similar function. Examples include proteins interacting: (1) in a *complex*, e.g. components of various BLOCs (*b*iogenesis of *l*ysosome-related *o*rganelle *c*omplexes) in Hermansky–Pudlak syndrome (see Fig. 65.8A); (2) as a *ligand and receptor*, e.g. endothelin-3 and the endothelin-B receptor in type 4 Waardenburg syndrome (see Fig. 65.3); or (3) in a *signaling pathway*, e.g. RAS/mitogen-activated protein kinase [MAPK] pathway proteins in cardio-facio-cutaneous syndrome (see below). However, some phenotypic differences can arise when these proteins also have distinct functions and/or tissue distributions. For example, the neurologic abnormalities in Griscelli syndrome 1 result from myosin Va expression in neurons, and the immunodeficiency and hemophagocytic syndrome that characterize Griscelli syndrome 2 reflect RAB27A expression in hematopoietic cells.

MOLECULAR CLASSIFICATION OF HEREDITARY SKIN DISORDERS

Molecular classification (see Table 55.1) represents a useful approach to the categorization of genodermatoses. Based on the pathogenetic defect rather than the clinical presentation, it can facilitate better understanding of important cellular pathways such as phosphatidylinositol 3-kinase (PI3K)/AKT or RAS/MAPK signaling (see Fig. 113.1). Several groups of genodermatoses for which molecular classification has been instructive are discussed below.

Keratin Defects

In 1991, EB simplex became the first human disease shown to be caused by intermediate filament mutations. Molecular defects in keratins have subsequently been identified in a diverse group of hereditary skin disorders, with manifestations including mechanical fragility (EB simplex), scaling/hyperkeratosis (keratinopathic ichthyoses, palmoplantar keratodermas [PPKs]), hyperpigmentation (Dowling–Degos disease), nail dystrophy (pachyonychia congenita), hair abnormalities (monilethrix), oral mucosal changes (white sponge nevus), and ectodermal dysplasia (Naegeli–Franceschetti–Jadassohn syndrome) (see Table 56.4)[16].

Keratin intermediate filaments are expressed in a tissue- and differentiation-specific fashion. They are composed of heterodimeric subunits formed by the specific pairing of a type I (acidic) and type II (basic–neutral) keratin (see Ch. 56). Many keratin disorders can be caused by mutations (often dominant negative) in either the type I or type II component of a particular keratin pair, thus exhibiting locus heterogeneity (e.g. KRT10 or KRT1 for epidermolytic ichthyosis; KRT14 or KRT5 for EB simplex). Allelic heterogeneity is also observed, with mutations in the highly conserved helix initiation and termination motifs leading to more severe phenotypes (e.g. severe EBS) than those in other regions (e.g. localized EBS) (see Fig. 56.5).

GROUPS OF MONOGENIC SKIN DISORDERS LISTED IN TABLES ELSEWHERE IN THE BOOK	
Category	**Table(s)**
Congenital insensitivity to pain and related neuropathies	Table 6.10
Epidermolysis bullosa and other blistering disorders	Tables 32.1 & 32.3
Sclerodermoid disorders	Table 43.7
Autoinflammatory diseases	Tables 45.2 & 45.7
Porphyrias	Table 49.3
Keratinopathies and desmosomal disorders	Table 56.4; Figs. 56.5 & 56.8
Ichthyoses	Tables 57.1, 57.2, 57.6, 57.7 & 57.8
Connexin disorders and keratodermas	Tables 58.5 & 58.6
Primary immunodeficiencies	Tables 60.4, 60.6, 60.8, 60.10, 60.13, 60.15 & 60.16
Disorders associated with multiple café-au-lait macules	Table 61.3
Epidermal nevi and other mosaic disorders	Tables 62.3 & 62.6
Progeroid syndromes/inherited poikilodermas and nuclear membrane disorders	Tables 63.9 & 63.10
Ectodermal dysplasias	Tables 63.11–63.13
Aplasia cutis congenita, cleft lip/palate, and digital anomalies	Tables 64.3–64.6
Disorders of hypopigmentation (diffuse or circumscribed)	Tables 65.1 & 66.4
Disorders with reticulated hyperpigmentation, dyskeratosis congenita, and dyschromatoses	Tables 67.8, 67.9 & 67.11
Hypotrichosis, hair shaft disorders, and hypertrichosis	Tables 69.7; 70.1 & 70.2
Xeroderma pigmentosa and other photosensitivity disorders	Table 87.4
Hyperlipidemias	Table 92.2
Ehlers–Danlos syndrome, cutis laxa, and other extracellular matrix disorders	Tables 95.5; 97.1, 97.2 & 97.7
Lipodystrophy syndromes	Table 101.1
Vascular anomalies and overgrowth syndromes	Tables 104.2 & 104.5
Lymphatic malformations/lymphedema	Table 105.7
Disorders with multiple lentigines	Table 112.2

Table 55.2 Groups of monogenic skin disorders listed in tables elsewhere in the book. In addition, other chapters (especially in the genodermatosis section) have tables that present more detailed information on monogenic skin disorders.

Defects in Intercellular Junctions

Mutations in genes encoding components of desmosomes and gap junctions underlie a variety of genodermatoses, several of which have prominent extracutaneous manifestations.

Desmosomal defects

Desmosomes are intercellular junctions that provide mechanical integrity to tissues by anchoring intermediate filaments to the cell surface and mediating strong cell–cell adhesion (see Fig. 29.3B). They are particularly important in stratified squamous epithelia and the myocardium, tissues that are subjected to substantial mechanical stress[17]. It is therefore not surprising that impaired keratinization (especially PPK), skin fragility, and cardiomyopathy represent features of disorders caused by defects in desmosomal proteins such as desmoplakin, plakoglobin, and plakophilin 1 (see Fig. 56.8). Abnormal hair (oftentimes woolly in nature) can also result from abnormalities in these proteins, and defects in other desmosomal components such as desmoglein 4 and corneodesmosin (which are highly expressed within the hair follicle) can lead to hypotrichosis and (for desmoglein 4) an autosomal recessive form of monilethrix (Fig. 55.1). Additional consequences of desmosomal defects include inflammatory peeling skin (corneodesmosin) and *s*evere dermatitis, *a*llergies, and *m*etabolic wasting (SAM; desmoglein 1, desmoplakin).



Fig. 55.1 Autosomal recessive monilethrix due to desmoglein 4 mutations. Sparse short hairs, stubble, and follicular papules on the scalp. Inset: Trichogram showing alternating elliptical nodes and constrictions.

Connexin defects

Gap junctions are intercellular channels that connect the cytoplasm of neighboring cells, facilitating communication that coordinates cellular growth, differentiation and responses to stimuli as well as tissue morphogenesis and homeostasis (see Ch. 58). Transmembrane connexin proteins undergo oligomerization to form the connexons that compose gap junctions. Connexin proteins such as Cx26, Cx30, Cx31, and Cx43 are preferentially expressed in ectoderm-derived epithelia of the inner ear and cornea as well as in the epidermis and its appendages[18]. This accounts for the sensorineural deafness, keratitis, and cutaneous abnormalities ranging from keratoderma to erythrokeratoderma to ectodermal dysplasias affecting the hair and nails that are observed in various connexin disorders (see Table 55.1). Several connexins are expressed in lymphatic cells, and mutations in the gene encoding Cx47 (*GJC2*) cause a hereditary type of lymphedema[19].

Defects in Keratinocyte–Extracellular Matrix Adhesion

The hemidesmosome links keratin intermediate filaments (KRT5, KRT14) within basal keratinocytes to proteins within the lamina densa (basement membrane proper) and sublamina densa regions of the epidermal basement membrane zone (see Ch. 28). Defects in protein components of these structures lead to various forms of EB (simplex, junctional, and dystrophic; see Ch. 32)[20]. The basement membranes of epithelia in other sites such as the eye, oral cavity, gastrointestinal tract, and genitourinary tract may also be affected in patients with EB. Additional clinical manifestations can result when the abnormal protein has important functions in extraepithelial tissues, such as the skeletal muscle for plectin (leading to EBS with muscular dystrophy).

Focal adhesions are structurally defined sites of linkage between the intracellular actin cytoskeleton and the extracellular matrix (ECM; see

Fig. 28.3B). Mutations in the gene encoding the focal adhesion protein kindlin-1 cause Kindler EB, an autosomal recessive disorder characterized by acral blistering and photosensitivity early in life, progressive poikiloderma, and erosive periodontal disease (see Ch. 32). Kindlin-1 is found within basal keratinocytes along the cell surface that faces the basement membrane, and it has roles in keratinocyte adhesion, polarity, proliferation, and motility. To date, Kindler EB represents the only skin fragility disorder known to be caused by disruption of linkage between actin microfilaments (rather than keratin intermediate filaments) and the ECM[20].

Transmembrane Transporter Defects

Abnormalities in transmembrane transporters underlie a variety of genodermatoses, ranging from oculocutaneous albinism due to defective transporters on lysosome-related organelles to metabolic disorders such as acrodermatitis enteropathica. This list also includes defects in a fatty acid transporter in ichthyosis prematurity syndrome[21] and an intracellular nucleoside transporter in H syndrome (Fig. 55.2)[22]. Disorders of calcium pumps and ATP-binding cassette (ABC) transporters, which underscore the important roles of transmembrane transporters in cutaneous homeostasis, are discussed below.

Calcium pump defects

Darier disease and Hailey–Hailey disease are distinct autosomal dominant disorders that share the histologic feature of epidermal acantholysis leading to suprabasal cleft formation; on an ultrastructural level, this corresponds to disruption of the desmosome–keratin intermediate filament complex. The two conditions also have some clinical similarities, including intertriginous involvement, vesiculobullous lesions (relatively uncommon in Darier disease), nail changes, exacerbation with heat, and frequent superinfections. As a result of these overlapping features, it was initially postulated that Darier disease and Hailey–Hailey disease were allelic disorders caused by defects in a gene encoding a structural component of the epidermis. In 1999, pathogenetic mutations in *ATP2A2*, which encodes a sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase, were identified in patients with Darier disease. Subsequently, mutations in *ATP2C1*, which encodes a Ca^{2+} ATPase localized to the Golgi apparatus, were shown to cause Hailey–Hailey disease (see Fig. 59.1). Determining the molecular bases of these genodermatoses thus demonstrated the pivotal role of calcium homeostasis in epidermal differentiation and cell–cell adhesion[23].

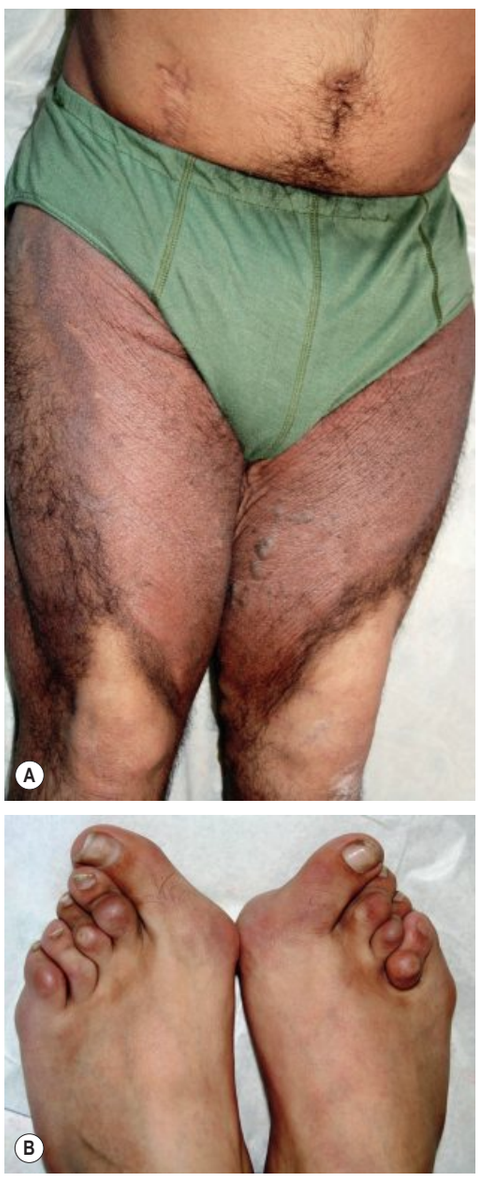


Fig. 55.2 H syndrome (histiocytosis-lymphadenopathy plus syndrome). This autosomal recessive disorder due to mutations in the *SLC29A3* gene (which encodes a nucleoside transporter) presents with *h*yperpigmentation, *h*ypertrichosis, induration, and varicose veins in a characteristic distribution pattern on the thighs with sparing of the knees (**A**). Additional features include *h*allux valgus and flexion contractures of the toes (**B**), *h*epatosplenomegaly, *h*eart anomalies, *h*earing loss, *h*ypogonadism, low *h*eight and *h*yperglycemia/diabetes mellitus.

ATP-binding cassette transporter defects

Members of the ABC transporter superfamily bind and hydrolyze adenosine triphosphate (ATP) in order to transport various molecules across a cell membrane or into a vesicle. Well-known examples include the CFTR (cystic fibrosis transmembrane conductance regulator) chloride ion channel that is defective in patients with cystic fibrosis and the P glycoprotein that mediates multidrug resistance. Several phenotypically diverse genodermatoses are also caused by mutations in ABC transporters (see Table 55.1)[24].

Because pseudoxanthoma elasticum (PXE) features fragmentation and calcification of elastic fibers, this autosomal recessive disorder was initially postulated to result from mutations in an extracellular matrix protein with roles in the skin, eyes, and cardiovascular system. Surprisingly, PXE was instead found to be caused by mutations in *ABCC6*, which encodes a hepatocyte efflux pump that transports ATP to the extracellular space. Extracellular ATP is rapidly converted to AMP and inorganic pyrophosphate (PPi), with the latter representing a physiologic anti-mineralization factor. PXE therefore actually represents a metabolic disorder with secondary connective tissue manifestations.

Biallelic mutations in *ABCA12*, which encodes a transporter that secretes lipids into lamellar granules, cause both harlequin ichthyosis and a form of lamellar ichthyosis[25] (see Fig. 56.2). Patients with harlequin ichthyosis tend to have nonsense mutations, whereas those with lamellar ichthyosis typically have missense mutations. This represents one of the most clearcut genotype–phenotype correlations observed to date for nonsyndromic autosomal recessive ichthyoses. Defective formation of intercellular lipid layers, which are essential for epidermal barrier function, due to genetic defects in lipid metabolism also represents the pathomechanism of an expanding list of other ichthyosiform disorders (see Table 55.1 and Fig. 56.2)[25].

Nuclear Envelope Defects

"Nuclear envelopathies" represent a clinically heterogeneous group of inherited disorders caused by defects in structural components of the nuclear envelope (see Table 63.10). In addition to a variety of extracutaneous findings – e.g. skeletal dysplasia, muscular dystrophy, cardiomyopathy, and neuropathy – dermatologic manifestations include: premature aging of the skin, e.g. in progeria and "atypical Werner syndrome" due to *LMNA* mutations; cutaneous fibrosis, e.g. in restrictive dermopathy and Buschke–Ollendorff syndrome/melorheostosis due to *LMNA* and *LEMD3* mutations, respectively; and partial lipodystrophy, e.g. familial Dunnigan and "acquired" Barraquer–Simons types due to *LMNA* and *LMNB2* mutations, respectively.

"Laminopathies" represent the largest subgroup of envelopathies and result from mutations in the genes that encode the lamin A/C and lamin B2 proteins of the nuclear membrane lamina, which lies just inside the inner nuclear membrane[26]. *LEMD3* encodes MAN1, an inner nuclear membrane protein that associates with lamin A. In addition to "true" envelopathies, mutations in *ZMPSTE24*, which encodes a zinc metallopeptidase involved in the processing of prelamin A into mature lamin A, can result in restrictive dermopathy and mandibuloacral dysplasia characterized by lipodystrophy, premature aging, and skeletal defects. The study of patients with envelopathies has provided insight into the importance of lamins and other nuclear envelope proteins to the structural integrity of the nucleus, chromatin organization, transcriptional regulation, control of differentiation, and mechanisms of aging[26].

Defects in Pyrin/NOD Family Members and Related Proteins

The molecular bases of several hereditary periodic fever syndromes and other autoinflammatory disorders have been found to be due to defects in proteins containing *n*ucleotide-binding *o*ligomerization *d*omains (NODs) and/or pyrin domains (see Table 45.2)[27]. This has drawn attention to the NOD and pyrin families and related proteins (see Fig. 4.2), helping to uncover their importance in innate immune responses and acquired inflammatory disorders. Defects in such proteins lead to diverse cutaneous phenotypes, ranging from urticarial papules in cryopyrin-related disorders and erysipeloid erythema in familial Mediterranean fever to nodulocystic acne and pyoderma gangrenosum in PAPA syndrome to granulomatous dermatitis (together with arthritis and uveitis) in Blau syndrome (see Fig. 45.11C). Upon uncovering *NOD2* mutations as the defect in Blau syndrome, it was also established that this autosomal dominant disorder and sporadic "early-onset sarcoidosis" are identical on a genetic as well as phenotypic level (with the latter resulting from *de novo NOD2* mutations), thus representing a single disease entity. However, other *NOD2* variants have been implicated in Crohn disease and susceptibility to leprosy.

Defects in DNA Repair Genes, Tumor Suppressor Genes, and Oncogenes

Hereditary tumor syndromes that affect the skin can be divided into groups based upon whether the associated neoplasms are primarily benign skin tumors (Table 55.3), skin cancers (Table 55.4), or extracutaneous malignancies (Table 55.5); individuals in the latter group may have either benign cutaneous neoplasms (e.g. Cowden syndrome) or non-neoplastic skin lesions (e.g. ataxia–telangiectasia)[28]. To complement this clinical approach, molecular classification of such syndromes can help to explain relationships among disorders, understand the

SELECTED HEREDITARY DISORDERS CHARACTERIZED BY BENIGN SKIN TUMORS			
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**
Familial cylindromatosis; Brooke–Spiegler syndrome; multiple familial trichoepitheliomas	AD	CYLD (deubiquitinating enzyme)	*CYLD*
Familial mastocytosis ± gastrointestinal stromal tumors*	AD	KIT proto-oncogene (stem cell factor receptor)	*KIT*
Lipomatosis, familial multiple	AD		
Lipomatosis, benign symmetric (Madelung disease)†	mt	Mitochondrial tRNA-lysine	*MT-TK*
	AR	Mitofusin 2	*MFN2*
	AR	Lipase E, hormone sensitive	*LIPE*
Ferguson–Smith multiple self-healing squamous epitheliomas	AD	Transforming growth factor-β receptor 1 (loss-of-function mutations)	*TGFBR1*
Neurofibromatosis type 1‡	AD	Neurofibromin 1 (GTPase activating protein)	*NF1*
Neurofibromatosis type 2	AD	Neurofibromin 2 (merlin)	*NF2*
Tuberous sclerosis complex	AD	Hamartin	*TSC1*
	AD	Tuberin	*TSC2*

*Occasionally malignant.
†Associated with myoclonic epilepsy with ragged red fibers (MT-TK mutations), neuropathy (MFN2 mutations), or partial lipodystrophy and myopathy (LIPE mutations).
‡Also associated with malignant peripheral nerve sheath tumors.

Table 55.3 Selected hereditary skin disorders characterized by benign skin tumors. Disorders associated with extracutaneous cancer as well as benign skin tumors are listed in Table 55.5. These conditions are discussed in Chapters 61, 62, 104, 117, and 118. mt, mitochondrial inheritance.

SELECTED HEREDITARY DISORDERS ASSOCIATED WITH SKIN CANCER			
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**
Bazex–Dupré–Christol syndrome	XD	Actin-related protein T1	*ACTRT1*
Epidermodysplasia verruciformis	AR	Transmembrane channel-like 6	*TMC6*
	AR	Transmembrane channel-like 8	*TMC8*
BAP1 tumor predisposition syndrome*	AD	BRCA-associated protein 1	*BAP1*
Familial atypical mole and melanoma (FAMM) syndrome*	AD	Cyclin-dependent kinase inhibitor 2A†	*CDKN2A*
	AD	Cyclin-dependent kinase 4	*CDK4*
Basal cell nevus syndrome	AD	Patched 1	*PTCH1*
	AD	Patched 2	*PTCH2*
	AD	Suppressor of fused homolog (Drosophila)	*SUFU*
Huriez syndrome (sclerotylosis)	AD		
Palmoplantar keratoderma with cutaneous SCC and sex reversal	AR	R-spondin 1	*RSPO1*
Pigmentation defects, palmoplantar keratoderma, and cutaneous SCC	AR	SAM and SH3 domain-containing 1	*SASH1*
Xeroderma pigmentosum (see Table 87.4)			

*Also associated with melanocytic nevi.
†Also associated with increased risk of developing pancreatic cancer.

Table 55.4 Selected hereditary disorders associated with skin cancer. These conditions are discussed in Chapters 79, 87, 99, 108, and 112. SCC, squamous cell carcinoma.

SELECTED HEREDITARY SKIN DISORDERS ASSOCIATED WITH EXTRACUTANEOUS CANCER				
Disorder	**Mode of inheritance**		**Gene or gene product**	**Gene symbol**
Ataxia–telangiectasia	AR		Ataxia–telangiectasia mutated (phosphatidylinositol 3-kinase-like serine/threonine protein kinase)	*ATM*
Birt–Hogg–Dubé syndrome	AD		Folliculin	*FLCN*
Bloom syndrome	AR		RecQ protein-like 3 (DNA helicase)	*BLM (RECQL3)*
Costello syndrome (see text)	AD		v-Ha-ras Harvey rat sarcoma viral oncogene homolog	*HRAS*
	AD		v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	*KRAS*
Dyskeratosis congenita (see Table 67.9)				
Ectodermal dysplasia–neoplastic syndrome	AD		Axis inhibitor 2	*AXIN2*
Gardner syndrome (variant of familial adenomatous polyposis)	AD		Adenomatous polyposis coli	*APC*
Howel–Evans syndrome (tylosis–esophageal carcinoma)	AD		Rhomboid 5 homolog 2	*RHBDF2*
Leiomyomatosis, cutaneous and uterine (Reed syndrome)	AD		Fumarate hydratase	*FH*
Muir–Torre syndrome (variant of Lynch syndrome)	AD		MutS homolog 2 (mismatch repair enzyme)	*MSH2*
	AD		MutS homolog 6 (mismatch repair enzyme)	*MSH6*
	AD		MutL homolog 1 (mismatch repair enzyme)	*MLH1*
MUTYH-associated polyposis	AR		MutY homolog	*MUTYH*
Constitutional mismatch repair deficiency syndrome (childhood tumor syndrome with neurofibromatosis type 1 phenotype)	AR		MutS homolog 2 (mismatch repair enzyme)	*MSH2*
	AR		MutS homolog 6 (mismatch repair enzyme)	*MSH6*
	AR		MutL homolog 1 (mismatch repair enzyme)	*MLH1*
	AR		Postmeiotic segregation increased 2 (mismatch repair enzyme)	*PMS2*
Multiple endocrine neoplasia (MEN)	MEN 1	AD	Menin	*MEN1*
	MEN 2A	AD	Ret proto-oncogene (cysteine-rich extracellular domain)	*RET*
	MEN 2B	AD	Ret proto-oncogene (particularly Met918Thr in substrate recognition pocket)	*RET*
	MEN 4	AD	Cyclin-dependent kinase inhibitor 1B (p27, Kip1)	*CDKN1B*
PTEN hamartoma tumor syndrome (including Cowden and Bannayan–Riley–Ruvalcaba syndromes)	AD		Phosphatase and tensin homolog	*PTEN*
Rothmund–Thomson syndrome	AR		RecQ protein-like 4 (DNA helicase)	*RECQ4*

Table 55.5 Selected hereditary skin disorders associated with extracutaneous cancer. These conditions are discussed in Chapters 60, 63, 67, 87, and 117.

disrupted pathway or process, and suggest candidate genes for patients with similar phenotypes for which the underlying molecular defect has not yet been identified. In addition to characterization based on the specific pathomechanism (e.g. RAS–MAPK pathway activation[29]; see below), hereditary cancer syndromes can be separated into three general categories: (1) defective DNA repair and protection of genomic integrity ("caretaker" genes); (2) defective tumor suppressor ("gatekeeper") genes; and (3) activated oncogenes.

Defective DNA repair and protection of genomic integrity

Inactivation of caretaker genes causes an increased mutation rate in all genes, including gatekeeper genes with critical roles in controlling tumor growth (see below). Classic examples of caretaker dysfunction include defects in the nucleotide excision repair of UV-induced DNA damage in xeroderma pigmentosum and abnormal mismatch repair in the Muir–Torre syndrome subtype of the hereditary non-polyposis colorectal cancer syndrome. Defects in RecQ helicases, which function in DNA replication, recombination, and repair, underlie Bloom, Rothmund–Thomson, and Werner syndromes. This leads to genomic instability, as evidenced by findings such as accumulation of chromosomal aberrations, increased sister chromatid exchange (Bloom syndrome), and shortened telomeres (Werner syndrome). The compromised telomere maintenance observed in dyskeratosis congenita can result from defects in telomerase subunits (RNA and reverse transcriptase) or associated proteins (e.g. dyskerin, a Cajal body protein, ribonucleoprotein homologs, shelterin complex components; see Table 67.9).

Defective tumor suppressor genes

In hereditary cancer syndromes caused by a defective tumor suppressor gene, there is classically a heterozygous germline loss-of-function mutation followed by a somatic "second hit" that leads to loss of heterozygosity and abrogation of protein function in affected tissues. Examples include *PTCH* (encoding patched) in basal cell nevus syndrome, *CDKN2A* (encoding $p16^{INK4a}$ and $p14^{ARF}$, which maintain activity of the retinoblastoma [Rb] and p53 tumor suppressor proteins, respectively) in the familial atypical mole and melanoma syndrome (see Fig. 107.4), and *PTEN* in the PTEN hamartoma tumor syndrome (see Table 63.3). The PTEN protein negatively regulates the PI3K/AKT cascade, which is positively regulated by the RET oncogene (Fig. 55.3; see below). The *PIK3CA*-related overgrowth spectrum and Proteus syndrome are caused by mosaicism for an activating mutation in *PIK3CA* and *AKT1* oncogenes, respectively. The roles of these proteins in the same pathway explains these conditions' clinical similarity to one another as well as to mosaic forms of PTEN hamartoma tumor syndrome (see Table 104.5 and below).

Activated oncogenes

Germline *gain*-of-function mutations in oncogenes have been identified in some autosomal dominant hereditary tumor syndromes, including *RET* in multiple endocrine neoplasia (MEN) 2A/2B (see Fig. 55.3), *KIT* in familial mastocytosis plus gastrointestinal stromal tumors, and those encoding RAS–MAPK pathway components in some "RASopathies" (Fig. 55.4). The latter include Costello (Fig. 55.5), Noonan, and

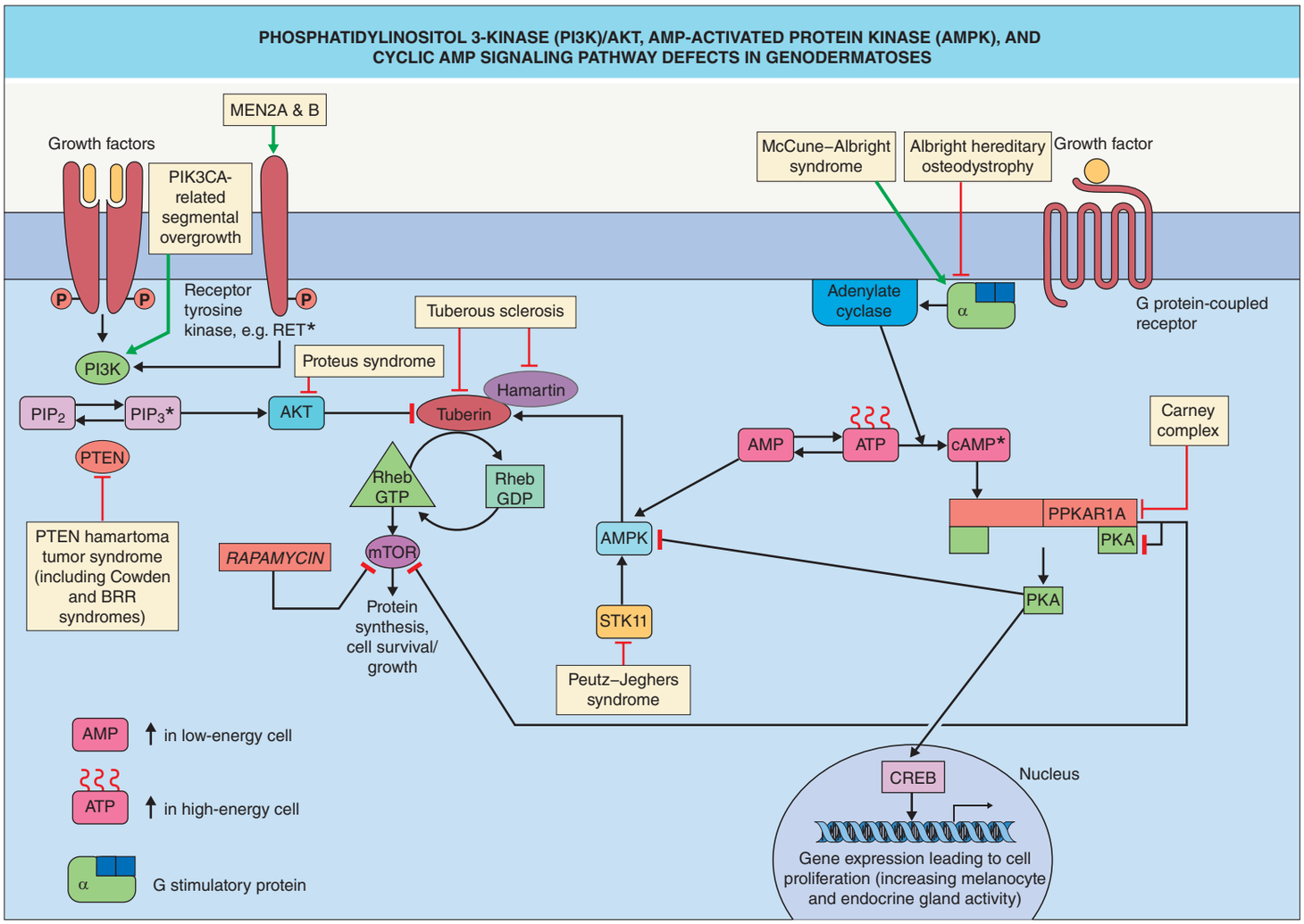


Fig. 55.3 Phosphatidylinositol 3-kinase (PI3K)/AKT, AMP-activated protein kinase (AMPK), and cyclic AMP signaling pathway defects in genodermatoses. The PI3K/AKT pathway is negatively regulated by the PTEN tumor suppressor protein and can be stimulated by a variety of receptor tyrosine kinases as well as by RAS (via cross-talk with the RAS–ERK pathway; see Fig. 55.4). AKT (protein kinase B) inhibits the GTPase activating-protein tuberin, which leads to increased *m*ammalian *t*arget *o*f *r*apamycin (mTOR) activity and resultant cell growth. During periods of nutrient depletion (high AMP/low ATP), serine–threonine kinase 11 (STK11) promotes AMPK-mediated activation of tuberin, which results in decreased mTOR activity and less protein synthesis. Ligand binding to G protein-coupled receptors activates adenylate cyclase, producing increased intracellular cAMP and activation of protein kinase A catalytic subunits (PKA; via release from *p*rotein *k*inase *A* regulatory subunit 1α [PRKAR1A]); this leads to transcription of *c*AMP *r*esponse *e*lement *b*inding protein (CREB)-controlled genes as well as inhibition of AMPK (which is also negatively regulated by AKT). *Other effector pathways include activation of RAS–ERK (see Fig. 55.4). AMP, adenosine monophosphate; ATP, adenosine triphosphate; BRR, Bannayan–Riley–Ruvalcaba; ERK, *e*xtracellular signal-*r*egulated *k*inase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; PIP_2, phosphatidylinositol diphosphate; PIP_3, phosphatidylinositol triphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome 10.

cardio-facio-cutaneous (CFC) syndromes as well as Noonan with multiple lentigines (LEOPARD) syndrome[29,30]. In addition, neurofibromatosis type 1 (NF1), Legius syndrome (previously referred to as NF1-like syndrome), and capillary malformation–arteriovenous malformation (CM-AVM) represent RASopathies due to germline *loss*-of-function mutations in tumor suppressor genes that normally downregulate RAS–MAPK signaling[29].

RASopathies share extracutaneous features such as ocular hypertelorism, macrocephaly, cardiac defects (especially pulmonary stenosis), and developmental delay, as well as a spectrum of skin findings that includes hair abnormalities (e.g. curly, woolly, loose anagen), pigmented lesions (e.g. lentigines, melanocytic nevi, café-au-lait macules)[31], keratosis pilaris, acanthosis nigricans, and distal phalangeal transverse creases (see Fig. 55.5B&C). Some RASopathies also have more specific cutaneous manifestations, such as neurofibromas in NF1, lax acral skin in Costello syndrome (see Fig. 55.5B), and capillary and arteriovenous malformations in CM-AVM. Different RASopathies are associated with variably increased risks for the development of benign (e.g. neurofibromas in NF1) and malignant (e.g. rhabdomyosarcoma in Costello syndrome) tumors. Targeted drugs aimed at proteins in the RAS–MAPK pathway hold promise for the treatment of sporadic cancers (e.g. BRAF inhibitors for melanoma) as well as RASopathies themselves (e.g. MEK inhibitors for plexiform neurofibromas)[32].

Defects in WNT/β-Catenin Signaling

WNT (*w*ingless-type *int*egration site) family members are lipid-modified, secreted signaling proteins that play important roles in numerous physiologic and pathologic processes, ranging from stem cell differentiation, cell polarity/adhesion, and tissue morphogenesis/maintenance (including hair follicle development) to wound repair, inflammation, oncogenesis, and aging. WNT signaling can be divided into canonical (β-catenin-dependent) and non-canonical (β-catenin-independent) pathways. Several genodermatoses result from defects in proteins that function in the WNT/β-catenin pathway (Fig. 55.6). Goltz syndrome (focal dermal hypoplasia; Fig. 55.7) is caused by mutations in *PORCN*, which encodes an O-acyltransferase in the endoplasmic reticulum that palmitoylates and thereby facilitates secretion of WNT proteins. Mutations in *WNT10A* produce several relatively common forms of ectodermal dysplasia as well as Schöpf–Schulz–Passarge syndrome (featuring hidrocystomas and palmoplantar keratoderma with eccrine syringofibroadenomatosis). Gardner syndrome (a variant

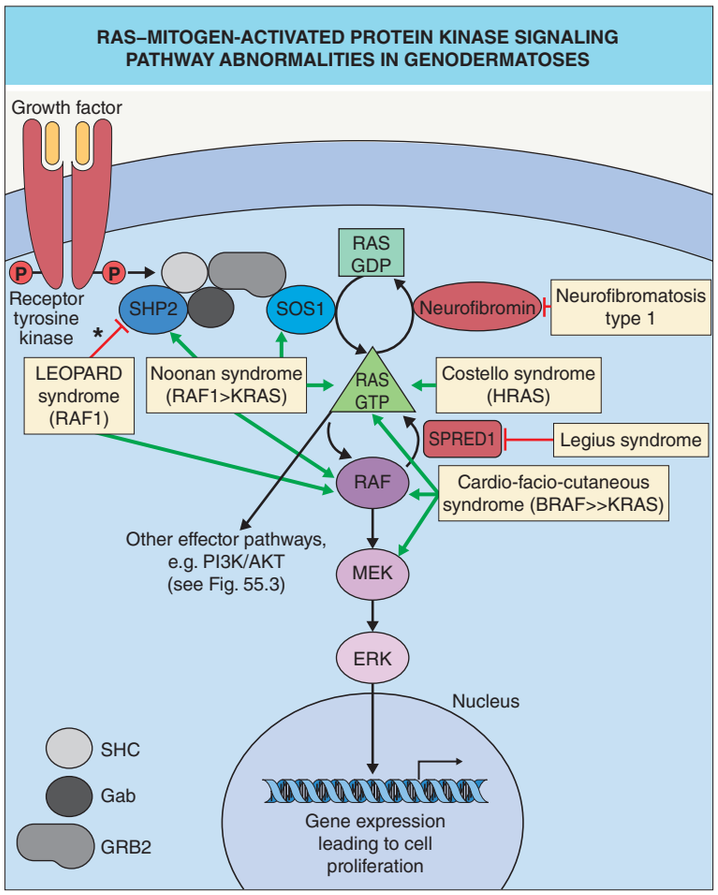


Fig. 55.4 RAS–mitogen-activated protein kinase (MAPK) signaling pathway abnormalities in genodermatoses. The phenotypic overlap among neurofibromatosis type 1 and Legius, Noonan, cardio-facio-cutaneous, Costello, and Noonan with multiple lentigines (also referred to as LEOPARD) syndromes is explained by underlying germline mutations in different components of the RAS–MAPK pathway that lead to activation of this signaling cascade. Of note, similar *somatic* activating mutations are found in a variety of benign and malignant tumors (e.g. *BRAF* or *NRAS* mutations in the majority of melanocytic nevi and melanomas; see Ch. 113) as well as epidermal/sebaceous nevi (see Ch. 62). Growth factor binding to receptor tyrosine kinases results in activated receptor complexes containing adapters such as Src *h*omology 2 domain-*c*ontaining (SHC), *g*rowth factor *r*eceptor-*b*ound 2 (GRB2), and GRB2-*a*ssociated *b*inding (Gab) proteins as well as SH2 domain-containing protein tyrosine phosphatase 2 (SHP2; encoded by *PTPN11*), which relays signals from activated receptors to RAS and deactivates negative regulators of RAS (e.g. Sprouty). The activated receptor complex recruits son of sevenless homolog 1 (SOS1), a guanine nucleotide exchange factor that increases levels of active RAS–guanosine triphosphate (GTP). In contrast, neurofibromin is a GTPase activating protein that promotes hydrolysis of RAS–GTP to RAS–guanosine diphosphate (GDP), which terminates signaling. **In vitro* studies suggest a dominant negative effect, but the consequences could vary depending on the substrate, cell type, or developmental stage.







Fig. 55.5 Costello syndrome due to a heterozygous activating *HRAS* mutation in a 3-year-old girl. **A** Verrucous periorificial (periocular, perinasal) plaques. **B** Loose acral skin with deep palmoplantar creases. Note the distal phalangeal transverse crease on the thumb. **C** Acanthosis nigricans.

of *a*denomatous *p*olyposis *c*oli) is due to mutations in the *APC* tumor suppressor gene that encodes an inhibitor of WNT/β-catenin signaling[33], and mutations in the APC downregulated 1 gene (*APCDD1*) underlie hereditary hypotrichosis simplex. Lastly, anonychia congenita and "palmoplantar keratoderma with cutaneous SCC and sex reversal" are caused by mutations in genes encoding R-spondins that activate WNT/β-catenin signaling.

CONTIGUOUS GENE SYNDROMES

Certain syndromic associations actually represent contiguous gene syndromes caused by large deletions that affect two or more neighboring genes. For example, deletions in the Xp22.3 region can give rise to X-linked recessive ichthyosis, X-linked recessive chondrodysplasia punctata, Kallmann syndrome (hypogonadotrophic hypogonadism with anosmia), ocular albinism type 1, short stature, and intellectual disability. Of note, more than 90% of patients with X-linked recessive ichthyosis have complete deletion of the *STS* gene and flanking sequences, which represents one of the highest incidences of chromosomal deletions among all genetic disorders. Additional genodermatoses that can present as contiguous gene syndromes include Ehlers–Danlos syndrome (due to tenascin-X deficiency) plus congenital adrenal hyperplasia (due to 21-hydroxylase deficiency), tricho-rhino-phalangeal syndrome plus multiple cartilaginous exostoses (together referred to as Langer–Giedion syndrome), and MIDAS (*mi*crophthalmia, *d*ermal *a*plasia, and *s*clerocornea) syndrome plus Aicardi syndrome (agenesis of the corpus callosum with a chorioretinal abnormality).

CUTANEOUS MOSAICISM

The current medical definition of a mosaic is: the coexistence of at least two genotypes in an individual derived from a single zygote, by the time

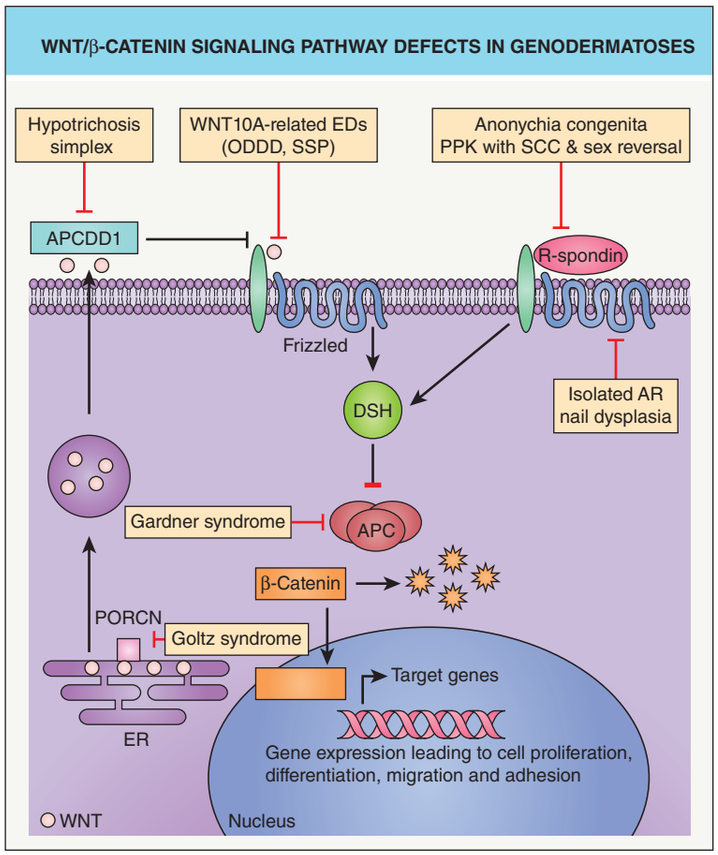


Fig. 55.6 WNT/β-catenin signaling pathway defects in genodermatoses. The porcupine homolog (PORCN) O-acyltransferase in the endoplasmic reticulum (ER) palmitoylates WNT proteins, facilitating their secretion. Extracellular WNT binds to the frizzled transmembrane receptor, which activates dishevelled (DSH), a cytosolic protein that inhibits the "destruction complex" (containing the adenomatous polyposis coli [APC] tumor suppressor protein) that mediates proteasomal degradation of β-catenin. As a result, β-catenin accumulates and is translocated to the nucleus, where it induces the transcription of genes that lead to cell proliferation, differentiation, migration, and adhesion. APC downregulated 1 (APCDD1) can inhibit WNT signaling. R-spondins are other secreted proteins that bind to frizzled and activate the WNT/β-catenin pathway. AR, autosomal recessive; EDs, ectodermal dysplasias; ODDD, odonto-onycho-dermal dysplasia; PPK, palmoplantar keratoderma; SCC, squamous cell carcinoma; SSP, Schöpf–Schulz–Passarge syndrome.

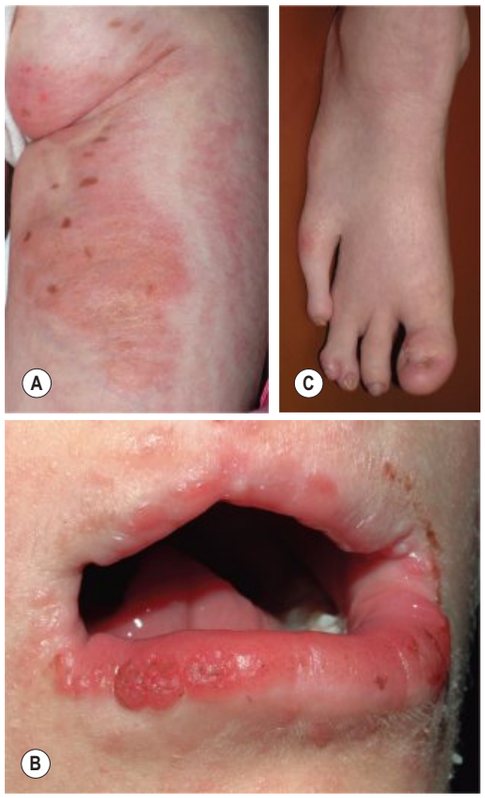


Fig. 55.7 Goltz syndrome (focal dermal hypoplasia). **A** Hyperpigmented macules and dermal atrophy with fat "herniation" on the posterior thigh. **B** Raspberry-like papillomas on the lower lip. **C** Ectrodactyly.

of birth, and which gives rise to a disease phenotype[34] (see Ch. 62). As a uniquely accessible organ, the skin provides an excellent opportunity to visualize and study mosaicism[35]. Patterns on the skin due to mosaicism include the lines of Blaschko, phylloid (see below), segmental with quadrilateral shapes, and non-segmental with circular shapes (see Fig. 62.1). Mosaicism for activating mutations affecting RAS-MAPK signaling or G protein α-subunits have been found to underlie a variety of birthmarks, including congenital melanocytic, epidermal, and sebaceous nevi as well as port-wine birthmarks and dermal melanocytosis. A single heterozygous mutation in a multipotent progenitor cell can lead to multiple types of birthmarks involving different skin lineages, such as nevus spilus (melanocytic) plus nevus sebaceus in phakomatosis pigmentokeratotica (*HRAS*) or port-wine birthmarks (vascular) plus dermal melanocytosis in phakomatosis pigmentovascularis (*GNAQ* or *GNA11*)[36,37]. Extracutaneous manifestations may occur if the mutation involves other organs such as the brain, eye, or bones.

Mosaic forms of autosomal dominant genodermatoses include: (1) a heterozygous postzygotic mutation occurring on a wild-type ("normal") background (type 1); and (2) a postzygotic "second hit" leading to loss-of-heterozygosity in the setting of a heterozygous constitutional mutation (type 2). The latter manifests clinically as a superimposed area of earlier onset or more severe disease than the background of generalized disease, e.g. linear porokeratosis in a patient with disseminated superficial actinic porokeratosis. Examples of type 1 mosaicism that have been confirmed on a molecular level include epidermolytic (*K1* or *K10*) and non-epidermolytic (fibroblast growth factor receptor 3 *[FGFR3]*) epidermal nevi; constitutional mutations in these genes produce epidermolytic ichthyosis and craniosynostosis syndromes associated with severe acanthosis nigricans (Fig. 55.8), respectively. Both type 1 and type 2 mosaicism have been documented for Darier disease (*ATP2A2*) and Hailey–Hailey disease (*ATP2C1*) (Fig. 55.9), while type 2 mosaicism has been confirmed for several genodermatoses due to a defective tumor suppressor gene, such as NF1, basal cell nevus syndrome (*PTCH1*), and PTEN hamartoma tumor syndrome.

All women and girls are *functional* mosaics due to the random, irreversible, stably inherited inactivation of one of the two X chromosomes that occurs in each cell during early embryonic development (lyonization). However, 15% of genes on the human X chromosome escape lyonization and 10% are variably inactivated. In women heterozygous for X-linked disorders, functional mosaicism can result in skin lesions that follow the lines of Blaschko or have other mosaic distribution patterns. This occurs in female patients with X-linked dominant, male-lethal disorders such as incontinentia pigmenti (*IKBKG/NEMO*), CHILD (*c*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects) syndrome (*NSDHL*), Conradi–Hünermann–Happle syndrome (*EBP*), and Goltz syndrome (*PORCN*; see Fig. 55.7) as well as in female "carriers" of X-linked dermatoses such as hypohidrotic ectodermal dysplasia (*EDA*; Fig. 55.10) and *i*chthyosis *f*ollicularis–*a*trichia–*p*hotophobia (IFAP) syndrome (*MBTPS2*; Fig. 55.11). The gene encoding steroid sulfatase escapes lyonization, explaining why skin lesions in a mosaic pattern are not observed in female carriers of X-linked recessive ichthyosis.

REVERTANT MOSAICISM

Revertant mosaicism is a means of "natural gene therapy" in which a spontaneous secondary genetic phenomenon leads to rescue of a disease-causing mutation, allowing a mosaic clone of heterozygous cells to regain wild-type ("normal") function[38]. It has been described most often in patients with EB (see Ch. 32), potentially explaining the tendency of some forms of this condition to improve with age. A growth advantage and selective pressures (e.g. blistering) may help to increase the number of revertant cells over time. Revertant mosaicism via mitotic recombination accounts for the numerous small "islands" of normal skin in a

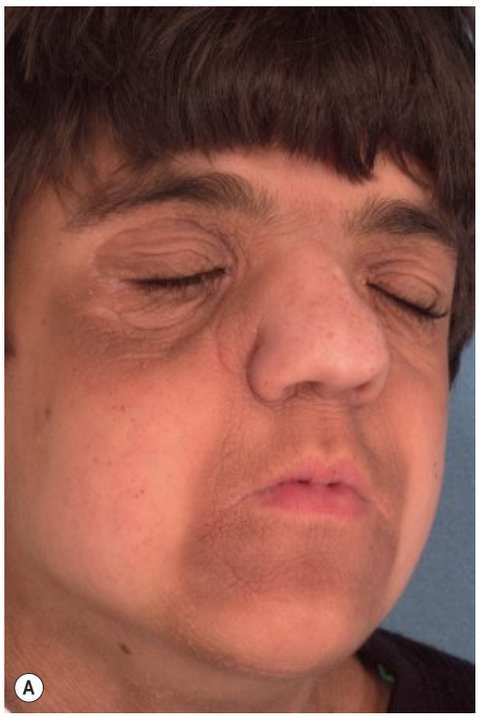


Fig. 55.8 Skin disease due to fibroblast growth factor receptor 3 (FGFR3) defects. **A** Severe acanthosis nigricans in a patient with the Crouzon craniosynostosis syndrome. **B** Systematized epidermal nevus in a young boy who had developmental delay. These conditions can be caused by germline and mosaic *FGFR3* mutations, respectively. *A, Courtesy Seth J. Orlow, MD, PhD.*

background of ichthyosiform erythroderma that characterize ichthyosis en confetti[39]. Affected individuals have specific frameshift mutations in *KRT10* or *KRT1*, which produce mutant proteins with an arginine-rich C-terminus that redirects them to the nucleolus; this mislocalization may have a role in promoting the reversion.

CHROMOSOMAL DISORDERS

Chromosomal disorders represent abnormalities in the number or structure of chromosomes. Aneuploidy refers to having an additional or missing chromosome; examples that are compatible with postnatal survival include complete trisomies for chromosomes 21 (Down syndrome; Fig. 55.12), 18 (Edwards syndrome), and 13 (Patau syndrome) as well as monosomy for the X chromosome (Turner syndrome) and XXY (Klinefelter syndrome) or XYY karyotypes. Mosaic aneuploidies or partial trisomies and monosomies due to duplications, deletions, or translocations of portions of chromosomes can also occur. The cutaneous and extracutaneous features of several relatively common chromosomal disorders are presented in Table 55.6.

Phylloid hypomelanosis, characterized by leaf-like hypopigmented patches (Fig. 55.13), usually results from mosaic trisomy 13. In contrast, hypo- or hypermelanotic streaks and swirls that follow the lines of Blaschko, occasionally with associated extracutaneous findings, can be caused by mosaicism for a variety of chromosomal aberrations (see Ch. 62).





Fig. 55.9 Type 2 segmental Hailey–Hailey disease. This 7-year-old girl had a history of recurrent blistering on the right abdomen, groin, and thigh since infancy.





Fig. 55.10 Female "carriers" of X-linked hypohidrotic ectodermal dysplasia. **A** The skin within hyperpigmented streaks and swirls following the lines of Blaschko is slightly depressed and very smooth, in contrast to follicular prominence in the surrounding areas. Starch-iodine testing on the back disclosed a patchy distribution of active sweat glands. This 2-year-old girl also had whorled areas of sparse hair on the posterior scalp and several cone-shaped teeth. **B** A color thermogram demonstrates an asymmetric distribution of skin temperature on the anterior trunk. *B, From Clark RP, Goff MR, MacDermot KD. Identification of functioning sweat pores and visualization of skin temperature patterns in X-linked hypohidrotic ectodermal dysplasia by whole body thermography. Hum Genet 1990;86:7–13.*



Fig. 55.11 Ichthyosis follicularis with atrichia and photophobia (IFAP) syndrome. Note the confluent psoriasiform plaques on the scalp.





Fig. 55.12 Cutaneous manifestations of Down syndrome (trisomy 21). A Full lips with cheilitis and a protruding, fissured tongue. **B** Multiple facial syringomas.

INSIGHT INTO ACQUIRED SKIN DISORDERS PROVIDED BY THE STUDY OF GENODERMATOSES

Inherited monogenic skin disorders can serve as models to improve our understanding of the pathogenesis of more common acquired skin diseases. For example, basement membrane proteins that are defective in JEB (e.g. type XVII collagen [bullous pemphigoid antigen 2], laminin 332 subunits) and dystrophic EB (type VII collagen) are also targeted in autoimmune blistering diseases such as bullous pemphigoid, mucous membrane (cicatricial) pemphigoid, and EB acquisita (see Fig. 28.7). The excessive granulation tissue that develops due to a truncated laminin α3 subunit in patients with laryngo-onycho-cutaneous syndrome has also provided clues to the role of this protein in regulating angiogenesis and granulation tissue formation during normal wound healing. Likewise, observation of similar dermal hyalinization in lichen sclerosus and the rare genodermatosis lipoid proteinosis led to the discovery of autoantibodies against extracellular matrix protein 1, the protein that is defective in the latter disorder, in the majority of patients with lichen sclerosus[40]. In addition, investigation of monogenic type I interferonopathies such as Aicardi–Goutières syndrome, familial chilblain lupus, and STING-associated vasculopathy with onset in infancy (SAVI; see Ch. 45) that are caused by abnormal processing of and immune responses to nucleic acids has provided pathogenic insights and potential targeted therapeutic approaches for lupus erythematosus and dermatomyositis[41,42].

Loss-of-function variants in the gene that encodes filaggrin, the protein that aggregates keratin filaments during keratinocyte terminal differentiation (see Ch. 56), not only cause ichthyosis vulgaris but also represent a major predisposing factor for atopic dermatitis, with a significantly higher prevalence (20%–50%) in individuals with atopic dermatitis compared to the general population (<5%–10%). Defective filaggrin also represents a predisposing factor for asthma, but specifically that occurring in individuals with pre-existing atopic dermatitis. Barrier dysfunction due to abnormalities in the serine protease inhibitor (SPINK5) involved in Netherton syndrome may also play a role in the pathogenesis of atopic dermatitis, and polymorphisms in *SPINK5* have been shown to be associated with this common acquired skin disease.

PRENATAL AND PREIMPLANTATION GENETIC DIAGNOSIS

In the past, prenatal diagnosis was based on techniques such as ultrastructural and immunohistochemical analysis of fetal skin biopsy specimens obtained between 18 and 22 weeks' gestational age (GA). Today, such methods have been largely replaced by DNA-based testing that is less invasive and more reliable. The diagnosis of genodermatoses for which the molecular basis is known can be established prenatally by performing chorionic villus sampling (at 10–12 weeks' GA) or amniocentesis (at 14–16 weeks' GA) and analyzing fetal DNA (after determining the underlying genetic defect in family members)[43]. Non-invasive prenatal diagnostic techniques that utilize fetal cells or cell-free DNA in the maternal circulation have also been developed[44,45]. Preimplantation genetic diagnosis is another option for severe genetic skin diseases. This involves analysis of DNA from single cells (blastomeres) extracted from late cleavage stage embryos following *in vitro* fertilization[46]. In this way, knowing the genetic bases of heritable skin conditions may be of tremendous value to affected families.

TREATMENT FOR HEREDITARY SKIN DISORDERS

Gene Therapy

The accessibility of the skin makes it an excellent target for gene therapy. In recent years, particular progress has been made in developing approaches to gene therapy for EB. For example, *ex vivo* gene therapy has led to functional correction of the skin fragility phenotype in patients with JEB due to *LAMB3* mutations and dystrophic EB due to *COL7A1* mutations, demonstrating for the first time successful

SKIN FINDINGS ASSOCIATED WITH CHROMOSOMAL ABERRATIONS				
Disorder	**Chromosomal aberration**	**Mucocutaneous anomalies**	**Extracutaneous anomalies**	**Comments**
Turner syndrome	45, XO	Congenital lymphedema (usually resolves by age 2 years), low posterior hairline, numerous melanocytic nevi, small hyperconvex nails, tendency to form keloids	Short stature, webbed neck, "shield-like" chest with widely spaced nipples, absence of sexual development, cardiovascular defects, renal malformations, sensorineural hearing loss, autoimmune hypothyroidism	Mosaicism (e.g. 45, XO/46, XX or 45, XO/46, XY) in ~40% of patients
Klinefelter syndrome	47, XXY	Varicose veins, leg ulcers	Tall stature, gynecomastia, small testes, infertility	Mosaicism 46, XY/47, XXY in ~20% of patients; uncommon variants include 48, XXXY and 48, XXYY
Trisomy 21 (Down syndrome)	47, XY, +21 47, XX, +21	Single palmar crease, protruding scrotal tongue, cheilitis (see Fig. 55.12A), multiple syringomas (often with calcification; see Fig. 55.12B), alopecia areata, ichthyosiform hyperkeratosis, keratosis pilaris, milia-like calcinosis cutis, elastosis perforans serpiginosa, multiple collagenomas, cutis marmorata/acrocyanosis; a predisposition to developing folliculitis, dermatophyte infections and Norwegian scabies; vesiculopustular eruptions associated with neonatal transient myeloproliferative disorder	Brachycephaly, characteristic facial appearance (e.g. epicanthal folds, flat nasal bridge), Brushfield spots (speckled irides), broad hands, brachydactyly, atlantoaxial instability, mental disability, immunodeficiency, congenital heart defects, duodenal atresia, leukemia (especially acute myeloid leukemia), hearing loss, autoimmune hypothyroidism	
Phylloid hypomelanosis (see Fig. 55.13)	Mosaic trisomy 13	Round, oval, or oblong hypopigmented macules resembling floral ornaments	Absence of corpus callosum, retinal coloboma, craniofacial defects, brachydactyly, clinodactyly, camptodactyly, conductive hearing loss	
Pallister–Killian syndrome	Mosaic tetrasomy 12p (isochromosome 12p)	Hypopigmented and/or hyperpigmented streaks; fine, sparse hair during infancy	Postnatal growth deficiency, characteristic facies (anteverted nostrils, down-turned mouth with thin upper lip), mental disability	

Table 55.6 Skin findings associated with chromosomal aberrations.



Fig. 55.13 Phylloid hypomelanosis due to mosaic trisomy 13. This condition is characterized by leaf-like and oblong patches of hypopigmentation in a pattern reminiscent of a floral ornament. *Courtesy Arne König, MD and Rudolf Happle, MD.*

gene therapy for a disease of solid tissue[47]. The technique involves retroviral-mediated transduction of autologous epidermal cells with a wild-type copy of the *LAMB3* or *COL71A* gene, followed by grafting of epidermal sheets grown from the genetically corrected cells. *In vivo* topical gene therapy with beremagene geperpavec (B-VEC), a non-replicating *COL7A1*-containing herpes simplex virus type 1 vector, was recently FDA-approved as a treatment to promote wound healing in patients with dystrophic EB[48]. Gene editing using technologies such as CRISPR-Cas9 and base editing to restore expression of functional proteins in EB is also under investigation[49] (see Fig. 3.13). Additional strategies include the use of drugs such as aminoglycoside antibiotics (e.g. topical or intravenous gentamicin) to induce read-through of nonsense mutations in recessive forms of EB as well as utilization of small interfering RNA to specifically "knock down" expression of the mutant protein in dominant-negative disorders such as EB simplex and pachyonychia congenita.

Therapy Targeting Affected Molecular Pathways

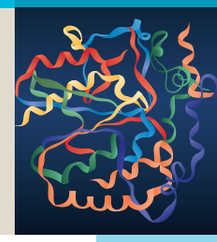
Understanding the molecular pathway that is affected in genodermatoses can translate into effective therapy. For example, loss-of-function mutations in tumor suppressor genes that negatively regulate the growth-promoting mTOR (*m*echanistic *t*arget *o*f *r*apamycin) signaling pathway underlie several hamartoma syndromes, including tuberous sclerosis complex, the PTEN hamartoma tumor syndrome, and Peutz–Jeghers syndrome (see Fig. 55.3). Recognition of the mTOR overactivation common to these disorders has led to successful treatment of affected individuals with the mTOR inhibitors sirolimus (rapamycin) and everolimus. For example, use of these agents in patients with tuberous sclerosis complex has resulted in regression of subependymal giant cell astrocytomas, renal angiomyolipomas, pulmonary lymphangioleiomyomatosis and (with topical as well as oral therapy) facial angiofibromas[50]. Additional examples of molecular advances resulting in successful targeted therapy include the use of the MEK inhibitor selumetinib for NF1-associated plexiform neurofibromas, the PI3K inhibitor alpelisib for the PIK3CA-related overgrowth spectrum, and the AKT inhibitor miransertib for Proteus syndrome[51,52].



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56 Biology of Keratinocytes



Peter J. Koch, Anna L. Bruckner and Maranke I. Koster

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Key features

- The epidermis functions as a barrier that provides protection against harmful substances, ultraviolet radiation, and water loss
- Through a complex terminal differentiation program, the progeny of epidermal stem cells undergo molecular and biochemical changes that generate the morphologically and functionally distinct layers of the epidermis
- Keratinocyte terminal differentiation culminates in the replacement of the plasma membrane with the cornified cell envelope
- Keratin intermediate filaments, which are expressed by keratinocytes in a differentiation-specific manner, are required to maintain epidermal integrity and have additional roles in the regulation of basic cell functions
- Desmosomes, which integrate the keratin cytoskeleton into the cell membrane and establish adhesive points between adjacent cells, are necessary for epidermal stability and stress resistance; these cell–cell junctions also function as signaling centers in epidermal morphogenesis and homeostasis
- Other cell–cell junctions that are found in keratinocytes include adherens junctions, tight junctions, and gap junctions
- A variety of inherited skin diseases are caused by a failure of normal epidermal differentiation and function

INTRODUCTION

The main function of the epidermis is to provide a barrier between the organism and the environment. This barrier is the result of a complex terminal differentiation program in which the progeny of epidermal stem cells undergo a series of molecular and biochemical changes that lead to the generation of the morphologically distinct layers of the epidermis (Fig. 56.1). This chapter reviews the molecular and cellular mechanisms that control this terminal differentiation program. It also discusses inherited skin diseases that are caused by a failure of normal epidermal differentiation.

THE EPIDERMIS: STRUCTURE AND FUNCTION

The epidermis, the outermost layer of the skin, functions as a barrier that protects the organism against harmful substances and water loss. The barrier function is established during embryogenesis and maintained in the mature epidermis through a continuous program of self-renewal[1]. Under homeostatic conditions, this self-renewal is mediated by epidermal stem cells located in the basal layer of the interfollicular epidermis. Another population of stem cells, located in the bulge region of the hair follicles, contributes to the interfollicular epidermis; however, this occurs in response to injury but not under homeostatic conditions. Like other types of stem cells, epidermal stem cells can generate daughter stem cells as well as transit-amplifying cells destined for differentiation. Transit-amplifying cells undergo several cell divisions before beginning a terminal differentiation program, which is associated with irreversible withdrawal from the cell cycle.

Terminally differentiating keratinocytes detach from the basement membrane and move suprabasally, a process that is facilitated by the inactivation of integrins, which are extracellular matrix receptors that anchor basal cells to the basement membrane (see Ch. 28). The cells are termed *spinous* keratinocytes when they reach the first suprabasal cell layer. As they continue to move upward, further differentiation leads to the formation of *granular* keratinocytes. These cells contribute to barrier function via their tight junctions which create a seal between neighboring keratinocytes[2]. Further differentiation culminates in the development of *corneocytes* that have lost their nuclei and cytoplasmic organelles as well as having their plasma membranes replaced by cornified cell envelopes.

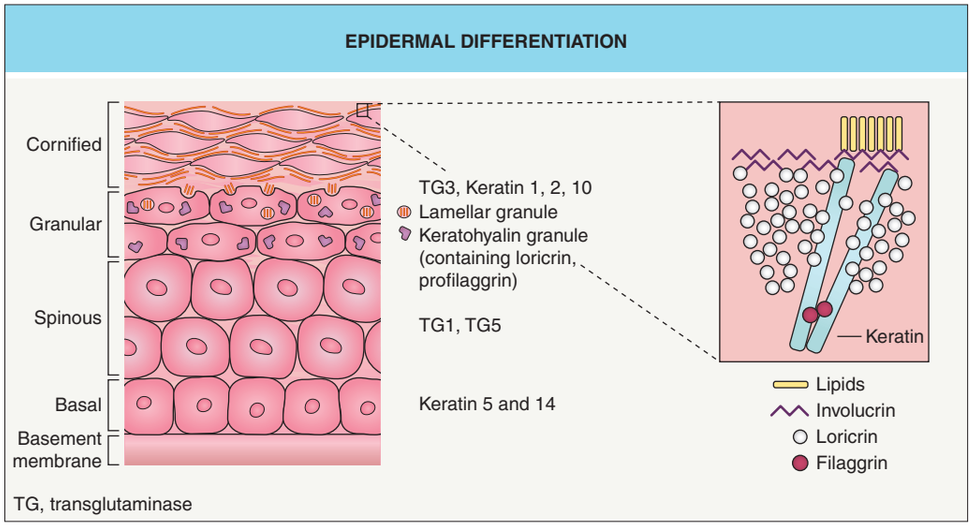


Fig. 56.1 Epidermal differentiation. As keratinocytes are transformed from mitotically active cells in the basal layer to fully differentiated, anucleated squames in the cornified layer, specific proteins are expressed at particular locations within the epidermis. Keratohyalin (profilaggrin- and loricrin-containing) and lamellar (lipid-containing) granules extrude their contents in the granular layer, leading to bundling of keratin filaments and replacement of the plasma membrane with the highly cross-linked, lipid-covered cornified cell envelope (see inset and Fig. 56.2).
Courtesy Julie V. Schaffer, MD.

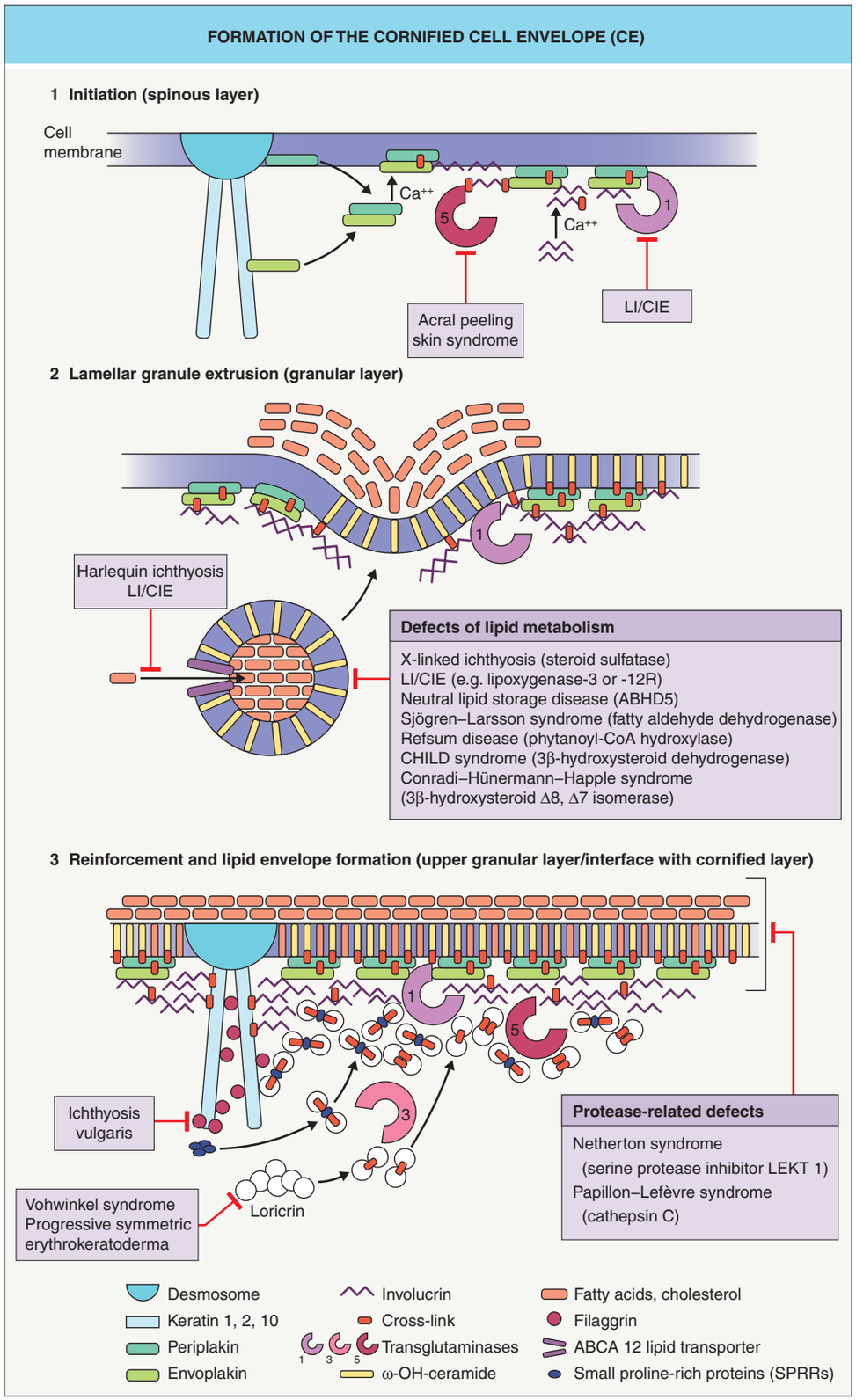


Fig. 56.2 Formation of the cornified cell envelope (CE). Terminal differentiation of keratinocytes is triggered by an increase in the intracellular Ca^{2+} concentration of the suprabasal epidermis. CE assembly is initiated in the upper spinous layer via formation of a cross-linked scaffold composed of envoplakin, periplakin, and involucrin along the inner surface of the cell membrane (**1**). This is followed by (or perhaps coincident with) extrusion of lamellar granules into the extracellular space (**2**). Specialized ω-hydroxyceramides are delivered to and eventually replace the cell membrane, where they become linked to scaffold proteins. Reinforcement occurs via cross-linking and translocation to the cell periphery of loricrin (which accounts for >80% of the mass of the CE) and small proline-rich proteins (SPRRs) (**3**). Complexes of keratin and filaggrin also become cross-linked to the CE. In addition, proteases play important roles in processing of CE proteins and the proteolysis of corneodesmosomes that is required for desquamation. A mature, terminally differentiated cornified cell thus consists of keratin filaments covalently attached to the CE, which is composed of protein and lipid envelope components and imbedded in extracellular lipid lamellae. Defects in transglutaminases, lipid metabolism, CE structural proteins and proteases lead to a variety of diseases characterized by ichthyosis and/or keratoderma (**1–3**). ABHD5, abhydrolase domain containing 5, lysophosphatidic acid acyltransferase; CHILD, congenital hemidysplasia with ichthyosiform erythroderma and limb defects; CIE, congenital ichthyosiform erythroderma; LI, lamellar ichthyosis. *Courtesy Julie V. Schaffer, MD.*

The *cornified cell envelope* (CE) is a composite of several covalently cross-linked proteins, most of which are encoded by genes located in the epidermal differentiation cluster on human chromosome 1. Examples of CE components include involucrin, small proline-rich proteins (SPRR), XP-5/late envelope proteins (LEP), loricrin, cystatin, envoplakin, periplakin, elafin, repetin, filaggrin, and S100 proteins, in addition to keratins and desmosomal proteins (Fig. 56.2)[3]. Mutations in some of the genes that encode these proteins can lead to skin disorders (see below). The extracellular surface of the CE is covered by lipids, which form the *cornified lipid envelope* (CLE) (see Ch. 124).

The stratum corneum, which serves to cover the body surface of terrestrial mammals, is composed of corneocytes. The CE and CLE of corneocytes are major contributors to the cutaneous water barrier. Failure or impairment of the water barrier leads to increased transcutaneous water loss and susceptibility to infections, a major problem in premature infants and in genetic disorders such as Netherton syndrome[4].

CE assembly begins within the upper spinous and granular cell layers, where proteins are chemically cross-linked, primarily by ε-(γ-glutamyl) lysine isopeptide bonds (Fig. 56.3). This reaction is catalyzed by a

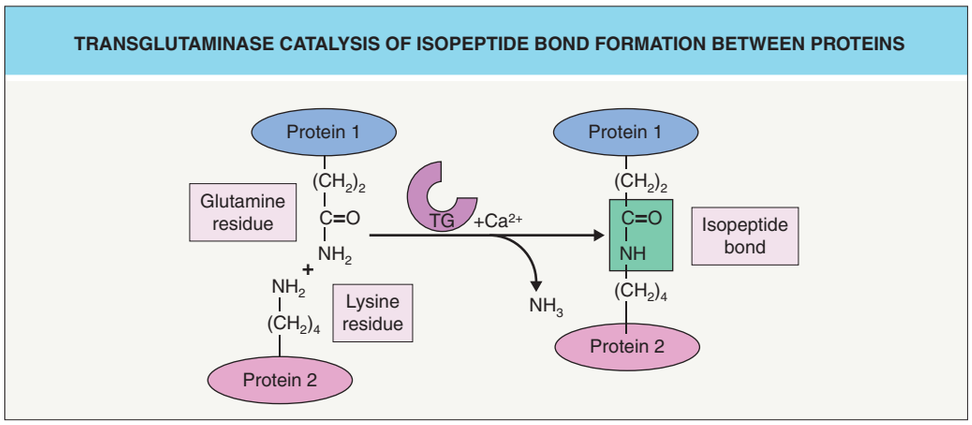


Fig. 56.3 Transglutaminase catalysis of isopeptide bond formation between proteins. Transglutaminases (TGs) are calcium-dependent enzymes that catalyze the formation of γ-glutamyl lysine isopeptide bonds between proteins. TGs also have a role in the creation of ester bonds between proteins and ω-hydroxyceramides. Such cross-linking is essential for assembly of the CE. Four TGs are expressed in the epidermis: TG1 (keratinocyte TG; membrane-bound), TG2 (tissue TG; basal layer), TG3 (epidermal TG; hair follicle and terminally differentiating keratinocytes) and TG5 (upper epidermis). *Courtesy Julie V. Schaffer, MD.*

TYPES OF INTERMEDIATE FILAMENTS					
Type I	**Type II**	**Type III**	**Type IV**	**Type V**	**Others**
Keratins (acidic)	Keratins (basic)	Vimentin Desmin GFAP Peripherin	Neurofilament-L Neurofilament-M Neurofilament-H α-Internexin Syncoilin Nestin Synemin	Lamin A/C Lamin B1 Lamin B2	Filensin Phakinin

Table 56.1 Types of intermediate filaments. GFAP, glial fibrillary acidic protein; L, M, and H, low-, medium-, and high-molecular-weight.

class of enzymes termed transglutaminases (TGases). Loss-of-function mutations in the gene that encodes TGase 1 lead to lamellar ichthyosis and congenital ichthyosiform erythroderma, both of which are generalized forms of autosomal recessive congenital ichthyosis that result from a failure to form proper CEs.

Because the CE is highly resistant to chemical attack, very harsh conditions (e.g. boiling the epidermal cells in buffers containing high concentrations of detergents) are required to isolate and purify CE proteins. One surprising finding is that a loss of *individual* CE components in knockout mice does not necessarily have a major impact on barrier function. One possible explanation is the presence of compensatory gene regulatory pathways that maintain barrier function even in the absence of major CE components. Further investigations of these regulatory pathways will hopefully provide additional insights into how the barrier is established and maintained, thereby leading to the development of new strategies for the treatment of diseases caused by impaired barrier function.

KERATIN INTERMEDIATE FILAMENTS

Keratin intermediate filaments provide resilience to keratinocytes and represent the largest group of intermediate filament proteins (Table 56.1). Compared to microfilaments and microtubules, the other two major classes of filaments, intermediate filaments lack intrinsic polarity. The current classification system includes 54 human keratin genes which can be divided into three categories: (1) epithelial keratin genes; (2) hair keratin genes; and (3) keratin pseudogenes[5]. Based upon their biochemical properties, keratins are classified as either type I (KRT9–KRT28, KRT31–KRT40) or type II (KRT1–KRT8, KRT71–KRT86) (Table 56.2). Type I and type II keratins form obligatory heteropolymers, i.e. pairs composed of one keratin from each group. These heteropolymers represent the basic building blocks of epithelial intermediate filaments (Fig. 56.4).

Similar to other intermediate filament proteins, keratins have a structure composed of domains[6]. The central α-helical *rod domain* consists of 310 amino acid residues and is divided into four segments (1A, 1B, 2A, 2B), which are interrupted by three non-helical segments of variable lengths, termed linkers (Fig. 56.5). The rod domain is composed of seven-residue amino acid sequence repeats $(a\text{-}b\text{-}c\text{-}d\text{-}e\text{-}f\text{-}g)_n$ termed "heptad repeats", where positions "a" and "d" represent hydrophobic residues that are considered crucial for stabilization of the heterodimer. In the middle of the 2B domain, the heptad pattern is interrupted, giving rise to the "stutter". This helical segment is highly conserved among intermediate filaments and does not participate in the formation of the coiled-coil dimer (see Fig. 56.4).

The beginning and end of the α-helical rod domain, referred to as the *helix initiation* and *helix termination* motifs, are highly conserved within different keratins and play a pivotal role in keratin intermediate filament assembly (e.g. filament elongation). These helix boundary peptides represent genetic "hot spots" for mutations in many of the hereditary keratin disorders (see Fig. 56.5). The severity and other phenotypic features of genodermatoses caused by keratin defects often correlate with the position of the underlying mutation, with more severe disease resulting from mutations in the helix initiation and termination motifs (see Table 56.4).

The head and tail regions that flank the rod domain are subdivided into extreme end (E), variable (V), and (in type II keratins) homologous (H) domains. Epithelial keratins possess glycine- and serine-rich head and tail domains, whereas these regions in hair keratins have a high content of cysteine and proline. Variations in the head and tail domains account for much of the diversity among different keratin proteins, suggesting that these domains play an important role in cell type-specific functions such as interactions with cytosolic proteins.

Keratins and Signaling

Keratins are markers of keratinocyte differentiation and are required to maintain epidermal integrity. However, keratins may also influence other basic cell functions, such as cell cycle progression, metabolic activity, apoptosis, and migration[7]. The mechanisms by which keratins regulate these processes are not well understood, but accumulating evidence suggests that intermediate filaments directly interact with several cell signaling pathways including TNF receptor 2-induced apoptosis, Src-mediated migration, and Akt/mTOR-related growth. Interestingly, deletion of the entire murine type II keratin gene cluster, which completely prevented the assembly of keratin intermediate filaments, resulted in an early embryonic lethal phenotype with growth retardation and defects in yolk sac hematopoiesis and vasculogenesis. This underscores the importance of keratins in cellular signaling and differentiation of non-epithelial cell lineages.

PREVIOUS AND CURRENT HUMAN KERATIN NOMENCLATURE							
Type I				**Type II**			
Previous name	**Current name**	**Previous name**	**Current name**	**Previous name**	**Current name**	**Previous name**	**Current name**
KRT9	KRT9	KRT25irs1	KRT25	KRT1	KRT1	KRT6hf	KRT75
KRT10	KRT10	KRT25irs2	KRT26	KRT2e	KRT2	KRT2p	KRT76
KRT12	KRT12	KRT25irs3	KRT27	KRT3	KRT3	KRT1b	KRT77
KRT13	KRT13	KRT25irs4	KRT28	KRT4	KRT4	KRT5b	KRT78
KRT14	KRT14	Ha1	KRT31	KRT5	KRT5	KRT6l	KRT79
KRT15	KRT15	Ha2	KRT32	KRT6a	KRT6a	KRTb20	KRT80
KRT16	KRT16	Ha3-I	KRT33a	KRT6b	KRT6b	Hb1	KRT81
KRT17	KRT17	Ha3-II	KRT33b	KRT6e/h	KRT6c	Hb2	KRT82
KRT18	KRT18	Ha4	KRT34	KRT7	KRT7	Hb3	KRT83
KRT19	KRT19	Ha5	KRT35	KRT8	KRT8	Hb4	KRT84
KRT20	KRT20	Ha6	KRT36	KRT6irs1	KRT71	Hb5	KRT85
KRT23	KRT23	Ha7	KRT37	KRT6irs2	KRT72	Hb6	KRT86
KRT24	KRT24	Ha8	KRT38	KRT6irs3	KRT73	–	–
–	–	KRTa35	KRT39	KRT6irs4	KRT74	–	–
–	–	KRTa36	KRT40	–	–	–	–

Table 56.2 Previous and current human keratin nomenclature. Darker shading indicates keratins with names that were changed. irs, inner root sheath; Ha, type I hair keratins; Hb, type II hair keratins. *From Schweizer J, Bowden PE, Coulombe PA, et al. J Cell Biol 2006;174:169–74.*

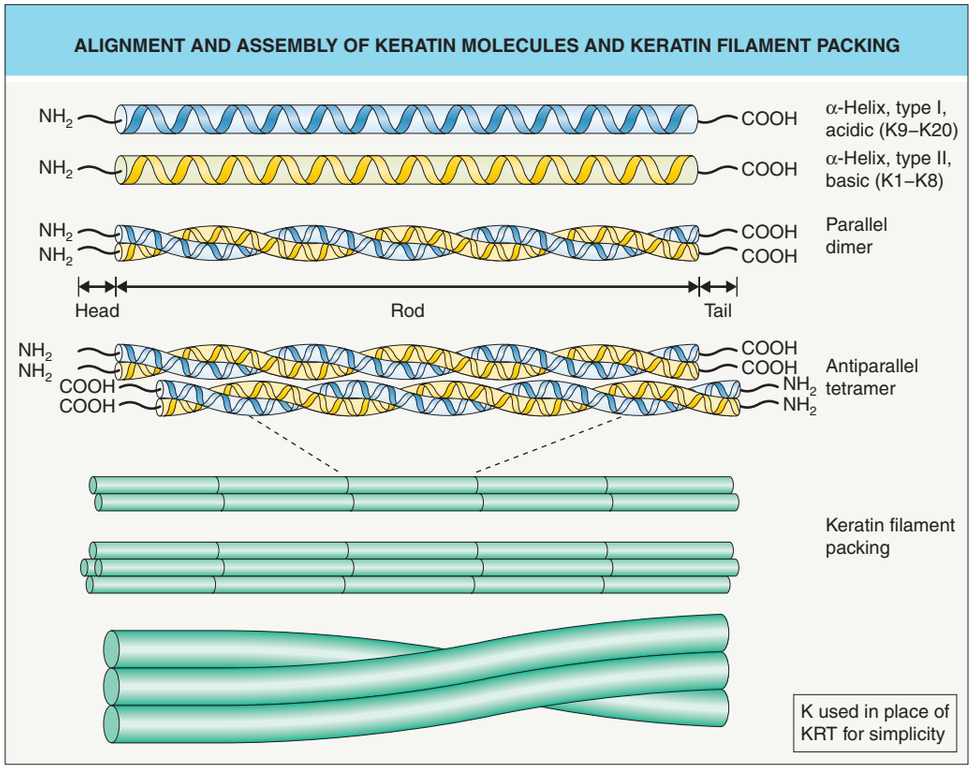


Fig. 56.4 Alignment and assembly of keratin molecules and keratin filament packing. Intermediate filament assembly takes place in several stages and begins with the heterodimerization of one type I and one type II keratin protein in a coiled-coil fashion. Two heterodimers then associate to form a tetramer. Lateral aggregation of tetramers yields higher-order polymers which eventually make up the filament network of the keratinocyte. *Courtesy Julie V. Schaffer, MD.*

Hair Keratins

The mature hair is the differentiation product of trichocytes and is found within the central core of the hair follicle. The anagen (growing) follicle is a complex structure consisting of eight distinct, concentrically arranged cell layers (see Fig. 68.5). The innermost compartment is the hair shaft, which is composed of a medulla, cortex, and one-layered cuticle; the latter serves as a protective coat for the hair shaft. The innermost living cell layer of the hair follicle is the inner root sheath (IRS). It surrounds the growing hair shaft and consists of the IRS cuticle as well as Huxley and Henle layers. The outermost compartment is the outer root sheath (ORS), which is continuous with the interfollicular epidermis. The companion layer is located between the IRS and the ORS.

The medulla contains a mixture of epithelial keratins (KRT17, KRT75) and hair keratins (KRT33, KRT34, KRT36, KRT37, KRT81), whereas the cortex contains type I hair keratins (KRT31–KRT38) and type II hair keratins (KRT81, KRT83, KRT85, and KRT86) (Fig. 56.6, see Fig. 68.6). The cuticle expresses hair keratins KRT32 and KRT35 (type I) and their partners KRT82 and KRT85 (type II). KRT71, KRT74, and KRT73 can be detected in the three IRS layers. The epithelial keratins KRT5 and KRT14 are found throughout the full thickness of the ORS, while expression of KRT6, KRT16, and KRT17 is limited to the isthmus and the lower ORS. Additional keratins expressed in the ORS are KRT15 and KRT19.

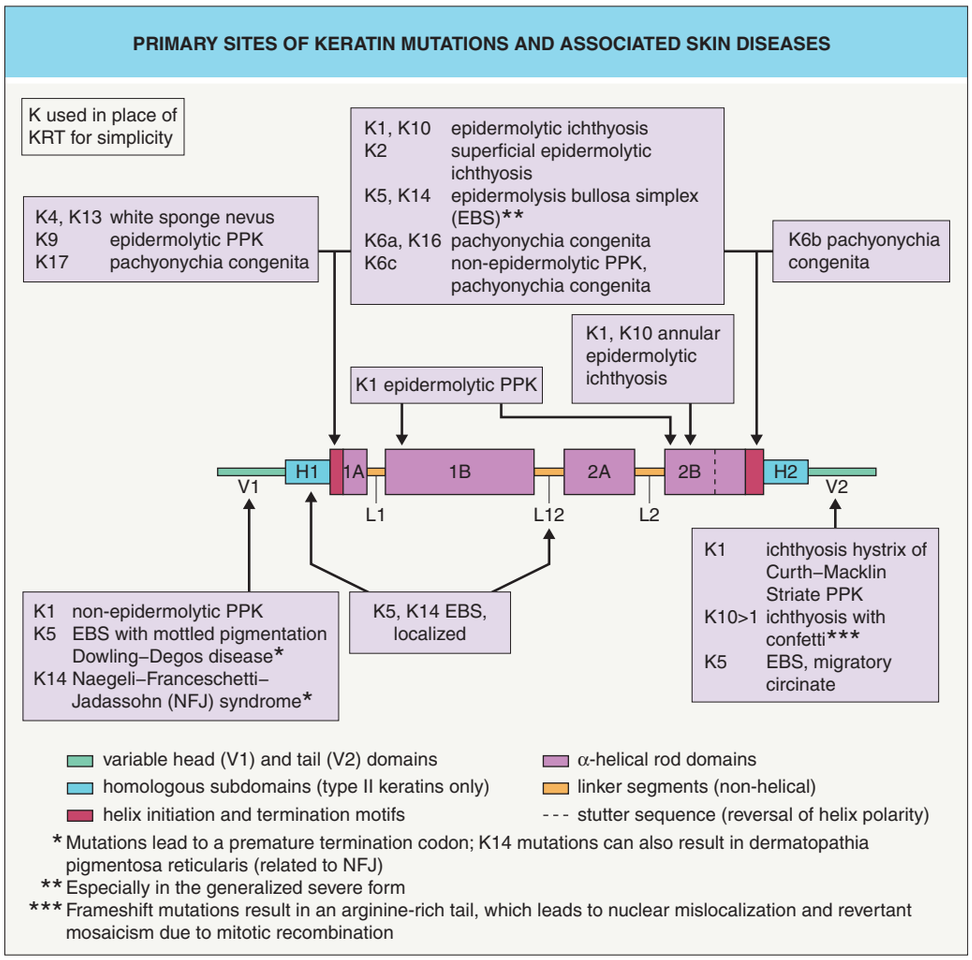


Fig. 56.5 Primary sites of keratin mutations and associated skin diseases. Over 90% of pathogenic alterations in keratins are missense mutations. Genotype–phenotype correlations are particularly well established for EBS. In the *severe* form of EBS, many patients have a "hot spot" mutation in a highly conserved arginine (Arg125) located within the helix initiation motif of KRT14. The corresponding arginine (Arg156) in KRT10 is also a mutational "hot spot" in epidermolytic ichthyosis. In the *intermediate* EBS subtype, mutations are more centrally located in the rod domains of KRT5 and KRT14. In contrast, mutations in the *localized* form of EBS are often outside the rod domain, e.g. in the L12 linker motifs of KRT5 and KRT14 or the H1 homologous subdomain of KRT5. Mutations in the variable head (V1) and tail (V2) domains of KRT1 can lead to non-epidermolytic PPK and ichthyosis hystrix Curth–Macklin. Rather than interfering with keratin intermediate filament assembly, mutations in these domains may cause intracellular maldistribution of loricrin. K or KRT, keratin; PPK, palmoplantar keratoderma. *Courtesy Julie V. Schaffer, MD.*

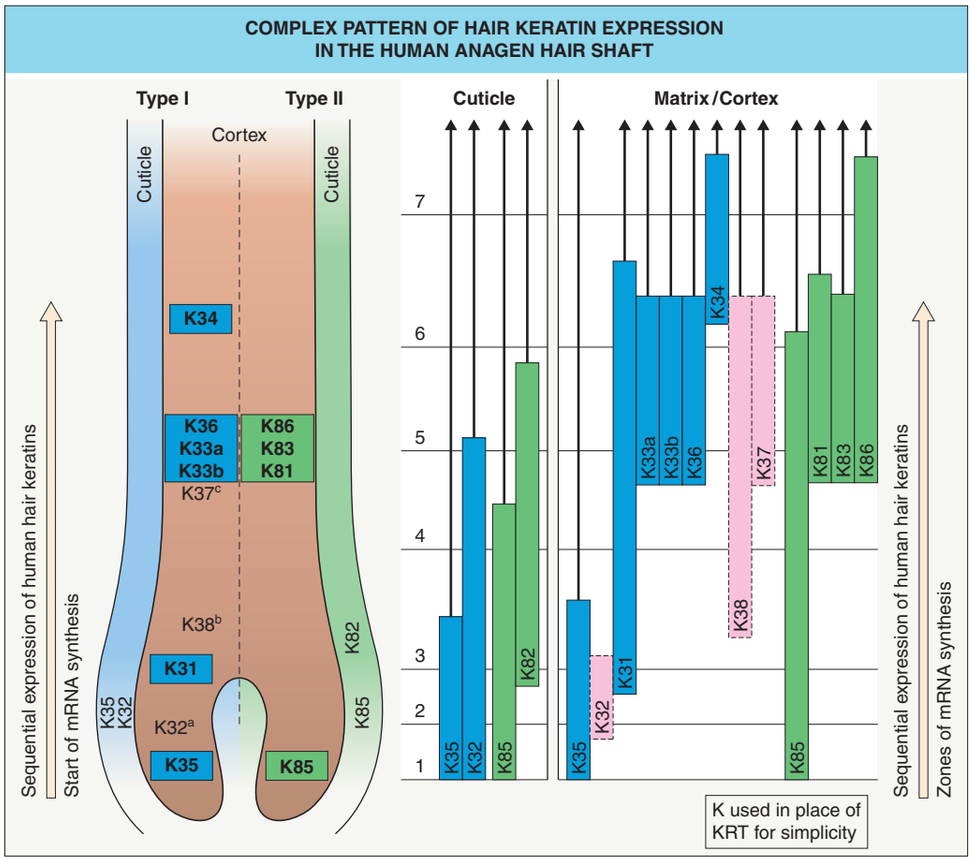


Fig. 56.6 Complex pattern of hair keratin expression in the human anagen hair shaft. Major type I hair keratins are in blue, and major type II hair keratins are in green. Minor hair keratins are in pink. [a]This protein is weakly expressed at this site. [b]To date, expression of this protein has only been detected in single cortex cells. [c]To date, this protein has only been detected in vellus hairs. Autosomal dominant monilethrix is caused by mutations in *KRT81*, *KRT83*, and *KRT86*. *Redrawn from Langbein L, et al. The catalog of human hair keratins. J Biol Chem 2001;276:35123–32.*

EPIDERMAL DIFFERENTIATION

Epidermal differentiation is a tightly regulated process that involves the transformation of proliferating cells in the basal layer into the dead corneocytes of the stratum corneum. During this process, the keratins and junctional proteins (see below) that are expressed are highly specific for the state of differentiation (Fig. 56.7). The mitotically active keratinocytes in the basal layer primarily express the keratin pair KRT5 and KRT14, with less abundant expression of KRT15. KRT15 is also able to assemble with KRT5, thereby providing mechanical stability to the keratinocyte in the absence of K14.

As keratinocytes move suprabasally to the spinous layer, they withdraw from the cell cycle. This process is associated with a downregulation of KRT5 and KRT14 and an induction of the differentiation-specific keratins, KRT1 and KRT10. Further maturation of spinous keratinocytes into granular keratinocytes results in expression of KRT2, a reinforcement keratin. With further maturation, filaments containing the suprabasal keratins are bundled parallel to the surface and, eventually, keratinocytes lose their cytoplasmic organelles and differentiate into lifeless corneocytes that are shed into the environment.

Interestingly, a number of epidermal keratins have a more restricted anatomic distribution pattern. For example, KRT9 is specifically expressed in the suprabasal cells of palmoplantar skin. KRT6, KRT16, and KRT17 are expressed in the palmoplantar epidermis as well as in the keratinocytes of the nail bed, hair follicle, and sebaceous and sweat glands. In addition, this group of keratins is rapidly induced by injury and ultraviolet radiation and appears in hyperproliferative conditions.

Regulatory Pathways Involved in Epidermal Development and Differentiation

The regulatory pathways necessary for normal epidermal differentiation include those that: (1) establish and maintain basal keratinocytes; (2) initiate and execute keratinocyte terminal differentiation; and (3) form the embryonic epidermis. Examples of these pathways are discussed below.

Genes required for establishing and maintaining basal keratinocytes

The importance of *TP63* in epidermal and adnexal development became apparent with the generation of knockout mouse models[8]. The p63 protein encoded by this gene has at least six different isoforms that activate or repress transcription, depending on the cellular context. p63 is essential for epidermal morphogenesis, as highlighted by the failure of *Trp63*-null mice to develop a stratified epidermis. After birth, exposure of these mice to the environment leads to rapid death due to dehydration. The failure of p63-deficient epithelial cells to adopt an epidermal fate underscores the critical role of p63 in specifying an epidermal lineage.

The p63 protein regulates the transcription of multiple genes in basal keratinocytes[9]. For example, p63 induces expression of epidermal keratins KRT5 and KRT14 while simultaneously repressing expression of KRT18, a keratin expressed in single-layered epithelia. Another key function of p63 is to maintain the proliferative state of basal keratinocytes by repressing cell cycle inhibitors.

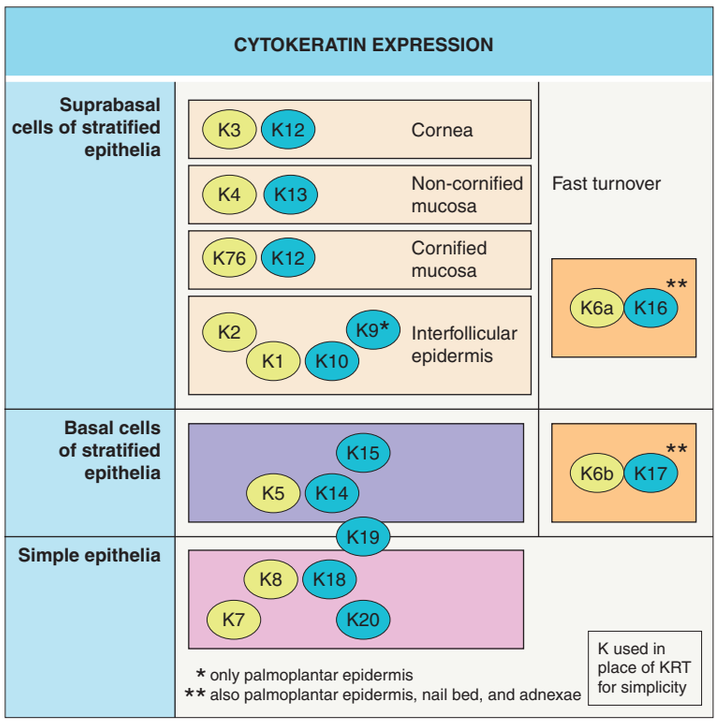


Fig. 56.7 Cytokeratin expression. Type II (basic) keratins are in yellow (KRT1–KRT8; KRT76) and type I (acidic) keratins are in blue (KRT9–KRT20). Keratin disorders are presented in Fig. 56.5 and Table 56.4.

Genes required for differentiation in mature epidermis

After basal keratinocytes have undergone a few rounds of cell division, they irreversibly withdraw from the cell cycle, move suprabasally, and become spinous keratinocytes. This process is also regulated by p63, in particular its ΔNp63α isoform[8]. In this context, p63 mediates cell cycle exit and induces expression of KRT1. The importance of p63 for normal epidermal development and differentiation is further underscored by the finding that p63 mutations underlie a subset of ectodermal dysplasias characterized by abnormalities in the skin and its adnexae (see Ch. 63).

Notch signaling is also required for the formation of the spinous layer[10]. In mouse models, ablation of Notch signaling resulted in the development of an extremely thin spinous layer, whereas constitutively active Notch signaling resulted in an expanded spinous layer. Notch signaling is essential for controlling the balance between proliferation and differentiation in the developing and postnatal epidermis.

Roles of Ca^{2+} in epidermal differentiation

The extracellular concentration of Ca^{2+} also plays an important role in keratinocyte differentiation[11]. In a mature epidermis, there is a gradient of increasing extracellular Ca^{2+} concentration from the basal layer to the cornified layer. Increasing the Ca^{2+} concentration in the media of cultured keratinocytes can induce a differentiation program similar to that of keratinocytes *in vivo*, with successive expression of markers of keratinocyte terminal differentiation.

Several Ca^{2+}-responsive proteins in the epidermis have key roles in the formation of the granular cell layer[12]. For example, the protein kinase C (PKC) family is activated by Ca^{2+} signaling and functions specifically in the transition from spinous to granular cells. PKC proteins have a dual role, contributing to the downregulation of KRT1 and KRT10 expression while also inducing markers of granular keratinocytes such as loricrin, filaggrin, and transglutaminases.

In addition to the PKC family, other proteins that undergo conformational changes upon binding to Ca^{2+} are expressed in mouse and human epidermis. Of these, the calcium-sensing receptor is specifically expressed in granular keratinocytes. Mice lacking a functional calcium-sensing receptor fail to properly form a granular layer, while overexpression of the calcium-sensing receptor in basal keratinocytes leads to expansion of the spinous and granular cell layers[13].

Genes required for development of the embryonic epidermis

During epidermal morphogenesis, basal keratinocytes do not directly differentiate into spinous keratinocytes as they do in postnatal skin[14]. Instead, basal keratinocytes initially differentiate into *intermediate* keratinocytes that, like spinous cells, express KRT1. However, unlike spinous keratinocytes, intermediate keratinocytes still undergo proliferation. The intermediate cell layer exists only transiently during epidermal morphogenesis, and intermediate keratinocytes ultimately differentiate into spinous and granular keratinocytes, which then undergo further terminal differentiation.

The importance of the intermediate cell layer for normal epidermal development has been demonstrated by mouse models in which intermediate cells fail to mature into spinous and granular cells. Such a block in differentiation occurs in mice lacking expression of inhibitor of κB kinase-α (IKKα), interferon regulatory factor 6 (IRF6), or ovo-like 1 (Ovol1), as well as in mice expressing a mutant form of the 14–3–3σ protein[14]. In all instances, an expanded intermediate cell layer develops, terminal differentiation is disrupted, and the consequent failure to establish barrier function results in neonatal lethality.

KERATINOCYTE ADHESION

Desmosomes

Desmosomes are multi-protein complexes that function as cell–cell adhesion structures (junctions) in epidermal cells (Fig. 56.8)[15]. They form within areas of specialized plasma membrane, termed *lipid raft domains*, that are enriched with sphingolipids and cholesterol[16]. Desmosomes also provide attachment sites for the keratin intermediate filament cytoskeleton of keratinocytes. Consequently, these junctions are critical components of a supracellular keratin network that traverses the interfollicular epidermis and epithelia of cutaneous adnexae, such as hair follicles.

Although the biochemical composition of desmosomes varies from tissue to tissue, the core of the desmosome is formed mainly by transmembrane glycoproteins that belong to the desmoglein (Dsg) and desmocollin (Dsc) subfamilies of Ca^{2+}-dependent cell adhesion proteins (cadherins). Heterophilic and homophilic interactions between Dsg and Dsc proteins are required to establish cell–cell coupling (see Ch. 29)[17]. Another protein, termed Perp, is also crucial for this process[18]. The transmembrane proteins are linked to the keratin intermediate filament network via a complex of several proteins, including desmoplakin, plakoglobin, one of several plakophilin (PKP) isoforms, and additional accessory proteins (see Fig. 29.3B)[19].

To complicate matters, several desmosomal components are encoded by multigene families. In humans, for example, there are four *DSG* genes, three *DSC* genes, and three *PKP* genes. In the epidermis, several Dsg and Dsc isoforms can be present in the same cell and even in the same desmosome[20]. The specific composition of the desmosome is thought to affect its adhesive properties. Similar to the epidermis, a differential expression pattern of desmosomal proteins is observed in the living layers of the hair follicle[21].

Regulating adhesiveness of junctions via changes in the protein composition or through protein modifications is also a crucial prerequisite for regulating cell migration, cell sorting, and the formation of the proper tissue histoarchitecture during embryonic development. An example of differential regulation of desmosomes during tissue/organ development is the formation of adnexae (e.g. hair follicles) and mammary glands. Regardless of the type of adnexal structure that is being formed, the initial steps are very similar. First, keratinocytes from the basal cell layer change their polarity and downregulate desmosomal proteins[22]. Next, these cells migrate into the underlying dermal tissue. Eventually, the cells begin to differentiate in order to form the various cell layers that constitute the new adnexal structure. During this process, desmosomal adhesion is re-established.

The molecular pathways that control differential expression of desmosomal genes during such developmental processes are not well understood. However, based on work focusing on the regulation of classical cadherins (e.g. E-cadherin), it is likely that major epidermal signaling pathways, such as the Wnt and NF-κB, are involved (see Figs. 55.6 and 130.4). Of note, the phenomenon of local proliferation of keratinocytes followed by invasion into dermal tissue also occurs in cutaneous wound healing and the initial stages of cancer progression. It is therefore likely that the same gene regulatory pathways that govern adnexal development also control these biological processes.

Desmosomes act as signaling centers that affect the basic characteristics of epithelial cells. For example, induction of epidermal Dsg1 expression is thought to counteract epidermal growth factor (EGF) signaling, triggering cell cycle withdrawal, expression of differentiation-associated proteins, and delamination of keratinocytes from the basal layer[20]. Desmosomal proteins are also involved in nuclear signaling. Plakoglobin (also known as junction plakoglobin) is associated with both desmosomes (see Fig. 56.8) and adherens junctions (see below) and is involved in relaying signals to the nucleus. Plakoglobin belongs to the armadillo protein family, the prototype of which is β-catenin. In addition to binding desmosomal cadherins (Dsg, Dsg) at the plasma membrane, plakoglobin forms complexes with Tcf/Lef transcription factors to control gene expression, thereby influencing cell proliferation, migration, and apoptosis[15]. Plakophilins can also affect cytoplasmic signaling pathways, and at least two isoforms (PKP1, PKP2) have nuclear functions[23].

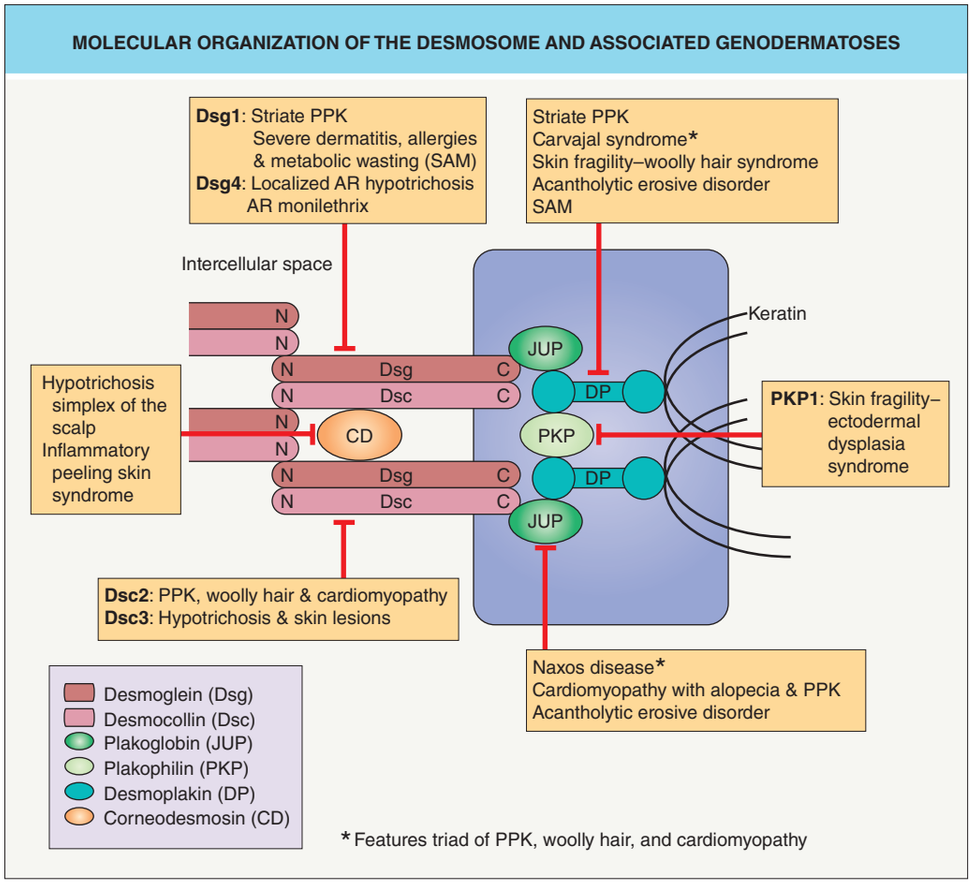


Fig. 56.8 Molecular organization of the desmosome and associated genodermatoses. Type 1 transmembrane glycoproteins from the cadherin family (desmogleins and desmocollins) are linked to intermediate filaments via a complex that contains catenins (plakoglobin, plakophilins) and plakin proteins (desmoplakin). Both homophilic and heterophilic interactions have been postulated to participate in establishing desmosomal adhesion. Examples of inherited skin diseases affecting the components of desmosomes are shown. AR, autosomal recessive; PPK, palmoplantar keratoderma.

What happens when desmosomes do not function properly?

Tissues that are subjected to mechanical stress, such as the skin and its adnexae, mucous membranes (e.g. oral cavity), and the heart, are often affected by desmosomal defects. The clinical symptoms of desmosomal diseases typically reflect tissue fragility, with mucocutaneous blistering and cardiomyopathy representing major manifestations[15,22]. In fact, skin and/or heart diseases have been linked to dysfunction of at least 12 desmosomal proteins, including Dsc1–3, Dsg1–4, desmoplakin, plakoglobin, plakophilin 1–2, and corneodesmosin (see Fig. 56.8). These disorders include genodermatoses, autoantibody-mediated diseases such as pemphigus vulgaris (PV) and pemphigus foliaceus (PF), and bacterial toxin-induced staphylococcal scalded skin syndrome.

The first mucocutaneous disorders linked to a desmosomal defect were PV and PF (see Ch. 29). In these diseases, autoantibodies bind to Dsg and induce epidermal and/or mucous membrane blistering via acantholysis, a process thought to be caused by loss of Dsg. In contrast to the blisters observed in patients with epidermolysis bullosa simplex due to keratin mutations, PV and PF blisters are caused by cell–cell separation, not cytolysis. Nevertheless, both groups of diseases illustrate the point that desmosomes and the associated keratin intermediate filaments must function properly to maintain tissue integrity.

The decreased function of desmosomal proteins may also lead to abnormal distribution of gap junction proteins, contributing to the development of cardiomyopathy in patients with mutations in desmosomal genes[24]. These findings support the emerging picture that desmosomes are part of a highly dynamic network of cellular junctions that interact with each other and the keratinocyte cytoskeleton in signal transduction and regulation of cell properties such as mechanical stress resistance, proliferation, migration, and differentiation[25].

Adherens Junctions

Adherens junctions consist of classical cadherins, in particular, E- and P-cadherin, as well as a complex of cytoplasmic plaque proteins (α-catenin, β-catenin, γ-catenin [also known as plakoglobin]) that connect the transmembrane proteins to the actin microfilament cytoskeleton (see Fig. 29.3A). Note that the armadillo protein plakoglobin can bind to both desmosomal and classical cadherins (see above).

P-cadherin is expressed primarily in the basal layer of mouse epidermis, whereas E-cadherin is expressed throughout the interfollicular epidermis. Genetically engineered loss of P-cadherin in mice has little effect on the interfollicular epidermis, whereas loss of E-cadherin can lead to severe defects in the homeostasis and function of the epidermis. Interestingly, it appears that loss of E-cadherin can affect tight junctions and thus the skin barrier function of the epidermis. Based on an analysis of genetically engineered mice, it has become evident that normal expression of the plaque proteins α-catenin, β-catenin, and plakoglobin is also required for normal epidermal function.

Similar to desmosomal cadherins, classical cadherins are differentially regulated during the development of adnexae within the skin[26]. For example, E-cadherin is downregulated in keratinocytes that invade the underlying dermis. A failure to downregulate cadherin-based adhesion suppresses invasive growth of keratinocytes and thus formation of adnexal structures.

As indicated above, armadillo proteins (e.g. β-catenin, plakoglobin) are involved in signaling from cell junctions to the nucleus. While β-catenin is a downstream effector of the classical (canonical) Wnt pathway, plakoglobin appears to be able to signal either via Wnt components or independently. Interestingly plakoglobin also counteracts classical Wnt signaling[27].

Tight Junctions

Tight junctions *(zonula occludens)* "seal" the intercellular space, thus preventing the free diffusion of macromolecules. The seal formed by tight junctions in the granular layer is required for maintaining the water barrier function of the epidermis (see Fig. 124.1)[28]. Together, tight junctions, adherens junctions, and desmosomes form the apical junctional complex in polarized epithelial cells.

KERATINOCYTE INTEGRIN RECEPTORS	
Integrin	**Ligand**
β1 family	
$\alpha_1\beta_1$	Fibrillar collagen, laminin
$\alpha_2\beta_1$	Fibrillar collagen, laminin
$\alpha_3\beta_1$	Fibronectin, laminin 332 (formerly laminin 5), denatured collagen
$\alpha_5\beta_1$	Fibronectin
$\alpha_6\beta_1$	Laminin
β4 family	
$\alpha_6\beta_4$	Laminin 332
αv family	
$\alpha_v\beta_1$	Fibronectin, vitronectin
$\alpha_v\beta_3$	Vitronectin, fibronectin, fibrinogen, denatured collagen
$\alpha_v\beta_5$	Vitronectin
$\alpha_v\beta_6$	Fibronectin, tenascin

Table 56.3 Keratinocyte integrin receptors. *Courtesy Irene M. Leigh, MD.*

KERATINOCYTE–MATRIX INTERACTIONS

The epidermis is separated from the underlying dermis by a basement membrane (see Ch. 28), which consists of proteins secreted by epidermal keratinocytes and dermal fibroblasts[29]. The main components of the skin basement membrane are glycoproteins, including laminins, collagens, proteoglycans, and fibronectin. Keratinocytes are anchored to the basement membrane through integrins, transmembrane receptors for extracellular matrix proteins (Table 56.3). In addition to their structural role, integrins function by transducing signals from the extracellular matrix to the epidermal keratinocytes.

Another family of proteins required for basement membrane integrity during embryogenesis consists of Fras1, Frem1, and Frem2, three proteins that form a complex within the basement membrane. Loss-of-function mutations in any of these three genes destabilize this protein complex, causing aberrant basement membrane formation and skin blistering in mouse models. In humans, loss-of-function mutations in *FRAS1* or *FREM2* underlie Fraser syndrome, a multisystem autosomal recessive disorder characterized by embryonic (but not postnatal) blistering of the skin, cutaneous syndactyly, cryptophthalmos, and renal defects[30].

RELATED DISEASES

Keratin Disorders

Mutations in keratin genes cause a variety of disorders of the skin and other epithelia, usually with an autosomal dominant pattern of inheritance. The underlying mutations typically act in a dominant-negative fashion, interfering with normal intermediate filament assembly. This causes aggregation of disorganized keratin bundles, which often leads to clinically evident cell fragility. Mutations in the helix initiation and termination motifs are generally associated with relatively severe disease phenotypes, whereas mutations affecting other keratin domains usually cause milder disease (see Fig. 56.5). The location of mutations and genetic "hot spots" in skin disorders caused by mutations in keratin genes are presented in Table 56.4.

Epidermolysis bullosa simplex

Epidermolysis bullosa (EB) comprises a group of heritable skin fragility disorders characterized by skin and sometimes mucosal blistering following minor mechanical trauma[31] (see Ch. 32). Mutations in genes encoding desmosomal components can lead to several disorders associated with skin fragility (see Fig. 56.8). Genotype–phenotype correlations are well established for EB simplex due to *KRT5* and *KRT14* mutations (see Table 56.4). The clinical severity is related to the location of the mutations and the degree to which they perturb keratin

TYPES OF KERATIN MUTATIONS IN MUCOCUTANEOUS DISORDERS			
Disorder	**Inheritance**	**Gene(s)**	**Type/location of mutation(s)**
EBS, localized	AD	*KRT5, KRT14*	L12; H1 of *KRT5*
EBS, intermediate	AD		L12, L2; central portions of 1A & 2B
EBS, severe	AD		Helix initiation & termination motifs; "hot spot" Arg125Cys/His in *KRT14*
EBS, AR-KRT14	AR		Truncating or splice-site mutations
EBS with mottled pigmentation	AD	*KRT5* ≫ *KRT14*	Pro25Leu in V1 of *KRT5*
EBS, migratory circinate	AD	*KRT5*	Frameshift mutation leading to extended V2 region
Dowling–Degos disease	AD		V1 – truncating (leading to haploinsufficiency)
Naegeli–Franceschetti–Jadassohn syndrome & dermatopathia pigmentosa reticularis	AD	*KRT14*	V1 – truncating (leading to haploinsufficiency)
Epidermolytic ichthyosis	AD	*KRT1, KRT10*	Helix initiation & termination motifs; "hot spot" Arg156 in KRT10
	AR	*KRT10*	2B – truncating
Annular/cyclic epidermolytic ichthyosis	AD	*KRT1, KRT10*	2B
Ichthyosis hystrix Curth–Macklin	AD	*KRT1*	V2 – truncated tail
Ichthyosis with confetti	AD	*KRT10* ≫ *KRT1*	Frameshift mutations leading to arginine-rich tail; revertant clones via mitotic recombination
Superficial epidermolytic ichthyosis	AD	*KRT2*	Helix termination > initiation motifs
Epidermolytic PPK	AD	*KRT1*	1B (diffuse with "tonotubular" keratin), 2B (mild diffuse/focal)
		KRT9	Helix initiation > termination motifs, with "hot spot" Arg163
Non-epidermolytic PPK	AD	*KRT1*	V1 (diffuse), V2 (striate)
Pachyonychia congenita-6a & 16	AD	*KRT6A, KRT16*	Helix initiation > termination motifs
Pachyonychia congenita-6b & 17	AD	*KRT6B, KRT17*	Helix termination motif of *KRT6B*; helix initiation motif with "hot spots" Asn92 & Arg94 in *KRT17*
Pachyonychia congenita-6c & non-epidermolytic PPK (focal > diffuse)	AD	*KRT6C*	Helix termination > initiation motifs
Pseudofolliculitis barbae	Risk factor	*KRT75*	1A
Monilethrix	AD	*KRT81, KRT83, KRT86*	Helix termination (*KRT86* > *KRT81* > *KRT83*) & initiation (*KRT86*) motifs
"Pure" hair–nail type ectodermal dysplasia	AR	*KRT85*	V1 (more severe phenotype), V2
White sponge nevus	AD	*KRT4, KRT13*	Helix initiation > termination motifs

Table 56.4 Types of keratin mutations in mucocutaneous disorders. Also see Fig. 56.5. AD, autosomal dominant; AR, autosomal recessive; EBS, epidermolysis bullosa simplex; H1, homologous subdomain 1; KRT, keratin; L12/L2, linker segments (non-helical); PPK, palmoplantar keratoderma; V1, variable head domain; V2, variable tail domain; 1A/1B/2A/2B, α-helical rod domain segments.

structure[32]. Interestingly, hyperpigmentation is a major feature of Dowling–Degos disease, Naegeli–Franceschetti–Jadassohn syndrome, and dermatopathia pigmentosa reticularis (disorders that do not feature prominent blistering; see Ch. 67) as well as EBS with mottled pigmentation, demonstrating that mutations in keratin genes expressed in the basal epidermis can lead to pigmentary changes in addition to skin fragility (see Fig. 56.5).

Epidermolytic ichthyosis and palmoplantar keratoderma

Epidermolytic ichthyosis (EI) is a disorder of keratinization caused by mutations in *KRT1* or *KRT10* (see Ch. 57)[33]. It is usually inherited in an autosomal dominant fashion due to heterozygous missense mutations (typically involving the helix initiation and termination motifs) that lead to clumping of keratin filaments in the suprabasal layers of the epidermis and subsequent cytolysis. EI associated with PPK is mainly due to *KRT1* mutations, while EI without palmoplantar involvement is primarily due to *KRT10* mutations. *KRT1* mutations (outside of the critical helix initiation and termination regions) have also been identified in non-epidermolytic and epidermolytic variants of isolated PPK, which is more commonly caused by mutations in *KRT9*[34]. A recessive form of EI characterized by a complete absence of the KRT10 protein has also been described. Somatic mutations in *KRT1* or *KRT10* that occur during embryogenesis can present as an epidermolytic epidermal nevus (see Ch. 62), representing a mosaic form of EI. Vertical transmission of the mutation is possible if the gonads are involved, causing generalized disease in affected offspring. The types of mutations in keratin disorders are outlined in Table 56.4.

White sponge nevus

White sponge nevus is characterized by white plaques involving the oral mucosa, with occasional involvement of other mucosal surfaces such as the esophagus, vagina, rectum, and nasal cavity. The plaques may wax and wane over time, and suprabasal cytolysis and keratin clumping are observed histologically. Mutations in the genes encoding KRT4 and KRT13, which are specifically expressed in mucosal keratinocytes, cause this condition.

Gastrointestinal disorders

KRT8 and KRT18 are the major keratins that are expressed in gastrointestinal epithelia, including the liver, pancreas, and gut. Mutations in these simple keratins are typically located within the head and tail domains and do not involve the highly conserved helix boundary regions. KRT8 and KRT18 mutations are considered as risk factors for developing liver and gastrointestinal disorders (e.g. cirrhosis, inflammatory bowel disease) with additional genetic and environmental alterations likely required for disease development[35]. The

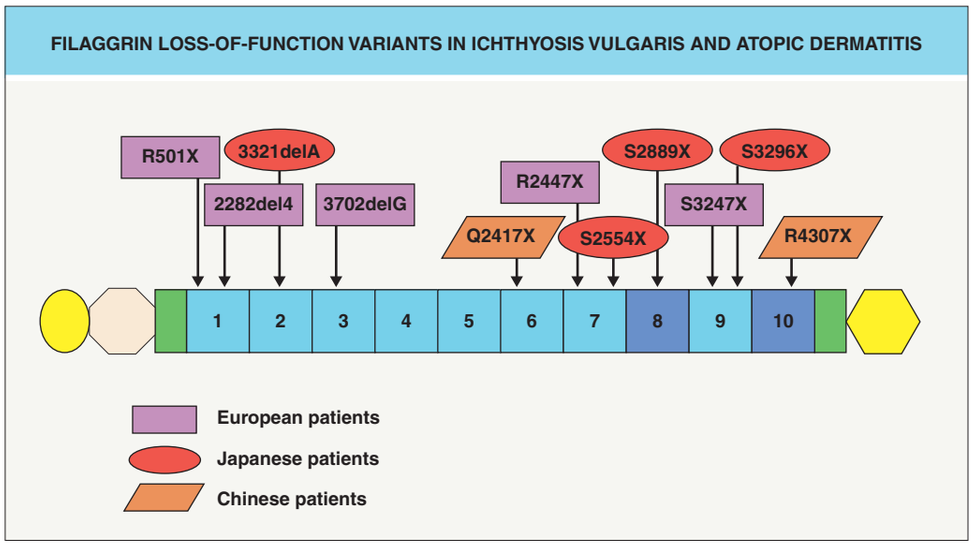


Fig. 56.9 Filaggrin loss-of-function variants in ichthyosis vulgaris and atopic dermatitis. The filaggrin protein consists of several domains: an S100 Ca^{2+}-binding domain (yellow oval), a B-domain (beige octagon), two imperfect filaggrin repeats (green rectangles), 10 filaggrin repeats (blue numbered rectangles; some individuals have two copies of repeat 8 and/or 10), and a C-terminal domain (yellow hexagon). Mutations in filaggrin that have been identified in patients with ichthyosis vulgaris and atopic dermatitis are indicated.

mutation-associated predisposition to tissue injury is likely related to mechanical and non-mechanical keratin functions, including maintenance of cell integrity and protection from oxidative injury and apoptosis.

Filaggrin Deficiency Disorders

Filaggrin is a component of the cornified cell envelope and is responsible for aggregating keratins. It represents the processed product of profilaggrin, which is cleaved into individual filaggrin polypeptides by caspase 14. Loss-of-function mutations in filaggrin underlie ichthyosis vulgaris (Fig. 56.9), a semidominant condition with incomplete penetrance (~90% in homozygotes and ~60% in heterozygotes; see Ch. 57)[36]. Whereas patients with a heterozygous filaggrin mutation display mild scaling or no phenotype, those with homozygous or compound heterozygous mutations have more severe ichthyosis vulgaris with dry, scaly skin and a substantially altered cutaneous barrier.

In addition to causing ichthyosis vulgaris, loss-of-function mutations in filaggrin also predispose to atopic dermatitis (see Ch. 12). Approximately 20%–50% of patients with atopic dermatitis have at least one filaggrin null allele. Furthermore, individuals who carry filaggrin mutations and develop atopic dermatitis are also predisposed to the subsequent onset of asthma, suggesting that epicutaneous sensitization and inflammation of the skin in the context of an abnormal epidermal barrier may play a role in the development of airway hyperreactivity.

Mouse Models for Structural and Desmosomal Proteins

The generation of mouse models has significantly increased our understanding of skin biology and the pathophysiology of genodermatoses. Animals harboring mutational "hot spots" that have been identified in humans are important for testing novel disease-targeted treatments and can help to bring new technologies closer to clinical use[37]. For example, a reporter mouse model was developed to assess topical formulations that deliver short interfering RNAs (siRNAs) into the skin to silence dominant-negative mutant alleles[38].

CONCLUSION

We have made great progress in understanding the structure and function of the epidermis. Another challenge is to better elucidate the gene regulatory mechanisms and cell signaling pathways required for the development and maintenance of the skin. Identification of epigenetic factors and modifier genes will help to explain phenotypic variations and establish more precise genotype–phenotype correlations. This knowledge will form the foundation for the development of new therapeutic strategies for acquired and inherited skin diseases.

Additional table on Mouse models for human skin diseases due to abnormalities in structural and desmosomal proteins, available in our eBook (see inside front cover for access code).

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MOUSE MODELS FOR HUMAN SKIN DISEASES DUE TO ABNORMALITIES IN STRUCTURAL AND DESMOSOMAL PROTEINS		
Gene/protein	**Human diseases**	**Genotype and phenotype of mouse models**
Structural proteins		
Keratin 14	Epidermolysis bullosa simplex	R125C: blistering due to collapse of keratin network in basal keratinocytes
Keratin 1	Epidermolytic ichthyosis (See also Fig. 56.5)	KO: perinatal lethality
Keratin 10	Epidermolytic ichthyosis (See also Fig. 56.5)	R156C: blistering at birth, hyperkeratosis later in life KO: severe blistering and hyperkeratosis
Keratin 2	Superficial epidermolytic ichthyosis	KO: localized hyperkeratosis (ear, tail)
Keratin 9	Epidermolytic PPK	KO: footpad calluses
Keratin 6a	Pachyonychia congenita-6a	KO: delayed wound healing N172del: nail dystrophy
Keratin 6b	Pachyonychia congenita-6b	KO: starvation due to upper GI constriction
Keratin 16	Pachyonychia congenita-16	KO: oral leukokeratosis, footpad calluses
Keratin 17	Pachyonychia congenita-17 Steatocystoma multiplex	KO: alopecia
Loricrin	Vohwinkel syndrome Progressive symmetric erythrokeratoderma	KO: transient neonatal erythroderma 372insC: neonatal erythrokeratoderma, tail constriction bands, footpad hyperkeratosis
Filaggrin	Ichthyosis vulgaris Atopic dermatitis	KO*: impaired epidermal barrier, enhanced contact hypersensitivity
Desmosomal proteins		
Desmocollin 1	Subcorneal pustular dermatosis	KO: skin fragility with acantholysis, localized hair loss
Desmocollin 3	Hypotrichosis and skin lesions	Conditional KO: skin blistering with acantholysis, telogen hair loss
Desmoglein 3	Pemphigus vulgaris (PV)	KO or PV model (anti-Dsg3 Ab in Rag2 KO): mucous membrane blistering and hair loss
Desmoglein 4	Localized autosomal recessive hypotrichosis Autosomal recessive monilethrix	Y196S (biallelic): hair defects ("lanceolate hair")
Desmoplakin	Striate PPK Carvajal syndrome Skin fragility/woolly hair syndrome Acantholytic erosive disorder	KO: embryonic lethality; heart defects in tetraploid rescued mice
Plakoglobin	Naxos disease Cardiomyopathy with alopecia & PPK Acantholytic erosive disorder	KO: embryonic lethality, heart defects
Corneodesmosin	Hypotrichosis simplex of the scalp Inflammatory peeling skin syndrome	Conditional KO: loss of adhesion between granular and cornified cell layers, skin water barrier defects, hair loss
Plakophilin 1	Skin fragility–ectodermal dysplasia syndrome	KO: fragile skin, sparse and small desmosomes, abnormal tight junctions

*Similar findings in the "flaky tail" mouse with a biallelic single nucleotide deletion (5303delA) that results in a frameshift mutation and truncated protein.

eTable 56.1 Mouse models for human skin diseases due to abnormalities in structural and desmosomal proteins. Ab, antibodies; KO, knockout; PPK, palmoplantar keratoderma.

57 Ichthyoses, Erythrokeratodermas, and Related Disorders

Gabriele Richard

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Key features

- Ichthyoses and erythrokeratodermas are heterogeneous groups of disorders of cornification
- Ichthyoses are characterized by scaling of the skin in a widespread distribution
- Erythrokeratodermas feature discrete areas of erythema and hyperkeratosis, usually without substantial scale
- Most inherited ichthyoses and erythrokeratodermas are evident at birth or manifest in infancy
- Clinical features and pattern of inheritance as well as the underlying structural, biochemical, and molecular abnormalities help to differentiate these disorders
- Therapy is symptomatic and primarily aimed at reducing hyperkeratosis. Topical management consists of emollients, keratolytics, and retinoids
- Many, but not all, disorders respond well to oral retinoids. Treatment is initiated at low doses and titrated to response. Benefits and side effects must be carefully considered because of the chronic nature of these conditions

INTRODUCTION

Ichthyoses and erythrokeratodermas are disorders of cornification in which abnormal differentiation and desquamation of the epidermis result in a defective cutaneous barrier. Ichthyoses represent a large clinically and etiologically heterogeneous group of conditions that feature generalized scaling of the skin (Tables 57.1 and 57.2). Erythrokeratodermas are characterized by circumscribed areas of erythema and hyperkeratosis without obvious scaling. Willan introduced the term "ichthyosis", derived from the Greek root "*ichthy*" meaning fish, in his textbook of dermatology in 1808[1]. Since then, nomenclature and nosology of ichthyoses have continuously evolved, including a variety of descriptive names, eponyms, and synonyms.

Milestones in recognizing distinct entities include the description of harlequin ichthyosis in the nineteenth century, separation of the bullous and non-bullous types of ichthyosis by Brocq (who also coined the name "congenital ichthyosiform erythroderma") in the early 20th century[2], and differentiation between autosomal dominant "epidermolytic hyperkeratosis" and autosomal recessive "lamellar ichthyosis" by Frost and Van Scott in 1966[3]. Alibert mentioned the autosomal dominant inheritance of ichthyosis vulgaris as early as 1806[4]. X-linked ichthyosis, despite several earlier reports, was only fully recognized in Wells and Kerr's study in 1966[5], followed by the identification of steroid sulfatase deficiency in the 1970s[6]. Advances in the molecular etiology and biology of ichthyoses and erythrokeratodermas have provided tools to categorize these disorders of cornification, at least in part, based on their underlying genetic defects. In 2009, an international group of clinical and research experts developed a revised nomenclature and classification system for ichthyoses and other disorders of cornification, incorporating molecular causes as well as functional aspects of disease pathogenesis[7].

Establishing the correct diagnosis in a patient with ichthyosis is a prerequisite for making prognostic predictions, planning therapy, and offering genetic counseling. This may pose a considerable challenge, as these disorders are uncommon and have overlapping clinical spectra. However, a systematic approach utilizing clinical and laboratory-based clues in conjunction with genetic testing can aid in making the diagnosis (Fig. 57.1).

In general, it is helpful to determine whether an ichthyosis presented at birth (e.g. as a collodion baby) or later in life and whether manifestations are limited to the skin or are part of a multisystem disorder. The quality and distribution of the scale as well as the presence or absence of erythroderma, blistering, and abnormalities of cutaneous adnexa are other useful clinical features. A thorough family history is essential for recognizing the inheritance pattern, and examination of both parents (even in a seemingly sporadic case) may reveal valuable diagnostic hints such as an epidermal nevus representing a mosaic presentation of epidermolytic ichthyosis. Patients whose parents are clinically unaffected may have: (1) a recessive ichthyosis, especially in the setting of consanguinity and/or affected siblings; (2) a dominant ichthyosis due to a "new" mutation; or (3) for a male patient, an X-linked recessive ichthyosis where the mother may be an asymptomatic carrier but her male relatives could be affected. A few disorders are recognizable by characteristic histopathologic and ultrastructural features, such as epidermolytic ichthyosis and ichthyosis hystrix Curth–Macklin. Laboratory studies suggest the diagnosis in other conditions, including enzyme analysis in steroid sulfatase deficiency and observation of lipid vacuoles in circulating leukocytes in neutral lipid storage disease (see Fig. 57.1).

This strategy allows the clinician to identify some ichthyoses based on their key features. Genetic testing can confirm the diagnosis in ~90% of patients with ichthyosis[8,9], allowing for more precise genetic counseling and providing the basis for prenatal testing.

FEATURES OF SELECTED NONSYNDROMIC ICHTHYOSES AND ERYTHROKERATODERMAS							
Diagnosis	**Gene (protein)**	**Mode of inheritance**	**Incidence**	**Onset**	**Primary cutaneous features**	**Associated features**	**Diagnosis (in addition to molecular testing*)**
Common ichthyoses							
Ichthyosis vulgaris	*FLG* (filaggrin)	Autosomal semi-dominant; more severe with biallelic variants	1:100–1:250	Infancy/ childhood	Fine, adherent, grayish scales on extremities and trunk with sparing of flexures; larger scales on lower legs; hyperlinear palms/soles, furrowed heels	Keratosis pilaris; atopic dermatitis (in ~50%)/ atopic diathesis	Clinical; diminished/absent stratum granulosum; absent/ reduced filaggrin immunostaining
Steroid sulfatase deficiency (X-linked recessive ichthyosis)	*STS* (steroid sulfatase) Deletion in ~90% of patients	XL recessive	1:2000–1:9500 boys/men	Infancy	Fine to large, dark, rhomboidal, adherent scales on extremities, trunk, neck, and lateral face; sparing of skin folds, palms/soles	Corneal opacities; cryptorchidism; ADHD or autism spectrum *Female carriers*: corneal opacities; prolonged labor with affected child	FISH or chromosomal microarray to identify gene deletion; increased plasma (hydroxy) cholesterol sulfate; lipoprotein electrophoresis (increased mobility of β-fraction); decreased steroid sulfatase activity in leukocytes
Nonsyndromic autosomal recessive congenital ichthyoses (ARCI)							
ARCI phenotypic continuum ranges from lamellar ichthyosis (LI) to congenital ichthyosiform erythroderma (CIE), with intermediate phenotypes[8,9,36,39,52]	**Often LI phenotype:** *TGM1* (transglutaminase-1) *ABCA12* (ABC lipid transporter); also CIE, harlequin ichthyosis *NIPAL4* (transporter protein involved in lipid processing) *CYP4F22* (cytochrome P450 enzyme that forms acylceramides) *PNPLA1* (patatin-like phospholipase directing acylceramide synthesis) *SULT2B1* (cholesterol sulfotransferase) *CERS3* (ceramide synthase) **Often CIE phenotype:** *ALOX12B* and *ALOXE3* (lipoxygenases) *ABCA12* *NIPAL4* *PNPLA1* (synthesis of omega-O-acylceramides) *SDR9C7* (short chain dehydrogenase/ reductase) **Childhood-onset:** *LIPN* (lipase N)	AR†	1:100 000–1:200 000 (up to 1:60 000 in some European countries)	Birth	Frequently CM at birth‡, then a generalized distribution; variable PPK (esp. *ABCA12, NIPAL4, LOX, SDR9C7*) or hyperlinear palms (esp. *CYP4F22, CERS3, PNPLA1*) **LI**: large, thick, plate-like brown scales; absent or mild erythroderma **CIE**: fine, white scales; prominent erythroderma Prematurely aged skin appearance (*CERS3*) Sparing of skin folds and central face (*SULT2B1*) Occasional EKV-like lesions (*ABCA12, PNPLA1*)	Heat intolerance; frequent (LI) or variable (CIE) scarring alopecia and ectropion (esp. *TGM1*), eclabium; secondary hearing or eye problems; ear malformations (*ABCA12, LOX*); nails hyperconvex (*ABCA12*) or ridged (*LOX*); tapered fingers (*ABCA12);* frequent fungal infections of skin and nails (*SDR9C7*)	Clinical; LI: transglutaminase-1 immunostaining or *in situ* assay in skin biopsy specimen

Table 57.1 Features of selected nonsyndromic ichthyoses and erythrokeratodermas.

Continued

FEATURES OF SELECTED NONSYNDROMIC ICHTHYOSES AND ERYTHROKERATODERMAS							
Diagnosis	**Gene (protein)**	**Mode of inheritance**	**Incidence**	**Onset**	**Primary cutaneous features**	**Associated features**	**Diagnosis (in addition to molecular testing*)**
Harlequin ichthyosis	*ABCA12* *KDSR* (3-ketodihydrosphingosine reductase)	AR	Rare	Birth	Very thick, yellow–brown plates of scale that tightly encase the neonate; large, deep, bright red fissures; survivors develop severe CIE-like phenotype with PPK	Premature delivery; often neonatal death due to sepsis or respiratory insufficiency; extreme ectropion, eclabium, and ear deformities; later heat intolerance, skin infections, growth delay, joint contractures and arthritis; thrombocytopenia (*KDSR*)	Clinical
Ichthyosis prematurity syndrome[60,61]	*SLC27A4* (solute carrier family 27 member 4, encoding fatty acid transport protein 4 [FATP4]) Common founder mutation Asn176Asp in Scandinavian families	AR	Rare	Birth	Erythroderma; thick, yellow–white, spongy hyperkeratosis (resembling vernix caseosa) with cobblestone-like appearance favoring scalp, forehead, and trunk; neonatal findings resolve within a few months, leaving variable mild, fine scaling and follicular keratoses	Polyhydramnios; premature birth, neonatal asphyxia and respiratory distress; later peripheral eosinophilia and atopy	Clinical
AD lamellar ichthyosis[71]	*ASPRV1* (skin aspartic protease responsible for cleaving profilaggrin)	AD	Very rare	Birth to first few months	Generalized, large, plate-like scales; absent or mild erythema; PPK	Hypohidrosis	Clinical
Keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK) syndrome[165]	*POMP* (proteasome maturation protein)	AR	Very rare	Birth	Mild generalized fine scaling; linear distribution of keratotic papules in flexural sites; hyperkeratotic plaques on knees, PPK with digital constriction bands	Digital flexion contractures	Clinical
Keratinopathic ichthyoses							
Epidermolytic ichthyosis[9]	*KRT10* (keratin 10; ~75%); *KRT1* (keratin 1; ~25%)	AD (very rarely AR)	1:200 000–1:350 000	Birth	*At birth:* erythroderma, blistering, erosions *Later:* hyperkeratosis with cobblestone pattern (most prominent over joints), ridging of the flexures; generalized or localized; thick PPK (*KRT1*)	Frequent skin infections; malodor; contractures; gait and posture abnormalities	Clinical; histopathology showing epidermolytic hyperkeratosis

Table 57.1 Features of selected nonsyndromic ichthyoses and erythrokeratodermas.

FEATURES OF SELECTED NONSYNDROMIC ICHTHYOSES AND ERYTHROKERATODERMAS							
Diagnosis	**Gene (protein)**	**Mode of inheritance**	**Incidence**	**Onset**	**Primary cutaneous features**	**Associated features**	**Diagnosis (in addition to molecular testing*)**
Superficial epidermolytic ichthyosis	*KRT2* (keratin 2 intermediate filaments)	AD	Rare	Birth	Erythroderma and blistering at birth; later, hyperkeratosis with flexural accentuation, "molting" of the skin; palms and soles spared	Hypertrichosis	Clinical; histopathology
Ichthyosis with confetti	*KRT10* or *KRT1* splice or frameshift mutations altering keratin tail; revertant mosaicism	AD	Very rare	Birth	Ichthyosiform erythroderma; PPK; during childhood, development of small spots of normal-appearing skin, which increase in number/size over time	Micropinnae, alopecia universalis, ectropion (MAUIE variant); increased risk of melanoma and keratinocyte carcinomas	Clinical
Ichthyosis hystrix Curth–Macklin	*KRT1*	AD	Rare	Birth	Mild to severe, mutilating PPK; hyperkeratosis with verrucous, cobblestone, or hystrix-like pattern on extremities and trunk	Pseudoainhum; digital contractures	Clinical; electron microscopy
Nonsyndromic erythrokeratodermas							
Erythrokeratodermia variabilis et progressiva	*GJB3* (connexin 31) *GJB4* (connexin 30.3) *GJA1* (connexin 43; rare)	AD (very rarely AR) AR	Rare	Birth/infancy	Transient, variable erythematous patches (esp. during childhood); more stable, geographic, hyperkeratotic plaques over knees, elbows, Achilles tendons, extremities, buttocks, lateral trunk; face and scalp often spared; less common generalized hyperkeratosis; PPK in ~50% of patients	Burning or stinging sensation preceding or accompanying erythema	Clinical, particularly history or presence of transient, migratory erythema
Progressive symmetric erythrokeratoderma (encompasses multiple entities)	*KRT83*, keratin 83 *TRPM4* (transient receptor potential cation channel) *LOR* (loricrin)	AD	Rare	Infancy/childhood	Fixed, slowly progressive, erythematous, hyperkeratotic plaques with sharp, figurate borders; favor cheeks, knees, elbows; periorificial distribution (*TRPM4*); PPK (transgredient with *TRPM4*, mutilating/pseudoainhum with *LOR*)		Clinical

*Genetic testing is available for all types of ichthyosis with a known molecular basis; multigene panels are preferable over single gene testing if the diagnosis is not evident based on clinical and laboratory findings.
†There are also rare reports of autosomal dominant inheritance of LI or CIE phenotypes (occasionally with a collodion membrane at birth) with unknown genetic bases. Biallelic small deletions in the caspase 14 gene (*CASP14*) were identified in patients from two Algerian families who presented with generalized fine whitish scales with no erythema and no collodion membrane.
‡A CM presentation is common in patients with underlying mutations in *TGM1*, *ALOX12B* (>*ALOXE3*), *CERS3*, *PNPLA1*, and *SULT2B1*; a CM presentation occurs less often with *NIPAL4* and *CYP4F22* mutations.

Table 57.1 Features of selected nonsyndromic ichthyoses and erythrokeratodermas. ADHD, attention deficit/hyperactivity disorder; AD, autosomal dominant; AR, autosomal recessive; ARCI, autosomal recessive congenital ichthyosis; CIE, congenital ichthyosiform erythroderma; CM, collodion membrane; EI, epidermolytic ichthyosis; EK, erythrokeratoderma; FISH, fluorescence in situ hybridization; FTT, failure to thrive; HI, harlequin ichthyosis; ID, intellectual disability; LI, lamellar ichthyosis; PPK, palmoplantar keratoderma; XL, X-linked

FEATURES OF SELECTED SYNDROMIC ICHTHYOSES AND ERYTHROKERATODERMAS							
Diagnosis	**Gene**	**Mode of inheritance**	**Incidence**	**Onset**	**Primary cutaneous features**	**Associated features**	**Diagnosis (in addition to molecular testing*)**
Syndromic ichthyoses							
Netherton syndrome	*SPINK5* (KAZAL type serine protease inhibitor 5)	AR	1:50 000	Birth/infancy	Congenital erythroderma and peeling; later develop two principal phenotypes: ichthyosis linearis circumflexa (ILC, polycyclic erythematous plaques with double-edged scale) and CIE-like; pruritus and eczematous plaques reminiscent of atopic dermatitis	Trichorrhexis invaginata and other hair shaft abnormalities; brittle, lusterless hair; highly elevated serum IgE; neonatal temperature instability, electrolyte imbalance, FTT; recurrent infections; food and other allergies; nonspecific aminoaciduria	Clinical; psoriasiform histopathology; trichoscopy, light microscopic hair shaft analysis; serum IgE measurement
Sjögren–Larsson syndrome	*ALDH3A2* (microsomal fatty aldehyde dehydrogenase)	AR	<1:100 000	Birth	Fine to plate-like scaling or non-scaling hyperkeratosis; favors abdomen, neck, flexures; lichenification; pruritus	Spastic di- and tetraplegia; perifoveal glistening white dots; ID; white matter disease of the brain	Clinical; fatty aldehyde hydrogenase activity assay in cultured fibroblasts (limited availability), MRI
Neutral lipid storage disease with ichthyosis	*ABHD5* (abhydrolase 5, activator of adipose triglyceride lipase)	AR	Rare	Birth	Generalized fine, white scales with variable erythema; very rarely figurate erythematous, hyperkeratotic plaques	Developmental delay; hepatomegaly; liver steatosis; myopathy; hearing impairment; cataracts; ataxia; reduced thyroid function in adulthood; lipid-containing vacuoles in leukocytes	Peripheral blood smear to detect leukocyte lipid vacuoles (Jordan anomaly); oil stains of frozen skin biopsy specimens
Trichothiodystrophy with ichthyosis	*ERCC2, ERCC3, GTF2H5* (subunits of general transcription factor TFIIH) For additional forms, see text	AR XL	Rare	Birth	Generalized scaling with absent or minimal erythroderma, except during infancy; CM in ~30% of patients	Brittle hair and nails; photosensitivity in ~50% of patients; ID; gonadal abnormalities; short stature	Clinical; tiger tail pattern by microscopic hair shaft examination under polarizing light; analysis of hair sulfur/cysteine content
Syndromic erythrokeratodermas							
Keratitis–ichthyosis–deafness (KID) syndrome	*GJB2* (connexin 26) *(GJB6*, connexin 30 – single reported patient)	AD	Rare, ~90% *de novo*	Birth/infancy	Transient neonatal erythroderma; erythematous, hyperkeratotic plaques with well-demarcated borders on face and extremities; follicular keratoses; progressive thickening of the skin with an appearance of "coarse-grained leather"; stippled PPK	Congenital SNHL; progressive keratitis with corneal neovascularization, conjunctivitis; recurrent mucocutaneous infections, especially with *Candida albicans*; increased susceptibility to oral and cutaneous squamous cell carcinoma; nail, hair and dental anomalies; follicular occlusion triad, cysts, proliferating pilar tumors; very rare fatal form with respiratory problems	Clinical

Table 57.2 Features of selected syndromic ichthyoses and erythrokeratodermas.

FEATURES OF SELECTED SYNDROMIC ICHTHYOSES AND ERYTHROKERATODERMAS							
Diagnosis	**Gene**	**Mode of inheritance**	**Incidence**	**Onset**	**Primary cutaneous features**	**Associated features**	**Diagnosis (in addition to molecular testing*)**
Periorificial and ptychotropic erythrokeratoderma (PERIOPTER) syndrome (erythrokeratoderma with thrombocytopenia)[45,132]	*KDSR* (3-ketodihydrosphingosine reductase involved in ceramide synthesis)	AR	Rare	Birth to early childhood	Variable presentations: harlequin ichthyosis-like, CM, erythroderma; later sharply demarcated, erythematous, hyperkeratotic plaques with predilection for cheeks, periorificial regions, and skin folds; transgredient PPK; may resemble Olmsted syndrome; spontaneous remission after puberty possible	Thrombocytopenia	Clinical; thrombocytopenia; *histology*: acanthosis, marked hyperkeratosis with parakeratosis
Severe dermatitis, multiple allergies, metabolic wasting (SAM) syndrome[166]	*DSG1* (desmoglein 1) *DSP* (desmoplakin)	AR (*DSG1*) AD (*DSP*)	Rare	Birth	Congenital erythroderma; PPK; dermatitis, erosions or pustules; PSEK-like plaques; findings and severity vary	Markedly elevated IgE levels in blood; multiple food and other allergies; recurrent infections; malabsorption, hypoalbuminemia, and marked metabolic wasting in some patients; developmental delay; hypotrichosis	Clinical; elevated IgE in blood; *histopathology*: acantholysis
Erythrokeratodermia-cardiomyopathy syndrome[167]	*DSP* (desmoplakin)	AD	Very rare	Birth	Congenital, generalized erythrokeratoderma/ichthyosiform erythroderma; PPK; pruritus	Early childhood onset of progressive dilated cardiomyopathy; sparse, coarse hair; nail dystrophy; enamel defects, hypodontia; variable photophobia/corneal opacities, ID; response to ustekinumab reported	Clinical; echocardiography; *histopathology:* psoriasiform
Erythrokeratodermia with spinocerebellar ataxia (Giroux–Barbeau syndrome; variant of spinocerebellar ataxia-34)[168]	*ELOVL4* (elongase-4 for very long-chain fatty acids; involved in ceremide synthesis)	AD (initially in French-Canadian family)	Rare	Infancy (skin manifestations)	Migratory erythematous patches and/or erythematous, hyperkeratotic plaques with fine, white, adherent scales on extremities (knees, ankles, elbows, wrists); diminish or disappear during adulthood	Progressive neurologic symptoms develop during 4th–5th decades of life, including nystagmus, ataxia, dysarthria, and hyporeflexia	Clinical, *histopathology*: acanthosis, hyperkeratosis, focal parakeratosis, perinuclear vacuoles, clumped keratohyalin granules
Ichthyotic keratoderma, spasticity, hypomyelination, and dysmorphic features (IKSHD) syndrome[169]	*ELOVL1* (elongase-1 for very long-chain fatty acids, involved in ceramide synthesis)	AD	Very rare	Infancy–early childhood	Hyperkeratotic, rough, darkened skin with accentuation over joints (ridged) and on neck (acanthosis nigricans-like); yellow, adherent scale on scalp	SNHL, hypomyelination of central white matter with progressive spastic paraplegia; nystagmus, optic atrophy; dysmorphic facies	Clinical

*Genetic testing is available for all types of ichthyosis with a known molecular basis; multigene panels are preferable over single gene testing if the diagnosis is not evident based on clinical and laboratory findings.

Table 57.2 Features of selected syndromic ichthyoses and erythrokeratodermas. AD, autosomal dominant; AR, autosomal recessive; CIE, congenital ichthyosiform erythroderma; CM, collodion membrane; FTT, failure to thrive; ID, intellectual disability; IgE, immunoglobulin E; MRI, magnet resonance imaging; PPK, palmoplantar keratoderma; PSEK; progressive symmetric erythrokeratoderma; SNHL, sensorineural hearing loss; XL, X-linked.

The latter can potentially utilize circulating fetal cells as well as samples of chorionic villi or amniotic fluid[10]. However, despite advances in our understanding of the pathomechanisms underlying ichthyoses, effective therapies are available for only a subset of these conditions, and safety concerns may limit long-term use of treatments such as oral retinoids[11]. Hopefully, ongoing research will lead to the development of targeted treatments that will be of greater benefit to ichthyosis patients. Patient organizations such as the Foundation for Ichthyosis and Related Skin Types (FIRST; www.firstskinfoundation.org) can provide valuable support to affected individuals and their families.

COMMON ICHTHYOSES

ICHTHYOSIS VULGARIS

Synonyms: ■ Ichthyosis simplex ■ Autosomal dominant ichthyosis

History

In 1806, Alibert[4] described "ichthyose nacrée", which represented the first well-documented report of ichthyosis vulgaris. In 1966, Wells and Kerr[5] separated autosomal dominant and X-linked recessive forms of ichthyosis and delineated their clinical and epidemiological features.

Epidemiology

Ichthyosis vulgaris represents the most common disorder of cornification and is estimated to affect ~1 in 100 to 1 in 250 individuals[12]. It is inherited in an autosomal semi-dominant manner, with minimal to mild ichthyosis in individuals with heterozygous filaggrin mutations and more severe ichthyosis in those with complete filaggrin deficiency due to mutations on both alleles[13]. The overall penetrance in heterozygotes is ~80%–95% for ichthyosis vulgaris and/or associated findings (e.g. hyperlinear palms, keratosis pilaris, atopic dermatitis)[12–14], although there is variable phenotypic expression between and within families.

Pathogenesis

Ichthyosis vulgaris is caused by loss-of-function mutations in the filaggrin gene (*FLG*) (see Fig. 56.9) that result in haploinsufficiency[15]. Approximately 8% of European and 3% of East Asian individuals harbor at least one *FLG* mutation, compared to <1% among those of Mediterranean or African descent[13]. R501X and c.2282del4 account for up to 80% of mutations in Northern Europeans, while different null mutations are common in other population groups.

Profilaggrin represents a major component of the keratohyalin granules located in the granular layer of the epidermis. During keratinocyte differentiation, profilaggrin is cleaved into filaggrin peptides, which aggregate keratin intermediate filaments. These complexes are cross-linked to the cornified cell envelope and are responsible for proper formation of compact squamous cells (see Figs. 56.1 & 56.2). Filaggrin is eventually degraded into water-retaining amino acids, in particular histidine, that serve as a natural moisturizer.

Filaggrin deficiency results in impaired cornification, increased transepidermal water loss, enhanced penetration of allergens and irritants, and a propensity to develop inflammatory responses upon exposure to the latter. This explains the association of *FLG* mutations with atopic dermatitis (see Ch. 12) as well as hand eczema, irritant contact dermatitis, and nickel contact sensitization[13]. In addition, an association between *FLG* mutations and elevated serum vitamin D levels may result from increased UVB-induced vitamin D production in the skin, perhaps related to a paucity of urocanic acid, a photoprotective histidine metabolite. The flaky-tail mouse with biallelic loss-of-function mutations in *Flg* represents an animal model that serves as a tool for the study of ichthyosis vulgaris and other filaggrin-deficient conditions.

Clinical Features

Ichthyosis vulgaris in *FLG* heterozygotes is usually not evident at birth. Dry skin and mild to moderate scaling appear during infancy or early childhood. Fine, white, flaky scales typically develop on the extremities, especially the extensor surfaces (Fig. 57.2). The groin and flexural areas are spared because of increased humidity in those regions. On the lower legs, the scales are often larger with an adherent center and detached, outward-turning edges. Mild hyperkeratosis of the palms and soles leading to accentuated skin markings (hyperlinearity) is common (Fig. 57.3).

In more severe disease due to a complete lack of filaggrin, ichthyosis vulgaris may present at birth with mild erythema and generalized scaling or peeling. Later, large scales reminiscent of lamellar ichthyosis may develop and the trunk, scalp, forehead, and cheeks can be affected in addition to the extremities. Palmoplantar involvement is also more pronounced with furrows or painful fissures of the heels.

Severity and symptoms such as pruritus depend on the season and climate, improving during the summer and with higher humidity, and worsening in a dry, cold environment. Although the ichthyosis may be progressive during childhood, it usually improves with age. Ichthyosis vulgaris is frequently associated with keratosis pilaris and the atopic triad of asthma, hay fever, and atopic dermatitis. The latter is encountered in at least 25%–50% of patients with ichthyosis vulgaris and can obscure the characteristic sparing of the flexures. Conversely, 10%–15% of all individuals with atopic dermatitis and up to 50% of those of Northern European descent with atopic dermatitis also have moderate to severe ichthyosis vulgaris[15].

Pathology

Mild orthokeratotic hyperkeratosis is seen and a diminished granular layer is often but not always observed (Fig. 57.4). Approximately 30%–50% of affected individuals have no detectable granular layer and no keratohyalin granules by electron microscopy, while others have structural abnormalities in keratohyalin granules[13]. Immunohistochemistry demonstrates diminished or absent filaggrin staining in most patients.

Differential Diagnosis

The boundary between dry skin (xerosis) and mild ichthyosis vulgaris is not always clear-cut. In male patients, X-linked ichthyosis may be differentiated by larger, darker scales and involvement of the neck and other flexures; cryptorchidism, a maternal history of delayed or prolonged labor, and the inheritance pattern can represent additional clues. Chromosomal microarray or fluorescence *in situ* hybridization (FISH) testing can exclude steroid sulfatase deficiency. A rare mild form of autosomal recessive congenital ichthyosis that presents with generalized fine, whitish scaling similar to ichthyosis vulgaris results from mutations in *CASP14* (caspase 14), which is involved in the proteolytic degradation of profilaggrin. Acquired ichthyosis is distinguished by its development later in life and association with conditions such as malnutrition, infections (e.g. leprosy), neoplasms (e.g. lymphoma), inflammatory disorders (e.g. sarcoidosis), and medications (e.g. statins, ponatinib, immune checkpoint inhibitors)[15a]. Some individuals with other heritable forms of ichthyosis also have a partial or complete filaggrin deficiency, which may result in a more severe phenotype than is usually observed for those ichthyoses.

Treatment

The mainstay of treatment is application of emollients, humectants, and keratolytic agents to reduce scaling. Preparations that contain urea and/or glycolic, lactic, or salicylic acid are usually beneficial; with the latter, care must be taken to prevent salicylate toxicity (see Ch. 129). Skin irritation from topical retinoids limits their use for ichthyosis vulgaris, and vitamin D analogues are typically ineffective. Systemic treatment with acitretin or isotretinoin is rarely indicated. The use of moisturizing cleansers and humidifiers may also be helpful. Research is underway to identify compounds that could upregulate filaggrin expression and, for those patients with nonsense mutations, modify protein translation[13].

STEROID SULFATASE DEFICIENCY

Synonym: ■ X-linked recessive ichthyosis

History

A type of ichthyosis occurring only in boys and men was first reported in the early nineteenth century, and its X-linked recessive inheritance was clearly recognized in the 1920s. In 1966, the clinical features of this entity were distinguished from those of ichthyosis vulgaris[5]. The underlying steroid sulfatase deficiency was identified in the late 1970s[6].

Epidemiology

The worldwide incidence is between 1 in 2000 and 1 in 9500 male births. It is an X-linked recessive disorder that is transmitted by asymptomatic female carriers and almost exclusively affects boys and men.

Pathogenesis

Diminution or complete absence of steroid sulfatase activity is caused by a deletion of the entire *STS* gene on chromosome Xp22.31 in ~90% of patients and inactivating mutations in others[16]. Steroid sulfatase deficiency results in impaired hydrolysis of cholesterol sulfate and dehydroepiandrosterone sulfate (DHEAS), with subsequent accumulation of cholesterol 3-sulfate in the epidermis. High levels of this metabolite can inhibit transglutaminase-1, explaining the partial overlap with lamellar ichthyosis.

In women pregnant with an affected fetus, steroid sulfatase deficiency in the fetal placenta causes low or absent levels of estrogen in the urine and amniotic fluid because of inadequate deconjugation of DHEAS, which is necessary for estrogen synthesis. As a result, labor often fails to initiate spontaneously or progress, due to insufficient dilation of the cervix. This can only be partially overcome by oxytocin administration, often necessitating cesarean delivery.

Clinical Features

In ~90% of affected boys, steroid sulfatase deficiency presents during the neonatal period with mild erythroderma and generalized peeling, often with exfoliation of large, translucent scales. The typical polygonal, dark-brown, adherent scales develop later during infancy or childhood and are distributed symmetrically on the extremities, trunk, and neck (Fig. 57.5). The scales are occasionally grayish or white, and they tend to be larger on the lower extremities. Involvement of the preauricular area and neck is highly characteristic, which has resulted in the descriptive term "dirty neck disease" (see Fig. 57.5D); however, other skin folds are often not affected. The palms, soles, and remainder of the face are typically spared. Fine scaling of the scalp is frequently seen during early childhood but diminishes over time. The ichthyosis tends to improve in the summer; however, in contrast to ichthyosis vulgaris, it does not significantly subside with age.

Asymptomatic corneal opacities occur in 10%–50% of male patients and in some female carriers, but other ocular abnormalities such as deuteranopia (green color-blindness) are rare. Male patients have a 20-fold increased incidence of cryptorchidism[12]. A higher prevalence of attention deficit hyperactivity and mood disorders has also been reported as has an increased risk of atrial fibrillation/flutter in men[12,17]. Approximately 5% of patients with steroid sulfatase deficiency have a larger contiguous gene deletion, which may include the genes that underlie Kallmann syndrome (hypogonadotropic hypogonadism with anosmia), X-linked chondrodysplasia punctata, ocular albinism, intellectual disability/autism, and short stature.

Steroid sulfatase activity is measurably reduced in 85% of female carriers, but the remaining activity is sufficient to prevent skin manifestations. Because the *STS* gene at least partially escapes X-chromosome inactivation, mosaic ichthyotic changes are not seen.

Pathology

Histopathologic findings include hyperkeratosis or parakeratosis overlying a normal or slightly thickened granular layer. Follicular hyperkeratosis may be present. Electron microscopy shows an increased size and number of keratohyalin granules. In the stratum corneum,

APPROACH TO THE NEONATE OR INFANT WITH SIGNS OF ICHTHYOSIS AND DIAGNOSTIC CLUES

History
- Prenatal/birth history: prenatal diagnoses (e.g. heart defects), prolonged labor (suggestive of steroid sulfatase deficiency), prematurity (characteristic of harlequin ichthyosis, ichthyosis with prematurity)
- Consanguinity makes an autosomal recessive ichthyosis more likely
- Family history of epidermal nevi, ichthyosis, or erythrokeratoderma

Physical examination
- Types of skin findings (see Table 57.3): collodion membrane, bullae/erosions, erythroderma, peeling, diffuse scaling, circumscribed areas of erythema/hyperkeratosis
- Distribution of skin findings: generalized, unilateral, following lines of Blaschko, regional
- Evaluate the scalp hair, eyebrows, and eyelashes (including with trichoscopy); nails; and mucous membranes
- Evaluate for microcephaly, dysmorphic facies, asymmetry, contractures, hepatosplenomegaly, and other extracutaneous abnormalities

↓

Basic laboratory evaluation and additional assessment
- Complete blood count, electrolytes, hepatic panel, immunoglobulin levels (including IgE)
- Peripheral blood smear to evaluate for vacuoles in leukocytes
- Hearing screen (e.g. via the auditory brainstem response or oto-acoustic emission test)
- Ophthalmologic examination
- Consider X-rays to evaluate epiphyses, especially if ichthyosiform lesions are unilateral or in a mosaic distribution pattern
- Consider a skin biopsy, in particular if bullae/erosions (to assess for epidermolysis), if suspect ichthyosis vulgaris (to assess for a diminished granular layer; more evident in severe forms), or if genetic testing is not possible

↓

Consider genetic testing
- A multigene panel is preferable over single gene testing if the diagnosis is not evident based on clinical and laboratory findings
- FISH and microarray are alternatives if suspect steroid sulfatase deficiency

Other possible diagnostic testing (see Tables 57.1, 57.2, & 57.6–8)
- Following resolution of the collodion membrane if present, immunohistochemical staining of a skin biopsy specimen for transglutaminase-1, LEKTI, or filaggrin
- Lipid antibodies (e.g. adipophilin) or stains (e.g. oil red O, Sudan III) to detect cytoplasmic lipid droplets in paraffin-embedded or fresh frozen skin sections, respectively, if suspect neutral lipid storage disease
- Fibroblast or keratinocyte cultures of skin biopsy specimen to measure FALDH activity or check for elevated free fatty alcohols if suspect Sjögren–Larsson syndrome
- Electron microscopy of a skin biopsy specimen using ruthenium tetroxide fixation, to assess for abnormalities in the epidermal lipid system

Ⓐ

Fig. 57.1 Approach to the neonate or infant with signs of ichthyosis and diagnostic clues.

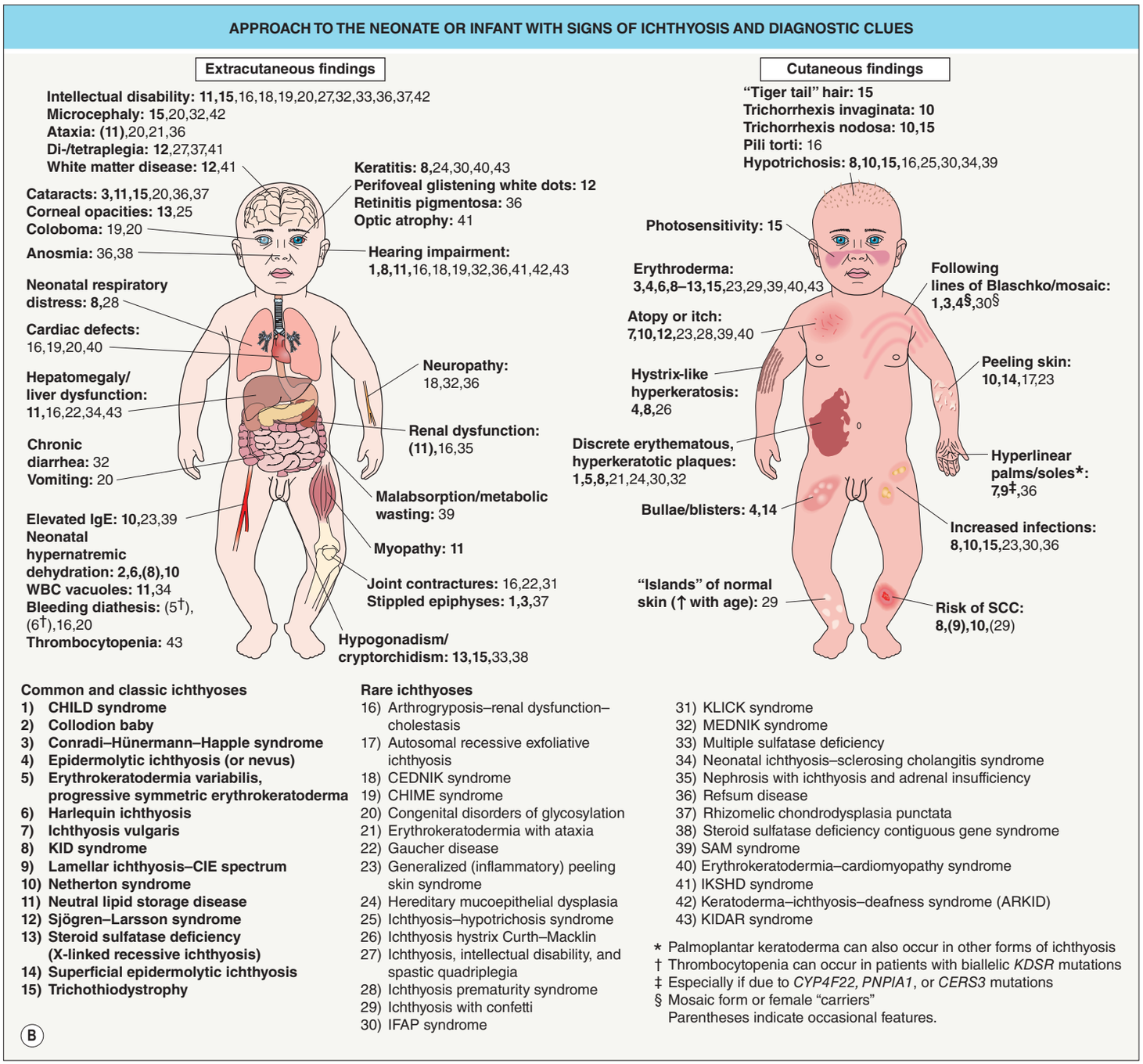


Fig. 57.1 Approach to the neonate or infant with signs of ichthyosis and diagnostic clues. IKSHD, ichthyotic keratoderma, spasticity, hypomyelination, and dysmorphic features; SAM, severe dermatitis, multiple allergies, metabolic wasting.

desmosomes are retained and cells contain a large number of melanosomes. Biochemical and cell kinetic studies show normal epidermal cell turnover and water homeostasis.

Other diagnostic tests

Underlying deletions can be identified by chromosomal microarray analysis or FISH, and molecular testing of *STS* is available. Prenatal diagnosis can also be performed (see Introduction)[10]. However, non-invasive prenatal diagnosis may be accomplished by identifying decreased maternal serum estriol levels or the presence of non-hydrolyzed sulfated steroids in maternal urine. Accumulation of (hydroxy) cholesterol sulfate can be detected indirectly by increased migration of the β-fraction in serum lipoprotein electrophoresis, or measured directly by liquid chromatography-mass spectrometry (LC-MS) of serum, epidermal scale, placental tissue, or amniotic fluid. In addition, steroid sulfatase enzymatic activity can be measured in leukocytes, fibroblasts, keratinocytes, or placental tissue.

Differential Diagnosis

Clinically, ichthyosis vulgaris is distinguished by its sparing of the neck and other flexural areas as well as the presence of hyperlinear palms and keratosis pilaris. As discussed above, an identical ichthyosis phenotype can be associated with extracutaneous findings in patients with larger contiguous gene deletions. Chromosomal microarray analysis, refined karyotyping, or FISH can be utilized to detect Xp deletions and X;Y translocations in patients who present with these additional findings. Autosomal recessive congenital ichthyosis due to defective cholesterol sulfotransferase (*SULT2B1* mutations) has a phenotype similar to that of steroid sulfatase deficiency, with lamellar scaling that spares the central face and skin folds[18].

Treatment

Topical humectants (especially propylene glycol), keratolytics, and retinoids are helpful alone or in combination. In contrast, vitamin D

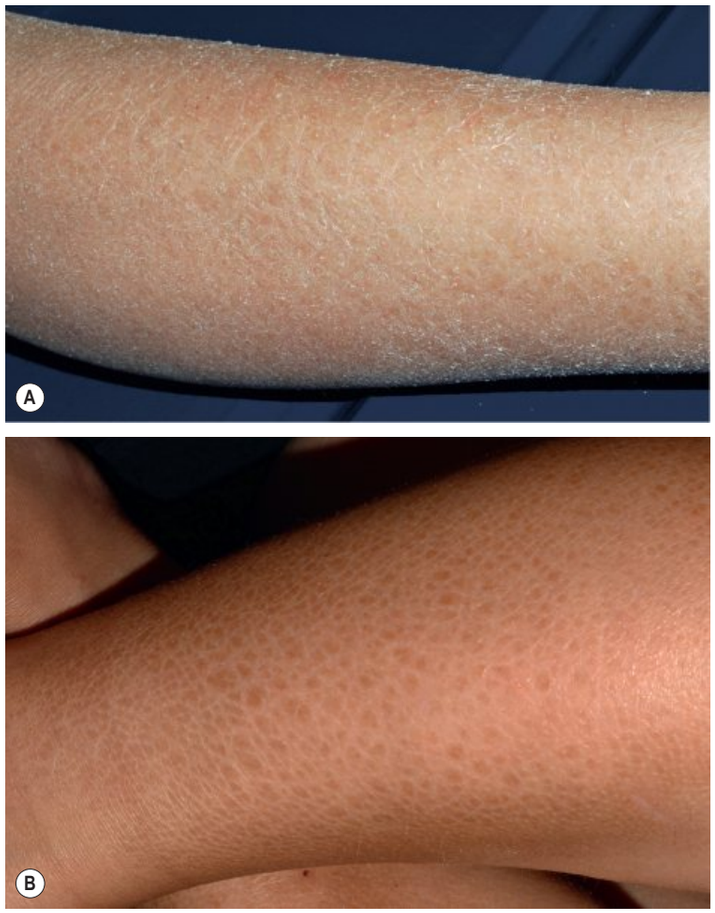


Fig. 57.2 Ichthyosis vulgaris. Fine, whitish, flaky scales **(A)** and larger, darker scales **(B)** on the legs of children. *Courtesy Julie V. Schaffer, MD.*



Fig. 57.3 Hyperlinear palms in ichthyosis vulgaris. *Courtesy Karynne Duncan, MD.*

analogues are less effective and cause significant irritation. Systemic retinoids are rarely necessary.

KERATINOPATHIC ICHTHYOSES

EPIDERMOLYTIC ICHTHYOSIS

Synonyms: ■ Bullous congenital ichthyosiform erythroderma (Brocq) ■ Epidermolytic hyperkeratosis ■ Bullous ichthyosis
Superficial epidermolytic ichthyosis subtype: ■ Ichthyosis bullosa of Siemens ■ Ichthyosis exfoliativa

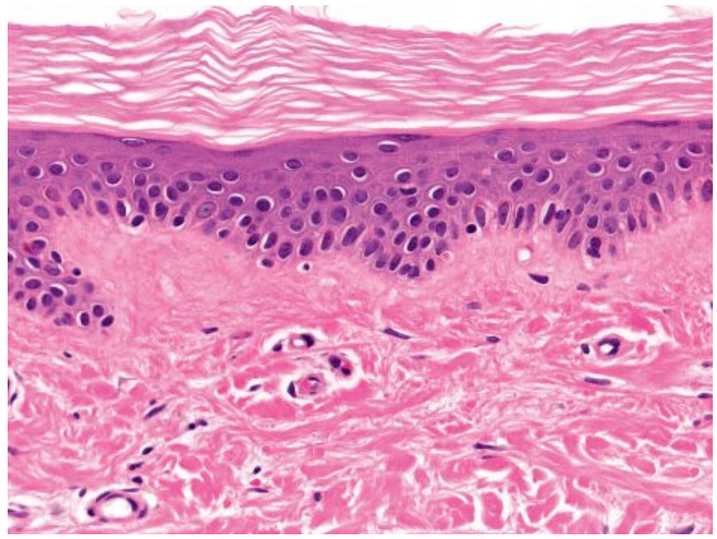


Fig. 57.4 Histologic features of ichthyosis vulgaris. Orthokeratotic hyperkeratosis and a diminished granular layer are evident. *Courtesy Lorenzo Cerroni, MD.*

History

Nikolsky first recognized the characteristic histopathology of the bullous form of congenital ichthyosis in 1897, and Brocq differentiated the dry (non-bullous) form from the wet (bullous) form of congenital ichthyosiform erythroderma in 1902[2]. Based on the distinctive histopathologic features of the epidermis, Frost and Van Scott[3] introduced the name "epidermolytic hyperkeratosis" for this autosomal dominant blistering form of congenital ichthyosis in 1966. In 1937, Siemens[19] first recognized a superficial form of epidermolytic ichthyosis as a distinct entity ("ichthyosis bullosa of Siemens").

Epidemiology

Epidermolytic ichthyosis (EI), which includes the superficial subtype (SEI), has an estimated worldwide prevalence of 1 in 200 000[20]. It is generally an autosomal dominant disorder with complete penetrance, with rare reports of autosomal recessive inheritance. Both sexes are affected equally. At least 50% of all cases occur sporadically due to new mutations.

Pathogenesis

EI is caused by heterozygous mutations in the genes encoding keratin 1 *(KRT1)*, keratin 10 *(KRT10)*, and (for SEI) keratin 2 (*KRT2*)[21]. There are rare reports in consanguineous families of a severe autosomal recessive form of EI due to biallelic loss-of-function mutations[22]. Keratins 1 and 10 are coexpressed in the differentiated spinous and granular layers of the epidermis, whereas keratin 2 is found in the uppermost spinous and granular layers; these represent the sites of disease pathology in classic EI and SEI, respectively. *KRT1* mutations are usually associated with palmoplantar keratoderma (PPK), which may be severe, while most *KRT10* mutations result in sparing of the palms and soles because there is less expression of *KRT10* in these locations[23]. Pathogenic mutations alter highly conserved amino acid residues located at the boundaries of the α-helical rod region; these sites represent mutational "hot spots" that impact the helix initiation and termination motifs (see Fig. 56.5)[21]. Mutations in other sites are uncommon and generally associated with a milder or unusual phenotype[21].

Mutations perturb keratin alignment, oligomerization, and filament assembly. This weakens the cytoskeleton, compromises the mechanical strength and cellular integrity of the epidermis, and leads to cytolysis and blistering. Epidermal acanthosis and hyperkeratosis result from hyperproliferation, decreased desquamation, and other factors. The barrier function of the skin is markedly disturbed, leading to increased transepidermal water loss and bacterial colonization of the stratum corneum.

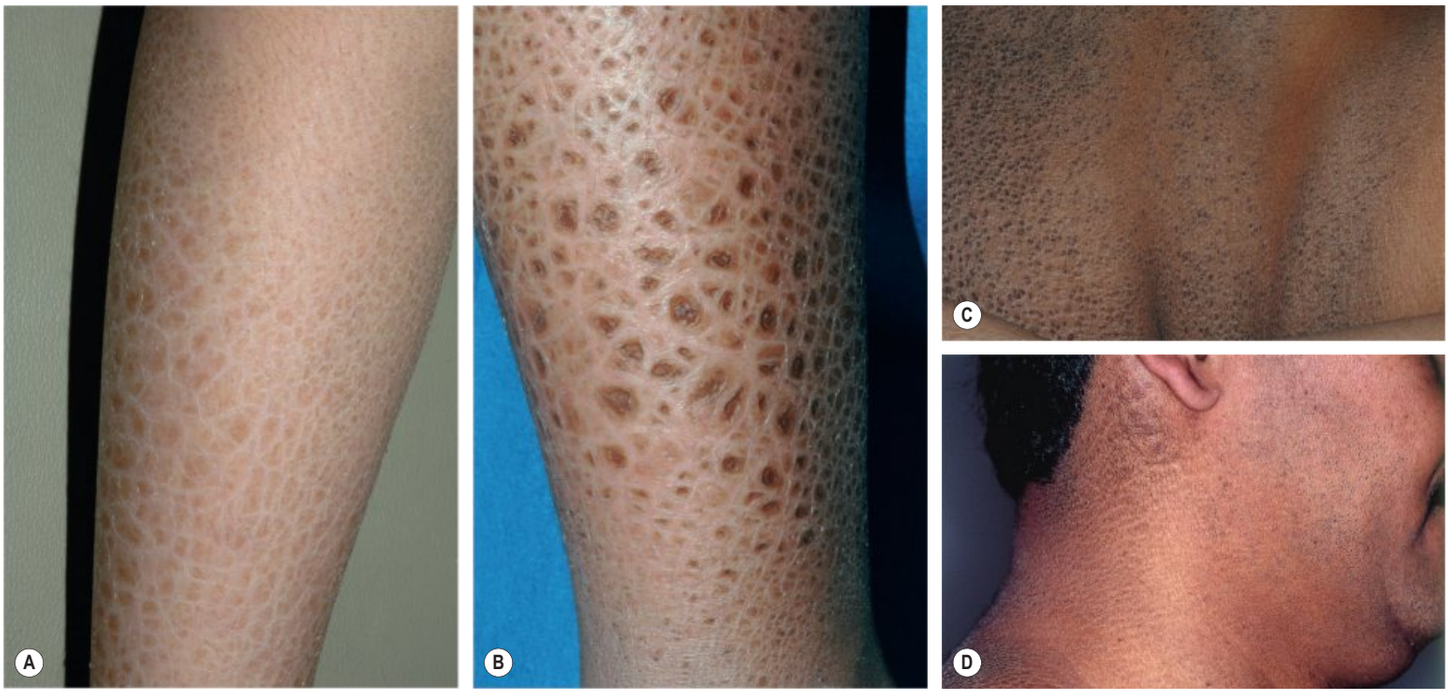


Fig. 57.5 Steroid sulfatase deficiency. Large light-brown (**A**) and more prominent dark-brown (**B**) scales on the lower legs. **C** Smaller dark-brown scales on the trunk, with sparing of the skin folds. **D** Dark scales on the neck, sometimes referred to as a "dirty neck". *A–C, Courtesy Julie V. Schaffer, MD.*

Clinical Features

Classic epidermolytic ichthyosis and variants

Classic EI presents at birth with erythroderma (Fig. 57.6A), peeling, erosions, and often widespread areas of denuded skin (see Fig. 34.16). Hyperkeratosis may be present, but it usually develops later during infancy. Skin fragility, blistering, and erythema decrease over time, and severe hyperkeratosis prevails (Fig. 57.6B–E). However, patients may still periodically shed large plates of superficial epidermis, revealing a tender, erythematous base. Ridges along skin lines are common in flexures (see Fig. 57.6C,D), while hyperkeratosis over the extensor surfaces of the joints often forms a cobblestone pattern (see Fig. 57.6E). When present, PPK may be severe and associated with digital contractures (Fig. 57.6F).

The clinical presentation of EI varies considerably, and six characteristic clinical patterns with or without PPK have been described[23]. Unusual clinical variants of EI include "cyclic ichthyosis with epidermolytic hyperkeratosis" and "annular epidermolytic ichthyosis", which are caused by distinct mutations outside the helix boundaries of *KRT1* and *KRT10*, respectively[21].

EI is disfiguring and has tremendous impact on patients' quality of life and social interactions. Sepsis as well as fluid and electrolyte imbalances can be life threatening in the neonatal period. Episodes of blistering and secondary skin infections are also problematic later in life. The disorder is accompanied by a pungent body odor, and it is occasionally associated with posture and gait abnormalities. Angular cheilitis and severe scalp involvement leading to encasement of hair shafts and hair loss are additional associated findings.

Superficial epidermolytic ichthyosis (SEI)

SEI is less severe than classic EI. At birth, the skin may appear normal or have mild blistering. Trauma-induced vesicles on the extremities occur during infancy but usually subside by early childhood, as hyperkeratosis develops. The skin overlying the joints, the flexures, and the dorsa of the hands and feet (Fig. 57.7) are sites of predilection, whereas the palms and soles are spared. Involved skin may appear ridged, shiny, or lichenified. A characteristic feature is superficially denuded areas with collarette-like borders, described as "molting" or "Mauserung", which develop due to superficial blistering and shedding of the stratum corneum[21].

Epidermolytic epidermal nevi (mosaic epidermolytic ichthyosis)

The mosaic form of EI is characterized by unilateral or bilateral streaks of hyperkeratosis that follow the lines of Blaschko[24]. Extensive involvement with marked hyperkeratosis leading to protruding, porcupine-like spines has been referred to as "ichthyosis hystrix", but this is a descriptive term rather than the name of a distinct disorder. Epidermolytic epidermal nevi are caused by a postzygotic mutation in *KRT1, KRT10*, or rarely *KRT2* that arises during embryogenesis. If this mutation involves gonadal cells, it can potentially be transmitted to the patient's offspring, resulting in full-blown, generalized disease[24]. Examination of both parents of a child with sporadic EI and genetic counseling are therefore recommended.

Pathology

Highly characteristic structural and ultrastructural abnormalities described as "epidermolytic hyperkeratosis" allow EI and SEI to be distinguished from other congenital ichthyoses. Key features of EI on routine histologic examination are dense orthokeratotic hyperkeratosis, prominent acanthosis, hypergranulosis, and cytolysis of the suprabasal and granular layers leading to small intraepidermal blisters (Fig. 57.8). In SEI, cytolysis is limited to the granular cell layers and can occasionally lead to superficial intraepidermal separation. Keratinocytes within the affected cell layers exhibit marked intracellular vacuolization and dense clumps of keratin intermediate filaments (KIFs). A mild perivascular lymphohistiocytic infiltrate is usually present in the upper dermis. Ultrastructural analysis of EI reveals fragmented, clumped KIFs in the lower epidermis and perinuclear KIF shells in the upper epidermis, while SEI has tonofilament clumping in the upper spinous and granular cell layers.

Other diagnostic tests

Mutation screening and complete sequencing of *KRT1, KRT10*, and *KRT2* are available. Prenatal diagnosis can be performed when the underlying mutation has been identified in affected family members.

Differential Diagnosis

In the neonatal period, the presence of blisters and erosions differentiates EI from non-bullous congenital ichthyoses (Table 57.3). Clinical distinction from the various forms of epidermolysis bullosa,



Fig. 57.6 Epidermolytic ichthyosis. A Erythroderma with fine scaling and erosions on the face and thigh in an infant. **B** Later development of marked hyperkeratosis with focal erosions. **C, D** Corrugated hyperkeratosis in the antecubital fossa. **E** Hyperkeratosis with a cobblestone pattern on the dorsal hand. **F** Severe palmoplantar keratoderma with digital contractures in a patient with a *KRT1* mutation. *A, Courtesy Angela Hernández-Martín, MD; B–D, F, Courtesy Julie V. Schaffer, MD; E, Courtesy S.J. Bale, PhD and J.J. DiGiovanna, MD.*



Fig. 57.7 Superficial epidermolytic ichthyosis. Increased skin markings and "collarettes" where the skin has been superficially shed ("Mauserung"). *Courtesy Anthony J. Mancini, MD.*

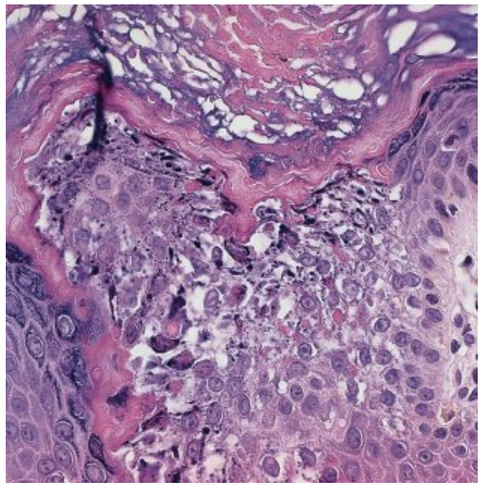


Fig. 57.8 Histology of epidermolytic ichthyosis. Striking ortho-hyperkeratosis, intracellular vacuolization of keratinocytes, and a prominent granular layer with clumped keratin filaments are seen.

staphylococcal scalded skin syndrome, and other vesiculobullous and erosive disorders that can present in neonates may require skin biopsy specimens and cultures (see Chs. 32 and 34).

Later in life, EI can be distinguished from other congenital ichthyoses by the history of blistering at birth with focal recurrences, frequent superinfections, characteristic clinical appearance, and distinctive histologic features. The latter may also be seen in epidermolytic PPK (see Ch. 58), but it is limited to the palms and soles. Ichthyosis hystrix Curth–Macklin sometimes resembles EI, with ridged, verrucous hyperkeratosis over joints and in flexures. In contrast to EI, there is neither blister formation nor histologic evidence of epidermolysis, and the KIFs have specific ultrastructural abnormalities (see below).

Infants with SEI usually do not present with the marked erythroderma and widespread blistering seen in classic EI. Later in life, SEI is differentiated by the lack of erythema and milder course with "molting" of the superficial epidermis. Peeling skin syndromes can have a clinical appearance similar to that of SEI but do not feature vacuolization of the granular layer.

NEONATAL PRESENTATION OF SELECTED ICHTHYOSES AND RELATED DISORDERS					
Disorder	**Collodion membrane**	**Bullae/blisters/ erosions**	**Erythroderma**	**Generalized ichthyosis**	**Peeling/exfoliation**
Epidermolytic ichthyosis		+	+	(+)	(+)
Superficial epidermolytic ichthyosis		(+)	(+)	(+)	+
Ichthyosis with confetti	(+)	(+)	+	+	
Lamellar ichthyosis	+		(+)	+	
Congenital ichthyosiform erythroderma	+		+	+	
Self-improving collodion ichthyosis	+				
Sjögren–Larsson syndrome	(+)		+	+	
Neutral lipid storage disease	(+)		+	+	
Trichothiodystrophy	(+)		+	+	
Netherton syndrome			+	+	+
Steroid sulfatase deficiency			+	(+)	+
Peeling skin syndromes (see Table 57.8)			(+)	(+)	+
Conradi–Hünermann–Happle syndrome	(+)		+ (lines of Blaschko)	+ (lines of Blaschko)	
CHILD syndrome			Unilateral	Unilateral*	
KID syndrome			+	(+)	
Loricrin keratoderma	(+)				

*Some attenuated or band-like involvement may occasionally be appreciated on the contralateral side.

Table 57.3 Neonatal presentation of selected ichthyoses and related disorders. Parentheses indicate less frequent or occasional findings.

Treatment

Treatment is symptomatic and depends on the age of the patient, disease severity, and clinical issues. In the neonatal period, infants with classic EI typically require management in an intensive care nursery to provide protective isolation and prevent or treat dehydration, electrolyte imbalance, and cutaneous superinfection. Sepsis should be treated with broad-spectrum antibiotics. When the neonate is handled carefully and protective padding and lubricants are used, erosions and denuded skin usually heal rapidly.

In children and adults with classic EI, therapy is aimed at reducing hyperkeratosis, removing scale, and softening the skin. Topical products containing urea, salicylic acid, α-hydroxy acids, and N-acetylcysteine can be effective but are often not well tolerated, especially in children, because of burning and stinging. Widespread topical application of higher-concentration salicylic acid preparations should be avoided because of the risk of systemic salicylism. Topical tretinoin and vitamin D may be beneficial but often cause skin irritation. Frequent use of emollients and humectants can be combined with hydration (e.g. soaking of the skin during bathing) and mechanical abrasion of keratotic skin via gentle scrubbing with a soft brush or sponge.

Bacterial skin infections are common in patients with classic EI and often trigger blistering; they require topical or systemic antibiotic treatment. Use of antiseptics such as antibacterial soaps, chlorhexidine, or dilute sodium hypochlorite baths may help to control bacterial colonization. Continuous use of oral or topical antibiotics should be avoided due to the risk of developing antibiotic resistance. Because of the increased skin fragility, it is also important to prevent mechanical trauma, e.g. by wearing comfortable clothing and shoes.

Oral retinoids may drastically reduce hyperkeratosis and the frequency of infections in patients with generalized EI, but they also increase epidermal fragility and blistering. Low initial doses with gradual increase and careful monitoring are advisable, with use of the lowest effective maintenance dose[11,25]. Responses to topical and systemic retinoids tend to be better in patients with EI due to *KRT10* mutations than in those with *KRT1* mutations; the latter individuals are vulnerable to retinoid-related down-regulated expression of KRT2, which can function as a substitute for KRT1[20]. Promising therapeutic approaches utilizing gene editing technologies to inactivate keratin genes with dominant-negative mutations are under development (e.g. *ex vivo* use of a transcription activator-like effector nuclease [TALEN])[26].



Fig. 57.9 Ichthyosis with confetti. Numerous small, confetti-like "islands" in the background of ichthyosiform erythroderma reflect revertant mosaicism. *Courtesy Antonio Torrelo, MD.*

ICHTHYOSIS WITH CONFETTI

Synonyms: ■ Ichthyosis en confetti ■ Confetti ichthyosis ■ Congenital reticular ichthyosiform erythroderma (CRIE) ■ Ichthyosis variegata ■ MAUIE (*m*icropinnae, *a*lopecia *u*niversalis, congenital *i*chthyosis, and *e*ctropion) syndrome

Ichthyosis with confetti is a rare autosomal dominant disorder in which affected individuals are born with an ichthyosiform erythroderma and PPK[27]. During childhood, hundreds to thousands of small, confetti-like "islands" of normal skin appear in a widespread distribution (Fig. 57.9), increasing in size and number over time. The MAUIE – *m*icropinnae,

*a*lopecia *u*niversalis, congenital *i*chthyosis, and *e*ctropion – variant is associated with an increased risk of melanoma and keratinocyte carcinomas, which have also been reported in other ichthyosis with confetti patients[28].

Histologic findings in ichthyotic skin include acanthosis, perinuclear vacuolization of keratinocytes in the upper epidermis, and parakeratotic hyperkeratosis, while the white macules lack epidermal abnormalities by light microscopy.

This ichthyosis is caused by heterozygous splice or frameshift mutations in *KRT10* or less often *KRT1*[27]. The resulting mutant keratin protein is often extended and has an arginine-rich carboxy terminus. This leads to varying degrees of mislocalization of KIFs to the nucleus instead of the cytoplasm. Each island of normal skin represents a revertant clone that arises via loss-of-heterozygosity due to mitotic homologous recombination, i.e. a "crossing-over" process that leads to homozygous mutant and homozygous normal daughter cells. The exact role of the frameshift mutations in the markedly elevated rate of mitotic recombination remains to be determined.

ICHTHYOSIS HYSTRIX CURTH–MACKLIN

Synonyms: ■ Ichthyosis hystrix ■ "Porcupine man" ■ Ichthyosis hystrix gravior type Lambert ■ Systematized verrucous nevus

Introduction

Ichthyosis hystrix is a descriptive term for massive hyperkeratosis that leads to a verrucous surface or protruding porcupine-like spines. Of note, it does not represent a distinct clinical entity. This phenotype is most commonly observed in patients with EI, but can also be seen in clinically and genetically heterogeneous disorders ranging from ichthyosis hystrix Curth–Macklin to verrucous epidermolytic nevi to hystrix-like ichthyosis with deafness (HID) syndrome. The latter is a variant of keratitis–ichthyosis–deafness (KID) syndrome and is due to mutations in *GJB2*[29].

History

In 1954, Ollendorff-Curth and Macklin[30] described a family with hystrix-like spiky hyperkeratosis and PPK. Electron microscopic examinations by Anton-Lamprecht et al.[31] revealed binucleated keratinocytes and peculiar ultrastructural abnormalities of the cytoskeleton. Since the initial description, several large families with autosomal dominant inheritance have been reported as have sporadic cases. A well-known example of the ichthyosis hystrix phenotype is the "porcupine men" of the Lambert family from Suffolk, England[32]. Since no blister formation was mentioned in the records of this kindred, it remains unclear if they had ichthyosis hystrix Curth–Macklin or a form of EI.

Pathogenesis

In several unrelated patients with ichthyosis hystrix Curth–Macklin, heterozygous mutations in the keratin 1 (*KRT1*) or keratin 10 (*KRT10*) genes have been demonstrated. In contrast to EI, the mutations were small nucleotide deletions/insertions that mostly led to a frameshift and produced a keratin protein with an aberrant tail. Because the latter lacks the usual glycine loop motifs, protein–protein interactions are altered[33].

Clinical Features

The hyperkeratotic areas in ichthyosis hystrix Curth–Macklin can clinically mimic EI, but there is no skin fragility. Clinical expression varies even within families, ranging from isolated PPK (which may be severe and mutilating) to localized keratotic verrucous plaques to generalized hystrix-like hyperkeratosis with horny rigid spikes. Hyperkeratosis is present at birth or develops during early childhood. It has a cobblestone-like or ridged surface over large joints and in skin folds. Circular constriction bands (pseudoainhum), starfish-like keratoses, knuckle pads, digital flexion contractures, and secondary bacterial infections have been described.

Pathology

Most histopathologic features, including orthokeratotic hyperkeratosis, hypergranulosis, acanthosis, and church spire-like papillomatosis, are nonspecific. Cells in the differentiated cell layers may be vacuolated or binucleated. Ultrastructural abnormalities in the upper epidermis are diagnostic, with a shell-like, interspersed network of tangled KIFs, often associated with perinuclear vacuolization and formation of binucleated cells. In contrast to EI, there is no epidermolysis or keratin clumping.

Differential Diagnosis

Ichthyosis hystrix Curth–Macklin can be differentiated from EI by the absence of blistering and skin fragility as well as by electron microscopic findings.

Treatment

The most effective treatments are systemic retinoids and topical keratolytic agents (see EI above).

AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSES

AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSIS (ARCI): CLINICAL AND GENETIC SPECTRUM

Synonyms: ■ Nonsyndromic ARCI ■ Ichthyosis congenita

Introduction

Autosomal recessive congenital ichthyosis (ARCI) encompasses a clinically and genetically heterogenous group of nonsyndromic ichthyoses that are present at birth or shortly thereafter and feature generalized scaling with variable erythema. Approximately one-third of patients with ARCI are born preterm, and the most common presentation at birth is a collodion membrane (~70%; see below)[7,34]. Ectropion (eversion of the eyelids) occurs in ~50% of neonates and may persist, while eclabium (eversion of the lips), observed in ~25% of neonates, often resolves[34].

The spectrum of fully developed ARCI phenotypes ranges from large, dark, plate-like scales with no or minimal erythema in lamellar ichthyosis (LI) to fine white scales and pronounced erythroderma in congenital ichthyosiform erythroderma (CIE). In addition, there are many intermediate phenotypes with variable degrees of erythema as well as size and quality of the scales. Other frequent accompanying features include PPK, hypohidrosis, heat intolerance, scarring alopecia, and conductive hearing loss. Patients may also develop recurrent infections, arthritis or arthralgia, anemia, and vitamin D deficiency.

ARCI is caused by pathogenic variants in at least 13 genes which encode proteins that contribute to the structure and function of lipid and cornified cell envelopes, in particular via their roles in epidermal lipid processing and transport (see Chs. 56 and 124). As a result, affected individuals have perturbed homeostasis of the stratum corneum and abnormal skin barrier function.

History

In 1966, Frost and Van Scott[3] coined the term "lamellar ichthyosis" for all autosomal recessive forms of non-bullous congenital ichthyosis. Williams and Elias[35] further separated this group into two distinct phenotypes, lamellar ichthyosis (LI) and (non-bullous) congenital ichthyosiform erythroderma (CIE), which now have been recognized to reside along a continuum with intermediate phenotypes. In the current classification system, the LI–CIE spectrum as well as harlequin ichthyosis (HI) and ichthyosis–prematurity syndrome (IPS) fall within the nonsyndromic ARCI category[7,36].

Epidemiology

ARCI occurs worldwide with an estimated overall prevalence of 1 in 100 000 to 200 000 live births. It is more common in certain regions such as Norway (1 in 90 000) and Spain (1 in 60 000) as well as in highly consanguineous populations[12]. The various forms of ARCI are inherited as autosomal recessive traits.

Pathogenesis and Clinical Features

Approximately 85%–90% of patients with ARCI have identifiable mutations in one of the ≥13 genes currently known to underlie this group of ichthyoses (see Table 57.1)[9,34]. Most common is *transglutaminase-1* deficiency due to deleterious mutations in both copies of ***TGM1***, accounting for ~30%–70% of all patients with ARCI and 70%–90% of those with classic LI[37–39]. Transglutaminase-1 (TGM1) catalyzes the calcium-dependent cross-linking of proteins through the formation of ε-(γ-glutamyl) lysine isopeptide bonds; it also creates ester bonds between proteins and ω-hydroxyceramides (see Fig. 56.3). This enzyme is expressed in the upper differentiated layers of the epidermis, where it facilitates the formation of the cornified cell envelope via cross-linking of multiple structural proteins (e.g. involucrin, small proline-rich proteins, loricrin, keratins, desmosomal proteins) to one another as well as to the lipid envelope.

Many patients of northern European descent share a German founder mutation that leads to alternative splicing of *TGM1* mRNA[40]. Certain *TGM1* variants can also result in self-improving collodion ichthyosis with very mild residual scaling after the collodion membrane has been shed (see below). In addition, mutations that result in temperature-sensitive TGM1 cause an LI variant known as "bathing suit ichthyosis" that primarily affects warmer body sites such as the trunk and scalp.

Biallelic loss-of-function mutations in *ATP-binding cassette subfamily A member 12* (***ABCA12***) that lead to complete absence of this transporter protein in the skin underlie the most severe form of ARCI, harlequin ichthyosis (HI). The presence of at least one *ABCA12* splice site or missense variant that permits residual protein function may result in a CIE or LI phenotype. Overall, this gene plays a role in ~5%–10% of all ARCI patients[41]. A germline missense *ABCA12* mutation plus mosaicism for a postzygotic frameshift *ABCA12* mutation ("recessive mosaicism") has been reported in a patient with erythematous, scaly lesions following the lines of Blaschko[42]. Rarely, *ABCA12* mutations may result in a phenotype resembling erythrokeratodermia variabilis et progressiva (see Table 57.1)[9].

ABCA12 is responsible for the energy-dependent transmembrane transport of glucosylceramides and proteolytic enzymes (e.g. kallikrein 5 and 7) required for normal epidermal desquamation. This transporter is found in lamellar bodies, which are absent, reduced, or improperly formed in patients with HI[43,44]. A lack of functional ABCA12 prevents the formation of lipid bilayers in the stratum corneum and results in compensatory massive hyperkeratosis and a severe breakdown of the permeability barrier with increased transepidermal water loss. Rarely, individuals with biallelic mutations in *3-ketodihydrosphingosine reductase* gene (***KDSR***), which encodes an enzyme involved in *de novo* ceramide synthesis, may have a HI presentation associated with thrombocytopenia[45].

Depending on their ethnic background, 10%–30% of ARCI patients without *TGM1* mutations harbor biallelic inactivating mutations in one of two *lipoxygenase (LOX)* genes, either ***ALOX12B*** or ***ALOXE3***, with *ALOX12B* accounting for approximately two-thirds of cases[34,36,39,46,47]. Up to 70% of these individuals (most with *ALOX12B* variants) are born with a collodion membrane and subsequently develop mild to moderate CIE that may improve with age. Additional clinical features can include mild PPK, ridged nails, and an anteriorly overfolded outer rim of the ears[34]. As noted for *TGM1*, certain *ALOX12B* and *ALOXE3* variants (and rarely *NIPAL4* or *CYP4F22*) result in self-improving collodion ichthyosis. The lipoxygenase enzymes encoded by these genes are involved in the arachidonic acid degradation pathway and are preferentially synthesized in the epidermis, where their successive actions play a role in the creation of protein-bound ceramides in the corneocyte lipid envelope[48].

Mutations in ***NIPAL4***, which encodes *NIPA-like domain containing 4 (ichthyin)*, account for 5%–25% of ARCI, with a higher frequency in Northern Europe[49,50]. In a Scandinavian study, 16 of 18 ARCI families with ultrastructurally abnormal lamellar bodies in the granular layer (elongated perinuclear membranes [ARCI EM type III]) had mutations in this gene[34,50,51]. Affected individuals have variable patchy erythema and widespread coarse, gray–white scales with a predilection for the neck and skin folds but sparing of the face. Diffuse yellowish PPK and hypohidrosis are common manifestations while a collodion membrane at birth (<30%), ectropion, eclabium, nail abnormalities, cataracts, and keratoconus occur less frequently[34,50,51].

NIPAL4 is a Mg^{2+} transporter protein that associates with FATP4, an acyl-CoA synthetase critical for epidermal lipid processing that is implicated in ichthyosis prematurity syndrome (see below)[52]. Ichthyosis may result from disrupted lipid envelope formation due to a lack of sphingolipid end products. Cytotoxic events due to accumulation of long-chain free fatty acids that disrupt processing and transport of intracellular membrane components may also play a role.

Approximately 5%–10% of individuals with ARCI harbor mutations in ***CYP4F22***, which encodes a *cytochrome P450 enzyme* involved in the ω-hydroxylation of ultra-long-chain fatty acids to form acylceramides. The latter are important to skin barrier function[34,52,53]. Affected individuals have a mild form of LI or CIE, with a variable collodion membrane at birth and palmoplantar hyperlinearity[54]. Ultrastructurally, the stratum corneum shows fragmented and disorganized lamellar lipid bilayers and entombment of lipids and lamellar bodies[55].

ARCI is occasionally caused by mutations in ***CERS3*** which encodes *ceramide synthase 3*. This enzyme is involved in the synthesis of ultra-long-chain, epidermis-specific ceramides. Affected individuals often present with a collodion membrane and develop a prematurely aged appearance of the skin, generalized gray–brown scales, mild erythema, and palmoplantar hyperlinearity[9,56].

Mutations in the gene that encodes *patatin-like phospholipase domain-containing 1* (***PNPLA1***), an enzyme involved in acylceramide biosynthesis, account for ~5% of ARCI overall. This form of ARCI is more common in northern Africa, Spain, and Iran, where common founder mutations or consanguinity may result in pseudo-dominant inheritance[57,58]. Affected individuals have relatively mild generalized scaling, along with scalp involvement and variable erythema; approximately half are born with a collodion membrane. Occasional manifestations include a cyclic course, palmoplantar hyperlinearity, and sharply demarcated erythrokeratodermic plaques.

Loss-of-function variants in *cholesterol sulfotransferase* (***SULT2B1***), which encodes a cytosolic enzyme involved in the sulfoconjugation, synthesis and metabolism of steroids, may lead to LI with variable mild erythema and often a collodion presentation. Sparing of the skin folds and face (reminiscent of steroid sulfatase deficiency) and thickened, scaly gray plaques over large joints and in areas of friction distinguish this form of ARCI[18].

Mutations in *short chain dehydrogenase/reductase family 9C member 7* (***SDR9C7***), which contributes to skin barrier function via the covalent binding of acylceramides to the cornified cell envelope, can underlie a mild form of ARCI. Affected individuals present with generalized scaling with variable erythema and PPK; recurrent fungal infections of the skin and nails have been reported[59]. This ichthyosis tends to spare face and scalp, and it lessens in severity with age.

Pathogenic variants in *lipase N* (***LIPN***) can result in childhood-onset ichthyosis with generalized fine white scales but minimal erythema. This gene accounts for ~5% of Israeli families with nonsyndromic ARCI[47].

Lastly, *ichthyosis prematurity syndrome* (IPS), a clinically distinct form of ARCI first described in Scandinavia, results from mutations in *solute carrier family 27 member 4* (***SLC27A4***; see Table 57.1)[60–62]. The protein product of *SLC27A4* is FATP4 (fatty acid transport protein 4), which acts as an acyl-CoA synthetase and functions in the formation of very-long- and ultra-long-chain fatty acids. Its dysfunction leads to disruption of acylceramide production and skin barrier defects. Of note, FATP4 interacts with NIPAL4 and TGM1 in lipid metabolism and processing[63].

FATP4 is preferentially expressed in fetal murine epidermis, while the related FATP1 predominates in adult murine epidermis. If this pattern is also true for human skin, rescue of FATP4 deficiency by upregulation of another fatty acid transport protein after birth could explain the distinct clinical features and course of IPS. Clinically, hallmarks of IPS are premature birth, neonatal asphyxia, and massive verrucous or spiky hyperkeratosis favoring the scalp, forehead, and trunk. The hyperkeratosis resolves during the neonatal period, transitioning to mild generalized scaling and follicular keratoses[60].

COLLODION BABY

Synonyms: ■ Collodion fetus
Self-improving collodion ichthyosis/baby: ■ Self-healing collodion baby ■ Lamellar exfoliation of the newborn

Epidemiology

The collodion baby is a shared presentation of several congenital ichthyoses, most with autosomal recessive inheritance. It is not a distinct disorder.

Pathogenesis

The pathomechanisms leading to formation of a collodion membrane are not completely understood, but this presentation points to disturbed adaptation of the fetal epidermis to postnatal life. The most common causes of collodion ichthyosis are deficiencies of the crucial cross-linking enzyme TGM1[64] or various lipid-processing enzymes and lipid transporters. This includes *ALOX12B* (>*ALOXE3*), *CERS3*, *PNPLA1*, and *SULT2B1* (see ARCI). Less common etiologies are fatty aldehyde dehydrogenase deficiency in Sjögren–Larsson syndrome, deficiency of an activator of the adipose triglyceride lipase in neutral lipid storage disease, and β-glucocerebrosidase deficiency in Gaucher disease (see Fig. 56.2).

In ~10% of collodion babies[12], a milder "self-healing" phenotype known as *self-improving collodion ichthyosis* occurs. This has been reported in association with *TGM1, ALOX12B, ALOXE3*, *NIPAL4*, or *CYP4F22* mutations that fully inactivate the encoded protein *in utero* but not after birth[46,65]. It has been postulated that this "dynamic" phenotype is dependent on environmental conditions, which influence the stability of the mutant protein. A form of self-improving collodion ichthyosis in which membranes are localized to acral areas due to compound heterozygous *TGM1* mutations has also been described[66].

Clinical Features

Collodion babies are often born prematurely and small for gestational age, and they have increased perinatal morbidity and mortality. At birth, the neonate is covered with a taut, shiny, transparent membrane formed by the thickened stratum corneum, which resembles a plastic wrap (Fig. 57.10). Its tautness often leads to ectropion, eclabium, and hypoplasia of nasal and auricular cartilage. Sucking and pulmonary ventilation may also be impaired, resulting in dehydration, malnutrition, hypoxia, and pneumonia. After birth, the parchment-like membrane gradually dries, cracks, and breaks up. In the process, fissures develop that impair epidermal barrier function, which can lead to percutaneous loss of water and permit the entry of microorganisms; fluid and electrolyte imbalances, skin infections, and sepsis may follow. In addition, circular bands of hardened skin can lead to vascular constriction, ischemia, and distal edema. Growth hormone resistance and an increased prevalence of hypothyroidism have also been described.

Within two to four weeks after birth, the membrane peels off in sheets and a transition to the underlying disease phenotype takes place. Most commonly, CIE or LI ensues. Other ichthyoses may rarely present as a collodion baby (Table 57.4). In self-improving collodion ichthyosis, desquamation of the collodion membrane leaves normal skin or variable clinical findings including xerosis, fine or focal scaling, palmar hyperlinearity, mild PPK, red cheeks, and hypohidrosis[65].

Pathology

Light and electron microscopic abnormalities of the collodion membrane are nonspecific and reveal mostly an excessively thickened,

DIFFERENTIAL DIAGNOSIS OF A COLLODION BABY	
Disorder	**Frequency**
Self-improving collodion ichthyosis	Always
Lamellar ichthyosis	Common
Congenital ichthyosiform erythroderma	Common
Trichothiodystrophy	Fairly common
Sjögren–Larsson syndrome	Rare
Infantile Gaucher disease	Rare
Ichthyosis, intellectual disability, and spastic quadriplegia	Rare
Ichthyosis with confetti	Very rare
Autosomal dominant lamellar ichthyosis	Very rare
Neutral lipid storage disease	Very rare
Male *EBP* disorder with neurologic defects (MEND) syndrome	Very rare
Ectodermal dysplasias (EDs)*	Very rare
*e.g. hypohidrotic ED or ankyloblepharon–ED–clefting (AEC) syndrome.	

Table 57.4 Differential diagnosis of a collodion baby. A collodion membrane has also been described in a patient with neonatal inflammatory skin and bowel disease due to a homozygous ADAM17 mutation.

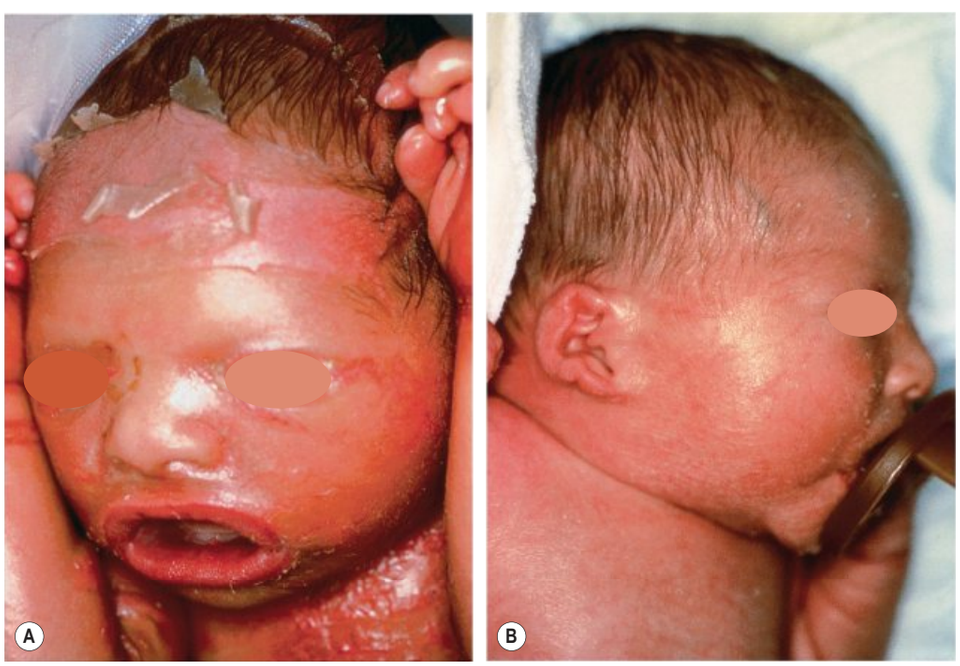


Fig. 57.10 Collodion baby. A Day 1 with eclabium. **B** Day 8 with erythema and diffuse mild scaling and misshapen ears.

orthokeratotic stratum corneum. Therefore, it is usually preferable to perform multigene molecular testing or to defer a skin biopsy until transition to the underlying disease phenotype occurs. At that time, immunostaining can demonstrate the presence or absence of TGM1 protein in the upper epidermis[67]. *In situ* assays of transglutaminase activity can also be performed on skin biopsy sections and allow rapid identification of patients with TGM1 deficiency, even as a collodion baby[67]. However, interpretation of the transglutaminase activity assay requires experience, and this test is not widely available.

Differential Diagnosis

The phenotype of harlequin ichthyosis is much more severe and so striking that a clinical distinction between the two disorders is, in most circumstances, not difficult.

Treatment

Collodion babies are at risk for thermoinstability, hypernatremic dehydration, skin infections, and sepsis. It is therefore essential to keep them in a controlled environment and to carefully monitor for fluid and electrolyte imbalances. Collodion babies are also at risk for pneumonia secondary to restricted ventilation and aspiration of amniotic fluid containing scales. To facilitate gradual desquamation of the collodion membrane, it is generally recommended that infants be placed in a humidified incubator and the skin treated with wet compresses and light emollients to increase its elasticity and pliability. Manual removal of the collodion membrane and use of topical keratolytic agents are not advisable because of the increased risk of infections and percutaneous absorption. Distal constriction bands occasionally require surgical release. Systemic retinoid therapy is rarely necessary but may be of benefit in selected cases of delayed membrane shedding or severe underlying ichthyosis[11].

LAMELLAR ICHTHYOSIS

Synonyms: ■ Non-erythrodermic autosomal recessive lamellar ichthyosis ■ Ichthyosis congenita type 2

Clinical Features

Classic LI is typically a severe disorder that is apparent at birth and persists throughout life, although milder variants also occur. Most affected neonates are encased in a collodion membrane that is gradually replaced over the first few weeks of life by large scales in a generalized distribution. These large, brown, plate-like scales form a mosaic or bark-like pattern, and there is minimal to no associated erythroderma (Fig. 57.11A,B). The scales are centrally attached and have raised borders, often leading to superficial fissures. "Bathing suit ichthyosis", which is caused by temperature-sensitive *TGM1* mutations, affects primarily the trunk and scalp; it was first reported in South Africans and subsequently described in individuals from around the world[68].

Tautness of facial skin commonly results in ectropion (Fig. 57.11C), eclabium, and hypoplasia of nasal and auricular cartilage. Severe ectropion may lead to lagophthalmos, madarosis, conjunctivitis, and ensuing corneal exposure and keratitis. Traction and compression exerted by the taut skin can cause scarring alopecia, especially at the periphery of the scalp. Although hair shafts are normal, they are often encased by the thickened stratum corneum. At least half of individuals with LI have PPK, which can range from accentuated skin markings to severe thickening with cracking and fissuring. Secondary nail dystrophy with thickened nail plates and ridging sometimes develops. Intraepidermal constriction of sweat ducts often results in severe heat intolerance, while accumulation of scale in the external ear canals can lead to occlusion, bacterial colonization, and recurrent infections.

Pathology

The histologic abnormalities are not diagnostic. Massive orthokeratotic hyperkeratosis covers an acanthotic epidermis, sometimes with psoriasiform or papillomatous hyperplasia. In contrast to CIE, the epidermal proliferation rate is normal or only slightly elevated. Elongated cholesterol clefts, variable numbers of translucent lipid droplets in the stratum corneum, and a thin or absent cornified cell envelope have been observed by electron microscopy, although these findings overlap with those of CIE[69].

Other diagnostic tests

In addition to measuring TGM1 activity in cultured keratinocytes, procedures to detect TGM1 deficiency in skin biopsy specimens include immunostaining with anti-TGM1 antibodies, *in situ* measurement of TGM1 activity (via covalent incorporation of biotinylated substrate peptides into skin cryostat sections)[67], and testing for the presence of cross-linked cell envelopes[70]. However, these assays are not widely available for diagnostic purposes.

Massively parallel (next-generation) sequencing panels that include the genes associated with ARCI have a diagnostic yield of >85%[9,34,39]. Alternatively, single-gene testing starting with *TGM1* can be considered, especially in patients with classic LI. ARCI patients with a collodion membrane at birth, plate-like scale, ectropion, and/or alopecia are approximately four times more likely to have *TGM1* mutations than those without at least one of these features[37]. Establishing a molecular diagnosis not only enables genetic counseling and family planning but can also provide prognostic information and help direct therapy. In families with known mutations, molecular prenatal diagnosis may be performed utilizing samples of chorionic villi, amniotic fluid, or circulating fetal cells obtained at an early gestational age[10].



Fig. 57.11 Lamellar ichthyosis. **A** Large, plate-like scales on the lower extremities forming a tile-like pattern. **B** Brown scales of various sizes with accentuation on the neck and in the axilla. **C** Obvious ectropion as well as plate-like scales. *B, Courtesy Julie V. Schaffer, MD.*

Differential Diagnosis

In the neonatal period, there is considerable clinical overlap of LI with other congenital ichthyoses that present with a collodion membrane, especially CIE and self-improving collodion ichthyosis (see Tables 57.3 and 57.4). Later in life, the large, dark, plate-like scales, ectropion, and no discernible erythroderma of LI can be readily distinguished from most other ichthyoses. Of note, a rare autosomal dominant form of LI with prominent PPK can occur due to heterozygous mutations in *ASPRVI* (aspartic peptidase retroviral-like 1), which encodes a protease important for profilaggrin processing[71]. Although classic CIE is differentiated by marked erythroderma and small white scales, some patients exhibit intermediate LI/CIE phenotypes with variable degrees of erythroderma as well as quality and size of scales.

Treatment

Neonatal care is detailed in the collodion baby section. Severe disease often necessitates oral retinoids from early childhood. Treatment is usually initiated at a low dose and then titrated to the minimal effective dose, which is dictated by the course and severity of the disease[11,25]. In addition to alleviating hyperkeratosis and scaling, there may be improvement of the ectropion, thus avoiding eye complications and reconstructive eyelid surgery. However, the benefits of long-term systemic retinoid therapy must be weighed against the potential toxicities. Of note, liarozole, a retinoic acid metabolism blocking agent that is not available in the US, had a similar efficacy to acitretin but with a more favorable tolerability profile[72]. In a randomized controlled study of 64 patients with moderate-to-severe LI, a 40%–50% response rate was observed in patients receiving liarozole, compared to 11% with placebo (p=0.056)[73].

Topical management strategies should take into consideration the severely impaired desquamation and barrier function of the skin as well as the patient's age and preferences. Addition of sodium bicarbonate to bath water (e.g. 2 handfuls of baking soda in a half-full standard tub) to raise the pH to ~7.9 one to three times weekly may facilitate scale removal. The use of keratolytics is often limited due to skin irritation and an increased risk of systemic absorption, especially in children; systemic absorption of topical tacrolimus and vitamin D_3 derivatives can also occur. Topical calcipotriene (calcipotriol), tazarotene, and formulations combining either lactic acid with propylene glycol or urea with N-acetylcysteine may be of benefit[52,74]. A topical isotretinoin formulation is currently under investigation in patients with LI.

Systemic therapies targeting interleukin (IL)-17 (e.g. secukinumab) or IL-12/23 (e.g. ustekinumab) may suppress the Th2-associated inflammation that has been documented in patients with ARCI. Because these antibodies have little impact on scaling, their potential benefit is greater for CIE than for LI[75]. Notably, in a small randomized controlled study of adults with several types of erythrodermic ichthyosis (ARCI, EI, Netherton syndrome), treatment with secukinumab for 16 weeks did not significantly decrease Th2-related biomarkers or disease severity[75]. Topical enzyme replacement (e.g. recombinant human TGM1) and acylceramide supplementation are being investigated as treatment strategies for ARCI, and a clinical trial of topical gene therapy utilizing a replication-defective herpes simplex virus type 1 vector encoding human TGM1 is underway in patients with TGM1-deficient ARCI[52,76].

Heat intolerance can be ameliorated by frequent moistening of the skin with water or the use of air conditioning and humidifiers. Severe ectropion requires longitudinal ophthalmologic evaluation. Surgical repair and/or topical retinoids (e.g. tazorotene) can be used to prevent irreversible corneal damage.

Because LI and other severe forms of ARCI are often disfiguring, they may hinder the psychosocial development of affected children and adolescents. An increased risk of depression and reduced quality of life scores have been reported. Families and patients need to be supported, and patient advocacy groups such as FIRST (www.firstskinfoundation.org) are excellent resources.

CONGENITAL ICHTHYOSIFORM ERYTHRODERMA

Synonyms: ■ Non-bullous congenital ichthyosiform erythroderma ■ Erythrodermic autosomal recessive lamellar ichthyosis ■ Ichthyosis congenita type 1

Clinical Features

CIE usually presents at birth with either erythroderma or a collodion membrane, followed by generalized erythroderma and scaling that remain throughout life. The clinical features of CIE tend to be milder than those of classic LI, but there is variability in the intensity of erythema as well as the size and type of scale. In severely affected patients, CIE is characterized by an intense, bright red erythroderma; generalized white, small scales with a "powdery" consistency (Fig. 57.12); and additional findings such as ectropion and scarring alopecia. Scales may become larger, darker, or plate-like, especially on the extensor surface of the lower extremities. The palms and soles

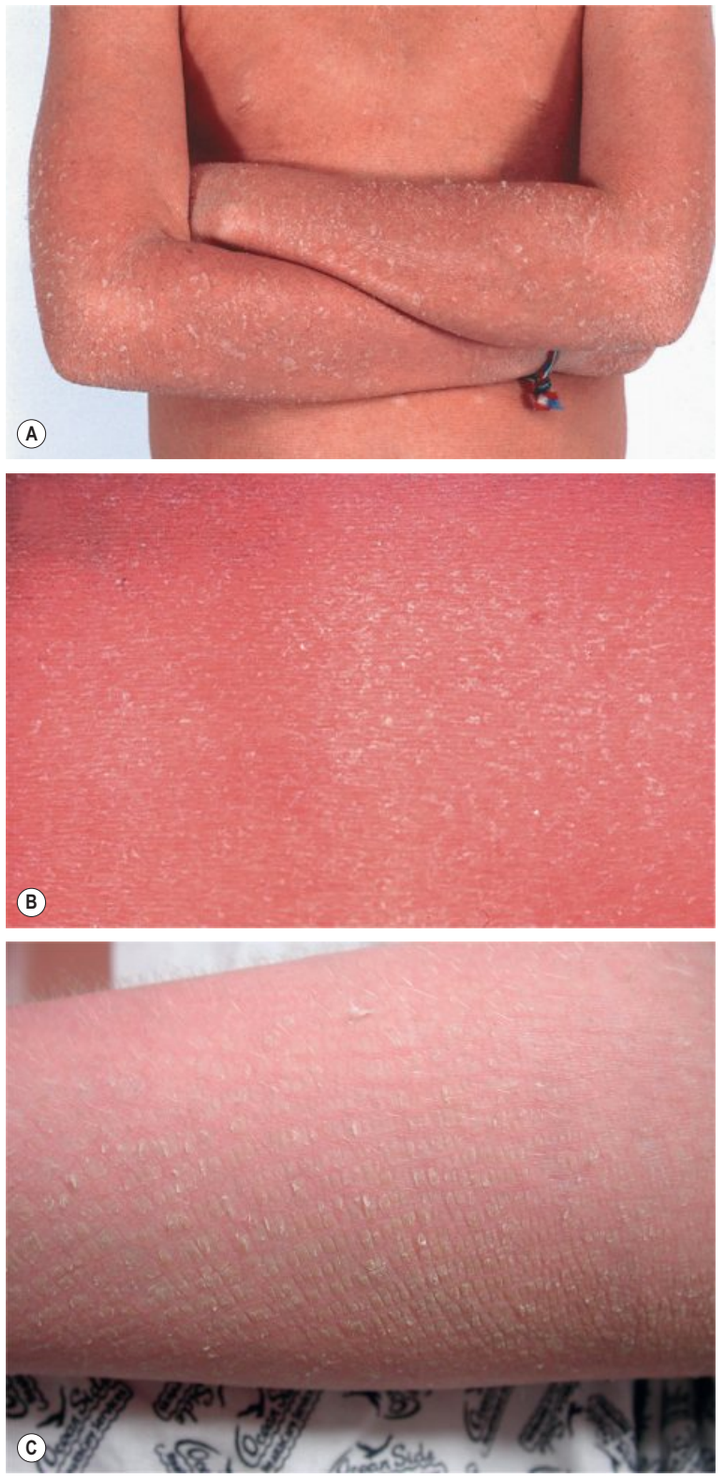


Fig. 57.12 Congenital ichthyosiform erythroderma. A Intense redness and fine, flaky, white scale on the trunk and arms. Close-up of fine white (**B**) and coarser yellowish (**C**) scale in a background of prominent erythema. *A, Courtesy S.J. Bale, PhD and J.J. DiGiovanna, MD.*

are often severely affected with a diffuse, fissuring keratoderma that contrasts with the fine, translucent scales elsewhere on the body; palmoplantar hyperlinearity is observed in some subtypes. Patients with milder disease exhibit less intense erythroderma and scaling, although the latter still tends to be generalized, and they have variable palmoplantar involvement.

Obstruction of sweat ducts and pores often results in hypohidrosis and heat intolerance. Secondary nail dystrophy, onychomycosis, and digital flexion contractures are not uncommon. Severe exfoliative erythroderma can cause metabolic stress in growing children, and failure to meet their high caloric needs can lead to growth retardation[77]. However, most children with CIE have normal growth and development. Adults with CIE may have an increased risk of developing cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), so longitudinal skin surveillance should be considered[78].

Pathology

The histopathologic and ultrastructural features of CIE are non-diagnostic. Compared to LI, there is more parakeratosis (focal or extensive) and the acanthosis is typically more pronounced and accompanied by hypergranulosis. Unlike LI, the epidermal cell turnover rate in CIE is markedly increased. Ultrastructural abnormalities in CIE include an increased number of lamellar bodies, an accumulation of lipid droplets in the stratum corneum (often more prominent than in LI), and disorganized intercellular lipid lamellae. While characteristic of CIE, these findings overlap with those seen in LI and other hyperproliferative epidermal disorders[79].

Other diagnostic tests

As in LI, TGM1 deficiency can be detected by immunostaining or assessing the activity of this enzyme in skin biopsy specimens. Genetic testing utilizing multigene panels is the only reliable method for distinguishing the different forms of CIE. Prenatal molecular diagnosis is possible when disease-causing mutations have been identified in family members.

Differential Diagnosis

A collodion membrane at birth requires consideration of LI, self-improving collodion ichthyosis, and other forms of ichthyosis (see Tables 57.3 and 57.4). After transition to the ichthyosis phenotype, pronounced erythroderma and fine white scales in classic CIE differentiate it from classic LI, which is characterized by less erythema, large dark scales, and more frequent ectropion, eclabium, and scarring alopecia. However, many intermediate phenotypes with variable degrees of erythema and size and quality of scale exist. As noted below, harlequin ichthyosis survivors typically develop an extremely severe CIE-like phenotype. A variety of clinical, histologic, and laboratory findings differentiate CIE from other erythrodermic forms of ichthyosis, including syndromic as well as nonsyndromic conditions (see Tables 57.1 and 57.2 and Fig. 57.1).

Treatment

A summary of therapeutic strategies is provided above in the section on LI. Erythrodermic patients have a special need for increased intake of fluids, calories, iron, and protein to balance substantial loss through the skin, which can be 3–10 times higher than normal[77]. Therapy with oral retinoids can reduce scaling, but it is less beneficial in suppressing the erythroderma.

HARLEQUIN ICHTHYOSIS

Synonyms: ■ Harlequin baby ■ Harlequin fetus ■ Ichthyosis congenita gravior

History

This most extreme and distinct form of ARCI was described as early as 1750 by the Reverend Oliver Hart. In 1900, Riecke recognized the histopathologic features of dramatic thickening of the stratum corneum and follicular hyperkeratosis, and he distinguished this disorder from other types of congenital ichthyosis. "Harlequin" refers to the resemblance of the facial features and diamond-shaped scales in affected neonates to the costume of the comic servant character with this name. Initially called a "harlequin fetus" because of the premature delivery and fatal outcome, increasing survival rates due to improved neonatal care and systemic retinoid treatment have resulted in evolution to the terms "harlequin baby" and (currently) "harlequin ichthyosis" (HI).

Epidemiology

This rare disorder has an estimated incidence of 1 in 300 000 births and is inherited in an autosomal recessive manner. HI has been reported in patients with a wide variety of ethnic backgrounds[80].

Clinical Features

Individuals with HI are usually born prematurely (mean gestational age, 35 weeks) and may die within a few days or weeks because of respiratory insufficiency or sepsis[80]. Affected neonates are encased in a hard, armor-like, tremendously thickened stratum corneum that results in severe immobilization and restricts ventilation. Shortly after birth, the hyperkeratotic cast cracks and forms large, yellow, adherent plates separated by broad, deep, intensely red fissures (Fig. 57.13). Increased transcutaneous loss of water and heat results in dehydration, electrolyte imbalances (e.g. hypernatremia), and temperature instability. The latter may impede recognition of skin infections or sepsis, which are promoted by the large fissures.

The tautness of the skin results in marked eversion of the eyelids (ectropion) and lips (eclabium), rudimentary development of ear and nasal cartilage, and sometimes microcephaly, giving the face an extremely distorted appearance. The hands and feet are edematous and swollen, often covered by a mitten-like casing. Although the digits are well developed, autoamputation due to constricting skin bands occasionally occurs. Eyelashes and eyebrows are usually missing, while scalp hair may be present. Eclabium and taut facial skin prohibit effective suckling by the infant.

Over the past two decades, improved postnatal care and oral retinoid therapy have led to prolonged survival in an increasing number of HI patients. More than half of affected individuals now live beyond the neonatal period, with the oldest HI patient to date being >25 years of age[80]. All survivors develop a severe, exfoliative ichthyosiform erythroderma, and half have a painful PPK; dystrophic nails (e.g. small, thickened) and poor hair growth are also common. Complications in these patients include recurrent skin infections, reduced sweating with heat intolerance, ocular problems related to persistent ectropion, chronic constipation, vitamin D deficiency, anemia, arthralgias, arthritis, and joint contractures[80]. Affected children often have delayed growth and development of motor skills, while intelligence is normal[34].



Fig. 57.13 Harlequin ichthyosis. Severe hyperkeratosis with fissuring as well as eclabium and ectropion. *Reproduced from Morillo M, Novo R, Torrelo A, et al. Feto arlequin. Actas Dermosifiliogr 1999;90:185–7.*

Pathology

The histologic hallmark is an extraordinarily thickened and compact orthokeratotic stratum corneum, although parakeratosis is occasionally observed. Hair follicles and sweat ducts have prominent hyperkeratotic plugging. Ultrastructural features include abnormal or missing lamellar bodies in the granular layer, absent extracellular lipid lamellae, and the presence of lipid inclusions or remnant organelles in the stratum corneum[44]. However, similar findings may be found in other forms of ARCI. Hair follicles show concentric accumulation of keratotic material around hair shafts, a highly characteristic feature that was historically used to establish the diagnosis based on prenatal skin biopsy specimens obtained in the second trimester[81].

Other diagnostic tests

Molecular diagnosis and prenatal testing are available for HI families. Ultrasonography can establish the diagnosis in affected fetuses during the last trimester of pregnancy based on facial features, acral edema, intrauterine growth retardation, polyhydramnios, and the "snowflake sign" due to floating scales in the amniotic fluid[80,82].

Differential Diagnosis

The clinical presentation of HI at birth is striking and highly characteristic. Hyperkeratosis and associated abnormalities, such as ectropion and eclabium, are usually much milder in collodion babies. However, the clinical findings in children and adults with HI overlap with severe forms of CIE. The facial features and taut, scaling skin in Neu–Laxova syndrome may be reminiscent of HI, but this rare autosomal recessive disorder also features microcephaly, lissencephaly (few and shallow convolutions of the brain), syndactyly, and other congenital malformations.

Treatment

HI remains a life-threatening and often fatal disorder, and survivors require long-term multidisciplinary management[80,82]. During the neonatal period, intensive care is needed to provide sufficient nutrition; monitor and manage body temperature and pain; correct fluid and electrolyte imbalances; and prevent and treat respiratory dysfunction, pneumonia, or sepsis. Severe ectropion necessitates ophthalmologic care. Infants should be kept in humidified incubators and treated with wet wraps and light emollients. Early administration of systemic retinoids, in particular acitretin, usually with an initial dose of 0.5–1 mg/kg once daily, has been shown to result in shedding of the large, keratotic plates within weeks as well as improvement of the ectropion and eclabium[80,82]. Subsequent titration to the lowest effective dose is recommended. It is important to discuss the overall prognosis, therapeutic options, and potential medication side effects with each family before beginning treatment.

SYNDROMIC ICHTHYOSES

NETHERTON SYNDROME

Synonyms: ■ Comèl–Netherton syndrome ■ Ichthyosis linearis circumflexa ■ Trichorrhexis invaginata

History

Comèl, an Italian dermatologist, first described the clinical features of ichthyosis linearis circumflexa in 1949. Netherton, an American dermatologist, subsequently discovered a hair shaft abnormality that he termed "bamboo hair" in a child with a CIE phenotype. Wilkinson et al.[83] delineated the triad of congenital ichthyosis, trichorrhexis invaginata, and atopy as "Netherton syndrome" in 1964. It was later recognized that this disorder encompasses different cutaneous presentations including ichthyosiform erythroderma, localized ichthyosis linearis circumflexa, and continuous skin peeling[84].

Epidemiology

Netherton syndrome (NTS) is an autosomal recessive disorder that occurs worldwide, with a higher prevalence in inbred populations. Considering the phenotypic variability and clinical overlap with atopic dermatitis as well as other forms of ichthyosis, it has been estimated that the incidence of NTS might be as high as 1 in 50 000[84]. In one series, 18% of patients who presented with erythroderma during the neonatal period had NTS[85].

Pathogenesis

NTS is caused by biallelic mutations in the serine protease inhibitor Kazal type 5 gene (*SPINK5*)[86,87]. Approximately 100 *SPINK5* mutations have been identified to date, with functional null alleles in ~65% of cases and missense mutations that compromise enzyme function in the remainder.

SPINK5 encodes the multi-domain serine protease inhibitor LEKTI that is expressed in the lamellar granules of epithelia and lymphoid tissues. A lack of functional LEKTI leads to uncontrolled activity of serine proteases, and NTS patients have an up to five-fold increase of trypsin-like proteolytic activity in their stratum corneum[88]. This disturbs the regulation of lipid-processing enzymes, which are critical to proper formation of the lamellar lipid bilayer system in the stratum corneum. Hastened degradation of desmoglein 1 results in disintegration and shedding of horny cells, ultimately producing superficial clefts within the stratum corneum and severely disrupted skin barrier function[89]. In addition, LEKTI deficiency leads to a loss of crucial anti-inflammatory and antimicrobial mechanisms in the skin.

Histochemical analysis of hair shafts in NTS demonstrates a reduced number of disulfide bonds, which is suggestive of diminished cross-linkage of hair keratin structures and a weaker coherence of cortical cells. Such focal softening of the hair shaft may allow intussusception of the distal shaft into the dilated proximal cup.

Clinical Features

NTS presents in most (but not all) patients at or soon after birth with CIE-like generalized erythroderma and scaling or with continuous peeling of the skin (Fig. 57.14A). A collodion membrane is not a feature of NTS. Approximately 20% of neonates develop potentially fatal complications such as hypernatremic dehydration, electrolyte imbalances, perturbed thermoregulation, failure to thrive, pneumonia, and sepsis. In patients with severe disease, generalized ichthyosis and erythroderma persist throughout life (Fig. 57.14B–D). However, in the majority of patients, the ichthyosis gradually evolves into serpiginous or circinate scaling and erythematous plaques, which are bordered by a peculiar double-edged scale and descriptively named "ichthyosis linearis circumflexa" (ILC; Fig. 57.15). The plaques are usually distributed on the trunk and extremities and change over time in size, shape, and location, reflecting the undulating course of NTS. The lesions are pruritic, and many patients develop eczematous plaques and/or lichenification in flexural sites, especially the wrists and antecubital and popliteal fossae. Scalp involvement with thick scale is common.

Hair shaft abnormalities usually develop during infancy and early childhood and improve with age, but they vary tremendously in the age of onset, extent, severity, and type. While in some patients the scalp hair grows slowly and is sparse, thin, and fragile, it has a normal appearance in others. Light microscopic examination of clipped hair from the scalp and (of particularly high yield) the eyebrows often reveals trichorrhexis invaginata (bamboo hair) with a ball-and-socket appearance (Fig. 57.16) or nodular thickening of the distal end of broken hair shafts ("golf tee", "matchstick"). Multiple additional abnormalities may be observed, including pili torti, trichorrhexis nodosa, and "helical" hair. Eyelashes and secondary sexual hair can also be affected.

The third characteristic feature of NTS is immune dysregulation that involves memory B, T, and NK cells, resulting in atopic manifestations as well as susceptibility to infections. There is increased secretion of both interferon-γ and tumor necrosis factor by T and NK cells, and the proportion of activated B cells correlates with frequency of bacterial skin infections. Serum levels of IgE are usually markedly elevated, ranging from 100 to >10 000 IU/ml. Eosinophilia and allergic



Fig. 57.14 Netherton syndrome. A, B Generalized involvement with features of congenital ichthyosiform erythroderma in an infant (**A**) and child (**B**). **C** Close-up showing "peeling" quality of the scale. **D** Short, thin hair on the scalp, sparse eyebrows, and a lack of eyelashes.



Fig. 57.15 Ichthyosis linearis circumflexa. Note the double-edged scale. *Courtesy Antonio Torrelo, MD.*

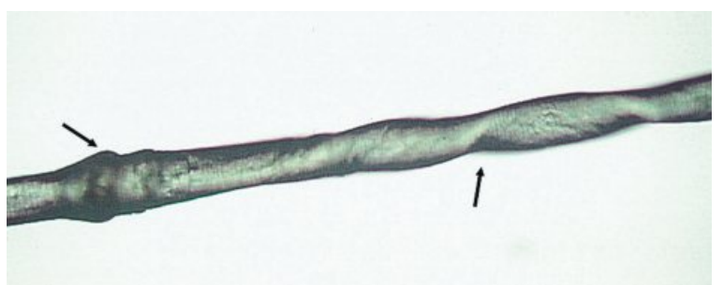


Fig. 57.16 Abnormal hair shaft in Netherton syndrome. Trichorrhexis invaginata with its ball-and-socket appearance (left arrow) and twist in the hair shaft (right arrow).

reactions to foods and other antigens are common, with clinical manifestations ranging from urticaria and angioedema to anaphylactic shock. Increased IL-17 signaling has been described in NTS and other ichthyoses (e.g. EI, LI, CIE), and clinical studies of IL-17 or IL-12/23 blockade are underway[90].

Patients with NTS often develop recurrent respiratory tract and staphylococcal skin infections, and they are at increased risk of sepsis[91]. Human papilloma virus (HPV) infections are frequent and can result from epidermodysplasia verruciformis-associated HPV types. HPV infections may increase the incidence of SCC of the anogenital area or other cutaneous sites in these patients. Development of multiple SCCs and BCCs in the third decade of life has been described[92].

During infancy and early childhood, patients with generalized skin involvement often continue to experience failure to thrive, which may be related to an enteropathy with villus atrophy as well as the increased caloric needs associated with erythroderma; this often results in short stature[93]. Intermittent aminoaciduria can occur, and a few patients with substantial developmental delay have been reported[94].

Pathology

On light microscopic examination, the epidermis shows pronounced parakeratotic hyperkeratosis with a diminished or absent granular layer, acanthosis, and papillomatosis. There are often dense, almost band-like, lymphohistiocytic perivascular infiltrates in the papillary dermis. Subcorneal clefting, spongiosis, exocytosis, and Munro microabscesses can occur. Trichorrhexis invaginata, in which the distal hair shaft is telescoped into the proximal segment, is a highly characteristic light microscopic finding in clipped hairs; other hair shaft abnormalities may also be evident (see above). A band-like pattern in hairs with polarized microscopy has also been described[95]. Trichoscopy of eyelashes and eyebrow hair may also reveal a "matchstick" or "golf tee" appearance.

Ultrastructural abnormalities in the epidermal lipid system that are not present in other erythrodermic disorders have historically assisted in differentiating NTS from CIE and erythrodermic psoriasis. Premature secretion of lamellar body contents in the upper epidermis as well as the presence of intercellular electron-dense accumulations and abnormal splitting in the superficial stratum corneum are specific for NTS and represent indicators of accelerated desquamation[89,96]. Other variable ultrastructural abnormalities include round cytoplasmic inclusion bodies in the upper cell layers, a decreased tonofilament–desmosome system, and a lack of lamellar bodies.

Other diagnostic tests

Molecular testing of *SPINK5* can facilitate diagnosis of NTS, and prenatal diagnosis may be performed in families with known *SPINK5* mutations[87]. In addition, immunostaining of skin biopsy specimens with anti-LEKTI antibodies can be used to determine absence or aberrant distribution of LEKTI protein in the epidermis[97].

Differential Diagnosis

During infancy, NTS often presents a diagnostic challenge due to its clinical overlap with CIE, erythrodermic psoriasis, and other primary immunodeficiencies. Although the presence of trichorrhexis invaginata and other hair shaft abnormalities can distinguish NTS from these conditions, characteristic hair shaft abnormalities may not be present at birth or in early infancy, and their detection requires repeated analysis of many hairs from different locations (e.g. scalp, eyebrows). Elevated serum IgE levels can also help to differentiate NTS from CIE and psoriasis.

Autosomal dominant hyper-IgE syndrome (AD-HIES) also features elevated serum IgE levels in association with atopic-like dermatitis and recurrent skin and respiratory tract infections. However, AD-HIES presents with a neonatal papulopustular eruption rather than erythroderma, and eventually characteristic facial, dental, and skeletal anomalies that are not seen in NTS develop. Other primary immunodeficiencies characterized by erythematous, scaly skin and elevated IgE levels include Wiskott–Aldrich, Omenn, and IPEX (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked) syndromes (see Ch. 60). Infants with failure to thrive and generalized eczematous or scaling skin require a comprehensive immunologic evaluation.

In acrodermatitis enteropathica, erythematous, sometimes figurate plaques with scale-crust are usually restricted to periorificial areas and the distal extremities (see Ch. 51). If zinc deficiency cannot be excluded with certainty, an empirical trial of zinc treatment is indicated. The migratory, serpiginous plaques of ichthyosis linearis circumflexa can also resemble those seen in erythrokeratodermia variabilis. Prominent borders with a double-edged scale and associated hair shaft abnormalities are specific for NTS, while transient, variable erythematous patches are characteristic of erythrokeratodermia variabilis.

Peeling skin syndromes (PSSs) are clinically and genetically heterogeneous disorders characterized by perpetual peeling and desquamation of the skin with variable associated erythema (see Table 57.8). They share many features with NTS, including pruritus, congenital erythroderma in the generalized inflammatory subtype of PSS, and histologic and ultrastructural abnormalities. Although mutations in the corneodesmosin gene (*CDSN*) cause generalized inflammatory PSS[98], *SPINK5* mutations have been identified in some patients with erythroderma and generalized skin peeling[94].

Treatment

Treatment is symptomatic and should be adjusted to the patient's specific needs. Neonates with exfoliative erythroderma and severe impairment of skin barrier function often require management in an intensive care nursery. Patients who develop failure to thrive and enteropathy need nutritional support to ensure sufficient intake of calories and protein.

Topical emollients, keratolytics, retinoids, calcipotriene, and corticosteroids alone or in combination are variably effective. Although the skin lesions of NTS may respond to topical tacrolimus, dramatically increased percutaneous absorption of this medication has been described in NTS patients, due to their severe skin barrier dysfunction[99]. Use of topical tacrolimus therefore requires monitoring of plasma drug levels. Topical pimecrolimus has also been successfully used, with considerably less systemic absorption[100]. Topical or systemic antimicrobial agents are often required to treat bacterial and fungal skin infections, but continuous preventive antibiotic therapy (oral or topical) should be avoided because of the risk of developing antibiotic resistance. In NTS patients receiving intravenous immunoglobulin (IVIg) therapy, fewer infections, reduced skin inflammation, growth, weight gain, and improvement in some immune imbalances have been observed[91].

Sedating oral antihistamines may be helpful in decreasing pruritus. Systemic retinoids have variable efficacy, leading to dramatic improvement in some patients and exacerbation in others. Benefit from treatment with narrowband UVB, psoralen plus UVA (PUVA), UVA1, and balneophototherapy (broadband UVB plus saltwater baths) has been reported. Treatment with anti-IL-17 or IL-12/23 agents (e.g. secukinumab, ixekizumab, ustekinumab) have been reported to decrease skin inflammation, reduce flares of ILC, and improve pruritus in patients with NTS[101,102], although significant benefit was not observed in a small clinical trial that included patients with NTS (see above)[75]. Additional treatment approaches that are under investigation include TNF and IL-4/13 inhibitors, topical protein replacement, and kallikrein-related peptidase inhibitors. Exploration of gene therapy strategies utilizing *ex vivo* gene transfer and *in vivo* viral vectors is also in progress.

SJÖGREN–LARSSON SYNDROME

History

In 1957, Sjögren and Larsson[103] defined the clinical triad of congenital ichthyosis, gradually developing di- or tetraplegia, and intellectual disability as a distinct disorder in 28 Swedish patients. In 1988, Rizzo et al.[104] discovered an underlying deficiency in the oxidation of long-chain fatty acids due to malfunction of the fatty alcohol dehydrogenase : fatty aldehyde dehydrogenase enzyme complex. Subsequently, De Laurenzi et al.[105] identified the underlying defect in the fatty aldehyde dehydrogenase gene (*ALDH3A2/FALDH*).

Epidemiology

Sjögren–Larsson syndrome (SLS) is an autosomal recessive neurocutaneous disorder. It occurs worldwide with an estimated prevalence of ~1 in 250 000. It is most common in northern Sweden, where the carrier frequency is estimated to be 1.3%[103].

Pathogenesis

SLS is caused by a deficiency of the microsomal fatty aldehyde dehydrogenase enzyme (FALDH) due to mutations in *ALDH3A2*[105]. More than 140 distinct mutations, including whole gene deletions, have been identified to date. Mutation analysis of *ALDH3A2* has an almost 100% sensitivity in patients with a clinical diagnosis of SLS. A few mutations have a high allelic frequency in northern European and Middle Eastern populations due to a founder effect[106].

FALDH catalyzes NAD-dependent oxidation of long-chain aliphatic aldehydes into fatty acids. This pathway is important for the recycling of epidermal ceramides as well as the catabolism of ether glycerolipids and sphingolipids in the brain[107]. The symptoms of SLS result from membrane alterations due to accumulation of fatty alcohol- or fatty aldehyde-modified lipids and proteins. In addition, FALDH catalyzes steps that are downstream of the lipoxygenases (12R-LOX and eLOX)

in the hepoxilin pathway of arachidonic acid metabolism, which is modulated by NIPAL4. FALDH also degrades leukotriene B_4, and the accumulation of leukotrienes may contribute to pruritus in SLS patients.

Clinical Features

SLS presents at birth with varying degrees of erythema, hyperkeratosis, and scaling. Preterm birth is common, while collodion membrane and ectropion are rare. After infancy, the erythema tends to fade, while hyperkeratosis and scaling become more prominent and darker in color. The ichthyosis varies from fine, white scales to larger, plate-like scales to non-scaling, yellowish hyperkeratosis (Fig. 57.17). Predilection sites include the lower abdomen (especially around the umbilicus), the neck (especially the sides and nape), and flexural areas. Approximately 70% of patients develop PPK. Accentuated skin markings and lichenification of flexural areas are common. Almost half of SLS patients experience persistent pruritus, which often leads to excoriations.

An important diagnostic and almost pathognomonic finding in SLS is the presence of perifoveal glistening white dots in the ocular fundus, which represents a form of juvenile macular dystrophy (Fig. 57.18)[108]. These dots can be detected in many, but not all, patients during the first year of life, and they increase in number over time. Involvement of the CNS usually manifests at the end of the first year of life with delayed motor development, an abnormal gait, pyramidal signs, spasticity, and contractures. The lower extremities are usually more severely affected than the arms. The di- or tetraplegia is gradually progressive and accompanied by speech defects and mild to severe intellectual disability. Seizures are present in almost 40% of affected individuals, and MRI of the brain shows white matter disease in most patients. Other variable clinical features of SLS include superficial corneal defects and photophobia, dental and/or osseous dysplasia, and hypertelorism. Despite the multisystem manifestations, most patients have a normal life expectancy.



Fig. 57.17 Sjögren–Larsson syndrome. Yellowish-brown hyperkeratosis with accentuated skin markings. *Courtesy Julie V. Schaffer, MD.*

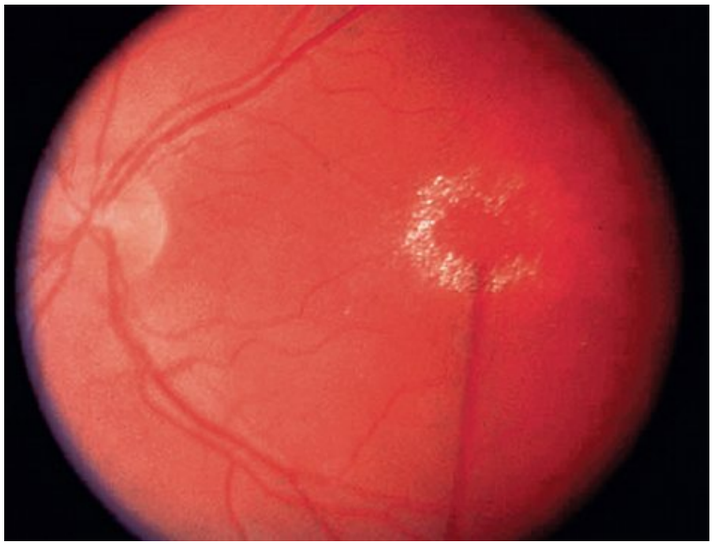


Fig. 57.18 Sjögren–Larsson syndrome. Perifoveal glistening white dots of the ocular fundus. *Courtesy William B. Rizzo, MD.*

Pathology

The histopathologic features are nonspecific and include primarily orthokeratotic hyperkeratosis, papillomatosis, and moderate acanthosis with a well-developed granular layer. Similarly, the ultrastructural abnormalities are not diagnostic. Keratinocytes may show mitochondrial proliferation and a prominent Golgi apparatus, with lamellar membranous inclusions and clefts in corneocytes.

Other diagnostic tests

Cultured skin fibroblasts, keratinocytes, and leukocytes have drastically reduced or absent FALDH activity. This assay also allows detection of unaffected carriers, who exhibit half of the normal levels. Another sensitive marker in SLS is the detection of elevated free fatty alcohols in cultured fibroblasts and plasma. However, these specialized tests are not widely available and the preferred method for confirming the diagnosis of SLS is DNA-based molecular testing. Prenatal molecular diagnosis can also be performed.

Differential Diagnosis

The combination of congenital ichthyosis with spasticity and retinal glistening dots is diagnostic for SLS, although ichthyosis, intellectual disability, and spastic quadriplegia can also result from biallelic *ELOVL4* mutations (see Table 57.2). The skin findings of SLS can overlap with those of steroid sulfatase deficiency, severe ichthyosis vulgaris, and mild forms of CIE or lamellar ichthyosis. In contrast to the latter two disorders, ectropion, eclabium, and alopecia are usually absent in SLS.

Treatment

Management of SLS requires a multidisciplinary approach, including dermatologic, neurologic, ophthalmologic, and orthopedic care as well as developmental support. Topical keratolytics and vitamin D preparations in combination with hydration of the skin are helpful in reducing hyperkeratosis and scaling. Systemic retinoids, especially acitretin, are effective and relatively safe even in children when a minimal effective dose is maintained and patients are monitored for side effects. Administration of a 5-lipoxygenase inhibitor (e.g. zileuton) to block the synthesis of leukotriene B_4 may decrease pruritus in some SLS patients (1 of 10 in a randomized controlled study) but does not improve the ichthyosis or CNS manifestations[109]. Topical application of the reactive aldehyde species inhibitor reproxalap is under investigation. Unfortunately, various forms of a fat-reduced diet have yet to provide consistent and reproducible results.

NEUTRAL LIPID STORAGE DISEASE WITH ICHTHYOSIS

Synonym: ▪ Chanarin–Dorfman syndrome

History

This disorder of lipid metabolism was first recognized as a distinct entity by Dorfman et al.[110] in 1974, and Chanarin et al.[111] coined the name in 1975.

Epidemiology

This is a rare autosomal recessive disorder. Most cases have been observed in consanguineous families from the Middle East and Mediterranean basin.

Pathogenesis

Neutral lipid storage disease with ichthyosis (NLSDI) is an inborn error of lipid metabolism with accumulation of triglycerides in the skin and

other organs. The disorder is caused by deleterious germline mutations in *ABHD5*, which encodes an activator of adipose triglyceride lipase (ATGL); this enzyme catalyzes the first step in triacylglycerol hydrolysis[112]. In patients with NLSDI, decreased ATGL activity results in cytoplasmic accumulation of triglyceride droplets. A profound decrease in the PNPLA1-dependent synthesis of acylceramides has been identified *in vitro* and in mice with Abhd5 deficiency[113].

Clinical Features

The disorder presents at birth with generalized, fine, white scaling of the skin and a variable degree of erythema, thus resembling CIE[111,112,114]. At least one patient with a collodion membrane has been reported and several patients have had ectropion, eclabium, and alopecia[114]. On the lower extremities and scalp, the scales may be grayish, larger, and plate-like with detached borders. Erythrokeratodermia variabilis et progressiva-like presentations have also been reported.

The widespread tissue deposition of neutral lipids results in a broad array of systemic manifestations during childhood. Serum liver enzymes and muscle phosphocreatine kinase are usually elevated, although the myopathy may be mild and detectable only by neurologic examination. Hepatomegaly is common, and liver biopsy often reveals severe fatty degeneration and fibrosis, which may not be reflected in liver function studies.

Cataracts, sensorineural deafness, and developmental delay are frequent features, while growth retardation, ataxia, microcephaly, renal insufficiency, splenomegaly, thyroid dysfunction, and intestinal malabsorption have only been occasionally observed. The prognosis of NLSDI depends primarily on the course of the liver disease and extent of hepatic fibrosis.

Pathology

A highly characteristic feature is the presence of numerous lipid-containing vacuoles in circulating granulocytes (Jordan anomaly) and monocytes, a finding detectable on a fresh peripheral blood smear but not by automated blood-counting methods (Fig. 57.19). Similar findings (but to a lesser extent) may be seen in heterozygous carriers. Lipid stains (e.g. oil red O, Sudan III) or antibodies (e.g. adipophilin) can detect cytoplasmic lipid droplets in fresh frozen or paraffin-embedded skin sections, respectively, particularly in the epithelium of eccrine sweat glands and ducts but also in fibroblasts and basal and sometimes suprabasal keratinocytes. Ultrastructural abnormalities of the epidermis include globular electron-lucent inclusions, which disrupt the normal structure of lamellar bodies in the cells of the granular layer and change the conformation of intercellular lipid lamellae throughout the stratum corneum[115].

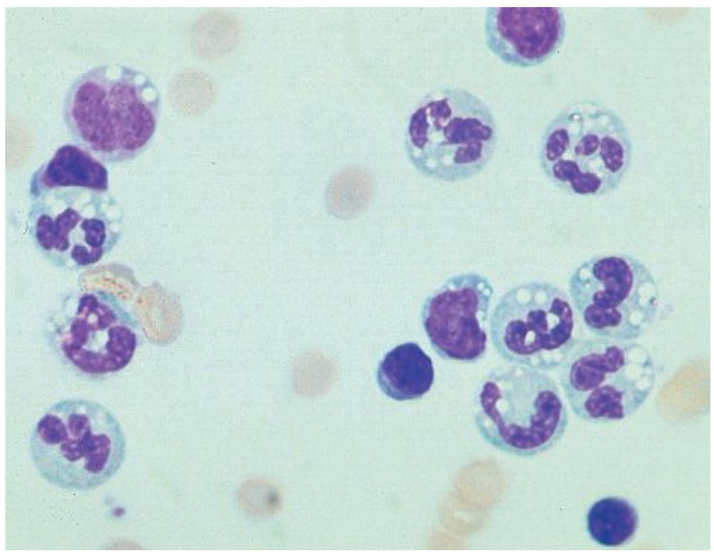


Fig. 57.19 Neutral lipid storage disease. Lipid droplets in circulating granulocytes and monocytes but not lymphocytes or erythrocytes. *Courtesy Mary L. Williams, MD.*

Differential Diagnosis

The associated ichthyosis is clinically similar to CIE, but the microscopic detection of lipid vacuoles in circulating white blood cells points to the diagnosis of NLSDI. In Refsum disease, a peroxisomal disorder characterized by accumulation of phytanic acid, the ichthyosis is not congenital and is more reminiscent of ichthyosis vulgaris (see Table 57.7). Although cytoplasmic lipid accumulations in basal keratinocytes may be found in both disorders, lipid droplets on a peripheral blood smear are not seen in Refsum disease. Neonatal ichthyosis–sclerosing cholangitis (NISCH) syndrome features vacuoles within circulating eosinophils but not neutrophils (see Table 57.7).

Treatment

Therapy is symptomatic. Topical emollients and keratolytics as well as systemic retinoids have been shown to improve the ichthyosis. A diet low in long-chain but enriched in medium-chain fatty acids has been reported to be beneficial in a few patients, but data are too limited to determine if systemic complications can be prevented.

TRICHOTHIODYSTROPHY WITH ICHTHYOSIS

Synonyms: ■ IBIDS: ichthyosis, brittle hair, infertility, developmental delay, short stature ■ Tay syndrome ■ PIBIDS: photosensitivity + IBIDS ■ Sulfur-deficient brittle hair syndrome

History

The first description of this disorder was in 1968, when Pollitt et al.[116] reported siblings with brittle hair, trichorrhexis nodosa, short stature, and intellectual disability. In 1971, Tay[117] described three siblings with similar features and additional skin involvement resembling CIE. Several years later, the term "trichothiodystrophy" was proposed to encompass a heterogeneous group of neuroectodermal disorders that share the finding of sulfur-deficient, short, brittle hair.

Epidemiology

With the exception of a few reported cases with X-linked transmission, the disorder is inherited in an autosomal recessive fashion, affecting both sexes equally.

Pathogenesis

Trichothiodystrophy (TTD) is a heterogeneous group of neuroectodermal disorders. Types of TTD that are associated with clinical and cellular photosensitivity result from severe instability and reduced amounts of general transcription factor IIH (TFIIH; see Ch. 86). This leads to reductions in the basal transcription of multiple genes expressed in the skin and CNS as well as defective transcription-coupled nucleotide excision repair (NER). Photosensitive trichothiodystrophy (PS-TTD) is due primarily to recessive mutations in two genes that encode helicase subunits of TFIIH, *ERCC2*/XPD and, less frequently, *ERCC3*/XPB. These genes are also mutated in patients with xeroderma pigmentosum (XP) and combined Cockayne syndrome–XP. Mutations in *GTF2H5*, which encodes the TFIIH subunit p8/TTD-A, have also been implicated in a small subset of patients with PS-TTD[118]. Non-photosensitive forms of trichothiodystrophy (NPS-TTD) with proficient NER typically *lack* ichthyosis and are caused by genetic defects that result in impaired transcription initiation or altered mRNA processing. Genes implicated in NPS-TTD include: (1) *MPLKIP (TTDN1)* – encodes the M-phase specific PLK1 interacting protein; (2) *GTF2E2* – β-subunit of TFIIE; (3) X-linked *RNF113A* – a ring finger protein; (4) *AARS1* – alanyl-tRNA synthetase; and (5) *TARS1* – threonyl-tRNA synthetase.

The TFIIH deficiency in patients with TTD due to abnormal XPD or XPB results in two major consequences: (1) impaired *transcription-coupled* NER, which leads to photosensitivity; and (2) repression of the basal transcription of genes that are highly expressed in differentiated cells of various tissues. The latter mechanism is thought to underlie

the defective synthesis of high-sulfur matrix proteins in hair and nails, growth retardation, short stature, and neurologic abnormalities seen in TTD, and this is supported by findings in transgenic animals[119]. In addition, the ichthyosis of TTD has been linked to decreased transcription of LXR (liver X receptor)-responsive genes that encode lipid transporters such as ABCA12 (see ARCI)[120].

In contrast, the TFIIH defect in XP profoundly impairs *global genome* NER, which is particularly important for UV-induced DNA damage, thereby leading to cancer formation as well as photosensitivity. Residual NER function of TFIIH in TTD explains the lack of increased carcinogenesis in affected individuals. In Cockayne syndrome, abnormal transcription-coupled NER results in apoptosis of metabolically active cells (e.g. neurons) rather than carcinogenesis.

Clinical Features

TTD is characterized primarily by hair, skin, and neurologic abnormalities. The obligatory finding in all types is short, unruly, fragile hair of the scalp, eyebrows, and eyelashes due to an abnormally low sulfur content, i.e. deficient cysteine and/or methionine. Body, axillary, and pubic hair may also be affected. Nail changes are common and can include thinning, longitudinal ridging, yellow discoloration, splitting, and onychogryphosis.

Patients with TTD are often born prematurely and small for their gestational age, and approximately one-third have a collodion membrane presentation that is not associated with ectropion or eclabium. Erythroderma and generalized fine scaling similar to that seen in CIE may be evident at birth or develop in the neonatal period[121]. The erythema usually resolves during infancy. The size and color of the associated scale is variable, ranging from fine and translucent to large and dark.

Photosensitivity occurs in half of patients; however, as in Cockayne syndrome, there is no propensity to develop cutaneous malignancies[119]. Additional cutaneous findings that have been described in TTD patients include follicular keratoses, folliculitis, erythema, atopic-like dermatitis, cheilitis, hypohidrosis, pruritus, hyperpigmentation of the eyelids, lentigines, hypopigmented macules, telangiectasias, poikiloderma, "hemangiomas", lipoatrophy, pyoderma, and palmar pustules.

Neurologic manifestations include intellectual disability, microcephaly, ataxia, and spastic paralysis; brain MRI may show dysmyelination, cerebellar atrophy, and dilated ventricles. Patients often fail to thrive and have short stature. Other potential associated abnormalities depend upon the type of TTD and include recurrent infections, gonadal abnormalities, progeria-like features (e.g. decreased subcutaneous fat), cataracts, joint contractures, and (very rarely) osteosclerosis.

Pathology

By light microscopy, hair shafts show transverse fractures (trichoschisis) in conjunction with an irregular surface and diameter. Occasionally, a nodal appearance similar to trichorrhexis nodosa or 180° twists as in pili torti may be evident. Polarizing light microscopy is the gold standard for detecting the characteristic light and dark bands, the so-called "tiger-tail" or "zigzag" pattern (see Ch. 69), which has been incorrectly referred to as alternating birefringence[119]. Transmission electron microscopy reveals an abnormal arrangement of microfibers and absence of the exocuticle and cuticular A-layer. If ichthyosis is present, histopathologic changes are typically similar to those found in ichthyosis vulgaris (see above), occasionally with perinuclear vacuoles.

Other diagnostic tests

Molecular genetic testing panels are available. Hair sulfur content can be semi-quantitatively analyzed by scanning electron microscopy. Determination of cysteine content via amino acid analysis of hydrolyzed hair is also possible.

Differential Diagnosis

Although Cockayne syndrome shares several features with the photosensitive form of TTD, the former lacks ichthyosis and tiger-tail hairs. Likewise, the characteristic microscopic hair findings distinguish TTD from other conditions with congenital alopecia or hypotrichosis, including Menkes disease. Polarized hairs can also have a tiger-tail pattern in healthy infants, but this is usually not prominent in all hairs as it is in TTD. Hair shaft abnormalities (including trichorrhexis nodosa and a band-like pattern with polarized microscopy), ichthyosiform erythroderma, and failure to thrive are also seen in NTS; although differentiation from TTD can be difficult in the neonatal period, elevated serum IgE levels are suggestive of NTS. Patients with SLS and ARCI have no hair shaft abnormalities.

Treatment

If photosensitivity is present, sun protection is essential. Treatment of the ichthyosis should be tailored to its severity. Symptomatic relief is best achieved with humectants, keratolytics, and in more severe cases, systemic retinoids. Multidisciplinary care is necessary to address neurologic issues and other manifestations.

ERYTHROKERATODERMAS

Erythrokeratodermas are disorders of cornification characterized by sharply demarcated keratotic plaques that are symmetrically distributed on the extremities, trunk, and/or face. The plaques tend to slowly expand over time and may be accompanied by migratory erythematous patches with circinate borders, as observed in erythrokeratodermia variabilis et progressiva. In addition to the conditions described below and in Tables 57.1 and 57.2 in which erythrokeratoderma (syndromic or nonsyndromic) represents the primary cutaneous finding, patients with other ichthyoses and PPKs occasionally present with erythrokeratoderma-like well-circumscribed keratotic plaques and/or circinate erythematous patches.

ERYTHROKERATODERMIA VARIABILIS ET PROGRESSIVA

Synonyms: ■ Erythrokeratoderma variabilis ■ Erythrokeratodermia figurata variabilis ■ Mendes da Costa disease ■ Progressive symmetric erythrokeratoderma

History

De Buy Wenninger published the first description of this entity in 1907. Mendes da Costa subsequently presented detailed clinical descriptions of patients with keratotic plaques plus migratory erythematous patches, and he coined the name "erythro-et keratodermia variabilis" (EKV)[122]. Darier provided the original description of progressive symmetric erythrokeratoderma (PSEK) in 1911, and Gottron coined the name in 1922. Although PSEK does not share the fleeting erythematous patches that characterize EKV[123,124], these two disorders otherwise have indistinguishable clinical characteristics and have been observed within the same family. Moreover, identical underlying *GJB4* mutations have been reported in patients with EKV and PSEK. Therefore, the unifying term erythrokeratodermia variabilis et progressiva (EKVP) was proposed by van Steensel et al.[125] in 2009.

Epidemiology

EKVP is a rare disorder that is predominantly inherited in an autosomal dominant pattern, with nearly complete penetrance but considerable intra- and interfamilial variability. In a few families, EKVP with autosomal recessive inheritance has been documented. It has been reported in individuals from a variety of ethnic backgrounds.

Pathogenesis

EKVP is caused by heterozygous mutations in *GJB3*, *GJB4*, or occasionally *GJA1* (see Table 57.1)[126–128]. These genes encode the gap junction proteins β3 (connexin 31), β4 (connexin 30.3), and α1 (connexin 43), which belong to a large family of transmembrane proteins that form intercellular channels (see Ch. 58). All reported mutations result in amino acid substitutions of conserved residues, thereby altering

the structure/activity of gap junction channels, impairing cytoplasmic trafficking of the mutant gap junction proteins to the cell membrane, and/or inducing cell death. The end result is impaired epidermal differentiation[125,129].

Clinical Features

The hallmark of classic EKV is the coexistence of transient erythematous patches and more stable keratotic plaques, with one of these features frequently predominating. The erythematous component is most prevalent during childhood, but it later slowly subsides and can be absent in adults. More than 50% of patients present at birth or in the neonatal period, and 90% within the first year of life, with transient erythematous patches that have a random distribution. These lesions are well demarcated with a geographic, circinate, or target-like appearance, and they can coalesce into large figurate patches (Fig. 57.20A). Circinate or gyrate erythematous patches have been associated primarily with mutations in *GJB4*, and this variant might be identical to the previously described "erythrokeratodermia en cocarde". The erythema is of variable intensity and is sometimes surrounded by a blanched halo. Individual lesions usually persist for only minutes to hours, although they may last for days. In about 35% of patients, the erythema is preceded or accompanied by a burning sensation, which may cause discomfort. The remarkable variability in number, size, shape, location, and duration of erythematous patches is reflected in the name of the disease.

Hyperkeratosis evolves simultaneously with or following the appearance of transient erythematous lesions. Sharply demarcated, yellow–brown to pink–brown thickened plaques with geographic borders progressively develop on the limbs, buttocks, and trunk in an almost symmetric distribution, descriptively termed progressive symmetric erythrokeratoderma (PSEK) (Figs. 57.20B–D & 57.21). In approximately half of all patients, the thickening of the skin extends onto the palms and soles, while the flexures, face, and scalp tend to be spared. The surface can be ridged, verrucous, or velvety, and it may have collarette-like peeling or fine, adherent scales. Lesions on the elbows, knees, Achilles tendons, dorsal aspect of the feet, and waistline are particularly common and tend to persist for months to years. In a subset of patients with severe disease, hyperkeratosis is generalized and persistent, with a yellow–brown–gray thickening of the skin and accentuated skin markings. Hypertrichosis may be observed. Some patients develop thick, dark plates of hyperkeratosis with a spiny, hystrix-like appearance, especially on the lower extremities.

After gradual progression throughout infancy and childhood, EKVP tends to stabilize after puberty. Improvement over time and periodic clearing of the skin are not unusual. Skin lesions may be triggered by factors such as emotional stress, sudden temperature changes, mechanical friction, and sun exposure.

Pathology

Histopathologic features are orthokeratotic, basket-weave hyperkeratosis, moderate to severe acanthosis with a prominent granular layer, and papillomatosis. There are dilated, elongated capillaries with minimal perivascular inflammation in the papillary dermis. Severe papillomatosis with suprapapillary thinning may result in a "church spire" configuration of the epidermis. Ultrastructural studies have had variable results, including a reduced number of lamellar bodies in the granular layer.

Other diagnostic tests

Molecular testing is available for the associated genes.

Differential Diagnosis

Not all published cases clinically categorized as PSEK fit into the EKVP clinical spectrum. For example, in a Japanese family with PSEK-like features plus mutilating PPK that included pseudoainhum, a heterozygous frameshift mutation in the loricrin gene was detected[130]. In addition, a homozygous loss-of-function mutation in *KRT83* (also implicated in autosomal dominant monilethrix) was found to underlie PSEK in a Pakistani kindred[131]. The lack of pathogenic variants in either connexin or loricrin genes in six unrelated patients with clinical findings of PSEK also pointed to a role for additional genes[125,126].

Autosomal recessive *periorificial and ptychotropic erythrokeratoderma* (*PERIOPTER*) *syndrome* due to *KDSR* mutations is distinguished by predilection of the hyperkeratotic plaques for periorificial sites and skin folds as well as associated transgredient PPK and thrombocytopenia (see Table 57.2)[45,132]. Nonsyndromic autosomal dominant *TRPM4* (transient receptor potential cation channel subfamily M



Fig. 57.20 Erythrokeratodermia variabilis et progressiva. A Transient erythematous patches and generalized brownish hyperkeratosis. **B** Barely elevated plaques with mild hyperkeratosis and a well-demarcated pink–brown border on the abdomen. **C** Symmetrically distributed hyperkeratotic plaques with hypertrichosis. **D** Brown hyperkeratotic plaques with geographic borders in a child. *B, Courtesy Lorenzo Cerroni, MD; D, Courtesy Julie V. Schaffer, MD.*



Fig. 57.21 Progressive symmetric erythrokeratoderma. Well-demarcated, symmetrically distributed hyperkeratotic plaques on the buttocks and lower extremities; note the white scale with underlying erythema and hyperpigmentation. *Courtesy Antonio Torrelo, MD.*

member 4)-*related PSEK* also features a periorificial distribution and transgredient PPK[133], and *Olmsted syndrome* presents with periorificial and intertriginous hyperkeratotic plaques plus mutilating PPK (see Ch. 58). Whereas heterozygous mutations in *PERP* (p53 effector related to PMP22), a component of desmosomes, underlie a form of Olmsted syndrome, biallelic *PERP* mutations have been associated with variable cutaneous manifestations including ichthyosis, erythrokeratoderma, PPK, psoriasiform plaques, and recalcitrant dermatophyte infections. In *erythrokeratodermia with spinocerebellar ataxia* due to mutations in *ELOVL4* (elongase-1 for very long-chain fatty acids), an autosomal dominant disorder that was first described in a French-Canadian family, EKVP-like findings during childhood are followed by the development of progressive ataxia due to cerebellar atrophy during adulthood. *MEDNIK syndrome* (mental disability, enteropathy, deafness, peripheral neuropathy, ichthyosis, keratoderma) features erythematous patches and hyperkeratotic plaques similar to EKVP (see Table 57.2). Lastly, generalized erythrokeratoderma, severe PPK, and ectodermal dysplasia as well as cardiac involvement distinguish *erythrokeratoderma–cardiomyopathy syndrome* due to *DSP* (desmoplakin) mutations.

The migratory, serpiginous erythematous plaques of ichthyosis linearis circumflexa in NTS are typically bordered by a double-edged scale, and patients have additional manifestations such as hair shaft abnormalities, eczematous lesions, and pruritus. Patients with erythrokeratolysis hiemalis develop erythematous circinate plaques with centrifugal peeling that primarily affect the palms and soles but occasionally extend to the arms and legs (see Table 57.8). Sharply demarcated hyperkeratotic plaques that wax and wane may also be seen in rare cyclic and annular subtypes of epidermolytic ichthyosis due to *KRT1* and *KRT10* mutations, respectively (see above). Greither syndrome, a heterogeneous condition that may also be due to *KRT1* mutations, features a transgredient PPK as well as erythrokeratoderma-like hyperkeratotic plaques (see Ch. 58). The presence of perifollicular papules, islands of sparing, and a salmon color distinguish pityriasis rubra pilaris and CARD14-associated papulosquamous eruption, while psoriasis has micaceous scale and a characteristic distribution pattern.

Treatment

Therapy is symptomatic and depends on the severity and extent of the hyperkeratosis, which varies over time. Topical management with keratolytic agents (e.g. α-hydroxy acids, salicylic acid), urea, and/or retinoids (e.g. tretinoin, tazarotene) may be sufficient for mild disease. Systemic retinoids such as acitretin and isotretinoin are the treatment of choice for more extensive or severe EKVP. These agents often produce dramatic improvement or complete clearing of hyperkeratosis and significant reduction in the development of erythematous lesions, although the latter cannot be completely suppressed. The minimal maintenance dose for patients with EKVP is usually considerably lower than that required for other disorders of cornification[134]. Nevertheless, the use of retinoids should always be considered carefully, since chronic therapy is necessary to avoid relapse and long-term side effects, especially in children, may ensue. Of note, other forms of PSEK do not tend to respond as well to systemic retinoids. The red patches in EKVP often result in cosmetic concerns, which can be limited by using camouflaging makeup. Avoidance of sudden temperature changes, friction, and irritation may be beneficial.

KERATITIS–ICHTHYOSIS–DEAFNESS SYNDROME

Synonyms: ■ KID syndrome ■ Erythrokeratodermia progressiva Burns Subtype: Hystrix-like ichthyosis with deafness [HID] syndrome ■ Ichthyosis hystrix gravior type Rheydt

History

In 1915, Frederick Burns provided a detailed clinical description delineating all the key features of this syndrome. Subsequently, several case reports emerged in the literature using different names to describe the skin involvement, such as "atypical erythrokeratodermia with deafness", "atypical ichthyosiform erythroderma", and "ichthyosiform dermatosis". In 1981, Skinner summarized the previous reports and coined the acronym "KID" (keratitis–ichthyosis–deafness) syndrome[135]. Although several authors argued that the skin findings represent erythrokeratoderma rather than ichthyosis[84,136], the widely-used acronym prevailed. KID syndrome presents an overlap between disorders of cornification and ectodermal dysplasias. Hystrix-like ichthyosis with deafness (HID) syndrome, which was first described as ichthyosis hystrix gravior type Rheydt, was originally considered to represent a distinct entity but is now classified as a clinical subtype of KID syndrome with more severe skin findings but less severe keratitis[29].

Epidemiology

KID syndrome is a rare disorder, with ~300 published cases. Although it is primarily inherited in an autosomal dominant manner, >90% of reported cases have been sporadic.

Pathogenesis

The vast majority of KID syndrome patients harbor mutations in *GJB2*, which encodes connexin 26 (Cx26), a β-type gap junction protein[137]. In a single patient with features of KID syndrome and congenital atrichia, a causative mutation was identified in *GJB6* (encoding connexin 30)[138]. All pathogenic *GJB2* variants identified to date have been heterozygous missense substitutions; D50N is particularly common and is detected in >80% of KID patients[137,139]. This latter mutation can also underlie KID syndrome associated with the follicular occlusion triad and hystrix-like-ichthyosis–deafness (HID) syndrome[29,139a]. Other *GJB2* mutations affecting the amino terminus or transmembrane domains of Cx26 have been associated with atypical clinical features such as a lack of PPK or corneal involvement, generalized spiny or verrucous keratoses, mucosal involvement, and the follicular occlusion triad. Two *GJB2* mutations, G45E and A88V, cause a very severe neonatal form of KID syndrome that is typically fatal during infancy or early childhood[140].

In vivo and *in vitro* functional studies have shown that *GJB2* mutations increase connexin hemichannel permeability, leading to ATP release, Ca^{2+} overload, and cell death. Mutations altering the Cx26 amino terminus may also allow the formation of constitutively active heteromeric Cx43/Cx26 hemichannels, whereas gap junction channels are not functional[141]. Cx26 hemichannels containing the substitutions N14K, N14Y, A40V, and A88V were shown *in vitro* to abolish the sensitivity of Cx26 to CO_2, providing a possible explanation for breathing abnormalities in patients with fatal KID syndrome[142].

Of note, somatic heterozygous *GJB2* mutations have been identified in porokeratotic eccrine ostial and dermal duct nevi (PEODDN), nevoid spiny hyperkeratosis, and other epidermal nevus variants, which could be considered to represent mosaic forms of KID syndrome. If these mutations involve the gonads, their transmission to the offspring of such individuals can result in KID syndrome[143]. Revertant mosaicism has also been documented in a KID syndrome patient with progressive development of normal-appearing spots within erythrokeratodermic lesions[144].

Clinical Features

There is considerable variability in the type, extent, and severity of cutaneous features in patients with KID syndrome (Table 57.5). The first manifestation is often transient erythroderma at birth or during infancy. Later, most patients develop symmetrically distributed, well-demarcated, hyperkeratotic plaques with an erythematous base and a rough, ridged, or verrucous surface (i.e. erythrokeratoderma); psoriasiform plaques may also occur. The plaques favor the knees, elbows, and face, often with radial furrows around the mouth (Fig. 57.22A,B). The helices, scalp, groin, other skin folds, extremities, and, less often, trunk may be affected. A plaque-like or diffuse PPK with a grainy, reticulated, or stippled surface (reminiscent of Vohwinkel syndrome) is almost always present (Fig. 57.22C,D). Prominent follicular keratoses and cheilitis (especially perlèche) are common. Some patients develop diffuse thickening of the skin with a coarse, grainy appearance, which may also lead to deep facial furrows (see Fig. 57.22A).

Nails may be dystrophic and show leukonychia. Although most patients have normal hair, some affected individuals have lusterless hair or alopecia of the scalp, eyelashes, and eyebrows. Heat intolerance occasionally occurs.

ADDITIONAL MUCOCUTANEOUS MANIFESTATIONS OF KID (KERATITIS–ICHTHYOSIS–DEAFNESS) SYNDROME
Inflammatory
• Follicular occlusion triad (onset usually at puberty): acne conglobata, dissecting cellulitis of the scalp, hidradenitis suppurativa • Folliculitis • Cheilitis with red, "chapped", fissured lips (especially at the angles of the mouth*) • Stomatitis with erythematous patches, adherent white plaques, and erosions*
Infectious
• Recurrent or chronic mucocutaneous bacterial (e.g. *Staphylococcus aureus*), fungal (e.g. *Candida* spp.), and viral infections • Sepsis in the neonatal period (may be fatal)
Neoplastic
• Cutaneous and oral squamous cell carcinoma (10%–20% of patients; median age 25 years) • Epidermoid and pilar cysts • Proliferating pilar tumors, benign or malignant (the latter aggressive/metastasizing)
*May have candidal superinfection.

Table 57.5 Additional mucocutaneous manifestations of KID (keratitis–ichthyosis–deafness) syndrome. The spectrum of hyperkeratotic manifestations is described in the text.

The spectrum of cutaneous lesions in KID syndrome also includes folliculitis, the follicular occlusion triad, cysts, and proliferating pilar tumors (rarely aggressive/metastasizing)[139a]. Another serious complication is the development of SCC of the skin and oral mucosa, which occurs in 10%–20% of patients at a median age of 25 years, but as early as the first decade of life[136]. KID syndrome is also associated with increased susceptibility to mucocutaneous bacterial, viral, and fungal infections, in particular with *Candida albicans*.

All KID patients have congenital sensorineural hearing impairment that (in contrast to the keratitis) is not progressive. Hearing loss is generally severe and bilateral, although some patients have unilateral or moderate hearing impairment. Approximately 95% of patients have ocular involvement, which typically presents at birth, during infancy, or in early childhood with photophobia and blepharitis. Vascularizing keratitis and conjunctivitis develop and worsen with age. Scarring and neovascularization often cause a progressive decline in visual acuity and may eventuate in blindness. Dental abnormalities may include small or absent teeth, delayed eruption, or excessive caries. The Dandy–Walker malformation of the cerebellar vermis and fourth ventricle, short heel cords, other joint contractures, facial dysmorphism, and developmental abnormalities have also been reported.

A rare severe form of KID syndrome with a fatal outcome during infancy or early childhood presents with erythroderma and areas of massive, fissured hyperkeratosis on the scalp, periorificial skin, and extremities[140]. These patients also have a grainy PPK, atrichia, and nail dystrophy. Other features may include facial dysmorphism, congenital absence of the foreskin, edema and dyskeratosis of the laryngeal



Fig. 57.22 KID syndrome. A Diffusely thickened, hyperkeratotic skin with a coarse-grained texture and an erythematous component; note the characteristic radial furrows around the mouth. **B** Bright pink, keratotic periorificial plaques with crusting. Palmar (**C**) and plantar (**D**) keratoderma with a grainy surface. *A, B, Courtesy Julie V. Schaffer, MD; C, Courtesy J. Tercedor, MD; D, Courtesy Richard Antaya, MD.*

mucosa, and hydrocephalus. Complications include apnea and other breathing problems requiring mechanical ventilation, severe failure to thrive, and recalcitrant bacterial and fungal infections leading to enterocolitis and sepsis.

Pathology

Histology is not specific. Acanthosis and papillomatosis of the epidermis with basket-weave hyperkeratosis and follicular plugging are the most frequent features. Vacuolization of the cells in the granular layer has also been described. The corneal epithelium may be dyskeratotic, atrophic, or absent centrally, and Bowman's membrane may be absent. The eccrine glands may be diminished in number and atrophic. In the inner ear, the organ of Corti is immature or atrophic.

Other diagnostic tests

Molecular genetic testing is available. A rapid molecular diagnosis can provide important prognostic information in infants with the severe fatal form of KID syndrome.

Differential Diagnosis

Autosomal recessive keratitis–ichthyosis–deafness syndrome results from biallelic mutations in *AP1B1* (see Table 57.7). It encodes adaptor related protein complex 1 subunit β1, which is involved in intracellular vesicular trafficking. Patients present by early infancy with ichthyosiform erythroderma accompanied by ectropion, pruritus, sensorineural hearing loss, and failure to thrive. Photophobia and PPK develop over time, and additional features distinct from those of classic KID syndrome include chronic diarrhea, hepatomegaly, thrombocytopenia, low plasma levels of copper and ceruloplasmin, and large numbers of basophilic vesicles within the epidermis[145,146]. *Autosomal recessive keratoderma–ichthyosis–deafness (ARKID) syndrome* features diffuse PPK, mild generalized ichthyosis, intellectual disability, microcephaly, short stature, and occasionally hip dislocation, pancreatic insufficiency, or copper overload. Both ARKID and the more severe arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome are caused by biallelic mutations in *VPS33B* (see Table 57.7). This gene encodes vacuolar protein sorting 33 homolog B, which is involved in vesicular trafficking and biogenesis of organelles such as epidermal lamellar bodies[36,147].

EKVP and most other erythrokeratodermas are not associated with impaired hearing or keratitis. However, *MEDNIK syndrome* features EKVP-like skin findings, PPK, and sensorineural hearing loss (see Table 57.7). X-linked *ichthyosis follicularis with atrichia and photophobia (IFAP) syndrome* (*MBTPS2*; Table 57.6) and autosomal dominant *hereditary mucoepithelial dysplasia* (*SREBF1* [sterol regulatory element binding transcription factor 1]) are both characterized by follicular keratoses, psoriasiform plaques, alopecia, keratitis, and susceptibility to mucocutaneous infections, but not hearing impairment; in the latter disorder, the plaques favor the perineal area and fiery red oral mucosal patches are present. *Keratosis follicularis spinulosa decalvans* (allelic to IFAP; see Ch. 38) also features follicular keratoses and keratitis, but it progresses to scarring alopecia and does not manifest with hyperkeratotic plaques, PPK, or hearing impairment. Lastly, ichthyosis follicularis together with punctate PPK and sensorineural hearing loss due to biallelic *GJB2* mutations has been reported[148].

Treatment

Skin treatment includes use of emollients and keratolytics; topical retinoids may be beneficial. Oral retinoid therapy (e.g. acitretin) yields mixed results: the hyperkeratosis may or may not respond, the PPK is recalcitrant, and ocular side effects may aggravate keratitis and neovascularization in some patients. Successful use of oral alitretinoin (not available in the US; see Ch. 126) for patients with recalcitrant disease has also been described[149]. Use of allele-specific small interfering RNA (siRNA) to inhibit expression of mutant *GJB2* is under investigation in a human–murine chimeric skin graft model[150].

Gas-permeable contact lenses can improve vision in KID patients, while corneal transplants may have limited efficacy because of revascularization[136,151]. Hearing aids and cochlear implants have been used successfully. Mucocutaneous infections often require prolonged systemic therapy. Surveillance for the development of SCC and other tumors via periodic examination of the mucous membranes as well as the skin (including the scalp) is required.

X-LINKED DOMINANT ICHTHYOSIFORM DISORDERS

CHILD SYNDROME

Synonyms: ■ Congenital hemidysplasia with ichthyosiform erythroderma (or nevus) and limb defects ■ CHILD nevus

History

The first description of this condition in 1948 was followed by 17 case reports before Happle delineated the key features and proposed the acronym CHILD syndrome in 1980[152].

Epidemiology

This is a rare X-linked dominant disorder that occurs primarily in girls and women, as it is generally lethal in affected male embryos. Very few affected boys have been reported, one of whom had a normal karyotype and a mosaic *NSDHL* mutation[153].

Pathogenesis

CHILD syndrome is a disorder of lipid metabolism that results in disturbed cholesterol biosynthesis. Inactivating mutations in *NSDHL*, which encodes the enzyme 3β-hydroxysteroid-dehydrogenase, were initially identified in five families with right-sided skin and skeletal involvement[154]; such mutations were subsequently described in additional patients with left-sided involvement. The striking hemilateral phenotype is postulated to result from skewed X-inactivation and deficient sonic hedgehog signaling in the cells expressing the X-chromosome with an *NSDHL* mutation, resulting in selection against these cells on one side of the body. This hypothesis reflects the role hedgehog signaling plays in conferring left–right asymmetry during embryogenesis. Cholesterol has critical functions during mammalian development, including hedgehog signaling, and inborn errors in cholesterol biosynthesis cause several other malformation syndromes.

Clinical Features

CHILD syndrome classically presents at birth or in the neonatal period with a striking unilateral distribution of erythema and thickened skin with a waxy surface or yellowish adherent scale (Fig. 57.23A). The erythema most often involves the right side of the body and is sharply demarcated at the anterior and posterior midline of the trunk. The face is typically spared. Occasionally, there is partial spontaneous resolution or periodic exacerbation of the cutaneous inflammation[152]. During infancy, the erythema lessens, while hyperkeratotic plaques or bands with a verrucous surface prevail and often become more pronounced. They may follow the lines of Blaschko or uniformly affect large areas on half of the body, with affinity for the skin folds (ptychotropism). Because of the clinical resemblance to inflammatory linear verrucous epidermal nevus (ILVEN), the terms "CHILD nevus" and "psoriasiform epidermal nevus" have been used. The contralateral side of the body may have mild skin involvement in a mosaic pattern, but symmetric distribution is extremely rare. Ipsilateral linear alopecia and claw-like nail dystrophy or onychorrhexis are common.

Ipsilateral skeletal abnormalities range from hypoplasia of digits or ribs to complete amelia. Congenital or secondary scoliosis may also occur. Stippled epiphyses can be identified on radiologic examination in early infancy but tend to resolve during childhood. The teeth are typically normal but mild hearing loss and cleft palate may be present. Asymmetric organ hypoplasia most commonly affects the brain, kidneys, heart, and lungs on the affected side of the body. Occasionally, there is contralateral involvement.

FEATURES OF SELECTED SYNDROMIC X-LINKED ICHTHYOSIFORM DISORDERS							
Diagnosis	**Gene**	**Mode of inheritance**	**Incidence**	**Onset**	**Primary cutaneous features**	**Associated features**	**Diagnosis (in addition to molecular testing*)**
CHILD syndrome	*NSDHL* (3-beta-hydroxysteroid-dehydrogenase)	XL dominant	Rare	Birth	At birth, unilateral erythema and waxy, yellowish adherent scale; later, verrucous; hyperkeratosis of variable extent, with affinity for skin folds	Ipsilateral skeletal hemidysplasia, organ hypoplasia	Clinical
Conradi–Hünermann–Happle syndrome (chondrodysplasia punctata 2)	*EBP* (emopamil-binding protein)	XL dominant	Rare	Birth	*Females (>95%):* at birth, inflammatory ichthyosiform erythroderma with feathery, adherent scale along lines of Blaschko; later, follicular atrophoderma along lines of Blaschko	Unilateral or sectorial cataracts; chondrodysplasia punctata (during infancy); asymmetric skeletal abnormalities; patchy scarring alopecia	Clinical; histopathologic finding of keratotic follicular plugs with calcification; epiphyseal stippling on X-rays during infancy; accumulation of 8(9)-cholestenol and 8-dehydrocholesterol in plasma, scales, or cultured fibroblasts
Male *EBP* disorder with neurologic defects (MEND) syndrome		XL recessive			*Affected males*: occasional collodion membrane, later ichthyosis with variable erythema	Dandy–Walker malformation, hydrocephalus; cataracts; craniofacial, skeletal, and cardiovascular anomalies; cryptorchidism	
Ichthyosis follicularis, atrichia, and photophobia (IFAP) syndrome†,[170] with or without BRESHECK syndrome	*MBTPS2* (membrane-bound transcription factor peptidase site 2, a zinc metalloprotease with roles in cholesterol homeostasis and the ER stress response)	XL			*Affected males*: congenital atrichia with absence of eyebrows and lashes; follicular keratoses ("nutmeg grater" skin); psoriasiform plaques; occasionally PPK; nail dystrophy; increased susceptibility to mucocutaneous bacterial and fungal infections *"Carrier" females*: linear streaks with follicular keratoses or scaling; patchy hypotrichosis	Vascularizing keratitis and corneal ulcers leading to progressive vision impairment; BRESHECK syndrome multisystem involvement may include cerebral atrophy, brain malformations, ID, seizures; inguinal hernias; Hirschsprung disease, cleft palate; urogenital, renal, and vertebral malformations	Clinical; *histopathology*: hyperkeratosis, absent/atretic hair follicles and sebaceous glands

*Genetic testing is available for all ichthyosiform disorders and erythrokeratodermas with a known molecular basis; multigene panels are preferable over single gene testing if the diagnosis is not evident based on clinical and laboratory findings.
†Allelic with *keratosis follicularis spinulosa decalvans*, which features scarring alopecia (see Table 38.2), and Olmsted syndrome, which features mutilating PPK and perioral/perianal keratotic plaques (see Ch. 58). Similar clinical findings, with additional features of plaques favoring the perineal area and fiery red oral mucosal patches, are present in *hereditary mucoepithelial dysplasia*, an autosomal dominant disorder due to mutations in *SREBF1* (sterol regulatory element binding transcription factor 1).

Table 57.6 Features of selected syndromic X-linked ichthyosiform disorders. BRESHECK, brain anomalies, ectodermal dysplasia, skeletal malformations, Hirschsprung disease/hernias, ear/eye anomalies, cleft palate/cryptorchidism, kidney dysplasia/hypoplasia; ER, endoplasmic reticulum; ID, intellectual disability; PPK, palmoplantar keratoderma; XL, X-linked

Pathology

Histopathologic changes include an acanthotic and papillomatous epidermis with marked ortho- and parakeratosis, overlying a mild superficial perivascular infiltrate. Parakeratotic nuclei characteristically retain a round shape[155], and numerous vacuoles are present within the cells of the lower stratum corneum. Multiple layers of granular cells surround the sweat ducts, while the granular zone in the surrounding epidermis may be absent, normal, or thickened[155]. Over time, foamy histiocytes accumulate within the dermal papillae, giving the appearance of a verruciform xanthoma (Fig. 57.23B). Ultrastructural abnormalities include abundant pale-staining mitochondria, cytoplasmic glycogen, lipid retention in the stratum corneum, and altered intracellular and intercellular lamellar granule content.

Other diagnostic tests

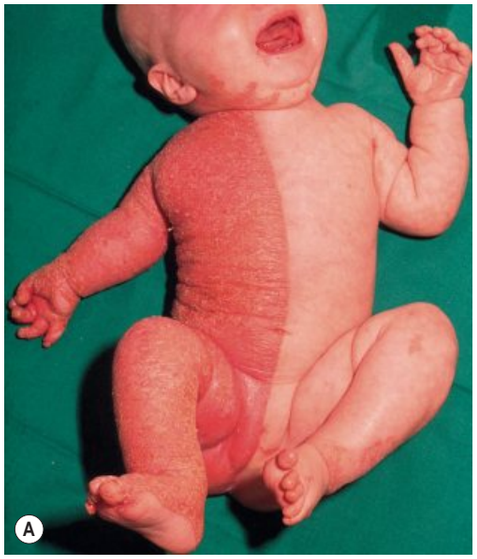
Molecular analysis of the *NSDHL* gene is available. Plasma cholesterol is normal despite defective cholesterol biosynthesis.

Differential Diagnosis

Sebaceous nevus syndrome may resemble CHILD syndrome but can be differentiated clinically by its distribution pattern and the lack of erythema and scaling. ILVEN is a less extensive condition that is not associated with visceral abnormalities. Punctate epiphyseal calcifications and asymmetric limb shortening, together with CIE along the lines of Blaschko, may be seen in Conradi–Hünermann–Happle syndrome (see below). However, the skin manifestations are not unilateral and are replaced by atrophoderma by 2 years of age. In addition, skeletal defects are usually less severe than in CHILD syndrome[154].

Treatment

Case reports have noted variable improvement of skin lesions with topical tretinoin or systemic retinoid therapy, but emollients and corticosteroids are ineffective. Substantial benefit has been described with pathogenesis-based therapy targeting the underlying



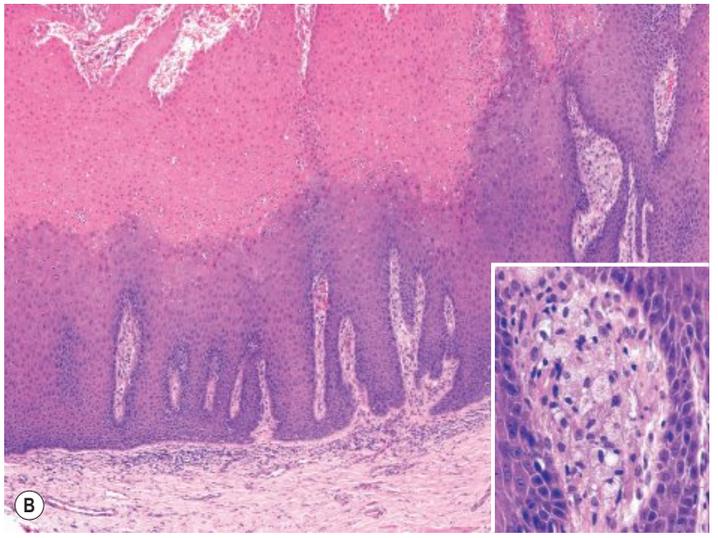


Fig. 57.23 CHILD syndrome. A Note the sharp midline demarcation on the trunk. **B** Histologic features include an acanthotic and papillomatous epidermis with marked parakeratosis and vacuoles within the lower stratum corneum. Note the foamy histiocytes in the dermal papillae (inset). The findings can mimic those of a verruciform xanthoma. *A, Courtesy R. Happle, MD, from Happle R, Mittag H, Kuster W. Dermatology. 1995;191:210–6, with permission; B, Courtesy Luis Requena, MD.*



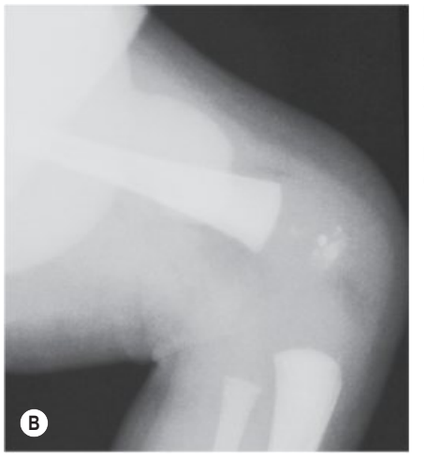


Fig. 57.24 Conradi–Hünermann–Happle syndrome. A Erythroderma and linear streaks and whorls of hyperkeratosis. **B** Epiphyseal stippling at the knee. *A, Courtesy R. Happle, MD; B, Courtesy Jean L. Bolognia, MD.*

cholesterol pathway defect via topical application of an ointment or lotion containing 5% simvastatin or 2% lovastatin or simvastatin plus 2% cholesterol[156,157]. A single report noted improvement with topical ketoconazole, possibly due to inhibition of the sterol 14α-demethylase (CYP51)[158]. Cosmetically and functionally satisfactory results from dermabrasion of affected skin followed by placement of split-thickness skin grafts obtained from the clinically normal contralateral side of the body have also been described[159]. Requirements for multidisciplinary care depend on the extent of associated organ involvement.

CONRADI–HÜNERMANN–HAPPLE SYNDROME

Synonyms: ■ X-linked dominant chondrodysplasia punctata ■ Chondrodysplasia punctata type 2 (CDPX2) ■ Conradi–Hünermann syndrome ■ Happle syndrome

History

In 1971, the dominant Conradi–Hünermann type of chondrodysplasia was differentiated from the autosomal recessive rhizomelic form. Happle subsequently reviewed the literature and established that the Conradi–Hünermann type has an X-linked dominant mode of inheritance[160].

Epidemiology

Conradi–Hünermann–Happle (CHH) syndrome is a rare X-linked dominant disorder that occurs primarily in girls and women. It is lethal in male embryos outside the setting of an XXY karyotype or mosaicism due to a postzygotic mutation in *EBP*. However, an X-linked recessive multiple congenital anomaly syndrome (MEND – male EBP disorder with neurologic defects) in which male patients often die by early childhood and female carriers are unaffected has been described with less severe germline mutations in *EBP*[161].

Pathogenesis

Conradi–Hünermann–Happle syndrome results from a cholesterol biosynthesis defect caused by mutations in *EBP*, which encodes emopamil-binding protein (EBP)[162,163]. The resulting deficiency of EBP, a widely expressed integral membrane protein with Δ8-Δ7-sterol isomerase activity, leads to accumulation of 8-dehydrocholesterol and 8(9)cholestenol[163], which can be detected in plasma, scales, and cultured fibroblasts. However, levels of the end product cholesterol sulfate are normal in plasma and fibroblasts because of X-inactivation[162,163]. Impaired cholesterol synthesis during a critical period of mammalian development is thought to be responsible for the phenotype. Hemizygous missense mutations affecting the first transmembrane domain of EBP, presumably with less deleterious effects on enzyme function, have been identified in boys with MEND syndrome[161].

Clinical Features

CHH is a multisystem disorder that involves primarily the skin, eyes, and skeletal system. Clinical presentations in female patients are variable as they depend on the pattern of X-chromosome inactivation in relevant tissues. At birth, most CHH syndrome patients have generalized erythema with thick, adherent, feathery scale; streaks and whorls of hyperkeratosis following the lines of Blaschko are often observed (Fig. 57.24A). The erythroderma resolves substantially, if not completely, within the first weeks

or months of life. In older children, hyperkeratosis is largely replaced by linear or patchy follicular atrophoderma with dilated follicular openings, ice-pick-like scars, and mild residual scaling. The atrophoderma is most pronounced on the forearms and dorsal hands, whereas the palms and soles are usually spared. Hyper- or hypopigmentation along the lines of Blaschko may coexist separately from atrophodermic areas[160]. Scalp involvement results in patchy scarring alopecia. In addition, hair may be sparse, coarse, or lusterless. Nail changes include onychoschizia and flattening of the nail plate, while teeth are normal.

Skeletal anomalies include asymmetric shortening of the proximal limbs, kyphoscoliosis, frontal bossing, malar hypoplasia, a flat nasal bridge, and a short neck. Widespread premature calcifications manifest as stippling (chondrodysplasia punctata) of the long bone epiphyses, tracheal cartilage, and vertebrae. These can be detected by fetal ultrasound in severe cases or postnatally in radiographs during infancy (Fig. 57.24B), but they are not apparent once bone maturation progresses (after ~9 months of age).

Unilateral, asymmetric, and/or sectorial cataracts, which are present at birth or develop within the first months of life, are the most common ocular abnormality and may be accompanied by microphthalmia or microcornea. Less common features include congenital heart defects, sensorineural hearing loss, CNS malformations, and congenital renal anomalies. Attenuated cases with characteristic skin findings but mild or no associated systemic anomalies have been observed[164]. Psychomotor development and life expectancy are normal.

Boys with the allelic X-linked recessive MEND syndrome have a collodion-like presentation at birth and evolution to a variable ichthyosis phenotype[161]. Additional features include cardiovascular, craniofacial, and skeletal anomalies as well as the Dandy–Walker malformation, hydrocephalus, cataracts, and cryptorchidism.

Pathology

Hyperkeratosis with focal parakeratosis is common and most prominent in follicular ostia, where dystrophic calcification may be observed within keratotic plugs. The granular layer is diminished and keratinocytes contain small vacuoles with needle-like calcium inclusions on electron microscopy.

Other diagnostic tests

Radiographs reveal premature calcifications in the cartilage of the trachea, spine, and long bones during the first year of life (Fig. 57.24B). Accumulation of 8(9)cholestenol and 8-dehydrocholesterol in plasma can be detected by gas chromatography–mass spectrophotometry in order to confirm the diagnosis. Molecular analysis of *EBP* is available.

Differential Diagnosis

Stippled epiphyses during infancy and asymmetric limb shortening are also seen in girls with CHILD syndrome, but the skin involvement usually shows striking lateralization and does not fade completely. However, some overlap in the clinical findings of CHILD and CHH syndromes is not surprising, since both represent disorders of cholesterol biosynthesis (see Table 57.6). Ichthyosis linearis circumflexa in NTS is readily distinguished by its double-edged scale, and the lesions do not follow the lines of Blaschko. Cutaneous manifestations in CIE are more generalized. Hyper- and hypopigmentation in "pigmentary mosaicism", incontinentia pigmenti, and epidermal nevi (including epidermolytic variants) follow the lines of Blaschko but lack follicular atrophoderma.

Treatment

Although the erythema gradually resolves, residual mild scaling may benefit from application of emollients and products containing urea or a keratolytic agent. Orthopedic and ophthalmologic care are essential.

OTHER ICHTHYOSES, PEELING SKIN SYNDROMES, AND RELATED DISORDERS

Additional rare ichthyoses, erythrokeratodermas, and peeling skin syndromes for which the genetic basis is known are presented in Tables 57.7 and 57.8.

FEATURES OF ADDITIONAL RARE SYNDROMIC ICHTHYOSES AND ICHTHYOSIFORM DISORDERS

Disorder	Gene (protein)	Mode of inheritance	Dermatologic features	Associated features	Diagnosis (in addition to molecular testing*)
Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome[147] (allelic with ARKID syndrome, see below)	*VPS33B* (vacuolar protein sorting 33 homolog B, in ~75%; involved in organelle biogenesis) *VIPAS39* (VPS33B-interacting protein, in ~25%)	AR	In ~half of patients, generalized fine to large scales on trunk and extremities with sparing of skin folds	Severe FTT, often lethal within first year of life; arthrogryposis; renal tubular dysfunction; neonatal jaundice, cholestasis; hemorrhage due to platelet dysfunction; osteopenia; SNHL, CNS abnormalities, congenital heart defects	Clinical; metabolic acidosis and aminoaciduria
Autosomal recessive keratoderma, ichthyosis, deafness (ARKID) syndrome[36,171]	*VPS33B* (vacuolar protein sorting 33 homolog B)	AR	Diffuse PPK, mild generalized ichthyosis without erythema; reminiscent of *GJB2*-related Vohwinkel syndrome	Progressive SNHL; microcephaly, ID; digital contractures, acromicria, short stature, hip dislocation; exocrine pancreatic insufficiency and hepatic copper overload (in single patient)	Clinical
Cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma (CEDNIK) syndrome[172]	*SNAP29* (SNARE protein involved in intracellular vesicle transport)	AR	Normal skin in infancy, later widespread large scale with variable erythema; PPK	Microcephaly, neuropathy, ID; hearing impairment, optic nerve atrophy; cachexia; dysmorphic facial features; usually fatal within first decade of life	MRI showing cortical dysplasia and abnormal corpus callosum; electron microscopy showing clear vesicles within the epidermis
Mental disability, enteropathy, deafness, neuropathy, ichthyosis, keratoderma (MEDNIK) syndrome[173]	*AP1S1* (adaptor-related protein complex 1 σ-1 subunit; role in vesicular trafficking, intracellular transport of copper pumps)	AR	Erythematous patches and hyperkeratotic plaques of variable sizes and shapes; mucosal involvement	Chronic diarrhea and enteropathy; SNHL; peripheral neuropathy; ID and growth delay; abnormal copper metabolism	Clinical; elevated plasma very-long-chain fatty acids

Table 57.7 Features of additional rare syndromic ichthyoses and ichthyosiform disorders.

Continued

FEATURES OF ADDITIONAL RARE SYNDROMIC ICHTHYOSES AND ICHTHYOSIFORM DISORDERS					
Disorder	**Gene (protein)**	**Mode of inheritance**	**Dermatologic features**	**Associated features**	**Diagnosis (in addition to molecular testing*)**
Keratitis–ichthyosis–deafness, autosomal recessive (KIDAR) syndrome (MEDNIK-like syndrome; includes Desmons [Senter] syndrome)[145,146]	*AP1B1* (adaptor-related protein complex 1 β-1 subunit; role in vesicular trafficking)	AR	Ichthyosiform erythroderma from birth or early infancy; thick, adherent yellow scale on the scalp; mild PPK; pruritus	SNHL; ectropion, photophobia, and corneal scaring; FTT during infancy, mild growth and developmental delay; variable enteropathy and hepatomegaly; tooth loss; mild–moderate thrombocytopenia	*Histology*: large number of basophilic vesicles in spinous and granular layers
Congenital disorders of glycosylation (CDG)[174,175]	*DOLK* (dolichol kinase; essential for N- and O-glycosylation; CDG-Im) *MPDU1* (mannose-P-dolichol utilization defect 1; CDG-If) *SRD5A3* (steroid 5-α-reductase 3; CDG-Ig)	AR	Highly variable: dry skin, patchy desquamation (cheeks, trunk, lower legs), transient eczematous lesions, ichthyosiform erythroderma; hyper-/hypotrichosis; cutis laxa (*SRD5A3*)	FTT; severe ID, seizures, hypo-/hypertonia, ataxia, microcephaly; optic atrophy, cataracts, coloboma; vomiting, abdominal pain; congenital heart defects, cardiomyopathy (*DOLK*); abnormal coagulation	Clinical; low serum cholesterol
CHIME syndrome	*PIGL* (phosphatidylinositol glycan anchor biosynthesis class L)	AR	Migratory *i*chthyosiform dermatosis	*C*olobomas, *h*eart defects, *m*ental/intellectual disability, *e*ar anomalies, including conductive hearing loss	Clinical
Neonatal ichthyosis–sclerosing cholangitis (NISCH) syndrome[176]	*CLDN1* (claudin 1, a tight junction protein)	AR	Fine to large scales on trunk and extremities with sparing of flexures; hypotrichosis, coarse hair, scarring alopecia of scalp, eyebrows	Neonatal jaundice and hepatomegaly due to sclerosing cholangitis or congenital paucity of biliary ducts; hypodontia and enamel dysplasia	Clinical; peripheral blood smear to detect eosinophil vacuoles
Ichthyosis–hypotrichosis syndrome[177]; ichthyosis, follicular atrophoderma, and hypotrichosis[178]	*ST14* (matriptase, a transmembrane serine protease)	AR	Large scales on trunk, extensor extremities, and scalp; woolly, sparse, brittle scalp hair; absent eyebrows, eyelashes; variable follicular atrophoderma and hypotrichosis	Photophobia, corneal opacities, pitted or conical teeth	Clinical; scalp hairs with pili torti/pili bifurcati
Multiple sulfatase deficiency (mucosulfatidosis)[179]	*SUMF1* (sulfatase-modifying factor 1, responsible for post-translational modification of all sulfatases, including steroid sulfatase)	AR	Scaling develops within first two years of life; similar to steroid sulfatase deficiency, but often less severe	Findings depend upon residual sulfatase activity; may resemble metachromatic leukodystrophy or various mucopolysaccharidoses (see Ch. 48); coarse facies; broad great toes, chondrodysplasia calcificans, dysostosis multiplex; deafness; hypotonia, hydrocephalus, intellectual disability, neurologic deterioration	Reduced arylsulfatase A/B/C, heparan sulfatase, and iduronate-2 sulfatase activity/levels in fibroblasts (cultured), leukocytes, plasma, or chorionic villi
Rhizomelic chondrodysplasia punctata (autosomal recessive chondrodysplasia punctata type 1)[180]	*PEX7* (peroxisomal type 2 targeting signal receptor; functions in peroxisomal biogenesis)	AR	Ichthyosis and alopecia in ~25% of patients; at birth, erythroderma and thick, sticky vernix with underlying adherent scale; diffuse or patchy scales with feather-like edges in infancy; later, follicular atrophoderma, scarring alopecia of the scalp, sparse or absent eyebrows, eyelashes *Histology*: (during infancy) hyperkeratosis, focal parakeratosis, follicular plugging	Symmetric skeletal anomalies with rhizomelia (short proximal limbs), scoliosis, chondrodysplasia punctata (in infancy); facial dysmorphism (frontal bossing, flat nasal bridge); bilateral congenital cataracts; neurodegeneration usually results in death by 2 years of age; occasional survival with spastic tetraplegia	Stippled epiphyses on X-rays prenatally and during infancy; in plasma/RBCs: low plasmalogen in first month of life, later increased phytanic acid

Table 57.7 Features of additional rare syndromic ichthyoses and ichthyosiform disorders.

FEATURES OF ADDITIONAL RARE SYNDROMIC ICHTHYOSES AND ICHTHYOSIFORM DISORDERS					
Disorder	**Gene (protein)**	**Mode of inheritance**	**Dermatologic features**	**Associated features**	**Diagnosis (in addition to molecular testing*)**
Refsum disease (hereditary sensory motor neuropathy type IV)[181–184]	*PHYH* (phytanoyl-CoA hydroxylase, a peroxisomal enzyme) *PEX7* (peroxisomal biogenesis factor 7)	AR	Childhood onset, ichthyosis vulgaris-like in ~50% of patients; small, white scales on extremities and trunk; larger, adherent scales on legs; hyperlinear or hyperkeratotic palms and soles	Insidious onset of night blindness and neurologic symptoms in adolescence, with undulating but progressive course; mixed motor/sensory peripheral polyneuropathy, cerebellar ataxia; atypical retinitis pigmentosa; hypo-/anosmia; later SNHL, cataracts, renal tubular dysfunction, cardiomyopathy, arrhythmias, and skeletal hyperostosis *Treatment:* drastic reduction of dietary phytanic acid intake (<5 mg daily; found in dairy products, animal fats) can arrest neurologic progression but not reverse retinal changes; less strict diet can be combined with orlistat (intestinal lipase inhibitor)	Elevated plasma phytanic acid level >200 mcmol/L (normal <3); elevated CSF protein levels *Histology*: orthokeratotic hyperkeratosis and lipid-containing vacuoles in basal keratinocytes
Nephrosis with ichthyosis and adrenal insufficiency[185]	*SGPL1* (sphingosine-1-phosphate lyase 1)	AR	Generalized fine scaling; diffuse hyperpigmentation; occasionally calcinosis cutis	Steroid-resistant nephrotic syndrome by early childhood; primary adrenal insufficiency; immunodeficiency; variable neurodegeneration	Clinical

*Genetic testing is available for all types of ichthyosis with a known molecular basis; multigene panels are preferable over single gene testing if the diagnosis is not evident based on clinical and laboratory findings.

Table 57.7 Features of additional rare syndromic ichthyoses and ichthyosiform disorders. Ichthyosis can also be a presentation of *PSAT1*-related serine deficiency disorder. AR, autosomal recessive; CNS, central nervous system; CSF, cerebrospinal fluid; FTT, failure to thrive; ID, intellectual disability; MRI, magnetic resonance imaging; PPK, palmoplantar keratoderma; RBC, red blood cells; SNHL, sensorineural hearing loss.

PEELING SKIN SYNDROMES					
Disorder	**Gene (protein)**	**Mode of inheritance**	**Dermatologic features**	**Associated features**	**Diagnosis (in addition to molecular testing*)**
Generalized inflammatory peeling skin syndrome[98†]	*CDSN* (corneodesmosin, a desmosomal protein)	AR	Erythroderma with fine white scales; widespread, patchy superficial (subcorneal) peeling of the skin; pruritus; fine hair during infancy	Mild FTT and staphylococcal skin infections during infancy; atopic manifestations (e.g. asthma, food allergies); elevated serum IgE	Clinical; *histopathology*: hyperkeratosis, parakeratosis, and subcorneal or intracorneal separation
Acral peeling skin syndrome	*TGM5* (transglutaminase 5) *CSTA* (cystatin A, a protease inhibitor)	AR	Peeling and erosions (on the hands and feet, more superficial with *TGM5*); diffuse fine scaling (*CSTA*)	None	Clinical; *histopathology*: subcorneal or intracorneal separation
Autosomal recessive exfoliative ichthyosis[186]	*CSTA* (cystatin A, a protease inhibitor) *SERPINB8* (serine protease inhibitor B8)	AR	Peeling skin on palms, soles, elbows, and knees; fine white scale on trunk and extremities	None	Clinical; *histopathology*: lack of epidermolysis
Generalized non-inflammatory peeling skin syndrome[187,188]	*CHST8* (carbohydrate sulfotransferase 8) *FLG2* (profilaggrin 2)	AR	Generalized peeling skin, especially on the extremities *FLG2*: blisters or erythroderma at birth; later generalized fine scaling; trauma- and heat-induced skin peeling, most severe acrally; hyperkeratotic plaques on elbows and knees; marked improvement during childhood	None	Clinical; *histopathology* (perilesional; *FLG2*): separation in the lower stratum corneum with parakeratosis; *ultrastructure* (*FLG2*): abnormal keratin bundles, swollen corneocytes with globular inclusions
PLACK syndrome	*CAST* (calpastatin, a protease inhibitor)	AR	Generalized *p*eeling skin, *l*eukonychia, *a*cral punctate keratoses, *c*heilitis, *k*nuckle pads	None	Clinical
Erythrokeratolysis hiemalis (keratolytic winter erythema, Oudtshoorn disease)[189]	*CTSB* (cathepsin B; segmental duplications of upstream intergenic enhancer element)	AD (South African founder mutation)	Episodic or seasonal circinate erythematous plaques with scaling and centrifugal peeling; predominantly on palms/soles, may extend to legs and arms (rarely trunk and face); occasional blisters in center of new plaques; triggered by viral infection or fever; improves with age	None	Clinical; *histopathology*: parakeratosis, necrosis in the stratum spinosum, and basaloid proliferation

*Genetic testing is available for all ichthyosiform disorders and erythrokeratodermas with a known molecular basis; multigene panels are preferable over single gene testing if the diagnosis is not evident based on clinical and laboratory findings.
†Netherton syndrome can also present with a phenotype of generalized peeling skin and erythroderma.

Table 57.8 Peeling skin syndromes. AD, autosomal dominant; AR, autosomal recessive; FTT, failure to thrive; IgE, immunoglobulin E.

Additional figures available in our eBook (see inside front cover for access code).

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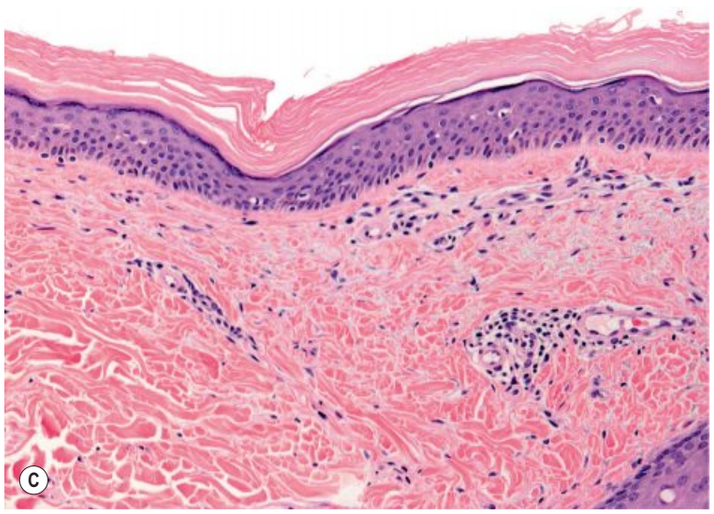
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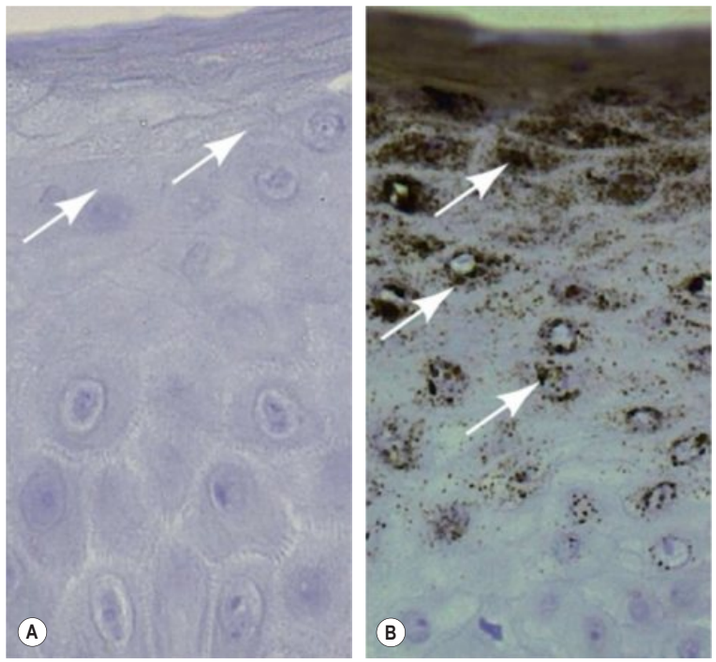




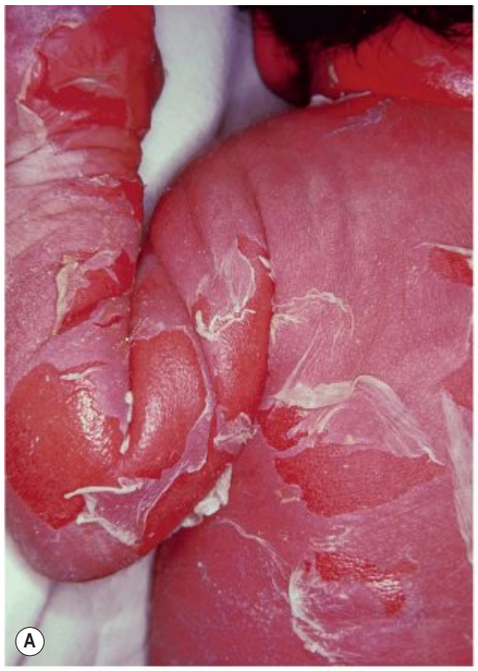
eFig. 57.1 Ichthyosis vulgaris. A Fine, white scales on the leg. **B** Polygonal brown scales on the lower leg. **C** Histologically, orthokeratotic hyperkeratosis and a diminished granular layer are evident. *A, Courtesy Angela Hernández-Martín, MD; B, C, Courtesy Lorenzo Cerroni, MD.*

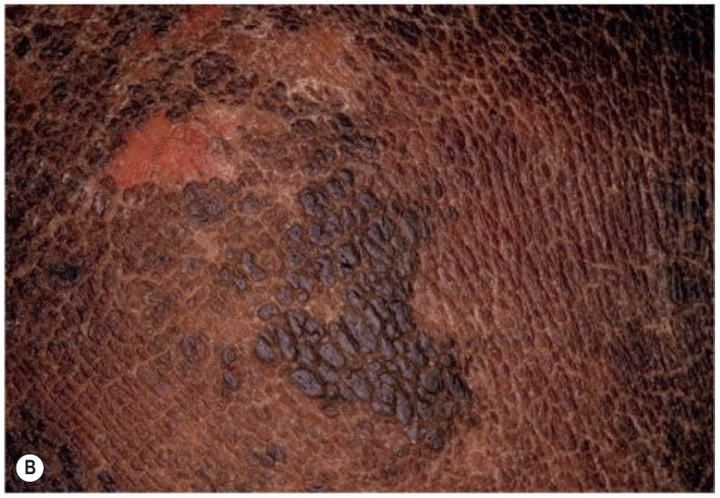


eFig 57.2 Hyperlinear palms in ichthyosis vulgaris. *Courtesy S.J. Bale, PhD and J.J. DiGiovanna, MD.*



eFig. 57.3 Filaggrin expression in ichthyosis vulgaris. Immunostaining with an anti-filaggrin antibody demonstrates a complete absence of filaggrin in an ichthyosis vulgaris patient homozygous for a deleterious *FLG* mutation (**A**), while filaggrin is strongly expressed throughout the granular layer (arrows) in normal skin (**B**). *Courtesy W.H. Irwin McLean, PhD.*







eFig. 57.4 Epidermolytic ichthyosis. A Erythroderma with widespread peeling and erosions during the neonatal period. **B** Hyperkeratosis with focal erosions. **C** Corrugated hyperkeratosis on the neck. *A, B, Courtesy Gene Mirrer, MD; C, Courtesy Julie V. Schaffer, MD.*



eFig. 57.5 Ichthyosis with confetti. Numerous small, confetti-like "islands" in the background of ichthyosiform erythroderma reflect revertant mosaicism. *Courtesy Antonio Torrelo, MD.*



eFig. 57.6 Harlequin ichthyosis. Encasement by a markedly thickened stratum corneum with development of large erythematous fissures and adherent plates. *Reproduced from Morillo M, Novo R, Torrelo A, et al. Feto arlequin. Actas Dermosifilogr 1999;90:185–7.*



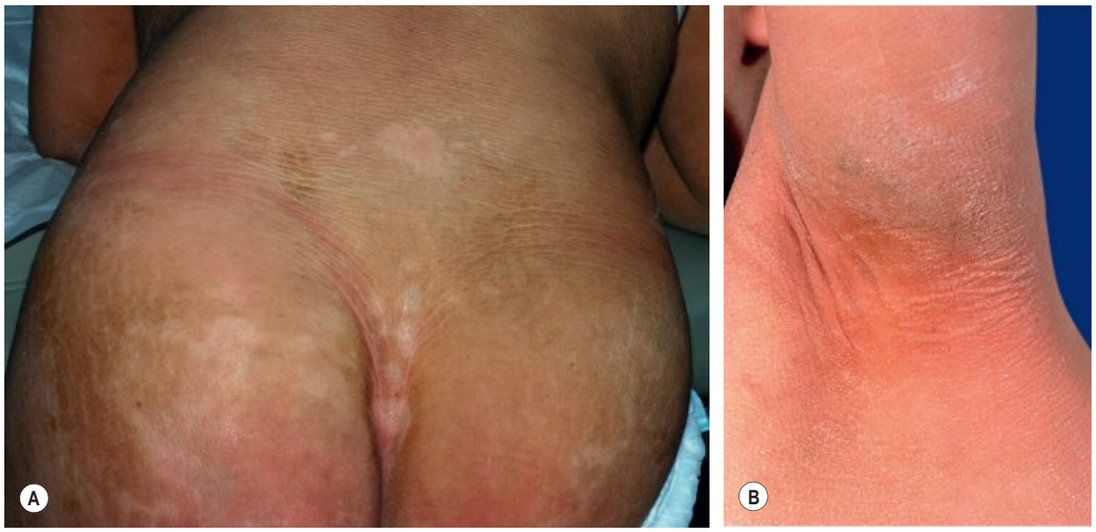




eFig. 57.7 Netherton syndrome. A Erythroderma in a neonate who also presented with hypernatremic dehydration. **B** Generalized erythema and scaling in an infant. **C** Peling scale on the hand. *Courtesy Julie V. Schaffer, MD.*



eFig. 57.8 Ichthyosis linearis circumflexa. Note the double-edged scale.



eFig. 57.9 Sjögren–Larsson syndrome. **A** Yellowish-brown hyperkeratosis, accentuated skin markings and areas of scaling on the lower back and buttocks. **B** Scaling and accentuated skin markings are seen. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy William B. Rizzo, MD.*



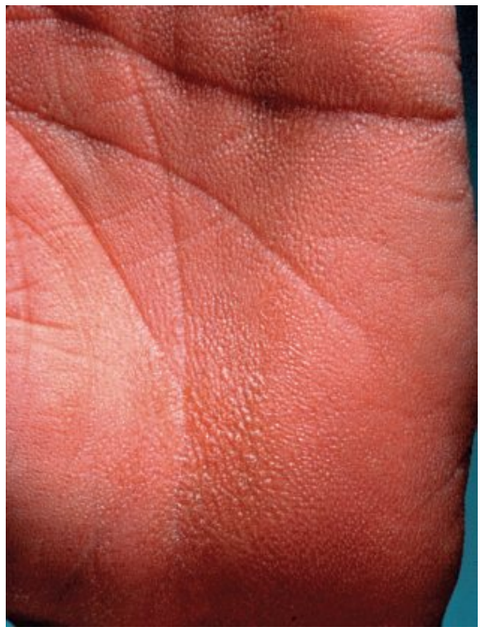
eFig. 57.10 Erythrokeratodermia variabilis et progressiva. **A** Barely elevated plaques with mild hyperkeratosis and a well-demarcated pink–brown border on the trunk. **B** Brown hyperkeratotic plaques with geographic borders in a 7-year-old child. *A, Courtesy Lorenzo Cerroni, MD; B, Courtesy Julie V. Schaffer, MD.*



eFig. 57.11 Progressive symmetric erythrokeratoderma. **A, B** Two patients with well-demarcated, symmetrically distributed hyperkeratotic plaques with underlying erythema and scale. They also had a plantar keratoderma. *B, Courtesy Antonio Torrelo, MD.*



eFig. 57.12 KID syndrome. In addition to the erythematous plaques, characteristic radial furrows are seen. *Courtesy L. Russell, MD and S.J. Bale, PhD.*



eFig. 57.13 KID syndrome. Palmar keratoderma with a grainy surface.

Palmoplantar Keratodermas 58

Dieter Metze, Kira Süßmuth and Vinzenz Oji

Key features

- Palmoplantar keratodermas can be inherited or acquired
- The three major patterns of involvement are diffuse, focal, and punctate
- The clinical presentation may be different on the hands and feet, e.g. diffuse on the soles and focal on the palms
- Additional distinguishing features include an erythematous border, transmigration to areas beyond the palmoplantar skin, and digital constrictions (pseudoainhum)
- Patients may also suffer from hyperhidrosis, maceration, blistering, fungal infections, malodor, and pain
- It is important to determine whether other features are present, e.g. nail dystrophy, hypotrichosis, oral lesions, hyperkeratosis of non-volar skin, impaired hearing, ocular findings, cardiomyopathy (in patients with woolly hair)
- Histologic examination sometimes shows findings such as epidermolytic hyperkeratosis that provide diagnostic clues

INTRODUCTION

Palmoplantar keratodermas (PPKs) represent a heterogeneous group of hereditary and acquired disorders of cornification characterized by prominent hyperkeratosis of the skin on the palms and soles. Inherited PPK sometimes represents a component of a syndromic phenotype with extracutaneous manifestations such as cardiomyopathy or deafness. Likewise, acquired PPK can be drug-induced or associated with cancer. Early diagnosis with determination of the specific subtype of PPK and recognition of associated features is therefore important[1–4] (Table 58.1).

Several classification systems for PPKs have been proposed, but none of these satisfactorily incorporates clinical presentation, pathology, and molecular pathogenesis. Traditional nomenclature is non-uniform and includes many eponyms[2]. In addition, PPK may represent a component of other genodermatoses such as ichthyoses, erythrokeratodermas, epidermolysis bullosa, and ectodermal dysplasias (Table 58.2).

A simple working classification divides PPKs into three major types based on the clinical pattern of involvement[3,5]:

- ***diffuse PPK*** – involvement of the entire palmoplantar surface, usually but not always including the central palmar skin and instep (Fig. 58.1).
- ***focal PPK*** – localized areas of hyperkeratosis, with two major patterns: (1) the *areata/nummular type* – oval lesions, located mainly over pressure points; and (2) the *striate type* – linear hyperkeratotic lesions, most commonly extending from the palms to the volar surface of the fingers, overlying flexor tendons (Fig. 58.2; see Fig. 58.15A)
- ***punctate PPK*** – multiple small keratotic papules or pits (usually from removal of a keratotic plug) that are scattered or aggregated on the palms and soles (Fig. 58.3).

Many hereditary forms of PPK do not develop until the first months or years of life. The onset and severity of disease expression depend in part on mechanical stress, e.g. exposure of the feet to friction and pressure. Some patients have diffuse PPK on the soles and focal PPK (e.g. striate) on the palms. In addition, focal involvement may evolve into a diffuse PPK over time, e.g. from infancy to adulthood. Some types of PPK don't even manifest until adulthood, while others have spontaneous improvement and recurrences over time. In addition, substantial variability can often be observed within the same family.

Further clinical classification depends upon whether there are associated cutaneous and extracutaneous features (see Table 58.1). Many PPKs demonstrate *transgrediens*, which refers to extension of the hyperkeratosis onto the dorsal aspects of the fingers, toes, hands, and feet as well as the flexor aspects of the wrists and heels, either diffusely or as callosities on pressure points (e.g. the knuckles). Confluent hyperkeratosis may also extend circumferentially around entire digits. In scarring PPKs, keratotic constriction bands (pseudoainhum) can develop around digits and may lead to autoamputation (Table 58.3). Additional associated findings include hyperhidrosis, maceration, blistering, malodor, pain, and fungal infections.

When evaluating a patient with a PPK, a thorough family history should be obtained and the entire skin surface examined as well as the mucous membranes, nails, and hair. Hearing and the ability to sweat should also be assessed. Exclusion of extracutaneous manifestations may require referral for cardiac, audiologic, ophthalmologic, or dental evaluation.



Fig. 58.1 Diffuse palmoplantar keratoderma. Hyperkeratosis of the entire palmar **(A)** and plantar **(B)** surface with sharp demarcation. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Alfons Krol, MD, and Dawn Siegel, MD.*

PRIMARY PALMOPLANTAR KERATODERMAS (PPKS)	
Disorder	**Additional features**
Hereditary PPKs	
Diffuse PPK, isolated	
Vörner–Unna–Thost	Epidermolytic
Kimonis	Non-epidermolytic
Bothnian, Nagashima	Transgrediens and white/spongy upon water exposure; non-epidermolytic
"Greither"	Transgrediens & progrediens; variable pathology
Mal de Meleda (including Gamborg Nielsen)	Mutilating, frequent superinfections; non-epidermolytic
Keratolytic winter erythema	Recurrent erythema and peeling; see Table 58.4
Diffuse PPK with associated features	
Hearing impairment	
Vohwinkel syndrome	Mutilating, "honeycomb" PPK; starfish keratoses on knuckles
Bart–Pumphrey syndrome	Knuckle pads, leukonychia
PPK due to connexin 26 defect	"Honeycomb" PPK
Mitochondrial PPK	
*High risk of acral SCC**	
Huriez syndrome	Scleroatrophy
PPK with sex reversal	Female-to-male sex reversal
Hair & nail abnormalities	
Clouston syndrome	Pebbled/grid-like acral papules, thick nails with distal elevation, hypotrichosis
Odonto-onycho-dermal dysplasia (OODD)	Hypodontia, facial telangiectasias/erythema, thin to absent nails, hypotrichosis
Schöpf–Schulz–Passarge syndrome	Hidrocystomas, other adnexal neoplasms, features of OODD
Keratoderma–hypotrichosis–leukonychia totalis	Total leukonychia, hypotrichosis
PPK & exuberant scalp hair	Leukonychia, thick "bushy" scalp hair
*Mutilating**	
Olmsted syndrome	Periorificial/intertriginous keratotic plaques
Papillon–Lefèvre syndrome†	Periodontitis, pyogenic infections, psoriasiform plaques
Loricrin keratoderma	Mild generalized ichthyosis, "honeycomb" PPK
KLICK	Keratosis linearis, ichthyosis congenita, sclerosing keratoderma
Vohwinkel syndrome (see above)	
Mal de Meleda (see above)	
Cardiomyopathy	
Naxos disease‡	Woolly hair, arrhythmias in adolescence
Focal PPK, isolated	
Brünauer–Fuhs–Siemens, Wachters	Striate on palms, nummular on soles; see Table 58.6 for genetic subtypes
Focal PPK with associated features	
Pachyonychia congenita	Painful soles, dystrophic nails, oral leukokeratosis, steatocystomas/other cysts
Focal palmoplantar and gingival keratosis	Painful soles, gingival leukokeratosis; epidermolytic
Howel–Evans syndrome	Esophageal carcinoma
Richner–Hanhart syndrome (oculocutaneous tyrosinemia)	Dendritic keratitis, corneal ulcers, intellectual disability, painful keratosis
Carvajal syndrome‡	Striate on palms; woolly hair, dilated cardiomyopathy; occasionally skin fragility, nail dystrophy, and hypodontia
PPK and woolly hair	Striate on palms; woolly hair, hypotrichosis, leukonychia
Punctate PPK, isolated	
Buschke–Fischer–Brauer (type 1 punctate PPK)	
Spiny keratoderma (type 2 punctate PPK)	
Marginal papular keratoderma: acrokeratoelastoidosis, focal acral hyperkeratosis (type 3 punctate PPK)	
Punctate keratoses of the palmar creases	
Porokeratosis punctata palmaris et plantaris	
Punctate PPK with associated features	
Cole disease	Guttate hypopigmentation, calcinosis cutis
PLACK syndrome	*P*eeling skin, *l*eukonychia, *a*cral punctate keratoses, *c*heilitis, *k*nuckle pads

Table 58.1 Primary palmoplantar keratodermas (PPKs).

PRIMARY PALMOPLANTAR KERATODERMAS (PPKS)	
Disorder	**Additional features**
Acquired PPKs	
Keratoderma climactericum	
Aquagenic PPK	
Pityriasis rubra pilaris	
Associated with hypothyroidism/myxedema	
Associated with cancer	
Associated with lymphedema	
Arsenical keratosis	
Drug-induced keratoderma[¶] (e.g. BRAF inhibitors, tyrosine kinase inhibitors [e.g. regorafenib, sorafenib; see Table 21.16], 5-fluorouracil prodrugs [tegafur, capecitabine] > lithium, verapamil, venlafaxine, glucan)	
Induced by dioxin or halogenated herbicides	
Associated with dermatomyositis: pityriasis rubra pilaris-like (Wong) type, "mechanic's hands" in antisynthetase syndrome	

*Acral SCC can also develop in patients with mutilating PPK.
†*Haim–Munk syndrome* is an allelic disorder that also features arachnodactyly, atrophic nail changes, and acro-osteolysis.
‡The PPK in Naxos disease is occasionally focal/striate, overlapping with Carvajal syndrome.
¶Sticky palms can also be caused by oral retinoids and proton pump inhibitors.

Table 58.1 Primary palmoplantar keratodermas (PPKs). More common disorders are in **bold**. Other genodermatoses that feature PPK are listed in Table 58.2. Of note, the pattern can be different on the hands and feet, e.g. diffuse on the feet and focal on the hands. Progrediens means progressive, referring to the tendency to involve additional sites (e.g. the elbows and knees) over time. Mutilating refers to the development of digital constrictions and possible autoamputation (pseudoainhum; see Table 58.3). SCC, squamous cell carcinoma.



Fig. 58.2 Focal palmoplantar keratoderma. A Striate type with linear hyperkeratosis on the palm overlying flexor tendons. **B** Areata type on the soles. *B, Courtesy Alfons Krol, MD, and Dawn Siegel, MD.*

A skin biopsy for histologic examination may provide additional diagnostic clues (Table 58.4). The molecular defect underlying PPKs may involve epidermal proteases as well as proteins of the keratinocyte cytoskeleton, cornified envelope, desmosome (see Fig. 56.8), or gap junction (Fig. 58.4, Table 58.5); the known underlying genetic mutations are summarized in Table 58.6[5,6]. Genetic analysis is sometimes helpful to establish the specific diagnosis, facilitate identification of affected family members, and enable prenatal diagnosis.

HEREDITARY KERATODERMAS

DIFFUSE PALMOPLANTAR KERATODERMA WITHOUT ASSOCIATED FEATURES (ISOLATED, NON-SYNDROMIC)

Diffuse Epidermolytic Palmoplantar Keratoderma (EPPK)

Synonyms: ■ Unna–Thost disease ■ Vörner disease ■ Vörner–Unna–Thost type PPK ■ Keratosis palmoplantaris diffusa Vörner–Unna–Thost

History

In 1880, Thost described a family with diffuse non-transgrediens PPK. This was followed by Unna's description of a clinically identical, autosomal dominant PPK in two families. Although "Unna–Thost type" has been used to designate non-epidermolytic PPK (NEPPK), in 1992, Küster et al.[7] reviewed the family described by Thost and found the histologic features of epidermolytic hyperkeratosis, which characterize the "Vörner type" of PPK. Subsequently, after keratin mutations were reported in epidermolytic PPK (EPPK), identical mutations were found in the descendants of the family studied by Thost[8]. This confusion underscores the need for careful histologic examination and sometimes multiple biopsy specimens to identify epidermolytic hyperkeratosis.

Epidemiology

EPPK is likely the most common form of diffuse keratoderma, with an estimated incidence of ≥4.4 per 100 000 in Northern Ireland[9].

Pathogenesis

Mutations in *KRT1* and *KRT9* (encoding keratins 1 and 9) underlie diffuse EPPK. The expression of keratin 9 is limited to the suprabasal cell layers of palmar and plantar skin. In patients with diffuse EPPK, the majority of keratin 9 mutations are localized to a very small area within

OTHER GENODERMATOSES THAT FEATURE PALMOPLANTAR KERATODERMA (PPK)
Erythrokeratodermas (see Ch. 57)
Keratitis–ichthyosis–deafness (KID) syndrome*
Erythrokeratodermia variabilis*
Progressive symmetric erythrokeratoderma*
KDSR-related erythrokeratoderma*
Erythrokeratodermia–cardiomyopathy syndrome*
Other ichthyoses (see Ch. 57)
Epidermolytic ichthyosis (due to keratin 1 mutations)*
Ichthyosis hystrix Curth–Macklin*
Nonsyndromic autosomal recessive congenital ichthyoses†
Sjögren–Larsson syndrome*
Refsum syndrome
CEDNIK (*c*erebral *d*ysgenesis, *n*europathy, *i*chthyosis and *k*eratoderma) syndrome*
MEDNIK (*m*ental retardation, *e*nteropathy, *d*eafness, *n*europathy, *i*chthyosis and *k*eratoderma) syndrome*
Autosomal recessive exfoliative ichthyosis (peeling skin syndrome 4, cystatin A deficiency)
Autosomal recessive keratoderma–ichthyosis–deafness syndrome*
Other ectodermal dysplasias (see Chs. 63 and 67)
Ectodermal dysplasia–ectrodactyly–clefting (EEC) syndrome
Cleft lip/palate ectodermal dysplasia
Oculo-dento-digital dysplasia
Naegeli–Franceschetti–Jadassohn syndrome, dermatopathia pigmentosa reticularis
Ectodermal dysplasia-skin fragility syndrome*
Autosomal recessive ectodermal dysplasia due to grainyhead-like 2 (*GRHL2*) mutations*,‡
Epidermolysis bullosa (EB; see Ch. 32)
EB simplex: severe*, with mottled pigmentation > localized
Junctional EB: intermediate, with pyloric atresia
Kindler EB
Erosive skin fragility disorders*, e.g. skin fragility–woolly hair syndrome, ectodermal dysplasia–skin fragility syndrome, plakoglobin deficiency
Other
SAM (severe dermatitis–multiple allergies–metabolic wasting) syndrome
Erythropoietic protoporphyria
Rothmund–Thomson syndrome
Poikiloderma with neutropenia, Clericuzio-type
CARD14-associated papulosquamous eruption*
Dyskeratosis congenita
Darier disease (usually punctate)
Cowden syndrome (punctate)
Linear PPK associated with epidermal nevus*
Porokeratotic adnexal ostial nevus (PAON; encompasses porokeratotic eccrine ostial and dermal duct nevus [PEODDN])*
Cardio-facio-cutaneous syndrome
HOPP (*h*ypotrichosis, acro-*o*steolysis/onychogryphosis, *p*almoplantar keratoderma, and *p*eriodontitis) syndrome*
Cantu syndrome*: hyperkeratosis–hyperpigmentation syndrome
Pigmentation defects, PPK, and cutaneous SCC (see Table 67.11)*
*PPK is a major feature of the disorder.
†Include congenital ichthyosiform erythroderma, lamellar ichthyosis, and harlequin ichthyosis.
‡Features include nail dystrophy/loss, marginal PPK, hypodontia, enamel hypoplasia, oral hyperpigmentation, dysphagia, and deafness.

Table 58.2 Other genodermatoses that feature palmoplantar keratoderma (PPK).

GENODERMATOSES ASSOCIATED WITH DIGITAL CONSTRICTION BANDS (PSEUDOAINHUM)
Palmoplantar keratodermas (PPKs)
Mal de Meleda*
Vohwinkel syndrome*
Loricrin keratoderma*
KLICK (*k*eratosis *l*inearis with *i*chthyosis *c*ongenita and sclerosing *k*eratoderma)*
Olmsted syndrome*
Papillon–Lefèvre syndrome*
Clouston syndrome
Pachyonychia congenita
Diffuse epidermolytic PPK
Other disorders of cornification
Epidermolytic ichthyosis
Autosomal recessive congenital ichthyoses, including Harlequin and lamellar ichthyosis
Erythrokeratodermia variabilis
Progressive symmetric erythrokeratoderma
Other genodermatoses
Epidermolysis bullosa
Kindler epidermolysis bullosa
Tuberous sclerosis complex
Erythropoietic protoporphyria
*Digital constriction bands represent a common feature.

Table 58.3 Genodermatoses associated with digital constriction bands (pseudoainhum). This is referred to as "mutilating" keratoderma. Congenital digital constriction bands can occur in the amniotic band sequence.

this gene that encodes the helix initiation motif in the 1A domain (see Ch. 56). Such mutations are highly disruptive to keratin filament assembly, causing tonofilament clumping and cytolysis that result in blistering as well as hyperkeratosis.

Within palmoplantar skin, keratin 9 is thought to partner with keratin 1. Of note, mutations in *KRT1* and *KRT10* are associated with epidermolytic ichthyosis (EI), in which epidermolytic hyperkeratosis is seen histologically (see Ch. 57). PPK in EI is predictive of a mutation in *KRT1*, which is the only type II keratin expressed in palmoplantar skin. In contrast, EI due to *KRT10* mutations rarely has involvement of palmoplantar skin, likely reflecting compensation by keratin 9, which is also a type I keratin. The majority of mutations in EI patients are in the critical 1A and 2B domains of the keratin molecule[10]. However, when keratin 1 defects underlie diffuse EPPK alone, including the "tonotubular" subtype, the mutations are typically in the beginning of the 1B domain[11]. Although *KRT1* mutations have been reported in some families with the Greither type of EPPK, other Greither variants with NEPPK not associated with *KRT1* mutations have also been described. Of note, *KRT1* mutations have also been identified in patients with focal PPK (see below).

Clinical features

The palmoplantar skin is initially red, followed by the appearance of thick, yellow hyperkeratosis by 3–4 years of age. In adults, there is confluent hyperkeratosis with a smooth, waxy surface and sharply demarcated erythematous border, sparing the dorsal aspects of the palms and soles (Fig. 58.5). Blistering and fissuring are not common but may occur during childhood or during oral retinoid therapy. Knuckle pads and thickened nails are occasionally present[2,12], and digital or palmar constriction has been described[13]. Disabling pain, especially of the palms, can occur in the "tonotubular" EPPK subtype[11]. The *Greither type* (PPK transgrediens and progrediens) presents with limited transgredient lesions, e.g. overlying the Achilles tendon, elbows, and knees.

Pathology

EPPK shows the typical pattern of epidermolytic hyperkeratosis, which is characterized by vacuolated suprabasal keratinocytes with round or ovoid eosinophilic inclusions that represent large tonofilament aggregates at an ultrastructural level[14]. In the "tonotubular" subtype, electron microscopy shows whorls of keratin containing tubular structures[11]. Histologic findings also include coarse keratohyalin granules, acanthosis, and marked orthohyperkeratosis. Intraepidermal blistering and a mild superficial dermal inflammatory infiltrate may result from keratinocyte cytolysis (Fig. 58.6A). The findings of epidermolytic hyperkeratosis are often subtle and patchy, requiring a careful search and often multiple biopsy specimens to enable their identification.



Fig. 58.3 Punctate palmoplantar keratoderma. Keratotic papules, some coalescing to form plaques, on the palms **(A–C)** and soles **(D, E)**. *C, Courtesy Kalman Watsky, MD.*

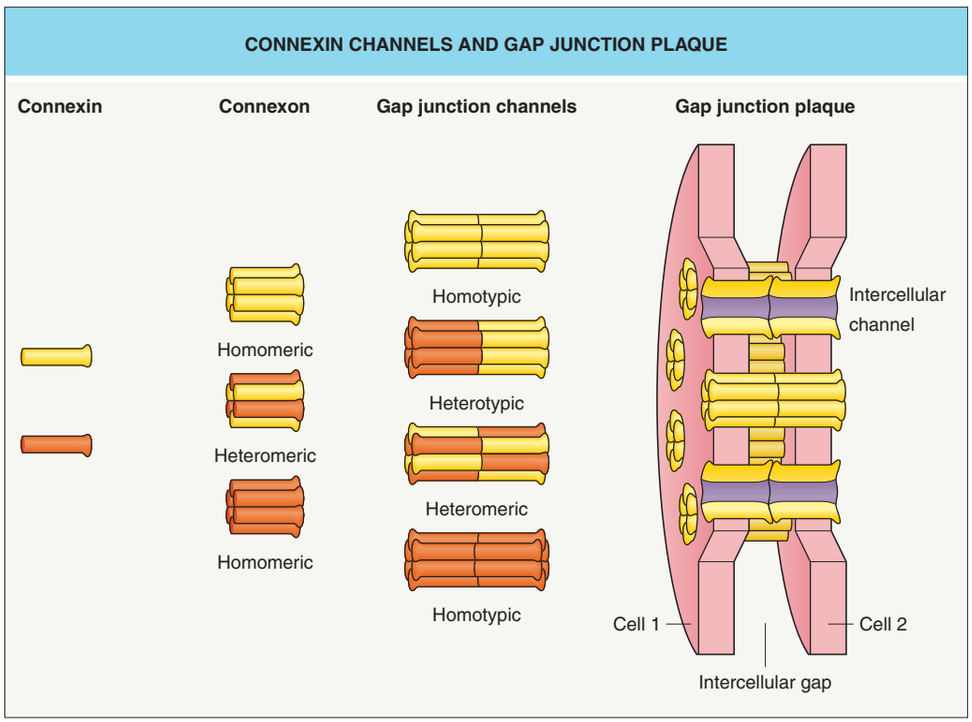


Fig. 58.4 Connexin channels and the gap junction plaque. Gap junctions are specialized transmembrane channels that connect the cytoplasm of neighboring cells, facilitating cell-to-cell communication. The status of the channels (i.e. open or closed) is controlled by mechanisms, including voltage, calcium concentration, pH, and phosphorylation. Each gap junction channel is composed of integral membrane proteins called connexins. The half-life of each connexin is short (i.e. hours), which results in a constant state of assembly and degradation of channels. Different connexins are expressed in a tissue- and differentiation-specific manner as well as in response to stimuli. Six connexin molecules oligomerize to form a connexon hemichannel with a central pore that has a maximum diameter of 2 nm. Connexons may be homomeric if all the participating molecules are of the same connexin species, or heteromeric if they differ. Connexons of adjacent cells dock in the intercellular gap to form a complete gap junction intercellular channel. *Redrawn with permission from Richard G, Smith LE, Bailey RA, et al. Mutations in the human connexin gene GJB3 cause erythrokeratoderma variabilis. Nat Genet 1998;20:366–9.*

HISTOLOGIC PATTERNS IN SELECTED HEREDITARY PALMOPLANTAR KERATODERMAS (PPKS)
Epidermolytic hyperkeratosis*
Diffuse epidermolytic PPK: Vörner–Unna–Thost, "Greither" (epidermolytic variant) Focal palmoplantar and gingival keratosis
Orthohyperkeratosis, acanthosis, and papillomatosis
Diffuse non-epidermolytic PPK: Bothnian, Nagashima, Kimonis, "Greither" (non-epidermolytic variant) Mal de Meleda (including Gamborg Nielsen type) Huriez, Howel–Evans, Papillon–Lefèvre, and Vohwinkel syndromes
Orthohyperkeratosis with focal parakeratosis, acanthosis, and papillomatosis
KLICK (*k*eratosis *l*inearis with *i*chthyosis *c*ongenita and sclerosing *k*eratoderma) Erythrokeratodermia variabilis KID (keratitis–ichthyosis–deafness) syndrome
Orthohyperkeratosis with parakeratosis and hypergranulosis with transitional cells
Loricrin keratoderma
Eccrine syringofibroadenoma
Schöpf–Schulz–Passarge syndrome, odonto-onycho-dermal dysplasia Clouston syndrome (acral papular lesions)
Widening of intercellular spaces and partial dehiscence of keratinocytes
Striate PPK types 1 and 2 Diffuse PPK due to a *DSG1* mutation Carvajal syndrome Erosive skin fragility disorders*, e.g. ectodermal dysplasia-skin fragility and skin fragility–woolly hair syndromes
Ballooning degeneration, eosinophilic granular material and parakeratosis with absence of the granular layer
Keratolytic winter erythema
Epithelia with pale cytoplasm and eosinophilic inclusions
Pachyonychia congenita Richner–Hanhart syndrome
Orthohyperkeratotic, focally parakeratotic column overlying depressed epidermis
Punctate PPK, Buschke–Fischer–Brauer type Punctate keratoses of the palmar creases Focal acral hyperkeratosis
Orthohyperkeratotic, focally parakeratotic column overlying depressed epidermis with fragmentation and loss of elastic fibers
Acrokeratoelastoidosis
Parakeratotic column overlying depressed epidermis devoid of vacuolization and dyskeratosis
Spiny keratoderma
Parakeratotic column overlying depressed epidermis with vacuolization and dyskeratosis
Porokeratosis
*When epidermolytic hyperkeratosis is present, oral retinoid therapy can exacerbate skin fragility and should be avoided.

Table 58.4 Histologic patterns in selected hereditary palmoplantar keratodermas (PPKs).



Fig. 58.5 Diffuse epidermolytic palmoplantar keratoderma (Vörner–Unna–Thost). Diffuse, hyperkeratosis with waxy surface on the palm **(A)** and soles **(B, C)**, with sharp demarcation. Note the red borders **(A, C)**. *C, Courtesy Alfons Krol, MD, and Dawn Siegel, MD.*

Differential diagnosis

EI can be distinguished clinically by the cutaneous involvement beyond the palms and soles. EPPK and NEPPK can be differentiated histologically by the absence of epidermolytic hyperkeratosis in the latter; they are not distinguishable clinically, although the erythematous border of EPPK tends to be more pronounced.

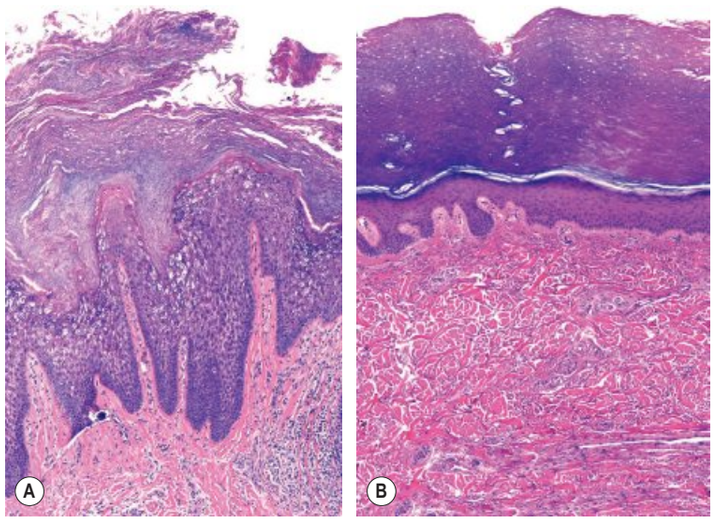


Fig 58.6 Histologic features of palmoplantar keratoderma. A In epidermolytic hyperkeratosis, suprabasal keratinocytes show vacuolated cytoplasm, intracytoplasmic eosinophilic granules, and coarse keratohyalin granules. **B** In non-epidermolytic keratoderma, an extremely thick orthohyperkeratotic horny layer and acanthotic epidermis are seen. *Courtesy Luis Requena, MD.*

Management

Factors to consider when selecting treatment for diffuse PPK include the severity of symptoms, degree of hyperkeratosis, and age of the patient. Mechanical debridement can be performed with a blade, foot file, or pumice stone and followed by application of a keratolytic agent to help avoid fissure formation. Options for keratolytic therapy include 50% propylene glycol in water under plastic occlusion several nights per week, lactic acid- and urea-containing creams and lotions, and salicylic acid 4%–6% in petrolatum; the latter should not be applied to large areas in young children to avoid salicylism from systemic absorption (see Ch. 129). Oral retinoids may improve the hyperkeratosis, but even low doses can lead to excessive peeling and increased fragility of volar skin in EPPK[15]. Topical calcipotriene (calcipotriol) has reportedly been helpful[16]. Genome editing utilizing CRISPR/Cas9 technology was shown to decrease expression of mutant keratin 9 and lead to phenotypic improvement in an EPPK-like transgenic mouse model[17].

Diffuse Non-epidermolytic Palmoplantar Keratoderma (NEPPK)

Diffuse NEPPK represents a heterogeneous group of non-syndromic forms of PPK that do not show epidermolytic hyperkeratosis histologically. This category includes *Bothnia(n)*[18], *Kimonis*[19], and *Nagashima*[20] *types* of PPK as well as *Mal de Meleda*[21]. The *Greither type* (PPK transgrediens

HUMAN CONNEXIN DISORDERS				
Disorder	**Inheritance**	**Connexin**	**Gene**	**Major organ distribution**
Non-syndromic hearing impairment (DFNB1)	AR	Cx26	*GJB2*	Ubiquitous, including liver, cochlea, mammary gland, skin and appendages, mucous membranes, pancreas, kidney, intestine, lung
Non-syndromic hearing impairment (DFNA3)	AD	Cx26	*GJB2*	
Palmoplantar keratoderma and hearing impairment, including Vohwinkel syndrome	AD	Cx26	*GJB2*	
Bart–Pumphrey syndrome	AD	Cx26	*GJB2*	
Keratitis–ichthyosis–deafness (KID) syndrome & hystrix-like–ichthyosis–deafness (HID) syndrome	AD	Cx26 (Cx30)*	*GJB2 (GJB6)**	
Porokeratotic adnexal ostial nevus (PAON)	Mosaic	Cx26	*GJB2*	
Non-syndromic hearing impairment (DFNA3)	AD	Cx30	*GJB6*	Brain, cochlea, skin
Clouston syndrome	AD	Cx30	*GJB6*	
Erythrokeratodermia variabilis	AD≫AR	Cx30.3	*GJB4*	Skin, kidney
Erythrokeratodermia variabilis	AD≫AR	Cx31	*GJB3*	Skin, eye, placenta, kidney, testes, cochlea, Schwann cells
Non-syndromic hearing impairment	AR≫AD	Cx31	*GJB3*	
Peripheral sensory neuropathy and hearing impairment	AD	Cx31	*GJB3*	
Charcot–Marie–Tooth disease	X-linked dominant	Cx32	*GJB1*	Brain, Schwann cells, liver, thyroid, kidney, pancreas, uterus
Increased risk for atherosclerotic plaque development		Cx37	*GJA4*	Gonads, lung, endothelium, heart, skin
Oculo-dento-digital dysplasia	AD	Cx43	*GJA1*	Ubiquitous, including eyes, teeth, musculoskeletal, brain, heart, skin
Erythrokeratodermia variabilis et progressiva	AD	Cx43	*GJA1*	
Keratoderma–hypotrichosis–leukonychia totalis	AD	Cx43	*GJA1*	
ILVEN	Mosaic	Cx43*	*GJA1**	
Syndactyly, type III	AD	Cx43	*GJA1*	
Hypoplastic left heart syndrome	Oligogenic	Cx43	*GJA1*	
Cataract, zonular pulverulent-3	AD	Cx46	*GJA3*	Lens, heart, kidney, peripheral nervous system
Atrial fibrillation, familial 11	AD	Cx40	*GJA5*	Heart
Hereditary lymphedema	AD	Cx47	*GJC2*	Lymphatic vessels, CNS
Hypomyelinating leukodystrophy	AR	Cx47	*GJC2*	
Cataract, zonular pulverulent-1	AD	Cx50	*GJA8*	Lens, cornea, heart

*Reported in a single patient to date.

Table 58.5 Human connexin disorders. Disorders in **bold** feature palmoplantar keratoderma. AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; GJ, gap junction. *Adapted with permission from Richard G. Connexin disorders of the skin. Adv Dermatol 2001;17:243–77.*

PALMOPLANTAR KERATODERMAS (PPKS) – UNDERLYING GENETIC MUTATIONS			
Disorder	**Inheritance**	**Mutated genes**	**Protein products**
Diffuse without associated features			
Vörner–Unna–Thost EPPK	AD	*KRT9* > *KRT1*	Keratin 9 Keratin 1 (1B domain)
Kimonis NEPPK	AD	*KRT1*	Keratin 1 (V1 domain)
Bothnia NEPPK	AD	*AQP5*	Aquaporin 5
Nagashima NEPPK	AR	*SERPINB7*	Serpin family B member 7
SERPINA12-related NEPPK	AR	*SERPINA12*	Serpin family A member 12
Mal de Meleda	AR	*SLURP1*	Secreted Ly6/PLAUR-domain containing 1
Keratolytic winter erythema	AD	*CTSB*	Cathepsin B
Diffuse with associated features			
Loricrin keratoderma	AD	*LOR*	Loricrin
KLICK	AR	*POMP*	Proteasome maturation protein
Vohwinkel syndrome, Bart–Pumphrey syndrome, PPK with deafness	AD	*GJB2*	Connexin 26
Mitochondrial PPK with deafness	Mt	*MT-TS1*	Mt tRNA serine 1
Huriez syndrome	AD	*SMARCAD1*	SWI/SNF-related, matrix-associated actin-dependent regulator of chromatin, subfamily a, containing DEAD/H box 1
PPK with sex reversal & SCC	AR	*RSPO1*	R-spondin 1
Clouston syndrome	AD	*GJB6*	Connexin 30
Keratoderma–hypotrichosis–leukonychia totalis	AD	*GJA1*	Connexin 43
PPK & exuberant scalp hair	AR	*FAM83G*	Family with sequence similarity 83 member G
OODD, SSP syndrome	AR	*WNT10A*	Wnt 10A
Olmsted syndrome	AD > AR	*TRPV3*	Transient receptor potential vanilloid 3
	XR	*MBTPS2*	Membrane-bound transcription factor peptidase, site 2
	AD	*PERP*	p53 effector related to PMP22
Papillon–Lefèvre syndrome, Haim–Munk syndrome	AR	*CTSC*	Cathepsin C
Naxos disease	AR	*JUP*	Junction plakoglobin
Focal without associated features			
Striate PPK type 1	AD	*DSG1*	Desmoglein 1
Striate PPK type 2	AD	*DSP*	Desmoplakin
Striate PPK type 3	AD	*KRT1*	Keratin 1 (V2 tail)
Focal PPK	AD	*KRT6C* *KRT16*	Keratins 6C and 16
Focal with associated features			
Pachyonychia congenita	AD	*KRT6A* *KRT6B* *KRT6C* *KRT16* *KRT17*	Keratins 6A, 6B, 6C, 16, and 17
Richner–Hanhart syndrome	AR	*TAT*	Tyrosine aminotransferase
Howel–Evans syndrome	AD	*RHBDF2*	Rhomboid 5 homolog 2
Carvajal syndrome	AR > AD	*DSP*	Desmoplakin
PPK and woolly hair	AR	*KANK2*	KN motif and ankyrin repeat domains 2
Punctate without associated features			
Buschke–Fischer–Brauer (type 1)*	AD	*AAGAB*	α- and γ-adaptin-binding protein p34
Punctate with associated features			
Cole disease	AD	*ENPP1*	Ectonucleotide pyrophosphate/phosphodiesterase 1
PLACK syndrome	AR	*CAST*	Calpastatin

*A second locus for punctate PPK on 8q was found to be potentially associated with a heterozygous missense mutation in the collagen type XIV α1 chain gene (*COL14A1*) in a single Chinese family.

Table 58.6 Palmoplantar keratodermas (PPKs) – underlying genetic mutations. The protein products represent epidermal proteases/related proteins/enzymes (*gray*) or components of the keratinocyte cytoskeleton (*purple*), cornified envelope (*yellow*), desmosome (*blue*), gap junction/other transmembrane channels (*green*), or WNT/β-catenin signaling pathway (*orange*). AD, autosomal dominant; AR, autosomal recessive; GJA1, gap junction α1; GJB2/6, gap junction β2/6; KLICK, keratosis linearis–ichthyosis congenital–sclerosing keratoderma; Mt, mitochondrial; OODD, odonto-onycho-dermal dysplasia; PLACK, *p*eeling skin, *l*eukonychia, *a*cral punctate keratoses, *c*heilitis, *k*nuckle pads; SCC, squamous cell carcinoma; SSP, Schöpf–Schulz–Passarge; tRNA, transfer RNA.

and progrediens) lacks a clear definition and is heterogeneous, with both epidermolytic and non-epidermolytic variants (see EPPK above)[22]. The *Gamborg Nielsen (Norrbotten) type*[23] is currently regarded as a variant of Mal de Meleda[24].

Epidemiology and pathogenesis

An autosomal dominant form of NEPPK that was initially described in families from Bothnia in Northern Sweden and the United Kingdom is due to heterozygous missense mutations in *AQP5*, which encodes aquaporin 5. Aquaporins are transmembrane proteins that allow the osmotic movement of water across the cell membrane. Aquaporin 5 is expressed by keratinocytes in the granular layer, and the gain-of-function mutations that cause Bothnian-type NEPPK lead to increased keratinocyte water uptake rather than transepidermal water loss[18].

The form of NEPPK described by *Kimonis* is caused by a heterozygous mutation in a highly conserved lysine residue in the V1 domain of keratin 1 that does not result in epidermolytic hyperkeratosis[19].

Nagashima-type NEPPK, an autosomal recessive disorder most commonly observed in Asians and also described in Finns, is caused by biallelic nonsense mutations in *SERPINB7*. More recently, biallelic mutations in *SERPINA12* were found to underlie another autosomal recessive form of NEPPK. These genes encode *ser*ine *p*rotease *in*hibitor family B member 7 and family A member 12, respectively, which are thought to regulate proteolytic activity in the skin[25,26].

Mal de Meleda is an autosomal recessive condition that was first described in inhabitants of the island of Mljet (Meleda) off the Dalmatian coast. It is caused by biallelic mutations in *SLURP1* (secreted *l*eukocyte antigen-6/*u*rokinase-type plasminogen activator related *p*rotein *1*), which is expressed in the granular layer of the epidermis[27]. *SLURP1* acts as a ligand of the α7-nicotinic acetylcholine receptor and plays a role in epidermal differentiation. Heterozygous female carriers may have a mild clinical phenotype.

Clinical features

The clinical findings and time course of the different types of NEPPK are overall similar to those of EPPK (see above). The hyperkeratosis is variably thick and hyperhidrosis is common, with frequent dermatophyte infections and pitted keratolysis. The Bothnian, Nagashima, and *SERPINA12*-related types feature transgrediens and a white spongy appearance upon exposure to water[18,28]. Acrokeratoelastoidosis-like papules have been reported in Bothnian-type PPK as has acral melanoma in Japanese patients with Nagashima-type PPK; the latter is also characterized by "soft" hyperkeratosis, prominent erythema, and a nonprogressive course[28].

In Mal de Meleda, progressive transgredient hyperkeratosis begins during early infancy and becomes severe, impairing the mobility of hands and resulting in hyperhidrotic maceration, severe malodor, and fissures (Fig. 58.7). Fungal superinfection is common, and hyperkeratosis of the fingers may lead to sclerodactyly and digital constrictions (pseudoainhum). The elbows, knees, wrists, and ankles as well as the dorsal surfaces of the hands and feet can be involved, and the nails show thickening, koilonychia, and subungual hyperkeratosis. Angular cheilitis and involvement of the lips and perioral skin may be observed[21,29]. Hyperpigmented macules, melanoma, and Bowen disease within the keratotic areas have been reported[30].

Differential diagnosis

In addition to diffuse EPPK, diagnostic considerations may include aquagenic PPK, acral peeling skin syndrome, and keratolytic winter erythema.

Pathology

Histologically, palmoplantar skin shows orthohyperkeratosis, hypergranulosis or normogranulosis, and acanthosis (Fig. 58.6B). A moderate perivascular lymphocytic infiltrate may be present. In Mal de Meleda, papillomatosis is a characteristic finding. PAS staining should be performed to exclude infection by dermatophytes.

Management

Keratolytic therapy may be helpful, such as 5%–10% salicylic acid in white soft paraffin, or 5%–6% salicylic acid in 70% propylene glycol gel; occlusion for a few nights per week enhances efficacy, and mechanical debridement can also be performed. However, salicylic acid should not be applied to large areas in young children. Low-dose acitretin (0.2–0.5 mg/kg daily) may be considered, especially for patients with functional impairment. Fungal superinfection and bacterial overgrowth should be treated. Responses to oral erythromycin and topical tacrolimus have been described in the Bothnian and Nagashima types, respectively[31,32]. Nonsense-suppression (readthrough) therapy with topical gentamicin has been shown to reduce hyperkeratosis in Nagashima-type PPK[33]. Excision of hyperkeratotic skin with split-thickness skin grafting represents an option to relieve functional impairment.



Fig. 58.7 Mal de Meleda. Diffuse, yellow hyperkeratosis characterized by maceration, erythema in areas with reduced hyperkeratosis, progression beyond the palmar area (transgrediens), and a well-defined red border.

Keratolytic Winter Erythema and *CTSB*-Related Palmoplantar Keratoderma

Synonyms: ■ Erythrokeratolysis hiemalis ■ Oudtshoorn disease

Keratolytic winter erythema (KWE) is an autosomal dominant disorder of cornification characterized by recurrent erythema followed by centrifugal peeling on the palms (Fig. 58.8), soles, occasionally the extremities, and rarely elsewhere; episodes typically occur during the winter (see Table 57.8). The term "Oudtshoorn disease" derives from a town in South Africa, where the condition was first described and is common due to a founder effect. KWE is caused by genomic duplications in a noncoding region containing an enhancer element for the cathepsin B gene (*CTSB*), which lead to upregulation of this cysteine protease that functions in keratinocyte homeostasis[34]. In addition, a missense gain-of-function *CTSB* mutation was found to underlie an autosomal dominant form of diffuse transgredient PPK with an erythematous border and associated peeling[35].

Histologically, KWE demonstrates ballooning degeneration in the upper epidermis associated with eosinophilic granular material, absence of the granular layer, parakeratosis, and variable spongiosis[34]. Regenerative basal cell hyperplasia may be evident. In *CTSB*-related PPK, orthohyperkeratosis and areas of intra- and subcorneal separation have been described[35].

DIFFUSE PALMOPLANTAR KERATODERMAS WITH ICHTHYOSIS

Loricrin keratoderma and *k*eratosis *l*inearis–*i*chthyosis *c*ongenita–sclerosing *k*eratoderma (KLICK) have distinctive skin findings beyond the palms and soles. PPK is also a component of other ichthyoses that are discussed in Chapter 57 (see Table 58.2).



Fig. 58.8 Keratolytic winter erythema ("Oudtshoorn disease"). Recurrent erythema followed by centrifugal peeling of the hands and feet. *Courtesy Sian Hartshorne, MD.*

Loricrin Keratoderma

Synonyms: ■ Camisa variant of Vohwinkel syndrome ■ Mutilating keratoderma with ichthyosis ■ Variant Vohwinkel syndrome ■ Vohwinkel syndrome with ichthyosis

This disorder is caused by mutations in the gene encoding loricrin, a glycine-rich cornified envelope protein[36] (see Ch. 56). Mutant loricrin is transported to the nucleus, where it is thought to interfere with regulation of cornification[37,38]. Recombination-induced revertant mosaicism leading to small "islands" of unaffected skin has been described[39].

Clinical and histologic features

Generalized desquamation or features of a collodion baby may be evident at birth, with subsequent evolution to a mild generalized ichthyosis. During childhood, diffuse NEPPK develops, with a "honeycomb" pattern and associated findings that overlap with those of Vohwinkel syndrome, including keratotic digital constrictions (pseudoainhum), knuckle pads, and warty keratoses on extensor surfaces[40]. However, the absence of deafness as well as the presence of ichthyosis distinguish loricrin keratoderma from Vohwinkel syndrome[41]. The differential diagnosis may also include ichthyosis hystrix Curth–Macklin due to mutations in the variable tail region of keratin 1 (see Ch. 57).

Histologic features of loricrin keratoderma include hyperkeratosis with parakeratotic cells, scattered transitional cells, and a broad stratum granulosum with focal perinuclear vacuolization[40,41]. Keratinocyte nuclei demonstrate distinctive immunoreactivity for loricrin[37].

Management

Isotretinoin has been reported to improve hyperkeratosis and prevent digital amputation[42].

Keratosis Linearis–Ichthyosis Congenita–Sclerosing Keratoderma (KLICK)

Synonym: ■ KLICK syndrome

KLICK is an autosomal recessive disorder caused by mutations in *POMP*, which encodes proteasome maturation protein[43]. The resulting proteasome insufficiency disturbs terminal epidermal differentiation and interferes with processing of profilaggrin.

Patients present with mild congenital ichthyosis and diffuse, transgredient PPK with development of digital constriction bands[44]. Other features include flexion deformity of the fingers with associated sclerosis and parallel linear arrays of keratotic papules in the flexural areas of the extremities. Erythrokeratoderma, presenting as well-demarcated erythematous, hyperkeratotic plaques on the extremities and trunk, has also been described[45]. Development of aggressive squamous cell carcinoma (SCC) in affected skin has been reported[46].

Histologic evaluation shows orthohyperkeratosis, focal parakeratosis, acanthosis, and hypergranulosis with characteristic irregular keratohyalin granules. Immunostaining for filaggrin is positive in the cornified layer rather than the granular layer.



Fig. 58.9 Mutilating palmoplantar keratoderma in Vohwinkel syndrome. A Diffuse honeycombed keratoderma of the sole. **B** Pseudoainhum formation. *A, Courtesy Alfons Krol, MD, and Dawn Siegel, MD.*

DIFFUSE PALMOPLANTAR KERATODERMAS WITH ASSOCIATED FEATURES/SYNDROMIC

Vohwinkel Syndrome

Synonyms: ■ Keratoderma hereditaria mutilans ■ Cicatrizing keratoderma with hearing impairment ■ Keratoderma with sensorineural deafness ■ Vohwinkel syndrome with deafness

Vohwinkel syndrome is autosomal dominantly inherited and caused by mutations in the gap junction β2 gene (*GJB2*) encoding connexin 26[47,48]. This gene is also implicated in Bart–Pumphrey and keratitis–ichthyosis–deafness (KID) syndromes[49] (see Table 58.5 and Ch. 57). Connexin 26 is expressed in the palmoplantar epidermis, sweat glands, and cochlea of the inner ear. As a major gap junction protein, it is crucial for signal transduction involved in epithelial differentiation and sensorineural functions[50,51].

Vohwinkel syndrome is characterized by pitted and stippled, honeycomb-like diffuse PPK and characteristic stellate ("starfish") keratoses on the knuckles (Fig. 58.9A). Digital constriction bands may lead to autoamputation (pseudoainhum) (Fig. 58.9B)[52]. Patients may have non-progressive high-tone sensorineural hearing loss, which may be overlooked during infancy.



Fig. 58.10 Bart–Pumphrey syndrome. Leukonychia and knuckle pads in a patient with sensorineural deafness. *Courtesy Alfons Krol, MD, and Dawn Siegel, MD.*

Bart–Pumphrey syndrome is characterized by keratoses over the interphalangeal and metacarpophalangeal joints ("knuckle pads") and leukonychia (Fig. 58.10), which may improve with age, as well as a honeycomb-like PPK and hearing loss as in Vohwinkel syndrome[53,54].

Histologic findings are nonspecific, with papillomatosis and prominent orthohyperkeratosis.

Treatment with oral retinoids can improve the PPK[55], while the cicatricial bands require surgical intervention which occasionally includes the use of distant flaps[56]. Cochlear implantation may be performed for the hearing loss.

Mitochondrial Palmoplantar Keratoderma With Hearing Impairment

This PPK has a honeycomb appearance and may be either focal or diffuse, often with calluses on the heels and toes. Sensorineural hearing loss typically develops during childhood[57]. The causative mutation in mitochondrial DNA (mtDNA) affects a serine transfer RNA (tRNA)[58].

Huriez Syndrome

Synonyms: ■ Palmoplantar keratoderma with scleroatrophy ■ Sclerotylosis

This rare autosomal dominant disease is caused by mutations in *SMARCAD1* (*S*WI/SNF-related, *m*atrix-associated *a*ctin-dependent *r*egulator of *c*hromatin, subfamily *a*, containing *D*EAD/H box *1*) that lead to haploinsufficiency for a skin-specific isoform with a role in the repair of double-strand DNA breaks[59]. Diffuse scleroatrophy of the hands typically becomes evident during infancy, and there is eventual development of sclerodactyly and absent dermatoglyphs. The mild PPK presents as diffuse parchment-like skin on the palms and, to a lesser degree, the soles; circumscribed hyperkeratosis over pressure points may develop during adulthood. Hypoplastic nail changes (e.g. thinning, longitudinal ridging, fissuring) are also seen[60]. The risk of developing SCC in areas of atrophic skin is increased by ≥100-fold, and early metastasis often occurs[61]. The differential diagnosis may include Kindler epidermolysis bullosa, PPK with sex reversal and SCC, and dyskeratosis congenita.

Histologic features of the keratoderma include orthohyperkeratosis, acanthosis, and hypergranulosis. A characteristic finding is almost complete absence of Langerhans cells in the affected skin.

Palmoplantar Keratoderma With Sex Reversal and Squamous Cell Carcinoma

This rare autosomal recessive syndrome, initially described in several consanguineous Italian kindreds, is due to mutations in the R-spondin 1 gene (*RSPO1*), which encodes a protein that activates β-catenin signaling and has an important role in gonadal development[62,63]. In addition to a diffuse NEPPK that develops during infancy, there is a marked predisposition to the development of acral SCC. Affected individuals with a 46,XX genotype have either: (1) a male phenotype (i.e. female-to-male sex reversal), often associated with hypospadias and hypogonadism; or (2) ambiguous genitalia, sometimes with hermaphroditism (existence of both male and female gonadal structures). Other manifestations include sclerodactyly with variable cutaneous atrophy resembling Huriez syndrome, ichthyosiform scale on the lower legs, nail dystrophy (e.g. hypoplasia, longitudinal ridging, skin growth over the nail plate), periodontitis leading to early loss of teeth, ocular anomalies (e.g. cataracts, colobomas), and microcephaly[62,63].



Fig. 58.11 Clouston syndrome. Note the "pebbled" skin on the dorsal aspect of the toes as well as the dystrophic nail plates. *Courtesy D. Sasseville, MD, and R. Wilkinson, MD.*

Clouston Syndrome

Synonym: ■ Hidrotic ectodermal dysplasia 2

Clouston syndrome is an autosomal dominant disorder caused by missense mutations in the gap junction β6 gene (*GJB6*), which encodes connexin 30[64]. The dysfunctional connexin 30 disturbs cell–cell communication in epithelial cells. Although first reported in a large French-Canadian kindred, Clouston syndrome has also been described in a variety of other ethnic groups.

This condition features diffuse PPK in conjunction with hypotrichosis and nail dystrophy[65], thereby qualifying as an ectodermal dysplasia (see Ch. 63). The PPK initially develops over pressure points and then becomes diffuse, increasing in severity with age. In addition, thickened skin with a "pebbled" appearance is often evident on the dorsal aspects of the digits, knees, and elbows (Fig. 58.11). Small papules in a grid-like array that corresponds to eccrine acrosyringia may be seen, especially on the distal digits where the dermatoglyphs are most prominent.

Progressive hypotrichosis that can eventuate in complete alopecia affects the scalp, eyebrows, eyelashes, and axillary and genital regions; the hair is typically wiry, brittle, and pale. The nails, which may be normal or milky white at birth, gradually become thickened and dystrophic, displaying short nail plates that are easily shed (see Fig. 58.11). The nail abnormalities may mimic those of pachyonychia congenita or other syndromes of "hair–nail hypoplasia"[66].

Histologic evaluation of thickened palms and soles shows orthohyperkeratosis with a normal granular layer. Papular lesions may demonstrate proliferation of eccrine ductal structures within a fibrovascular stroma (eccrine syringofibroadenomas). Ultrastructural examination of the hair shows disorganization of the hair fibers, with a loss of the hair shaft cuticle.

Odonto-onycho-dermal Dysplasia

Synonyms: ■ Tricho-odonto-onycho-dermal dysplasia ■ Schöpf–Schulz–Passarge syndrome

Odonto-onycho-dermal dysplasia encompasses a diverse group of autosomal recessive disorders caused by mutations in *WNT10A*, which encodes a signaling molecule with a critical role in the development of ectodermal appendages[67] (see Fig. 55.6). The clinical features include various combinations of diffuse PPK, facial telangiectasias or reticulate erythema, dental anomalies (e.g. hypodontia, small teeth), nail dystrophy, and hypotrichosis (see Table 63.13)[68]. Patients with Schöpf–Schulz–Passarge syndrome also develop hidrocystomas of the eyelids and other adnexal tumors (e.g. poromas, tumors of the follicular infundibulum) during adulthood[69]. Histologic examination of the PPK demonstrates eccrine syringofibroadenomas.

Olmsted Syndrome

Synonym: ■ Mutilating PPK with periorificial keratotic plaques

Autosomal dominant and the less common autosomal recessive variants of Olmsted syndrome are caused by different gain-of-function mutations in the *t*ransient *r*eceptor *p*otential *v*anilloid *3* gene (*TRPV3*)[70,71]. TRP cation-selective ion channels are involved in epidermal differentiation, hair growth, and the modulation of inflammation, pain, and pruritus. The X-linked recessive variant of Olmsted syndrome, which presents with total alopecia and severe nail dystrophy, results from specific mutations in the *m*embrane-*b*ound *t*ranscription factor *p*eptidase *s*ite *2* gene (*MBTPS2*). The zinc metalloprotease encoded by this gene is essential for cholesterol homeostasis and endoplasmatic reticulum stress response[72]. *MBTPS2* mutations also underlie IFAP syndrome (ichthyosis follicularis with atrichia and photophobia) and KFSD (keratosis follicularis spinulosa decalvans) (see Chs. 38 and 57). In addition, heterozygous mutations in *PERP* (p53 effector related to PMP22), a component of desmosomes, underlie an autosomal dominant form of Olmsted syndrome[73].

Olmsted syndrome features a sharply defined, diffuse PPK with an erythematous border, and progression over time leads to flexion contractures and digital constriction or autoamputation. Erythema and warty hyperkeratosis develop in the perioral and perianal regions as well as in other intertriginous sites[74], resulting in pain and pruritus[75]. Keratoses in linear streaks and with a perifollicular distribution also appear in the flexures of the extremities[76]. Additional findings may include alopecia, blonde curly hair (*PERP*-related form), nail dystrophy, oral involvement (e.g. keratotic plaques, periodontal disease), corneal dysplasia, erythromelalgia, deafness, and joint laxity[76]. Recurrent skin infections are common, and the development of SCC and melanoma within areas of keratoderma has been reported[77,78].

The differential diagnosis may include Mal de Meleda, Vohwinkel syndrome, *KDSR*-related erythrokeratoderma (see Ch. 57), pachyonychia congenita, acrodermatitis enteropathica, chronic mucocutaneous candidiasis, and (early on or in milder cases) psoriasis. Histology of affected skin demonstrates acanthosis with orthohyperkeratosis and parakeratosis, papillomatosis, and a perivascular inflammatory infiltrate; an increased number of mast cells has also been observed[79].

There are reports of dramatic improvement of the PPK in patients with gain-of-function mutations in *TRPV3* following administration of the epidermal growth factor receptor (EGFR) inhibitor erlotinib[80]. This targeted therapy is based upon the observation that EGFR activation can lead to enhanced TRPV3 activity. Systemic treatment with a retinoid or sirolimus and excision of hyperkeratotic areas with skin grafting may also be of benefit[81].

Papillon–Lefèvre and Haim–Munk Syndromes

Papillon–Lefèvre syndrome is an autosomal recessive condition caused by mutations in *CTSC* which encodes cathepsin C, a lysosomal cysteine protease that activates serine proteases found in inflammatory cells as well as the skin[82,83]. This disorder is characterized by a diffuse, transgredient PPK with associated erythema. Pseudoainhum and hyperkeratotic psoriasiform plaques on the elbows and knees often develop. An additional feature is periodontitis with onset during childhood, which leads to premature loss of teeth. There is a predisposition to pyogenic infections of the skin and internal organs, including hepatic abscesses[84]. Haim–Munk syndrome is an allelic condition that also features onychogryphosis, arachnodactyly, and acro-osteolysis[85]. Acral melanoma and SCC have been reported in patients with Papillon–Lefèvre syndrome[86,87].

Oral retinoid therapy lessens the hyperkeratosis and may also decrease the risk of periodontal and infectious complications[88].

Naxos Disease

Synonym: ■ Diffuse NEPPK with woolly hair and arrhythmogenic cardiomyopathy

This autosomal recessive disorder described in families from the Greek island of Naxos is defined by keratoderma, woolly hair, and a life-threatening cardiomyopathy[89,90]. Naxos disease results from a homozygous truncating mutation in the gene encoding plakoglobin (*JUP*), a component of both desmosomes and adherens junctions in the epidermis, hair follicle, and cardiac muscle[91] (see Fig. 29.3). A member of the armadillo protein family, plakoglobin links the inner and outer portions of the desmosomal plaque by binding to the cytoplasmic domain of cadherins (e.g. desmoglein, desmocollin) (see Fig. 56.8). Other biallelic mutations in *JUP* can result in alopecia (rather than woolly hair) together with focal PPK and cardiomyopathy as well as *erosive skin fragility disorders* (see Ch. 32).

Naxos disease classically presents during the first year of life with a diffuse NEPPK, but some patients have focal (striate/areata) involvement. Woolly scalp hair is usually evident at birth. The right ventricular cardiomyopathy has virtually 100% penetrance, typically manifesting with arrhythmias, heart failure, and/or sudden death during adolescence. Therefore, cardiac evaluation is mandatory for any patient with a PPK plus woolly hair (or alopecia) and their potentially affected family members. Treatment with an automatic cardioverter-defibrillator, antiarrhythmic drugs, and heart transplantation improves outcomes[92].

The triad of PPK, woolly hair, and cardiomyopathy can also result from biallelic desmoplakin mutations (Carvajal syndrome; see below), which generally features a striate/areata PPK, and rarely desmocollin 2 mutations. PPK plus woolly hair without cardiac findings has also been reported to result from homozygous mutations in *KANK2* (*K*N motif and *ank*yrin repeat domains *2*), which encodes a sequestering protein for steroid receptor coactivators.

FOCAL PALMOPLANTAR KERATODERMA WITHOUT ASSOCIATED FEATURES (ISOLATED, NON-SYNDROMIC)

Striate/Focal Palmoplantar Keratoderma

Synonyms: ■ Brünauer–Fuhs–Siemens PPK ■ Keratosis palmoplantaris areata et striata ■ Keratosis palmoplantaris varians Wachters ■ Keratosis palmoplantaris nummularis ■ Hereditary painful callosities (historical)

Striate palmoplantar keratoderma (SPPK) is an autosomal semidominant condition caused by mutations in at least three different genes that encode proteins with roles in desmosomal function (see Fig. 56.8)[93]: (1) type 1 – desmoglein 1 (*DSG1*)[94]; (2) type 2 – desmoplakin (*DSP*)[95]; and (3) type 3 – keratin 1 (*KRT1*), V2 tail domain[96]. In addition, heterozygous mutations in *DSG1* sometimes produce SPPK with blistering or diffuse PPK[97]. SAM syndrome – *s*evere dermatitis, multiple *a*llergies, and *m*etabolic wasting – features focal PPK and can result from biallelic *DSG1* mutations; affected individuals' parents with heterozygous *DSG1* mutations have isolated milder focal PPK[98]. SAM syndrome can also be caused by a heterozygous *DSP* mutation. Focal areata NEPPK with absent or very mild associated nail dystrophy is occasionally due to mutations in keratin 6c or 16 (see Pachyonychia congenita below).

The characteristic clinical features of all three types of SPPK are linear keratotic bands on the palms and flexor aspects of the fingers and island-like areas of hyperkeratosis over pressure points on the soles (see Fig. 58.2). Lesions usually develop in adolescence or early adulthood and are exacerbated by mechanical stress (e.g. from manual labor). Larger plantar keratoses are often painful.

In addition to orthohyperkeratosis, widening of the intercellular spaces and partial dehiscence of the suprabasal keratinocytes represent characteristic findings shared by SPPK types 1 and 2, diffuse PPK due

to a *DSG1* mutation, Carvajal syndrome, ectodermal dysplasia–skin fragility syndrome (plakophilin 1 deficiency), and other erosive skin fragility disorders (see Ch. 32)[99]. At the ultrastructural level, the size of the desmosomes is reduced in type 1 SPPK, while marked perinuclear aggregation of keratin filaments is seen in type 2 SPPK[100].

There is often a good response to oral acitretin and/or application of keratolytic agents. Treatment with erlotinib 1% ointment plus salicylic acid 10% cream has been reported to improve PPK due to a keratin 16 mutation[100a].

FOCAL PALMOPLANTAR KERATODERMA WITH ASSOCIATED FEATURES/SYNDROMIC

Pachyonychia Congenita

Synonyms: ■ Pachyonychia congenita type 1 (Jadassohn–Lewandowsky; historic) ■ Pachyonychia congenita type 2 (Jackson–Lawler; historic)

History, epidemiology, and pathogenesis

Pachyonychia congenita (PC) is a group of autosomal dominant genodermatoses caused by mutations in keratins 6A, 6B, 6C, 16, and 17; ectodermal structures that are affected include the nail bed, palmoplantar skin, pilosebaceous unit, oral mucosa, and teeth[101,102]. Historically, PC was classified as type 1 (Jadassohn–Lewandowsky) due to keratin 6a/16 defects, featuring more severe PPK and oral leukokeratosis, and type 2 (Jackson–Lawler) due to 6b/17 defects, featuring pilosebaceous cysts and neonatal teeth. However, extensive genotype–phenotype analysis led to recognition of the considerable overlap between these groups, and the current classification system is based on the affected keratin: PC-6a (~40% of PC patients), PC-6b (~5%–10%), PC6c (<5%), PC-16 (~30%), and PC-17 (~15%–20%)[101–104]. The different expression patterns of the mutant keratins account for the frequencies of various phenotypic features. For example, keratin 6a is more highly expressed in the oral mucosa and nails than other keratins[105], while keratin 17 is constitutively expressed in the pilosebaceous unit[106]. Mutations in keratin 6c or 16 and keratin 17 have also been reported in patients with focal PPK[107] and steatocystoma multiplex[108], respectively, without any other features of PC.

Clinical features

Clinically, three cardinal manifestations are present in >90% of PC patients, regardless of which keratin is affected: toenail dystrophy, focal keratoderma, and plantar pain (Fig. 58.12A–D)[101,102,109]. Wedge-shaped subungual hyperkeratosis leads to elevation, thickening, and darkening of the nail plate, which may assume an "omega" shape with more prominent involvement distally than proximally. There may or may not be involvement of all of the digits, but the toes, thumbs, and index fingers tend to have more severely affected nails. In infants, erythema of the nail bed can precede the appearance of dystrophic changes. Thick yellow plantar keratoses develop in sites of pressure, with the formation of calluses, fissures, and blisters in areas of friction, particularly during the summer; spread to the dorsal feet occasionally occurs in association with trauma or infection. Severe pain often makes it difficult for patients to walk, and palmoplantar hyperhidrosis and paronychia are common findings.

Other variable features include follicular keratoses on the knees and elbows, angular cheilitis, oral leukokeratosis (Fig. 58.12E), natal teeth (primarily in PC-17), and less often pili torti or other hair abnormalities[109,110]. Steatocystomas, vellus hair cysts, and other pilosebaceous cysts (e.g. epidermoid) develop in approximately half of patients overall and >90% of those with PC-17[101,109] (Fig. 58.12F). Mucosal involvement may lead to feeding difficulties in affected infants[111], and laryngeal involvement can result in hoarseness and occasionally respiratory tract obstruction.

Pathology

In hyperkeratotic skin and oral plaques, the keratinocytes in the superficial epidermis and mucosal epithelium have a characteristic pale cytoplasm and eosinophilic inclusions. At the ultrastructural level, these findings correlate with perinuclear condensation of mutated keratin filaments and vacuolization of the peripheral cytoplasm[110]. Similar histologic findings are seen in white sponge nevus, which is caused by keratin 4 and 13 mutations.

Differential diagnosis

The differential diagnosis for PC-like nail changes includes Clouston syndrome, which is distinguished by diffuse (rather than focal) PPK and more prominent alopecia, and isolated autosomal recessive nail dysplasia due to mutations in the frizzled 6 gene (*FZD6*)[112,113].

Treatment

Symptomatic treatment for the hyperkeratotic skin and dystrophic nails includes mechanical modalities (e.g. cutting, filing, grinding) following softening via soaking, as well as application of emollients and keratolytics[114]. Surgical removal of nails with attempts at matrix ablation is usually not effective, as the keratins involved in PC are expressed in the nail bed. Use of orthotics and treatment of hyperhidrosis with botulinum toxin type A injections may reduce blistering and pain. Oral retinoids can reduce hyperkeratosis but may increase tenderness[114]. Treatment with oral erlotinib or lapatinib (an EGFR/Her2 inhibitor) has been reported to reduce plantar pain and hyperkeratosis in patients with PC, which is associated with overactive EGFR signaling[114a]; less substantial benefit was observed with application of erlotinib 0.2% cream. Treatment with small interfering RNAs (siRNAs) that specifically target and silence expression of dominant-negative mutant *K6a* has been investigated, with the pain of intradermal injection representing a limiting factor. Use of topical sirolimus or oral statins to down-regulate *K6a* promoter activity in patients with K6a defects is under investigation[115,116]. Multimodal pain control strategies may also be of benefit.

Richner–Hanhart Syndrome

Synonyms: ■ Tyrosinemia type II ■ Tyrosine aminotransferase deficiency ■ Tyrosine transaminase deficiency ■ Oculocutaneous tyrosinemia

This is a rare autosomal recessive disorder of tyrosine metabolism caused by mutations in the gene that encodes hepatic tyrosine aminotransferase (TAT)[117–119]. Photophobia and dendritic keratitis with corneal ulcerations often appear in the first year of life. Tyrosine crystal deposition is seen on slit-lamp examination, and serum and urinary tyrosine levels are elevated. Painful, focal hyperkeratotic plaques on the palms and soles represent the characteristic cutaneous finding (Fig. 58.13). The skin changes can appear during early childhood or be delayed until adolescence; blistering and hyperhidrosis may be seen. Progressive intellectual disability occurs if the patient is not treated with a restrictive diet.

The histologic findings of pale epithelia with eosinophilic inclusions resemble those of pachyonychia congenita. Electron microscopy reveals clumped tonofilaments with adherent globoid keratohyalin granules and needle-shaped tyrosine crystalline inclusions within keratinocytes[118].

A diet in which tyrosine and phenylalanine are restricted will clear the keratitis and keratoderma, and it may delay or prevent cognitive impairment[120].

Howel–Evans Syndrome

Synonyms: ■ Focal non-epidermolytic PPK with carcinoma of the esophagus ■ Tylosis–esophageal carcinoma ■ Tylosis type A

This autosomal dominant disorder, which has been reported in several families over many generations, is caused by missense mutations in the rhomboid 5 homolog 2 gene (*RHBDF2*) encoding an intramembrane protease[121]. Functional data suggest that mutant RHBDF2 increases signaling through the epidermal growth factor receptor (EGFR), which promotes epithelial hyperproliferation and dysregulation of wound repair[121].

Affected individuals develop focal PPK by 5–15 years of age, often limited to the pressure areas of the balls of the feet, with milder involvement of the palms (Fig. 58.14). Keratosis pilaris, dry rough skin, and oral leukokeratosis are often present. Affected individuals have a high risk of esophageal carcinoma, which developed by the fifth decade of life in ~40% of affected members of the originally reported family[122].



Fig. 58.12 Pachyonychia congenita. A–C Plantar hyperkeratosis accentuated over pressure points and hypertrophic nail dystrophy with wedge-shaped subungual hyperkeratosis. **D** Painful focal plantar keratoderma with associated erythema and blistering. **E** Oral leukokeratosis. **F** Steatocystomas in the axilla. *A,B,E, Courtesy Julie V. Schaffer, MD; D, Courtesy Alfons Krol, MD, and Dawn Siegel, MD; F, Courtesy Dr. J. Valverde.*

Carvajal Syndrome

Synonyms: ■ Carvajal–Huerta syndrome ■ Striate PPK with woolly hair and dilated cardiomyopathy

This condition, first described in families from Ecuador, is characterized by PPK of the areata and striate type together with woolly hair and cardiomyopathy (Fig. 58.15)[123]. It can be caused by either biallelic or heterozygous mutations in the desmoplakin gene (*DSP*), which encodes a major constituent of desmosomes and is critical to providing strength to the epidermis and cardiac tissue (see Fig. 56.8)[124,125]. The mutations typically affect the protein's carboxy-terminal tail, which binds to intermediate filaments and is important in cardiac myocytes.

The PPK usually develops during infancy, and the woolly hair is generally present at birth. Additional skin findings may include scaly plaques and keratoses on the elbows and knees or in flexural sites. Although the cardiac ventricular involvement was predominantly left-sided in the original kindred, the right or both ventricles can be affected. The onset of cardiac disease ranges from early childhood to adolescence, and it typically leads to heart failure with cardiac enlargement[124]. Patients with an autosomal dominant form of Carvajal syndrome may also have leukonychia and oligodontia, and a variant autosomal



Fig. 58.13 Richner–Hanhart syndrome (tyrosinemia II). Focal painful keratoses on the plantar surface in a patient with corneal ulcers and mental retardation. *Courtesy Jean L. Bolognia, MD.*



Fig. 58.14 Howel–Evans syndrome. Focal palmoplantar keratoderma in association with carcinoma of the esophagus. *Courtesy Alfons Krol, MD, and Dawn Siegel, MD.*

recessive form features skin fragility with acantholysis, nail dystrophy, and dental enamel defects.

Histologic findings include widening of the intercellular spaces and partial dehiscence of suprabasal keratinocytes, which have dense eosinophilic cytoplasm surrounding a pyknotic nucleus. Immunohistochemistry demonstrates perinuclear localization of keratin in these keratinocytes, suggesting a collapsed intermediate filament network. Early cardiac diagnosis and intervention is essential for survival of affected individuals[125].

The differential diagnosis of the triad of PPK, woolly hair, and cardiomyopathy includes Naxos disease, which more often presents with a diffuse PPK (see above), and desmocollin 2 defects. Other phenotypes due to genetic defects in desmoplakin include: isolated striate PPK or cardiac anomalies; skin fragility–woolly hair syndrome and other erosive skin fragility disorders (see Ch. 32); erythrokeratodermia–cardiomyopathy syndrome (see Ch. 57); and SAM syndrome (see Striate PPK above)[126–128].





Fig. 58.15 Carvajal syndrome. A Focal plaque-like hyperkeratosis over pressure points on the soles. **B** Woolly hair.

PUNCTATE PALMOPLANTAR KERATODERMA WITHOUT ASSOCIATED FEATURES (ISOLATED, NON-SYNDROMIC)

Punctate Palmoplantar Keratoderma, Buschke–Fischer–Brauer type

Synonyms: ■ Punctate palmoplantar keratoderma type 1 ■ Palmoplantar keratoderma punctata type 1 ■ Keratosis punctata palmoplantaris type Buschke–Fischer–Brauer ■ Keratoma dissipatum ■ Disseminated clavus

Punctate PPK is an autosomal dominant condition that can be caused by heterozygous mutations in *AAGAB*, which encodes the *α- a*nd *γ-a*daptin-*b*inding protein p34. This protein is involved in the intracellular trafficking of clathrin-coated vesicles[129]. Accordingly, a large number of small vesicles and a dilated Golgi apparatus can be visualized via electron microscopy of affected skin. The AAGAB defect results in impaired endocytic recycling of receptor tyrosine kinases such as EGFR and Axl, leading to increased signaling and cellular proliferation[129]. A second locus for punctate PPK on 8q was found to be associated with a heterozygous missense mutation in the collagen type XIV α1 chain gene (*COL14A1*) in a Chinese family[130].

Multiple small keratotic papules usually begin to appear on the palmoplantar surfaces during adolescence or early adulthood, although onset can be in childhood or as late as the sixth decade of life[131].



Fig. 58.16 Punctate keratoses of the palmar creases. Keratotic papules lined along a crease in an African-American.

DIFFERENTIAL DIAGNOSIS OF PALMOPLANTAR PITS
Hereditary disorders
Basal cell nevus syndrome
Basaloid follicular hamartoma syndrome
Darier disease
Reticulate acropigmentation of Kitamura
Punctate PPK (including punctate keratoses of the palmar creases)*
Cowden syndrome*
Porokeratotic adnexal ostial nevus (PAON; encompasses porokeratotic eccrine ostial and dermal duct nevus [PEODDN])*
Acquired disorders
Pitted keratolysis
Associated with Dupuytren contracture
Punctate porokeratoses*
*Characterized primarily by keratoses, which may leave a pit upon removal of the keratotic plug.

Table 58.7 Differential diagnosis of palmoplantar pits. They are rarely seen in alkaptonuria, epidermodysplasia verruciformis, Blau syndrome, and lesions of lichen nitidus, lichen planus, or psoriasis. Occasionally, lesions of circumscribed palmar or plantar hypokeratosis can be multiple and <5 mm. PPK, palmoplantar keratoderma.

The central keratotic core is initially translucent but may become opaque or verrucous over time, and a depression remains upon its removal (see Fig. 58.3). The papules can be painful or tender, and they may enlarge and aggregate to form plaques over pressure points. Environmental factors can affect the degree of hyperkeratosis. Although some older studies suggested a possible association between punctate PPK and the development of breast and colon carcinomas, it is not clear whether there is truly an excess of malignancies in affected individuals[129,132].

Histologically, there is a slight epidermal depression with an overlying column of compact orthohyperkeratosis. Focal hypogranulosis with parakeratosis and elongated, curved rete ridges may be evident. Cytologic features of HPV infection are lacking.

Punctate keratoses frequently develop in the palmar creases of adults with African ancestry (Fig. 58.16); the creases of the digits and soles may also be involved, and the lesions are worsened by mechanical stress. The relationship of this variant to other forms of punctate PPK remains to be determined[133]. The differential diagnosis of punctate PPK often includes verrucae, which are distinguished by multiple bleeding points upon paring, and punctate porokeratoses, which demonstrate a cornoid lamella rather than a column of orthohyperkeratosis histologically. Keratotic papules on palms and soles can also occur after exposure to arsenic or dioxin and in patients with Darier disease, acrokeratosis verruciformis of Hopf, and Cowden syndrome. Conditions that present with palmoplantar pits, which may be confused with punctate PPK, are listed in Table 58.7.

Comfortable footwear and mechanical paring can provide relief. Although topical retinoids and keratolytic ointments have limited efficacy, oral retinoids may be helpful[131]. Receptor tyrosine kinase inhibitors represent a possible future treatment option[134].

Spiny Keratoderma

Synonyms: ■ Punctate palmoplantar keratoderma type 2 ■ Palmoplantar keratoderma punctata type 2 ■ Music box spine keratoderma ■ Filiform hyperkeratosis ■ Digitate keratosis

Spiny PPK is an autosomal dominant condition characterized by numerous tiny keratotic spines projecting from the palms and soles, usually beginning in the first to third decades of life[135] (Fig. 58.17). Discomfort can be caused by a tendency to catch on clothing and other objects[136]. This disorder should be differentiated from acquired forms of spiny PPK, which typically develop after 50 years of age; possible associations with the latter based upon case reports include various malignancies (visceral carcinoma, melanoma, leukemia, multiple myeloma), hyperlipidemia type IV, chronic kidney disease, and polycystic kidney disease with liver cysts[137]. Some authors group this entity under the umbrella term multiple minute digitate hyperkeratosis.

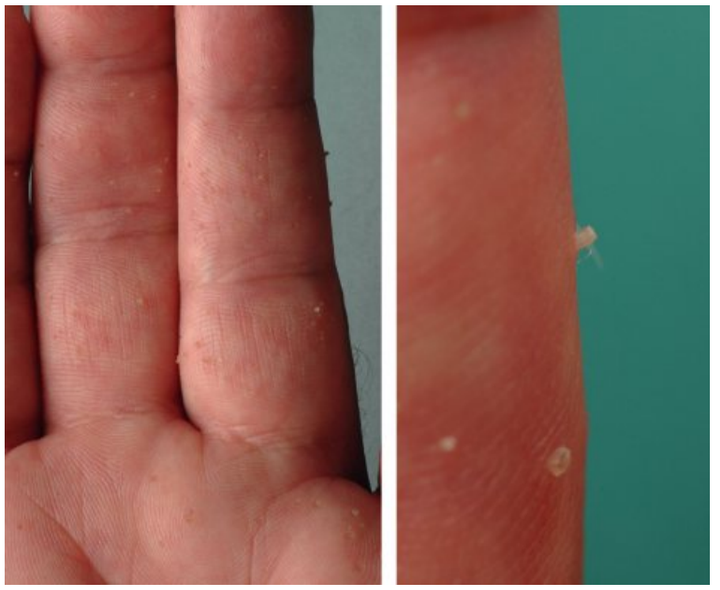


Fig. 58.17 Spiny palmoplantar keratoderma. Multiple tiny keratotic spines project from palms and soles.

Histologically, an epidermal depression with an overlying column of parakeratosis is seen. In contrast to porokeratosis and porokeratotic adnexal ostial nevus, the stratum granulosum is preserved while vacuolization, pleomorphism, and dyskeratosis of underlying keratinocytes are not evident.

Mechanical debridement, including via dermabrasion, may be more effective than topical keratolytics. Oral retinoids may provide temporary benefit. Topical 5-fluorouracil ointment has been tried with variable results[136].

Marginal Papular Keratoderma: Acrokeratoelastoidosis and Focal Acral Hyperkeratosis

Synonyms: ■ Punctate palmoplantar keratoderma type 3 ■ Palmoplantar keratoderma punctata type 3 ■ Acrokeratoelastoidosis of Costa

Both forms of marginal papular keratoderma can have an autosomal dominant inheritance pattern, and onset is typically in childhood or adolescence. Focal acral hyperkeratosis (FAH) classically favors female patients with African ancestry. These conditions are both characterized by small, keratotic papules along the margins of the palms, soles, and digits (Fig. 58.18). The papules tend to be skin-colored to hyperpigmented in FAH and yellowish in acrokeratoelastoidosis. Lesions may be umbilicated and occasionally they extend to the dorsal aspect of the hands and feet. While acrokeratoelastoidosis histologically shows fragmentation and degeneration of elastic fibers in the dermis as well as hyperkeratosis, FAH lacks elastorrhexis[138].

There is ongoing debate as to whether a form of acral keratosis with polygonal papules in a "jigsaw puzzle" pattern reported in African patients represents a variant of marginal keratoderma[139]. The primary sites of involvement in these patients are the ankles, shins, and dorsal aspect of the hands and feet. *Keratoelastoidosis marginalis* (digital papular calcific elastosis) is an acquired condition that presents with degenerative collagenous plaques forming a linear band around the thumb and index finger at the margin of the volar and dorsal surfaces in patients with severe photodamage[140].

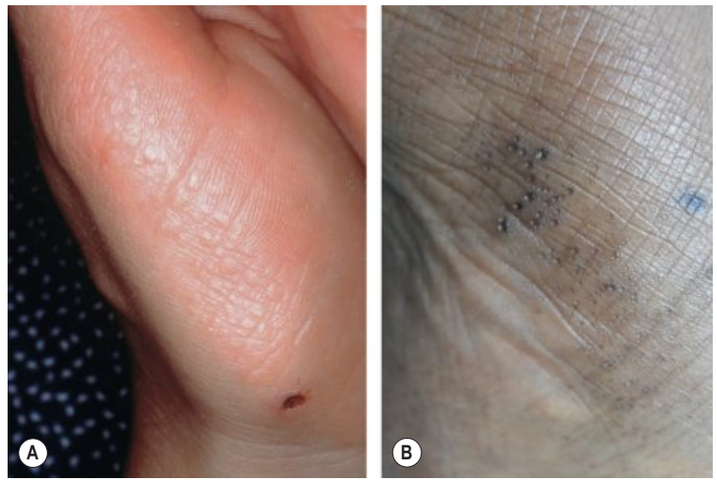


Fig. 58.18 Marginal papular keratoderma. A Acrokeratoelastoidosis presenting with multiple skin-colored to yellowish papules at the margin of the palmar skin. **B** Focal acral hyperkeratosis presenting with umbilicated keratotic papules at the margin of volar skin in an African-American woman. *B, Courtesy Boni Elewski, MD.*

PUNCTATE PALMOPLANTAR KERATODERMA WITH ASSOCIATED FEATURES/SYNDROMIC

Cole Disease

Synonym: ▪ Guttate hypopigmentation and punctate palmoplantar keratoderma with or without ectopic calcification

Cole disease is a rare autosomal dominant condition characterized by a congenital or early childhood onset of punctate PPK together with irregularly shaped hypopigmented macules on the extremities[141]. Electron microscopy shows defective melanosome transfer from melanocytes to keratinocytes. Cole disease is caused by heterozygous mutations in *ENPP1*, which encodes ectonucleotide pyrophosphate/phosphodiesterase 1. The latter is a cell-surface protein that catalyzes the hydrolysis of ATP to AMP and generates extracellular inorganic pyrophosphate, which is a major inhibitor of mineralization[142]. Recessive mutations in *ENPP1* underlie inherited forms of ectopic calcification, and calcific tendinopathy and calcinosis cutis have been observed in patients with Cole disease.

ACQUIRED KERATODERMAS AND RELATED CONDITIONS

Keratoderma Climactericum

This common, acquired form of focal plantar hyperkeratosis favoring women >45 years of age was first described by Haxthausen in 1934. It is often associated with obesity, cold dry climates, and wearing backless shoes (e.g. sandals). Hyperkeratosis begins over pressure points on the heels, and the formation of fissures makes walking painful. If present, involvement of the hands is much milder. Endocrine dysfunction, vitamin A deficiency, contact dermatitis, and fungal infection were excluded in reported patients[143]. Treatment options include keratolytic preparations containing 20%–40% urea or 12% ammonium lactate and, if severe, a low-dose oral retinoid. Similar changes described in young women following bilateral oophorectomy responded to estrogen replacement therapy.

Keratoderma and Cancer

Acquired diffuse PPK has been observed in association with bronchial carcinoma[144], and filiform PPK has been reported in patients with cancer of the breast, colon, and kidney[145]. "Tripe palms" refers to velvety, thickened palmar skin with exaggerated ridges. It is often associated with acanthosis nigricans and may herald malignancies of the lung, stomach, or genitourinary tract[146]. Bazex syndrome (acrokeratosis paraneoplastica) is discussed in Chapter 53. Esophageal carcinoma in association with focal PPK (Howel–Evans syndrome) as well as the increased risk of acral SCC in patients with Huriez syndrome and PPK with sex reversal are discussed above. Acral melanoma and the epithelioma cuniculatum variant of SCC have also been reported in individuals with mutilating forms of PPK and (for acral melanoma in Asians) Nagashima-type PPK. In addition, an autosomal recessive syndrome featuring pigmentation defects, PPK, and cutaneous SCC can result from mutations in *SASH1* (SAM and SH3 domain-containing 1; see Table 67.11). Mycosis fungoides represents another diagnostic consideration in patients with acquired PPK[147].

Arsenical keratoses present as small, corn-like areas of hyperkeratosis on the palms and soles (see Fig. 88.8). Over time, the lesions enlarge, thicken, and increase in number, spreading to the dorsal surfaces of the hands and feet. Ulceration often occurs when SCC develops. On histologic examination, epidermal changes vary from benign hyperplasia to moderate atypia or frank SCC. The latent period between ingestion of inorganic arsenic and onset of keratoses is 10 to 30 years or longer[148]. Visceral malignancies, particularly of the lung and genitourinary tract, usually develop after the onset of skin tumors.

Other Etiologies of Acquired Keratoderma

Diffuse or focal palmoplantar hyperkeratosis can develop in association with *hypothyroidism*, often in the setting of myxedema. The PPK improves or resolves with thyroid replacement therapy[149].

With the increasing use of targeted therapies for the treatment of malignancies, in particular tyrosine kinase inhibitors, drug-induced palmoplantar hyperkeratosis also needs to be considered (see Table 21.16).

Other conditions that have been associated with keratoderma are listed in Table 58.1[150–152].

Aquagenic Palmoplantar Keratoderma

Synonyms: ▪ Transient reactive papulotranslucent acrokeratoderma ▪ Aquagenic syringeal acrokeratoderma ▪ Acquired aquagenic palmoplantar keratoderma ▪ Aquagenic wrinkling of the palms and soles ▪ Transient aquagenic keratoderma

Patients with aquagenic PPK develop thickening and white to translucent, "pebbly" changes on their palms shortly after immersion in water (e.g. within 3 minutes) (Fig. 58.19). Often, there is associated edema and burning pain[153,154]. Involvement of the dorsal hands or soles is less frequently observed[155]. These findings disappear shortly after drying the hands. Onset is typically during the second decade of life, with a predilection for girls and women. By dermoscopy, the papular lesions are at sites of dilated acrosyringeal ostia[156]. Histologically, normal skin or dilated eccrine ostia and a mildly hyperkeratotic stratum corneum may be seen.



Fig. 58.19 Aquagenic wrinkling of the palms. These exaggerated changes occur after water immersion. *Courtesy Cindy E. Owen, MD.*

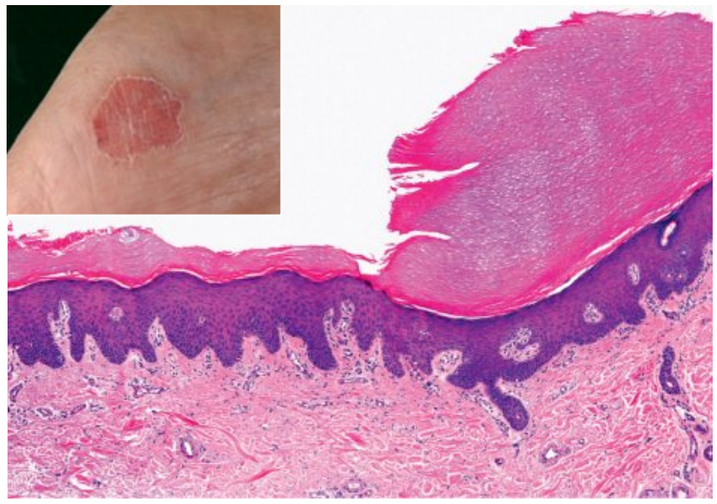


Fig. 58.20 Circumscribed palmar hypokeratosis. A sharp drop-off is seen between the lesional epidermis, which has a very thin stratum corneum, and the surrounding skin. Clinically, a well-circumscribed pink depression is seen (inset). *Courtesy Luis Requena, MD.*

Autosomal recessive or dominant inheritance of aquagenic PPK has been described, and an onset associated with the use of cyclooxygenase-2 inhibitors was reported[157]. Aquagenic wrinkling of the palms can be observed in ~50% of patients with cystic fibrosis and ~10%–25% of heterozygous carriers of *CFTR* mutations[158]. Aquagenic PPK should be differentiated from hereditary papulotranslucent acrokeratoderma, in which lesions are persistent once they appear[159], and other forms of PPK that are accentuated upon exposure to water, e.g. the Bothnian and Nagashima types of diffuse NEPPK (see above).

Improvement has been described with botulinum toxin injections, application of 20% aluminum chloride hexahydrate followed by urea cream, tap water iontophoresis, and oral acitretin[160].

Circumscribed Palmar or Plantar Hypokeratosis

This entity, which was first described in 2002, presents as a well-circumscribed, mildly erythematous, circular depression on the thenar or hypothenar region of the palm or less often the medial sole (Fig. 58.20)[161]. Lesions are solitary, or rarely few in number, and have a maximum diameter of 3 cm. They typically develop in women 40–85 years of age[162], although congenital lesions have been described. Sometimes there is a history of prior trauma or a burn at the site. The clinical differential diagnosis may include Bowen disease or porokeratosis.

Histologically, abrupt thinning of the stratum corneum over a diminished granular layer forms a sharp drop-off between normal and involved skin (see Fig. 58.20). To date, malignant transformation has not been reported. The etiology remains unknown, with postulated roles for trauma and loss of the keratinocytes' ability to undergo palmoplantar differentiation. The latter is supported by the observation of diminished keratin 9 expression[163]. Molecular studies have failed to detect human papillomavirus (HPV) apart from a single report of HPV type 4 DNA[164].

Treatments that have been reported include topical calcipotriene or 5-fluorouracil, cryotherapy, photodynamic therapy, fractional carbon dioxide laser, and excision[165].

Additional figures available in our eBook (see inside front cover for access code).

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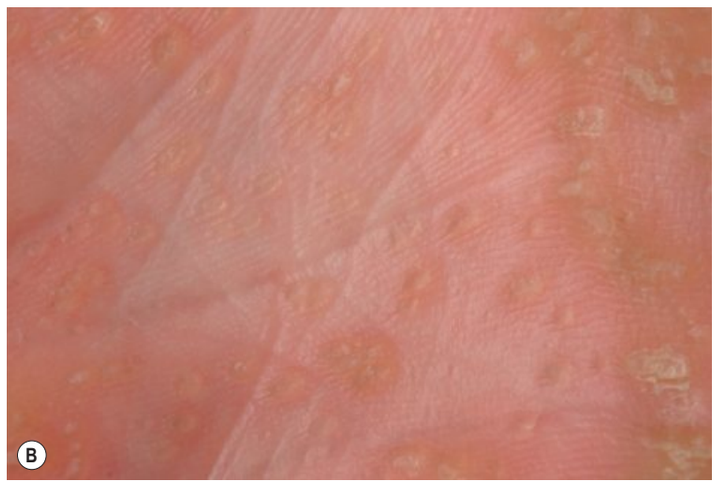
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eFig. 58.1 Diffuse palmoplantar keratoderma. Hyperkeratosis of the entire palmar surface.





eFig. 58.3 Punctate palmoplantar keratoderma. A Lesions can coalesce over pressure points on the sole. **B** Close-up view of coalescing small keratotic papules on the palm.







eFig. 58.2 Focal palmoplantar keratoderma. A, B Striate type on the palm. **C** Areata type on the soles; this patient has an incidental digital anomaly.





eFig. 58.4 Diffuse epidermolytic palmoplantar keratoderma. **A** Diffuse hyperkeratosis on the soles. **B** Erythema is present at the border on the flexor wrist as well as in areas where there is reduced hyperkeratosis. *Courtesy Alfons Krol, MD, and Dawn Siegel, MD.*



eFig. 58.5 KLICK syndrome. Diffuse keratoderma and hyperkeratotic papules in parallel lines around the wrist.



eFig. 58.6 Diffuse palmar keratoderma in an infant with keratitis–ichthyosis–deafness (KID) syndrome. Note the associated erythroderma.





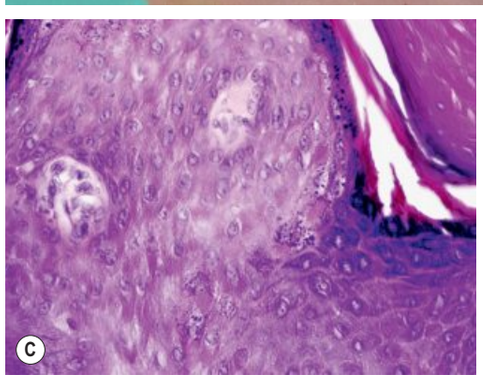
eFig. 58.7 Huriez syndrome. A Mild palmar hyperkeratosis. **B** Hypoplastic nail changes and scleroatrophic skin.



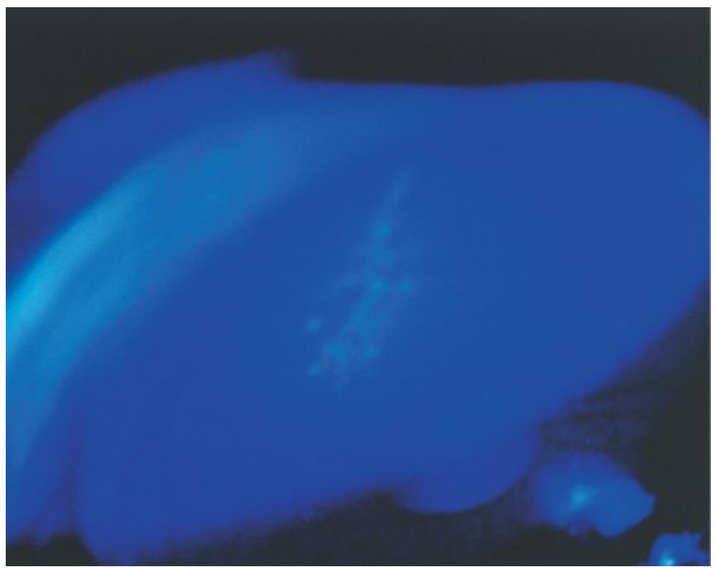
eFig. 58.8 Palmar keratoderma in ectodermal dysplasia–skin fragility syndrome due to plakophilin 1 deficiency. Note the fissuring and accentuation in areas of friction. *Courtesy Antonio Torrelo, MD.*



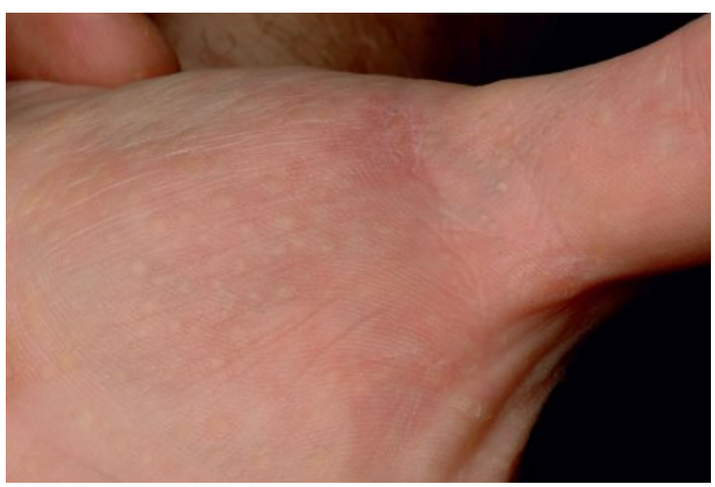




eFig. 58.9 Pachyonychia congenita. A Hypertrophic nail dystrophy with wedge-shaped subungual hyperkeratosis. **B** Focal hyperkeratosis over pressure points on the sole. **C** Characteristic histologic finding of pale keratinocytes with eosinophilic inclusions.



eFig. 58.10 Richner–Hanhart syndrome (tyrosinemia II). Dendritic keratitis detected by slit-lamp examination. *Courtesy Jean L. Bolognia, MD.*



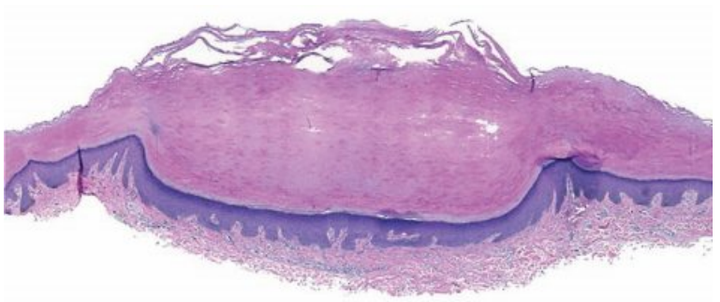
eFig. 58.11 Marginal papular keratoderma. Multiple skin-colored papules at the margin of the palmar skin.



eFig. 58.12 Keratoderma climactericum. Hyperkeratosis of the heels accompanied by fissures. *Courtesy Jean L. Bolognia, MD.*



eFig. 58.13 Aquagenic keratoderma. White "pebbly" changes on the palm following immersion in water. *Courtesy Julie V. Schaffer, MD.*



eFig. 58.14 Focal acral hyperkeratosis – histopathologic features. Marked thickening of the stratum corneum overlying an invagination of the epidermis. *Courtesy Lorenzo Cerroni, MD.*

Darier Disease and Hailey–Hailey Disease

59

Daniel M. Hohl

Chapter Contents

Darier Disease 951
Hailey–Hailey Disease. 957

DARIER DISEASE

Synonyms: ■ Darier–White disease ■ Keratosis follicularis ■ Dyskeratosis follicularis

Key features

- Autosomal dominant disorder in which mutations in *ATP2A2* result in dysfunction of an endoplasmic reticulum Ca^{2+} ATPase (SERCA2), thus interfering with intracellular Ca^{2+} signaling
- Keratotic and crusted papules and plaques favor seborrheic areas; additional features include palmoplantar papules, variable nail changes, and whitish oral mucosal papules
- Clinical subtypes include an acral hemorrhagic variant and segmental forms due to type 1 and type 2 mosaicism
- Characterized histologically by acantholytic dyskeratosis with suprabasilar clefting, "corps ronds", and "grains"

Introduction

Darier disease is an autosomal dominant genodermatosis with characteristic mucocutaneous findings such as keratotic papules on the upper trunk and longitudinal erythronychia. Insufficient function of the 2b isoform of the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA2b) leads to abnormal intracellular Ca^{2+} signaling, notably involving the endoplasmic reticulum. The result is a loss of suprabasilar cell adhesion (acantholysis) and an induction of apoptosis (dyskeratosis).

History

In 1889, the French dermatologist Jean Darier[1], at the Hôpital Saint-Louis in Paris, and James C. White[2], Professor of Dermatology at Harvard University, independently reported a skin disease characterized by brown, crusted, malodorous lesions with a follicular distribution. Darier called the disease "psorospermose folliculaire végétante" because of his histopathologic studies, where throughout the malpighian layer he saw a large number of round bodies surrounded by a double-layered membrane. He and others thought that these bodies represented psorosperms, a type of parasitic protozoa now referred to as coccidia, which they postulated were the causative agents for the disease. However, attempts to culture or inoculate the supposed parasites failed, and the histologic changes were subsequently recognized as sequelae of abnormal keratinization. The supposed follicular origin of the disease could not be confirmed either, as lesions were noted to occur outside the pilosebaceous unit. It was White who first suggested the hereditary character of the disorder, when the daughter of his initially described patient developed similar skin lesions.

Epidemiology

The reported prevalence of Darier disease ranges from 1 in 100 000 in Denmark to 1 in 30 000 in Scotland, and the estimated incidence is 4 per million per 10 years[3]. Men and women are equally affected. Darier disease has an autosomal dominant mode of inheritance with complete penetrance and variable expressivity. For example, in a series of 42 patients with Darier disease, 7 of 18 affected individuals who recalled no family history were found to be members of known Darier kindreds with mildly affected parents[4]. The clinical severity varies among different families carrying identical mutations and among members of the same family. Indeed, subtle changes of the skin or nails may remain unnoticed by affected persons.

Pathogenesis

Mutations in *ATP2A2* which encodes an endoplasmic reticulum (ER) Ca^{2+} ATPase pump, SERCA2, leads to both acantholysis and apoptosis, accounting for the characteristic histologic finding of acantholytic dyskeratosis. SERCA2 haploinsufficiency has been hypothesized to underlie the condition's dominant inheritance pattern[5], but a more recent study found that aggregates of mutant SERCA2 may exert a dominant negative effect by inducing ER stress and keratinocyte apoptosis[6]. Although both SERCA2a and SERCA2b isoforms are found within the epidermis, SERCA2b is the major protein product and its dysfunction alone can produce Darier disease[7]. While SERCA2 is ubiquitously expressed, a lack of compensatory SERCA3 expression in keratinocytes may explain the particular vulnerability of these cells to SERCA2 deficiency.

Close to 300 pathogenic *ATP2A2* mutations have been identified, primarily missense and frameshift alterations. In general, there is no clear genotype–phenotype correlation[8]. Likely exceptions include a particular *ATP2A2* mutation underlying the allelic acrokeratosis verruciformis of Hopf[9,10] (see below) and mutations in the S4-M4 region associated with more severe neuropsychiatric manifestations[11]. Several pathogenic mechanisms have been proposed for the acantholytic dyskeratosis of Darier disease. *ATP2A2* mutations result in chronically low Ca^{2+} stores within the ER (Fig. 59.1)[12], which is aggravated by cellular stress. This Ca^{2+} depletion leads to *acantholysis* via impaired processing, folding and trafficking of junctional proteins such as desmoplakin[13] and E-cadherin[14]. Impaired membrane translocation of protein kinase C α, an important Ca^{2+}-dependent regulatory enzyme that interacts with membrane phospholipids, is thought to mediate the disruption of desmosome assembly[15]. Studies have also shown that SERCA2 inhibition in keratinocytes causes increased levels of sphingosine, which inhibits protein kinase C α[14,16].

ER stress due to depleted Ca^{2+} stores and accumulation of unfolded proteins produces the "unfolded protein response", which can induce apoptosis[16,17]. ATP receptors, which are thought to have roles in apoptosis and calcium signaling, localize abnormally in lesional Darier disease epidermis, with decreased P2Y2 (a G protein-coupled receptor) but increased P2X7 (a death receptor) in the plasma membrane of acantholytic cells[18].

Clinical Features

Onset and clinical pattern

In ~70% of patients, Darier disease becomes apparent between the ages of 6 and 20 years, with a peak onset during puberty (ages 11–15 years)[19]. The primary lesions are keratotic, sometimes crusted, red to brown papules, which develop preferentially in a "seborrheic" distribution involving the trunk (Fig. 59.2), scalp (especially its margins; Fig. 59.3), face, and lateral aspects of the neck (Fig. 59.4). Despite its initial description as follicular dyskeratosis, the papules are not limited to a perifollicular location. The lesions tend to become confluent and may form papillomatous masses (Fig. 59.2B,D). Small (2–3 mm) hypomelanotic macules may be admixed with the keratotic papules

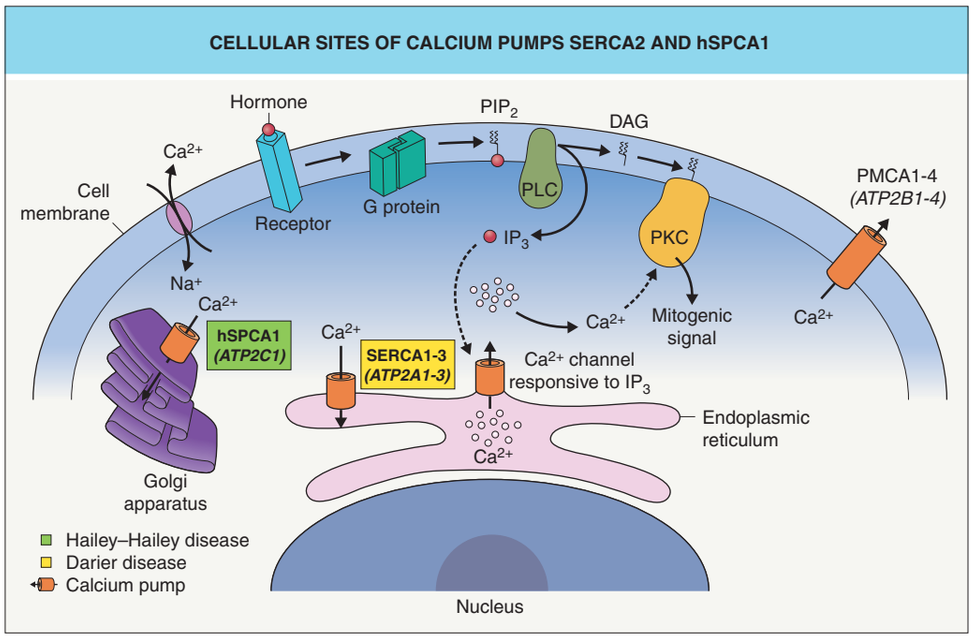


Fig. 59.1 Cellular sites of calcium pumps SERCA2 and hSPCA1. Darier disease is due to mutations in *ATP2A2* which encodes SERCA2. PIP_2, phosphoinositol diphosphate; IP_3, inositol triphosphate; PLC, phospholipase C; DAG, diacylglycerol; PKC, protein kinase C.



Fig. 59.2 Darier disease. A–D Truncal involvement with a predilection for seborrheic areas. Keratotic papules can vary from red (**A, B**) to brown (**C, D**) in color and may become confluent. **E** Papules with scale-crust and focal erosions on the leg. *A & C, Courtesy Julie V. Schaffer, MD; E, Courtesy Kalman Watsky, MD.*



Fig. 59.3 Darier disease. **A** Crusted papules at the hairline on the face and in the posterior auricular area. **B** Extensive facial involvement leading to ectropion.

and occasionally are the predominant feature (Fig. 59.5). Rarely, sterile vesicles or bullae are prominent, and, in these cases, herpetic infection (Kaposi varicelliform eruption) must be excluded[20,21].

Most patients have lesions in the axillae, groin, and/or inframammary area (Fig. 59.6). Although these intertriginous lesions are usually mild, they are occasionally the predominant finding and may result in the misdiagnosis of Hailey–Hailey disease (HHD)[22]. Occasionally, macerated, fungating masses are seen in the axillae or groin. Malodor is a frequent and distressing feature of Darier disease.

In ~50% of patients, 2–4 mm, skin-colored or brownish, flat-topped papules, reminiscent of flat warts, are found on the dorsal aspects of the hands and feet, and less often, on the forearms and legs (Fig. 59.7). Rarely, acral hemorrhagic vesicles may also be seen. Palmoplantar papules, many of which are keratotic, and keratin-filled depressions are almost invariably present (Fig. 59.8). Subtle changes can be detected by obtaining finger or palm prints, which show interruption of the dermatoglyphic pattern. Nail changes include longitudinal red and/or white lines, longitudinal ridging and fissuring, and wedge-shaped subungual hyperkeratosis (Fig. 59.9). The nails are brittle and tend to break distally, forming V-shaped notches[23].

Painless whitish papules or rugose plaques are noted on the oral mucosa in 15%–50% of patients with Darier disease. The hard palate is the most common site of involvement, followed by the gingiva, buccal mucosa, and tongue (Fig. 59.10)[19].

Symptoms

Most patients complain of moderate itching. Equally distressing are the appearance and the odor, which can lead to social isolation.

Modifying factors

This condition frequently worsens during the summer. In patients with Darier disease, characteristic lesions can be experimentally induced in clinically uninvolved skin by UV irradiation, and UVB irradiation has been shown to suppress *ATP2A2* expression in keratinocytes[23]. Sweating, heat, and occlusion represent additional factors that trigger exacerbations primarily in covered and intertriginous areas (e.g. after a long airplane flight), and this predisposes patients to infections (see below). Interferon β-1a or lithium carbonate[24,25] can provoke flares of Darier disease.

Course of the disease

Darier disease follows a chronic course with fluctuations in disease severity. While some patients report improvement over time, others experience worsening.

Infectious complications

Areas of skin affected by Darier disease are prone to secondary infections with bacteria, yeast, and dermatophytes, often leading to malodor and vegetating plaques. A study of 75 adult patients found a high prevalence of *Staphylococcus aureus* colonization in lesional skin (~70%) and the nares (~50%), which correlated with a more severe phenotype[26].

Affected individuals are also susceptible to the development of widespread cutaneous infections with human papillomaviruses (HPV) and herpes simplex virus (HSV). When there is a sudden onset and rapid spread of vesicular and crusted lesions, often accompanied by fever and malaise, the clinician should have a high index of suspicion for the development of Kaposi varicelliform eruption (KVE; Fig. 59.11)[21]. The latter requires systemic antiviral therapy (e.g. valacyclovir, acyclovir). Generalized cowpox infection has also been reported.

Disruption of the epidermal barrier likely plays an important role in the increased frequency and severity of skin infections in patients with Darier disease. Immunologic studies have shown no consistent systemic abnormalities[27]. However, an immunohistochemical analysis found evidence for an impaired local immune response, with a decrease in Langerhans cells and plasmacytoid dendritic cells[28]. In a recent study, SERCA2 activity was shown to be required for efficient V(D)J recombination, and 6/16 patients with Darier disease were found to have an abnormally low proportion of $CD19^+$ B cells in their peripheral blood lymphocytes[29].

Salivary glands

In some patients, obstruction of salivary gland ducts can lead to painful glandular swelling. Darier-like histologic changes within the ducts are thought to be responsible for the obstruction[30].

Neuropsychiatric disorders

Various neuropsychiatric conditions such as intellectual impairment, mood disorders, and epilepsy have been reported in association with Darier disease. Neuropsychiatric assessment of Darier disease patients from the UK revealed higher lifetime rates of major depression (30%), suicide attempts (13%), bipolar disorder (4%), and epilepsy (3%) than in the general population[31]. In a study based on the Swedish national registry, Darier disease patients (n = 770) were more likely to be diagnosed with intellectual disability (6.2-fold), bipolar disorder (4.3-fold), and schizophrenia (2.3-fold) than matched individuals from the general population[32].

More severe neuropsychiatric manifestations have been observed in patients with *ATP2A2* mutations in the S4-M4 region[11,31]. *ATP2A2* is expressed in the brain, and hypotheses regarding potential mechanisms for neuropsychiatric findings in Darier disease include disruption of intracellular calcium signaling, an impaired endoplasmic reticulum stress response, and accumulation of insoluble SERCA2 aggregates within neurons[6,11]. In addition, the disfigurement and social isolation associated with severe skin conditions often lead to psychological morbidity, which may contribute to depression and suicidal ideation in patients with Darier disease[22].

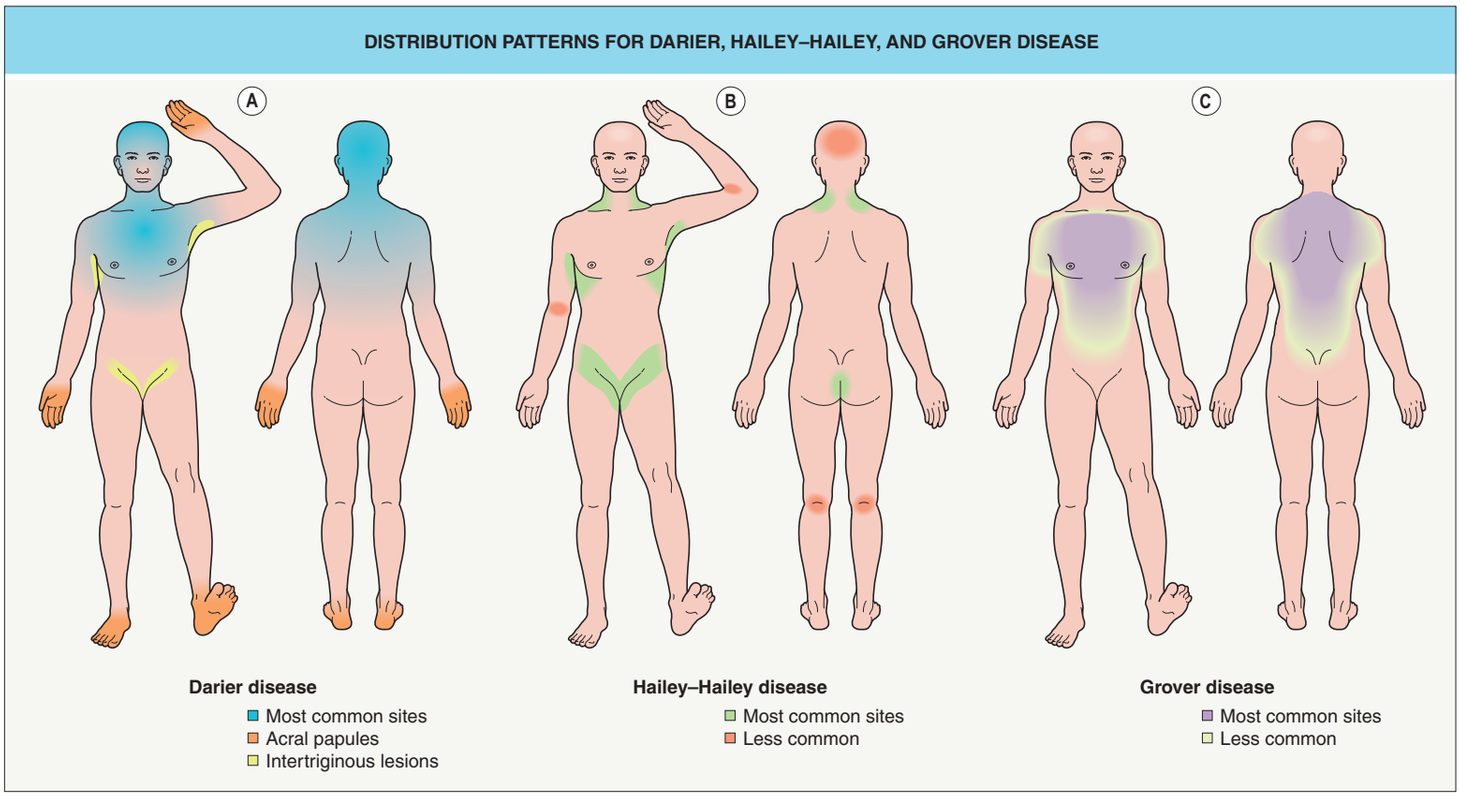


Fig. 59.4 Distribution patterns for Darier, Hailey–Hailey, and Grover disease.



Fig. 59.5 Darier disease. Observed most commonly in individuals with darkly pigmented skin, a guttate leukoderma may be seen in patients with Darier disease, including the segmental form. *Courtesy Julie V. Schaffer, MD.*



Fig. 59.6 Darier disease. Severe involvement in intertriginous zones, including the abdominal fold and groin.

Others

Dry eyes and blepharitis are common in patients with Darier disease[33], although more serious ocular complications, e.g. corneal ulcerations or staphylococcal endophthalmitis, are rare. There have been a few reports of squamous cell carcinomas arising in cutaneous or mucosal sites chronically affected by Darier disease[34]. Malignant transformation is a rare event and may be related to infection with oncogenic types of HPV or changes in keratinocyte adhesion and proliferation secondary to SERCA2 haploinsufficiency, which has been associated with squamous cell carcinomas of the skin and upper gastrointestinal tract in mice. Swedish cross-sectional case–control and population-based studies have suggested that Darier disease is associated with an increased risk of heart failure and type 1 diabetes mellitus[35]. Observations of bone cysts, renal agenesis, and autoimmune thyroiditis in patients with Darier disease are thought to represent chance associations.

Clinical subtypes of darier disease

Acral hemorrhagic type (Table 59.1)

In addition to classic clinical features, a small subset of patients develop sharply demarcated, red to blue–black macules on the palms and soles as well as the dorsal aspects of the hands. These irregularly shaped lesions represent hemorrhage into acantholytic vesicles. A particular *ATP2A2* missense mutation (N767S) has been identified in several non-related families with the acral hemorrhagic type of Darier disease[11], as well as in individuals with a classic Darier disease phenotype[8].

Segmental types 1 and 2

Two types of segmental Darier disease have been described, both with a distribution of lesions along the lines of Blaschko (see Ch. 62). With the more common type 1 mosaicism (Fig. 59.12), the age of onset, severity, and histologic findings within the streaks are similar to those of generalized Darier disease. Type 1 segmental Darier disease results from a postzygotic mutation in *ATP2A2* during embryogenesis, which leads to a mosaic pattern of skin involvement. Heterozygous *ATP2A2*



Fig. 59.7 Darier disease. Multiple flat-topped papules on the dorsal aspect of the hand.



Fig. 59.9 Darier disease. Alternating longitudinal red and white streaks as well as notching of the free edge of the nail plate. *Courtesy Antonella Tosti, MD.*





Fig. 59.8 Palmar involvement in Darier disease. A Both keratotic papules and keratin-filled depressions are seen. **B** Less commonly, a thick, spiked focal keratoderma is observed. *A, Courtesy Kalman Watsky, MD; B, Courtesy Julie V. Schaffer, MD.*



Fig. 59.10 Oral mucosal Darier disease. Whitish papules on the palate.



Fig. 59.11 Darier disease with superimposed HSV infection (Kaposi varicelliform eruption). Multiple hemorrhagic crusts (**A**) and punched-out erosions (**B**) of a similar size are seen. *B, Courtesy Kalman Watsky, MD.*

mutations in affected, but not background, skin have been documented in patients with this form of segmental Darier disease[36]. If there are mutant cells in the gonads, a patient with type 1 segmental manifestations may have offspring with generalized Darier disease.

Patients with type 2 mosaicism have generalized Darier disease plus linear streak(s) with increased severity[37]. Type 2 segmental manifestations of autosomal dominant disorders occur when patients with a heterozygous germline mutation also have a postzygotic inactivating mutation in the *other* allele of the same gene (i.e. a "second hit" causing loss of heterozygosity), which leads to more severe manifestations in a mosaic distribution (see Fig. 62.2). Of note, a second hit in *ATP2A2* was identified in skin from erosive patches following the lines of Blaschko in a 1-year-old boy with a family history of Darier disease[38].

LESS COMMON PRESENTATIONS OF DARIER DISEASE
Morphologic variants
• Guttate hypopigmentation (see Fig. 59.5) > hyperpigmented flat-topped papules and macules ("freckle-like")*
• Vesiculobullous lesions
• Acral hemorrhagic lesions
• Keratoderma (spiked; see Fig. 59.8B)
• "Cornifying" (e.g. with cutaneous horns)
• Comedones†, facial cysts, acne conglobata
• Periocular nodulocystic lesions
• Alopecia, cutis verticis gyrata
Distribution patterns
• Predominantly involving intertriginous areas, sun-exposed skin, the extremities, acral sites, or the scalp (pityriasis amiantacea-like)
• Segmental (type 1 > 2) (see Fig. 59.12)
Extracutaneous
• Oral mucosal erosions
• Corneal opacities or ulcers
• Salivary gland obstruction
• Laryngeal involvement
*A persistent acantholytic dermatosis and extensive lentiginous "freckling" without an underlying *ATP2A2* mutation has also been described.
†The differential diagnosis may include familial dyskeratotic comedones.

Table 59.1 Less common presentations of Darier disease.



Fig. 59.12 Type 1 segmental Darier disease. Note the distribution of the papules along the lines of Blaschko.

Pathology

There are two prominent histologic features in Darier disease, acantholysis and dyskeratosis (Fig. 59.13). Acantholysis is due to a disturbance in cell adhesion that leads to suprabasilar cleft formation. At the ultrastructural level, this corresponds to a loss of desmosomes and detachment of keratin filaments from the desmosomes[39]. Dyskeratosis is due to apoptosis of keratinocytes and is characterized by nuclear condensation and perinuclear keratin clumping. Two types of dyskeratotic cells are observed in Darier disease[40]:

- "Corps ronds" – acantholytic enlarged keratinocytes in the malpighian layer with darkly staining and partially fragmented nuclei surrounded by a clear cytoplasm and encircled by a bright ring of collapsed keratin bundles.

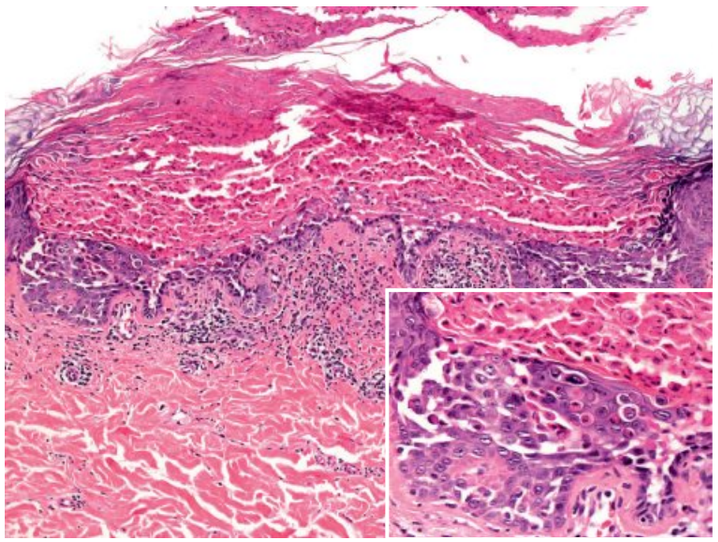


Fig. 59.13 Histopathology of Darier disease. Hyperkeratosis, grains and corp ronds (inset) are seen in addition to acantholysis leading to suprabasilar clefting. *Courtesy Lorenzo Cerroni, MD.*

- "Grains" – small, oval cells in the stratum corneum characterized by an intensely eosinophilic cytoplasm composed of collapsed keratin bundles containing shrunken parakeratotic nuclear remnants. "Grains" are likely derived from "corps ronds", but formal proof that they indeed represent different stages of the same pathologic process has not been provided.

The epidermis overlying acantholytic and dyskeratotic foci is thickened and shows papillomatosis and hyperkeratosis. In the superficial dermis, there is a mild to moderate perivascular inflammatory infiltrate. Diagnostic histologic changes are often focal, necessitating a careful search. Similar histologic features may be observed in Grover disease, but in the latter there tends to be more acantholysis, less dyskeratosis, and fewer "corps ronds" or "grains". The two conditions can be histologically indistinguishable, but the findings are typically broader in Darier disease, i.e. in a given biopsy specimen a larger portion of the epidermis is affected, sometimes with skip areas. Presence of eosinophils within the inflammatory infiltrate favors Grover disease.

Differential Diagnosis

Acrokeratosis verruciformis of Hopf

Flat-topped, wart-like papules on the dorsal aspects of the extremities are a common manifestation of Darier disease. They are clinically indistinguishable from the lesions that characterize the autosomal dominant disorder described by Hopf as "acrokeratosis verruciformis" (Fig. 59.14)[41]. There has been debate as to whether acrokeratosis verruciformis is a separate entity or an allelic forme fruste of Darier disease. A particular *ATP2A2* missense mutation that leads to Pro602Leu in SERCA2 has been identified in families with isolated acrokeratosis verruciformis as well as a Swiss kindred with acral warty lesions followed by the development of more widespread papules after intense sun exposure (author's unpublished observation), but not classic Darier disease[9,10].

Acrokeratosis verruciformis and Darier disease have traditionally been separated on the basis of their histologic features, with the former lacking acantholysis and dyskeratosis. However, serial sectioning is often required to find foci of acantholysis and dyskeratosis in acral skin biopsy specimens from patients with Darier disease[42]. In addition, Hopf actually described nail changes and palmoplantar keratotic papules in his initial report of acrokeratosis verruciformis[41], and there have been subsequent observations of families where some members had only acrokeratosis verruciformis while others exhibited the classic skin findings of Darier disease[43]. Because patients with Darier disease often develop warty lesions on the extremities before keratotic papules appear in a seborrheic distribution, some individuals who present with acrokeratosis verruciformis may later be diagnosed as actually having Darier disease[4].



Fig. 59.14 Acrokeratosis verruciformis of Hopf. Involvement of the dorsal aspect of the foot with flat-topped papules.

Other conditions

Although the clinical differential diagnosis may include severe seborrheic dermatitis and Grover disease (transient acantholytic dermatosis; see Fig. 59.4 and Ch. 87), Darier disease is readily distinguished by involvement of acral skin, the nails, and the oral mucosa. A family history may also be a clue to the diagnosis of Darier disease, and histologic findings differentiate it from seborrheic dermatitis. In Grover disease, the pruritic crusted papules are not confluent, and they typically develop after occlusion and/or sweating. However, in a persistent form of acantholytic dermatosis that affects patients with significant actinic damage, the papules are scalier and the histologic features closely resemble those of Darier disease[44].

In patients with predominantly flexural involvement, pemphigus vegetans (Hallopeau type), pemphigoid vegetans, blastomycosis-like pyoderma (pyoderma vegetans), and HHD may represent diagnostic considerations. Pemphigus vegetans usually develops at an older age and is characterized histologically by exocytosis of eosinophils as well as acantholysis but not dyskeratosis; direct immunofluorescence (DIF) shows the intercellular pattern of the pemphigus group, and antidesmoglein antibodies can be detected by ELISA. Pyoderma vegetans features a neutrophilic infiltrate, and acantholysis is not observed. HHD is sometimes difficult to separate clinically from primarily intertriginous Darier disease. The presence of palmoplantar papules, longitudinal erythronychia, distal notching of the nails, mucosal lesions, and prominent dyskeratosis as well as acantholysis histologically can serve as clues to the diagnosis of Darier disease. Occasionally, a sporadic disorder referred to as "papular acantholytic dyskeratosis" may be localized to the vulvocrural area and in an affected individual, identical somatic *ATP2A2* mutations have been detected within the papules.

Treatment

General measures

Therapies directed against hyperkeratosis, inflammation, and infection are employed as needed. Lightweight clothes and sun protection help prevent aggravation due to heat, sweating, and exposure to UV radiation. Skin care includes the use of antimicrobial cleansers and/or bleach baths (0.5 cup of household bleach [6%–8.25% sodium hypochlorite] in a full standard bathtub once or twice weekly) to prevent malodorous bacterial colonization as well as keratolytic emollients to reduce scaling and irritation.

Topical and intralesional therapy

Topical retinoids are more effective as monotherapy[45,46] than topical vitamin D analogues[47], which had no benefit in a small randomized controlled study[48], or corticosteroids. However, retinoid-associated irritation is common and can be reduced by alternate-day application, liberal use of emollients[45,49], and combination therapy with mid-potency topical corticosteroids[45,49]. Improvement following treatment with topical calcineurin inhibitors has also been reported[48]. Intermittent use of topical antibiotics and antifungal agents is helpful in reducing malodor due to microbial colonization and mild secondary infections.

Several case reports have suggested that topical 5-fluorouracil (1% or 5%) may be efficacious alone or in combination with oral alitretinoin (see below)[50]. Benefit from topical application of diclofenac sodium 3% gel has also been described[51], and cyclooxygenase-2 (COX-2) inhibition has been shown to rescue keratinocytes from UVB-induced downregulation of *ATP2A2* expression[52].

Systemic therapy

Isotretinoin, acitretin, and alitretinoin represent effective treatments for Darier disease, producing significant improvement in ~90% of patients[22,53]. However, the use of these agents is limited by their side effects, and relapse occurs after cessation of therapy. Thus, it is generally recommended that systemic retinoids be reserved for patients with severe disease unresponsive to topical treatment. Because of the teratogenic potential of systemic retinoids, contraception is mandatory for women of childbearing potential (see Ch. 126). Individual dose titration is important to optimize the benefit–risk balance and avoid excessive dose-related side effects, such as mucocutaneous dryness and elevation of serum lipids. Intermittent therapy to prevent exacerbations during the summer months is a useful approach. In patients with predominantly bullous or intertriginous lesions, oral retinoids may aggravate the disease and are not recommended[54].

Oral contraceptives may mitigate symptoms in women with premenstrual exacerbations[55]. Cyclosporine represents an option for patients with severe Darier disease who cannot tolerate or do not respond to oral retinoids[56]. Low-dose intravenous immunoglobulin was also reported to reduce crusting and pruritus in a patient with Darier disease[57]. Oral antibiotics and antifungal medications are often required for significant infections, and oral antivirals (e.g. valacyclovir) are necessary for KVE.

Surgical therapy

Surgical therapy may be an effective alternative for focal recalcitrant lesions, particularly in the flexural and gluteal areas. Excision followed by split-thickness grafting, dermabrasion, or laser removal (CO_2 or erbium:YAG) may yield a long-term remission[58]. Destructive treatment must include the follicular infundibulum in order to prevent recurrences. Experience is necessary to avoid scarring, particularly in body areas at risk for hypertrophic scar or keloid formation. From this standpoint, the erbium:YAG laser might have an advantage over the CO_2 laser[59]. In small case series, improvement has been observed following pulsed dye laser and photodynamic therapy[60].

HAILEY–HAILEY DISEASE

Synonym: ■ Familial benign chronic pemphigus

Key features

- An uncommon autosomal dominant disorder in which mutations in *ATP2C1* result in dysfunction of a Golgi-associated Ca^{2+} ATPase, thus interfering with intracellular Ca^{2+} signaling
- Clinically, flaccid blisters and erosions are seen in intertriginous areas, especially the axillae and groin; moist, malodorous vegetations and fissures may develop
- Segmental variants (types 1 and 2 mosaicism) can occur
- The major histologic finding is acantholysis throughout the spinous layer, sometimes referred to as a "dilapidated brick wall"

Introduction

HHD is an autosomal dominant genodermatosis characterized by vesicular and erosive lesions that favor the intertriginous areas,

especially the axillae and groin. Mutations in *ATP2C1*, which encodes the Golgi-associated Ca^{2+} ATPase hSPCA1, lead to abnormal intracellular Ca^{2+} signaling, resulting primarily in a loss of cellular adhesion (acantholysis) in the stratum spinosum.

History

In 1939, Howard and Hugh Hailey, brothers working in the Department of Dermatology at Emory University School of Medicine in Atlanta, Georgia, described a chronic dermatosis in two sets of brothers. The disorder was characterized by recurrent blisters and erosive, crusted lesions on the neck (in one pair of brothers) and in the axillae and groin (in the second pair)[61]. Histologic sections from all four patients showed similar features – intraepidermal vesicles, mild dyskeratosis, hyperkeratosis, and a moderate dermal lymphocytic infiltrate. Different dermatopathologists interpreted these findings variably as pemphigus, pemphigus-like, or Darier disease. The authors themselves rightly believed that they were dealing with a novel entity separate from Darier disease and coined the name "familial benign chronic pemphigus".

A disease called "pemphigus congénital familiale héréditaire" had been described 6 years prior to the report by the Hailey brothers. Therefore, some believe that HHD should also bear the name of the French dermatologists Gougerot and Allée. However, they did not perform a biopsy, and the early onset and initial localization on pressure points suggest that their patients may have actually suffered from epidermolysis bullosa simplex[62]. The subsequent controversy as to whether "familial benign chronic pemphigus" was a distinct disorder or a phenotypic variant of Darier disease was eventually solved by our understanding of the molecular genetics of both disorders.

Epidemiology

There are no data regarding the exact prevalence of HHD. Based upon clinical experience, HHD is seen nearly as often as Darier disease. The mode of inheritance is autosomal dominant with complete penetrance, but the age of onset and expressivity vary markedly amongst affected family members[63,64]. Particular mutations may be associated with primarily genitoperineal involvement[65] or milder phenotypes[66].

Pathogenesis

HHD is caused by mutations in *ATP2C1*[67,68], which encodes hSPCA1, a Ca^{2+} ATPase that is localized to the Golgi apparatus[69,70] (see Fig. 59.1). hSPCA1 transports Ca^{2+} and Mn^{2+}, and it sequesters Ca^{2+} within the Golgi lumen. HHD is likely caused by haploinsufficiency and most *ATP2C1* mutations encode premature termination codons[71,72].

Acantholysis due to *ATP2C1* mutations appears to be mediated via impaired Ca^{2+} sequestration, resulting in depletion of Ca^{2+} within the Golgi lumen[69]. Normal Golgi Ca^{2+} levels are required for proper protein processing[73], and Golgi Ca^{2+} depletion in HHD keratinocytes impairs the processing and translocation of junctional proteins that function in cell–cell adhesion. Lesional skin from HHD patients shows decreased staining for extracellular desmosomal components[74], and altered synthesis of tight junction proteins has been observed in hSPCA1-deficient keratinocytes[75]. Reduced ATP levels in HHD keratinocytes have also been associated with impaired actin reorganization, which may affect adherens junction formation[76]. Lastly, decreased calcium levels in basal keratinocytes of lesional HHD epidermis may be linked to abnormal localization of ATP receptors and aberrant expression of keratins 10 and 14[18].

Clinical Features

Onset and clinical pattern

The initial lesions and associated symptoms usually develop during the second or third decade of life but may be delayed until the fourth or fifth decade[63]. HHD has a predilection for intertriginous sites, such as the axillae, groin, lateral aspects of the neck, and perianal region (Fig. 59.15A & C; see Fig. 59.4). The scalp, antecubital and popliteal fossae, and trunk are less frequently involved[77] (Fig. 59.15D). Inframammary and vulvar lesions are common in women (Fig. 59.15B), and female patients occasionally present with isolated vulvar disease[78].

The primary lesion is a flaccid vesicle on erythematous or normal-appearing skin, which ruptures easily and therefore is often overlooked (see Fig. 59.15A). The blisters give rise to macerated or crusted erosions (see Fig. 59.15B–D), which tend to spread peripherally, producing a circinate border with crusts and small vesicles when examined carefully



Fig. 59.15 Hailey–Hailey disease. A Erythematous, eroded plaque in the axilla. Note the intact flaccid vesicles at 2 and 7 o'clock. **B** Chronic submammary lesion with erosions in a worm-eaten pattern. **C, D** Vegetative plaques with erosions on the neck (**C**) and central chest (**D**). *C, D, Courtesy Jonathan S. Leventhal, MD.*



Fig. 59.16 Hailey–Hailey disease. Circinate plaques on the back with erosions and crusting in the active borders. *Courtesy Louis A. Fragola, Jr, MD.*

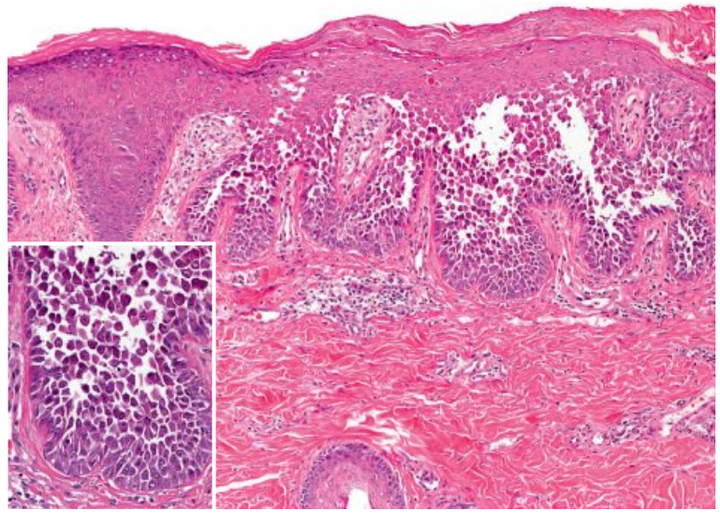


Fig. 59.17 Histopathology of Hailey–Hailey disease. Focal crusting and acantholysis beginning in the suprabasilar area and extending throughout the epidermis. The latter has been likened to a "dilapidated brick wall". *Courtesy Lorenzo Cerroni, MD.*

(Fig. 59.16). Development of chronic, moist, malodorous vegetations and painful fissures is common. Healing occurs without scarring, leaving postinflammatory hyperpigmentation.

Longitudinal leukonychia of the fingernails may serve as a subtle diagnostic clue in patients with limited or atypical disease[79]. Involvement of the buccal, vaginal, or conjunctival mucosae is rare[80–82].

Symptoms

Painful intertriginous erosions and crusting may interfere with activities of daily living. Fetid odor and pruritus add to the psychosocial distress experienced by HHD patients.

Modifying factors

Given the abnormal cell–cell adhesion within the epidermis, friction can induce new lesions. Heat and sweating can also exacerbate HHD, and patients often note worsening during the summer months. Although *ATP2C1* mRNA expression in keratinocytes can be suppressed by UVB irradiation[23], UV exposure does not appear to influence the course of HHD[63]. Microbial colonization and secondary infections are important modifying factors, as discussed below. In particular, staphylococcal infection potentiates acantholysis and may lead to severe and widespread blistering[83].

Course of the disease

Complete remissions as well as flares are common, and the clinical course in an individual patient is difficult to predict. Some patients report attenuation of the disease at an older age, whereas others experience no change or worsening over time[77]. Life expectancy is not altered.

Complications

Infections

As in Darier disease, colonization and secondary bacterial, fungal, and viral infections play an important role in disease exacerbation and persistence[84,85]. Vegetating lesions and malodor suggest bacterial and/or fungal overgrowth. Topical and/or systemic antimicrobial agents may be required to induce a clinical remission.

Recalcitrant intertriginous lesions have been described in association with HSV infections[84]. PCR-based testing, direct fluorescent antibody assays, or viral culture of infected keratinocytes can confirm this diagnosis; occasionally, a skin biopsy is required. KVE due to HSV is a rare complication of HHD[86]. It is characterized by fever and a rapidly spreading vesicular eruption, and prompt treatment with a systemic antiviral medication (e.g. valacyclovir, acyclovir) is required.

Malignant transformation

There are a few case reports of cutaneous squamous cell carcinoma developing within chronic lesions of HHD in the anogenital region[87]. It is possible that impairment of the structural integrity of the epidermis may predispose patients to infection with oncogenic strains of HPV (see Ch. 79).

Clinical subtypes of Hailey–Hailey disease

Segmental type 1

Segmental type 1 HHD is caused by a heterozygous postzygotic mutation in an otherwise normal embryo, resulting in a mosaic distribution of disease with age of onset and severity similar to the non-mosaic phenotype. Only a few cases of segmental type 1 involvement in HHD have been reported.

Segmental type 2

There are rare patients with generalized HHD who also have a segmental area of more pronounced involvement with earlier onset, analogous to type 2 segmental lesions described previously for Darier disease. This results from postzygotic inactivation of the normal *ATP2C1* allele (loss of heterozygosity), which leads to more severe disease in a mosaic pattern[88]. Unlike HHD due to a heterozygous mutation, the affected segments display acantholysis within adnexal structures, which might make it impossible to eradicate foci of blistering using superficial ablative methods (see below).

Pathology

Whereas acantholysis in Darier disease occurs primarily within discrete foci, the loss of intercellular bridges in HHD is generally more widespread within the epidermis. Thus, larger areas of dyscohesion with single or groups of acantholytic cells are seen, which have been likened to a "dilapidated brick wall". Dermal papillae, lined by a single layer of basal cells, protrude into the blister cavities and are referred to as "villi" (Fig. 59.17). In contrast to Darier disease, necrotic keratinocytes are uncommon, and only rare acantholytic dyskeratotic cells (e.g. "corps ronds") may be observed. In more chronic lesions, epidermal hyperplasia, parakeratosis, and focal crusts are found. A moderate perivascular lymphocytic infiltrate is observed in the superficial dermis.

Histologically, Grover disease may be indistinguishable from HHD, but these two entities are readily distinguished on the basis of clinical features. DIF is negative, thus excluding pemphigus vulgaris.

Differential Diagnosis

The blisters in HHD are typically fragile and rupture easily. Therefore, clinical experience and a high index of suspicion may be necessary to diagnose HHD, especially in patients with limited disease. Lesions confined to the axillae or groin may be mistaken for intertrigo or candidiasis (see Fig. 13.4). Isolated perianal maceration is easily misdiagnosed as irritant dermatitis, and vulvar involvement may resemble lichen simplex chronicus[78]. Histologic examination of affected skin is often the key to the diagnosis.

The lesions of inverse psoriasis have sharper borders, fewer erosions, and less crusting. A total skin examination, looking for additional sites of involvement and associated signs, e.g. nail pitting, will aid in the diagnosis. Vegetating intertriginous lesions in HHD may be identical to those of pemphigus vegetans (Hallopeau type) or pemphigoid vegetans, but the latter can be differentiated by positive DIF of perilesional skin.

The cutaneous features of HHD and Darier disease may overlap. Older reports described patients with characteristic skin findings of both genodermatoses who therefore carried two diagnoses[89], but genetic analysis can now establish a single diagnosis in such individuals. In general, the two disorders have different patterns of distribution that are fairly easily distinguished (see Fig. 59.4). Moreover, a predominantly vesicular eruption in patients with Darier disease is rare[20]. Additional features such as V-shaped notches in the distal free edge of the nail plate, longitudinal erythronychia, and oral papules point to the diagnosis of Darier disease.

Treatment

General measures

There is no specific therapy for the acantholysis. Wearing lightweight clothes is recommended to avoid friction and sweating, and adhesive dressings should be avoided. Colonization and secondary bacterial, fungal, and viral infections are addressed via antimicrobial cleansers or bleach baths and appropriate topical and/or systemic antimicrobial agents, respectively.

Topical and intralesional therapy

Topical corticosteroids often help to reduce inflammation and can be combined with topical antimicrobials and cleansers. Early application of corticosteroids may ameliorate flares[63], and injections of intralesional corticosteroids can be tried for persistent lesions. In order to minimize the potential side effects of topical corticosteroids in intertriginous zones (e.g. atrophy, striae, telangiectasias), the lowest potency that is effective should be used and they should be applied intermittently. Both improvement and worsening following treatment with topical calcineurin inhibitors have been described[90,91].

In case reports, improvement has been observed with topical application of 5-fluorouracil[92] and vitamin D analogues[93]. Of note, there are multiple reports of substantial improvement of HHD in the axillae, inframammary area, and groin after chemodenervation of sweat glands with botulinum toxin injections[94,95]. Application of zinc oxide paste in skin folds to protect against friction and moisture may also be helpful[90].

Surgical and physical therapy

Surgical therapy may be considered for disease unresponsive to general measures and topical treatments. While wide excision followed by grafting has been reported to be successful[96], this aggressive approach has been replaced by more superficial ablative techniques. The most well-documented method is dermabrasion[97], but laser vaporization of the epidermis (scanned CO_2 or erbium:YAG) seems to be equally effective[59]. Removal of the diseased epidermis plus its dermal niche of fibroblasts, which can extend to the level of the mid dermis, is recommended. Re-epithelialization from the spared adnexal structures normally occurs within 7–14 days. Benefit has also been reported with electron beam radiation[98], photodynamic therapy[99], and combination of narrowband UVB phototherapy with an oral retinoid[100].

Systemic therapy

With the exception of antimicrobial agents for secondary infections, there is no strong evidence to support the use of systemic therapies in HHD. A case series described improvement with long-term continuous or intermittent doxycycline administration in 6 patients with HHD[101], but the benefits of this treatment regimen vary (author's personal observations). Low-dose naltrexone may have some efficacy and is well-tolerated; results in case series have ranged from clinical improvement in 7 of 8 patients, with a 77% mean reduction in areas of involvement, to a sustained response in only 2 of 14 patients, with initial improvement then relapse in 6 and no response in 6 individuals[102]. Oral acitretin and isotretinoin also have variable efficacy[63], while successful results with alitretinoin have been reported in several patients[103]. There are anecdotal reports of severely affected individuals improving with the use of immunomodulatory drugs, e.g. prednisone, cyclosporine, methotrexate, dapsone, or afamelanotide[104–106]. In one case series, apremilast led to improvement in 4 patients (with relapse in 2 individuals after >6 months of treatment), but another report described no response to apremilast in 4 of 5 patients[107–109].

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eFig. 59.1 Darier disease. Red–brown keratotic papules scattered on the abdomen. *Courtesy Julie V. Schaffer, MD.*



eFig. 59.4 Hailey–Hailey disease. Erythematous plaque with erosions and maceration of the inguinal canal and scrotum.



eFig. 59.2 Darier disease. Pink keratotic papules with areas of confluence on the chest and neck as well as scar centrally on the chest. *Courtesy Julie V. Schaffer, MD.*







eFig. 59.3 Darier disease. Nail changes with longitudinal erythronychia and notching of the free edge of the nail plate.

eFig. 59.5 Hailey–Hailey disease. A, B Pink and pink–brown plaques with erosions and crusts. *Courtesy Jeffrey P. Callen, MD.*

60 Primary Immunodeficiencies

Julie V. Schaffer and Amy S. Paller

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INTRODUCTION

Primary immunodeficiencies represent a heterogeneous group of inherited disorders characterized by immune system defects that result in susceptibility to infections as well as additional manifestations such as autoimmunity, allergy, and malignancy. The molecular bases have been defined for >450 monogenic primary immunodeficiency diseases, providing valuable insight into the functions of the human immune system[1–4].

Patients with genetic immunodeficiency disorders often manifest with cutaneous abnormalities[1,3]. Some of these skin findings are highly characteristic of a particular disorder, while others, such as eczematous or granulomatous dermatitis, are shared by other immunodeficiencies[5,6] (Table 60.1). Table 60.2 provides an overview of the current classification system for immunodeficiency disorders and lists conditions that are covered in other chapters.

In general, immunodeficiency should be suspected when patients have recurrent infections of longer duration and greater severity or caused by unusual organisms. Additional signs may include incomplete clearance of infections or a poor response to antimicrobial therapy. Screening laboratory tests for a patient with recurrent cutaneous infections that raise suspicion of a primary immunodeficiency are listed in Table 60.3[7]. Determination of the genetic etiology, which may require multigene panels or whole-exome sequencing, can provide prognostic information and improve management[8].

ATAXIA–TELANGIECTASIA

Synonym: ■ Louis–Bar syndrome

Key features

- Progressive cerebellar ataxia
- Oculocutaneous telangiectasias, initially of the bulbar conjunctivae
- Selective deficiency of humoral and cell-mediated immunity, leading to sinopulmonary infections
- Increased sensitivity to ionizing radiation
- Leukemias and lymphomas

Introduction

Ataxia–telangiectasia (AT) is characterized by oculocutaneous telangiectasias, progressive cerebellar ataxia beginning in infancy, a variable immunodeficiency with a tendency to develop sinopulmonary infections, and chromosomal instability with persistent DNA damage after exposure to ionizing radiation.

Epidemiology

AT is an autosomal recessive disorder that occurs in 1 in 40 000 to 100 000 live births, with a carrier rate of up to 1% of the population.

Pathogenesis

AT results from mutations in the ataxia–telangiectasia mutated gene (*ATM*), which encodes a phosphatidylinositol 3-kinase-like serine/threonine protein kinase that plays a central role in activating apoptotic and cell cycle responses to DNA damage, particularly double-stranded breaks[9]. These DNA breaks are sensed directly by the MRN (MRE11–RAD50–nibrin [NBN]) complex, which recruits ATM and triggers its dissociation from inactive multimers to active monomers[10,11]. Autophosphorylated ATM monomers subsequently activate (via phosphorylation) a variety of targets, including p53, BRCA1, FANCD2, and Artemis in addition to NBS1 and MRE11. The result is cell cycle arrest and facilitation of DNA repair, both in the setting of external insults (e.g. ionizing radiation) and in the processing of physiologic DNA breaks that occur during V(D)J recombination in lymphocytes, telomere maintenance, and meiosis[9]. This provides an explanation for the sensitivity to ionizing radiation, immunodeficiency, premature aging, and defective spermatogenesis that are observed in patients with AT. Progressive neurologic deterioration in affected individuals likely reflects defective DNA repair in a cell population that cannot replicate. Oxidative stress related to ATM dysfunction has also been implicated in the pathogenesis of the disease.

Of note, mutations in genes encoding components of the MRN complex cause conditions with manifestations similar to AT. *MRE11* mutations underlie the *AT-like disorder*, which features radiosensitivity and neurologic manifestations but no telangiectasias, and *NBN* or rarely *RAD50* mutations result in *Nijmegen breakage syndrome* characterized by microcephaly, immunodeficiency, chromosomal instability, and cancer predisposition.

Clinical Features

The first manifestation of AT is usually ataxia, which typically appears when the affected child begins to walk. However, the diagnosis is often not recognized until the oculocutaneous telangiectasias are well developed, at a median age of 6 years[12]. The telangiectasias first appear at 3–6 years of age on the lateral and medial bulbar conjunctivae as red, symmetric horizontal streaks (Fig. 60.1A). Telangiectasias subsequently develop on the ears, eyelids, malar prominences, antecubital and popliteal fossae, and presternal area, and less commonly on the dorsal aspects of the hands and feet as well as the hard and soft palate. The non-facial cutaneous telangiectasias are often subtle, resembling fine petechiae (Fig. 60.1B).

Progeric changes of the skin and hair are noted in almost 90% of patients. Subcutaneous fat is lost early and the facial skin tends to become atrophic and sclerotic. Gray hairs frequently appear in young children, and diffuse graying of the hair may occur by adolescence. Another common manifestation of AT is cutaneous granulomas (Fig. 60.1C), which are often associated with persistent rubella virus

CUTANEOUS FINDINGS IN PRIMARY IMMUNODEFICIENCY DISORDERS										
Disorder	***S. aureus* infections**		**CMC**	**Warts**	**Eczematous dermatitis**	**Granulomatous dermatitis***	**LE**	**SVV**	**Ulcers (PG-like)**	**Other findings**
	Superficial pyodermas	**Abscesses**								
Ataxia–telangiectasia	+	+			+	+ (often ulcerate)				Oculocutaneous telangiectasias, progeric changes, CALM, BCC
Chédiak–Higashi syndrome	+	+							+	Pigmentary dilution, hyperpigmentation in sun-exposed sites, silvery hair, bleeding diathesis, gingivitis
Chronic granulomatous disease	++	++	+		+	++ (nodular, necrotic)	+		+	DLE in female carriers, Sweet syndrome, oral ulcers
Chronic mucocutaneous candidiasis			++			(++, but infectious due to *Candida*)				Dermatophyte infections, vitiligo, alopecia areata
Common variable immunodeficiency	+	+	+	+	+	++	+	+	+	Dermatophyte infections, vitiligo, alopecia areata
Complement deficiencies	+	+	+				++	+	+	Dermatomyositis, urticaria, lipodystrophy (C3), JIA
DiGeorge syndrome†			+		+	+				
Hyper-IgE syndromes (HIES)	++	++ (cold)	+	‡	++					Neonatal papulopustular eruption (STAT3)
Hyper-IgM syndrome	+	+		+		+	+		+	Oral ulcers
Idiopathic $CD4^+$ lymphocytopenia			+	++			+			$CD4^+$ T cells <300/mm^3 or <20%¶, severe HSV infections, cryptococcal meningitis, non-tuberculous mycobacterioses, lymphoma
IgA deficiency	+	+	+		+		+	+	+	Vitiligo, lipodystrophia centrifugalis abdominalis
IgM deficiency	+	+		+	+		+			
IL-1 receptor-associated kinase-4 (IRAK-4) deficiency	++	++ (cold)	+							
Leukocyte adhesion deficiency		++ (necrotic)							++	Poor wound healing, delayed separation of the umbilical stump, gingivitis
SCID	+	+	+	+	+	+*				GVHD, erythroderma; Omenn syndrome
TAP deficiency						++		+	+	
WHIM syndrome	+	+		++		+				
Wiskott–Aldrich syndrome	++	+			++	+		+		Bleeding diathesis
X-linked agammaglobulinemia	+	++			+	+				Dermatomyositis-like eruption (due to echovirus); ecthyma gangrenosum

*Granulomatous dermatitis associated with persistent rubella virus infection (vaccine derived > wild type) has been identified in patients with these and other disorders characterized by T cell lymphopenia and/or defective lymphocyte cytotoxicity, including Griscelli syndrome type 2 and familial hemophagocytic lymphohistiocytosis. Extensive cutaneous and extracutaneous granulomatous disease (including destructive midfacial granulomas) has also been described in children with hypomorphic *RAG1* or *RAG2* mutations.
†Defective thymic function, hypocalcemia secondary to hypoparathyroidism, congenital heart defects, and craniofacial anomalies; due to 22q11 deletions.
‡Patients with DOCK8 deficiency are also at increased risk of developing mucocutaneous squamous cell carcinoma and severe warts, molluscum contagiosum, and herpes simplex or varicella–zoster viral infections.
¶On more than one occasion with no evidence of HIV infection and the absence of any defined immunodeficiency or immunosuppressive therapy.

Table 60.1 Cutaneous findings in primary immunodeficiency disorders. +, occasional finding; ++, common finding; BCC, basal cell carcinoma; CALM, café-au-lait macules; CMC, chronic mucocutaneous candidiasis; DLE, discoid lupus erythematosus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; IL, interleukin; JIA, juvenile idiopathic arthritis; LE, lupus erythematosus; PG, pyoderma gangrenosum; SCID, severe combined immunodeficiency; SVV, small vessel vasculitis; TAP, transporter associated with antigen processing; WHIM, warts, hypogammaglobulinemia, infections and myelokathexis.

PRIMARY IMMUNODEFICIENCIES: CLASSIFICATION FROM THE INTERNATIONAL UNION OF IMMUNOLOGICAL SOCIETIES EXPERT COMMITTEE AND DISORDERS DISCUSSED IN OTHER CHAPTERS			
Group	**Type of primary immunodeficiency disorder**	**Examples (including disorders discussed in other chapters)**	**Table(s)**
1	Immunodeficiencies affecting cellular and humoral immunity	Severe combined immunodeficiency (SCID) and other combined immunodeficiencies	Table 60.16
2	Combined immunodeficiencies with associated/syndromic features	Hyper-IgE syndromes and Netherton syndrome (Ch. 57); hypohidrotic ectodermal dysplasia with immune deficiency and ORAI-1 deficiency (Ch. 63); Bloom syndrome (Ch. 87); Hennekam lymphangiectasia–lymphedema syndrome (Ch. 104)	Table 60.14
3	Predominantly antibody deficiencies	See text	Table 60.15
4	Diseases of immune dysregulation	Chédiak–Higashi, Hermansky–Pudlak and Griscelli syndromes (Ch. 66); familial hemophagocytic lymphohistiocytosis	Table 60.5 Table 60.6
5	Congenital defects of phagocyte number or function	Leukocyte adhesion deficiency; poikiloderma with neutropenia (Clericuzio type; Ch. 63)	Table 60.10 Table 60.13
6	Defects in intrinsic and innate immunity	Chronic mucocutaneous candidiasis; epidermodysplasia verruciformis (Ch. 79)	Table 60.4 Table 60.13
7	Autoinflammatory disorders*	Interferonopathies and disorders of the inflammasome (Ch. 45)	Table 45.2 Table 45.7
8	Complement deficiencies	See text	Table 60.8
9	Bone marrow failure disorders	Fanconi anemia and dyskeratosis congenita (Ch. 67)	Table 67.9 Table 67.10
10	Phenocopies of inborn errors of immunity		
*Characterized by immune dysregulation that often includes a component of immunodeficiency.			

Table 60.2 Primary immunodeficiencies: classification from the International Union of Immunological Societies Expert Committee and disorders discussed in other chapters.

SCREENING LABORATORY TESTS TO ASSESS FOR A PRIMARY IMMUNODEFICIENCY IN A PATIENT WITH RECURRENT CUTANEOUS INFECTIONS		
Test	**Finding**	**Immunodeficiency identified**
Complete blood count with differential, platelet count, and examination of smear	• Giant granules within neutrophils, ± neutropenia • Neutrophilia • Small platelets, thrombocytopenia	Chédiak–Higashi syndrome Leukocyte adhesion deficiency Wiskott–Aldrich syndrome
Hair shaft examination	• Small, regular clumps of melanin • Large, irregular clumps of melanin	Chédiak–Higashi syndrome Griscelli syndrome (type 2; *RAB27A*)
Quantitative immunoglobulins	• All Ig ↓ • IgA ↓, IgG ↓, ± IgM ↓ • IgA ↓ or IgM ↓ • IgM ↑, all other Ig ↓ • IgM ↑, ± IgA ↑, ± IgG ↓ • IgA ↓, IgE ↓, $IgG_{2,4}$ ↓ • IgE ↑↑ • IgM ↓, ± IgG ↓, IgA ↑, IgE ↑	X-linked agammaglobulinemia Common variable immunodeficiency Selective IgA or IgM deficiency Hyper-IgM syndrome Hypohidrotic ectodermal dysplasia with immunodeficiency Ataxia–telangiectasia Hyper-IgE syndrome Wiskott–Aldrich syndrome
Total hemolytic complement (CH50)	• Marked ↓	Various complement deficiencies
Dihydrorhodamine (DHR) flow cytometric assay	• Marked ↓ fluorescence (% of neutrophils and intensity)	Chronic granulomatous disease
T and B cell analysis by flow cytometry	• Lack of T cells ± B cells	Severe combined immunodeficiency

Table 60.3 Screening laboratory tests to assess for a primary immunodeficiency in a patient with recurrent cutaneous infections.

infection (vaccine strain > wild type)[13,14]. These granulomatous plaques tend to be persistent and ulcerate, leading to significant discomfort. Children with AT often have hyper- or hypopigmented macules as well as hyper- and/or hypopigmentation along the lines of Blaschko, with chromosomal instability likely explaining their predisposition to pigmentary mosaicism. Other dermatologic findings that have been described in individuals with AT include a facial papulosquamous rash, poikiloderma, hypertrichosis favoring the arms, warts, and acanthosis nigricans[15].

Cerebellar ataxia usually begins during infancy and is characterized by swaying of the head and trunk. Choreoathetosis, dysarthric speech, oculomotor abnormalities, and myoclonic jerks often become prominent during childhood. Despite good muscle strength, patients are typically confined to a wheelchair by 11 years of age. The facies become dull and hypotonic, with mask-like changes developing concurrently with progressive progeric features. Of note, milder AT with onset of neurologic manifestations in adulthood has been described in individuals with *ATM* mutations that result in residual kinase activity.

Chronic or recurrent sinopulmonary infections occur in >80% of AT patients[16], with the most common cause of death being bronchiectasis with respiratory failure. The majority of affected individuals also have evidence of glucose intolerance, hyperinsulinemia, and insulin resistance. Additional manifestations of AT include growth delay (>70%), hypogonadism (especially in female patients), and intellectual disability (~30%)[17].

Although lymphoid malignancy has been reported as the presenting sign of AT during infancy, most neoplasias occur in young adults. Patients who survive into their late teenage years have an up to 40% risk of developing a malignancy, especially leukemia (70-fold increase compared to unaffected individuals) and lymphoma (200-fold increase). Occasionally, patients develop basal cell carcinomas (BCCs) during the third decade of life.

Carriers of heterozygous ATM mutations have a two- to threefold increase in both the risk of developing breast cancer and the likelihood of death from cancer, including malignancies of the stomach, colon, and lung as well as the breast. There is greater excess mortality in individuals <50 years of age[18].

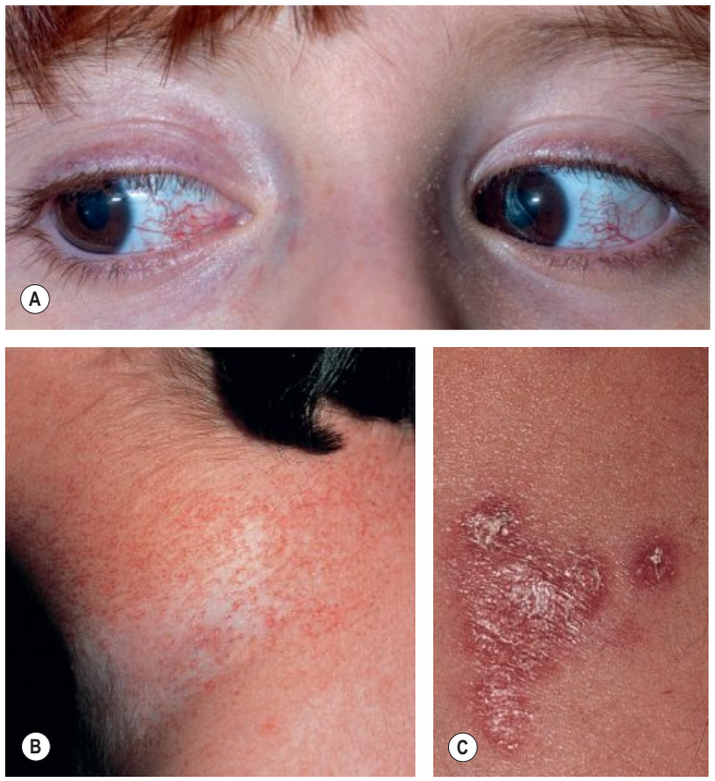


Fig. 60.1 Ataxia–telangiectasia (AT). A Linear telangiectasias on the medial and lateral bulbar conjunctivae of a girl with AT. Punctate and smaller linear telangiectasias are also present on the eyelids. **B** Extensive telangiectasias on the neck of a young woman with AT. **C** Persistent granulomatous plaques on the leg of a child. These lesions often ulcerate and are difficult to manage. *A, Courtesy Edward Cowen, MD.*

Laboratory Findings

Immunologic defects in patients with AT include: (1) decreased serum levels of IgE, IgA, and IgG (especially IgG_2 and IgG_4) in ~80%, 70%, and 60% of patients, respectively; (2) low-molecular-weight (8 S) IgM (in 80% of patients) and increased serum levels of IgM (in a minority of patients); and (3) defects in cell-mediated immunity such as lymphopenia (in 70% of patients) and deficient *in vitro* responses to antigens and mitogens[16]. Affected individuals tend to have a relative deficiency of $CD4^+$ T cells and an excess of γ/δ T cells as well as elevated serum levels of interleukin-8 (IL-8), a chemokine that may contribute to pathogenic inflammation in AT. Most patients have an absent or abnormal thymus. Individuals with no ATM activity have more severe immunologic deficits than those with low levels of ATM activity[19].

Spontaneous chromosomal abnormalities such as fragments, breaks, gaps, and translocations occur 2–18 times more frequently in patients with AT than in unaffected individuals, and an increased rate of telomeric shortening is also observed. Rearrangements of chromosomes 7 and 14 are particularly common and may predict the development of lymphoma. Fibroblast DNA from both patients and carriers is extremely sensitive to ionizing radiation and to radiomimetic agents such as bleomycin.

Almost all patients with AT have elevated levels of α-fetoprotein and carcinoembryonic antigen, and measuring the former can support the diagnosis in individuals ≥2 years of age. Hepatic transaminase levels are also mildly elevated in approximately half of patients, and MRI often shows cerebellar atrophy by early childhood. Additional traditional diagnostic clues include radiosensitivity testing with the colony survival assay, analysis of radioresistant DNA synthesis (which demonstrates an abnormal S phase checkpoint), and karyotyping to identify 7;14 translocations. Sequencing the *ATM* gene or immunoblotting for the ATM protein may be utilized to confirm the diagnosis. Prenatal diagnosis of AT can be performed when parental mutations have been identified.

Differential Diagnosis

Children with AT may be thought to have Friedreich ataxia until the ocular telangiectasias become apparent. The conjunctival telangiectasias are occasionally misdiagnosed as conjunctivitis, but the chronicity and size of the telangiectatic vessels distinguish AT. Bloom syndrome can present with facial and occasionally conjunctival telangiectasias, café-au-lait macules, decreased immunoglobulin levels, recurrent respiratory infections, and hematologic malignancies, but patients do not have neurologic abnormalities (see Ch. 87). FILS syndrome – *f*acial dysmorphism, *i*mmunodeficiency, *l*ivedo, and *s*hort stature – due to polymerase ε 1 (*POLE1*) mutations has overlapping features and can also present with telangiectasias or poikiloderma. RIDDLE syndrome is an autosomal recessive condition that features *r*adiosensitivity, *i*mmunodeficiency, facial *d*ysmorphism, *d*ifficulty *le*arning, abnormal motor control, and short stature due to mutations in *RNF168*, which encodes a protein that mediates ubiquitin-dependent signaling at sites of DNA double-stranded breaks.

Treatment

The median lifespan in patients with AT is now >25 years. More than half of patients die from chronic sinopulmonary disease and up to a third succumb to a malignancy or complications of cancer treatment. Some of the patients who survive into adulthood show improvement in neurologic and immunologic status.

Therapy is supportive:

- antibiotics for infections; prophylactic antibiotics and IVIg replacement therapy for patients with severe immunodeficiency
- avoidance of sun exposure and use of sunscreens
- early physiotherapy for patients with bronchiectasis and consideration of systemic corticosteroid therapy for interstitial lung disease
- physical therapy to prevent contractures related to neurologic dysfunction
- screening for the development of malignancy.

If malignancy occurs, chemotherapy is typically necessary; radiation and radiomimetic chemotherapeutic agents, especially bleomycin, should be avoided. AT patients have a decreased threshold for postradiation erythema, tissue necrosis, and radiation-induced cutaneous malignancy. If radiation is necessary, restriction of the fractions to 1 Gy and total radiation to <20 Gy is recommended. Allogeneic hematopoietic stem cell transplantation with a reduced intensity conditioning regimen has been utilized in AT patients with hematopoietic malignancies or severe manifestations of immunodeficiency, including destructive rubella virus-associated cutaneous granulomas[20]. Because oxidative stress is thought to contribute to chromosomal instability, neurodegeneration, and malignancy in patients with AT, administration of antioxidants such as α-lipoic acid is often recommended; however, treatment with the latter together with nicotinamide did not improve neurologic or pulmonary function in a small controlled study[21]. In patients with truncating *ATM* mutations, treatment with aminoglycosides can induce read-through of premature termination codons and restore production of functional ATM protein, providing the basis for a potential therapeutic approach[22].

CHRONIC MUCOCUTANEOUS CANDIDIASIS

Key features

- Heterogeneous group of conditions characterized by recurrent and progressive candidal infections of the skin, nails, and mucosae
- Due to an impaired interleukin-17 response, which has a critical role in immune defense against *Candida*
- May be associated with additional autoimmune and infectious manifestations

Introduction

Chronic mucocutaneous candidiasis (CMC) represents a heterogeneous group of disorders characterized by progressive and recurrent infections of the skin, nails, and mucous membranes with *Candida* spp[23]. Affected individuals demonstrate an ineffective immune response against this

organism, and patients with an earlier onset and greater severity of candidal infections typically have more severe underlying immunologic abnormalities.

Epidemiology

*A*utoimmune *p*olyendocrinopathy–*c*andidiasis–*e*ctodermal *d*ystrophy syndrome (APECED) has autosomal recessive inheritance[24], and other familial forms of CMC have autosomal dominant or recessive inheritance patterns (Table 60.4).

Pathogenesis

Patients with CMC have an abnormal immune response to *Candida* spp. and sometimes to other infectious organisms (Table 60.4).The immune defects that underlie selective predisposition to *Candida* infections in both APECED and non-APECED CMC patients involve an impaired response by T helper 17 (Th17) cells, which have a critical role in immune defense against *Candida* (Fig. 60.2)[25–27].

APECED results from mutations in the *AIRE* (*a*uto*i*mmune *re*gulator) gene, which encodes a transcription factor[28]. The AIRE protein regulates

VARIANTS OF CHRONIC MUCOCUTANEOUS CANDIDIASIS (CMC) IN CHILDREN AND ADOLESCENTS	
Subgroup	**Features**

CMC due to increased STAT1 signaling (most common form)	• Autosomal dominant due to gain-of-function *STAT1* mutations; see Fig. 60.2
	• Onset of mucocutaneous candidal infections at a mean age of 1 year – oropharynx (>95%), nails (60%), skin (50%)
	• Dermatophyte infections of skin and/or nails (15%)
	• Cutaneous autoimmune disorders, e.g. vitiligo, alopecia areata (10%)
	• Autoimmunity (40%)
	  • thyroid disease (25%)
	  • type 1 diabetes mellitus (5%)
	  • cytopenias (5%)
	  • colitis or celiac disease (5%), hepatitis (2%)
	  • systemic lupus erythematosus (2%)
	• Other infections (variable)
	  • cutaneous staphylococcal
	  • demodicosis
	  • bacterial pneumonia (e.g. pneumococcal, *Pseudomonas*; 50%), otitis, sinusitis
	  • recurrent/severe viral (e.g. HSV, VZV, EBV, CMV, orf; 40%)
	  • invasive fungal (e.g. *Candida*, *Aspergillus*, *Cryptococcus*, endemic dimorphic, mucormycosis, *Fusarium*; 10%)
	  • mycobacterial (tuberculosis, non-tuberculous; 5%)
	• Aneurysms (e.g. cerebral, aortic; 5%), mucocutaneous SCC (5%), dental enamel defects

CMC representing the main clinical phenotype (“CMC disease”)	• Autosomal dominant due to mutations in IL-17F (*IL17F*) or Jun N-terminal kinase 1 (JNK1; *MAPK8*); autosomal recessive due to mutations in IL-17 receptor A or C (*IL17RA* or *IL17RC*) and TRAF3-interacting protein 2 (*TRAF3IP2*; *ACT1*); see Fig. 60.2 • Oral candidiasis usually begins by age 6 months to 2 years • Cutaneous and ungual candidiasis also common • No associated endocrinopathy • Cutaneous staphylococcal infections (IL17RA or TRAF3IP2 deficiency) • Ehlers–Danlos syndrome-like joint hypermobility, skin hyperextensibility (mild), and atrophic scarring (JNK1 deficiency)

Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome (APECED)*	• Caused by mutations in *AIRE*, usually with autosomal recessive inheritance
	• Increased prevalence among Finns, Iranian Jews, and Sardinians
	• *Mucocutaneous candidal infections*† with mean onset at age 3 years
	• Candidal granulomas, especially of the face and scalp
	• Autoimmune endocrinopathies, which may not be apparent until teenage or even adult years
	  • *hypoparathyroidism*† (90%)
	  • *hypoadrenocorticism*† (80%)
	  • hypogonadism (30%–50%)
	  • thyroid disease (20%)
	  • type 1 diabetes mellitus (20%)
	  • hypopituitarism (e.g. growth hormone deficiency; 15%)
	• Cutaneous autoimmune disorders
	  • alopecia areata (30%)
	  • vitiligo (20%)
	  • urticarial eruption‡ (up to 60%)
	  • lupus-like panniculitis
	• Other autoimmune disorders
	  • pernicious anemia (15%)
	  • hepatitis (15%–40%)
	  • pneumonitis (15%–40%)
	  • Sjögren-like syndrome (20%–40%)
	• Dental enamel hypoplasia (70%), chronic diarrhea (20%–80%), keratoconjunctivitis (20%), hyposplenism (15%), hypertension (15%), oral/esophageal SCC
	• Anti-type I interferon antibodies (nearly 100%); anti-thyroglobulin, anti-microsomal, anti-parietal cell, and anti-adrenal antibodies; rheumatoid factor
	• An autosomal dominant form of CMC associated with autoimmune thyroid disease may occur due to dominant-negative *AIRE* mutations and has also been linked to chromosome 2p in one family

CMC plus susceptibility to mycobacterial infections	• Autosomal recessive due to mutations in the retinoic acid receptor-related orphan receptor C gene (*RORC*) that lead to decreased IL-17 and interferon-γ production
CARD9-associated CMC	• Autosomal recessive form of CMC due to mutations in *CARD9*; see Fig. 60.2 • Chronic oral and vulvovaginal candidiasis; also dermatophytosis • Invasive fungal infections, e.g. candidiasis (especially of the brain during the second decade of life), dermatophytosis, phaeohyphomycosis

Table 60.4 Variants of chronic mucocutaneous candidiasis (CMC) in children and adolescents.

VARIANTS OF CHRONIC MUCOCUTANEOUS CANDIDIASIS (CMC) IN CHILDREN AND ADOLESCENTS	
Subgroup	**Features**
Dectin-1 deficiency	• Due to biallelic polymorphisms that result in a truncated dectin-1 protein; see Fig. 60.2 • Chronic/recurrent vulvovaginal candidiasis and onychomycosis
Late-onset CMC	• Initial infections in late childhood or early teenage years • Milder involvement than in other subgroups • Responses against *Candida albicans* may normalize after effective therapy
Familial chronic nail candidiasis	• Autosomal dominant form of CMC mapped to the pericentromeric region of chromosome 11 in a five-generation Italian family • Onset in infancy of candidiasis limited to the nails of the hands and feet • Association with low serum levels of intercellular adhesion molecule-1 (ICAM-1)
CMC associated with other immunodeficiency disorders	• Hyper-IgE syndromes due to STAT3 and DOCK8 deficiencies • Severe combined immunodeficiency • DiGeorge syndrome • Interleukin-12 receptor β1 and interleukin-12B (p40) deficiencies (see Fig. 60.2 and Table 60.13) • Autosomal dominant hypohidrotic ectodermal dysplasia with immunodeficiency (*NFKBIA* mutations) • Keratitis–ichthyosis–deafness (KID) syndrome
CMC associated with metabolic disorders	• Multiple carboxylase deficiency • Acrodermatitis enteropathica • Ectodermal dysplasia–ectrodactyly–clefting syndrome

*Ectodermal dystrophy refers primarily to dental enamel hypoplasia; also known as autoimmune polyendocrine syndrome type 1.
†*Two of these three manifestations are classically required for diagnosis.*
‡Mean onset at age 1.5 years; histologically, focal vacuolar interface dermatitis plus mixed superficial and deep dermal perivascular infiltrates with karyorrhexis.

Table 60.4 Variants of chronic mucocutaneous candidiasis (CMC) in children and adolescents. CARD9, caspase recruitment domain family member-9; IL, interleukin; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; MAPK9, mitogen-activated protein kinase 8; SCC, squamous cell carcinoma; STAT, signal transducer and activator of transcription; VZV, varicella–zoster virus.

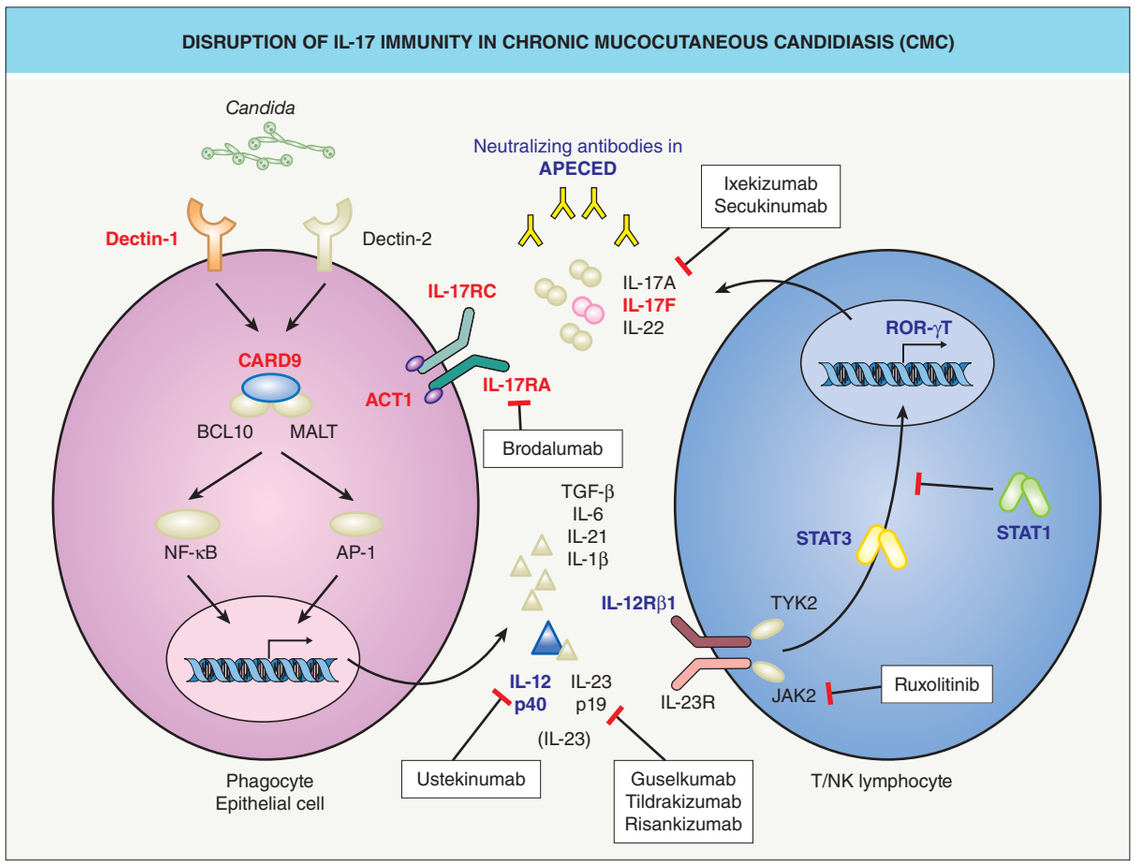


Fig. 60.2 Disruption of IL-17 immunity in chronic mucocutaneous candidiasis (CMC). Phagocytes, keratinocytes, and other epithelial cells detect *C. albicans* via pattern recognition receptors such as dectin-1/2 and produce proinflammatory cytokines including interleukin (IL)-6 and IL-23. This results in activation of T cells via signal transducer and activator of transcription 3 (STAT3) signaling, which upregulates expression of retinoic acid receptor-related orphan receptor γT (encoded by *RORC*) and leads to production of IL-17A, IL-17F, and IL-22. IL-17A/F signal via the IL-17 receptor (IL-17RA/C) and its ACT1 adaptor protein (TRAF3-interacting protein 2). Of note, STAT1 activation represses IL-17 production. In addition to genetic disorders that lead to CMC, several targeted immune modulators disrupt IL-17 immunity and can increase the risk of candidiasis, especially IL-17A and IL-17 RA inhibitors. **Red**: genetic defects implicated in *nonsyndromic* CMC ("CMC disease"). **Blue**: genetic defects and neutralizing antibodies implicated in *syndromic* CMC. See Table 60.4 for additional information on genetic forms of CMC. AP-1, activator protein 1; APECED, *a*utoimmune *p*olyendocrinopathy–*c*andidiasis–*e*ctodermal *d*ystrophy syndrome; CARD9, caspase recruitment domain family member-9; JAK2, Janus kinase 2; TGF-β, transforming growth factor β; TYK2, tyrosine kinase 2. *Adapted from Okada S, Puel A, Casanova JL, Kobayashi M. Chronic mucocutaneous candidiasis disease associated with inborn errors of IL-17 immunity. Clin Transl Immunol 2016;5:e114.*

the ectopic expression of self antigens in the thymus, which allows the development of peripheral tolerance via negative selection of autoreactive T cells and the generation of antigen-specific regulatory T cells[29,30]. In APECED patients, failure to delete autoreactive T cells leads to autoimmune disease[31]. Neutralizing autoantibodies targeting Th17-associated cytokines (e.g. IL-17A/F, IL-22) have been identified in APECED patients as well as individuals with thymoma-associated CMC[32].

Heterozygous gain-of-function mutations in *STAT1* (*s*ignal *t*ransducer and *a*ctivator of *t*ranscription *1*) have emerged as the most common cause of CMC[27,33]. The resulting STAT1 protein activation leads to increased interferon-α/β and -γ signaling as well as repression of IL-17 production, and clinical manifestations can include predisposition to other infections, autoimmunity, and aneurysms (Fig. 60.3; see Table 60.4)[34,35]. Other autosomal dominant forms of CMC are caused by deficiency in IL-17F or rarely Jun N-terminal kinase 1 (JNK1); the latter leads to decreased transforming growth factor β (TGF-β) as well as IL-17 signaling, producing features of hypermobile Ehlers–Danlos syndrome[36] (see Ch. 97). In addition, autosomal recessive forms of CMC can result from: (1) biallelic *IL17RA* or *IL17RC* mutations that disrupt function of the IL-17 receptor; or (2) *TRAF3IP2* (*ACT1*) mutations that prevent interaction between the IL-17 receptor and its TRAF3-interacting protein 2 adaptor molecule[27,37–40] (see Fig. 60.2).

CMC variants with autosomal recessive inheritance can also result from defects in the genes encoding dectin-1, a pattern-recognition receptor that binds to β-glucan in the *Candida* cell wall, and CARD9 (*ca*spase *r*ecruitment *d*omain family member-*9*), proteins that act together to activate a Th17 response (see Table 60.4)[41,42]. Decreased neutrophil function is also thought to contribute to invasive fungal infections in patients with CARD9 deficiency[32]. In other types of CMC, inadequate production of IL-23 and overproduction of IL-6, which result in an inefficient IL-17 response, have been observed.

Clinical Features

The clinical severity of CMC ranges from recurrent, treatment-resistant thrush (see Fig. 60.3A) or a few erythematous scaly plaques and dystrophic nails to severe, generalized, crusted granulomatous plaques. The cutaneous plaques occur most frequently on the scalp and in periorificial and intertriginous sites. Scalp infections may lead to scarring alopecia. Affected nails are thickened, brittle and discolored, with associated paronychia (Fig. 60.4). Although mucosal involvement is usually limited to oral thrush with hyperkeratotic plaques, chronic lesions of esophageal, genital, and laryngeal mucosae with resultant stricture formation may occur. Systemic candidiasis is rare, but cutaneous dermatophyte infections are common (see Fig. 60.3B,C). Up to 80% of patients with childhood-onset CMC develop recurrent or severe infections with organisms other than *Candida*, including occasional bacterial septicemia.

Subgroups of CMC in children and adolescents include those described in Table 60.4. An association of CMC with abnormalities of iron metabolism or (as noted above) thymoma has also been described in adult patients.

Laboratory Findings

Candidal organisms are confined to the stratum corneum and are demonstrable in scrapings and cultures. Approximately 70% of patients have direct evidence of an immunologic defect, including decreased lymphocyte proliferation *in vitro*, impaired cytokine production, and absent delayed-type hypersensitivity (DTH) in response to *Candida*, as well as nonspecific findings such as abnormal leukocyte chemotaxis or phagocytosis, depressed IgA levels, and complement dysfunction. These heterogeneous immune abnormalities reflect the variety of underlying etiologies. Candidal polysaccharides may act as serum factors that inhibit the immune response, and, in some patients, DTH to candidal antigens has been restored after antifungal therapy[28]. Autoantibodies against type I interferons have been shown to represent a sensitive and specific marker for APECED.

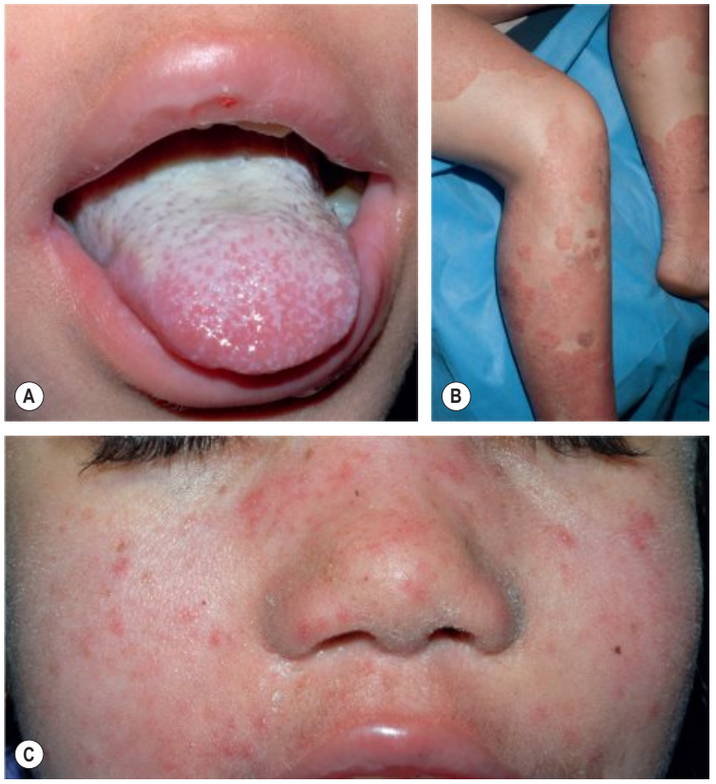


Fig. 60.3 Chronic mucocutaneous candidiasis and dermatophytosis due to increased STAT1 signaling. A Recalcitrant thrush on the tongue of a 6-year-old child. **B** Extensive tinea corporis with coalescing annular and polycyclic plaques on the legs. **C** Tinea faciei presenting as small pustules and diffuse scaling.
B, Courtesy Edward Cowen, MD.



Fig. 60.4 Chronic mucocutaneous candidiasis. A, B Marked onychodystrophy with significant paronychial swelling and erythema (**A**) and crusted plaques on the palm (**B**) in patients with chronic mucocutaneous candidiasis. **C** Recurrent cutaneous candidiasis presenting as erythema, pustules, and scale-crust near the site of an intravenous line on the arm in an infant with DiGeorge syndrome.

Differential Diagnosis

Candidal infections, particularly thrush, are fairly common in infants. Recurrent thrush in young children with frequent otitis media may reflect alterations in bacterial flora caused by the administration of systemic antibiotics; this is seen much more often than CMC or other immunodeficiencies. Recurrent or recalcitrant candidal infections should prompt consideration of HIV infection. Clearance after traditional therapy helps to distinguish secondary candidal infections from mild CMC.

The IPEX (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked) syndrome (see below) can present with autoimmune skin conditions and endocrinopathies together with recurrent infections, but the latter are typically bacterial rather than candidal. Autoimmune endocrinopathies, enteropathy, eczematous dermatitis, and a predisposition to bacterial, viral, and fungal infections have also been described in patients with IL-2 receptor α-chain deficiency (see Table 60.6).

Treatment

Patients with CMC do not respond well to standard topical medications, and the cutaneous granulomas are especially difficult to treat. Most patients benefit from long-term therapy with systemic antifungal agents such as itraconazole and fluconazole, and alternative drugs that can be helpful in treating fluconazole-resistant *Candida* isolates include posaconazole, voriconazole, and echinocandins[43]. Adjunctive therapy with granulocyte colony-stimulating factor (G-CSF) may increase IL-17 production[44]; nail avulsion, drainage of abscesses, and debridement of thick crusted cutaneous plaques can also be beneficial. In patients with gain-of-function *STAT1* mutations, JAK inhibitors such as ruxolitinib may improve associated infectious and autoimmune disease[45].

Patients should be evaluated at least annually for the development of endocrinopathies, particularly if they have a diagnosis or family history of APECED or other forms of CMC with autoimmune manifestations.

CARTILAGE–HAIR HYPOPLASIA SYNDROME

Synonym: ■ McKusick-type metaphyseal chondrodysplasia

Key features

- Fine, sparse, hypopigmented hair
- Short-limbed dwarfism with metaphyseal dysostosis
- Doughy skin with abnormal elastic tissue
- Defective cell-mediated and (in a minority of patients) humoral immunity

Cartilage–hair hypoplasia (CHH) syndrome is a pleiotropic autosomal recessive disorder that occurs most commonly in Amish individuals and Finns. The condition results from mutations in *RMRP* which encodes the RNA component of a ribonucleoprotein endoribonuclease, RNase MRP; the latter cleaves RNA primers responsible for DNA replication in mitochondria and processes pre-rRNA in the nucleolus[46]. Impaired telomerase activity leading to decreased telomere length in lymphocytes may also have a pathogenic role in the immune deficiency associated with CHH[47].

Affected individuals are most likely to visit the dermatologist for their fine, sparse, hypopigmented hair, although they may also have soft, doughy skin with degenerated elastic tissue[48]. The short-limbed dwarfism results from metaphyseal dysostosis, and ligamentous laxity is often observed. Most patients have some degree of defective cell-mediated immunity, which predisposes them to severe varicella and herpes simplex viral (HSV) infections. Approximately a third of patients also have abnormal humoral immunity[49], most frequently an IgA or IgG deficiency, which increases their susceptibility to recurrent respiratory tract infections that can lead to bronchiectasis. Occasionally, affected individuals present with severe combined immunodeficiency and an Omenn syndrome-like phenotype with erythroderma, eosinophilia, chronic diarrhea, lymphadenopathy, and hepatosplenomegaly (see below). Neutropenia and anemia can develop due to autoimmunity or bone marrow hypoplasia. Hirschsprung disease, other autoimmune disorders, and impaired spermatogenesis represent additional manifestations of CHH. Patients also have an increased risk of developing non-Hodgkin lymphoma and BCCs.

Hematopoietic stem cell transplantation, which can restore function of the immune system and bone marrow, should be considered in patients with severe immunodeficiency or cytopenias.

CHÉDIAK–HIGASHI SYNDROME

Synonyms: ■ Béguez César–Steinbrinck syndrome ■ Chédiak–Higashi disease ■ Chédiak–Steinbrinck–Higashi syndrome ■ Chédiak–Steinbrinck anomaly

Key features

- Autosomal recessive disorder of vesicle trafficking that results in giant organelles, including melanosomes, leukocyte granules, and platelet dense granules
- Silvery hair is accompanied by mild diffuse pigmentary dilution, often with an admixture of hyper- and hypopigmentation in sun-exposed sites; a variable degree of photophobia and nystagmus
- Recurrent pyogenic infections and a mild bleeding diathesis
- An "accelerated phase" with pancytopenia and organomegaly due to lymphohistiocytic infiltration, which is fatal without hematopoietic stem cell transplantation
- Progressive neurologic deterioration in survivors

Epidemiology

Chédiak–Higashi syndrome (CHS) is a rare autosomal recessive disease reported most often in individuals of Northern European, Spanish, Middle Eastern, and Japanese ancestry[50]. Patients of African descent have also been described[51].

Pathogenesis

CHS represents a disorder of vesicle trafficking and is caused by mutations in the *lys*osomal *t*rafficking regulator gene (*LYST*)[52]. Most patients have frameshift or nonsense mutations that result in a truncated protein and lead to a severe phenotype with progression to a fatal lymphoproliferative "accelerated phase" during childhood, but 10%–15% of affected individuals have missense mutations that are associated with a milder phenotype and survival to adulthood[53].

The giant intracytoplasmic granules that characterize CHS result from dysregulated fission/fusion of lysosome-related organelles, which include melanosomes, platelet dense granules, and leukocyte cytolytic granules[50]. The latter granules cannot effectively migrate or discharge their peroxidative and proteolytic enzymes, leading to defective target cell killing. Localization of cytotoxic T lymphocyte-associated antigen (CTLA-4) to enlarged vesicles rather than the cell surface may play a role in the development of lymphoproliferative disease. In addition, defective autophagic lysosome reformation in neurons, generalized impairment in plasma membrane repair, and abnormal antigen presentation by B cells may contribute to the pathogenesis of CHS.

Clinical Features

Patients with CHS usually present in infancy with mild diffuse pigmentary dilution of the skin, hair, and eyes. In individuals with relatively dark constitutive pigmentation, areas of bronze to slate-gray hyperpigmentation may be evident in sun-exposed sites, often admixed with guttate hypopigmented macules. Hair color is variable, but a silvery, metallic sheen is characteristic. Decreased ocular pigment can result in photophobia, nystagmus, and strabismus, but visual acuity is usually normal.

Infections primarily involve the skin and respiratory tract, and they are typically caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. The skin infections are most often superficial pyodermas. Cutaneous ulcerations resembling pyoderma gangrenosum, gingivitis, and ulceration of the oral mucosa have also been described. Although the bleeding diathesis of CHS is generally mild, some patients experience easy bruising, petechiae, and epistaxis.

Approximately 85% of patients with CHS enter a lymphoproliferative "accelerated phase" characterized by pancytopenia and lymphohistiocytic infiltration of the liver, spleen, lymph nodes, oral mucosa, and other internal organs. This "hemophagocytic syndrome" results from uncontrolled T cell and macrophage activation, possibly associated with Epstein–Barr virus (EBV) infection, and typically leads to death by age 10 years from overwhelming infection or hemorrhage unless hematopoietic stem cell transplantation is performed.

Patients with CHS who survive the first decade of life experience progressive neurologic deterioration with abnormal gait, paresthesias, and developmental delay. Peripheral and cranial neuropathies, spinocerebellar degeneration, spastic paraplegia, parkinsonism, and dementia can manifest in adult patients who were treated with hematopoietic stem cell transplantation as children as well as in those with otherwise mild disease.

Pathology

The silvery hair of patients with CHS is characterized by clumps of melanin microscopically (Fig. 60.5), and giant melanosomes may be evident within melanocytes in skin biopsy specimens. A peripheral blood smear demonstrating abnormally large granules in the perinuclear area of granulocytes can assist in establishing the diagnosis. Immunologic defects in CHS include neutropenia, diminished leukocyte chemotaxis, impaired antibody-dependent cell-mediated cytotoxicity, reduced cytotoxic and regulatory T cell activity, and markedly decreased natural killer (NK) cell function.

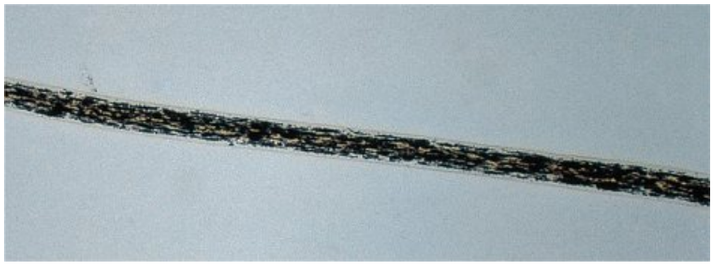


Fig. 60.5 Chédiak–Higashi syndrome. Light microscopic examination of hair shows small, regularly spaced clumps of melanin in patients with Chédiak–Higashi syndrome.

Differential Diagnosis

The features of CHS and the three types of Griscelli syndrome (GS), another autosomal recessive disorder that can present with immune dysfunction and silvery hair, are compared in Table 60.5 (see also Ch. 66). Although leukocytes generally have a normal appearance in GS, hypogammaglobulinemia can be observed. Hermansky–Pudlak syndrome (HPS) types 2, 9, and 10 (*AP3B1*, *BLOC1S6*, and *AP3D1* mutations, respectively; see Table 65.1) can result in recurrent infections due to abnormal cytotoxic T cell function; additional manifestations include a bleeding diathesis, neurologic manifestations (in HPS9 & HPS10), and diffuse pigmentary dilution, but not silvery hair. Trichohepato-enteric syndrome, an autosomal recessive disorder caused by mutations in *SKIC2* or *SKIC3* which encode the SKI2 and SKI3 subunits of superkiller complex, can present with diffuse pigmentary dilution of the skin and hair, immunodeficiency, and platelet abnormalities; unlike CHS, it is also characterized by brittle hair with trichorrhexis nodosa, intractable diarrhea during infancy, primary liver disease, facial dysmorphism, and cardiac defects. Other inherited disorders characterized by lymphoproliferation due to immune dysregulation are presented in Table 60.6.

Treatment

Hematopoietic stem cell transplantation (HSCT) can reverse the immunodeficiency of CHS and may also be performed following immunochemotherapy to abrogate the lymphoproliferative accelerated phase. However, HSCT has no effect on pigmentary alteration and does not halt neurologic degeneration. Management of the CHS is otherwise largely supportive, with administration of prophylactic antibiotics to prevent recurrent infections.

FEATURES OF CHÉDIAK–HIGASHI SYNDROME AND GRISCELLI SYNDROME				
	CHS	**GS1***	**GS2**	**GS3**
Gene defect	*LYST*	*MYO5A*	*RAB27A*	*MLPH*
Major sites of gene expression	Melanocytes, platelets, granulocytes, CNS	Melanocytes, CNS	Melanocytes, cytotoxic T cells	Melanocytes
Cellular defect	Vesicle trafficking (e.g. fission/fusion)	Vesicle movement/transfer		
Pigmentary dilution of the skin†	+	+	+	+
Silvery/metallic hair	+	+	+	+
Hair microscopy: clumps of melanin	Small, regularly spaced	Larger, irregularly distributed		
Melanocytes	Giant melanosomes	"Stuffed" with melanosomes		
Neutrophils	Giant granules	Normal-appearing granules		
Ocular findings	+	–	–	–
Bleeding diathesis	+	–	–	–
Recurrent infections	+	–	+	–
Accelerated phase	+	–	+	–
Primary neurologic abnormalities	+	+	–‡	–

*A form of GS with manifestations limited to the skin and hair can result from deletion of the *MYO5A* F-exon, which is only expressed in melanocytes.
†Often accompanied by hyperpigmentation ± guttate hypopigmented macules in acral and sun-exposed sites.
‡May develop neurologic symptoms secondary to the hemophagocytic syndrome of the accelerated phase.

Table 60.5 Features of Chédiak–Higashi syndrome (CHS) and Griscelli syndrome (GS). The latter is caused by defective attachment of organelles to the actin cytoskeleton (see Ch. 65). Elejalde syndrome (neuroectodermal melanolysosomal disease), which presents with pigmentary features of GS plus severe neurologic dysfunction, likely represents a variant of GS1. CNS, central nervous system.

INHERITED DISORDERS CHARACTERIZED BY LYMPHOPROLIFERATION DUE TO IMMUNE DYSREGULATION				
Disorder	**Inh**	**Gene**	**Protein (function)**	**Clinical features**
Chédiak–Higashi syndrome	AR	*LYST*	See Table 60.5	See Table 60.5
Griscelli syndrome type 2	AR	*RAB27A*		
Familial hemophagocytic lymphohistiocytosis	AR	*PRF1*	Perforin (major cytolytic granule protein of CTL and NK cells)	• HLH • Absent NK cell cytotoxicity • Fatal during early childhood unless hematopoietic stem cell transplantation is performed
	AR	*UNC13D*	Unc13 homolog D (primes cytolytic granules for secretion)	
	AR	*STX11*	Syntaxin 11 (involved in cytolytic granule trafficking and fusion)	
	AR	*STXBP2*	Syntaxin-binding protein 2 (regulates cytolytic granule trafficking)	
NOCARH	AD	*CDC42*	Cell division cycle 42	• *N*eonatal-onset cytopenias with dyshematopoiesis, *a*utoinflammation, *r*ash, and *H*LH
X-linked lymphoproliferative syndrome (Duncan disease)	XR	*SH2D1A*	Signaling lymphocyte activation molecule-associated protein (adaptor protein that regulates B, T, and NK cell function; particularly important for immune responses to EBV)	• Severe EBV-related infectious mononucleosis in childhood or adolescence (e.g. fever, pharyngitis, LAN, HSM), often associated with morbilliform eruptions, purpura and/or jaundice • Hypogammaglobulinemia • Fatal EBV-related B cell lymphoma (70%) • Lymphocytic vasculitis
	XR	*XIAP*	X-linked inhibitor of apoptosis	
EBV-associated lymphoproliferative syndrome	AR	*ITK*	IL-2-inducible T cell kinase	
XMEN (*X*-linked immunodeficiency with *m*agnesium defect, *E*BV infection, and *n*eoplasia)	XR	*MAGT1*	Magnesium transporter 1	• Decreased $CD4^+$ T cells • EBV infection with persistent viremia; recurrent sinopulmonary infections • EBV-associated lymphoma
STK4 deficiency	AR	*STK4*	Serine/threonine kinase 4	• EBV-associated lymphoproliferation and lymphoma • Recurrent bacterial, viral (including warts, molluscum, HSV), and candidal infections • Autoimmune cytopenias
Autoimmune lymphoproliferative syndrome (Canale–Smith syndrome) and related conditions*	AD >AR	*TNFRSF6*	CD95 (Fas; cell-surface apoptosis receptor)	• Massive LAN and/or splenomegaly • Increased $CD4^-/CD8^-$ α/β T cells • Autoimmune cytopenias, LE, small vessel vasculitis • Recurrent bacterial and viral infections (*CASP8*) • Increased risk of lymphoma
	AD >AR	*TNFSF6*	CD95L (Fas ligand)	
	AR	*FADD*	Fas-associated death domain	
	AD > AR	*CASP10*	Caspase 8 and 10 (proteases in intracellular apoptosis cascade)	
	AR	*CASP8*		
	Mosaic	*NRAS*, *KRAS*	NRAS, KRAS (gain of function leads to decreased lymphocyte apoptosis)	
	AR	*PRKCD*	Protein kinase C δ (regulates B cell proliferation)	
	AD	*CTLA4*	Cytotoxic T lymphocyte-associated protein 4 (costimulation of T cells)	
Immunodeficiency with lymphoid proliferation	AR	*IL2RA*	IL-2 receptor α-chain (apoptosis of developing T cells in the thymus)	• Bacterial, viral, and fungal infections • Extensive lymphocytic infiltration of the liver, lung, gut, and bones • Eczematous dermatitis; autoimmune polyendocrinopathy, cytopenias, and enteropathy
	AR	*IL2RB*	IL-2 receptor β-chain	
SOCS1 haploinsufficiency	AD	*SOCS1*	Suppressor of cytokine signaling	• Early-onset multisystem autoimmunity, HSM, psoriasis, eczematous dermatitis, discoid LE • Recurrent bacterial infections

*LRBA mutations (see Table 60.15) and gain-of-function *CARD11* or *STAT3* mutations can also lead to autoimmune lymphoproliferative syndrome-like disorders.

Table 60.6 Inherited disorders characterized by lymphoproliferation due to immune dysregulation. Hemophagocytic lymphohistiocytosis (HLH) results from uncontrolled T cell and macrophage activation, manifesting with fever, pancytopenia, hepatosplenomegaly (HSM), lymphadenopathy (LAN), hypertriglyceridemia, and hypofibrinogenemia. AD, autosomal dominant; AR, autosomal recessive; CTL, cytotoxic T lymphocytes; Inh, inheritance; LE, lupus erythematosus; NK, natural killer; XR, X-linked recessive.

COMPLEMENT DISORDERS

Key features

- Deficiency or dysfunction of early complement components increases susceptibility to pyogenic infections caused by encapsulated bacteria and autoimmune disorders, especially systemic lupus erythematosus
- Deficiency of late complement components leads to a markedly increased risk of neisserial infections

Introduction

The complement system represents an important effector of the innate immune response (see Ch. 4). An enzymatic cascade of complement activation can be triggered by three different pathways: classical, alternative, and lectin (Fig. 60.6). In addition to their roles in killing microbial pathogens, complement proteins serve as regulators of a variety of humoral and cellular immune functions (Table 60.7). As a result, clinical manifestations of complement deficiency include autoimmune diseases as well as increased susceptibility to infection[54,55].

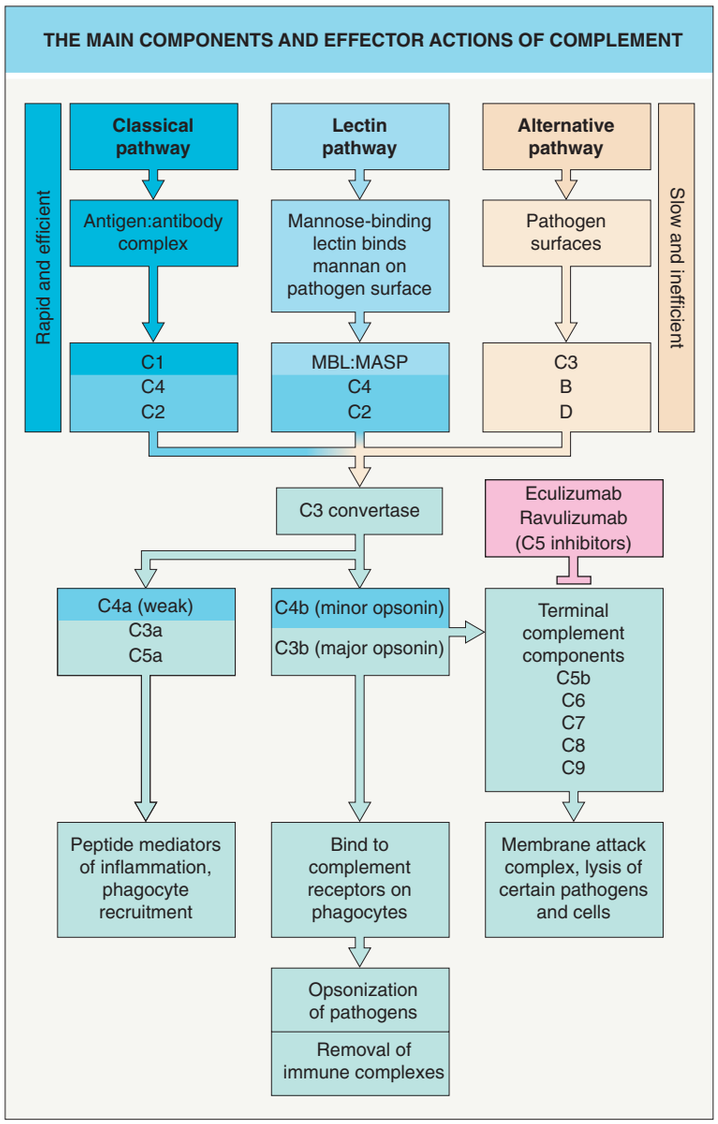


Fig. 60.6 The main components and effector actions of complement. The C3b bound to the C3 convertase binds C5, allowing the C3 convertase to generate C5b, which associates with the bacterial membrane and triggers the late events. MBL, mannose-binding lectin; MASP, MBL-associated serine protease. *© 2005 from Immunobiology by Charles A. Janeway, et al. Adapted with permission of Garland Science/Taylor & Francis Books, Inc.*

Epidemiology

Deficiency of C2 represents the most common hereditary complement disorder[54]. Homozygous C2 deficiency occurs in ~1 in 20 000 individuals, and 1%–2% of the population has the heterozygous form. Homozygous deficiencies of C1q, C1r, C1s, and C4 are rare, but affected individuals manifest with autoimmune disease more frequently than those with homozygous C2 deficiency. Heterozygotes usually make enough protein to ensure function and are generally asymptomatic, so most of the complement disorders are inherited as autosomal recessive traits. One exception is hereditary angioedema (HAE), an autosomal dominant condition due to deficiency or dysfunction of the C1 inhibitor (see Ch. 18).

In contrast to the low prevalence of deficiencies in components of the classical complement pathway, 5% of the population is homozygous or compound heterozygous for alleles that lead to a lack of functional mannose-binding lectin (MBL), the major recognition factor of the lectin pathway of complement activation[56]. Although the clinical penetrance of MBL deficiency is low, it may have a substantial impact on immunity and autoimmunity at the population level. In addition, ~1 in 10 000 individuals has a homozygous deficiency in the MBL-associated serum protease (MASP) that functions in this pathway.

Pathogenesis

Deficiency of C2 can result from a defect in either protein synthesis (type 1) or secretion (type 2). Defects involving the early components of the classical complement pathway (C1, C4, C2) manifest with an increased risk of autoimmune disorders, especially systemic lupus erythematosus (SLE)[57] (Table 60.8). The genes that encode these complement components, including four highly polymorphic genes for C4 (two each for C4A and C4B), are located within the HLA region on chromosome 6. C4-null alleles have been linked with SLE, and *C4A* is deleted in the HLA A1-B8-DR3 extended haplotype that is strongly associated with SLE.

The pathogenesis of SLE in the setting of complement deficiency may also be related to impaired physiologic clearance of autoantigen-containing apoptotic cells[57]. Epidermal keratinocytes undergoing UVB-induced apoptosis preferentially display autoantigens such as SSA/Ro in plasma membrane blebs. Binding of C1q to these blebs and the nucleolus results in activation of the classical complement pathway and removal of the apoptotic cells by phagocytes[58]; in the absence of C1q, autoantibodies have the opportunity to bind to SSA/Ro, leading to activation of B and T cells and loss of immune tolerance. Decreased MBL-mediated clearance of apoptotic debris and DNA might likewise explain the predisposition to SLE associated with MBL deficiency. Furthermore, the complement system may enhance the elimination of self-reactive B cells during lymphocyte development, with complement deficiency leading to a lack of B cell self-tolerance. Complement components are also important for handling immune complexes and regulating production of cytokines (e.g. type I interferons) that have a key role in SLE pathogenesis.

The variety of recurrent infections associated with complement deficiencies underscores the central role of complement in bacterial clearance. Patients deficient in the early classical components, especially C2, have increased susceptibility to infections with encapsulated bacteria, especially *Str. pneumoniae*. Opsonization of bacteria and fungi may be ineffective in disorders of the classical pathway because of the slow, inadequate formation of C3b. However, because the lectin and alternative pathways can bypass early classical components to intersect with the cascade at the level of C3 (see Table 60.7 & Fig. 60.6), these deficiencies do not usually lead to overwhelming infections. C5 deficiencies result in impaired generation of chemotactic factors, which may lead to inadequate neutrophil function.

Individuals with C5 to C9 (membrane attack complex; MAC), properdin, and factor D deficiencies develop recurrent neisserial infections in their teenage years. This underscores the importance of the bactericidal MAC complex and the alternative complement pathway (which requires properdin and factor D) in the destruction of these organisms. However, because a lack of lytic activity limits release of bacterial products (e.g. lipopolysaccharide) that stimulate a damaging cytokine response, the mortality of meningococcal infections in patients with MAC deficiency is actually lower than that in immunocompetent individuals. In contrast, patients with a properdin or factor D deficiency are unable to eradicate *Neisseria* spp. via opsonophagocytosis and have severe disease that is often fatal.

Clinical Features

Individuals with homozygous deficiencies in the early components of the classical complement pathway (C1, C4, C2) have a risk of SLE that ranges from >90% for C1q to 10%–20% for C2. Among those with C2 deficiency, features of lupus erythematosus (especially photosensitivity and subacute cutaneous lupus erythematosus) are most common in women, with the age at onset ranging from early childhood to adulthood (median 30 years). Other manifestations of C2 deficiency-associated SLE are presented in Table 60.9. SLE in the setting of C1q/r/s or C4 deficiency usually develops during childhood, affects boys and girls equally, and is often associated with renal disease and palmoplantar keratoses as well as photosensitivity. Other autoimmune and/or inflammatory disorders and susceptibilities to infection associated with complement deficiencies are listed in Table 60.8. C2 deficiency may coexist with common variable immunodeficiency, and the development of Hodgkin lymphoma has occasionally been reported.

COMPLEMENT SPLIT PRODUCTS AND COMPLEXES			
Split product	**Function**	**Complex**	**Function**
C1q	Recognition factor of CP (binds Ag–Ab complexes) Activates C1r	C1inh-C1r-C1s	Formed during C1 activation
C1r	Cleaves C1s to an active protease		
C1s	Cleaves C4 and C2		
C4a	Anaphylatoxin (weak)	C4b2a	CP C3 convertase
C4b	Part of the CP C3 and C5 convertases Opsonization		
C2a	Part of the CP C3 and C5 convertases		
C2b	Unknown		
C3(H_2O)	Recognition factor of AP (binds bacterial surfaces, including lipopolysaccharide)	C3bBb	AP C3 convertase
C3a	Anaphylatoxin Chemotaxis (eosinophils) Direct antimicrobial effect	C4b2a3b	CP C5 convertase
C3b	Part of CP C5 and AP C3/C5 convertases		
	Opsonization	C3b(n)Bb	AP C5 convertase
C5a	Anaphylatoxin (strong) Chemotaxis (neutrophils and monocytes) Regulation of apoptosis		
C5b	Part of membrane attack complex	C5b-9n SC5b-9	Membrane attack complex Soluble terminal complement complex

Table 60.7 Complement split products and complexes. Dark blue, classical pathway (CP); medium blue, CP and lectin pathway; yellow-tan, alternative pathway (AP); green, all three pathways. Anaphylatoxins are inflammatory mediators that increase vascular permeability and cause mast cell degranulation. Opsonization represents binding of a protein to the pathogen surface in order to target it for destruction. C1 inh, C1 esterase inhibitor; SC, soluble complex.

MBL deficiency may confer an increased risk of acute respiratory infections in children aged 6–18 months, who no longer have maternal antibodies but are not yet able to mount an efficient antibody response to the carbohydrate antigens of encapsulated bacteria[56]. Several studies have shown that MBL deficiency is associated with an increased risk of developing SLE or dermatomyositis and a higher incidence of infections in the setting of immunosuppressive therapy.

Pathology

The total hemolytic complement (CH50) is markedly decreased or undetectable in complement deficiencies other than hereditary angioedema. The alternative pathway lytic test (AP50) can be used to screen for deficiencies in components of this pathway, although it is less sensitive than the CH50. Immunoprecipitation assays (e.g. radial immunodiffusion, ELISA) can determine the levels of specific complement components and MBL[59], and functional studies of individual components may be informative when antigen levels are normal. Genetic analysis can be utilized to confirm the diagnosis.

Differential Diagnosis

Complement components may be specific targets of autoimmune responses; for example, anti-C1q antibodies are found in 30%–50% of patients with SLE (often with renal involvement) and virtually all of those with hypocomplementemic urticarial vasculitis. The "*Leiner phenotype*" of exfoliative dermatitis, failure to thrive, chronic diarrhea, and recurrent infections has been observed in infants with C3 or C5 deficiency or C5 dysfunction. However, this constellation of findings can also develop in patients with other disorders such as X-linked agammaglobulinemia, hyper-IgE syndrome, and severe combined immunodeficiency. Low complement levels related to bacterial and viral infections should also be differentiated from primary complement deficiencies. Of note, patients treated with the C5 inhibitors eculizumab and ravulizumab are at risk for the development of severe meningococcal infections.

Treatment

Conservative therapy is often effective for patients with autoimmune manifestations of complement deficiency. The use of topical corticosteroids and sun protection may be sufficient to treat cutaneous lupus erythematosus in these individuals. Antimalarial drugs, systemic corticosteroids, and other immunomodulatory medications are required in more severe cases, with consideration of the increased risk of infections in patients with complement deficiencies. The use of plasma transfusions to replace the deficient components may actually activate the cascade and accelerate immune complex deposition.

Infections should be treated with early, aggressive antibiotic therapy. Pneumococcal vaccination is recommended for individuals with an early component complement deficiency and meningococcal vaccination for those with a C3, C5–C9, properdin, factor D, or factor H deficiency.

CHRONIC GRANULOMATOUS DISEASE

Synonyms: ■ Chronic granulomatous disorder ■ Bridges–Good syndrome ■ Quie syndrome

Key features

- Inability to kill intracellular organisms through generation of oxidative metabolites
- X-linked recessive or autosomal recessive inheritance
- Recurrent pneumonias and cutaneous infections, lymphadenopathy, and hepatosplenomegaly
- Patients develop granulomas as a compensatory effort to confine organisms

Introduction

Chronic granulomatous disease (CGD) is a group of disorders characterized by severe, recurrent infections due to an inability of leukocytes to kill phagocytosed bacteria and fungi by generating oxidative metabolites[60]. The activity of the nicotinamide dinucleotide phosphate (NADPH) oxidase complex is reduced in all forms of CGD.

COMPLEMENT DISORDERS		
Complement component	**Common infectious agents**	**Autoimmune/inflammatory disorders**
Classical pathway		
C1q	Encapsulated bacteria, *Candida* spp.	SLE*, dermatomyositis, GN
C1r	Encapsulated bacteria	SLE*, GN
C1s	Encapsulated bacteria	SLE*
C1 inhibitor		Hereditary angioedema ≫ SLE, GN, partial lipodystrophy, vasculitis
C4	Encapsulated bacteria	SLE* with PPK and scars, HSP, GN, urticaria, JIA‡
C2†	Encapsulated bacteria, especially *Streptococcus pneumoniae*	SLE*, SCLE, DLE, dermatomyositis, HSP, other vasculitides, atrophoderma, cold urticaria, JIA‡, IBD, atherosclerosis
Lectin pathway		
MBL¶	Encapsulated bacteria, especially *N. meningitides*	SLE, dermatomyositis, atherosclerosis, chronic pulmonary disease
MASP-2	Encapsulated bacteria, especially *S. pneumoniae*	SLE, IBD
C3 and alternative pathway		
C3	Encapsulated bacteria (severe infections)	SLE, vasculitis, lipodystrophy (partial [cephalo]thoracic), GN, "Leiner phenotype"
Factor H	Encapsulated bacteria	SLE, HUS, GN, age-related macular degeneration
Factor I (C3b inactivator)	Encapsulated bacteria	SLE, HUS, aquagenic urticaria, angioedema
Properdin (XLR)	*Neisseria* spp. (fulminant infections)	
Factor D	*Neisseria* spp.	
Membrane attack complex		
C5 dysfunction	Gram-negative bacteria	"Leiner phenotype"
C5 deficiency	*Neisseria* spp., *S. pneumoniae*	SLE
C6	*Neisseria, Brucella, Toxoplasma* spp.	SLE, JIA, GN
C7	*Neisseria* spp.	SLE, limited systemic sclerosis, ankylosing spondylitis
C8α	*Neisseria* spp.	SLE, fever with HSM, eosinophilia, hypergammaglobulinemia
C8β	*Neisseria* spp.	SLE, JIA
C9	*Neisseria* spp.	

*Hierarchy of SLE risk with homozygous mutations: C1q (~90%) > C1r/s > C4 > C2 (~10%–20%).
†Most common of the homozygous complement deficiencies.
‡Especially in heterozygous girls.
¶Very low penetrance.

Table 60.8 Complement disorders. Unless otherwise specified, affected individuals usually have biallelic defects. Pyogenic infections caused by encapsulated organisms (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes*) in individuals with classical pathway component deficiencies are not as frequent as neisserial infections in those with membrane attack complex component deficiencies. The C3 inhibitor pegcetacoplan is FDA-approved for the treatment of paroxysmal nocturnal hemoglobinuria. DLE, discoid lupus erythematosus; GN, glomerulonephritis; HSM, hepatosplenomegaly; HSP, Henoch–Schönlein purpura; HUS, hemolytic uremic syndrome; IBD, inflammatory bowel disease; INH, inhibitor; JIA, juvenile idiopathic arthritis; MBL, mannose-binding lectin; MASP, MBL-associated serum protease; PPK, palmoplantar keratoderma; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; XLR, X-linked recessive. *Adapted with permission from Torrelo A (ed). Schachner and Hansen's Pediatric Dermatology, 5th edn. London: Mosby, 2023.*

Epidemiology

The incidence of CGD is ~1 in 200 000 live births[61,62]. Ninety percent of patients are boys. Approximately three-quarters of cases have X-linked recessive transmission, while the remainder are autosomal recessive[63]. A small subset of male patients with X-linked CGD due to a contiguous gene deletion also have McLeod neuroacanthocytosis syndrome, with additional central nervous system, neuromuscular, cardiovascular, and hematologic (e.g. reduced Kell antigens on red blood cells) manifestations.

Pathogenesis

The defects in CGD involve subunits of the NADPH oxidase found in phagocytes. These include: (1) membrane-bound gp91^{phox} (phagocyte oxidase) and p22^{phox} as well as the EROS (*e*ssential for *r*eactive *o*xygen *s*pecies) chaperone protein required for their expression; and (2) cytoplasmic p47^{phox}, p67^{phox}, and p40^{phox} (Table 60.10). The failure of microbial killing that characterizes CGD results from an inability of the NADPH oxidase system to rapidly generate toxic reactive oxygen species (ROS) by transferring electrons from NADPH to molecular O_2 (the "respiratory burst") after phagocytosis of a pathogen. Regardless of the gene affected in patients with CGD, having residual NADPH oxidase activity and the resultant ability to generate ROS is associated with less severe disease and longer survival[64,65].

NADPH oxidase activity results in the activation of antimicrobial proteases within the phagosome and the formation of microbicidal "neutrophil extracellular traps" (NETs)[66,67]. In addition to killing and degrading microorganisms, ROS produced by the NADPH oxidase system have roles in the regulation of cytokine synthesis as well as induction of neutrophil apoptosis, which prevents tissue damage at sites of inflammation. Animal models of CGD have shown that a lack of ROS leads to excess inflammation via decreased regulatory T cell activity, unrestrained γ/δ T cell activity, and augmented production of cytokines such as IL-1β, IL-8, and IL-17. NADPH oxidase also has a role in modulating MHC class II antigen presentation by B cells[68].

Clinical Features

The skin, perianal area, lymph nodes, and lungs are the sites most often affected by CGD. In general, the X-linked form tends to be more severe than the autosomal recessive forms, with a younger mean age at diagnosis (3 years vs 8 years)[61]. Organisms that commonly cause

infections in patients with CGD are listed in Table 60.11[69]. Most carriers of CGD do not have an increased susceptibility to infections.

The earliest manifestations of CGD are usually staphylococcal infections of the skin around the ears and nose, which may begin in the neonatal period and progress to extensive purulent dermatitis with regional lymphadenopathy during infancy. Initial presentation of CGD as ecthyma gangrenosum in the neonatal period has also been described[70]. Cutaneous abscesses occur in 40% of patients, usually due to *S. aureus* but also *Serratia marcescens*; these infections sometimes present as large, poorly healing cutaneous ulcers[71]. Non-infectious purulent inflammatory reactions may develop at sites of minor cutaneous trauma or regional lymph node drainage and heal slowly with scarring. Sterile cutaneous granulomas, which are often nodular and necrotic, occur less frequently than infections.

Additional cutaneous manifestations include acute or chronic cutaneous lupus erythematosus-like skin lesions, most commonly discoid[72] (Fig. 60.7A,B); Sweet syndrome-like lesions; ulcers involving the oral mucosa (resembling aphthous stomatitis), the perioral area, and other cutaneous sites (Fig. 60.7C); and seborrheic dermatitis or folliculitis of the scalp. Female carriers of X-linked CGD occasionally present with discoid lesions, lymphocytic infiltrate of Jessner, photosensitivity, Raynaud phenomenon, severe aphthous stomatitis, and granulomatous cheilitis.

The extracutaneous organs most frequently involved in CGD are the lymph nodes, lungs, liver, spleen, and gastrointestinal tract (Table 60.12). Suppurative lymphadenitis develops in half of patients, most often affecting cervical nodes and leading to abscess and fistula formation. Granulomas of the lungs, liver, spleen, and gastrointestinal and genitourinary tracts occur more frequently than those of the skin. These granulomas can lead to obstruction of the gastric outlet or urinary tract. Excessive inflammatory responses may also lead to wound dehiscence, pneumonitis, and hemophagocytic lymphohistiocytosis. Approximately 40%–80% of CGD patients develop gastrointestinal manifestations (e.g. chronic diarrhea, fistulas) similar to those of inflammatory bowel disease; clinical presentations can also mimic sarcoidosis, rheumatoid arthritis, and IgA nephropathy[62,73,74].

Pathology

Common nonspecific abnormalities in CGD include leukocytosis, anemia, elevated ESR, hypergammaglobulinemia, a decreased number of T cells, and an abnormal chest radiograph. Skin testing for delayed-type hypersensitivity is normal, as are studies of phagocytosis and chemotaxis.

FEATURES OF SYSTEMIC LUPUS ERYTHEMATOSUS IN C2 DEFICIENCY	
Common features	**Features more suggestive of C2 deficiency-associated SLE than classic SLE**
• Photosensitivity* • SCLE*, ACLE, or DLE • Cicatricial alopecia • Oral ulcerations (50%) • Fever (>50%) • Arthralgias and/or arthritis (80%) • Leukopenia (50%) • Anti-SSA/Ro antibody (75%) • Rheumatoid factor (40%)	• Childhood onset • Extensive, treatment-resistant skin lesions • Mild or absent renal disease • Absent or low-titer ANA and anti-dsDNA antibodies • Negative lupus band test • Less severe disease overall • Pyogenic infections with encapsulated bacteria, e.g. *Streptococcus pneumoniae* • Increased risk of atherosclerosis
*Most common cutaneous manifestations.	

Table 60.9 Features of systemic lupus erythematosus (SLE) in C2 deficiency. Less frequent manifestations include central nervous system vasculitis, pleuritis, pericarditis, Raynaud phenomenon, thrombocytopenia, anti-Sm or anti-RNP antibodies, circulating immune complexes and a positive RPR. ACLE, acute cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus. *Adapted with permission from Torrelo A. Schachner and Hansen's Pediatric Dermatology, 5th edn. London: Mosby, 2023.*

ORGANISMS THAT CAUSE INFECTIONS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE		
Type of organism	**Common causes**	**Less frequent causes**
Gram-positive bacteria	*Staphylococcus aureus** *Nocardia* spp.	*Cutibacterium* (formerly *Propionibacterium*) spp.
Gram-negative bacteria	*Burkholderia cepacia* *Klebsiella* spp. *Serratia marcescens*†	*Acinetobacter* spp. Other *Burkholderia* spp. *Chromobacterium violaceum* *Enterobacter* spp. *Escherichia coli* *Granulobacter bethesdensis* *Francisella philomiragia* *Proteus* spp. *Pseudomonas* spp. *Salmonella* spp.
Mycobacteria		*Mycobacterium tuberculosis* Atypical mycobacteria Bacillus Calmette–Guérin (BCG)‡
Fungi	*Candida* spp. *Aspergillus* spp.¶	*Paecilomyces* spp. *Talaromyces (Penicillium)* spp. Phaeohyphomycetes *Phellinus* spp. *Trichosporon* spp.
*Most common cause of cutaneous infections, abscesses, and suppurative adenitis. †Most common cause of osteomyelitis; also a frequent cause of cutaneous abscesses and ulcers. ‡Including severe and disseminated infections. ¶Most common cause of pneumonia.		

Table 60.11 Organisms that cause infections in patients with chronic granulomatous disease.

GENETIC DEFECTS AFFECTING COMPONENTS OF THE PHAGOCYTE NADPH OXIDASE					
Disorder	**Gene**	**Protein**	**Location within NADPH oxidase**		**Approximate % of CGD patients**
			Resting state	**Active state**	
X-linked recessive chronic granulomatous disease	*CYBB*	gp91^{phox}	Membrane-bound subunits of flavocytochrome b_{558} and their chaperone protein (EROS)	Same	70
Autosomal recessive chronic granulomatous disease	*CYBA*	p22^{phox}			≤5
	CYBC1	EROS			Rare
	NCF1	p47^{phox}	Cytosolic complex	Associated with flavocytochrome b_{558}	20
	NCF2	p67^{phox}			≤5
	NCF4	p40^{phox}			Rare
Neutrophil immunodeficiency syndrome	*RAC2*	Rac2 GTPase*	Cytosolic complex with RhoGDI	Membrane- and GTP-bound	–
*Also has a role in actin cytoskeletal dynamics, integrin-dependent adhesion, and neutrophil migration; see Table 60.13.					

Table 60.10 Genetic defects affecting components of the phagocyte NADPH oxidase. CGD, chronic granulomatous disease; *CYBC1*, cytochrome b-245 chaperone 1; Eros, essential for reactive oxygen species; *NCF*, neutrophil cytosolic factor; RhoGDI, Rho GDP-dissociation inhibitor.



Fig. 60.7 Chronic granulomatous disease. Lupus erythematosus-like annular plaques and papules on the infraorbital cheek (**A**) and neck (**B**). Pyoderma gangrenosum-like ulcers at an ostomy stoma site (**C**). *Courtesy Edward Cowen, MD.*

Biopsy specimens from cutaneous granulomas that develop in CGD patients demonstrate histiocytic infiltrates associated with foreign body giant cells and accumulation of neutrophils with necrosis. Lupus erythematosus-like skin lesions in CGD patients and carriers may have histologic features similar to classic discoid lesions, but they sometimes lack vacuolar degeneration of basal keratinocytes; immunofluorescence examination of lesional skin is negative in most cases.

The traditional screening test for CGD was the nitroblue tetrazolium (NBT) reduction assay. NBT is yellow in its soluble, oxidized form; when reduced, the dye precipitates and becomes blue (formazan precipitate). Only 5%–10% of leukocytes from patients with CGD are able to reduce NBT during phagocytosis, compared to 80%–90% of leukocytes from unaffected individuals and ~20%–70% of leukocytes from carriers of X-linked CGD. The dihydrorhodamine (DHR) flow cytometric assay is more accurate and quantitative in measuring the neutrophil respiratory burst, and it is commercially available for verifying the diagnosis of CGD[75]. However, the DHR assay is not sensitive for detecting $p40^{phox}$-related CGD.

Immunoblot analysis may demonstrate lack of the $gp91^{phox}$ and $p22^{phox}$ proteins; however, gene sequencing must still be done to ascertain which gene is affected, since mutations resulting in the absence of one of these proteins or EROS lead to the absence of the other(s). A lack of the $p47^{phox}$, $p67^{phox}$, or $p40^{phox}$ protein by immunoblot analysis indicates the affected gene.

FREQUENCY OF SIGNS AND SYMPTOMS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE	
Symptom	**Approximate % of patients**
Lymphadenopathy	90
Hepatosplenomegaly	85
Pneumonia	80
Underweight	75
Short stature	50
Persistent diarrhea and/or abdominal pain	40
Hepatic/perihepatic abscess	35
Pleuritis/empyema	35
Septicemia or meningitis	35
Osteomyelitis	25
Conjunctivitis and/or chorioretinitis	25
Facial periorificial dermatitis	20
Perianal abscess	15
Lung abscess	15
Ulcerative stomatitis	15
Peritonitis	10
Onset by age 1 year	65
Onset with lymphadenitis	25

Table 60.12 Frequency of signs and symptoms in patients with chronic granulomatous disease.

Differential Diagnosis

Laboratory tests allow differentiation of CGD from other immunodeficiency disorders characterized by increased susceptibility to bacterial infections. Additional inherited phagocyte disorders are listed in Table 60.13.

Treatment

The use of antibiotics and antifungals has markedly reduced the morbidity and mortality rates of CGD. Although cutaneous and nodal infections are often readily apparent, localized foci of internal infection (which may or may not be associated with fever) can be difficult to detect. Thorough periodic evaluation of the lungs, liver, and bones by routine radiographs, ultrasounds or CT, MRI, positron emission tomography (PET), and bone scans often uncovers occult foci of inflammation or infection. Cultures should be performed to identify the infectious agent, and invasive procedures may be necessary to obtain adequate tissue samples. While awaiting culture results or in situations where material from the affected site cannot be obtained, patients with evidence of infection should be treated empirically with broad-spectrum parenteral antibiotics that cover *S. aureus* as well as Gram-negative bacteria, with a high index of suspicion for fungal infection if despite antibiotics symptoms persist. Surgical interventions such as debridement, irrigation, and prolonged drainage are important for deeper infections.

Chronic prophylaxis with trimethoprim–sulfamethoxazole has been shown to decrease the incidence of bacterial infection in CGD patients.

OTHER INHERITED DEFECTS OF PHAGOCYTES AND INNATE IMMUNITY				
Disorder	**Inh**	**Gene**	**Protein (defect or function)**	**Clinical features**
Selected disorders featuring neutropenia or neutrophil defects				
Severe congenital neutropenia	AD	*ELANE*	Neutrophil elastase (abnormal elastase trafficking and accumulation)	• Neutropenia • MDS, AML
	AD	*GFI1*	Transcriptional repressor of elastase (abnormal elastase accumulation)	• Neutropenia, lymphopenia • Circulating myeloid progenitors
	AR	*HAX1*	Mitochondrial HS1-associated protein X1 (protects against apoptosis in myeloid cells)	• Neutropenia • Increased apoptosis of myeloid cells
	AD	*CSF3R*	Granulocyte colony-stimulating factor receptor	• Neutropenia • Severe myeloid hypoplasia
	AR	*G6PC3*	Glucose 6 phosphatase catalytic subunit 3 (glucose metabolism)	• Neutropenia, thrombocytopenia • Urogenital and cardiac malformations • Ectatic veins on trunk/extremities
Cyclic neutropenia	AD	*ELANE*	Neutrophil elastase	• Alternating 21-day cycles of neutropenia & monocytopenia • Fever and oral ulcers at nadir
X-linked neutropenia	XR	*WASP*	WASP (gain of function; see text, Wiskott–Aldrich syndrome)	• Neutropenia
p14 deficiency	AR	*LAMTOR2*	Endosomal adaptor protein p14 (p14; endosomal biogenesis)	• Neutropenia • Pneumococcal infections • Diffuse pigmentary dilution of the skin and hair • Short stature, coarse facies
Shwachman–Bodian–Diamond syndrome	AR	*SBDS*	SBDS protein (ribosomal RNA metabolism)	• Neutropenia > pancytopenia • MDS, AML • Exocrine pancreatic insufficiency • Chondrodysplasia
Poikiloderma with neutropenia, Clericuzio type	AR	*USB1*	U6 snRNA biogenesis phosphodiesterase 1	• Neutropenia • Dermatitis → poikiloderma, keratotic papules • Recurrent skin & respiratory infections
Specific granule deficiency	AR	*CEBPE*	C/EBPε transcription factor (granulocyte differentiation)	• Bilobed neutrophils • Recurrent bacterial infections
Myeloperoxidase deficiency	AR	*MPO*	Myeloperoxidase (microbial killing by granulocytes)	• *Candida* spp. and *S. aureus* infections • Often asymptomatic
Leukocyte adhesion deficiencies (LADs) and related conditions				
LAD-I	AR	*ITGB2*	β_2-integrin subunit of LFA-1, CR3, and p150 (see text)	• Neutrophilia; ↓ tissue neutrophils • Necrotic abscesses, ulcers • Poor wound healing, delayed umbilical stump separation • Gingivitis • Bleeding diathesis (LAD-III)
LAD-II	AR	*SLC35C1 (FUCT1)*	GDP-fucose transporter 1 (sialyl-Lewis X expression; see text)	
LAD-III	AR	*FERMT3*	Kindlin-3 (defective integrin activation; see text)	
Rac2 deficiency	AD	*RAC2*	Rac2 GTPase (NADPH oxidase, integrin-dependent adhesion, and neutrophil migration; see Table 60.10)	
Defects resulting in predisposition to specific infections				
Defects of the interleukin-12/interferon-γ axis	AR	*IL12B*	Subunit of IL-12 and IL-23 (stimulation of IFN-γ production)	• Severe mycobacterial and *Salmonella* infections • Disseminated BCG infection • Chronic mucocutaneous candidiasis (*RORC*, *IL12RB1* > *IL12B*) • Viral infections (*STAT1, TYK2*) • Hyper-IgE syndrome (*TYK2*; see text)
	AR	*IL12RB1*	IL-12 and IL-23 receptor β1 chain	
	AR, AD	*IFNGR1*	IFN-γ receptor (ligand binding)	
	AR	*IFNGR2*	IFN-γ receptor (signaling)	
	AR, AD	*STAT1**	Signal transducer and activator of transcription 1 (STAT1)* (IFN receptor signaling is impaired by loss-of-function mutations)	
	AR	*TYK2*	Tyrosine kinase 2 (IFN/IL-12/other cytokine receptor signaling)	
	AD	*IFR8*	IFN regulatory factor 8 (IL-12 signaling)	
	AR	*ISG15*	IFN-α/β-inducible ubiquitin-like modifier	
	AR	*RORC*	Retinoic acid receptor-related orphan receptor C (IFN-γ and IL-17 signaling)	

Table 60.13 Other inherited defects of phagocytes and innate immunity.

Continued

OTHER INHERITED DEFECTS OF PHAGOCYTES AND INNATE IMMUNITY				
Disorder	**Inh**	**Gene**	**Protein (defect or function)**	**Clinical features**
Defects in Toll-like receptor (TLR) signaling	AD	*TLR3*	TLR3 (signals IFN-α/β production)	• Herpes simplex encephalitis
	AR	*UNC93B1*	UNC-93B (endoplasmic reticulum protein required for TLR3 signaling)	
	AD	*TRAF3*	TNF receptor-associated protein 3 (TLR3 signaling)	
	AD, AR	*TICAM1* (*TRIF*)	TLR-adaptor molecule 1 (TLR3/4 signaling)	
	AD	*TBK1*	TANK-binding kinase 1 (TLR3 signaling)	
	AR	*IRAK4*	IL-1 receptor associated kinase-4 (IL-1 receptor & TLR signaling)	• Recurrent pyogenic sinopulmonary and skin infections with *Streptococcus pneumoniae* and *S. aureus*, respectively
	AR	*MYD88*	Myeloid differentiation primary response gene 88 (recruits IRAK4 to the IL-1 receptor and TLRs)	
GATA2 deficiency/ MonoMAC syndrome	AD	*GATA2*	GATA binding protein 2	• Monocytopenia, B/NK lymphopenia, myelodysplasia, myeloid leukemia • Mycobacterial and fungal infections (e.g. histoplasmosis) • Recalcitrant warts • Lymphedema, panniculitis, granulomatous dermatitis • Alveolar proteinosis

*Gain-of-function *STAT1* mutations lead to chronic mucocutaneous candidiasis (see Table 60.4) and/or confer susceptibility to endemic dimorphic fungal infections; *loss*-of-function *STAT3* mutations underlie AD hyper-IgE syndrome (see text) while *gain*-of-function *STAT3* mutations can result in lymphoproliferation, autoimmunity, hypogammaglobulinemia, mycobacterial infections, and occasionally psoriasiform dermatitis; defects in STAT5B, which is involved in IL-2 and growth hormone receptor signaling, lead to an AR syndrome of growth hormone insensitivity, decreased $CD4^+/CD25^+$ regulatory T cells, viral infections, and eczematous dermatitis.

Table 60.13 Other inherited defects of phagocytes and innate immunity. See text and Tables 60.5 and 60.10 for Chédiak–Higashi syndrome and chronic granulomatous disease. AD, autosomal dominant; AML, acute myeloid leukemia; AR, autosomal recessive; BCG, bacillus Calmette–Guérin; IFN, interferon; IL, interleukin; Inh, inheritance; LFA-1, lymphocyte function-associated antigen-1; MDS, myelodysplastic syndrome; WASP, Wiskott–Aldrich syndrome protein; XR, X-linked recessive.

The frequency and mortality of invasive fungal infections (e.g. with *Aspergillus* spp.) have likewise been reduced with itraconazole prophylaxis as well as treatment with other azoles (e.g. voriconazole, posaconazole, isavuconazonium sulfate)[76,77]. However, invasive fungal infections remain the most common cause of death in CGD. Administration of interferon-γ, which likely augments oxidant-independent antimicrobial pathways, may help to decrease the risk of serious infections[78]. Granulocyte transfusions have been used for rapidly progressive, life-threatening infections.

Short courses of systemic corticosteroids have been helpful for patients with obstructive granulomas of the bronchopulmonary, gastrointestinal, or genitourinary tract[58]. Additional immunomodulatory therapies with potential benefit for inflammatory manifestations of CGD include azathioprine, hydroxychloroquine, anakinra, thalidomide, pioglitazone (increases ROS production and efferocytosis), ustekinumab, and sirolimus[79,80]; tumor necrosis factor (TNF) inhibitors may improve colitis but increase the risk of infectious complications.

Hematopoietic stem cell transplantation represents a potentially curative treatment for CGD. Although younger patients without infection at the time of transplantation have the best outcomes (survival >95%), use of reduced-intensity conditioning regimens has enabled successful transplantation of higher-risk patients such as adults and individuals with recalcitrant infections or inflammatory manifestations[81]. Children with CGD who undergo transplantation have improved growth and fewer infections, surgical interventions, and hospital admissions than those managed conservatively[82].

In the 1990s, gene therapy was performed in five adults with the $p47^{phox}$-deficient form of CGD, and a single infusion of transduced $CD34^+$ peripheral blood stem cells led to peak levels of corrected granulocytes in 3–6 weeks with persistence for as long as 6 months[83]. Subsequently, two young men with X-linked recessive CGD were treated with non-myeloablative conditioning prior to the infusion of $CD34^+$ peripheral blood stem cells transduced *ex vivo* with a retroviral vector expressing $gp91^{phox}$; this led to sustained engraftment of functionally corrected phagocytes. However, following initial resolution of infections, the transgene was silenced due to methylation of the viral promoter in both patients, and within 3 years they developed myelodysplasia with monosomy 7 as a result of insertional activation of ecotropic viral integration site 1 (*EVI1*)[84]. To increase the safety and efficacy of gene therapy for CGD, current investigations are utilizing approaches such as self-inactivating lentiviral vectors, targeted integration of transgenes into a genomic "safe harbor" site, or the CRISPR-Cas9 site-specific nuclease system to encourage repair of the endogenous gene via homologous recombination (see Ch. 3)[77]. In a recent study, 6 of 9 patients with severe X-linked CGD who received *ex vivo* autologous $CD34^+$ hematopoietic stem/progenitor cell-based lentiviral gene therapy following myeloablative conditioning recovered functional oxidase activity, with no new CGD-related infections or evidence of genotoxicity after a follow-up period of 1 year[85].

DHR flow cytometric studies may be utilized in determining the carrier status of the sisters and other female relatives of patients with X-linked CGD, which is important for genetic counseling prior to pregnancy. Prenatal diagnosis of CGD is also possible.

HYPERIMMUNOGLOBULIN E SYNDROMES

Synonyms: ■ Hyper-IgE syndromes ■ Job syndrome ■ Buckley syndrome

Key features

- Characterized by recurrent skin and sinopulmonary tract infections, early-onset eczematous dermatitis, and extremely elevated IgE levels
- The classic form, an autosomal dominant disorder due to STAT3 deficiency, features skin infections caused primarily by *S. aureus* (in particular "cold abscesses") and, especially during infancy, *C. albicans*, in addition to a neonatal papulopustular eruption, progressively coarse facies, osteopenia with fractures, scoliosis, and dental abnormalities
- Autosomal recessive forms have a broader spectrum of infectious complications

Introduction and History

Hyperimmunoglobulin E syndromes (HIESs) are characterized by the triad of recurrent cutaneous and sinopulmonary infections, dermatitis beginning in infancy or early childhood, and extremely elevated IgE levels[86]. Job syndrome is a subgroup of autosomal dominant (AD) HIES that was originally described in female patients with fair skin, red hair, and hyperextensible joints as well as the typical features of HIES. In 2007, classic AD HIES was found to result from STAT3 deficiency[87,88] (see Pathogenesis). Since then, multiple additional forms of HIES caused by defects in proteins with roles in STAT3 signaling or other pathways of immune regulation have been identified[89].

Epidemiology

As noted above, classic HIES is inherited in an AD fashion with variable expression. Additional AD and autosomal recessive (AR) forms of HIES with variable clinical features have also been described[89–93].

Pathogenesis

Heterozygous mutations in the gene encoding STAT3 (*s*ignal *t*ransducer and *a*ctivator of *t*ranscription *3*) cause classic AD HIES, commonly referred to as STAT3-HIES[87,88]. Different combinations of receptor-associated Janus kinases (JAKs) and STAT proteins transduce cytokine signals; upon phosphorylation by JAKs, the latter dimerize, translocate to the nucleus, and activate target genes (see Fig. 128.11). Susceptibility to bacterial and candidal infections in HIES reflects the roles of STAT3-dependent cytokines (e.g. IL-6, IL-21, IL-23) in the differentiation of IL-17-producing $CD4^+$ T cells that help to defend against these organisms (see Fig. 4.10)[94]. A lack of stimulation of β-defensin production by IL-22, which is produced by Th17 cells and signals via STAT3, may contribute to the development of infections at epithelial surfaces (e.g. skin, lungs) in STAT3-HIES.

STAT3 is critical to the signaling pathways for both IL-6, which promotes acute phase responses and acts as a pyrogen, and IL-10, an anti-inflammatory cytokine. STAT3 dysfunction provides an explanation for the "cold" abscesses and destructive inflammation (e.g. in the lung) that characterize HIES. Defective generation of IL-10-induced tolerogenic dendritic cells and $FOXP3^+$-induced regulatory T cells may contribute to other inflammatory features of HIES, such as the atopic-like dermatitis and high IgE levels[95]. STAT3 also downregulates differentiation of osteoclasts, and osteoporosis represents a feature of STAT3 deficiency in mice as well as HIES. Lastly, leukocytes from STAT3-deficient individuals produce higher levels of interferon-γ and tumor necrosis factor (TNF) upon stimulation with IL-12 and lipopolysaccharide/interferon-γ, respectively, than do leukocytes from unaffected controls[87,88].

Other variants of HIES can also result from disruption of STAT3 signaling, including deficiencies in the following proteins: the *IL-6 receptor* (AR) and *IL-6 signal transducer* (*gp130*; AD or AR); *phosphoglucomutase 3* (PGM3; AR), which promotes gp130 expression; *ZNF341* (AR), which regulates STAT3 expression; and *ERBIN* (AD), expression of which is stimulated by STAT3. In general, these disorders have clinical findings that overlap with those of STAT3-HIES, with additional manifestations such as autoimmunity and neurocognitive abnormalities in PGM3 deficiency and craniosynostosis in AR gp130 deficiency[89,93].

DOCK8 (dedicator of cytokinesis 8) deficiency is an AR condition with features of HIES (see below)[91,92]. The DOCK8 protein interacts with the Wiskott–Aldrich syndrome protein (WASP) in a complex that links T cell receptors to the actin cytoskeleton[96]. DOCK8 deficiency results in an increase in Th2 cells and production of the pruritogen IL-31, but a decrease in Th1 and Th17 cells[97,98].

CADINS (CARD11-associated atopy with dominant interference of NF-κB signaling) results from heterozygous dominant negative mutations in *CARD11*, which encodes a scaffolding protein involved in lymphocyte receptor signaling[99]. Patients present with the characteristic HIES triad together with additional atopic manifestations and B cell lymphopenia. The features of HIES have also been identified in a subset of patients with homozygous mutations in the gene encoding *tyrosine kinase 2 (TYK2)*, a member of the JAK family[100]. Affected individuals have defects in signaling pathways for IL-12 and interferon-α/β, which lead to susceptibility to mycobacterial and viral infections (see Table 60.13), as well as IL-6 and IL-10.

Clinical Features

Patients with *STAT3-HIES* typically present during the first month of life with a non-infectious, folliculocentric papulopustular eruption involving the face, scalp, neck, axillae, and diaper area[101,102]. Chronic candidiasis of the oral mucosa, periungual areas, and nails occurs in ~80% of HIES patients and may represent the initial infectious manifestation during infancy.

Cutaneous staphylococcal infections include impetiginized plaques and retroauricular fissures, folliculitis, furunculosis, abscesses, cellulitis, lymphangitis, and paronychia leading to nail dystrophy[102]. The cutaneous abscesses are often large, and they most commonly involve the neck, scalp (Fig. 60.8A), periorbital area, axillae, and groin. Such lesions are referred to as "cold abscesses" because they are not as red or tender as those that develop in healthy individuals. Patients are often afebrile or have only a low-grade fever. Although the abscesses tend to be staphylococcal, many patients have recurrent skin infections with other organisms, including *Str. pyogenes* as well as *C. albicans*.

The eczematous rash of HIES shares many clinical features with atopic dermatitis, including severe pruritus, lichenification, and staphylococcal superinfection[102]. It is almost always present in young children with STAT3-HIES but frequently clears by adolescence. Unlike individuals with atopic dermatitis, patients with STAT3-HIES do not commonly exhibit allergic rhinitis, asthma, or other cutaneous signs of atopy.

Although some STAT3-HIES patients have only cutaneous manifestations, most also develop recurrent bronchitis and pneumonias. *S. aureus* and *Haemophilus influenzae* usually cause the pulmonary infections, which may result in empyema, bronchiectasis, and pneumatocele formation. The pneumatoceles tend to persist and become the site of further infections with bacterial or fungal organisms, particularly *Aspergillus*

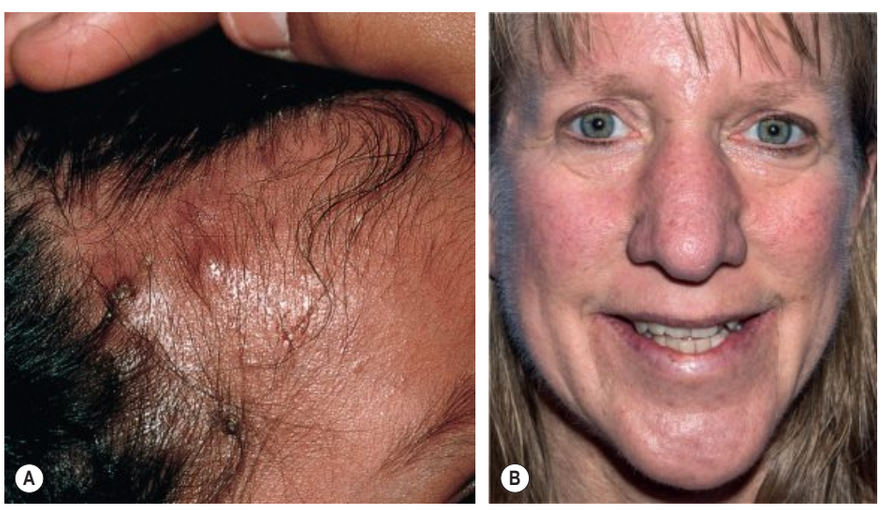


Fig. 60.8 STAT3-hyperimmunoglobulin E syndrome. A Several erythematous, slightly purulent "cold" abscesses are apparent on the forehead and scalp of this infant. **B** Coarse facial features that developed progressively over time in an affected woman. Note the prominent follicular ostia, doughy skin, and broad nasal bridge. *B, Courtesy Edward Cowen, MD.*

spp. Massive hemoptysis occasionally ensues. *Pneumocystis jirovecii* pneumonia can also occur in infants and children with STAT3-HIES. Other common sites of infection include the ears, oral mucosa, sinuses, and eyes. Visceral infections other than pneumonia are unusual.

STAT3-HIES patients develop progressive facial coarsening with thickened doughy skin, large follicular ostia, pitted scarring, a broad nasal bridge, a wide fleshy nasal tip, deep-set eyes, a prominent forehead, and irregularly proportioned cheeks and jaw (Fig. 60.8B). Osteopenia is frequently present and is associated with an increased risk of fractures of the long bones, ribs, and pelvis. More than half of adolescents and adults with STAT3-HIES have had at least three fractures, often due to unrecognized or minor trauma. Scoliosis occurs in 75% of patients ≥16 years of age, and joint hyperextensibility affects ~70% of patients. Approximately half of individuals with STAT3-HIES have a high-arched palate, and retention of primary teeth due to failure of root resorption and lack of eruption of secondary teeth are characteristic dental manifestations. Several brain abnormalities have been described, including Chiari malformations, lacunar infarctions, and focal hyperintensities in white matter on T2-weighted MRI sequences. Development of coronary artery aneurysms during adulthood has also been reported. HIES is associated with an increased risk of non-Hodgkin lymphoma of B cell origin.

DOCK8 deficiency shares some features with STAT3-HIES, including highly elevated serum IgE levels, peripheral eosinophilia, chronic eczematous dermatitis (Fig. 60.9A), recurrent staphylococcal skin infections (including cold abscesses), respiratory tract infections, and mucocutaneous candidiasis. However, skeletal and dental abnormalities, facial coarsening, and pneumatoceles are not characteristic features[90,103]. Patients with DOCK8 deficiency are predisposed to the development of warts, molluscum contagiosum, severe herpes simplex and varicella–zoster viral infections, and opportunistic infections[90,103,104] (Fig. 60.9B,C). Additional manifestations include asthma, food allergies resulting in anaphylaxis, autoimmunity, cerebral vasculitis, mucocutaneous squamous cell carcinomas, and lymphomas. Up to half of patients die by 20 years of age from infection, malignancy, or CNS disease[90,103].

Laboratory Findings and Pathology

HIES patients have markedly elevated serum levels of polyclonal IgE, usually peaking at >2000 IU/ml and sometimes declining during adulthood. Patients develop particularly high levels of anti-staphylococcal and anti-candidal IgE antibodies and often have immediate wheal-and-flare reactions to a variety of foods and environmental allergens. Many affected individuals also have eosinophilia of the peripheral blood and sputum. Cell-mediated immunity is often abnormal, as manifested by anergy to skin testing and impaired *in vitro* lymphoproliferative responses to specific antigens. Serum levels of IgG, IgA and IgM are usually normal in STAT3-HIES, as are lymphocyte subsets. In contrast, DOCK8 deficiency represents a combined immunodeficiency that is characterized by lymphopenia with a paucity of $CD4^+$ T cells > $CD8^+$ T cells > B cells, low IgM levels, and variable IgG levels as well as elevated IgE levels and peripheral eosinophilia[91,92].

The infantile papulopustular eruption of STAT3-HIES is characterized histologically by eosinophilic folliculitis, eosinophilic spongiosis, and a superficial and deep perivascular infiltrate with abundant eosinophils[101,102].

Differential Diagnosis

Current diagnostic criteria for STAT3-HIES include an IgE level >1000 IU/ml and a weighted score of five clinical features (Table 60.14)[105]; these characteristics plus a lack of Th17 cells or the detection of a heterozygous *STAT3* mutation allow for a probable or definitive diagnosis, respectively.

HIES must be differentiated from a number of other disorders that can feature elevated IgE levels and a cutaneous eruption, including atopic dermatitis, Wiskott–Aldrich syndrome, Netherton syndrome, Omenn syndrome, DiGeorge syndrome, IPEX syndrome, ARPC1B (actin-related protein 2/3 complex subunit 1B) deficiency, Loeys–Dietz syndrome, and GVHD. Atopic dermatitis and Wiskott–Aldrich syndrome are most easily confused with HIES because they present with eczematous dermatitis and staphylococcal infections. However, the development of cold abscesses, recurrent pneumonia, coarse facial features, and osteopenia help to differentiate STAT3-HIES from these disorders, and platelet abnormalities distinguish Wiskott–Aldrich syndrome as well as ARPC1B syndrome. In a series of pediatric patients who had a serum IgE level of >2000 IU/ml, 69% (48/70) had atopic dermatitis and only 8% (6/70) had HIES; no correlation was observed between the IgE level and diagnosis of HIES[106]. Elevated IgE levels, susceptibility to pyogenic infections, and eczematous dermatitis have



Fig. 60.9 DOCK8 deficiency. **A** Eczematous dermatitis with prurigo nodularis lesions. **B** Extensive molluscum contagiosum. **C** Numerous coalescing facial warts. *A, B, Courtesy Edward Cowen, MD.*

DIAGNOSTIC GUIDELINES FOR HYPERIMMUNOGLOBULIN E SYNDROME (AD-HIES) DUE TO *STAT3* MUTATIONS							
Clinical finding	**Points**						**Multiplication factor**
	0	**2**	**4**	**5**	**6**	**8**	
Pneumonias (X-ray proven, total #)	none	1	2	–	3	>3	2.5
Newborn papulopustular eruption (during first 3 weeks of life)	absent	–	present	–	–	–	2.1
Pathologic bone fractures	none	–	1–2	–	–	>2	3.3
Characteristic facies	absent	mild	–	present	–	–	3.3
High-arched palate	absent	present	–	–	–	–	2.5
Possible AD-HIES: IgE >1000 IU/ml *plus* weighted score of >30 **Probable AD-HIES**: As above plus lack of Th17 cells by peripheral blood flow cytometry *or* a family history of definitive AD-HIES **Definitive AD-HIES:** As above plus a dominant-negative heterozygous mutation in *STAT3*							

Table 60.14 Diagnostic guidelines for autosomal dominant hyperimmunoglobulin E syndrome (AD-HIES) due to *STAT3* mutations[105].

also been described in patients with prolidase deficiency, an autosomal recessive condition due to *PEPD* mutations that also features chronic leg ulcers, facial dysmorphism, and intellectual disability. Patients with CGD and myeloperoxidase deficiency develop bacterial and candidal abscesses, but they do not typically have markedly elevated levels of IgE.

In addition to DOCK8 deficiency and the other six conditions noted in Table 60.1, primary immunodeficiencies that result in increased susceptibility to warts include epidermodysplasia verruciformis (see Ch. 79), Netherton syndrome (see Ch. 57), and activated phosphoinositide-3-kinase δ syndrome (see Table 60.15) as well as deficiencies of serine/threonine kinase 4 (STK4), GATA2 (see Table 60.13), TNF-like weak inducer of apoptosis (TWEAK; see Table 60.15), coronin 1A (see Table 60.16), RhoH GTPase, minichromosome maintenance complex component 4 (MCM4; also herpesvirus infections), and capping protein regulator and myosin 1 linker 2 (CARMIL2; also severe molluscum contagiosum). Of note, $CD4^+$ lymphocytopenia can be a prominent feature of DOCK8 deficiency and other wart-prone immunodeficiency syndromes.

Treatment

Treatment of the infectious complications of HIES includes incision and drainage of abscesses as well as therapeutic and prophylactic administration of antibiotics. Interferon-γ has been shown to help control infections, and IVIg may improve the dermatitis, prevent infections, and lower IgE levels. Treatment with dupilumab and omalizumab has been reported to improve the eczematous dermatitis of HIES[107].

IMMUNOGLOBULIN DEFICIENCIES

Synonyms: ■ X-linked agammaglobulinemia ■ Bruton agammaglobulinemia ■ Bruton–Gitlin syndrome ■ Congenital hypogammaglobulinemia ■ X-linked hypogammaglobulinemia

Key features

Agammaglobulinemia

- The inheritance pattern is X-linked recessive in ~90% of patients and autosomal recessive in ~10%
- Recurrent bacterial infections begin in the first few years of life

Common variable immunodeficiency (CVID)

- Heterogeneous group of disorders with defects in both humoral and cell-mediated immunity
- May manifest during childhood or adulthood, with clinical onset at an average age of 30 years
- Variable severity of infectious and autoimmune complications

Selective IgA deficiency

- Most common immunoglobulin deficiency, but usually asymptomatic, with clinical manifestations in only 10%–15% of affected individuals
- Bacterial sinopulmonary infections and autoimmune disorders may occur

Hyper-IgM syndromes

- Usually has an X-linked recessive inheritance pattern, but autosomal recessive forms also exist
- Recurrent sinopulmonary and gastrointestinal infections with pyogenic bacteria and opportunistic organisms
- Oral ulcerations and verrucae may develop

The most common immunoglobulin deficiency is selective IgA deficiency, overall found in ~1 in 500 persons with an equal sex distribution. Panhypogammaglobulinemia has a prevalence of 1 in 25 000, with X-linked agammaglobulinemia[102] (affecting primarily boys) and common variable immunodeficiency[108] (CVID; no sexual predilection) representing the most frequent forms. CVID has its clinical onset at a mean age of 30 years whereas X-linked agammaglobulinemia often manifests during the first few years of life, after levels of maternal antibodies wane at ~6 months of age. Approximately 15% of patients with CVID have family members with selective IgA deficiency. The pathogenesis and clinical features of immunoglobulin deficiencies are presented in Fig. 60.10 and Table 60.15[108–115].

The treatment of hypogammaglobulinemia is antibody replacement by IVIg or subcutaneous immunoglobulins and antibiotic therapy for infections[116]. However, IVIg and other blood products containing IgA should be avoided in individuals with profound IgA deficiency, who may develop anti-IgA antibodies; fatal anaphylactic reactions have been reported. Recalcitrant non-infectious cutaneous and extracutaneous granulomas in patients with CVID may respond to treatment with TNF inhibitors.

Female carriers of X-linked agammaglobulinemia may be detected via examination of B cell X-inactivation patterns, which show skewing towards cells with inactivation of the mutated X chromosome. DNA-based prenatal diagnosis is possible when the genetic defect in affected family members has been identified.

IPEX SYNDROME

Key features

- X-linked recessive disorder due to mutations in *FOXP3*
- Cutaneous findings include a widespread eczematous dermatitis during infancy and a variety of autoimmune skin conditions
- Also features enteropathy and endocrinopathies with autoimmune etiologies

IPEX – *i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked – syndrome is an X-linked recessive disorder caused by *FOXP3* mutations that result in abnormal development of regulatory T cells. Affected individuals typically present during infancy with severe diarrhea secondary to autoimmune enteropathy and develop a variety of autoimmune endocrinopathies such as early-onset type 1 diabetes mellitus, thyroiditis, and cytopenias. Most IPEX patients have a widespread eczematous dermatitis and elevated IgE levels during early infancy, and this is often complicated by staphylococcal superinfections and sepsis. Cutaneous manifestations of IPEX can also include psoriasiform dermatitis, cheilitis, nail dystrophy, and autoimmune skin conditions such as alopecia areata, chronic urticaria, and bullous pemphigoid[117].

IPEX-like clinical presentations can occur in patients with IL-2 receptor α-chain (CD25) deficiency[118], LPS-responsive beige-like anchor protein (LRBA) deficiency, *gain*-of-function *STAT1* or *STAT3* mutations, and *loss*-of-function *STAT5B* mutations[119] (see Tables 60.4, 60.13, 60.15). In addition, an autosomal recessive disorder due to mutations in *ADAM17*, which encodes the TNF converting enzyme, features a widespread psoriasiform dermatitis with pustular flares, brittle hair, staphylococcal skin infections, and chronic diarrhea[120].

LEUKOCYTE ADHESION DEFICIENCY

Key features

- Group of autosomal recessive disorders characterized by decreased ability of leukocytes to adhere to the vascular endothelium and migrate to sites of tissue injury and infection
- Gingivitis and periodontitis
- Necrotic ulcerations clinically resembling pyoderma gangrenosum
- Poor wound healing; delayed separation of the umbilical stump
- Life-threatening bacterial and fungal infections

Introduction

Leukocyte adhesion deficiency (LAD) comprises three autosomal recessive disorders that affect the ability of neutrophils, monocytes, and lymphocytes to adhere to the vascular endothelium and migrate to sites of infection and tissue injury[121,122].

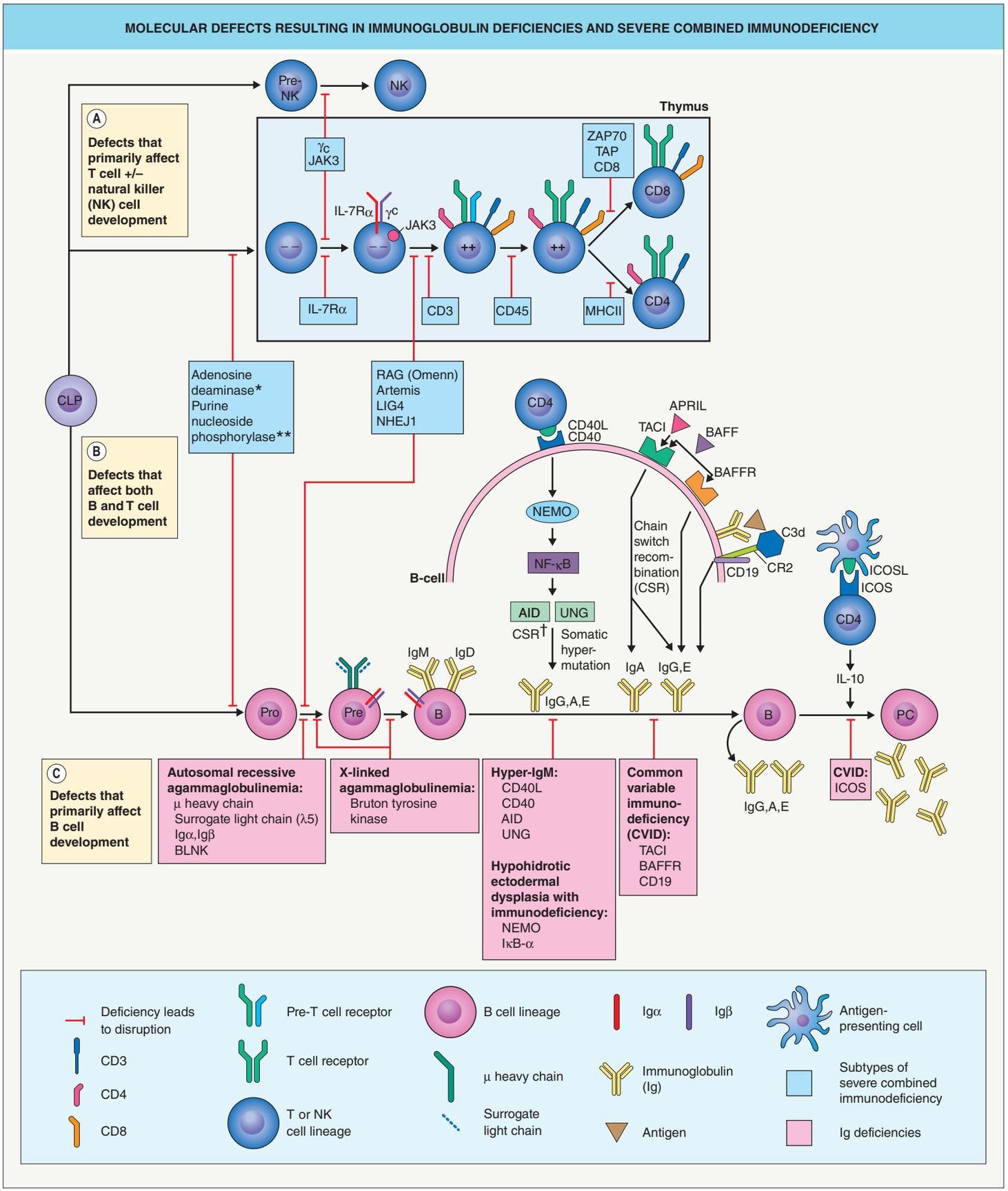


Fig. 60.10 Molecular defects resulting in immunoglobulin deficiencies and severe combined immunodeficiency (SCID). *Also important for B cell maturation in germinal centers. **Affects T cells more than B cells. †Switch from IgM to IgG, IgA, or IgE. AID, activation-induced cytidine deaminase; APRIL, *a p*roliferation-*i*nducing *l*igand; BAFF(R), B cell activating factor (receptor); BLNK, B cell linker protein (binds Bruton tyrosine kinase); CD40L, CD40 ligand; CLP, common lymphoid precursor; CR2, complement receptor 2; γ_c, common γ chain; ICOS(L), inducible costimulator on activated T cells (ligand); IκB-α, inhibitor of κB-α; IL, interleukin; IL-7Rα, IL-7 receptor α-chain; MHC, major histocompatibility complex; NEMO, NF-κB essential modulator; NHEJ1, non-homologous end-joining 1 (Cernunnos); NK, natural killer cell; PC, plasma cell; TACI, transmembrane activator and CAML interactor; TAP, transporter associated with antigen processing; UNG, uracil-DNA glycosylase; _ _, double-negative thymocyte; ++, double-positive thymocyte.

PRIMARY IMMUNOGLOBULIN DEFICIENCY DISORDERS						
Disorder	**Gene**	**Protein (function)**	**Ig levels**	**B cells**	**Infectious and systemic manifestations**	**Cutaneous manifestations**
Block in B cell differentiation at the pro-B to pre-B cell transition						

X-linked agammaglobulinemia	*BTK*	Bruton tyrosine kinase (pre-B cell receptor [BCR] signaling)	All ↓	↓↓	• Recurrent infections with *Staphylococcus, Streptococcus, Pneumococcus, Haemophilus* and *Pseudomonas* spp.
					• Hepatitis B and enteroviral infections
					• Lymphomas (~5%)
						• The skin is the most common site of infection
						  • Furuncles and cellulitis
						  • Ecthyma gangrenosum
						• Eczematous dermatitis
						• Papular dermatitis due to lymphohistiocytic infiltration
						• Non-infectious granulomas
						• Dermatomyositis-like disorder associated with chronic echoviral meningoencephalitis

AR agammaglobulinemia	*IGHM*	μ heavy chain of IgM (component of pre-BCR)				
	CD79A, CD79B	Igα chain, Igβ chain (bind μ heavy chain)				
	IGLL1	λ5 (surrogate light chain of pre-BCR)				
	BLNK	B cell linker protein (binds Bruton tyrosine kinase)				
AD agammaglobulinemia	*LRRC8A*	Leucine-rich repeat-containing 8 family member A				
Defective class switch recombination (e.g. from IgM to IgG, IgA or IgE), somatic hypermutation*, and related mechanisms						
Common variable immunodeficiency (CVID)[†]	*ICOS*	Inducible costimulator on activated T cells (T cell help for B cell differentiation)	IgG, A ↓; ± IgM ↓	Nl or ↓	• Bacterial sinopulmonary infections (organisms similar to X-linked agammaglobulinemia) • *Giardia* spp. gastroenteritis • Autoimmune diseases, especially hemolytic anemia and idiopathic thrombocytopenic purpura • Increased risk of cancer (10-fold overall) and lymphoma (400-fold)	• Pyodermas and mucocutaneous candidiasis • Extensive warts and dermatophyte infections • Eczematous dermatitis • Non-infectious granulomas (Fig. 60.11), which may also involve the lungs, liver and spleen • Autoimmune conditions such as vitiligo, alopecia areata and vasculitis • Clonal $CD8^+$ lymphocytic infiltration of the skin • Clinical manifestations of LRBA deficiency variable; include an IPEX-like presentation (see text) and autoimmune lymphoproliferative syndrome (see Table 60.6)
	TNFRSF13B (AD or AR)	Transmembrane activator and CAML interactor (TACI; B cell isotype switching)				
	TNFRSF13C	B cell activating factor receptor (BAFFR; B cell isotype switching)				
	CD19[‡]	CD19 antigen (B cell survival and differentiation)				
	MSH5 (AD)	Mismatch repair protein (regulates class switch recombination)				
	LRBA (AR)	LPS-responsive beige-like anchor protein				
Selective IgA deficiency	*TNFRSF13B* (AD)	See CVID section above	IgA ↓[¶]; anti-IgA antibodies in ~half	Nl	• Clinical manifestations in 10%–15% • Similar to CVID	• Mucocutaneous candidiasis • Eczematous dermatitis • Autoimmune conditions such as SLE, vitiligo, and lipodystrophia centrifugalis abdominalis
	MSH5 (AD)					
Selective IgM deficiency	?	?	IgM ↓	Nl	• Recurrent bacterial infections • Autoimmune diseases	• Extensive warts • Eczematous dermatitis • SLE
TWEAK deficiency	*TWEAK*	TNF-like weak inducer of apoptosis	IgM, A ↓	Nl	• Pneumonia, other bacterial infections • Thrombocytopenia, neutropenia	• Warts
Activated PI3Kδ syndrome	*PIK3CD, PIK3R1*	Phosphoinositide-3-kinase catalytic subunit δ (gain-of-function) or regulatory subunit 1 (loss-of-function)	IgG/G_2, A ↓; IgM ↑; also often CD4 lymphopenia	Nl or ↓	• Recurrent sinopulmonary infections • Chronic EBV and CMV infections • LAN, HSM • Lymphoma • Autoimmune diseases, e.g. cytopenias • Growth retardation (*PIK3R1*)	• Staphylococcal abscesses, cellulitis • Severe/recurrent HSV and VZV infections, warts, molluscum contagiosum

Table 60.15 Primary immunoglobulin deficiency disorders.

Continued

PRIMARY IMMUNOGLOBULIN DEFICIENCY DISORDERS						
Disorder	**Gene**	**Protein (function)**	**Ig levels**	**B cells**	**Infectious and systemic manifestations**	**Cutaneous manifestations**
X-linked hyper-IgM syndrome	*CD40LG*	CD40 ligand (on T cells)	IgM ↑; isohemagglutinins ↑; IgA, E, G ↓↓	NI	• Recurrent sinopulmonary and GI infections with pyogenic bacteria and opportunistic organisms (e.g. PCP) • Neutropenia • Small lymph nodes • Autoimmune diseases, especially thyroiditis and hemolytic anemia	• Pyodermas • Extensive warts • Oral and anogenital ulcers • Non-infectious granulomas • Autoimmune conditions such as SLE
AR hyper-IgM syndromes	*CD40*	CD40 (on B cells)				
	AICDA	Activation-induced cytidine deaminase			• As above, but massive HSM/LAN (with germinal centers) and no opportunistic infections	• Pyodermas
	UNG	Uracil-DNA glycosylase				
Hypohidrotic ectodermal dysplasia with immunodeficiency	*IKBKG (NEMO)* (X-linked recessive)	NF-κB essential modulator (activates NF-κB, which is involved in CD40 signaling)	IgM ↑; ± IgA ↑; ± IgG ↓	NI	• Pyogenic bacterial and opportunistic infections • Subset of *NEMO* patients with osteopetrosis and lymphedema	• Pyodermas • Ectodermal dysplasia (see Ch. 63)
	NFKBIA (AD, gain of function)	NF-κB inhibitor α				
	IKBKB	Inhibitor of NF-κB kinase β				
Abnormal DNA methylation leading to defective B cell negative selection and terminal differentiation						
*I*mmunodeficiency, centromeric instability, and *f*acial anomalies (ICF) syndrome	*DNMT3B, ZBTB24*	DNA methyltransferase 3β, zinc finger and BTB-containing 24	All ↓	NI or ↓	• Bacterial sinopulmonary and GI infections • Abnormal facies, intellectual disability	• Telangiectasias (uncommon) • Nevoid hyperpigmentation
Aberrant chemokine signaling						
WHIM syndrome§	*CXCR4* (AD, gain-of-function)	CXC chemokine receptor 4 (binds CXCL12; key role in bone marrow homeostasis and lymphocyte trafficking)	IgG ↓; ± IgA, M ↓	↓	• Recurrent bacterial sinopulmonary infections • Myelokathexis (mature neutrophils fail to exit the bone marrow)	• Cellulitis and pyodermas • Extensive verruca vulgaris and condyloma acuminata (Fig. 60.12) • Treatment with mavorixafor, a CXCR4 inhibitor, decreased warts and other infections in a phase 3 clinical trial
Delayed maturation of helper T cell function						
Transient hypogammaglobulinemia of infancy	?	?	IgG, A ↓ (resolves by age 3 y)	NI	• Failure to thrive in infancy • Recurrent sinopulmonary and GI infections	• Recurrent pyodermas and abscesses • Eczematous dermatitis

*T cell priming may also be defective, particularly in CD40–CD40L disorders (leading some authors to classify the latter as subtypes of severe combined immunodeficiency).
†Relatively common, heterogeneous group of disorders characterized by decreased levels of at least two classes of immunoglobulins (IgG, IgA > IgM) and variable defects in T cell function; currently, ≤10% of patients have an identifiable disease-causing mutation; several additional genes have also been associated with CVID[114].
‡*CD81* is required for CD19 expression, and a homozygous mutation in the *CD81* gene was reported in a patient with hypogammaglobulinemia and autoimmune vasculitis.
¶Symptomatic patients often develop the immunodeficiency pattern of CVID.
§Warts, hypogammaglobulinemia, infections, and myelokathexis; in a phase 1 trial, treatment with plerixafor (AMD 3100), a CXCR4 antagonist, led to higher neutrophil counts and improvement of warts.

Table 60.15 Primary immunoglobulin deficiency disorders. Conditions are autosomal recessive (AR) unless otherwise specified. AD, autosomal dominant; CAML, calcium-modulating cyclophilin ligand; GI, gastrointestinal; HSM, hepatosplenomegaly; HSV, herpes simplex virus; Ig, immunoglobulin; *IKBKG*, inhibitor of NF-κB kinase regulatory subunit γ; LAN, lymphadenopathy; NI, normal; PCP, *Pneumocystis jirovecii* pneumonia; SLE, systemic lupus erythematosus; VZV, varicella–zoster virus.

Pathogenesis

Leukocyte adhesion requires a group of cell surface integrins that share the 95-kDa β_2-subunit known as CD18. This β_2-subunit can be linked to different α-chains to form distinct cell surface glycoproteins including: (1) lymphocyte function antigen 1 (LFA-1 – CD18 paired with CD11a); (2) complement receptor type 3 (CR3/$iC3_b$ receptor/Mac-1 – CD18 paired with CD11b); and (3) p150,95 (complement receptor type 4 – CD18 paired with CD11c). The primary ligand for these glycoproteins is intercellular adhesion molecule-1 (ICAM-1), which participates in the initiation and evolution of localized inflammation in the skin and other tissues (see Fig. 102.10). LAD-I is caused by mutations in *ITGB2* which encodes CD18, and it manifests with dysfunction of all three glycoproteins. This leads to profound impairment of leukocyte firm adhesion to the vascular endothelium and mobilization into extravascular sites of inflammation, as well as defective neutrophil and monocyte chemotaxis and phagocytosis.

LAD-II is due to mutations in *SLC35C1* (solute carrier family 35 member C1), which encodes the GDP-fucose transporter-1 (FUCT1) that is required for formation of sialyl-Lewis X, the fucosylated ligand for selectins on the surface of leukocytes[123]. This causes a defect in the initial steps of tethering and rolling of leukocytes on the endothelial cell surface via interaction of sialyl-Lewis X on leukocytes with E- or



Fig. 60.11 Persistent granulomatous plaques in a patient with common variable immunodeficiency (CVID). *Courtesy Edward Cowen, MD.*



Fig. 60.12 Extensive, recalcitrant perianal warts in a child with WHIM syndrome. *Courtesy Edward Cowen, MD.*

P-selectin on endothelial cells. These contacts are required for their targeting to sites of infection and inflammation.

In order to undergo firm adhesion and subsequently extravasate from the bloodstream, circulating leukocytes must activate integrins *in situ* to rapidly increase their affinity and avidity for endothelial ligands. Patients with LAD-III have impaired integrin activation in hematopoietic cells, which leads to impaired leukocyte β_1- and platelet β_3-integrins in addition to leukocyte β_2-integrins as in LAD-I. It is caused by loss-of-function mutations in the fermitin family member 3 gene (*FERMT3*) that encodes kindlin-3, an effector of integrin activation in hematopoietic cells[124].

Clinical Features

The most common manifestation of LAD is gingivitis with periodontitis, which often leads to tooth loss and alveolar bone resorption and is thought to be related to excessive production of interleukin-17. Minor injuries to the skin may rapidly expand to form large, chronic ulcerations that can resemble "burnt out" pyoderma gangrenosum (Fig. 60.13). Poor wound healing also results in paper-thin, atrophic scars. A history of delayed separation of the umbilical stump represents a clue to the diagnosis.

Patients with LAD develop recurrent otitis media, pneumonia, and cutaneous infections caused by pyogenic bacteria. The latter often present as cellulitis and necrotic abscesses with relatively little production of purulent material, typically located in the perianal area or on the face. Life-threatening bacterial, fungal, or (less frequently) viral infections may also occur. More than three-quarters of patients with severe LAD-I (<1% of normal CD18 levels) die within the first 5 years of life, whereas approximately half of patients with moderate disease (1%–10% of normal CD18 levels) live to age 30 years[122].

Additional clinical manifestations of LAD-II include intellectual disability, microcephaly, hypotonia, short stature, and facial dysmorphism[123]. Patients with LAD-III often present with a bleeding tendency as well as variable osteopetrosis and hepatosplenomegaly. Dermal hematopoiesis with a "blueberry muffin" appearance secondary to myelodysplastic syndrome has been described in infants and children with LAD-III[125].



Fig. 60.13 Chronic ulcer in leukocyte adhesion deficiency type I. This 7-year-old boy was scratched by his sister, resulting in a large gaping wound that healed poorly. *Reprinted with permission from Torrelo A (ed). Schachner and Hansen's Pediatric Dermatology, 5th edn. London: Mosby, 2023.*

Pathology

Individuals with LAD have marked *peripheral blood neutrophilia* (5–20 times normal levels). Although cutaneous ulcerations may resemble pyoderma gangrenosum clinically, histologic examination reveals a relative *paucity of tissue neutrophils*. Flow cytometric analysis reveals markedly decreased leukocyte CD18 expression in individuals with LAD-I. Patients with LAD-II have the Bombay red blood cell type due to a lack of the H blood group antigen, and those with LAD-III have abnormal platelet aggregation due to defective activation of β_3-integrin and less often have anemia.

Differential Diagnosis

A mutation in the gene encoding the Rac2 GTPase, which has a role in phagocyte NADPH oxidase activation as well as integrin-dependent adhesion and neutrophil migration, can lead to clinical features similar to those of LAD, including delayed separation of the umbilical stump, poor wound healing, neutrophilia, and recurrent perirectal abscesses with an absence of pus (see Tables 60.10 & 60.13).

Treatment

Soft tissue infections in LAD patients require prolonged courses of antimicrobial therapy and, in some cases, surgical debridement. Meticulous dental hygiene is important in reducing the severity of the periodontitis. Granulocyte transfusions have potential benefit in LAD-I and -III, and oral administration of fucose may improve immune function in patients with LAD-II[123]. In LAD-I, healing of chronic oral and cutaneous ulcers following administration of IVIg or ustekinumab has been reported[126]. Hematopoietic stem cell transplantation represents the only definitive therapy for LAD, but it is limited by infectious complications and GVHD.

Two patients with severe LAD-I were treated without prior conditioning with an infusion of autologous hematopoietic stem cells that had been corrected *ex vivo* with a retroviral vector encoding CD18, but circulating $CD18^+$ cells persisted for <2 months[122]. However, canine LAD-I has been successfully treated with non-myeloablative conditioning followed by infusion of autologous hematopoietic stem cells transduced *ex vivo* by a CD18-expressing foamy virus vector, which has less potential for genotoxicity than a retroviral vector; this led to complete reversal of the LAD phenotype that was sustained for more than 4 years[127]. Preclinical studies have also investigated lentiviral-mediated gene therapy for LAD-I, with correction of the phenotype in a mouse model.

SEVERE COMBINED IMMUNODEFICIENCY AND OMENN SYNDROME

Synonyms: ■ Severe combined immunodeficiency (SCID) syndrome ■ Severe mixed immunodeficiency syndrome ■ Glanzmann–Riniker syndrome ■ Alymphocytosis ■ Thymic alymphoplasia

Key features

- Group of conditions characterized by defective function of both cell-mediated and humoral immunity
- Recurrent infections, diarrhea, and failure to thrive within the first 3–6 months of life
- Risk of GVHD, especially from unirradiated blood products
- Lack of lymphoid tissue

Introduction

Severe combined immunodeficiency (SCID) is a heterogeneous group of disorders that share clinical manifestations related to defective function of both cell-mediated and humoral immunity[128–130] (Table 60.16).

Epidemiology

SCID occurs in ~1 in 50 000 live births[131], and three-quarters of affected patients are boys. Approximately 40% of cases have X-linked recessive inheritance, primarily due to defects in the gene encoding the common γ (γ_c) chain of the IL-2 receptor, while the remainder are autosomal recessive. Other relatively frequent causes of autosomal recessive SCID include deficiencies of adenosine deaminase (ADA), the IL-7 receptor, or JAK3, each accounting for 5%–15% of cases[131].

Pathogenesis

Molecular defects that can lead to the SCID phenotype are presented in Fig. 60.10 and Table 60.16.

Clinical Features

Infants with SCID may present with widespread seborrheic-like dermatitis or morbilliform eruptions, often reflecting maternofetal GVHD. Cutaneous findings may also resemble lichen planus, acrodermatitis enteropathica, Langerhans cell histiocytosis, ichthyosiform erythroderma, and systemic sclerosis. Extensive eczematous dermatitis or exfoliative erythroderma, often associated with diffuse alopecia, may also occur in infants with *Omenn syndrome (RAG1* or *RAG2)*, which also features lymphadenopathy, hepatosplenomegaly, chronic diarrhea, peripheral eosinophilia, leukocytosis, and elevated IgE levels in the setting of SCID (see Tables 10.2 and 60.16). Of note, extensive cutaneous and extracutaneous granulomas (including destructive midfacial lesions) can develop in children with hypomorphic *RAG1* or *RAG2* mutations (Fig. 60.14).

Recurrent infections, chronic diarrhea, and failure to thrive are apparent within the first few months of life. Common early infections include mucocutaneous candidiasis, persistent viral gastroenteritis, and pneumonias due to bacteria, viruses, or *P. jirovecii*. Cutaneous infections are most often caused by *C. albicans*, *S. aureus*, and *Str. pyogenes*. Despite recurrent infections, patients with SCID typically lack tonsillar buds and palpable lymphoid tissue. SCID due to ADA deficiency is associated with an increased risk of developing dermatofibrosarcoma protuberans, often multiple and morpheaform, during the first two decades of life[130].

Laboratory Findings and Pathology

Nearly all patients with SCID have a profound T cell deficiency and a low absolute lymphocyte count. Patients are further classified by the results of fluorescent activated cell sorter (FACS) analysis into those with and without B lymphocytes and NK cells. The laboratory abnormalities observed in different types of SCID are noted in Table 60.16. Certain forms of SCID show distinctive radiographic manifestations; for example, patients with ADA deficiency demonstrate cupping and flaring of the costochondral junction on chest radiographs. Flow cytometric analysis of peripheral blood mononuclear cells with antibodies directed against a particular protein that is missing from the cell surface (e.g. γ_c, JAK3) as well as genetic testing (e.g. a multigene panel) can help to establish a specific diagnosis.

Maternal T cell engraftment accounting for ≥1% of peripheral blood leukocytes is present in approximately half of infants with SCID. The presence of maternal T cells is often asymptomatic, but a third of patients have mild changes such as cutaneous erythema and scale, a morbilliform eruption, elevated hepatic transaminases, and eosinophilia. Skin biopsy specimens show the histopathologic features of GVHD (see Ch. 52). Maternofetal GVHD is typically less severe than that resulting from postnatal inoculation of allogeneic lymphocytes, such as from unirradiated blood product transfusions, which can be fatal.

Histologically, the erythroderma of Omenn syndrome shares some features with GVHD such as necrotic keratinocytes but also has epidermal acanthosis, parakeratosis, and a dense dermal infiltrate composed primarily of T cells.

Differential Diagnosis

SCID must be differentiated from other immunodeficiency disorders, especially HIV infection. The latter is distinguished by normal to increased immunoglobulin levels, a relative decrease in $CD4^+$ T cells, and the presence of anti-HIV antibodies and HIV RNA.

Treatment

Without intervention, the outcome for SCID patients is death by 1 year of age. Early diagnosis of SCID is critical, preferably before the administration of live vaccines or unirradiated blood products. Newborn screening for SCID is performed in the US and several other countries. Infants with SCID should be kept in protective isolation and monitored for the development of infections, which should be treated aggressively; administration of IVIg and prophylaxis for *P. jirovecii* pneumonia are also recommended.

Hematopoietic stem cell transplantation (HSCT) during infancy is currently the first-line treatment for SCID. Because the patient's immune system is unable to reject the transplanted cells, myeloablative therapy is not required. The result is engraftment of donor T and NK cells, but usually not B cells. With an HLA-identical sibling donor, T cell reconstitution typically occurs within 3–4 months, GVHD is uncommon, and the long-term survival rate is >90%. Transplantation of haploidentical parental stem cells, which can be depleted of postthymic T cells to reduce the risk of GVHD, often requires some chemotherapeutic conditioning to facilitate engraftment and results in ≤80% survival. *In utero* injection of haploidentical $CD34^+$ cells has also been used to treat X-linked SCID. SCID patients often require IVIg replacement therapy for persistent B cell deficiency following HSCT, and T cell function may decline over time. Administration of virus-specific T cells from their stem cell donor or a third-party donor may be useful for the treatment and prevention of viral infections (e.g. with EBV or cytomegalovirus) in HSCT recipients with SCID[132].

Enzyme replacement via injection of polyethylene glycol-conjugated ADA can lead to improved immune function in children with ADA deficiency. Gene therapy has been successfully performed in more than 50 children with X-linked SCID or ADA deficiency via retroviral-mediated *ex vivo* gene transfer into $CD34^+$ cells[133,134]. Follow-up studies on 19 of these patients (4 months–4 years after treatment) showed

TYPES OF SEVERE COMBINED IMMUNODEFICIENCY (SCID)			
Disorder	**Gene**	**Protein function and specific clinical features**	**Cells**
Defects in cytokine receptors and their signaling			
X-linked SCID	*IL2RG*	Common γ chain (γ_c) of the receptors for IL-2, 4, 7, 9, 15, and 21	$T^-/B^+/NK^-$
JAK3 deficiency	*JAK3*	Tyrosine kinase with a role in signal transduction via the receptors for IL-2, 4, 7, 9, 15, and 21	$T^-/B^+/NK^-$
Interleukin-7 receptor deficiency	*IL7R*	α-chain of the IL-7 receptor; critical for development and differentiation of T cells; possible Omenn syndrome phenotype	$T^-/B^+/NK^-$
Increased apoptosis of lymphocytes ± other hematopoietic cells			
Defects in purine pathway enzymes that result in the build-up of toxic metabolites			
Adenosine deaminase (ADA) deficiency	*ADA*	Enzyme in the purine salvage pathway	$T^-/B^-/NK^-$
Purine nucleoside phosphorylase (PNP) deficiency	*PNP*	Enzyme in the purine salvage pathway (downstream of ADA)	$T^-/B^-/NK^-$
Defects disrupting mitochondrial energy production			
Reticular dysgenesis (aleukocytosis)	*AK2*	Adenylate kinase 2, a mitochondrial enzyme that regulates ADP levels in leukocytes; profound neutropenia and sensorineural deafness	$T^-/B^-/NK^-$
Defects disrupting actin polymerization			
Coronin 1A deficiency	*CORO1A*	Actin regulator expressed in T cell precursors; severe warts, molluscum contagiosum, and herpesvirus infections	$T^-/B^-/NK^+$
Defects in (pre-)T cell receptors (TCRs) ± B cell receptors (BCRs) and their signaling			
Omenn syndrome	*RAG1* and *RAG2*	Mediate V(D)J recombination of the genes that encode BCRs (immunoglobulins) and TCRs*; erythroderma, alopecia, LAN, HSM, diarrhea, eosinophilia, elevated IgE levels (see text)	$T^-/B^-/NK^+$
Artemis deficiency	*DCLRE1C (Artemis)*	Repairs the DNA double-stranded breaks that occur during V(D)J recombination and from ionizing radiation*; possible Omenn syndrome phenotype	$T^-/B^-/NK^+$
PRKDC deficiency	*PRKDC*	DNA-activated protein kinase catalytic subunit critical for V(D)J recombination*	$T^-/B^-/NK^+$
LIG4 syndrome	*LIG4*	Ligase component of the DNA non-homologous end-joining (NHEJ) machinery required for the repair of DNA double-stranded breaks*; photosensitivity, telangiectasias, bird-like facies, microcephaly	$T^-/B^-/NK^+$
NHEJ1 (Cernunnos) deficiency	*NHEJ1*	NHEJ factor required for the repair of DNA double-stranded breaks*; bird-like facies, microcephaly	$T^-/B^-/NK^+$
T cell receptor deficiencies	*CD3γ, CD3δ, CD3ε*, and *CD3ζ*	TCR-associated proteins required for cell surface expression of and signal transduction by the TCR; most severe with defective CD3δ	$T^-/B^-/NK^+$
	TRAC	TCR-α constant region; relatively mild immunodeficiency	
CD45 deficiency	*PTPRC*	Transmembrane tyrosine phosphatase with a role in TCR signaling	$T^-/B^+/NK^+$
ZAP70 deficiency	*ZAP70*	Tyrosine kinase with a role in TCR signaling	$CD4^+CD8^+/B^+/NK^+$
CD8 deficiency†	*CD8A*	Co-receptor for TCRs recognizing MHC class I-associated peptides; role in TCR signaling	$CD4^+CD8^+/B^+/NK^+$
Calcium channel deficiency	*ORAI1*	Pore-forming subunit of calcium channel with a role in TCR signaling; hypohidrotic ectodermal dysplasia and myopathy	$T^+/B^+/NK^+$
	STIM1	Calcium channel component with a role in TCR signaling; LAN, HSM, autoimmune cytopenias, dental dysplasia, myopathy	$T^+/B^+/NK^+$
Antigen presentation defects (bare lymphocyte syndromes)			
MHC class II deficiency	*CIITA, RFXANK, RFX5, and RFXAP*	Transactivate the MHC class II promoter; MHC class II molecules are required for the positive selection of $CD4^+$ T cells in the thymus as well as for antigen presentation to $CD4^+$T cells	$T^+/B^+/NK^+$, but fewer and dysfunctional $CD4^+$ T cells
MHC class I deficiency†	*TAP1, TAP2, TAPBP, B2M*	Transporter associated with antigen processing (TAP) and the TAP binding protein (tapasin); translocate peptides from the cytosol to MHC class I molecules in the ER; cutaneous granulomas in TAP deficiency	$CD4^+CD8^-/B^+/NK^+$
Defective thymic development			
Winged helix nude (forkhead box N1) deficiency	*WHN (FOXN1)*	Transcription factor important to thymic development; complete congenital alopecia and nail dystrophy (human equivalent of "nude" mice)	$T^-/B^+/NK^+$

*Patients have increased sensitivity to ionizing radiation.
†Not true SCID

Table 60.16 Types of severe combined immunodeficiency (SCID). "Leaky SCID" refers to less severe deficits in T cell number and function due to hypomorphic (milder) mutations in SCID-associated genes. Cartilage–hair hypoplasia (see text) also occasionally presents as SCID with an Omenn-like phenotype. Two most common forms of SCID, accounting for approximately two-thirds of cases, are shaded. B2M, β2-microglobulin; *DCLRE1C*, DNA cross-link repair protein 1C; ER, endoplasmic reticulum; HSM, hepatosplenomegaly; LAN, lymphadenopathy; MHC, major histocompatibility complex; V(D)J, variable/diversity/joining.



Fig. 60.14 Non-infectious ulcerated granulomatous plaque in an adolescent with hypomorphic RAG1 deficiency. *Courtesy Edward Cowen, MD.*

that transcriptional start sites and coding regions of active genes were the preferred retroviral integration sites in circulating T cells as well as in pre-infusion transduced CD34$^+$ cells; in the former cells, ~25% of all integrations were clustered at common sites, suggesting *in vivo* selection of transduced cells with a higher capacity for engraftment, survival, and proliferation[135]. Although T and NK cell function was restored, at least five patients with X-linked SCID have developed T cell leukemias (2–6 years after treatment) related to activation of proto-oncogenes such as *LMO2* by the retroviral vector[136]. These complications raised serious concerns, which led to protocol modifications and investigation of alternative approaches such as lentiviral vectors, *in situ* gene transfer, and gene editing techniques (e.g. CRISPR/Cas)[137]. More recently, gene therapy with self-inactivating lentivirus vectors following low-dose busulfan conditioning has been safely and successfully utilized in patients with X-linked SCID and ADA deficiency, resulting in functional immune reconstitution and high survival rates[138,139].

Prenatal diagnosis of SCID can be performed by fetal DNA analysis in families with a known genetic defect.

WISKOTT–ALDRICH SYNDROME

Synonyms: ■ Wiskott–Aldrich–Huntley syndrome ■ Eczema–thrombocytopenia–immunodeficiency syndrome

Key features

- X-linked recessive immunodeficiency disorder characterized by the classic triad of atopic-like dermatitis, a bleeding tendency due to microthrombocytopenia, and recurrent sinopulmonary infections
- Onset of bacterial infections is early in life, with later development of viral and *P. jirovecii* infections
- Patients are also at risk of autoimmune diseases and lymphomas

Introduction

Wiskott–Aldrich syndrome (WAS) is characterized by recurrent pyogenic infections, bleeding due to thrombocytopenia and platelet dysfunction, and recalcitrant eczematous dermatitis[140,141]. The full triad develops in a minority of patients, with platelet abnormalities representing the most constant feature.

Epidemiology

Most patients with this X-linked recessive immunodeficiency are boys, but girls are occasionally affected in the setting of non-random X-chromosome inactivation or homozygosity for a mild mutation. WAS has an incidence of ~1 in 250 000 live male births in European populations; it is less common in Black individuals and Asians.

Pathogenesis

WAS is caused by loss-of-function mutations in *WASP*, which is constitutively expressed in hematopoietic cell lineages. The WAS protein (WASP) controls the assembly of actin filaments, which are required for microvesicle and pro-platelet formation as well as T cell activation and polarization toward antigen-presenting cells[142]. Loss-of-function *WASP* mutations also cause isolated X-linked recessive thrombocytopenia, while gain-of-function *WASP* mutations can lead to X-linked congenital neutropenia.

Abnormal T cell function is central to the immunologic defect in WAS, with resultant diminution of both cell-mediated and humoral responses[142]. Although the number of T cells in WAS patients has been observed to decrease with age, affected infants also have reduced numbers of T cells (especially naive T cells) and B cells[143]. This suggests that impaired lymphocyte maturation and output from the thymus are central to the immunodeficiency of WAS. WASP function is required for the activation of regulatory T cells, helping to explain the autoimmune manifestations of WAS. Defects in B cell migration, differentiation, and organization into germinal centers have roles in the impaired humoral immunity of WAS, with reduced expression of the CD21 and CD35 complement receptors involved in antigen capture and presentation also potentially contributing to autoimmunity[143,144]. Although NK cells are not decreased in number, their cytolytic activity is abnormal in WAS. Lastly, small, structurally abnormal platelets with a reduced half-life (due in part to splenic destruction) account for the thrombocytopenia of WAS[142].

Clinical Features

Because thrombocytopenia and platelet dysfunction are present from birth, the first clinical signs of WAS are usually petechiae and ecchymoses of the skin and oral mucosa. Spontaneous bleeding from the oral cavity, epistaxis, hematemesis, melena, and hematuria are commonly observed.

The dermatitis of WAS typically develops during the first few months of life, and it fulfills the diagnostic criteria for atopic dermatitis (see Table 12.1). The face, scalp, and flexural areas are most severely affected, although patients often have widespread involvement with progressive lichenification. Exfoliative dermatitis occasionally develops. Excoriated areas frequently have serosanguineous crusts and petechiae (Fig. 60.15). Secondary bacterial infections are common, as are eczema herpeticum and molluscum contagiosum.

Recurrent bacterial infections begin during the first 3 months of life, coincident with diminishing levels of placentally transmitted maternal antibodies. These infections include otitis externa and media, pneumonia, sinusitis, conjunctivitis, furunculosis, meningitis, and septicemia. Encapsulated bacteria such as *Str. pneumoniae, H. influenza*, and *Neisseria meningitidis* are the predominant organisms. With advancing age, there is increased susceptibility to infections with viruses (e.g. herpes simplex) and *P. jirovecii*.

Most children with WAS develop at least one autoimmune disease, most commonly cutaneous small vessel vasculitis (often associated with painful edema), autoimmune cytopenias, arthritis, inflammatory bowel disease, and cerebral vasculitis[145]. IgE-mediated conditions such as urticaria, food allergies, and asthma also occur with increased frequency. Lymphomas develop at a mean age of 10 years in ~15% of WAS patients who do not undergo successful HSCT, especially those with a history of autoimmune disease. Non-Hodgkin lymphomas predominate, most often diffuse large B cell types with extranodal and brain involvement as in AIDS-related lymphomas.

The median survival for WAS patients who do not receive a HSCT is ~15 years, with infection (50%), bleeding (25%), and malignancy (25%) representing the most common causes of death.



Fig. 60.15 Severe atopic dermatitis in an infant with Wiskott–Aldrich syndrome. This young boy was successfully treated with bone marrow transplantation, and his dermatitis virtually cleared owing to the T cell engraftment.
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Laboratory Findings and Pathology

The most frequent laboratory abnormalities in WAS are persistent thrombocytopenia (platelet counts <70 000/mm^3) and low mean platelet volume (<5.0 fl). WAS patients may also have lymphopenia and eosinophilia. Serum IgM and IgG_2 levels are typically low, while IgA, IgE, and IgD levels tend to be elevated. Antibody responses to polysaccharide antigens are markedly diminished. Delayed-type hypersensitivity skin test reactions are usually absent, and responses to mitogens are often depressed, especially in older patients. Monocyte and neutrophil chemotaxis may also be defective.

Assessment of WASP expression in peripheral blood mononuclear cells by flow cytometry-based assays or immunoblot analysis can be performed in patients suspected to have WAS prior to mutational analysis. Patients with a complete lack of WASP expression in circulating cells tend to have a more severe phenotype.

Differential Diagnosis

Although several other immunodeficiency syndromes feature eczematous dermatitis together with susceptibility to infection (see HIES Differential Diagnosis), WAS can usually be differentiated by the bleeding tendency and laboratory evidence of microthrombocytopenia. Of note, deficiency of the actin-related protein 2/3 complex subunit 1b (ARPC1B), which interacts with WASP, presents with overlapping features including eczematous dermatitis, thrombocytopenia (with variably sized platelets), recurrent infections, autoimmune manifestations, vasculitis, and colitis[146].

An approach to the differential diagnosis of infantile erythroderma is presented in Fig. 10.11.

Treatment

HSCT is the treatment of choice for patients with WAS. Full engraftment results in normal platelet numbers and function, restoration of immunologic status, and clearance of the dermatitis. Affected children who receive a HSCT have an overall survival rate of >90%, with lower rates in those transplanted at >5 years of age with an unrelated donor[147,148]. Gene therapy using lentivirally transduced, WASP-reconstituted, autologous $CD34^+$ cells can lead to sustained resolution of the dermatitis and susceptibility to infection as well as improvement in the bleeding diathesis and autoimmunity, without the high risk of leukemic transformation that was observed with utilization of a retroviral vector[149–151].

Prophylactic use of antibiotics can decrease the risk of fatal infections in WAS patients[152]. IVIg therapy also helps to prevent infections and may potentially improve the dermatitis. Topical corticosteroids remain a mainstay of treatment for the latter. Although splenectomy may reduce bleeding complications in patients with recurrent severe hemorrhage, it further increases the risk of infections with encapsulated organisms. Platelet transfusions may be given prior to surgery and in the setting of life-threatening hemorrhage. Systemic corticosteroids, rituximab, and other immunosuppressive agents may be utilized for autoimmune disorders.

Genetic counseling is important for the sisters and other female relatives of WAS patients. Female carriers may be detected by genetic analysis or detection of selective inactivation of the abnormal X chromosome in lymphocytes and platelets. Prenatal diagnosis can be performed by mutational analysis.

Additional figures available in our eBook (see inside front cover for access code).

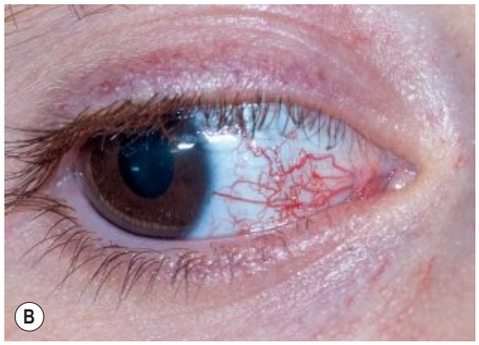
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eFig. 60.1 Ataxia–telangiectasia. Linear telangiectasias on the bulbar conjunctivae of a young woman (**A**) and girl (**B**). *Courtesy Jean L. Bolognia, MD.*



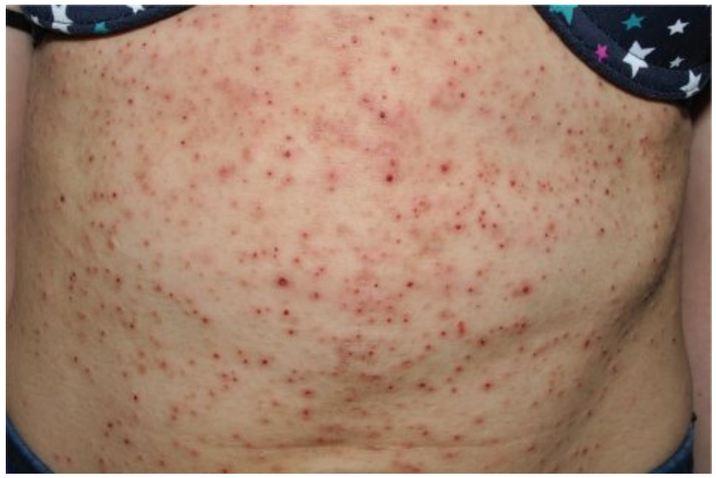
eFig. 60.2 Alopecia universalis in a patient with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome. *Courtesy Edward Cowen, MD.*



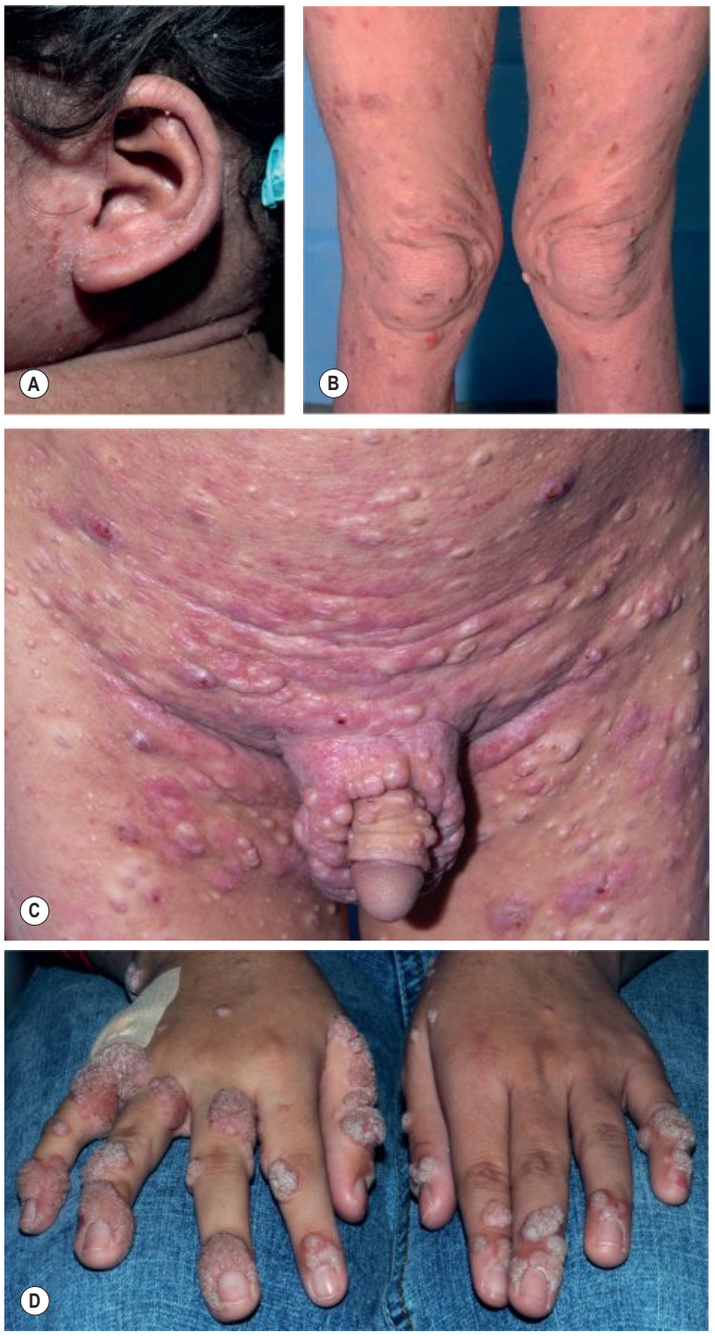
eFig. 60.3 Tinea corporis and tinea unguium in a patient with increased STAT1 signaling. The latter is due to a gain-of-function mutation in *STAT1*. *Courtesy Edward Cowen, MD.*



eFig. 60.4 Lymphedema in a patient with GATA2 deficiency. *Courtesy Edward Cowen, MD.*



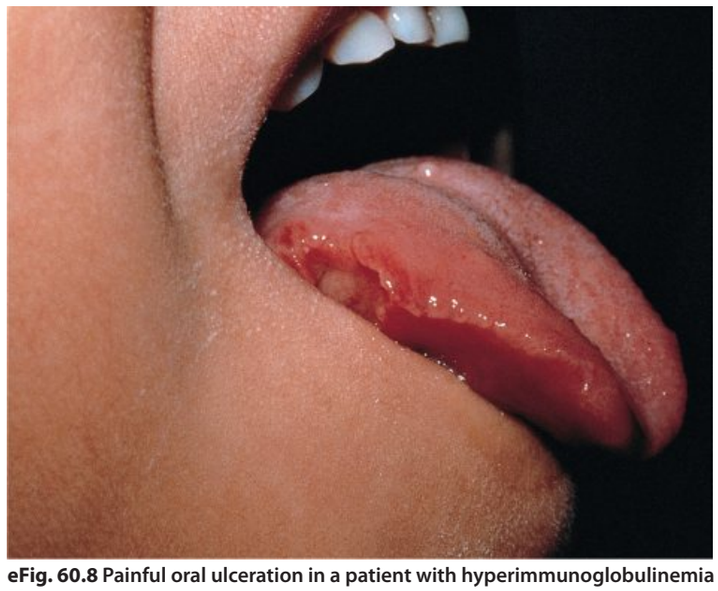
eFig. 60.5 Papulovesicular eruption in a patient with STAT3-hyperimmunoglobulin E syndrome. Histologically, eosinophilic pustulosis was observed. *Courtesy L. Noguera-Morel, MD.*



eFig. 60.6 DOCK8 deficiency. A Widespread eczematous dermatitis. **B** Eczematous dermatitis admixed with molluscum contagiosum. **C** Extensive nodular molluscum contagiosum in a child. **D** Numerous coalescing warts on the hands. *A–C, Courtesy Edward Cowen, MD.*



eFig. 60.7 Grouped ulcerations due to herpes simplex viral infection in a patient with DOCK8 deficiency. *Courtesy Edward Cowen, MD.*



eFig. 60.8 Painful oral ulceration in a patient with hyperimmunoglobulinemia M syndrome. *Reprinted with permission from Torrelo A (ed). Schachner and Hansen's Pediatric Dermatology, 5th edn. London: Mosby, 2023.*



eFig. 60.9 Hyper IgM syndrome. A Confluent verrucae on the hands. **B** The verrucae on the trunk and arms have a pityriasis (tinea) versicolor-like appearance. *Courtesy Jonathan S. Leventhal, MD.*



eFig. 60.10 Widespread eczematous dermatitis in an infant with transient hypogammaglobulinemia. *Courtesy Antonio Torrelo, MD.*

61 Neurofibromatosis and Tuberous Sclerosis Complex

Hensin Tsao and Su Luo

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INTRODUCTION

Neurofibromatosis (NF) and tuberous sclerosis complex (TSC) are neurocutaneous disorders, or phakomatoses. They are characterized by cutaneous lesions as well as peripheral and/or central nervous system neoplasms. Like most hereditary cancer syndromes, NF and TSC are autosomal dominant in inheritance. Despite a high penetrance for both diseases, new cases of NF type 1 (NF1) and TSC frequently represent *de novo* mutations. The pleiotropic nature of these two neurocutaneous syndromes has led to complex schemes for their classification and diagnosis. Dermatologists are frequently asked to participate in the clinical diagnosis of patients with NF1 and TSC due to the early appearance of cutaneous, especially pigmentary, findings. Advances in the molecular characterization of these disorders have revealed related, but distinct, pathogenic mechanisms.

In 1982, Riccardi proposed a classification scheme for patients with NF that included seven subtypes. Elucidation of the molecular bases of NF1, NF2, mosaic/segmental NF1 (formerly known as NF5), and "NF1-like" syndromes has further refined the categorization of patients. Among these conditions, NF1 has the most well-characterized and diagnostic skin findings and is the main focus in this chapter.

NEUROFIBROMATOSIS TYPE 1

Synonym: ■ von Recklinghausen disease

Key features

- NF1 is an autosomal dominant disorder with an incidence of ~1 in 2000–3000 births
- Characteristic clinical features include café-au-lait macules, neurofibromas, freckling in the axillae and groin, Lisch nodules, and bony defects. Nevus anemicus represents another common early finding.
- Patients with NF1 have an increased risk of developing juvenile xanthogranulomas, juvenile myelomonocytic leukemia and a variety of extracutaneous tumors, including optic pathway gliomas, malignant peripheral nerve sheath tumors, pheochromocytomas, and other CNS tumors
- Up to 50% of patients with NF1 have a new spontaneous mutation rather than an inherited mutation
- The protein product of *NF1* (neurofibromin) is involved in the negative regulation of RAS signaling
- Other well-characterized forms of NF include mosaic/segmental NF1 and NF2 (vestibular schwannomas)

History

Individuals with NF1 have been described throughout history[1,2]. In 1882, von Recklinghausen[3] provided the first in-depth report of the clinical and pathologic nature of the neurofibromas. Fifty years later, the Viennese ophthalmologist Lisch described the iris nodules that were more recently recognized as an important criterion in the clinical diagnosis of NF. In the mid twentieth century, Crowe, Schull, and Neel compiled a landmark monograph with a comprehensive description of the manifestations of this disease[4].

Epidemiology

NF1 occurs worldwide. Its incidence is ~1 in 2000 to 3000 births[5–7].

Pathogenesis

NF1 is inherited in an autosomal dominant manner. Most large series have found that 30%–50% of patients have no affected relatives and thus likely harbor new spontaneous mutations[4,8,9]. There is also the possibility of germline mosaicism in a parent, especially when two siblings develop NF1 in the absence of a prior family history. The penetrance of NF1 approaches 100% in carefully examined adults[10], but expressivity is variable. A wide range of clinical findings and complications can develop among individuals with the same underlying mutation. The specific *NF1* mutation is therefore not the only factor that determines phenotype.

In 1987, an international consortium found evidence of linkage to the pericentromeric region of chromosome 17 in families with NF1[11]. Subsequent descriptions of two NF1 patients with balanced translocations involving the long arm of chromosome 17 (17q11.2) further refined the position of the *NF1* locus[12,13]. The localization data derived from these studies led to the cloning of the *NF1* gene[14–16].

NF1 encodes neurofibromin, a 327 kDa protein composed of 2818 amino acids, and consists of at least 59 exons (Fig. 61.1)[17]. Over 80% of NF1 patients have a mutation that predicts truncation of the neurofibromin protein, and ~5% of patients have a large deletion ("microdeletion") that encompasses the entire *NF1* gene plus variable flanking genes[18]. Although there is usually no clear genotype–phenotype correlation, exceptions include: (1) the single amino acid deletion p.Met922del and a missense mutation affecting p.Met1149 or p.Arg1809 are all associated with an absence of neurofibromas and the latter two with a Noonan syndrome-like phenotype[19–21]; (2) p.Arg 1276 or p.Lys1423 are associated with cardiovascular abnormalities, a Noonan syndrome-like phenotype, and (for the former) symptomatic spinal neurofibromas[21]; (3) missense mutations in *NF1* codons 844–848 result in a higher likelihood of major plexiform neurofibromas, symptomatic spinal neurofibromas, optic gliomas, skeletal abnormalities, and malignancies[22]; and (4) a recurrent 1.4-mega-base pair deletion ("type 1 microdeletion") results in a more severe phenotype[23]. The latter includes an earlier onset and larger number of neurofibromas, an increased risk of malignant peripheral nerve sheath tumors, intellectual disability, facial dysmorphism, overgrowth, connective tissue dysplasia (e.g. hyperextensible skin, joint laxity), and cardiac defects[23].

Sequence similarities between a central 300–400 amino acid domain within neurofibromin and *G*TPase-*a*ctivating *p*roteins (GAPs) led to recognition of neurofibromin's role in the negative regulation of the RAS–*m*itogen-*a*ctivated *p*rotein *k*inase (MAPK) pathway that promotes cell survival and proliferation (see Fig. 61.1 and Fig. 55.4)[24]. Like all G proteins, RAS activity requires GTP. Neurofibromin and other GAPs accelerate the hydrolysis of GTP to GDP, thereby terminating the RAS signal and functioning as tumor suppressor proteins. Neurofibromin also associates with microtubules[25], although the consequences remain unclear.

As observed in other autosomal dominant genodermatoses (e.g. basal cell nevus syndrome) caused by a defective tumor suppressor gene, a *somatic* "second-hit" mutation inactivating the remaining allele of the gene (i.e. causing loss of heterozygosity [LOH]) can be found within skin lesions of NF1. Biallelic *NF1* inactivation has been identified in

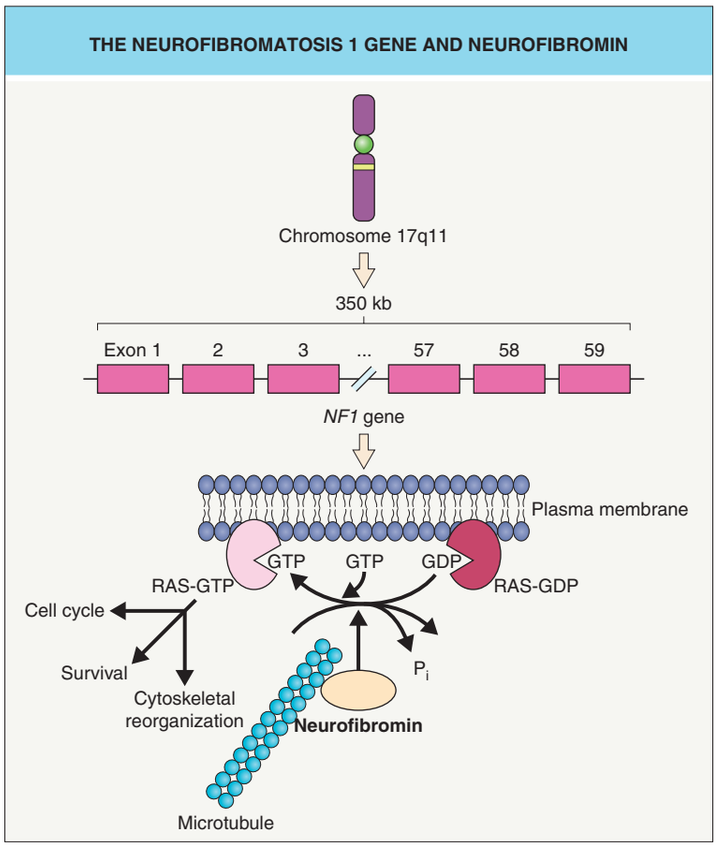


Fig. 61.1 The neurofibromatosis 1 gene and neurofibromin. *NF1* is located on chromosome 17q11.2 and encodes the *G*TPase-*a*ctivating *p*rotein (GAP)-related protein neurofibromin. One of the functions of neurofibromin is to negatively regulate the activity of RAS proteins. RAS, like other related G proteins, is dependent upon GTP binding for its full activity, and GAP proteins shut off the signal by accelerating the hydrolysis of GTP to GDP.

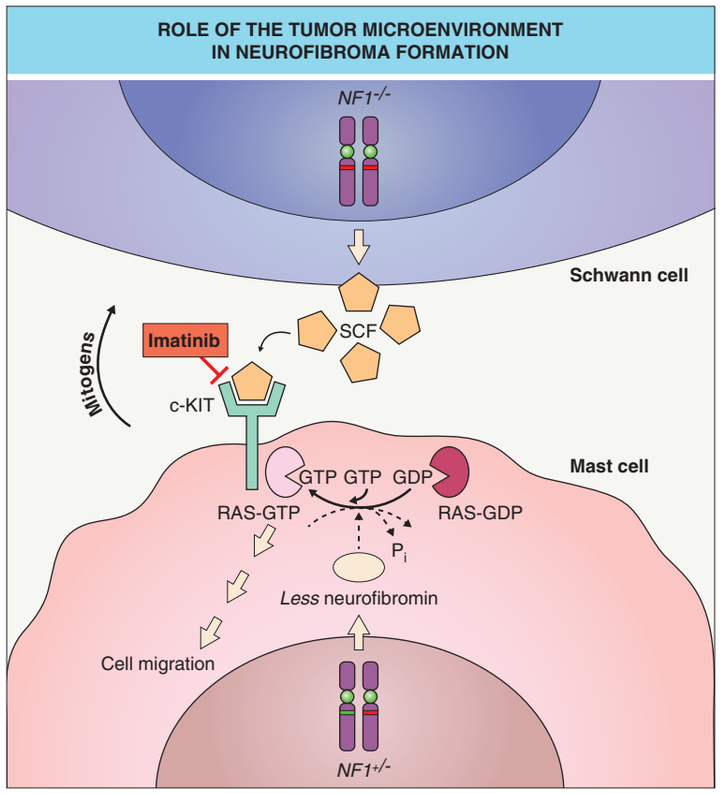


Fig. 61.2 Role of the tumor microenvironment in neurofibroma formation. *NF1* nullizygous (*NF1*$^{-/-}$) Schwann cells oversecrete stem cell factor (SCF), which binds the KIT receptor on *NF1* heterozygous (*NF1*$^{+/-}$) mast cells. This leads to mast cell recruitment and their activation to produce growth factors that stimulate neurofibroma development. Inhibition of KIT signaling by imatinib mesylate can block neurofibroma formation and progression.

Schwann cells from neurofibromas as well as melanocytes from café-au-lait macules in patients with NF1[26,27]. In a mouse model, *Nf1* nullizygosity (*Nf1*$^{-/-}$) in Schwann cells was shown to be necessary, but not sufficient, for neurofibroma formation[28]; however, plexiform neurofibromas did arise from *Nf1*$^{-/-}$ Schwann cells when the microenvironment included *Nf1*$^{+/-}$ (rather than wild-type) mast cells[29]. The latter cells appear early in neurofibroma development and are hypermotile in response to the KIT ligand (stem cell factor), which is oversecreted by *Nf1*$^{-/-}$ Schwann cells. Once recruited, mast cells produce growth factors that likely promote neurofibroma tumorigenesis (Fig. 61.2). Of note, genetic or pharmacologic attenuation of KIT signaling in *Nf1*$^{+/-}$ mast cells has been found to diminish neurofibroma initiation and progression (see Management section below).

Clinical Features

The clinical features of NF1 (Table 61.1) are myriad and vary in frequency[4,8,9,30–40]. Almost every organ system has been found to be involved in NF1, which can lead to a wide range of morbidities and mortality[7]. The cutaneous manifestations of NF1 represent particularly important clinical features that have a central role in its diagnosis[41].

Oculocutaneous manifestations

Café-au-lait macules (CALMs) are tan to dark brown (depending on the degree of constitutive pigmentation), uniformly pigmented macules and patches that are randomly distributed on the body, with the exception of the scalp, palms, and soles. The CALMs of NF1 are sharply demarcated with regular borders and often have an oval shape (Fig. 61.3); the diameter can vary from a few millimeters to >4 cm. CALMs may not be apparent at birth and frequently become more noticeable during the first year of life; fading of these lesions during later adulthood has also been described[42]. When located within areas of dermal melanocytosis, CALMs may be surrounded by a rim of normally pigmented skin (see Ch. 112). Larger CALMs, especially those with associated hypertrichosis, should be palpated to exclude the possibility of an underlying plexiform neurofibroma (see below).

Crowe et al.[4] reported that 10% of the normal population has one to five CALMs, and Burwell et al.[43] found that 26% of 732 White schoolchildren had at least one CALM >1 cm in diameter. In the latter study, ≥6 CALMs were found in only three children (0.4%) and they were siblings with a parent who had NF1. For the clinical diagnosis of NF1, a minimum of six CALMs is required to meet the specificity of this criterion (Table 61.2 and 61.3). To avoid confusion with lentigines, CALMs must be >5 mm in prepubertal individuals and >15 mm in postpubertal individuals in order to satisfy this diagnostic criterion for NF1.

"Freckling" in the axillae and groin in NF1 patients was first noted by Crowe[4] and is referred to as "Crowe sign" (see Fig. 61.3B). Numerous 1–3 mm brown macules (more akin to lentigines than ephelides) typically populate these intertriginous zones, the neck, and occasionally the majority of the skin surface (see Fig. 61.3C,D & 61.4). Involvement of the axillae is most common, occurring in ~80% of NF1 patients[44,45]. The lesions usually arise by 4–6 years of age, following the emergence of CALMs but preceding the development of neurofibromas. As a result, intertriginous "freckling" is a useful clinical sign in the evaluation of a young child with multiple CALMs[46].

In its fullest expression, NF1 can manifest with thousands of neurofibromas in an affected individual, hence the appellation *neurofibromatosis* (Fig. 61.4). Several variants of neurofibromas are observed in NF1. Most commonly, proliferations of spindle cells occur within the dermis, leading to *cutaneous* neurofibromas (CNFs). CNFs are skin-colored to pink, tan, or brown papulonodules that are soft or slightly rubbery in texture and can range from a few millimeters to several centimeters in diameter. While fully formed CNFs are often dome-shaped or pedunculated, early lesions may be barely elevated. They invaginate easily with gentle pressure, exhibiting the pathognomonic "buttonhole" sign. Although usually asymptomatic, lesions may become pruritic or, occasionally, irritated. CNFs appear as early as 4–5 years of age but

MAJOR CLINICAL FEATURES OF NEUROFIBROMATOSIS TYPE 1
Cutaneous
• Neurofibromas (60%–90%) • Café-au-lait macules (>90%) • Axillary and/or inguinal freckling (~80%) • Plexiform neurofibroma (25%; up to 50% with detection via whole-body MRI) • Nevus anemicus (30%–50%) • Juvenile xanthogranuloma (15%–35% in first 3 years of life)
Ocular
• Lisch nodules (~90% by 20 years of age) • Choroidal abnormalities (>80% of adults, 60%–70% of children) • Neovascular glaucoma, retinal vasoproliferative tumors
Skeletal
Cranial
• Macrocephaly (20%–50%) • Hypertelorism (25%) • Sphenoid wing dysplasia (<5%)
Spinal
• Scoliosis (5%–10%) • Spina bifida
Limbs
• Dysplasia of long bone cortex (5%), pseudarthrosis (2%)
Other
• Generalized osteopenia (~50%), osteoporosis (~20%) • Short stature (~30% <3rd percentile) • Pectus deformity (30%–50%)
Tumors
• Optic pathway glioma (15%–20% of children) (± precocious puberty) • Malignant peripheral nerve sheath tumors (3%–15%) • Pheochromocytoma (~1%) • Juvenile myelomonocytic leukemia • CNS tumors other than optic pathway gliomas (~5%) • Rhabdomyosarcoma, especially of the genitourinary tract • Duodenal carcinoid • Somatostatinoma • Parathyroid adenoma • Gastrointestinal stromal tumors (GIST) • Breast cancer (~5- and ~10-fold increased risk in women <50 and <40 years of age, respectively)
Neurologic
• T2 hyperintensities on brain MRI (50%–75%) • Learning difficulties (30%–50%) • Seizures (~5%) • Intellectual impairment (severe in <5%) • Aqueductal stenosis and hydrocephalus (~2%)
Cardiovascular
• Hypertension (~30%): essential > renal artery stenosis or pheochromocytoma • Pulmonic stenosis (~1%) • Renal artery stenosis (~2%) • Cerebrovascular anomalies (2%–5%), including vascular stenoses and aneurysms

Table 61.1 Major clinical features of neurofibromatosis type 1.

more typically develop around puberty, with occasional acceleration of growth during pregnancy.

Subcutaneous neurofibromas (SNFs) occur deeper in the dermis and subcutis, tending to be firmer and less well-circumscribed than CNFs. Nearly one-fifth of NF1 patients have at least one SNF[44], and one-quarter of these individuals develop tumor-related local complications. Less common cutaneous presentations of neurofibromas in patients with NF1 include: (1) *blue–red macules* due to thick-walled blood vessels as well as neurofibromatous tissue within the papillary dermis (Fig. 61.5); and (2) *pseudo-atrophic macules* due to replacement of collagen in the reticular dermis with neurofibromatous tissue[47].

Plexiform neurofibromas (PNFs; Fig. 61.6) may track along nerves to create tender, firm nodules or masses in the subcutaneous tissue with a "bag of worms" consistency upon palpation, or they can infiltrate diffusely to involve various layers of the skin, fascia, muscle, or even internal structures. Approximately 25% of NF1 patients have clinically apparent PNFs. Larger lesions may cause soft tissue and bony hypertrophy, and massive distortion of the head and neck or extremities occasionally develops. Impingement upon nerves can lead to neurologic deficits, and (peri)orbital PNFs may result in visual loss as well as facial deformity[48].

Unlike other neurofibromas, PNFs are probably all congenital in origin. Superficial and/or diffuse lesions usually become clinically apparent by the age of 4 or 5 years[30], while deep/internal nodular lesions may remain undetected even in adulthood unless full-body magnetic resonance imaging (MRI) is performed[49]. Older children without evidence of soft tissue overgrowth related to a PNF are unlikely to develop this finding later in life. Both hyperpigmentation and hypertrichosis can overlie PNFs[50], sometimes leading to the misdiagnosis of congenital melanocytic nevus (see Fig. 61.6).

The transformation of PNFs into malignant peripheral nerve sheath tumors (MPNSTs, also known as "neurofibrosarcomas") occurs in 8%–15% of patients with NF1[9,44,51], with a peak incidence in young adults. The onset of rapid growth, increased firmness, or persistent pain within an established PNF or the development of a new neurologic deficit may herald malignant degeneration (Table 61.4; see Management section). MPNSTs can be very aggressive and are often fatal[52]. As many as 15%–35% of children with NF1 develop one or more juvenile xanthogranulomas (JXGs) during the first 2–3 years of life, making these lesions a potential early sign of NF1 when they coexist with multiple CALMs[53–55]. Young children with NF1 also have a 200- to 500-fold greater risk of developing juvenile myelomonocytic leukemia (JMML; incidence 1/2000–1/5000) than does the general pediatric population. Although a "triple association" between NF1, JMML, and JXG has been described[56], the magnitude of additional risk of JMML in children with NF1 plus JXGs compared to NF1 alone remains to be determined. Neurofibromin is known to regulate the proliferation of myeloid cells, but the exact etiopathogenesis of the "triple association" remains unclear.

Vascular anomalies that have been recognized as manifestations of NF1 include nevus anemicus and glomus tumors[54,57,58]. In two prospective studies, a nevus anemicus was identified in a total of 55% (92/166) of children and 36% (19/53) of adults with NF1, compared to only 2% (6/302) of age- and sex-matched controls[57,58]. These lesions favor the trunk, especially the mid chest, and become more evident after rubbing the skin. Because nevus anemicus is prevalent in NF1 patients and apparent by early childhood, its use as a diagnostic criterion has been proposed but not yet adopted[54,57,58].

Biallelic inactivation of *NF1* has been documented within glomus tumors in NF1 patients[59]. The tumors are often multiple and develop on the fingers > toes; like their sporadic counterpart, they can present with paroxysmal pain and sensitivity to cold (see Ch. 114). Focal swelling, ill-defined reddish discoloration (often of the nail bed), and nail dystrophy may be observed.

Pigmented iris hamartomas, or Lisch nodules, begin to develop at about 3 years of age and are found in ~90% of NF1 patients by 20 years of age[36,44,60,61]. These 1–2 mm, dome-shaped, yellow–brown papules are best seen on slit-lamp examination (Fig. 61.7). Lisch nodules rarely lead to symptoms or complications. Asymptomatic choroidal nodules are also present in 80%–100% of adults and 60%–70% of children with NF1, and this finding has been added to the recently published revised diagnostic criteria[62]. However, the near-infrared reflectance imaging required for detection of these lesions may be technically challenging in younger children[41].

In mosaic (segmental) NF1 (formerly known as NF5), CALMs, "freckling", and/or neurofibromas are present in mosaic distribution patterns such as blocks with midline demarcation, often with relative hyperpigmentation in the background of the affected segment[63–65] (Fig. 61.8). This form of NF1 results from a postzygotic *NF1* mutation, and up to 30% of patients also have extracutaneous manifestations of NF1[63]. If the mutation involves the gonads (germline mosaicism) as well as the skin, there is a chance of full-blown NF1 in the patient's offspring.



Fig. 61.3 Café-au-lait macules and "freckling". Oval-shaped, light- to medium-brown patches with regular borders and uniform pigmentation (**A**–**C**). Numerous 1–3 mm lentigines are most commonly found in the axillae (Crowe's sign) (**B**) but can also develop in other locations such as the chest (**C**) and perioral region (**D**). *A–D, Courtesy Julie V. Schaffer, MD.*

REVISED DIAGNOSTIC CRITERIA FOR NEUROFIBROMATOSIS TYPE 1 (NF1) AND MOSAIC NF1
Diagnostic criteria for NF1
Requires **two or more** of the following in an individual ***without a parent diagnosed with NF1*** and **one or more** of the following in an individual ***with a parent diagnosed with NF1***: • Six or more café-au-lait macules >5 mm in prepubertal individuals and >15 mm in postpubertal individuals* • "Freckling" in the axillary or inguinal region* • Two or more neurofibromas of any type *or* one plexiform neurofibroma • Optic pathway glioma • Two or more Lisch nodules (iris hamartomas) or two or more choroidal abnormalities† • A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudoarthrosis of a long bone • A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue (e.g. white blood cells)
Diagnostic criteria for mosaic NF1
Requires any of the following in an individual ***without a parent diagnosed with NF1***: • A heterozygous pathogenic *NF1* variant with a variant allele fraction of significantly <50% in apparently normal tissue (e.g. white blood cells) **AND** one of the other NF1 criteria above • An identical heterozygous pathogenic *NF1* variant in two anatomically independent affected tissues, in the absence of a pathogenic *NF1* variant in unaffected tissue • A clearly segmental distribution of café-au-lait macules or cutaneous neurofibromas **AND** *either* another NF1 criterion‡ *or* offspring diagnosed with NF1 • One of the *clinical* NF1 criteria above *other than* café-au-lait macules **AND** offspring diagnosed with NF1
*If only café-au-lait macules and freckling are present, at least one should be bilateral; in this scenario, the diagnosis is most likely NF1 but may rarely be another condition such as Legius syndrome. †Defined as bright, patchy nodules imaged by optical coherence tomography/near-infrared reflectance imaging. ‡If only café-au-lait macules and freckling are present, the diagnosis is most likely mosaic NF1 but may rarely be mosaic Legius syndrome or constitutional mismatch repair deficiency syndrome (see Table 61.3).

Table 61.2 Revised diagnostic criteria for neurofibromatosis type 1 (NF1) and mosaic NF1.

DISORDERS ASSOCIATED WITH MULTIPLE CAFÉ-AU-LAIT MACULES	
Disorder	**Notes**
Neurofibromatosis and related disorders	
Neurofibromatosis type 1 (NF1)	AD; six or more CALMs in >90% of patients; mutations in *NF1* gene; see text
Neurofibromatosis type 2	AD; six or more CALMs in minority of patients; mutations in *NF2* gene; see Table 61.5
Mosaic (segmental) NF1 (formerly neurofibromatosis type 5)	Neurofibromas alone or CALMs ± "freckling" in a block-like or other mosaic pattern; due to a postzygotic *NF1* mutation, which may involve the gonads in some patients
Legius syndrome	AD; six or more CALMs in >80% and intertriginous "freckling" in ~50% of patients; lack neurofibromas, Lisch nodules, optic pathway gliomas, and typical osseous lesions of NF1; macrocephaly and learning disabilities are common; lipomas, hypopigmented macules, and vascular anomalies in minority; loss-of-function mutations in *SPRED1* gene, the protein product of which inhibits MAPK signaling
Watson syndrome	AD; short stature; pulmonic stenosis; ID; may also have Lisch nodules, axillary/inguinal freckling, and neurofibromas; allelic with NF1; 60/100*
Jaffe–Campanacci syndrome	AD; disseminated non-ossifying fibromas of long and jaw bones; hypogonadism or cryptorchidism; ID; giant cell granulomas (jaws); usually due to *NF1* mutation
Noonan syndrome	AD; short stature; pterygium colli; characteristic facies; cardiac defects, esp. pulmonic valve stenosis; skeletal and testicular abnormalities; keratosis pilaris atrophicans; lymphedema; melanocytic nevi; activating mutations in *PTPN11* > *SOS1, RAF1, RIT1* > *KRAS, NRAS, MAP2K1, LZTR1, SHOC2* (with loose anagen hair), and rarely other genes; patients with an NF1–Noonan overlap phenotype may have mutations in *NF1* gene
Noonan syndrome with multiple lentigines (LEOPARD syndrome)	AD; darker "café noir" macules; *L*entigines, *E*CG abnormalities, *O*cular hypertelorism, *P*ulmonic stenosis, *A*bnormal genitalia, *R*etardation of growth, *D*eafness syndrome; mutations in *PTPN11*; 38/100*
Cardio-facio-cutaneous syndrome	AD; short stature; characteristic facies; low-set ears; cardiac defects; ID; sparse curly hair; dry skin to generalized ichthyosiform eruption; activating mutations in MAPK pathway genes – *BRAF* > *MEK1, MEK2* > *KRAS*
Constitutional mismatch repair deficiency syndrome (formerly Turcot syndrome type 1)	AR; multiple CALMs ± axillary freckling, neurofibromas and/or CNS gliomas (features of NF1) as well as hypopigmented macules, pilomatricomas, hematologic malignancies, and colorectal carcinoma; NF1-like skin findings are often in a mosaic distribution pattern; patients have mutations in both copies of a DNA mismatch repair gene (*PMS2* > *MSH6* > *MLH1, MSH2*) and evidence of microsatellite instability (e.g. in peripheral blood leukocytes); hereditary non-polyposis colorectal cancer (HNPCC; Lynch) syndrome in heterozygotes
McCune–Albright syndrome	Sporadic, presumably lethal unless in mosaic state; polyostotic fibrous dysplasia; hyperfunction of endocrine glands, esp. gonads (e.g. precocious puberty); CALMs are usually apparent during infancy and often several shades darker than background skin with irregular borders; CALMs classically end at midline (as may larger CALMs of NF) and may follow lines of Blaschko in broad bands; activating mutations in the *GNAS1* gene that encodes $G_s\alpha$; 35/100*
Other disorders¶	
Tuberous sclerosis complex (TSC)	AD; ID; seizures; hypopigmented macules; angiofibromas; fibrous plaques; mutations in *TSC1* and *TSC2* genes; see text
Piebaldism	AD; CALMs in involved as well as uninvolved skin; mutations in *KIT* proto-oncogene
Familial progressive hyper- and hypopigmentation	AD; CALMs of variable sizes admixed and overlapping with lentigines and hypopigmented macules and patches; activating mutations in *KITLG* gene
Westerhof syndrome	AD; congenital hypo- and hyperpigmented macules; ID; growth retardation
Carney complex (NAME and LAMB syndromes)	AD; darker "café-noir" macules, lentigines, blue nevi; cutaneous and atrial myxomas; endocrine neoplasia of adrenal glands, pituitary gland, and/or testes; mutations in *PRKAR1A*
Partial unilateral lentiginosis	Unilateral agminated lentigines; unilateral CALMs may also be present; debatable if associated neurologic or psychiatric problems; possible relationship to mosaic NF1
Bannayan–Riley–Ruvalcaba syndrome‡	AD; penile lentigines; vascular malformations; lipomas; intestinal hamartomas; macrocephaly; mutations in *PTEN* gene; ≤10% of patients have CALMs
Cowden syndrome‡	AD; multiple tricholemmomas; cobblestoning of oral mucosa; palmoplantar keratoses; sclerotic fibromas, hamartomas and carcinoma of breast, thyroid, genitourinary system, colon; mutations in *PTEN* gene; ≤10% of patients have CALMs
Ataxia–telangiectasia	AR; telangiectasias of conjunctivae, head/neck, and acral sites; premature canities; cerebellar ataxia; abnormal DNA repair; lymphomas and leukemias; immunodeficiency; sinopulmonary infections; mutations in *ATM* gene; 20/100*
Bloom syndrome	AR; telangiectatic erythema of face; photosensitivity; growth retardation; increased sister chromatid exchanges; malignancies; hypogonadism; mutations in *BLM* gene that encodes the RecQ protein-like-3 DNA helicase
Fanconi anemia	AR; generalized hyperpigmentation, esp. flexural ± guttate hypopigmented macules; pancytopenia; skeletal malformations, e.g. aplasia radii; chromosomal fragility and malignancies, e.g. acute myelogenous leukemia; see Table 67.10
Mosaic chromosomal anomalies	In particular, ring chromosomes (7, 11, 12, 15, 17); rearrangements of 7 and 14; ring 7 also associated with vascular lesions (hemangiomas and capillary malformations) and congenital melanocytic nevi
Extensive epidermal and sebaceous nevi	Mosaic; "syndrome" includes seizures, ID, musculoskeletal and ocular abnormalities; hypophosphatemic vitamin D-resistant rickets; see Table 62.6 for genes
Multiple endocrine neoplasia 1	AD; tumors of the pituitary, parathyroid, and pancreatic islet cells; multiple facial angiofibromas, collagenomas, gingival papules, confetti-like hypomelanotic macules, lipomas; *MEN1* gene
Multiple endocrine neoplasia 2B	AD; mucosal neuromas; marfanoid habitus; medullary thyroid carcinoma; intestinal ganglioneuromatosis; pheochromocytoma; mutations in *RET* proto-oncogene

Table 61.3 Disorders associated with multiple café-au-lait macules (CALMs).

DISORDERS ASSOCIATED WITH MULTIPLE CAFÉ-AU-LAIT MACULES	
Disorder	**Notes**
Silver–Russell syndrome	Growth retardation; triangular face; clinodactyly 5th finger; hemihypertrophy; epigenetic changes on chromosome 15p13 or maternal uniparental disomy of chromosome 7; 45/100*
Tricho-hepato-enteric syndrome	AR; CALM and lentigines on hips and legs; diffuse pigmentary dilution (skin & hair), woolly hair; dysmorphic facies with hypertelorism; intractable diarrhea, liver disease; immune deficiency; mutations in *TTC37* or *SKIV2L*
Tay syndrome†	?AR; growth retardation; ID; triangular face; cirrhosis; trident hands; premature canities; vitiligo
Gastrocutaneous syndrome†	AD; multiple lentigines; peptic ulcer/hiatal hernia; hypertelorism; myopia
Mukamel syndrome	AR; premature graying (infancy); lentigines; depigmented macules; ID; spastic paraparesis, microcephaly, scoliosis
Johnson–McMillin syndrome	Probable AD; alopecia; anosmia; deafness; hypogonadism; microtia

*Estimates of prevalence of CALMs[90].
†To date, observed in a single family.
‡Overlapping conditions collectively referred to as PTEN hamartoma tumor syndrome.
¶To date, single case reports of multiple CALMs in association with X-linked hypohidrotic ectodermal dysplasia, woolly hair, and osteoma cutis.

Table 61.3 Disorders associated with multiple café-au-lait macules (CALMs). Multiple CALMs may also be seen in patients with segmental pigmentation disorder (see Ch. 67). AD, autosomal dominant; AR, autosomal recessive; ID, intellectual disability; *KITLG*; KIT ligand; MAPK, mitogen-activated protein kinase.

Neurologic manifestations

Optic pathway gliomas occur in 15%–20% of children with NF1, usually developing prior to 10 years of age and leading to symptoms in 30%–50% of affected individuals[66]. The behavior of these CNS neoplasms is variable, ranging from spontaneous regression to progressive visual compromise and proptosis due to tumor expansion[5]. Precocious puberty occurs in about 3% of children with NF1, typically in association with an optic pathway glioma[67,68]. Non-optic CNS tumors occur in ~5%[45] and pheochromocytomas in ~1% of NF1 patients[30,69].

Hyperintense lesions on T2-weighted MRI of the brain (T2 hyperintensities; "unidentified bright objects") can be observed in 50%–75% of children with NF1[70]. These are most commonly seen in the basal ganglia, brainstem, and cerebellum. T2 hyperintensities have been shown to evolve over time[71], and they may contribute to cognitive impairment via thalamocortical dysfunction[72].

Although severe intellectual impairment is uncommon, learning difficulties occur in 30%–50% of affected children[44,73]; there is also an increased likelihood of attention deficit disorder, headaches, and sleep disturbances. Seizures develop in about 5% of NF1 patients, although no specific cortical lesions have been linked to the abnormal EEG activity[35].

Skeletal manifestations

Macrocephaly[31,74], hypertelorism, and scoliosis[39,73] are common cranioskeletal abnormalities in individuals with NF1. Osteopenia is another frequent finding, with potential pathogenic factors including vitamin D deficiency and increased bone turnover[75]. A highly distinctive but less common manifestation is pseudarthrosis of the long bones, most often the tibia. This congenital defect begins as bowing and eventually results in erosion of the bone cortex, leading to pathologic fractures and false joint formation (pseudarthrosis)[30,44]. Sphenoid wing dysplasia is a congenital, typically unilateral bony defect in the posterior wall of the orbit that may present as pulsating exophthalmos[44].

Cardiovascular manifestations

Hypertension is a common finding in NF1 patients. Although essential hypertension is most frequent, renovascular stenosis[76] (especially in children) and unsuspected pheochromocytomas[77] may be the cause in some patients. Other cardiovascular manifestations are listed in Table 61.1.

Timing of onset of clinical manifestations

The prevalence of various clinical features in patients with NF1 evolves over the first two decades of life (Fig. 61.9). PNFs and skeletal defects are probably congenital, while CALMs and nevus anemicus may be evident at birth or become apparent during the first few years of life. Intertriginous "freckling", Lisch nodules, and optic pathway gliomas usually occur by the school-age years, and multiple CNFs typically start to develop closer to puberty. A diagnosis of NF1 can be established via classic clinical criteria (i.e. not including genetic testing) in 97% of affected individuals by age 8 years and 100% by age 20 years (see Table 61.2)[36].

Pathology

The CALMs, CNFs, and MPNSTs associated with NF1 are histologically similar to their sporadic counterparts. CALMs from affected individuals are characterized primarily by increased epidermal melanin; other nonspecific findings may include giant melanosomes and a higher number of melanocytes compared to the surrounding skin[78].

CNFs feature a well-circumscribed but unencapsulated dermal collection of small nerve fibers and loosely arranged spindle cells; the latter have scanty pale cytoplasm and elongated wavy nuclei (see Ch. 115). These spindle cells represent a mixture of fibroblasts, Schwann cells, and perineural cells all set in a collagenous stroma with varying amounts of mucin and scattered mast cells. The nuclei are bland and mitotic activity should raise a suspicion of malignancy.

PNFs are specific to NF1. Histologically, they are composed of large, hypertrophied nerves surrounded by spindle-shaped fibroblasts and Schwann cells embedded in a myxoid matrix and growing in a plexiform pattern (see Ch. 115). In some PNFs, neurofibromatous changes extend diffusely into the papillary and reticular dermis. The stroma may be more collagenous than myxoid and organoid differentiation may occur, forming structures resembling Meissner corpuscles.

MPNSTs are characterized by tight intersecting bundles of spindle cells. There are often alternating cellular and myxoid areas. The cells (as in neurofibromas) stain positively with S100, but they are much more pleomorphic, with wavy and hyperchromatic nuclei (see Ch. 115). Increased mitotic activity and perivascular whorling of tumor cells are often observed. Areas of bony or cartilaginous differentiation may also be present, along with hyalinized nodules.

Differential Diagnosis

In an affected individual with complete expression of NF1, *classic* clinical criteria[79] are met and the diagnosis is usually straightforward. In infants, establishing the diagnosis can sometimes be difficult because age-dependent features have not yet developed[80]. Recently published revised diagnostic criteria for NF1 developed by an international consensus group incorporate genetic testing, update the clinical features (primarily the addition of choroidal abnormalities), and emphasize distinction from mosaic NF1 and conditions with overlapping findings (e.g. Legius syndrome) (see Table 61.2)[62].

An approach to children with multiple CALMs (NF1 suspect)[81] is outlined in Figure 61.10. In a series of 110 children (median age 3 years; range, 1 month to 17 years) who presented to an NF1 clinic with CALMs but no other features of NF1, 34/44 (77%) of those with ≥6 "typical" CALMs (distinct regular borders, uniform pigmentation) eventually met criteria for NF1 (almost all before age 6 years), compared to 2/15 (15%) of those with ≥6 "atypical" CALMs (smudgy irregular borders, non-homogeneous pigmentation) and 0/51 of those with <6 CALMs[82].

Comprehensive, highly sensitive analysis of *NF1* is available, with methods including targeted massively parallel/next-generation sequencing (NGS), multiplex ligation-dependent probe amplification (MLPA; assesses copy number variation), and RNA-based testing[83].



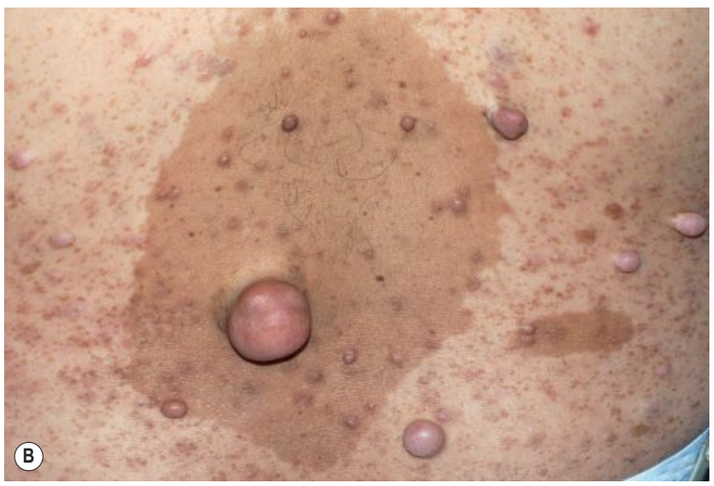




Fig. 61.4 Multiple cutaneous neurofibromas. Soft, skin-colored to pinkish-tan, dome-shaped or polypoid, well-demarcated papules and nodules of various sizes (**A**–**C**) can occur in patients with NF1. Neurofibromas may be superimposed on café-au-lait macules and lentigines (**B**, **C**). *A,B, Courtesy Julie V. Schaffer, MD.*





Fig. 61.5 Spectrum of cutaneous neurofibromas. Lesions range from subtle blue–red macules (**A**) to exophytic nodules with associated hypertrichosis (**B**). *Courtesy Julie V. Schaffer, MD.*

These techniques can identify the underlying pathogenic variant in ≥95%–98% of non-founder patients who fulfill classic clinical diagnostic criteria[79]. This is because they can detect low-level mosaicism (down to 3%–5% variant allele frequency with NGS) as well as deep intronic splice variants and deletions that are missed by conventional genomic DNA-based sequencing. Molecular testing allows for more accurate diagnoses in young children and individuals with atypical clinical presentations. It also makes prenatal or preimplantation diagnosis an option for affected families.

In addition to mosaic NF1 (see above), unilateral lentigines in the axilla or groin may be seen in patients with partial unilateral lentiginosis (PUL) or a large speckled lentiginous nevus (nevus spilus)[84]. These segmental conditions are characteristically sharply demarcated at the midline, but bilateral involvement occasionally occurs. The presence of CALMs in addition to lentigines increases the likelihood of NF1. When individuals suspected of having mosaic NF1 do not have a detectable mutation in the peripheral blood, the diagnosis can be confirmed by analyzing *NF1* in melanocytes or Schwann cells cultured from a lesional skin biopsy specimen (e.g. of a CALM or neurofibroma, respectively).

Some patients with a familial tendency to develop multiple "typical" NF1-like CALMs, often in association with intertriginous "freckling", do not develop neurofibromas or Lisch nodules and lack an underlying *NF1* mutation. Approximately 70% of such individuals have a heterozygous germline mutation that inactivates *SPRED1*, which encodes a protein that inhibits RAS–RAF interaction and thereby (like neurofibromin) negatively regulates MAPK signaling (see Fig. 55.4)[85,86]. This autosomal dominant condition, known as *Legius syndrome*, accounts for ~2% of all patients who meet classic clinical NF1 criteria[86].

Constitutional mismatch repair deficiency (CMMRD) due to biallelic germline mutations in a mismatch repair gene frequently presents with multiple CALMs, sometimes together with other features of NF1 such as intertriginous freckling, neurofibromas, and gliomas (Fig. 61.11A). There is often a segmental/regional distribution of skin findings, and postzygotic *NF1* mutations have been documented in affected tissues[87].



Fig. 61.6 Plexiform neurofibromas. Clinical presentations include: hyperpigmented plaques that may be misdiagnosed as a café-au-lait macule (if not palpated) (**A**) or congenital melanocytic nevus (**B**); and a poorly circumscribed, sagging pink mass (**C**). *A, Courtesy Antonio Torrelo, MD; B,C, Courtesy Julie V. Schaffer, MD.*

EVALUATION AND MANAGEMENT OF PATIENTS WITH NEUROFIBROMATOSIS TYPE 1 (NF1)
At the time of diagnosis and annually

• Offer genetic testing at the time of diagnosis, especially if atypical clinical features or helpful for reproductive planning
• Dermatologic examination, especially if a plexiform neurofibroma (PNF) involves the skin
  • Surgical consultation if painful, disfiguring, or bothersome neurofibromas
  • Consider baseline MRI if deeper extension of PNF
  • Urgent PET-CT if rapid growth, increased firmness, or persistent pain within an established PNF or the development of a new neurologic deficit
• Neurologic evaluation
  • Consider baseline brain/orbital MRI in pediatric patients*
  • Brain/orbital and/or spinal MRI if neurologic signs/symptoms develop
• Cardiac assessment (*at initial diagnosis*) and measurement of blood pressure
  • Renal MRA (or spiral CT/CT angiography if impaired renal function) and plasma free metanephrines if hypertension develops
• Evaluation for scoliosis (via forward bend test), other skeletal abnormalities (e.g. tibial bowing), and vitamin D deficiency†
  • Referral to orthopedics and vitamin D supplementation as indicated

At the time of diagnosis ± annually, *depending on the age of the patient*
• Ophthalmologic examination with visual testing and assessment for pubertal development/accelerated linear growth (*prior to puberty; consider twice yearly ophthalmologic examination until age 6 years*)   • Brain/orbital MRI if signs/symptoms of optic pathway glioma • Neurodevelopmental/behavioral evaluation (*annually only in children/adolescents*) • Measurement of head circumference (*annually only in young children*) • Screening for breast cancer with clinical examination + mammography ± MRI (*beginning at age 30 years*)
Potentially affected family members
• Consider genetic testing for the mutation identified in the proband • Dermatologic examination for cutaneous manifestations of NF1 • Ophthalmologic examination for Lisch nodules
*The role of neuroimaging in asymptomatic patients is controversial. †Considering that osteoporosis occurs at an earlier age in individuals with NF1, screening with dual-energy X-ray absorptiometry can be considered based on age and other risk factors.

Table 61.4 Evaluation and management of patients with neurofibromatosis type 1 (NF1)[94,95]. During yearly visits, patients with NF1 should also be asked about fingertip pain from glomus tumors, other chronic pain or itch, signs/symptoms of pheochromocytoma (e.g. palpitations, sweating), and depression. CT, computed tomography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography–computed tomography.

Additional findings suggestive of this diagnosis in children with manifestations of NF1 but who lack an *NF1* or *SPRED1* mutation include siblings but not parents with features of NF1, a personal or family history of malignancies (especially Lynch syndrome-related cancers; see Ch. 63), and consanguinity[88].

Additional disorders associated with multiple CALMs, some of which are caused by other genetic defects that lead to increased MAPK signaling, are presented in Table 61.3. NGS panels are now available to assess *NF1*, *SPRED1*, and other "RASopathy" genes.

Historically, *neurofibromatosis type 2* (NF2) has been discussed in the context of NF1. However, the clinical manifestations and molecular genetics of NF2 are distinct from those of NF1 (Table 61.5). NF2 is less common and has a lower frequency of cutaneous findings than NF1; Lisch nodules are not a feature of NF2. The tumor upon which a diagnosis of NF2 typically rests is the vestibular schwannoma. In the 1990 diagnostic criteria for NF2, neurofibromas were included as one of the index tumors[89]. However, in a 1997 update, neurofibromas were excluded from the diagnostic criteria for NF2[90]. Mautner et al.[91] found that 60% of NF2 patients had skin tumors, usually schwannomas appearing as flat or spherical, nodular subcutaneous tumors of the peripheral nerves on the limbs and trunk. Although one-third of the

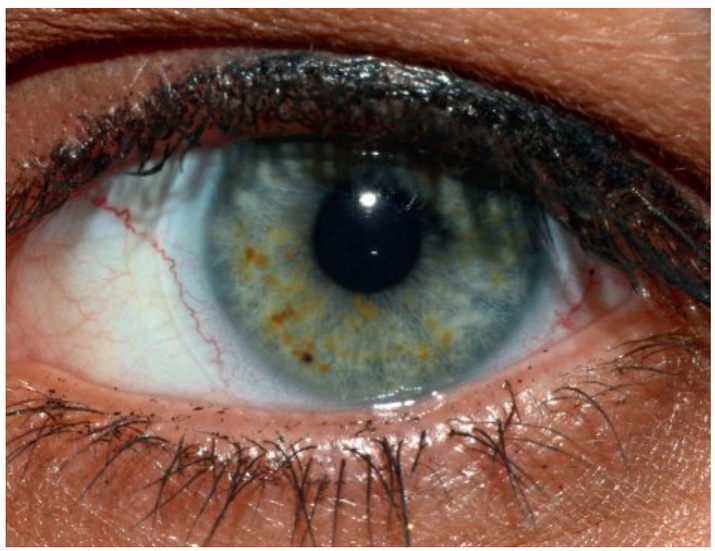


Fig. 61.7 Lisch nodules. Multiple yellow–brown papules on the iris. Although best seen using a slit lamp, Lisch nodules may also be evident on clinical examination in patients with lightly pigmented eyes. *Courtesy Julie V. Schaffer, MD.*

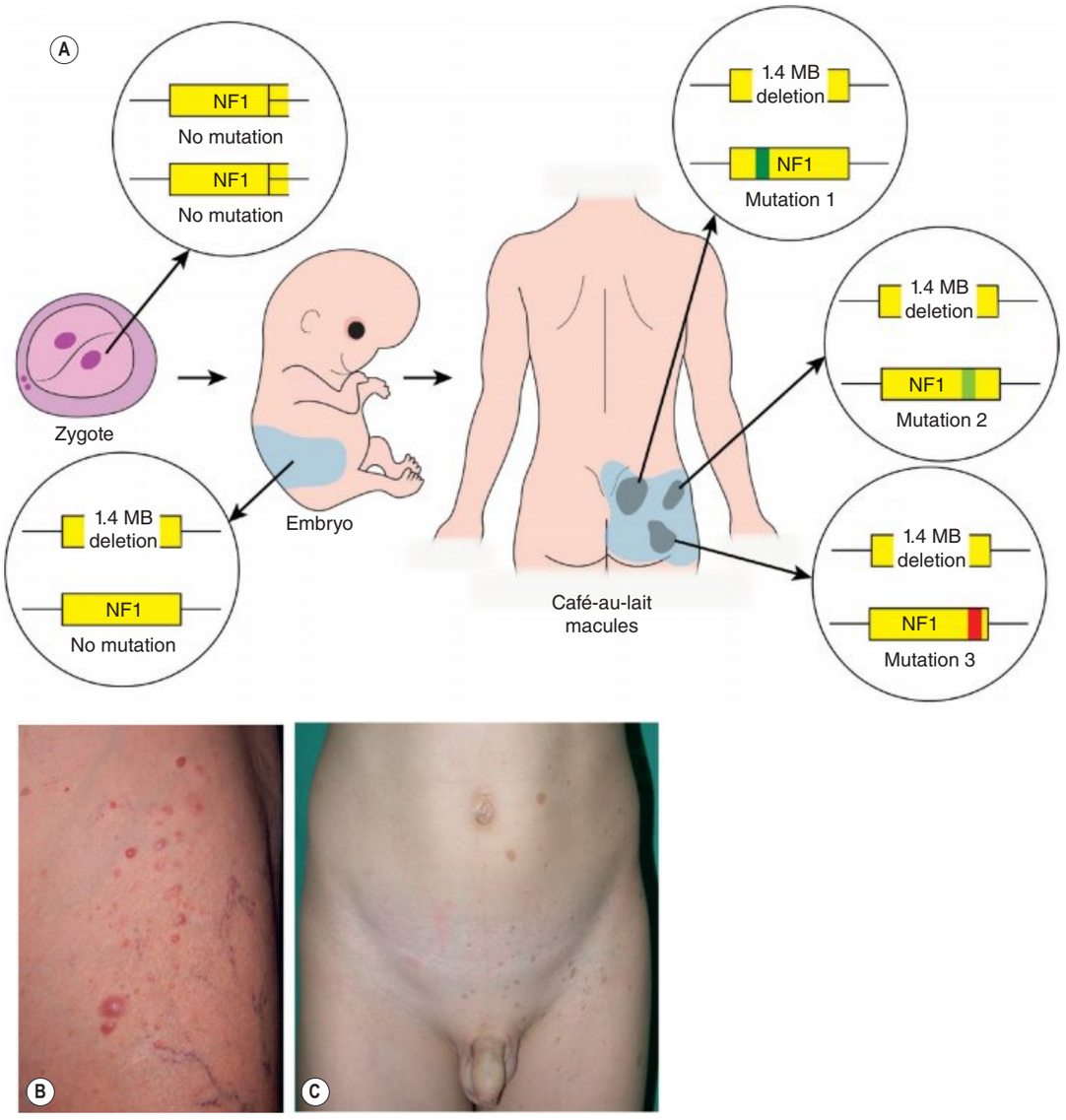


Fig. 61.8 Mosaic neurofibromatosis type 1 (NF1). A Mosaic NF1 results from a heterozygous postzygotic *NF1* mutation (e.g. the deletion depicted here), which can affect one or more regions of skin. Within such areas, somatic "second-hit" mutations that inactivate the remaining *NF1* allele result in skin lesions such as café-au-lait macules, lentigines, and neurofibromas. **B** A cluster of soft, pink to pink–brown papules limited to the thigh. There were no associated café-au-lait macules. **C** Multiple small café-au-lait macules and "freckling" limited to the left side of the trunk and groin, with slight extension past the midline. *A, Courtesy Jean L. Bolognia, MD; B, Courtesy Antonio Torrelo, MD.*

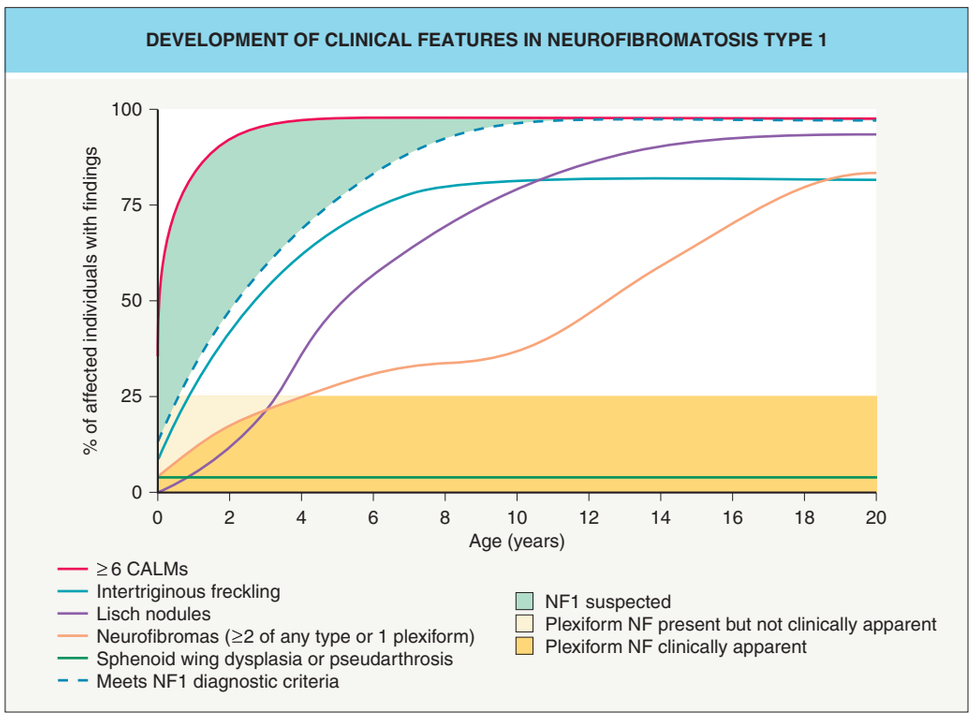


Fig. 61.9 Development of clinical features in neurofibromatosis type 1. The time course of major diagnostic lesions that develop in NF1. During the first few years of life, a child may have only café-au-lait macules. *Adapted from DeBella K, Szudek J, Friedman JM. Use of the National Institutes of Health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics 2000;105:608–14.*

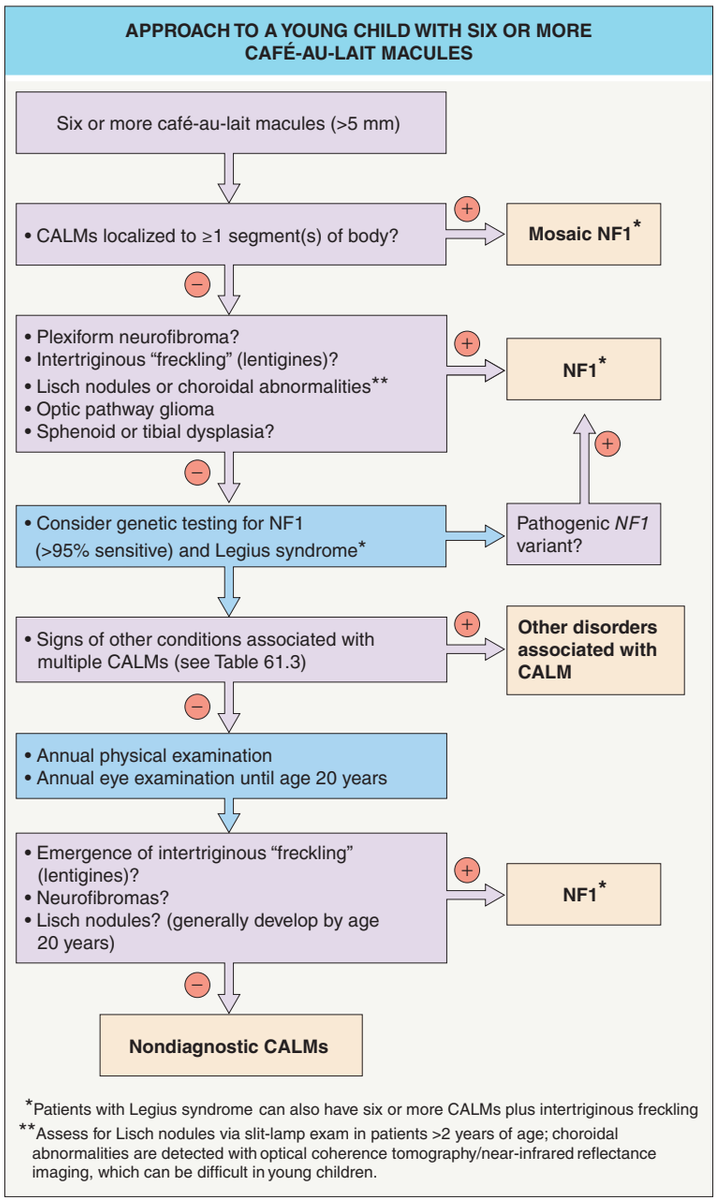


Fig. 61.10 Approach to a young child with six or more café-au-lait macules. More than half of these patients have NF1 or, less often, one of the other CALM-associated syndromes (see Table 61.3). Additional early signs of NF1 that are not included in the diagnostic criteria include nevus anemicus, juvenile xanthogranulomas, macrocephaly, and T2 hyperintensities on brain MRI.



Fig. 61.11 Entities in the differential diagnosis of neurofibromatosis type 1. A Grouped café-au-lait macules and lentigines in a 6-year-old boy with constitutional mismatch repair deficiency. **B** A cutaneous schwannoma with hypertrichosis and slight hyperpigmentation in a 2-year-old boy with neurofibromatosis type 2; such lesions may be misdiagnosed as a congenital melanocytic nevus or smooth muscle hamartoma. *Courtesy Julie V. Schaffer, MD.*

KEY FEATURES OF NEUROFIBROMATOSIS TYPE 2
• Autosomal dominant transmission; affects approximately 1 in 40 000 individuals
• Approximately half of the cases are due to *de novo* mutations rather than inherited germline mutations (similar to NF1)
• Bilateral vestibular schwannomas, meningiomas, and spinal tumors
• Two-thirds of patients develop cutaneous schwannomas, and approximately 50% develop café-au-lait macules (CALMs), but fewer in number compared to NF1*
• No Lisch nodules or mental retardation/learning disabilities
• *NF2* gene is located on chromosome 22q12 and encodes a cytoskeleton-associated protein of ~600 amino acids named merlin/neurofibromin 2, which is structurally related to the ERM (ezrin-radixin-moesin) protein family of membrane-cytoskeleton linkers
*In two large series of patients with NF2 (n = 161), only two individuals had more than five CALMs of the required size to meet NF1 criteria and over half of those with any CALMs had only one (41 of 72).

Table 61.5 Key features of neurofibromatosis type 2 (NF2).

affected individuals in this series had CALMs, only 2 of 88 patients had six or more CALMs. In young children with NF2, schwannomas may present as hypertrichotic, slightly hyperpigmented plaques (Fig. 61.11B).

McCune–Albright syndrome also features CALMs that are present at birth or become apparent during infancy. Additional manifestations of this sporadic mosaic disorder include polyostotic fibrous dysplasia and endocrine hyperfunction, most commonly precocious puberty. Affected tissues harbor an *activating* mutation in the gene encoding $G_s\alpha$ (i.e. the α-subunit of the G protein that stimulates adenylate cyclase), which leads to increased intracellular levels of cyclic AMP. Compared to the CALMs that occur in NF1, those of McCune–Albright syndrome and other forms of "pigmentary mosaicism" are generally larger, have a linear (e.g. broad bands along the lines of Blaschko) or segmental distribution pattern, usually do not cross the midline, and have an irregular border that may resemble the "coast of Maine". The most common sites are the head, neck, trunk, and buttocks.

PNFs need to be distinguished from congenital melanocytic nevi, especially when they are hyperpigmented with hypertrichosis. It is equally important not to misdiagnose patients who have large congenital melanocytic nevi with smaller "satellite" lesions and prominent neurotization as having NF1.

Management

Management of NF1 patients requires a multidisciplinary approach[79,90]; if available, a multispecialty NF clinic can help to optimize care. Dermatologists are often consulted to assist in establishing the diagnosis in affected children. Evaluation of individuals newly diagnosed with NF1 should include a thorough history (personal and family) and physical examination, with particular attention to signs and symptoms of disease manifestations (see Table 61.1). As part of the initial care of NF1 patients, an in-depth educational discussion should include the natural history of the condition, possible medical complications and neurodevelopmental sequelae, and psychosocial considerations; genetic counseling should also be provided. Table 61.4 summarizes recommendations for the evaluation and management of NF1 patients[92–95]. Goals of longitudinal care include early recognition and treatment of complications, maximization of academic and vocational achievement, and minimization of the disease's psychosocial impact.

The cutaneous lesions of NF1 can lead to a variety of age-dependent management issues. PNFs may grow into large, bulky tumors during

early childhood. Multidisciplinary teams are often required to excise deep and extensive neurofibromatous tissue, and the lesions tend to recur following surgery. CALMs do not need or respond well to treatment, although it may be desired for cosmetic purposes. When laser therapy is performed, CALMs tend to persist or recur (see Ch. 137). During adolescence and adulthood, removal of CNFs may be indicated for functional or cosmetic reasons. Simple surgical excision is the treatment of choice for selected bothersome lesions; laser ablation or electrocautery can be used to remove numerous small CNFs[96,97], but recurrences are common and hypertrophic scarring may develop.

Lifelong surveillance for the development of MPNSTs is essential, particularly for patients at increased risk of this malignancy due to the known presence of PNFs, polyneuropathy secondary to multiple nerve root tumors, a history of radiation therapy (with reports of MPNSTs arising in the radiation field), or a germline *NF1* microdeletion[49]. An increase in the growth rate, firmness, pain, or neurologic symptoms associated with a PNF merits further evaluation. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET-CT) or functional MRI with diffusion-weighted imaging/apparent diffusion coefficient (DWI/ADC) mapping can aid in the early detection of malignant transformation within PNFs and guide biopsy of suspicious areas[98,99]. Histologic evaluation has been recommended for symptomatic lesions with a maximum standardized uptake value (SUVmax) of ≥3.5 on PET-CT with delayed imaging (4 hours after ^{18}F-FDG injection).

The MEK inhibitor selumetinib was FDA approved in 2020 for treatment of symptomatic, inoperable PNFs in pediatric patients (≥2 years of age) with NF1; clinical trials showed durable tumor shrinkage (median 28%)[100]. Selumetinib and other MEK inhibitors (e.g. trametinib) have shown clinical benefit for gliomas as well as PNFs in patients with NF1[101]. Targeted therapies that are under investigation for PNFs and other tumors in NF1 patients also include inhibitors of the KIT receptor on mast cells and other tyrosine kinases (e.g. imatinib mesylate, cabozantinib; see Pathogenesis section and Fig. 61.2), mechanistic target of rapamycin (mTOR; e.g. sirolimus), vascular endothelial growth factor receptors (VEGFRs), and other components of the MAPK pathway as well as the *p*hosphatidyl*i*nositol 3-*k*inase (PI3K)/AKT, JAK/STAT3, and Hippo/YAP pathways[102–105].

Resources for patients and families include Neurofibromatosis Network (www.nfnetwork.org), the Neurofibromatosis Clinics Association (www.nfpittsburgh.org), the Children's Tumor Foundation (www.ctf.org), and Nerve Tumours UK (www.nervetumours.org.uk).

TUBEROUS SCLEROSIS COMPLEX

Synonyms: ■ Tuberous sclerosis ■ Bourneville disease ■ Bourneville–Pringle disease ■ Epiloia (*epi*lepsy, *l*ow *i*ntelligence, *a*ngiofibroma)

Key features

- Tuberous sclerosis complex is an autosomal dominant disorder with an incidence of ~1 in 10 000 births
- Key cutaneous features include hypopigmented macules, facial angiofibromas, collagenomas, and ungual fibromas
- The characteristic oral findings are gingival fibromas and dental enamel pits
- Hamartomas can be found in the eye as well as several internal organs, including the brain, kidneys, heart and lungs
- Seizures, mental deficits, and neuropsychiatric disturbances are common
- Up to 75% of cases are due to new spontaneous mutations
- Mutations have been identified in two genes: *TSC1* and *TSC2*; their protein products are hamartin and tuberin, respectively

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by seizures, intellectual deficits, and skin findings including hypomelanotic macules and facial angiofibromas. As with NF1, cutaneous lesions are often the initial clinical features, and dermatologists are routinely called upon to assist in the diagnosis of TSC.

History

During the mid-1800s, Virchow recognized scleromas in the brain and von Recklinghausen described a similar patient with both scleromas and myomata in the heart[44]. Between 1880 and 1900, Bourneville provided the first systematic descriptions of the disease, including neural and cutaneous findings. Vogt posited the classic triad of epilepsy, low intelligence, and angiofibromas (termed the Vogt triad) in 1908, and Sherlock coined the term "epiloia" a few years later. In 1920, van der Hoeve described the significance of retinal hamartomas, which he termed "phakomas" (hence the designation "phakomatosis")[106]. At that time, examination of the ocular fundi was the only external access to the CNS before death.

Epidemiology

TSC has an incidence of ~1 in 10 000 births, and the overall prevalence is estimated to be between 1 in 10 000 and 1 in 30 000[107,108].

Pathogenesis

TSC is a hamartomatous condition characterized by disordered cellular proliferation, migration, and differentiation. It has an autosomal dominant pattern of inheritance. However, the majority of affected individuals have new spontaneous mutations.

In the 1980s, TSC kindreds from around the world were analyzed and the disease locus was mapped to chromosome 9q34 in a subset of affected families. Further study led to the discovery of a second disease locus on chromosome 16p13[109]. In 1994, Povey et al.[110] studied 32 TSC families and found that about half demonstrated linkage to chromosome 9q34 (*TSC1*), whereas the other half showed linkage to chromosome 16p13 (*TSC2*).

In 1993, the *TSC2* gene on chromosome 16 was identified and found to be deleted or mutated in the subset of TSC families linked to this region[111]. *TSC2* is composed of 41 exons that encode an 1807 amino acid, 200 kDa protein referred to as *tuberin*. Like neurofibromin, tuberin contains a GAP domain (Fig. 61.12). Tuberin stimulates the GTPase activities of RAB5, a protein involved in endocytosis[112], and RHEB, a RAS-related protein that activates the mTOR pathway. By "turning off" RHEB, tuberin inhibits the cell growth and proliferation that result from mTOR signaling. The latter is a central regulator of cellular responses to nutrition, energy levels, and a variety of growth factors.

The *TSC1* gene, which was identified in 1997, consists of 23 exons that encode a 130 kDa protein termed *hamartin*[113]. Hamartin shares no sequence homology with tuberin or other known tumor suppressor genes. However, hamartin interacts with tuberin[114] and other cytoskeletal components, and it functions together with tuberin to negatively regulate mTOR signaling[115,116]. In patients with TSC, mTOR inhibition by sirolimus (rapamycin) and related agents can have therapeutic benefit (see Fig. 61.12 and Management section).

In large series of TSC patients, *TSC2* mutations have been identified more frequently than *TSC1* mutations, with an overall ratio of approximately 3 : 1[117,118]. However, in familial cases, there is a more equal proportion of *TSC2* and *TSC1* mutations. Of note, individuals with *TSC2* mutations tend to have a more severe phenotype than those with *TSC1* mutations. Familial TSC due to *TSC2* mutations tends to have a milder phenotype than *de novo* cases[117,118], which likely reflects a decreased likelihood of reproduction in more severely affected individuals. Some patients with mild sporadic TSC are mosaics for a mutation in *TSC1* or *TSC2*; if there is gonadal involvement, they may pass on generalized disease to their offspring.

In mouse models, heterozygous TSC1 mutant (*Tsc1*$^{+/-}$) mice develop renal and extrarenal tumors such as hepatic hemangiomas with loss of the wild-type *Tsc1* allele. Heterozygous TSC2 mice (*Tsc2*$^{+/-}$) display a high incidence of multiple bilateral renal cystadenomas, liver hemangiomas, and lung adenomas. Progression to renal carcinoma, fatal bleeding from the liver hemangiomas, and angiosarcomas are occasionally observed[119]. These mice also have abnormalities in learning and memory associated with hyperactive hippocampal mTOR signaling. Treatment of adult mice with the mTOR inhibitor sirolimus resulted in improved cognitive function[120].

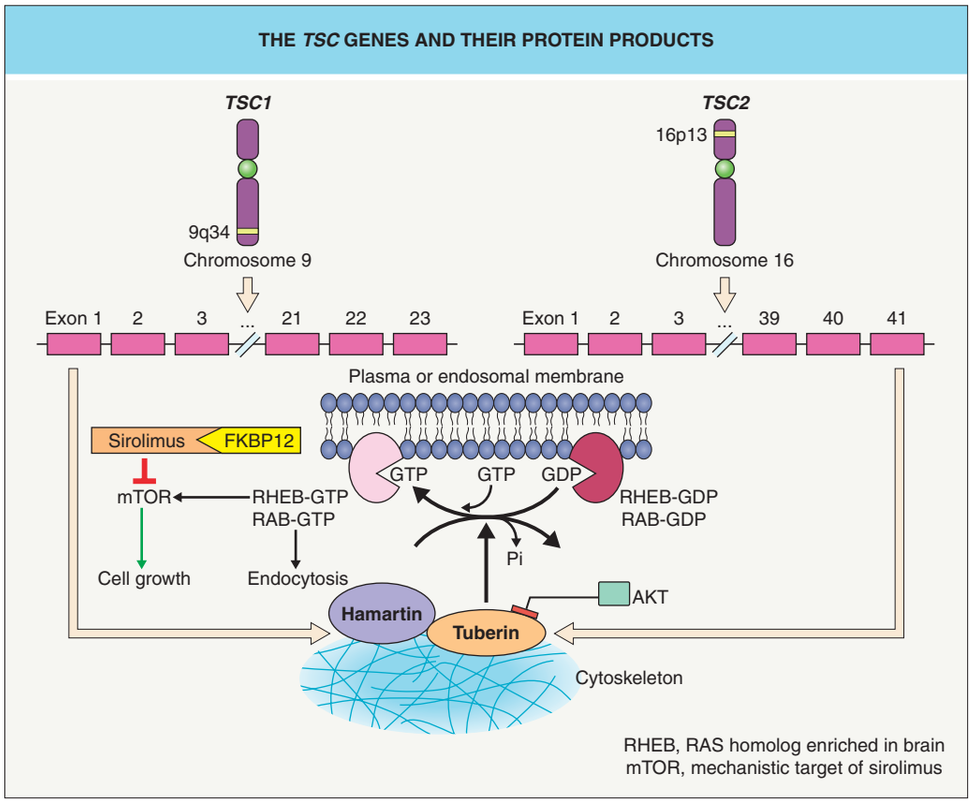


Fig. 61.12 The *TSC* genes and their protein products. *TSC1* and *TSC2* are located on chromosomes 9q34 and 16p13, respectively. The *TSC1* product, hamartin, interacts with the *TSC2* product, tuberin, and negatively regulates signaling by the small GTPases RAB and RHEB. Like RAS, the activity of RAB and RHEB is dependent upon bound GTP, and tuberin (like neurofibromin) accelerates hydrolysis of GTP to GDP in order to turn off RAB and RHEB. Sirolimus (rapamycin) and its analogues (e.g. everolimus) form a complex with the FK506-binding protein-12 (FKBP12), and together they bind to and inhibit mTOR. AKT, human homolog of the murine AKT8 retrovirus transforming sequence.

Clinical Features

As with NF1, the diagnosis of TSC often involves a dermatologist, as some of the earliest findings of TSC are cutaneous (Table 61.6).

Oculocutaneous manifestations

The time course for developing the cutaneous findings of TSC is shown in Fig. 61.13. The hypomelanotic macules are not depigmented, as in vitiligo, but instead are hypopigmented (Fig. 61.14). A Wood's lamp can help to detect these lesions, which may be very subtle in children with lightly pigmented skin. The macules are usually present at birth or within the first few months of life, although their appearance is sometimes delayed until early childhood in individuals with fair skin. They may adopt several configurations, and small (<2 cm) polygonal or "thumbprint"-shaped macules are most common[121]. The lance-ovate hypopigmented macule or "ash leaf spot" (named after the Eastern Mountain ash tree) is rounded at one end and tapered at the other, and it can range from 1 to 12 cm in size. Although less frequent than polygonal macules, ash leaf spots are characteristic of TSC.

Over 90% of TSC patients have more than one hypomelanotic macule[122], and some have >100 lesions. Scores of 1–2 mm, "guttate" hypopigmented macules (also known as "white freckles" or "confetti" macules) may also be seen, especially on the extremities (Fig. 61.15). Although these guttate lesions occur in <5% of affected infants, they are probably the most specific pigmentary manifestation of TSC[121,122].

Approximately 1%–4% of healthy infants and children have a circumscribed hypopigmented macule or patch, i.e. a nevus depigmentosus (see Ch. 66)[121,123,124]. Debard and Richardet[123] examined the skin of 9737 infants aged 1–18 months and found that 0.7% had one or two white spots that were larger than 1 cm; however, no unaffected infant had more than three spots. Thus, the presence of three or more hypomelanotic macules (≥5 mm in diameter) was chosen as a major criterion for diagnosis of TSC[125,126] (Table 61.7). Clusters of scalp hair, eyebrows, or eyelashes may be lighter or white (poliosis) when the underlying skin is affected.

Café-au-lait macules (CALMs) have been reported in up to 30% of patients with TSC and are usually evident within the first few months of life[121,122]. Most TSC patients, however, have fewer than the six CALMs required to diagnose NF1.

Angiofibromas, previously referred to as "adenoma sebaceum", are not typically present at birth. They begin to appear in the centrofacial area as early as the first 2 years of life, and by adolescence angiofibromas are present in ~80% of TSC patients. A high frequency of somatic second-hit CC>TT "UV signature" mutations has been identified in TSC-related facial angiofibromas, suggesting a role for UV light in their pathogenesis[127]. The lesions may begin as erythematous macules on the cheeks and forehead and then mature into pink to red or red–brown papules or papulonodules, which may coalesce into plaques. The papules are often dome-shaped and have a smooth, shiny surface (Fig. 61.16A,B). With the exception of mosaic TSC, facial angiofibromas have a bilateral and symmetric distribution. Because one or two angiofibromas (fibrous papules) are relatively common in the general population, the presence of at least 3 angiofibromas is required as a diagnostic criterion for TSC[125].

The fibrous cephalic plaque represents a larger variant of an angiofibroma that develops on the face or scalp in ~20% of TSC patients[122,125]. These plaques favor the forehead and are usually firm and yellow–brown to pink–tan in color (Fig. 61.16C). They may slowly enlarge over time and when on the scalp typically lack hair.

A characteristic truncal lesion is the shagreen ("leather") patch, which represents a type of collagenoma (see Ch. 116). Shagreen patches occur most commonly in the lumbosacral area and typically begin to develop at around 2 years of age, although occasionally they are apparent earlier. Eventually these lesions are observed in approximately half of TSC patients[122]. Clinically, they typically appear as skin-colored to hyperpigmented plaques that can reach up to 10 cm in diameter and often have an uneven surface (Fig. 61.17A). Multiple lesions may be present. A distinctive feature is prominent, but slightly depressed, follicular openings, giving rise to a pigskin-like appearance. A "folliculocystic and collagen hamartoma" (FCCH) featuring comedones and keratin-containing cysts as well as collagen deposition has also been described in patients with TSC (Fig. 61.17B)[128]. When present in patients with TSC, fibrous cephalic plaques, shagreen patches and FCCH, in addition to segmental forms of hypomelanosis, congenital lymphedema and lipomatosis, are thought to reflect superimposed (type 2) mosaicism due to a second-hit mutation arising during an early stage of prenatal development[129] (see Ch. 62).

Ungual fibromas (Koenen tumors) begin to develop later in childhood and can continue to form throughout adulthood. *Periungual* fibromas

MAJOR CLINICAL FEATURES OF TUBEROUS SCLEROSIS COMPLEX
Cutaneous
• Facial angiofibromas (~80%) and fibrous plaque of the forehead (~20%) • Hypomelanotic macules (90%–100%) – polygonal; lance-ovate (ash leaf); confetti • Shagreen patch (40%–50%) • Ungual fibromas (30%–60%) • Molluscum pendulum • Café-au-lait macules
Ocular
• Retinal hamartomas (~40%) • Achromatic retinal patches (~40%) • Retinal astrocytoma
Skeletal
• Cystic areas of bone rarefaction, especially phalanges
Dental
• Pitted enamel (>90%) • Intraoral fibromas (up to 70%)
Pulmonary
• Lymphangioleiomyomatosis (≥30%–40% of women)
Renal
• Multiple bilateral angiomyolipomas (75%–90%) • Cysts (30%) • Carcinoma
Endocrine
• Precocious puberty • Hypothyroidism
Neurologic
• Cortical dysplasia (cortical tubers and cerebral white matter radial migration lines) (>90%) • Subependymal nodules* (>80%) • Subependymal giant cell astrocytoma† (5%–15%) • Seizures (70%–95%), including infantile spasms (~60%) • Intellectual impairment (>50%)
Cardiovascular
• Myocardial rhabdomyoma‡ (80% of infants) • Wolff–Parkinson–White syndrome
*Nearly all patients by puberty. †Also known as subependymal giant cell tumor ‡Increasingly difficult to distinguish from normal myocardium after the first few years of life.

Table 61.6 Major clinical features of tuberous sclerosis complex.

arise from the proximal or lateral nail fold and occur most commonly around the toenails (Fig. 61.18A). In contrast, *subungual* fibromas that originate under the nail plate and longitudinal red streaks with proximal narrowing ("red comets") favor the fingernails (Fig. 61.18B). In addition, lesions can lead to distortion of the nail plate (e.g. a longitudinal groove) without a visible tumor (see Fig. 61.18A).

Soft, pedunculated, skin-colored papules and nodules (molluscum pendulum) develop in some TSC patients. These lesions resemble large acrochordons and favor flexural areas, such as the neck, axillae, and groin.

Intraoral fibromas have been described in 20%–70% of individuals with TSC, with a higher prevalence in adults than in children[121,130]. The gingiva is the most common location, but lesions can also occur on buccal or labial mucosa and occasionally the tongue. Dental enamel pits are seen in nearly all TSC patients, compared with <10% to (upon close examination) 70% of unaffected individuals[131,132]. However, one study found >10 pits in 70% of TSC patients but only 4% of controls[132].

Retinal lesions are present in about half of TSC patients, with retinal hamartomas seen in ~40% (Fig. 61.19). The most common morphologic type of hamartoma is the flat, translucent lesion (70%), followed by the multinodular "mulberry" lesion (55%) and the transitional-type



Fig. 61.14 Hypomelanotic macules in tuberous sclerosis complex. Lance-ovate and oval hypomelanotic (ash leaf) macules. *Courtesy Julie V. Schaffer, MD.*

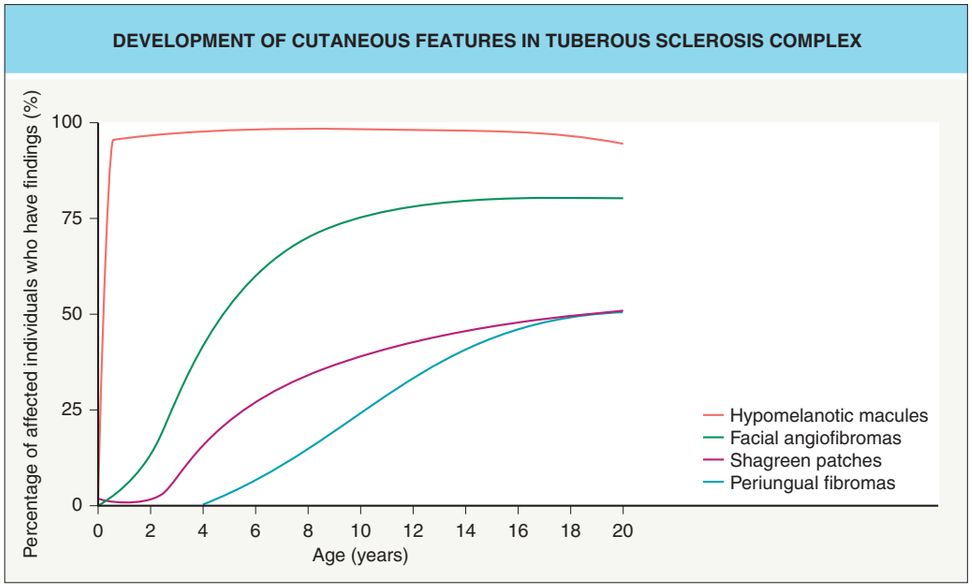


Fig. 61.13 Development of cutaneous features in tuberous sclerosis complex. Hypomelanotic macules are usually the only cutaneous finding at birth.



Fig. 61.15 Guttate leukoderma of tuberous sclerosis complex. Multiple 1–2 mm hypopigmented "confetti" macules. *Courtesy Jean L. Bolognia, MD.*





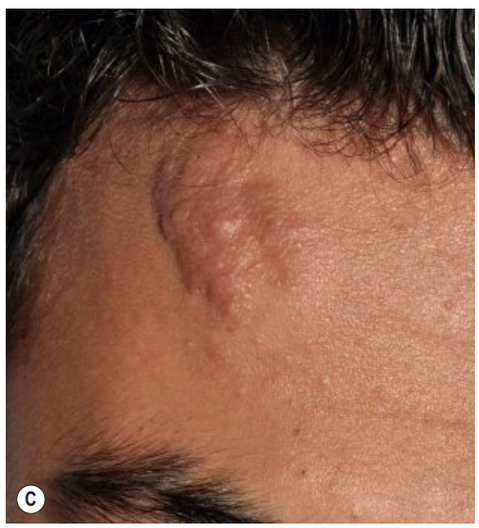


Fig. 61.16 Facial angiofibromas and fibrous plaque in tuberous sclerosis complex. A Multiple small, dome-shaped pink–tan papules and a fibrous cephalic plaque on the cheeks of a 5-year-old boy. **B** Larger, coalescing dome-shaped, pink–tan papules on the cheeks and nose of an adolescent. **C** Fibrous plaque on the forehead, which represents the most common location. *A,B, Courtesy Julie V. Schaffer, MD; C, Courtesy Ángela Hernández-Martín, MD.*

2012 REVISED DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS COMPLEX (TSC)	
Major Features	
Hypomelanotic macules (≥3, diameter ≥5 mm)	
Facial angiofibromas (≥3) or fibrous cephalic plaque	
Ungual fibromas (≥2)	
Shagreen patch	
Multiple retinal hamartomas	
Cortical dysplasias (including tubers and cerebral white matter radial migration lines)	
Subependymal nodules	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis	
Angiomyolipomas (≥2; renal >> other organs, e.g. liver)	
Minor Features	
"Confetti" skin lesions	
Dental enamel pits (≥3)	
Intraoral fibromas (≥2)	
Retinal achromic patch	
Multiple renal cysts	
Non-renal hamartomas	
Definite *clinical* diagnosis	
• Either two major features* *or* one major feature plus ≥2 minor features	
Possible *clinical* diagnosis	
• Either one major feature *or* ≥2 minor features	
Definite *genetic* diagnosis	
• Identification of a pathogenic variant in either *TSC1* or *TSC2* in DNA from the blood or normal tissue	
Key:	
Cutaneous	*Extracutaneous*
*With the exception of lymphangioleiomyomatosis + angiomyolipomas.	

Table 61.7 2012 revised diagnostic criteria for tuberous sclerosis complex (TSC)[125,141].

lesion (9%). Punched-out areas of retinal depigmentation can also be found in about 40% of affected individuals[133]. Most ocular lesions in TSC patients do not lead to visual loss.

Neurologic manifestations

Infantile spasms occur in ~70% of infants with TSC. These seizures last for several minutes and are characterized by massive flexion or extension of the limbs, trunk, and head for <1–3 seconds, occurring in series separated by intervals of a few seconds. These spasms typically begin at about 3 months of age, as opposed to other types of TSC-associated seizures, which usually develop after 1 year of age[134]. The EEG changes that characterize infantile spasms are termed hypsarrhythmia[134,135].

Intellectual disabilities of varying degrees occur with a high frequency in children and adults with TSC[134,135]. The spectrum of *T*SC-*a*ssociated *n*europsychiatric *d*isorders (TAND) also includes autism, attention deficit disorder, aggressive behaviors, and psychiatric conditions[136–138].

Multiple subependymal nodules along the ventricular surface can be seen on MRI (more sensitive) or CT scan in >80% of TSC patients by 2 years of age. These nodules progressively calcify and are found in almost all patients by puberty[139]. Subependymal giant cell astrocytomas (SEGAs), which affect 5%–15% of patients with TSC, usually develop during childhood[140]. Unlike subependymal nodules, SEGAs tend to enlarge over time, which may lead to hydrocephalus and neurologic symptoms; they exhibit contrast enhancement on MRI or CT[141]. Types of cortical dysplasia in TSC include cerebral white matter radial migration lines as well as the highly characteristic tubers (glioneuronal hamartomas) that can be detected by MRI in ~90% of patients[139].

Cardiovascular manifestations

Cardiac rhabdomyomas, which can be detected prenatally as well as after birth by echocardiography or MRI, are found in >80% of infants with TSC[139]. However, cardiac rhabdomyomas tend to involute during





Fig. 61.17 Collagenomas in tuberous sclerosis complex. A Shagreen patches are actually plaques, which can be hyperpigmented or skin-colored. The surface is said to resemble leather or pigskin. **B** The "folliculocystic and collagen hamartoma" features comedones and keratin-filled cysts as well as collagen deposition. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Antonio Torrelo, MD.*





Fig. 61.18 Ungual fibromas in tuberous sclerosis complex. A Multiple fibromas of the toes arising in a periungual location. Note the associated longitudinal grooves. **B** Longitudinal red streaks ("red comets") that narrow proximally and favor the fingernails. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Thomas Darling, MD.*

the first 3 years of life[142], and they often disappear altogether by adulthood. Arrhythmias, especially Wolff–Parkinson–White syndrome, appear to be more common in affected individuals[143].

Renal manifestations

Multiple bilateral angiomyolipomas are frequently noted on routine renal ultrasounds of TSC patients. Most of these lesions are asymptomatic, especially during childhood and when they measure <4 cm in diameter[142]. However, angiomyolipomas tend to enlarge and increase in number with age, and they may lead to life-threatening hemorrhage[144]. Children with TSC who develop severe renal cysts often have a contiguous gene syndrome in which both *TSC2* and the polycystic kidney disease (*PKD*) genes are lost in a single large chromosomal deletion[145]. Occasionally, renal cell carcinomas develop in TSC patients.

Other manifestations

Pulmonary lymphangioleiomyomatosis is often asymptomatic and occurs in at least 30%–40% of women with TSC. On high-resolution CT scan, these lesions appear as cysts. Men rarely develop this manifestation of TSC[146], and estrogen is suspected to be involved in stimulating growth of smooth muscle cells in the lung[147]. Of note, lymphangioleiomyomatosis can occur sporadically due to biallelic somatic *TSC2* mutations, and renal angiomyolipomas also develop in a subset of these patients. Multifocal micronodular pneumonocyte hyperplasia, hamartomatous gastrointestinal polyps, congenital segmental lymphedema, other vascular anomalies, segmental lipomatosis, and hemihypertrophy have also been reported in individuals with TSC[129,148–150].

Pathology

Hypopigmented macules have a reduction in the amount of epidermal melanin but a normal number of melanocytes. The melanocytes have poorly developed dendrites[151]. On electron microscopy, small, immature melanosomes are seen whose number, degree of melanization, and transfer to keratinocytes are reduced[151–153].

Angiofibromas consist of an irregular proliferation of fibrous tissue and blood vessels. Expansion of the hamartomatous process can lead to compression of adnexae. Characteristically, there is concentric perifollicular fibrosis. *Fibrous cephalic plaques* have similar histopathologic findings[154].



Fig. 61.19 Retinal hamartomas of tuberous sclerosis complex. *Courtesy Jean L. Bolognia, MD.*

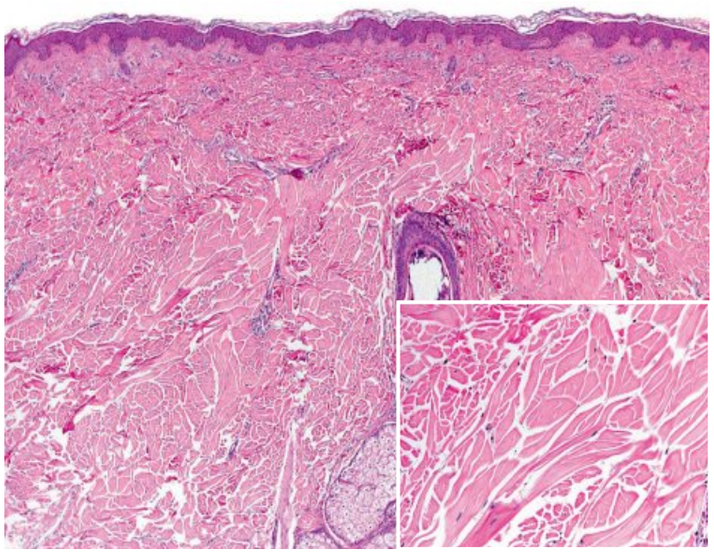


Fig. 61.20 Histology of a shagreen patch. Increased collagen forming thickened bundles in the dermis. *Courtesy Lorenzo Cerroni, MD.*

The *shagreen patch* (Fig. 61.20) and *ungual fibromas* represent collagenomas. The dermis is replaced by thick bundles of collagen, and elastin fibers are typically absent. The fibroblasts may be large and morphologically atypical. It is thought that the various fibrous lesions seen in TSC belong to the same histopathologic spectrum, with perifollicular fibrosis representing a characteristic feature; a cystic component is occasionally evident, as observed in FCCH[154,155].

Differential Diagnosis

The diagnostic criteria for TSC were revised in 1998 and then updated in 2012 (see Table 61.7)[125,126,141]. Four of the major features are cutaneous, and a thorough dermatologic examination frequently helps to establish the diagnosis. Although seizures occur in the majority of affected infants, the possibility of TSC is often considered in asymptomatic infants with multiple hypomelanotic macules. An approach to this clinical situation is outlined in Fig. 61.21. Echocardiography can be helpful in establishing the diagnosis in infants and is easier to perform in this age group than is a brain MRI to detect CNS lesions.

Conventional genetic testing, including sequencing and deletion/duplication analysis, identifies a pathogenic variant in *TSC1* or *TSC2* in ~85% of individuals who meet the clinical criteria for TSC. Use of targeted next-generation sequencing (including deletion/duplication analysis) can increase the yield to ~95%, enabling detection of intronic splice site and mosaic pathogenic variants that tend to result in relatively mild disease[156,157]. Analysis of DNA from a lesional skin biopsy specimen (e.g. angiofibroma) may be necessary for mosaic TSC with more limited involvement[156].

Multiple facial angiofibromas, collagenomas, gingival papules, and confetti-like hypomelanotic macules can occur in patients with multiple endocrine neoplasia type 1 (MEN 1; see Ch. 63). Multiple facial angiofibromas and collagenomas have also been observed in adults with Birt–Hogg–Dubé syndrome (see Ch. 111), whereas multiple collagenomas can occur in Cowden syndrome (storiform variant, also referred to as sclerotic fibromas; see Ch. 63), Buschke–Ollendorf syndrome (dermatofibrosis lenticularis disseminata; see Ch. 116), and familial cutaneous collagenoma. The clinical differential diagnosis for facial angiofibromas may include acne vulgaris and trichoepitheliomas, but individual acneiform lesions should resolve over a period of weeks. Trichoepitheliomas are usually less red in color, although a biopsy is often required to establish the diagnosis. Additional causes of multiple facial papules are listed in Table 36.2 and Figure 111.5.

As discussed above, a nevus depigmentosus represents a common cause of a congenital hypopigmented macule or patch, and some infants have more than one of these lesions. A larger nevus depigmentosus that has a segmental distribution (segmental pigmentation disorder) or follows the lines of Blaschko may be composed of multiple hypopigmented macules and patches within the affected areas. Features that distinguish the hypopigmented lesions of TSC from postinflammatory hypopigmentation (e.g. due to atopic or seborrheic dermatitis) and the amelanosis of piebaldism or vitiligo are presented in Figure 61.21. Idiopathic guttate hypomelanosis (IGH) may resemble the confetti-like leukoderma of TS; however, IGH is an acquired condition that favors the shins and extensor forearms of older adults.

A congenital smooth muscle hamartoma can present during infancy as a firm, skin-colored to hyperpigmented plaque that may resemble a shagreen patch; however, it accentuates with rubbing (pseudo-Darier sign), contains follicular papules due to hyperplastic arrector pili muscles, and has associated hypertrichosis rather than prominent but depressed follicular orifices. Histologically, smooth muscle hamartomas feature intradermal bundles of smooth muscle rather than collagen.

Management

Nearly every organ can be affected by TSC, and clinical findings vary tremendously even within families. Certain signs and complications typically appear at birth, whereas others develop much later in life. The 2012 International TSC Consensus Conference Recommendations and 2019 United Kingdom Guidelines for the evaluation and management of individuals with TSC are summarized in Table 61.8[142,158–160]. Investigations in TSC patients should focus on detecting disease manifestations and complications that are potentially significant and treatable, and it is important to provide genetic counseling to affected individuals and families. In clinical trials involving TSC patients, systemic therapy with the mTOR inhibitors sirolimus and everolimus has led to regression of SEGAs, control of recalcitrant seizures, reduction in the size of renal angiomyolipomas, and improvement of lung function in women with lymphangioleiomyomatosis[161–163].

Considering the UV-induced mutations implicated in facial angiofibromas, sun protective measures may be of utility[127]. Use of electrosurgery, dermabrasion, and ablative fractional or pulsed dye lasers has led to variable results.

Topical sirolimus (rapamycin) has been employed to treat angiofibromas as well as fibrous plaques and hypomelanotic macules, with limited systemic absorption. More irritation is produced by topical application of the commercially available 0.1% solution (Rapamune® 1 mg/ml) than with compounded 0.1%–1% ointment, cream, and gel formulations[164–167]. Reduced erythema and flattening of the angiofibromas are typically seen within 3 months of initiating daily topical therapy, especially if treatment is initiated at ≤10 years of age. In randomized placebo-controlled studies in adults and children with TSC, angiofibromas improved in 60% (18/30) of patients treated topically with sirolimus 0.2% gel twice daily for 3 months and 82% (45/55) of those treated with sirolimus 1% daily for 6 months (vs 0% [0/31] and 25% [13/51], respectively, with placebo; $p<0.001$)[167,168]. Relapses typically occur upon discontinuation; although maintenance with thrice weekly

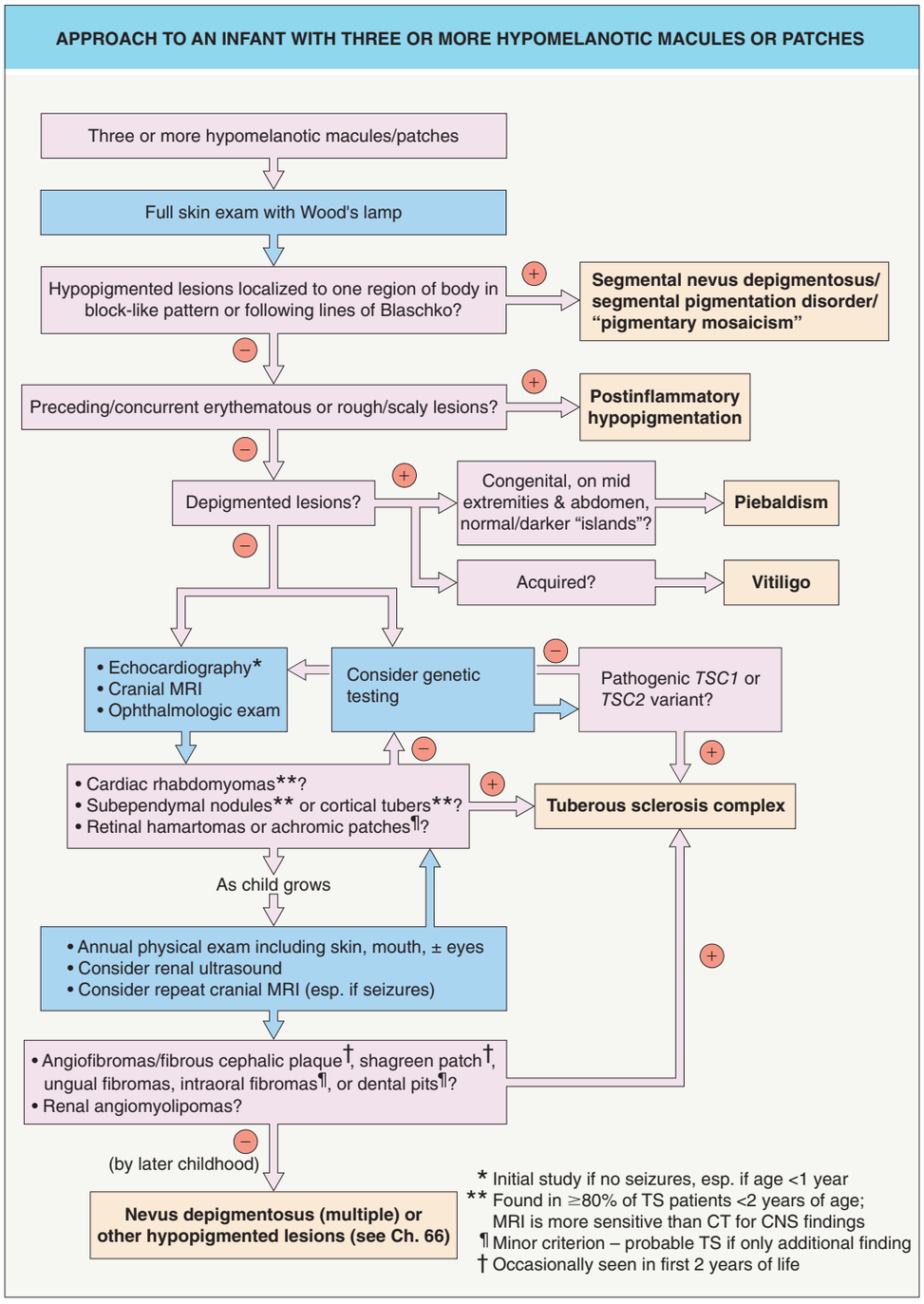


Fig. 61.21 Approach to an infant with three or more hypomelanotic macules or patches. A child with fewer than three macules and no family history of tuberous sclerosis complex (TSC) has an extremely low likelihood of having this disease.

applications has limited efficacy[166], a combination of topical sirolimus 0.1% and calcitriol 0.0003% may result in a more durable response than sirolimus alone[169].

Resources for patients and families include the TSC Alliance (www.tscalliance.org), the National Institute of Neurological Disorders and Stroke (www.ninds.nih.gov/health-information/disorders/tuberous-sclerosis-complex), and the Tuberous Sclerosis Association (www.tuberous-sclerosis.org).

Additional figures and table on Riccardi's classification of neurofibromatosis, available in our eBook (see inside front cover for access code).

EVALUATION AND MANAGEMENT OF TUBEROUS SCLEROSIS (TSC) PATIENTS
Newly diagnosed
• Offer genetic testing, especially if the TSC diagnosis cannot be clinically confirmed or would provide helpful information for reproductive planning • Neurodevelopmental and behavioral evaluation (especially for children) for features of TSC-associated neuropsychiatric disorder (TAND) • Brain MRI with and without gadolinium to assess for tubers, migrational defects, subependymal nodules, and SEGA* • Electroencephalogram (EEG); consider 24-hour video EEG if cognitive, behavioral, neurological, or sleep symptoms not explained by EEG; educate parents to recognize infantile spasms • Ophthalmologic examination including dilated fundoscopy • Electrocardiogram (ECG); echocardiography in children (especially if <3 years) and symptomatic adults • Abdominal MRI to detect angiomyolipomas and renal cysts (favored over CT or ultrasonography) • Assess blood pressure and determine glomerular filtration rate (GFR) • High-resolution chest CT and pulmonary function tests (PFTs) to detect LAM (all women ≥18 years of age; adolescents and men if symptomatic); counsel on risks of estrogen use and smoking as appropriate • Detailed dental assessment and dermatologic examination using a Wood's lamp
Established (to monitor for complications)
• Screening for TAND annually; comprehensive formal evaluation for TAND at transition periods, e.g. ages 0–3, 3–6, 6–11, and 12–18 years • Brain MRI every 1–3 years until age 25 to monitor for SEGA*; in patients with SEGA, perform MRI more frequently if symptoms or a large/growing lesion† and after age 25 as indicated • EEG if known/suspected seizure activity or behavior change/cognitive decline • Ophthalmologic examination with fundoscopy annually • ECG every 3–5 years in asymptomatic patients; echocardiography every 1–3 years in asymptomatic pediatric patients with cardiac rhabdomyomas until regression is documented • Abdominal MRI for angiomyolipomas and renal cysts every 1–3 years until early adulthood if no known renal lesions and yearly if renal lesions‡; may consider alternating with ultrasonography or fast low-dose CT, especially if general anesthesia is needed for MRI • Assess blood pressure and determine GFR at least annually in patients with renal lesions • High-resolution chest CT every 5–10 years until menopause in women without known LAM; annual PFTs in patients with LAM‡ • Dental examination every 6–12 months; panoramic radiographs by age 7 years if asymmetry, swelling, or abnormal tooth development • Annual dermatologic examination; counsel on sun protection • Offer genetic counseling/testing in patients of reproductive age or considering having children
Potentially affected family members (especially first-degree relatives)
• Consider genetic testing for the mutation identified in the proband • Dermatologic and (if skin findings not diagnostic) ophthalmologic examinations for manifestations of TS
*CT (or head ultrasound in infants with open fontanelles) is suboptimal but may be done if MRI is not possible. †Treatment options for enlarging and/or symptomatic SEGA include surgical resection (first-line) and mTOR inhibitors. ‡mTOR inhibitors represent first-line therapy for asymptomatic enlarging angiomyolipomas >3 cm in diameter and LAM resulting in progressive loss of lung function; embolization followed by corticosteroid therapy is recommended for acute hemorrhage of an angiomyolipoma.

Table 61.8 Evaluation and management of tuberous sclerosis (TSC) patients[159,160]. CT, computed tomography; MRI, magnetic resonance imaging; SEGA, subependymal giant cell astrocytoma; LAM, lymphangioleiomyomatosis.

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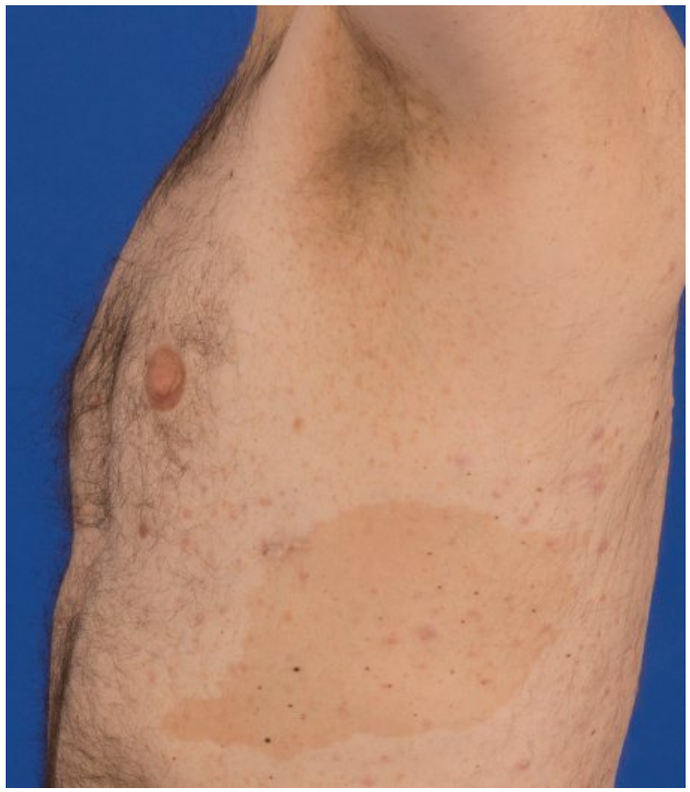


eFig. 61.1 Neurofibromatosis type 1. Axillary lentigines and a café-au-lait macule. *Courtesy Julie V. Schaffer, MD.*





eFig. 61.2 Neurofibromatosis type 1. A, B Multiple lentigines plus café-au-lait macules and in **B**, neurofibromas. The multiple lentigines are often referred to as "freckling". *Courtesy Julie V. Schaffer, MD.*



eFig. 61.3 Neurofibromatosis. Large café-au-lait macule, soft raised neurofibromas and axillary "freckling" (Crowe sign). *Courtesy Edward Cowen, MD.*



eFig. 61.4 Neurofibromatosis type 1. Multiple soft, skin-colored to pink neurofibromas in addition to lentigines. *Courtesy Julie V. Schaffer, MD.*



eFig. 61.5 Neurofibromatosis 1. A common location for neurofibromas in women is the areola. Note the numerous lentigines on the breast.



eFig. 61.6 Plexiform neurofibromas. The pink-brown plaques are soft and large lesions often have a sagging bag-like appearance. *Courtesy Julie V. Schaffer, MD.*



eFig. 61.7 Plexiform neurofibroma in a patient with neurofibromatosis type 1. This sharply demarcated reddish-brown plaque had a "bag of worms" texture upon palpation. *Courtesy Julie V. Schaffer, MD.*



eFig. 61.8 Plexiform neurofibroma. Initial presentation can be hyperpigmentation with mild hypertrichosis, as in this 4-year-old girl. The lesion was initially misdiagnosed as a congenital melanocytic nevus. *Courtesy Anthony J. Mancini MD.*



eFig. 61.9 Plexiform neurofibromas. Clinical presentations of a hyperpigmented plaque that may be misdiagnosed as a congenital melanocytic nevus or (if not palpated) a café-au-lait macule. *Courtesy Julie V. Schaffer, MD.*



eFig. 61.10 Plexiform neurofibroma in a child with neurofibromatosis type 1. Light brown plaque with a "bag of worms" texture upon palpation. *Courtesy Julie V. Schaffer, MD.*



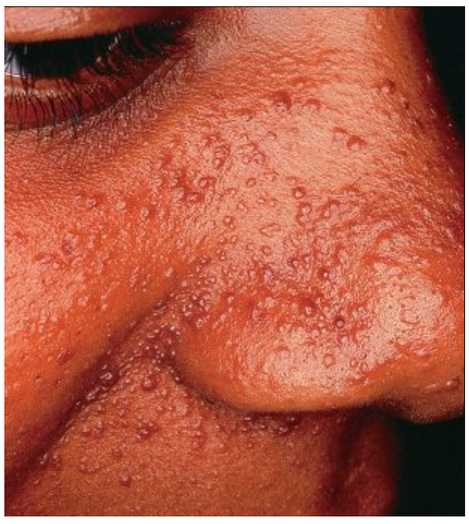
eFig. 61.11 Ash leaf macules in a boy with tuberous sclerosis complex. *Courtesy Ángela Hernández-Martín, MD.*



eFig. 61.12 Hypomelanotic macules of tuberous sclerosis complex. Both the confetti and polygonal types are present. *Courtesy Jean L. Bolognia, MD.*



eFig. 61.13 Facial angiofibromas and fibrous plaque in tuberous sclerosis complex. Multiple small dome-shaped papules as well as a larger fibrous plaque on the cheek.



eFig. 61.14 Facial angiofibromas of tuberous sclerosis. Multiple shiny, dome-shaped papules on the cheeks and nose in an adult.



eFig. 61.15 Fibrous plaque of the forehead in a patient with tuberous sclerosis. The plaque is firm to palpation.



eFig. 61.16 Large fibrous cephalic plaque in a patient with tuberous sclerosis complex. *Courtesy Luis Requena, MD.*



eFig. 61.17 Shagreen patch in tuberous sclerosis complex. A hypomelanotic macule ("ash leaf spot") is also present. *Courtesy Thomas Darling, MD.*



eFig. 61.18 Shagreen patch in tuberous sclerosis complex. *Courtesy Ángela Hernández-Martín, MD.*



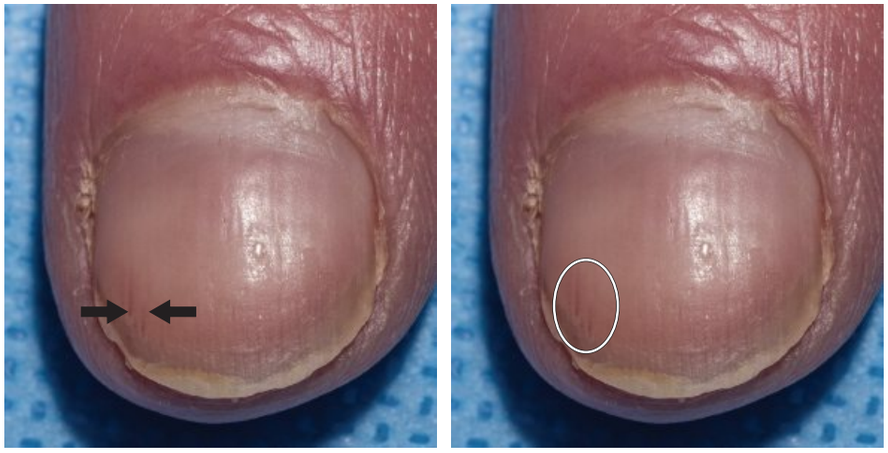
eFig. 61.19 Collagenomas in tuberous sclerosis complex. Shagreen patch with a hyperpigmented surface that resembles leather or pigskin.



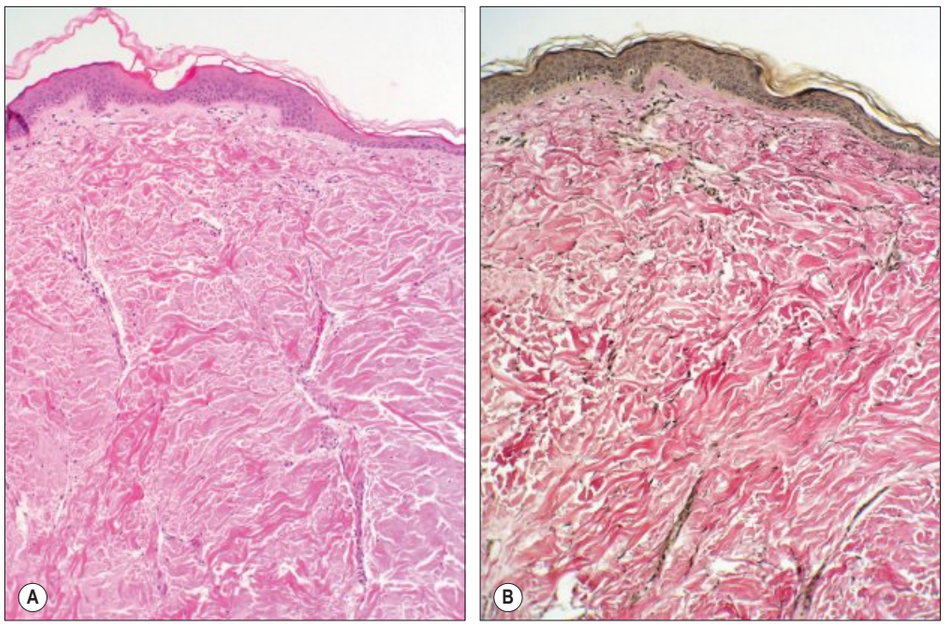
eFig. 61.20 Multiple ungual fibromas in a patient with tuberous sclerosis complex. *Courtesy Luis Requena, MD.*



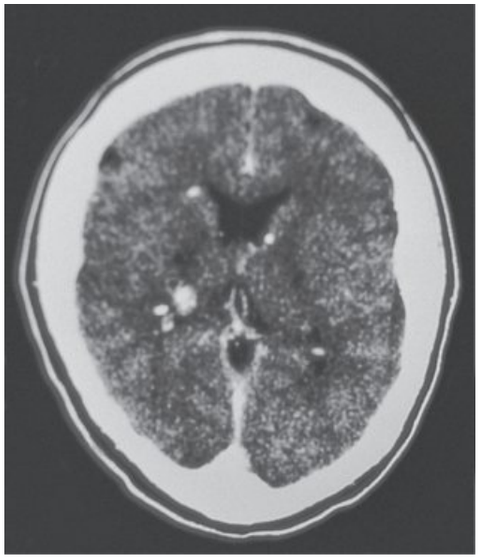
eFig. 61.22 Ungual fibromas of tuberous sclerosis complex. Multiple fibromas of the toes arising in a periungual location.



eFig. 61.21 Longitudinal red streaks ("red comets") in tuberous sclerosis complex. The streaks narrow proximally and favor the fingernails. *Courtesy Thomas Darling, MD.*



eFig. 61.23 Histology of a shagreen patch. A Increased collagen in dermis with H&E stain. **B** Verhoeff-van Gieson stain demonstrates increased red collagen and sparse black elastic fibers. *A,B, Courtesy Ronald P. Rapini MD.*



eFig. 61.24 Cranial CT demonstrating multiple calcified subependymal nodules in a paraventricular location. *Courtesy Jean L. Bolognia, MD.*

RICCARDI'S CLASSIFICATION OF NEUROFIBROMATOSIS	
Category	**Description**
NF1	von Recklinghausen disease
NF2	Acoustic schwannoma
NF3*	Mixed (central and peripheral neurofibromas)
NF4*	Variant
NF5*,†	Segmental café-au-lait macules, neurofibromas, or both, affecting one or more dermatomes
NF6*,‡	Café-au-lait macules only
NF7*	Late onset
NF-NOS	Not otherwise specified

*Primarily of historical/conceptual interest.
†Now referred to as mosaic (segmental) NF1.
‡Includes Legius (NF1-like) syndrome.

eTable 61.1 Riccardi's classification of neurofibromatosis.

62 Mosaicism and Linear Lesions

*Julie V. Schaffer**

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Introduction and history 1012
Patterns and pathogenesis of cutaneous mosaicism 1012
Approach to Molecular Testing for Genomic Mosaicism 1015
Functional mosaicism in X-linked germline disorders 1017
Epidermal nevi and related syndromes. 1023
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Key features

- Mosaicism for genes expressed in the skin presents as a patchy distribution of affected and unaffected skin
- The classical pattern follows the lines of Blaschko but varies according to cell type and timing of mosaicism
- Epidermal nevi represent mosaicism for a variety of genes with variable associated features
- Some mosaic disorders are recognizable as segmental forms of autosomal dominant skin disorders
- If there is also gonadal mosaicism, offspring may have the corresponding generalized condition

INTRODUCTION AND HISTORY

The term "mosaic" is used to describe individuals composed of cells of different genotypes that are derived from a genetically homogeneous zygote. For example, patients with mosaic Turner syndrome have both 45,XO and 46,XX cells. Based on this traditional definition, all humans are actually mosaics due to high rates of postzygotic mutations both *in utero* and throughout life (e.g. in cutaneous neoplasms)[1a,1b]. Consequently, a recent consensus expert review proposed redefinition of a *mosaic skin abnormality* or *mosaic disorder* to specify that the genetically distinct cell populations: (1) are present *by the time of birth*; and (2) *lead to a disease phenotype*, either in the skin or the entire disorder, respectively[1c]. Of note, a *postzygotic* mutation occurs after the single-cell stage and is thus not inherited from one's parents; this is also referred to as a *somatic* mutation if it does not affect the germ cells/gametes. In contrast, a *germline* (constitutional) mutation affects the whole individual and can either be inherited from a parent or arise *de novo* (see Ch. 54).

The skin provides an ideal canvas to visualize patterns of mosaicism.In 1901, Alfred Blaschko[1] documented the characteristic lines and whorls that are followed by epidermal nevi and other skin conditions now known to result from mosaicism (Fig. 62.1A). In 1961, Mary Lyon postulated that similar striped patterns in female mice heterozygous for coat color genes on the X chromosome reflected two populations of cells, one expressing the maternal X chromosome and one the paternal X chromosome. She hypothesized that all women are *functional* mosaics with regard to the X chromosome. In 1965, Curth and Warburton[2] used the Lyon hypothesis to explain the linear pattern of skin findings in the X-linked disorder incontinentia pigmenti. A decade later, Happle recognized lyonization as the reason that skin lesions follow the lines of Blaschko in heterozygous female patients with other X-linked genodermatoses[3,4].

We now recognize that mosaicism affecting autosomes as well as X chromosomes may result from either: (1) changes in the DNA sequence due to mutations or chromosomal alterations (*genetic* or *genomic* mosaicism); or (2) changes in gene expression (*epigenetic* or *functional* mosaicism) as in lyonization[4] (Table 62.1). Autosomal mosaic conditions usually result from *de novo* postzygotic mutations and are not inherited. However, the clinical manifestations of some autosomal dominant disorders reflect a mosaic "second hit" in affected tissues, such as the skin lesions of neurofibromatosis type 1 (NF1). The unusual familial occurrences of autosomal mosaic disorders may be explained by inheritance of either an unstable "premutation" or a transposon ("jumping gene") of retroviral origin that can modulate the expression of other genes when the disorder has a genetic versus epigenetic etiology, respectively[5].

The idea that the lines of Blaschko represent the embryonic migration pathways of skin cells was first expressed in English by Douglass Montgomery, who proposed that the linear patterns of epidermal nevi "may be due to the streams or trend of growth of the tissues"[6]. Although both Montgomery and Blaschko presented their findings in May 1901, Montgomery's contribution was eclipsed by that of his German contemporary. In fact, the now widely held theory that the lines of Blaschko reflect routes of embryonic cell migration did not surface again until the late 1970s[3,7].

PATTERNS AND PATHOGENESIS OF CUTANEOUS MOSAICISM

Blaschko's original diagram (see Fig. 62.1A) omitted the midface, scalp, lateral neck, and genital area. The trajectories of the lines of Blaschko in these areas have now been established[8] (Fig. 62.1B–E), as have analogous patterns in the eyes, teeth, and oral mucosa. Considerable variability occurs in the degree of whorling on the flanks and the directions of lines on the face; the posterior midline may be shifted to the left or right, but the anterior midline tends to be sharply centered from the upper sternum to the pubis.

Mosaic skin conditions do not always follow the lines of Blaschko (Fig. 62.1F-H). Happle categorized patterns of cutaneous mosaicism into seven types[8a]: (1,2) narrow or broad bands along the lines of Blaschko; (3) checkerboard (block- or flag-like); (4) lateralization, i.e. one side of the body only; (5) phylloid (leaf- or flower-like); (6) patchy without midline separation; and (7) sash. To date, all patterns, except for sash, have been shown to be mosaic at the molecular level in at least one condition. Other patterns have also been described in genetically proven mosaic conditions, such as multiple small, relatively circular congenital melanocytic nevi. Assuming that the pattern is determined by cell migration, it depends on both the *timing* of the genetic alteration (Table 62.2) and the *cell type* affected. These two factors also contribute to other aspects of the mosaic phenotype. A mutation occurring early in embryonic development tends to affect a higher proportion of that individual's cells and a greater number of tissue types. For example, an early mutation in a vascular precursor cell can give rise to Sturge-Weber syndrome involving the skin, eyes and brain, while the same mutation

*This chapter was written by Drs Celia Moss and Fiona Browne for the previous edition of this textbook. It has been updated here by Dr Schaffer, but much of their original chapter has been retained. We remain most grateful to them both for their work on earlier editions.

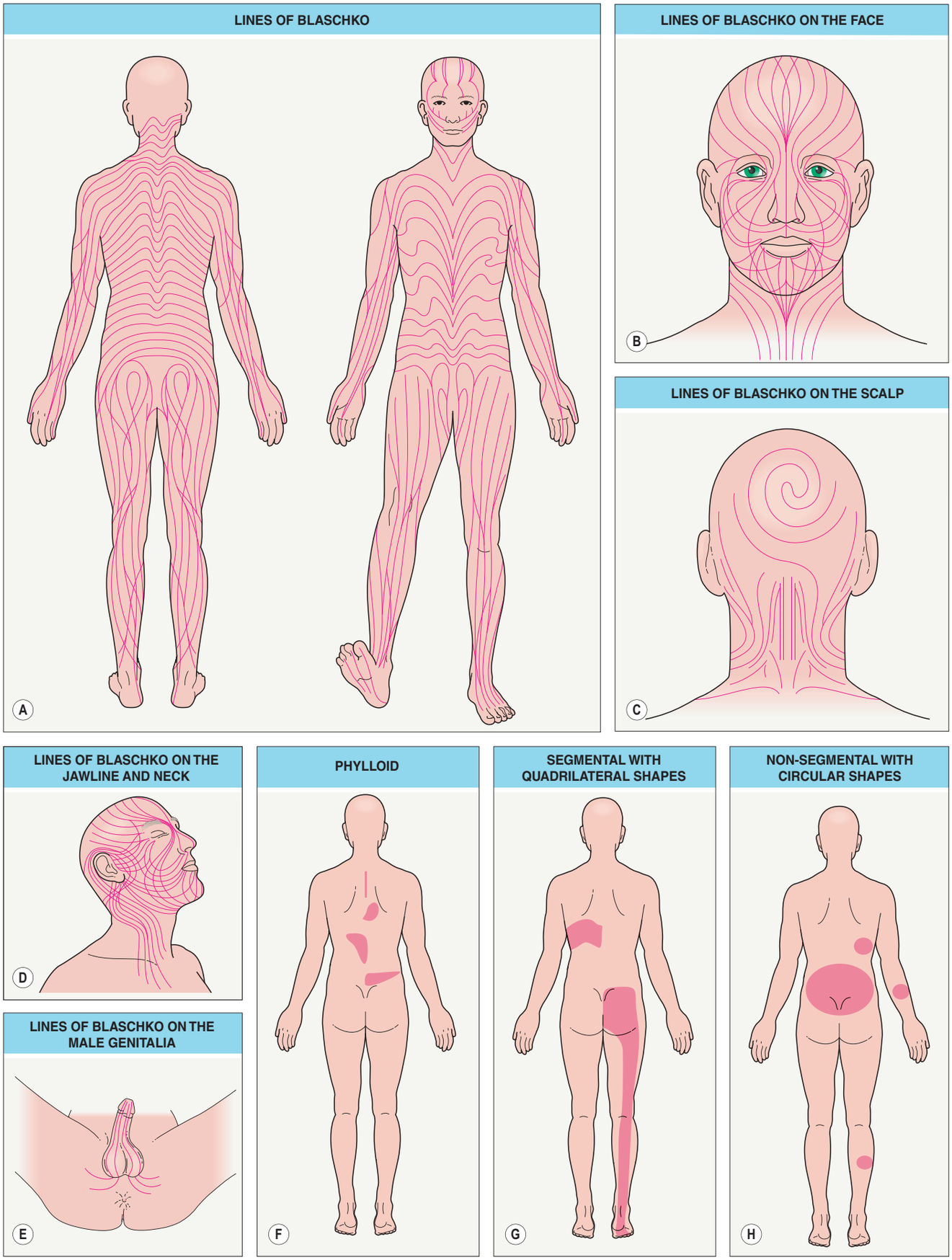


Fig. 62.1 Lines of Blaschko and other mosaic patterns. A These diagrams are taken from Blaschko's original drawings[1]. Note the S-shape of the abdominal lines and the V-shape on the central back. **B** Lines of Blaschko on the face, based on personal observations and ref. 8. **C** Lines of Blaschko on the scalp, based on ref. 8. **D** Lines of Blaschko on the jawline and neck, based on personal observations and ref. 8. **E** Lines of Blaschko on the male genitalia, based on ref. 1. **F** Phylloid pattern, with multiple "leaf-like" or "floral" lesions of different shapes and sizes, without a dominant larger lesion. Often includes linear streaks with midline demarcation. **G** Segmental pattern with quadrilateral shapes. The linear edges are often roughly parallel, with midline demarcation. Involvement may be unilateral or bilateral, ranging from a single relatively small area to an entire "quadrant" such as the arm, shoulder and upper trunk. This pattern encompasses broad bands along the lines of Blaschko and the checkerboard (flag-like) pattern. **H** Non-segmental with circular shapes (encompasses the "patchy pattern without midline separation"). The edges are rounded, and the affected areas may extend around the body, e.g. to form a bathing-trunk pattern. Lesions are of variable sizes and may be single or multiple, with or without a dominant larger lesion that may cross the midline. *F-H, Courtesy Veronica Kinsler, MD, PhD.*

CAUSES OF MOSAICISM AND CHIMERISM			
Cause	**Timing**	**Pathogenesis**	**Consequence**
Genetic (genomic)			
Half-chromatid mutation	First meiotic division of gametogenesis	An incorrect base is added, resulting in a mismatched double strand. When this separates in mitosis, it provides two templates that are not exactly complementary, giving rise to two lines of daughter cells	An individual composed of two different cell lines in approximately equal proportions
Somatic mutation	Postzygotic (i.e. any time after fertilization); not in germ cells/gametes	Any DNA change	A mutant clone within an otherwise normal individual
Chromosomal non-disjunction	Postzygotic	Chromosomes fail to separate correctly during either meiosis or mitosis, resulting in daughter cells with aberrations in chromosome number or structure	An individual composed of two or more different cell lines
Chimerism	Pre- or post-zygotic	Fertilization of one egg by two sperm, or fusion of two zygotes	An individual composed of two cell lines with completely different genotypes
Epigenetic (functional)			
Lyonization	Early embryonic development	Random inactivation in each cell of either the paternal or maternal X chromosome, which then forms the Barr body; once this occurs, it is the same in all daughter cells	A female composed of 2 different cell lines, expressing either the maternal or paternal X chromosome
Epigenetic modification	Inherited or postzygotic	A switch in gene expression, usually involving DNA packaging, resulting from DNA methylation or histone modifications; passed on to daughter cells	Cells with gene expression different from the other cells in that individual

Table 62.1 Causes of mosaicism and chimerism.

EXPECTED PATTERN OF CUTANEOUS MOSAICISM ACCORDING TO ITS TIMING OF ONSET				
Timing	**Configuration/shape of skin lesions**	**Number of skin lesions**	**Laterality**	**Organs affected**
Meiosis	Linear	Multiple	Bilateral	Multi-organ
Very early blastocyst (includes lyonization)	Linear	Multiple	Bilateral	Multi-organ
Later blastocyst	Linear	Fewer	Uni- or bilateral	Multi-organ
Later in first trimester, pre-organogenesis	Linear or oval	Fewer	Uni- or bilateral	Multi-organ
First trimester, post-organogenesis	Linear or oval	Few or single	Uni- or bilateral	Skin only
Second/third trimester	Oval or round	Single	Unilateral	Skin only
Postnatal	Round (smaller)	Single	Unilateral	Skin only

Table 62.2 Expected pattern of cutaneous mosaicism according to its timing of onset.

at a later developmental stage may only lead to a port-wine birthmark. Likewise, the identical mutation in a keratinocyte, melanocyte or pluripotent precursor cell can result in a nevus sebaceus, nevus spilus, or both of these birthmarks, respectively.

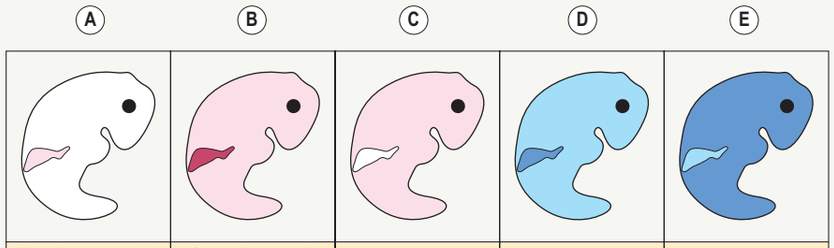
The classic pattern defined by Blaschko is seen in disorders of epidermal cells[9], which is not surprising since Blaschko based his diagrams on epidermal nevi. Investigation of patterns in congenital pigmentary disorders led to the proposal that *narrow* bands following Blaschko's lines reflect mosaicism involving keratinocytes, but not melanocytes[9a]. For example, *KITLG* mutations in keratinocytes can result in narrow hyperpigmented bands[9b]. Embryonic keratinocytes move via directional proliferation, in more-or-less continuous lines that are affected by the complex interplay between cell migration and surface remodeling. In contrast, melanoblasts migrate from the neural crest to the skin, where they then proliferate antenatally. This as well as other characteristics of the aberrant cells and the timing of the genetic alteration may explain the *broad* bands along Blaschko's lines as well as checkerboard and phylloid patterns seen in mosaic pigmentary conditions and the patchy or garment-like distribution of larger congenital melanocytic nevi. For *melanocytic* mosaic disorders, two major patterns have been proposed: (1) *segmental* - characterized by quadrilateral shapes with midline demarcation, encompassing broad Blaschko-linear and checkerboard patterns; and (2) *non-segmental* - characterized by circular shapes without midline demarcation[9a] (see Fig. 62.1G and H).

Cutaneous blood vessels, fibroblasts, other mesodermal derivatives, and nerve cells take different routes; mosaic disorders involving these tissues typically display patterns that correspond to embryonic segments or dermatomes rather than the lines of Blaschko. For example, the patterns of facial capillary malformations and their association with ophthalmologic and neurologic involvement are thought to relate to embryonic placodes[9c]. The distribution of skin lesions along the lines of Blaschko in Goltz syndrome (focal *dermal* hypoplasia) and linear morphea are thought to reflect mutated genes that are expressed in the epidermis but lead to changes in the underlying dermis.

The phenotypic consequences of mosaicism also vary according to: (1) whether the trait is dominant or recessive; (2) whether the mutation is "forward" (pathogenic; gain- or loss-of-function) or revertant (correcting; "backward"/"back"); and (3) whether the individual's background germline genome is "normal" or contains an autosomal dominant or autosomal recessive mutation (Fig. 62.2). In individuals with a "normal" germline genome, the postzygotic mutation can result in *simple segmental mosaicism*. Such mutations are further categorized as either lethal or compatible with life if in the germline. When compatible with life, this has been referred to as *type 1 mosaicism*, defined as a postzygotic mutation in one allele of a gene that underlies an autosomal dominant disorder (e.g. epidermolytic ichthyosis) resulting in one or more regions of affected skin (Fig. 62.2A). The latter may have a linear distribution, e.g. an epidermolytic epidermal nevus. On the other hand, if the postzygotic mutation is lethal when in the germline (e.g. Proteus syndrome), there is no correlate of generalized disease.

Sometimes, a more severe segmental lesion is *superimposed* upon the background of a generalized autosomal dominant disease. This phenomenon, which has been referred to as *type 2 mosaicism*, occurs

MOSAICISM FOR AUTOSOMAL TRAITS



	Simple segmental (type 1) forward in AD	Superimposed (type 2) forward in AD	Revertant in AD	Forward in AR	Revertant in AR
Background genotype	Wild type	Heterozygous	Heterozygous	Heterozygous	Homozygous abnormal
Background phenotype	Normal	Abnormal	Abnormal	Normal	Abnormal
"Line" genotype	Heterozygous	Homozygous abnormal	Homozygous normal	Homozygous abnormal	Heterozygous
"Line" phenotype	Abnormal	Very abnormal	Normal	Abnormal	Normal
Mosaic event	Somatic mutation ("gain of heterozygosity")	Loss of heterozygosity	Reversion to normal*	Loss of heterozygosity	Reversion to heterozygous state**
Example	Type 1 linear Darier disease	Type 2 linear Darier disease	Ichthyosis with confetti	Mosaic AR congenital ichthyosis	Revertant recessive dystrophic EB

*Additional mechanisms include mitotic recombination, with crossing over of homologous chromosomes leading to homozygous mutant and homozygous normal daughter cells, and a second site mutation (e.g. that silences a dominant negative allele).

**Additional mechanisms include gene conversion (where the donating chromosome is unchanged) and a second-site mutation (e.g. that restores the reading frame, prevents a termination codon, or aff ects RNA splicing).

Fig. 62.2 Mosaic mutations in autosomal skin disease genes. The phenotype depends partly on whether the background genotype is wild type (**A**), heterozygous for a dominant condition (**B, C**), heterozygous for a recessive condition (**D**), or homozygous/compound heterozygous for a recessive condition (**E**). Mosaicism for "forward" mutations results in an abnormal streak or segment of skin (**A, B, D**), with mosaic loss of heterozygosity in an individual with a generalized dominant condition resulting in a more severely affected area (**B**). In contrast, revertant mosaicism ("back" mutation) creates a spared area (**C, E**). The revertant phenotype depends on the degree of gene reversion (complete or partial), the timing of the "back" mutation (larger or multiple areas if earlier in development versus a smaller spot if postnatally), and a selective advantage of the revertant cells (e.g. lack of blistering in revertant epidermolysis bullosa).

when an individual with a heterozygous germline mutation in the gene for an autosomal dominant disorder develops a "second hit" postzygotic mutation in the other allele that leads to loss of heterozygosity (or rarely a "double [cis]" mutation in the same allele). This results in a region (e.g. a linear streak) where the genetic burden is doubled (Fig. 62.2B). Superimposed (type 2) mosaicism has been proven on a molecular level in Hailey–Hailey disease, Darier disease[10], PTEN hamartoma tumor syndrome[11], NF1, and basal cell nevus syndrome.

Clonal loss of heterozygosity leading to clinical manifestations may also occur in carriers of autosomal recessive skin conditions such as epidermal dysplasia-skin fragility syndrome and autosomal recessive congenital ichthyosis[12,12a] (Fig. 62.2D). The opposite phenomenon – regional absence of skin disease attributed to a correcting mutation (revertant mosaicism) – can occur in both autosomal recessive and autosomal dominant conditions, including ichthyosis with confetti and several forms of epidermolysis bullosa (EB)[13,14] (Fig. 62.2C, E). Revertant mosaicism has therapeutic potential and has been employed to create pluripotent stem cells and autologous grafts for patients with recessive dystrophic EB[15,16].

Mosaic skin conditions can also be categorized based upon the nature of the corresponding generalized condition (Table 62.3). When assessing a linear skin disorder, it is helpful to consider what the most likely diagnosis would be were the condition to affect the entire skin surface. While the lesional morphology and histology of the mosaic condition are typically similar to the generalized form, the connection may not be immediately obvious due to differences in distribution and overall appearance. If no generalized disorder exists to match the linear lesions, then the patient could have a dominant mutation (autosomal or X-linked) that is only survivable in the mosaic form.

Mosaicism for autosomal dominant disorders can arise after fertilization (postzygotic/somatic mutation) or less often during gametogenesis (half-chromatid mutation). Although a simple segmental (type 1) mosaic condition itself is not heritable, there is a risk of passing on the full-blown disorder to the next generation if mutant cells are present not just in the skin but also in the gonads (gonadal mosaicism). Examples include an epidermolytic epidermal nevus (due to *KRT1* or *KRT10* mosaicism) passed on as epidermolytic ichthyosis, a porokeratotic eccrine and ostial dermal duct nevus (*GJB2* [gap junction β2]) passed on as keratitis-ichthyosis-deafness (KID) syndrome, and segmental neurofibromatosis type 1 (*NF1*) passed on as generalized NF1. A correlation between the size or site of the parent's mosaic lesion and the risk to offspring has not been established. If the parental mutation is known, prenatal diagnosis is possible if clinically appropriate, and men can theoretically undergo DNA analysis of sperm to quantify the risk to their offspring[17].

Fig. 62.3 provides an approach to the differential diagnosis of skin lesions that follow the lines of Blaschko. Selected mosaic disorders will be discussed in more detail below.

APPROACH TO MOLECULAR TESTING FOR GENOMIC MOSAICISM

Although mosaic mutations are sometimes present in the peripheral blood (especially when findings are widespread), a sample of *affected tissue* (e.g. skin biopsy specimen) is more likely to contain mutant cells. In addition to the skin biopsy, it is often recommended that a blood sample be sent for comparative analysis. For DNA-based tests (including whole-exome or whole-genome sequencing, multi-gene panels, and arrays), DNA can be extracted directly from the skin biopsy, which is typically used in its entirety if it is not known with certainty which cell type is affected (e.g. keratinocytes vs melanocytes).

Many phenotypically distinct mosaic diseases have been found to have the same genetic basis and therefore have been grouped together as part of a spectrum. For example, depending on the cell type(s) affected, manifestations of the *PIK3CA*-related overgrowth spectrum (PROS) can include vascular malformations, lipomatosis, and epidermal nevi. This enables genotype-driven targeted therapies, such as treatment of PROS with phosphatidylinositol 3-kinase (PI3K) inhibitors, when the genetic etiology has been identified[17a].

MOSAIC SKIN CONDITIONS WITH CORRESPONDING GENERALIZED CONDITIONS AND ASSOCIATED GENES			
Mosaic condition	**Generalized condition**	**Gene symbol [? = likely candidate for mosaic condition]**	**Protein**
X-linked dominant mutations: mosaic patterns in females, usually lethal in males			
Incontinentia pigmenti	(Hypomorphic mutations: hypohidrotic ectodermal dysplasia with immune deficiency)	*IKBKG (NEMO)*	Inhibitor of nuclear factor κB kinase regulatory subunit γ
Goltz syndrome	NR	*PORCN*	Porcupine homolog
Conradi–Hünermann–Happle syndrome	NR	*EBP*	Emopamil binding protein
CHILD syndrome	NR	*NSDHL*	NAD(P)-dependent steroid dehydrogenase like
Linear skin defects with multiple congenital anomalies (LSDMCA) 1 (MIDAS syndrome), 2, and 3	NR	1: *HCCS;* 2: *COX7B;* 3: *NDUFB11*	Holocytochrome c synthase; 2: cytochrome c oxidase, subunit 7B; 3: NADH:ubiquinone oxidoreductase
Oral–facial–digital syndrome type 1	NR	*OFD1*	OFD1 centriole and centriolar satellite protein
Terminal osseous dysplasia with pigmentary defects*	NR	*FLNA*	Filamin A
X-linked recessive mutations: variable mosaic patterns in females, generalized in males			
Linear hypohidrosis, alopecia/lack of adnexa, ± hyperpigmentation	Hypohidrotic ectodermal dysplasia	*EDA*	Ectodysplasin A
Incontinentia pigmenti-like lesions (stages 3 and 4)	Hypohidrotic ectodermal dysplasia with immune deficiency	*IKBKG (NEMO)*	See above
Linear hyperpigmentation	X-linked reticulate pigmentary disorder	*POLA1*	DNA polymerase-α1, catalytic subunit
Linear hyperpigmentation	X-linked dyskeratosis congenita	*DKC1*	Dyskerin
Linear hypopigmentation	Menkes disease	*ATP7A*	ATPase, copper-transporting, α polypeptide
Linear hypotrichosis and scaling	Ichthyosis follicularis with atrichia and photophobia (IFAP), X-linked keratosis follicularis spinulosa decalvans, X-linked Olmsted syndrome	*MBTPS2*	Membrane-bound transcription factor peptidase, site 2
See text for other X-linked etiologies of Blaschko-linear hypo- and hyperpigmentation			
Autosomal dominant mutations (including lethal conditions)			
Various types of epidermal and sebaceous nevi	See Table 62.6		
Linear Darier disease	Darier disease	*ATP2A2*	ATPase, calcium-transporting
Linear Hailey–Hailey disease	Hailey–Hailey disease	*ATP2C1*	ATPase, calcium-transporting
Linear porokeratosis	Porokeratosis	*MVD, PMVK*	Mevalonate diphosphate decarboxylase, phosphomevalonate kinase
Linear basal cell nevus	Basal cell nevus syndrome	*PTCH1*	Patched 1
Happle–Tinschert/Curry–Jones syndrome	NR	*SMO*	Smoothened
Segmental café-au-lait macules, lentigines, and/or neurofibromas	Neurofibromatosis type 1	*NF1*	Neurofibromin 1
Segmental café-au-lait macules and lentigines	Legius syndrome	*SPRED1*	Sprouty-related EVH1 domain-containing 1
Linear/segmental angiofibromas	Tuberous sclerosis complex	*? TSC1, TSC2*	Hamartin, tuberin
Segmental leiomyomas	Multiple cutaneous and uterine leiomyomatosis	*FH*	Fumarate hydratase
Linear trichoepitheliomas, spiradenomas, and/or cylindromas	Multiple familial trichoepitheliomas, Brooke–Spiegler syndrome, familial cylindromatosis	? *CYLD*	Cylindroma lysine 63 deubiquitinase
Venous malformation	Multiple cutaneous and mucosal venous malformations (VMCM), blue rubber bleb nevus syndrome	*TEK(TIE2)*	TIE-2 endothelial tyrosine kinase
Segmental plaque-type glomuvenous malformations	Hereditary glomuvenous malformations	*GLMN*	Glomulin
Verrucous venous malformation ("verrucous hemangioma")	NR	*MAP3K3*	MAPK kinase kinase 3
Parkes Weber syndrome/arteriovenous malformation (AVM)	Capillary malformation (CM)–AVM syndrome	*RASA1, EPHB4*	RAS p21 protein activator 1 EPH receptor B4

Table 62.3 Mosaic skin conditions with corresponding generalized conditions and associated genes.

MOSAIC SKIN CONDITIONS WITH CORRESPONDING GENERALIZED CONDITIONS AND ASSOCIATED GENES			
Mosaic condition	**Generalized condition**	**Gene symbol [? = likely candidate for mosaic condition]**	**Protein**
Sturge–Weber syndrome, port-wine stains, dermal melanocytosis, phakomatosis pigmentovascularis type II, congenital hemangiomas	NR	*GNAQ, GNA11*	Q-type G proteins, α-stimulating
Becker nevus	Baraitser-Winter syndrome, juvenile-onset dystonia**	*ACTB*	β-actin
McCune–Albright syndrome	NR for activating mutations	*GNAS*	G protein, α-stimulating
Nevus spilus, phakomatosis pigmentokeratotica	Costello syndrome**	*HRAS*	HRAS
Nevus spilus, phakomatosis pigmentovascularis type III	Noonan syndrome with multiple lentigines	*PTPN11*	Protein tyrosine phosphatase non-receptor
Classic CMN, nevus spilus-type CMN	Noonan syndrome**	*NRAS*	NRAS
Agminated melanocytic nevi; linear syringocystadenoma papilliferum; arteriovenous malformations (also *MAP2K1, KRAS*, and *HRAS*)	Cardio-facio-cutaneous syndrome**	*BRAF*	BRAF
Encephalocraniocutaneous lipomatosis; arteriovenous malformations (*KRAS*)	Craniosynostosis/skeletal dysplasia syndromes* *(FGFR1);* Noonan and cardio-facio-cutaneous syndromes* (*KRAS*)	*FGFR1, KRAS*	Fibroblast growth factor receptor 1, KRAS
Linear hyperpigmentation with syndromic findings	Smith-Kingsmore syndrome	*MTOR*	Mechanistic target of rapamycin
RHOA-related neuroectodermal syndrome	NA	*RHOA*	Ras homolog family member A
Autosomal recessive mutations			
Linear scaling and erosions	Ectodermal dysplasia with skin fragility	*PKP1*	Plakophilin 1
Linear scaling and erythema	Autosomal recessive congenital ichthyosis	*ABCA12*	ATP binding cassette subfamily A member 12

*Features hyperpigmented, atrophic (with dermal hypoplasia) facial macules and digital fibromas.
**In general, the mutations in this gene that cause generalized disease are different (e.g. less severe) than those that underlie mosaic disorders.

Table 62.3 Mosaic skin conditions with corresponding generalized conditions and associated genes. Epidermal nevi with known genetic bases are presented in Table 62.6. CMN, congenital melanocytic nevus; MIDAS, *mi*crophthalmia, *d*ermal *a*plasia and *s*clerocornea; NR, not reported (presumably lethal).

FUNCTIONAL MOSAICISM IN X-LINKED GERMLINE DISORDERS

In women heterozygous for X-linked disorders, functional mosaicism due to random X-chromosome inactivation (lyonization) may produce skin lesions following the lines of Blaschko. Sons who inherit the abnormal X chromosome carry and express the mutation in all cells; if "recessive", the disorder is generally compatible with survival (e.g. hypohidrotic ectodermal dysplasia), but if "dominant", the disorder is typically so severe that males die before birth (e.g. incontinentia pigmenti, Goltz syndrome). Occasionally, male patients present with skin lesions following the lines of Blaschko because they themselves are mosaic for an X-linked dominant disorder, and therefore, protected by the presence of some normal X chromosomes. X-chromosome mosaicism in boys and men can result from Klinefelter syndrome (where the extra X chromosome permits lyonization) or a postzygotic or half-chromatid mutation (see Tables 62.1 and 62.4).

Lyonization occurs synchronously in all cells at about the 1000-cell stage, so the two clones are intimately mixed from the beginning. Female patients with X-linked genodermatoses typically have numerous skin lesions that follow the lines of Blaschko in narrow bands. A curious exception is CHILD (*c*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects) syndrome, which characteristically shows large unilateral blocks of abnormal skin. This lateralization pattern may reflect the effects of expression of the mutant versus normal X-chromosome in organizer cells that control large developmental fields. Alternatively, a deficiency in sonic hedgehog signaling (which normally helps to confer left–right asymmetry) in cells expressing the *NSDHL* mutation may result in selection against these cells on one side of the body.

Not all X-linked skin disorders follow the lines of Blaschko. For example, women who are heterozygous for the gene defects that underlie Fabry disease, Wiskott–Aldrich syndrome, and chronic granulomatous disease have either no lesions or scattered lesions in a non-linear pattern. This is likely because the cells that express the mutated gene are circulating leukocytes or non-epidermal cells (e.g. endothelial cells) for which lyonization does not produce a clinically apparent pattern. In the case of steroid sulfatase-deficient ichthyosis, where the defect is epidermal but not evident in female carriers, the steroid sulfatase gene is on a part of the X chromosome that does not undergo lyonization.

Incontinentia Pigmenti

Synonym: ■ Bloch–Sulzberger syndrome

Key features

- An X-linked dominant disorder with skin lesions that follow the lines of Blaschko
- Four cutaneous stages: (1) inflammatory/vesicular; (2) verrucous; (3) hyperpigmented; and (4) hypopigmented/atrophic
- Other ectodermal abnormalities may be present, e.g. alopecia, nail dystrophy, pegged or missing teeth
- May also have ocular (~20–40%) and neurologic (~30%) involvement
- Caused by mutations in *IKBKG* (*NEMO*)

Introduction

Incontinentia pigmenti (IP) is a multisystem disorder with an estimated birth prevalence of 1:140 000 and a female:male ratio of ~20:1. Patients may present to neonatologists, neurologists, ophthalmologists, or dentists as well as dermatologists. However, the diagnosis typically rests on recognition of the cutaneous findings[17b]. The name refers to the pathologic finding of pigmentary incontinence, i.e. dermal melanophages, in the third stage of the disease. The linear skin lesions reflect *functional* mosaicism secondary to X inactivation (lyonization).

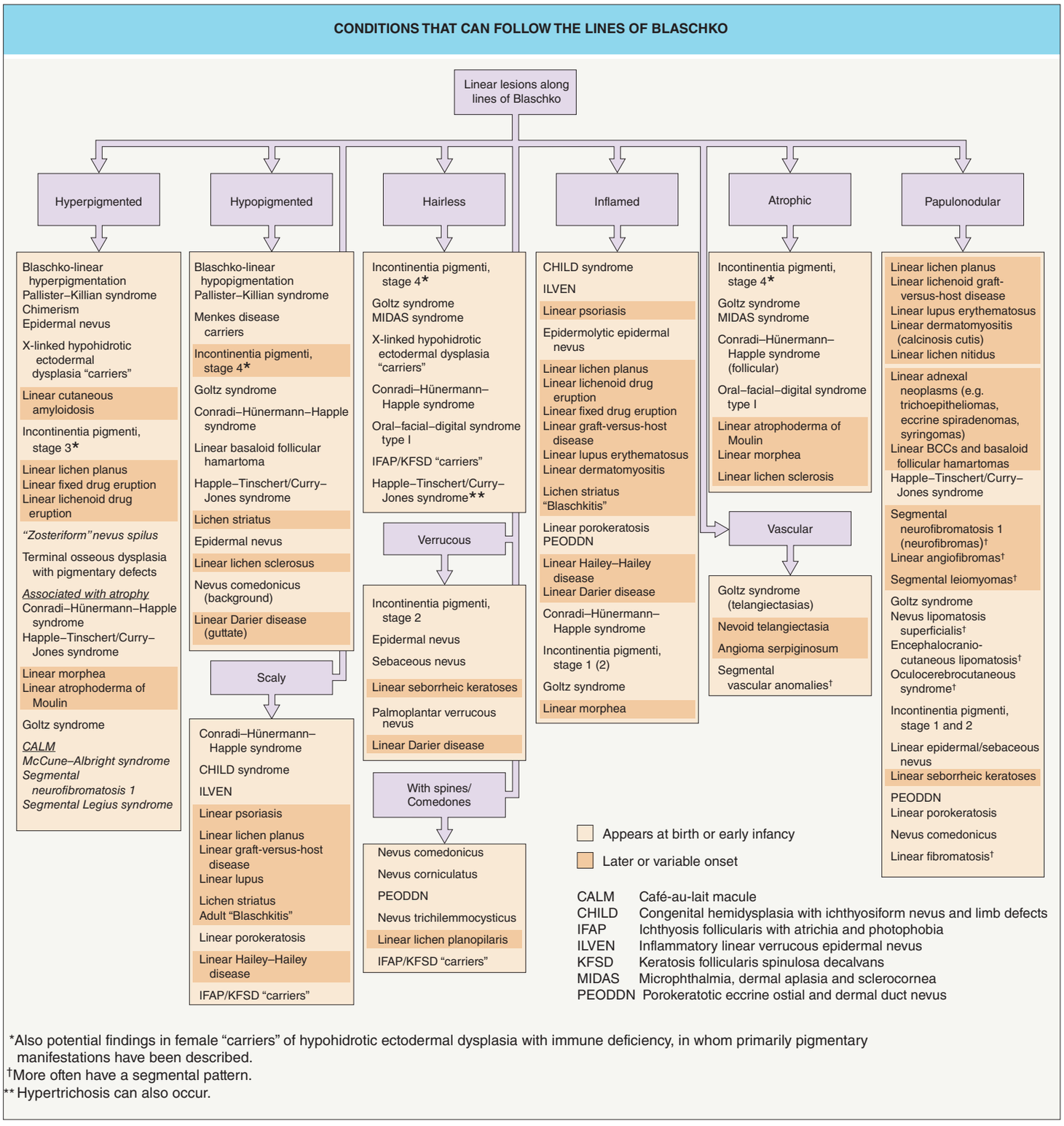


Fig. 62.3 Conditions that can follow the lines of Blaschko. Most of these conditions occur in narrow bands as shown in Fig. 62.2A-E. However, those in italics typically have the segmental pattern with quadrilateral shapes shown in Fig. 62.2G, which includes broad bands along the lines of Blaschko.

History

Although Garrod probably first described IP in 1906, Bloch's 1926 report of a "previously unreported pigment disorder" and that 2 years later by Sulzberger are remembered eponymously. In 2000, the International Incontinentia Pigmenti Consortium established that IP is caused by mutations in *IKBKG*, which encodes inhibitor of nuclear factor κB kinase regulatory subunit γ, also known as *NEMO* (*N*F-κB *e*ssential *mo*dulator).

Genetics

IP is an X-linked dominant disorder, usually antenatally lethal in boys, that is caused by mutations in *IKBKG* located at Xq28[18]. Approximately 80% of patients have a common large deletion of exons 4–10 that tends to arise during paternal meiosis (male gametogenesis). Occasional occurrences of clinically typical IP in boys are attributed to Klinefelter syndrome (~10% of male patients) or to genomic mosaicism due to a half-chromatid or postzygotic *NEMO* mutation (Table 62.4)[19]. In the latter patients, the

FINDINGS IN GIRLS AND BOYS WITH *NEMO* MUTATIONS					
	Girl with IP	**Boy with IP + Klinefelter syndrome**	**Son of mother with classic IP**	**Somatic mosaic boy with IP**	**Boy with HED-ID†**
Karyotype	XX	XXY	XY	XY	XY
***IKBKG* genotype**	Heterozygous for typical mutation*	Heterozygous for typical mutation*	Hemizygous for typical mutation*	Mosaic hemizygous for typical mutation* (half-chromatid or postzygotic)	Hemizygous for milder ("hypomorphic") mutation that does not abolish activity
Skin findings	Classic IP	Classic IP	NA	Classic IP, although may have a more limited distribution (e.g. unilateral or localized)	Hypotrichosis, hypohidrosis, recurrent pyogenic infections, extensive seborrheic- or atopic-like dermatitis, reticulated hyperpigmentation (less common)
Immunodeficiency	No	No	Yes, extremely severe	No	Yes, with dysgammaglobulinemia (↑IgM, ↓IgG)
Life expectancy	Normal	Normal	Usually lethal before birth	Normal	Typically shortened due to pyogenic and opportunistic infections; may improve with hematopoietic stem cell transplantation

*A particular large deletion that removes exons 4–10 is found in ~65% of female patients with IP; a NEMO mutation may be difficult to detect in peripheral blood samples from mosaic male patients (since mutant leukocytes are prone to apoptosis), so analysis of DNA from lesional skin may be required.
†Mother may have a mild variant of IP; affected boys typically have missing/conical teeth. An allelic variant features osteopetrosis and lymphedema, and an autosomal dominant condition with a similar phenotype can result from mutations in NF-κB inhibitor α gene (NFKBIA).

Table 62.4 Findings in girls and boys with *NEMO* mutations. HED-ED, hypohidrotic ectodermal dysplasia with immune deficiency; IP, incontinentia pigmenti; NA, not applicable; *IKBKG*, inhibitor of nuclear factor κB kinase regulatory subunit γ.

distribution of the skin lesions may be relatively limited. A large genetic biobank has been established to facilitate IP research[19a].

Pathogenesis

The NEMO protein is a subunit of a kinase that activates NF-κB, a transcription factor that protects against TNF-α-induced apoptosis (Fig. 62.4). Defective linear ubiquitination has been described in association with a truncated NEMO protein[19b]. The idea of IP as a pro-apoptotic state explains male lethality, destruction of epidermal cells, and progressive replacement of cells expressing the mutant X chromosome by those expressing the normal allele[18]. In one report, a liveborn boy whose mother had classic IP died hours after birth due to lethal hematopoietic and immunologic disturbances[20]. Milder hypomorphic *NEMO* mutations are responsible for hypohidrotic ectodermal dysplasia with immune deficiency (HED-ID) in boys, whose mothers often have relatively subtle features of IP (see Table 62.4 and Ch. 63)[21].

Clinical features

IP typically presents with linear erythema and vesicles (stage 1) during the first few weeks to months of life in an otherwise healthy baby girl (see Fig. 34.13)[22]. Vesiculobullous lesions are most common on the limbs and scalp, frequent on the trunk, and rare on the face (Fig. 62.5A). They resolve within days to weeks and are often replaced by verrucous linear plaques (stage 2) that favor the extremities (Fig. 62.5B) and usually disappear later in infancy. Streaks and swirls of reticulate grayish-brown hyperpigmentation (stage 3) develop next and have a predilection for the trunk and intertriginous sites, with scalloped edges that are thought to reflect the growth of normal keratinocytes into affected skin (Fig. 62.5B, C). Gray-brown dots in a linear array represent a characteristic dermoscopic finding of stage 3 IP. The inflammatory sequence sometimes recurs within pigmented areas during later infancy or childhood together with intercurrent febrile illnesses. In addition, acral keratotic nodules (including subungual lesions) occasionally arise after puberty (Fig. 62.5D). The hyperpigmented streaks tend to fade by adolescence, although a few areas of slate-gray pigmentation may persist lifelong. From puberty onward, linear hypopigmented bands lacking hair and sweat glands (stage 4) appear on the posterior aspects of the limbs (especially the calves; Fig. 62.5E) and may be the only stigmata of the disease during adulthood[23]. Individual stages of IP may be absent or overlap. Extracutaneous manifestations of this condition are listed in Table 62.5.

Pathology

The early inflammatory phase of IP demonstrates eosinophilic spongiosis and scattered dyskeratotic keratinocytes. The epidermis of verrucous lesions is acanthotic with hyperkeratosis and foci of dyskeratosis. In stage 3, there is pigmentary incontinence as well as variable vacuolization of basal keratinocytes, whereas stage 4 is characterized by a thinned epidermis and dermis devoid of adnexa[23].

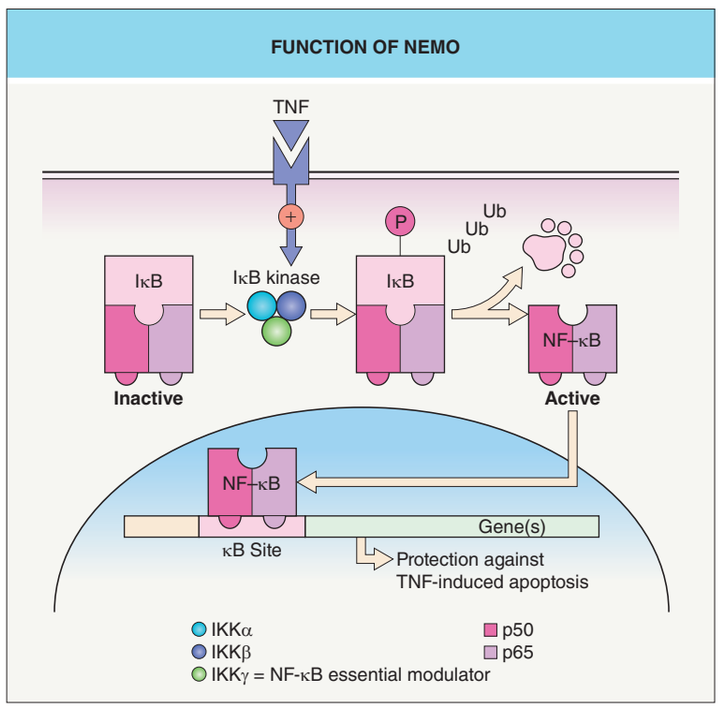


Fig. 62.4 Function of NEMO. In incontinentia pigmenti, lack of NEMO (NF-κB essential modulator; also known as IKBKG [*i*nhibitor of nuclear factor κB kinase regulatory subunit γ]) results in failure to activate NF-κB, which normally protects against tumor necrosis factor (TNF)-induced apoptosis.

Differential diagnosis

Neonatal IP can usually be distinguished from infectious conditions (e.g. herpes zoster, varicella, herpes simplex viral infections) by the wellbeing of the child and characteristic patterning of the skin lesions. Peripheral eosinophilia and leukocytosis are common in neonates with IP, and histologic examination can confirm the diagnosis. In Blaschko-linear hyper- or hypopigmentation due to pigmentary mosaicism, there is no preceding inflammatory phase, the hyperpigmentation is epidermal, and adnexa are typically normal.



Fig. 62.5 Incontinentia pigmenti. A Stage 1 with streaks of erythema and vesicles in a neonate. **B** Stages 2 (verrucous) and 3 (hyperpigmented). Note the keratotic lesions on the toes (**B**). **C** Residual stage 3 involvement in the axilla of a young girl. The scalloped edges of the hyperpigmented streaks are thought to reflect growth of normal keratinocytes into areas of apoptosis. **D** Hyperkeratotic nodules on the leg of a teenage girl. **E** Stage 4 (atrophic and hypopigmented). Note absence of hairs within the streaks on the calf. *A, Courtesy Robert A. Silverman, MD; B, E, Courtesy Celia Moss, MBBS, MA, DM.*

Treatment

Baseline and longitudinal ophthalmologic (especially during infancy) and neurologic evaluations represent the most important aspects of IP management early in life[17b]. Prompt laser therapy can reduce the likelihood of visual sequelae in patients with retinal vasculopathy[23a]. MRI and electroencephalogram are indicated for infants with neurologic symptoms, and European consensus guidelines also recommend a brain MRI at ~2 years of age in children without neurologic manifestations[17b]. Initial dental assessment is recommended at 2-3 years of age, with further intervention by specialists as indicated. The mother should be examined for subtle atrophic streaks, usually most visible on the calves, and genetic testing can assist with family planning. Rare cases of transmission from a mosaic father to a daughter have been reported[23b].

Hypohidrotic Ectodermal Dysplasia With Immune Deficiency

This condition is discussed in detail in Chapter 63.

Goltz Syndrome (Focal Dermal Hypoplasia)

Synonym: ■ Goltz–Gorlin syndrome

Key features

- X-linked dominant condition in which skin lesions follow the lines of Blaschko and consist of dermal atrophy in association with variable fat "herniation", telangiectasias, and pigmentary changes
- "Raspberry-like" papillomas favor the perioral and anogenital regions
- Nail dystrophy, ocular defects, dental anomalies, and limb malformations such as ectrodactyly (split hand/foot) are common
- Caused by mutations in *PORCN*

Introduction

This uncommon genetic disorder was first described by Goltz in 1962 and ectodermal and mesodermal structures – primarily the skin, eyes, teeth, and bones – are affected in a mosaic pattern.

ADDITIONAL MANIFESTATIONS OF INCONTINENTIA PIGMENTI
Surface ectodermal defects
• Missing and conical *teeth* (40–50% of patients) • Linear absence of *hair* (swirled at the vertex in 30–40% of patients) and *sweat glands* • Dystrophic *nails* (ridging, pitting > subungual keratoses; 10–20% of patients) • Asymmetric *breast* development or supernumerary *nipples*
Eye anomalies (20–40% of patients)
• Retinal vascular abnormalities • Strabismus • Cataracts • Microphthalmia • Optic atrophy
Central nervous system abnormalities (30–60% of patients)
• Seizures • Motor and intellectual delay • Microcephaly • Hemorrhagic stroke
Skeletal defects (uncommon)
• Skull anomalies • Scoliosis
Other organs (uncommon)
• Pulmonary hypertension

Table 62.5 Additional manifestations of incontinentia pigmenti.

Genetics

Goltz syndrome is an X-linked dominant condition caused by mutations in *PORCN*, with the mosaic distribution of skin lesions in female patients reflecting lyonization. Although Goltz syndrome is antenatally lethal in boys with non-mosaic hemizygous mutations (as in IP; see Table 62.4), male patients with genomic (e.g. due to a postzygotic mutation) or functional (in the setting of Klinefelter syndrome) mosaicism account for ~10% of affected individuals.

Approximately 95% of all Goltz syndrome cases are sporadic, which likely reflects both a decreased likelihood of reproduction by severely affected women and the lethality of *PORCN* mutations with widespread expression. Some authors have postulated that either preferential inactivation of the mutant X chromosome or a postzygotic mutation is required for survival of affected female fetuses[24]. Rare familial cases often show anticipation, with the offspring being more severely affected than the parent and having a higher proportion of cells expressing the mutant X chromosome. The possibility that an apparently normal mother is a carrier must therefore be considered.

Pathogenesis

PORCN belongs to the evolutionarily conserved porcupine gene family and is expressed in the skin, craniofacial and long bones, tooth buds, and eyes – structures affected in Goltz syndrome. PORCN is an endoplasmic reticulum protein with multiple transmembrane domains. It functions as an O-acyltransferase involved in palmitoylation and secretion of Wnt, a morphogen important in ectomesodermal tissue development[24,25]. Wnt signaling stimulates fibroblast proliferation, inhibits adipogenesis, and induces osteogenesis, explaining the dermal hypoplasia, fat "herniations", and osteopathia striata (streaks of decreased bone density) observed in Goltz syndrome. Wnt also has key roles in early limb patterning and tooth formation.

Although the primary cutaneous abnormality in Goltz syndrome is in the dermis, the distribution of skin lesions along the lines of Blaschko reflects embryonic migration pathways of epidermal cells. Ectoderm-specific deletion of *PORCN* in mice has shown that expression of this gene in the epidermis and resultant Wnt signaling regulate development of the underlying dermis and fat[26]. Of note, patients with Goltz syndrome have a thin epidermis and abnormal adnexal structures. This is not surprising considering that Wnt signaling, including β-catenin-dependent pathways, is known to have critical roles in epidermal regeneration and adnexal morphogenesis/maintenance (see Fig. 55.6).

In 3 of 24 patients in one series, a microdeletion affected both *PORCN* and the adjacent *EBP* gene responsible for Conradi–Hünermann–Happle syndrome (see below). Curiously, however, these patients showed no features of the latter disorder. This implies that the *PORCN*-related hypoplastic skin phenotype predominates over the ichthyosis and follicular changes of Conradi–Hünermann–Happle syndrome[24].

Clinical features

The phenotype of Goltz syndrome is highly variable, depending on the proportion and distribution of cells expressing the mutant X chromosome[25,27]. Streaks of vermiculate dermal atrophy and/or telangiectasias are often present from birth (Fig. 62.6A–C). Later, hypo- and hyperpigmentation as well as "herniations" of fat develop. Although "raspberry-like" papillomas with a verrucous surface and fibrovascular core may appear in any location, they favor the anogenital region as well as the lips (Fig. 62.6D), larynx, and acral sites. Limb malformations affect >80% of patients and include ectrodactyly (split hand/foot malformation), asymmetric syndactyly, oligodactyly, and long bone reduction defects. Radiographs of the midportion of the lower extremities characteristically show osteopathia striata. Eye abnormalities, often unilateral, include iritic and chorioretinal colobomas, microphthalmia, anophthalmia, and cataracts. Dystrophic nails (e.g. longitudinal fissures, hypoplasia), sparse hair, abnormal teeth (e.g. vertical grooving, hypodontia), and dysmorphic facies (e.g. notched nasal alae, pointed chin, large malformed ears) may be observed. Other reported features include aplasia cutis congenita, ventral body wall defects, cleft lip/palate, obstructive sleep apnea, gastrointestinal dysfunction, impaired hearing, intellectual impairment, and anomalies of the CNS, spine, urinary tract, or uterus.

Pathology

Affected skin shows a marked reduction in the thickness of the dermis, with fewer adnexal structures[25]. As a consequence of the decreased dermal thickness, adipose tissue may be found just below the epidermis. An increase in papillary dermal blood vessels may also be seen.

Differential diagnosis

The distinctive cutaneous and extracutaneous findings of Goltz syndrome, especially dermal atrophy/fat "herniations" and osteopathia striata, distinguish it from other X-linked dominant genodermatoses. Examples of such conditions include MIDAS (which does not involve the distal extremities), Conradi–Hünermann–Happle, and oral–facial–digital type 1 syndromes. Although an inflammatory component is occasionally observed, the skin lesions of Goltz syndrome are relatively static compared to the evolving lesions of IP.

Treatment

Treatment is supportive, with appropriate subspecialist referral based on the associated abnormalities. The telangiectasias may be improved by pulsed dye laser treatment. Troublesome exophytic papillomas can be treated with curettage or photodynamic therapy.

Conradi–Hünermann–Happle Syndrome (X-Linked Dominant Chondrodysplasia Punctata)

This rare X-linked dominant disorder presents in female neonates with ichthyosiform erythroderma characterized by feathery, adherent scale distributed along the lines of Blaschko (see Ch. 57). Characteristic extracutaneous findings include asymmetric shortening of the proximal limbs with epiphyseal stippling (chondrodysplasia punctata) and ocular anomalies such as cataracts and microphthalmia[28]. Patients often have swirled cicatricial alopecia and coarse, lusterless hair. After infancy, the skin changes evolve into follicular atrophoderma. Conradi–Hünermann–Happle syndrome is caused by mutations in the *emopamil binding protein* (*EBP*) gene[29], which lies on the X chromosome adjacent to *PORCN* and encodes an isomerase essential for cholesterol biosynthesis. The cardinal biochemical abnormality is increased plasma 8(9)-cholestenol and 8-dehydrocholesterol[28].

CHILD Syndrome (*C*ongenital *H*emidysplasia With *I*chthyosiform Erythroderma [or Nevus] and *L*imb *D*efects)

CHILD syndrome is a rare X-linked dominant disorder that presents with unilateral skeletal hypoplasia ranging from amelia to mild distal



Fig. 62.6 Goltz syndrome (focal dermal hypoplasia). A, B Hypopigmented streaks of vermiculate atrophy. Note the fat herniation (**A**). **C** Streaks of telangiectasias plus erosions on the leg. **D** Several erythematous, raspberry-like papules on the lips. The most prominent lesion is at the angle of the mouth. Similar lesions can occur in the anogenital region and may be confused with warts. *D, Courtesy Celia Moss, MBBS, MA, DM.*

defects, chondrodysplasia punctata, and occasionally defects in internal organs (see Ch. 57). Erythematous, thickened skin with yellowish scaling may have a striking unilateral distribution with sharp midline demarcation, follow the lines of Blaschko, and/or favor skin folds. With time, lipid accumulates and lesions develop features of a verruciform xanthoma. CHILD syndrome results from mutations in *NSDHL* located on Xq28, which encodes a 3β-hydroxysteroid dehydrogenase enzyme involved in cholesterol biosynthesis[30]. Pathogenesis-based topical therapy with lovastatin or simvastatin plus cholesterol is highly beneficial[31].

Linear Skin Defects With Multiple Congenital Anomalies (Including MIDAS Syndrome)

Linear skin defects with multiple congenital anomalies (LSDMCA) represents a group of X-linked dominant conditions that are antenatally lethal in males and characterized by *mi*crophthalmia, *d*ermal *a*plasia, and *s*clerocornea (MIDAS syndrome; see Table 64.4)[32]. Aplastic linear skin lesions with stellate borders are usually confined to the face and neck. Other reported features include agenesis of the corpus callosum, developmental delay, short stature, cardiac anomalies, and genital malformations. LSDMCA can be caused by mutations in several genes that encode mitochondrial enzymes – *HCCS* (holocytochrome c synthase), *COX7B* (cytochrome c oxidase), and *NDUFB11* (NADH:ubiquinone oxidoreductase subunit B11)[33].

Oral–Facial–Digital Syndrome Type I

Oral–facial–digital syndrome type I is an X-linked dominant condition characterized by cleft (or pseudocleft) lip/palate, lobulations and hamartomas of the tongue, hypertrophic oral frenula associated with alveolar clefts, digital malformations, structural brain abnormalities, intellectual disability, polycystic kidneys, facial milia (primarily during infancy), and patchy alopecia that is typically whorled at the vertex. It is caused by mutations in *OFD1*, which encodes a centrosomal protein located at the base of primary (non-motile) cilia[34]. The latter structures are present on most cells and mediate signaling pathways such as Hedgehog and Wnt during embryonic development.

X-linked Etiologies of Blaschko-Linear Hypo- and Hyperpigmentation

Several X-linked disorders can present with hypo- or hyperpigmentation along the lines of Blaschko in affected girls and women. *Börjeson-Forssman-Lehmann syndrome*, due to germline mutations in *PHF6*, presents with Blaschko-linear hyperpigmentation that favors the axillae; additional features include dental and digital anomalies, hypoplastic nails, intellectual disability, and facial features such as prominent supraorbital ridges and frontotemporal hypotrichosis[34a].

TFE3-associated neurodevelopmental disorder is characterized by linear hypopigmentation or (less often) hyperpigmentation as well as lysosomal storage disorder-like findings such as skeletal anomalies, intellectual disability, seizures, and coarse facial features. Although most affected individuals are female, there are reports of male patients with this disorder, some of whom were shown to be mosaic[34b]. The TFE3 transcription factor functions in mTOR signaling and has roles in lysosomal biogenesis and embryonic stem cell differentiation[34b].

Female-restricted X-linked syndromic intellectual development disorder-99 due to germline mutations in *USP9X* (encodes ubiquitin-specific peptidase 9) is associated with pigmentary alteration (hypopigmentation documented) along the lines of Blaschko in the majority of patients[34c]. Other features include structural brain abnormalities, facial dysmorphism, cleft palate, short stature, polydactyly, cardiac defects, breast underdevelopment, and scoliosis[34c].

X-Linked Hypohidrotic Ectodermal Dysplasia (Female Patients)

Female patients ("carriers") with the X-linked form of hypohidrotic ectodermal dysplasia may have mild dental anomalies, patchy alopecia, and variable degrees of reduced sweating, with a lack of adnexa and sometimes hyperpigmentation in a distribution corresponding to the lines of Blaschko (see Ch. 63 and Fig. 55.10).

Menkes Disease (Female Carriers)

Menkes disease, an X-linked recessive disorder caused by dysfunction of a Cu^{2+}-transporting ATPase (α-polypeptide), is discussed in Ch. 69. Female carriers may have patchy pili torti and hypopigmentation along the lines of Blaschko, attributable to functional mosaicism for cells with abnormal copper metabolism.

X-Linked Reticulate Pigmentary Disorder

X-linked reticulate pigmentary disorder is caused by mutations in *POLA1* that encodes the catalytic subunit of DNA polymerase-α, a regulator of the type I interferon response. Female patients have hyperpigmented streaks following the lines of Blaschko, whereas male patients have generalized reticulated hyperpigmentation and systemic manifestations (see Ch. 67). Histologic findings, which are similar in both sexes, include increased epidermal melanin, dermal melanophages, and necrotic keratinocytes; in some adult patients, amyloid deposits are present in the papillary dermis. The latter finding led to an initial description of the condition as "familial cutaneous amyloidosis".

EPIDERMAL NEVI AND RELATED SYNDROMES

Classification and Clinical Features of Epidermal Nevi

Epidermal nevi represent a heterogeneous group of mosaic lesions that are typically distributed along the lines of Blaschko, although those with a later developmental origin may be smaller with a round to oval shape. They may be warty, smooth, or barely palpable; brown, pink, yellow, tan, or hypopigmented (Fig. 62.7); localized or extensive; unilateral or widespread; and isolated or (for more extensive lesions) associated with extracutaneous abnormalities. The appearance is affected by both the age of the patient and the site of the lesion. Epidermal nevi are often whitish or pink in color and macerated at birth. Sometimes they first become evident later in infancy or seem to extend over time, a phenomenon parents find worrisome and difficult to reconcile with the term "birthmark".

Epidermal nevi may be purely *keratinocytic* or demonstrate *organoid* differentiation (see Chs. 109 & 111). Organoid subtypes include nevus sebaceus, Munro acne nevus, nevus comedonicus, woolly (or rarely straight) hair nevus, linear syringocystadenoma papilliferum, and porokeratotic adnexal ostial nevus (Table 62.6 and Fig. 62.8). A nevus sebaceus typically presents as a congenital hairless plaque on the scalp or face, with a characteristic yellowish-pink to orange-brown color and waxy texture (see Fig. 62.8A). These lesions tend to thicken after puberty and can become verrucous. In a patient with widespread epidermal nevi, it is not uncommon for lesions to be keratinocytic on the trunk and extremities but have sebaceous differentiation when they involve the head and neck region. In general, epidermal nevi on the scalp tend to have overlying alopecia or hair with an abnormal (e.g. woolly) texture (see Fig. 62.8B).

Keratinocytic epidermal nevi can be divided clinically into inflammatory (e.g. inflammatory linear verrucous epidermal nevi [ILVEN]) (see below and Ch. 109) and noninflammatory categories. The latter may be further classified histologically into non-epidermolytic and epidermolytic variants (Fig. 62.9), although this is not an absolute distinction and even organoid nevi occasionally display epidermolysis. Keratinocytic epidermal nevi are often thicker and more pronounced within skin folds (see Fig. 62.7B), where they can have an appearance similar to acanthosis nigricans; softening and decreased hyperkeratosis may also be observed in intertriginous sites.

Two rare epidermal nevus variants are RAVEN (*r*ounded *a*nd *v*elvety *e*pidermal *n*evus) and PENS (*p*apular *e*pidermal *n*evus with "*s*kyline" basal cell layer). RAVEN, also referred to as nevoid acanthosis nigricans, is characterized by lesions with a distinctive rounded outline arranged in a linear pattern[34d]. Patients with PENS present with congenital skin-colored or pinkish hyperkeratotic papules or small plaques that are typically circular/ovoid or polygonal in shape, with only one report to date of a lesion following the lines of Blaschko[34e,34f]. Although usually sporadic, familial cases have been reported as have associated neurodevelopmental abnormalities[34e,34f]. Characteristic histopathologic findings include basal cells with palisaded nuclei in a pattern reminiscent of a city skyline[34e].

Genetics of Epidermal Nevi

The genetic bases of multiple types of epidermal nevi have been established[35–49] (see Table 62.6). Several variants as well as their syndromic associations (see below) are caused by activating postzygotic mutations in genes that encode proteins in two major signaling pathways: (1) RAS/MAPK (mitogen-activated protein kinase), resulting in mosaic RASopathies (see Fig. 55.4); and (2) FGFR (fibroblast growth factor receptor)/PIK3CA (phosphatidylinositol-3-kinase catalytic subunit α)/AKT1, which is negatively regulated by PTEN (phosphatase and tensin homolog) (see Fig. 55.3). For example, mosaic *HRAS* or *KRAS* mutations account for ~40% of noninflammatory, non-epidermolytic keratinocytic epidermal nevi, with *FGFR2/3* or *PIK3CA* mutations in another ~50% of these lesions[35,36] (Fig. 62.10). Nevus sebaceus is also



Fig. 62.7 Non-epidermolytic verrucous epidermal nevi. A S-shaped hyperpigmented papillomatous streaks on the abdomen with sharp midline demarcation. **B** Hyperpigmented keratotic streaks accentuated in skin folds. **C** Tan lesions in a V-shaped pattern on the mid-back. **D** Velvety papillomatous streaks along the midline abdomen. **E** Extensive hypopigmented streaks with variable adherent scale, which is accentuated in the popliteal fossae, in a patient with darkly pigmented skin. *D, Courtesy Lorenzo Cerroni, MD.*

EPIDERMAL NEVI: ASSOCIATED GENES AND POTENTIAL SYNDROMIC ASSOCIATIONS				
Type of epidermal nevus (EN)	**Gene**	**Protein**	**Generalized conditions caused by germline mutations***	**Potential syndromic associations with the EN**
Verrucous (keratinocytic) epidermal nevi				
	Mosaic keratinopathies			None
Epidermolytic keratinocytic EN	*KRT1, KRT10, KRT2*	Keratin 1, 10, and 2	Epidermolytic ichthyosis, PPK (*KRT1*)	None
Palmoplantar non-epidermolytic EN	*KRT16*	Keratin 16	Pachyonychia congenita, focal PPK	None
	Mosaic RASopathies (also woolly hair and sebaceous nevi; see below)			Ocular, skeletal, neurologic
Non-epidermolytic keratinocytic EN (NEKEN)	*NRAS* (<5% of NEKEN)	NRAS	Noonan syndrome (see Table 61.3)	Cutaneous skeletal hypophosphatemic syndrome (*NRAS* or *HRAS* Q61R, *HRAS* G13R); phakomatosis pigmentokeratotica with nevus spilus (*HRAS* Q61R or G13R in both nevus types) or with agminated melanocytic nevi + focal cortical dysplasia (*BRAF*)
	HRAS (~30% of NEKEN)	HRAS	Costello syndrome (see Table 97.7)	
	KRAS (~5% of NEKEN)	KRAS	Cardio-facio-cutaneous (CFC) andNoonan syndromes	
	BRAF (K601Q; <1% of KEN)	BRAF	CFC syndrome	
	Mosaic "FiGRopathies" (also sebaceous and acneiform nevi; see below)			Craniofacial, acral skeletal, neurologic
	FGFR2 (5-10% of NEKEN)	Fibroblast growth factor receptor 2	See below	"Twisted" hair, syndactyly, overgrowth of hands/feet, macrocephaly, nevus simplex complex
	FGFR3[**,§] (~30% of NEKEN)	Fibroblast growth factor receptor 3	Thanatophoric dysplasia**, Crouzon syndrome with acanthosis nigricans, SADDAN	Garcia–Hafner–Happle syndrome: asymmetric craniofacial malformations, intellectual disability
	Mosaic "AKTopathies"			Overgrowth; vascular and adipose anomalies
	PIK3CA[§] (~10% of NEKEN)	Phosphatidylinositol 3-kinase catalytic subunit α	?Cowden syndrome variant (type 5)	CLOVE(S) syndrome: *c*ongenital *l*ipomatous *o*vergrowth, *v*ascular anomalies, *EN*, and *s*coliosis/other *s*keletal abnormalities (especially broad hands and feet); see Table 104.5
	AKT1	AKT serine/threonine kinase 1	Not reported	Proteus syndrome (see text)
	PTEN	Phosphatase and tensin homolog	PTEN hamartoma tumor syndrome (PHTS), including Cowden syndrome	"Proteus-like" features: *s*egmental *o*vergrowth, *l*ipomatosis, *a*rteriovenous *m*alformations, *EN* (SOLAMEN; due to postzygotic "second hit"); macrocephaly and other features of PHTS (see Ch. 63)
Other epidermal nevi				
Woolly hair nevus	*HRAS* (G12S)	HRAS	Costello syndrome	
	BRAF (K601Q)	BRAF	CFC syndrome	See NEKEN above
Nevus sebaceus (NS)	*HRAS* (G13R in ~90% of NS)	HRAS	Costello syndrome	Schimmelpenning syndrome (CNS, ocular, skeletal); cutaneous skeletal hypophosphatemic syndrome
	KRAS	KRAS	CFC and Noonan syndromes	
Nevus sebaceus, papillomatous pedunculated	*FGFR2* (C382R)	Fibroblast growth factor receptor 2	Craniosynostosis syndromes: Beare–Stevenson cutis gyrata, Apert***	Cleft palate
Munro acne nevus	*FGFR2* (S252W, P252R)			Acral skeletal anomalies (e.g. syndactyly, broad thumb), developmental delay
Nevus comedonicus	*NEK9*	NIMA-related kinase 9	Skeletal dysplasia (with biallelic mutations)	Digital anomalies, scoliosis
Porokeratotic adnexal ostial nevus (PAON)[¶]	*GJB2*	Connexin 26	Keratitis–ichthyosis–deafness (KID) syndrome	
Inflammatory linear verrucous epidermal nevus (ILVEN)	*GJA1*, *?NSHDL*	Connexin 43	Erythrokeratodermia variabilis, ? CHILD syndrome (mosaic skin findings)	Ipsilateral distal limb reductions (*NSHDL*)
	CARD14	CARD14	Psoriasis, CARD14-associated papulosquamous eruption	
	ABCA12	ABCA12	Autosomal recessive congenital ichthyosis (biallelic)	

*Can potentially occur in the offspring of an epidermal nevus patient who has gonadal as well as cutaneous mosaicism.
**Usually caused by the R248C activating FGFR3 mutation; thanatophoric dysplasia presents with widespread acanthosis nigricans, short-limbed dwarfism, craniofacial malformations, CNS defects, and perinatal lethality
§Somatic activating mutations are also found in seborrheic keratoses, dermatosis papulosa nigra, stucco keratoses, and solar lentigines.
***Manifestations of Apert syndrome, which is usually caused by S252W and P253R FGFR2 mutations, include craniosynostosis, digital anomalies (syndactyly, broad thumbs), severe acne, diffuse pigmentary dilution, and developmental delay.
¶Includes porokeratotic eccrine ostial and dermal duct nevus (PEODDN); spiny hyperkeratotic EN without histologic features of PAON have also been reported.

Table 62.6 Epidermal nevi: associated genes and potential syndromic associations. Mosaic RAS mutations found in epidermal nevi are often (but not always) different from those in generalized conditions, suggesting that the former represent more severe, lethal mutations rescued by mosaicism. Other mosaic genetic changes reported within epidermal nevi include *PTCH* deletion (in a nevus sebaceus), a chromosomal breakpoint at 1q23, and trisomy 6[36,37]. *ABCA12*, ATP-binding cassette subfamily A member 12; *CARD14*, caspase recruitment domain family member 14; CHILD, *c*ongenital *h*emidysplasia with *i*chthyosiform erythroderma/nevus and *l*imb *d*efects; CNS, central nervous system; FGF, fibroblast growth factor; *GJA1/B2*, gap junction α1/β2; PPK, palmoplantar keratoderma; SADDAN, *s*evere *a*chondroplasia with *d*evelopmental *d*elay and *a*canthosis *n*igricans.



Fig. 62.8 Epidermal nevi with organoid differentiation. A A small nevus sebaceus with an oval shape. **B, C** Woolly hair and epidermal nevi due to a mosaic *HRAS* mutation in a young girl. Focal areas of curly hair with a woolly texture are evident amid a background of straight hair **(B)**. A thin tan epidermal nevus with subtle elevation more evident with side lighting. **D** Comedones and cribriform scarring along the lines of Blaschko, with an inflammatory nodule in the superior portion of the lesion. *A, Courtesy Veronica Kinsler, MD, PhD.*



Fig. 62.9 Epidermolytic verrucous epidermal nevus. A Hyperpigmented streaks with central shedding of scale and associated pink color. **B** Histology shows verrucous epidermal hyperplasia with prominent compact hyperkeratosis associated with granular and vacuolar degeneration of keratinocytes in the spinous and granular layers (epidermolytic hyperkeratosis). *B, Courtesy, Luis Requena, MD.*



Fig. 62.10 Epidermal nevus due to *FGFR3* mutation and seborrheic keratoses following the lines of Blaschko. A This lesion represents a mosaic counterpart of the acanthosis nigricans in patients with thanatophoric dysplasia, perhaps reflected in its flexural prominence. **B** Unilateral seborrheic keratoses in bands following the lines of Blaschko. Seborrheic keratoses often have a somatic activating mutation in *FGFR3* or *PIK3CA*. *A, Courtesy Celia Moss, MBBS, MA, DM; B, Courtesy, Luis Requena, MD.*

primarily caused by mosaic mutations in *HRAS* and to a lesser degree *KRAS*[47]. *FGFR2* mutations have been found to underlie a less common papillomatous/cerebriform nevus sebaceus variant and the Munro acne nevus as well as a subset of keratinocytic epidermal nevi that includes RAVEN, which can also result from *FGFR3* mutations[43]. Mutations in either *HRAS* or *BRAF*, whose protein product is also in the RAS/MAPK pathway, have been identified in woolly hair nevi[49](see Fig. 62.8B), and *BRAF* mutations can result in linear syringocystadenoma papilliferum.

Epidermal Nevus Syndromes

Introduction

"Epidermal nevus syndromes" (ENSs) represent a group of heterogeneous disorders in which keratinocytic and organoid epidermal nevi are associated with ocular, neurologic, and/or musculoskeletal abnormalities[50–53]. *Schimmelpenning syndrome* can be caused by somatic mutations in *HRAS* or *KRAS*[52], and the genetic etiologies of other ENSs are presented in Table 62.6. Overgrowth syndromes resulting from activation of the PIK3CA/AKT1 pathway include Proteus syndrome, PTEN hamartoma tumor syndrome (PHTS), and the *PIK3CA*-related overgrowth spectrum (PROS). These disorders, which are discussed below and summarized in Table 104.5 can have cutaneous manifestations including lipomatosis and vascular malformations as well as epidermal nevi. Additional skin findings that have been described in association with epidermal nevi include hypo- or hyperpigmentation (e.g. café-au-lait macules [CALMs]) in a mosaic distribution, melanocytic nevi (e.g. in phakomatosis pigmentokeratotica; see below), and aplasia cutis congenita.

History and terminology

Reports of epidermal nevi occurring in conjunction with abnormalities in other organ systems date back over a century. Various authors are credited with descriptions of these associations, including Jadassohn, Schimmelpenning, Feuerstein, and Mims. Solomon and Esterly reviewed epidermal nevi and related extracutaneous findings in 1973[50], and Solomon is often credited with the term "epidermal nevus syndrome". Happle later extended ENSs to encompass multiple additional mosaic entities such as Proteus and CHILD syndromes[51], while others limited the term to the Schimmelpenning phenotype classically associated with sebaceous nevi[53].

Phakomatosis Pigmentokeratotica, Schimmelpenning Syndrome, and Cutaneous Skeletal Hypophosphatemia Syndrome

Phakomatosis pigmentokeratotica (*phakomatosis spilosebacea*) is defined as the association of a nevus spilus (see below and Ch. 112) with a nevus sebaceus, while *Schimmelpenning syndrome* is the term classically used for the association of extracutaneous findings with a nevus sebaceus. These clinical diagnoses exist on a spectrum, as they result from mosaic *HRAS* or, for a small subset of Schimmelpenning syndrome, mosaic *KRAS* mutations[34,57]. Additional cutaneous features may include keratinocytic epidermal nevi and CALMs, with the latter potentially representing a nevus spilus prior to the appearance of superimposed nevi. The distributions of the various skin findings can be overlapping or distinct.

Extracutaneous manifestations of these mosaic RASopathies most often involve the CNS (e.g. hemimegalencephaly, seizures, hemiparesis, intellectual impairment)[53], eye (e.g. [lipo]dermoids, colobomata, choristomas), and skeleton (e.g. hemihypertrophy, scoliosis). Epidermal nevi involving the head are thought to be more likely to have associated cerebral defects than those in other sites, although this has not been systematically evaluated. Neurologic abnormalities are also more likely when sebaceous nevi on the scalp are linear rather than round, presumably reflecting their earlier origin and the consequent wider tissue dissemination (see Table 62.2). Epidermal nevi due to *RAS* mutations have also been associated with extracutaneous malignancies, in particular rhabdomyosarcoma and urothelial carcinoma, which occur at increased frequency in patients with Costello syndrome due to germline *HRAS* mutations (see Table 97.7).

The *cutaneous skeletal hypophosphatemia syndrome* may occur in patients with an extensive keratinocytic and/or sebaceous nevus caused by particular *HRAS* and *NRAS* mutations[48]. Affected individuals develop vitamin D-resistant rickets due to overproduction of fibroblast growth factor 23 (FGF-23), which is normally secreted by osteocytes to regulate vitamin D and phosphate homeostasis. There are reports of successful treatment with the FGF23 inhibitor burosumab or the MEK inhibitor trametinib, with the latter also leading to improvement of the patient's nevus sebaceus[48a,48b].

PIK3CA-Related Overgrowth Spectrum (PROS)

PROS encompasses a variety of mosaic conditions with dermatologic manifestations, including: CLOVE(S) syndrome (*c*ongenital *l*ipomatous *o*vergrowth, *v*ascular malformations, *e*pidermal nevi, *s*coliosis/skeletal/spinal anomalies); megalencephaly-capillary malformation; CLAPO syndrome (*c*apillary and *l*ymphatic malformations of the tongue/neck with *a*symmetry and *p*artial *o*vergrowth); Klippel-Trenaunay syndrome; fibroadipose hyperplasia/overgrowth; and hemihyperplasia multiple lipomatosis[53a,53b]. Depending on the tissue(s) involved, characteristic findings in addition to epidermal nevi (which are present in a subset of patients) include asymmetric overgrowth, lipomatosis, and vascular malformations (see Table 104.5).

Proposed diagnostic criteria require documentation of a mosaic *PIK3CA* mutation, which can be done via genetic analysis (e.g. an overgrowth syndrome panel) of DNA extracted from a biopsy of affected skin[53a]. Although there is some clinical overlap with Proteus syndrome (see below), PROS is distinguished by congenital, less progressive overgrowth, and the cerebriform connective tissue nevi that characterize Proteus syndrome are typically absent[53a,53b].

Management of PROS depends on the types and distribution of the clinical manifestations. Patients with PROS have an increased risk of venous thromboembolism, with potential contributing factors including venous malformations, impaired mobility, decreased anticoagulant proteins, and effects of the underlying mutation on the vascular endothelium[53c]. There is debate regarding whether routine screening for Wilms tumor via serial abdominal ultrasounds until age 8 years is indicated, as only a few Wilms tumors have been reported in PROS patients[53b].

Targeted therapy with the PI3K inhibitor alpelisib is FDA-approved for patients ≥2 years of age with severe manifestations of PROS. In a retrospective study (n = 32 patients), administration of alpelisib for 24 weeks improved vascular malformations and overgrowth in ~75% of PROS patients. A 6-month course of low-dose oral sirolimus was also found to result in a small reduction in the bulk of affected tissues in PROS patients, but adverse effects (e.g. infections, cytopenias) were common.

Proteus Syndrome

Proteus syndrome is a rare mosaic disorder characterized by overgrowth of a variety of tissues due to activating mutations in *AKT1*. The 1999 diagnostic criteria were revised in 2019 to include the genotype as well as clinical manifestations[54]. A hallmark of Proteus syndrome is progressive and disproportionate postnatal overgrowth, which is distinct from the relatively stable congenital overgrowth seen in PROS. Manifestations of overgrowth in Proteus syndrome include asymmetric macrodactyly or limb gigantism, typically with abnormal bones and soft tissue in the affected areas, as well as scoliosis related to megaspondylodysplasia. Another characteristic feature is cerebriform palmar or plantar connective tissue nevi, which tend to expand and thicken during childhood and adolescence[55,56]. EN in patients with Proteus syndrome are often "soft" but have variable clinical morphologies[56]. Other cutaneous manifestations include slow-flow vascular malformations, papulonodular connective tissue nevi on the face and digits, patchy dermal hypoplasia, hyper- and hypopigmented macules/patches, asymmetric hypertrichosis, and abnormal fat deposition resulting in lipomas and/or lipoatrophy[56,56a].

Management of Proteus syndrome includes genetic analysis (e.g. an overgrowth syndrome panel) of DNA from affected tissue and radiologic evaluation to assess and monitor bony and soft tissue disease. Similar to PROS, patients with Proteus syndrome have an elevated risk of venous thromboembolism, which represents the leading cause of death in this condition and requires individualized surveillance and management[56b]. Targeted therapy with the AKT inhibitor miransertib has shown promising results in early clinical studies[56c].

Superimposed (Type 2) Mosaic PTEN Hamartoma Tumor Syndrome

The growth-promoting PIK3CA/AKT pathway that is activated in the affected tissues of Proteus syndrome patients is negatively regulated by PTEN (see Fig. 55.3). In the autosomal dominant PTEN hamartoma tumor syndrome (PHTS, including Cowden syndrome; see Ch. 63), patients have a heterozygous germline *PTEN* mutation, and the hamartomas/tumors result from a "second hit" causing loss of heterozygosity. The same mechanism, occurring earlier during embryogenesis, can lead to a "Proteus-like" phenotype distinguished from true Proteus syndrome by macrocephaly, thicker and more verrucous epidermal nevi, vascular anomalies with a fast-flow component, and a lack of cerebriform palmoplantar connective tissue nevi. This superimposed (type 2) mosaic PHTS/Cowden syndrome is also referred to as *SOLAMEN syndrome* – *s*egmental *o*vergrowth, *l*ipomatosis, *a*rteriovenous *m*alformation, and *e*pidermal *n*evus (Fig. 62.11)[11,55].

PTEN negatively regulates mechanistic target of rapamycin (mTOR) signaling downstream of AKT1. The mTOR inhibitor sirolimus has been anecdotally reported to slow overgrowth in superimposed mosaic PHTS[56], and further investigation of this agent in PHTS is in progress.

ILVEN (Inflammatory Linear Verrucous Epidermal Nevus)

ILVEN represents a spectrum of inflammatory mosaic disorders that manifest as linear, erythematous, scaly plaques that follow the lines of Blaschko and are characteristically pruritic[57] (Fig. 62.12; see Ch. 109). While occasionally present at birth, ILVEN usually appears during childhood (or, less often, adult life) and extends over months to years. It responds temporarily, if at all, to topical anti-inflammatory agents and rarely remits spontaneously.

Reported genetic etiologies of ILVEN include heterozygous postzygotic mutations in *GJA1* (encoding connexin 43; mosaic erythrokeratodermia variabilis et progressiva) and *CARD14* as well as germline plus postzygotic mutations in *ABCA12* (mosaic autosomal recessive congenital ichthyosis)[57,57a,57b]. The differential diagnosis of ILVEN includes linear psoriasis (see Fig. 62.15), which may be difficult to distinguish but tends to be less recalcitrant to therapy, and secondary inflammation within an epidermal nevus (e.g. with an underlying postzygotic *HRAS* or *KRT10* mutation). Linear porokeratosis (e.g. due to germline plus superimposed somatic *PMVK* mutations) can mimic ILVEN clinically and histologically, with potential misinterpretation of the cornoid lamella as alternating ortho- and parakeratosis[57]. In addition, some patients presenting with an ILVEN phenotype actually have a forme fruste of CHILD syndrome due to a germline *NHDSL* mutation. An alternative acronym for this variant is PEN/PENCIL (*p*soriasiform *e*pidermal *n*evus ± *c*ongenital *i*psilateral *l*imb defects)[58]. Knowing the genetic basis of these lesions can direct targeted therapies such as topical statin/cholesterol (*PMVK* or *NSDHL*) and ustekinumab (*CARD14*).



Fig. 62.11 SOLAMEN – *s*egmental *o*vergrowth, *l*ipomatosis, *a*rteriovenous *m*alformation, and *e*pidermal *n*evus – syndrome. Epidermal nevus, vascular malformations, and localized fatty infiltration on the thigh. *Courtesy Celia Moss, MBBS, MA, DM.*

MOSAICISM IN OTHER AUTOSOMAL DOMINANT DISORDERS

Mosaicism for other autosomal dominant disorders may present with a linear or segmental distribution of cutaneous findings that are usually generalized.

Linear Darier Disease (Acantholytic Dyskeratotic Epidermal Nevus)

Linear and segmental presentations of Darier disease are usually morphologically identical to the generalized form (Fig. 62.13). Heterozygous mutations in *ATP2A2* have been found in lesional but not normal-appearing skin, documenting simple segmental (type 1) mosaic Darier disease on a molecular level[59]. Less commonly, linear streaks with an earlier onset and



Fig. 62.12 Inflammatory linear verrucous epidermal nevus. Scaly psoriasiform plaques distributed in a linear array.

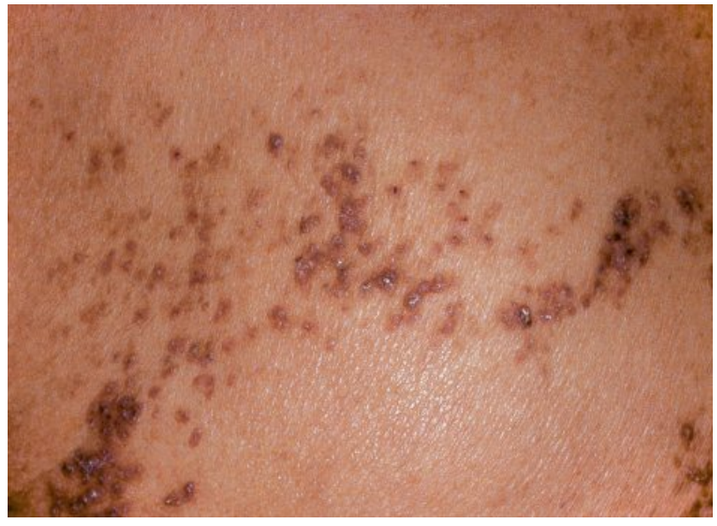


Fig. 62.13 Linear Darier disease with hyperpigmented, keratotic papules. Sometimes lesions of guttate leukoderma are also seen within the streak.

increased severity due to a "second hit" in *ATP2A2* are found in patients with generalized Darier disease, reflecting superimposed (type 2) mosaicism.

Linear Hailey–Hailey Disease (Relapsing Linear Acantholytic Dermatosis)

Linear Hailey–Hailey disease is characterized by relapsing erosions and crusting within a segmental area; histologically, acantholysis resembling a "dilapidated brick wall" is observed (see Ch. 59). Heterozygous postzygotic *ATP2C1* mutations reflecting type 1 mosaicism have been identified in such patients. Inactivation of the second *ATP2C1* allele (loss of heterozygosity) has also been found in linear regions with earlier and more severe involvement in patients with generalized Hailey–Hailey disease, confirming superimposed (type 2) mosaicism[60].

Linear Porokeratosis

Linear porokeratosis is composed of multiple plaques with keratotic borders that represent cornoid lamellae. These plaques are usually congenital and persistent, with a higher risk of developing squamous cell carcinoma than other porokeratosis variants[61]. Linear porokeratosis sometimes coexists with familial forms of porokeratosis such as disseminated superficial actinic porokeratosis (DSAP), which result from germline heterozygous mutations in genes encoding various enzymes in the mevalonate biosynthesis pathway such as *MVD* (mevalonate diphosphate decarboxylase; see Fig. 109.8). Mosaic "second hit" mutations in *MVD* and *PMVK* (phosphomevalonate kinase) have been found to underlie linear porokeratosis[61a]. Pathogenesis-directed topical treatment of linear porokeratosis with cholesterol 2%/lovastatin 2% cream or ointment has been reported[61b].

Porokeratotic Adnexal Ostial Nevus (PAON)

PAON, which includes the porokeratotic eccrine ostial and dermal duct nevus (PEODDN), features keratotic spines and/or punctate pits with keratotic plugs (see Fig. 111.40). Histologically, parakeratotic columns arise from the eccrine ducts and/or hair follicles. PAON is caused by postzygotic mutations in *GJB2*, which encodes connexin 26, and therefore represents the mosaic form of the autosomal dominant keratitis–ichthyosis–deafness (KID) syndrome[62] (see Ch. 57). Erosions during the neonatal period, development of SCC, and psoriasiform lesions have been described in association with PAON, but extracutaneous features of KID syndrome have not yet been reported.

Linear Basal Cell Nevus Syndrome

Superimposed mosaic manifestations of basal cell nevus syndrome can include congenital basaloid skin tumors and palmoplantar pits in a linear pattern. This has been confirmed on a molecular level, with identification of a germline *PTCH1* mutation in addition to a "second hit" mutation in affected skin[63]. A heterozygous mosaic *PTCH1* mutation has also been identified within multiple superficial BCCs in a Blaschko-linear distribution pattern[63a].

Curry-Jones and Happle-Tinschert Syndromes

Curry-Jones and Happle–Tinschert syndromes, which were described in 1995 and 2008, respectively, represent mosaic disorders with genotypic and phenotypic overlap[64,65]. Both conditions are caused by postzygotic activating mutations in the gene encoding Smoothened (SMO), which is inhibited by Patched in the Hedgehog signaling pathway (see Fig. 107.6)[66]. Patients present with a linear or segmental distribution of basaloid follicular hamartomas that are variably accompanied by hyperpigmentation, hypopigmentation, atrophoderma, hypertrichosis, and hypotrichosis. Extracutaneous manifestations can include dental, digital, cranial, cerebral, and gastrointestinal anomalies[64–66].

Mosaic Neurofibromatosis Type 1 and Legius Syndrome

Patients with café-au-lait macules (CALMs) and/or neurofibromas limited to a segmental distribution may have a type 1 mosaic form of NF1 or (for CALMs) Legius syndrome due to a postzygotic mutation in the gene encoding neurofibromin or SPRED1 (*sp*routy-related *E*VH1 *d*omain-*1*), respectively[67,68] (see Ch. 61). The distribution of the CALMs, which are often accompanied by lentigines, may be block-like or rarely in a broad Blaschko-linear distribution, sometimes with subtle relative hyperpigmentation of the background skin. In contrast, neurofibromas usually occur in a segmental pattern. Like other simple segmental (type 1) mosaic conditions with nonlethal underlying mutations, offspring may have full-blown NF1[69]. In addition, plexiform neurofibromas and CALMs represent manifestations of superimposed (type 2) mosaicism (i.e. due to a postzygotic "second hit") in patients with NF1 and (for CALMs) Legius syndrome.

Linear or Segmental Angiofibromas and Mosaicism in Tuberous Sclerosis Complex

Mosaicism accounts for ~5–10% of patients diagnosed with tuberous sclerosis complex (TSC) based on clinical criteria, many of whom have relatively mild clinical manifestations but not an obvious segmental distribution of skin lesions[70]. However, mosaic TSC can also present with an asymmetric distribution of facial angiofibromas[70a]. Of note, "second hit" mutations have been identified within angiofibromas, fibrous cephalic plaques, and shagreen patches in patients with TSC[70b].

Linear or Segmental Benign Tumors

Trichoepitheliomas, spiradenomas, and/or cylindromas occasionally occur in a linear distribution. These may represent mosaic forms of autosomal dominant *CYLD* cutaneous syndrome caused by heterozygous germline *CYLD* mutations, and heterozygous *postzygotic CYLD* mutations have been identified in clustered cylindromas[71]. A somatic *BRAF* V600E mutation has been associated with linear syringocystadenoma papilliferum.

Leiomyomas can occur in a segmental pattern as a manifestation of autosomal dominant hereditary leiomyomatosis and renal cell cancer due to fumarate hydratase mutations, most often representing superimposed (type 2) mosaicism (i.e. with a germline mutation plus "second hit" in the affected segment).

An autosomal dominant tendency to develop seborrheic keratoses is recognized, although no gene has yet been implicated. An adult onset of seborrheic keratoses distributed along the lines of Blaschko has also been described (see Fig. 62.10B); in one patient, activating *FGFR3* and/or *PIK3CA* mutations were variably present within the lesions, some of which showed keratinocytic atypia histologically, but were not found in the background skin[72].

Encephalocraniocutaneous Lipomatosis (Haberland Syndrome)

Encephalocraniocutaneous lipomatosis (ECCL) is a rare mosaic condition caused by postzygotic activating mutations in *FGFR1* or *KRAS*[73,74]. Patients present with cerebral malformations, ipsilateral eye abnormalities (usually choristomas), and papulonodular skin lesions including lipomas, fibromas, fibrolipomas, and angiolipomas. These lesions favor the eyelids and scalp, and alopecia overlying scalp lipomas, referred to as *nevus psiloliparus*, is occasionally associated with aplasia cutis congenita. The cranial and eye lesions are usually unilateral, but lipomas may be found on both sides of the scalp. Of note, *germline* activating *FGFR1* mutations lead to autosomal dominant craniosynostosis and skeletal dysplasia syndromes. *Oculocerebrocutaneous (Delleman–Oorthuys) syndrome* has similar clinical features and is thought to exist on a spectrum with ECCL[74].

VASCULAR MALFORMATIONS

Mosaic mutations have been identified as the cause of multiple types of sporadic and familial vascular malformations (see Ch. 104). In addition to the entities discussed below, mosaic mutations underlying lymphatic (*PIK3CA*) and arteriovenous (*MAP2K1, BRAF, KRAS, HRAS*) malformations have also been identified (see Table 104.2).

Venous and Glomuvenous Malformations

Heterozygous somatic activating mutations in *TEK*, which encodes the TIE-2 endothelial cell tyrosine kinase receptor, or *PIK3CA* are frequently



Fig. 62.14 Dermal melanocytosis (A) and port wine birthmarks (B) in phakomatosis pigmentovascularis type II. Note the block-like segmental distributions. *Courtesy Veronica Kinsler, MD, PhD.*

found in sporadic *venous malformations*. A subset of these lesions therefore represents a simple segmental (type 1) mosaic form of the autosomal dominant multiple cutaneous and mucosal venous malformation syndrome caused by *germline TEK* mutations[75]. *Verrucous venous malformations* ("verrucous hemangiomas") result from heterozygous somatic mutations in *MAP3K3* (MAPK kinase kinase 3)[76]. Large segmental plaque-type *glomuvenous malformations*, which are typically congenital, can occur as a superimposed (type 2) mosaic manifestation of hereditary glomuvenous malformations due to heterozygous germline *GLMN* (glomulin) mutations.

Capillary Malformations (Port-Wine Birthmarks)

Somatic activating mutations in *GNAQ* are found within affected tissues in most patients with *Sturge–Weber syndrome* and non-syndromic *port-wine birthmarks*[77]. This gene encodes a Q-class G protein α-subunit, activation of which increases MAPK signaling. Somatic mutations in *GNAQ* and the related *GNA11* are also found in blue nevi and nevus of Ota. It is therefore not surprising that patients with *phakomatosis pigmentovascularis type II* have the same activating *GNAQ* or *GNA11* mutation in both their port-wine stain and dermal melanocytosis[78] (Fig. 62.14). Of note, somatic activating mutations in *GNAQ*, *GNA11*, *GNA14*, and *RAS* have been identified in congenital hemangiomas (noninvoluting and rapidly involuting variants), pyogenic granulomas (*RAS*), and other vascular tumors. *GNAQ*, *GNA11*, and *GNA14* mutations have only been reported in mosaic form and are likely otherwise lethal. *RASA1* and *EPHB4* mutations are responsible for the autosomal dominant capillary malformation–arteriovenous malformation syndrome, in which lesions have been shown to demonstrate loss of heterozygosity[79].

PIGMENTED LESIONS WITH A MOSAIC DISTRIBUTION PATTERN

Congenital Melanocytic Nevi (CMN)

CMN have more recently been viewed as forms of mosaicism and are discussed in Chapter 112. In addition to *classic CMN*, which are categorized based upon their size, the *nevus spilus-type CMN* is characterized by multiple small to medium-sized CMN superimposed on a CALM-like background. A single, small classic CMN is the most common presentation. Rarely, numerous widespread classic CMN are seen. Such patients, who sometimes also have a large or giant CMN in a "cape"- or "bathing trunk"-like distribution pattern, are at risk of neurocutaneous melanocytosis and other involvement beyond the skin. Additional manifestations of this "CMN syndrome" may include non-melanotic CNS findings (e.g. Dandy-Walker malformation, arachnoid cysts), endocrine abnormalities, and characteristic facial features.

Classic CMN of all sizes are most often caused by postzygotic *NRAS* mutations (~70%; e.g. Q61K, Q61R), with *BRAF* mutations accounting for 5-10%[80,81]. Nevus spilus-type CMN most often result from *NRAS* mutations (e.g. Q61H, Q61L) that differ from those typically observed in classic CMN[82]. The same *NRAS* mutations are found in skin and CNS lesions in patients with neurocutaneous melanocytosis[80]. *SCALP syndrome* refers to the rare association of *s*ebaceous nevi, *C*NS malformations, *a*plasia cutis congenita, and *l*imbal dermoid with CMN (*p*igmented nevi) on the scalp; underlying mosaic *NRAS* and germline biallelic *DOCK6* mutations have been reported in one affected individual to date.

Nevus Spilus

Nevus spilus (speckled lentiginous nevus) is defined as CALM-like hyperpigmentation with superimposed smaller pigmented lesions that may represent lentigines or a variety of types of melanocytic nevi. The macular background hyperpigmentation is often subtle and may not be evident at birth. Subtypes of this mosaic condition include: (1) nevus spilus-type CMN due to *NRAS* mutations (see above)[82]; (2) nevus spilus due to *HRAS* mutations (primarily "papular" type), which may have superimposed Spitz nevi and can occur together with nevus sebaceus in phakomatosis pigmentokeratotica (see above)[46,83]; and (3) nevus spilus due to *PTPN11* mutations (primarily "macular" type), which can occur together with a light red-pink capillary malformation ("nevus roseus") in phakomatosis pigmentovascularis type III[83a] (spilorosea; see Table 104.4). A variant of phakomatosis pigmentokeratotica due to an activating *BRAF* mutation in both an epidermal nevus and agminated melanocytic nevi (without background hyperpigmentation) has also been reported.

Extracutaneous findings described in *PTPN11*-associated nevus spilus and PPV spilorosea include neurodevelopmental impairment, macrocephaly, scoliosis, skeletal muscle weakness, overgrowth/hemihypertrophy, and ocular pigmentation[84]. Considering that *germline PTPN11* mutations are responsible for Noonan syndrome with multiple lentigines (formerly LEOPARD syndrome), individuals with *PTPN11*-associated mosaic skin conditions may be at risk of having offspring affected by Noonan syndrome. Of note, cutaneous melanoma has been reported to arise within all subtypes of nevus spilus.

McCune–Albright Syndrome

McCune–Albright syndrome features large blocks of café-au-lait pigmentation, demarcated at the midline and sometimes following the lines of Blaschko in broad bands, together with polyostotic fibrous dysplasia of the bone and/or endocrine hyperfunction (classically precocious puberty). It is due to particular postzygotic activating mutations in *GNAS*, the gene encoding the α-subunit of the G protein that stimulates adenylate cyclase activity. This results in increased signaling in pathways where cyclic AMP acts as a "second messenger", explaining endocrine overactivities and increased pigmentation due to stimulation of tyrosinase. Associated bone involvement can be asymptomatic or present with manifestations such as pain, a limp, pathologic fractures, facial asymmetry, and FGF23-related phosphate wasting. Evaluation may include X-rays of the long bones, bone scintigraphy, and laboratory assessment of phosphate homeostasis[83b].

LINEAR INFLAMMATORY DISORDERS

Several inflammatory skin conditions are occasionally distributed along the lines of Blaschko. When generalized, these disorders are multifactorial, typically with both a genetic susceptibility and environmental contributions. Linear presentations likely result from mosaicism for a "susceptibility" mutation. In some cases, a streak of more severe disease is superimposed on a generalized background of the same condition, perhaps reflecting clonal loss of heterozygosity[85]. Such conditions provide an opportunity to identify the genes involved in multifactorial cutaneous diseases.



Fig. 62.15 Linear psoriasis. Erythema and scale are seen within the streak as well as in small scattered lesions. *Courtesy Lorenzo Cerroni, MD.*

Linear Psoriasis

Linear psoriasis is rare (Fig. 62.15)[86] and can be difficult to distinguish from ILVEN (see above). Psoriasis following the lines of Blaschko may also be confused with the Koebner phenomenon where linearity is imposed by exogenous injury. However, both can occur in the presence of generalized psoriasis, as can psoriasis superimposed on an epidermal nevus. Linear psoriasis may be "unmasked" when the generalized component clears with treatment[87].

Linear Lichen Planus

Linear lichen planus (LP) is more common than linear lupus and can occur at any age[88]. It presents as typical LP lesions distributed along the lines of Blaschko, and postinflammatory hyperpigmentation is often the most prominent feature. Histology may be required to distinguish this disorder from other causes of linear pigmentation (see Fig. 62.3). If the LP lesions extend to the end of a digit, the nail is often affected.

Lichen Striatus

This self-limited linear inflammatory condition usually occurs during childhood, most commonly on an extremity in an atopic individual (see Ch. 11)[89]. The condition is not particularly pruritic, but it has histologic features similar to those of both eczema and lichen planus. Although both lichen striatus and linear lichen planus can be associated with nail dystrophy, postinflammatory hypopigmentation points to the diagnosis of lichen striatus.

"Blaschkitis"

"Blaschkitis" refers to a rare inflammatory dermatosis that typically presents as pruritic papules and vesicles along multiple lines of Blaschko, particularly on the trunk. More common in adults than children, it follows a relapsing course, with episodes often resolving spontaneously within days. Although the histology is more eczematous and less lichenoid than in lichen striatus, they may represent variants of the same condition[90].

Other Linear Inflammatory Disorders

Several other inflammatory disorders occasionally occur in a distribution along the lines of Blaschko. These conditions include atopic dermatitis, lupus erythematosus (with morphea-like/"sclerodermiform" features in one variant)[91,92], dermatomyositis, lichenoid and fixed drug eruptions[93,94], lichenoid GVHD[95], morphea[96], and atrophoderma of Pasini and Pierini (linear atrophoderma of Moulin[97]; Fig. 62.16).

PIGMENTARY MOSAICISM

Both hypo- and hyperpigmentation can occur in a linear or segmental pattern as a reflection of mosaicism. Traditionally, such presentations have been split into the disorders described below, but there is considerable overlap between these heterogeneous conditions, and distinctions can become blurred.



Fig. 62.16 Linear atrophoderma of Moulin. Hyperpigmented depressions with "cliff-drop" borders following the lines of Blaschko. The morphology of the lesions resembles that of atrophoderma of Pasini and Pierini.

Linear and Block-Like Hypo- and Hyperpigmentation

Synonyms/variants: ■ Linear nevoid hypo- and hyperpigmentation ■ Blaschkoid dyspigmentation ■ Pigmentary mosaicism ■ Hypomelanosis of Ito (becoming historical) ■ Linear and whorled nevoid hypermelanosis ■ Segmental pigmentation disorder ■ Incontinentia pigmenti achromians (historical)

Key features

- Descriptive terms rather than specific diagnoses, with a variety of genetic etiologies
- Hypo- or hyperpigmentation following the lines of Blaschko or in a block-like pattern can be evident at birth or appear later
- Variable extracutaneous involvement, which can include CNS, musculoskeletal, and ocular abnormalities

Introduction

Hypo- or hyperpigmentation following the lines of Blaschko reflects *epidermal* mosaicism and has a wide variety of genetic etiologies[98]. Block-like hypo- or hyperpigmentation, which has been referred to as "*segmental pigmentation* disorder"[99], is also presumed to result from mosaicism. Associated extracutaneous findings are found in a minority of affected individuals with either distribution pattern[99–101].

History

The first published description of hypopigmentation along Blaschko's lines was by Ito in 1951, resulting in the eponym "hypomelanosis of Ito." This term is becoming historical and should be reserved for patients with extracutaneous manifestations due to the presence of the mosaic abnormality in tissues other than the skin[98,100,101].

Epidemiology

Linear and block-like pigmentary alterations affect both sexes and are typically easier to see in darkly pigmented skin. The areas of patterned hypo- or hyperpigmentation may be apparent at birth or become evident during childhood, especially in those with lightly pigmented skin.

Genetics and pathogenesis

Blaschko-linear hypo- or hyperpigmentation can have a variety of genetic etiologies, which range from mosaic chromosomal alterations (up to 50% of cases; e.g. trisomy 18 or 20) or point mutations (e.g. *MTOR*) to *germline* X-linked conditions (e.g. Börjeson-Forssman-Lehmann syndrome; see above) and rarely chimerism (see below)[102,103]. The pattern of narrow bands along Blaschko's lines is thought to reflect mosaicism at the level of keratinocytes, with the pigmentary changes resulting from interactions between altered keratinocytes and neighboring melanocytes[9a,102]. This is supported by the identification of

postzygotic mutations in genes such as *TP63* and *KITLG*, which are primarily expressed by keratinocytes, in patients with Blaschko-linear hyperpigmentation[9b].

Clinical features

Streaks and swirls of hypo- or hyperpigmentation along the lines of Blaschko can occur anywhere on the cutaneous surface, with unilateral or bilateral involvement. Superimposed lentigines, hypertrichosis, and alopecia are occasionally observed. Only a small proportion (<15–30%) of children with Blaschko-linear hypo- or hyperpigmentation who present to a pediatric dermatologist at a tertiary referral center have extracutaneous abnormalities, which generally became apparent during infancy[100,101]. The extracutaneous abnormalities are highly variable, depending on the genetic etiology and tissues affected; they most often involve the CNS, eyes, and musculoskeletal system. In a recent series, neurodevelopmental abnormalities were significantly more common in children with Blaschko-linear hypopigmentation affecting ≥4 vs <3 of 5 body areas[101a].

Block-like hypo- or hyperpigmentation favors the trunk, but any site can be affected. Midline demarcation is more often present ventrally than dorsally, and the lateral borders tend to be less distinct. Segmental hyperpigmentation occasionally coexists with a light red-pink capillary malformation ("phakomatosis melanorosea"). Associated extracutaneous findings are uncommon, affecting <2–5% of patients[99].

Some patients have linear streaks of both hypo- and hyperpigmentation or a combination of linear and block-like hypopigmentation. When involvement is extensive, it may be difficult to determine whether the lighter or darker skin represents the background color.

Associated syndromes

The most common known single-gene cause of Blaschko-linear *hypopigmentation* is mosaic activating *MTOR* mutations. In a recent French series of 71 patients with "hypomelanosis of Ito", 15 (21%) had an underlying mosaic *MTOR* mutation[103a]. Additional findings in affected individuals can include macrocephaly, (hemi)megalencephaly, intellectual disability, seizures, facial dysmorphism, ocular anomalies, and asymmetric overgrowth[103b]. *RHOA-related neuroectodermal syndrome* results from mosaic mutations that lead to inactivation of a RAS-related Rho GTPase. Clinical features include Blaschko-linear *hypopigmentation* (Fig. 62.17), scarring alopecia, leukoencephalopathy (usually asymptomatic), facial dysmorphism, and hemihypoplasia as well as digital, dental, and ocular anomalies[103c]. X-linked syndromes that present with Blaschko-linear hypo- or hyperpigmentation are discussed above.

Pallister-Killian syndrome due to mosaic tetrasomy 12p, which usually results from gonadal mosaicism in a parent, is a distinct disorder that presents with *hypopigmentation* following the lines of Blaschko or in an irregular pattern. Frontotemporal alopecia and hypohidrosis represent additional cutaneous manifestations. Extracutaneous features include facial dysmorphism, intellectual disability, and broad first digits in addition to cardiac, renal, genitourinary, and gastrointestinal abnormalities[104].

Phylloid hypomelanosis in a pattern of leaf-like and floral shapes represents a distinct entity due to mosaic copy number variation involving chromosome 13[105]. Additional features may include telangiectatic macules, thick eyebrows, long eyelashes, intellectual disability, agenesis of the corpus callosum, conductive hearing loss, colobomas, and digital anomalies. A few patients with phylloid hypermelanosis have also been reported, with variable extracutaneous manifestations and underlying mosaic chromosomal aberrations (e.g. involving 5p)[105].

Pathology

Hypopigmented skin may appear normal or have a reduced number of melanocytes, while hyperpigmented skin shows increased epidermal pigmentation.

Differential diagnosis

Fig. 62.3 shows the differential diagnosis of hypo- and hyperpigmented lesions following the lines of Blaschko. Diagnostic considerations for block-like hyperpigmentation may include McCune–Albright syndrome, which tends to have darker, sharply demarcated lesions that follow the broad lines of Blaschko, as well as a large CALM, Becker nevus, and early nevus spilus. Block-like hypopigmentation is usually distinguishable from the amelanotic lesions of segmental vitiligo.



Fig. 62.17 Blaschko-linear hypopigmentation on the foot and leg of a child with a mosaic *RHOA* mutation. *Courtesy Veronica Kinsler, MD, PhD.*

Evaluation and management

A thorough history and physical examination should be performed to assess for extracutaneous involvement, with further evaluation directed by abnormal findings and/or recognition of distinct syndromes (see above). Growth and development should be followed in conjunction with the child's pediatrician.

In patients with extracutaneous abnormalities, identification of the underlying genetic alteration may provide better understanding of the overall diagnosis, help direct further evaluation, and potentially impact future family planning. For example, mosaic *MTOR* mutations involving the gonads have been implicated in transmission of Smith-Kingsmore syndrome, which presents with megalencephaly, seizures, and intellectual disability due to heterozygous germline *MTOR* mutations. In addition, recognizing the genetic etiology can provide the basis for targeted therapies such as sirolimus or other mTOR inhibitors.

Although mosaic mutations are sometimes present in the peripheral blood, a sample of affected tissue (e.g. a skin biopsy specimen) is more likely to contain mutant cells. If no specific single-gene disorder is suspected, genetic testing should start with an assessment for chromosomal mosaicism, which can be performed via microarray-based tests, e.g. single nucleotide polymorphism (SNP) array or array comparative genomic hybridization (CGH). If initial evaluation of DNA from a blood sample is not diagnostic, the test can be repeated on DNA extracted from a 4 mm punch skin biopsy of affected skin. The latter is generally of higher yield than the fibroblast cultures routinely performed by cytogenetics laboratories, as the mutation may not be present in that cell type. Keratinocyte cultures may be of utility when available[102], and whole exome or whole genome sequencing represents an additional testing option.

Nevus Depigmentosus

A nevus depigmentosus is another hypopigmented skin lesion that is thought to reflect cutaneous mosaicism. However, it is limited in extent and generally lacks extracutaneous associations. The most common presentation is a localized patch that breaks apart into smaller macules

at its periphery, resembling a splash of paint. Although classically evident at birth, a nevus depigmentosus sometimes becomes apparent later in childhood, especially in lightly pigmented individuals.

CHIMERISM

Block-Like Hyper- and Hypopigmentation Due to Chimerism

Chimerism differs from mosaicism in that the different clones originate from different organisms. Human chimeras can result from fusion of two zygotes (i.e. fused dizygotic twins) or fertilization of one egg by two sperm. Usually detected by hematologists as anomalous blood groups, or by endocrinologists as ambiguous sexual differentiation, chimerism is exceedingly rare. Findlay and Moores[106] studied more than a million routine blood samples and found evidence of chimerism in only two. Pigmentary variation in chimerism typically presents in a checkerboard pattern; however, streaks along the lines of Blaschko and mixtures of light and dark skin that do not correspond to recognized patterns of mosaicism have also been described[107]. In cases of XX/XY chimerism, the karyotype of dermal fibroblasts does not necessarily correspond to the overlying skin color, probably reflecting the different embryonic migration routes in the dermis and epidermis[9].

Additional figures available in our eBook (see inside front cover for access code).

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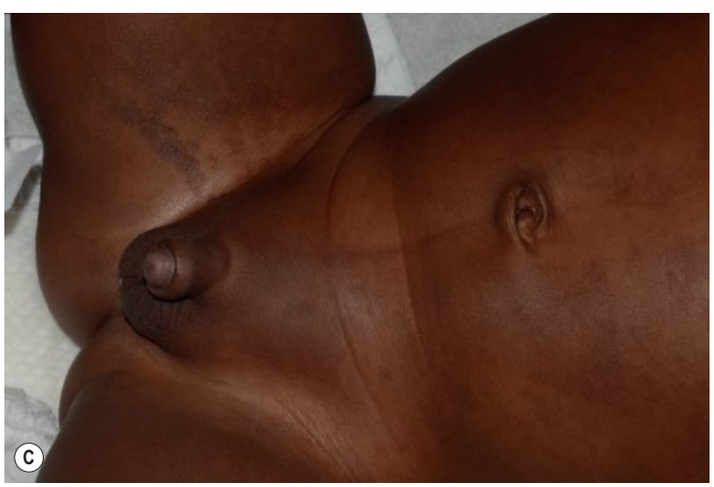
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eFig. 62.1 Epidermal nevi. A Extensive involvement on the trunk and arm. The lesions on the neck are more verrucous. **B, C** Accentuation in the groin. *B, C, Courtesy Julie V. Schaffer, MD.*





eFig. 62.2 Extensive epidermal nevus. *Courtesy Julie V. Schaffer, MD.*



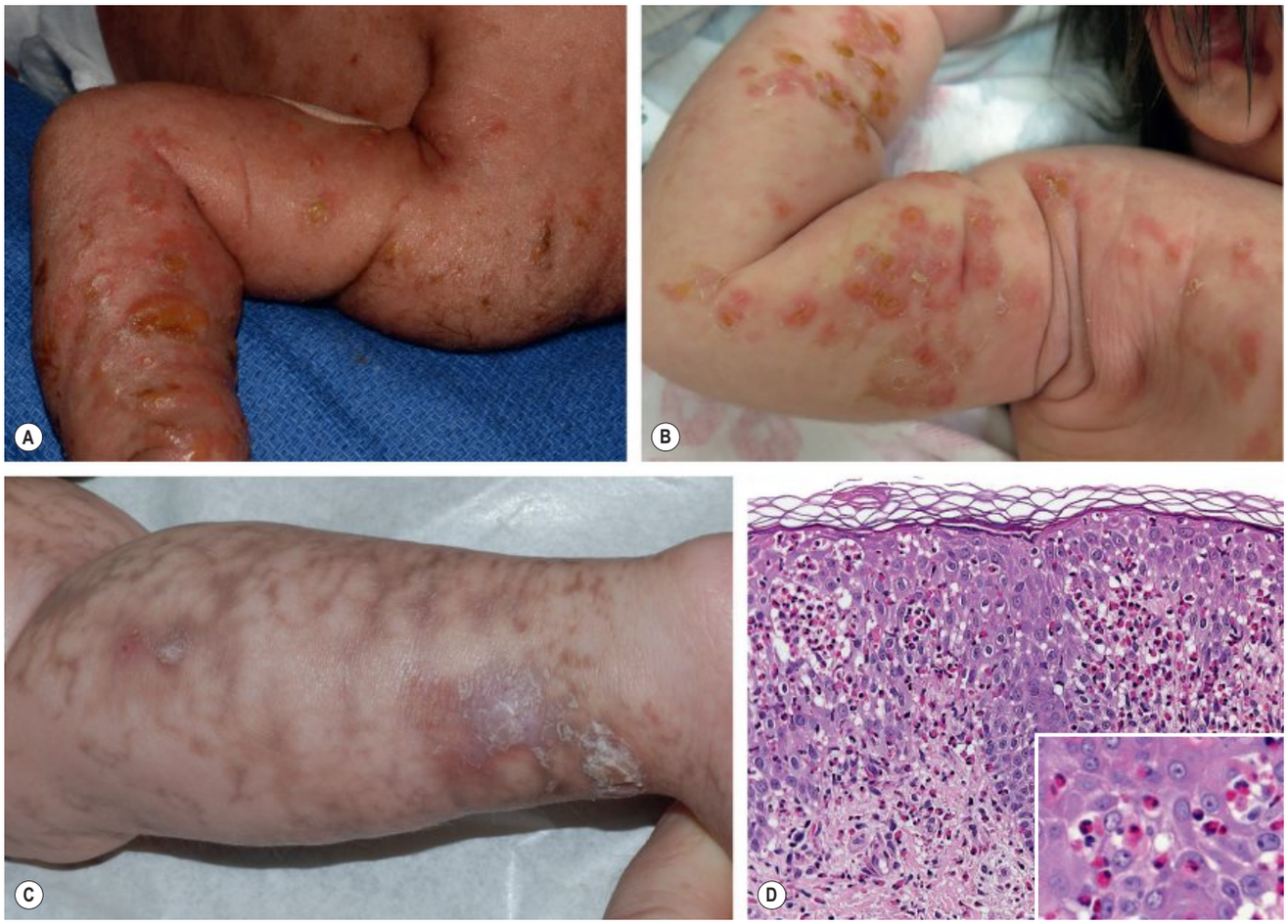
eFig. 62.3 Non-epidermolytic verrucous epidermal nevus. *Courtesy Kathyrn Schwarzenberger, MD.*



eFig. 62.5 Superimposed (type 2) segmental Hailey–Hailey disease. This 7-year-old girl had a history of recurrent blistering on the right abdomen, groin, and thigh since infancy. *Courtesy Julie V. Schaffer, MD.*



eFig. 62.4 Porokeratotic eccrine ostial and dermal duct nevus. Hyperkeratotic spines arise from dilated eccrine ostia, corresponding to the histologic finding of cornoid lamellae. Note the linearity of several of the lesions. *Courtesy Julie V. Schaffer, MD.*



eFig. 62.6 Incontinentia pigmenti. A, B Stage 1 presenting as vesicular and crusted lesions. **C** Stages 2 and 3 with hyperpigmented and hyperkeratotic lesions. **D** Histologically, numerous eosinophils are present within the dermis and epidermis (inset). Eosinophilic spongiosis can be seen in incontinentia pigmenti as well as disorders such as pemphigus and pemphigoid. *A, Courtesy Helen T. Shin, MD; B, Courtesy Andrea Zaenglein, MD; C, Courtesy Julie V. Schaffer, MD; D, Courtesy Lorenzo Cerroni, MD.*









eFig. 62.7 Incontinentia pigmenti, stage 1. A Admixture of erythematous streaks containing vesicles and yellow–brown streaks with scale on the lower extremity. **B–D** Streaks of vesicles and erythema in female neonates. *A, B, Courtesy Julie V. Schaffer, MD. C, Courtesy Lorenzo Cerroni, MD. D, Courtesy Luis Requena, MD.*



eFig. 62.8 Incontinentia pigmenti, stage 3 (hyperpigmented streaks). The scalloped edges of the lesions are consistent with growth of normal keratinocytes into the damaged areas.



eFig. 62.9 Incontinentia pigmenti, stage 4. Lack of terminal hair follicles is associated with relative hypopigmentation. *Courtesy Julie V. Schaffer, MD.*



eFig. 62.10 Nail dystrophy in a girl with incontinentia pigmenti. There is thickening and roughness of the surface of the nails. *Courtesy Antonio Torrelo, MD.*



eFig. 62.11 Conradi–Hünermann–Happle syndrome. Linear hyperpigmentation along the lines of Blaschko. *Courtesy Julie V. Schaffer, MD.*



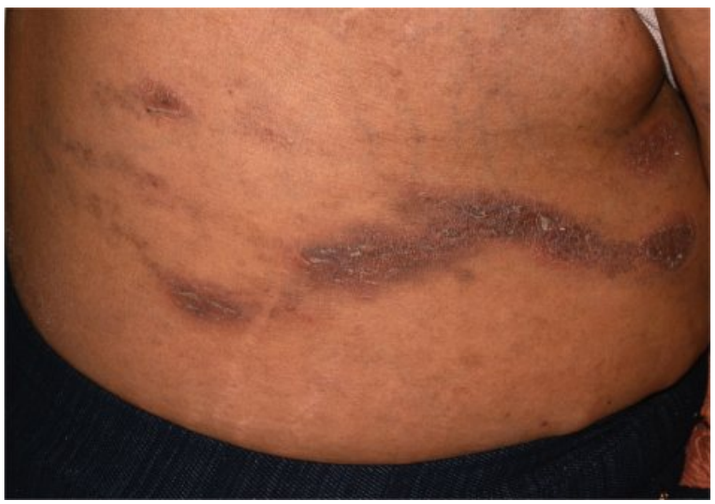
eFig. 62.12 Linear psoriasis. Streaks of erythematous papules and plaques with scale. *Courtesy Julie V. Schaffer, MD.*



eFig. 62.13 Linear lichen planus. More active lesions are seen on the calf, while postinflammatory hyperpigmentation predominates on the thigh. *Courtesy Anthony J. Mancini, MD.*



eFig. 62.14 Exaggerated dermatitis along the lines of Blaschko in a child with generalized atopic dermatitis. *Courtesy Antonio Torrelo, MD.*



eFig. 62.15 Linear lichenoid GVHD. Violet–brown scaly band following the lines of Blaschko. *Courtesy Julie V. Schaffer, MD.*



eFig. 62.16 Linear atrophoderma of Moulin. *Courtesy Julie V. Schaffer, MD.*

Other Genodermatoses 63

Susan J. Bayliss, Monique G. Kumar, Ángela Hernández-Martín, Bernard A. Cohen, Teresa Martínez-Menchón, Encarna Guillén-Navarro and Virginia P. Sybert

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Introduction

In this chapter, a number of genodermatoses are discussed that are not covered in other chapters of this textbook (Table 63.1).

Disorders characterized by cutaneous or mucosal tumors in conjunction with a variety of extracutaneous neoplasias, both benign and malignant, as well as endocrine abnormalities are the focus of the first section. It includes multiple endocrine neoplasia types 1, 2A, and 2B in addition to PTEN hamartoma tumor syndrome (including Cowden syndrome), Gardner syndrome, and Muir–Torre syndrome. This is followed by sections on: enzyme deficiencies; premature aging syndromes and poikilodermas; and ectodermal dysplasias.

DISORDERS FEATURING TUMORIGENESIS

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MULTIPLE ENDOCRINE NEOPLASIA

Multiple endocrine neoplasia (MEN) refers to a group of disorders marked by the presence of neoplasia or hyperplasia in two or more endocrine organs, often in association with mucocutaneous findings. Three major MEN syndromes with mucocutaneous findings – termed types 1, 2A, and 2B – have been clinically and genetically defined and are described in Table 63.2[1,2].

Mucocutaneous features are most prominent in MEN types 1 and 2B. In MEN1, multiple facial angiofibromas and collagenomas are present in the majority of affected individuals (Fig. 63.1), and lipomas are another common finding[3,4]. Compared to those in tuberous sclerosis, facial angiofibromas in MEN1 tend to be smaller and fewer in number, and they are more likely to arise on the upper lip and its vermilion border in addition to the nose and medial cheeks. Although melanoma has been reported in patients with MEN1 and there is evidence that *MEN1* expression is frequently lost in sporadic melanomas[5,6], it remains unclear whether individuals with this syndrome have an increased risk of melanoma.

MEN2B is notable for multiple mucosal neuromas, especially of the conjunctivae, lips, and anterior tongue (Fig. 63.2). These lesions, which may be evident at birth or develop during early childhood, represent a relatively specific marker that can enable timely diagnosis and thyroidectomy, as medullary thyroid cancer typically develops during the first few years of life in patients with MEN2B[7,8]. However, mucosal neuromas are also occasionally observed in patients with the PTEN hamartoma tumor syndrome (PHTS; see below). Cutaneous neuromas are rare in MEN2B and when present are usually in a perinasal location.

PTEN HAMARTOMA TUMOR SYNDROME, INCLUDING COWDEN SYNDROME

Synonyms: ■ Multiple hamartoma syndrome ■ Cowden disease

Key features

- Spectrum of disorders with autosomal dominant inheritance characterized by multiple hamartomatous tumors of ectodermal, mesodermal, and endodermal origin
- Mucocutaneous findings include tricholemmomas, acral keratoses, oral papillomas, neuromas, sclerotic fibromas, genital pigmented macules, vascular anomalies, and lipomas
- Patients have especially high risks of breast, thyroid, and endometrial carcinoma
- Caused by mutations in *PTEN*

Introduction

PTEN hamartoma tumor syndrome (PHTS) refers to a spectrum of disorders with overlapping clinical features caused by mutations in the phosphatase and tensin homolog (*PTEN*) gene (Table 63.3). PHTS encompasses Cowden syndrome (CS), Bannayan–Riley–Ruvalcaba syndrome (BRRS), and SOLAMEN syndrome (segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus; see Ch. 62). CS represents the most common phenotype of PHTS and is characterized by multiple hamartomas of ectodermal, mesodermal, and endodermal origin. Macrocephaly and mucocutaneous lesions (e.g. tricholemmomas, acral keratoses, oral papillomas) are the most constant and characteristic features[9]. Up to 85% of CS patients develop at least one malignant neoplasm, most often of the breast, thyroid, or endometrium[10].

GENODERMATOSES
Hereditary connective tissue disorders (Chs. 64, 95, 97, 98) Disorders of keratinization (Chs. 57–59) Hereditary epidermolysis bullosa (Ch. 32) Hereditary disorders of hair and nails (Chs. 69–71, 99) Hereditary disorders of pigmentation (Chs. 66 & 67) Hereditary vascular disorders (Ch. 104) Hereditary lipodystrophy syndromes (Ch. 101) Metabolic skin disorders (including enzyme deficiencies – see below; Chs. 48, 49, 92) Hereditary disorders of calcification/ossification (Ch. 50) Hereditary photosensitivity disorders (Chs. 49 & 87) Hereditary autoinflammatory diseases (Ch. 45) Primary immunodeficiencies (Ch. 60) Disorders featuring cutaneous cancer (Ch. 108) Disorders featuring benign tumors (Chs. 61 & 111) or multiple lentigines (Ch. 112) Mosaic skin disorders (Ch. 62)
Skin disorders associated with extracutaneous cancer • MEN1, 2A, 2B* • Cowden syndrome/PTEN hamartoma tumor syndrome* • Gardner syndrome* • Muir–Torre syndrome* • Birt–Hogg–Dubé syndrome (Ch. 111) • Peutz–Jeghers syndrome (Ch. 112) • Hereditary leiomyomatosis and renal cell cancer (Reed syndrome; Ch. 117) Ectodermal dysplasias* Premature aging syndromes* Poikilodermas* Enzyme deficiencies* • Alkaptonuria • Biotinidase & holocarboxylase synthetase deficiencies • Fabry disease & fucosidosis • Gaucher disease • Hartnup disease • Mitochondrial respiratory chain defects • Niemann–Pick disease • Phenylketonuria
*Discussed in this chapter.

Table 63.1 Genodermatoses. See also Chapter 55.



Fig. 63.1 Multiple endocrine neoplasia type 1. A Multiple large angiofibromas are a characteristic finding, including on the lips. **B** Multiple collagenomas are present on the abdomen. *A, Courtesy Edward Cowen, MD.*

History

In 1963, Lloyd and Dennis reported a multisystem disorder with characteristic mucocutaneous lesions and tumors of the breast, thyroid, and gastrointestinal tract[9]. They named the disorder "Cowden disease" after their first patient.

Epidemiology

PHTS is probably more common than is reflected by the number of cases reported, because the clinical findings can be subtle. It is inherited as an autosomal dominant trait with variable expressivity; a female predominance has been noted in some series[11]. Most of the reported patients have been White, and it is estimated to affect 1 in 200 000 individuals[12].

Pathogenesis

The PTEN protein is a lipid and protein phosphatase that plays a role in cell-cycle regulation and apoptosis[13,14]. In particular, PTEN *downregulates* the PI3K (phosphatidylinositol 3-kinase)/AKT/mTOR (mechanistic target of rapamycin) pathway that promotes cellular proliferation and survival (see Fig. 55.3). Like other autosomal dominant disorders caused by a defective tumor suppressor gene, PHTS is caused by a heterozygous germline *PTEN* mutation, with hamartomas and neoplasms resulting from a "second-hit" somatic mutation that inactivates the remaining allele of the gene (loss of heterozygosity). Lack of PTEN function leads to excessive mTOR signaling in affected tissues, in particular those with physiologic proliferation, such as the epidermis, oral and gastrointestinal mucosa, and thyroid and breast epithelium. PTEN also has phosphatase-independent activities and nuclear functions independent of the PI3K/AKT/mTOR pathway[14].

Clinical presentations of PHTS vary substantially even among patients with the same germline *PTEN* mutation, and in some families both CS and BRRS phenotypes are observed. Although genotype/phenotype correlations have not been established, mutations leading to an inactive protein may produce a more severe phenotype than those resulting in partially retained protein function[15]. Mosaicism due to a very early postzygotic *initial* mutation may produce a phenotype with disseminated findings clinically similar to germline disease[16]. Manifestations such as vascular anomalies and epidermal nevi with segmental distribution patterns can reflect an early postzygotic *second-hit* mutation (type 2 mosaicism; see Ch. 62) in a patient with a germline mutation, with different clinical findings depending on the tissue type affected.

Clinical Features

The 2013 revised clinical diagnostic criteria for PHTS are outlined in Table 63.4[17].

Mucocutaneous manifestations

Cutaneous involvement occurs in >80% of patients with PHTS and often serves as an early sign of the disorder. Characteristic mucocutaneous lesions usually begin to appear during the second to third decades of life (average, 22 years; range, birth to 75 years). Facial tricholemmomas present as multiple skin-colored to yellowish-tan, verrucous, or keratotic papules that resemble common warts[18] (Fig. 63.3A; see Ch. 111).

TYPES OF MULTIPLE ENDOCRINE NEOPLASIA (MEN)							
MEN type (synonyms)	**Mode of inheritance**	**Gene locus**	**Gene**	**Protein product**	**Location and type of mutations**	**Clinical manifestations**	
						Systemic	**Mucocutaneous**
1 (Wermer syndrome)	AD	11q13	*MEN1** [*MENIN*]	Menin (a nuclear protein)	Variable; truncating mutations in >70%	**Parathyroid**: hyperplasia or adenoma, hyperparathyroidism **Pancreas**: islet cell hyperplasia, adenoma or carcinoma, e.g. gastrinoma, insulinoma, glucagonoma **Pituitary**: prolactinoma > acromegaly, Cushing syndrome Less common: foregut carcinoid tumors, adrenocortical tumors, follicular adenomas (thyroid) Uncommon: pheochromocytoma	Multiple facial angiofibromas Collagenomas Lipomas (cutaneous and visceral) Less common: multiple gingival papules, confetti-like hypopigmented macules, CALM, possibly melanoma
2A (MEN type 2, Sipple syndrome)	AD	10q11.2	*RET*†	Tyrosine kinase receptor	Point mutations in the cysteine-rich extracellular domain, especially codon 634‡	**Thyroid**: C-cell hyperplasia, medullary carcinoma§ **Adrenal**: pheochromocytoma (50% bilateral) **Parathyroid**: hyperplasia or adenoma; hyperparathyroidism (less frequent than in MEN 1) Unusual: Cushing syndrome, Hirschsprung disease	Pruritus¶ Lichen amyloidosis¶ Notalgia paresthetica¶ Macular amyloidosis¶
2B (MEN type 3, multiple mucosal neuroma syndrome)	AD	10q11.2	*RET*†	Tyrosine kinase receptor	>95% of patients have missense mutation ($Met^{918}Thr$) in substrate-recognition pocket	**Thyroid**: medullary carcinoma (in first few years of life)§ **Adrenal**: pheochromocytoma (50% bilateral) **GI**: Diffuse ganglioneuromatosis (constipation, megacolon) Tearless crying (alacrima) Medullated corneal nerve fibers Marfanoid habitus Reduced subcutaneous fat High-arched palate Flat nasal bridge Pectus excavatum Proximal myopathy Other: Bilateral pes cavus, high patella, scoliosis, kyphosis, lordosis, joint laxity Rare: Cushing syndrome	Multiple mucosal neuromas, especially eyelid margins, conjunctivae, lips, anterior tongue > gingiva, palate, nasal and laryngeal mucosa Increased nerve fibers in normal skin Prominent, everted lips Everted eyelids Hyperpigmentation around mouth and overlying small joints of hands and feet CALM Circumoral lentigines Hypertrichosis, synophrys Rare: multiple neuromas of perinasal skin

*A tumor suppressor gene.
†Rearranged during transfection of proto-oncogene; mutations in the same gene can be responsible for Hirschsprung disease and familial medullary thyroid carcinoma.
‡Induces dimerization and activation of receptor in the absence of its ligand.
¶Onset usually prior to medullary thyroid carcinoma.
§Screen via measurement of serum calcitonin level after calcium or pentagastrin injection; prophylactic thyroidectomy prior to age 1 year is recommended for patients with MEN2B.

Table 63.2 Types of multiple endocrine neoplasia (MEN). A rare fourth type of MEN (MEN4) is caused by mutations in cyclin-dependent kinase inhibitor 1B (*CDKN1B*) and characterized by pituitary and parathyroid tumors; familial medullary thyroid carcinoma can result from *NTRK1* mutations as well as *RET* mutations. A woman with medullary thyroid carcinoma, macular amyloidosis, and multiple cutaneous neuromas in a widespread distribution (overlapping features of MEN2A and MEN2B) with a RET mutation in codon 768 has also been reported. AD, autosomal dominant; CALM, café-au-lait macules; NTRK1, neurotrophic tyrosine kinase receptor type 1.



Fig. 63.2 Multiple endocrine neoplasia type 2B. Enlarged lips and multiple neuromas on the tip of the tongue.

Both tricholemmomas and nonspecific cutaneous papules show a predilection for the central face, and they may coalesce around facial orifices (especially the nostrils) and on the ears. Papules on the head and neck of PHTS patients may also represent inverted follicular keratoses or acrochordons.

Multiple sclerotic fibromas of the skin are a relatively specific cutaneous marker of CS[19]. These lesions present as sharply circumscribed, firm dermal papules that display a strikingly uniform storiform pattern of collagen bundles on histologic examination (see Ch. 116). Punctate palmoplantar keratoses, often translucent with a central depression, are present in more than half of patients[20] (Fig. 63.4). Keratotic papules can also be seen on the heels, the dorsal aspects of the hands and feet, and the extensor surfaces of the forearms and lower legs.

Other skin and soft tissue manifestations include lipomas (especially testicular lipomatosis), angiolipomas, and vascular anomalies. The cutaneous vascular anomalies tend to be fast-flow lesions with intramuscular involvement and associated ectopic fat[21]. A distinctive "PTEN hamartoma of soft tissue" that presents as a subcutaneous and intramuscular mass with adipocytic, fibrous, and vascular (arterial, venous) components and sometimes lymphoid, bony, and neural elements has also been described[22]. Lastly, PHTS patients may have a slightly increased risk of melanoma, with a lifetime incidence of ~5%[10].

Oral lesions of PHTS appear as 1–3 mm, asymptomatic, mucosa-colored papules that often lead to a cobblestone appearance (Fig. 63.3B). They have a predilection for the lips and tongue, but extensive involvement of the entire oral cavity can occur[20].

CLINICAL MANIFESTATIONS OF PTEN HAMARTOMA TUMOR SYNDROME AND SCREENING RECOMMENDATIONS			
Clinical manifestations			
	Onset typically at birth or in childhood	**Onset typically in adolescence or adulthood**	**Variable onset**
Mucocutaneous	Pigmented macules of genitalia (glans and shaft of penis, vulva) Lipomas Vascular anomalies* PTEN hamartoma of soft tissue (see text) Neuromas (facial, acral, mucosal) Epidermal nevi Café-au-lait macules	Multiple facial papules† Multiple oral papillomas (lips, tongue)‡ Sclerotic fibromas Inverted follicular keratoses Multiple acrochordons Acanthosis nigricans	Acral/palmoplantar keratoses Scrotal tongue Perioral pigmented macules (rare)
Craniofacial and skeletal	Macrocephaly Down-slanting palpebral fissures Frontal bossing High-arched palate, long philtrum Pectus excavatum Joint hyperextensibility Hand and foot abnormalities¶		Scoliosis, kyphoscoliosis
Thyroid		Goiter and/or adenomas Carcinoma (follicular form over-represented)	
Breast		Fibrocystic disease Virginal hypertrophy Ductal papillomas Fibroadenomas Adenocarcinoma	
Gastrointestinal tract	Hepatic vascular anomalies	Adenocarcinoma (rare)	Multiple polyps (usually <5 mm in diameter)§ Ganglioneuromas Diffuse glycogenic acanthosis of esophagus
Genitourinary system		Ovarian cysts Uterine leiomyomas Menstrual irregularities Testicular lipomatosis Endometrial carcinoma Renal cell carcinoma Testicular tumors (e.g. seminoma)	
Central nervous system	Developmental delay, autism Seizures Hypotonia Developmental venous anomalies	Lhermitte–Duclos disease (LDD) – hamartomatous overgrowth of cerebellar ganglion cells that can lead to elevated intracranial pressure, ataxia, and seizures‖	Meningioma Spinal neurinoma
Ocular	Prominent corneal nerves Prominent Schwalbe lines Strabismus, amblyopia Retinal vascular anomalies Pseudopapilledema		Cataracts Myopia Angioid streaks
Muscular	Lipoid storage myopathy		
Other	Neonatal macrosomia Persistent drooling		
Screening recommendations			
• Yearly comprehensive *physical examination*, including skin, thyroid and breast, beginning at age 18 years (or 5 years before the youngest age of cancer diagnosis in the family); in women, breast examination every 6–12 months beginning at age 25 years (or 5–10 years prior to first breast cancer diagnosis in the family) in addition to monthly self-examinations • Yearly *thyroid ultrasound* starting at age 7 years • *Colonoscopy* beginning at age 35 years (or earlier if symptomatic or a family history of colon cancer before age 40 years); repeat at least every 5 years • In women, *annual mammogram and consideration of tomosynthesis and breast MRI* beginning at age 30–35 years (or 5–10 years before the youngest breast cancer diagnosis in the family) • Consider: (1) prophylactic mastectomies on an individual basis; (2) endometrial biopsy every 1–2 years and/or endometrial ultrasound beginning at menopause; and (3) renal ultrasound every 1–2 years beginning at age 40 years			
*Typically multifocal lesions with fast-flow channels, intramuscular involvement, and associated ectopic fat; may have capillary, venous, and/or lymphatic components. †Includes tricholemmomas, lesions with histologic features of verrucae, and very rarely tumors of the follicular infundibulum. ‡May represent epithelial hyperplasia, sclerotic fibromas, or glycogenic acanthosis. ¶Includes accelerated growth of the first metacarpal and first and second middle phalanges, syndactyly, and brachydactyly. §Can be hamartomatous, adenomatous, ganglioneuromatous, or inflammatory. ‖May occur as an isolated finding or in association with Cowden syndrome; patients with adult-onset LDD usually have a mutation in PTEN.			

Table 63.3 Clinical manifestations of PTEN hamartoma tumor syndrome and screening recommendations. In general, the clinical manifestations that are usually evident at birth or during childhood have classically been associated with Bannayan–Riley–Ruvalcaba syndrome and those that usually develop during adolescence or adulthood have classically been associated with Cowden syndrome.

REVISED CLINICAL DIAGNOSTIC CRITERIA FOR PTEN HAMARTOMA TUMOR SYNDROME (2013)
Major criteria

• Multiple mucocutaneous lesions (any of the following):
  • Tricholemmomas (≥3, at least 1 biopsy-proven)
  • Acral keratoses (≥3 papules or palmoplantar pits)
  • Mucocutaneous neuromas (≥3)
  • Oral papillomas, particularly on tongue & gingiva (≥3, biopsy-proven, or dermatologist-diagnosed)
• Pigmented macules on the glans penis
• Macrocephaly (>97th %ile; 58 cm in adult women, 60 cm in adult men)
• Lhermitte–Duclos disease (LDD; in an adult)
• Breast cancer
• Endometrial cancer (epithelial)
• Thyroid cancer (follicular)
• Gastrointestinal (GI) hamartomas, including ganglioneuromas, but *not* hyperplastic polyps (≥3)

Minor criteria
• Vascular anomalies, including multiple intracranial developmental venous anomalies • Lipomas (≥3) • Testicular lipomatosis • Autism spectrum disorder • Intellectual disability (IQ ≤75) • Renal cell carcinoma • Colon cancer • Esophageal glycogenic acanthosis • Thyroid cancer (papillary or follicular variant of papillary) • Thyroid structural lesions (e.g. adenoma, multinodular goiter)
Operational diagnosis in an individual: 3 major criteria including macrocephaly, LDD, or GI hamartomas –*or*– 2 major criteria + 3 minor criteria **Operational diagnosis when a family member meets diagnostic criteria or has a *PTEN* mutation:** 2 major criteria –*or*– 1 major + 2 minor criteria –*or*– 3 minor criteria

Table 63.4 Revised clinical diagnostic criteria for PTEN hamartoma tumor syndrome (2013). A scoring system incorporating age and clinical findings developed to estimate a patient's risk of having a *PTEN* mutation is available online (http://www.lerner.ccf.org/gmi/ccscore/). *Adapted from Pilarski R. PTEN hamartoma tumor syndrome: a clinical overview. Cancers (Basel) 2019;11;844.*





Fig. 63.3 Facial lesions in Cowden syndrome. **A** Multiple skin-colored papules on the face, especially the nose, some of which are verrucous. **B** Coalescing papules with a cobblestone-like appearance on the vermilion lips. *A, Courtesy Kalman Watsky, MD; B, Courtesy Jean L. Bolognia, MD.*

Extracutaneous manifestations

Multinodular goiter or thyroid adenomas occur in more than two-thirds of patients with PHTS, and the lifetime risk of thyroid carcinoma is estimated to be 10% to >30%. Fibrocystic disease and fibroadenomas of the breast affect three-quarters of female patients. Breast carcinoma develops in up to 85% of female patients with PHTS and is diagnosed at a mean age of ~40 years[10,23]; it has also been reported in affected men[24].

Multiple polyps may be found anywhere in the gastrointestinal tract but most frequently affect the colon (≥85% of patients). The lifetime risk of colon carcinoma is estimated to be ~10%[17,23]. Benign ovarian cysts and uterine leiomyomas commonly develop and endometrial carcinoma occurs in as many as 20%–30% of women with PHTS. The lifetime risk of renal carcinoma is estimated to be as high as ~30%[23].

Pathology

Histologically, tricholemmomas are characterized by a lobular proliferation of pale keratinocytes, often in association with a hair follicle. Basal keratinocytes are oriented to form a palisade, and hyperkeratosis can lead to a cutaneous horn. Demonstration of complete loss of PTEN expression within a tricholemmoma via immunohistochemical staining is suggestive that the patient has PHTS[25]. Histologically, some facial papules in patients with PHTS may simply be squamous papillomas, while others show follicular infundibular hyperplasia. Oral lesions often represent fibromatous nodules with collagen fibers arranged in whorls. On biopsy, extrafacial and palmoplantar papules tend to be hyperkeratotic papillomas, and they may have changes reminiscent of verrucae or acrokeratosis verruciformis[26].



Fig. 63.4 Cowden syndrome. Multiple palmar keratoses, many of which have a glassy appearance. A few have a central depression. *Courtesy Joyce Rico, MD.*

Differential Diagnosis

The clinical differential diagnosis of the oral papillomas of PHTS includes verrucae, focal epithelial hyperplasia (Heck disease), traumatic fibromas, mucosal neuromas of MEN2B, papillomas of Goltz

syndrome, and papular lesions of lipoid proteinosis. A combination of acral keratoses (including palmoplantar) plus oral and facial papules can also be seen in Darier disease, whereas multiple facial angiofibromas and gingival fibromas are characteristic of tuberous sclerosis. These disorders can usually be differentiated from PHTS by other characteristic features as well as histologic evaluation.

The clinical differential diagnosis of multiple facial tricholemmomas may include angiofibromas (as seen in tuberous sclerosis complex or MEN1), trichoepitheliomas, and fibrofolliculomas (Birt–Hogg–Dubé syndrome); in addition to their histologic features, the tendency of tricholemmomas to have a verrucous appearance clinically may help to distinguish them from these lesions. Common warts, seborrheic keratoses, basaloid follicular hamartoma syndrome, and epidermodysplasia verruciformis may represent additional diagnostic possibilities. Less commonly, multiple syringomas or the basal cell nevus syndrome might be considered (see Fig. 111.5).

The differential diagnosis for SOLAMEN syndrome includes the *PIK3CA*-related overgrowth spectrum and Proteus syndrome (see Table 104.5).

Treatment

Although the recognition of PHTS is based upon clinical and histologic evaluation, genetic testing allows confirmation of the diagnosis and facilitates identification of affected family members. Due to the high risk of malignancy, cancer surveillance is a critical part of PHTS management (see Table 63.3).

Agents that downregulate the mTOR pathway, such as sirolimus (rapamycin), can lead to improvement in vascular anomalies, lipomatosis, cutaneous papules, gastrointestinal polyps, and cerebellar function[27]. Facial papules respond variably to topical 5-fluorouracil, oral isotretinoin, curettage, laser ablation, or surgical excision[18].

GARDNER SYNDROME (VARIANT OF FAMILIAL ADENOMATOUS POLYPOSIS)

Synonym: ■ Familial polyposis of the colon

Key features

- Autosomal dominant disorder that is a variant of familial adenomatous polyposis (FAP) with prominent extraintestinal manifestations
- Features the intestinal polyps and adenocarcinoma that characterize FAP together with epidermoid cysts, fibromas, desmoid tumors, and osteomas
- Retinal pigment epithelial hamartomas represent an early sign
- Caused by mutations in the *APC* (adenomatous polyposis coli) gene

Introduction

The main features of Gardner syndrome are premalignant intestinal polyposis, epidermoid cysts, osteomas, and desmoid or fibrous tumors of the skin and other sites. It is considered to represent a phenotypic variant of the familial adenomatous polyposis syndrome (FAP) with prominent extraintestinal involvement[28,29].

History

In 1951, Gardner described a large family in which colonic polyps and carcinoma were associated with osteomas and "surface tumors". This FAP phenotype with prominent extraintestinal manifestations continues to bear Gardner's name.

Epidemiology

The prevalence of FAP is estimated to be 1 in 7000 to 1 in 30 000 live births. It is inherited as an autosomal dominant trait with high penetrance of the gastrointestinal manifestations but variable expressivity of extraintestinal findings, affecting men and women equally.

Pathogenesis

FAP (including Gardner syndrome) is caused by heterozygous germline mutations in the adenomatous polyposis coli (*APC*) tumor suppressor gene. *APC* encodes a protein that downregulates the Wnt/β-catenin signaling pathway, which has important functions in cellular proliferation, differentiation, and adhesion (see Fig. 55.6). Extraintestinal manifestations (especially desmoid tumors) are more likely in patients with mutations in the distal portion of *APC*[30,31].

Clinical Features

Cutaneous and soft tissue manifestations

Skin lesions appear during childhood and adolescence, frequently preceding the onset of polyposis. Cutaneous epidermoid cysts affect ~50% of patients with FAP and are often multiple[31]. The cysts typically begin to appear before puberty and favor the face, scalp, and extremities[31]. Multiple familial pilomatricomas have also been reported as a presentation of Gardner syndrome[32].

Gardner-associated fibromas may occur in the skin, subcutaneous tissues, mesentery, or retroperitoneum. The fibromas typically arise during the first two decades of life, favor the back (especially the paraspinal region), and can serve as a desmoid tumor precursor. Lipomas, leiomyomas, trichoepitheliomas, and neurofibromas are less frequently observed.

Desmoid tumors (also referred to as desmoid fibromatosis) are non-encapsulated, non-metastasizing, locally aggressive tumors that are usually rare but affect 10%–30% of patients with FAP. These lesions arise from musculoaponeurotic structures and can occur spontaneously or at surgical sites. In patients with APC, desmoid tumors most often develop within the abdominal wall or intra-abdominally following colectomy, with the latter location causing greater morbidity via obstruction of the small bowel and/or ureters. Extra-abdominal lesions affecting the shoulder girdle, chest wall, or inguinal region can also occur. Although cytologically benign, desmoid tumors represent a potential cause of mortality in FAP, e.g. due to compression of vital organs.

Other extraintestinal manifestations

Retinal pigment epithelial hamartomas (RPEH) are evident in ~75%–80% of patients with FAP. These lesions may be present at birth, serving as an early and specific sign of the disorder[33,34] (Fig. 63.5). Although often referred to as congenital hypertrophy of the retinal pigment epithelium (CHRPE), FAP-associated pigmented retinal lesions have irregular borders and a haphazard bilateral distribution that differentiate them from sporadic multifocal CHRPE[34].

Osteomas occur in ~65%–80% of patients with FAP and favor the frontal bone, mandible, and maxilla, although they can also develop in other bones of the skull and long bones. Seen in children as young as 8 years of age, osteomas are painless and can grow large enough to be clinically obvious or be detectable only by radiographic studies. Other skeletal lesions include exostoses, endostoses, and cortical thickening of the long bones. Dental anomalies are apparent in ~30% of patients with FAP and include supernumerary teeth, odontomas, unerupted teeth, and congenitally missing teeth.



Fig. 63.5 Retinal pigment epithelial hamartomas in Gardner syndrome. *Courtesy L. Tychsen, MD.*

Patients with FAP are at increased risk for the development of other tumors, including papillary carcinoma of the thyroid (particularly in women), hepatoblastoma (usually affecting children <3 years of age), pancreatic and biliary tract carcinomas, nasal angiofibromas, adrenal adenomas (or occasionally carcinomas), and sarcomas (e.g. fibrosarcoma, osteosarcoma). The association of brain tumors (most often medulloblastomas) with adenomatous polyposis in patients with heterozygous *APC* mutations has historically been referred to as Turcot syndrome type 2. The latter is distinct from the *constitutional mismatch repair deficiency syndrome* (previously referred to as Turcot syndrome type 1) that presents during childhood with brain tumors (primarily glioblastomas), colonic polyposis, hematologic malignancies, and multiple café-au-lait macules due to *biallelic* mutations in mismatch repair genes (see below and Table 61.3)[35].

Gastrointestinal manifestations

In adults, the diagnosis of FAP is commonly made when the patient presents with gastrointestinal bleeding secondary to adenomatous polyps. Other findings may include anemia, abdominal pain, diarrhea or constipation, and weight loss. Premalignant *adenomatous* polyps most commonly occur in the colorectum but are also found in the small intestine and stomach in over half of patients. Polyps are typically <1 cm in diameter and are rarely seen before the age of 10 years. By the age of 20 years, 50% of patients with FAP have demonstrable polyps. Without surgical intervention, colorectal carcinoma is inevitable; it usually develops before age 40 years and arises by early adolescence in ~5% of affected individuals[29,36]. Carcinomas of the small intestine (especially the duodenum) can also occur[29].

Pathology

Histologically, intestinal polyps show adenomatous hyperplasia of the mucosa. Cutaneous cysts in patients with FAP usually demonstrate the same microscopic changes as ordinary epidermoid cysts, with a lining of keratinizing epithelium that includes a granular layer. Pilomatricoma-like changes, with characteristic basophilic and shadow cell populations, have also been noted.

Differential Diagnosis

Although epidermoid cysts represent a common sporadic finding, multiple lesions with onset during childhood should prompt a thorough family history and evaluation for other findings of Gardner syndrome (e.g. RPEH, osteomas). Of note, mutations in the *MUTYH* base excision repair gene can cause an autosomal recessive form of colorectal adenomatous polyposis, with osteomas, RPEH, desmoid tumors, pilomatricomas, and sebaceous neoplasms (see below) having been described in affected individuals[37].

Management

The diagnosis of FAP is established by identifying a pathogenic variant in *APC* in an individual with multiple colorectal adenomatous polyps (≥100 for an adult pre-colectomy and without a relative with confirmed FAP). Genetic counseling is imperative, and family members should be evaluated for intestinal and extraintestinal signs of the disorder.

Because of the inevitable development of colorectal carcinoma, prophylactic colectomy is recommended when polyp formation becomes evident, and it is usually performed between 15 and 25 years of age. Initially, children with FAP should be monitored with sigmoidoscopy or colonoscopy every 1–2 years beginning at 10–12 years of age. Once polyps are detected, patients should undergo annual colonoscopy until a colectomy is done. Esophagogastroduodenoscopy is recommended every 6 months to 4 years (depending on polyp burden) beginning at 20–25 years of age, with careful inspection of the ampulla of Vater. Annual physical examination should include evaluation for neurologic deficits and other extraintestinal manifestations, including palpation of the abdomen (for desmoid tumors) and thyroid starting in the late teenage years. If there is a family history of desmoid tumors, abdominal CT or MRI beginning 1–3 years post colectomy and then every 5–10 years should be considered. Because of the increased risk of hepatoblastoma, some experts recommend abdominal ultrasound and measurement of serum α-fetoprotein every 3–6 months during the first 5 years of life.

Symptomatic epidermoid cysts can be surgically excised. Desmoid tumors are also treated by surgical excision, although there tends to be a high recurrence rate. Preoperative MRI of the abdomen can demonstrate the origin of the tumor and the extent of involvement. If wide surgical excision fails, radiotherapy, hormonal therapy (e.g. tamoxifen, raloxifene), chemotherapy, or a combination thereof can be tried. The osteomas of FAP may or may not be amenable to surgical intervention. Medications that affect prostaglandin metabolism, such as nonsteroidal anti-inflammatory drugs (NSAIDs), may reduce the risk of colorectal cancer and desmoids[38].

MUIR–TORRE SYNDROME (VARIANT OF LYNCH SYNDROME)

Synonym: ■ Cutaneous sebaceous neoplasms and keratoacanthomas, with gastrointestinal and other carcinomas

Key features

- An autosomal dominant disorder associated most commonly with adenocarcinoma of the colon, followed by genitourinary carcinomas
- The cutaneous manifestations are sebaceous neoplasms and keratoacanthomas
- Caused by mutations in DNA mismatch repair genes (*MSH2* >> *MLH1* > *MSH6, PMS2*)

Introduction

Muir–Torre syndrome (MTS) is an uncommon autosomal dominant genodermatosis that is characterized by sebaceous neoplasms (adenoma, sebaceoma, or carcinoma; see Ch. 111), and internal malignancies. It is considered to represent a variant of Lynch syndrome, which is also known as hereditary non-polyposis colorectal cancer (HNPCC) syndrome[39].

History

Muir in 1967 and Torre in 1968 independently reported the syndrome that bears their names. Their two patients had malignancies in several organs plus either keratoacanthoma-like lesions or multiple tumors of sebaceous origin.

Epidemiology

The male : female ratio in MTS is 3 : 2, and affected individuals present with cutaneous manifestations at a mean age of 55 years. The prevalence of Lynch syndrome in the general population is estimated to be ~1 in 350. In a study of Lynch syndrome patients, MTS was observed in 28% (14/50) of families and 9% (14/152) of individuals with a confirmed germline mismatch repair gene mutation[40].

Pathogenesis

MTS is caused by heterozygous germline mutations in one of several DNA mismatch repair (MMR) genes, including *MSH2* (90% of MTS cases), *MLH1*, and rarely *MSH6* or *PMS2*. MMR proteins are responsible for detecting and repairing DNA replication errors. In patients with MTS, somatic inactivation of the other allele of the affected gene (loss of heterozygosity) results in microsatellite instability, i.e. increased variability in the lengths of repetitive "microsatellite" sequences in the genome, as well as mutations that lead to tumor formation[41].

Clinical Features

Sebaceous tumors can present prior to (~30%), concurrently with (~10%), or after (~60%) the diagnosis of a visceral malignancy. The skin tumors sometimes appear decades before or after a visceral malignancy develops. In general, sebaceous tumors favor the head and neck region (Fig. 63.6), and sporadic sebaceous carcinomas tend to affect the

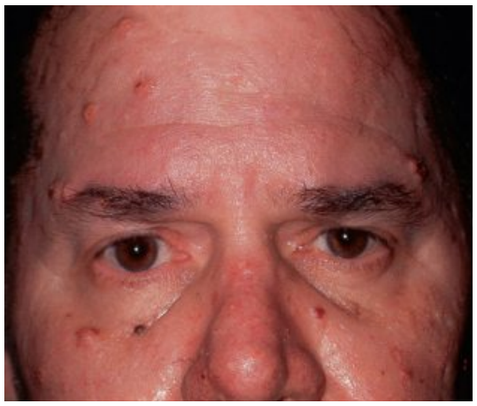


Fig. 63.6 Muir–Torre syndrome with multiple sebaceous neoplasms. *Courtesy Dan Ring, MD.*

periocular area. However, in patients with MTS, these neoplasms can occur in other locations (trunk > extremities)[42]. Sebaceous adenomas are the most common tumor type, and they present as slow-growing, yellow to pink papules or nodules, numbering from one to hundreds. Keratoacanthomas, which are keratotic skin-colored to erythematous papules or nodules that arise quickly, are seen in ~25% of patients with MTS and usually exhibit sebaceous differentiation. Fordyce granules ("free" sebaceous glands) on the vermilion lip and oral mucosa (especially the vestibule) are more common and prominent in patients with MTS than in the general population[43].

The most frequently observed malignancies in Lynch syndrome are colorectal (~50%–60% of patients with *MSH2* or *MLH1* mutations) and genitourinary (e.g. endometrium [15%–50% of women], ovary [10%–35% of women], urinary tract; highest risk with *MSH2* mutations) carcinomas[44]. Colorectal carcinoma in Lynch syndrome most often involves the proximal colon and develops at a median age of 45 years, about one decade before it typically occurs in the general population. Lynch syndrome patients are also at increased risk of neoplasms of the small intestine, stomach, pancreas, hepatobiliary system, CNS, and perhaps breast[45,46]; hematologic malignancies and sarcomas have also been reported.

RISK ASSESSMENT FOR MUIR–TORRE SYNDROME (MTS)	
Higher likelihood of MTS	**Lower likelihood of MTS**
Clinicopathologic characteristics of skin lesions	
• ≥2 sebaceous neoplasms **[2]** • Located outside of the head and neck region • Sebaceous neoplasm with high specificity for MTS, e.g. a cystic lesion or keratoacanthoma with sebaceous differentiation	• Single sebaceous neoplasm • Located in photodamaged facial skin • Sebaceous hyperplasia
Characteristics of patient and family history	
• Age <60 years **[1]** • Personal history of colorectal cancer* and/or other Lynch syndrome-related malignancies (e.g. small bowel, gastric, endometrial, bladder, ureteral, renal, biliary, pancreatic, glioblastoma) **[1]**, especially if more than one • Colorectal cancer and/or other Lynch syndrome-related malignancies in family member(s) **[1]**, especially if before 50 years of age and in first-degree relative(s)	• Elderly patient with no history of a Lynch syndrome-related malignancy • No family members with colorectal cancer/other Lynch syndrome-related malignancies
Additional analysis of sebaceous neoplasms	
• Loss of MSH2, MLH1, MSH6, and/or PMS2 expression shown by immunohistochemical staining† • Evidence of MSI in lesional tissue (more specific)‡	• Expression of MLH1, MSH2, MSH6, and PMS2 shown by immunohistochemical staining • No evidence of MSI in lesional tissue‡

*Especially if MSI-high histology – presence of tumor-infiltrating lymphocytes, Crohn disease-like lymphocytic reaction, medullary growth pattern, or signet ring/mucinous differentiation.
†MSH2 and MSH6 proteins form a heterodimer, so lack of one can lead to the absence of the other; likewise, PMS2 is unstable without a functional MLH1 protein.
‡Testing can be performed on paraffin-embedded tissue; diagnostic yield may be higher for colonic neoplasms.

Table 63.5 Risk assessment for Muir–Torre syndrome (MTS). A clinical score of ≥2 based on the sum of the applicable numbers in [ ] has a sensitivity of nearly 100% and a specificity of ~80% for predicting a germline mutation in a mismatch repair gene[48]. MSI, microsatellite instability.

Diagnosis

The diagnosis of MTS was traditionally based on the presence of at least one sebaceous tumor (or keratoacanthoma with sebaceous differentiation) and a visceral malignancy without another known predisposing factor. In the absence of a sebaceous tumor, the diagnosis can be made in a patient with multiple keratoacanthomas, multiple visceral malignancies, and a family history of MTS[47]. Findings that suggest a higher or lower likelihood of MTS in patients with sebaceous neoplasms are summarized in Table 63.5[48]. Testing for a mismatch repair gene mutation is helpful in confirming the diagnosis and facilitating identification and surveillance of affected family members.

Pathology

Skin tumors arising as part of MTS fall into two general categories: sebaceous neoplasms and keratoacanthomas. Sebaceous adenomas (with a predominance of mature sebocytes), sebaceomas (vertically oriented with a predominance of basaloid seboblastic cells), so-called sebaceous epitheliomas (inconsistently defined term used for various lesions with seboblastic differentiation), and sebaceous carcinomas may occur (see Ch. 111). A type of keratoacanthoma with sebaceous differentiation that may be specific to this syndrome has been called a sebo(kerato)acanthoma; it has the architecture of a keratoacanthoma but contains well-differentiated sebaceous lobules (Fig. 63.7)[49]. In addition, cystic sebaceous tumors, which are well-circumscribed, deep sebaceous lesions with a cystic growth pattern, occur in some MTS patients and are a strong clue for the presence of the syndrome.

Immunohistochemical (IHC) staining for MSH2, MSH6, MLH1, and PMS2 can be a valuable screening tool for MTS-associated tumors, which frequently show a lack of expression of one or more of these mismatch repair proteins (see Table 63.5)[43,45,50]. However, abnormal IHC staining is not diagnostic of MTS, as it is sometimes seen in sporadic sebaceous neoplasms, especially in immunocompromised patients; conversely, IHC staining may rarely be normal in lesions from patients with a mismatch repair gene mutation (see Ch. 111)[50,51]. PCR-based assays can also be used to demonstrate microsatellite instability (MSI) in tissue from MTS-associated neoplasms. Confirmatory testing for a germline

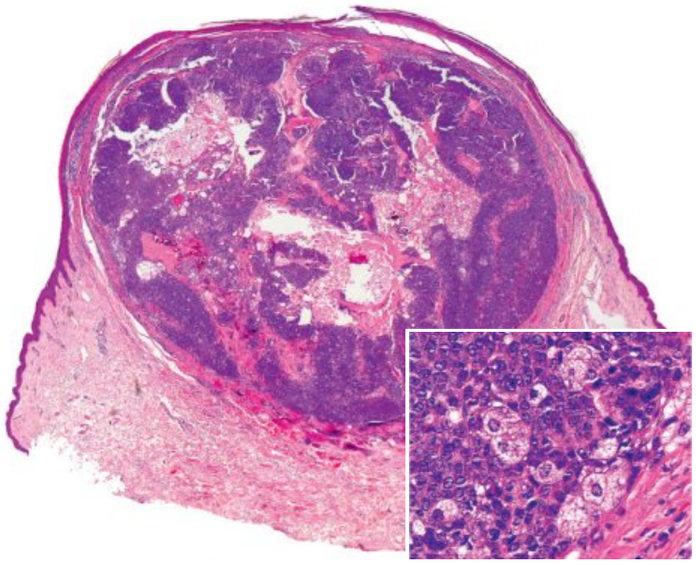


Fig. 63.7 Seboacanthoma in a patient with Muir–Torre syndrome. Well-circumscribed basaloid tumor with abundant secreted material, surrounded by a pseudocapsule of compressed fibrous tissue. Note the sebaceous differentiation (inset). *Courtesy Luis Requena, MD.*

SURVEILLANCE GUIDELINES FOR PATIENTS WITH LYNCH SYNDROME, INCLUDING MUIR–TORRE SYNDROME		
Test	**When to begin**	**Frequency**
• Comprehensive physical examination, including the skin, and neurologic assessment	• Age 20–25 years	• Yearly
• **Colonoscopy**	• Age 20–25 years • If diagnosed in a family member before age 25 years, 2–5 years younger than the earliest colon cancer in the family	• Every 1–2 years
• Consider endometrial biopsy and (in postmenopausal women) transvaginal ultrasound*	• Age 30–35 years*	• Every 1–2 years
• Consider esophagogastroduodenoscopy with biopsy of the proximal and distal stomach • Consider *H. pylori* testing and treatment when found	• Age 40 years	• Every 3–5 years, based on individual risk factors
• Consider urinalysis ± cytological examination	• Age 30–35 years	• Yearly, based on individual risk factors
• Consider prostate-specific antigen (PSA) testing and digital rectal examination	• Age 40 years	• Yearly, based on individual risk factors
*Consider hysterectomy and bilateral salpingo-oophorectomy when childbearing is completed, with timing depending on factors including menopause status, comorbidities, family history, and genetic etiology.		

Table 63.6 Surveillance guidelines for patients with Lynch syndrome, including Muir–Torre syndrome. Colonoscopy (in **bold**) is the only strong recommendation in these guidelines. For patients with a family history of pancreatic cancer, screening can be considered beginning at age 50 years (or 10 years younger than the earliest diagnosis in the family) with endoscopic ultrasound and/or magnetic resonance imaging/magnetic resonance cholangiopancreatography. Routine breast screening beyond that advised for the general population is not currently recommended. *Based on the National Comprehensive Cancer Network guidelines (http://nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf) and Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer. Dis Colon Rectum 2014;57:1025–48.*

mismatch repair gene mutation should be considered in patients with abnormal lesional IHC staining for these proteins, evidence of MSI, or a strong clinical suspicion of MTS.

Differential Diagnosis

Sebaceous hyperplasia is a common finding in the general population, and sebaceous adenomas and carcinomas can occur in patients without MTS. Sebaceous adenomas and carcinomas as well as colorectal carcinomas have also been described in patients with autosomal recessive colorectal adenomatous polyposis caused by mutations in the *MUTYH* base excision repair gene[37,52]. This disorder accounts for some of the patients with sebaceous neoplasms and visceral malignancy who meet the traditional criteria for MTS, but whose tumors do not exhibit microsatellite instability. Some authors have referred to patients without evidence of microsatellite instability due to mismatch repair dysfunction as having MTS type 2[47]. Additional manifestations of *MUTYH*-associated polyposis include other malignancies (e.g. small bowel, ovarian, bladder) and findings that overlap with Gardner syndrome, such as osteomas, RPEH, desmoid tumors, and pilomatricomas[53].

Multiple keratoacanthomas may occur as an isolated finding (i.e. without visceral malignancy), especially in patients with the Ferguson–Smith (multiple self-healing) or Grzybowski (generalized eruptive) types of keratoacanthomas. However, these patients should be evaluated to exclude the possibility of MTS.

Treatment

Patients with an internal malignancy require appropriate oncologic referral and management. Recommendations for surveillance of high-risk individuals are outlined in Table 63.6. Long-term aspirin therapy may decrease the risk of colorectal carcinoma in patients with Lynch syndrome[39].

Treatment options for benign sebaceous tumors include curettage, excision, and cryosurgery. Sebaceous carcinomas have metastatic potential and require wide local excision or Mohs micrographic surgery, with the latter recommended for facial lesions. Oral retinoids with or without interferon-α may be useful in the prevention of new sebaceous neoplasms.

ENZYME DEFICIENCY DISEASES

Ángela Hernández-Martín

ALKAPTONURIA

Synonym: ■ Ochronosis

Key features

- An autosomal recessive disorder due to deficiency of homogentisate 1,2-dioxygenase
- Clinical signs include discoloration of cartilage (e.g. the helices), sclerae, and skin (e.g. the axillae)
- Extracutaneous findings include urine that darkens on standing, arthritis, and valvular heart disease

Alkaptonuria is an autosomal recessive inborn error of metabolism in which homogentisic acid (HGA), an intermediate in phenylalanine and tyrosine metabolism, cannot be further metabolized and therefore accumulates in body fluids and tissues[54]. The disorder results from a deficiency of the enzyme homogentisate 1,2-dioxygenase. It is estimated to have a prevalence of ~1 in 250 000 in most ethnic groups, but as high as 1 in 20 000 in Slovakia and the Dominican Republic due to founder effects.

The cardinal clinical features of alkaptonuria include urine that turns dark on standing, discoloration of cartilage and other connective tissues, and arthritis (Fig. 63.8). The arthritis often presents in the third or fourth decade of life with chronic back pain and stiffness, and radiographs show flattened and calcified intervertebral discs. Later involvement of large peripheral joints can resemble rheumatoid arthritis clinically but osteoarthritis radiographically. Renal complications include an increased incidence of calculi and occasionally kidney failure. Aortic stenosis is common by the sixth or seventh decade of life and coronary artery calcifications may also develop[54]. Life expectancy is normal.

The dermatologic features of alkaptonuria are rarely noted prior to 10–15 years of age and typically become apparent during adulthood, often in the fourth decade of life. Axillary skin may be one of the initial sites to develop discoloration, which can range in color from blue to yellow to brown. The classic blue–grey color associated with this disorder is often first noted in the helices of the ear and sclerae (see Fig. 63.8). Later, it may affect the palmar and plantar surfaces as well as the entire face. Dermoscopy can show speckled white globular structures overlying a grayish-blue structureless area[55]. Collagenous and elastotic marginal plaques of the hand may also develop, typically during the fourth to sixth decades of life[56]. Features that may present early in life

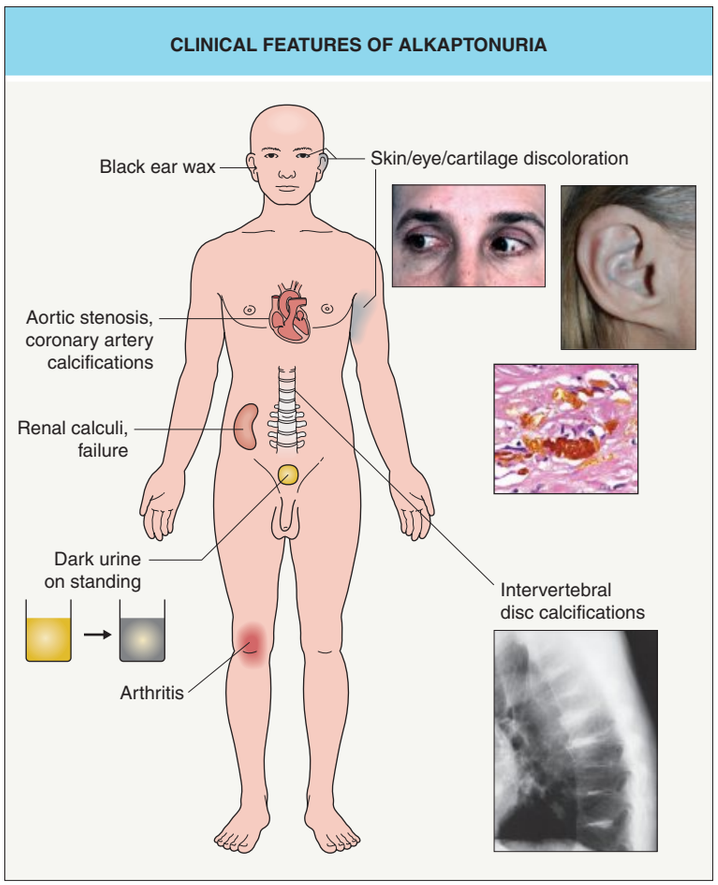


Fig. 63.8 Clinical features of alkaptonuria. *Eyes, courtesy William Gahl, MD PhD; ear, courtesy Julie V. Schaffer, MD; radiograph, courtesy Jean L. Bolognia, MD; photomicrograph, courtesy Lorenzo Cerroni, MD.*

include brownish discoloration of diapers (due to the dark urine) and cerumen that is brown to black in color. Histopathologic findings of discolored skin include orthohyperkeratosis and irregular, brownish-yellow, acellular deposits in the dermis[55].

Diagnosis of alkaptonuria can be confirmed by urine organic acid analysis. Management includes physical therapy and pain control as needed. Beginning at age 40 years, periodic cardiac assessment with echocardiography is recommended[54]. Administration of oral nitisinone, an inhibitor of HGA production, at a dose of 2–10 mg daily reduces urinary HGA excretion by >95% and has been shown to slow disease progression[57]; a low-protein diet in conjunction with this medication may help to prevent excessively high plasma tyrosine levels.

BIOTINIDASE AND HOLOCARBOXYLASE SYNTHETASE DEFICIENCIES

Synonym: ■ Late- and early-onset forms of multiple carboxylase deficiency

Key features

- As biotin is an essential cofactor for carboxylases, there is overlap in these two autosomal recessive disorders
- Cutaneous findings include alopecia, periorificial erythema and erosions (features of "nutritional dermatitis"), and sometimes flexural involvement reminiscent of seborrheic dermatitis
- Metabolic acidosis occurs in both disorders
- Biotinidase deficiency is associated with developmental delay, hearing loss, and seizures beginning during infancy or childhood, while patients with holocarboxylase synthetase deficiency classically develop encephalopathy and hypotonia within the first 3 months of life

Biotinidase deficiency and holocarboxylase synthetase deficiency are genetically distinct autosomal recessive disorders that result in multiple carboxylase deficiency; the former has its onset during infancy or childhood, while the latter presents during the first 3 months of life[58,59]. Dermatologic features, which overlap with other forms of "nutritional dermatitis" (see Fig. 51.13), occur in >50% of patients with biotinidase deficiency and a smaller proportion of those with holocarboxylase synthetase deficiency. Characteristic skin findings include progressive alopecia and a well-demarcated dermatitis with erythema and scaling that typically begins in perioral, perianal and/or flexural regions, sometimes mimicking seborrheic dermatitis, but then can become generalized. This eruption is often eroded or fissured, and superimposed candidiasis and other secondary infections may develop.

Biotinidase deficiency, a pan-ethnic disorder with an incidence of ~1 in 60 000 births, represents a defect in biotin recycling. Patients with this disorder become functionally biotin-deficient under conditions of *normal* dietary biotin intake. Since biotin is an essential cofactor for the activity of carboxylases, multiple carboxylase deficiency ensues. Both cutaneous and extracutaneous manifestations usually develop between 3 months and 2 years of age but may be delayed until later childhood. Extracutaneous features include developmental delay, hearing loss, seizures, conjunctivitis, optic atrophy, myelopathy, and metabolic acidosis[58].

Abnormalities on urine organic acid analysis are not consistently present. The diagnosis is established by an assay of biotinidase activity in blood or molecular genetic testing; prenatal diagnosis is possible via enzymatic and molecular analyses. Considering that the highly variable manifestations may go unrecognized, biotinidase deficiency is included in the newborn screening panel of many countries, including the US[58]. The clinical features of biotinidase deficiency are entirely preventable with administration of 5–20 mg of biotin daily.

Holocarboxylase synthetase deficiency is significantly less common than biotinidase deficiency. It represents a defect in biotinylation of the apocarboxylases, leading to a failure in synthesis of intact functional holocarboxylases[59]. Patients typically present within the first 3 months of life with symptoms of a metabolic encephalopathy, including poor feeding, lethargy, respiratory distress, and hypotonia. Metabolic acidosis, hyperammonemia, and organic aciduria are often observed. Definitive diagnosis is established by assays of carboxylases in leukocytes or cultured skin fibroblasts, or by molecular genetic testing; prenatal diagnosis is also possible via enzymatic and molecular analyses. Most patients exhibit significant improvement when treated with 10 mg of biotin daily.

FABRY DISEASE

Synonym: ■ Anderson–Fabry disease

Key features

- X-linked disorder due to a deficiency of α-galactosidase A
- Characteristic mucocutaneous finding is multiple angiokeratomas
- Additional features include pain and paresthesias of the extremities, hypohidrosis, and renal and coronary insufficiency

Fabry disease is an X-linked lysosomal storage disorder resulting from a defect in glycosphingolipid metabolism due to pathogenic variants in *GLA*, which encodes the enzyme α-galactosidase A (α-Gal A)[60]. It is a pan-ethnic condition that can be identified via newborn screening in ~1 in 7000 male neonates[61], including both *classic* severe disease (associated with minimal residual α-Gal A activity) and *later-onset* phenotypes with milder clinical involvement (cardiac > renal). Female heterozygotes may also be affected, with variable clinical manifestations that often have a later onset. The clinical manifestations result from accumulation of globotriaosylceramide and its deacylated form, globotriaosylsphingosine, in multiple cell types, including vascular endothelial cells, cardiomyocytes, renal podocytes, and neural cells[60]. This leads to sequelae such as apoptosis, inflammation, oxidative stress, ischemia, necrosis, and fibrosis[60,62].

Fabry disease has a wide spectrum of clinical findings with variable progression, ranging from severe multi-organ dysfunction in the classic phenotype to minimal symptoms[62]. Classic Fabry disease presents in boys during childhood or adolescence with the cardinal clinical features of acral pain (episodic or chronic), acral paresthesias, hypohidrosis, and angiokeratomas (Fig. 63.9). Characteristic whorled corneal opacities ("cornea verticillata") are evident in ~75% of both male hemizygotes and female heterozygotes by childhood or adolescence but are rarely of clinical significance. Posterior lenticular opacities and tortuous retinal or conjunctival vessels may also be observed. However, milder forms of Fabry disease with delayed onset often have subtle or absent early findings.

With increasing age, progressive renal insufficiency develops, typically leading to the need for dialysis or transplantation by the fourth or fifth decade of life in untreated men with classic disease. Cardiac sequelae such as hypertrophic cardiomyopathy, arrhythmias, myocardial fibrosis, valvular abnormalities, and coronary insufficiency occur in most men with classic disease by middle age and represent the most common cause of premature death in both men and women with Fabry disease. Manifestations in other organ systems can include transient ischemic attacks and strokes; abdominal pain, diarrhea, and vomiting (especially in children); obstructive lung disease; joint pain and osteopenia; and hearing loss[60,62]. Characteristic facial features such as periorbital fullness, bushy eyebrows, a broad nasal bridge, thick lips, prognathism, and prominent earlobes have been noted in men with Fabry disease. Although complications usually occur at a later age in female heterozygotes than in men with classic disease, some women do develop early symptoms followed by progressive organ involvement.

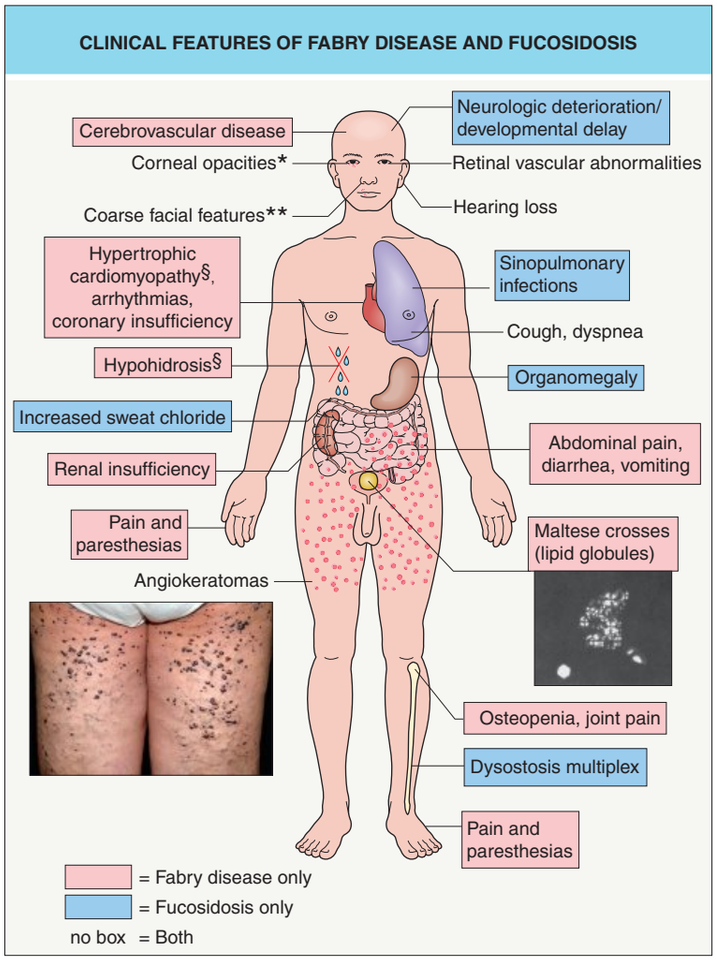


Fig. 63.9 Clinical features of Fabry disease and fucosidosis. Traditionally, polarizing microscopy of urinary sediment revealing birefringent lipid globules ("Maltese crosses") was utilized as a marker of Fabry disease. *Also lenticular in Fabry disease. **Milder in Fabry disease. §Occasionally observed in fucosidosis.
Angiokeratomas of Fabry disease, courtesy Luis Requena, MD; photomicrograph of Maltese crosses, courtesy Robert J. Desnick, MD PhD.

Angiokeratomas are one of the earliest signs of Fabry disease, typically beginning to appear during childhood or adolescence[63–65]. They develop in most male patients and ~30% of female heterozygotes. Angiokeratomas present as punctate, dark red to blue–black macules or papules (Fig. 63.10). The lesions do not blanch with pressure and may become slightly keratotic as they enlarge. The angiokeratomas of Fabry disease, referred to as angiokeratoma corporis diffusum, tend to be concentrated between the umbilicus and the knees but can develop at any cutaneous site (see Fig. 63.10); oral and conjunctival lesions are also seen. Less frequent vascular findings include linear telangiectasias favoring the face, lips, and oral mucosa; episodic acral vasospasm resembling Raynaud phenomenon, typically accompanied by pain and paresthesias; and peripheral edema and lymphedema[64,65]. Hypohidrosis is an early and almost constant feature of Fabry disease that can result in heat intolerance. Decreased body hair has also been described.

Histologically, angiokeratomas are composed of dilated capillaries in the uppermost dermis, partially enclosed by elongated rete ridges (see Ch. 114); hyperkeratosis may be seen in older lesions. In the skin, there is evidence of lipid storage in endothelial cells, pericytes, arteriolar smooth muscle, and arrector pili muscle. This can be detected by a lipid stain such as Sudan black B, or highlighted by periodic acid Schiff (PAS) staining. Lipid accumulation may also be observed in sweat gland epithelium (see Ch. 39) and perineural cells. Ultrastructural examination demonstrates characteristic cytoplasmic inclusions in all of these cell types.

The diagnosis of Fabry disease can be established by demonstration of deficient α-gal A activity in plasma, leukocytes, dried blood spots on filter paper, or cultures of amniocytes or chorionic villi obtained from prenatal testing. However, enzyme activity is within the normal range in up to a third of female heterozygotes. Molecular analysis of *GLA* can be helpful in: (1) determining disease status in females; (2) predicting disease severity in male patients via genotype–phenotype correlation; and (3) facilitating prenatal/preimplantation diagnosis and testing of at-risk family members[66,67]. Elevated plasma or urinary levels of globotriaosylsphingosine (lyso-Gb3), which correlate with disease severity, can confirm the diagnosis in individuals with a *GLA* variant of uncertain significance identified by genetic testing[61]. Although most commonly seen in association with Fabry disease, angiokeratoma corporis diffusum can also be observed in several other lysosomal storage disorders[68], as outlined in Table 63.7. Scrotal and vulvar angiokeratomas are also commonly found in older adults (see Ch. 114).

Enzyme-replacement therapy (ERT) with recombinant agalsidase-α or β is available (the latter FDA-approved) and is administered biweekly by intravenous infusion. Accumulated data indicate that it is effective in arresting progression of the disorder, especially when initiated early in the disease process. Current guidelines recommend considering ERT in all symptomatic patients, and at 7–10 years of age in asymptomatic boys with *GLA* pathogenic variants associated with classic disease[66,67,69]. Some authors recommend X-chromosome inactivation (XCI) analysis for asymptomatic girls ≥7 years of age and consideration of ERT in those with a skewed XCI pattern favoring expression of a *GLA* pathogenic variant that has been associated with classic disease[66]. Baseline assessment for organ involvement is also recommended by age 5 years and 12–15 years for asymptomatic boys and girls, respectively[66]. Controlled studies have found that treatment with migalastat, an oral pharmacologic chaperone that stabilizes specific mutant forms of α-galactosidase, may reduce renal glycosphingolipid accumulation, left ventricular hypertrophy, and gastrointestinal symptoms in Fabry disease patients with suitable mutations. Other interventions include gabapentin or carbamazepine for neuropathic pain and angiotensin-converting enzyme inhibitors to reduce proteinuria[61,70].

FUCOSIDOSIS

Key features

- Autosomal recessive disorder due to deficiency of α-fucosidase
- Multiple angiokeratomas of the skin and oral mucosa
- Extracutaneous findings include coarse facial features, dysostosis multiplex, and progressive mental and motor deterioration



Fig. 63.10 Angiokeratomas of Fabry disease. Multiple dark red to red–brown macules and papules located: (**A**) on the penis, an uncommon site for angiokeratomas in the general population, as well as on the scrotum; (**B**) on the lower trunk; and (**C, D**) in a more extensive "bathing trunk" distribution. *A,B, Courtesy Paula Luna, MD; C,D, Courtesy Edward Cowen, MD.*

Fucosidosis is a rare autosomal recessive lysosomal storage disorder resulting from pathogenic variants in *FUCA1*, which encodes the enzyme α-fucosidase. In the past, patients were classified into two groups: type I, a more severe form with onset in the first year of life; and type II, a milder form with onset in the second year or later. However, a continuous spectrum of severity is now recognized. The extracutaneous manifestations include coarse facial features, short stature, organomegaly, dysostosis multiplex, and neurologic deterioration with associated hypomyelination (see Fig. 63.9). Patients may also have corneal opacities, retinal vascular abnormalities, and frequent sinopulmonary infections[71].

Angiokeratomas virtually indistinguishable from those associated with Fabry disease are found in approximately one-third of fucosidosis patients <10 years of age and 85% of those 10–19 years of age. The lesions are distributed primarily on the trunk and lower extremities but can also develop within the mouth. Other reported cutaneous findings include telangiectasias, acrocyanosis, nevus anemicus, xerosis, and elevated sweat chloride levels[72]. The light microscopy findings of the angiokeratomas are similar to those seen in Fabry disease. Electron microscopic examination of clinically normal skin may reveal empty-appearing storage vesicles in endothelial cells, melanocytes, eccrine glands, and fibroblasts.

The diagnosis of fucosidosis is supported by demonstration of characteristic abnormalities on urine oligosaccharide analysis and established by an α-fucosidase assay utilizing leukocytes or cultured skin fibroblasts. Prenatal diagnosis is possible via enzyme analysis or genetic testing. There is no definitive treatment for fucosidosis, and the mortality rate is high, especially after the second decade of life. Hematopoietic stem cell transplantation has been attempted with some evidence of clinical improvement[73], and enzyme replacement therapy is under investigation in a canine model[71].

GAUCHER DISEASE

Key features

- Autosomal recessive disorder due to deficiency of glucocerebrosidase
- Extracutaneous findings include hepatosplenomegaly, bone disease, cytopenias, and highly variable neurologic manifestations
- Cutaneous manifestations of type 1 disease include yellow–brown pigmentation, easy tanning, and petechiae
- A subset of patients with type 2 (acute neuronopathic) Gaucher disease have ichthyosiform skin at birth

Gaucher disease is a relatively common autosomal recessive lysosomal storage disorder in which the glycolipid glucocerebroside accumulates as a result of a deficiency of the enzyme glucocerebrosidase (β-glucosidase). There are three clinical subtypes of the disorder, although the acute and chronic neuronopathic forms (types 2 and 3, respectively) are thought to exist on a continuum. Type 1 is by far the most common form of Gaucher disease and has a particularly high incidence of ~1 in 850 births in the Ashkenazi Jewish population.

Type 1 Gaucher disease is distinguished by a lack of primary involvement of the CNS, although Parkinson disease-like symptoms develop by the eighth decade of life in ~10% of affected individuals.

INHERITED METABOLIC DISORDERS ASSOCIATED WITH ANGIOKERATOMA CORPORIS DIFFUSUM				
Disorder	**Enzyme deficiency (gene)**	**Other clinical features**	**Inheritance pattern**	**Diagnostic tests***
Aspartylglucosaminuria	Aspartylglucosaminidase (*AGA*)	ID, coarse facial features, frequent respiratory infections	AR	Urine oligosaccharides; enzyme assay in leukocytes or fibroblasts
Galactosialidosis	β-Galactosidase and neuraminidase 1 secondary to a defect in cathepsin A (*CTSA*)	Coarse facial features, dysostosis multiplex, myoclonus, ataxia, neurologic deterioration, cherry-red macular spots	AR	Urine oligosaccharides; enzyme assay in leukocytes or fibroblasts
GM1 gangliosidosis	β-Galactosidase (*GLB1*)	Coarse facial features, dysostosis multiplex, neurologic deterioration, organomegaly, dermal melanocytosis	AR	Urine oligosaccharides; enzyme assay in leukocytes or fibroblasts
Fabry disease	α-Galactosidase A (*GLA*)	Pain and paresthesias of extremities, hypohidrosis, corneal and lenticular opacities, renal insufficiency, cardiac and cerebrovascular disease	X-L	Enzyme assay in plasma, monocytes or leukocytes
Fucosidosis	α-Fucosidase (*FUCA1*)	Coarse facial features, developmental regression, organomegaly, dysostosis multiplex	AR	Urine oligosaccharides; enzyme assay in leukocytes or fibroblasts
Kanzaki disease	α-*N*-Acetylgalactosaminidase (*NAGA*)	Highly variable, ranging from no other findings to lymphedema, hearing loss, and cardiomegaly; normal intelligence	AR	Urine oligosaccharides; enzyme assay in plasma or leukocytes
β-Mannosidosis	β-Mannosidase (*MANBA*)	ID, mild facial dysmorphism, hearing loss	AR	Urine oligosaccharides; enzyme assay in leukocytes or fibroblasts
Sialidosis	Neuraminidase [sialidase] 1 (*NEU1*)	Coarse facial features, dysostosis multiplex, ID, myoclonus, cherry-red macular spots	AR	Urine oligosaccharides and sialic acid; enzyme assay in fibroblasts

*Genetic testing is also available.

Table 63.7 Inherited metabolic disorders associated with angiokeratoma corporis diffusum. AR, autosomal recessive; ID, intellectual disability; X-L, X-linked (variable manifestations in female heterozygotes).

Presenting findings in type 1 may include hepatosplenomegaly, thrombocytopenia, anemia, and bone pain. The cutaneous manifestations of type 1 Gaucher disease are infrequent and relatively nonspecific[74]. They include diffuse brown or yellow–brown pigmentation of the skin and easy tanning. In addition, petechiae and ecchymoses may be observed due to the thrombocytopenia that results from infiltration of the bone marrow with glycolipid-filled macrophages (Gaucher cells) or from hypersplenism.

Type 2 Gaucher disease, the acute neuronopathic form of the disorder, is a severe and rapidly progressive condition that usually results in death before 2 years of age. Clinical manifestations develop within the first year of life and include hepatosplenomegaly, severe hypertonia, opisthotonus, oculomotor apraxia, and progressive neurologic deterioration. A subgroup of patients with this type of Gaucher disease presents at birth with a collodion baby phenotype or other ichthyosiform skin findings[75,76], suggesting that Gaucher disease should be considered in the differential diagnosis of congenital ichthyosis. Studies in a mouse model indicate that glucocerebrosidase is required to generate functionally competent membranes for normal epidermal barrier function. Electron microscopy of skin samples from patients with type 2 Gaucher disease, including those without clinically evident ichthyosis, shows immature lamellar membranes with characteristic electron-dense clefts[77]. The residual enzymatic activity present in patients with types 1 and 3 Gaucher disease is apparently adequate to protect them, since similar epidermal abnormalities are not observed in these forms. In fact, no specific cutaneous abnormalities have been described in patients with type 3 (chronic neuronopathic) Gaucher disease.

The diagnosis of Gaucher disease is established by demonstration of a glucocerebrosidase deficiency in leukocytes or cultured skin fibroblasts. Carrier detection is possible by genetic analysis, and prenatal diagnosis can be accomplished via chorionic villus sampling (CVS) or amniocentesis. Biomarkers with utility in determining prognosis and monitoring response to therapy include chitotriosidase, CC chemokine ligand 18 (CCL18), glucosylsphingosine, and ferritin[78]. There are two forms of specific treatment for Gaucher disease: (1) intravenous recombinant *enzyme-replacement therapy* for types 1 (when symptomatic) and 3; and (2) *substrate reduction therapy* with miglustat or eliglustat, inhibitors of glucosylceramide synthase, for type 1[78]. These treatments can improve organomegaly, hematologic abnormalities, and (to a variable degree) bone disease, but not the CNS manifestations of Gaucher disease.

HARTNUP DISEASE

Key features

- An autosomal recessive disorder associated with defective renal and intestinal neutral amino acid transport
- Marked aminoaciduria and tryptophan deficiency
- Typically presents with a pellagra-like dermatosis associated with photosensitivity
- Systemic manifestations include ataxia and tremors

Hartnup disease is an autosomal recessive disorder caused by pathogenic variants in *SLC6A19*, which encodes a transporter that mediates epithelial uptake of neutral amino acids in the kidneys and intestines[79]. The hallmark of the disorder is a specific hyperaminoaciduria due to diminished renal and intestinal reabsorption of neutral amino acids. Hartnup disease is one of the most common amino acid disorders, occurring in about 1 in 30 000 births. Most affected individuals, particularly those in high-income countries, remain asymptomatic throughout life, although symptoms can occur when exacerbating factors such as poor nutrition, celiac disease, or other causes of persistent diarrhea are present.

When clinical features develop, the most common finding is a recurrent photosensitive "pellagra-like" dermatosis[80]. This eruption is thought to be related to a relative niacin deficiency, as tryptophan is a precursor in niacin synthesis. It typically develops in children on exposed areas of the body and may initially resemble a sunburn or acute cutaneous lupus erythematosus. After the development of erythema following sun exposure, the affected skin becomes dry and scaly with well-defined margins; later findings include desquamation and hypo- or hyperpigmentation. The dermatosis is occasionally pruritic and blistering may occur; acrodermatitis enteropathica- and hydroa vacciniforme-like presentations have been described[80]. The second major manifestation of symptomatic Hartnup disease is intermittent ataxia, which may be accompanied by nystagmus and tremors. Psychiatric disturbances, developmental delay, and other neurologic abnormalities have been reported in some patients.

The diagnosis of Hartnup disease is established by urine amino acid analysis, which reveals markedly elevated levels of neutral amino

acids. In contrast, plasma levels of amino acids and niacin are typically normal, despite the clinical resemblance to pellagra. A high-protein diet or protein supplementation can help to prevent symptoms of Hartnup disease, and oral nicotinamide administration (50–300 mg/day) improves dermatologic and neurologic manifestations[80].

MITOCHONDRIAL DISORDERS

Synonyms: ■ Respiratory chain defects ■ Oxidative phosphorylation defects

Key features

- Marked phenotypic and genotypic heterogeneity
- 5%–10% of patients have pigmentary changes, alopecia, hypertrichosis, or hair shaft anomalies
- Myopathy, encephalopathy, cardiomyopathy, and visual impairment are frequent manifestations

Mitochondrial disorders represent a clinically and biochemically heterogeneous group of metabolic conditions characterized by impairment of the mitochondrial respiratory chain, which generates most of the adenosine triphosphate (ATP) required for cellular functioning[81]. The mitochondrial genome contains 37 genes and they encode subunits of the respiratory chain as well as the transfer and ribosomal RNAs (tRNAs and rRNAs) that translate mitochondrial DNA (mtDNA). However, some of the genes that encode respiratory chain components and other mitochondrial proteins are encoded by nuclear DNA. Mitochondrial disorders can therefore result from either maternal inheritance of mtDNA mutations or Mendelian inheritance of nuclear DNA mutations. The respiratory chain is organized into five enzyme complexes (I–V), the activity of which can be measured in muscle or other tissues to aid in the diagnosis of mitochondrial disorders. Although some mitochondrial syndromes are characterized by a particular constellation of clinical findings, there is often poor correlation between the enzyme complex involved and the clinical phenotype.

Mitochondrial disorders can present at any age and may potentially affect any organ system, but with a predilection for cells with high energy requirements such as neurons and muscle[81]. Common manifestations include developmental delay, seizures, stroke, weakness, hypotonia, and cardiomyopathy. Visual impairment, hearing loss, proximal renal tubular defects, hepatic dysfunction, poor growth, and fatigue are other frequent findings. The clinical course and progression are highly variable, even in patients with similar biochemical abnormalities[82].

A wide range of hair and skin abnormalities has been described in association with mitochondrial disorders (Table 63.8)[83]. These manifestations have been reported in about 5%–10% of patients with documented mitochondrial disorders and may develop early in the disease course. When such findings are noted in conjunction with seemingly unrelated abnormalities in other organ systems, the possibility of a mitochondrial disorder should be considered.

Biochemical and/or molecular genetic confirmation of the diagnosis of a mitochondrial disorder is rarely straightforward. Measurement of plasma lactate, plasma amino acids, and urine organic acids can be helpful in assessing mitochondrial function. Other components of the evaluation may include exercise testing, neuroimaging, muscle biopsy for histologic/histochemical evaluation, assays of respiratory chain enzyme complexes in muscle tissue or cultured skin fibroblasts, and genetic analysis[81].

Treatment of patients with mitochondrial disorders is largely symptomatic. A variety of dietary modifications have been tried and may be helpful for some patients. Coenzyme Q_{10}, L-carnitine, resveratrol, curcumin, sulforaphane, and riboflavin supplementation may also have some benefit.

CUTANEOUS MANIFESTATIONS OF MITOCHONDRIAL RESPIRATORY CHAIN DISORDERS
• Alopecia
• Hair shaft abnormalities – trichoschisis, pili torti, longitudinal grooving, trichorrhexis nodosa, trichothiodystrophy
• Hypertrichosis
• Absent or excessive sweating
• Pigmentary abnormalities – mottled or reticulated pigmentation
• Palmoplantar keratoderma (linked with deafness)
• Hypoplastic nails
• Lipomas
• Acrocyanosis
• Linear skin defects on the face and neck

Table 63.8 Cutaneous manifestations of mitochondrial respiratory chain disorders.

ACID SPHINGOMYELINASE DEFICIENCY (NIEMANN–PICK DISEASE)

Key features

- An autosomal recessive disorder due to deficiency of acid sphingomyelinase
- Rare skin involvement in type A consists of yellow–brown discoloration and facial papules
- Failure to thrive, hepatosplenomegaly, and neurologic deterioration occur in type A
- Minimal neurologic involvement and milder disease characterize type B

This is an autosomal recessive lysosomal storage disorder caused by acid sphingomyelinase deficiency, which results in the accumulation of sphingomyelin and other phospholipids[84]. There are two classic forms: type A, with an incidence of 1 in 40 000 births in the Ashkenazi Jewish population; and type B, with a lower incidence and no specific ethnic predilection. Type A (*infantile neurovisceral*) is a severe disorder associated with failure to thrive, hepatosplenomegaly, thrombocytopenia, and rapid neurologic degeneration leading to death by 2–3 years of age; cherry-red retinal spots are evident in ~50% of patients. Type B (*chronic visceral*) is characterized by little or no neurologic involvement, later onset, and survival into adult life. Progressive pulmonary infiltration may occur in either subtype, and the disease spectrum includes a *chronic neurovisceral* phenotype with intermediate severity (type A/B). Type C, which has primarily neurologic findings, results from defects in other genes (*NPC1* > *NPC2*) and is associated with an accumulation of unesterified cholesterol.

Cutaneous manifestations are typically observed only in patients with type A disease. The skin may exhibit a generalized ochre or brownish-yellow discoloration. Papular lesions, most commonly located on the face and upper extremities, may also be present. Histologically, these papules consist of foamy histiocytes, multinucleated cells, and a variable infiltrate of lymphocytes.

Diagnosis of type A or B disease is established by demonstration of deficient sphingomyelinase activity in leukocytes or cultured skin fibroblasts, or via molecular genetic analysis. Carrier detection for type A can also be performed via genetic testing, and prenatal diagnosis is available by CVS or amniocentesis. In recent clinical trials, recombinant enzyme-replacement therapy with olipudase-α has shown promising results for the non-neurologic manifestations of types A/B and B[85]. Treatment approaches utilizing gene therapy, molecular chaperones, and anti-inflammatory agents are also under investigation[84]. Lastly, hematopoietic stem cell transplantation may improve the non-neurologic features, but treatment-related complications limit its use[84].

PHENYLKETONURIA

Key features

- Autosomal recessive disorder due to a deficiency of phenylalanine hydroxylase
- Pigmentary dilution of the skin, eyes, and hair
- Atopic-like dermatitis and sclerodermatous skin changes
- Progressive developmental delay with severe intellectual disability if not treated



Fig. 63.11 Phenylketonuria (PKU). Infant with PKU and sclerodermoid skin changes. *Courtesy New York Medical College.*

Phenylketonuria (PKU) is one of the most common inborn errors of metabolism, occurring worldwide with an incidence of ~1 in 10 000 births. It is an autosomal recessive disorder resulting from a deficiency of the enzyme phenylalanine hydroxylase that is responsible for conversion of phenylalanine to tyrosine. As a result of this enzyme deficiency, phenylalanine levels rise in blood and tissues of the untreated patient on a phenylalanine-containing diet, and high levels of this amino acid are extremely toxic to the CNS. Progressive developmental delay ultimately leads to severe intellectual disability and may be accompanied by seizures, behavioral problems, and psychiatric symptoms[86].

In patients with PKU, a relative deficiency of tyrosine and/or competitive inhibition of tyrosinase by excess L-phenylalanine leads to diminished melanin production and resultant diffuse pigmentary dilution. The classic patient is described as blond and blue-eyed, although pigmentation varies depending on the family and ethnic background. Sweat with a musty or "mousy" odor can represent a clue to the diagnosis. Nonspecific dermatitis occurs with increased frequency, and early-onset atopic dermatitis affects up to half of patients with PKU. Progressive scleroderma-like skin changes that favor the proximal extremities may also be observed, often with an onset in the first year of life[87] (Fig. 63.11). This is in contrast to the acral predilection and older age of onset in systemic sclerosis.

Newborn screening for PKU is routinely performed in many countries, and the diagnosis is established by plasma amino acid analysis. Identification of affected infants at birth with early institution of a phenylalanine-restricted diet and careful control of blood phenylalanine levels prevents the development of skin changes and intellectual disability, although subtle neurocognitive consequences may be observed. Unfortunately, untreated patients are still encountered among children from low-income countries, and despite recommendations that dietary therapy be continued for life, some adolescents and adults do not adhere to the dietary restrictions, which may result in recurrent dermatologic manifestations. Dietary therapy involves not only restriction of phenylalanine, but also special medical foods containing phenylalanine-free protein substitutes. Close monitoring by an experienced nutritionist is vital. Enzyme substitution therapy with pegvaliase, a PEGylated recombinant phenylalanine ammonia lyase administered by subcutaneous injection, has been FDA-approved for adults with uncontrolled elevation of blood phenylalanine levels[88].

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PREMATURE AGING SYNDROMES AND POIKILODERMAS

Bernard A. Cohen

The study of rare progeroid syndromes has led to better understanding of the normal aging process. Distinct progeroid disorders are differentiated by their time courses, associated clinical findings, and biochemical and genetic markers (Table 63.9). Inherited congenital and childhood poikilodermas, including Kindler syndrome (see Ch. 32), can also demonstrate features associated with aging and may be considered in the differential diagnosis of progeroid syndromes (Fig. 63.12).



Fig. 63.12 Facial poikiloderma in a 3-year-old boy with Rothmund–Thomson syndrome. This child also had short stature and photosensitivity. *Courtesy Sarah Chamlin, MD.*

HUTCHINSON–GILFORD PROGERIA SYNDROME

Synonyms: ■ Progeria ■ Hutchinson–Gilford syndrome

Key features

- Rare, occurring in 1 in 4 to 8 million births
- Due to mutations in *LMNA*, which encodes nuclear lamins A and C
- Normal motor and mental development
- Characteristic facies with prominent scalp veins and a beaked nose
- Wrinkled as well as scleroderma-like skin, alopecia, and poor growth
- Generalized atherosclerosis with premature death from cardiovascular and cerebrovascular disease at a median age of 14 years
- Lonafarnib, an oral farnesyltransferase inhibitor that reduces the accumulation of farnesylated mutant prelamin A ("progerin"), is an FDA-approved therapy

Introduction

Hutchinson–Gilford progeria syndrome (HGPS) is a genetic disease characterized by accelerated aging that begins during infancy[89,90]. The term "progeria" originates from the Greek word for old age, "*geras*", and was proposed by Gilford when he delineated the clinical features and course of the disorder in 1904.

History

The syndrome was first reported in 1886 by Jonathan Hutchinson, with Hastings Gilford subsequently documenting the postmortem features. In 2003, mutations in the gene that encodes lamin A were first described[90,91].

Epidemiology

HGPS is estimated to occur in 1 in 4 to 8 million births, with an overall prevalence of ~1 in 20 million people[89,92,93]. The male : female ratio is 1.2 : 1[93], and it has been reported worldwide in patients with a wide variety of ethnic backgrounds.

In the 64 cases reviewed by DeBusk[89], median and mean paternal ages were advanced, consanguinity was uncommon, and the abortion

PROGEROID SYNDROMES AND INHERITED POIKILODERMAS					
	Hutchinson–Gilford progeria syndrome	**Werner syndrome**	**MDPL syndrome**	**Penttinen syndrome**	**Néstor–Guillermo progeria syndrome**
Inheritance/gene (if known)	Sporadic AD/*LMNA*	AR/*WRN (RECQL2)* Atypical variant – AD/*LMNA*	AD/*POLD1*	AD/*PDGFRB*	AR/*BANF1*
Gender ratio	M : F = 1.2 : 1	M = F	M = F	M = F	M = F
Onset	First year	Second decade	Childhood	Infancy to childhood	Third year
Stature	Short stature, low weight for height	Short stature, central obesity	Short to normal stature, central obesity	Normal	Short stature
Facial features	Prominent scalp veins and eyes, perioral cyanosis, frontal bossing, micrognathia, thin beaked nose, small mouth, thin lips	Thin beaked nose, prominent eyes, circumoral furrows, protuberant teeth, micrognathia	Thin beaked nose, prominent eyes, protuberant teeth, micrognathia	Malar hypoplasia with retracted maxilla, pseudoprognathism, proptosis, flat occiput	Prominent scalp veins and eyes, micrognathia, thin nose, midfacial hypoplasia, thin lips
Cutaneous features	Dryness, wrinkling, scleroderma-like tautness, mottled hyperpigmentation, loss of subcutaneous fat	Atrophy (epidermal, dermal, subcutaneous), mottled hyperpigmentation, scleroderma-like tautness, keratoses and ulcers over pressure points, subcutaneous calcifications	Atrophy with lack of subcutaneous fat, telangiectasias, scleroderma-like tautness, keratoses and ulcers over pressure points	Lipoatrophy, thin translucent skin, hypertrophic scar-like lesions over pressure points	Atrophy with generalized lack of subcutaneous fat, mottled hyperpigmentation, red swollen skin on phalanges
Nails	± Dystrophy, hypoplasia	± Dystrophy	Normal	Normal or loss related to acro-osteolysis	Dystrophy
Scalp hair	Thin and lightly pigmented, progressing to diffuse alopecia	Premature canities, thinning over time	± Premature canities and thinning over time	Thin and sparse	Progressive alopecia during late childhood
Musculoskeletal	Thin with narrow thorax, prominent joints, thoracic kyphosis, coxa valga, short clavicles	Spindly extremities, osteoporosis, osteosclerosis of phalanges	Thin extremities, muscle wasting, osteopenia, joint contractures	Thin extremities, acro-osteolysis, broad thumbs and halluces, kyphoscoliosis	Marked acro-osteolysis, resorption of mandible and clavicles, severe osteoporosis, scoliosis
Metabolic/ malignancy	Growth failure, insulin resistance	Lack of growth spurt at puberty; diabetes mellitus; increased risk of sarcomas, thyroid carcinomas, melanomas	Diabetes mellitus, hyperlipidemia	None	None
Cardiovascular	Premature atherosclerosis, myocardial fibrosis	Premature atherosclerosis, calcified aortic valve	Normal	Normal	Normal
Prognosis	Average survival 12 years	Average survival ~50 years	Normal lifespan expected	Survival into adulthood	Survival into early adulthood
Other	High-pitched voice, delayed and abnormal dentition, large open anterior fontanelle, sparse or absent eyebrows and eyelashes	Bilateral cataracts (99%), high-pitched voice, hypogonadism	Sensorineural hearing impairment, high-pitched voice, dental crowding, hypogonadism in males	Corneal clouding, ocular pterygia, delayed dentition	Delayed closure of anterior fontanelle

*Acrogeric phenotypes also occur in vascular Ehlers–Danlos syndrome, which is caused by mutations in the gene encoding type III collagen, and in progeroid laminopathies due to LMNA mutations (see Table 63.10).

Table 63.9 Progeroid syndromes and inherited poikilodermas. Disorders featuring poikiloderma are shaded. Hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis results from heterozygous mutations in *FAM111B*. Variants of cutis laxa and Ehlers–Danlos syndrome with progeroid features are discussed in Chapter 97 and ataxia–telangiectasia is covered in Chapter 60. Other rare progeroid conditions include Wiedemann–Rautenstrauch (neonatal progeroid), Hallermann–Streiff, Lenz–Majewski, Fontaine progeroid, Marbach–Rustad progeroid, Ruijs–Aalfs, and SHORT (*s*hort stature, *h*yperextensibility, hernia, *o*cular depression, *R*eiger anomaly [dysgenesis of cornea and iris], and *t*eething delay) syndromes (www.ncbi.nlm.nih.gov/omim). AD, autosomal dominant; AR, autosomal recessive; *ANAPC1*, anaphase promoting complex subunit 1; *BANF1*, barrier-to-autointegration factor 1; *FERMT1*, fermitin family homolog 1; MDPL, *m*andibular hypoplasia, *d*eafness, *p*rogeroid features, and *l*ipodystrophy; *PDGFRB*, platelet-derived growth factor receptor β gene; *POLD1*, DNA polymerase δ 1; PPK, palmoplantar keratoderma; SCC, squamous cell carcinoma; *USB1*, U6 snRNA biogenesis 1.

Acrogeria (Gottron syndrome)*	Metageria	Kindler syndrome (see Ch. 32)	Cockayne syndrome (see Ch. 87)	Rothmund–Thomson syndrome (see Ch. 87)	Poikiloderma with neutropenia, Clericuzio type ("Navajo poikiloderma")
AD, AR	AR	AR/*FERMT1* (*KIND1*)	AR/*ERCC8 (CSA), ERCC6 (CSB)*	AR/*RECQL4*, AR/*ANAPC1*	AR/*USB1*
F > M	M = F	M = F	M = F	M = F	M = F
Birth	Birth	Birth	After first year	First year	First year
Normal	Tall, thin	Normal	Dwarfism, low weight for height	Short stature	Short stature
Micrognathia, thin nose with atrophic tip, proptosis	Beaked nose, prominent eyes	Normal	Sunken eyes due to periorbital fat atrophy; senile "bird-like" facies, beak-like nose, prognathism	Frontal bossing, saddle nose, prognathism	Midfacial hypoplasia
Poikiloderma, marked skin atrophy on hands and feet, easy bruising, prominent veins on trunk	*Poikiloderma* with mottled hyperpigmentation, atrophy on extremities, rarely leg ulcers	Congenital acral blistering and photosensitivity; later *poikiloderma*, atrophy, acral hyperkeratosis; occasional eczematous dermatitis	At presentation: acute photosensitivity, healing with hyperpigmentation; later: wrinkling, loss of subcutaneous fat, *poikiloderma*	At presentation: acute eruption with erythema and edema, especially on face, ± photosensitivity; later: *poikiloderma* (Fig. 63.12), acral keratoses	At presentation: erythematous papular or ichthyosiform dermatitis on the extremities and face, ± photosensitivity; later: evolution to *poikiloderma*, PPK, keratotic papules on face and forearms, calcinosis cutis, skin infections and ulcers
Dystrophy, thickening	Normal	± Dystrophy	± Dystrophy	± Dystrophy	Dystrophy (especially first toenails) with subungual hyperkeratosis (pachyonychia-like)
Normal	Fine and thin	Normal	Dry, thin; premature canities	Fine and thin, alopecia	± Thin hair
Short phalanges, acro-osteolysis	Generalized loss of subcutaneous fat	Webbing of the fingers, toes	Long limbs, disproportionately large hands and feet, joint contractures, microcephaly	Radial ray defects, metaphyseal chondrodysplasia, delayed bone formation	Normal
None	Early-onset diabetes mellitus	Possible increased malignancy risk	Cellular sensitivity to sunlight and defective DNA repair, but no increase in neoplasia	Increased risk of malignancy, especially osteosarcoma and SCC (often acral)	Myelodysplasia/ myelodysplastic syndrome; cutaneous SCC (reported in adolescents)
Normal	Premature atherosclerosis	Normal	Normal	Normal	Normal
Normal lifespan	Depends on severity of diabetes and atherosclerosis	Normal lifespan	Death by age of 30 years from neurologic degeneration	Normal to shortened life expectancy (if malignancy)	Normal lifespan
		Mucous membrane involvement with stenoses (e.g. urethral), ectropion and erosive gingivitis resulting in poor dentition	Optic atrophy, deafness, unsteady gait, demyelination	Cataracts, hypogonadism, hypodontia	Neutropenia, recurrent sinopulmonary infections, lacrimal duct obstruction, carious teeth, hypogonadism, ± developmental delay

rate in affected families was normal. These observations favored a *de novo* dominant mutation, which was later confirmed by genetic studies (see below). Since HGPS patients usually do not become sexually mature and typically succumb to the disease early in the second decade of life, familial occurrence is rare; however, it can occur in the setting of gonadal mosaicism[93]. Consanguineous families with autosomal recessive variants of HGPS have been described, but additional clinical features such as clavicular aplasia/hypoplasia in affected individuals suggest an overlap with mandibuloacral dysplasia, which is caused by biallelic mutations in *LMNA* (Table 63.10)[94,95].

Pathogenesis

The vast majority of patients with both classic and atypical forms of HGPS have a *de novo* heterozygous point mutation that affects splicing of the lamin A gene (*LMNA*)[90,96]. This gene encodes two protein products, lamin A and lamin C, that represent major components of the nuclear membrane lamina and contribute to the structural scaffolding of the nucleus. *Classic HGPS* (80%–90% of affected individuals) is caused by a particular mutation, c.1824C>T, which activates a cryptic splice site within exon 11 and leads to an internal deletion of 50 amino acids. This deletion includes a cleavage site that is necessary for the conversion of prelamin A to mature lamin A[97] (Fig. 63.13). As a result, the cells contain a dominant-mutant prelamin A ("progerin") that disrupts the nuclear scaffolding. In the patients' cells, including lymphocytes and fibroblasts, there is evidence of altered nuclear sizes and shapes, as well as lobulation of the nuclei, extrusion of chromatin, and nucleolar alterations. Such structural changes result in functional defects such as abnormal DNA damage repair, mitochondrial impairment and aberrant cell-cycle regulation, which lead to premature aging[98].

Other heterozygous progerin-producing *LMNA* mutations cause either *atypical HGPS* with clinical findings similar to classic HGPS or *autosomal dominant progeroid laminopathies* with distinct phenotypes that share some features with HGPS (see Table 63.10). The severity of these disorders correlates with the ratio of progerin to lamin A, and extremely high progerin levels have been associated with neonatal-onset progeria and death in the first few years of life[99]. In families with *autosomal recessive progeroid laminopathies*, including the *progeria–mandibuloacral dysplasia overlap syndromes*, biallelic mutations in *LMNA* may affect both lamin A and C, disrupting interactions with nuclear proteins[94,95].

Other cellular and molecular changes that contribute to the pathogenesis of HGPS include altered epigenetic regulation and gene expression, shortened telomeres, and increased cellular senescence[98]. Of note, progressively decreasing telomere length is seen with normal aging and is associated with progerin production and low levels of telomerase activity[100]. In a telomerase knockout mouse model (see Ch. 4), some clinical features of accelerated aging have also been observed. Additional abnormalities associated with the normal aging process, such as insulin resistance and decreased survival of fibroblast cultures, are seen in patients with HGPS.

Clinical Features

HGPS is a multisystem disease with prominent involvement of the skin, bones, skeletal muscle, adipose tissue, and cardiovascular structures. Although affected children usually appear normal at birth, growth failure and other clinical features typically appear rather abruptly during the first year of life[89,91,93,101]. Weight gain is very slow, with marked loss during episodes of illness. Linear growth proceeds at half the normal pace and does not undergo the normal acceleration around puberty. Sexual maturation is absent in most patients, and affected individuals have both short stature and a low weight for height.

At birth or during early infancy, patients may have thick, inelastic, scleroderma-like skin, usually on the lower abdomen, flanks, thighs, and buttocks. Following the onset of growth failure, the skin becomes thin and dry, with less hair than normal. Some areas may appear taut and shiny, whereas others (especially the fingers and toes) lax and wrinkled. Infantile fat is rapidly lost with the onset of growth failure, resulting in prominent superficial veins and the appearance of perioral cyanosis. As the aged appearance progresses, irregular brown pigmentation becomes evident in sun-exposed areas.

NUCLEAR ENVELOPATHIES	
Primary feature and associated diseases	**Inheritance**
Laminopathies – due to mutations in the *LMNA* gene which encodes the lamin A and C proteins of the nuclear membrane lamina*	
Premature aging and/or cutaneous sclerosis	
Hutchinson–Gilford progeria syndrome (classic and atypical)	AD
Restrictive dermopathy†	AD > AR
"Atypical Werner syndrome"	AD
Other progeroid laminopathies	AD > AR
Skeletal dysplasia and/or arthropathy	
Mandibuloacral dysplasia†	AR
Arthropathy, tendinous calcinosis and progeroid features	AR
Lipodystrophy‡	
Familial partial lipodystrophy, type 2 (Dunnigan type)	AD
Muscular dystrophy	
Emery–Dreifuss muscular dystrophy	AD > AR
LMNA-related congenital muscular dystrophy	AD
Early-onset myopathy with progeroid features	AD
Cardiomyopathy	
Dilated cardiomyopathy type 1A	AD
Heart–hand syndrome	AD
Dilated cardiomyopathy with hypergonadotrophic hypogonadism	AD
Neuropathy	
Charcot–Marie–Tooth type 2B1	AR
Cutaneous disorders with inner nuclear membrane dysfunction – due to mutations in the *LEMD3* gene, whose protein product associates with lamin A	
Cutaneous sclerosis and/or skeletal dysplasia	
Buschke–Ollendorff syndrome	AD
Osteopoikilosis	AD
Melorheostosis	Type 2 segmental¶

*Heterozygous mutations in the *LMNB2* gene, which encodes the lamin B2 protein of the nuclear membrane lamina, can cause "acquired" partial lipodystrophy (Barraquer–Simons syndrome).
†Can also result from recessive mutations in the *ZMPSTE24* gene, which encodes a zinc metalloproteinase involved in the processing of prelamin A into mature lamin A (see Fig. 63.13); mandibuloacral dysplasia often presents with progeroid features and lipodystrophy.
‡Generalized lipodystrophy with pubertal onset and features that overlap with atypical Werner syndrome has also been described; whitish, fibrotic papules on a background of diffuse hyperpigmentation represent an additional finding in some of these patients.
¶Germline heterozygous mutation (resulting in Buschke–Ollendorff syndrome or osteopoikilosis) with a presumed second hit in area of melorheostosis.

Table 63.10 Nuclear envelopathies. Entities in this heterogeneous group of genetic disorders share the common findings of cutaneous fibrosis and bone dysplasia. Néstor–Guillermo progeria syndrome (see Table 63.9) is also characterized by abnormalities in the nuclear membrane lamina; this autosomal recessive disorder results from mutations in the barrier-to-autointegration factor 1 gene (*BANF1*), which encodes a protein that interacts with prelamin A (and progerin). AD, autosomal dominant; AR, autosomal recessive.

At the onset of growth failure, patients begin to develop characteristic facial features, including a disproportionately large cranium, frontal bossing, a large open anterior fontanelle, pronounced scalp veins, prominent eyes due to relatively slow growth of the facial bones, a thin beaked nose with a sculpted appearance, and micrognathia. The facial stigmata tend to become marked by age 2 to 3 years, giving a "plucked-bird" appearance.

Alopecia develops during the first year of life and becomes diffuse and generalized, with later hair growth tending to be fine and lightly pigmented. Eyebrows and eyelashes are often sparse or absent. Although the nails may be normal, dystrophy in the form of small, short and

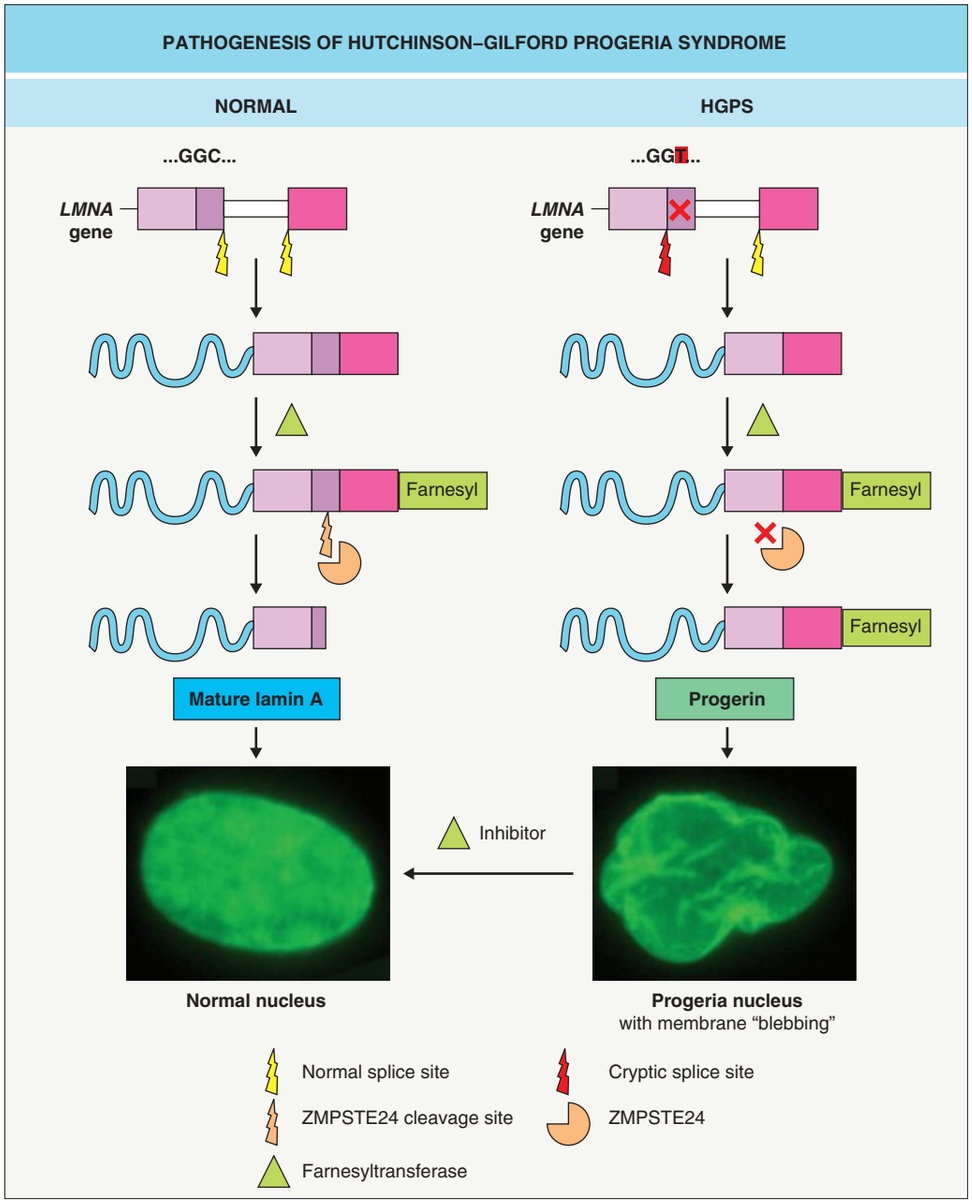


Fig. 63.13 Pathogenesis of Hutchinson–Gilford progeria syndrome (HGPS). Patients with classic HGPS have a C-to-T point mutation that activates a cryptic splice site and leads to an internal in-frame deletion of 50 amino acids. Because the deleted region includes a cleavage site for the ZMPSTE24 zinc metalloproteinase, removal of a farnesylated and methylated portion of prelamin A by this enzyme in order to produce mature lamin A does not occur in HGPS patients. Mutant "progerin" therefore remains farnesylated and, as a result, anchored to the nuclear membrane, where it disrupts nuclear scaffolding and causes blebbing. Administration of farnesyltransferase inhibitors can prevent this disruption of nuclear structure and function by progerin. Of note, *ZMPSTE24* mutations underlie some human cases of restrictive dermopathy and mandibuloacral dysplasia (see Table 63.10).

thin nails is common. Marked delay in the eruption of primary and secondary dentition has also been noted in most patients. Teeth may be crowded, rotated, overlapped and maloccluded, and the voice tends to be high-pitched and piping.

Truncal features include a narrow pyriform thorax, shoulders with thin and short clavicles, and prominent thoracic kyphosis giving a stooped appearance. Prominence of the abdomen (relative to the chest) and hypoplastic nipples also contribute to the distinctive habitus. The limbs are usually proportionate and become progressively thinner with increasing prominence of the joints, especially the knees, elbows, and small joints of the hand. Coxa valga is usually present by age 2 to 3 years and, in combination with increasing joint stiffness, contributes to a wide-based gait.

Patients are of normal intelligence and may be self-conscious about their appearance. Early onset of progressive coronary and cerebral atherosclerosis results in a median lifespan of approximately 14 years[102,103]. Other complications include osteopenia, low-frequency conductive hearing loss, corneal dryness, and hyperopia[91]. Although mild insulin resistance occurs in up to half of patients, overt diabetes mellitus is rare.

Pathology and Laboratory Findings

Cutaneous histopathology varies with the site and the age of the patient, and it is usually not helpful in diagnosing the condition[104,105]. The epidermis is fairly normal with minimal hyperkeratosis and a slight increase in melanin in the basal cell layer. Although dermal elastic tissue is normal, dermal collagen tends to be thickened and hyalinized. Adnexal structures are normal or decreased in density and arrector pili muscles are usually prominent.

Radiographic findings include hypoplasia of the facial bones, thinned cranial bones, open fontanelles, and hypoplasia of the mandible with crowding of the teeth. Progressive resorption of bone from the distal phalanges of the fingers and toes is also characteristic, but not diagnostic, of HGPS.

Differential Diagnosis

The differential diagnosis is outlined in Table 63.9 and includes Werner syndrome, "atypical Werner syndrome", Néstor–Guillermo progeria syndrome, metageria, and acrogeria[106]. In contrast to HGPS, patients with Werner syndrome have premature canities, cataracts, and an increased incidence of malignancy. HGPS should also be distinguished from the following disorders: Cockayne syndrome (Ch. 87), Rothmund–Thomson syndrome (Ch. 87), ataxia–telangiectasia (Ch. 60), Kindler syndrome (Ch. 32), Wiedemann–Rautenstrauch syndrome (neonatal progeroid syndrome), and forms of Ehlers–Danlos syndrome and cutis laxa with progeroid features (Ch. 97). Lastly, clinical overlap may be seen with other disorders that are due to mutations in *LMNA*, such as early-onset myopathy with progeroid features, restrictive dermopathy (Ch. 34), and mandibuloacral dysplasia (see Table 63.10).

Treatment

Management is directed toward the prevention and treatment of complications, particularly cardiovascular, cerebrovascular, and musculoskeletal. Regular cardiovascular monitoring is recommended and low-dose aspirin may be of benefit. No dietary regimen has been shown to alter the disease course. Although growth impairment in HGPS is not typically related to growth hormone deficiency, administration of exogenous growth hormone may increase weight and, to a lesser degree, height. Physical and occupational therapy can help to maintain joint mobility, and patients and families may benefit from psychological and genetic counseling.

Because farnesylation of the dominant-mutant progerin form of prelamin A causes it to be anchored to the nuclear membrane, thereby disrupting nuclear structure (see Fig. 63.13), inhibitors of farnesylation were identified as a potential treatment for HGPS. Initial studies found that administration of farnesyltransferase inhibitors (FTIs) restored normal nuclear morphology to human HGPS fibroblasts *in vitro*, and these inhibitors improved body weight, bone density, strength, and survival in mouse models of progeria[97,107]. Additional investigation in mouse models showed benefit from treatment with the combination of a bisphosphonate and statin, which inhibit farnesyl pyrophosphate synthase and HMG-CoA reductase, respectively. Each of these enzymes functions in the protein prenylation pathway essential to both farnesylation and the alternative pathogenic geranylgeranylation that occurs in the setting of FTI monotherapy.

Treatment of HGPS patients with the FTI lonafarnib, either alone or together with the bisphosphonate zoledronate and pravastatin, has been shown to result in small but significant increases in survival[102,108]. Mechanistic target of rapamycin (mTOR) inhibitors (e.g. sirolimus, everolimus) increase autophagic degradation of progerin[109], and a clinical trial investigating the combination of everolimus and lonafarinib is underway. Antisense oligonucleotides that reduce progerin transcript and protein levels were recently shown to partially rescue the cardiovascular phenotype and increase lifespan in an HGPS transgenic mouse model[110]. Other possible therapies being explored include inhibition of progerin–lamin A binding with the small molecule progerinin, inhibition of isoprenylcysteine carboxyl methyltransferase to mislocalize progerin away from the nuclear rim, vitamin D to potentially reduce progerin production, remodelin to inhibit N-acetyltransferase-10 and rescue nuclear shape, tocilizumab to reduce oxidative stress by neutralizing interleukin-6, and inhibition of the NLRP3 inflammasome[111–114]. Lastly, gene correction via base editing or CRISPR/Cas9-based methods is being investigated in HGPS mouse models[115,116].

WERNER SYNDROME

Synonym: ■ Progeria of the adult

Key features

- Occurs in 1 in 1 million births, with a higher incidence in Japan
- Autosomal recessive disorder due to mutations in *WRN (RECQL2)*, which encodes a DNA helicase
- Premature aging with the appearance of canities, cataracts, osteoporosis, diabetes mellitus, and atherosclerosis during the second decade
- Additional features include sclerodermoid changes, keratoses and ulcerations over bony prominences, short stature, and vascular and soft tissue calcification
- Similar facies to progeria patients, with a pinched appearance and micrognathia
- Increased risk of meningiomas, sarcomas, and (particularly in Japanese patients) thyroid carcinomas and melanomas

Introduction

Werner syndrome is a genetic disorder of accelerated aging with an onset in the second decade of life. This rare progeroid syndrome has a higher incidence in certain populations in Japan[117–121]. Although it is often referred to as progeria of the adult, Werner syndrome has some distinctive clinical findings not normally associated with aging, such as hypogonadism, laryngeal atrophy, and osteosclerosis of the distal extremities[117–120]. The discovery of underlying mutations in *WRN (RECQL2)* has allowed investigation into the molecular aspects of Werner syndrome[118].

History

In 1904, Otto Werner described a family with two brothers and two sisters between the ages 36 and 40 years who displayed clinical features of premature aging. In 1934, Oppenheimer and Kugel reported two similar cases and established the eponym Werner syndrome.

Epidemiology

Werner syndrome is a rare autosomal recessive disorder with an overall incidence of 1 in 1 million births. However, its incidence in Japan is higher and may approach 1 in 3500 in some communities owing to high rates of consanguinity. It was the study of several large Japanese families that led to identification of the gene responsible for this disorder[120]. Werner syndrome has been reported in all races and affects both sexes equally.

Pathogenesis

Werner syndrome is caused by mutations in *WRN (RECQL2)*, which encodes a homolog of the *Escherichia coli* RecQ DNA helicase. Almost all of the mutations identified to date predict a truncated protein, and over half of Japanese patients are homozygous for a specific splice-site mutation[118,122].

The Werner protein (WRN) has both exonuclease and helicase activities, and it plays a role both in optimizing DNA repair, particularly via base excision, and in suppressing illegitimate recombination. Therefore, loss of WRN activity results in genomic instability. The accumulation of senescent cells with decreasing replicative capacity and an increasing number of mutations is thought to lead to the clinical findings of premature aging and an increased risk of malignancy. Decreased heterochromatin stability is also thought to play a role in the accelerated cellular senescence of Werner syndrome as well as physiologic aging[123]. Loss of function of *WRN* may occur in the normal population as a function of age[118].

A subset of patients have "atypical Werner syndrome" and lack pathogenic changes in *WRN*. Rather, they have heterozygous missense mutations in *LMNA* (see HGPS section) that affect the heptad repeat region and are predicted to interfere with protein–protein interactions[124]. Compared to patients with *WRN* mutations, those with atypical Werner syndrome tend to have an earlier onset of disease and more severe age-related manifestations. Atypical Werner syndrome might therefore be better classified as a late-onset form of HGPS.

Clinical Features

In most affected individuals, growth progresses normally until the beginning of the second decade, when short stature and thin limbs become noticeable. Graying of the hair may first appear during childhood but characteristically develops in late adolescence or the early twenties, often accompanied by hair thinning. While other findings of Werner syndrome typically become evident during the second and third decades of life[117–120], diagnosis is often delayed until the fourth or fifth decade[125].

The typical patient is short, with an average height of 5 ft (1.5 m), and has spindly limbs but central obesity. The hands and feet are small, and the face is thin with a pinched appearance, prominent eyes, a beaked nose, circumoral radial furrows, taut lips, protuberant teeth, and micrognathia (Fig. 63.14). The voice is high-pitched and raspy.

Cutaneous changes include atrophy (epidermal, dermal and subcutaneous), scale, mottled hyperpigmentation, and tightness reminiscent of scleroderma. These findings are most prominent on the face, forearms, hands, legs, and feet. Nails may be dystrophic, hypoplastic, or absent, and plantar hyperkeratosis is common. Thick keratoses

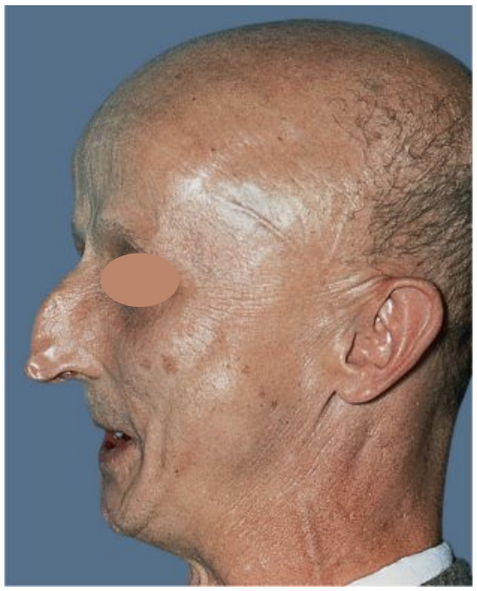


Fig. 63.14 Werner syndrome. Characteristic features include a beaked nose, taut skin, prominent veins, and micrognathia. *Courtesy Ronald P. Rapini, MD.*

develop over pressure points such as the fingers, toes, ankles, elbows and, occasionally, the ears. Removal of these keratoses by accidental or deliberate trauma leaves painful progressive ulcers. Ulcers may be resistant to therapy and prone to infection because of ischemia related to peripheral vascular disease. Dystrophic soft tissue calcification and osteomyelitis can also complicate chronic ulcers.

Other characteristic findings in Werner syndrome that reflect accelerated aging include bilateral cataracts, type 2 diabetes mellitus, hyperlipidemia, generalized atherosclerosis, osteoporosis, and less often hypertension. Additional features not normally associated with aging include hypogonadism, laryngeal atrophy, and osteosclerosis of the extremities. Affected individuals have an increased risk of meningiomas, soft tissue sarcomas, and osteosarcoma. Japanese patients are also at increased risk for thyroid follicular carcinomas and melanomas, especially in acral and mucosal locations[121].

The average lifespan is ~54 years, and death is usually related to cardiovascular and cerebrovascular disease. Some authors have postulated that heterozygous carriers may have higher rates of malignancy and myocardial infarction than the general population[118,119].

Pathology and Laboratory Findings

The epidermis is hyperkeratotic and atrophic, with focal hypermelanosis of the basal layer. Appendages are decreased in number and atrophic, and there is fibrosis and variable hyalinization of the dermis. The fat is also atrophic and often replaced by hyalinized connective tissue. Vessels may show changes typical of diabetic angiopathy.

Differential Diagnosis

A clinical diagnosis can usually be made when the characteristic skin findings, premature canities, "bird-like" facies, short stature, and bilateral cataracts are recognized. More detailed clinical diagnostic criteria are available at https://dlmp.uw.edu/research-center/werner/diagnostic-criteria, and genetic testing can be utilized to confirm the diagnosis if clinical features are inconclusive. There is considerable overlap with *m*andibular hypoplasia, *d*eafness, *p*rogeroid features, and *l*ipodystrophy (MDPL) syndrome caused by mutations in *POLD1*, which encodes DNA polymerase δ (see Table 63.9)[126]; this polymerase interacts with the Werner helicase during DNA replication and repair. However, MDPL is differentiated by frequent hearing impairment, absence of cataracts, and no predisposition to malignancy. In addition to other premature aging syndromes outlined in Table 63.9, Werner syndrome must be distinguished from ataxia–telangiectasia (see Ch. 60), prolidase deficiency (which features facial dysmorphism, telangiectasias, recalcitrant leg ulcers, and premature canities), and disorders associated with plantar keratoderma and scleroderma-like skin changes, such as Huriez syndrome (see Ch. 58).

Treatment

Genetic counseling should be provided, and prenatal diagnosis can be offered to affected families. Skin ulcers may prove resistant to therapy and should be treated aggressively and early, including with skin grafting; severe recalcitrant disease may lead to lower limb amputation[125,127]. Case reports have suggested that etidronate can ameliorate painful soft tissue calcifications. Management of diabetes mellitus and hyperlipidemia with proper diet and appropriate medications (e.g. thiazolidinediones, metformin, dipeptidyl peptidase 4 inhibitors ["gliptins"], lipid-lowering agents) can help to reduce complications, including atherosclerosis. Vitamin C supplementation was found to reverse age-related metabolic abnormalities and increase the lifespan in a mouse model of Werner syndrome, suggesting that vitamin C might be beneficial for Werner syndrome patients[128]. Other potential treatments that are under investigation include mTOR inhibitors and CRISPR/Cas9-mediated gene correction[129,130].

ECTODERMAL DYSPLASIAS

Encarna Guillén-Navarro, Teresa Martínez-Menchón and Virginia P. Sybert

Key features

- These genetic disorders share the central feature of abnormalities in at least two of the major ectodermally derived structures – hair, teeth, nails, and sweat glands
- Other ectodermal structures, such as mucous and sebaceous glands, as well as non-ectodermally derived structures may also be affected
- Different forms of ectodermal dysplasia are distinguished based on the types of ectodermal abnormalities, associated non-ectodermal anomalies, and mode of inheritance, as well as the underlying genetic defect
- Ectodysplasin, WNT, and p63 signaling pathways have been implicated in the pathogenesis of ectodermal dysplasias
- Some inherited abnormalities limited to one ectodermal structure (e.g. hair, nails) have a genetic basis related to that of ectodermal dysplasias, e.g. hypodontia due to heterozygous *WNT10A* mutations versus ectodermal dysplasia syndromes due to biallelic mutations in the same gene

Ectodermal dysplasias have long been recognized as a distinct group of inherited disorders that affect ectodermal appendages. Early descriptions of affected individuals were made by Danz in 1792, Wedderburn in 1838, and Darwin in 1875. The term "hereditary ectodermal dysplasia" was subsequently introduced by Weech in 1929. Ectodermal dysplasias are characterized by abnormalities in two or more of the major ectodermal structures – hair, teeth, nails, and sweat glands; other ectodermal structures, such as sebaceous and mucous glands, can also be affected[131–133].

Multiple ectodermal dysplasia classification schemes have been proposed over the years, including a descriptive clinical categorization by Pinheiro and Freire-Maia[134], a clinical–genetic model by Priolo and Lagana[135], and a functional classification by Lamartine[136]. Over the past two decades, the molecular basis of many ectodermal dysplasias has been elucidated, leading to better understanding of processes of cell signaling involved in the induction and development of ectodermal structures as well as their interactions with mesodermal structures[131,137]. International conferences were held in 2008, 2012, and 2017 with the aim of developing a classification system for ectodermal dysplasias that integrates clinical, genetic, and functional/pathway-based data and is fluid enough to incorporate new discoveries[133,138,139]. The current ectodermal dysplasia classification system recognizes approximately 100 conditions in which defects in ectodermal structures represent the major clinical features[133,133a]. Disorders recognized as within other genodermatosis groups (e.g. ichthyoses, keratodermas, skin fragility disorders) and complex syndromes with major non-ectodermal manifestations are not included in this classification[133].

CLASSIC ECTODERMAL DYSPLASIAS				
	Hypohidrotic ED*	**Hypohidrotic ED–immune deficiency**	**Hidrotic ED**	**Witkop tooth and nail syndrome**
Inheritance (associated gene)	XL† (*EDA*); AD, AR (*EDAR* > *EDARADD*)	XL recessive (*IKBKG*/*NEMO*) > AD (*NFKBIA*)	AD (*GJB6*)	AD (*MSX1*)
Protein product	Ectodysplasin A; EDAR; EDARADD	NF-κB essential modulator; NF-κB inhibitor-α	Connexin 30	MSH homeobox 1
Scalp hair	Sparse to absent; often lightly pigmented in children	Sparse	Wiry, brittle; patchy alopecia; often lightly pigmented	Normal to thin
Teeth	Hypodontia, conical	Hypodontia, conical	Normal	Hypo- or anodontia of secondary teeth; primary teeth normal or small/peg-shaped
Sweating	Markedly decreased	Mildly decreased	Normal	Normal
Nails	Normal	Normal	White and small during infancy; thickened, distal separation	Koilonychia improves with age; toenails worse than fingernails
Other	Characteristic facies; neonates may have collodion-like membrane; eczema common; thick nasal secretions and cerumen; frequent respiratory tract infections	Intertrigo, seborrheic-like dermatitis, erythroderma; colitis; recurrent infections (pyogenic or opportunistic); ↑ IgM and IgA, ↓ IgG; rare osteopetrosis and lymphedema, arthritis, and/or (esp. in AD form) autoimmune cytopenias and endocrinopathy	Stippled palmoplantar keratoderma; grid-like array of tiny acral papules; blepharitis, conjunctivitis	Prolonged retention of primary teeth

*_WNT10A_ and _TRAF6_ (TNF receptor-associated factor 6; single patient reported to date) pathogenic variants can also lead to a hypohidrotic ED phenotype (see Table 63.13 and text).
†In female patients, clinical manifestations vary considerably and may have a mosaic pattern (see text).

Table 63.11 Classic ectodermal dysplasias. AD, autosomal dominant; AR, autosomal recessive; ED, ectodermal dysplasia; EDAR, ectodysplasin A receptor; EDARADD, EDAR-associated death domain; *GJB6*, gap junction β6; *IKBKG*, inhibitor of NF-κB kinase regulatory subunit γ; XL, X-linked.

p63-RELATED ECTODERMAL DYSPLASIA SYNDROMES				
	AEC*	**EEC**	**Limb–mammary**	**ADULT**
Inheritance	AD	AD	AD	AD
Typical *TP63* pathogenic variants	Missense in SAM domain	Missense in DNA-binding domain	Truncating in C-terminal region†	Missense in hotspot at end of DNA-binding domain†,‡
Scalp hair	Lightly pigmented, wiry; sparse with patchy alopecia	Lightly pigmented, coarse; may be sparse	Normal	Lightly pigmented, sparse; frontal alopecia
Teeth	Hypodontia, misshapen (e.g. conical) teeth	Hypodontia, enamel hypoplasia	Hypodontia	Hypodontia, small teeth
Sweating	Hypohidrosis in some patients	Usually normal	Hypohidrosis in some patients	Usually normal
Nails	Hyperconvex, thickened or absent	Transverse ridges, pitting	Variable dystrophy	Ridges, pitting
Cleft lip/palate	Almost 100%; palate ± lip	~50%; usually lip + palate	~30%; palate only	None
Digital anomalies	Syndactyly in some patients; rarely ectrodactyly	Ectrodactyly > syndactyly	Ectrodactyly > syndactyly	Ectrodactyly, syndactyly
Skin findings	Neonatal erythroderma; erosive dermatitis, esp. of scalp; flexural reticulated hyperpigmentation	Xerosis, palmoplantar keratoderma	None	Xerosis, photosensitivity, freckling
Other	Ankyloblepharon; lacrimal duct defects; ectopic breast tissue; hypospadias; GER	Lacrimal duct defects; keratopathy, corneal scarring; GU anomalies	Lacrimal duct defects, hypoplastic nipples/breasts; GU anomalies	Lacrimal duct defects; hypoplastic nipples/breasts

*Rapp–Hodgkin syndrome is now included within the AEC spectrum.
†May also be caused by pathogenic missense variants in the proline-rich domain.
‡This variant is thought to constitutively activate a transactivation domain.

Table 63.12 p63-related ectodermal dysplasia syndromes. *TP63* mutations also occur in subsets of autosomal dominant (AD) non-syndromic split-hand/foot malformation (SHFM) and isolated cleft lip/palate. ADULT, *a*cro-*d*ermato-*u*ngual-*l*acrimal-*t*ooth; AEC, ankyloblepharon–ectodermal defects–cleft lip/palate; EEC, ectrodactyly–ectodermal dysplasia–clefting; GER, gastroesophageal reflux; GU, genitourinary; SAM, sterile alpha motif.

Tables 63.11, 63.12 and 63.13 summarize the key clinical and genetic features of selected ectodermal dysplasias with a known molecular basis. Several classic ectodermal dysplasias are discussed in detail in this chapter. Ectodermal dysplasias that are discussed in other chapters include: Goltz syndrome (Ch. 62); oculodentodigital dysplasia and Basan, Johanson–Blizzard, scalp–ear–nipple, and ulnar–mammary syndromes (Ch. 64); Naegeli–Franceschetti–Jadassohn syndrome and dermatopathia pigmentosa reticularis (Ch. 67); and Coffin–Siris and Zimmermann–Laband syndromes (Ch. 70).

OTHER SELECTED ECTODERMAL DYSPLASIAS (EDs) WITH CUTANEOUS MANIFESTATIONS AND A KNOWN MOLECULAR BASIS							
	Tricho-dento-osseous syndrome†	**Ellis–van Creveld syndrome**	**Cranioectodermal dysplasia (Sensenbrenner syndrome)**	**Nectinopathies: cleft lip/palate ED (CLPED), ED-syndactyly (EDS)†**	**ED, ectrodactyly and macular dystrophy (EEM)†**	**Odonto-onycho-dermal dysplasia***	**Pure hair–nail type ED**
Inheritance (associated gene)	AD (*DLX3*)	AR (*EVC*, *EVC2*)	AR (*IFT122, WDR35, WDR19, IFT43*)	AR (*NECTIN1* [CLPED], *NECTIN4* [EDS])	AR (*CDH3*)	AR (*WNT10A*)	AR (*KRT85, KRT74, HOXC13*)
Protein product	Distal-less homeobox-3	EVC and EVC2 (limbin)	Intraflagellar transport proteins	Nectin-1 (CLPED), nectin-4 (EDS)	Cadherin-3 (P-cadherin)	WNT10a	Keratin 85 or 74, homeobox C13
Scalp hair	Kinky (may straighten with age)	Normal	Thin, sparse	Brittle, sparse; involves eyebrows and eyelashes; pili torti; progressive alopecia	Sparse; involves eyebrows and eyelashes	Thin, sparse; involves eyebrows and eyelashes	Sparse to absent; fragile; involves eyebrows and eyelashes
Teeth	Small, widely spaced; thin enamel with pits; taurodontism (elongated pulp chamber)	Neonatal teeth; hypodontia; delayed eruption	Small, widely spaced; hypodontia; enamel defects, abnormally shaped	Hypodontia; peg-shaped teeth	Small, widely spaced; selective tooth agenesis	Hypodontia; small teeth	Normal
Sweating	Normal	Normal	Normal	Normal	Normal	Hyperhidrosis of palms and soles; occasionally hypohidrosis	Normal
Nails	Brittle	Dystrophic	Short, broad, thin	Dystrophic (variable)	Normal	Dystrophic or absent	Dystrophic; fragile, irregular distal ends
Other	Dolichocephaly, frontal bossing, increased bone density	Short-limbed dwarfism, postaxial polydactyly, skeletal dysplasia; congenital heart defects	Lax, redundant skin; short proximal limbs, brachydactyly, narrow thorax; dolichocephaly, frontal bossing; nephronophthisis	Cleft lip/palate (CLPED); PPK (esp. CLPED); partial cutaneous syndactyly (EDS > CLPED)	Macular dystrophy; syndactyly, ectrodactyly, camptodactyly	Facial telangiectasias, reticulated erythema, "atrophy"; xerosis, follicular keratoses; PPK; smooth tongue	Follicular papules on scalp

*Allelic with Schöpf–Schulz–Passarge syndrome, which has an overlapping phenotype but also features eyelid hidrocystomas and PPK with histologic evidence of eccrine syringofibroadenomas. In addition, approximately 5%–15% of patients with a hypohidrotic ED phenotype have *WNT10A* pathogenic variants, with milder manifestations in heterozygotes. Multiple milia, adnexal neoplasms (e.g. poromas, tumors of the follicular infundibulum), basal cell carcinomas, and pili annulati have also been described in patients with *WNT10A* pathogenic variants.
†The pathogenesis of these conditions as well as disorders with an underlying mutation in *TP63, RIPK4* (CHANDS), or *CHUK/IKKA* (see Table 63.12 and text) is thought to involve disruption of p63 signaling.

Table 63.13 Other selected ectodermal dysplasias (EDs) with cutaneous manifestations and a known molecular basis. The ED–short stature syndrome due to biallelic pathogenic variants in *GRHL2* (grainyhead-like 2) features nail dystrophy, hypodontia with enamel hypoplasia, marginal PPK, keratoses on the dorsal hands and feet, and oral hyperpigmentation. SOFT syndrome – *s*hort stature, *o*nychodysplasia, *f*acial dysmorphism, and hypo*t*richosis – is caused by pathogenic variants in *POC1A*. Additional genes that have been implicated in ED include *KREMEN1* (kringle-containing transmembrane protein 1; AR, hair/tooth), *TSPEAR* (thrombospondin-type laminin G domain and EAR repeats; AR, hair/tooth/±hypohidrotic), *CST6* (cystatin E/M; AR, hair/hypohidrotic), and *KDF1* (keratinocyte differentiation factor 1; AD, hair/tooth/nail/hypohidrotic). AD, autosomal dominant; AR, autosomal recessive; PPK, palmoplantar keratoderma.

HYPOHIDROTIC ECTODERMAL DYSPLASIA

Synonyms: ■ Anhidrotic ectodermal dysplasia ■ Christ–Siemens–Touraine syndrome

Hypohidrotic ectodermal dysplasia (HED) refers to a group of disorders that share the following features: sparse or absent hair; missing or peg-shaped teeth; and decreased ability to sweat. The most common form is X-linked, and traditionally the term HED has referred to this condition. However, clinically similar conditions with autosomal dominant and autosomal recessive inheritance can result from molecular defects that affect the same pathway as in X-linked HED.

Epidemiology

The X-linked form of HED is estimated to affect 0.5–2 in 10 000 live-born boys and occurs in all ethnic groups. The autosomal dominant and recessive forms are much less common.

Pathogenesis

HED is caused by pathogenic variants in genes that affect the ectodysplasin signal transduction pathway[140,140a] (Fig. 63.15). Epithelial cells in the developing tooth, hair follicle, and eccrine gland utilize this pathway during morphogenesis, and errors in signaling result in aplasia, hypoplasia, or dysplasia of these structures. Activation of the ectodysplasin pathway at a critical time during development leads to translocation of the nuclear factor-κB (NF-κB) transcription factor into the nucleus of these epithelial cells, thereby altering the expression of a variety of target genes. The change in gene expression likely has an effect on both cellular proliferation and survival[141].

The *EDA* gene that is altered in X-linked HED encodes a soluble ligand, ectodysplasin A. It is secreted by a subset of epithelial cells and binds to its receptor (*ecto*dysplasin-*A* receptor; EDAR) on another group of epithelial cells. Pathogenic variants in *EDAR* can cause autosomal recessive or autosomal dominant HED[142]. Less often, autosomal recessive and autosomal dominant HED is caused by pathogenic variants in *EDARADD* (EDAR-associated death domain), which encodes an intracellular adapter protein that assists in transducing the signal from the activated receptor to the nucleus[143]. A dominant-negative mutation in *TRAF6*

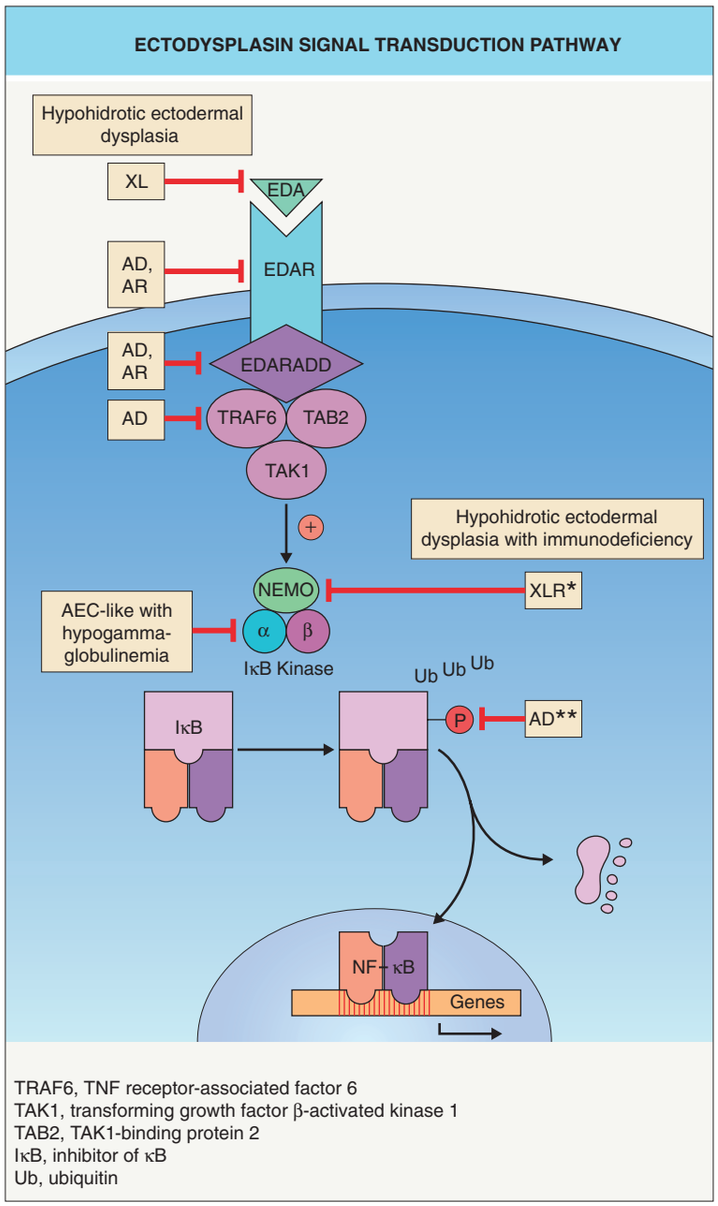


Fig. 63.15 The ectodysplasin signal transduction pathway. The IκB kinase α subunit (IKKα), which is also known as CHUK (component of IκB kinase complex), is upregulated by p63; this explains the ankyloblepharon–ectodermal defects–cleft lip/palate (AEC) syndrome-like phenotype in individuals with pathogenic variants in this gene. *Allelic with incontinentia pigmenti. **A hypermorphic mutation in the gene encoding IκBα that prevents this protein's phosphorylation (and subsequent ubiquitination/degradation) can result in continued inhibition of NF-κB and a phenotype of hypohidrotic ectodermal dysplasia with immunodeficiency. AD, autosomal dominant; AR, autosomal recessive; EDA, ectodysplasin A; EDAR, EDA receptor; EDARADD, EDAR-associated death domain adapter protein; NEMO, NF-κB essential modulator (also known as IKBKG, inhibitor of NF-κB kinase regulatory subunit γ); XL(R), X-linked (recessive).

(TNF receptor-associated factor 6), which encodes a protein that interacts with EDARADD, has also been reported in a patient with HED[144]. In addition, mutations in *WNT10A* are responsible for a subset (~5%–15%) of patients with an HED phenotype (see below and Table 63.12)[145].

Clinical Features

Affected newborns may present with a collodion-like membrane or with marked skin scaling. Scalp hair is sparse to absent (Fig. 63.16), and, when present, is usually lightly pigmented. Hair may darken at puberty and secondary sexual hairs are typically normal, although body hair is usually sparse or absent. Most male patients are unable to sweat to a detectable degree[146]. This can lead to elevation of core temperature in warm environments or with exertion, and symptomatic hyperthermia is a major problem. Affected infants often present with fever of unknown origin, and hyperthermia during the first few years of life can be fatal when HED is not recognized[146,147]. The skin is smooth and dermatoglyphics may be effaced because of absent eccrine pores. Atopy is a major cause of morbidity, with eczema affecting nearly two-thirds of HED patients. Periorbital wrinkling and hyperpigmentation are common. Sebaceous hyperplasia of the face, clinically resembling milia, can develop over time (see Fig. 63.16E). The nails are usually normal.

Both the primary and secondary dentition are affected. Teeth may be absent or reduced in number and abnormally shaped (e.g. peg-shaped). Dental radiographs are helpful in determining the extent of hypodontia, and prenatal tooth germ sonography can reliably identify affected fetuses between 18 and 28 weeks of gestation[148]. Individuals with HED typically have an alteration in their facial appearance characterized by a saddle nose, full everted lips and frontal bossing (see Fig. 63.16). Nasal secretions and cerumen are thick and viscous, and recurrent respiratory tract infections are common. The voice is frequently hoarse or raspy. Affected infants often develop gastroesophageal reflux and feeding problems. Unilateral or bilateral amastia is an occasional feature.

Female patients with the X-linked form of HED fall into one of three categories: (1) carriers with no detectable clinical features; (2) limited involvement with findings such as decreased hair density, one or more peg-shaped or missing teeth, patchy distribution of sweat glands along the lines of Blaschko, and relative hyperpigmentation of the skin that lacks adnexa (most evident on the back); or (3) full-blown features of the disorder (Fig. 63.17). Although this variability has been classically linked to the random nature of X-inactivation (see Ch. 62), hypomorphic *EDA* variants, genetic modifiers, and additional biologic mechanisms may also play a role[145].

Pathology

A skin biopsy is usually not necessary, although a scalp or palmar biopsy specimen lacking eccrine structures was traditionally considered diagnostic of HED[149]. Microscopic examination of hairs often shows small or variable shaft diameters and parallel dark bands of various lengths resembling a "bar code"[150].

Differential Diagnosis

In patients with clinical features of HED, options to confirm the diagnosis include single gene testing or a next-generation sequencing (NGS)-based multigene panel including *EDA, EDAR, EDARADD, TRAF6*, and *WNT10A*[145]. The majority of affected individuals, either male or female, have the X-linked form. *Homozygous* or *compound heterozygous* pathogenic variants in the *WNT10A* gene can give rise to an HED phenotype without associated facial dysmorphism, in addition to causing odonto-onycho-dermal dysplasia and Schöpf–Schulz–Passarge syndrome[145,151] (see Table 63.13 and Fig. 55.6). *Heterozygous WNT10A* pathogenic variants also represent a common etiology of mild HED or isolated hypodontia. At birth, HED can be confused with an ichthyosis if a collodion-like membrane is present (see Ch. 57, Table 57.4). Recurrent fevers in an infant may lead to consideration of infectious diseases before the features of HED are recognized. HED with immune deficiency (HED-ID) due to pathogenic variants in the *IKBKG* (*NEMO*) gene can be differentiated by the clinical and laboratory features of the associated immune system abnormalities and confirmed by genetic analysis (see below).

Treatment

Controlling ambient temperatures and external methods of cooling, e.g. wet T-shirts, wet headbands and cooling vests, are critical to prevent hyperthermia in children with HED. Regular use of moisturizers is helpful for dry skin. Dentures can be fitted in children as young as 3 years of age, and dental restoration through implants should be employed for older patients. Multidisciplinary care is required for treatment of other manifestations, which range from nasal concretions, asthma and recurrent respiratory infections to weight deficits and reduced salivary secretion. Patient organizations such as the National Foundation for Ectodermal Dysplasias (www.nfed.org) are also an important aspect of care, providing information and support to affected families.

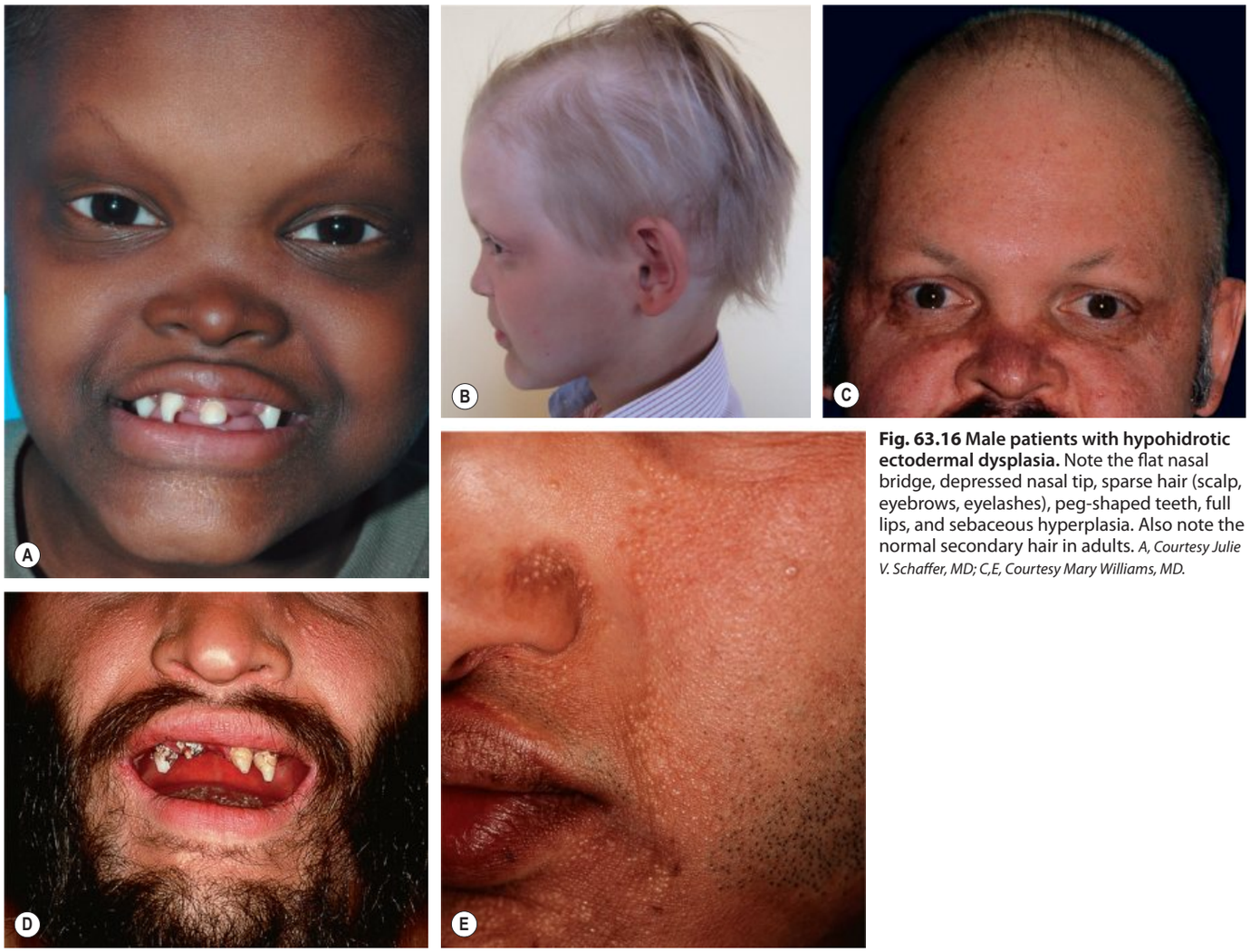


Fig. 63.16 Male patients with hypohidrotic ectodermal dysplasia. Note the flat nasal bridge, depressed nasal tip, sparse hair (scalp, eyebrows, eyelashes), peg-shaped teeth, full lips, and sebaceous hyperplasia. Also note the normal secondary hair in adults. *A, Courtesy Julie V. Schaffer, MD; C,E, Courtesy Mary Williams, MD.*

Prenatal administration of recombinant EDA protein is a promising approach to correct the X-linked HED phenotype. This method has been successfully utilized in murine and canine models[152–154]. Intra-amniotic administration of recombinant Fc-EDA fusion protein (constant domain of IgG1 plus receptor-binding portion of EDA) to three human fetuses with X-linked HED at 26 ± 31 weeks' gestation had positive effects on tooth development and restored sweating ability in the infants[155].

HYPOHIDROTIC ECTODERMAL DYSPLASIA WITH IMMUNE DEFICIENCY

HED-ID is a rare condition that shares many features with classic HED but is differentiated by the associated immune abnormalities (see also Ch. 60).

Pathogenesis

HED-ID is most commonly inherited in an X-linked recessive pattern due to hypomorphic mutations in *IKBKG* (inhibitor of NF-κB kinase regulatory subunit γ), which is also known as *NEMO* (*N*F-κB *e*ssential *mo*dulator). This gene encodes the γ subunit of a kinase that activates NF-κB downstream in the ectodysplasin (see Fig. 63.15) and tumor necrosis factor (TNF) pathways[156]. The condition primarily affects boys and is allelic to incontinentia pigmenti, which is caused by more detrimental *IKBKG* pathogenic variants that are lethal in male embryos unless in a mosaic state (e.g. due to a postzygotic mutation of Klinefelter syndrome; see Ch. 62). Patients with HED-ID have a high frequency of somatic mosaicism in their T cells, reflecting revertant mutations that are critical for survival in this cell type. An autosomal dominant form of HED-ID due to pathogenic variants in the *NFKBIA* gene has also been described[157]. These patients have decreased NF-κB signaling because the mutated α-component of the NF-κB inhibitor is resistant to degradation (see Fig. 63.15).

Clinical Features

Individuals with HED-ID often have milder abnormalities of ectodermal structures than do patients with classic HED. The findings can include hypodontia, conical teeth, hypotrichosis, and a reduced ability to sweat; frontal bossing, periorbital wrinkling, and everted lips may also be seen. A seborrheic- or atopic-like dermatitis that evolves into erythroderma may serve as a clue to the diagnosis[158], and reticulated hyperpigmentation is occasionally observed. Extracutaneous inflammatory manifestations can include colitis, which affects ~25% of patients, and chronic arthritis.

The immunodeficiency results in recurrent pyogenic bacterial infections, especially of the skin and respiratory tract, as well as opportunistic infections. It is characterized by a poor antibody response to polysaccharide antigens, dysgammaglobulinemia (typically elevated IgM and IgA but decreased IgG levels) and defective natural killer cell activity[156]. A T cell deficiency has also been described in some patients with the autosomal dominant variant of HED-ID. Occasionally, infants with X-linked HED-ID present with osteopetrosis (abnormally dense bones) and lymphedema. Female carriers, e.g. mothers of affected children, may have mild features of incontinentia pigmenti[156,159] (see Ch. 62).

Treatment

Intravenous immunoglobulin (IVIg) administration does not typically decrease the propensity to develop infections. Hematopoietic stem cell transplantation (HSCT) can correct the immune defects, although patients may experience engraftment difficulties and post-transplant complications such as worsening colitis[158,160].







Fig. 63.17 Female patients with X-linked hypohidrotic ectodermal dysplasia. Note the peg-shaped teeth, hypodontia, and full lips (**A**), as well as sparse eyelashes and periorbital hyperpigmentation (**B**) and sebaceous hyperplasia in a distribution following the lines of Blaschko (**C**). *A, Courtesy Julie V. Schaffer, MD.*



Fig. 63.18 Hidrotic ectodermal dysplasia (Clouston syndrome). Note the thickened, shortened nails with distal separation and tiny papules in a regular distribution on the fingertips.

HIDROTIC ECTODERMAL DYSPLASIA

Synonym: ▪ Clouston syndrome

Hidrotic ectodermal dysplasia was first described in a French-Canadian kindred[161] and the ancestry of many affected individuals was traced to a single founder. Subsequently, the disorder has been reported in individuals of varying ethnic backgrounds[162].

Pathogenesis

Hidrotic ectodermal dysplasia is an autosomal dominant condition that is caused by missense mutations in the *GJB6* gene, which encodes the connexin 30 protein and is thought to be regulated by the p63 transcription factor[163]. Connexins oligomerize to form gap junctions that are important for communication between cells (see Ch. 58), and *GJB6* is expressed in keratinocytes. Pathogenic variants in genes that encode other connexins cause skin disorders ranging from Vohwinkel and keratitis–ichthyosis–deafness (KID) syndromes (*GJB2*) to erythrokeratodermia variabilis (*GJB3* and *GJB4*) (see Table 58.5). Pathogenic variants in *GJB6* can also cause non-syndromic, autosomal dominant, digenic (together with a *GJB2* mutation) deafness, with normal teeth and hair in affected individuals; less often the inheritance pattern is autosomal recessive. A *GJB6* mutation has also been described in a patient with a KID syndrome-like phenotype that included congenital atrichia[164].

Clinical Features

Hidrotic ectodermal dysplasia is characterized by the triad of hypotrichosis, nail dystrophy, and palmoplantar keratoderma, with normal teeth and sweating. The hair is wiry, brittle, and pale; patchy alopecia is common. Both hair loss and nail changes may progress over time. In affected infants, the nails are typically milky white and smaller than normal with gradual thickening throughout childhood. In adults, the nail plates grow slowly, are thick, and separate from the nail bed distally (Fig. 63.18). Keratoderma with stippling of the palms and soles can also be progressive (see Ch. 58). Tiny papules in a grid-like array, corresponding to eccrine acrosyringia, or larger papules coalescing in a cobblestone-like pattern may extend from the palms and soles onto the dorsal surface of the digits, especially distally (see Fig. 63.18 and Fig. 58.11); the latter corresponds to where the dermatoglyphics are more prominent. Similar papules may also occur on the extensor surfaces of the extremities. Oral leukoplakia has been described, and sparse eyelashes may predispose patients to conjunctivitis and blepharitis.

Pathology

Histologically, the thickened palms and soles have orthohyperkeratosis with a normal granular layer. Eccrine syringofibroadenomatosis, which is characterized by proliferation of ductal structures within a fibrovascular stroma, may be observed when papular lesions are biopsied. The hair does not have specific microscopic changes.

Differential Diagnosis

The hair abnormalities in hidrotic ectodermal dysplasia distinguish it from pachyonychia congenita, which may have similar nail findings. A hidrotic ectodermal dysplasia-like phenotype plus deafness has been reported in a few patients with a *GJB2* mutation, and the dominant deafness–onychodystrophy syndrome results from pathogenic variants in *ATP6V1B2*.

Treatment

The National Foundation for Ectodermal Dysplasias can provide support to affected individuals and families. Ablation of the nail matrix is occasionally necessary for pain relief, and patients with substantial alopecia may choose to use hairpieces. Management of hyperkeratotic palms and soles is difficult; similar strategies to those used for the palmoplantar keratodermas, e.g. α-hydroxy acids, urea, soaking and paring, can be employed.

WITKOP TOOTH AND NAIL SYNDROME

Synonyms: ■ Tooth and nail syndrome ■ Witkop syndrome ■ Hypodontia with nail dysgenesis

First described in 1965, this autosomal dominant disorder is probably more common than suggested by the relatively small number of reports in the literature[165]. Affected individuals have small, thin, brittle nail plates that grow slowly, and koilonychia may be evident at birth. The toenails are usually more prominently involved than the fingernails, and nail abnormalities tend to improve with age. Thin, fine scalp hair is an occasional feature. The primary teeth may be normal or small and/or peg-shaped (Fig. 63.19). There is usually prolonged retention of primary teeth and partially or totally absent secondary dentition, especially the mandibular incisors, second molars, and maxillary canines.

A heterozygous mutation in *MSX1* (MSH homeobox 1), which is expressed in developing teeth and nail beds in mice, has been identified in at least one family with Witkop tooth and nail syndrome[166]. Pathogenic variants in *MSX1* have also been described in families with isolated tooth agenesis or non-syndromic cleft lip and/or palate. MSX1 is a transcription factor that has roles in the development of teeth and presumably nails. Fried tooth and nail syndrome represents a similar condition with autosomal recessive inheritance and more consistent hair abnormalities.



Fig. 63.19 Witkop tooth and nail syndrome. Small primary teeth, some conical, in a 7-year-old boy. Radiographs showed an absence of nearly all of the secondary teeth. *Courtesy Julie V. Schaffer, MD.*

ANKYLOBLEPHARON–ECTODERMAL DEFECTS–CLEFT LIP/PALATE SYNDROME

Synonyms: ■ Hay–Wells syndrome ■ Rapp–Hodgkin syndrome

This autosomal dominant ectodermal dysplasia, first described in 1976[167], has been reported in ethnically and geographically diverse individuals and families[168].

Pathogenesis

The ankyloblepharon–ectodermal defects–cleft lip/palate (AEC) syndrome is caused by *TP63* mutations that typically affect the sterile alpha motif (SAM) domain of the p63 protein[169]. p63, a transcription factor, is expressed within basal keratinocytes of the skin, which have a high proliferative capacity that is lost in differentiated keratinocytes. The p63 protein has multiple isotypes, with the SAM domain present in only some forms. This helps to explain the phenotypic differences between AEC syndrome and ectodermal dysplasia–ectrodactyly–clefting (EEC) syndrome (see Table 63.12 and below); the latter is usually due to mutations within the DNA-binding domain of p63[169,170].

Clinical Features

This disorder is evident at birth. Up to 90% of affected infants present with erythroderma, peeling skin, or erosions, which can result in life-threatening infectious complications (Fig. 63.20A). The scalp is almost always involved, and a chronic, erosive scalp dermatitis is a characteristic finding (Fig. 63.20B,C). The scalp hair is wiry and usually lightly pigmented and sparse, often with patchy alopecia. Some degree of nail dystrophy is typically evident, with findings ranging from hyperconvex, thickened nail plates to anonychia. Patients may have decreased sweating and heat intolerance[171,172].

Patients often develop abnormal granulation tissue and recurrent bacterial infections of the skin. Cribriform and stellate scarring tends to occur in a shawl-like distribution on the shoulders and upper trunk[171]. Progressive reticulated hyperpigmentation frequently appears in intertriginous areas, and hypopigmentation of the scalp and face may be seen in children with darkly pigmented skin.

Congenital strands of tissue between the eyelids (ankyloblepharon adnatum filiforme) are observed in approximately three-quarters of affected individuals (Fig. 63.20D). These may lyse spontaneously, even prior to birth, or require surgical correction. The lacrimal ducts may be atretic. Almost all patients with AEC syndrome are born with a cleft palate with or without a cleft lip. Malformed external ears and recurrent otitis media with secondary conductive hearing loss are common[173]. Dental abnormalities include hypodontia and misshapen (e.g. conical) teeth, and most patients have maxillary hypoplasia.

Gastroesophageal reflux develops in the majority of AEC patients, while one-quarter of affected children fail to thrive and require gastrostomy placement[174]. Hypospadias affects up to 80% of male patients, and supernumerary nipples and/or ectopic breast tissue have been described[175]. Limb abnormalities are more common in AEC syndrome than once thought[171,172,176]; these malformations, which are typically less severe than the defects seen in EEC syndrome (see below), can include syndactyly (partial or complete), camptodactyly, brachydactyly, and even ectrodactyly[175] (Fig. 63.20E).

Pathology

Hair shaft abnormalities such as pili torti and pili trianguli et canaliculi may be observed. Histopathologic changes are nonspecific and often include mild epidermal atrophy and dermal melanophages[177].

Differential Diagnosis

Rapp–Hodgkin syndrome, once considered to be a distinct entity, is now thought to fall within the AEC spectrum. Affected individuals have heterozygous pathogenic variants in *TP63*, generally affecting the SAM domain of p63. Other than a lack of ankyloblepharon, clinical findings overlap with those of AEC syndrome, including maxillary hypoplasia, cleft palate ± lip, nail dystrophy, and abnormalities of the teeth and hair[178]. The clinical features of AEC also overlap with those of *c*urly *h*air–*a*nkyloblepharon–*n*ail *d*ysplasia *s*yndrome (CHANDS), which is caused by biallelic mutations in the receptor-interacting serine-threonine kinase 4 gene (*RIPK4*) that is a direct transcriptional target of p63[179]. An AEC/EEC-like syndrome presenting with hypogammaglobulinemia as well as ankyloblepharon, cleft lip/palate, conical teeth, sparse hair, nail dystrophy, syndactyly/ectrodactyly, and hypoplastic genitalia can result from pathogenic variants in *CHUK/IKKA* (component of inhibitor of NF-κB kinase complex/inhibitor of NF-κB kinase subunit α; see Fig. 63.15), which is activated by p63[180]. The peeling erythroderma of neonates with AEC syndrome can lead to a misdiagnosis of epidermolysis bullosa or ichthyosis.

Treatment

Surgical repair of oral clefting is usually necessary. Treatment for the erosive scalp dermatitis should be gentle and non-occlusive, with surveillance for and treatment of secondary infections. Debridement often causes erosions to worsen, and skin grafts typically fail. Ulceration and granulation tissue may be very difficult to treat, and healing tends to be slow. A recent study found that topical application APR-246/eprenetapopt/PRIMA-1^{MET}, which was developed to activate mutant p53 in cancer cells, led to substantial re-epithelialization of erosions on the hands and scalp that had been present for 9–15 years in two patients with AEC[181].



Fig. 63.20 Ankyloblepharon–ectodermal defects–cleft lip/palate syndrome. A Extensive erosions in an infant who succumbed to sepsis. **B, C** Thick scale-crust and alopecia of the scalp. **D** Strands of tissue between the eyelids (ankyloblepharon adnatum filiforme). **E** Digital abnormalities (including syndactyly, brachydactyly) and nail dystrophy (yellowing and thickening of the nail plate). *B, Courtesy Jean L. Bolognia, MD; C, Courtesy Julie V. Schaffer, MD.*

ECTODERMAL DYSPLASIA–ECTRODACTYLY–CLEFTING SYNDROME

Synonym: ■ Split hand–split foot–ectodermal dysplasia–clefting syndrome

First described by Eckholdt and Martens in 1804, this disorder occurs in all ethnic groups and has been reported worldwide.

Pathogenesis

Ectodermal dysplasia–ectrodactyly–clefting (EEC) syndrome is an autosomal dominant disorder caused by pathogenic variants in the region of *TP63* that encodes the protein's DNA-binding domain[182,183]. These mutations disrupt the ability of the p63 transcription factor, which is expressed in proliferating epidermal basal cells, to regulate gene expression. *TP63* pathogenic variants also occur in several related autosomal dominant disorders, including non-syndromic split hand/foot malformation (minority of affected families), limb–mammary syndrome



Fig. 63.21 Ectodermal dysplasia–ectrodactyly–clefting syndrome. Note the characteristic split-hand (**A**) and foot (**B**) deformities in these three siblings.

and ADULT (*a*cro-*d*ermato-*u*ngual-*l*acrimal-*t*ooth) syndrome, as well as in AEC syndrome (see Table 63.12 and above). Patients with EEC syndrome usually have missense mutations within the p63 DNA-binding domain that differ from those seen in these other disorders[183].

Clinical Features

The ectodermal changes in this highly variable condition may be quite mild[184]. The scalp hair is usually light in color and coarse. It may be sparse and grow slowly. The secondary sexual hair may also be affected. Scalp folliculitis and dermatitis are rare manifestations[185,186]. Approximately 80% of affected individuals have transverse ridging, pitting, and slow growth of the nail plates. Xerotic skin and palmoplantar hyperkeratosis can occur, and sweating is usually normal.

Clefting of the palate/lip occurs in ~50% of affected individuals, and additional oral abnormalities include enamel hypoplasia, hypodontia, and premature loss of secondary teeth. Lacrimal duct defects leading to blepharitis and dacryocystitis are frequently present, and limbal stem cell deficiency can result in photophobia and keratopathy as well as corneal ulceration and scarring[187]. Secondary conductive hearing loss is also common, and choanal atresia is an occasional manifestation.

Ectrodactyly, a specific split-hand/foot malformation due to failure of normal development of the central digits, represents a defining feature of EEC syndrome (Fig. 63.21). The ectrodactyly is frequently asymmetric, usually with more severe involvement of the feet than the hands. Intrafamilial variability is marked. Genitourinary abnormalities are an under-appreciated manifestation of EEC syndrome and may be associated with dysplasia of the urogenital epithelium; renal and urogenital malformations affect more than one-third of patients and can result in hydronephrosis.

Pathology

Histologic features are neither diagnostic nor specific.

Differential Diagnosis

The presence of split-hand/foot malformations and the absence of ankyloblepharon or cutaneous erosions help to distinguish EEC syndrome from AEC syndrome. The findings that differentiate limb–mammary syndrome and ADULT syndrome from EEC are presented in Table 63.12. Other ectodermal dysplasias that feature digital abnormalities include ectodermal dysplasia–ectrodactyly–macular dystrophy (EEM) syndrome, cleft lip/palate ectodermal dysplasia, oculodentodigital dysplasia, and ulnar–mammary syndrome (see Table 63.13 and Table 64.6). Although Goltz syndrome (focal dermal hypoplasia) can present with split-hand/foot and other digital malformations, nail dystrophy, sparse hair, dental anomalies and (occasionally) cleft lip/palate, it is easily recognized based on the highly characteristic skin findings as well as ocular and additional skeletal (e.g. osteopathia striata) defects (see Ch. 62). Lastly, the popliteal pterygium syndrome, which is caused by pathogenic variants in the interferon regulatory factor 6 gene (*IRF6*) that is transcriptionally activated by p63, has features overlapping with EEC (see Ch. 64).

Treatment

As for the other ectodermal dysplasias with oral clefting and lacrimal abnormalities, management involves a multidisciplinary approach. Limb defects may be ameliorated by surgical interventions. All affected individuals should be screened with a renal ultrasound. Potential approaches to therapy include small interfering RNAs (siRNAs) that selectively silence mutant *TP63* alleles and the p53-activating compound APR-246/eprenetapopt/PRIMA-1^{MET}, which was found *in vitro* to rescue impaired epidermal and corneal differentiation in cells from EEC patients[188,189].

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Additional figures available in our eBook (see inside front cover for access code).

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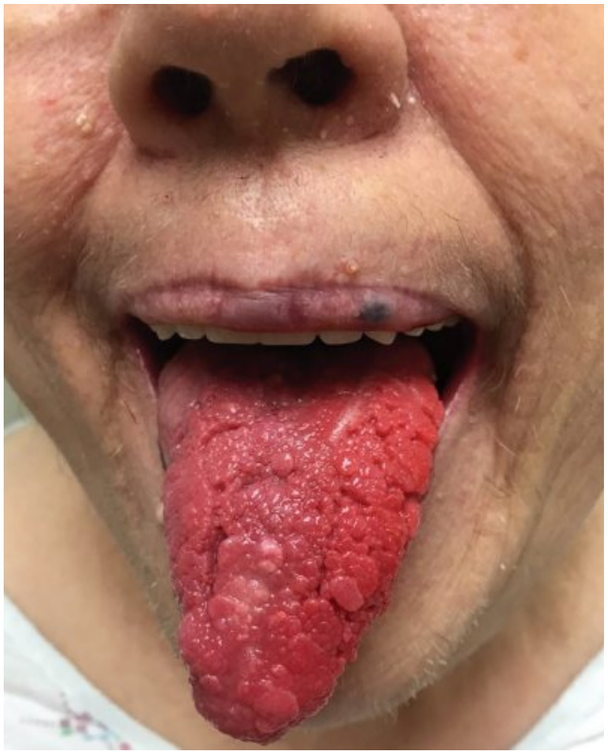
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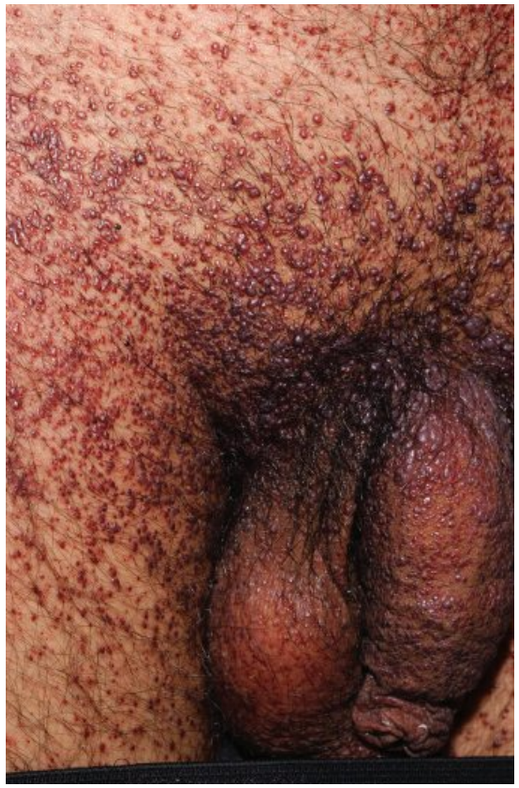
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eFig. 63.1 Multiple endocrine neoplasia type 2B. Enlarged nodular lips and multiple mucosal neuromas on the tongue.



eFig. 63.2 Cobblestoning of the tongue in a patient with Cowden syndrome. The patient also has trichilemmomas on the cheeks, nose, and upper cutaneous lip. *Courtesy Jonathan S. Leventhal, MD.*



eFig. 63.3 Angiokeratomas of Fabry disease. Multiple dark red to red–brown macules and papules in a "bathing trunk" distribution. *Courtesy Edward Cowen, MD.*



eFig. 63.4 Male patients with hypohidrotic ectodermal dysplasia. A–C Scalp and eyebrow hair is absent (**A**) to sparse (**B**) or thin (**C**). Note the flat nasal bridge and periorbital wrinkling and hyperpigmentation. **D** Hypodontia with peg-shaped teeth. Note the perioral wrinkling and sebaceous hyperplasia.

Developmental Anomalies 64

Richard J. Antaya and Julie V. Schaffer

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Key features

- The human neural tube is thought to close in an intermittent, multisite pattern, and neural tube defects that present as midline cutaneous lesions (e.g. cephaloceles, heterotopic brain tissue, rudimentary meningoceles) typically occur at the junction between two closure sites
- Midline lesions of the nose and scalp have a high likelihood of representing developmental defects with a potential intracranial connection, and an evaluation with CT or MRI prior to surgical intervention is critical
- The presence of a "hair collar" surrounding a lesion on the scalp is a sign of ectopic neural tissue or membranous aplasia cutis; the latter is thought to represent a forme fruste of a neural tube defect
- Cutaneous lesions overlying the spinal axis can serve as a marker for spinal dysraphism, and their presence is often an indication for radiologic evaluation
- Aplasia cutis congenita, a physical finding reflecting a disruption of intrauterine skin development, can be approached clinically based on the morphology and distribution of lesions as well as the presence or absence of associated abnormalities
- A number of other developmental anomalies affect the skin; although they usually represent isolated defects, it is important to be aware of potential associated conditions

INTRODUCTION

Developmental anomalies are a diverse group of congenital disorders that result from faulty morphogenesis. They include both *malformations*, defined as structural defects arising due to errors in embryologic development, and *disruptions*, which occur when a structure programmed to develop normally is damaged before it is fully formed. A classic example of the former is incomplete closure of the neural tube resulting in an encephalocele, while the latter process is illustrated by the anomalies associated with varicella embryopathy. Although developmental anomalies that affect the skin are often recognized at birth or during infancy, occasionally diagnosis is delayed until later in life. The cutaneous abnormalities range in severity from isolated, minor physical findings (e.g. rudimentary supernumerary digits) to deforming, potentially life-threatening defects (e.g. deep, irregular scalp aplasia cutis congenita in Adams–Oliver syndrome). Furthermore, some skin lesions that appear to be innocuous may serve as important clues to the presence of a multiple congenital anomaly syndrome or, particularly when involving the midline, the existence of a serious defect of the underlying tissues. Such associations reflect the complex interactions between various ectodermal and mesodermal elements that occur during the intricate processes of morphogenesis and differentiation.

This chapter begins with an overview of the midline lesion and its relationship to closure of the neural tube. A discussion of specific issues pertaining to midline lesions of the nose, scalp, and spine follows, including a review of the different types of anomalies that can present in these sites. An overview of aplasia cutis congenita is followed by presentation of a clinical approach based on the morphology and distribution of lesions and the presence or absence of associated abnormalities. Finally, a variety of non-midline developmental anomalies are discussed, including lip pits, accessory tragi, supernumerary nipples, skin dimples, malformations of the dermatoglyphics, rudimentary supernumerary digits, and the amniotic band sequence. Developmental anomalies that are covered in Chapter 110 include ear pits as well as branchial cleft, thyroglossal duct, bronchogenic, median raphe, omphalomesenteric duct, and urachal cysts.

THE MIDLINE LESION

A number of critical events occur during the third to fifth weeks of embryologic development (see Ch. 2). These include formation of the neural tube, separation of neuroectoderm from surface ectoderm, and interposition of mesodermal elements. Inherent in such a complicated process is the potential for error, which spans a spectrum from obvious, fulminant neural tube defects to subtle cutaneous anomalies. However, the latter may represent a sign of a significant underlying malformation.

Classically, closure of the human neural tube was thought to be a continuous process, beginning at a single focus in the cervical region and progressing bidirectionally in a "zipper-like" fashion to culminate in the closure of the anterior and subsequently posterior neuropores. However, evidence suggests that in humans as well as other mammals, the cranial segment of the neural tube closes in an intermittent or multisite pattern. Four distinct initiation sites of neural tube closure have been identified in the mouse, and a similar pattern of closure has been proposed for humans, with an additional caudal site (Fig. 64.1)[1]. In support of the multisite closure model, neural tube defects (e.g. cephaloceles, myelomeningoceles, heterotopic brain/meningeal tissue) cluster either entirely within one closure site or at the junction of two sites, such as the nasal root (2–3) or vertex (2–4; see Fig. 64.1). Neural tube

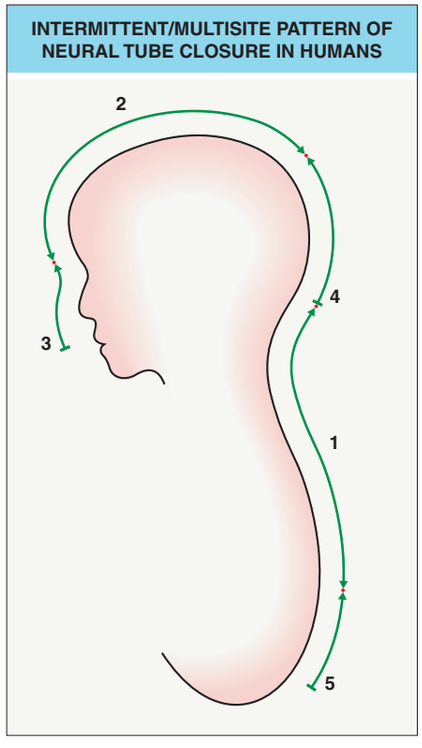


Fig. 64.1 Intermittent/multisite pattern of neural tube closure in humans. The five separate initiation sites are labeled (in chronological order, 1–5), the direction of neural tube closure is indicated by the arrows, and the junctions (where defects tend to occur) designated with dots. The 2–3 junction corresponds to the location of frontoethmoidal neural tube defects, the 2–4 junction to parietal defects, and the 1–4 junction to occipital defects. Closure in region 4 is thought to occur via membranous growth, proceeding in a superior direction; incomplete closure at this site could therefore result in a membranous defect at the 2–4 junction (i.e. the vertex).

closure in the posterior cranial area is thought to occur via a membrane rather than a midline fusion of folds, and the appearance of this site during embryologic development in animals resembles that of human membranous aplasia cutis[2]. Specific genes may control individual closure sites, explaining repetitive events within families.

Midline Lesions of the Head, Neck, and Anterior Trunk

The pathogenesis, differential diagnosis, and management of midline lesions of the nose (Fig. 64.2) and scalp are discussed below, followed by a review of the individual developmental anomalies that may present with a midline lesion on the head, neck, and anterior trunk. Midline cysts of this region (e.g. thyroglossal duct, bronchogenic) are discussed in Chapter 110.

Midline nasal lesions

It is important for physicians to recognize the potential intracranial connection of a midline nasal mass or pit[3]. Dermoid cysts, dermal sinuses, cephaloceles, and nasal glial heterotopia (nasal "gliomas") resulting from faulty embryologic development of the frontobasal skull and/or adjacent ectodermal/neuroectodermal tissues may present as congenital nasal lesions (Table 64.1). As a group, these midline nasal masses occur in ~2–5 per 100 000 live births. They are often misdiagnosed as more familiar entities such as epidermoid cysts and infantile hemangiomas.

The various congenital midline nasal masses have similar developmental origins. As the bones of the skull form during the second month of gestation, diverticula of dura mater project: (1) inferiorly into the prenasal space that extends from the base of the skull to the nasal tip, deep to the nasal bone and skin but superficial to the nasal cartilage; and (2) anteriorly through the nasofrontal fontanelle into the glabellar and inner canthal areas. These diverticula may make connections with the overlying dermis, but usually they regress completely, with subsequent bony fusion to form the base of the skull and the cribriform plate. However, if the dura mater does not separate from the dermis, an ectodermal residue, with or without a patent intracranial connection, can persist; furthermore, if faulty neural tube closure results in a bony defect, there may be herniation of brain tissue. Such ectopic elements can occur either within the prenasal space (nasoethmoidal, "intranasal") or superiorly at the glabella (nasofrontal, "extranasal")[4]. Depending on the contents of the lesion (e.g. cutaneous versus neural tissue, cyst versus tract only) and the patency of the intracranial connection, a dermoid cyst, dermal sinus, cephalocele, or nasal glial heterotopia may result (see below).

Many of these midline nasal lesions have the potential for intracranial communication and therefore present a risk for the development of serious CNS infections such as meningoencephalitis or a brain abscess. In addition, recurrent inflammation and progressive expansion of the mass may result in bony atrophy and nasal distortion. Early and complete surgical excision with repair of associated bony and dural defects is imperative. In order to prevent ascending infections, a biopsy, needle aspiration, or other preoperative manipulations should be avoided.

A thorough radiologic evaluation prior to surgery is mandatory. Ultrasound may detect some bony defects but has limited sensitivity. While CT is the most sensitive method for defining bony skull defects, false-positive studies are common in young children undergoing bone maturation. MRI is superior in demonstrating intracranial masses and other soft tissue changes and may aid in planning surgical approaches[5]. In addition, surgical exploration is often necessary to definitively exclude the presence of an intracranial connection, as small fibrous tracts may not be detectable with imaging studies.

Midline lesions of the scalp

Subcutaneous nodules of the scalp are common, and in adults they are usually acquired lesions, such as epidermoid and tricholemmal

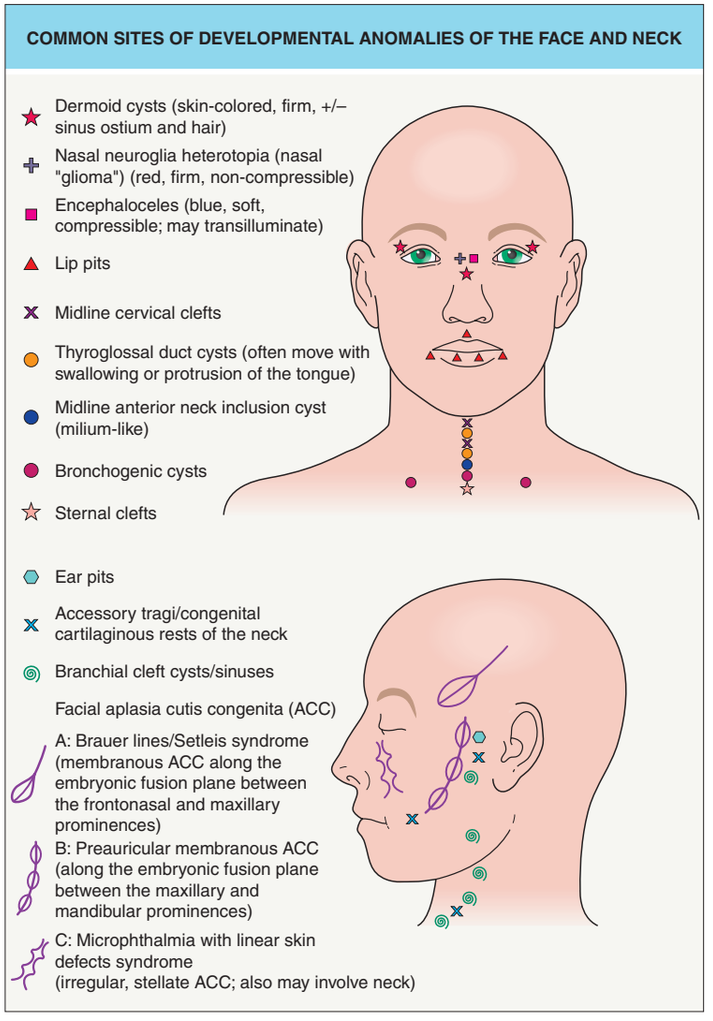


Fig. 64.2 Common sites of developmental anomalies of the face and neck.

THE DIFFERENTIAL DIAGNOSIS OF NASAL MASSES PRESENTING AT BIRTH OR DURING INFANCY
Developmental defects
• Dermoid cyst*,†
• Cephalocele (encephalocele > meningocele)*
• Nasal glial heterotopia (nasal "glioma")*
• Lymphatic malformation
• Nasolacrimal duct cyst
Other cysts
• Epidermoid cyst
• Pilomatricoma
• Ethmoid mucocele
Benign neoplasms and hamartomas
• Infantile hemangioma
• Hemangiopericytoma
• Neurofibroma
• Melanotic neuroectodermal tumor of infancy
• Hamartomas: chondromesenchymal, chondroid, lipomatous, or angiomatous
• Teratoma‡
Malignant neoplasms
• Rhabdomyosarcoma
• Fibrosarcoma
• Osteosarcoma
• Neuroblastoma
*Midline lesions.
†The most common cause of a congenital midline nasal mass.
‡May also be malignant.

Table 64.1 The differential diagnosis of nasal masses presenting at birth or during infancy.

cysts. However, midline scalp lesions that are noted at birth or in early childhood have a high likelihood of representing developmental defects, such as dermoid cysts, cephaloceles, heterotopic brain or meningeal tissue, sinus pericranii, and aplasia cutis congenita. In one series of 70 children presenting with a solitary, non-traumatic scalp nodule[6], 61% of the lesions were dermoid cysts and 4% cephaloceles. More importantly, 37% of the lesions were found to extend intracranially to the dura or brain.

In the evaluation of a patient with a subcutaneous nodule on the scalp, clinical clues that heighten suspicion of a developmental anomaly with potential intracranial extension include[7]:

- a patient who is an infant or child
- a lesion first noted at birth or during early childhood
- a family history of neural tube defects
- a history of meningitis
- the presence of neurologic signs or symptoms
- location of the lesion along the midline or over the suture lines of the scalp
- lesions that pulsate, transilluminate, or fluctuate in size with crying or straining
- lesions with a central pore in young children, who are less likely to have epidermoid cysts
- an overlying capillary malformation
- a positive hair collar sign or hair tuft (see below).

A congenital midline lesion, or a scalp nodule with other concerning features, requires imaging studies prior to surgical excision or biopsy. As noted previously, CT is superior in detecting bony defects and MRI is more sensitive in evaluating transcranial extension of soft tissue. Ultrasound is sometimes utilized as an initial study in infants, but it has a relatively high false-negative rate. A neurosurgical referral is indicated if these studies are positive and, as small communications may be missed, complete surgical removal may be prudent even if they are negative[8].

The *hair collar sign* consists of a ring of long, dark, coarse hair surrounding a congenital scalp lesion. The presence of a hair collar or a tuft of hair in the midline scalp is a relatively specific marker for ectopic neural tissue[8,9]. Hair collars are also seen in membranous aplasia cutis (Figs. 64.3 & 64.4), a disorder thought to represent a forme fruste of a neural tube defect (i.e. without the presence of ectopic neural tissue)[2]. Drolet et al.[8] hypothesized that cerebral herniation produces aberrant shearing forces during the formation of hair follicles early in development, causing them to point outward from the defect. The proximity of neuroectoderm expressing neural adhesion molecules may also alter normal epidermal–dermal interactions, thereby inducing the development of large, abnormal follicles[2]. These speculations correlate with the histologic and dermoscopic finding of numerous horizontally oriented, hypertrophic follicles emerging from the edge of scalp lesions to form the hair collar[10]. The differential diagnosis and evaluation of a positive hair collar sign is presented in Fig. 64.5.



Fig. 64.3 Hair collar sign. Membranous aplasia cutis congenita with a hair collar.



Fig. 64.4 Hair collar sign. Membranous aplasia cutis congenita with a bullous appearance and a surrounding hair collar.

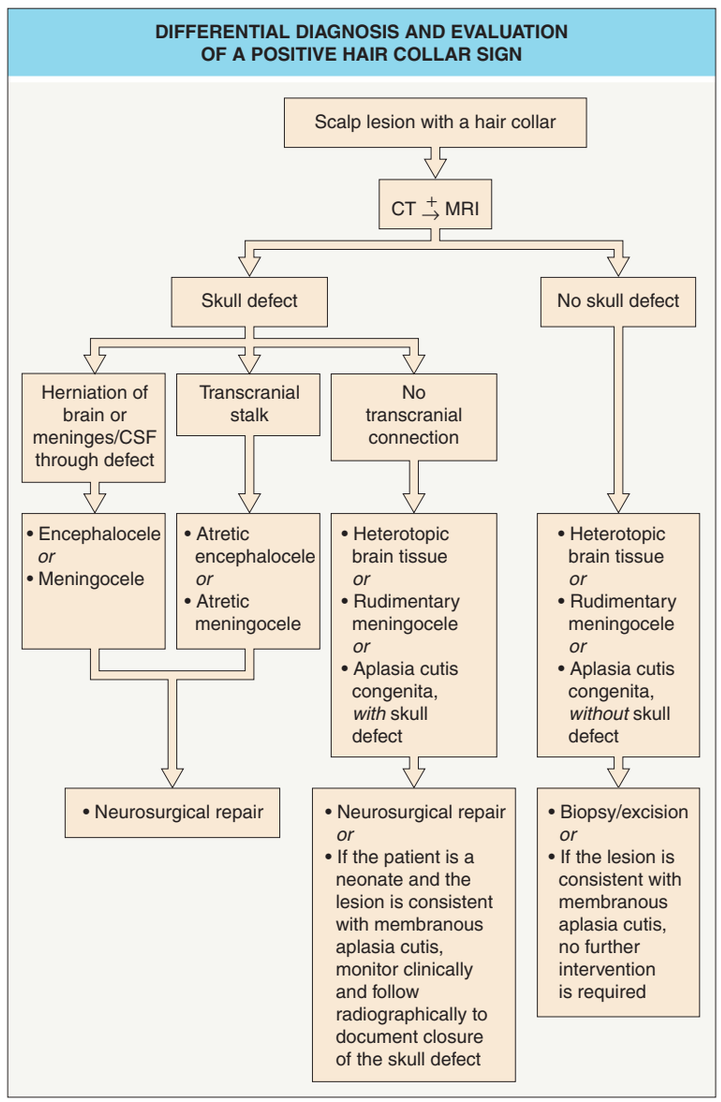


Fig. 64.5 Differential diagnosis and evaluation of a positive hair collar sign. In general, CT is the most accurate method of detecting skull defects. However, if a bony defect is detected by CT, a follow-up evaluation by MRI may be indicated to better determine whether there is extension of soft tissue transcranially.

Other developmental anomalies of the scalp

Sinus pericranii is a rare disorder characterized by a congenital, or occasionally acquired, epicranial venous malformation of the scalp that communicates with an intracranial dural sinus through dilated diploic cranial veins. The lesion is usually located near the midline, especially in the frontal region. Most are asymptomatic and appear as a compressible, fluctuant mass that varies in size with changes in intracranial pressure (Fig. 64.6). The differential diagnosis includes a simple venous or arteriovenous malformation, meningocele, and encephalocele; of note, sinus pericranii can also occur in association with heterotopic meningeal or brain tissue.

Hairless congenital scalp lesions such as a *nevus sebaceus* (see Chs. 62 & 111) and *nevus psiloliparus* (a hallmark of encephalocraniocutaneous lipomatosis; see Ch. 62) due to mosaic activating mutations may mimic developmental anomalies of the scalp.

Dermoid cysts

Dermoid cysts result from sequestration of ectodermal tissue along embryonic fusion planes during development. They are a separate entity from benign cystic teratomas, neoplasms that are also referred to as dermoids. Although dermoid cysts are congenital defects and may be recognized at birth, these lesions often escape notice until they become enlarged, inflamed, or infected. This typically occurs by early childhood, but diagnosis may be delayed until as late as the sixth decade of life. Dermoid cysts present as firm, non-compressible, non-pulsatile subcutaneous nodules that often reach a size of 1–4 cm in diameter.



Fig. 64.6 Sinus pericranii. This venous malformation involving the midline forehead and communicating with an intracranial dermal sinus was evident at birth. Fluctuations in fullness occurred with crying. *Courtesy Susan Psaila, MD.*

The lesions usually do not transilluminate. They are most commonly located around the eyes, particularly the lateral eyebrow (Fig. 64.7A), but may also be found on the nose (Fig. 64.7B), scalp (often over the anterior fontanelle or the midline occiput), neck, sternum, sacrum, and scrotum.

Dermoid cysts on the nose or midline scalp have a much higher likelihood of intracranial extension than those in a periocular location. Nasal lesions, which account for <10% of cervicofacial dermoid cysts, occur anywhere from the glabella to the tip of the nose (see above) and can result in a widened nasal bridge. The presence of a sinus ostium, which may be heralded by protruding hairs or a sebaceous discharge, increases the risk of intracranial involvement of a nasal dermoid cyst to almost 50%, versus ~25% overall[3]. A sinus ostium without an underlying subcutaneous mass may also connect with an intracranial dermoid cyst. These lesions favor the midline occipital area but can occur elsewhere on the face and scalp; recurrent drainage and inflammation may represent signs of deeper extension[11]. In addition to infectious complications, a chemical meningitis or even hydrocephalus due to release of keratinous and sebaceous material into the cerebrospinal fluid (CSF) can occur with intracranial dermoid cysts. Lastly, dermoid cysts and dermal sinuses overlying the spine may be associated with occult dysraphism (see below) and if the tract connects with the subarachnoid space, an increased risk of meningitis.

Histologically, dermoid cysts in any location are lined by keratinizing stratified squamous epithelium and contain mature adnexal structures (see Ch. 110)[12]. Treatment is by excision, and preoperative imaging studies are required for lesions located on the nose, midline scalp, or posterior axis or those with other suspicious features (e.g. a draining sinus ostium) in order to exclude a connection to the CNS.

Cephaloceles

Cephalocele is a general term for congenital herniation of intracranial structures through a defect in the skull. *Cranial meningoceles* are herniations in which the sac contains meninges and CSF, while *encephaloceles* contain both meninges and brain (Fig. 64.8). Therefore, by definition, all cephaloceles have an intracranial connection. These lesions result from faulty closure of the cephalic portion of the neural tube during development, and they are much less common than their caudal counterparts (e.g. myelomeningoceles). Cephaloceles occur in ~1–3 per 10 000 live births, with a higher incidence in those with a family history of neural tube defects and an ~5% risk of neural tube defects in subsequent siblings. They are usually midline or paramedian, occurring most frequently at the occiput or vertex (75%) (see Fig. 64.1), followed by extranasal (e.g. glabella or medial orbit; 15%) and intranasal or pharyngeal (10%) locations[4]. Encephaloceles are generally noted early in life due to the resultant deformity. Occasionally, small frontal lesions are misdiagnosed as deep infantile hemangiomas, vascular malformations, hypertelorism, or nasal polyps[3,4]; of note, the latter are almost never seen in children younger than 3 years of age.

Cephaloceles typically appear as a soft, compressible, pulsatile mass with a bluish color. They may be covered with either normal skin or a thin, glistening epithelial membrane. The size of cephaloceles varies tremendously, from 1 cm nodules to lesions containing nearly half of the brain, and the size does not necessarily correlate with the extent of the underlying bony defect. Patients with intranasal cephaloceles often present with a broadened nasal bridge but no palpable mass, whereas

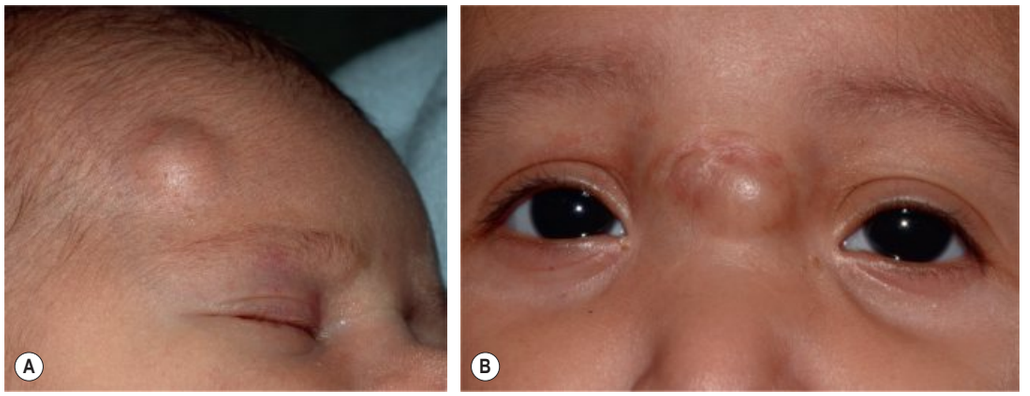


Fig. 64.7 Dermoid cysts. A This dermoid cyst presented in an infant as a firm subcutaneous nodule superior to the lateral right eyebrow. **B** Congenital firm, skin-colored nodule at the nasal root. Unlike those located in the more common lateral eyebrow location, nasal dermoid cysts have a substantial risk of intracranial extension.

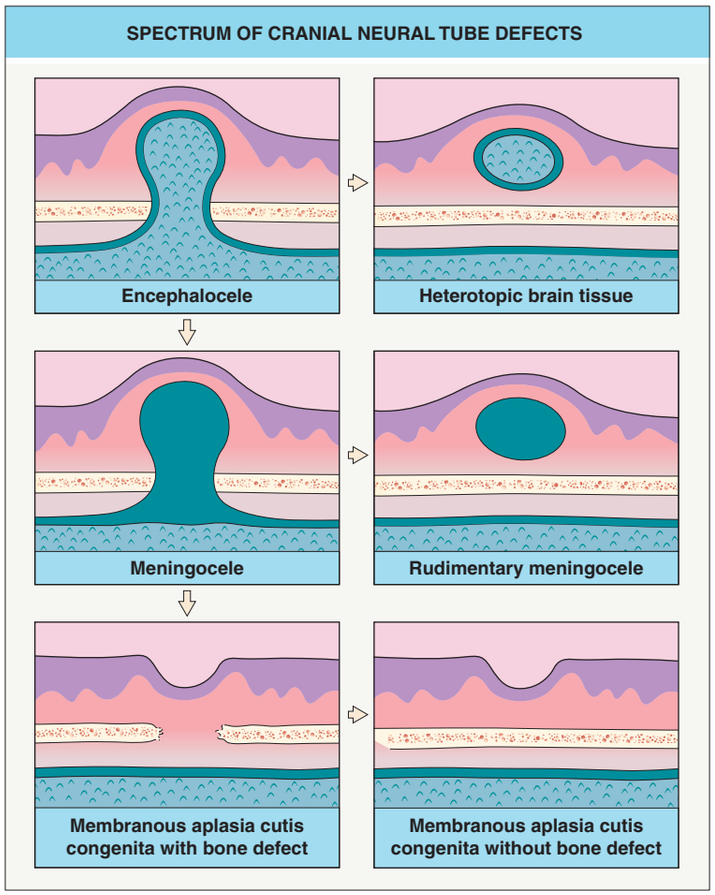


Fig. 64.8 Spectrum of cranial neural tube defects. When there is herniation of both the spinal cord and the meninges, this is referred to as a myelomeningocele.

lesions on the scalp may have an overlying capillary malformation and/or a surrounding hair collar (see above, Midline lesions of the scalp)[8]. Transillumination frequently indicates the presence of CSF; in addition, increased flow of CSF into lesions with crying, the Valsalva maneuver, or compression of the jugular veins (Furstenberg test) may result in transient expansion. Leaks of CSF can occur (e.g. CSF rhinorrhea), and patients may have a history of meningitis. Nasal cephaloceles may develop in conjunction with facial clefts and other midline defects, while encephaloceles are often associated with neurologic abnormalities.

On histologic examination, encephaloceles show mature neuroglial tissue embedded in varying amounts of fibrous stroma. Heterotopic brain tissue (see Fig. 64.8) demonstrates similar features, and these lesions cannot be reliably distinguished histologically. When a patient is suspected of having a cephalocele, imaging studies and subsequent neurosurgical repair should be performed.

Nasal glial heterotopia

Synonyms: ■ Nasal glioma ■ Nasal neuroglial heterotopia ■ Nasal heterotopic brain tissue

Nasal glial heterotopia (NGH) refers to extracranial rests of brain tissue located extranasally (e.g. at the nasal root or glabella; 60%), intranasally (30%), or both (10%)[13]. The previous term for NGH, nasal glioma, is a misnomer since this lesion represents a developmental anomaly rather than a neoplasm; it is also entirely separate from the similarly named glioma, a malignant brain tumor. NGH results when herniated brain tissue is sequestered extracranially by the bony fusion that forms the base of the skull during development (see Fig. 64.8). Although a vestigial fibrous stalk connecting with the intracranial space persists in 15%–25% of cases[13], unlike encephaloceles, there is no communication with the intracranial leptomeninges



Fig. 64.9 Nasal glial heterotopia (nasal glioma). A mass was noted on prenatal ultrasound, and this reddish, slightly pedunculated, rubbery nodule was evident at birth. *Courtesy Mary Chang, MD.*

or the CSF. NGH is present at birth, accounting for ~5% of congenital nasal midline masses[3,14], and it typically enlarges in proportion to the growth of the child.

*Extra*nasal NGH typically presents as a firm, non-compressible, non-pulsatile, non-transilluminating mass at or just lateral to the nasal root (Fig. 64.9; see Fig. 115.20). The overlying skin is often red with prominent telangiectasias, which may result in misdiagnosis as a hemangioma. *Intra*nasal NGH manifests as a widened nasal bridge or a polypoid nodule within the nasal cavity, sometimes protruding from a nostril. It occasionally causes nasal obstruction resulting in respiratory distress, and lesions involving the nasopharynx may be associated with a cleft palate[15]. Excessive lacrimation or strabismus may occur ipsilateral to the NGH[14].

Histologically, NGH demonstrates well-circumscribed nodules composed mostly of astrocytes, admixed with other glial cells and loosely textured intercellular glial substance interwoven with fibrous tissue (see Ch. 115). Neurons may or may not be present focally, and there are often prominent dilated blood vessels in the lesion and overlying skin. Immunoperoxidase staining for S100 protein and glial fibrillary acidic protein (GFAP) is positive. After imaging studies to determine whether an intracranial extension is present, NGH should be surgically excised.

Heterotopic brain tissue and rudimentary meningoceles

Synonyms: ■ Heterotopic brain tissue – neuroglial heterotopia, neuroglial choristoma ■ Rudimentary meningoceles – heterotopic meningeal tissue, sequestrated meningoceles, meningeal hamartomas, meningothelial hamartomas

Heterotopic brain tissue and rudimentary meningoceles are uncommon congenital anomalies thought to represent encephaloceles or meningoceles that have lost their intracranial attachment[8,16] (see Fig. 64.8). The bone underlying these lesions is usually intact. However, in intermediate forms known as *atretic encephaloceles* and *meningoceles*, a fibrotic stalk that extends intracranially with some degree of luminal ablation remains[8]. Heterotopic brain tissue may be located in the scalp, orbit, lip and oropharynx, as well as in the nasal area (nasal glial heterotopia; see above); rudimentary meningoceles are usually found on the scalp or overlying the spine[10,16].

Heterotopic brain tissue and rudimentary meningoceles typically present as a 1–4 cm solid or cystic subcutaneous nodule, often with a blue–red hue. Occasionally, rudimentary meningoceles have a bullous appearance and are clinically indistinguishable from membranous aplasia cutis[16]. Lesions are often located in the midline occipital or parietal scalp, where they can manifest with alopecia of the overlying skin and/or a surrounding hair collar. An overlying capillary malformation also may be present.

Histologic features of heterotopic brain tissue are as described for nasal glial heterotopia. Although classic findings such as cystic cavities lined by meningothelial cells are present in some cases of rudimentary meningocele, the histologic features are often subtle, with meningeal elements simulating the appearance of vascular or loose connective tissue. While signs such as the tendency of meningocytes to encircle collagen bundles and the presence of psammoma bodies may be helpful,



Fig. 64.10 Midline anterior neck inclusion cyst (MANIC) in an infant. *Courtesy Antonio Torrelo, MD.*

immunohistochemical staining for epithelial membrane antigen (EMA) and vimentin are critical in establishing the diagnosis[16]. Because the presence or absence of an intracranial connection cannot be reliably determined by clinical examination, imaging studies should be performed prior to surgical excision.

Midline anterior neck inclusion cyst

A midline anterior neck inclusion cyst (MANIC) presents as a congenital milia-like papule on the midline lower neck superior to the sternum. The small, superficial, yellow to white papule is not associated with underlying anomalies (Fig. 64.10). Histologically, a MANIC is lined by stratified squamous epithelium with intact keratohyalin granules, resembling an epidermoid cyst.

Midline cervical cleft

A midline cervical cleft is a rare congenital anomaly resulting from incomplete fusion of the branchial arches in the ventral midline of the neck. Approximately 200 cases have been reported worldwide, with a female-to-male ratio of 2 : 1[17]. Midline cervical clefts may be isolated or found in association with other defects, including other midline clefts (e.g. lower lip, tongue, mandible) and thyroglossal, branchial cleft, or bronchogenic cysts.

Patients present at birth with a vertically oriented, linear cleft on the midline neck at any point between the inferior edge of the mandible and the sternum. The lesion is covered with atrophic skin, which is often weeping in the neonatal period. Additional features may include a blind mucosal sinus tract inferiorly and a skin protuberance superiorly. A subcutaneous fibrous cord deep to the latter may extend upward to the chin, resulting in progressive cervical contracture and/or webbing of the neck with extension (pterygium colli medianum).

Histologically, midline cervical clefts consist of parakeratotic stratified squamous epithelium without normal adnexal structures. The subcutis often contains dense connective tissue, and fibrous cords may include bundles of skeletal muscle. Following ultrasonography to evaluate for an associated thyroglossal duct cyst (see Ch. 110), complete surgical excision and closure via Z-plasty (to reduce the risk of cicatricial contracture) should be performed during the first two years of life.

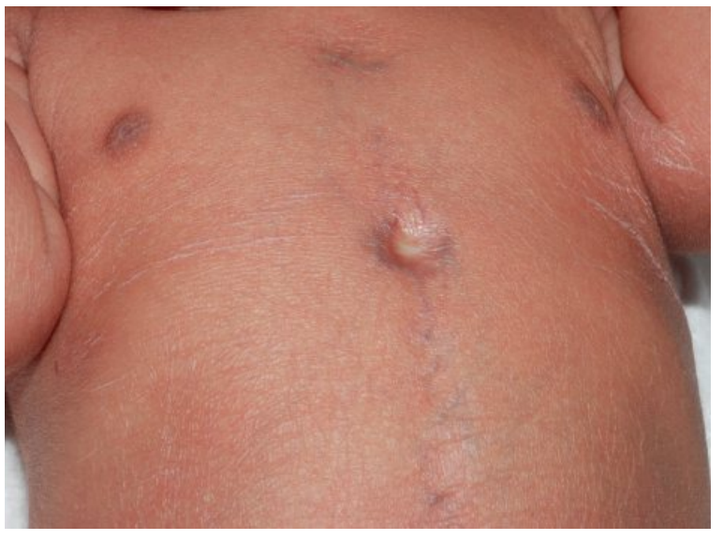


Fig. 64.11 Sternal cleft. Note the atrophic skin overlying the defect and prominent veins in the midline chest. Generalized desquamation is also evident in this 1-day-old post-term neonate. She did not develop an infantile hemangioma and had no cardiac defects or other features of PHACE syndrome.

Sternal clefts and supraumbilical raphae

Sternal clefts are rare congenital malformations that result from defective embryologic fusion of paired mesodermal bands in the ventral midline. These lesions most frequently involve the superior sternum, but inferior clefts and a complete bifid sternum can also occur. The skin overlying sternal clefts may be atrophic (Fig. 64.11), scarred, or ulcerated, and a dermal sinus tract is occasionally present. Approximately 40% of sternal clefts are associated with PHACE syndrome (*p*osterior fossa malformations; *h*emangiomas; *a*rterial, *c*ardiac and *e*ye anomalies; see Ch. 103)[18]. The sternal abnormality in PHACE syndrome may be limited to cutaneous atrophy or a pit in the presternal area, with intact underlying bone[19]. For sternal clefts associated with a substantial bony defect, surgical repair can be performed to protect the mediastinal organs and improve respiration as well as cosmesis. A supraumbilical raphe is a rare midline abdominal defect that presents as a firm, scar-like, linear protuberance extending cephalad from the umbilicus. Supraumbilical raphae often occur in association with sternal clefts, sometimes simultaneously as manifestations of PHACE syndrome.

Midline Lesions of the Spine

Spinal dysraphism refers to abnormal fusion of dorsal midline structures during embryologic development[20]. This term encompasses a wide variety of congenital spinal defects, ranging from myelomeningoceles (protrusion of the spinal cord and meninges with no overlying skin) and other overt anomalies in which neural tissue is exposed (*open spinal dysraphism*) to less obvious, skin-covered malformations (*closed* or *"occult" spinal dysraphism*). The latter include diastematomyelia (a split in the spinal cord), meningoceles, intraspinal lipomas, lipomyelomeningoceles (protrusion of the cord extraspinally into an attached lipoma), tight or fatty filum terminale, dermoid cysts, dermal sinuses, and isolated posterior spina bifida[21].

The degree of neurologic impairment associated with closed spinal dysraphism is variable. Any lesion that produces traction and/or pressure can cause progressive damage to the spinal cord, resulting in neurologic symptoms. Whereas isolated posterior spina bifida, an incidental radiographic finding in 15%–25% of the general population, is not clinically significant, other forms of dysraphism may become symptomatic during childhood or adolescence. Some patients, however, do not present until adulthood. When diagnosis is delayed, many of the aforementioned malformations can result in the tethered cord syndrome, which occurs when the conus medullaris (normally at the adult position of L1–L2 by 3 months of age) is low-lying and/or immobile. This syndrome is characterized clinically by back pain, urinary incontinence, motor and sensory deficits of the lower extremities, and orthopedic deformities (Fig. 64.12). Occasionally, an acute onset of symptoms is precipitated

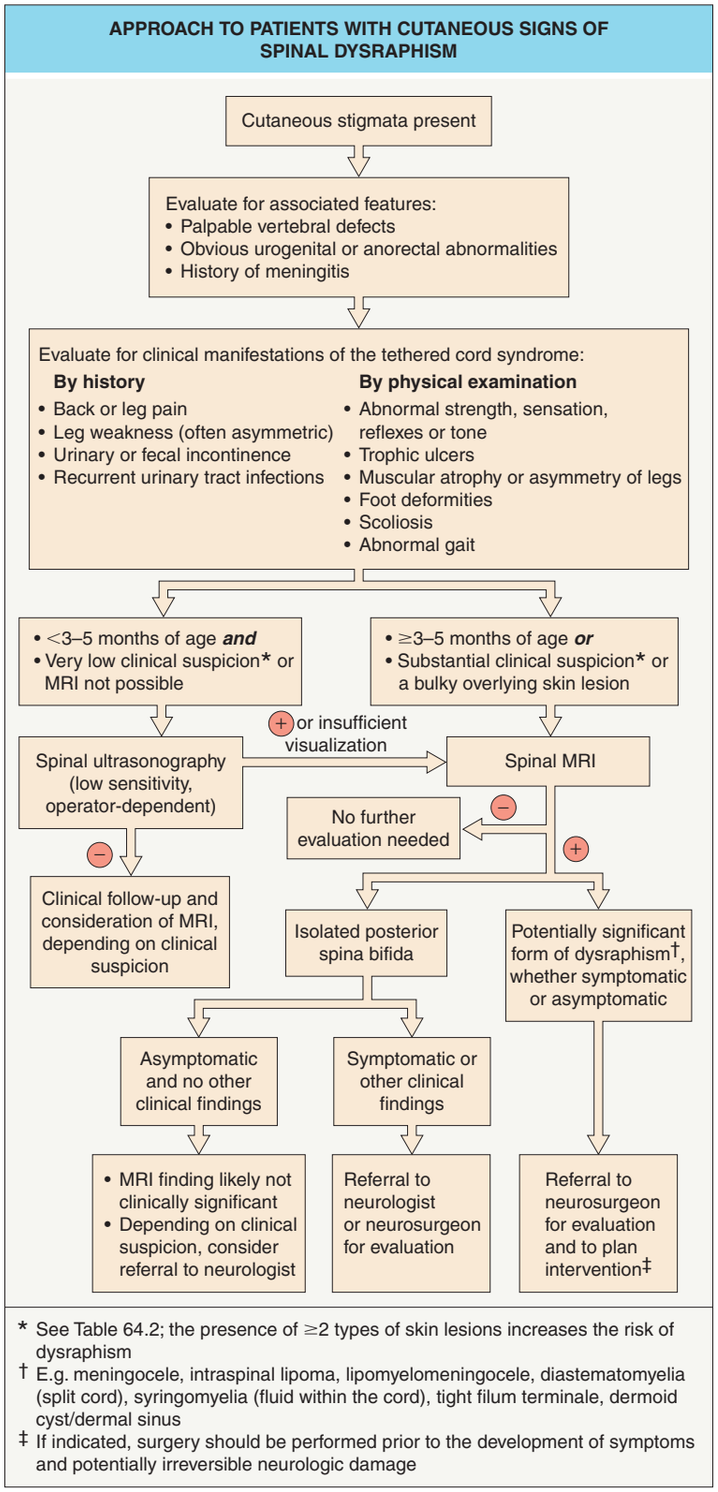


Fig. 64.12 Approach to patients with cutaneous signs of spinal dysraphism.



Fig. 64.13 Midline deep sacral dimple. The dimple was located above the gluteal cleft in association with a small tail. In contrast, a shallow dimple within the gluteal cleft is a common finding and not a sign of spinal dysraphism. *Courtesy Seth J. Orlow, MD, PhD.*

by childbirth, heavy lifting, or spinal trauma. Early diagnosis allows timely neurosurgical intervention that can halt progression and prevent potentially irreversible neurologic damage.

Because the skin and the nervous system share an ectodermal origin, concurrent anomalies of these tissues are common. Midline cutaneous lesions thus serve as a valuable marker for spinal dysraphism, and in the majority of patients, they are the finding that leads to the diagnosis. Approximately 80% of individuals with closed spinal dysraphism have paraspinal skin abnormalities, and the majority of them have more than one type of skin lesion[22,23]. In contrast, <3% of all neonates have cutaneous findings overlying the spine[24]. Shallow coccygeal dimples and deep gluteal clefts occur in an additional 4% of infants; however, in contrast to dimples located superior to the gluteal cleft (Fig. 64.13), these are considered as normal variants rather than a sign of an underlying malformation[24–26]. Most of the cutaneous lesions associated with spinal dysraphism are located in the lumbosacral area, reflecting the relative rarity of neural tube defects in the cervicothoracic region[27].

Hypertrichosis is the cutaneous marker of spinal dysraphism most often evident at birth. Affected individuals may be born with a V-shaped lumbosacral patch of long, coarse or silky hair on the dorsal midline (Fig. 64.14) known as a "faun tail"[28]. Overall, however, lumbosacral lipomas are the skin lesions most commonly associated with spinal dysraphism[22,23]. An intraspinal lipoma or lipomyelomeningocele often represents a portion of a larger subcutaneous lipoma, typically presenting as a soft mass located above the gluteal cleft and extending asymmetrically into one buttock. A curved gluteal cleft is suggestive of such a lesion, but clinical findings may be subtle initially, becoming more noticeable with time.

Infantile hemangiomas and vascular malformations located on or near the dorsal midline may also be signs of dysraphism. In addition to usually spanning the midline in the lumbosacral area, infantile hemangiomas associated with spinal dysraphism tend to have a segmental pattern and a superficial component, sometimes with minimal growth beyond reticular erythema and telangiectasias (Fig. 64.15; see Ch. 103)[29–31]. A patient with an isolated midline lumbosacral hemangioma >2.5 cm in diameter has an ~35% risk of having spinal dysraphism, which is higher if the hemangioma is larger, ulcerated, or associated with additional cutaneous markers[31]. Several acronyms have been proposed for the constellation of regional extracutaneous anomalies that can occur in individuals with segmental hemangiomas of the lower body; the most inclusive is ***LUMBAR*** *syndrome*: ***L***, *l*ower body/*l*umbosacral hemangioma and *l*ipomas or other cutaneous anomalies (e.g. "skin tags"); ***U***, *u*rogenital anomalies and *u*lceration; ***M***, *m*yelopathy (spinal dysraphism); ***B***, *b*ony deformities; ***A***, *a*norectal and *a*rterial anomalies; ***R***, *r*enal anomalies. Of note, a telangiectatic patch overlying a spinal defect may actually represent an infantile hemangioma with minimal or arrested growth.

Vascular malformations are most often an indicator of dysraphism when they occur together with other midline cutaneous lesions, most notably lipomas. In Cobb syndrome, a spinal arteriovenous malformation is associated with cutaneous involvement in the same segment; such findings may occur as a manifestation of the capillary malformation–arteriovenous malformation syndrome due to *RASA1* or *EPHB4* mutations. The cutaneous component may mimic a capillary malformation or angiokeratoma, and neurologic manifestations of cord compression can develop (see Ch. 104).

The common occipital nevus simplex ("stork bite") is *not* a marker for a spinal defect. In the lumbosacral region, nevus simplex lesions typically have rhomboidal or triangular shapes ("butterfly-like") or appear as grouped pink–red macules (Fig. 64.16), and they are frequently accompanied by nevus simplex lesions of the head, neck,

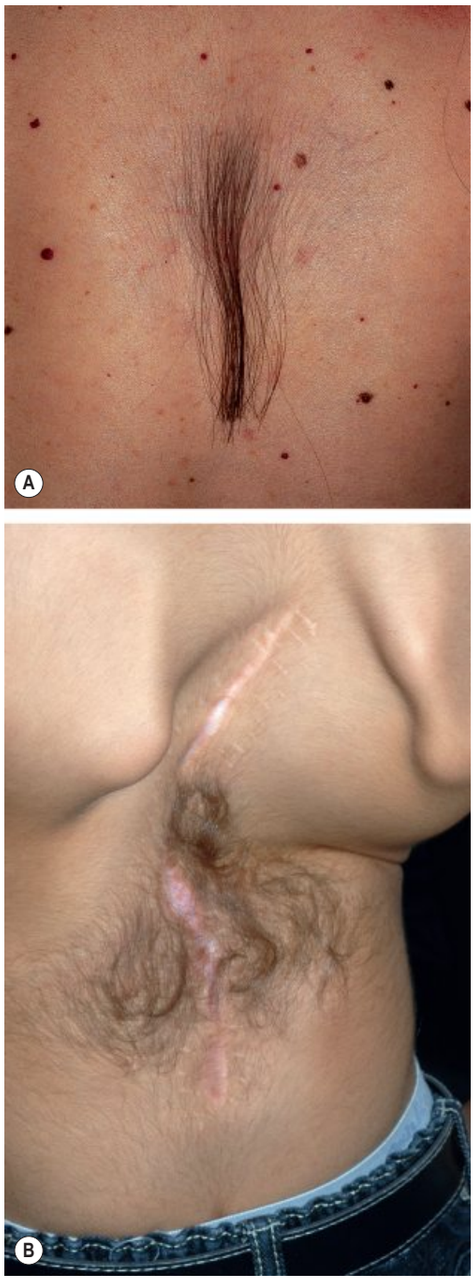


Fig. 64.14 Hypertrichosis associated with spinal dysraphism. **A** Circumscribed midline hypertrichosis overlying the lower thoracic spine in an adult with occult dysraphism. The patient periodically trims the hairs. **B** V-shaped patch of long, coarse hair on the mid back in a boy born with a large thoracic myelomeningocele. Severe scoliosis remains after multiple surgeries. *A, Courtesy Jean L. Bolognia, MD.*



Fig. 64.15 Multiple midline cutaneous stigmata overlying the sacral spine in LUMBAR syndrome. This infant with a segmental infantile hemangioma in the lumbosacral area, a large atypical dimple, a pseudotail, and a deviated gluteal cleft associated with a subcutaneous lipoma had an underlying lipomyelomeningocele.



Fig. 64.16 Nevus simplex of the lumbosacral region. Note the characteristic "butterfly-like" shape. The likelihood of spinal dysraphism is extremely low if there are no other local cutaneous findings (e.g. deviated gluteal cleft/lipoma, focal hypertrichosis, dermal sinus/pit), especially if there are additional nevus simplex lesions elsewhere.

and (occasionally) upper back. The current consensus is that regardless of spinal level, a nevus simplex without other local skin changes is rarely a sign of dysraphism, especially when there are nevus simplex lesions elsewhere[25,27]. While additional case series of lumbosacral nevus simplex have supported this expert opinion, i.e. they have not found an association with spinal dysraphism[32], a prospective study of 3623 neonates found that 1 of the 25 individuals with nevus simplex had diastematomyelia revealed by ultrasonography[33]. These neonates had no additional local skin findings, and it was not noted whether the individual with diastematomyelia had extrasacral vascular lesions.

Cutaneous lesions of the spinal axis that should alert the clinician to the possibility of dysraphism are summarized in Table 64.2. In one study[26], 39% (22/56) of neonates with "high-risk" stigmata such as hypertrichosis, subcutaneous masses, infantile hemangiomas, tails, or dimples above the gluteal cleft were found to have spinal dysraphism (see Figs. 64.14 & 64.15). The presence of *two or more skin lesions* is a particularly strong sign; in another series, 61% (11/18) of such patients had spinal dysraphism, compared to 8% (3/36) of those with only one skin lesion[34].

High-risk cutaneous stigmata overlying the spine represent an indication for radiologic evaluation, and superficial removal for cosmetic reasons is contraindicated until an underlying abnormality is excluded. MRI is highly sensitive and represents the imaging modality of choice in patients of all ages when occult spinal dysraphism is suspected. Although the vertebrae are not yet completely ossified in infants <5 months of age, ultrasonographic evaluation of the spinal cord is still less sensitive than MRI in this age group. In series comparing ultrasound to the gold standard of MRI in infants with cutaneous stigmata, ultrasound was ~75% sensitive for a low-lying conus but only 20%–40% sensitive for other findings such as a dermal sinus or abnormal filum terminale (e.g. thickened or fatty)[35]. Similarly, in a second series, ultrasound was 50% sensitive and 78% specific for detecting spinal anomalies (tethered cord, spinal lipoma > intraspinal hemangioma) in infants with lumbosacral infantile hemangiomas[31]. In infants with dysraphism associated with an anorectal malformation, spinal ultrasound had a sensitivity as low as 15%[36]. When infants are found to have anomalies with the potential to cause traction and/or pressure on the spinal cord, close follow-up is required and neurosurgical intervention may be recommended. Fig. 64.12 provides an algorithm for the approach to patients with cutaneous signs of spinal dysraphism.

SKIN LESIONS OF THE SPINAL AXIS ASSOCIATED WITH DYSRAPHISM	
Lesion	**Features**
Lipomas	Soft subcutaneous mass, asymmetric buttocks, curved gluteal cleft (Fig. 64.15)
Hypertrichosis	A V-shaped patch of long, coarse or silky hair ("faun tail") (Fig. 64.14)
Dimples	Above the gluteal cleft or >2.5 cm from the anal verge in neonates (Figs. 64.13 & 64.15); >0.5 cm in size or depth*
Dermal sinuses	Hair may be present at the ostium*
Acrochordons	May be associated with a dimple or dermal sinus
Pseudotails	Caudal protrusion due to prolonged vertebrae or hamartomatous elements, e.g. adipose tissue or cartilage (Fig. 64.15)
True tails	Persistent vestigial appendage with a central core of mature adipose tissue, muscle, blood vessels, and nerves
	May be capable of spontaneous or reflex motion
Infantile hemangiomas	Superficial, usually segmental pattern (Fig. 64.15), may be ulcerated
Telangiectasias	May represent an early, minimal/arrested growth, or regressed infantile hemangioma
Vascular malformations	Capillary malformations (CMs) are typically found together with other skin lesions
	Cobb syndrome: spinal arteriovenous malformation associated with skin involvement in the same segment mimicking a CM or angiokeratomas
Aplasia cutis congenita (ACC)	Ulcer, scar, or atrophic skin
Connective tissue nevus	Typically found together with other skin lesions
Hypo/depigmentation	May represent a nevus depigmentosus (typically found together with other skin lesions) or the residua of ACC
Hyperpigmentation	Typically found together with other skin lesions
Congenital melanocytic nevi	Spinal dysraphism has been reported in patients with neurocutaneous melanosis
Accessory breast tissue	Overlying nipple(s)
Subcutaneous masses†	May represent lipomas, meningoceles, lipomyelomeningoceles, teratomas, ependymomas, plexiform neurofibromas

*Due to a potential risk of meningitis, these lesions should not be probed.
†May result in a deviated gluteal cleft.

Table 64.2 Skin lesions of the spinal axis associated with dysraphism. The presence of two or more types of lesions increases the risk of a spinal anomaly.

APLASIA CUTIS CONGENITA

Synonyms: ■ Cutis aplasia ■ Congenital absence of skin ■ Congenital scars

Aplasia cutis congenita (ACC) is a condition in which localized or widespread areas of skin are absent or scarred at birth. It may occur as an isolated defect, in association with other developmental anomalies, or as a feature of a variety of disorders (Tables 64.3 & 64.4). There is no single underlying cause of ACC, which simply represents a physical finding that reflects an abnormality in intrauterine skin development. The many possible etiologies include genetic factors, vascular compromise, trauma, teratogens, and intrauterine infections[37,38].

As a result of its causal heterogeneity, the clinical appearance of ACC at birth is extremely variable, ranging from an erosion or deep ulceration to a scar due to healing *in utero* to a discrete ovoid defect covered by a membrane. The latter, referred to as *membranous aplasia cutis*, is the most common form. Occurring primarily on the scalp and often surrounded by a hair collar (see Figs. 64.3 & 64.4), such lesions may represent a forme fruste of a neural tube defect[2]. However, membranous aplasia cutis can also be seen along the embryonic fusion lines of the face (Table 64.4; Figs. 64.2 & 64.17)[39]. Membranous aplasia cutis typically presents at birth as a sharply marginated ("punched-out"), oval or round defect covered by a thin, translucent, glistening epithelial membrane. Lesions may contain serous fluid in the neonatal period, resulting in a bullous appearance (see Fig. 64.4). Eventually, they tend to flatten and transform into an atrophic scar (Fig. 64.18A). Dermoscopy typically shows a lack of follicular openings, telangiectatic vessels, and radially oriented hair follicles extending horizontally at the periphery ("starburst-like")[40]. Hypertrophic scarring can be a manifestation of an autosomal dominant form of scalp ACC in which mutations in the ribosomal GTPase BMS1 result in a cell cycle defect[41].

A second major type of ACC consists of stellate or angulated lesions, which are thought to result from vascular abnormalities and/or intrauterine ischemic events. Examples include irregular midline scalp defects in Adams–Oliver syndrome[42,43] and extensive, symmetric lesions on the trunk and/or extremities associated with fetus papyraceus, placental infarction, or other forms of vascular insufficiency (Fig. 64.19)[44]. These defects usually appear as ulcers of variable depth with a raw, hemorrhagic, or granulating base (Fig. 64.18B,C).

Other patterns of ACC include a lack of skin overlying embryologic malformations, either obvious or occult, and large erosions with jagged borders on the extremities of neonates with epidermolysis bullosa[45]. The latter likely result from the mechanical trauma of fetal movements in a setting of increased skin fragility. The morphology and distribution of the skin defects (see Fig. 64.19) as well as the presence or absence of associated abnormalities represent important clues to the etiology of ACC. Table 64.3 presents a classification scheme for ACC, and Table 64.4 describes several syndromes associated with ACC. However, because ACC is a physical finding that may result from *any* intrauterine event that disrupts skin development, not all cases can be neatly categorized. Unusual presentations of ACC range from an isolated defect on the ventral penis to an extreme form with absence of skin and subcutaneous tissue over >90% of the body surface area associated with extracutaneous anomalies ("systemic" ACC; see Table 64.3).

The scalp is the most common site for ACC, accounting for >85% of solitary lesions. The majority of cases of scalp ACC, whether membranous or irregular and scar-like, are located at or near the vertex, in proximity to the parietal hair whorl[46]. Approximately 25% of patients have more than one lesion, and multiple membranous lesions may occur in a linear arrangement. Most defects are 1–2 cm in diameter, although the size can range from 0.5 to >10 cm. A capillary malformation (see above, Midline lesions of the scalp) is sometimes present in the skin surrounding membranous ACC, and dilated scalp veins may also be evident, especially in patients with Adams–Oliver syndrome (see Table 64.3)[42]. Scalp ACC involves the underlying skull in 10%–30% of cases, with increased risk when the lesion has a midline vertex location, hair collar, size >5 cm, and associated capillary stain[47,48]. Large, irregular lesions are more likely to extend to deeper structures and may affect the dura and/or leptomeninges.

Histologic features of membranous aplasia cutis include an atrophic flattened epidermis, replacement of the dermis by loose connective tissue, and an absence of adnexal structures. Findings in other types of ACC vary but lesions that have healed generally show scarring, a lack of adnexa, and in some cases fragmented elastic tissue[49]. Although histologic examination may occasionally be helpful, the diagnosis of ACC is primarily clinical.

Cutaneous defects noted at birth may initially be erroneously attributed to obstetric trauma, such as injuries from forceps or fetal scalp electrodes. Evaluation of a patient with ACC is directed by the personal, obstetric, and family history as well as the physical examination; in a neonate, it may include specific investigations such as examination of the placenta and viral studies for herpes simplex and varicella zoster[50]. In patients with large, deep, irregular or membranous lesions of the scalp (Fig. 64.18B,E), especially when there is a hair collar and/or midline vertex location, imaging studies are indicated to assess for underlying bone defects, vascular anomalies, or brain malformations. Lastly, elevated α-fetoprotein in midtrimester maternal serum and amniotic fluid as well as elevated acetylcholinesterase in the amniotic fluid may represent early signs of ACC, although they are neither sensitive nor specific for this condition.

CLASSIFICATION SCHEME FOR APLASIA CUTIS CONGENITA (ACC)			
	Inheritance (Gene)	**Features**	**Associated abnormalities**
Group 1: Scalp ACC without multiple anomalies	Sporadic > AD	Usually at the vertex Membranous Hair collar	**No associated abnormalities** **Isolated abnormalities** (most often associated with membranous ACC): cleft lip and/or palate, tracheoesophageal fistula, high myopia and cone-rod dysfunction, patent ductus arteriosus, intestinal lymphangiectasia, omphalocele, polycystic kidneys, double cervix and uterus, intellectual disability, temporal triangular alopecia
	Often AD (*BMS1*)	Usually at the vertex Irregular and scar-like	
Group 2: Scalp ACC associated with Adams–Oliver syndrome	AD (*ARHGAP31*, *RBPJ*, *NOTCH1, DLL4*) AR (*DOCK6*, *EOGT*)	Midline scalp Often large, irregular lesions Skull defect Dilated scalp veins	**Adams–Oliver syndrome**: terminal transverse limb defects (e.g. reductions, syndactyly, nail dystrophy), cutis marmorata telangiectatica congenita, cardiac malformations, CNS abnormalities
Group 3: Scalp ACC associated with epidermal and sebaceous nevi (and, occasionally, congenital melanocytic nevi)	Sporadic due to mosaic RASopathy (e.g. *HRAS*, *KRAS*)	Scalp, often unilateral Membranous	**Epidermal nevus or nevus sebaceus**, usually in proximity to the ACC **Large congenital melanocytic nevus**: in a few reports* **Ipsilateral ophthalmologic abnormalities**: corneal opacities, scleral dermoids, eyelid colobomas, retinal dystrophy **CNS abnormalities**: intellectual disability, seizures
Group 4: ACC overlying embryologic malformations	Variable	Scalp, often with a hair collar if overlying a neural tube defect Lumbosacral Chest, abdomen	**Cranial malformations**: cephalocele, heterotopic brain or meningeal tissue, congenital midline porencephaly, holoprosencephaly, craniosynostosis, vascular malformation/aplasia/arteriovenous fistula **Spinal malformations**: occult dysraphism, myelomeningocele **Thoracic malformations**: sternal cleft **Abdominal malformations**: omphalocele, gastroschisis **Multiple malformations associated with generalized, lethal ACC ("systemic" ACC)**: corneal opacities, choanal atresia, hypoplastic lungs, absent greater omentum, intestinal malrotation & atresias, hepatosplenomegaly, skull defects, syndactyly, anonychia
Group 5: ACC associated with fetus papyraceus, placental infarcts, or other ischemic events	Sporadic	Scalp, chest, flanks, axillae and/or extremities (see Fig. 64.19) Multiple, symmetric Stellate/angulated configuration	**Associated fetus papyraceus** due to second-trimester death of twin/triplet or fetal reduction of higher-order pregnancies **Placental infarction**, single umbilical artery **Duodenal, ileal, and/or biliary atresias with intestinal infarction** Intracranial hemorrhage/CNS abnormalities
Group 6: ACC associated with epidermolysis bullosa (EB)	AD or AR, depending on EB type	Lower extremities ("Bart syndrome") or large areas of the extremities, trunk, and scalp	**EB simplex (EBS; especially *KLHL24*-related), junctional EB (JEB), and dystrophic EB**: blistering of skin and/or mucous membranes, skin fragility, nail dystrophy **If more widespread (most often in JEB or EBS with pyloric atresia)**: ureteral stenosis, renal abnormalities, arthrogryposis, abnormal ears and nose; may have intrauterine/neonatal death (*ITGB4*, *PLEC*)
Group 7: Localized ACC, presumably due to prenatal physical insult	Sporadic	Extremities, e.g. forearm, pretibial area	**Volkmann contracture** or **radial dysplasia** (with ACC on the forearm) **Amniotic band sequence** (see text)
Group 8: ACC caused by specific teratogens, maternal conditions, or intrauterine infections	Sporadic	Scalp with drugs Any site with congenital infections	**Methimazole (thiamazole), carbimazole**: imperforate anus, urachal malformations **Misoprostol** **Low-molecular-weight heparin** **Valproic acid** **Maternal antiphospholipid syndrome** **Intrauterine varicella, herpes simplex or rubella infection**: signs of these infections
Group 9: ACC associated with malformation syndromes	Variable	Variable	See Table 64.4

*Referred to as "SCALP" syndrome (*s*ebaceous nevus, *C*NS malformations, *A*CC, *l*imbal dermoid, *p*igmented nevus).

Table 64.3 Classification scheme for aplasia cutis congenita (ACC). Bold text in column 4 signifies main topics, followed by details. AD, autosomal dominant; AR, autosomal recessive; *ARHGAP31*, Rho GTPase activating protein 31; *BMS1*, ribosome biogenesis factor; CNS, central nervous system; *DLL4*, Delta-like 4; DOCK6, dedicator of cytokinesis 6; *EOGT*, EGF domain-specific O-linked N-acetylglucosamine transferase; *KLHL24*, Kelch-like member 24; *RBPJ*, recombination signal binding protein for immunoglobulin κ J region (transcriptional regulator for the Notch pathway). *Adapted from Frieden IJ. J Am Acad Dermatol. 1986;14:646–60, with permission.*

Most small lesions of ACC heal within the first few months of life, leaving an atrophic (see Fig. 64.18A) or, less often, hypertrophic ("lumpy") scar. In such instances, daily cleansing and application of petrolatum or a topical antibiotic ointment until healing is complete are often the only interventions required. Underlying skull defects also tend to resolve spontaneously during infancy. However, potential complications of deep ACC of the scalp include life-threatening sagittal sinus hemorrhage/thrombosis and meningitis. Because the risk of complications increases if the period of healing is prolonged, early surgical repair of large stellate scalp lesions or those associated with a dural defect or exposure of the sagittal sinus is recommended. Preoperative imaging studies are required to identify underlying vascular structures. Even without surgical intervention, residual scarred, hairless areas generally become less conspicuous as the child grows. If desired for cosmetic reasons, excision or hair transplants can be performed later in life.

SYNDROMES ASSOCIATED WITH APLASIA CUTIS CONGENITA (ACC, GROUP 9)			
	Inheritance (Gene)	**Features of ACC**	**Other features**
Facial ACC (see Fig. 64.2)			
Focal facial dermal dysplasia (FFDD) FFDD1 – Brauer FFDD2 – Brauer–Setleis FFDD3 – Setleis FFDD4 – preauricular	**FFDD1 & 2:** AD, variable expressivity **FFDD3:** AR (*TWIST2*) **FFDD4:** AR (*CYP26C1*) > AD	Round or oval, membranous, ± hair collar Linear arrangement **FFDD1–3:** bilateral temples ("forcep marks"), from lateral eyebrow to anterior hairline* **FFD4:** bilateral from preauricular cheek to angle of mouth†	**FFDD1**: sparse lateral eyebrows, distichiasis, flat nasal tip **FFDD2 & 3**: abnormal eyelashes, upward-slanting eyebrows, "leonine" facies (Fig. 64.17), imperforate anus **FFDD4**: buccal mucosal polyps
Linear skin defects with multiple congenital anomalies (LSDMCA) 1–3 LSDMCA1 – microphthalmia with linear skin defects (MIDAS)	X-linked dominant LSDMACA1: *HCCS* LSDMACA2: *COX7B* LSDMACA3: *NDUFB11*	Mid-cheek to bridge of nose, neck Stellate erosions that heal with reticulolinear scarring	Microphthalmia, sclerocornea, agenesis of the corpus callosum, genital anomalies, short stature
Scalp ACC			
Adams–Oliver syndrome (see Table 64.3, ACC group 2)			
Oculocerebrocutaneous (Delleman–Oorthuys) syndrome	Sporadic	Membranous on supra-auricular scalp (often crescentic shape) Also may occur on neck and lumbosacral area	Orbital cysts, microphthalmia, giant tectum-absent vermis, agenesis of the corpus callosum, facial appendages composed of skeletal muscle
Oculoectodermal syndrome	Mosaic (*KRAS*)	Membranous	Epibulbar dermoids, macrocephaly, truncal hyperpigmentation
UBA2-related phenotypic spectrum	AD (*UBA2*)	At/around vertex, may be multifocal	Ectrodactyly/other digital anomalies, hip dysplasia, peg-like teeth, thin hair, supernumerary nipples, hypertelorism, high forehead, developmental delay; ocular, cardiac, genital, and renal anomalies
Johanson–Blizzard syndrome	AR (*UBRI*)	Stellate or membranous	Dwarfism, hypoplastic nasal alae, hypodontia/peg-like teeth, deafness, microcephaly, hypothyroidism, pancreatic insufficiency
Scalp–ear–nipple syndrome (Finlay–Marks syndrome)	AD (*KCTD1*)	May heal with hypertrophic scarring	Nipple/breast hypo- or aplasia, abnormal ears and teeth, nail dystrophy, syndactyly, reduced apocrine secretion
Trisomy 13 (Patau syndrome)	Sporadic	Membranous Large defects	Holoprosencephaly, ocular abnormalities, deafness, cleft lip/palate, cardiac malformations, polydactyly, narrow and convex nails; early death
4p- (Wolf–Hirschhorn) syndrome	Sporadic	Midline	Microcephaly, ocular abnormalities, cleft lip/palate, preauricular pits, and accessory tragi; often early death

*Along the embryonic fusion line between the frontonasal prominence and the maxillary prominence of the first branchial arch.
†Along the embryonic fusion line between the maxillary and mandibular prominences of the first branchial arch.

Table 64.4 Syndromes associated with aplasia cutis congenita (ACC, group 9). ACC also may be found in patients with branchio-oculo-facial syndrome (see text), Goltz syndrome (focal dermal hypoplasia), encephalocraniocutaneous lipomatosis, and several types of ectodermal dysplasia, including the EEC syndrome (*e*ctrodactyly, *e*ctodermal dysplasia, *c*lefting), AEC syndrome (*a*nkyloblepharon, *e*ctodermal dysplasia, cleft lip/palate), cleft lip/palate–ectodermal dysplasia, and tricho-odonto-onychial dysplasia. In addition, there have been reports of scalp ACC in patients with Pallister–Killian syndrome (tetrasomy 12p), Opitz syndrome, popliteal pterygium syndrome, EVEN-plus syndrome, Xia–Gibbs syndrome, Marshall syndrome, and hereditary sensory and motor neuropathy type 1 (www.ncbi.nlm.nih.gov/omim). AD, autosomal dominant; AR, autosomal recessive; *COX7B*, cytochrome c oxidase, subunit 7B; *CYP26C1*, cytochrome P450 family 26 C, polypeptide 1; *HCCS*, holocytochrome c synthase; *KCTD1*, potassium channel tetramerization domain-containing 1; MIDAS, microphthalmia, dermal aplasia and sclerocornea; *NDUFB11*, NADH:ubiquinone oxidoreductase subunit B11; *UBA2*, ubiquitin like modifier activating enzyme 2; *UBR1*, ubiquitin-protein E3 component n-recognin 1.



Fig. 64.17 Facial aplasia cutis congenita. Atrophic cutaneous defect extending from the lateral eyebrow to the anterior hairline in a patient with Setleis syndrome. Note the upward-slanting eyebrows and "leonine" facial appearance. *Courtesy Seth J. Orlow, MD, PhD.*

OTHER DEVELOPMENTAL ANOMALIES

Congenital Lip Pits

Synonyms: ■ Lip sinuses ■ Congenital sinuses of the lower lip ■ Midline sinuses of the upper lip

Congenital lip pits are divided into three types based on their location: (1) commissural; (2) upper lip; and (3) lower lip. Commissural lip pits are by far the most common, occurring in 1%–2% of newborns. Lip pits likely result from defective embryologic fusion of facial processes with epithelial entrapment. They usually represent the opening of a blind sinus tract, which can extend inward through the orbicularis oris muscle to a depth of >10 mm. This tract occasionally communicates with the ducts of underlying minor salivary glands, and saliva or mucus may drain from the ostium. Lesions are sometimes associated with swelling of the lip or, particularly if located on the philtrum, recurrent infection.

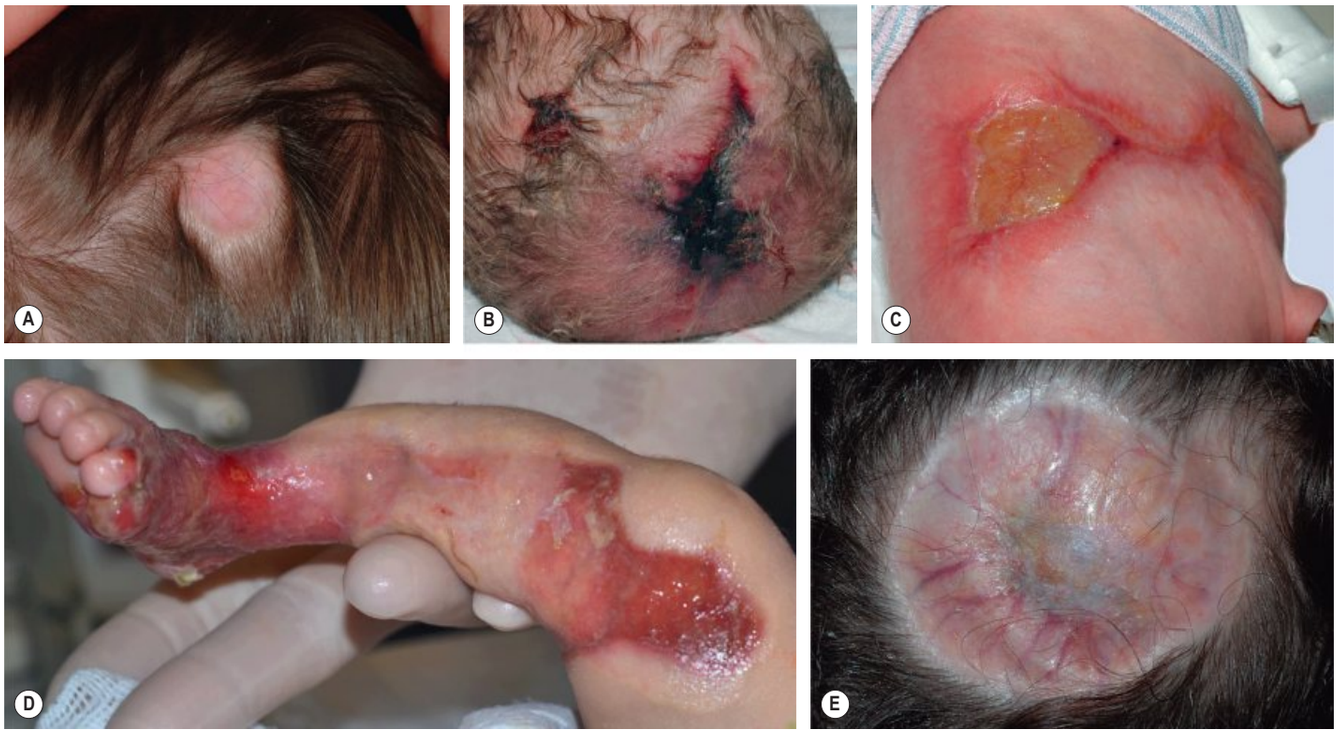


Fig. 64.18 Aplasia cutis congenita (ACC). A This hairless, round, scarred plaque on the scalp of a 6-month-old was present at birth. **B** Stellate ACC on the midline scalp of a neonate. This hemorrhagic lesion was associated with an underlying skull defect and cerebrovascular anomalies. **C** Stellate ACC on the lateral trunk of a neonate born of an initial sextuplet gestation for which fetal reduction was performed. The lesions had a bilateral, symmetric distribution. **D** ACC on the leg in a neonate with epidermolysis bullosa ("Bart syndrome"). **E** Membranous ACC associated with a large defect of the underlying skull in a patient with Goltz syndrome.
A, Courtesy Anthony J. Mancini, MD; D, Courtesy Emily Berger, MD.

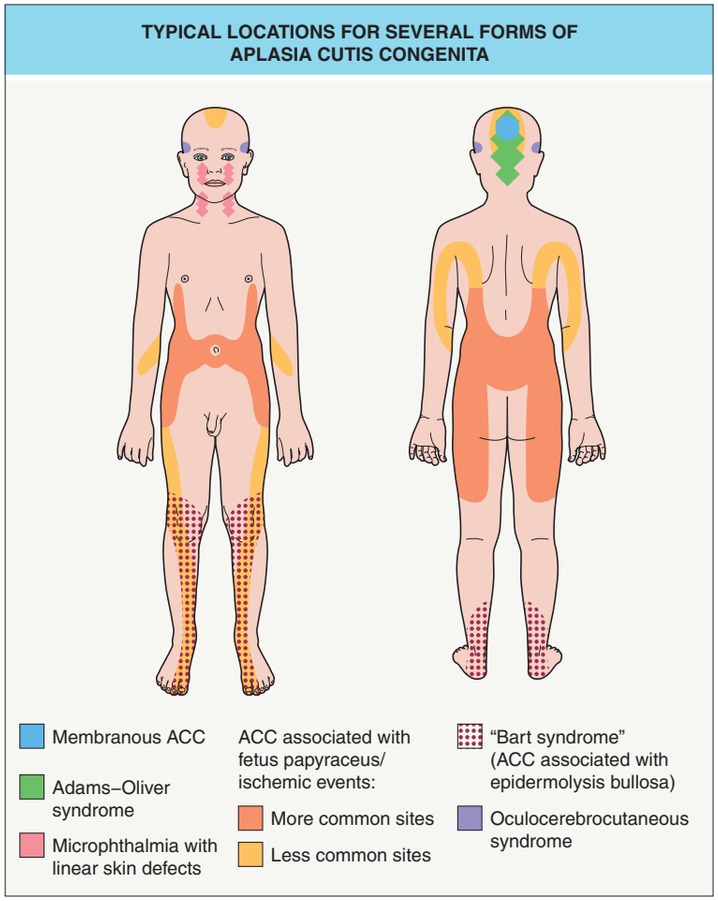


Fig. 64.19 Typical locations for several forms of aplasia cutis congenita (ACC). See Fig. 64.2 for Brauer lines/Setleis syndrome, preauricular membranous ACC, and microphthalmia with linear skin defects.

Commissural lip pits are typically found bilaterally in the mucosal surface at the angles of the mouth (Fig. 64.20A). Although most often an isolated anomaly, they may be inherited in an autosomal dominant fashion along with preauricular pits and hearing impairment in patients with a form of branchio-otic syndrome linked to chromosome 1q31[51]. Commissural lip pits also have been described in association with alveolar synechiae, ankyloblepharon filiforme adnatum (congenital adhesions between the upper and lower eyelids), and ectodermal defects.

Upper lip pits, also known as midline sinuses of the upper lip, are rare lesions that are typically located along the philtrum. Although usually an isolated defect, they may be associated with hypertelorism and other dysmorphic facial features. In addition, paramedian upper lip pits may occur (Fig. 64.20B) and are bilateral in patients with the branchio-oculo-facial syndrome (see below, Branchial Cleft Sinuses and Fistulae).

Lower lip pits may be an isolated finding or seen as a part of van der Woude syndrome, which is characterized by paramedian pits in the vermilion portion of the lower lip, cleft lip and/or palate, and hypodontia. The lip pits are usually bilateral, and they may be located on the apex of a conical elevation (Fig. 64.20C). Van der Woude syndrome, which occurs in ~1–3 per 100 000 live births, is an autosomal dominant disorder caused by mutations in the interferon regulatory factor 6 (*IRF6*)[52] or grainyhead-like 3 (*GRHL3*) gene. The popliteal pterygium syndrome is also due to *IRF6* mutations; in addition to lower lip pits, findings include cleft lip and/or palate, syngnathia, popliteal webbing, nail dysplasia, syndactyly, and genital anomalies. Lastly, lower lip pits are occasionally seen in oral–facial–digital syndrome type I (Table 64.5) and Kabuki syndrome (www.ncbi.nlm.nih.gov/omim).

Histologically, the sinus tracts associated with lip pits are lined by stratified squamous epithelium; associated salivary or mucous glands are occasionally observed. The evaluation of patients with lip pits should include a family history and a physical examination to exclude associated anomalies. If lip pits of any type are symptomatic or cosmetically undesirable, surgical excision is the treatment of choice. The extent of the sinus can be estimated preoperatively by injection of a radio-opaque contrast medium.



Fig. 64.20 Lip pits. A Bilateral commissural lip pits. **B** Unilateral right-sided upper lip pit. **C** Bilateral paramedian lower lip pits, each located on the apex of a conical elevation. All were isolated anomalies.

DISEASES AFFECTING THE SKIN THAT ARE ASSOCIATED WITH CLEFT LIP AND/OR PALATE	
Syndrome	**Other features**
Ectodermal dysplasias (see Ch. 63)	
• EEC syndrome	AD, *TP63*; ectodermal dysplasia, ectrodactyly, cleft lip/palate
• AEC syndrome	AD, *TP63*; ankyloblepharon, ectodermal dysplasia, cleft lip/palate
• Cleft lip/palate–ectodermal dysplasia	AR, *NECTIN1*; ectodermal dysplasia, pili torti, syndactyly
Branchio-oculo-facial syndrome	See text – branchial cleft sinuses
Oral–facial–digital syndrome, type 1	X-D, *OFD1*; lobulated tongue, hypertrophic oral frenula, digital malformations, whorled alopecia of the vertex, transient facial milia, polycystic kidneys, CNS anomalies
Oculocerebrocutaneous syndrome	See Table 64.4
4p- syndrome (Wolf–Hirschhorn syndrome)	See Table 64.4
Pai syndrome	Facial skin tags, nasal polyps, midline cleft lip, CNS lipomas
Basal cell nevus (Gorlin) syndrome	See Ch. 108
Goltz syndrome (focal dermal hypoplasia)	See Ch. 62
Waardenburg syndrome, type 1 or 3	See Ch. 66
Van der Woude syndrome*	See text – congenital lower lip pits
Popliteal pterygium syndrome*	See text – congenital lower lip pits
Nail–patella syndrome	See Ch. 71
Beare–Stevenson cutis gyrata syndrome	AD, *FGFR2*; craniosynostosis, cutis gyrata, acanthosis nigricans
Local lesions	
Dermal melanocytosis Encephaloceles or nasal gliomas	
*Allelic disorders.	

Table 64.5 Diseases affecting the skin that are associated with cleft lip and/or palate. Other disorders associated with cleft lip/palate that also can affect the skin include Cornelia de Lange, Roberts, Simpson–Golabi–Behmel, Pallister–Hall and CHIME (colobomas [ocular], *h*eart defects, *i*chthyosis, *m*ental retardation and *e*ar anomalies) syndromes, hemifacial microsomia, Meige disease (familial lymphedema praecox), and trisomy 13. AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; X-D, X-linked dominant.

Accessory Tragi

Synonyms: ■ Preauricular tags ■ Preauricular appendages

Accessory tragi are relatively common congenital anomalies of the first branchial arch, and they are found in 3–6 per 1000 live births. Familial occurrence has been reported, sometimes with a consistent anatomic site within kindreds. During development, the external ear is formed by the fusion of six tubercles, three each from the first and second branchial arches; the tragus and anterior crus of the helix are the only portions of the ear derived from the former[53]. Whereas preauricular pits and cysts reflect defective fusion of the tubercles (see Ch. 110), accessory tragi represent remnants of and/or extra tubercles originating from the first branchial arch.

Accessory tragi most often manifest as skin-colored papules or nodules in the preauricular area, but they also may be found on the mandibular cheek or on the neck along the anterior border of the sternocleidomastoid muscle (also referred to as congenital cartilaginous rests of the neck, see below)[54] (Fig. 64.21). The latter locations reflect the embryologic migration of the external ear from the neck to the side of the head as the mandible develops. Accessory tragi are occasionally multiple (see Fig. 64.21B) and are bilateral in ~10% of affected individuals. They are typically covered by vellus hairs and can be either soft or firm due to a cartilaginous core[53].

Although they usually represent an isolated malformation, accessory tragi are sometimes associated with other developmental anomalies of the first branchial arch, such as cleft lip and palate[55]. Together with ipsilateral facial hypoplasia, ear deformities, epibulbar dermoids, and vertebral abnormalities, accessory tragi are a cardinal feature of hemifacial microsomia (Goldenhar syndrome). Accessory tragi may be seen in a number of other multiple congenital anomaly syndromes, including Nager acrofacial dysostosis, Townes–Brocks syndrome, Treacher Collins–Franceschetti syndrome, VACTERL association, Wildervanck syndrome, and Wolf–Hirschhorn syndrome (www.ncbi.nlm.nih.gov/omim). Controlled studies have failed to confirm purported associations between isolated accessory tragi and urinary tract abnormalities or hearing impairment.

Histologically, accessory tragi are polypoid lesions with numerous tiny, mature hair follicles, a prominent connective tissue framework within abundant subcutaneous fat, and often a central plate of elastic cartilage. When accessory tragi are surgically excised for cosmetic reasons, care must be taken to remove any protruding portion of underlying cartilage[54]. Evaluation of an infant with an accessory tragus should include assessment of hearing and examination for other dysmorphic features.

Congenital Cartilaginous Rests of the Neck

Synonyms: ■ Wattles ■ Cervical accessory tragi ■ Cutaneous cervical tabs



Fig. 64.21 Accessory tragi. A Typical small preauricular papule. **B** Multiple skin-colored papulonodules on the mandibular cheek as well as in a preauricular location. **C** Congenital cartilaginous rest of the neck, which is considered to represent a cervical subtype of accessory tragus.

Congenital cartilaginous rests of the neck are branchial arch remnants that are considered to be the cervical variant of accessory tragi (see above). The alternative term "wattle" refers to the fleshy appendage that hangs from the throat of certain animals, such as turkeys and goats. Typically located over the lower anterior border of the sternocleidomastoid muscle (see Fig. 64.21C), these asymptomatic lesions may be unilateral or bilateral, and they are neither cystic nor fistulous. They may be attached to the underlying fascia by a fibrous band, which can be safely transected if excision is desired[56].

Branchial Cleft Sinuses and Fistulae

Synonym: ■ Lateral cervical sinuses and fistulae

Branchial cleft *sinuses* most often represent remnants of the second branchial (pharyngeal) cleft. They are usually detected at birth or during the first few years of life, unlike the more common branchial cleft *cysts* that lack a primary cutaneous opening and typically present in older children and adults (see Ch. 110). The ostium of a second branchial cleft sinus is located on the lateral lower third of the neck along the anterior border of the sternocleidomastoid muscle, and there is frequently a history of mucus discharge; the associated tract extends superiorly in the subcutis and may be palpable. The less common first branchial cleft sinus can manifest with a cutaneous opening located higher on the neck or in the periauricular region. Approximately 70% of branchial cleft sinuses are located on the right and 5%–10% are bilateral. There may be a history of recurrent infection, and a skin tag, sometimes with a cartilaginous component, can mark the ostium. Most branchial sinus tracts end blindly, but occasionally there is a fistulous connection with the tonsillar fossa of the pharynx or the external auditory canal[57]. Rarely, thyroid or squamous cell carcinoma develops within branchial cleft remnants.

Although usually an isolated malformation, branchial cleft sinuses and fistulae are also features of several multiple congenital anomaly syndromes. These include the branchio-otic and branchio-oto-renal syndromes, autosomal dominant disorders that also feature ear pits, hearing loss, and, in the latter, renal anomalies. These syndromes can be caused by mutations in the *EYA1* (both conditions), *SIX1* (branchio-otic), and *SIX5* (branchio-oto-renal) genes, which encode transcription factors that interact within a complex. Atrophic, eroded, or "hemangiomatous" skin overlying branchial cleft sinuses on the neck or in the periauricular area is a distinctive feature of the branchio-oculo-facial syndrome that is due to mutations in the gene encoding transcription factor AP2-α. Additional manifestations of this disorder include cleft lip/palate, imperforate nasolacrimal ducts, eye and ear anomalies, and early graying of the hair.

Histologically, a branchial sinus may be lined by stratified squamous or pseudostratified ciliated columnar epithelium. In order to prevent infectious complications, complete surgical excision of branchial sinuses and fistulae is indicated. Imaging may be helpful in delineating the course and extent of the lesion, although recommendations vary among otolaryngologists. Preoperative options include CT fistulography and MRI; in addition, intraoperative contrast fistulography and/or injection of methylene blue dye can be considered[57,58].

Supernumerary Nipples and Other Forms of Accessory Mammary Tissue

Variants/synonyms: ■ Supernumerary nipples – accessory nipples, polythelia ■ Pseudomamma (nipple + areola) ■ Supernumerary breasts – polymastia

Supernumerary nipples and other forms of accessory mammary tissue are remnants of the embryologic mammary ridges or "milk lines", symmetric ectodermal thickenings that extend from the anterior axillary fold to the upper medial thigh (Fig. 64.22). Normally, there is further development in the pectoral region to form the nipples, while the remainder of the milk line regresses; focal areas of persistence result in accessory mammary tissue. Supernumerary nipples, the most common type of accessory mammary tissue, are found in 1%–6% of the population[59]. They usually represent a sporadic developmental anomaly, although ~10% of cases are familial. The incidence of supernumerary nipples is similar in men and women. However, in women, accessory mammary tissue often becomes more apparent at puberty or during pregnancy. Conversely, changes in supernumerary nipples may actually represent an early cutaneous sign of pregnancy.

Supernumerary nipples are most commonly seen on the inframammary chest, but they may be located anywhere along the milk lines (including the vulva) and occasionally in other sites such as the upper back, shoulder, posterior thigh, face, neck, or even foot. In addition, supernumerary nipples sometimes overlie the primary nipple or areola. Lesions are most often single, but they may be multiple and/or bilateral. Supernumerary nipples typically present as a small, soft, pink or brown papule, with or without a surrounding areola (Fig. 64.23). An areola also can also develop in the absence of a nipple, and ectopic glandular breast tissue can be isolated or associated with a nipple and/or areola. When only breast tissue is present, it is most often located in the axilla or vulva and may demonstrate all of the functional changes of normal breasts, from tenderness and swelling related to the menstrual cycle to lactation through pores in the overlying skin. Of note, a tuft of hair located along the milk lines may be a marker of underlying mammary tissue (polythelia pilosa)[60].

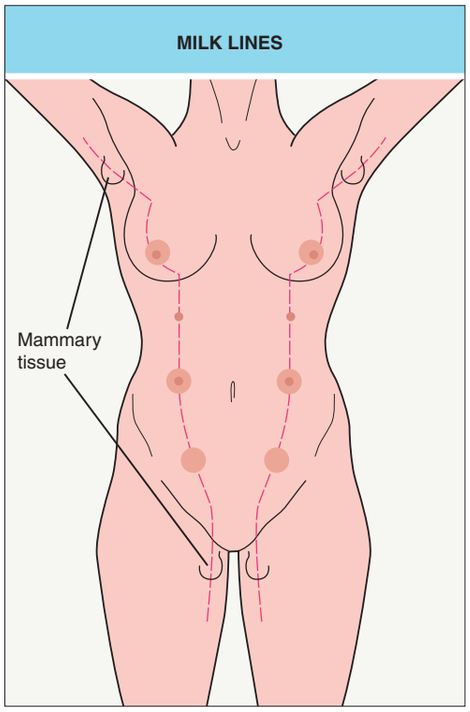


Fig. 64.22 "Milk lines". Supernumerary nipples and other forms of accessory mammary tissue represent focal remnants of the embryologic mammary ridges that extend from the anterior axillary fold to the upper medial thigh bilaterally.

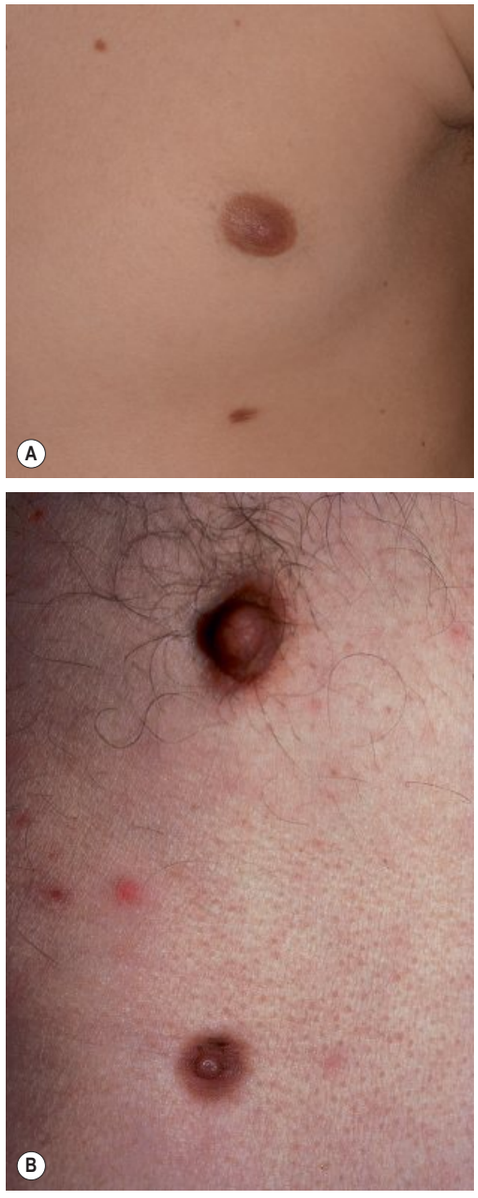


Fig. 64.23 Supernumerary nipples on the inframammary chest. A Brown papule that might be mistaken for a melanocytic nevus. **B** Nipple with a surrounding areola. *B, Courtesy Jean L. Bolognia.*

A number of other abnormalities have been described in patients with supernumerary nipples. The association between supernumerary nipples and malformations of the kidneys and urinary tract is controversial. Although early reports supported the existence of a "supernumerary nipple/renal field defect", several controlled studies failed to confirm this association[61]. However, a few studies have found supernumerary nipples to be significantly more common in patients with urogenital or renal malignancies than in control groups[62]. Supernumerary nipples have been noted in patients with Becker melanosis and are a feature of several multiple congenital anomaly syndromes (e.g. Simpson–Golabi–Behmel, Pallister–Killian), the *UBA2*-related phenotypic spectrum, cleft lip/palate–ectodermal dysplasia, and tricho-odonto-onychial dysplasia (www.ncbi.nlm.nih.gov/omim). Lastly, midline dorsal accessory breast tissue with underlying spinal dysraphism has been reported.

Histologic features of accessory mammary tissue are similar to those of normal breasts. For example, supernumerary nipples show acanthosis, pilosebaceous structures, smooth muscle, and in many cases, mammary glands. Fine-needle aspiration cytology can be helpful for evaluation of an axillary or vulvar mass suspected to represent breast tissue, although an incisional or excisional biopsy may be required for definitive diagnosis. Ectopic glandular breast tissue can develop any of the disorders that occur in normally positioned breasts, including galactorrhea, fibrocystic changes, mastitis, fibroadenomas, and carcinoma. Although such tissue does not have an increased malignant potential compared with the normal breast and prophylactic excision for cancer prevention is not required, routine screening should be performed with periodic physical examination and radiologic studies such as mammography or ultrasonography. Complete surgical excision is the treatment of choice for accessory mammary tissue that is symptomatic or cosmetically undesirable. Most authors do not recommend imaging studies to exclude an associated urinary tract malformation in asymptomatic individuals with accessory mammary tissue as an isolated anomaly.

Absent, Hypoplastic or Anomalous Nipples

Variants: ■ Athelia ■ Amastia ■ Hypomastia

Absence or hypoplasia of the nipples may occur either as an isolated developmental abnormality or together with other malformations in a variety of congenital syndromes. The Poland anomaly is a predominantly sporadic developmental field defect in which hypoplasia or absence of the nipple and/or breast is associated with ipsilateral aplasia of the sternal head of the pectoralis major muscle, patchy absence of axillary hair, and symbrachydactyly. The Becker nevus syndrome may also include hypoplasia of the ipsilateral nipple, breast, pectoralis major muscle, and/or arm; it results from mosaic mutations in the beta-actin gene that involve the mesenchymal lineage[63]. In addition, nipple and breast hypoplasia or aplasia may occur in association with ectodermal dysplasias, including X-linked hypohidrotic and tricho-odonto-onychial types, as well as the scalp–ear–nipple syndrome (see Table 64.4), limb–mammary syndrome (ectrodactyly, other hand/foot anomalies, and nail dysplasia), ulnar–mammary syndrome (Table 64.6), and ablepharon–macrostomia syndrome. In a rare, lethal form of dwarfism known as Blomstrand chondrodysplasia, loss-of-function mutations in the gene encoding parathyroid hormone receptor 1 result in lack of nipples. Mutations in *KMT2D* (lysine-specific methyltransferase 2D), *USP9X* (ubiquitin-specific protease 9, X-linked), or *PTPRF* (protein tyrosine phosphatase receptor F) can result in hypo- or athelia along with other dysmorphic features[64]. Both parathyroid hormone-related protein produced by the mammary bud epithelium and PTPRF produced by surrounding fibroblasts play a role in a Wnt-dependent pathway that regulates embryonic development of the mammary mesenchyme and is required for formation of the nipple and mammary ducts.

Inverted nipples are most often inherited as an isolated autosomal dominant trait, but they may also be found in congenital syndromes such as the congenital disorder of glycosylation type Ia. Widely spaced nipples are a feature of congenital disorders including Turner syndrome, Noonan syndrome,

DISEASES AFFECTING THE SKIN THAT ARE ASSOCIATED WITH CONGENITAL DIGITAL ANOMALIES						
	Digital anomaly (-dactyly)					
Syndrome	Syn-	Ectro-	Poly-	Clino-	Brachy-	Other features
Ectodermal dysplasias (see Ch. 63)						
• EEC syndrome*	x	x				AD, *TP63*; ectodermal dysplasia, ectrodactyly, cleft lip/palate
• EEM syndrome	x	x				AR, *CDH3*; ectodermal dysplasia, ectrodactyly, macular dystrophy
• Cleft lip/palate–ectodermal dysplasia	x					See Table 64.5
• ED–syndactyly	x					AR, *NECTIN4*; hypotrichosis with pili torti, hypodontia, PPK
• Oculodentodigital dysplasia	x				x	AD, *GJA1*; small eyes, enamel hypoplasia, midphalangeal hypoplasia, PPK, hypotrichosis
• Scalp–ear–nipple syndrome	x					See Table 64.4
• Ulnar–mammary syndrome		x	x			*TBX3*; absent/hypoplastic nipples, ulnar ray defects, genital anomalies, abnormal canine teeth
Oral–facial–digital syndrome, type 1	x		x			See Table 64.5
UBA2-related phenotypic spectrum	x	x	x	x		See Table 64.4
Goltz syndrome (focal dermal hypoplasia)	x	x	x			See Ch. 62
Terminal osseous dysplasia with pigmentary defects				x	x	X-D, *FLNA*; hyperpigmented, atrophic facial macules representing focal dermal hypoplasia, digital fibromas, multiple frenula, hypertelorism
Happle–Tinschert/Curry–Jones syndrome	x		x			Mosaic, *SMO*; basaloid follicular hamartomas ± hyper-/hypopigmentation; dental, skeletal, and cerebral anomalies
Epidermal/sebaceous nevus syndromes	x		x	x		See Ch. 62
Mosaicism/hypomelanosis of Ito	x		x	x		See Ch. 62
Klippel–Trenaunay syndrome†	x		x			See Ch. 104
Proteus syndrome†	x					See Ch. 62
Adams–Oliver syndrome	x				x	See Table 64.3
Megalencephaly–capillary malformation	x		x			See Ch. 104
Waardenburg syndrome, type 3	x					See Ch. 66
Apert syndrome	x					AD, *FGFR2*; craniosynostosis, severe acne, diffuse pigmentary dilution
Basal cell nevus (Gorlin) syndrome			x		x	See Ch. 108
Popliteal pterygium syndrome	x					See text – congenital lip pits
Trichorhinophalangeal syndrome					x	AD, *TRPS1*; cone-shaped epiphyses, pear-shaped nose, sparse hair
Anonychia–onychodysplasia	x			x	x	AD; absent/hypoplastic distal phalanges

*Caused by mutations in the *TP63* gene; allelic disorders with overlapping manifestations (e.g. ectrodactyly, nipple hypo-/aplasia) include ADULT (acro-dermato-ungual-lacrimal-tooth) syndrome and limb–mammary syndrome.
†Patients often have macrodactyly.

Table 64.6 Diseases affecting the skin that are associated with congenital digital anomalies. Other disorders associated with digital anomalies that also may affect the skin include Cornelia de Lange, Roberts, Simpson–Golabi–Behmel, Pallister–Hall, Russell–Silver, Rubinstein–Taybi, and Hurler syndromes, trisomy 13, Fanconi anemia, and the Poland anomaly. *Syndactyly*, fused digits; *ectrodactyly*, absent digits resulting in a split hand–foot deformity ("lobster claw"); *polydactyly*, extra digits; *clinodactyly*, laterally or medially "bent" digits; *brachydactyly*, short digits. AD, autosomal dominant; AR, autosomal recessive; *CDH3*, cadherin 3; *FGFR2*, fibroblast growth factor receptor 2; *FLNA*, filamin A; *GJA1*, gap junction α1; PPK, palmoplantar keratoderma; *SMO*, smoothened; X-D, X-linked dominant.

cerebro-oculo-facio-skeletal syndrome, renal hypoplasia syndromes, and various chromosomal abnormalities (www.ncbi.nlm.nih.gov/omim).

Skin Dimples

Synonym: ▪ Skin fossae

Skin dimples are deep cutaneous depressions that are seen most commonly on the cheeks or chin, occurring in a familial pattern suggestive of autosomal dominant inheritance. Unilateral or bilateral dimples also may be found in a variety of other locations, most often overlying bony prominences such as the acromion process of the scapula, elbow, patella, tibia, and sacrum. These represent regions in which there is close proximity of the skin to the underlying bone during fetal development, and the dimples are thought to result from early fixation of the skin and deficient formation of the subcutaneous tissue.

Bilateral skin dimples on the shoulders overlying the acromion processes can be inherited in an autosomal dominant fashion as an isolated anomaly. In addition, bilateral acromial dimples are a feature of several congenital malformation syndromes, including the 18q deletion syndrome, trisomy 9p syndrome, Say syndrome, and Russell–Silver dwarfism[65]. Skin dimples also may be seen in association with skeletal abnormalities. For example, dimpling may be found overlying the tibial bend in patients with camptomelic dysplasia and over bowing convexities or exostoses of long bones in those with hypophosphatasia. Distal arthrogryposis ("whistling face") syndrome type 2A features a characteristic H-shaped dimple on the chin. Although shallow coccygeal dimples are a common isolated finding[24–26], larger or deeper midline lumbosacral dimples may represent a cutaneous sign of spinal dysraphism (see above) or a malformation syndrome[65]. Congenital dimples on the thigh have been attributed to intrauterine friction from the opposite great toenail when in the fetal position[66]. Lastly, skin dimples overlying the knees and/or elbows have been reported in association with congenital rubella, Joubert syndrome, limb–mammary syndrome, ulnar–mammary syndrome, and multiple pterygium syndrome (www.ncbi.nlm.nih.gov/omim). In other sites, an enlarging dimple in a young child may indicate an atrophic dermatofibroma or nascent lipoblastoma (see Ch. 117).

Congenital Malformations of the Dermatoglyphics

Congenital malformations of the dermatoglyphics (fingerprints) are divided into four main categories based on the appearance of the dermal ridges of which they are composed: (1) ridge aplasia (absent); (2) ridge hypoplasia (poorly formed); (3) ridge dissociation (discontinuous pattern with short segments); and (4) ridges-off-the-end (run off the end of the fingertip rather than looping around). Embryologic development of the dermal ridges occurs in conjunction with that of the eccrine glands of the palms and soles, and the sweat pores are found on the ridges. The lack of eccrine ducts and glands in the palmar skin of patients with ridge aplasia reflects this close relationship[67]. Variants in the ADAM metallopeptidase with thrombospondin motif 9 antisense RNA 2 (*ADAMTS9-AS2*) influence the whorls within dermatoglyphics[68].

Congenital dermatoglyphic malformations of all types can be inherited in an autosomal dominant fashion as an isolated defect. A non-syndromic form of adermatoglyphia ("immigration delay disease") as well as Basan and Huriez syndromes are all autosomal dominant conditions caused by mutations affecting a skin-specific isoform of SMARCAD1, a member of the SNF subfamily of the helicase protein superfamily[69]. Basan syndrome is characterized by adermatoglyphia together with neonatal acral blistering and profuse facial milia; variable features include palmoplantar keratoderma (PPK), digital contractures, nail dystrophy, and acral hypohidrosis. Huriez disease features sclero-atrophy of the hands and feet with a predisposition to acral squamous cell carcinoma as well as adermatoglyphia, PPK, and hypoplastic nails. Dermatoglyphic malformations can also occur in association with chromosomal abnormalities, malformations of the distal limbs, and ectodermal dysplasias. The latter, which may present with ridge aplasia or hypoplasia, include hypohidrotic ectodermal dysplasia, AEC syndrome (*a*nkyloblepharon, *e*ctodermal dysplasia, *c*left lip/palate), dermatopathia pigmentosa reticularis, and Naegeli–Franceschetti–Jadassohn (NFJ) syndrome (see Chs. 63 & 67). Ridge dissociation can be seen in patients with Rosenthal–Kloepfer syndrome (acromegaloid changes, cutis verticis gyrata, and corneal leukoma) and cystic fibrosis. The spectrum of abnormal dermatoglyphics includes an acquired loss as is seen in Kindler syndrome and dyskeratosis congenita (see Chs. 32 & 67) and the stippled dermatoglyphics (pachydermatoglyphia) found in Costello syndrome, KID (*k*eratitis–*i*chthyosis–*d*eafness) syndrome, and hidrotic ectodermal dysplasia (see Chs. 55, 57, & 63). Lastly, aberrant dermatoglyphic patterns have been used to screen for a predisposition to early childhood dental caries, congenital orodental anomalies, hypertension, neurodevelopmental disorders, and schizophrenia.

Rudimentary Polydactyly

Synonym: ■ Rudimentary supernumerary digits

Rudimentary polydactyly represents duplication of digital soft tissue, but without a skeletal component. It is typically found on the lateral surface of a digit, more often the ulnar side of the fifth finger (postaxial) than the radial side of the thumb (preaxial). Rudimentary polydactyly is present in ~0.5–1 per 1000 White neonates and ~3–10 per 1000 Black neonates. It usually occurs as an isolated malformation with autosomal dominant inheritance; underlying mutations have been identified in *GLI3* (GLI family zinc finger 3) and other genes. The stump remaining after intrauterine amputation of a larger structure is sometimes referred to as an *amputation neuroma*. Rudimentary polydactyly lesions are frequently bilateral and range from small, fleshy or wart-like papules (Fig. 64.24) to larger, often pedunculated nodules that may contain cartilage or a vestigial nail. Congenital ectopic nails located on the tips of the fifth fingers are regarded as a separate entity.

Histologically, rudimentary supernumerary digits often show fascicles of nerve fibers in a pattern similar to that of an acquired neuroma (see Ch. 115). When removal is desired, surgical excision is the method of choice[70]. Removal via ligation with suture material increases the risk of infection and often leaves a residual papule, which may result in a painful neuroma later in life.

Amniotic Band Sequence and Disorganization Syndrome

Synonyms: ■ Amniotic band syndrome ■ Amniotic rupture sequence ■ Congenital constriction bands ■ ADAM (*a*mniotic *d*eformity, *a*dhesions and *m*utilations) complex

The amniotic band sequence (ABS) encompasses a variety of congenital anomalies of the limbs, head, body wall, and viscera with asymmetric, seemingly random distribution patterns that do not correspond to embryonic fusion planes. Characteristic findings include constriction rings and amputations of the limbs and digits that are associated with fibrous bands. Occurring in ~1–10 per 10 000 live births, ABS is primarily a sporadic disorder, although familial cases and one patient with a mutation in *IQCK* (IQ motif-containing K) have been reported. ABS may be more common in children born to primiparous versus multiparous women[71]. *Pseudoamniotic band syndrome* is a rare complication of invasive intrauterine procedures in monochorionic twins.

There are two classic hypotheses for the pathogenesis of ABS. The *extrinsic theory* postulates that rupture and repair of the amniotic membrane during the first trimester is followed by loss of amniotic fluid and entanglement of fetal parts in fibrous strands of torn amnion, which form rings that encircle and constrict the limbs, face, or trunk. The *intrinsic theory* proposes that an abnormal endogenous developmental process leads to production of fibrous bands as well as other anomalies (e.g. internal malformations, duplicated structures) not explained by bands alone. Although the extrinsic theory has traditionally been more widely accepted, the striking similarities between ABS and the human "disorganization syndrome" as well as the mouse disorganization mutant provide support for an intrinsic mechanism[72]. The disorganization syndrome features a haphazard pattern of defects such as limb duplications, reductions, and circumferential constrictions with attached fibrous bands; hamartomatous digit-like appendages and craniofacial > truncal clefts represent additional features. Alternatively, fibrosis due to altered activation of the epithelial–mesenchymal transition process during embryogenesis has been hypothesized.

The clinical spectrum of ABS is broad, ranging from isolated minor limb anomalies to major craniofacial and visceral defects. It includes the *limb–body wall complex* characterized by body wall defects with evisceration of thoracic and/or abdominal organs, irregular anencephaly/encephaloceles, and bizarre facial clefting[73]. Variations in severity may depend upon differences in the timing of amniotic rupture or variable expressivity of genetic trait(s). Constriction rings present as circumferential grooves of variable depth on the digits, extremities, neck, or trunk; this must be distinguished from the circumferential creases of the "Michelin tire baby" syndrome (see Ch. 97). Deep lesions located on an extremity may be associated with distal lymphedema, nerve compression,

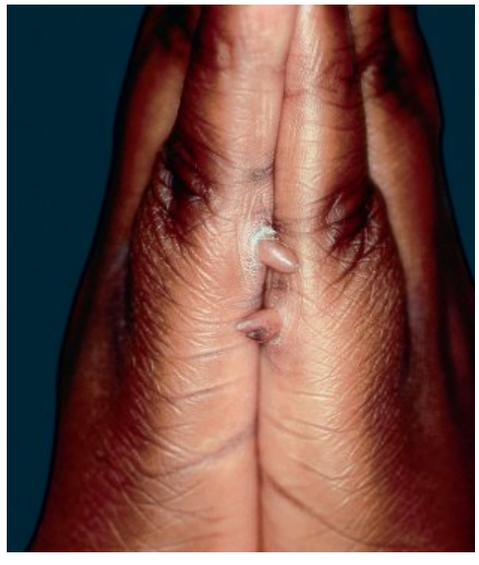


Fig. 64.24 Bilateral rudimentary supernumerary digits. The ulnar side of the fifth digit is the most common location, referred to as postaxial.

deformity, or intrauterine amputation. Acrosyndactyly can result from a constriction band that encircles adjacent digits. In addition to the distinctive fibrofatty appendages of the disorganization syndrome, other cutaneous manifestations of ABS may include aplasia cutis congenita, often with a stellate morphology, and abnormal dermatoglyphics.

Plastic surgery with wound closure via Z-plasty, anterior sheath Y–V plasty, or abdominal Scarpa fascia release is indicated for release of constriction bands that restrict growth, compress underlying nerves, or interfere with vascular and/or lymphatic circulation.

Other Developmental Anomalies Associated with Cutaneous Diseases

Skin disorders that are associated with cleft lip/palate or congenital digital anomalies are presented in Tables 64.5 and 64.6, respectively.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 64.1 Hair collar sign. Membranous aplasia cutis congenita with a hair collar and an associated capillary malformation. *Courtesy Kalman Watsky, MD.*



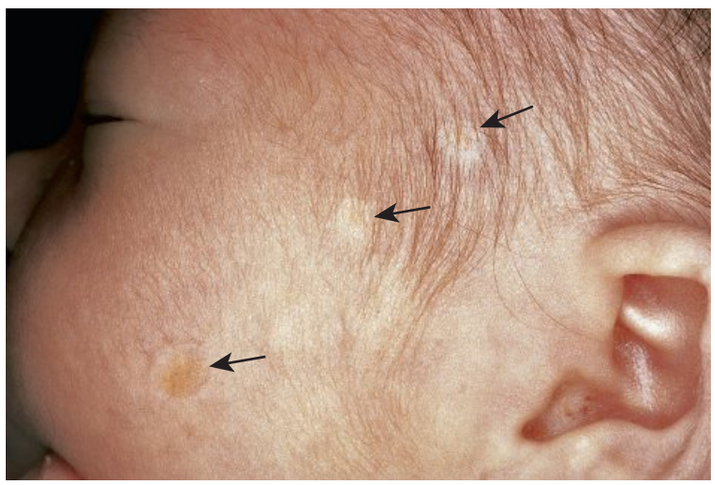
eFig. 64.2 Dermoid cyst on the scalp.



eFig. 64.3 Dermoid cyst. This dermoid cyst presented in an infant as a firm subcutaneous nodule superior to the lateral left eyebrow. *Courtesy Kalman Watsky, MD.*



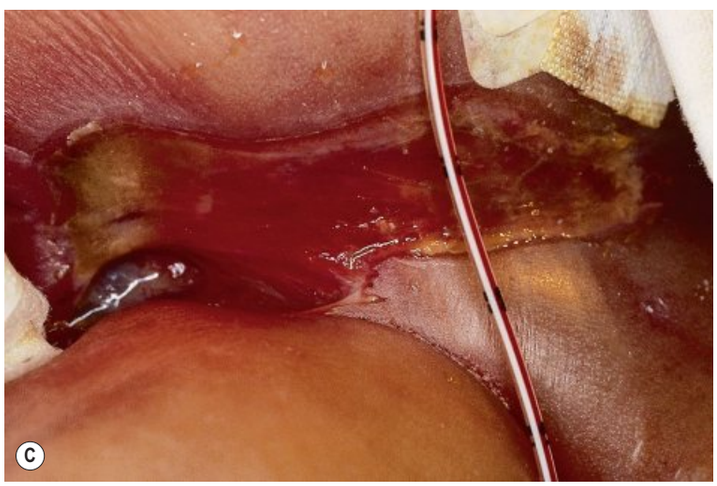
eFig. 64.4 Nevus simplex of the lumbosacral region. The likelihood of spinal dysraphism is extremely low if there are no other local cutaneous findings (e.g. deviated gluteal cleft/lipoma, focal hypertrichosis, dermal sinus/pit), especially if there are additional nevus simplex lesions elsewhere.



eFig. 64.5 Preauricular skin defects. Multiple discrete, round, atrophic skin defects in an infant, extending from the scalp line toward the angle of the mouth in a strikingly linear arrangement (arrows). *Courtesy Jean L. Bolognia, MD.*







eFig. 64.6 Aplasia cutis congenita (ACC). A ACC associated with fetus papyraceus due to the second-trimester death of a co-twin. **B** Stellate ACC on the lateral trunk of a neonate born of an initial sextuplet gestation for which fetal reduction was performed. The lesions had a bilateral, symmetric distribution. **C** ACC resulting from congenital varicella. Note the sharply demarcated, deep ulcer on the lower abdominal wall.





eFig. 64.7 Aplasia cutis congenita involving the leg and the vertex scalp. A, B Note the irregular outline of both lesions.



eFig. 64.8 Accessory tragus. Skin-colored papule in a typical preauricular location.

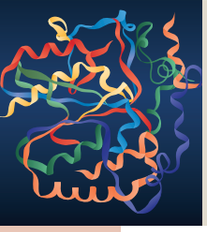


eFig. 64.9 Supernumerary nipple. Note the supernumerary nipple with a surrounding areola in a typical location on the inframammary chest.





eFig. 64.10 Bilateral supernumerary nipples. A, B This is a less common location than inferior to the breast. *Courtesy Kalman Watsky, MD.*



65 Melanocyte Biology

Jean L. Bolognia and Seth J. Orlow

Chapter Contents

Origin and Function of the Melanocyte *1086*
Formation and Function of the Melanosome *1089*
Regulation of Melanin Biosynthesis *1092*

Key features

- The major determinant of normal skin color is the activity of melanocytes, i.e. the quantity and quality of pigment production, not the density of melanocytes
- Melanocytes contain a unique intracytoplasmic organelle, the melanosome, which is the site of melanin synthesis and deposition
- Compared with lightly pigmented skin, darkly pigmented skin has melanosomes that contain more melanin and are larger; once transferred to keratinocytes, the melanosomes are singly dispersed and degraded more slowly
- Tyrosinase is the key enzyme in the melanin biosynthetic pathway
- Two major forms of melanin are produced in melanocytes: brown–black eumelanin and yellow–red pheomelanin
- The production of eumelanin versus pheomelanin is influenced by the binding of melanocyte stimulating hormone to the melanocortin 1 receptor

INTRODUCTION

In order to understand the underlying pathophysiology of cutaneous disorders of hypopigmentation and hyperpigmentation, as well as the process of normal physiologic pigment production, an appreciation of the structure and function of the melanocyte is required. A classic example of basic pathogenesis is type 1 oculocutaneous albinism (OCA1), in which pigmentary dilution of the skin, hair, and eyes is due to a reduction or absence of tyrosinase activity secondary to mutations in both copies of the tyrosinase gene (*TYR*). Physiologic pigmentation is influenced by variants in multiple genes. For example, melanocytes in individuals with red hair often express variants of the melanocortin 1 receptor (MC1R)[1]. As a consequence of the altered amino acid sequences of the variant MC1Rs, their cell surface expression and interactions with melanocyte stimulating hormone (MSH) can be affected, leading to an increase in the production of pheomelanin as opposed to eumelanin. Based upon population genetics, genes that are mutated in OCA (e.g. *TYR*, *OCA2*, *TYRP1*, *SLC45A2*, *SLC24A5*) also influence normal pigment variation (Table 65.1)[2–6].

ORIGIN AND FUNCTION OF THE MELANOCYTE

The melanocyte is a neural crest-derived cell. During embryogenesis, precursor cells (melanoblasts) migrate along a dorsolateral then ventral pathway via the mesenchyme to reach the epidermis and hair follicles of the trunk (see Ch. 2). More recently, it was shown that melanocytes can also arise from neural crest-derived Schwann cell precursors that migrate along nerves to the skin via a distinct ventral pathway[7]. Additional sites of melanocyte migration include the uveal tract of the eye (choroid, ciliary body, and iris), the leptomeninges, and the inner ear (cochlea) (Fig. 65.1). Presumably, the death of melanocytes within the leptomeninges, inner ear, and skin is responsible for the aseptic meningitis, auditory symptoms, and areas of vitiligo, respectively, seen in patients with the Vogt–Koyanagi–Harada syndrome (see Ch. 66).

In the inner ear, particularly in the stria vascularis, melanocytes are thought to play a role in the development of hearing. Aberrant migration or survival of melanocytes within the inner ear, the iris, and midportions of the forehead and extremities explains the presence of congenital deafness, heterochromia irides, and patches of leukoderma, respectively, in patients with Waardenburg syndrome, the classic neurocristopathy. Also, aberrant migration or survival of enteric ganglion cells, another neural crest-derived cell population, provides an explanation for the association of aganglionic megacolon (Hirschsprung disease) with Waardenburg syndrome or rarely piebaldism.

The survival and migration of neural crest-derived cells during embryogenesis depends upon interactions between specific receptors on their cell surface and extracellular ligands. For example, KIT ligand, also known as steel factor or stem cell growth factor, binds to the transmembrane KIT receptor on melanocytes and melanocyte precursors (melanoblasts) (Figs. 65.2 & 65.3); melanoblasts require expression of the KIT receptor in order to maintain their normal chemotactic migration directed by production of KIT ligand by the dermamyotome. Heterozygous germline mutations in *KIT* that decrease the ability of the KIT receptor to be activated by KIT ligand are responsible for human piebaldism, whereas in mice, mutations in either *kit* or *steel* can lead to white spotting.

In the developing embryo, melanoblasts expressing endothelin receptor type B (EDNRB) are stimulated to migrate by endothelin-3 (ET3 [EDN3]), which is produced by the ectoderm and dermamyotome. Loss-of-function mutations in one or both copies of *EDN3* or *EDNRB* can result in Waardenburg syndrome plus aganglionic megacolon, while overexpression of both has been observed in solar lentigines (see Fig. 65.3).

Transcription factors represent another group of proteins that play an essential role during embryogenesis. Because transcription factors bind DNA and influence the activity of other genes, they are able to regulate the complex interplay of various sets of genes that is required for embryonic development. Several of the genes that, when mutated, give rise to Waardenburg syndrome encode transcription factors (e.g. *PAX3, MITF, SOX10*; see Table 66.4). Fig. 65.4 demonstrates some of these interactions, e.g. PAX3 and SOX10 can control expression of MITF[8,9]. MITF is sometimes referred to as the master regulator of melanocyte development and function given its modulation of multiple differentiation genes and its early upregulation in neural crest cells that will eventually become melanocytes and emigrate from the dorsal neural tube.

During embryogenesis, melanin-producing melanocytes are found diffusely throughout the dermis. They first appear in the head and neck region at ~10 weeks of gestation. However, by the end of gestation, active dermal melanocytes have "disappeared", except in three primary anatomic locations – the head and neck, the dorsal aspects of the distal extremities, and the presacral area[10]. Some of the dermal melanocytes have clearly migrated into the epidermis, but, given the absolute numbers of cells in the two compartments, apoptosis of pigment cells has also occurred. The three sites where active dermal melanocytes are still present at the time of birth coincide with the most common sites for dermal melanocytoses and dermal melanocytomas (blue nevi). Hepatocyte growth factor may play a role in the survival and proliferation of these dermal melanocytes as well as somatic activating mutations in one of two genes that encode G proteins. In addition to blue nevi (see Table 112.3), gain-of-function mutations in *GNAQ* or *GNA11* are also found in primary uveal melanomas.

As depicted in Fig. 65.1, melanocytes also migrate to the basal layer of the hair matrix and the outer root sheath of hair follicles. Cells that are actively producing melanin are easily recognized in the matrices of pigmented anagen hairs, whereas melanocytes within the outer root sheath are usually amelanotic and more difficult to identify[11]. It has been hypothesized that there are two populations of melanocytes in the skin, one in the interfollicular epidermis and the second in the hair follicle[12].

DISORDERS CHARACTERIZED BY DIFFUSE PIGMENTARY DILUTION IN WHICH THE GENETIC DEFECT IS KNOWN			
Disorder	**Gene**	**Protein product**	**Comments**
Oculocutaneous albinism (OCA) [~40% of patients have OCA1 and ~50% have OCA2]			
OCA1A	*TYR*	Tyrosinase	• Complete absence of tyrosinase activity and melanin production • Retention of misfolded tyrosinase protein within the ER
OCA1B	*TYR*	Tyrosinase	• Decreased tyrosinase activity; can produce pheomelanin • Variant with temperature-sensitive tyrosinase (normal activity at 35°C, but diminished at 37°C) • Additional variants: minimal pigment, platinum, yellow
OCA2	*OCA2*	P protein (*OCA2* was previously known as *P*)	• Melanosomal transmembrane protein that is also present in the ER • Implicated in the regulation of melanosomal pH which influences tyrosinase activity • May also regulate intra-organelle glutathione levels and influence folding of tyrosinase proteins
OCA3	*TYRP1*	Tyrosinase-related protein 1*	• TYRP1 stabilizes tyrosinase in mice and humans, and it can function as a DHICA oxidase • Both "mutant" TYRP1 and tyrosinase are retained in the ER and then degraded • Rufous phenotype ≫ brown phenotype; latter seen in OCA2
OCA4	*SLC45A2*	Solute carrier family 45 member 2 (also known as MATP)	• Variable phenotype, with hair ranging from white to yellow–brown; most common in Asians • Proton/glucose exporter in melanosomes that maintains deacidification in later stage melanosomes • Acidification of melanosome impairs activity of tyrosinase
OCA5	Not known	–	• Locus linked to chromosome 4q24
OCA6	*SLC24A5*	Solute carrier family 24 member 5	• Cation exchanger that is a member of K^+-dependent Na^+/Ca^{++} exchanger family • May be involved in ion transport in melanosomes
OCA7	*LRMDA* (alias *C10orf11*)	Leucine-rich melanocyte differentiation-associated protein (previously known as chromosome 10 open reading frame 11)	• Expressed in melanoblasts and melanocytes • Possible role in melanocyte differentiation
OCA8	*DCT*	Dopachrome tautomerase	• Mild pigmentary dilution • Catalyzes conversion of DOPAchrome to DHICA • Also known as TYRP2
Hermansky–Pudlak syndrome (HPS)†			
HPS1	*HPS1*	HPS1 (BLOC-3 subunit 1)	• Defective trafficking of organelle-specific proteins to melanosomes, lysosomes and cytoplasmic granules (including platelet dense granules and lytic granules in cytotoxic T lymphocytes) • Pulmonary fibrosis and granulomatous colitis‡ • Component of BLOC-3 (see Fig. 65.8)
HPS2	*AP3B1*	Adaptor related protein complex 3 subunit β1	• AP-3 recognizes sorting signals within cytosolic tails of cargo molecules and is involved in the trafficking of proteins from the trans-Golgi network to appropriate organelles (see Fig. 65.8) • Pulmonary fibrosis (some patients) • Immunodeficiency, possibly related to abnormal trafficking of CD1B, reduced perforin levels in NK cells, and reduced elastase within neutrophils
HPS3	*HPS3*	HPS3 (BLOC-2 subunit 1)	• Component of BLOC-2
HPS4	*HPS4*	HPS4 (BLOC-3 subunit 2)	• Component of BLOC-3 • Pulmonary fibrosis
HPS5	*HPS5*	HPS5 (BLOC-2 subunit 2)	• Component of BLOC-2
HPS6	*HPS6*	HPS6 (BLOC-2 subunit 3)	• Component of BLOC-2
HPS7	*DTNBP1*	Dystrobrevin binding protein 1	• Component of BLOC-1 (subunit 8) • Granulomatous colitis (some patients)
HPS8	*BLOC1S3*	BLOC1S3 (BLOC-1 subunit 3)	• Component of BLOC-1
HPS9	*BLOC1S6* (*PLDN*)	BLOC1S6 (BLOC-1 subunit 6)	• Component of BLOC-1 • Protein product also referred to as pallidin
HPS10	*AP3D1*	Adaptor related protein complex 3 δ1 subunit	• See AP-3 above • Neurologic impairment (e.g. seizures), immunodeficiency
HPS11	*BLOC1S5*	BLOC1S5 (BLOC-1 subunit 5)	• Component of BLOC-1
Chédiak–Higashi syndrome			
	LYST	Lysosomal trafficking regulator	• Abnormal vesicle trafficking and fission/fusion of lysosome-related organelles result in giant organelles (e.g. melanosomes, neutrophil granules [lysosomes], platelet dense granules)

Table 65.1 Disorders characterized by diffuse pigmentary dilution in which the genetic defect is known.

DISORDERS CHARACTERIZED BY DIFFUSE PIGMENTARY DILUTION IN WHICH THE GENETIC DEFECT IS KNOWN			
Disorder	**Gene**	**Protein product**	**Comments**
Griscelli syndrome			
GS1	*MYO5A*	Myosin Va (attaches melanosomes to actin filaments)	• In all three forms, melanosomes are retained in the body of the melanocyte rather than trafficking to the tips of dendrites for transfer to keratinocytes (see Fig. 65.10) • Silvery hair seen in all three forms • Myosin Va expressed in neurons (as well as melanocytes) and dysfunction leads to neurologic abnormalities
GS2	*RAB27A*	RAB27A (melanosomal membrane GTPase that binds melanophilin)	• GTPase also expressed in hematopoietic cells; defective release of granule contents from cytotoxic T cells leads to recurrent infections and hemophagocytic lymphohistiocytosis (HLH) • Rarely, neurologic impairment independent of HLH
GS3	*MLPH*	Melanophilin (links myosin Va and RAB27A)	• Melanophilin only expressed in melanocytes, so only pigmentary dilution in type 3
	MYO5A	Myosin Va F-exon deletion	• F-exon only expressed in melanocytes

*Recognized by Mel-5 antibody.
†Reflecting a founder effect, individuals of Puerto Rican origin have HPS1 and HPS3 (3:1 ratio); non-Puerto Ricans most commonly have HPS1, followed by HPS3 and HPS4 with ~70% of patients having one of these three types.
‡In addition to bleeding diathesis which is a characteristic finding in all types of HPS.

Table 65.1 Disorders characterized by diffuse pigmentary dilution in which the genetic defect is known. See Chapter 66 for details of clinical findings. AP-3, adaptor protein complex 3; BLOC, *b*iogenesis of *l*ysosome-related *o*rganelles *c*omplex; DHICA, 5,6-dihydroxyindole-2-carboxylic acid; ER, endoplasmic reticulum; MATP, membrane associated transporter protein; TYRP, tyrosinase-related protein.

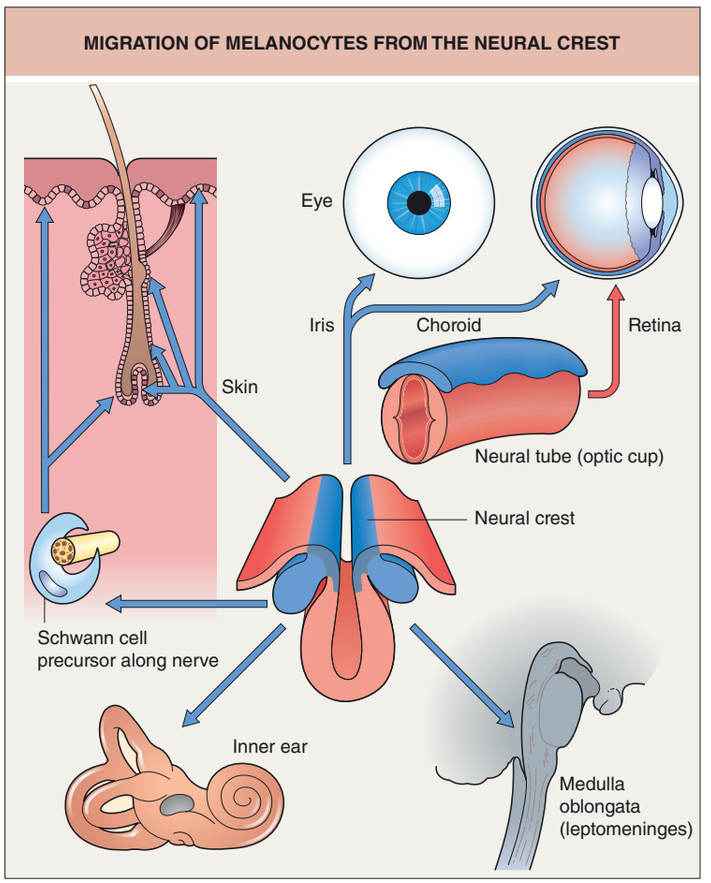


Fig. 65.1 Migration of melanocytes from the neural crest. Melanocytes migrate to the uveal tract of the eye (iris, ciliary body, and choroid), the leptomeninges, and the cochlea of the inner ear, as well as to the epidermis and hair follicle. Cutaneous melanocytes can also arise from Schwann cell precursors located along nerves in the skin, which also originate from the neural crest. The retina actually represents an outpouching of the neural tube. See Fig. 2.6 for location of melanocyte stem cells within the hair bulge.

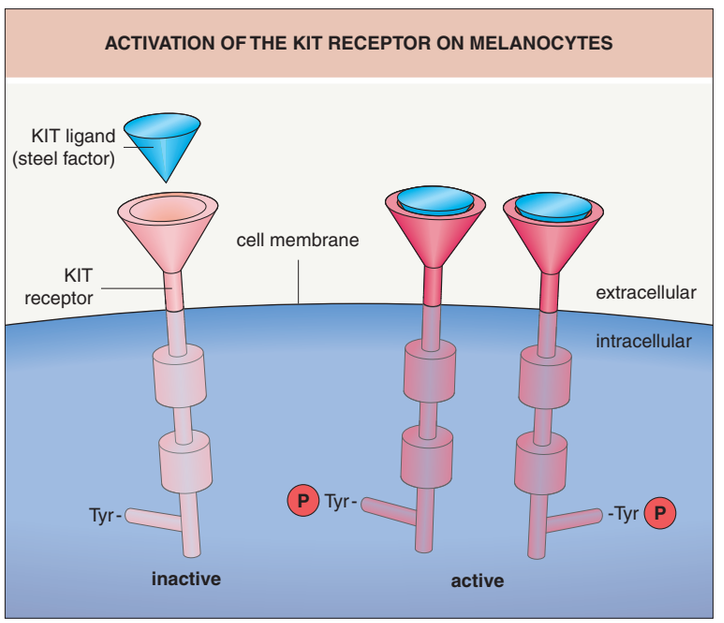


Fig. 65.2 Activation of the KIT receptor on melanocytes. Because the KIT receptor is a tyrosine kinase receptor, it has the ability to phosphorylate the tyrosine residues of other proteins as well as itself, i.e. autophosphorylation. Heterozygous germline mutations in *KIT* that prevent the activation of the KIT receptor by KIT ligand, also referred to as steel factor, lead to piebaldism, whereas somatic activating mutations in *KIT* are seen in patients with mastocytosis as well as melanomas (see Fig. 118.2). A form of familial progressive hyperpigmentation with or without hypopigmentation can result from heterozygous gain-of-function germline mutations in the gene that encodes KIT ligand[59]. P, phosphorylation; Tyr, tyrosine.

Based upon antigen expression and clinical observations, it is the former that is more sensitive to the destructive forces of vitiligo. As a result, repigmentation of patches of vitiligo in which the hairs are still pigmented relies upon activation and subsequent upward migration of the melanocytes present in the outer root sheath[11]. Of note, melanocyte stem cells have been identified within the lower portion of the hair follicle bulge, i.e. the lowermost permanent portion of the hair follicle (see Fig. 2.6). In addition, KROX20$^+$ cells, which give rise to the hair shaft, have been identified within the hair bulb. These hair progenitor cells produce KIT ligand/stem cell factor (SCF) which has been shown to be essential for hair pigmentation, i.e. mouse hairs turned white when *SCF* was deleted[13].

By immunohistochemical staining, melanocytes are identified within the fetal epidermis as early as 50 days of gestation[14]. Melanin-containing melanosomes are recognizable by electron microscopy during the fourth month of gestation. Except in benign and malignant neoplasms, melanocytes reside within the basal layer of the epidermis, a location they maintain throughout life (Fig. 65.5). Although the cell

body of the melanocyte sits on a specialized region of basal lamina, its dendrites come into contact with keratinocytes as far away as the mid stratum spinosum. This association of a melanocyte with ~30–40 surrounding keratinocytes to which it transfers melanosomes has been called the epidermal melanin unit[15]. However, melanocytes fail to form desmosomal connections with neighboring keratinocytes; their interactions with keratinocytes are via cadherins.

Although there is variation in the density of epidermal melanocytes/mm^2 when different *regions* of the body are analyzed via DOPA-stained epidermal sheets (Fig. 65.6), e.g. the density of melanocytes is greater in the genital region (~1500/mm^2) compared with the back (~900/mm^2), there are smaller differences between individuals when the same anatomic site is examined. This is despite the wide variation in pigmentation seen amongst humans. In other words, a person who has minimal baseline pigmentation and an inability to tan has a similar density of melanocytes when compared with a person whose skin is dark brown to black in color. Indeed, even patients with the most severe form of OCA, OCA type 1A, have a normal complement of epidermal melanocytes.

The major determinant of normal skin color is the activity of the melanocytes, i.e. the quantity and quality of pigment production, not the density of melanocytes[16]. Several factors play a role in determining the activity level of melanocytes; they include specific characteristics of the individual melanosomes (e.g. their dimensions) as well as both baseline (constitutive) and stimulated (facultative) levels and activity of the enzymes involved in the melanin biosynthetic pathway. The latter are influenced by receptor-mediated interactions with extracellular ligands such as MSH which then influence the expression of transcription factors including MITF (see Fig. 65.4). An example of an inhibitory signal is TGF-β1, which is expressed by adipose mesenchymal cells.

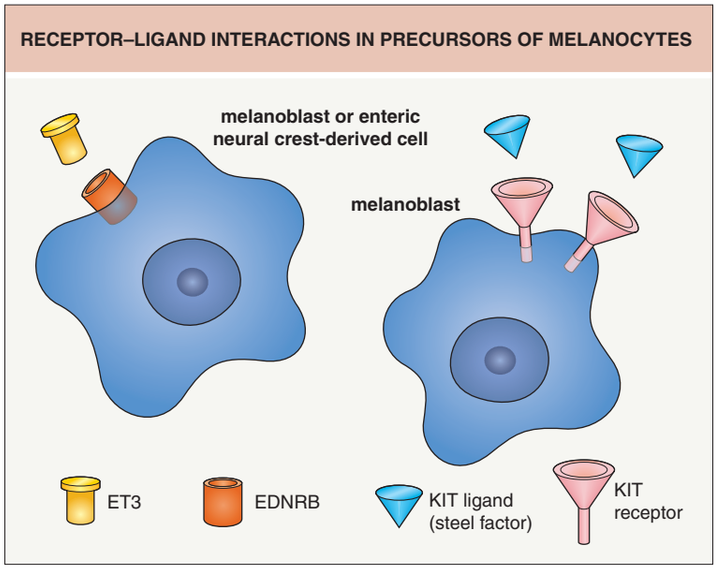


Fig. 65.3 Receptor–ligand interactions in precursors of melanocytes. In the developing embryo, melanoblasts expressing endothelin receptor type B (EDNRB) are stimulated to migrate by endothelin-3 (ET3) which is produced by the ectoderm and dermamyotome. Melanoblasts also require expression of the KIT receptor to maintain their normal chemotactic migration directed by production of KIT ligand/steel factor by the dermamyotome.

FORMATION AND FUNCTION OF THE MELANOSOME

Within the cytoplasm of melanocytes is a unique organelle known as the melanosome, in which melanin pigments are synthesized, deposited, and transported. The melanosome is most closely related to the lysosome and is referred to as a lysosome-related organelle[17]. Through compartmentalization, both organelles provide protection for the remainder of the cell – lysosomes protect against pro-enzymes such as proteases and melanosomes protect against melanin precursors (e.g. phenols, quinones) that can oxidize lipid membranes.

The melanosome contains both matrix proteins (chiefly PMEL/PMEL17/gp100), which form a scaffolding upon which the melanin is deposited, and enzymes such as tyrosinase that regulate melanin biosynthesis. Following their formation via ribosomes, all these proteins are found within the rough endoplasmic reticulum. In patients with OCA1 and OCA3, misfolded tyrosinase or aberrant tyrosinase-related protein 1 (TYRP1) plus tyrosinase polypeptides, respectively, accumulate within the endoplasmic reticulum (ER; Fig. 65.7)[18]. This retention leads to ER stress and activation of the unfolded protein response (UPR)[19]. As a result of the UPR, which acts as a form of quality control, these proteins

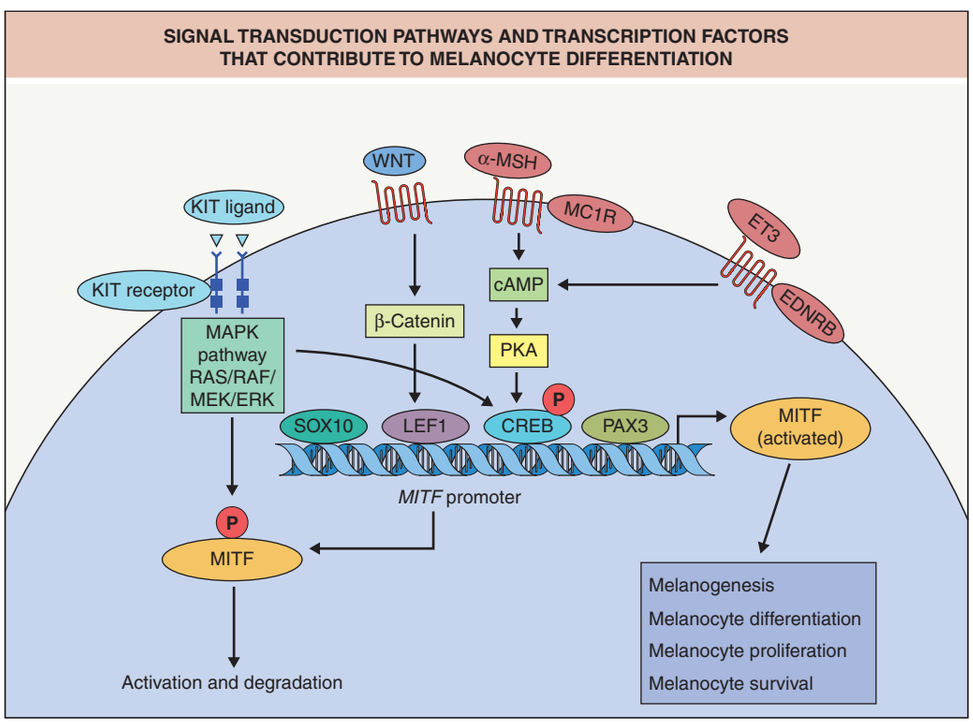


Fig. 65.4 Signal transduction pathways and transcription factors that contribute to melanocyte differentiation. MITF expression is activated early on during the transition from pluripotent neural crest cells to melanoblasts and is required for melanoblast survival[8]; mutations in *MITF* lead to Waardenburg syndrome, a classic neurocristopathy. MITF also regulates the expression of multiple pigment genes including those that encode tyrosinase, TYRP1, TYRP2, PMEL/PMEL17/gp100, and MART-1/Melan-A. Additional transcriptional targets are *CDK2*, *CDKN2A*, and *BCL-2* (whose protein product is an inhibitor of apoptosis)[9]. Small molecule inhibitors of SIK (salt-inducible kinase) can upregulate MITF, and application of these inhibitors to normal human skin led to an increase in pigmentation[60]. WNT signaling in melanocyte stem cells is critical for hair pigmentation[61]. Details of how activation of G-protein-coupled receptors leads to an increase in intracellular cAMP is shown in Fig. 65.14. Of note, EDNRB interacts with the G proteins GNAQ and GNA11, and activating mutations in the genes that encode these latter two proteins can lead to blue nevi and phakomatosis pigmentovascularis. EDNRB can also activate the MAPK pathway. Additional receptors include ET1 (activates protein kinase C), hepatocyte growth factor receptor, and GM-CSF receptor; the latter two activate the MAPK pathway. cAMP, cyclic adenosine monophosphate; CREB, cAMP response-element binding protein; ET3, endothelin-3; EDNRB, endothelin receptor type B; LEF1, lymphoid enhancer binding factor 1; MAPK, mitogen-activated protein kinase; MC1R, melanocortin 1 receptor; MITF, microphthalmia-associated transcription factor; MSH, melanoctye stimulating hormone; P, phosphorylation; PKA, protein kinase A; SOX10, SRY-box containing gene 10.

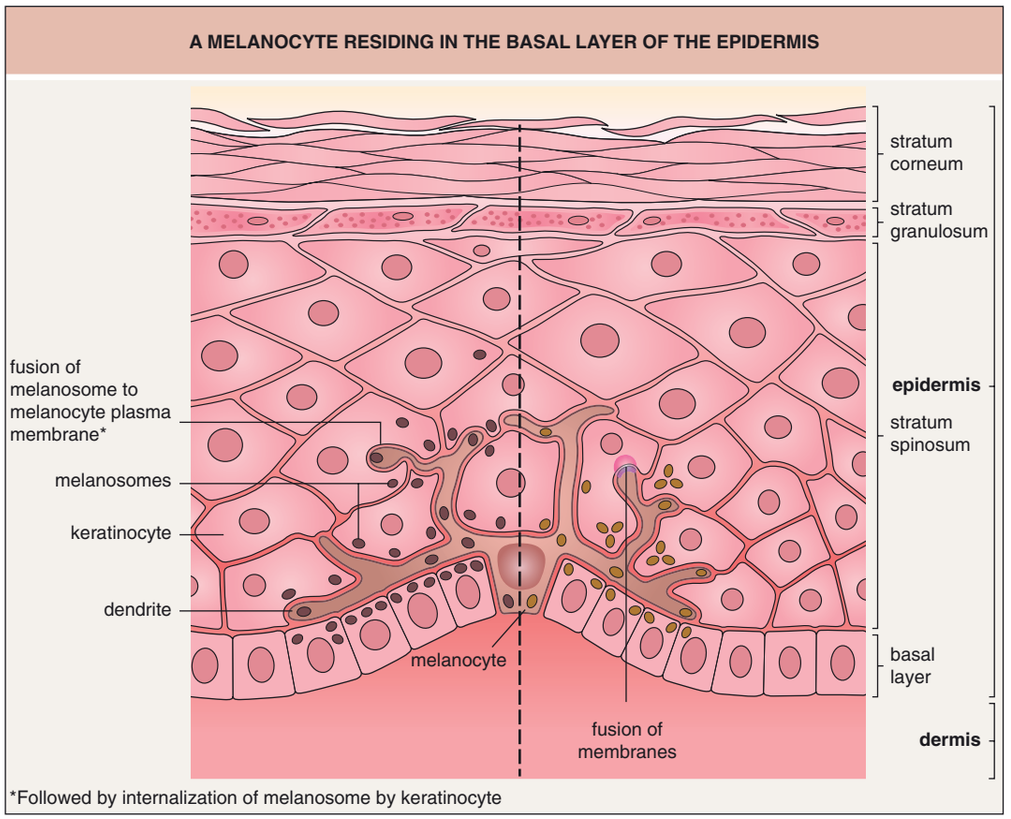


Fig. 65.5 A melanocyte residing in the basal layer of the epidermis. In normal skin, approximately every tenth cell in the basal layer is a melanocyte. Melanosomes are transferred from the dendrites of the melanocyte into neighboring keratinocytes of the epidermis, hair matrices, and mucous membranes; no transfer occurs in the pigment epithelium of the retina. The epidermal melanin unit refers to the association of a melanocyte with ~30–40 surrounding keratinocytes to which it transfers melanosomes. Note the different size and distribution of melanosomes in darkly pigmented skin (left) as compared to lightly pigmented skin (right).

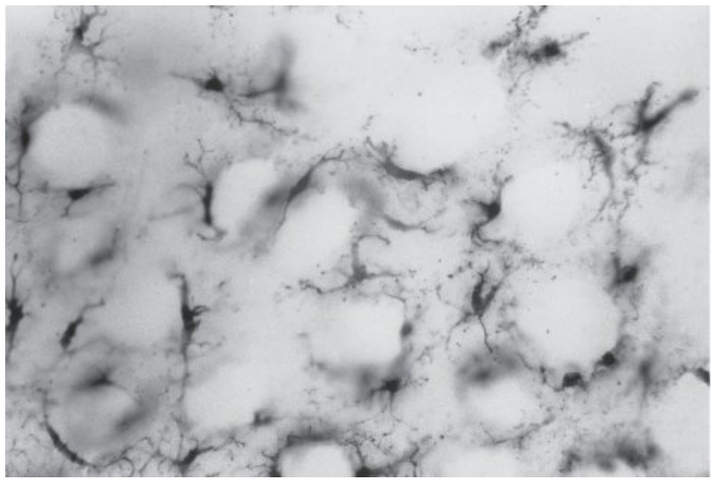


Fig. 65.6 Dihydroxyphenylalanine (DOPA)-stained epidermal sheet. Following incubation with 5 mM L-DOPA for 4–5 hours, the epidermal melanocytes turn black because they contain the enzyme tyrosinase, which converts DOPA to black DOPA-melanin. Note the multiple dendrites and regular spacing of the melanocytes.

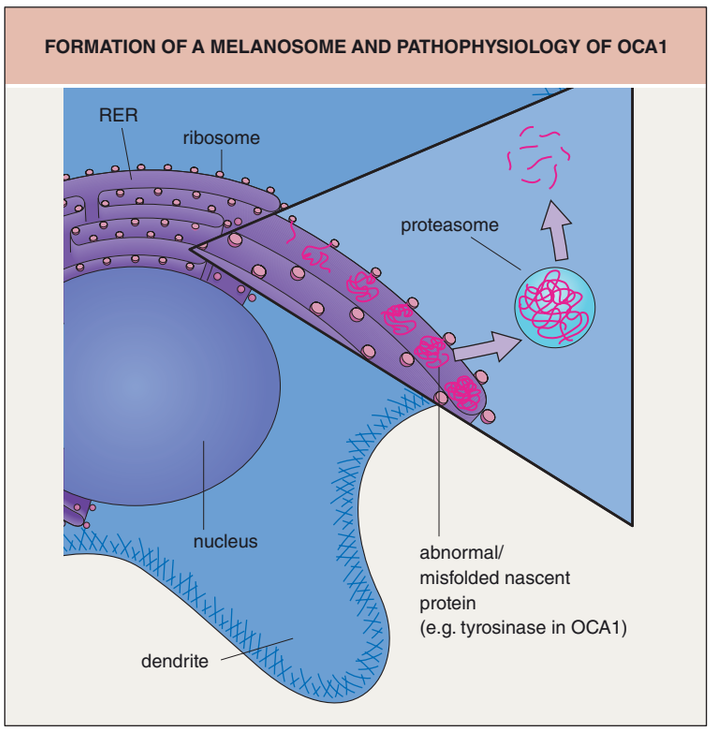


Fig. 65.7 Pathophysiology of oculocutaneous albinism type 1 (OCA1). In patients with OCA1 and OCA3, tyrosinase polypeptides are retained too long within the lumen of the RER and then become targets for destruction within proteasomes. Thus, they are not incorporated into melanosomes. RER, rough endoplasmic reticulum.

become targets for destruction by proteasomes and therefore are not incorporated into melanosomes.

Several of the enzymes in the melanin biosynthetic pathway are glycoproteins that require the attachment of sugars in order to gain full function. For this reason, they undergo post-translational modification in the ER and the Golgi apparatus and then join up with the matrix proteins (e.g. PMEL) to initiate melanogenesis. The targeting of proteins to the plasma membrane versus intracytoplasmic organelles and the targeting of specific proteins to the correct type of organelle are complicated processes. This triaging requires the equivalent of traffic police within the cell, an example of which is adaptor protein complex 3 (AP-3). Mutations in the gene that encodes the β3A subunit of AP-3 are responsible for a subset of patients with Hermansky–Pudlak syndrome (HPS2)[20]. Other forms of HPS are due to dysfunction of the proteins that serve as components of *b*iogenesis of *l*ysosome-related *o*rganelles complexes (BLOCs; Fig. 65.8)[21,22]. It then follows that these patients have dysfunction of more than one intracytoplasmic organelle, i.e. not just melanosomes but other lysosome-related organelles such as NK cell granules and platelet dense granules (see Table 65.1)[23]. The associated hypopigmentation can be explained by the failure to efficiently deliver melanogenic proteins, e.g. tyrosinase, TYRP1, to the melanosome.

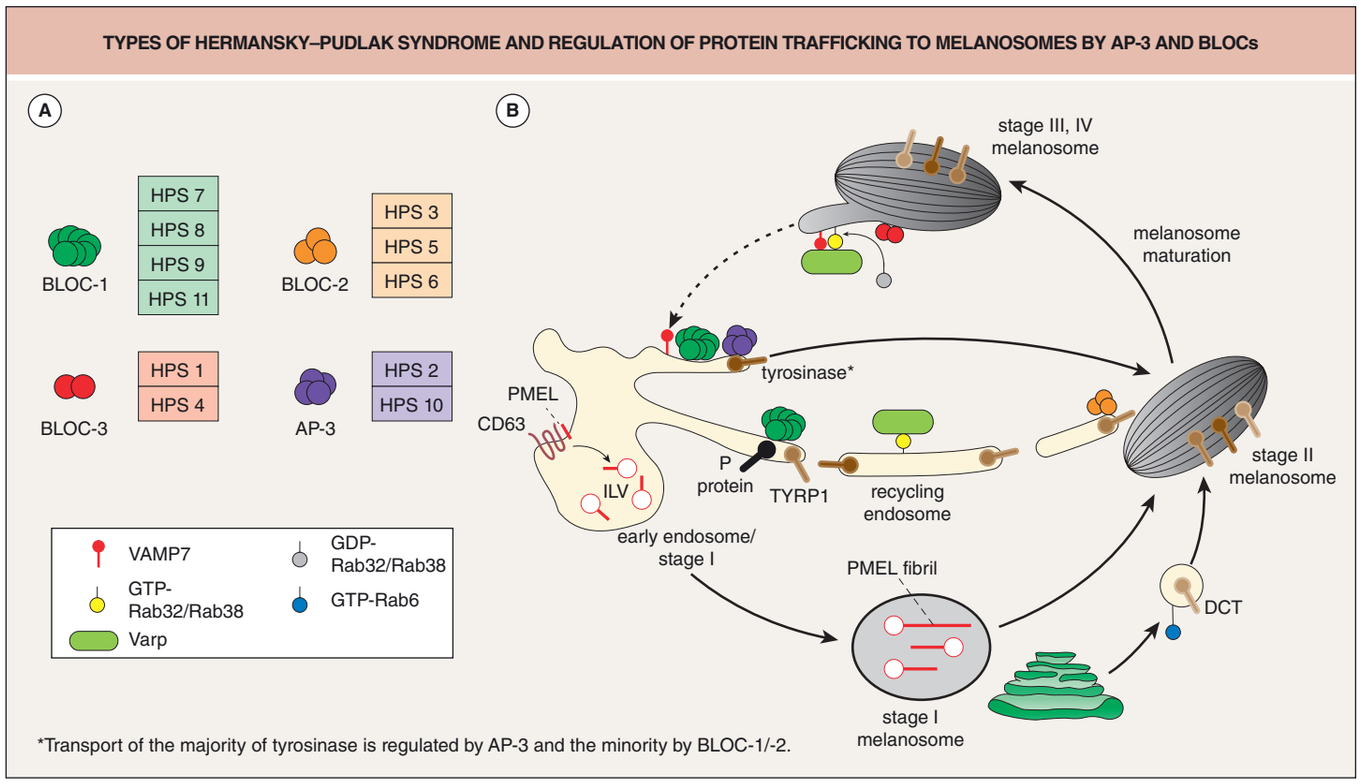


Fig. 65.8 Types of Hermansky–Pudlak syndrome and regulation of protein trafficking to melanosomes by adaptor protein complex 3 (AP-3) and biogenesis of lysosome-related organelles complexes (BLOCs). A Sorting of proteins to the correct organelles is a complex process and it requires regulators, in particular BLOCs and adaptor AP-3 in the case of lysosome-related organelles. The latter include melanosomes, platelet dense granules, and lytic granules of cytotoxic lymphocytes and natural killer cells. In Hermansky–Pudlak syndrome (HPS), there is abnormal routing of proteins to lysosome-related organelles due to dysfunction of components of BLOC-1, -2, or -3 or AP-3. **B** After glycosylation and processing within the endoplasmic reticulum and Golgi apparatus, several of the enzymes involved in the formation of melanin (including tyrosinase, TYRP1, and DCT) are packaged in vesicles and then combine with matrix proteins. The primary matrix protein is PMEL, also referred to as PMEL17 or gp100 and recognized by anti-HMB45 antibody; formation of the matrix fibers requires cleavage of PMEL by a proprotein convertase[62]. The Rab32/Rab38-Varp complex is required for the recovery of melanosomal cargoes, such as VAMP, from mature melanosomes (retrograde trafficking) and is also required for the transport of melanogenic enzymes from early endosomes to maturing melanosomes (anterograde trafficking). The dotted arrow indicates an as-yet-unidentified transport pathway. DCT, dopachrome tautomerase; ILV, intralumenal membrane vesicle; TYRP, tyrosinase-related protein; VAMP, vesicle-associated membrane protein; Varp, VPS9-ankyrin-repeat protein. *Adapted from Ohbayashi N, Fukuda M. Recent advances in understanding the molecular basis of melanogenesis in melanocytes. F1000Research 2020;9:608.*

FOUR MAJOR STAGES OF EUMELANIN MELANOSOMES

Stage	Description	Electron micrographs
I	Spherical; no melanin deposition	
II	Oval; obvious matrix in the form of parallel longitudinal filaments; minimal deposition of melanin; high tyrosinase activity	
III	Oval; moderate deposition of melanin; high tyrosinase activity	
IV	Oval; heavy deposition of melanin; electron-opaque; minimum tyrosinase activity	

Fig. 65.9 Four major stages of eumelanin melanosomes. *Courtesy Raymond Boissy, PhD.*

The progression of a melanosome from an organelle that lacks melanin to one that is fully melanized is arbitrarily divided, for convenience, into four stages (Fig. 65.9). Proteins that play a key role in the biogenesis of early-stage melanosomes are PMEL, MART-1/Melan-A, and the ocular albinism type 1 (OA1) G-protein-coupled receptor[24]. Cleavage and processing of PMEL, an amyloidogenic protein, leads to a fibrillar matrix that acts as a scaffold upon which melanin is deposited (see Fig. 65.8B)[25]. As melanin is deposited within the melanosome, the organelle migrates via microtubules into the dendrites in preparation for transfer into the neighboring keratinocytes, either within the epidermis or within the anagen hair matrix. In addition to microtubules, proteins such as kinesin and dynein are involved in the movement of melanosomes (Fig. 65.10)[26].

Within the dendrites, a specialized myosin protein, myosin Va, aids in the process of melanosome transfer by assisting attachment between the actin cytoskeleton beneath the plasma membrane and the organelle itself. RAB27A and melanophilin also play a role in ensuring this attachment. The importance of the interactions between these three proteins – myosin Va, RAB27A, and melanophilin – is illustrated by the three different forms of Griscelli syndrome in which there are mutations in the respective genes (see Table 65.1)[27,28]. The various phenotypes are explained by the tissue-specific expression of these three genes, e.g. neurons versus cytotoxic T cells. All three genes are expressed in melanocytes and as expected, the associated diffuse pigmentary dilution reflects a lack of transfer of melanosomes from the melanocytes to nearby keratinocytes. Histologically, numerous melanosomes are seen to congregate within the center of the melanocytes.

To reiterate, normal pigmentation of the skin is dependent on an orderly transfer of melanosomes from melanocytes to keratinocytes. When this transfer is disrupted, either in inherited diseases such as Griscelli syndrome or in acquired diseases such as atopic dermatitis, the result is hypopigmentation. In the former there is diffuse pigmentary dilution, whereas in the latter the hypopigmentation is circumscribed. Uptake of melanosomes by keratinocytes can be triggered by activation of the keratinocyte growth factor (KGF) receptor (KGFR/FGFR2b) by KGF, also referred to as fibroblast growth factor 7[29], as well as by activation of protease-activated receptor 2 (PAR-2)[30]. Inhibitors of PAR-2 receptor–ligand interactions, e.g. inhibitors of serine proteases, have led to cutaneous hypopigmentation in animal models[31].

In summary, the activity of melanocytes and their interactions with neighboring keratinocytes, rather than melanocyte density, is the

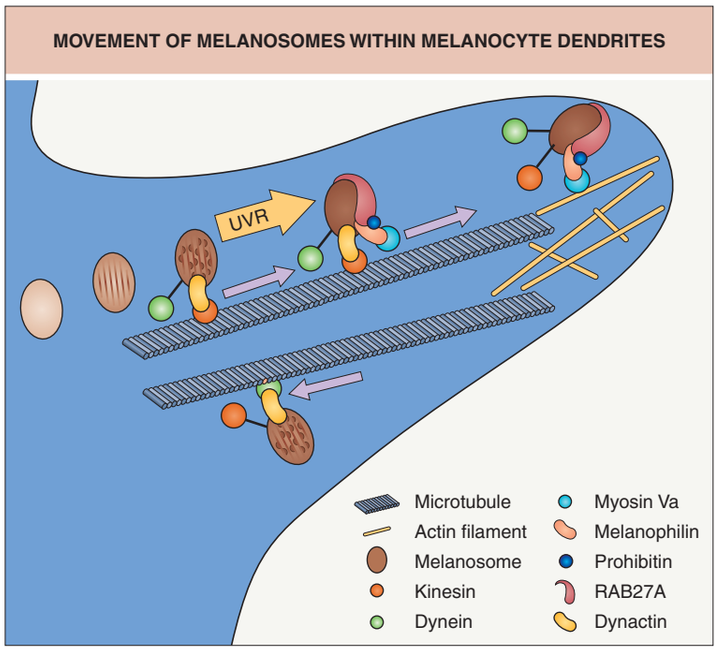


Fig. 65.10 Movement of melanosomes within melanocyte dendrites. As more melanin is deposited within the melanosomes, they migrate into the dendrites along microtubules in preparation for their transfer into neighboring keratinocytes. Kinesin and dynein serve as molecular motors for microtubule-associated anterograde and retrograde melanosomal transport, respectively, and UVR results in augmented anterograde transport via increased kinesin and decreased dynein activity. Myosin Va, which is linked to the melanosomal RAB27A GTPase by melanophilin, captures mature melanosomes when they reach the cell periphery and attaches them to the actin cytoskeleton.

VARIATION OF PREDOMINANT MELANOSOMAL STAGES WITH LEVEL OF CUTANEOUS PIGMENTATION

Pigmentation of skin	Predominant melanosomal stages	
	Melanocytes	Keratinocytes
Light	II, III	Occasional III
Medium	II, III, IV	III, IV
Dark	IV > III	IV

Table 65.2 Variation of predominant melanosomal stages with level of cutaneous pigmentation.

major determinant of normal skin color. The activity of a melanocyte is reflected in the number and size of melanized melanosomes it produces as well as in its efficiency at transferring those melanosomes to keratinocytes. For example, primarily stage II and stage III melanosomes are seen in lightly pigmented skin, whereas primarily stage IV melanosomes are seen in darkly pigmented skin (Table 65.2). An additional factor is the rate of degradation of the melanosomes once they are transferred to the surrounding keratinocytes and this is related in part to the size of the individual melanosomes. The smaller melanosomes of lightly pigmented skin are clustered in groups of two to ten within secondary lysosomes in the keratinocytes and are degraded by the mid stratum spinosum (Table 65.3)[16]. In lightly pigmented skin, increased autophagy also leads to increased degradation of melanosomes within both melanocytes and keratinocytes[32]. In darkly pigmented skin, the melanosomes are larger and singly dispersed within lysosomes of the keratinocytes; they are degraded more slowly, such that melanin granules can still be found in the stratum corneum. Melanosomes within the basal layer of the epidermis cap the nuclei and are more numerous within progenitor keratinocytes and stem cells[33].

REGULATION OF MELANIN BIOSYNTHESIS

This section begins with a review of the melanin biosynthetic pathway and then examines factors, both external and internal, that can

MELANOSOMES IN LIGHTLY PIGMENTED VERSUS DARKLY PIGMENTED SKIN

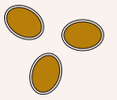
	Lightly pigmented skin	Darkly pigmented skin
Melanization	Stages II, III	Stage IV
Size (diameter)	0.3–0.5 microns	0.5–0.8 microns
Number per cell	<20	>200
Distribution of melanosomes within the lysosomes of keratinocytes	Groups of 2–10 	Single 
Degradation	Fast	Slow

Table 65.3 Melanosomes in lightly pigmented versus darkly pigmented skin.

influence the level of melanin production. The "starting material" for the production of melanin, both the brown–black eumelanin and the yellow–red pheomelanin, is the amino acid tyrosine. The key regulatory enzyme in the pathway is tyrosinase, which controls the initial biochemical reactions in this pathway (Fig. 65.11). It should then come as no surprise that the initial investigations into the molecular basis of OCA focused on the gene that encodes tyrosinase.

In OCA1A, the form of OCA where mutations in both copies of the tyrosinase gene lead to complete loss of enzyme activity, no melanin is found in the hair, skin, or eyes (see Table 65.1). However, in OCA1B, where there is decreased enzyme activity, pheomelanin is produced, especially in the hair as the patient ages. The formation of pheomelanin requires less tyrosinase activity than does the formation of eumelanin and therefore the formation of pheomelanin can be thought of as a default pathway (see Fig. 65.11).

The activity of tyrosinase is enhanced by DOPA and is stabilized by tyrosinase-related protein 1 (TYRP1) (see below). Competitive inhibitors of tyrosinase activity include hydroquinone, which is used to treat disorders of hyperpigmentation such as melasma, and L-phenylalanine. In patients with phenylketonuria (PKU), there is a diffuse pigmentary dilution due to elevated levels of L-phenylalanine resulting from a deficiency in the enzyme L-phenylalanine hydroxylase that converts L-phenylalanine to L-tyrosine[16]. The characteristic blonde hair of PKU can undergo darkening when the patient is on a low-phenylalanine diet. Of note, tyrosinase is a copper-requiring enzyme and it has two copper-binding sites. Rare cases of copper deficiency can lead to diffuse cutaneous pigmentary dilution, and in patients with Menkes disease, where a transmembrane Cu^{2+}-transporting ATPase that delivers copper to the trans-Golgi network and melanosomes is dysfunctional[34], the kinky hair is hypopigmented.

In a test tube, L-DOPA can spontaneously oxidize to form melanin, an insoluble biopolymer. For this reason, it was originally thought that tyrosinase was the sole enzyme involved in melanin biosynthesis. However, by the late 1970s, it was becoming clear that there were additional control points in the pathway (see Fig. 65.11). For example, dopachrome tautomerase, also known as tyrosinase-related protein 2 (TYRP2), which like TYRP1 shares similarities in its amino acid sequence with tyrosinase, converts DOPAchrome to 5,6-dihydroxyindole-2-carboxylic acid (DHICA). In mice and humans, TYRP1 stabilizes tyrosinase[35] and mutations in both copies of *TYRP1* lead to OCA3 (see Table 65.1).

Decreased function of yet another transmembrane protein, the P protein, leads to OCA2[36]. Based upon its amino acid sequence, a prediction was made that the P protein was involved in the transport of small molecules across the membrane of the melanosome. Originally, tyrosine, the initial precursor in the melanin biosynthetic pathway, was considered the most likely candidate for transmembrane transport. However, the P protein is now thought to play a role in increasing the internal pH of the melanosome, as acidification can reduce the activity of tyrosinase[37]. P protein may also regulate glutathione levels within the melanocyte's intracellular compartments.

Melanins represent a group of complex polymers whose functions vary from camouflage to the quenching of oxidative free radicals generated

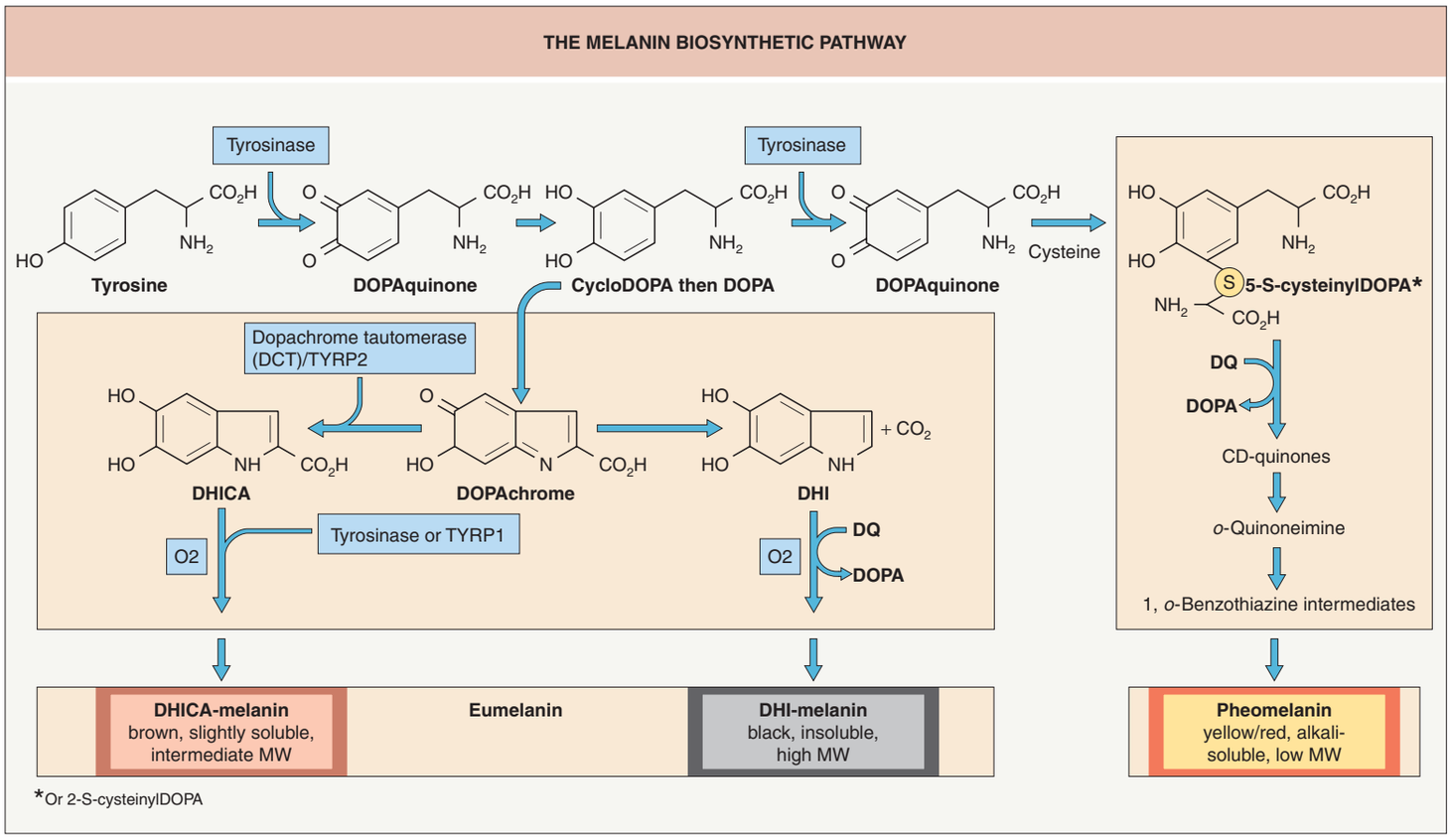


Fig. 65.11 The melanin biosynthetic pathway. The pathway includes the sites of dysfunction in OCA1 (tyrosinase) and OCA3 (TYRP1). The two major forms of melanin in the skin and hair are brown–black eumelanin and yellow–red pheomelanin. The enzymes are transmembrane proteins located within the melanosome. DHI, 5,6-dihydroxyindole; DHICA, 5,6-dihydroxyindole-2-carboxylic acid; DOPA, dihydroxyphenylalanine; MW, molecular weight; TYRP, tyrosinase-related protein.
Adapted from Hearing VJ. Determination of melanin synthetic pathways. J Invest Dermatol 2011;131:E8–E11.

via exposure to UV radiation (UVR). The level and type of melanin production is a complex interplay of the activity of the various enzymes involved in the biosynthetic pathway as well as the activity of proteins such as the P protein and those that stabilize the activity of tyrosinase (e.g. TYRP1). Several factors are known to influence the activity of these key proteins of melanogenesis, and they include α-MSH, basic fibroblast growth factor (bFGF), endothelin-1, KIT ligand, and UVR (see below).

Among the multiple protein products of the proopiomelanocortin (POMC) gene are adrenocorticotropic hormone (ACTH), β-endorphin, and the three forms of MSH (α, β, and γ) (Fig. 65.12); in humans, α-MSH represents the major biologically active form of MSH. The primary site of expression of *POMC* is the pituitary gland; however, other sites of expression include the testis, the endothelium, and, of particular importance, epidermal keratinocytes. Although MSH is classically associated with the pigmentary system, this peptide has a wide range of biologic properties, including suppression of inflammation and regulation of body weight. For example, mutations in *POMC* can result in severe early-onset obesity, adrenal insufficiency, and red hair[38]. It then follows that mutations in the genes that encode the melanocortin receptors to which the protein products of *POMC* bind can lead to similar clinical findings; for example, mutations in *MC4R* are associated with morbid obesity and variant alleles in *MC1R* are associated with red hair (see below). Of note, subcutaneous afamelanotide (4-norleucyl-7-phenylalanine-α-MSH), which has enhanced binding to MC1R compared to α-MSH, can lead to cutaneous hyperpigmentation. When subcutaneous implants of afamelanotide were administered monthly, patients with erythropoietic protoporphyria (EPP) experienced fewer phototoxic reactions and could tolerate more direct sunlight without pain while patients with vitiligo had more rapid and extensive repigmentation in response to treatment with UVB. More recently, once-daily dersimelagon, a novel oral MC1R agonist, improved sun exposure tolerance in patients with EPP[38a].

There are five major melanocortin receptors, all of which have seven transmembrane domains (Table 65.4; Fig. 65.13). Although the MC1R is present on a variety of cells within the skin, from endothelial cells to fibroblasts, the highest density of this receptor is found on melanocytes[39].

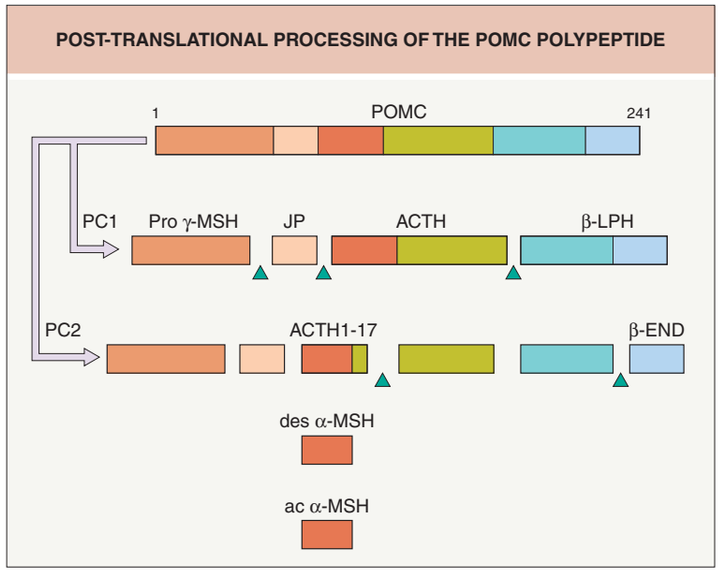


Fig. 65.12 Post-translational processing of the POMC polypeptide. Pituitary hypersecretion of ACTH and/or α-MSH can lead to generalized hyperpigmentation in patients with Addison disease. ac, acetylated; ACTH, adrenocorticotropic hormone; des, desacetyl; END, endorphin; JP, joining peptide; LPH, lipotropic hormone; MSH, melanocyte stimulating hormone; PC, prohormone-converting enzyme; POMC, proopiomelanocortin.

As in the case of the β-adrenergic receptor, the MC1R is a G-protein-coupled receptor, i.e. it uses proteins that bind guanosine triphosphate (GTP) and guanosine diphosphate (GDP) as intermediary messengers (Fig. 65.14). Following the binding of MSH to the MC1R, the protein pair interacts with a complex of G proteins. The GTP-$G_s\alpha$ subunit then

activates adenylate cyclase, leading to increased production of cyclic adenosine monophosphate (cAMP) within the melanocyte. An increase in the intracellular concentration of cAMP leads to an increase in tyrosinase activity and eumelanin production via MITF (see Fig. 65.4). If the MC1R is dysfunctional and fails to initiate a significant rise in the intracellular level of cAMP, then pheomelanogenesis is favored (Fig. 65.15). Of note, the majority of individuals with red hair are compound heterozygotes or homozygotes for a variant R allele in the gene that encodes the MC1R[1,40] (see Fig. 65.13). However, the variation in human hair color is complex, with over 120 genes identified[41].

MC1R also interacts with a protein known as the agouti protein (mouse) or agouti signaling protein (ASIP; human). Agouti is a term used to describe the banding of hairs seen in some mammals, including dogs, foxes and mice, that is due to alternating production of eumelanin and pheomelanin (Fig. 65.16). The production of agouti protein by the cells in the hair follicle papillae is cyclic, and, when the agouti protein is present, it effectively competes with MSH and the formation of pheomelanin within pheomelanosomes is favored[42,43] (see Fig. 65.15). Compared to eumelanosomes, pheomelanosomes are characterized by a more spherical shape and the presence of an unstructured matrix with vesicular bodies.

An enhancement of pigment production can be seen following exposure of melanocytes to agents that increase intracytoplasmic levels of cAMP such as cholera toxin, forskolin[44], dibutyryl cAMP, and MSH (see Fig. 65.14). The activation of protein kinase A (PKA) by cAMP leads to the phosphorylation of various proteins, which can result in their activation. One of the proteins that is phosphorylated by PKA is the *c*AMP *r*esponse-*e*lement *b*inding protein (CREB), which functions as a transcription factor, regulating the expression of other genes, including *MITF* (see Fig. 65.4). Patients with the McCune–Albright syndrome (polyostotic fibrous dysplasia) are mosaics for an activating mutation in the gene that encodes the G protein $G_s\alpha$ (see Fig. 65.14). As a result, the cAMP cascade is permanently "turned on" and, with continued transcription of CREB-controlled genes, there is hyperplasia of the bones and endocrine organs, albeit in a mosaic pattern. Presumably within the melanocytes of the segmental café-au-lait macules typical of this disorder, the increase in intracellular cAMP leads to increased tyrosinase activity and eumelanin production.

Exposure of melanocytes to phorbol esters, e.g. tetradecanoyl phorbol acetate (TPA), can lead to increased melanin formation via the activation of protein kinase C (PKC) (Fig. 65.17). Growth factors, including bFGF and KIT ligand, can also increase the pigment content within melanocytes whereas KIT receptor inhibitors (e.g. imatinib) can lead to hypopigmentation. Endothelin-1, a small peptide originally isolated from endothelial cells, is produced by keratinocytes and can lead to an increase in tyrosinase activity followed by an increase in melanin production.

In addition to ultraviolet radiation (see below), inflammation can lead to hyper- or hypopigmentation. Prostaglandin E_2/F_2 and interleukin (IL)-33, mediators produced by both keratinocytes and fibroblasts, can lead to activation of melanocytes. Inhibitors of pigment production include interferon-γ, tumor necrosis factor (TNF), IL-4, and IL-6[45].

Multiple genes have been implicated as playing a role in normal pigment variation in humans, including: (1) *MC1R* and *ASIP*; (2) several genes that play a role in OCA, e.g. *TYR*, *OCA2*, *TYRP1*, *SLC45A2*, *SLC24A5* (see Table 65.1); (3) *KITLG* which encodes KIT ligand; (4) *TPCN2* which encodes an ion channel transporter; and (5) *IRF4* which encodes interferon regulatory factor 4[2–4]. The presence of a variant (rather than the African ancestral) allele of *SLC24A5*, whose protein product is a putative cation exchanger in the melanosomal membrane, correlates with lighter skin color[5]. In addition, variants in *OCA2* are thought, at least in part, to determine the normal phenotypic variation in human eye color[2]. A haplotype with several polymorphisms in *ASIP* (and presumably a gain of ASIP function) has been associated with red or blonde hair, freckling, and a tendency to burn, while variants that lead to destabilized *ASIP* mRNA have been associated with darker skin phototypes[3,46,47]. A polymorphism in the regulatory region of *KITLG* that reduces its responsiveness to the WNT-activated transcription factor LEF1 is associated with blonde hair[48], and in mice, decreased lef1 leads to light-colored hair. Of note, some loss-of-function mutations in

MAJOR FORMS OF THE MELANOCORTIN RECEPTOR

Receptor	Distribution, major (minor)	Ligands
MC1R*	Melanocytes (keratinocytes, fibroblasts, endothelial cells, antigen-presenting cells)	α-MSH, ACTH > β-MSH
MC2R	Adrenal cortex (adipocytes)	ACTH
MC3R†	Brain (gut, placenta)	α-, β-, γ-MSH, ACTH
MC4R†	Brain	α-, β-MSH, ACTH
MC5R	Peripheral tissues, e.g. sebaceous glands, fibroblasts, adipocytes	α-, β-MSH, ACTH

*Antagonistic ligands – agouti protein (mouse) and agouti signaling protein (ASIP; human).
†Antagonistic ligand – agouti-related protein (AGRP).

Table 65.4 Major forms of the melanocortin receptor (MCR). ACTH, adrenocorticotropic hormone; MSH, melanocyte stimulating hormone.

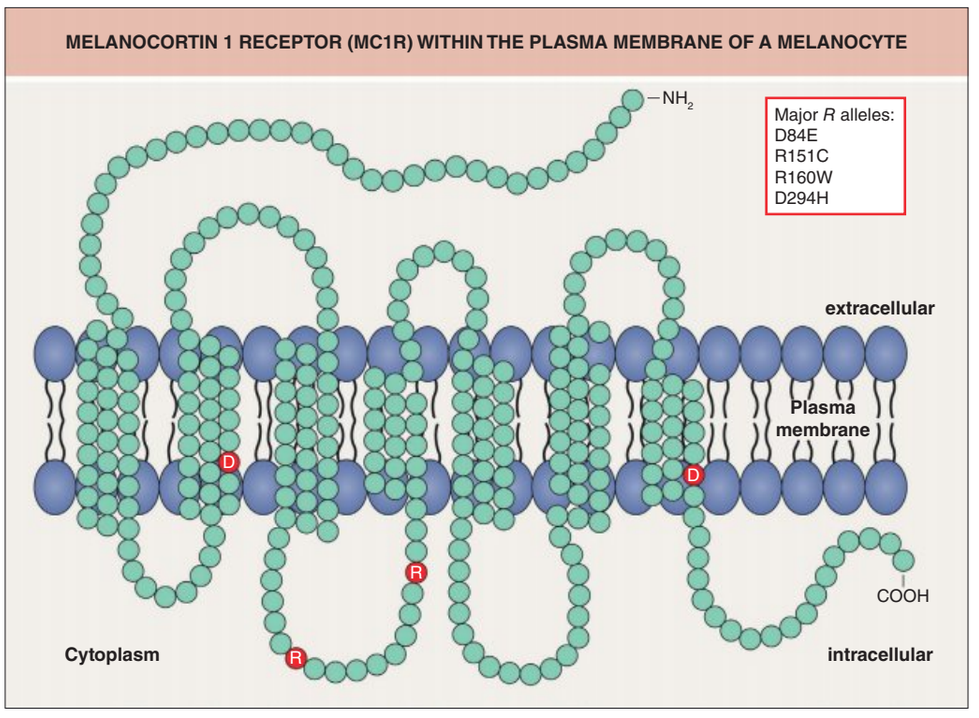


Fig. 65.13 Melanocortin 1 receptor (MC1R) within the plasma membrane of a melanocyte. MC1R has seven transmembrane domains and is a G-coupled receptor (see Fig. 65.14). There are numerous genetic variants of the MC1R. The null or hypomorphic *R* alleles D84E, R151C, R160W, and D294H have red hair odds ratios of 62, 118, 50, and 94, respectively; the low penetrance *r* alleles of V60L, V92M, and R163Q have red hair odds ratios of 6, 5, and 2, respectively[63]. In general, *R/R* individuals have red hair and lightly pigmented skin.

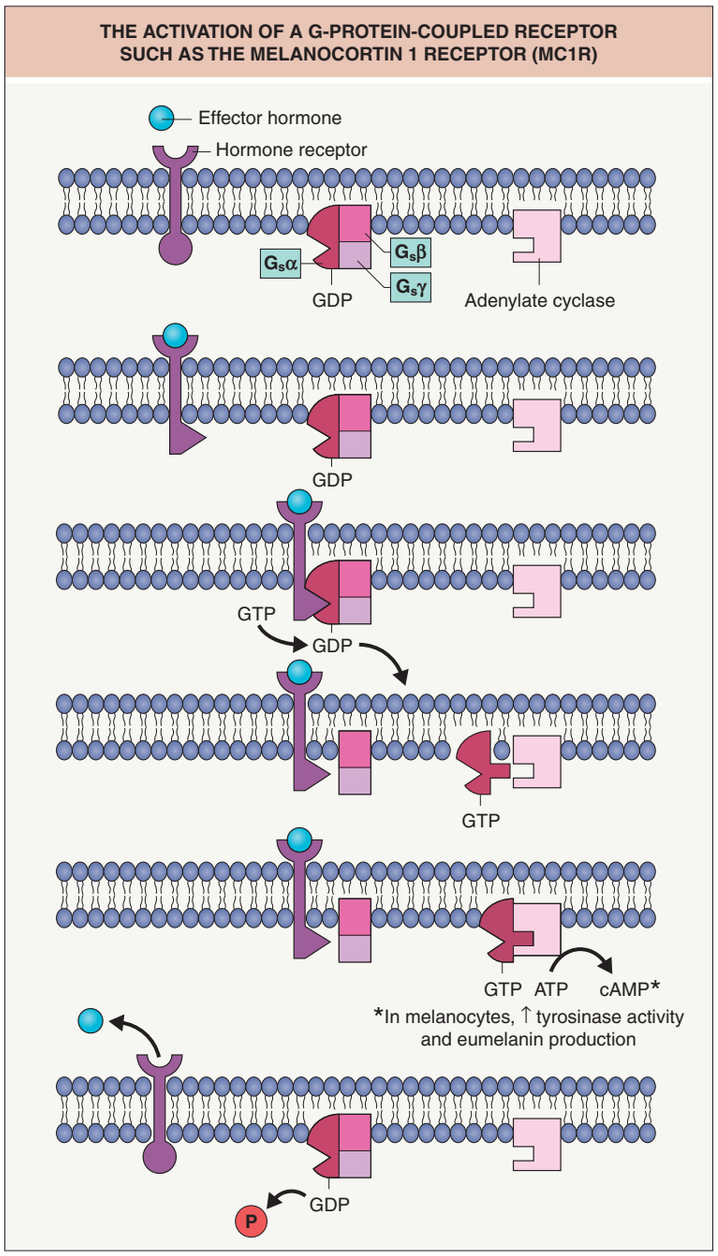


Fig. 65.14 Activation of a G-protein-coupled receptor such as the melanocortin 1 receptor (MC1R). In the case of the MC1R, the increase in the intracellular concentration of cAMP leads to an increase in tyrosinase activity and eumelanin production. GDP, guanosine diphosphate; GTP, guanosine triphosphate; P, phosphate group; S, stimulatory. *Adapted from Alberts B. Molecular Biology of the Cell. Garland Publishing; 1989.*

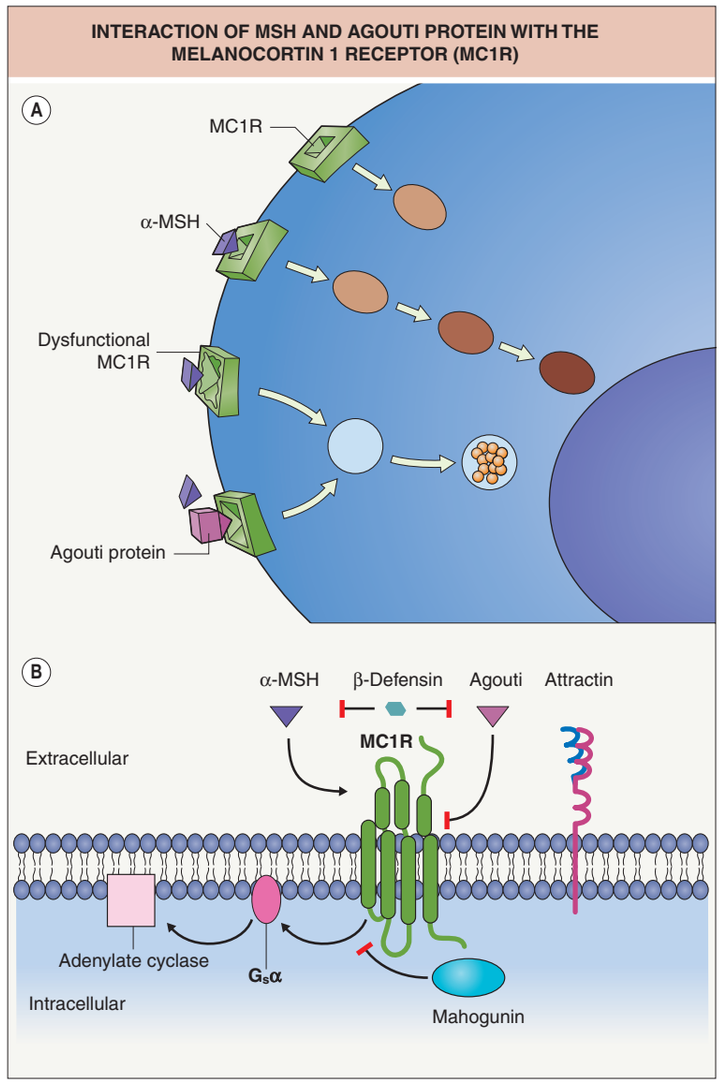


Fig. 65.15 Interaction of melanocyte stimulating hormone (MSH) and agouti protein with the melanocortin 1 receptor (MC1R). A There is baseline activity of the MC1R, enhanced by binding with MSH. Agouti protein represents an antagonist ligand for the MC1R whose binding can lead to pheomelanogenesis. Dysfunction of the MC1R can also lead to pheomelanogenesis, as in the case of humans with red hair. **B** Interactions are actually more complex, in that to be fully effective, agouti requires attractin and mahogunin; the former aids in the binding of agouti to MC1R while the latter acts on the cytosolic side. There is also a neutral agonist, β-defensin, which interferes with both agonist and antagonist binding. *Adapted from Schiaffino MV. Signaling pathways in melanosome biogenesis and pathology. Int J Biochem Cell Biol 2010;42:1094–104.*

MC1R confer a risk for developing cutaneous melanoma, independent of pigmentary phenotype[40].

In humans, graying or whitening of hair is a normal aging phenomenon. There is evidence that reactive oxygen species accumulate within affected hair follicles and lead to oxidative damage of hair follicle melanocytes[49]. Hair bulb melanocytes are thought to undergo apoptosis first, followed by depletion of precursor cells in the bulge region. However, more recent studies of graying hairs have pointed to a reduction in the migration of melanocyte stem cells from the bulge region[49a]. Hair bulb melanocytes that disappear fail to express TYRP2 and SOX10. The role of SCF production by KROX20$^+$ cells within the hair bulb was discussed previously. Lastly, hyperactivation of sympathetic nerves has been shown to drive depletion of melanocyte stem cells[50].

Ultraviolet Radiation (UVR)

Following a single exposure to UVR, an increase in the size of melanocytes can be observed, along with an increase in tyrosinase activity[16]. Repeated exposures to UVR lead to an increase in the number of stage IV melanosomes transferred to keratinocytes, as well as an increase in the number of active melanocytes. When chronically sun-exposed sites (e.g. the upper outer arm) are compared with non-sun-exposed sites (e.g. the upper inner arm), the density of melanocytes is up to two times greater in sun-exposed sites[51]. Melanocytes, like other neural-derived tissues, have a low mitotic rate, and whether this increase in number represents an increase in mitotic rate or an activation of "inactive" melanocytes or melanocyte precursors is not known. Senescent fibroblast-derived GDF15 may play a role in the hyperpigmentation of photoaged skin via β-catenin signaling[52].

Following exposure to UVA irradiation, an *immediate pigmentary darkening* can be observed, which occurs within minutes and fades over 20–30 minutes. It is clinically most obvious in darkly pigmented skin and is thought to represent oxidation of pre-existing melanin or melanin precursors. Given its transient nature, it does not provide photoprotection. *Delayed tanning* is visible within 24–72 hours after exposure to UVB and UVA radiation and represents new pigment production via an increase in tyrosinase activity. In addition to an increase in melanocyte

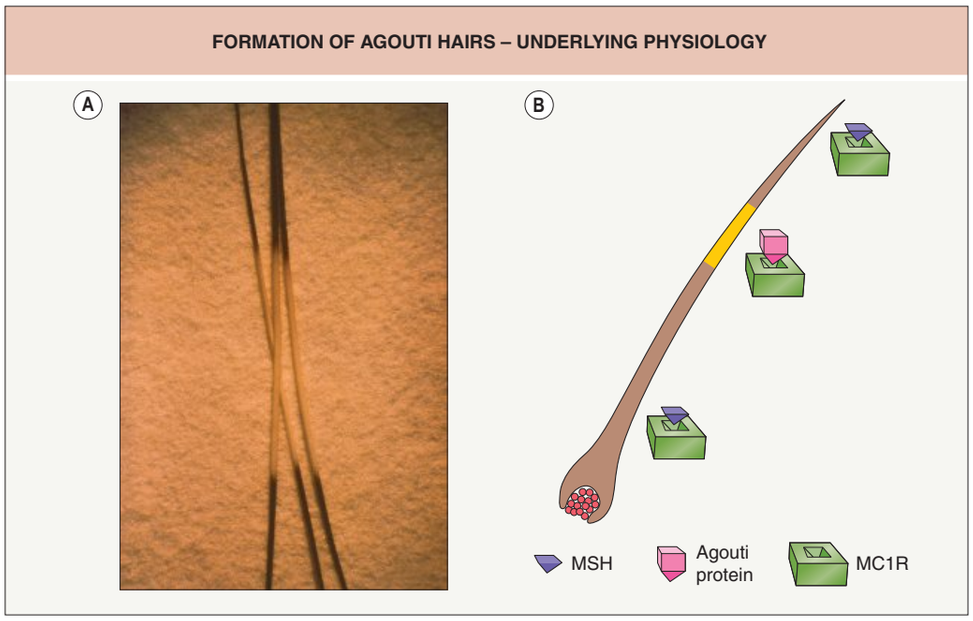


Fig. 65.16 Formation of agouti hairs – underlying physiology. A Fox hairs with alternating eumelanin and pheomelanin production within individual hairs, a pattern referred to as agouti. **B** Explanation for the agouti pattern based on different ligands interacting with the melanocortin 1 receptor (MC1R). Both gain-of-function mutations at the agouti locus and loss-of-function of MC1R can lead to yellow-haired mice. In the CNS, an abundance of agouti protein leads to obesity, and yellow mice with gain-of-function mutations at the agouti locus are also obese[64].

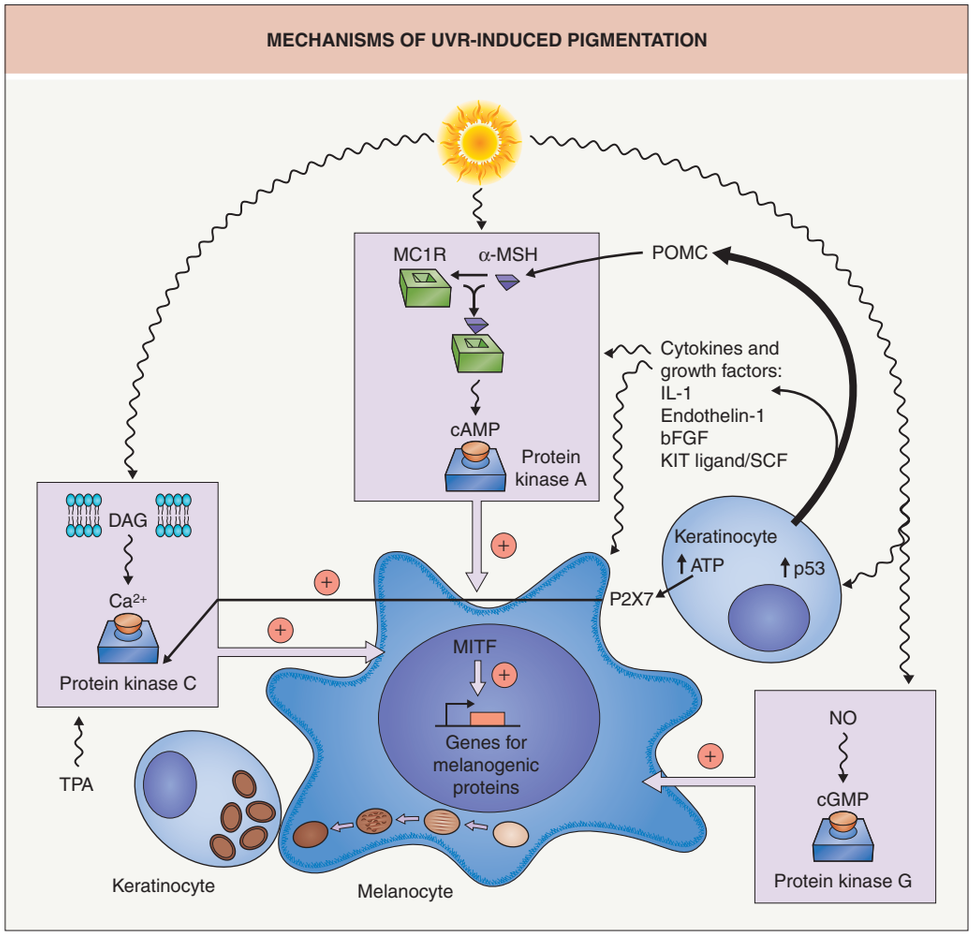


Fig. 65.17 Mechanisms of UVR-induced pigmentation. These include an increase in one or more of the following: (1) expression of proopiomelanocortin (POMC) and its derivative peptides by cells within the skin, in particular keratinocytes; (2) the number of melanocortin 1 receptors (MC1R) on melanocytes; (3) the release of diacylglycerol (DAG) from the plasma membrane, which activates protein kinase C; (4) the induction of an SOS response to UVR-induced DNA damage; (5) nitric oxide (NO) production, which activates the cGMP pathway; and (6) production of cytokines and growth factors by keratinocytes. As a result, there is enhanced transcription of the genes that encode microphthalmia-associated transcription factor (MITF) and melanogenic proteins including tyrosinase, tyrosinase-related protein 1 (TYRP1), TYRP2, and PMEL/PMEL17/gp100. In addition, melanocyte dendricity and transfer of melanosomes to keratinocytes is stimulated via increased activity of Rac1 (involved in dendrite formation), the ratio of kinesin to dynein, and expression of protease-activated receptor-2 (PAR-2; involved in melanosome transfer). Increased POMC expression in keratinocytes followed by processing to β-endorphin (in addition to α-MSH) may play a role in addiction to ultraviolet light. ATP, adenosine 5′-triphosphate; P2X7, purinergic receptors type 2 X7; TPA, tetradecanoyl phorbol acetate.

size and number, tyrosinase activity, and transfer of melanosomes to keratinocytes, the response to PUVA includes an alteration in size and aggregation pattern of melanosomes, i.e. from smaller and grouped to larger and singly dispersed (see Table 65.3).

UVR may work by increasing one or more of the following:

- transcription of the tyrosinase gene (via MITF)
- the number or activity of MC1R on melanocytes
- the expression of POMC and its derivative peptides by keratinocytes and several cell types within the dermis (e.g. endothelial cells, sebocytes, lymphocytes)
- the release of diacylglycerol from the plasma membrane, which activates protein kinase C
- an activation of the nitrous oxide/cGMP pathway
- the production of cytokines and growth factors by keratinocytes (e.g. endothelin-1)
- the induction of an SOS response to UVR-induced DNA damage[39,53,54]
- transactivation of the *POMC* promoter by p53[55,56]
- the ratio of kinesin to dynein, affecting melanosome transport (see Fig. 65.10).

The inability of the majority of red-haired individuals to develop a tan following exposure to UVR can be explained, at least in part, by dysfunction of their melanocyte MC1R. This phenomenon, along with the production of oxygen radicals following the UV irradiation of pheomelanins, probably contributes to the increased incidence of both cutaneous melanoma and keratinocyte carcinomas in persons with red hair. In addition, chemiexcitation of melanin derivatives induces DNA photoproducts long after UV exposure[57]. Based upon a large genome-wide association study in individuals of European ancestry, the ability to tan was associated with 20 loci, including ten that were not previously associated with pigment-related phenotypes[58].

Additional figure and table on Genes associated with physiologic variation in human pigmentation, available in our eBook (see inside front cover for access code).

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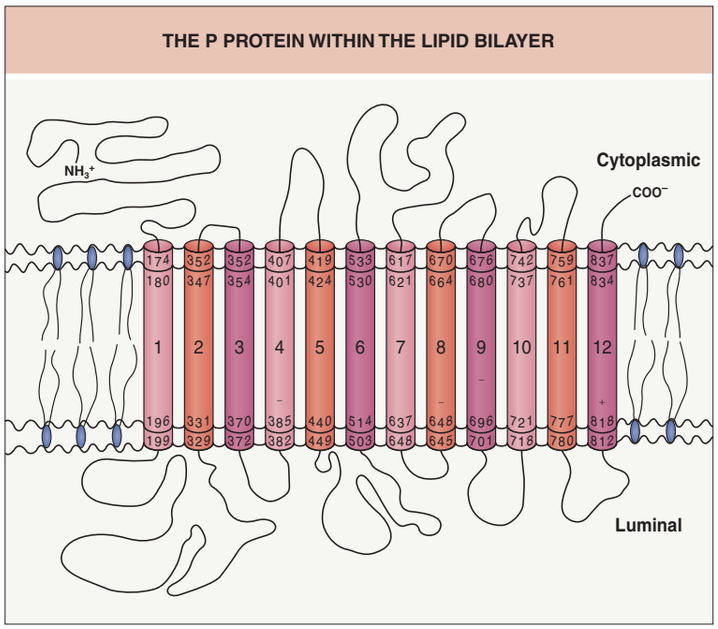
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eFig. 65.1 The P protein within the lipid bilayer. The polypeptide has 12 putative transmembrane domains. The solute carrier family 45 member 2 (previously known as membrane-associated transporter protein), which is dysfunctional in OCA4, has a similar configuration within the plasma membrane. *Adapted from Rinchik EM, Bultman SJ, Horsthemke B, et al. A gene for the mouse pink-eyed dilution locus and for human type II oculocutaneous albinism. Nature 1993;361:72–6.*

GENES ASSOCIATED WITH PHYSIOLOGIC VARIATION IN HUMAN PIGMENTATION									
Gene	**Protein**	**Selected variant(s): amino acid alteration (if applicable) or SNP**	**Skin color, sun sensitivity, and freckles**	**Hair color**	**Eye color**	**Skin cancer risk***	**Population frequencies of variant haplotype**		
							European	**East Asian**	**African**
TYR	Tyrosinase	Ser192Tyr	Freckles	–	–	SCC	0.4	0	0
		Arg402Gln	Fair, sun-sensitive	Light (weak)	Blue (vs green)	Melanoma, BCC	0.4	0	0.07
TYRP1	TYRP1	rs1408799 C>T	Sun-sensitive	Light	Blue	Melanoma	0.7	0.02	0.2
		rs2733832 C>T	–	Light	Blue	–	0.6	0.02	0.07
OCA2 (P)	P protein	Arg305Trp	–	–	Brown	–	0.07	0.04	0.02
		Arg419Gln	–	–	Green/hazel	Melanoma, BCC	0.07	–	0
		His615Arg	–	–	Brown	–	0	0.5	0
		rs12913832 T>C in HERC2†	Fair	Light	Blue	Melanoma (weak)	0.75	–	–
SLC45A2	MATP	Glu272Lys	Dark	Dark	Non-blue	–	0	0.4	0.05
		Leu374Phe	Fair	Light	Blue	Melanoma, NMSC	0.95	0.01	0
SLC24A5	NCKX5	Ala111Thr	Light	–	–	–	0.99	0.01	0.02
SLC24A4	SLC24A4	rs12896399 G>T	Sun-sensitive	Light	Blue (vs green)	–	0.6	0.5	0.01
MC1R	MC1R	R alleles‡	Fair, sun-sensitive, freckles	Red/light	–	Melanoma, NMSC	0.3	0	0
		r alleles¶	Variable	Variable	–	Melanoma, NMSC	0.3	0.4	0.01
ASIP	ASIP	g.8818A>G	Dark	Dark	Brown	–	0.15	–	0.6
		ASIP haplotype§	Fair, sun-sensitive, freckles	Red/light	Light	Melanoma, NMSC	0.1–0.3	0–0.2	0–0.1
KITLG	KIT ligand	rs642742 A>G	Fair	–	–	–	0.85	0.8	0.07
		rs12821256 T>C	–	Light	–	–	0.15	0	0
TPCN2	TPCN2	Met484Leu	–	Light	–	–	0.2	0	0
		Gly734Gln	–	Light	–	–	0.4	0.2	0.02
IRF4	Interferon regulatory factor 4	rs12203592 C>T	Fair, sun-sensitive	Dark	Blue	–	0.8	0	0
		rs1540771 G>A	Sun-sensitive, freckles	Dark (weak)	–	–	0.5	0.2	0.05

*Independent of pigmentary phenotype.
†Intronic regulatory region that determines expression of the OCA2 gene; other intronic polymorphisms in the HERC2 gene have also been linked to decreased pigmentation, with the same proposed mechanism.
‡High-penetrance "red hair color" alleles, e.g. Asp84Glu, Arg151Cys, Arg160Trp, and Asp294His.
¶Low-penetrance alleles, e.g. Val60Leu, Val92Met, and (especially in East Asians) Arg163Gln.
§Single long (~1.8 Mb) haplotype that includes multiple single nucleotide polymorphisms (SNPs; e.g. rs4911414 G>T and rs4911442 A>G) and encompasses several smaller haplotype blocks.

eTable 65.1 Genes associated with physiologic variation in human pigmentation[e1–e6]**.** Gray highlight = polymorphism associated with darker pigmentation. The genes in the first four rows are those responsible for OCA types 1 to 4. ASIP, agouti signaling protein; BCC, basal cell carcinoma; MATP, membrane-associated transporter protein; MC1R, melanocortin 1 receptor; NCKX5, Na-Ca-K exchanger 5; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma; SLC24A4/5, solute carrier family 24, member 4/5; SLC45A2, solute carrier family 45, member 2; TPCN2, two-pore segment channel 2; TYRP1, tyrosinase-related protein 1.
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66 Vitiligo and Other Disorders of Hypopigmentation

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Key features

- Leukoderma and hypopigmentation refer to lightening of the skin, which is classically due to decreased epidermal melanin (hypomelanosis)
- Melanocytopenic hypomelanosis, characterized by a reduction in the number of melanocytes, can result from a variety of defects in pigment cell differentiation, proliferation, migration, and/or survival
- Melanopenic hypomelanosis features a normal number of melanocytes but decreased melanin synthesis or transfer to keratinocytes, and the underlying abnormalities often involve melanosomes
- The age of onset (congenital or acquired), degree of pigment loss (hypo- versus amelanosis), presence or absence of preceding inflammation, anatomic location, and distribution pattern – circumscribed, diffuse, linear, or guttate – represent key considerations in the evaluation of a patient with hypopigmentation
- Vitiligo is a common multifactorial disorder involving the disappearance of melanocytes due to an immune disturbance; patients present with circumscribed depigmented macules and patches in a localized (including segmental) or generalized distribution
- Presentations of hereditary hypomelanosis range from congenital, stable, circumscribed areas of amelanosis in piebaldism and Waardenburg syndrome to diffuse pigmentary dilution of the skin, hair, and/or eyes in the various forms of oculocutaneous albinism and related conditions
- Postinflammatory, infectious, and chemical hypomelanosis as well as halo nevi and melanoma-associated leukoderma represent other etiologies of circumscribed hypo- or amelanosis
- Blaschko-linear hypopigmentation and idiopathic guttate hypomelanosis are the most common causes of linear and guttate hypopigmentation

INTRODUCTION

Leukoderma and hypopigmentation are general terms used to designate disorders characterized by lightening of the skin. They are classically the result of decreased epidermal melanin content (melanin-related), but they may be secondary to a decreased blood supply to the skin (hemoglobin-related). Hypomelanosis is a more specific term that denotes a reduction of melanin within the skin; amelanosis signifies the total absence of melanin. Depigmentation usually implies a total loss of skin color, most commonly due to disappearance of pre-existing melanin pigmentation, as in vitiligo. The term pigmentary dilution is used to describe a generalized lightening of the skin and hair, as in oculocutaneous albinism; this may only be apparent if the affected individuals are compared with unaffected relatives.

Cutaneous hypomelanosis is often classified into two groups:

- *melanocytopenic hypomelanosis*, caused by a reduction in the number of epidermal and/or follicular melanocytes
- *melanopenic hypomelanosis*, in which the number of epidermal and/or follicular melanocytes is normal, but the pigment cells fail to synthesize normal amounts of melanin and/or transfer it to surrounding keratinocytes.

Melanocytopenic hypomelanosis may be hereditary and/or congenital due to a defect in melanoblast differentiation, proliferation, migration, and/or survival, or it may be acquired. In the latter case, functional melanocytes can disappear as a result of their destruction from insults such as external trauma (e.g. cryosurgery) or an immune attack. The factors controlling melanocyte survival may also play a role in the postnatal disappearance of dermal melanocytes. Melanopenic hypomelanosis may result from complex pathologic mechanisms, including melanosomal abnormalities that affect biogenesis, melanization, transfer, or degradation.

Diagnosis of Leukodermas

Any patient with a leukoderma should be fully examined under visible light and using a Wood's lamp (~365 nm). The latter is particularly useful in circumscribed leukodermas, individuals who have very lightly pigmented skin (phototypes I or II), and neonates. Under visible light, it is sometimes difficult to distinguish between hypomelanosis and amelanosis, but the greater the loss of epidermal pigmentation, the more marked the contrast on Wood's lamp examination. This technique is also helpful in differentiating hypomelanotic macules from hemoglobin-related leukodermas; for example, nevus anemicus becomes inapparent.

Most leukodermas are diagnosed clinically following a complete history and physical examination. Determining whether the distribution pattern is *circumscribed* (e.g. vitiligo), *diffuse* (e.g. albinism), *linear*, or *guttate* (e.g. idiopathic guttate hypomelanosis) helps to narrow the differential diagnosis. The age of onset, presence or absence of preceding inflammation, anatomic location, and degree of pigment loss represent other pertinent features. Histologic examination of involved skin is most useful for several of the hypomelanoses associated with inflammatory processes (e.g. sarcoidosis, lichen sclerosus, mycosis fungoides).

VITILIGO

Vitiligo is an acquired disorder characterized by circumscribed depigmented macules and patches due to the loss of epidermal melanocytes. Leukotrichia within areas of involvement is due to a loss of follicular melanocytes.

Epidemiology

Worldwide, vitiligo affects ~0.5%–1% of the general population[1,2]. It may appear any time from shortly after birth to late adulthood, with an average age of ~30 years[3] at onset. Although patients with vitiligo may attribute the development of their disease to specific life events (e.g. physical injury, sunburn, emotional distress, illness, pregnancy), with the exception of the Koebner phenomenon, it has not been proven that these factors directly precipitate vitiligo.

Pathogenesis

The pathogenesis of vitiligo involves both genetic and non-genetic factors in processes that lead to the loss of epidermal melanocytes.

Genetics

Both twin and family studies point to the importance of genetic factors in the development of vitiligo[2]. For example, a survey in the US and UK found that 7% of the first-degree relatives of vitiligo probands had vitiligo. However, a 23% concordance rate in monozygotic twins supported the additional role of environmental factors[4]. Genome-wide linkage analyses have been performed in multiple patient populations, resulting in the identification of a number of susceptibility loci and candidate genes. Many of these genes are involved in melanogenesis, immune regulation, or apoptosis and have been associated with other pigmentary, autoimmune, or autoinflammatory disorders[3,5,6] (Table 66.1).

Pathogenic pathway

Multiple steps occur during the initiation and progression of vitiligo, ultimately leading to the loss of epidermal melanocytes (Fig. 66.1). With a background of genetic susceptibility, intrinsic abnormalities of melanocytes are thought to render them more vulnerable to damage from oxidative stress. Oxidative stress also results in impairment of WNT signaling; the latter normally promotes differentiation of melanocyte precursors and thereby facilitates repigmentation during vitiligo therapy[7].

In the cascade of events that leads to immune activation, an initial step is a release by melanocytes of damage-associated molecular patterns (DAMPs) such as HSP-70 (heat shock protein 70)[8] and HMGB1 (high mobility group box protein B1). This stimulates plasmacytoid dentritic cells and innate lymphoid cells in the skin to secrete interferon (IFN)-α[9,10] and IFN-γ. Activated keratinocytes produce C-X-C chemokine ligands 9 and 10 (CXCL9 & 10), which leads to the recruitment of both $CD4^+$ helper and $CD8^+$ cytotoxic T cells which express C-X-C chemokine receptor 3 (CXCR3). These T cells produce proinflammatory cytokines such as IFN-γ and tumor necrosis factor (TNF)[11,12], resulting in the destruction of melanocytes.

The recurrence of vitiligo within previously affected skin highlights the role of resident memory T cells (see Fig. 11.3). These cells have a distinct transcriptional program and express characteristic cell surface markers such as CD69, CD103 and CD49a[13], with the latter defining a subset of resident memory T cells with cytotoxic properties.

Clinical Features

Characteristics of vitiligo lesions

The most common presentation of vitiligo is totally amelanotic (milk- or chalk-white) macules or patches surrounded by normal skin. Well-developed lesions typically have discrete margins and may be round, oval, irregular, or linear in shape. The borders are usually convex, as if the depigmenting process were "invading" the surrounding normally pigmented skin[1,2,14]. However, at their onset or when actively spreading, areas of vitiligo may be more ill-defined and hypomelanotic rather than amelanotic. Vitiligo lesions occasionally have a hyperpigmented border, and a blue color can result when vitiligo develops in areas of postinflammatory dermal pigmentation.

Lesions enlarge centrifugally over time at a rate that can be slow or rapid. Vitiligo macules and patches range from millimeters to centimeters in diameter and often have variable sizes within an area of involvement. In lightly pigmented individuals, the lesions may be subtle or inapparent without Wood's lamp examination or tanning of uninvolved skin. In patients with darker skin phototypes, the contrast between vitiliginous areas and the surrounding skin can be striking (Fig. 66.2). Vitiligo is usually asymptomatic, but pruritus is occasionally noted, especially within active lesions.

Vitiligo may develop anywhere on the body. Interestingly, it frequently localizes to sites that are normally relatively hyperpigmented, such as the face, dorsal aspect of the hands, nipples, axillae, umbilicus, and sacral, inguinal, and anogenital regions (see Fig. 66.2). Typically, facial vitiligo occurs around the eyes and mouth (i.e. periorificial), and on the extremities it favors the elbows, knees, digits, flexor wrists, dorsal ankles, and shins (Figs. 66.3 & 66.4). Common sites of involvement also include areas subjected to repeated trauma, pressure, or friction (e.g. in body folds or via contact with clothing). Palmoplantar[15] and oral mucosal involvement in lightly pigmented individuals is often difficult to visualize without Wood's lamp examination. In acrofacial vitiligo, periungual involvement of one or more digits may be associated with lip depigmentation; however, either can be an isolated finding.

The incidence of body leukotrichia varies from 10% to >60%, as vitiligo often spares follicular melanocytes. The occurrence of leukotrichia does not correlate with disease activity.

One additional manifestation of vitiligo is the isomorphic Koebner phenomenon, which is characterized by the development of vitiligo within sites of trauma, such as a surgical excision or thermal burn. It is more common in patients with progressive vitiligo. There appears to be a minimal threshold of injury required, bringing into question the hypothesis that minor trauma, such as friction from clothes, can induce vitiligo lesions.

Clinical classification of vitiligo

The 2012 Vitiligo Global Issues Consensus Conference recommended that "vitiligo" be used as the umbrella term for all *non-segmental* forms of vitiligo[16]. *Segmental* vitiligo would refer to a clinically unambiguous segmental distribution of depigmented lesions, while *mixed* vitiligo represented the coexistence of segmental and non-segmental vitiligo.

An additional classification scheme subdivides vitiligo into two major groups, localized and generalized (see Fig. 66.4).

Localized:

- *Segmental*: involves one or more body segments, usually with roughly quadrilateral shapes and not crossing the midline (Fig. 66.5); this form typically has rapid onset and often associated leukotrichia (Fig. 66.6)
- *Focal*: undetermined/unclassified form in which depigmented macules are localized to one area but not clearly in a segmental distribution; after 1–2 years of follow-up, more definitive classification is frequently possible
- *Mucosal*: only the mucous membranes are involved

Generalized:

- *Vulgaris*: scattered patches that are widely distributed
- *Acrofacial*: distal extremities and face
- *Universal*: complete or, more commonly, nearly complete depigmentation

Overall, >90% of vitiligo patients have vulgaris or acrofacial variants. Segmental vitiligo is more common in children than adults, accounting for ~15%–30% of pediatric vitiligo (see below).

Clinical variants

Follicular vitiligo presents with leukotrichia in the absence of depigmentation of the surrounding epidermis[17]. Although vitiligo of the scalp, eyebrows, and eyelashes usually presents as one or more localized patches of white or gray hair (poliosis; see Fig. 66.6), scattered white hairs due to involvement of individual follicles or even total depigmentation of all scalp hair may occur.

Vitiligo ponctué, an unusual clinical presentation of vitiligo, is characterized by multiple, small, discrete amelanotic macules (confetti-like), sometimes superimposed upon a hyperpigmented macule. Erythema at the margin of a vitiligo macule is referred to as *"vitiligo with raised inflammatory borders"* or *inflammatory vitiligo* (Fig. 66.7); a figurate papulosquamous variant has also been reported.

Trichrome vitiligo is characterized by a hypopigmented zone between the normal and depigmented skin. This intermediate zone has a fairly uniform hue rather than a gradual progression from white to normally pigmented skin. The number of melanocytes is also intermediate in this zone, suggesting a slower centrifugal progression compared to classic vitiligo. *Quadrichrome and pentachrome vitiligo* have also been described.

Hypochromic vitiligo has been described in patients with skin phototypes V and VI[18]. They present with persistent hypopigmented macules in a seborrheic distribution, with lesions coalescing on the face and scattered on the neck, trunk, and scalp. There was no history of prior inflammation and a few individuals had additional achromic macules. Decreased melanocyte density was noted histologically.

SELECTED SUSCEPTIBILITY LOCI AND CANDIDATE GENES FOR VITILIGO	
Candidate gene	**Defective protein**
Involved in immune regulation	
PTPN22	Protein tyrosine phosphatase, non-receptor type 22
*FOXD3**	Forkhead box D3*
IFIH1	Interferon induced with helicase C domain 1
CTLA4	Cytotoxic T lymphocyte-associated protein 4
FOXP1	Forkhead box P1
CD80	CD80 molecule
LPP	LIM domain containing preferred translocation partner in lipoma
CLNK	Cytokine dependent hematopoietic cell linker
TSLP	Thymic stromal lymphopoietin
BACH2	BTB domain and CNC homolog 2
HLA (various genes), *BTNL2*	Major histocompatibility complex classes I–III, butyrophilin-like 2
CCR6	Chemokine (C-C motif) receptor 6
SMOC2	SPARC related modular calcium binding 2
SLA	Src-like-adaptor
IL2RA	Interleukin 2 receptor α
CD44	CD44 molecule
CXCR5	C-X-C motif chemokine receptor 5
IKZF4	IKAROS family zinc finger 4
SH2B3	SH2B adaptor protein 3
VDR	Vitamin D receptor
NLRP1 (formerly *NALP1*)	NOD-like receptor family, pyrin domain containing 1
TNFRSF11A	TNF receptor superfamily member 11a (RANK)
TICAM1	Toll-like receptor adaptor molecule 1
PTPN1	Protein tyrosine phosphatase, non-receptor type 1
UBASH3A, AIRE	Ubiquitin associated and SH3 domain containing A, autoimmune regulator
XBP1	X-box binding protein 1
C1QTNF6	C1q and tumor necrosis factor related protein 6
TOB2	Transducer of ERBB2, 2
FOXP3	Forkhead box P3
Involved in apoptosis and/or cytotoxicity	
FASL	Fas ligand
RERE	Arginine–glutamic acid dipeptide (RE) repeats
SLC29A3	Solute carrier family 29 member 3
CASP7	Caspase 7
GZMB	Granzyme B
Melanocyte-related	
IRF4	Interferon regulatory factor 4
FGFR1OP, RNASET2	Fibroblast growth factor receptor 1 oncogene partner, ribonuclease T2
ZMIZ1	Zinc finger MIZ-type containing 1
TYR	Tyrosinase
PMEL	Premelanosome protein
OCA2, HERC2	Oculocutaneous albinism 2 transmembrane protein, HECT and RLD domain containing E3 ubiquitin protein ligase 2
MC1R	Melanocortin-1 receptor
ASIP	Agouti signaling protein

*In one family to date, a functional variant in the promoter of the *FOXD3* melanoblast developmental regulator gene was associated with autosomal dominant inheritance of an atypical vitiligo phenotype (early onset, widespread, progressive depigmentation).

Table 66.1 Selected susceptibility loci and candidate genes for vitiligo. There is evidence that vitiligo has significant genetic heterogeneity in different ethnic populations. Genome-wide association studies have identified other susceptibility loci, including 7p13, 7q11, 9q22, and (in Chinese patients) 4q13–q21. HLA, human leukocyte antigen.

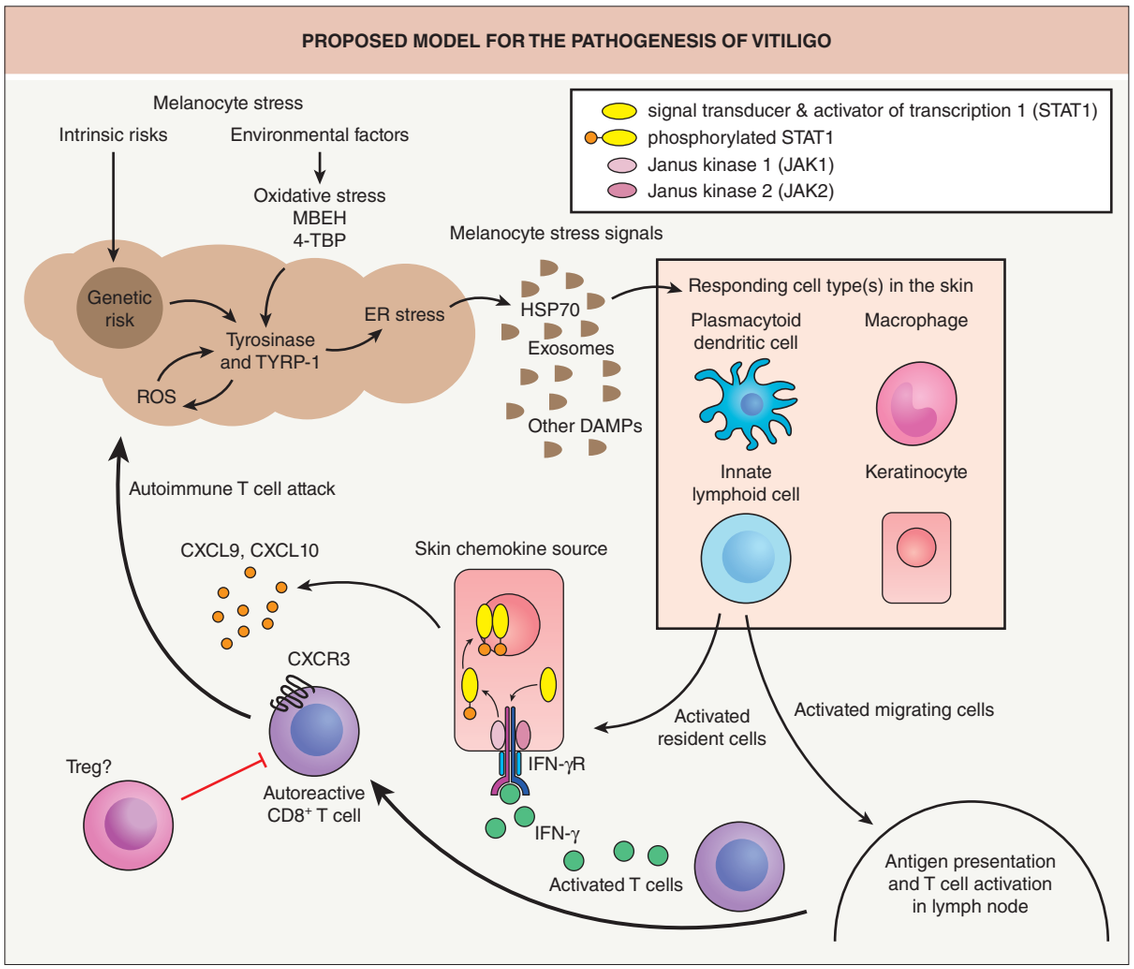


Fig. 66.1 Proposed model for the pathogenesis of vitiligo. Inherited genetic risk (see Table 66.1) and environmental insults (e.g. monobenzyl ether of hydroquinone [MBEH], 4-tertiary butyl phenol [4-TBP]) induce melanocyte stress, exemplified by endoplasmic reticulum (ER) stress. Stressed melanocytes signal to local innate and resident skin cell types via exosomes containing antigen and damage-associated molecular patterns (DAMPs), soluble heat shock protein 70 (HSP70), and other factors. These signals activate several cell types, some of which migrate to the draining lymph nodes and stimulate T cells, which secrete interferon-γ (IFN-γ). IFN-γ signals through the IFN-γ receptor (IFN-γR) on keratinocytes and/or other cells; this involves phosphorylation of the transcription factor STAT1 by Janus kinases (JAK) 1 and 2. Phosphorylated STAT1 homodimerizes and then translocates into the nucleus, where IFN-γ-dependent genes such as *CXCL9* and *CXCL10* (C-X-C chemokine ligand 9 and 10) are transcribed. Autoreactive $CD8^+$ T cells that express C-X-C chemokine receptor 3 (CXCR3) follow secreted CXCL9/10 to the skin, where they kill melanocytes. Approaches targeting this IFN-γ–STAT1–CXCL9/10 axis that drives melanocyte destruction (e.g. with JAK inhibitors or antibodies against CXCR3) can be utilized to treat vitiligo. ROS, reactive oxygen species; STAT1, signal transducer and activator of transcription 1; TYRP-1, tyrosinase-related protein 1. *Adapted from Strassner JP, Harris JE. Understanding mechanisms of autoimmunity through translational research in vitiligo. Curr Opin Immunol 2016;443:81–8.*



Fig. 66.2 Genital vitiligo. Complete loss of pigment on the penis and scrotum. Note the lack of any secondary changes. *Courtesy Lorenzo Cerroni, MD.*



Fig. 66.3 Vitiligo. Depigmentation of the volar wrists as well as the palmar surfaces. *Courtesy Jean L. Bolognia, MD.*

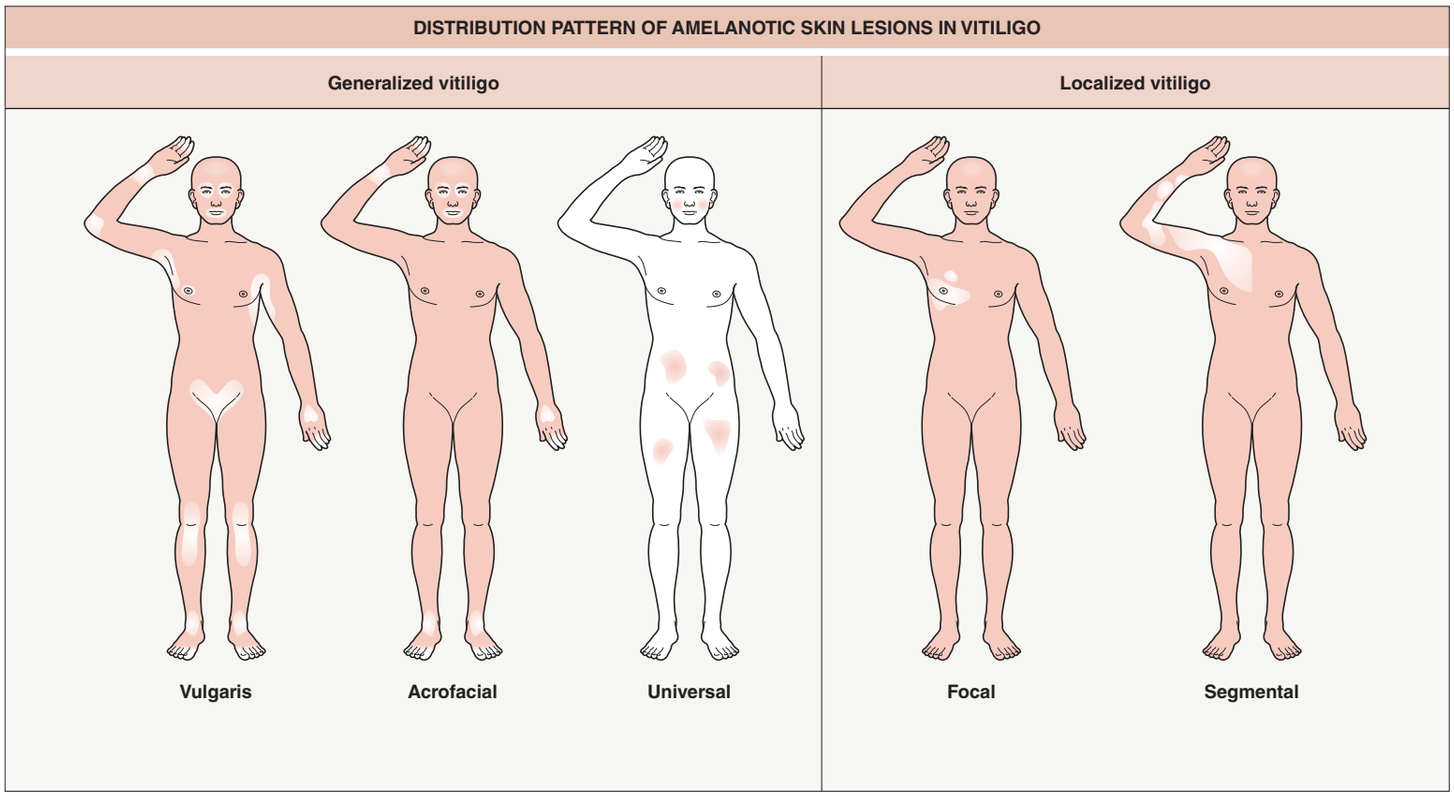


Fig. 66.4 Distribution pattern of amelanotic skin lesions in vitiligo. *Adapted with permission from Le Poole C, Boissy RE. Vitiligo. Semin Cutan Med Surg 1997;16:3–14.*



Fig. 66.5 Segmental vitiligo. Unilateral band of depigmentation on the face, the most common location for segmental vitiligo. Note the pigmented and depigmented hairs within the affected area. *Courtesy Kalman Watsky, MD.*



Fig. 66.6 Segmental vitiligo. Under normal light, vitiligo can be subtle in lightly pigmented individuals. The clue to the diagnosis is the poliosis of the eyelashes. *Courtesy Jean L. Bolognia, MD.*

Disease course

The onset of vitiligo is usually insidious. Many patients become aware of the depigmented macules and patches, especially in sun-exposed areas, during the summer when tanning increases the contrast between involved and uninvolved skin. Clinical erythema or pruritus rarely precedes vitiligo.

The course of vitiligo is unpredictable. It becomes more extensive by the appearance of new depigmented macules, centrifugal enlargement of pre-existing lesions, or both processes. Clinical features that have been associated with active progression include hypomelanotic lesions with poorly defined borders and confetti-like lesions[19–21].

The natural course of *generalized* vitiligo is usually one of slow spread, but it may stabilize for a long period of time or evolve rapidly. Rarely, total body involvement develops within a few weeks or even days. In contrast, *segmental* vitiligo usually reaches its full extent within 1–2 years and remains restricted to the initial segmental area. The presence of halo nevi and leukotrichia increases the likelihood of evolution from segmental to mixed vitiligo[22]. Some degree of sun-induced or spontaneous repigmentation of vitiligo is not uncommon, but complete and stable repigmentation is rare.

The *v*itiligo *a*rea *s*coring *i*ndex (VASI), *V*itiligo *E*uropean *T*ask *F*orce (VETF) score, and *v*itiligo *e*xtent *s*core (VES) represent validated quantitative assessment scales[14,23,24]. A *p*hysician *g*lobal *a*ssessment (PGA) that categorizes vitiligo extent and *v*itiligo *s*igns of *a*ctivity *s*core (VSAS) have also been developed[25,26].

Ocular involvement

The uveal tract (iris, ciliary body, and choroid) and retinal pigment epithelium contain pigment cells. *Uveitis* is the most significant ocular abnormality associated with vitiligo. *Vogt–Koyanagi–Harada*



Fig. 66.7 Inflammatory vitiligo. An erythematous inflammatory border is evident. Such lesions are sometimes misdiagnosed as tinea corporis.

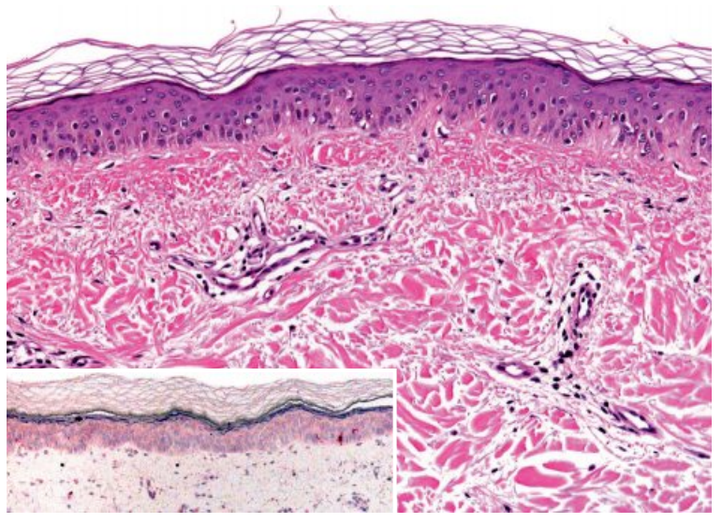


Fig. 66.8 Histology of vitiligo. The complete absence of melanocytes in the basal layer of the affected epidermis is highlighted by Melan-A (MART-1) staining (inset), in contrast to the normal number of melanocytes visible in adjacent unaffected skin on one lateral edge. *Courtesy Lorenzo Cerroni, MD.*

(VKH) syndrome is characterized by: (1) uveitis; (2) aseptic meningitis; (3) otic involvement (e.g. dysacusia); and (4) vitiligo, especially of the face or sacral region, and associated poliosis. Histologic examination of amelanotic skin, which classically appears after the extracutaneous symptoms, demonstrates an infiltrate consisting primarily of $CD4^+$ lymphocytes, suggesting a prominent role for cell-mediated immunity.

Non-inflammatory depigmented lesions of the ocular fundus are evident in some patients with vitiligo, presumably representing focal areas of melanocyte loss. An association between vitiligo and high-frequency sensorineural hearing loss has been noted in recent systematic reviews[27,28], possibly reflecting the role of cochlear melanocytes in regulation of auditory function. However, clearcut evidence of otic abnormalities remains to be demonstrated.

Alezzandrini syndrome is a rare disorder characterized by unilateral whitening of scalp hair, eyebrows, and eyelashes as well as ipsilateral depigmentation of facial skin and visual changes. In the affected eye, there is decreased visual acuity and an atrophic iris. The pathogenesis of Alezzandrini syndrome is unknown, but it is believed to be closely related to VKH syndrome.

Associated disorders

Although most vitiligo patients are otherwise healthy, generalized vitiligo is associated with an increased risk of developing additional autoimmune diseases, especially in patients with a family history of vitiligo and autoimmunity. Indeed, many vitiligo susceptibility genes are shared with other autoimmune or atopic diseases (see Table 66.1), usually with the same high-risk alleles. Up to 20% of patients with vitiligo have at least one comorbid autoimmune disorder[29], most commonly autoimmune thyroid disease, which affects ~15% of adults and ~5%–15% of children with vitiligo[27,30–33]. Other autoimmune conditions reported to be associated with vitiligo include alopecia areata (~2%–4% of vitiligo patients), pernicious anemia, type 1 diabetes mellitus, myasthenia gravis, and several connective tissue diseases – lupus erythematosus (discoid and systemic), Sjögren syndrome, and rheumatoid arthritis[27,29,34]. Epidemiologic studies have also linked vitiligo with psoriasis, atopic diseases, inflammatory bowel disease, and metabolic syndrome[27,35]. Vitiligo can also occur in the setting of chronic graft-versus-host disease. Lastly, psychosocial conditions such as depression, anxiety, and adjustment disorders also occur in patients with vitiligo[36].

Patients with the autosomal recessive *a*utoimmune *p*oly*e*ndocrinopathy–*c*andidiasis–*e*ctodermal *d*ystrophy (APECED) syndrome often develop vitiligo. The gene responsible for APECED, *AIRE* (*a*uto*i*mmune *re*gulator), encodes a transcription factor that promotes expression of tissue-specific self-antigens in the thymus, which facilitates development of peripheral tolerance. In APECED, failure to delete autoreactive T cells leads to autoimmune disease. In a mouse model, AIRE deficiency was found to result in tyrosinase-related protein-1 (TYRP1)-specific T cells that enhanced immune responses against melanoma[37].

Childhood vitiligo

Although vitiligo vulgaris is the most common clinical type observed in children, the frequency of segmental vitiligo (~15%–30%) is significantly increased compared to that in adults (<5%–10%)[38]. The incidence of associated endocrinopathies is less than in the adult vitiligo population. A family history of vitiligo is associated with an earlier age of onset[39].

Pathology

In lesions of vitiligo, melanocytes are typically absent or present in very small numbers (Fig. 66.8). The epidermal melanocyte density can be assessed with melanocyte-specific immunohistochemical stains, such as Melan-A (MART-1), MITF, and HMB45, or via incubation of biopsy specimens with dihydroxyphenylalanine (DOPA; detects tyrosinase activity; see Fig. 65.6). Although ultrastructural studies may be performed for research purposes, very few hypomelanotic disorders have specific ultrastructural findings.

Differential Diagnosis

When there is complete depigmentation/amelanosis, the differential diagnosis may include chemical or drug-induced (e.g. imatinib) leukoderma, postinflammatory depigmentation, the leukodermas associated with melanoma and scleroderma, the late stages of treponematosis and onchocerciasis, and (for congenital lesions) piebaldism. A single circular depigmented lesion on the trunk of a young person may represent a stage III halo nevus (see below). Early lesions or those with a partial loss of pigment need to be distinguished from postinflammatory hypopigmentation, idiopathic guttate hypomelanosis, tinea versicolor, and other cutaneous infections (e.g. leprosy). In addition to a decrease, rather than an absence, of pigment, nevus depigmentosus can be distinguished by its stability and early onset, although lesions may not become apparent until mid-childhood in lightly pigmented individuals. Treatment with potent topical corticosteroids can also lead to hypomelanosis.

Treatment

The major goals of vitiligo treatment are stabilization of the depigmentation process, repigmentation, and maintenance of repigmentation[39a,39b]. Immunomodulatory therapies are utilized to limit disease progression, with repigmentation requiring repopulation of epidermal melanocytes from neighboring pigmented hair follicles, surrounding uninvolved epidermis, and/or lesional interfollicular melanocyte precursors.

The therapeutic regimen depends on the extent, location, and activity of disease as well as the patient's age, skin type, and motivation for treatment. In general, a period of at least 6 months is needed to determine whether a particular treatment is effective. The face, neck, mid extremities, and trunk tend to have the best response to therapy, while the distal extremities and lips are the most resistant to treatment.

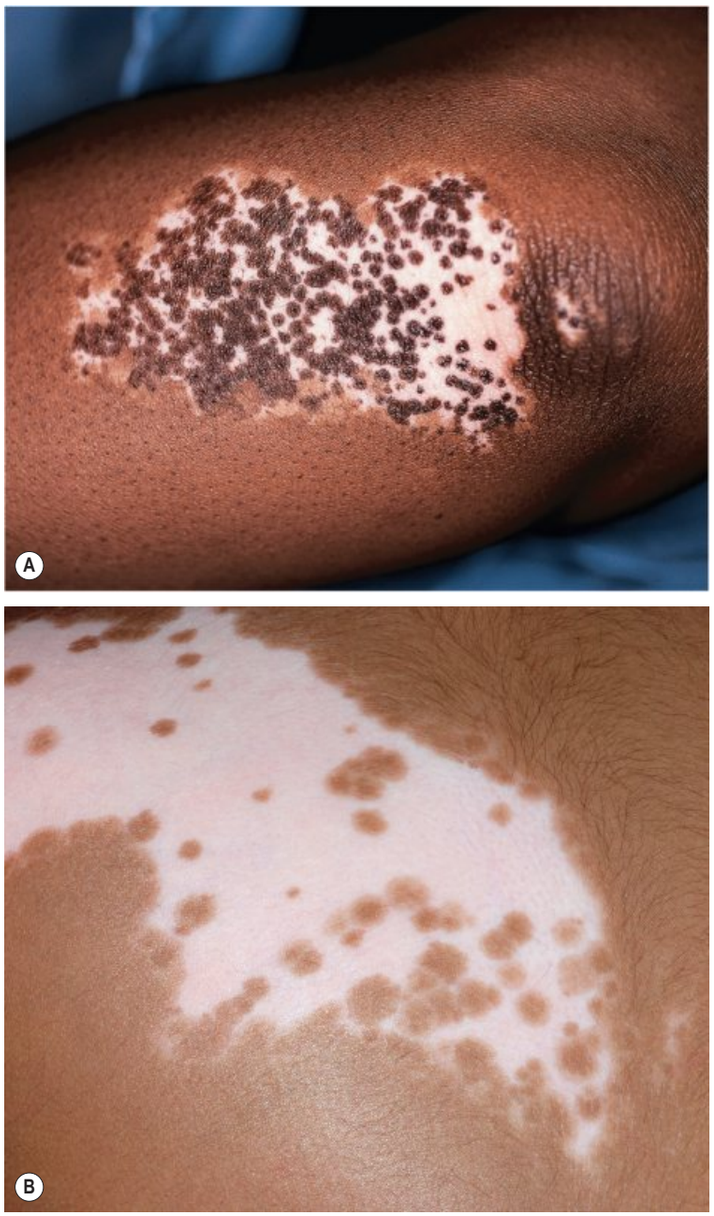


Fig. 66.9 Perifollicular repigmentation. Vitiligo on the elbow (**A**) and segmental vitiligo on the back (**B**) responding to PUVA and narrowband UVB therapy, respectively, with repigmentation in a prominent perifollicular pattern as well as from the periphery. The areas of repigmentation are darker in color than the uninvolved skin in (**A**) and have two shades (darker where well established and lighter at the expanding edge) in (**B**). *A, Courtesy Jean L. Bolognia, MD; B, Courtesy Julie V. Schaffer, MD.*

Repigmentation initially appears in a perifollicular pattern (unless the affected site is hairless or has depigmented hairs) and/or at the periphery of the lesions (Fig. 66.9). After therapeutic repigmentation, the rate of recurrent depigmentation of vitiligo lesions is ~40%[40].

Topical corticosteroids

Topical corticosteroids are useful for localized areas of vitiligo in adults and children, with the highest response rates in newer lesions and those on the face and neck. A meta-analysis showed that approximately half of patients with vitiligo affecting ≤20% of the body surface area (BSA) achieved >75% repigmentation with class 1 (superpotent) or 2–3 (high potency) topical corticosteroids; cutaneous atrophy was observed in 14% and 2% of these groups, respectively[41]. To minimize side effects, class 1 corticosteroids can be used in 6- to 8-week cycles or on a twice-weekly basis, alternating with topical tacrolimus, topical ruxolitinib, or a less potent topical corticosteroid. Treatment should be discontinued if there is no visible improvement after 4–6 months.

In general, intralesional corticosteroids are less commonly employed due to the pain associated with injection and the higher risk of cutaneous atrophy (≥30%).

Topical calcineurin inhibitors (TCIs)

For lesions on the face and neck, topical tacrolimus or pimecrolimus has similar efficacy as topical corticosteroids. A recent small randomized controlled trial (RCT) found that 65% of adults who applied tacrolimus 0.1% ointment twice daily for 24 weeks achieved ≥75% repigmentation of facial vitiligo, compared to 0% for a vehicle control[42]. However, TCIs are less effective than potent topical corticosteroids for vitiligo in extra-facial sites. In a recent systematic review (n=1499 vitiligo patients), TCI monotherapy for a median duration of 3 months produced ≥75% repigmentation in ~20% of patients overall, ~30% of children, and 35% of lesions on the face/neck versus only 2% of lesions on the trunk/extremities[43].

Combining a TCI with narrowband UVB or an excimer laser can provide a synergistic effect, resulting in repigmentation rates of ≥50%[43,44]. TCIs can also be used in conjunction with topical corticosteroids on a rotational basis (see above) or as maintenance therapy after repigmentation. In an RCT, bi-weekly application of tacrolimus 0.1% ointment to sites of previous vitiligo reduced the rate of recurrent depigmentation to 10%, compared to 40% with placebo[45].

Topical Janus kinase (JAK) inhibitors

Ruxolitinib 1.5% cream is a Janus kinase 1/2 (JAK1/2) inhibitor that was recently FDA-approved for treatment of non-segmental vitiligo involving ≤10% BSA in patients ≥12 years of age. In two phase III RCTs (total n=674 patients), ~30% of individuals treated with ruxolitinib 1.5% cream twice daily for 24 weeks achieved ≥75% improvement in the facial VASI, compared to 7%–11% for the vehicle control[46]. Acne at application sites was the most common adverse event, although the JAK inhibitor class-wide black box warning notes potential increased risks of serious infection, death, cancer, cardiovascular events, and thrombosis (see Chs. 128 & 129).

Photo(chemo)therapy

Narrowband UVB

Narrowband UVB (NB-UVB) has become first-line therapy for adults and children ≥6 years of age with generalized vitiligo[47], especially if it involves ≥15% BSA or cosmetically sensitive areas that typically respond to treatment (see Ch. 134). Several studies have demonstrated the effectiveness of NB-UVB monotherapy[48], which is superior to broadband UVB for the treatment of vitiligo.

The Vitiligo Working Group recommends initiating NB-UVB phototherapy at a dose of 200 mJ/cm^2 for all skin phototypes[49]. The dose is then increased by 10%–20% at each subsequent treatment until mild, asymptomatic lesional erythema is achieved, up to a maximum dose of 1500 mJ/cm^2 for the face and 3000 mJ/cm^2 for the body. Phototherapy is administered two to three times per week on non-consecutive days. If there is no evidence of repigmentation after 50 mildly erythrogenic exposures, then therapy should be discontinued. Short-term side effects include painful erythema, pruritus, and xerosis; to date, long-term side effects (e.g. cutaneous carcinogenesis) have not been reported. The advantages of NB-UVB over psoralen plus UVA (PUVA) therapy include shorter treatment times, no gastrointestinal side effects, reduced phototoxic reactions, less accentuation of the contrast between depigmented and normally pigmented skin, and no need for post-treatment photoprotection. In addition, NB-UVB can be used in children, pregnant or lactating women, and individuals with hepatic or kidney dysfunction. For reliable patients, home NB-UVB units represent a convenient option[50].

Psoralen plus UVA (PUVA)

PUVA consists of psoralens (usually 8-methoxypsoralen) combined with UVA light (see Ch. 134). Psoralens can be administered orally (oral PUVA) or applied topically (topical PUVA), followed by exposure to either artificial UVA light or natural sunlight (PUVASOL). Oral PUVA is no longer recommended for vitiligo therapy considering the greater efficacy, ease of administration, and lack of systemic side effects of NB-UVB[51]. Topical PUVA or PUVASOL can be useful for localized lesions[52], although there is a risk of phototoxicity with blistering or koebnerization.

A low concentration (≤0.1%) of psoralen should be used, which requires dilution of commercially available preparations, followed by an initial UVA dose of 0.25 J/cm^2 and subsequent increases in 10%–20% increments until mild erythema is achieved in the treated sites.

Excimer laser and lamp

The excimer laser and lamp deliver UVB light at a peak wavelength of 308 nm, which is similar to the 311 nm peak of NB-UVB. Compared with NB-UVB, excimer devices have equal to superior efficacy for vitiligo, typically requiring a shorter duration of treatment and avoiding darkening of unaffected skin[52]. However, excimer therapy is primarily indicated for segmental vitiligo and other forms involving <10% BSA.

Areas of vitiligo are treated two to three times weekly, typically for a total of 25 to 50 sessions; in general, the repigmentation rate depends on the total number of sessions, not their frequency[53]. Repigmentation may be enhanced by the concomitant use of treatments such as TCIs, topical corticosteroids, topical JAK inhibitors, or short-term oral corticosteroid mini-pulses (see next section).

Oral corticosteroid mini-pulse therapy

Mini-pulses of oral corticosteroids represent a treatment option for rapidly progressive vitiligo[54,55], although RCTs investigating their efficacy and safety are lacking. A typical regimen consists of oral dexamethasone 2.5–5 mg on two consecutive days each week for 3 to 6 months. This treatment has been reported to halt disease expansion in ~90% of patients[54,56], but it usually does not induce significant repigmentation. Side effects such as insomnia, agitation, weight gain, acne, and hypertrichosis frequently develop (see Ch. 125). As relapse of vitiligo often occurs after discontinuation of treatment, concomitant or maintenance therapy with other agents (e.g. NB-UVB) is recommended.

Other systemic immunomodulators

A few case reports and small studies have described improvement of vitiligo with systemic immunomodulators such as methotrexate and oral JAK inhibitors (e.g. tofacitinib, ruxolitinib, baricitinib; see Ch. 128)[55]. A recent phase II RCT in adults with active non-segmental vitiligo (n = 364 patients) found that ~20% of patients treated with the oral JAK3/TEC inhibitor ritlecitinib for 24 weeks (50 mg daily ± 100 or 200 mg loading dose daily for 4 weeks) achieved ≥75% improvement in the facial VASI, compared to ~2% for placebo[57]. Additional investigations are needed to determine the efficacy and safety of these systemic immunomodulators. Treatment strategies targeting interleukin-15 signaling are also under investigation.

Antioxidants

The rationale for this approach rests on the hypothesis that deficiencies in innate antioxidant processes play a role in vitiligo pathogenesis (Table 66.2). Oral α-lipoic acid, *Polypodium leucotomos*, *Ginkgo biloba*, and various vitamins (e.g. C, E) have been utilized as treatments for vitiligo, often in combination with phototherapy. Although individually none of these agents has strong evidence of efficacy, a recent meta-analysis concluded that oral antioxidants might have a benefit when administered in conjunction with phototherapy[58]. Small RCTs have found that administration of oral *Polypodium leucotomos* extract together with NB-UVB was associated with increased repigmentation in the head and neck region compared to NB-UVB alone[59]. In a recent small RCT, a statistically insignificant improvement in the vitiligo extent score (VES) was observed in patients treated with oral gliadin-protected superoxide dismutase plus NB-UVB compared to NB-UVB alone (20% vs 9%), suggesting potential benefit of this antioxidant[60].

Afamelanotide

Afamelanotide is an α-melanocyte stimulating hormone (α-MSH) analogue that stimulates melanogenesis and melanocyte proliferation by binding to the melanocortin-1 receptor (MC1R; see Ch. 65). An RCT found that the addition of afamelanotide (monthly subcutaneous implants) to NB-UVB therapy increased the speed and extent of repigmentation compared to NB-UVB alone in patients with generalized vitiligo, especially those with skin phototypes IV–VI[61]. However, afamelanotide-induced excessive tanning of non-lesional skin can increase the contrast with lesional skin, thereby reducing cosmetic acceptance in lightly pigmented patients[62]. Additional studies are needed to determine the indications and limitations of afamelanotide therapy for vitiligo.

Surgical therapies

For vitiligo patients who fail to respond to medical therapy, surgical treatment with autologous transplantation techniques may be an option[63,64]. The general selection criteria for autologous transplantation include stable disease for ≥6–12 months, absence of the Koebner phenomenon, no tendency for scar or keloid formation, and age >12 years. A minigraft test showing retention/spread of pigment at the recipient site and no koebnerization at the donor site after 2–3 months can also assist in patient selection.

Several methods of surgical repigmentation have been successfully utilized. *Minigrafting* is the simplest technique. Small punch grafts (1–2 mm) from uninvolved skin are implanted within achromic areas, separated from each other by 5–8 mm[65,66]. A cobblestone effect, a variegated appearance of the grafts, and sinking pits represent potential unfavorable outcomes. *Micropunch grafting* utilizes a motorized 0.8 mm punch instrument and can be used to reduce these complications[67]. Because scarring and dyspigmentation may occur at the donor sites, cosmetically insensitive areas are chosen. The advantages of *suction blister epidermal grafting* are the absence of scarring at the donor site and the possibility of reusing this area[68]. However, failure of the graft to take and koebnerization may occur. *Grafting of cultured autologous melanocytes* is an expensive technique that requires specialized laboratory expertise; grafts consist of pure melanocytes or melanocytes admixed with keratinocytes[69]. To avoid the need for *in vitro* culture, which involves mitogens to enhance cell growth, *grafting of non-cultured epidermal cell suspensions* that include melanocytes has been advocated[70]. *Grafting of individual hairs* to repigment vitiligo leukotrichia has also been successfully performed. Most of these techniques require clinical expertise.

Combination therapies

Combination therapy may produce higher rates of repigmentation compared to traditional monotherapies. Examples include phototherapy following surgical procedures as well as combining topical or systemic agents (e.g. TCIs, corticosteroids, JAK inhibitors, antioxidants) with NB-UVB or excimer laser therapy[71–76]. Of note, a recent meta-analysis did not demonstrate sufficient evidence to support the combination of excimer laser/lamp with topical vitamin D derivatives[75].

Maintenance therapies

As noted above, the relapse rate for repigmented vitiligo is ~40%[40]. There is evidence from one RCT that twice weekly application of tacrolimus 0.1% ointment can significantly reduce recurrent depigmentation in adults with successfully treated vitiligo[45]. Additional studies are needed to determine other agents and regimens that may have benefit as maintenance therapy for vitiligo.

Micropigmentation

The technique of permanent dermal micropigmentation utilizes a non-allergenic iron oxide pigment to camouflage recalcitrant areas of vitiligo. This tattooing method is especially useful for the lips, nipples, and distal fingers, which have a poor rate of repigmentation with currently available treatments. Although the color may not match perfectly with the normal surrounding skin and can fade over time, the result is immediate and can represent a dramatic aesthetic improvement.

Depigmentation

Depigmentation represents a treatment option for patients who have widespread, treatment-resistant vitiligo with limited areas of normally pigmented skin in exposed sites. The patients must be carefully chosen, i.e. adults who recognize that their appearance will be altered significantly and who understand that depigmentation requires lifelong strict photoprotection (e.g. sunscreens, clothing, umbrellas). The most commonly used agent is 20% monobenzyl ether of hydroquinone (MBEH), applied once to twice daily to the affected areas for 9–12 months or longer[77]. MBEH is a potent irritant and allergen, and an open application test can be performed before more widespread application. It typically takes 1–3 months to initiate a response, and a loss of pigment can occur at distant sites. Although depigmentation from MBEH is considered permanent, repigmentation (especially perifollicular in areas with pigmented hairs) can be seen following a sunburn or intense sun exposure. Monomethyl ether of hydroquinone (MMEH) in a 20% cream can be used as an alternative to MBEH. Side effects include contact dermatitis, exogenous

PATHOGENIC HYPOTHESES FOR VITILIGO		
Hypothesis	**Evidence for hypothesis**	**Evidence against hypothesis**
Autoimmune destruction of melanocytes	• Epidemiologic association with autoimmune disorders (see text) • Variants in immunoregulatory genes linked with vitiligo and associated autoimmune disorders (see Table 66.1) • Detection of antibodies against melanocyte proteins (e.g. TYR, TYRP1, DCT, MCHR1, SOX10) in the sera of patients with vitiligo • Destruction of melanocytes in normal human skin engrafted onto nude mice after injection with vitiligo patient sera • Infiltration of $CD8^+$ T cells into perilesional vitiligo skin • Skin-homing, melanocyte-specific cytotoxic T cells (e.g. against surface proteins such as Melan-A/MART-1) frequently detectable in the peripheral blood of vitiligo patients • Reports of generalized vitiligo following bone marrow transplantation from donors with vitiligo • T cell receptor transgenic mice that recognize an epitope of tyrosinase develop depigmented lesions with characteristics similar to human vitiligo	• Limited evidence for autoimmune pathogenesis of segmental vitiligo • Although there is strong evidence for an autoimmune etiology of generalized vitiligo, it is unclear whether a primary immune attack targets normal melanocytes or if immune activation is triggered by damage to melanocytes by an exogenous or endogenous factor

An intrinsic defect in melanocytes, their adhesive properties, and/or factors critical to their survival	• Abnormalities of cultured vitiligo melanocytes:
	  • Dilation of the rough endoplasmic reticulum
	  • Abnormal synthesis/processing of TYRP1
	• Increased sensitivity to oxidative stress (e.g. UVB)
	• Evidence for *transepidermal melanocytorrhagy* due to defective melanocyte adhesion:
	  • Detachment and transepidermal loss of melanocytes observed in *in vivo* studies of vitiligo skin
	  • Induction of detachment by mechanical stress, which could explain the Koebner phenomenon
	  • Decreased adhesion to collagen type IV and "stubby" dendrites in melanocytes cultured from perilesional skin of unstable vitiligo
	• Evidence for reduced melanocyte survival and dysregulation of melanocyte apoptosis in vitiligo:
	  • The progressive loss of hair follicle melanocytes observed in *bcl-2*$^{-/-}$ mice provides a model of apoptotic loss of melanocytes
	  • Variants in genes that regulate apoptosis associated with vitiligo (see Table 66.1)
	  • Deficiency of factors important for melanocyte maintenance (e.g. SCF, KIT, MITF) in vitiligo skin
	  • Vitiligo-like depigmentation and hair graying observed in patients treated with tyrosine kinase inhibitors that target KIT
		• Melanocytorrhagy is observed only in lesional and perilesional areas of vitiligo and appears to be a secondary process
		• No alteration in the expression of apoptosis regulatory molecules in vitiligo melanocytes compared with normal melanocytes

Defective defense against oxidative stress leading to destruction of melanocytes	• Detection of high *in vivo* levels of epidermal H_2O_2 in vitiligo skin, with potential sources including:
	  • Accumulation of oxidized pteridines, e.g. 6-biopterin (bluish fluorescence) and 7-biopterin (yellow/green fluorescence)
	  • Increased catecholamine biosynthesis in association with increased monoamine oxidase A activity
	  • Inhibition of thioredoxin/thioredoxin reductase by calcium in the setting of defective calcium transfer/homeostasis in vitiligo epidermis
	• Oxidative degradation of catalase resulting in low levels of this protective enzyme in vitiligo skin
		• Whether these abnormalities are the cause of vitiligo lesions, versus secondary consequences of immune attack or an intrinsic defect in melanocytes, has not been determined
		• No conclusive evidence of benefit from therapeutic approaches using pseudocatalase or systemic antioxidant agents in clinical studies

Table 66.2 Pathogenic hypotheses for vitiligo. A "convergence theory" that vitiligo results from a combination of several of these pathogenic mechanisms has also been proposed. Hypotheses with less support include destruction of melanocytes by neurochemical substances or a viral infection (e.g. cytomegalovirus). DCT, dopachrome tautomerase; MCHR1, melanin-concentrating hormone receptor 1; MITF, microphthalmia-associated transcription factor; SCF, stem cell factor; TYR, tyrosinase; TYRP1, tyrosinase-related protein 1; UVB, ultraviolet B.

ochronosis, and leukomelanoderma en confetti. Depigmentation via Q-switched ruby laser therapy was reported to achieve faster depigmentation than that achieved with a bleaching agent[78], and this laser has also been used in combination with topical 4-methoxyphenol to induce depigmentation[79]. Lastly, depigmentation with the Q-switched alexandrite laser has been described[80].

Psychological support

The impact of vitiligo on quality of life is severe in many affected individuals, and it is critical for physicians to recognize this aspect of the condition and address their patients' psychological needs. Although a "magic" treatment is not yet available, there is always something beneficial that can be done for vitiligo patients. They first need to know what their skin disorder is. Explaining the nature of the disease process and the potential and limits of available therapies is important and more productive than a fatalistic attitude that there is no cure and vitiligo is "only" a cosmetic disorder. Even helping patients to conceal the condition so that it is not visible can be part of the management plan. The use of support groups and, if indicated, psychological counseling are important supplementary therapies.

HEREDITARY HYPOMELANOSIS

Oculocutaneous Albinism

Oculocutaneous albinism (OCA) consists of a group of genetic disorders characterized by diffuse pigmentary dilution due to a partial or total absence of melanin pigment within melanocytes of the skin, hair follicles, and eyes[81]. The number of epidermal and follicular melanocytes is normal. Hypopigmentation involving primarily the retinal pigment epithelium is termed ocular albinism (OA).

Epidemiology

OCA is the most common inherited disorder that leads to diffuse hypomelanosis. In most populations, the estimated frequency is 1 : 20 000; however, it is as high as 1 : 1500 in some African tribes.

Pathogenesis

All well-characterized types of OCA have an autosomal recessive inheritance pattern, although a few rare families with autosomal dominant OCA have been described[82]. Based upon molecular studies, eight types of OCA have been defined (see Table 65.1). OCA type 1 (OCA1) results from reduced (OCA1B) or absent (OCA1A) tyrosinase activity; >400 distinct mutations in the tyrosinase gene (*TYR*) have been identified in patients with OCA1[83]. OCA2 is due to mutations in *OCA2* (previously *P*), which encodes the P (pink-eyed dilution) transmembrane protein present in melanosomes and the endoplasmic reticulum (ER)[84]. The P protein is thought to influence tyrosinase activity via regulation of melanosomal pH, and it may also regulate intra-organelle glutathione levels.

OCA3 results from mutations in *TYRP1* (tyrosinase-related protein 1)[85]. TYRP1 is a melanocyte-specific protein that stabilizes tyrosinase and is involved in eumelanin synthesis (see Fig. 65.11). In both OCA1 and OCA3, the abnormal protein (tyrosinase or TYRP1) never leaves the ER to become incorporated into melanosomes[86] (see Fig. 65.7). Of note, dysfunction of the P protein can also lead to abnormal processing and trafficking of tyrosinase. OCA4 is caused by mutations in *SLC45A2* which encodes solute carrier family 45 member 2 (formerly membrane-associated transporter protein [MATP]), a proton/glucose exporter that maintains the deacidification in later stage melanosomes that is required for tyrosinase activity[87,88].

OCA5 has been linked to chromosome 4q24, but the responsible gene has not yet been identified. OCA6 results from mutations in *SLC24A5*, which encodes a cation exchanger localized to the melanosomal membrane[89]. Of note, this gene was previously identified as one of the determinants of the physiologic variation in human pigmentation. Mutations in *LRMDA* (formerly *C10orf11*) underlie OCA7; the leucine rich melanocyte differentiation-associated protein is expressed in melanoblasts as well as melanocytes and is thought to have a role in melanocyte differentiation[90]. Lastly, OCA8 is due to mutations in *DCT* (*TYRP2*) which encodes DOPAchrome tautomerase, an enzyme that catalyzes tautomerization of DOPAchrome to 5,6-dihidroxyindole-2-carboxylic acid in the melanin biosynthetic pathway[91] (see Fig. 65.11).

OA type 1 is an X-linked recessive disorder caused by mutations in *GPR143* (G protein-coupled receptor 143; formerly *OA1*). This pigment cell-specific intracellular G protein-coupled receptor regulates melanosome formation and transport within melanocytes and cells of the retinal pigment epithelium[92]. Mutations in *GPR143* that lead to ocular albinism can result in retention of the aberrant protein within the ER. Autosomal recessive OA is no longer regarded as a distinct disorder, since many patients actually have OCA1B or OCA2 with subtle cutaneous findings.

Clinical features

Ocular manifestations

The many ocular manifestations of OA and OCA reflect a reduction in melanin within eye structures or misrouting of optic nerve fibers during development. The former leads to a translucent iris that transmits light upon globe transillumination, as well as a relatively hypopigmented retina and fovea that are associated with photophobia and reduced visual acuity; the severity of these findings correlates with the amount of reduction in melanin pigment. Misrouting of the optic fibers is thought to be responsible for the characteristic strabismus, nystagmus, and lack of binocular vision.

OCA1

There are two clinical subtypes of OCA1, based upon whether tyrosinase activity is reduced (OCA1B) or absent (OCA1A).

OCA1A

OCA1A corresponds to the classic "tyrosinase-negative" OCA. The melanocytes of the skin, hair, and eyes synthesize no melanin. The characteristic phenotype includes white hair, milky white skin, and blue–gray eyes at birth. With age, the skin color remains white and melanocytic nevi amelanotic, but the hair may develop a slight yellow tint due to denaturing of hair keratins. These patients have an extreme sensitivity to UV light and a strong predisposition to skin cancer. Reduced visual acuity is most severe in OCA1A, and some patients are legally blind.

OCA1B

Because the decrease in tyrosinase activity varies, the phenotype ranges from obvious to subtle pigmentary dilution when compared with first-degree relatives. One of the original OCA1B phenotypes was called "yellow albinism" because of the eventual color of the patient's hair, since the formation of yellow pheomelanin requires less tyrosinase activity. Other clinical types of OCA1B have been referred to as "minimal pigment OCA", "platinum OCA", and "temperature-sensitive OCA". All of these patients have little or no pigment at birth, but they develop some pigmentation of the hair and skin during the first and second decades of life. The majority burn without tanning after sun exposure, and some degree of iris translucency is often present. Amelanotic or pigmented melanocytic nevi can develop.

In the temperature-sensitive OCA1B phenotype, patients are born with white hair and skin and blue eyes. During puberty, scalp and axillary hairs remain white, but arm hairs turn light reddish brown and leg hairs turn dark brown. The abnormal tyrosinase enzyme is temperature-sensitive, losing its activity above 35°C. As a result, melanin synthesis does not occur in warmer areas of the body, akin to the phenotype of a Siamese cat, which also has temperature-sensitive tyrosinase activity.

OCA2

The OCA2 phenotype (in addition to OCA1B) corresponds to the classic "tyrosinase-positive" OCA. The clinical spectrum of OCA2 is broad, ranging from minimal to moderate pigmentary dilution of the hair, skin, and iris, with little to no ability to tan. The vast majority of Black individuals with "tyrosinase-positive" OCA have OCA2. With time, pigmented melanocytic nevi and lentigines may develop in sun-exposed areas (Fig. 66.10); the latter can become rather large and darkly colored (Fig. 66.11). Another phenotype previously referred to as "brown OCA" in Black populations results primarily from mutations in the *P* gene. In these individuals, the hair and skin are light brown, the irides are gray to tan at birth, and sunburns are unusual.

The hypopigmentation seen in a subset of patients with Prader–Willi syndrome (PWS) and Angelman syndrome (AS) represents a form of OCA2. PWS features hyperphagia, obesity, hypogonadism, and intellectual disability, whereas AS is characterized by severe intellectual disability, microcephaly, ataxic movements, and inappropriate laughter. Due to genomic imprinting (see Ch. 54), deletions of the 15q region (which includes *OCA2*) in the paternal chromosome lead to PWS, while deletions in the maternal chromosome give rise to AS. Approximately 1% of patients with AS or PWS also have OCA2, which occurs when the deletion of one *OCA2* allele is accompanied by a mutation in the second allele.

OCA3

OCA3 is most common in Black individuals, and phenotypes previously referred to as "rufous" (vast majority of OCA3 patients) and "brown" (more often seen in OCA2; see above) have been described. The "rufous" phenotype includes a red–bronze skin color, ginger-red hair, and blue or brown irides.



Fig. 66.10 Oculocutaneous albinism type 2 (OCA2). African patient with obvious squamous cell carcinomas on the cheek as well as multiple pigmented lentigines. *Courtesy James Nordlund, MD.*

OCA4

OCA4 is most common among individuals with albinism who are from Japan (~25% of patients), China (10%–20% of patients), or India (~10% of patients), and it accounts for ~5% of albinism in White individuals[93]. The phenotype of OCA4 is variable; hair color ranges from white to yellow or brown, and patients may or may not develop increased pigmentation of the skin and hair over time.

OCA5–8

OCA5 was described in a consanguineous Pakistani family, in which affected individuals had white skin and golden hair. OCA6 has been reported in patients from Asia, Africa, and Europe. Affected individuals have white to light brown skin with a variable ability to tan, yellow to brown hair that often darkens with age, and blue to light brown irides[89]. OCA7 has been described primarily in patients from the Faroe Islands of Denmark; affected individuals have lighter skin than their relatives and hair color ranging from light yellow to brown[90]. OCA8 presents with mild pigmentary dilution of the skin and hair, often together with more pronounced ocular findings including nystagmus, reduced visual acuity, and foveal hypoplasia[91].



Fig. 66.11 Oculocutaneous albinism type 2 (OCA2). African patient with hypopigmented hair and large pigmented lentigines. *Courtesy James Nordlund, MD.*

Ocular albinism type 1 (OA1)

Ocular albinism type 1 is characterized by a substantial reduction in visual acuity, hypopigmentation of the retina, and the presence of macromelanosomes in the eyes. Affected boys have nystagmus, photophobia, and foveal hypoplasia[92]. Their skin is usually clinically normal without notable pigmentary dilution, although hypopigmented macules have been described in affected individuals who have darkly pigmented skin. Macromelanosomes are evident on histologic examination of the skin. Female carriers of OA1 may have a "mud-splattered" fundus due to interspersed regions of pigmentation.

Pathology

Although there is a reduction in melanin content, a normal number of melanocytes are present within the epidermis.

Differential diagnosis

This is outlined in Fig. 66.12. Occasionally, patients with total body vitiligo may be thought to have OCA, but their epidermis lacks melanocytes.

Treatment

No specific treatment is available. Photoprotection (sunscreens, hats, clothing, sun avoidance) is mandatory in patients who have minimal or no pigmentation, in order to avoid cutaneous photocarcinogenesis, in particular the development of squamous cell carcinomas. The latter are a significant cause of morbidity and mortality, especially in tropical regions (see Fig. 66.10). All patients should undergo ophthalmologic evaluation early in life, with longitudinal care as required.

Nitisinone, which is FDA approved for treating hereditary tyrosinemia type 1, represents a potential therapy for OCA. In a mouse model of OCA1B, nitisinone elevated plasma tyrosine levels and led to increased pigmentation of the hair and eyes[94]. A pilot study in 5 adults with OCA1B found that visual acuity as well as skin and hair pigmentation increased after 1 year of treatment with oral nitisinone (2 mg/day)[95].

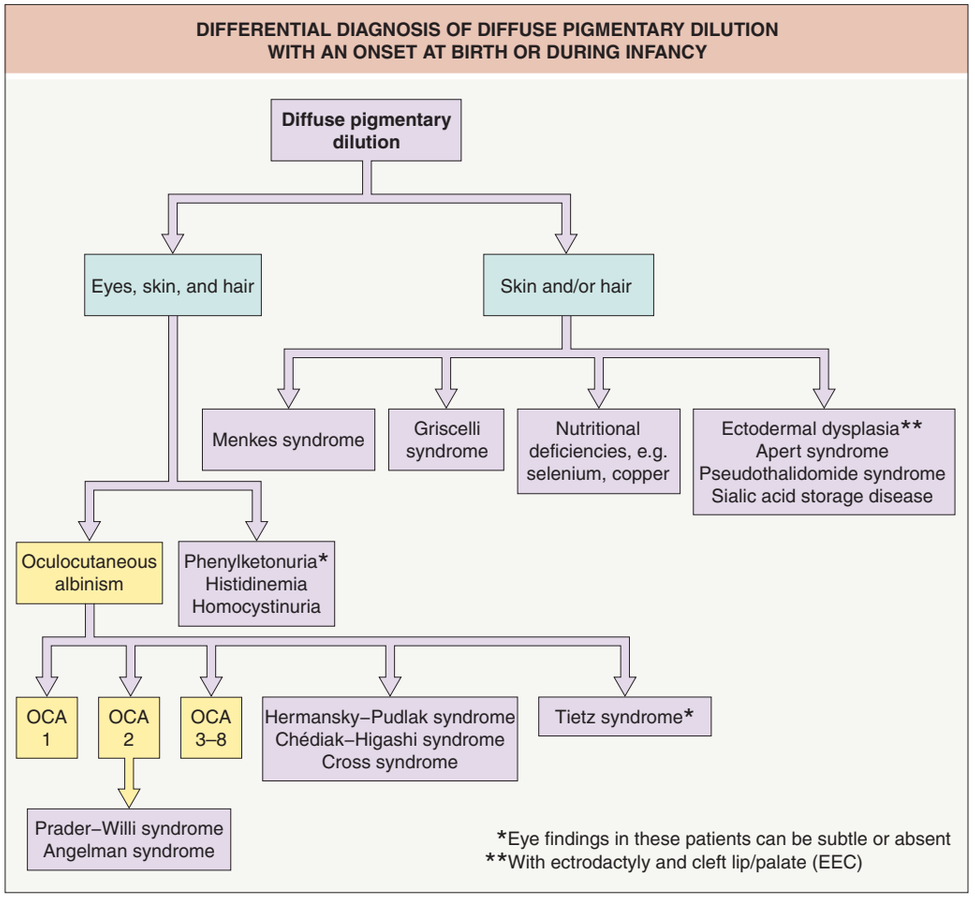


Fig. 66.12 Differential diagnosis of diffuse pigmentary dilution with onset at birth or during infancy. Patients with Griscelli syndrome and Chédiak–Higashi syndrome (CHS) have silvery hair and those with CHS can have an admixture of hyper- and hypopigmentation in chronically sun-exposed skin. Additional rare causes of diffuse pigmentary dilution include deficiency of the endosomal adaptor p14, tricho-hepato-enteric syndrome, and biallelic *KIT* mutations. *Adapted from Bolognia JL. A clinical approach to leukoderma. Int J Dermatol 1999;38:568–72.*

Piebaldism

Piebaldism is an uncommon autosomal dominant disorder characterized by poliosis and congenital, stable, circumscribed areas of leukoderma due to an absence of melanocytes within involved sites.

Epidemiology

The exact prevalence of this condition is not known, but it is estimated to occur in approximately 1 in 40 000 White individuals.

Pathogenesis

Piebaldism results from mutations in the *KIT* proto-oncogene[96], which encodes a member of the tyrosine kinase family of transmembrane receptors that is found on the surface of melanocytes (see Fig. 65.2). A functioning KIT receptor is required for the normal development of melanocytes, both immediately before melanoblast migration from the neural crest and postnatally. Although heterozygous deletion of *SNAI2* was previously identified in a few patients, this gene is no longer thought to be associated with piebaldism[97].

Clinical features

The leukoderma has a characteristic distribution pattern that favors the central anterior trunk, mid extremities, central forehead, and midfrontal portion of the scalp; the latter results in a white forelock (Fig. 66.13). The lesions are present at birth and classically spare the posterior midline. The white forelock, which is found in 80%–90% of patients, is the most familiar feature of piebaldism. However, its absence does not exclude the diagnosis. All the hairs of the forelock are white, and the underlying skin is also amelanotic. This depigmented patch is midline in location, triangular or diamond-shaped, and often symmetrical. The apex can reach the vertex posteriorly, and the affected area may extend to the root of the nose and include the medial third of the eyebrows; involvement of the nose is rare.

The areas of leukoderma are distinctive and can establish the diagnosis of piebaldism, even in the absence of a white forelock. They are irregular in shape, well-circumscribed, and milk-white in color. Normally pigmented and hyperpigmented macules and patches, ranging from a few millimeters to several centimeters in diameter, are typically apparent within the leukodermic patches (Fig. 66.14). Hyperpigmented patches also occur within uninvolved skin and should not be misinterpreted as evidence of neurofibromatosis type 1; axillary freckling has also been observed in patients with piebaldism. Poliosis of the eyebrows and eyelashes is a common finding, as are white hairs within areas of leukoderma. Limited contraction of the areas of involvement over time is occasionally observed, and premature graying of the hair is not uncommon.

Pathology

By light and electron microscopy, no melanocytes can be identified in either the interfollicular epidermis or the hair follicles of amelanotic skin[98]. The hyperpigmented macules are characterized by an abundance of melanosomes in the melanocytes and keratinocytes.

Differential diagnosis

The presence of stable amelanotic patches since birth, the characteristic distribution pattern, and the distinctive normally pigmented or hyperpigmented macules within the areas of leukoderma allow the differentiation of piebaldism from vitiligo. The differential diagnosis of circumscribed poliosis of scalp hairs is broad and includes both inherited and acquired causes (Table 66.3)[99]. Of note, an isolated white forelock can also be inherited as an autosomal dominant trait. The diagnosis of piebaldism should prompt the clinician to exclude the possibility of Waardenburg syndrome via an ocular examination and evaluation of hearing. *Albinism–deafness syndrome* (Ziprkowski–Margolis or Woolf syndrome), a rare X-linked disorder linked to Xq26.3–q27.1, presents with congenital sensorineural deafness and a severe piebald-like phenotype with extensive areas of hypopigmentation[100].

Treatment

Autografting of normal skin or melanocytes into amelanotic areas represents a therapeutic option, but this typically requires multiple procedures. Cosmetic products can be used to camouflage affected areas; protection against sunburn is also necessary.

Waardenburg Syndrome

Waardenburg syndrome (WS) is a rare autosomal dominant or less often autosomal recessive disorder that is characterized by various combinations of the following features[101]:

- achromia of the hair, skin, or both in the same pattern as piebaldism (see above)
- congenital deafness
- partial or total heterochromia irides (including isohypochromia)
- medial eyebrow hyperplasia (synophrys)
- a broad nasal root
- dystopia canthorum (increased distance between the inner canthi, with a normal interpupillary distance).

Four clinical subtypes of WS have been described (Table 66.4): WS type I, the classic form (WS1); WS type II, which lacks dystopia canthorum (WS2); WS type III, with associated limb abnormalities (WS3, Klein–Waardenburg syndrome); and WS type IV, with Hirschsprung disease (WS4, Shah–Waardenburg syndrome).

Epidemiology

The incidence of WS in the Netherlands has been estimated as ~1 in 200 000. In the US, deafness in the setting of WS afflicts 1 in 50 000. WS has been observed in various races and from all regions of the world. Men and women are equally affected.



Fig. 66.13 Piebaldism. White forelock and characteristic triangular amelanotic patch on the mid-forehead. *Courtesy Julie V. Schaffer, MD.*



Fig. 66.14 Piebaldism. Characteristic involvement of the mid extremities. Note the normally pigmented and hyperpigmented macules within the leukoderma. *Courtesy Julie V. Schaffer, MD.*

Pathogenesis

The facial dysmorphism seen in WS points to abnormal fetal development. It is therefore not surprising that several of the genes responsible for WS (*PAX3, MITF, SOX10*; see Table 66.4) encode transcription factors that, by binding DNA and regulating the expression of other genes, have important functions during embryogenesis (see Fig. 65.4). The neural crest is the source of the connective tissues of the head and neck and intestinal ganglion cells as well as melanoblasts, explaining the manifestations of this neurocristopathy. Presumably, the deafness in WS reflects the role of melanocytes in the development of the inner ear.

The PAX3 transcription factor that is mutated in WS1 and WS3 activates melanoblasts and other cells to proliferate and then migrate from the neural crest. The abnormalities of the upper extremities that characterize WS3 imply that PAX3 also regulates limb development[102]. Mutations in the *mi*crophthalmia-associated *t*ranscription *f*actor gene (*MITF*; expression of which is regulated by PAX3 and SOX10; see Fig. 65.4), which encodes a helix-loop-helix/leucine zipper transcription factor, can result in WS2. Of note, a mutation in *MITF* that affects the nuclear localization of this protein underlies Tietz syndrome (see below)[103]. In addition to its critical role in melanocyte development, MITF regulates the expression of a number of melanocyte-specific genes (e.g. tyrosinase; see Ch. 65). KIT signaling also interacts with MITF in melanocyte development (see Fig. 65.4), and biallelic mutations in *KITLG* (encodes KIT ligand) have been found to result in WS2 as well as other pigmentary phenotypes, including diffuse pigmentary dilution (skin and hair) and familial progressive hyperpigmentation ± hypopigmentation (see below)[104]. Homozygous deletion of *SNAI2* (the expression of which is regulated by MITF) is no longer thought to represent a cause of WS2[97].

The SOX10 transcription factor plays an essential role in the development of melanoblasts and ganglion cells, and mutations in this gene can cause WS4 or (if milder) WS2[105]. WS4 can also be caused by mutations in the genes encoding the endothelin B receptor and its endothelin-3 ligand[106]. The endothelin B receptor is found on melanoblast-ganglion cell precursors in the developing neural crest, and its binding to endothelin-3 is essential for the generation of these cell types (see Fig. 65.3).

DIFFERENTIAL DIAGNOSIS OF CIRCUMSCRIBED SCALP POLIOSIS
Inflammatory, autoimmune, or traumatic
• Vitiligo • Halo nevus • Alopecia areata (primarily initial cycle of growth) • Postinflammatory (e.g. discoid lupus, blepharitis [eyelashes]) • Postinfectious (e.g. zoster) • Post-traumatic • Vogt–Koyanagi–Harada syndrome • Alezzandrini syndrome • Melanoma-associated leukoderma (spontaneous or following immunotherapy)
Inherited
• Tuberous sclerosis* • Piebaldism (midline frontal) • Waardenburg syndrome (primarily midline frontal) • Isolated white forelock† • Isolated occipital white lock (X-linked recessive) • White forelock with osteopathia striata (autosomal or X-linked dominant) • White forelock with multiple malformations (autosomal or X-linked recessive) • Neurofibromatosis type 1 – overlying a neurofibroma • Prolidase deficiency and Marfan syndrome (single case reports)
Nevoid
• Angora hair nevus • Associated with nevus comedonicus • Scalp heterochromia secondary to mosaicism*
Pharmacologic agents
• Imiquimod • Latanoprost (eyelash poliosis) • Tyrosine kinase inhibitors (e.g. eyelash poliosis with cetuximab)
Idiopathic
*May be lighter than surrounding hair rather than white (e.g. blond streaks in a patient with brown hair). †Separate entity vs possible forme fruste of piebaldism.

Table 66.3 Differential diagnosis of circumscribed scalp poliosis. *Adapted from Bolognia JL, Shapiro PE. Albinism and other disorders of hypopigmentation. In: Arndt KA, et al (eds). Cutaneous Medicine and Surgery. Philadelphia: WB Saunders, 1995.*

Clinical features

Waardenburg syndrome type 1 (WS1)

A white forelock, generally similar to that of piebaldism, is the most frequently observed pigmentary abnormality in WS (20%–60% of patients). Although the forelock is usually white, patches of red, brown, or black hair have also been described. A few patients have additional areas of poliosis in the frontoparietal or occipital scalp. Premature graying can involve the scalp hair, eyebrows, and body hair, and the onset may be as early as the teens. Areas of leukoderma with an appearance, distribution pattern, and natural history similar to piebaldism have been observed in ~15% of patients. The prevalence of

DISORDERS OF MELANOCYTE DEVELOPMENT					
Human disease		**Mouse model**	**Inheritance**	**Gene**	**Protein**
Piebaldism*		Dominant spotting	AD	*KIT*	KIT tyrosine kinase
Waardenburg syndrome					
WS1		Splotch	AD	*PAX3*	Paired box 3 transcription factor
WS2†	A	Microphthalmia	AD	*MITF*	Microphthalmia-associated transcription factor
	E		AD	*SOX10*	SRY-box 10 transcription factor
	F		AR	*KITLG*	KIT ligand
WS3		Splotch	AD≫AR‡	*PAX3*	Paired box 3 transcription factor
WS4	A	Piebald spotting	AD, AR	*EDNRB*	Endothelin B receptor
	B	Lethal spotting	AD, AR	*EDN3*	Endothelin-3
	C	Dominant megacolon	AD	*SOX10*	SRY-box containing 10
Tietz syndrome			AD	*MITF*	Microphthalmia-associated transcription factor
Albinism, black lock, cell migration disorder of the neurocytes of the gut, and deafness (ABCD) syndrome			AR	*EDNRB*	Endothelin receptor type B

*Diffuse pigmentary dilution of the skin, hair, and eyes as well as deafness and developmental delay have been described in patients with biallelic *KIT* mutations.
†Other forms of WS2 have been linked to 1p21–p13.3 (WS2B) and 8p23 (WS2C).
‡Homozygous *PAX3* mutations have been described in individuals with WS3 whose parents were affected with WS1.

Table 66.4 Disorders of melanocyte development. AD, autosomal dominant; AR, autosomal recessive.

hearing impairment ranges from 10% to >35%[107]; it may be bilateral or unilateral and severe or moderate.

Heterochromia irides, partial (sectorial) or complete, is found in >20% of patients (Fig. 66.15). Complete heterochromia irides gives rise to irides of different colors, one being whitish blue. Bilateral involvement results in bilateral pale blue eyes (isohypochromia). Hypomelanotic fundi may be present.

The eyebrows may be confluent (synophrys) or show hyperplasia of their medial portions (15%–70% of patients). The characteristic dystopia canthorum represents an increase in the distance between the inner canthi, with normal distances between the pupils and between the outer canthi. This is accompanied by a shortening in the length of the palpebral fissure (blepharophimosis) and a lateral displacement of the inferior lacrimal points, which are then situated in front of the cornea. The dystopia is usually symmetric but may be asymmetric. Dystopia canthorum is a characteristic feature of WS1 and WS3.

Waardenburg syndrome type 2 (WS2)

WS2 differs from WS1 primarily by the absence of dystopia canthorum. In addition, deafness is probably more common in patients with WS2.

Klein–Waardenburg syndrome (WS3)

WS3 is similar to WS1 but is also associated with upper limb abnormalities (e.g. hypoplasia, syndactyly).

Shah–Waardenburg syndrome (WS4)

In WS4, the characteristic findings of WS occur in association with Hirschsprung disease. In many patients, a white forelock, amelanotic macules, and heterochromia irides are present. Deafness is fairly common, but dystopia canthorum and a broad nasal root are uncommon. Additional rare manifestations (associated with *SOX10* mutations) include central nervous system dysfunction, neonatal hypotonia, and arthrogryposis.

Tietz syndrome

Tietz syndrome is a rare autosomal dominant disorder characterized by diffuse pigmentary dilution of the skin and hair together with deafness and hypoplasia of the eyebrows. Although the eyes are blue, affected individuals do not have photophobia or nystagmus and the fundi are normal. The clinical phenotype is significantly different from WS2, despite being allelic.

Pathology

As in piebaldism, the areas of involvement in WS have an absence or minimal number of melanocytes when examined by light or electron microscopy.

Diagnosis

In patients with the complete WS phenotype, the diagnosis is clear. However, there is significant clinical heterogeneity, and in some forme fruste cases the diagnosis can be difficult to establish. Examination of family members can be helpful as they may have other features of the disease.



Fig. 66.15 Waardenburg syndrome type 2. Heterochromia irides in the absence of dystopia canthorum. The white forelock is seen in the upper left corner.
Courtesy Daniel Albert, MD.

Treatment

No specific treatment is available. However, early diagnosis permits appropriate management of the deafness.

Disorders of Melanosome Biogenesis

Melanosomes are considered members of the lysosome-related organelle family, which includes platelet dense granules and the lytic granules of cytotoxic lymphocytes and natural killer (NK) cells. When the biogenesis of these organelles is disrupted, affected individuals present with the clinical findings of OCA due to their defective melanosomes together with additional symptoms (e.g. bleeding diathesis, immunodeficiency) that reflect abnormalities in other lysosome-related orgenelles[108,109]. These genetic diseases include Hermansky–Pudlak syndrome (HPS) and Chédiak–Higashi syndrome (CHS).

Hermansky–Pudlak syndrome

To date, eleven subtypes of HPS have been identified, each of which is inherited in an autosomal recessive manner (see Table 65.1)[110].

Pathogenesis

Most forms of HPS result from mutations in genes that encode components of the *b*iogenesis of *l*ysosome-related *o*rganelles *c*omplexes 1–3 (BLOC1/2/3; see Table 65.1 & Fig. 65.8). These complexes are involved in the formation of lysosome-related organelles, including melanosomes, by a mechanism distinct from that of the adaptor protein 3 (AP-3) complex. The exceptions are HPS2 and HPS10, which are caused by mutations in *AP3B1* and *AP3D1*, respectively[111]. These genes encode the β1 and δ1 subunits of the AP-3 complex, which is involved in protein sorting to lysosomes and lysosome-related organelles (see Fig. 65.8). AP-3 also functions in CD1b-associated antigen presentation and secretion of lytic granules from cytotoxic T cells, explaining the additional clinical feature of immunodeficiency in patients with HPS2 and 10. In addition, a neuron-specific AP-3 heterotetramer requires δ1 but not β1; as a result, HPS10 but not HPS2 has neurologic manifestations.

Clinical features

Compared to unaffected first-degree relatives, patients with HPS have pigmentary dilution of the skin, hair, and eyes. The degree varies, depending upon the underlying mutations and the patient's constitutive pigmentation. With age, an increase in pigmentation is usually seen, but patients still have difficulty tanning. Ocular manifestations of albinism, such as nystagmus and reduced visual acuity, are also present.

Systemic manifestations due to organelle dysfunction include a bleeding tendency (e.g. with tooth extraction or childbirth) as well as interstitial pulmonary fibrosis and granulomatous colitis secondary to ceroid lipofuscin accumulation within lysosomes. Granulomatous plaques and "knife-cut" ulcers of the vulva, intertriginous areas, and peristomal skin similar to cutaneous Crohn disease have also been described[112]. Less often, renal failure and cardiomyopathy develop, usually during adulthood. Patients with HPS2 and 10 experience recurrent bacterial infections due to neutropenia and abnormal cytotoxic T cell function, and HPS10 presents with neurodevelopmental delay and seizures.

Laboratory findings and pathology

By electron microscopy, macromelanosomes as well as stage I to III (rarely stage IV) melanosomes are seen. Although the platelet count is normal, the bleeding time and platelet function analyzer (PFA)-100 time are prolonged due to platelet dysfunction. Ultrastructurally, there is an absence of dense bodies within platelets. Ceroid deposits, derived from the degradation of lipids and glycoproteins, are found within lysosomes in affected internal organs, including the lungs and gastrointestinal tract. Presumably, this reflects a defect in lysosomal function.

Differential diagnosis

In addition to the entities in Fig. 66.12, diagnostic considerations may include the autosomal recessive *deficiency of the endosomal*

adaptor p14, which features diffuse pigmentary dilution of the skin and hair, neutropenia, and recurrent pulmonary infections.

Treatment

The development of progressive pulmonary fibrosis often leads to premature death in patients with HPS, who have an average lifespan of only 30–50 years. Although the antifibrotic agent pirfenidone appeared to slow the progression of pulmonary fibrosis in HPS1 patients in an initial controlled study, a controlled trial found no benefit of this agent in HPS1 patients with mild to moderate pulmonary disease[113]. Platelet transfusions can be administered prior to surgical procedures in HPS patients.

Cross syndrome

Cross syndrome is characterized by diffuse pigmentary dilution, silvery hair, ocular anomalies, and neurologic abnormalities (e.g. psychomotor retardation, ataxia, and spasticity). A family with overlapping features of HPS and Cross syndrome has raised the possibility that this latter syndrome may be a clinical variant of HPS[114].

Chédiak–Higashi syndrome

Chédiak–Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by OCA with a silvery-gray cast to the hair, photophobia, nystagmus, and ocular hypopigmentation; an admixture of hyper- and hypopigmentation may be evident in chronically sun-exposed skin, especially in patients with relatively dark constitutive pigmentation. Additional findings include a bleeding diathesis due to diminished function of platelet dense granules, progressive neurologic dysfunction, and severe immunodeficiency due to abnormal lytic granules in lymphocytes, NK cells, and neutrophils (see Ch. 60). A hallmark of the disorder is the presence of giant lysosome-related organelles, including melanosomes, platelet dense granules, and neutrophil granules. Examination of a peripheral blood smear for the latter represents a simple method of screening for this condition. CHS is caused by mutations in the *lys*osomal *t*rafficking regulator gene (*LYST*), which encodes a cytoplasmic protein that regulates fission/fusion of lysosome-related organelles[115].

Tricho-hepato-enteric syndrome (phenotypic diarrhea of infancy)

This autosomal recessive disorder caused by mutations in the SKI3 subunit of superkiller complex gene (*SKIC3*) can present with diffuse pigmentary dilution of the skin and hair, platelet defects (including abnormal granules) and immunodeficiency. Unlike CHS, it is also characterized by brittle hair with trichorrhexis nodosa, intractable diarrhea during infancy, primary liver disease, facial dysmorphism, and cardiac defects.

Disorders of Melanosome Transport and/or Transfer

Identification of the defective proteins in various forms of Griscelli syndrome (GS) has led to better understanding of processes of melanosome transport.

Epidemiology

Griscelli syndrome is a rare autosomal recessive disorder.

Pathogenesis

On the basis of molecular genetics (as well as clinical findings), GS has been separated into three entities, GS1, GS2, and GS3 (see Table 65.1). GS1 is due to mutations in the gene that encodes myosin Va[116]. One end of the myosin Va protein binds the actin cytoskeleton, while the other can bind an organelle, e.g. a melanosome. This linkage plays a key role in the transfer of melanosomes from melanocytes to keratinocytes. GS2 is caused by mutations in *RAB27A*[117], which encodes a small Ras-like GTPase (belonging to the Rab family) that is present in melanosomes. GS3 is due to mutations in *MLPH*, whose protein product, melanophilin, serves to link myosin Va to Rab27a[118] (see Fig. 65.10). Because *MLPH* is expressed only in melanocytes, the associated phenotype is limited to diffuse pigmentary dilution and silvery hair. On the other hand, expression of *MYO5A* in neurons explains the associated neurologic abnormalities in GS1, and expression of *RAB27A* in hematopoietic cells accounts for the immunodeficiency and hemophagocytic syndrome observed in GS2. *Elejalde syndrome* is now thought to likely represent a variant of GS1.

Clinical features

All three types of GS are characterized by pigmentary dilution of the skin and silvery-gray hair due to pigment clumping within melanocytes. As noted above, patients with GS1 exhibit primarily neurologic impairment[116], while those with GS2 have immune abnormalities due to defective release of cytotoxic lysosomal contents from hematopoietic cells. A hemophagocytic syndrome can also occur in GS2, with uncontrolled T lymphocyte and macrophage activation leading to death[117]; this process can involve the CNS in a secondary manner.

Treatment

Hematopoietic stem cell transplantation is indicated for the treatment for GS2, but not GS1 or GS3.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) represents an autosomal dominant disorder characterized by hamartomas in multiple organs, most commonly the skin, brain, eye, heart, and kidney (see Ch. 61).

Clinical features

The classic TSC triad of facial angiofibromas ("adenoma sebaceum"), seizures, and intellectual disability is preceded by the appearance of white macules. In one study utilizing Wood's lamp examination, hypomelanotic macules were found in 64 of 65 patients with TSC.

Hypomelanotic macules are often evident at birth or during the neonatal period. In fact, all lesions are probably present at birth, but they may be inapparent, particularly in infants with lightly pigmented skin, until the skin is exposed to UV light or the patient is examined with a Wood's lamp. The number of lesions varies from one to >100 per patient. The vast majority of patients have 2–20 hypomelanotic macules, with 50% having <6 and 50% having ≥6 macules. Lesions may be polygonal, lance-ovate, "thumbprint-like", guttate ("confetti-like"), or (rarely) segmental (see Fig. 61.14). The most characteristic, but not the most frequent, configuration is lance-ovate (rounded at one end, pointed at the other), which resembles the leaflet of the mountain ash tree, hence the name "ash leaf spot".

Hypomelanotic macules are usually found on the trunk, particularly posteriorly, but they can be found on any cutaneous surface. They occur more commonly on the lower extremities than on the upper extremities or the head and neck; lesions on the scalp are often associated with more lightly pigmented hairs. The long axis of the lance-ovate (ash leaf) macules is predominantly in the cephalocaudal direction on the extremities and in the transverse direction on the trunk. The margins of the lesions are usually smooth but may be irregular. The macules and patches are a dull white color (hypomelanotic), not the "pure-white" color (amelanotic) of vitiligo. As a result, they may be inapparent on casual examination of lightly pigmented skin. Wood's lamp examination reveals a reduction, but not an absence, of pigmentation. The relative size and number of hypomelanotic macules do not change with age, and spontaneous disappearance does not occur. Café-au-lait macules are seen in some patients.

Pathogenesis

Circumscribed hypomelanosis in TSC does not appear to result from a reduction in the number of melanocytes but rather from decreased size and poor melanization of melanosomes, which (regardless of racial background) are grouped within the lysosomes of keratinocytes (see Table 65.3). Decreased melanosome size is not a feature of other circumscribed congenital hypomelanoses. TSC is caused by mutations in two tumor suppressor genes, *TSC1* and *TSC2*, which encode the hamartin and tuberin proteins, respectively. These proteins associate physically *in vivo*, functioning together to negatively regulate mechanistic target of rapamycin (mTOR) signaling.

Diagnosis

If an infant has three or more hypopigmented macules, especially if lance-ovate in shape, a diagnosis of TSC should be considered and (if there is no history of seizures) echocardiography performed as an initial

DIFFERENTIAL DIAGNOSIS OF GUTTATE LEUKODERMA
Idiopathic guttate hypomelanosis
Pityriasis lichenoides chronica
Lichen sclerosus
Achromic verrucae planae*
Leukoderma punctata (after PUVA therapy)
Vitiligo ponctué
Darier disease (usually admixed with keratotic lesions)
Confetti-like lesions of tuberous sclerosis
Xeroderma pigmentosum
In association with punctate palmoplantar keratoderma (Cole disease)
In association with chromosomal abnormalities
Disseminated hypopigmented keratoses (after PUVA therapy)*
Frictional lichenoid dermatitis*
Pityriasis alba
Tinea versicolor (especially on the face of children)
Clear cell papulosis*
*Minimally elevated flat-topped papules.

Table 66.5 Differential diagnosis of guttate leukoderma. Guttate hypopigmentation may also be seen in the setting of dyschromatoses (see Table 67.11). *Adapted from Bolognia JL, Shapiro PE. Albinism and other disorders of hypopigmentation. In: Arndt KA, et al (eds). Cutaneous Medicine and Surgery. Philadelphia: WB Saunders, 1995.*



Fig. 66.16 Linear nevoid hypopigmentation. Hypopigmented streaks with various widths along the lines of Blaschko on the posterior lower extremities. *Courtesy Antonio Torrelo, MD.*



Fig. 66.17 Nevus depigmentosus. Hypomelanotic patch with a decrease, but not absence, of pigmentation.

investigation (see Fig. 61.21). The combination of white macules and seizures increases the likelihood of TSC. Although the presence of only one or two hypopigmented macules or patches in an otherwise healthy infant does not exclude TSC, the diagnosis of nevus depigmentosus is much more likely.

It is usually fairly easy to distinguish vitiligo, given its characteristic distribution pattern and pure-white color. Postinflammatory hypopigmentation is typically easily excluded by the lack of preceding or concurrent inflammatory or trauma-induced lesions. Nevus anemicus is readily distinguished by its "disappearance" upon diascopy; in addition, vigorous rubbing or application of ice produces erythema in the hypopigmented lesions of TSC significantly more than in nevus anemicus. Hypomelanotic macules may be observed in patients with ataxia telangiectasia (likely reflecting "pigmentary mosaicism"). *Westerhof syndrome* is characterized by hypo- and hyperpigmented macules, possibly in association with growth retardation; autosomal dominant inheritance has been proposed, but the etiology is not known. *Familial progressive hyperpigmentation with or without hypopigmentation*, which also has autosomal dominant inheritance and features lesions ranging from small macules to large patches, is caused by heterozygous activating mutations in *KITLG*[119].

Rarely, the hypopigmentation in TSC has a segmental pattern, for which the differential diagnosis includes segmental vitiligo (which progresses over a few months to 2 years and is amelanotic) and "pigmentary mosaicism" (see below). Idiopathic guttate hypomelanosis (IGH) may resemble the confetti lesions of TSC, but IGH is an acquired disorder that usually develops in adults. The diagnosis of TSC should be considered in any child or infant with a guttate leukoderma. Other causes of a guttate leukoderma are outlined in Table 66.5.

"Pigmentary Mosaicism": Blaschko-Linear Hypopigmentation, Segmental Pigmentation Disorder, and Nevus Depigmentosus

Hypopigmentation along the lines of Blaschko reflects epidermal mosaicism characterized by streaks of skin with decreased pigment production ("pigmentary mosaicism"; see Ch. 62). The eponym "hypomelanosis of Ito" is becoming historical and should be reserved for patients with associated extracutaneous findings due to the presence of the mosaic mutation in tissues other than the skin. Although cytogenetic data are less substantial, "segmental pigmentation disorder" and nevus depigmentosus are also considered to represent manifestations of cutaneous mosaicism[120].

Clinical features

Blaschko-linear hypopigmentation may be apparent at birth or become evident during infancy or early childhood. The characteristic pattern of streaks and whorls can occur unilaterally or bilaterally (Fig. 66.16)[120]. Abnormalities of the CNS, eye, or musculoskeletal system are found in <15%–30% of patients with Blaschko-linear hypopigmentation who present to a pediatric dermatologist at a tertiary referral center.

Nevus depigmentosus occurs in 1 in 50–75 individuals. The name is a bit of a misnomer, as the areas of leukoderma are actually hypomelanotic rather than amelanotic. Most lesions measure a few centimeters in diameter and have irregular but well-defined borders, often breaking apart into smaller macules at the periphery (Fig. 66.17). A block-like variant of nevus depigmentosus, also referred to as the hypopigmented form of "segmental pigmentation disorder", typically features midline demarcation and less distinct lateral borders[121].

Phylloid hypomelanosis is a distinctive pattern of hypomelanosis that occurs in patients with mosaic forms of trisomy (or tetrasomy) 13 or 13q. The hypomelanosis consists of: (1) round or oval lesions; (2) large asymmetric areas reminiscent of the leaves of a begonia; and (3) pear-shaped or oblong macules. Additional features may include telangiectatic macules, hypertrichosis, CNS defects (especially absence of the corpus callosum), conductive hearing loss, choroidal and retinal colobomas, craniofacial anomalies, and digital malformations[122].

Pathology

The number of melanocytes in affected skin may be normal or decreased[123].

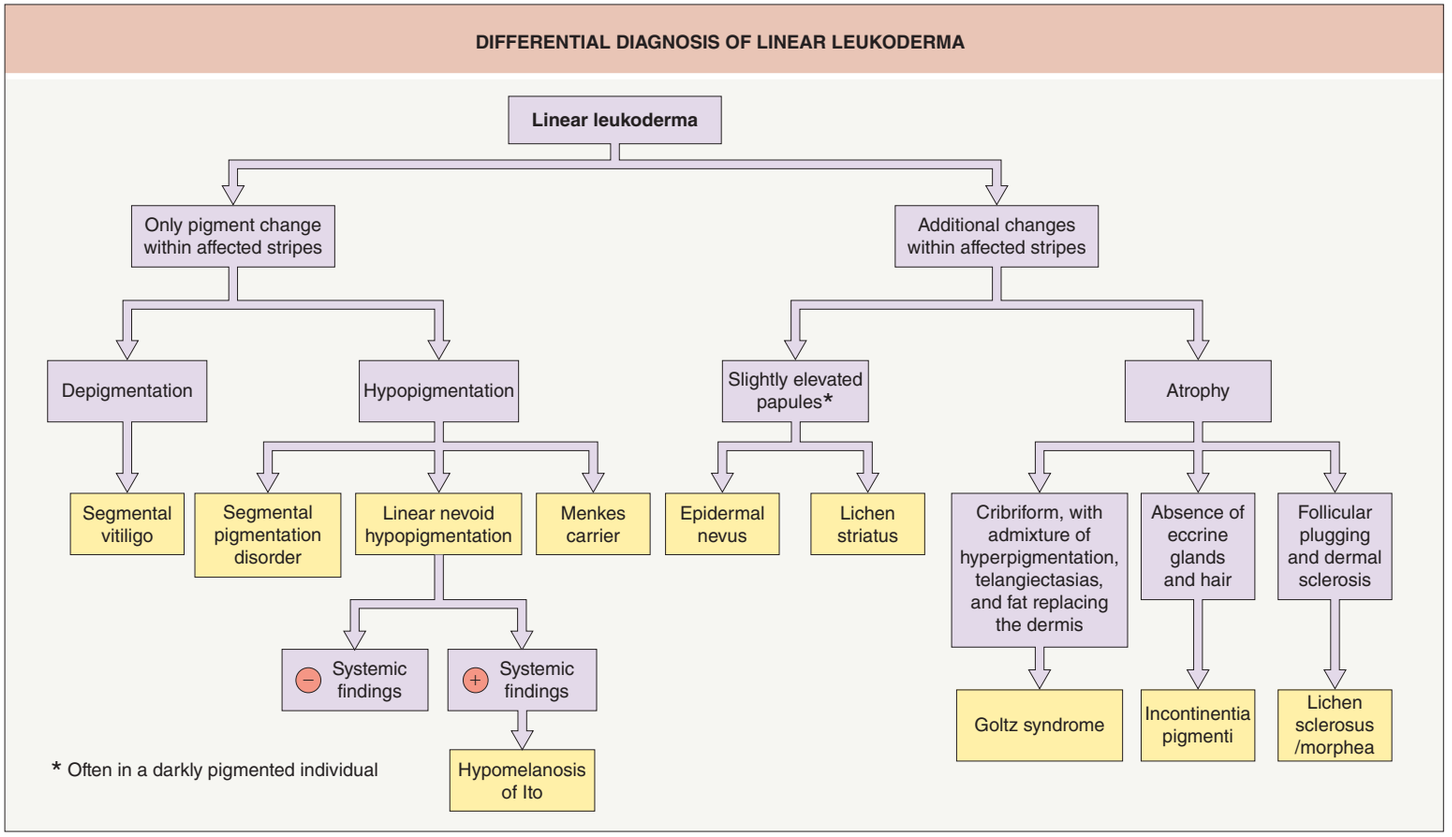


Fig. 66.18 Differential diagnosis of linear leukoderma.

Pathogenesis (see Ch. 62)

A wide variety of mosaic cytogenetic abnormalities in peripheral blood lymphocytes and/or lesional fibroblasts have been detected in patients with Blaschko-linear hypopigmentation. Single-gene causes of Blaschko-linear hypopigmentation include: (1) mosaic activating *MTOR* mutations, which are often associated with macrocephaly, (hemi)megalencephaly, and asymmetric overgrowth; (2) *RHOA-related neuroectodermal syndrome* with associated leukoencephalopathy and hemihypoplasia due to mosaic *RHOA* mutations; (3) X-linked disorders that result in functional mosaicism in female patients, e.g. *TFE3-associated neurodevelopmental disorder* with lysosomal storage disease-like features and *female-restricted X-linked syndromic intellectual development disorder-99 (USP9X)*[124] (see Ch. 62).

Diagnosis

The differential diagnosis of linear leukoderma is presented in Fig. 66.18 and Table 66.6. Diagnostic considerations for the common type of nevus depigmentosus are discussed above (see TSC).

DISORDERS WITH LINEAR HYPOPIGMENTATION
Lesions usually follow lines of Blaschko
• Blaschko-linear hypopigmentation*
• Lichen striatus
• Focal dermal hypoplasia (Goltz syndrome)
• Menkes kinky hair disease (female carrier)
• Conradi–Hünermann–Happle syndrome
• Epidermal nevus
• In association with nevus comedonicus
• Linear lichen sclerosus/morphea
• Guttate macules in linear keratosis follicularis and linear basaloid follicular hamartoma
Lesions may follow lines of Blaschko
• Segmental vitiligo
• Segmental ash leaf spot
• Fourth stage of incontinentia pigmenti
Lesions do not follow lines of Blaschko
• Linear hypopigmentation secondary to intralesional corticosteroids
• Pigmentary demarcation lines, type C
*Block-like hypopigmentation (segmental pigmentation disorder) represents another pattern of "pigmentary mosaicism" and may coexist with linear lesions; previous terms include "systematized" nevus depigmentosus with a linear configuration.

Table 66.6 Disorders with linear hypopigmentation. *Adapted from Bolognia JL, Shapiro PE. Albinism and other disorders of hypopigmentation. In: Arndt KA, et al (eds). Cutaneous Medicine and Surgery. Philadelphia: WB Saunders, 1995.*

NUTRITIONAL HYPOMELANOSIS

In *kwashiorkor*, which is due to severe protein deficiency, the skin initially becomes erythematous to red–brown in color with marked desquamation (see Ch. 51). Both hypomelanosis and patchy postinflammatory hypermelanosis can be seen, with striking pigmentary changes in florid cases. The hypomelanosis usually begins on the face. The hair is dry and lusterless, and it may become light red–brown in color. Upon resumption of dietary protein intake, the skin repigments slowly. Diffuse pigmentary dilution due to *deficiencies of copper* or *selenium* have also been reported (see Fig. 66.12).

HYPOMELANOSIS SECONDARY TO CUTANEOUS INFLAMMATION

Epidemiology

Postinflammatory hypomelanosis (PIH) represents a very common skin disorder that is more obvious in darkly pigmented or tanned individuals. A large number of dermatoses can lead to PIH[125], including seborrheic dermatitis, atopic dermatitis, lichen striatus, pityriasis lichenoides chronica, psoriasis, and lupus erythematosus (Fig. 66.19); mycosis fungoides, sarcoidosis, and lichen sclerosus can also present as hypopigmented lesions. In some patients, repeated examinations are required to identify primary inflammatory lesions.

Pathogenesis

The various steps that determine skin color, including melanogenesis, are controlled by multiple factors (e.g. growth factors, cytokines) that exert their actions directly or indirectly on keratinocytes and



Fig. 66.19 Postinflammatory hypopigmentation. Hypopigmentation secondary to psoriasis (**A**), seborrheic dermatitis in an infant (**B**), pityriasis lichenoides chronica (**C, D**), and lichen striatus (**E**). Note the subtle flat-topped papules in the latter. Complete pigment loss in patients with severe atopic dermatitis (**F**), neonatal lupus erythematosus (**G**), and discoid lupus erythematosus (**H**). *B, Courtesy Jean L. Bolognia, MD; E, G, Courtesy Julie V. Schaffer, MD.*

melanocytes. Dysregulation of these processes can induce abnormal melanocyte–keratinocyte interactions. Cutaneous inflammation, for example, is able to alter melanosome biogenesis, melanin production, melanosome transport, and especially transfer of melanosomes to keratinocytes. Severe local inflammation can lead to a loss of functional melanocytes or even melanocyte death.

Clinical features

Hypomelanosis usually follows or coexists with inflammatory lesions, but, occasionally, only hypopigmented lesions are seen, e.g. in sarcoidosis or mycosis fungoides. PIH, either localized or widespread, is usually associated with a decrease, but not absence, of pigment. Complete depigmentation is most commonly seen in the setting of severe atopic dermatitis and discoid lupus erythematosus (see Fig. 66.19F,H). Whether this lack of pigment represents koebnerization of vitiligo into areas of inflammation versus the consequence of severe inflammation is debatable.

Pathology

In certain dermatoses (e.g. sarcoidosis, mycosis fungoides), histologic examination of hypopigmented lesions can aid in establishing the diagnosis, whereas in others (e.g. pityriasis lichenoides chronica) the findings are less specific and the diagnosis is made primarily on a clinical basis.

Treatment

Once the underlying inflammatory disorder is effectively treated, PIH usually gradually resolves. Sun exposure or UVB phototherapy may be helpful, although tanning can also accentuate the contrast with normal skin. In amelanotic lesions with complete loss of melanocytes, epidermal or melanocyte grafting may be considered (see above).

Pityriasis Alba

Pityriasis alba is a very common condition, consisting of slightly scaly, round to oval, ill-defined macules and patches with mild to moderate hypopigmentation (see Ch. 12). Although it occurs in all skin phototypes, pityriasis alba is more noticeable in darkly pigmented individuals. It is generally a disorder of childhood and adolescence, and it becomes more apparent during the summer months when the surrounding skin is tanned. The lesions usually vary in size from 0.5 to 3 cm, but larger lesions can also occur.

The earliest lesions may be pink in color, but after a few weeks, the erythema fades and the cutaneous surface assumes a whitish, dry, powdery appearance, sometimes with a slightly raised, pinkish border. The face, especially the malar region, is the most frequent site of involvement. Occasionally, lesions of pityriasis alba are seen on the neck, trunk, and extremities. This dermatosis is generally asymptomatic, but some patients complain of itching and burning. With Wood's lamp examination, more lesions may become apparent and a decrease, but not absence, of pigment is observed. Although the patches of hypomelanosis often remain stationary and unchanged for several years, they usually (but not always) clear spontaneously after puberty.

Light and electron microscopy reveal reduced numbers of active melanocytes and a decrease in the number and size of melanosomes in the affected skin.

The differential diagnosis includes tinea versicolor, vitiligo (see above), "eruptive hypomelanosis" associated with viral symptoms[126], and other forms of PIH, in particular pityriasis lichenoides chronica when the lesions are extrafacial.

Topical hydrocortisone may be helpful, but emollients seem to be equally effective.

Sarcoidosis

The true incidence of leukoderma in sarcoidosis is unknown. In one series, hypopigmentation was observed in 6% of sarcoidosis patients. The female-to-male ratio is ~2:1. Lesions are described as circumscribed or poorly marginated papules or plaques that vary from one to a few centimeters in diameter, and they may or may not be indurated. In addition, dermal nodules surrounded by hypomelanosis may be seen[127]. The lesions appear most commonly on the extremities, are asymptomatic, and have no other secondary changes. They appear to carry no specific prognostic significance, and spontaneous repigmentation may occur.

Histologically, non-caseating granulomas are seen in the dermis. By electron microscopy, some melanocytes appear normal, while others have a vacuolated appearance; the number of melanosomes within keratinocytes is decreased. The clinical and histologic features of leprosy differ enough to allow a distinction.

Hypopigmented Mycosis Fungoides

Hypopigmented mycosis fungoides (MF) is a variant of early-stage MF that is most frequently observed in individuals with darkly pigmented skin (Fig. 66.20). The hypomelanotic lesions occur on the trunk or extremities and may be pruritic. Some authors distinguish patients, often children and adolescents, with primarily hypopigmented patches from those, usually adults, with classic erythematous plaques of MF admixed with postinflammatory hypopigmentation. Although the most common age range at the time of diagnosis of MF is 30–40 years, the hypopigmented variant accounts for a higher proportion (~25%–50%) of MF in children and adolescents. Successful treatment (e.g. photo[chemo] therapy or topical mechlorethamine [nitrogen mustard]) usually results in repigmentation. Routine histology shows the typical features of MF and electron microscopy demonstrates decreased numbers of melanosomes within epidermal keratinocytes. Numerous morphologically normal melanosomes are present in melanocytes. These observations suggest a defect in melanosomal transfer, a change seen in most postinflammatory hypomelanoses.

Systemic Sclerosis (Scleroderma) and Lichen Sclerosus

Patients with systemic sclerosis can develop diffuse hypermelanosis[128] with accentuation in sun-exposed sites, a mixture of hypo- and hyperpigmentation in areas of chronic sclerosis (e.g. the hands), and a characteristic leukoderma in both sclerotic and non-sclerotic skin. The latter is characterized by circumscribed areas of complete pigment loss except for perifollicular and supravenous retention of pigment (Fig. 66.21). When this peculiar leukoderma is seen, systemic sclerosis must be excluded, as it is only known to occur in two other settings: overlap syndromes (i.e. those that include systemic sclerosis) and scleromyxedema. The origin and pathogenesis of the pigmentary disturbances in systemic sclerosis are unknown.

Genital and extragenital lesions of lichen sclerosus are often hypomelanotic. Additional changes include epidermal atrophy, follicular plugging and, especially in the anogenital region, purpura. Occasionally, extragenital lichen sclerosus presents as a guttate leukoderma (see Table 66.5; Fig. 66.22). Electron microscopy reveals a loss of pigment cells or decreased number of melanocytes with degenerative changes.





Fig. 66.20 Hypopigmented mycosis fungoides. A Variant with an admixture of classic erythematous lesions and hypopigmented patches with scale on the legs in an adolescent. **B** Purely hypopigmented lesions of variable sizes on the back and buttocks of a child. *A, Courtesy Edward Cowen, MD; B, Courtesy Julie V. Schaffer, MD.*



Fig. 66.21 Leukoderma of systemic sclerosis (scleroderma). Uniform retention of perifollicular pigment within areas of leukoderma. Hyperpigmentation is also seen overlying a superficial vein.



Fig. 66.22 Guttate lichen sclerosus involving the areola.

Lupus Erythematosus

In discoid lupus erythematosus (DLE), hypomelanosis or amelanosis is almost always associated with cutaneous atrophy and scarring (see Fig. 66.19H). Hypomelanosis favors the center of the lesions, and it is often accompanied by a rim of hyperpigmentation. In chronic scarring DLE, the pigmentary changes are persistent. Histologically, in addition to a decreased number of epidermal melanocytes, changes that help to establish the diagnosis include epidermal atrophy, vacuolar degeneration of the basal layer, a variably dense inflammatory infiltrate rich in $CD123^+$ plasmacytoid dendritic cells, pigmentary incontinence, and fibrosis. Hypomelanosis is also frequently seen in the center of annular lesions of subacute cutaneous LE, but this is usually reversible.

INFECTIOUS AND PARASITIC HYPOMELANOSIS

Tinea (Pityriasis) Versicolor

The primary lesion is round to oval, hypomelanotic, and usually measures several millimeters to 1–3 cm in diameter (Fig. 66.23). Within the areas of involvement, the lesions are often coalescent centrally. Associated fine scale may be obvious or only apparent upon scratching or stretching the skin. The distribution is usually symmetric and favors the upper trunk and shoulders; lesions sometimes develop on the lower trunk, body folds, neck, and face (see Ch. 77). Of note, facial tinea versicolor may occur in association with protective mask use[128a]. While the contrast between the hypomelanotic infected skin and the surrounding normal skin is striking in darkly pigmented patients, or following a tan in lightly pigmented patients, Wood's lamp examination may be required to locate all the lesions.

In the hypopigmented skin, there is a decreased density of melanosomes within keratinocytes, but no change in the melanocyte density. Abnormal melanosome production, decreased melanin synthesis, and a partial block in melanosome transfer to keratinocytes have all been suggested as underlying defects. Azelaic acid, a competitive inhibitor of tyrosinase produced by *Malassezia furfur*, may play a role in the decreased melanin synthesis. Although the differential diagnosis may include postinflammatory hypopigmentation (e.g. secondary to parapsoriasis), progressive macular hypomelanosis, and early vitiligo, the diagnosis of tinea versicolor is easily confirmed by examination of the associated scale in a potassium hydroxide preparation.

Hypomelanosis without scaling may remain for months after spontaneous or treatment-induced eradication of the hyphal form of the organism.



Fig. 66.23 Tinea versicolor. A Hypopigmented variant with obvious scale. **B** Guttate hypopigmented lesions on the lateral cheek of a child; note the classic scaly lesions in the posterior auricular area. *B, Courtesy Julie V. Schaffer, MD.*

Hansen Disease (Leprosy)

Hypomelanotic macules may be the earliest expression of *lepromatous leprosy*. The lesions are usually small, multiple, subtle, and ill-defined; they may be difficult to recognize, particularly in lightly pigmented skin. The face, extremities, and buttocks are favored, and the warmer parts of the body are usually spared. There is little or no anhidrosis or loss of sensation. Later, plaques, nodules, or diffuse infiltration of the skin appear (see Ch. 75).

The hypopigmented patches of *tuberculoid leprosy* are much different from those of lepromatous leprosy. Tuberculoid lesions have discrete edges and can be quite large, up to 30 cm in diameter (Fig. 66.24). A raised border, uniform infiltration, or a characteristic pebbled appearance may be observed. The surface can be slightly scaly, dry, or minimally atrophic. The lesions are asymmetrically distributed on the posterolateral aspects of the extremities, back, buttocks, and face. There is associated alopecia, anhidrosis, and loss of tactile and heat sensations.

In *borderline leprosy*, plaques and annular lesions are more common than hypomelanotic macules; the latter, if present, have ill-defined borders. A "Swiss cheese" appearance with erythematous annular lesions and hypomelanotic areas, all bound by vague outer borders, characterizes this form of leprosy. In *indeterminate leprosy*, the macules are usually hypomelanotic, but they can also be erythematous; hypoesthesia may be present. They are asymmetrically distributed and favor exposed sites.

The mechanism of hypopigmentation in leprosy is unknown, and there are no histologic or ultrastructural alterations in the melanocytes. Treatment usually, but not always, results in repigmentation of the hypomelanotic macules.

Treponematoses

In *pinta*, hypomelanotic lesions occur during the late phase of the disease, a few months to several years after the appearance of secondary lesions. Irregular, vitiligo-like areas of depigmentation favor skin overlying bony prominences and are often surrounded by brown to blue–gray hyperpigmentation. Atrophy, xerosis, and alopecia may be evident. Longstanding amelanotic lesions do not typically repigment.



Fig. 66.24 Tuberculoid leprosy. Large, thin hypopigmented plaque on the elbow with a raised light pink border.

Hypomelanosis occasionally develops in untreated tertiary *yaws*. Symmetric hypomelanotic macules enlarge until an entire area is affected. The most common sites are the dorsal aspects of the wrists and hands and over the metacarpophalangeal and interphalangeal joints.

Hypomelanosis may occur in the late stages of *bejel (endemic syphilis)*. Hypomelanotic macules have well-defined borders and may be admixed with pigmented macules. The lesions are usually symmetrically distributed on the extremities, genitalia, areolae, and trunk. Early penicillin treatment results in satisfactory repigmentation.

In *secondary syphilis*, hypomelanosis is an occasional finding that is called "leukoderma syphiliticum". In the "necklace of Venus", small (1–2 mm) hypomelanotic macules are scattered within a larger area of hyperpigmentation on the neck. Hypopigmentation may also develop at sites of previously inflamed lesions, which favor the neck, proximal extremities, upper trunk, abdomen, axillae, and groin. Leukoderma syphiliticum regresses with treatment and usually disappears completely within several months to a year.

Onchocerciasis

Initially, small (punctate), yellowish, hypomelanotic macules appear on the middle third of the shin medial to the tibial crest. Later, the macules enlarge, coalesce, and undergo progressive lightening until there is amelanosis (Fig. 66.25). Pigmented macules persist within the hypopigmented patches, hence the designation "leopard skin" (see Fig. 83.31). Other sites of involvement may include the lateral aspects of the legs, groin, and skin overlying the bony prominences of the pelvis.

Post-Kala-Azar Dermal Leishmaniasis

Small hypomelanotic macules in a symmetric distribution that favors the upper trunk and arms constitute the prenodular stage of the disease. The lesions become elevated over a period of months to years. Total repigmentation following systemic treatment with antimonials is almost impossible to achieve.

Herpes Zoster

Hypo- or depigmentation is sometimes seen in the sites of previous herpes zoster. Amelanosis can result from melanocyte destruction during the inflammatory and healing process, which may also lead to atrophy and fibrosis.

HALO NEVUS AND MELANOMA-ASSOCIATED LEUKODERMA

Halo Nevus

The halo nevus phenomenon most often occurs in children and young adults with multiple melanocytic nevi (see Ch. 112); it is unusual in adults over 40 years of age. A central melanocytic nevus is surrounded by a round or oval amelanotic annulus. The lesions are asymptomatic and the most common site is the trunk, particularly the back. There are four stages in halo nevus evolution, which occurs over a period of months to ≥10 years: (1) appearance of the halo; (2) loss of pigment within the central nevus; (3) disappearance of the nevus; and (4) disappearance of the halo. Patients often develop multiple halo nevi and some have associated vitiligo. The exact relationship between halo nevi and vitiligo has been the subject of controversy.

Both nevus cells and epidermal melanocytes in the surrounding skin are destroyed, as demonstrated by histologic and ultrastructural studies. Both $CD4^+$ and $CD8^+$ T cells infiltrate halo nevi. Peripheral T cells from a patient with halo nevi were shown to lyse *in vitro* melanocytes obtained from a normal nevus, implicating T cells in the pathogenesis of halo nevi. Oligoclonality of the T cell response in patients with halo nevi further suggests that the destruction of melanocytes could represent the lysis of a distinctive cell type through an immune process mediated by a limited number of T cell clones[129].

The clinical diagnosis of halo nevus is usually fairly straightforward, but Wood's lamp examination may occasionally be required to detect the halo. The halo phenomenon can occur with a variety of types of melanocytic nevi (e.g. congenital, blue) and melanoma. Careful examination of the central lesion is therefore required. Typical halo nevi require no treatment other than reassurance. Individuals beyond 40 years of age with new-onset halo nevi should be examined carefully for melanoma (ocular and cutaneous).

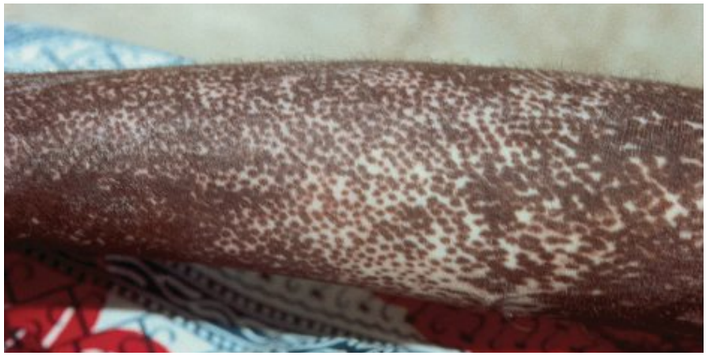


Fig. 66.25 Onchocerciasis (leopard skin). Depigmentation of the shin with follicular repigmentation or retention of perifollicular pigment, a common site for the associated leukoderma.

Melanoma-Associated Leukoderma

Vitiligo-like depigmentation can occur in patients with cutaneous or ocular melanoma. At least three types of leukoderma are associated with melanoma: (1) hypomelanosis within tumors (primary or metastatic) due to regression (see Ch. 113); (2) amelanosis around tumors (halo phenomenon; see above); and (3) vitiligo-like depigmentation remote from the tumors. In the latter, involvement of ocular melanocytes (e.g. uveitis, retinopathy, VKH-like changes) has also been reported.

Increasing evidence suggests that melanoma-associated, vitiligo-like leukoderma results from an immune reaction directed against antigenic determinants shared by normal and malignant melanocytes. Although antibodies to pigment cells are commonly found in patients with melanoma, growing evidence points towards an important role for cellular immune responses (Fig. 66.26). Vitiligo-like lesions have been observed in melanoma patients following successful immunotherapy with immune checkpoint inhibitors targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4; e.g. ipilimumab; Fig. 66.27), programmed cell death-1 (PD-1; e.g. pembrolizumab, nivolumab), and PD-ligand 1 (PD-L1; e.g. atezolizumab); IL-2; tumor-infiltrating lymphocytes specific for tyrosinase-, gp100- or TYRP1-derived antigens; and peptide vaccines based upon these antigens. Vitiligo-like depigmentation induced by immune checkpoint inhibitors favors chronically sun-exposed areas; although most common in melanoma patients, it occasionally occurs with treatment of other malignancies. Lastly, cytotoxic T lymphocyte clones derived from melanoma patients efficiently lyse cultured human melanocytes.

Clonally expanded T cells with identical Vp regions have been identified in a primary melanoma and a depigmented halo surrounding the tumor, again suggesting a role for a T cell-mediated antitumoral response in the development of melanoma-associated, vitiligo-like leukoderma. Melan-A/MART-1-specific $CD8^+$ T cells have been identified in inflammatory hypomelanotic skin lesions following the infusion of Melan-A/MART-1-specific $CD8^+$ T cell clones in a patient with metastatic melanoma[130]. Thus, in melanoma patients, "vitiligo" may be a visible effect of a spontaneous or therapy-induced antitumoral immune response against melanocyte differentiation antigens (see Ch. 113). In addition to occasionally preceding spontaneous resolution of metastatic melanoma, the development of vitiligo-like leukoderma is associated with a survival benefit in patients receiving immunotherapy for metastatic melanoma[131].

CHEMICAL AND PHARMACOLOGIC HYPOMELANOSIS

A large number of chemical and pharmacologic agents can cause hypomelanosis of skin and hair[132,133]. The three major groups of depigmenting compounds (Table 66.7) are:

- phenols/catechols
- sulfhydryls
- miscellaneous.

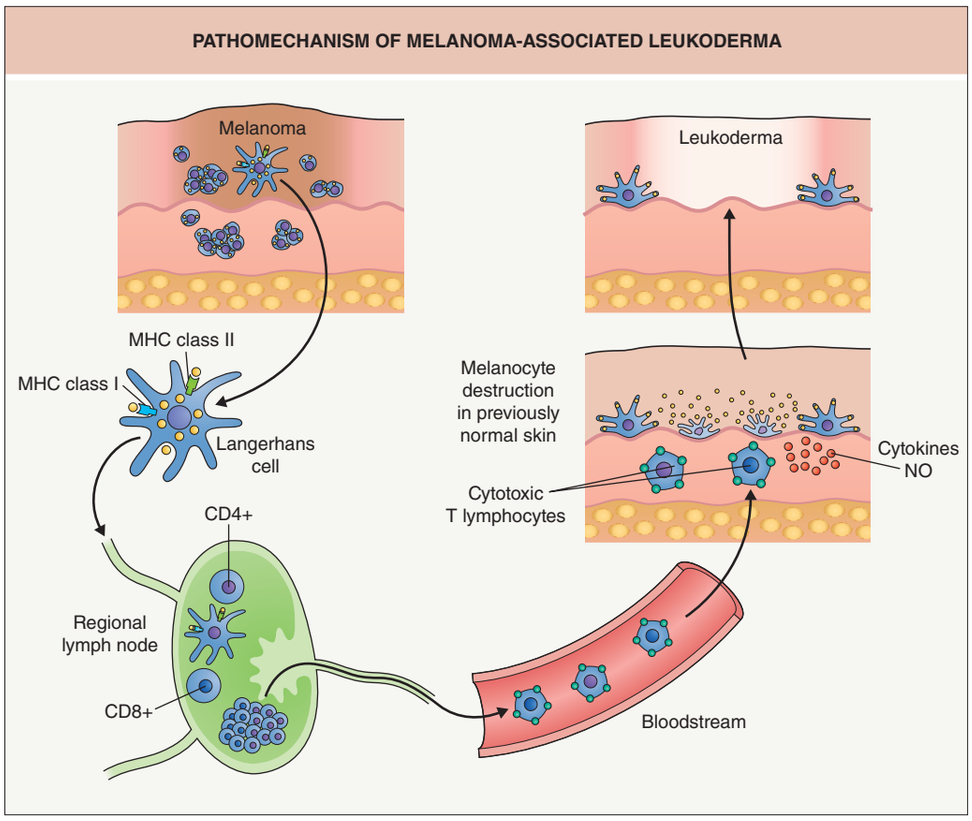


Fig. 66.26 Pathomechanism of melanoma-associated leukoderma. NO, nitric oxide. *From Schaffer JV, Bolognia JL. The biology of the melanocyte. In: Rigel DS, et al (eds). Cancer of the Skin, 2nd edn. Philadelphia: Elsevier Saunders, 2011.*



Fig. 66.27 Vitiligo-like leukoderma associated with anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) therapy for metastatic melanoma. *Courtesy Jean L. Bolognia, MD.*

Hydroquinone (HQ) and its derivatives (MMEH, MBEH) are the most widely used "bleaching" agents. HQ induces a reversible hypopigmentation of the skin, and it is used to treat disorders such as melasma. In contrast, depigmentation from MBEH is often permanent and occurs not only in the areas of application but also in distant sites; as a result, its only indication is as depigmentation therapy for widespread, treatment-resistant vitiligo (see above). Of note, MMEH and MBEH were identified as depigmenting agents after outbreaks of occupational leukoderma in workers exposed to these chemicals in rubber products.

Hypomelanosis can follow the use of either topical or intralesional corticosteroids, particularly in darkly pigmented individuals. Potent topical corticosteroids are unfortunately widely used as lightening agents in many areas of the world, especially Africa and Asia. In most cases, the hypomelanosis is incomplete, but the risk of significant side effects (e.g. acne, atrophy, striae) is high. Hypomelanosis induced by intralesional or intra-articular corticosteroids can be stellate or linear, has an irregular outline, and is often ill-defined (Fig. 66.28). The cutaneous hypopigmentation appears several weeks to months after the injection. In most instances, repigmentation occurs within 1 year after discontinuation of the injections.

In any patient, particularly adults, presenting with new-onset "vitiligo" (Fig. 66.29), a detailed history to detect exposure to known depigmenting agents or use of topical or oral medications (e.g. imiquimod, imatinib) implicated in depigmentation is mandatory (see Table 66.7). Patch testing can be useful for confirming the diagnosis of chemical leukodermas, but delayed readings are essential (e.g. at 2 weeks, then again at 4–6 weeks). Spontaneous repigmentation may occur following avoidance of the causative agent, but treatment, as for vitiligo, is usually required (see above).

In chemical leukoderma induced by HQ and its derivatives, melanocytes are decreased in number or absent. Other depigmenting agents inhibit tyrosinase (thus blocking melanogenesis) or prevent melanosome transfer.

Patients treated with imatinib mesylate have been noted to develop various forms of hypomelanosis, including generalized lightening of the skin, hypopigmentation of the distal digits, difficulty in maintaining a suntan, and progression of vitiligo. These changes appear to be reversible and potentially dose-dependent, and they have been observed more commonly in darkly pigmented individuals[134]. Imatinib mesylate is a tyrosine kinase inhibitor that targets the bcr-abl fusion protein that is characteristic of chronic myelogenous leukemia; it also inhibits three other tyrosine kinases – platelet-derived growth factor (PDGF) receptor-α, PDGF receptor-β, and the KIT receptor. Imatinib mesylate-induced inhibition of the KIT receptor, which is involved in melanogenesis and melanocyte homeostasis, is the most likely explanation for the hypopigmentation. Loss of hair color has been noted in patients receiving sunitinib malate, another inhibitor of tyrosine kinase receptors (including the KIT receptor). Sunitinib-induced hair depigmentation appears to be reversible with cessation of treatment[135].

SELECTED CHEMICALS ASSOCIATED WITH LEUKODERMA
Phenol/catechol derivatives
Monobenzyl ether of hydroquinone (MBEH)
Monomethyl ether of hydroquinone (MMEH) (*p*-methoxyphenol; *p*-hydroxyanisole)
Monoethyl ether of hydroquinone (MEEH) (*p*-ethoxyphenol)
Hydroquinone (HQ) (1,4-dihydroxybenzene; 1,4-benzenediol; quinol; *p*-hydroxyphenol)
Rhododendrol
p-tert-butylcatechol (PTBC)
p-tert-butylphenol (PTBP)
p-tert-amylphenol (PTAP)
p-phenylphenol
p-octylphenol
p-nonylphenol
p-isopropylcatechol
p-methylcatechol
Butylated hydroxytoluene (BHT)*
Butylated hydroxyanisole (BHA)*
Pyrocatechol (1,2-benzenediol)
p-cresol
Sulfhydryls
β-mercaptoethylamine hydrochloride (MEA) (cysteamine)
N-(2-mercaptoethyl)-dimethylamine hydrochloride (MEDA)
Methimazole (1-methyl-2-mercaptoimidazole – MMI)
Sulfanilic acid
Cysteamine dihydrochloride
3-mercaptopropylamine hydrochloride
Miscellaneous
Mercurials
Arsenic
Cinnamic aldehyde
p-phenylenediamine (PPD)
Benzyl alcohol
Azelaic acid
Corticosteroids
Imiquimod
Methylphenidate patches
Optic preparations • Physostigmine (eserine) • Diisopropyl fluorophosphates • Thiotepa (N,N′,N″-triethylenethiophosphoramide) • Guanonitrofuracin
Systemic medications • Chloroquine • Fluphenazine (Prolixin®) • Tyrosine kinase inhibitors (e.g. imatinib mesylate, pazopanib, cabozantinib)
*Depigmentation weak or not known.

Table 66.7 Selected chemicals associated with leukoderma.

HYPOMELANOSIS FROM PHYSICAL AGENTS

Various types of physical injuries can induce cutaneous hypomelanosis or amelanosis, including thermal burns, freezing, UV radiation, lasers, ionizing radiation, and physical trauma from surgical procedures. The combination of the history of an insult, the shape of the hypopigmentation, and associated findings usually makes the diagnosis relatively straightforward.

Repigmentation is based on a host of factors, including the type and depth of the insult or injury, the anatomic location, and the presence of hair follicles and pigmented hairs.



Fig. 66.28 Hypopigmentation due to injection of corticosteroids into the anatomic snuff box. The outline is both stellate and linear.



Fig. 66.29 Chemical leukoderma. Depigmentation developed at sites of contact with rubber swimming goggles. *Courtesy Kalman Watsky, MD.*

MISCELLANEOUS

Idiopathic Guttate Hypomelanosis

Idiopathic guttate hypomelanosis (IGH) is a very common disorder, the incidence of which increases with age. It is seen in up to 80% of patients over the age of 70 years. IGH occurs in all races and skin types, but it is more striking in darkly pigmented skin. In White individuals, IGH may favor those with brown eyes and brown hair. An apparent female predominance is probably the result of heightened perception of a cosmetic problem.

The typical IGH lesion is a circumscribed, sharply defined, asymptomatic porcelain white macule[136]. The lesions are usually 0.5–6 mm in diameter and often delineated by the skin furrows; occasionally, lesions are up to 2.5 cm in size (Fig. 66.30). Once present, they do not change in size or coalesce; their surface is smooth but not atrophic. Spontaneous repigmentation has not been reported. Hairs within the lesions usually retain their pigment. In most patients, there are multiple lesions on the extensor forearms and shins; the remainder of the extremities can be affected, but rarely the face.

The most consistent histologic features of IGH are a flattening of the dermal–epidermal junction, moderate to marked reduction or focal absence of melanin granules in the basal and suprabasal layers, and a basket-weave hyperkeratosis. There is a moderate to relatively marked reduction in the number of DOPA-positive epidermal melanocytes (10%–50% compared with normal skin), but these cells are never totally

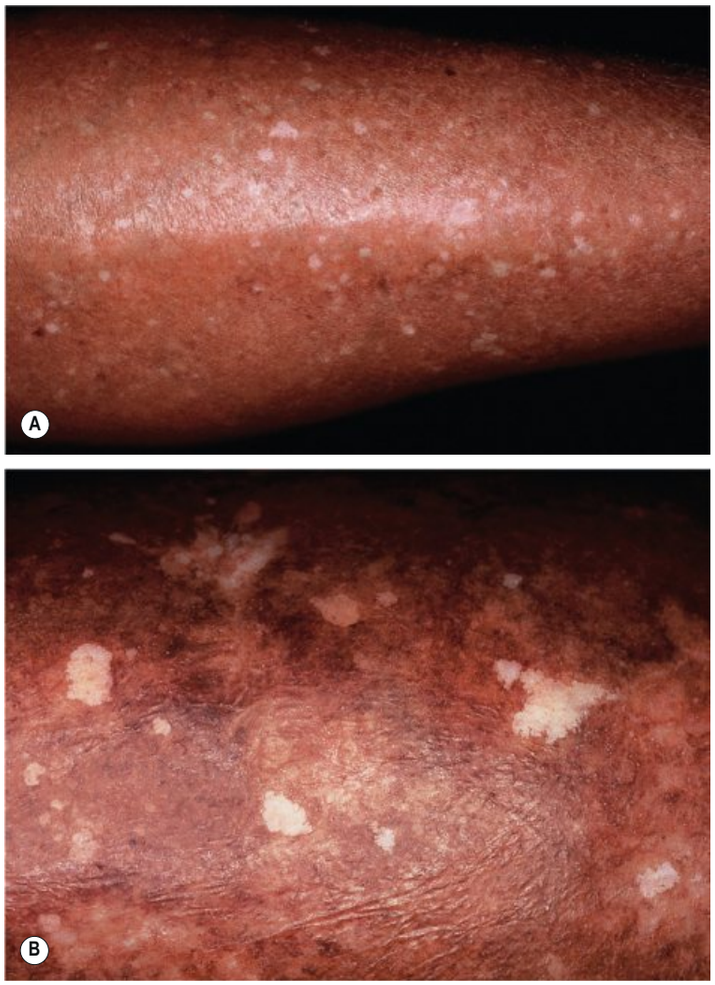


Fig. 66.30 Idiopathic guttate hypomelanosis. A Typical 1–5 mm macules on the shin. **B** Occasionally there is admixture of larger lesions.

absent. At the ultrastructural level, some melanocytes have normal melanogenic activity, while others lack mature melanosomes. The keratinocytes show marked variation in their content of melanin, which may be absent or markedly decreased.

The diagnosis of IGH is usually made clinically; the differential diagnosis of guttate leukoderma includes achromic verrucae planae, pityriasis lichenoides chronica, disseminated hypopigmented keratoses that follow PUVA therapy, and clear cell papulosis (Fig. 66.31; see Table 66.5). Although lesions of atrophie blanche favor the distal shins and ankles, these porcelain white scars are usually depressed and encircled by papular telangiectasias. The cause of IGH is unknown, but sun exposure probably plays a role.

Cryotherapy with liquid nitrogen has been described as a possible therapy for IGH. As sunlight is most likely a precipitating factor, use of sunscreens and physical barriers should be recommended.



Fig. 66.31 Guttate leukoderma. A Disseminated hypopigmented keratoses presenting as >200 guttate, minimally elevated hypopigmented papules. The lesions developed after several months of PUVA therapy. Histologically, there was no evidence of verruca plana. **B** Clear cell papulosis presenting as multiple hypopigmented, barely elevated, small flat-topped papules and macules in the suprapubic area and on the abdomen along the "milk lines" in a 2-year-old boy. Histologically, these lesions are characterized by large clear cells in the lower epidermis that have a pattern of immunohistochemical staining similar to clear cells of Toker and extramammary Paget disease. **C** Guttate hypopigmentation in sun-exposed areas on the extensor aspect of the arm in a 3-year-old Hispanic boy with xeroderma pigmentosum. Note the sparing of the proximal upper arm, which is normally covered by a T-shirt. *A, Courtesy Jean L. Bolognia, MD; B, C, Courtesy Julie V. Schaffer, MD.*

Vagabond's Leukomelanoderma

This skin disorder occurs in older persons in whom dietary deficiency is combined with lack of cleanliness and heavy infestation with *Pediculus humanus* var. *corporis*. These patients have small macules of hypomelanosis (related to scratching) superimposed on a background of diffuse hypermelanosis, especially of the wrists, axillae, groin, medial thighs, and posterior neck.

Progressive Macular Hypomelanosis

Progressive macular hypomelanosis (PMH) is a fairly common skin disorder, observed more frequently in young women with darkly pigmented skin who originate from or reside in tropical climates. The condition is characterized by poorly defined, nummular, non-scaly hypopigmented macules and small patches on the trunk, with rare extension onto the proximal extremities or head and neck region; confluence of lesions may occur centrally (Fig. 66.32)[137]. Another variant of PMH features large circular lesions. There is no associated pruritus or preceding inflammation, and patients are sometimes misdiagnosed as having residual hypopigmentation related to tinea versicolor. Histologically, there is decreased pigment in the epidermis and a normal-appearing dermis. Electron microscopy demonstrates a shift from large melanosomes in uninvolved skin to small aggregated membrane-bound melanosomes in hypopigmented skin. Proliferation of *Cutibacterium* (previously *Propionibacterium*) *acnes*, in particular the *elongatum* subspecies (phylotype III), is thought to play a role in PMH pathogenesis[138]. The fact that this strain is rarely present on the face may explain why PMH is not typically found in this location. Treatment regimens include various combinations of topical 1% clindamycin, 5%

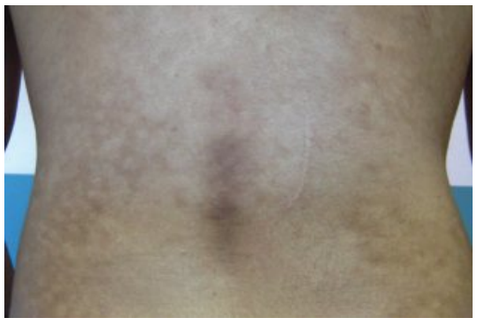


Fig. 66.32 Progressive macular hypomelanosis. Note the coalescence of the non-scaly hypopigmented macules on the center of the back.

DISORDERS ASSOCIATED WITH PREMATURE GRAYING OF SCALP HAIR
• Piebaldism
• Waardenburg syndrome
• Vitiligo
• Sudden whitening of hair
• Hereditary premature canities
• "Bird-headed" dwarfism
• Progeria
• Werner syndrome
• Ataxia telangiectasia
• Rothmund–Thomson syndrome
• Dyskeratosis congenita
• Fisch syndrome
• Myotonic dystrophy
• Prolidase deficiency (also in Table 66.9)
• Oasthouse disease

Table 66.8 Disorders associated with premature graying of scalp hair.

benzoyl peroxide, and phototherapy with NB-UVB or UVA (e.g. three times weekly for 12 weeks).

Hair Hypomelanosis

Poliosis refers to a circumscribed hypomelanosis of hair (see Table 66.3), whereas canities implies a more generalized depigmentation of hair. Graying of hair, localized or generalized, is characterized by an admixture of normally pigmented, hypomelanotic, and amelanotic hairs. Whitening of hair is the endpoint of canities and graying of hair. The graying and whitening of human hair that occurs with aging was thought to be due to defective maintenance of melanocyte stem cells[139,140], with more recent work suggesting a reduction in the migration of melanocyte stem cells from the bulge region.

A number of genetic disorders are associated with premature graying of hair (Table 66.8), while there are both hereditary and acquired causes of diffuse hypomelanosis of hair (Table 66.9). In Chédiak–Higashi and Griscelli syndromes, the scalp hairs have a silvery hue due to pigment clumping (see Fig. 60.5).

Leukodermas Without Hypomelanosis

Woronoff's ring

Woronoff's ring is a blanched halo of fairly uniform width surrounding psoriatic lesions after phototherapy or topical treatments. There is an element of vasoconstriction, but it is uncertain whether there is any decrease in pigmentation.

DISORDERS ASSOCIATED WITH DIFFUSE HYPOMELANOSIS OF SCALP HAIR
• Fanconi syndrome
• Book syndrome
• Down syndrome
• Hallermann–Streiff syndrome
• Treacher Collins syndrome
• Prolidase deficiency (also in Table 66.8)
• Hyperthyroidism
• Chronic protein loss or deficiency (e.g. due to kwashiorkor, nephrosis, ulcerative colitis, malabsorption)
• Vitamin B_{12} deficiency
• Tyrosine kinase inhibitors (e.g. sunitinib, imatinib, dasatinib, cabozantinib)
• Antimalarials (chloroquine > hydroxychloroquine)

Table 66.9 Disorders associated with diffuse hypomelanosis of scalp hair. See also Fig. 66.12.

Nevus anemicus

Nevus anemicus presents as a pale area of variable size (often 3–6 cm) with an irregular, "broken up" outline (see Ch. 106). It is usually unilateral and located on the trunk. Present since birth, the lesion is most commonly detected later in life, and it is most noticeable when there is surrounding vasodilation due to heat or emotional stress. On diascopy, the lesion becomes indistinguishable from surrounding skin. Histologically, there are no abnormalities in the melanocytes or melanin content. Nevus anemicus is caused by decreased blood flow through the capillaries in the dermal papillae, due to a localized hypersensitivity of the blood vessels to catecholamines. Although ~30%–60% of patients with neurofibromatosis type 1 (NF1) have a nevus anemicus, this skin finding is not included in the 2021 revised NF1 diagnostic criteria (see Ch. 61).

Cutaneous edema and anemia

Cutaneous edema and anemia also produce lightening of the skin and mucous membranes. In the case of anemia, it is due to decreased hemoglobin levels in the skin.

Angiospastic macules (Bier spots)

Pale macules, usually 3–6 mm in diameter, are seen primarily on the extremities and are often more noticeable on the legs (see Ch. 106). The lesions are due to localized vasoconstriction and occur most often in young women. Their appearance may be induced by a dependent position or placing a tourniquet on the limb. Prominent or widespread angiospastic macules have been described in association with pregnancy, lymphedema, cryoglobulinemia, capillary malformation–arteriovenous malformation syndrome (especially type 2 due to *EPHB4* mutations), tuberous sclerosis complex, and aortic hypoplasia. *BASCULE* syndrome features *B*ier *a*nemic *s*pots, *c*yanosis, and an *u*rticaria-*l*ike *e*ruption in association with orthostatic intolerance[141].

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 66.1 Vitiligo. Complete loss of pigment of the glans penis. Note the lack of any secondary changes. *Courtesy Jean L. Bolognia, MD.*



eFig. 66.2 Inflammatory vitiligo. There is a figurate outline to the inflammatory border, which is sometimes misdiagnosed as tinea corporis.





eFig. 66.3 Treatment of segmental vitiligo via epidermal transplants. A Before surgery. **B** After surgery. *Courtesy National Skin Centre, Singapore.*



eFig. 66.4 Piebaldism. A White forelock and characteristic triangular amelanotic patch on the mid-forehead. **B** Mother and son with the characteristic involvement of the mid extremities. **C** Amelanotic patch on the upper calf. In all of these examples, note the normally pigmented macules of varying sizes within the leukoderma, especially at the periphery. *A, Courtesy Diane Davidson, MD; B, Courtesy Jean L. Bolognia, MD; C, Courtesy Julie V. Schaffer, MD.*



eFig. 66.5 Piebaldism. Note the normally pigmented and hyperpigmented macules within the area of leukoderma on the upper calf. These macules favor the edge of the amelanotic patch. *Courtesy Jean L. Bolognia, MD.*



eFig. 66.6 Type I oculocutaneous albinism in a newborn. Patients with types IA and 1B can have a similar appearance at birth.



eFig. 66.7 Type II oculocutaneous albinism in a patient from sub-Saharan Africa. Note the severe photodamage in the form of solar elastosis. *Courtesy Rosemarie Moser, MD.*



eFig. 66.8 Hypomelanotic macules of tuberous sclerosis complex. Both the confetti and polygonal types are present. *Courtesy Jean L. Bolognia, MD.*



eFig. 66.9 Linear nevoid hypopigmentation. Note the S-shaped pattern of the hypopigmented streaks along the lines of Blaschko on the flank and abdomen.



eFig. 66.10 Lichen striatus. Hypopigmented band along the lines of Blaschko on the trunk.



eFig. 66.11 Postinflammatory hypopigmentation in a child with atopic dermatitis. *Courtesy Antonio Torrelo, MD.*



eFig. 66.12 Hypopigmented variant of cutaneous sarcoidosis . This variant is more noticeable in individuals with darkly pigmented skin. *Courtesy Louis A. Fragola, Jr, MD.*



eFig. 66.13 Hypopigmented mycosis fungoides. This condition is most often observed in individuals with darkly pigmented skin.



eFig. 66.14 Lichen sclerosus of the distal penile shaft and periurethral skin initially diagnosed as vitiligo. *Courtesy Kalman Watsky, MD.*



eFig. 66.15 Guttate lichen sclerosus. Wrinkling can be seen in some of the hypopigmented lesions. *Courtesy Louis A. Fragola, Jr, MD.*



eFig. 66.16 Perianal dermatitis and vitiligo-like leukoderma due to ipilimumab.



eFig. 66.17 Vitiligo-like leukoderma in the setting of combination anti-CTLA-4/anti-PD-1 antibody therapy for metastatic melanoma. Depigmented macules and patches on the trunk in a patient with complete response to immune checkpoint inhibitor therapy. *Courtesy Jonathan S. Leventhal, MD.*



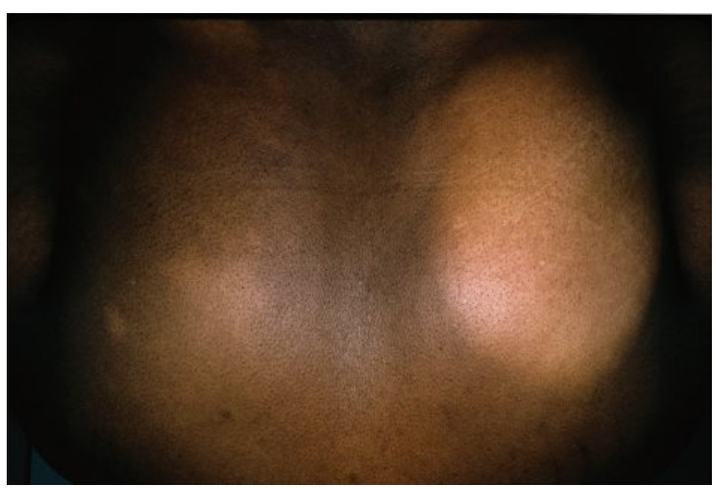
eFig. 66.18 Hypopigmentation due to injection of corticosteroids into the anatomic snuff box. The outline is both stellate and linear.



eFig. 66.19 Hypopigmentation due to injection of corticosteroid into the knee joint. *Courtesy Kalman Watsky, MD*



eFig. 66.20 Thin serpentine hypopigmentation and atrophy due to distal injection of corticosteroid. The configuration is due to either lymphatic or vascular spread. *Courtesy Jeffrey P. Callen, MD.*



eFig. 66.21 Progressive macular hypomelanosis – variant with large circular lesions. *Courtesy Jean L. Bolognia, MD.*

Disorders of Hyperpigmentation 67

Gillian K. Weston and Mary Wu Chang

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Skin color depends upon the amount and distribution of melanin and other pigments such as hemoglobin, which can influence light absorption, reflection, and scattering. Disorders of hyperpigmentation usually result from an increase in melanin production and, on occasion, from an increase in the density of active melanocytes. Discoloration of the skin may also be caused by deposition of exogenous substances such as drugs, drug complexes (e.g. with melanin or iron), or heavy metals within the dermis.

To aid in the clinical approach, disorders of hyperpigmentation can be divided into diffuse, circumscribed, linear, and reticulated subsets (Fig. 67.1). A discussion of each of these categories is followed by an overview of dyschromatoses, disorders characterized by both hypo- and hyperpigmentation. Keratinocytic disorders that present with hyperpigmentation are listed in Table 67.1, and benign melanocytic neoplasms are covered in Chapter 112.

DIFFUSE AND CIRCUMSCRIBED HYPERPIGMENTATION

Introduction

Diffuse and circumscribed hyperpigmentation are discussed together because both postinflammatory hyperpigmentation (PIH) and reactions to systemic drugs, two major causes of hyperpigmentation, can assume either of these patterns. Melasma is another common cause of circumscribed hyperpigmentation, whereas diffuse hyperpigmentation can also be a manifestation of metabolic diseases, sclerodermoid disorders, nutritional deficiencies, and occasionally HIV infection.

POSTINFLAMMATORY HYPERPIGMENTATION

Synonym: ■ Postinflammatory hypermelanosis

Key features

- Extremely common, especially in individuals with more darkly pigmented skin
- Develops after inflammation or injury to the skin, but preceding inflammation may be transient or subclinical
- The increased melanin can be primarily within the dermis (e.g. following lichen planus) or in the epidermis (e.g. following acne or atopic dermatitis)
- Epidermal hyperpigmentation fades more readily than dermal hyperpigmentation

Introduction

PIH represents an acquired excess of melanin pigment following cutaneous inflammation or injury. It can occur anywhere on the skin surface, including the mucous membranes and the nail unit. PIH is extremely common and can have significant cosmetic and psychosocial consequences.

Epidemiology

PIH can occur at any age and there is no sex preference. Individuals with darkly pigmented skin tend to have a greater frequency, severity, and duration of PIH than those with lighter complexions.

Pathogenesis

In the *epidermal* form of PIH, there is increased melanin production and/or transfer to keratinocytes. Inflammatory mediators (e.g. prostaglandins E_2 and D_2, IL-33) that enhance pigment production may play a role in this process. In *dermal* hyperpigmentation, melanin enters ("falls into") the dermis via a damaged basement membrane, where it is phagocytosed by and subsequently resides within dermal macrophages (referred to as melanophages). Macrophages may also migrate into the epidermis, phagocytose melanosomes, and then return to the dermis. Melanin within dermal melanophages tends to persist for long periods of time (e.g. years).

Clinical Features

Asymptomatic hyperpigmented macules and patches range in color either from tan to dark brown (epidermal melanin) or from gray–blue to gray–brown (dermal melanin). Primary lesions of the underlying inflammatory disorder may be admixed with the hyperpigmentation or present elsewhere. When primary lesions are absent, the size, shape, and distribution pattern of the hyperpigmented lesions may provide clues to the underlying etiology (Table 67.2). PIH can be exacerbated by continued inflammation, trauma, exposure to ultraviolet (UV) irradiation, or treatment-related irritation.

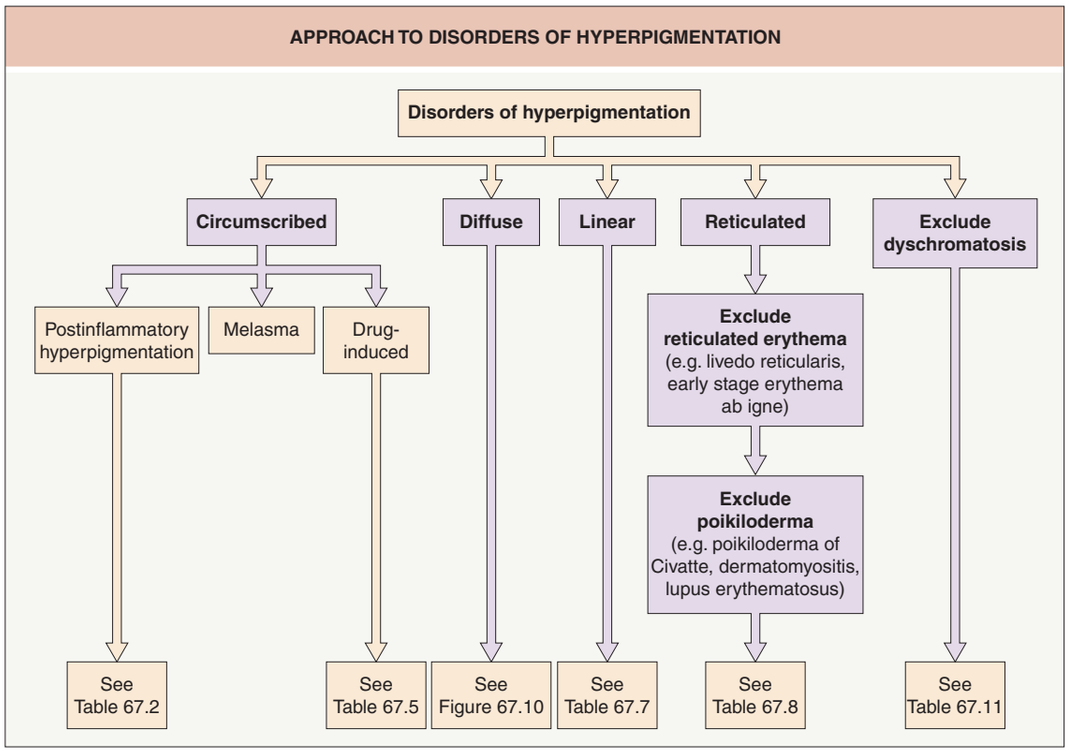


Fig. 67.1 Approach to disorders of hyperpigmentation. Hyperpigmentation can also result from keratinocytic (epidermal) disorders (see Table 67.1).

HYPERPIGMENTATION RELATED TO KERATINOCYTIC (EPIDERMAL) DISORDERS	
Disorder	**Key clinical features**
Acanthosis nigricans	Velvety and corrugated hyperpigmentation of flexural sites (e.g. neck, axillae) > extensor surfaces; often associated with insulin resistance (see Fig. 53.14)
Confluent and reticulated papillomatosis	Hyperpigmented papules and thin plaques with a corrugated and papillomatous surface; form a reticulated pattern primarily on the central trunk, neck, and axillae; onset typically around puberty (see Figs. 67.20 and 109.22)
Terra firmaforme dermatosis	Retention hyperkeratosis presenting as hyperpigmented plaques that favor concave surfaces of the face, neck, chest, and ankles; removed by wiping with 70% isopropyl alcohol pads
Nevoid hyperkeratosis of the nipple and areola	Hyperpigmentation and thickening of the areola(s), more commonly bilateral; typically begins after puberty in women or men receiving hormonal therapy (see Fig. 109.21)
Epidermal nevus	Linear hyperpigmented streaks following the lines of Blaschko (rarely hypopigmented); a variably papillomatous or verrucous texture; congenital or apparent by early childhood (see Chs. 62 and Fig. 109.18)

Table 67.1 Hyperpigmentation related to keratinocytic (epidermal) disorders. Therapeutic options are discussed in cited chapters.

Disorders that commonly lead to epidermal PIH include acne, insect bites, pyodermas, atopic dermatitis, psoriasis, and pityriasis rosea (Fig. 67.2A–C,E). In contrast, dermal PIH is associated with dermatoses characterized by degeneration of the basal layer of the epidermis and inflammation at the dermal–epidermal junction, such as lichen planus, lichenoid drug reactions, lupus erythematosus, and fixed drug eruptions (Fig. 67.2D). Upon treatment of the underlying disorder, epidermal PIH generally resolves over time, although fading may require months or years in darkly pigmented individuals. Dermal melanosis tends to persist longer and is sometimes permanent.

Pathology

Epidermal PIH is characterized by increased pigment in keratinocytes and dermal PIH by melanophages within the superficial dermis.

Differential Diagnosis

The size, shape, and distribution of the hyperpigmented lesions can provide clues to the inflammatory disease or injury that preceded PIH (see Table 67.2), and a thorough skin examination may detect active primary lesions. A history of prior inflammatory lesions and medication use (including prescription, over-the-counter, and alternative products) should be obtained. Disorders such as erythema dyschromicum perstans, melasma, tinea (pityriasis) versicolor, and atrophoderma of Pasini and Pierini should be considered in patients without evidence of preceding inflammation by history or on examination. Occasionally, a biopsy may assist in establishing the diagnosis.

Treatment

Provided that the underlying dermatosis is successfully treated, PIH eventually improves in most patients, especially those with epidermal hypermelanosis. Sun protection, including daily application of a broad-spectrum sunscreen, can help to prevent accentuation of the pigmentation by UV exposure. Topical hydroquinone (2%–4%) may lead to lightening over 3–6 months if the increase in pigmentation is limited to the epidermis. As with melasma (see below), use of a topical retinoid and corticosteroid together with hydroquinone may be more effective than monotherapy. Topical azelaic, α-hydroxy, L-ascorbic, tranexamic, and kojic acids as well as cysteamine, arbutin, licorice extracts, mequinol, niacinamide, *N*-acetyl glucosamine, and soy are additional potential therapeutic options[1]. However, it is important to avoid irritant contact dermatitis from topical agents, as this may exacerbate the hyperpigmentation. Chemical peels (e.g. with salicylic or glycolic acid) and laser therapy may be of benefit but can also result in hyper- or hypopigmentation, especially in patients with darkly pigmented skin. Laser therapy (e.g. 1927-nm non-ablative fractional thulium fiber laser, Q-switched Nd:YAG, ruby, and alexandrite lasers) are variably successful in removing dermal pigment (see Ch. 137).

ERYTHEMA DYSCHROMICUM PERSTANS

Synonyms: ■ Ashy dermatosis ■ Dermatosis cenicienta

DISORDERS ASSOCIATED WITH POSTINFLAMMATORY HYPERPIGMENTATION	
Inflammatory disease	**Clinical clues**
Common	
Acne vulgaris	Head/neck region, upper trunk; <1 cm; perifollicular
Atopic dermatitis	Atopic diathesis; face and extensor extremities in infants, then later flexural involvement; excoriations; atopic pleats; xerosis; lichenification; transverse nasal crease ("allergic salute")
Impetigo	Favors face; most common in children
Insect bites	Favor exposed areas; usually <1 cm; lower extremities common with flea bites; clustered and sometimes linear patterns ("breakfast–lunch–dinner"; see Fig. 67.2B)
Lichen simplex chronicus	Common locations: posterior neck, ankle, scrotum
Transient neonatal pustular melanosis	Black neonates; pustules precede pigmentation (see Fig. 67.2C)
Less common	
Irritant and allergic contact and photocontact dermatitis	Sites determined by etiologic agent and form of exposure; phytophotodermatitis associated with linear hyperpigmentation in sun-exposed areas
Pityriasis rosea	Favors trunk and proximal extremities; lesions follow skin cleavage lines; oval-shaped
Psoriasis	Scalp/nail involvement; knees/elbows most common sites (see Fig. 67.2E)
Seborrheic dermatitis	Favors face (especially forehead, upper eyelids, nasolabial folds, mental fold), skin folds, and presternal area; scalp/ear involvement; may also have hypopigmentation
Polymorphous light eruption	Extensor upper extremities, mid upper chest, face; seasonal (e.g. spring or early summer)
Discoid lupus erythematosus	Face and conchal bowls, with follicular plugging in latter site; oral lesions; in scarred lesions, central hypopigmentation with rim of hyperpigmentation
Lichen planus	Wrists, shins, presacral; nail/oral involvement
Erythema dyschromicum perstans (EDP; ashy dermatosis)*	Neck, proximal upper extremities, trunk; round or oval in shape with gray–brown to blue–gray color; long axis can follow skin cleavage lines (similar to pityriasis rosea); less commonly observed in fair-skinned individuals
Idiopathic eruptive macular pigmentation*	Trunk, proximal extremities, neck, face; round or oval, discrete brown macules and small patches; sometimes barely elevated plaques with a subtle velvety texture; histologically, basal epidermal hyperpigmentation ± papillomatosis, with no vacuolar alteration and relatively few dermal melanophages compared to EDP; affects primarily children and adolescents, lasting months to years
Hyperpigmented macules on the forehead in infants*	Irregular brown macules on the forehead and temples; onset at age 2–24 months, with variable fading over several years; histologically, mild lymphocytic dermal infiltrate with melanophages
Fixed drug eruption	Circular; favors perioral, acral and genital sites; recurrence at same site(s) with repeated exposure (see Fig. 67.2D)
Morbilliform drug eruption	Widespread; usually discrete lesions, history of drug exposure
Viral exanthem	Widespread, usually with discrete lesions; history of associated symptoms; chikungunya fever: diffuse or reticulated hyperpigmentation, especially in infants, that characteristically includes the tip of the nose ("chik sign")
Morphea	Trunk or extremities; large-sized except in guttate variant; may be linear; associated induration and later dermal atrophy
Atrophoderma of Pasini and Pierini	Trunk; large-sized; depressed with "cliff sign" at periphery; no induration
Neurotic (psychogenic) excoriation, acne excoriée	Favors face, scalp, extensor surface of arms, upper back (reachable areas); linear or angular shapes; multiple stages of evolution, from erosions/ulcerations to scars
Flagellate erythema	Associated with bleomycin use, shiitake mushroom ingestion, dermatomyositis, and Still disease
*Typically no preceding inflammatory phase evident clinically or histologically.	

Table 67.2 Disorders associated with postinflammatory hyperpigmentation. Cutaneous injury (e.g. thermal burn, radiation therapy) may also result in localized postinflammatory hyperpigmentation. *Adapted from Bolognia JL. Disorders of hypopigmentation and hyperpigmentation. In: Harper J, Oranje A, Prose N (eds). Textbook of Pediatric Dermatology, 2nd edn. Oxford: Blackwell Science, 2006:997–1040.*

Key features

- Most common in individuals with skin phototypes III–IV
- Gray–brown to blue–gray macules and patches in a symmetric distribution
- Favors the neck, trunk, and proximal extremities
- A consistently effective treatment is not currently available

Introduction

Ramirez first described erythema dyschromicum perstans (EDP) in 1957, referring to affected individuals as *los cenicientos* (ashen ones). This is an asymptomatic, slowly progressive eruption that is characterized by circumscribed areas of dermal pigmentation[2].

Epidemiology

Although EDP occurs worldwide, it is most common in Latin America. There is no sex preference. The disorder usually presents during the second to third decade, but it occasionally develops in younger children or older adults.

Pathogenesis

The etiology of EDP is not known. Although it has been postulated that a cell-mediated immune reaction to an ingestant, contactant, or microorganism underlies the discrete areas of pigmentary incontinence, no causal agent has consistently been identified[2]. In most patients, a trigger is never found. However, there have been reports of EDP developing in association with the ingestion of ammonium nitrate, oral X-ray contrast media, and medications (e.g. benzodiazepines, penicillin, proton pump inhibitors, epidermal growth



Fig. 67.2 Postinflammatory hyperpigmentation (PIH). The lesions were caused by pemphigus foliaceus (**A**), insect bite reactions (**B**), transient neonatal pustular melanosis (**C**), a fixed drug eruption induced by trimethoprim-sulfamethoxazole (**D**), and psoriasis (**E**). Note the residual inflammation and "breakfast–lunch–dinner" configuration in **B**.
A–C, Courtesy Julie V. Schaffer, MD; D, E Courtesy Justin Finch, MD.

factor receptor inhibitors, cyclin-dependent kinase 4/6 inhibitors); exposure to various pesticides, fungicides or toxins; endocrinopathies such as thyroid disease; and whipworm and HIV infections. The presence of the HLA-DR4 allele may represent a risk factor for EDP in Mexican patients.

Clinical Features

Oval, circular, or irregularly shaped macules and patches that are 0.5 to 3 cm in diameter and slate-gray to blue–brown in color develop gradually in a symmetric pattern and may coalesce (Fig. 67.3A). The initial site of involvement is often the trunk, with subsequent spread to the neck, proximal upper extremities, and sometimes the face. The mucous membranes are spared, and the palms, soles, and scalp are rarely affected. Occasionally, early lesions have a thin, raised, erythematous border, which tends to resolve over a few months, and the long axis of lesions may follow skin cleavage lines. Peripheral hypopigmentation may be seen in older lesions. Characteristic dermoscopic features of EDP include pigmentation in the crista cutis and small brown to gray dots, described as having a "Wagyu beef-like" appearance[3].

EDP is usually asymptomatic but can be mildly pruritic. The disease progresses slowly and typically does not regress in adults. However, in one study of 33 prepubertal children, the majority of whom were White children, the disease spontaneously resolved in two-thirds, with no recurrences over the ensuing 2–3 years[4].

Pathology

In early ("active") lesions, vacuolar degeneration of the basal cell layer, a perivascular mononuclear cell infiltrate and melanophages in the upper dermis, and increased epidermal melanin are seen (Fig. 67.3B). Colloid bodies (apoptotic basal keratinocytes) and dermal hemosiderin may be present. In later ("inactive") lesions, the number of melanophages in the superficial dermis is increased but hydropic changes within the basal cell layer are absent and the dermal mononuclear cell infiltrate is minimal or absent.

Differential Diagnosis

Idiopathic eruptive macular hyperpigmentation (IEMH) features discrete brown macules and small patches with a distribution similar to that of EDP but with more prominent epidermal pigment. Some reports have noted a velvety surface and papillomatosis histologically[5,6] (see Table 67.2). Considering the substantial clinical and histologic overlap of EDP, IEMH, lichen planus pigmentosus, and pigmented contact dermatitis (see Table 67.3), the umbrella term *acquired dermal macular hyperpigmentation* has been proposed for this group of disorders[7,8]. The differential diagnosis of EDP also includes PIH secondary to a lichenoid drug eruption (see Ch. 11), lichen planus, or a generalized fixed drug eruption as well as mastocytosis and (less often) infectious diseases such as leprosy or pinta.

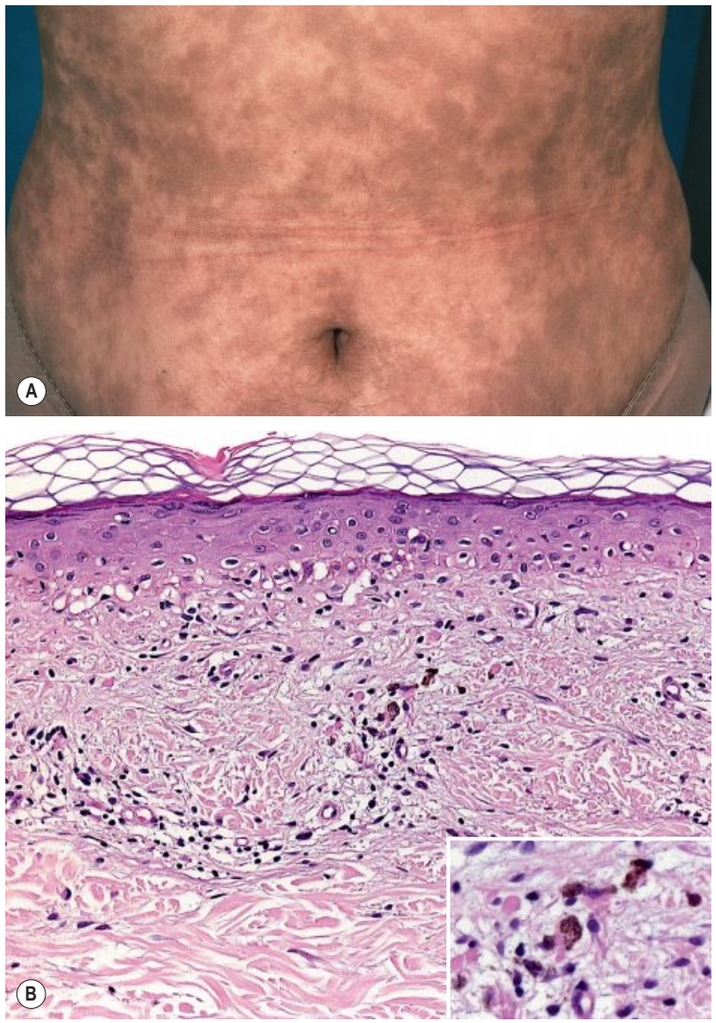


Fig. 67.3 Erythema dyschromicum perstans (ashy dermatosis). A Multiple gray–brown macules and patches on the abdomen; note the coalescence of lesions. The "ashy" color is characteristic. **B** Histopathologic features include vacuolar degeneration of the basal layer, a sparse perivascular lymphocytic infiltrate, and prominent dermal melanophages (see inset). *B, Courtesy Lorenzo Cerroni, MD.*

Treatment

There is no consistently effective therapy for EDP. Topical corticosteroids and hydroquinone are generally of no benefit. Successful treatment with topical tacrolimus, narrowband UVB phototherapy, and oral dapsone, clofazimine, or isotretinoin has been reported in small series.

LICHEN PLANUS PIGMENTOSUS

Key features

- Variant of lichen planus most commonly described in adults with skin phototypes III–V
- Gray–brown to dark brown macules and patches either in a photodistribution or in an inverse (intertriginous) pattern

Lichen planus pigmentosus (LPP) is an uncommon variant of lichen planus that most often affects young to middle-aged adults with skin phototypes III–V, including those from India, Latin America, and the Middle East[9,10]. It presents as irregularly shaped or oval, brown to gray–brown macules and patches that favor sun-exposed areas (especially the forehead, temples, and neck) as well as intertriginous zones (Fig. 67.4). It is usually asymptomatic, but some patients experience mild pruritus or burning. In contrast to EDP, early lesions with an erythematous border are not a feature of LPP.



Fig. 67.4 Lichen planus pigmentosus. Multiple coalescing brown to gray–brown macules in the axilla of a middle-aged woman.

Diffuse, reticulated, blotchy, and follicular patterns of LPP have all been described[9]. While the distribution is typically symmetric, a unilateral linear variant has also been reported. The palms, soles, nails, and oral mucosa are usually not involved. Other lichen planus variants, including frontal fibrosing alopecia, can be observed in ~15%–20% of patients with LPP[10]. Histologic findings include a flattened, often atrophic epidermis with basal cell degeneration and a variably dense, band-like, or perivascular lymphoid infiltrate in the upper dermis admixed with melanophages.

The etiology of LPP is unknown. The photodistribution in some patients suggests that UV exposure may play a pathogenic role. Possible associations with hepatitis C viral infection and the use of mustard oil, amla oil, henna, or hair dyes has also been reported[9]. The differential diagnosis includes other forms of acquired dermal macular hyperpigmentation (e.g. EDP, pigmented contact dermatitis) and PIH, especially that due to actinic and inverse variants of lichen planus or a lichenoid drug eruption (see Ch. 11). When there is facial involvement, melasma and the entities listed in Table 67.3 also need to be considered.

LPP is a chronic disorder with exacerbations and remissions. Treatment is often ineffective, although some patients may respond to topical tacrolimus, oral dapsone, and low-dose isotretinoin[9]. Depending upon the distribution, photoprotection is recommended.

MELASMA

Synonyms: ■ Chloasma ■ Mask of pregnancy

Key features

- At least 90% of patients are women
- Increased prevalence in individuals who are Hispanic, or of Asian or African descent
- Most common location is the face, followed by the forearms
- Symmetric patches of hyperpigmentation with irregular borders due to increased melanin within the epidermis and/or dermis

Introduction and Epidemiology

Melasma is a common acquired disorder characterized by symmetric, hyperpigmented patches with an irregular outline, occurring most commonly on the face. It is most prevalent among young to middle-aged women who are Hispanic, Black, or of Asian or Middle Eastern descent. Exacerbating factors include sun exposure, pregnancy, and use of oral contraceptives.

DIFFERENTIAL DIAGNOSIS OF MELASMA	
Disorder	**Key differences from melasma/comments**
Drug-induced hyperpigmentation or discoloration	• History of medication use (e.g. doxycycline, amiodarone; see Table 67.5) • Hyperpigmentation less patterned and less irregular in outline; may involve tip of nose • Discrete oval or round shape of fixed drug eruption rarely confused with melasma • May follow phototoxic drug reaction • Oral contraceptives and phenytoin may exacerbate melasma
Postinflammatory hyperpigmentation, e.g. due to cutaneous lupus erythematosus, photosensitivity reactions, contact dermatitis (e.g. irritant contact dermatitis to hydroquinone or tretinoin), or other forms of dermatitis	• History of inflammatory phase with erythema, scale, and possible pruritus or burning • Primary lesions – may be admixed or elsewhere on body
Pigmented contact dermatitis (Riehl melanosis)	• Favors sites of application of contactants, especially cosmetics; reported due to masks with a sponge insert • May be reticulated • Brown–grey color due to dermal melanin deposits • Histologic features: vacuolar degeneration of basal layer and lichenoid infiltrate in early lesions
Acquired bilateral nevus of Ota-like macules (Hori nevus)	• Asian women, usually during the fourth or fifth decade of life • Multiple brown–gray to brown–blue macules, primarily in the malar region • Less common sites: lateral forehead, temples, upper eyelids, nasal root, or alae • Lack of ocular or mucosal involvement • Histologic features: pigment-producing dermal melanocytes
Actinic lichen planus	• Fine scale overlying violaceous lesions if inflammatory phase still present • Histologic features: hydropic degeneration of basal layer, lichenoid infiltrate
Lichen planus pigmentosus	• Often begins on the temples/in the preauricular area and involves the neck • Coexistent classic lichen planus (~20% of patients) • Histologic features: vacuolar degeneration of basal layer; variable lichenoid infiltrate and epidermal atrophy
Erythema dyschromicum perstans	• Inflammatory phase with rim of erythema occasionally seen • Lesions slate-gray to blue–brown • Distribution includes sun-protected areas
Exogenous ochronosis	• History of hydroquinone application to areas of hyperpigmentation followed by progressive darkening • Superimposed small pigmented papules may also be seen • Histologic features: banana-shaped, yellow–brown deposits in the dermis (see Fig. 67.8)
Cutaneous mercury deposits	• History of use of mercury-containing soaps or creams • Dermatitis often present • Histologic features: brown–black granules free in dermis, in association with elastic fibers and within macrophages
Erythromelanosis follicularis faciei et colli	• Red–brown patches on lateral cheeks and neck • Superimposed tiny pale follicular papules
Poikiloderma of Civatte	• Presence of atrophy and telangiectasias • Favors lateral and inferior aspects of anterior neck; sparing of perifollicular skin and submental region
Acanthosis nigricans	• Velvety plaques in the hollow of the cheek and preauricular

Table 67.3 Differential diagnosis of melasma.

Pathogenesis

Although the exact pathogenesis of melasma is unknown, it is hypothesized that following exposure to UV irradiation or another inducer, hyperfunctional melanocytes within involved skin produce increased amounts of melanin[11,12]. The key role of UV irradiation is supported by fading of lesions during winter months and a distribution pattern characterized by involvement of sun-exposed regions with sparing of relatively sun-protected sites such as the philtrum. In addition to oral contraceptive use and hyperestrogenic states, other medications (e.g. phenytoin, phototoxic drugs) and disorders (e.g. autoimmune thyroid disease) have the potential to aggravate melasma. Increased expression of KIT and stem cell factor within lesional epidermis and dermis, respectively, may play a role in the hyperpigmentation of melasma[13]. Furthermore, reduced expression of Wnt-inhibitory factor 1 (WIF-1) and microRNAs may lead to tyrosinase upregulation via increased Wnt signaling[13a].

The presence of enhanced blood flow within areas of melasma has also been investigated. An increase in both blood vessel size and density has been observed that correlates with the increase in pigmentation. When compared to perilesional normal skin, increased expression of vascular endothelial growth factor (VEGF) was detected within lesional skin. These findings have led to alternative therapeutic strategies.

Clinical Features

Light to dark brown or brown–gray patches with irregular borders appear primarily on the face (Fig. 67.5). The areas of hypermelanosis are distributed symmetrically in three classic patterns: (1) *centrofacial* (most common), involving the forehead, cheeks, nose, upper lip (sparing the philtrum and nasolabial folds), and chin; (2) *malar*, affecting the cheeks and nose; and (3) *mandibular*, along the jawline. Less common sites include the extensor aspect of the forearms and mid upper chest. Lesions often first appear or are accentuated following exposure to UV irradiation or during pregnancy. In lightly pigmented individuals, this "mask of pregnancy" frequently diminishes or disappears after parturition, but it tends to persist in women with more darkly pigmented skin.

Melasma has classically been subdivided into four types based upon the primary location of the pigment: epidermal, dermal, mixed, or indeterminate (e.g. in patients with very dark skin pigmentation). In theory, lesions with increased epidermal melanin are accentuated and those with increased dermal melanin become less obvious (i.e. blend with uninvolved skin) with Wood's lamp examination. However, clinicopathologic studies utilizing adjacent uninvolved skin as controls have shown that Wood's lamp examination does not correlate with histologic findings[12,14]. Considering that epidermal pigmentation is more likely to respond to topical therapies, further studies are needed to determine the



Fig. 67.5 Various forms of melasma and melasma-like hyperpigmentation. A Malar variant. **B** Mild centrofacial type with sparing of the philtrum. **C** Extension of the hyperpigmentation onto the mandible. **D** Involvement of the extensor forearm; note the same irregular outline as is seen on the face. **E** Melasma-like appearance in a patient with previous acute cutaneous lupus erythematosus. *C–E, Courtesy Jean L. Bolognia, MD.*

clinical utility and prognostic significance of Wood's lamp examination and perhaps optical coherence tomography.

Pathology

Compared to uninvolved adjacent skin, increased melanin deposition is observed in all layers of the epidermis, particularly the basal layer. An increased number of melanophages may also be seen in the upper dermis. Epidermal melanocytes are normal to slightly increased in number, and they are enlarged with prominent dendrites[12,14].

Ultrastructurally, lesional melanocytes contain an increased number of melanosomes. In addition, the mitochondria, Golgi apparatus, and rough endoplasmic reticulum are increased in number. These findings support the theory of hyperfunctional melanocytes, presumably stimulated by UV irradiation or hormones (see Pathogenesis above).

Differential Diagnosis

The differential diagnosis of melasma is reviewed in Table 67.3. These disorders are distinguished from melasma based upon historical aspects (e.g. drug ingestion, previous inflammation), color, distribution pattern, histologic features, and, if present, primary inflammatory lesions.

Treatment

The treatment of melasma is summarized in Table 67.4. Diligent sun protection and patient motivation are necessary for any melasma treatment regimen to be successful. For epidermal melasma, 2 months of therapy are typically required to initiate lightening and 6 months of treatment are often needed to achieve satisfactory results.

ADDITIONAL FORMS OF CIRCUMSCRIBED HYPERPIGMENTATION

Segmental Pigmentation Disorder

This term was coined by Metzker et al. in 1983 and re-introduced by Hogeling and Frieden in 2010[15]. This block-like pattern of hyper- or hypopigmentation represents a type of pigmentary mosaicism, i.e. a postzygotic genetic alteration leading to a regional change in pigment production potential (Fig. 67.6; see Ch. 62). The hyperpigmented patches are evident at birth or become apparent during infancy. They favor the trunk, with midline demarcation more often evident ventrally than dorsally and less distinct lateral borders. There are usually no associated extracutaneous anomalies.

Familial Progressive Hyperpigmentation

Familial progressive hyperpigmentation is an autosomal dominant disorder characterized by hyperpigmented patches in a widespread distribution including the palms, soles, lips, and conjunctiva. The lesions begin to develop during infancy and increase in size, number, and confluence with age. Heterozygous gain-of-function mutations in the KIT ligand gene (*KITLG*) can cause this condition[16] as well as *familial progressive hyper- and hypopigmentation*, which has the additional finding of hypopigmented macules and patches.

GIST-Cutaneous Hyperpigmentation Disease

Familial gastrointestinal stromal tumors (GISTs), which are derived from the interstitial cells of Cajal in the stomach or small intestine, can result from germline heterozygous gain-of-function *KIT* mutations. Affected individuals (typically with mutations in codon 11 or 13) may also develop hyperpigmented patches or multiple lentigo-like macules, referred to as GIST–cutaneous hyperpigmentation disease[17]. The hyperpigmentation is progressive and favors the face, acral areas, the anogenital region, and sites of friction or trauma. It is usually apparent at birth or by early childhood, thus preceding the development of GIST, and may eventually become generalized. Treatment with imatinib has been reported to improve the hyperpigmentation as well as GIST[18].

Primary (Localized) Cutaneous Amyloidosis

Macular and lichenoid forms of primary (localized) cutaneous amyloidosis are associated with hyperpigmentation (see Ch. 47). The most common locations are the upper back (macular amyloidosis) or the extensor surface of the lower extremities (lichen amyloidosis), and there is a characteristic rippled pattern with parallel bands or ridges of hyperpigmentation. Areas of involvement are often pruritic, and rubbing plays a key role in the production of lesions. Histologically,

TREATMENT OPTIONS FOR MELASMA
Recommendations for all patients
• Avoidance of sun exposure and tanning beds • Daily use of broad-spectrum sunscreen (ideally SPF ≥30 with physical blocker such as zinc oxide or titanium dioxide) • Sun-protective hats and clothing • Camouflage makeup (with iron oxide to block visible light) • Discontinue oral contraceptives, if possible
Active treatment*,†
First-line topical therapies • Triple combination of HQ + retinoid + corticosteroid‡ at bedtime • 4% HQ daily, typically at bedtime • Azelaic acid (15%–20%) **Adjunctive topical therapies** • L-ascorbic acid (10%–15%) • Kojic acid (1%–4%) • Tranexamic acid (2%–5%) • Niacinamide (4%) **Adjunctive oral therapies** • Tranexamic acid (250 mg BID for 8–12 weeks)¶ **Second-line therapies** • Glycolic (start at 30% and increase as tolerated) or salicylic acid peels (20%–30%) every 4–6 weeks **Third-line therapies§** • Non-ablative fractional laser • Intense pulsed light (IPL) • Low fluence Q-switched lasers • Picosecond lasers
Long-term maintenance
• Continue daily sunscreen and sun-protective measures (see above) • Topical retinoid • Topical α-hydroxy acid (e.g. glycolic acid cream) • Other topicals, e.g. L-ascorbic acid (10%–15%), azelaic acid (15%–20%), kojic acid (1%–4%), tranexamic acid (2%–5%)
*Results from topical treatments may take up to 6 months to appreciate; depending on the patient, HQ or a combination HQ + retinoid + corticosteroid are typically used daily for 2–4 months and then decreased in frequency to 1–2 times per week; prolonged daily use can result in side effects such as perioral dermatitis and atrophy (corticosteroid) or exogenous ochronosis (HQ; see Ch. 129). †While topical HQ can cause allergic contact dermatitis, all topical agents may lead to irritant contact dermatitis, which can worsen the dyspigmentation; if this is a concern, can test on a small, non-facial site prior to widespread facial application. ‡Typically a class 5–7 topical corticosteroid is used (see Ch. 125). ¶Patients should be screened for history of and risk factors for thromboembolism. §Potential risk of post-procedural dyspigmentation; a small test site should be performed prior to widespread facial laser or light therapy.

Table 67.4 Treatment options for melasma. HQ, hydroquinone.



Fig. 67.6 Segmental pigmentation disorder. Unilateral block-like hyperpigmentation on the chest, abdomen, and upper arm of an infant. Note the midline demarcation inferiorly. *Courtesy Julie V. Schaffer, MD.*

melanophages as well as amyloid deposits that stain positively with anti-keratin antibodies are seen within the upper dermis.

Mastocytosis

Cutaneous mastocytosis is characterized by the accumulation of mast cells within the skin and sometimes other organs (see Ch. 118). The maculopapular form of mastocytosis classically features hyperpigmented lesions, with patients developing a few to several hundred brown to red–brown macules and papules ("urticaria pigmentosa"). Mastocytomas can also have a light brown color. Lesions of cutaneous mastocytosis typically urticate after they are stroked (Darier's sign), and an increased number of mast cells is seen in biopsy specimens. The hyperpigmentation in mastocytosis is thought to result from stimulation of melanocytes by mast cell-derived mediators such as KIT ligand or α-melanocyte-stimulating hormone[19]. Somatic activating mutations in *KIT* often underlie mastocytosis in both children and adults. Whereas the prognosis for childhood-onset mastocytosis is good, with spontaneous resolution by adolescence in many patients, adult-onset disease is frequently persistent (see Ch. 118).

Tinea (Pityriasis) Versicolor

Tinea versicolor is a superficial skin infection caused by the yeast *Malassezia globosa* and other *Malassezia* spp. (see Ch. 77). Hypo- or hyperpigmented macules or very thin papules and plaques covered with fine scale are usually found on the upper trunk and proximal upper extremities but may also appear in other sites such as the neck, face, and groin. There is often coalescence of lesions centrally, especially on the trunk. In light and electron microscopy studies, a similar number of melanocytes was noted in uninvolved skin as in hypo- and hyperpigmented lesions; the latter had a thickened stratum corneum that contained more organisms. The clinical differential diagnosis for the hyperpigmented form of tinea versicolor may include PIH and confluent and reticulated papillomatosis, but a KOH preparation of the scale showing both hyphal and yeast forms of *Malassezia* distinguishes tinea versicolor from these entities.

Atrophoderma of Pasini and Pierini

Atrophoderma of Pasini and Pierini is usually seen in young adults and has been postulated to represent an atrophic form of morphea (see Ch. 99). Most often, multiple oval hyperpigmented patches measuring 4–10 cm in diameter appear on the posterior trunk. There is a subtle depression of the entire lesion, but no induration or secondary changes. The depression can be appreciated by palpation of the edge of the lesion, with a characteristic "cliff sign" at the peripheral margin.

PIGMENTED LESIONS

Lentigines

Lentigines are reviewed in Chapters 109 and 112.

Café-au-Lait Macules

Café-au-lait macules (CALMs) are hyperpigmented macules or patches two to three shades darker than uninvolved skin (see Ch. 112). They are found in at least 10% of the population. CALMs may be evident at birth or, especially in individuals with lightly pigmented skin, become apparent during infancy or early childhood. The presence of multiple CALMs raises the possibility of neurofibromatosis type 1 or another genetic syndrome (see Table 61.3); Fig. 61.10 outlines an approach to a young child with multiple CALMs. A CALM is usually easily distinguished from a fully developed congenital melanocytic nevus, but in infants there may be overlap in the clinical appearance of these two entities. The differential diagnosis also includes the earliest stage of a nevus spilus (before the "speckles" appear), Becker melanosis (nevus) or smooth muscle hamartoma, and a mastocytoma; in addition, segmental CALMs and "pigmentary mosaicism" have significant overlap. Although laser treatment of CALMs is possible (see Ch. 137), responses vary and recurrence of pigmentation is common.

DRUG-INDUCED HYPERPIGMENTATION OR DISCOLORATION

Key features

- Localized or generalized hypermelanosis or discoloration may be seen
- Several medications and drug classes are known to induce hyperpigmentation or discoloration, especially minocycline, antimalarials, chemotherapeutic agents, and zidovudine
- Longitudinal, transverse, or diffuse melanonychia may also be present

Cutaneous hypermelanosis or discoloration can result from exposure to chemicals and a wide range of medications, most commonly chemotherapeutic agents, antimalarials, minocycline, and zidovudine (Table 67.5, Figs. 67.7–67.9). The underlying mechanisms vary from induction of melanin production to deposition of drug complexes or heavy metals within the dermis. The pigmentation can be circumscribed or generalized. Although it usually resolves with discontinuation of the offending drug, the course may be prolonged. Longitudinal, transverse, or diffuse melanonychia and oral mucosal pigmentation may also be observed.

ADDITIONAL FORMS OF DIFFUSE HYPERPIGMENTATION

In addition to medications, diffuse hyperpigmentation can be caused by metabolic abnormalities, nutritional deficiencies, and several inherited and acquired syndromes. An approach to the patient with diffuse hyperpigmentation is provided in Fig. 67.10.

DRUGS AND CHEMICALS ASSOCIATED WITH HYPERPIGMENTATION OR DISCOLORATION

Drug or chemical	Clinical features	Histopathology/comment
Chemotherapeutic agents (see Ch. 21)		
BCNU (carmustine)	• Hyperpigmentation at sites of topical application (not with parenteral administration)	• Hyperplasia of basal melanocytes • Increased melanin within the epidermis
Bleomycin (intravenous or intralesional)	• Linear, flagellate bands that favor the trunk and may be associated with minor trauma (see text) • Transverse melanonychia • Hyperpigmentation overlying joints/pressure points or localized to striae and palmar creases • Sclerodermoid changes	• Increased epidermal melanin but no increase in the number of melanocytes • Usually relatively few dermal melanophages
Busulfan	• Generalized hyperpigmentation resembling Addison disease; sometimes associated with drug-induced pulmonary fibrosis	• Increased melanin within basal keratinocytes and dermal macrophages
Cyclophosphamide	• Diffuse hyperpigmentation of the skin and mucous membranes • Pigment localized to the nails (transverse, longitudinal, or diffuse melanonychia), palms and soles, or teeth	• Cutaneous hyperpigmentation usually regresses within 6 to 12 months after therapy is discontinued
Dactinomycin	• Generalized hyperpigmentation, most prominent on the face	• Pigmentation fades after treatment is discontinued
Daunorubicin	• Hyperpigmentation of sun-exposed areas • Transverse brown–black melanonychia	
Doxorubicin	• Hyperpigmentation overlying the small joints of the hands and involving the palms (especially the creases), soles, and oral mucosa (buccal, tongue) • Transverse melanonychia	• Increased epidermal melanin • Increased number of melanocytes
5-Fluorouracil	• Hyperpigmentation in sun-exposed areas (~5% of patients treated systemically; often follows an erythematous photosensitivity reaction) • Increased pigmentation of skin overlying veins in which the drug was infused • Other sites include the dorsal aspects of the hands, palms/soles, and radiation ports • Transverse or diffuse melanonychia; lunular pigmentation	• Postinflammatory hyperpigmentation • Capecitabine (the 5-fluorouracil prodrug) may also lead to acral or oral hyperpigmentation
Hydroxyurea	• Reversible hyperpigmentation over pressure points and on the back • Longitudinal, transverse, or diffuse melanonychia; lunular pigmentation	• Lichenoid eruption with postinflammatory hyperpigmentation can also occur
Imatinib (also dasatinib, gefitinib)	• Localized or diffuse hyperpigmentation (<5% of patients) • Diffuse melanonychia, repigmentation of gray hair, and pigmentation of the gingiva and teeth	• Localized or diffuse hypo- or depigmentation is more common (40%–60% of darkly pigmented patients)
Mechlorethamine (nitrogen mustard)	• Topical use for cutaneous T cell lymphoma may result in generalized hyperpigmentation • More intense in lesional skin	• Disaggregation of melanosomes within keratinocytes • Increased number of melanocytes

Table 67.5 Drugs and chemicals associated with hyperpigmentation or discoloration.

Continued

DRUGS AND CHEMICALS ASSOCIATED WITH HYPERPIGMENTATION OR DISCOLORATION		
Drug or chemical	**Clinical features**	**Histopathology/comment**
Methotrexate	• Uniform hyperpigmentation in sun-exposed areas (occasionally follows an erythematous photosensitivity reaction)	• Uncommon
Antimalarials		
Chloroquine, hydroxychloroquine, quinacrine	• Gray to blue–black pigment, usually pretibial, with (hydroxy) chloroquine; face, hard palate, sclerae, and subungual areas may be involved • Diffuse yellow to yellow–brown discoloration with quinacrine • Discoloration affects up to 25% of patients	• Dermal deposition of melanin–drug complexes; hemosiderin around capillaries • May fade after discontinuation of drug, but rarely resolves completely
Heavy metals		
Arsenic	• Areas of bronze hyperpigmentation ± superimposed "raindrops" of lightly pigmented skin; favors axillae, groin, palms, soles, nipples, and pressure points • Dyspigmentation appears 1–20 years after arsenic exposure, with a strong dose–response relationship • Palmoplantar keratoses and squamous cell carcinoma typically develop after dyspigmentation (see Ch. 88)	• Dermal and epidermal deposition of arsenic • Increased epidermal melanin synthesis
Bismuth	• Generalized blue–gray discoloration of the face, neck and dorsal hands • Oral mucosa and gingivae may be involved	• Bismuth granules in the papillary and reticular dermis
Gold (chrysiasis)	• Permanent blue–gray discoloration in sun-exposed areas, particularly around the eyes	• Gold particles within lysosomes in dermal macrophages, especially in perivascular and perieccrine areas
Iron	• Permanent brown pigment at injection sites or in areas of application of ferric subsulfate (Monsel's) solution as a hemostatic agent • Dermal hemosiderin deposits (due to lysis of extravasated red blood cells and release of their iron stores) are commonly observed in the setting of venous hypertension, in pigmented purpuric dermatoses, and as a side effect of sclerotherapy of superficial veins	• Pigment coats collagen fibers and is deposited in dermal macrophages
Lead	• "Lead line" in gingival margin • Nail discoloration	• Lead line is due to subepithelial deposition of lead granules
Mercury	• Slate-gray discoloration, particularly in skin folds	• Brown–black granules free in dermis, in association with elastic fibers and within macrophages
Silver (argyria)	• Diffuse slate-gray discoloration (see Fig. 67.7A), increased in sun-exposed areas; occurs in settings of occupational exposure, alternative medications, or systemic absorption from use of silver sulfadiazine on extensive burns/wounds • The nail unit (diffuse or localized to the lunulae) and sclerae may also be affected • Sites of topical application, e.g. of silver sulfadiazine to burns or ulcers	• Silver granules in the basement membrane of eccrine glands; also often seen in elastic fibers, in the tissue around hair follicles, and in arrector pili muscles; highlighted by darkfield illumination (see Fig. 67.7B)
Hormones		
Oral contraceptives	• Melasma; increased pigmentation of nipples and nevi	• Increased melanocytes and increased melanin synthesis
ACTH/MSH (ACTH is rarely used; [NIe4-D-Phe7]-α-MSH/afamelanotide orphan drug for EPP)	• Diffuse brown or bronze hyperpigmentation, accentuated in sun-exposed sites	• Increased melanin synthesis
Miscellaneous compounds		
Amiodarone	• Slate-gray to violaceous discoloration of sun-exposed skin, especially the face (less common than erythema from photosensitivity) • Fair-skinned patients after long-term, continuous therapy	• Yellow–brown granules in dermal macrophages, mostly in a perivascular distribution • By EM, lysosomal inclusions composed of a lipid-like substance • Usually fades completely over months to years after discontinuation of drug, but sometimes persists
Azidothymidine (zidovudine, AZT)	• Longitudinal > transverse and diffuse melanonychia (up to 10% of patients); blue lunulae • Mucocutaneous hyperpigmentation (e.g. widespread diffuse, acral, oral macules); most common in patients with darkly pigmented skin, and may be accentuated in areas of friction or sun exposure	• Skin biopsy shows increased melanin in the epidermis and dermal melanophages • Fades gradually after drug is discontinued

Table 67.5 Drugs and chemicals associated with hyperpigmentation or discoloration.

DRUGS AND CHEMICALS ASSOCIATED WITH HYPERPIGMENTATION OR DISCOLORATION		
Drug or chemical	**Clinical features**	**Histopathology/comment**
Clofazimine	• Diffuse red to red–brown discoloration of skin, conjunctivae • Violet–brown to blue–gray discoloration, especially of lesional skin	• Red color secondary to drug in fat (highly lipophilic) • Blue–violet color secondary to brownish granular pigment within dermal macrophages • By EM, phagolysosomes contain amorphous granular material and lamellar structures characteristic of lipofuscin • Fades gradually after discontinuation of drug
Diltiazem (rarely amlodipine)	• Slate-gray to gray–brown discoloration of sun-exposed skin in patients with skin phototypes IV–VI; perifollicular accentuation and a reticular pattern may be observed	• Sparse lichenoid infiltrate and numerous dermal melanophages
Dioxins	• Hyperpigmentation may occur in sun-exposed areas • Chloracne is a more common skin finding	• Rare, except in accidental exposure
Eltrombopag (thrombopoietin receptor agonist)	• Subtle grey discoloration, usually on sun-exposed areas	• Dermal deposition of Fontana-Masson- and Prussian blue-positive brown granules
Ezogabine/retigabine (anticonvulsant no longer available in the US)	• Blue–gray discoloration, most often lips, face, nail beds, and hard palate • Black pigment deposits on conjunctivae	• Permanent vision changes • Perivascular and periadnexal intracellular deposits of coarse melanin granules
Gardenia fruit (herbal medicine)	• Blue–gray discoloration of face and chest • Diffuse and patchy	• Mesenteric phlebosclerosis • Dermal melanophages • Ionized genipin, a metabolite of geniposide, detected by ToF-SIMS
Hydroquinone	• Hyperpigmentation in areas of application due to irritant contact dermatitis (i.e. postinflammatory) or exogenous ochronosis; the latter may also result in small "caviar-like" papules	• In exogenous ochronosis, yellow–brown banana-shaped fibers in papillary dermis (see Fig. 67.8)* • Presumed mechanism is metabolism by melanocytes of hydroquinone into ringed structures that serve as precursors of ochronotic fibers • May fade upon discontinuation of hydroquinone; variable improvement with pigment-directed Q-switched lasers
Interferon-α	• Hyperpigmentation of the oral mucosa and face • Longitudinal melanonychia	• More common in patients with darkly pigmented skin and sun exposure
Minocycline	• *Type I:* blue–black discoloration in sites of inflammation and scars, including those due to acne or ablative laser therapy (see Fig. 127.7A) • *Type II:* blue–gray macules/patches (1 mm–10 cm in size) within previously normal skin, most often on the shins (see Figs. 67.9 & 127.7B–D); sometimes misdiagnosed as ecchymoses • *Type III:* diffuse "muddy brown" pigmentation that is most prominent in sun-exposed areas • Blue–black discoloration may also involve nails, sclerae, oral mucosa, bones, thyroid, and teeth	• Iron-containing (types I, II) or melanin-containing (type II) pigment granules within the dermis†; the former can be intra- or extracellular and may represent hemosiderin and/or a minocycline derivative plus chelated iron • Increased melanin within the basal epidermis and/or dermal melanophages (type III) • Minocycline is a highly lipid-soluble, yellow, crystalline material that turns black with oxidation • Fades after discontinuation of medication, but may take months or even years; for types I and II, treatment with Q-switched pigment-directed lasers (similar to tattoo removal) may decrease the discoloration
Nicotine (smoker's melanosis)	• Localized brown hyperpigmentation of oral mucosa, favoring gingiva and lips	• May fade upon cessation of smoking
Psoralens	• Diffuse hyperpigmentation after exposure to UVA light following oral administration (PUVA) • Circumscribed or linear streaks of hyperpigmentation can be seen with topical exposure, e.g. topical PUVA or phytophotodermatitis (exposure to psoralen-containing plants plus sunlight)	• Proliferation of follicular melanocytes, with increased synthesis and transfer of melanin • Singly dispersed melanosomes within keratinocytes • Psoralens are furocoumarin compounds originally derived from plants
Psychotropic drugs (chlorpromazine, thioridazine, imipramine, desipramine, amitriptyline)	• Slate-gray to brown (with amitriptyline) discoloration in sun-exposed areas	• Golden-brown granules in the upper dermis • Electron-dense inclusion bodies
Prostaglandin analogues (bimatoprost, latanoprost)	• Periocular reddish-brown to brown hyperpigmentation, hyperpigmentation of iris	• Increased melanin within the basal epidermis and dermal melanophages

*Similar histologic findings are seen in alkaptonuria (also referred to as ochronosis), an autosomal recessive disease caused by deficiency in homogentisic acid oxidase, which results in accumulation of homogentisic acid in the tissues; this insoluble pigment binds to collagen and leads to blue–black discoloration (e.g. of the helices and sclerae; see Ch. 63).
†Occasionally, the type I clinical pattern shows a calcium-containing melanin-like substance but no iron; in addition, both iron and melanin deposits have been described in pigmentation within pre-existing leprosy lesions.

Table 67.5 Drugs and chemicals associated with hyperpigmentation or discoloration. ACTH, adrenocorticotropic hormone; BCNU, 1,3-bis (2-chloroethyl)-1-nitrosourea; EM, electron microscopy; EPP, erythropoietic protoporphyria; MSH, melanocyte-stimulating hormone; ToF-SIMS, time-of-flight secondary ion mass spectrometry. *Adapted from Kang S, Lerner EA, Sober AJ, Levine N. In: Levine N (ed.). Pigmentation and Pigmentary Disorders. Boca Raton: CRC Press, 1993:417–31.*



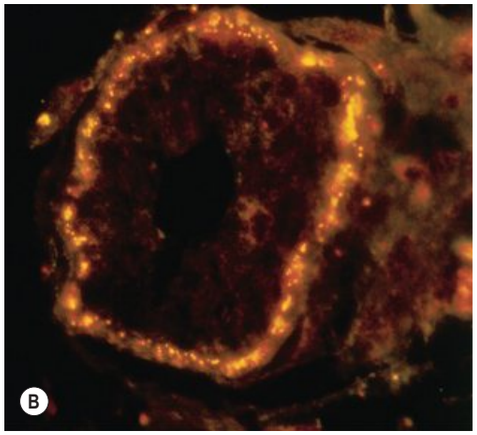


Fig. 67.7 Argyria. **A** Diffuse slate-gray discoloration of the palms. **B** Darkfield microscopy of an eccrine gland. Note the refractile nature of the granules and their location in the membrana propria. *A, Courtesy Mary Beth Cole, MD, and Michael L. Smith, MD.*

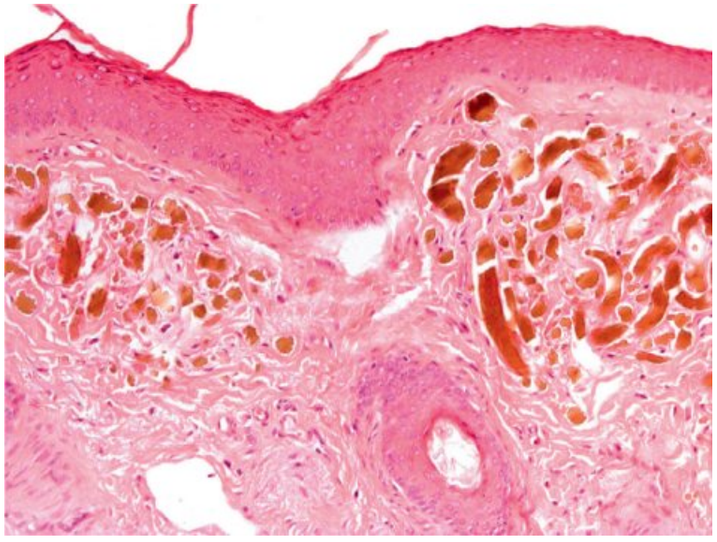


Fig. 67.8 Exogenous ochronosis secondary to topical hydroquinone – histopathologic features. Yellow–brown banana-shaped fibers are seen in the papillary dermis. *Courtesy Lorenzo Cerroni, MD.*

LINEAR HYPERPIGMENTATION

Linear hyperpigmentation can have a variety of etiologies, including postinflammatory changes, drug reactions, and mosaic genetic alterations that result in hypermelanosis along the lines of Blaschko (see Ch. 62). Pigmentary demarcation lines reflect normal dorsal–ventral patterning of the skin. In the evaluation of a patient with linear hyperpigmentation, an initial step is to determine whether or not the hypermelanosis follows the lines of Blaschko.

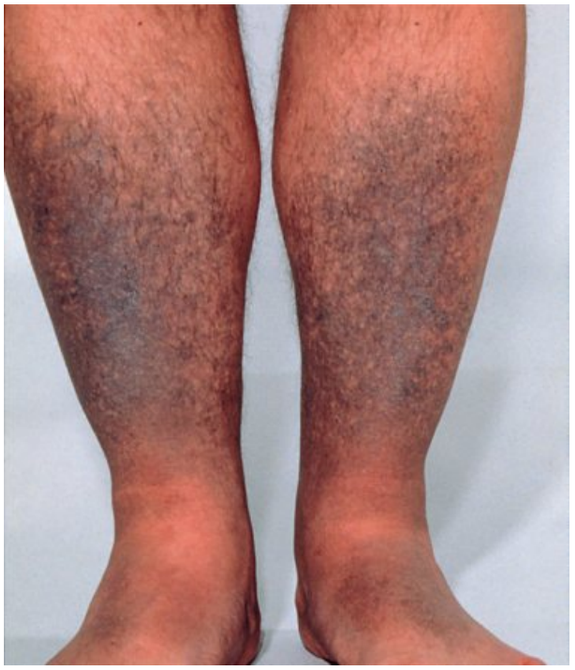


Fig. 67.9 Minocycline-induced pigmentation. The distribution on the shins and the gray–blue color can be similar to that seen with antimalarials.

PIGMENTARY DEMARCATION LINES

Synonyms: ■ Futcher lines ■ Voight lines ■ Ito lines

Key features

- Lines of demarcation between dorsal surfaces (which are relatively hyperpigmented) and ventral surfaces
- Physiologic pattern of human pigmentation
- More often apparent in individuals with darkly pigmented skin
- Most commonly seen on the anterolateral upper arm and posteromedial thigh

Introduction

In all skin types, the dorsal skin surfaces are relatively hyperpigmented compared to the ventral surfaces. In individuals with darkly pigmented skin, visible lines of demarcation between dorsal and ventral surfaces are more conspicuous, especially on the anterolateral portion of the upper arm (Fig. 67.11A). These demarcation lines are bilateral, symmetric, and present from infancy through adulthood. Additional lines occur on the posteromedial aspect of the thighs (Fig. 67.11B), upper chest (Fig. 67.11C), paraspinal region of the back, and face (Table 67.6; Fig. 67.12).

Differential Diagnosis

PIH may occasionally be confused with pigmentary demarcation lines types A, B, D, and F–H. However, in the latter there is no preceding inflammation or injury and the lines are perfectly symmetric and stable over time. Types C and E pigmentary demarcation lines may be confused with linear nevoid hypopigmentation. Linea nigra, the linear hyperpigmentation that extends from the umbilicus to the pubis in pregnant women (see Fig. 27.11A), is easily distinguished from a pigmentary demarcation line.

Treatment

These are normal pigmentation patterns, and no treatment is indicated.

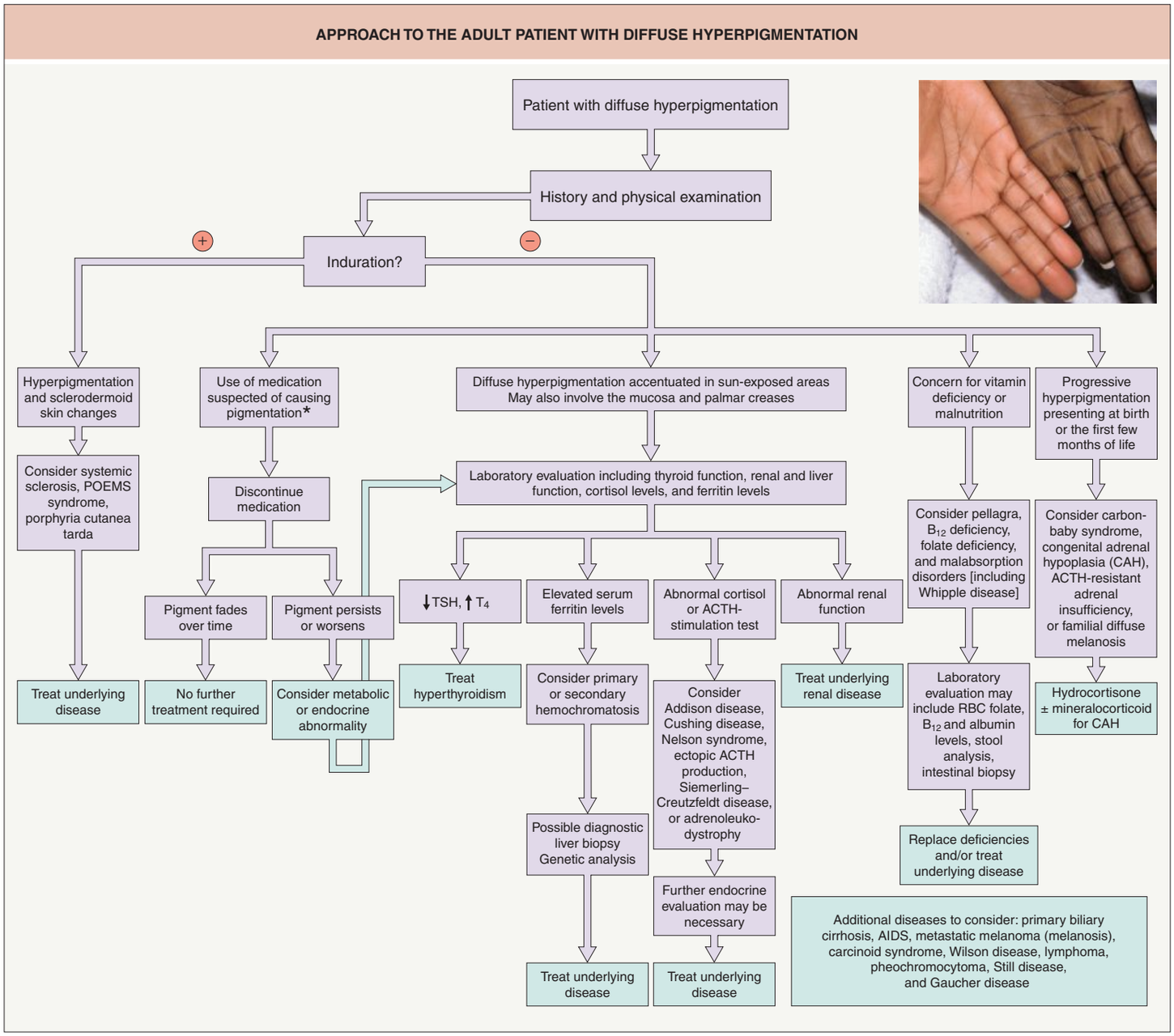


Fig. 67.10 Approach to the adult patient with diffuse hyperpigmentation. The palm on the right in the inset photograph shows diffuse hyperpigmentation in a patient with POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal gammopathy and *s*kin lesions). ACTH, adrenocorticotropic hormone; T_4, thyroxine; TSH, thyroid-stimulating hormone. *See Table 67.5 for drugs and chemicals associated with diffuse hyperpigmentation.

LINEAR POSTINFLAMMATORY HYPERPIGMENTATION

PIH is the most common cause of acquired hyperpigmentation, with the circumscribed variant (see above) seen more often than diffuse or linear forms. In general, PIH is more clinically apparent in individuals with darkly pigmented skin than in those with lightly pigmented skin.

Clinical Features

Linear PIH can occur following skin injuries, dermatitis, and other inflammatory conditions with a linear pattern, e.g. phytophotodermatitis (Table 67.7; Fig. 67.13). Occasionally, PIH follows the lines of Blaschko because the antecedent inflammatory dermatosis did so, e.g. linear lichen planus. The color ranges from brown (epidermal) to brown–gray (dermal). PIH slowly fades over time, provided that further injury to the skin does not occur. However, resolution may not occur for months to years, especially in more darkly pigmented individuals and when the melanin is primarily dermal. The pathogenesis, histology, and treatment of linear PIH are similar to those of the circumscribed form (see above).

Differential Diagnosis

Linear PIH is relatively easy to recognize when there is a history of preceding cutaneous injury or inflammation, but it is more difficult if the preceding event was transient or unnoticed. The differential diagnosis includes rare conditions such as flagellate pigmentation due to bleomycin or shiitake dermatitis (see below) as well as the common phenomenon of black dermographism. The latter occurs when metals, including those in jewelry (nickel, gold, silver), are abraded by harder substances such as powders that contain zinc oxide. The color varies from dark grey to black, and the deposits of metallic powder can be easily removed. Black lacquer deposits associated with poison ivy dermatitis can also result in linear pigmentation, but the color is jet black (see Ch. 17).

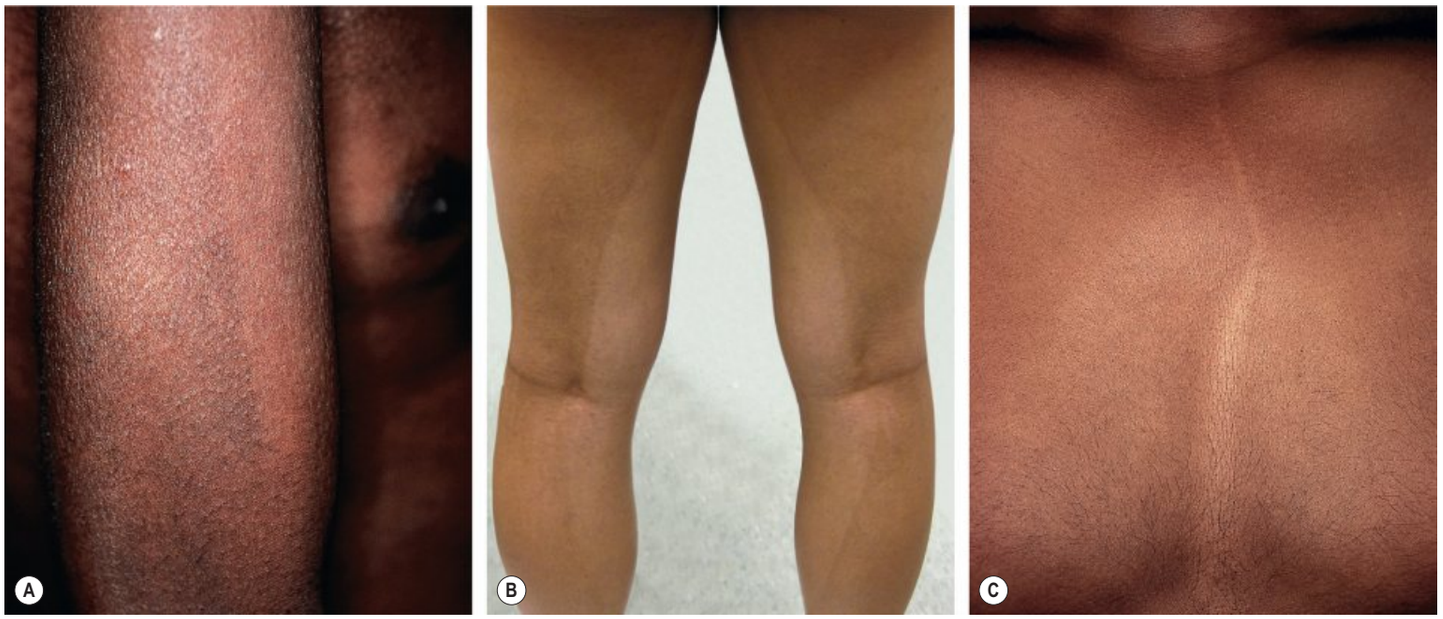


Fig. 67.11 Pigmentary demarcation lines (PDLs). A The most common PDL (type A) is on the upper arm, with relative hypopigmentation on the ventral surface. **B** Type B PDLs on the posterior thighs, with relative hypopigmentation medially. **C** Type C PDL (composed of parallel lines) may be confused with linear nevoid hypopigmentation. *A, C, Courtesy Jean L. Bolognia, MD; B, Courtesy Justin Finch, MD.*

PIGMENTARY DEMARCATION LINES: FIVE MAJOR TYPES (A–E) ANDPROPOSED FACIAL TYPES (F–H)	
Type	**Description**
A	A vertical line along the anterolateral portion of the upper arm that may extend into the pectoral region (most commonly observed type) (see Fig. 67.11A)
B	A curved line on the posteromedial thigh that extends from the perineum to the popliteal fossa and occasionally to the ankle (see Fig. 67.11B)
C	A vertical or curved hypopigmented band on the mid chest that results from two parallel pigmentary demarcation lines (see Fig. 67.11C)
D	A vertical line in a pre- or paraspinal location
E	Bilateral chest markings (hypopigmented macules and patches) in a zone that runs from the mid third of the clavicle to the periareolar skin
F & G	"V"- or "W"-shaped lines between the lateral temple and malar prominence; a curved line may extend medially in the infraorbital area
H	A diagonal line from the angle of the mouth to the lateral aspect of the chin

Table 67.6 Pigmentary demarcation lines: five major types (A–E) and proposed facial types (F–H). Also see Fig. 67.12.

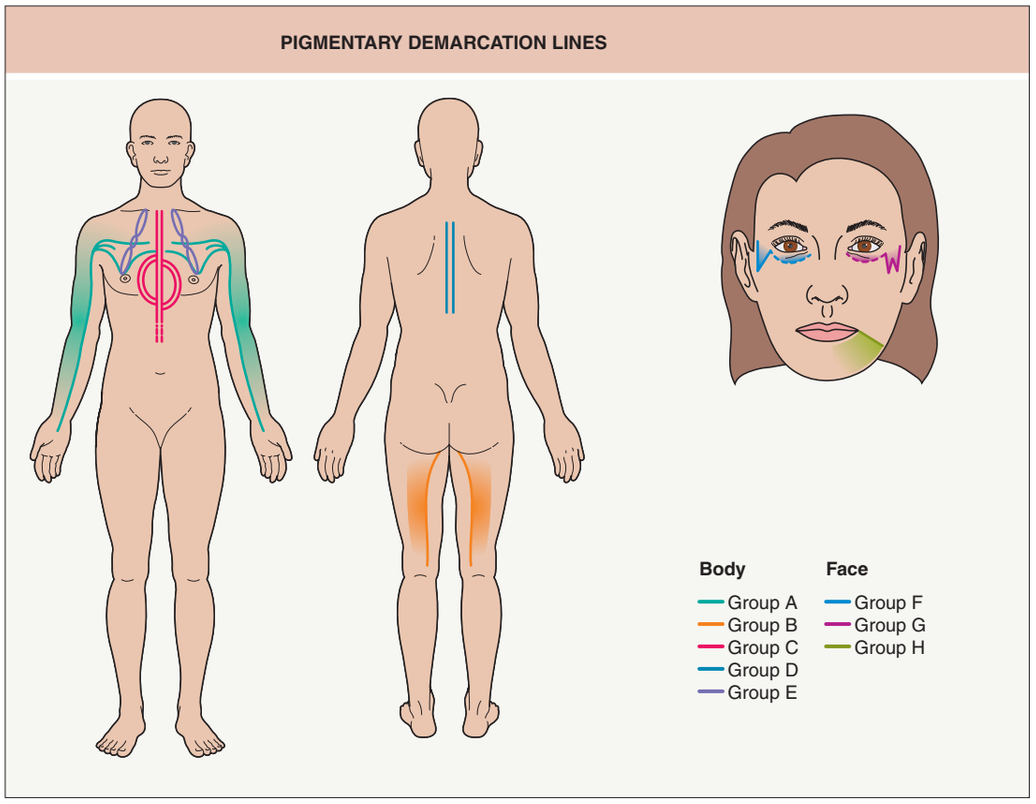


Fig. 67.12 Pigmentary demarcation lines.

DISORDERS WITH LINEAR HYPERPIGMENTATION
Follows the lines of Blaschko
Inherited/early onset
• Linear and whorled nevoid hypermelanosis ("pigmentary mosaicism"*; see Fig. 67.15) • Early or subtle epidermal nevus • Third stage of incontinentia pigmenti† (see Fig. 67.19) • X-linked reticulate pigmentary disorder† • Focal dermal hypoplasia† (Goltz syndrome; hyperpigmented macules within linear streaks, along with cribriform dermal atrophy, fat "herniation", hypopigmentation, and/or telangiectasias) • X-linked hypohidrotic ectodermal dysplasia† • Conradi–Hünermann–Happle syndrome† • X-linked dyskeratosis congenita (rare)† • Börjeson–Forssman–Lehmann syndrome† (favors axillae; also dental/digital anomalies, frontotemporal hypotrichosis, facial dysmorphism) • *TFE3*-associated neurodevelopmental disorder† (lysosomal storage disease-like findings) • Café-au-lait macules of McCune–Albright syndrome (more often broad bands or block-like) • Chimerism (more often block-like or ill-defined pattern)
Acquired/often later onset
• Linear lichen planus, lichen planus pigmentosus, erythema dyschromicum perstans, or fixed drug eruption • Linear atrophoderma of Moulin (see Fig. 67.17), possibly linear morphea • Postinflammatory hyperpigmentation due to Blaschkitis • Linear biphasic cutaneous amyloidosis‡
Does *not* follow the lines of Blaschko
• Pigmentary demarcation lines (see Figs. 67.11 & 67.12, Table 67.6) • Linea nigra (see Fig. 27.11A) • Phytophotodermatitis (see Fig. 67.13) • Sock- or mitten-line hyperpigmentation • Flagellate hyperpigmentation – e.g. from bleomycin (see Fig. 67.14), shiitake dermatitis, dermatomyositis, persistent plaques of Still disease • Serpentine supravenous hyperpigmentation, e.g. from phlebitis, intravenous drug use, systemic sclerosis, chemotherapeutic agents (e.g. 5-fluorouracil, docetaxel) • Additional causes of linear postinflammatory hyperpigmentation – excoriations, trauma/abuse, burns, allergic contact dermatitis (especially to plants), koebnerized lesions (e.g. psoriasis, lichen planus), coining
*Pigmentary mosaicism can also present with hyperpigmentation in a block-like pattern, referred to as segmental pigmentation disorder (see text). †Linear findings are found primarily in female patients due to functional mosaicism (via lyonization) in these X-linked disorders; occasionally in male patients with somatic mosaicism or Klinefelter syndrome. ‡Single case.

Table 67.7 Disorders with linear hyperpigmentation.

FLAGELLATE PIGMENTATION FROM BLEOMYCIN

Synonym: ■ Scratch dermatitis

Key features

- Occurs in 10%–20% of patients treated with systemic bleomycin
- Linear hyperpigmented streaks are most often seen on the chest and back
- Reversible once the drug is discontinued
- Additional findings may include circumscribed hyperpigmentation of the skin overlying joints, transverse melanonychia, and sclerodermoid changes

Introduction

Bleomycin is a cytotoxic antibiotic used to treat malignancies such as Hodgkin disease and testicular carcinoma. It is also occasionally used intralesionally for treatment of warts or sclerotherapy of vascular malformations. Flagellate or "streaked" hyperpigmentation due to bleomycin was first recognized in 1970[20].



Fig. 67.13 Linear hyperpigmentation due to phytophotodermatitis. Hyperpigmented streaks developed on the arms of this mother and her toddler son following contact with citrus juice on a sunny day.

Epidemiology

Flagellate hyperpigmentation is a fairly common side effect, occurring in 10%–20% of patients treated with systemic bleomycin and occasionally in those who receive intralesional bleomycin. Due to its potential pulmonary toxicity, other agents (e.g. brentuximab, immune checkpoint inhibitors) are increasingly being employed as substitutes for bleomycin in the treatment of Hodgkin lymphoma.

Pathogenesis

The pigmentation appears to be dose-dependent, but the pathogenesis is poorly understood. The pigmentation may represent a form of PIH, and preceding flagellate erythema is observed in a subset of patients. The configuration of the lesions is suggestive of a relationship to scratching. However, attempts to reproduce the lesions by scratching the skin of patients receiving bleomycin have often been unsuccessful, and some patients deny pruritus or previous scratching[21]. Other hypotheses include a bleomycin-induced local increase in melanogenesis or alteration of "pigment maturation"[20].

Clinical Features

Bleomycin-associated pigmentation can be circumscribed, diffuse, or flagellate. Circumscribed lesions are typically found over joints or in other pressure points, but hyperpigmentation can also be localized to the palmar creases, striae, or sites of adhesive electrode pads. Flagellate pigmentation usually occurs after cumulative doses of 100–300 mg; however, it has been reported after doses as low as 15 to 30 mg, including following intralesional injections of warts or vascular malformations[20,21]. Flagellate pigmentation appears from 1 day to 9 weeks after administration of the drug. Some patients have pruritus (ranging from mild to severe) or linear urticarial lesions preceding the pigmented streaks, but others have neither associated symptoms nor antecedent lesions. The linear bands or streaks are brown in color and are most commonly seen on the chest and back (Fig. 67.14).

Additional cutaneous side effects of bleomycin include painful nodules on the fingers, verrucous plaques on the knees and elbows, sclerodermoid changes, and digital gangrene due to Raynaud phenomenon. Nail changes can include melanonychia (typically transverse) as well as Beau's lines, onychomadesis, and onycholysis.

Pathology

Varying histologic findings have been reported in bleomycin-induced flagellate hyperpigmentation, from basal layer hypermelanosis to



Fig. 67.14 Flagellate pigmentation. This young man had received bleomycin as a treatment for his lymphoma. Note the linear excoriations. *Courtesy David E. Cohen, MD MPH.*

spongiosis confined to the basal layer in association with a perivascular lymphohistiocytic infiltrate admixed with melanophages. By electron microscopy, an increased number and size of melanosomes within the basal keratinocytes may be seen; the melanocytes sometimes contain enlarged mitochondria[22].

Differential Diagnosis

Linear forms of PIH should be considered in the differential diagnosis (see Table 67.7). However, a history of systemic bleomycin administration coupled with the characteristic clinical picture usually points to the correct diagnosis. Shiitake dermatitis (see below) can also present as flagellate lesions, but a history of ingestion of or occupational exposure to raw shiitake mushrooms allows a distinction to be made, as does the presence of a prominent papular component. Flagellate erythema can occur in patients with dermatomyositis, and fixed reddish-brown plaques and hyperpigmented streaks in irregular linear arrays have been observed in patients with Still disease (juvenile or adult-onset); histologically, these eruptions are characterized by an interface dermatitis (in dermatomyositis) and necrotic keratinocytes in the upper epidermis plus a dermal neutrophilic infiltrate (in Still disease).

Treatment

While there is no specific therapy, recognition that bleomycin is the culprit is important as these patients are usually receiving multiple medications. Pruritus can be treated with topical corticosteroids and oral antihistamines. The pigmentation usually fades over 3 to 4 months, once the course of chemotherapy is complete and the bleomycin is discontinued.

SHIITAKE DERMATITIS (FLAGELLATE MUSHROOM DERMATITIS)

Synonyms: ■ Shiitake mushroom dermatitis ■ Lentinan dermatitis ■ Shiitake-induced toxicoderma

Key features

- Occurs after eating large amounts of raw or partially cooked shiitake mushrooms
- Flagellate streaks initially composed of erythematous papules or petechiae develop on the face, trunk, and extremities

Introduction

Shiitake dermatitis occurs in individuals who have ingested raw or undercooked shiitake mushrooms (*Lentinula edodes*)[23,24]. It presents with linear streaks of erythematous papules or petechiae, which occasionally evolve to flagellate pigmentation similar to that induced by bleomycin[23]. Of note, occupational skin and respiratory conditions can develop in workers who cultivate shiitake mushrooms, with manifestations including protein contact dermatitis and hypersensitivity pneumonitis ("mushroom worker's disease").

History and Epidemiology

Toxicoderma caused by shiitake mushroom ingestion was first described in the Japanese literature in 1977. Since then, several hundred cases of "shiitake dermatitis" have been reported, initially mostly from Japan and Europe but nowadays globally due to the widespread popularity of East Asian cuisines. Similar eruptions due to ingestion of wood ear (*Auricularia auricula-judae*) or porcini (*Boletus* spp.) mushrooms have also been described[25].

Pathogenesis

Lentinan, a thermolabile toxin in shiitake mushrooms, is probably responsible for this dermatosis. Prick and patch tests using shiitake mushroom extract are typically negative in patients who have ingestion-related dermatitis, and oral rechallenge may be negative as well. A phototoxic mechanism has also been proposed[23].

Clinical Features

In shiitake mushroom dermatitis, pruritic erythematous papules, vesicles, and edema develop on the face, scalp, trunk, and extremities 1–2 days after mushroom ingestion. Scratching leads to long, flagellate streaks composed of erythematous papules and/or petechiae on the extremities and the trunk, with sparing of the difficult-to-reach mid upper back. This can be followed by a linear pattern of either discoloration due to hemosiderin or PIH. Diffuse erythema and edema in photo-exposed areas have been observed in half of Japanese patients with shiitake dermatitis, and fever and malaise are occasional associated findings[23].

Pathology

Spongiosis and necrotic keratinocytes are seen within the epidermis in addition to a lymphocytic dermal infiltrate, which is admixed with melanophages in cases with hyperpigmentation[23].

Treatment

The acute dermatitis can be treated with topical corticosteroids and oral antihistamines. Resolution occurs within 1 to 8 weeks if the mushrooms are avoided. Thoroughly cooking shiitake mushrooms prevents the disorder.

HYPERPIGMENTATION ALONG THE LINES OF BLASCHKO

The lines of Blaschko are characterized by a V-shape on the posterior midline, an S-shape on the abdomen, and spirals on the posterior scalp[26,27] (see Ch. 62). Dermatoses that follow the lines of Blaschko result from mosaicism.

Linear and Whorled Nevoid Hypermelanosis

Synonyms: ■ Linear nevoid hyperpigmentation ■ Reticulate and zosteriform hyperpigmentation ■ Progressive cribriform and zosteriform hyperpigmentation

Key features

- Hyperpigmentation in whorls and streaks following the lines of Blaschko
- Usually becomes apparent within the first year of life
- Associated systemic findings occur in a minority of affected individuals
- Increased melanin within the epidermis and few melanophages

Introduction

Linear and whorled nevoid hypermelanosis (LWNH), first described in the 1970s, is characterized by swirls and streaks of macular hyperpigmentation along the lines of Blaschko[28]. Occasionally, there are associated extracutaneous abnormalities.

Epidemiology

LWNH is a sporadic disorder with no sex preference. It is viewed as an uncommon condition but is probably under-recognized.

Pathogenesis

LWNH is a genetically heterogeneous, mosaic skin condition characterized by a clone of skin cells with increased pigment production[29]. A variety of underlying mosaic chromosomal anomalies have been reported. Mosaicism for a gain-of-function mutation in the KIT ligand gene (*KITLG*) was reported in a patient with extensive LWNH, thus representing a mosaic presentation of familial progressive hyperpigmentation.

Clinical features

Swirls and streaks of brown pigmentation usually appear early during the first year of life (Fig. 67.15). The full extent of skin involvement is typically apparent by the time the child is 2–3 years of age[28]. The linear hyperpigmentation tends to persist indefinitely. Occasionally, patients with "pigmentary mosaicism" will develop both hypo- and hyperpigmented streaks.

Approximately 10%–25% of patients with LWNH who present to a pediatric dermatologist have extracutaneous findings, which typically become apparent during infancy and may be neurologic, musculoskeletal, or (less often) cardiac in nature[29]. However, the exact incidence of extracutaneous abnormalities in LWNH is unknown and is likely lower in the general pediatric population.

Pathology

LWNH is characterized by increased melanin within basal keratinocytes and in some cases a slight increase in the density of melanocytes. There are a few dermal melanophages.

Differential diagnosis

The differential diagnosis includes other disorders characterized by hyperpigmentation along the lines of Blaschko (see Table 67.7; Figs. 67.16 & 67.17). The hyperpigmented stage (stage 3) of incontinentia pigmenti (IP) is distinguished by its grayish-brown color, a predominance of melanophages rather than epidermal pigment (Fig. 67.18), fading over time, and in most patients a history of previous inflammatory vesicular and verrucous stages (stages 1 and 2, respectively). Some epidermal nevi initially have minimal or no palpable component,



Fig. 67.15 Linear and whorled nevoid hypermelanosis on the trunk. This young Black girl had developmental delay. Note the distribution along the lines of Blaschko. *Courtesy Julie V. Schaffer, MD.*

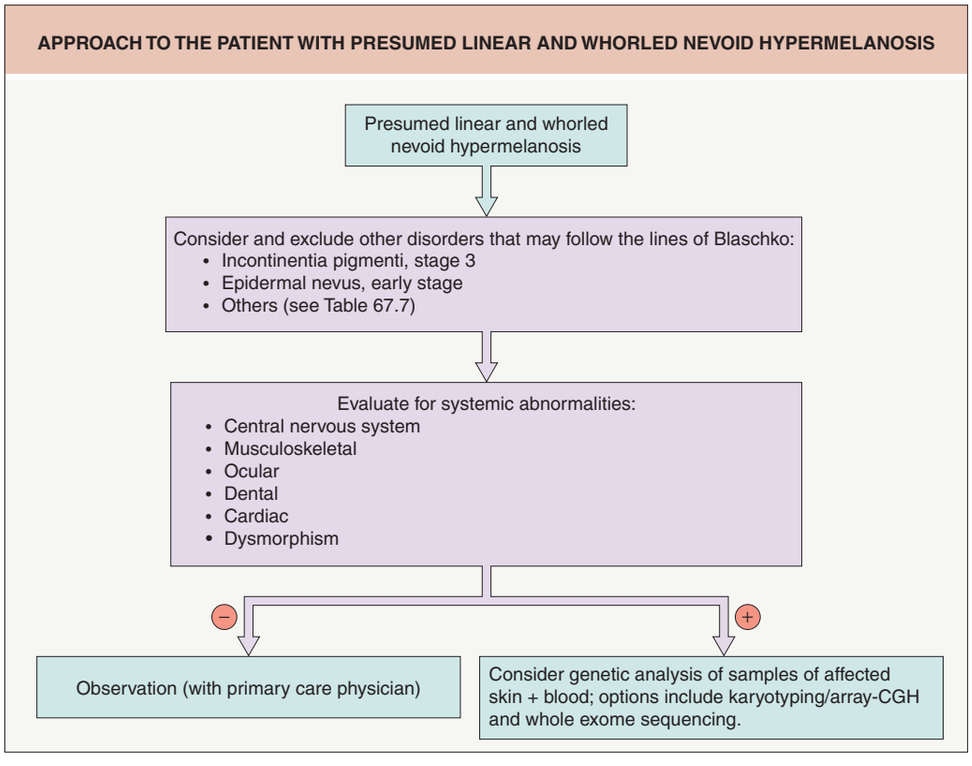


Fig. 67.16 Approach to the patient with presumed linear and whorled nevoid hypermelanosis. In general, the initial evaluation is clinical, with additional studies as indicated based on abnormalities that are evident. Karyotyping from a skin sample requires a fresh biopsy for cell culture; this is routinely done for fibroblasts, with keratinocyte or melanocyte cultures performed in specialized labs. Other tests use extracted DNA, with higher yield from a fresh biopsy than formalin-fixed paraffin-embedded tissue. CGH, comparative genomic hybridization.

but they often eventually develop some elevation. Of note, a mother and child previously reported as an example of "familial LWNH" (with histologic findings of increased epidermal melanin but no pigment incontinence in affected skin) were subsequently found to have hypohidrotic ectodermal dysplasia with immunodeficiency due to a hypomorphic *IKBKG* (*NEMO*) mutation[30].

Treatment

There is currently no effective treatment, although camouflage cosmetics may be helpful.

Incontinentia Pigmenti

A full discussion of IP can be found in Chapter 62. This X-linked dominant multisystem disorder is characterized by skin lesions distributed along the lines of Blaschko, including vesicles (stage 1), verrucous lesions (stage 2), hyperpigmentation (stage 3) and, eventually, hypopigmentation (stage 4). The third stage usually presents within the first year of life and is characterized by gray to gray–brown streaks and whorls along the lines of Blaschko (Fig. 67.19). The trunk is a common area of involvement. The pigmentation fades gradually during late childhood to adolescence, often persisting primarily in intertriginous sites. IP is due to mutations in the *IKBKG* (*NEMO*) gene. The gradual fading of stage 3 lesions reflects increased apoptosis within the affected streaks, followed by replacement with normal skin.



Fig. 67.17 Linear hyperpigmentation due to atrophoderma of Moulin. Note the subtle depression of the lesions. *Courtesy Antonio Torrelo, MD.*

RETICULATED HYPERPIGMENTATION

Disorders characterized by true reticulated macular hyperpigmentation are rare. Initial evaluation should exclude other more common entities such as confluent and reticulated papillomatosis of Gougerot and Carteaud (see Table 67.1 and Ch. 109), where the lesions are elevated and favor the neck and upper trunk (Fig. 67.20), and the hyperpigmentation of erythema ab igne, which has a widely spaced net-like pattern corresponding to the arrangement of the cutaneous venous plexus (see Ch. 88). A similar violaceous to brown-colored net-like pattern can also be seen on the lower extremities of patients with livedo reticularis. Reticulated hyperpigmentation is an occasional feature of other skin disorders, such as its occurrence on the anterolateral neck in patients with atopic dermatitis ("atopic dirty neck") and in association with epidermolysis bullosa herpetiformis.

When a true reticulated pigmentary disorder exists, the family history should be reviewed and the patient carefully examined for associated abnormalities. The following section discusses prurigo pigmentosa and six genodermatoses associated with reticulated hyperpigmentation. Additional entities that feature reticulated hyperpigmentation are listed in Table 67.8.

PRURIGO PIGMENTOSA

First described by Nagashima in 1971[31], this disorder is characterized by a markedly pruritic eruption of erythematous papules and papulovesicles on the back, neck, and chest (Fig. 67.21A). Crops of inflammatory lesions develop rapidly and then involute within a week, leaving macular reticulated hyperpigmentation (Fig. 67.21B). Recurrences tend to occur at the same site, and lesions in multiple stages are often



Fig. 67.19 Stage 3 incontinentia pigmenti in a 2-year-old child. Note the characteristic gray–brown color and the distribution along the lines of Blaschko.

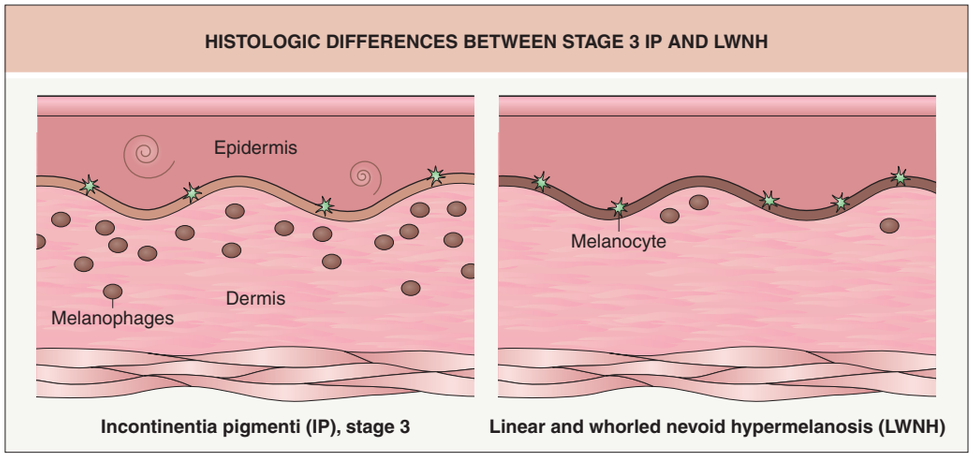


Fig. 67.18 Histologic differences between stage 3 incontinentia pigmenti (IP) and linear and whorled nevoid hypermelanosis (LWNH).



Fig. 67.20 Confluent and reticulated papillomatosis. **A** On the neck and back of a teenage girl. **B** On the chest of an older woman. *A, Courtesy Seth Orlow, MD PhD.*

DISORDERS CHARACTERIZED BY RETICULATED PIGMENTATION	
Disorder	**Key features**
Confluent and reticulated papillomatosis	See Table 67.1 and Fig. 67.20
Erythema ab igne	Widely spaced net that corresponds to vascular pattern; due to heat injury (see Ch. 88)
Atopic dirty neck	Anterolateral neck
Prurigo pigmentosa	Favors young Japanese women; may be associated with ketosis, e.g. due to a ketogenic diet or bariatric surgery; favors the back, neck, and chest; recurrent crops of pruritic papulovesicles that resolve with a reticulated pattern of hyperpigmentation (Fig. 67.21A,B)
Dyskeratosis congenita*	XLR > AD and AR forms (see Table 67.9 and Fig. 67.23); pterygium/nail dystrophy, leukoplakia, pancytopenia; increased risk of mucosal squamous cell carcinoma and leukemia
Naegeli–Franceschetti–Jadassohn syndrome	AD due to *KRT14* mutations; fading reticulated hyperpigmentation, dental anomalies, hypohidrosis, palmoplantar keratoderma, hypoplastic dermatoglyphics, nail dystrophy
Dermatopathia pigmentosa reticularis	AD due to *KRT14* mutations; persistent reticulated hyperpigmentation (see Fig. 67.24), alopecia, nail dystrophy; palmoplantar keratoderma and hypoplastic dermatoglyphics in some patients
X-linked reticulate pigmentary disorder	XLR due to *POLA1* mutations; generalized reticulated pigmentation in male patients (see Fig. 67.25); neonatal colitis, recurrent pneumonia, hypohidrosis, photophobia; amyloid deposits in adults
Dowling–Degos disease (DDD)	AD due to mutations in *KRT5*, *POFUT1*, and *POGLUT1* genes; reticulated hyperpigmentation favoring major flexures (see Fig. 67.26); may be composed of or admixed with discrete hyperpigmented macules and papules; variant associated with hidradenitis suppurativa due to *PSENEN* mutations
Galli–Galli disease	Acantholytic variant of DDD
Haber syndrome	Rosacea-like facial eruption plus the clinical features of DDD
Pigmentatio reticularis faciei et colli	Possible variant of DDD; hyperpigmentation of the face and neck plus multiple epidermoid cysts
Reticulate acropigmentation of Kitamura	AD due to *ADAM10* mutations; atrophic acral lentigo-like lesions, palmoplantar and dorsal phalangeal pitting
Epidermolysis bullosa simplex (EBS) with mottled pigmentation* and generalized EBS	AD due to *KRT5/14* mutations, with a specific P25L *KRT5* mutation usually underlying EBS with mottled pigmentation (see Ch. 32)
Mendes da Costa disease*	Traumatic bullae and hyperpigmentation, usually acral; dwarfism, atrichia
Cantu syndrome	Reticulated pigmentation of face, forearms, and feet; palmoplantar keratoderma
Reticulate genital hyperpigmentation associated with localized vitiligo*	Congenital or acquired reticulate hyperpigmentation of the genitalia, followed by the development of vitiligo in the same region
Mitochondrial disorders	Sun-exposed areas (e.g. cheeks, dorsal aspects of the forearms and hands); additional cutaneous findings include hypertrichosis, hair shaft abnormalities, and acrocyanosis (see Ch. 63)
Postinflammatory	Lichenoid dermatoses (e.g. lichen planus pigmentosus, graft-versus-host disease); contact dermatitis (e.g. due to benzoyl peroxide); chikungunya fever
Drug-induced	Diltiazem (sun-exposed areas); chemotherapeutic agents such as 5-fluorouracil, cyclophosphamide, paclitaxel, idarubicin, and cytarabine (see Table 67.5)

*Also dyschromatosis.

Table 67.8 Disorders characterized by reticulated pigmentation. Entities in the rows with a darker shade are covered in this chapter. Fanconi anemia is discussed in Table 67.10. *ADAM10; a d*isintegrin and *m*etalloproteinase *10*; AD, autosomal dominant; AR, autosomal recessive; *KRT5/14*, keratin 5 or 14; *POFUT1*, protein O-fucosyltransferase 1; *POGLUT1*, protein O-glucosyltransferase 1; *POLA1*, DNA polymerase-α1, catalytic subunit; *PSENEN*, presenilin enhancer protein 2; XLR, X-linked recessive.



Fig. 67.21 Prurigo pigmentosa. A Eroded and crusted erythematous papules and plaques. A few patches of hyperpigmentation are seen inferiorly. **B** Erythematous crusted papules admixed with reticulated macular hyperpigmentation. **C** Histopathologic features include intraepidermal vesiculation, necrotic keratinocytes, and a patchy lichenoid infiltrate. *A, Courtesy Luis Requena, MD; B, C, Courtesy Lorenzo Cerroni, MD.*

evident. The condition favors young adults, with a female : male ratio of ≥2 : 1; the majority of reported patients have been from East Asia. Prurigo pigmentosa triggered by ketosis due to bariatric surgery, a ketogenic diet, or type 1 diabetes mellitus has been reported in patients with a variety of ethnic backgrounds[32].

Three histopathologic stages have been identified: (1) neutrophilic exocytosis, spongiosis, papillary dermal edema, and a superficial perivascular infiltrate of neutrophils; (2) intra-/subepidermal vesiculation, necrotic keratinocytes, and a patchy lichenoid infiltrate of predominantly lymphocytes admixed with eosinophils (Fig. 67.21C); and (3) variable parakeratosis, acanthosis, and hyperpigmentation of the epidermis as well as dermal melanophages[33]. Treatment with oral minocycline, doxycycline, or dapsone is often effective for the inflammatory component of prurigo pigmentosa. The condition does not respond to corticosteroids (topical or systemic) or antihistamines. Prurigo pigmentosa associated with ketosis may improve with reintroduction of carbohydrates[32].

DYSKERATOSIS CONGENITA

Synonym: ■ Zinsser–Engman–Cole syndrome

Key features

- Genetically heterogeneous disorder due to defective telomere maintenance, with X-linked recessive inheritance in the most common form
- Triad of reticulated hyperpigmentation, nail dystrophy (e.g. pterygium), and leukoplakia
- Bone marrow failure resulting in thrombocytopenia, anemia, or pancytopenia
- Continuous lacrimation (epiphora) due to lacrimal duct atresia, pulmonary fibrosis, and liver cirrhosis may develop
- Predisposition to malignancy, especially mucosal squamous cell carcinoma (e.g. mouth, anus)

Introduction

First described in 1906 by Zinsser, dyskeratosis congenita (DKC) is a genetically heterogeneous disorder caused by defective telomere maintenance. DKC is characterized by progressive bone marrow failure and the mucocutaneous triad of reticulated hyperpigmentation, nail dystrophy, and leukoplakia. In addition, affected individuals have an increased risk of developing pulmonary fibrosis, liver cirrhosis, and malignancies including squamous cell carcinoma (especially mucosal) and acute myeloid leukemia[34].

Epidemiology

The most common form of DKC has an X-linked recessive pattern of inheritance, but autosomal dominant and autosomal recessive forms also exist (Table 67.9). The overall male : female ratio is ~3 : 1[34].

Pathogenesis

DKC is caused by defective telomere maintenance, which leads to the characteristic feature of markedly shortened telomeres[35]. Telomeres are repetitive nucleotide sequences that protect the ends of eukaryotic chromosomes. The enzyme telomerase prevents the progressive shortening of chromosomes that would otherwise occur with DNA replication (Fig. 67.22). Tissues with high replication rates, such as the bone marrow and skin, are particularly vulnerable when telomerase is not functioning properly. When telomeres reach a critically short length, cell cycle arrest occurs and the cells undergo either senescence or apoptosis. However, telomerase dysfunction also leads to chromosome instability, which can result in tumorigenesis.

In 1998, mutations in *DKC1*, which encodes the dyskerin protein that interacts with telomerase, were found to underlie the X-linked recessive form of DKC[36]. Since then, 11 additional genes have been implicated in both autosomal dominant and recessive forms of DKC that have variable clinical manifestations. These genes encode the telomerase RNA component (TERC) and reverse transcriptase (TERT) as well as other factors with roles in telomerase function and additional aspects of telomere protection (see Table 67.9 & Fig. 67.22). Advances in understanding of the pathogenesis of DKC and other telomere biology disorders may provide insights into telomere maintenance in general processes such as aging and cancer[35].

GENETIC ETIOLOGIES OF DYSKERATOSIS CONGENITA (DKC)				
Gene	**Gene product (see Fig. 67.22)**	**Mode of inheritance**	**Proportion of DKC patients (%)**	**Comments**
DKC1	Dyskerin (in telomerase complex)	XR*	20–30	Classic DKC, often relatively severe, in male patients; clinical manifestations in female heterozygotes are extremely rare
TINF2	Telomere repeat binding factor 1 (TERF1)-interacting nuclear factor 2 (in shelterin telomere protection complex)	AD*	10–20	Often severe with bone marrow failure in childhood; mutations in this gene also cause the Revesz syndrome variant (see text)
TERC	Telomerase RNA component	AD	5–10	Often less severe
TERT	Telomerase reverse transcriptase	AD, AR*	~5	Later onset and less severe in AD form
RTEL1	Regulator of telomere elongation helicase 1	AD, AR*	~5	Later onset in AD form
CTC1	Conserved telomere maintenance component 1 (in telomere capping complex)	AR	1–3	
WRAP53 (TCAB1)	Telomerase Cajal body protein 1 (regulates telomerase transport)	AR	<1	
NHP2, NOP10	NHP2 and NOP10 ribonucleoprotein homologs (in telomerase complex)	AR	<1	
PARN	Poly(A)-specific ribonuclease (regulates TERC interaction with telomeres)	AD, AR*	<1	
ACD (TINT1)	TINF2-interacting protein 1 (in shelterin telomere protection complex)	AD, AR*	<1	Later onset in AD form
RPA1	Replication protein A1 (functions in telomere maintenance)	AD	<1	

*Also reported to present as the more severe *Hoyeraal–Hreidarsson syndrome* variant (see text).

Table 67.9 Genetic etiologies of dyskeratosis congenita (DKC). ACD, adrenocortical dysplasia homolog; AD, autosomal dominant; AR, autosomal recessive; WRAP53, WD repeat-containing antisense to TP53; XR, X-linked recessive.

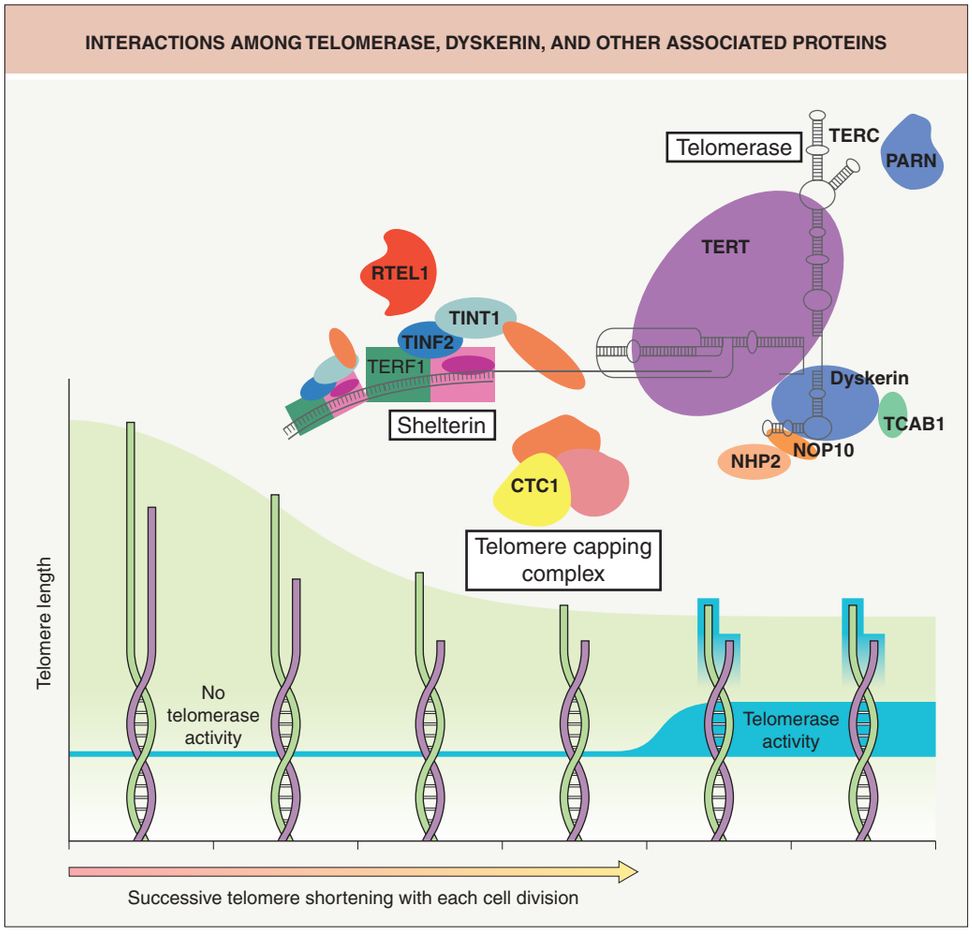


Fig. 67.22 Interactions among telomerase, dyskerin, and other telomere-associated proteins implicated in dyskeratosis congenita. Telomerase, the enzyme that protects against progressive shortening of the chromosomes with successive cell divisions, is composed of two subunits: an RNA component (**TERC**) and reverse transcriptase (**TERT**). **Dyskerin** interacts with telomerase and plays a role in its proper function. The **NHP2** and **NOP10** ribonucleoprotein homologs are also in the telomerase complex, while telomerase Cajal body protein-1 (**TCAB1**) controls telomerase trafficking. Poly(A)-specific ribonuclease (**PARN**) regulates TERC's interaction with telomeres. TERF1-interacting nuclear factor 2 (**TINF2**) and TINF2-interacting protein 1 (**TINT1**) are components of the shelterin complex that protects the ends of telomeres. **RTEL1** is a DNA helicase that regulates telomere elongation, and conserved telomere maintenance component 1 (**CTC1**) functions in a telomere capping complex. TERF1, telomere repeat binding factor 1.

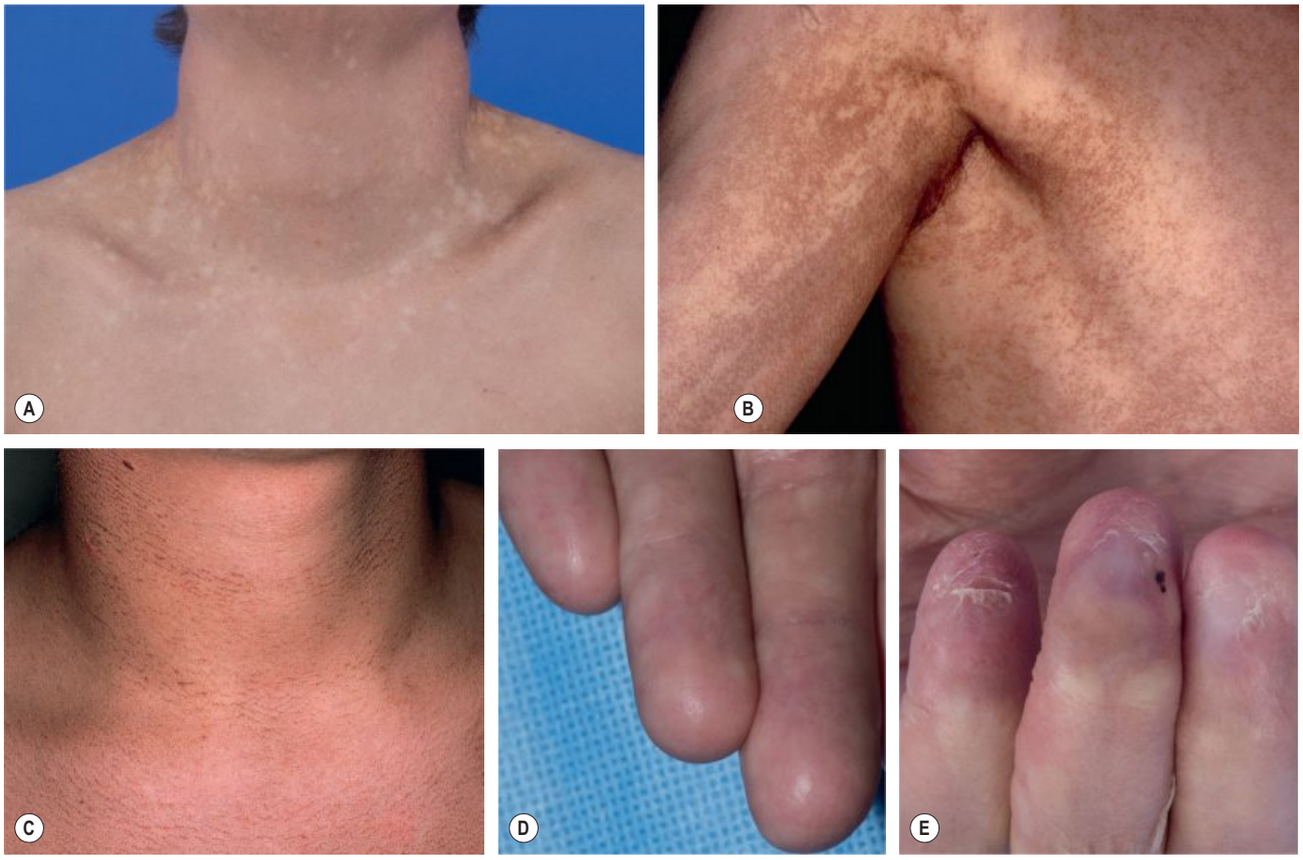


Fig. 67.23 Dyskeratosis congenita. A Diffuse and reticulated hyperpigmentation of the neck and upper chest as well as multiple hypopigmented macules. **B** More pronounced reticulated and confluent hyperpigmentation on the shoulder and axilla. **C** Reticulated hyperpigmentation on the chest and neck of a teenage boy. **D** Mild scaling and erythema of fingers as well as absent dermatoglyphics. **E** Micronychia and anonychia. *A, D, E, Courtesy Edward Cowen, MD; B, Courtesy Eugene Mirrer, MD; C, Courtesy Seth Orlow, MD PhD.*

Clinical Features

A lacy reticulated pattern of hyperpigmentation generally develops during the first decade of life. This occurs primarily on the neck, upper chest, and upper arms and is sometimes admixed with macules of hypopigmentation (Fig. 67.23A–C). Telangiectasias and epidermal atrophy may also be seen, i.e. poikiloderma. Additional cutaneous features include wrinkled skin on the extremities, dorsal aspects of the hands, and genitalia; palmoplantar hyperhidrosis and hyperkeratosis; loss of dermatoglyphics (Fig. 67.23D); frictional bullae; acrocyanosis; and premature graying of the hair.

Nail involvement is present in the vast majority of patients, typically appearing during early childhood. Initial changes include longitudinal ridging and splitting, followed by pterygia formation and occasionally complete nail loss (Fig. 67.23E). Leukoplakia occurs in most patients, usually manifesting during early adolescence. White plaques on the oral mucosa are observed most commonly, with a predilection for the lateral portions of the tongue. Involvement of the urethra, vagina, and anus may also be seen. The teeth may be malformed, missing, or have aberrant spacing or extensive caries. Epiphora (continuous lacrimation) due to lacrimal duct atresia is common.

Bone marrow failure occurs in 50%–90% of patients and is a major cause of mortality. It presents during the second or third decade with anemia, thrombocytopenia, or pancytopenia. Malignancies tend to develop during the third or fourth decade, most notably squamous cell carcinomas of the mouth, anus, cervix, vagina, esophagus, and skin. There is also an increased risk of myelodysplastic syndrome, acute myeloid leukemia, and gastrointestinal carcinomas.

Other potential systemic manifestations include pulmonary fibrosis, liver cirrhosis, developmental delay, short stature, avascular necrosis of the femoral head, esophageal or urethral stenosis, cryptorchidism, male hypogonadism, and immunologic dysfunction leading to opportunistic infections. Of note, increased severity in successive generations (anticipation) due to progressive telomere shortening has been observed in autosomal dominant forms of DKC. *Hoyeraal–Hreidarsson syndrome* is a severe variant of DKC characterized by early bone marrow failure, immunodeficiency, cerebellar hypoplasia, microcephaly, enteropathy, and growth retardation (intrauterine and postnatal). Caused by mutations in several DKC genes (see Table 67.9), it typically leads to death in early childhood. *Revesz syndrome* is another related disorder that features progressive neurologic deterioration, intracranial calcifications, and exudative retinopathy together with the manifestations of DKC; it is caused by heterozygous mutations in *TINF2*.

Pathology

Histologically, the features of poikiloderma vasculare atrophicans are seen, with telangiectasias and epidermal thinning as well as foci of increased pigment within the basal layer. In the early stage, hydropic degeneration of basilar keratinocytes and a band-like inflammatory infiltrate in the upper dermis may be evident. In the late stage, the epidermis is markedly thinned and flattened and melanophages are present in the upper dermis.

Short telomere length can be detected in leukocytes from patients with DKC by flow-fluorescence *in situ* hybridization (FISH)[37].

Differential Diagnosis

Fanconi anemia is also associated with pigmentary abnormalities, pancytopenia, and an increased risk of neoplasia (e.g. leukemia); this disorder is compared to DKC in Table 67.10. Naegeli–Franceschetti–Jadassohn (NFJ) syndrome and dermatopathia pigmentosa reticularis (DPR) differ by their lack of leukoplakia and bone marrow involvement (see below). Patients with chronic GVHD may develop poikilodermatous skin changes and lacy white patches of the oral mucosa. However, GVHD is usually easily distinguished by the history of a hematopoietic stem cell transplant (or, rarely, a solid organ transplant). Additional entities associated with poikiloderma are discussed in Chapter 63.

COMPARISON OF DYSKERATOSIS CONGENITA AND FANCONI ANEMIA		
	Dyskeratosis congenita	**Fanconi anemia (FA)**
Pigmentation	Lacy reticulated hyperpigmentation favoring the neck and upper chest, with onset during the first decade of life Sometimes admixed with hypopigmented macules Poikiloderma may be present (telangiectasias and epidermal atrophy)	More generalized, diffuse hyperpigmentation; less often reticulated Sometimes admixed with hypopigmented macules Multiple café-au-lait macules may be present
Hematologic abnormalities	Anemia, leukopenia, thrombocytopenia, pancytopenia Onset typically in 2nd decade	Anemia, leukopenia, thrombocytopenia, pancytopenia Onset typically in 1st decade
Associated malignancies	Increased risk, in particular SCC (esp. mucosal), acute myeloid leukemia	Increased risk, in particular SCC (esp. of head & neck), acute myeloid leukemia, hepatocellular cancer; increased risk of breast and pancreatic cancer with heterozygous mutations in some FA genes*
Additional clinical findings	Nail abnormalities (e.g. pterygium), leukoplakia, hyperhidrosis, palmoplantar hyperkeratosis, frictional bullae, acrocyanosis, epiphora (continuous lacrimation)	Radial ray bony defects involving the thumb, short stature, renal and cardiac malformations, hypogonadism and other endocrinopathies
Exposure of lymphocytes to mitomycin C or diepoxybutane	No chromosomal breakage; shortened telomeres via flow-fluorescence in situ hybridization (FISH)	Enhanced chromosomal breakage and rearrangement
Inheritance	12 associated genes identified (see Table 67.9); X-linked recessive > autosomal dominant or autosomal recessive	Autosomal recessive with at least 11 complementation groups; rarely X-linked recessive (1 complementation group; ~1% of patients)

*For example, BRCA2 (FAD1).

Table 67.10 Comparison of dyskeratosis congenita and Fanconi anemia. SCC, squamous cell carcinoma.

Treatment

Management of DKC patients requires multidisciplinary care. Longitudinal surveillance of all mucosal surfaces is indicated to monitor for the development of squamous cell carcinoma within areas of leukoplakia. Sun and cigarette avoidance are advisable. Bone marrow failure can be treated with supportive transfusions of blood products and the use of androgens (e.g. oxymetholone, danazol), erythropoietin, granulocyte colony-stimulating factor, and eltrombopag or romiplostim. Although hematopoietic stem cell transplantation (HSCT) can potentially cure bone marrow failure and leukemia in patients with DKC, the three-year overall survival rate following HSCT is ~65%.

NAEGELI–FRANCESCHETTI–JADASSOHN SYNDROME

Key features

- Autosomal dominant disorder due to heterozygous mutations in the keratin 14 gene
- Reticulated hyperpigmentation beginning by 2 years of age and often fading during adolescence
- Ectodermal dysplasia with hypohidrosis and heat intolerance as well as dental anomalies, including early loss of teeth
- Palmoplantar keratoderma, with absent or hypoplastic dermatoglyphics

Introduction

NFJ syndrome is a rare autosomal dominant genodermatosis that is characterized by reticulated hyperpigmentation as well as ectodermal dysplasia (primarily dental anomalies and hypohidrosis) and hypoplastic dermatoglyphics.

History

First described by Naegeli in 1927, NFJ was initially confused with incontinentia pigmenti. In 1954, Franceschetti and Jadassohn re-examined the original family and noted the autosomal dominant pattern of inheritance.

Epidemiology

Affected families have been primarily of Swiss and British descent.

Pathogenesis

NFJ syndrome is caused by truncating mutations in the non-helical head domain of the keratin 14 gene (*KRT14*) that result in haploinsufficiency (see Fig. 56.5)[38]. This leads to increased susceptibility of keratinocytes to tumor necrosis factor (TNF)-induced apoptosis, which explains the hyperpigmentation secondary to pigment incontinence observed in affected individuals. It also points to a role for the N-terminal portion of keratin 14 in regulating apoptosis during morphogenesis of cutaneous appendages.

Clinical Features

Brown or gray–brown reticulated hyperpigmentation develops by the age of 2 years, without a preceding inflammatory stage. The pigmentary changes are most often observed on the abdomen and periocular and perioral regions, with variable involvement of the neck, trunk, proximal extremities, axillae, and groin. The hyperpigmentation often fades after puberty and may eventually disappear. Some infants have bullae on their feet during the newborn period. Decreased sweat gland function with lifelong heat intolerance is a problem for many patients. Other cutaneous manifestations include absent or hypoplastic dermatoglyphics, palmoplantar keratoderma (diffuse or punctate), and onychodystrophy (onycholysis, subungual hyperkeratosis, and congenital malalignment of the great toenails). Dental anomalies are common and include abnormally shaped teeth, supernumerary teeth, and yellow spotted tooth enamel. Early total loss of teeth may occur.

Pathology

Histologically, the hyperpigmented skin demonstrates pigment incontinence, i.e. melanophages in the upper dermis.

Differential Diagnosis

The lack of leukoplakia, bone marrow failure, or an increased risk of malignancies in patients with NFJ syndrome differentiates it from *DKC*. Although NFJ syndrome lacks the prominent alopecia and more persistent hyperpigmentation that characterize *DPR*, there is significant overlap between these allelic disorders. *X-linked reticulate pigmentary disorder* often presents with hypohidrosis and dental anomalies as well as reticulate hyperpigmentation, but additional systemic manifestations as well as the inheritance pattern distinguish it from NFJ. Reticulated hyperpigmentation and palmoplantar keratoderma may develop in patients with *epidermolysis bullosa simplex* due to mutations in keratin 5 or 14, but blistering is more prominent. In addition, patients with *Kindler epidermolysis bullosa* may have absent or hypoplastic

dermatoglyphics, but they develop poikiloderma rather than reticulated hyperpigmentation (see Ch. 32). Obviously, hypohidrosis, onychodystrophy, dental anomalies, and hypoplastic or absent dermatoglyphics can be seen in other forms of ectodermal dysplasia (see Ch. 63).

Treatment

Treatment is supportive. Genetic counseling should be offered to affected individuals and families.

DERMATOPATHIA PIGMENTOSA RETICULARIS

Key features

- Autosomal dominant disorder due to mutations in the keratin 14 gene
- Persistent reticulated hyperpigmentation with truncal predominance
- Non-scarring alopecia of the scalp, eyebrows, and axillae
- Onychodystrophy
- Absent dermatoglyphics and punctate keratoderma in some patients

Introduction and Pathogenesis

DPR is a rare genodermatosis that was recognized as a distinct entity in the 1970s. Like NFJ (see above), a heterozygous truncating mutation in the non-helical head domain of the keratin 14 gene has been shown to cause DPR[38].

Clinical Features

DPR presents by the second year of life with the triad of reticulated hyperpigmentation, non-scarring alopecia, and onychodystrophy[39]. The reticulated hyperpigmentation has a predilection for the trunk but also occurs on the proximal extremities, and it persists during adulthood (Fig. 67.24). The nail involvement may result in pterygia formation. Variable features include absent dermatoglyphics, hypo- or hyperhidrosis, and a punctate palmoplantar keratoderma.

Pathology

Histologically, the hyperpigmented skin demonstrates pigment incontinence, i.e. melanophages in the upper dermis.



Fig. 67.24 Dermatopathia pigmentosa reticularis. Persistent hyperpigmentation in a reticulated pattern extending from the lower abdomen to the thigh in a young man. *Courtesy Julie V. Schaffer, MD.*

Differential Diagnosis

There is clinical overlap with the NFJ syndrome (e.g. reticulated hyperpigmentation, nail dystrophy, punctate keratoderma, absent dermatoglyphics), but the latter lacks alopecia and has less persistent hyperpigmentation. Additional diagnostic considerations are as discussed above for NFJ.

X-LINKED RETICULATE PIGMENTARY DISORDER

Synonyms: ■ Partington syndrome type II ■ Familial cutaneous amyloidosis ■ X-linked reticulate pigmentary disorder with systemic manifestations

Key features

- Reticulated hyperpigmentation along the lines of Blaschko in women and in a generalized pattern in men
- Recurrent infections and multiple systemic manifestations in male patients
- Some adult patients have amyloid deposits within the dermis

Introduction and Pathogenesis

This rare genodermatosis is characterized by reticulated brown hyperpigmentation that is generalized in male patients and along the lines of Blaschko in female patients. Affected males have severe systemic complications that may lead to premature death. The disorder was first described by Partington et al. in 1981[40], and several additional families have subsequently been identified[41–43]. It is caused by mutations in *POLA1* which encodes the catalytic subunit of DNA polymerase-α, a regulator of the type I interferon response[43].

Epidemiology

Partington's original kindred had English and Scottish heritage[40]. Other reported families had Maltese, Lebanese, Spanish, and mixed Dutch, French and German ancestries[41–43].

Clinical Features

In *female* patients with this X-linked disorder, manifestations appear to be limited to the skin. At birth or within the first few weeks of life, female infants develop lacy or reticulated areas of hyperpigmentation in streaks that follow the lines of Blaschko. Although the lesions are reminiscent of stage 3 IP, there are no preceding vesicular or verrucous stages. The hypermelanosis may fade during adulthood.

In *male* patients, the reticulated hyperpigmentation is generalized (Fig. 67.25), initially developing on the inner thighs, buttocks, or cheeks between 4 months and 5 years of age. Affected boys often have systemic manifestations, including a low birth weight, neonatal colitis, failure to thrive during infancy, seizures and hemiplegia, as well as gastroesophageal reflux, urethral strictures, and inguinal hernias. Recurrent pneumonias and chronic obstructive pulmonary disease are nearly always present in male patients and can lead to premature death. Intelligence may be normal or developmentally delayed. Additional features include dental anomalies, hypohidrosis, xerosis, photophobia, corneal clouding, and skeletal changes such as delayed bone age and shortened metacarpals. Blonde unruly hair with a frontal upsweep is a frequent clinical finding; in fair-skinned patients, the hair may become silver–gray[40–42].

Pathology

Histologic features of the cutaneous hyperpigmentation are similar in male and female patients. Findings include increased epidermal melanin, pigment incontinence with dermal melanophages, and dyskeratosis[40]. Amyloid deposits in the upper dermis (keratin-positive as in macular amyloidosis) were also noted in some adults (but not children), including those from the original Canadian family[40]. As with macular amyloidosis, deposits were not found in other tissues.



Fig. 67.25 X-linked reticulate pigmentary disorder. There is reticulated hyperpigmentation of the face and neck in this 11-year-old boy, as well as blond, coarse hair. *Courtesy K. Robin Carder, MD.*

Differential Diagnosis

In boys, other entities with reticulated hyperpigmentation should be considered (see Table 67.8), particularly DKC and NFJ syndrome, especially when there are recurrent infections (DKC), hypohidrosis (NFJ syndrome), or dental anomalies (DKC and NFJ syndrome). In female carriers, the differential diagnosis includes the disorders listed in Table 67.7 that follow the lines of Blaschko.

Treatment

Improvement of autoinflammatory manifestations with JAK inhibitor therapy has been reported[44]. Genetic counseling is indicated for affected families.

DOWLING–DEGOS DISEASE

Synonyms:
- Reticular pigmented anomaly of the flexures
- Reticulated pigmented anomaly of the flexures

Key features

- Reticulated hyperpigmentation in flexural sites
- Comedo-like lesions on the back and neck
- Pitted facial scars
- Autosomal dominant with variable penetrance
- Caused by loss-of-function mutations in the gene that encodes keratin 5

Introduction

Dowling–Degos disease (DDD) is an uncommon autosomal dominant condition characterized by acquired reticular hyperpigmentation in intertriginous sites.

Epidemiology

There is no racial or sex predilection in classic DDD, and it has been reported worldwide. A founder mutation has been observed in Jewish Ashkenazi families with DDD plus hidradenitis suppurativa.



Fig. 67.26 Dowling–Degos disease. Hyperpigmented macules forming a reticulated pattern in the axilla. *Courtesy Thomas Schwarz, MD.*

Pathogenesis

Classic DDD is often caused by loss-of-function mutations in the non-helical head domain of the keratin 5 gene (*KRT5*) (see Fig. 56.5) that lead to haploinsufficiency[45]. Interestingly, a missense mutation in the same region of *KRT5* underlies epidermolysis bullosa simplex with mottled pigmentation (see Ch. 32). The head domain of keratin 5 has been found to interact with Hsc70, a chaperone involved in vesicle uncoating, and it has been postulated that keratin 5 has a role in melanosome trafficking. In addition, a form of DDD with more prominent involvement of non-flexural sites can result from heterozygous loss-of-function mutations in *POFUT1* and *POGLUT1*, which encode O-fucosyltransferase 1 and O-glucosyltransferase 1, respectively. Both of these enzymes perform post-translational modifications that regulate the Notch signaling pathway, which has roles in controlling proliferation and differentiation of melanocytes and keratinocytes as well as their interactions with one another[46]. A variant of DDD associated with hidradenitis suppurativa is caused by mutations in the presenilin enhancer protein 2 gene (*PSENEN*), which encodes a component of the γ-secretase protein complex that functions in Notch signaling[47].

Clinical Features

Onset is typically during the third to fourth decade of life. The reticulated hyperpigmentation is admixed with and sometimes composed of lentigo-like brown macules; small brown papules with variable hyperkeratosis may also develop. These findings progressively increase over time, initially appearing in the axillae (Fig. 67.26) and groin followed by the intergluteal and inframammary folds, neck, trunk, and inner aspects of the arms and thighs. Some patients report pruritus of the affected flexural areas. Hypopigmented macules, comedo-like lesions on the back or neck, pitted perioral scars, epidermoid cysts, and hidradenitis suppurativa represent additional features in some patients[48].

Pathology

Histologically, there is increased pigmentation of the basal layer and finger-like elongation of the rete ridges with thinning of the suprapapillary epithelium. This results in an "antler-like" pattern arising from the under surface of the epidermis and hair follicles. Dermal melanophages and a mild perivascular lymphohistiocytic infiltrate are also observed[49]. *Galli–Galli disease* represents a variant of DDD (also caused by *KRT5* mutations) with prominent suprabasal non-dyskeratotic acantholysis in biopsy specimens of lesional skin in addition to the usual clinical and histologic features[50].

Differential Diagnosis

Acanthosis nigricans is distinguished clinically by velvety plaques and histologically by less pronounced elongation of the rete ridges. In

addition, there is no follicular involvement. Patients with neurofibromatosis type 1 develop lentigines (oftentimes referred to as "freckles") in the axillae and groin, but this disorder is usually easy to distinguish from DDD.

The spectrum of DDD-like disorders that feature reticulate pigmentation include reticulate acropigmentation of Kitamura (see below) and Haber syndrome. Patients with *Haber syndrome* develop a photosensitive rosacea-like facial eruption during adolescence, which is followed by the appearance of keratotic papules, comedo-like lesions, pitted scars, and reticulate hyperpigmentation on the trunk and proximal extremities as well as in the axillae.

Treatment

Topical hydroquinone, tretinoin, adapalene, and corticosteroids have been used with varying success. Improvement following treatment with the erbium:YAG or Q-switched Nd:YAG plus fractional CO_2 lasers has also been reported[48].

RETICULATE ACROPIGMENTATION OF KITAMURA

Synonym: ■ Kitamura reticulate acropigmentation

Key features

- Atrophic reticulated or lentigo-like hyperpigmentation that favors the dorsal aspects of the hands and feet and appears during childhood
- Pits on the palms, soles, and dorsal phalanges
- Autosomal dominant inheritance

Introduction and Pathogenesis

Reticulate acropigmentation of Kitamura (RAK) is a rare genodermatosis characterized by atrophic hyperpigmented macules that appear during childhood and initially have an acral distribution. Two-thirds of reported patients have been Japanese, but the condition has been described in individuals with other ethnic backgrounds. Heterozygous loss-of-function mutations in the *a d*isintegrin *a*nd *m*etalloproteinase *10* gene (*ADAM10*), which encodes a zinc metalloproteinase that activates Notch signaling (see above), have been found to underlie RAK.

Clinical Features

During childhood, slightly depressed lentigo-like hyperpigmented macules develop on the dorsal aspects of the hands and feet and often assume a reticulated pattern. These macules slowly darken over time and subsequently may spread to other sites of the body during adulthood. Sunlight may aggravate the condition. Pits are found on the palms, soles, and dorsal phalangeal surfaces, and breaks in the dermatoglyphics are often evident.

Pathology

The hyperpigmented macules show epidermal atrophy and elongated rete ridges that contain an increased amount of melanin. An increased number of DOPA-positive melanocytes are seen in the basal layer of the epidermis.

Differential Diagnosis

In contrast to the more common solar lentigines, the hyperpigmented macules of RAK are slightly atrophic and develop at an earlier age. Unlike dyschromatosis symmetrica hereditaria (see below), white macules are not admixed with the brown macules.

Treatment

Treatment options are similar to those listed above for Dowling–Degos disease.

DYSCHROMATOSES

Dyschromatoses are characterized by the presence of both hypo- and hyperpigmentation (Figs. 67.27–67.29). Often, at least one component of the dyspigmentation is guttate. The two classic dyschromatoses, dyschromatosis symmetrica hereditaria and dyschromatosis universalis hereditaria, are discussed in this section. A more recently recognized entity, acquired brachial cutaneous dyschromatosis, is also described. Additional dyschromatoses are listed in Table 67.11.

DYSCHROMATOSIS SYMMETRICA HEREDITARIA

Synonyms: ■ Acropigmentation of Dohi ■ Symmetrical dyschromatosis of the extremities

Key features

- Small, irregular hypopigmented and hyperpigmented macules on the dorsal aspects of the distal extremities, especially the hands and feet
- Autosomal dominant disorder caused by mutations in *ADAR*, which encodes an RNA-specific adenosine deaminase



Fig. 67.27 Dyschromic amyloidosis cutis. An admixture of reticulated hyperpigmentation and guttate hypopigmentation are evident. *Courtesy Seth J. Orlow, MD PhD.*



Fig. 67.28 Dyschromatosis symmetrica hereditaria. An admixture of multiple hypo- and hyperpigmented macules on the hands more so than on the forearms. *Courtesy Peter Ehrnstrom, MD.*

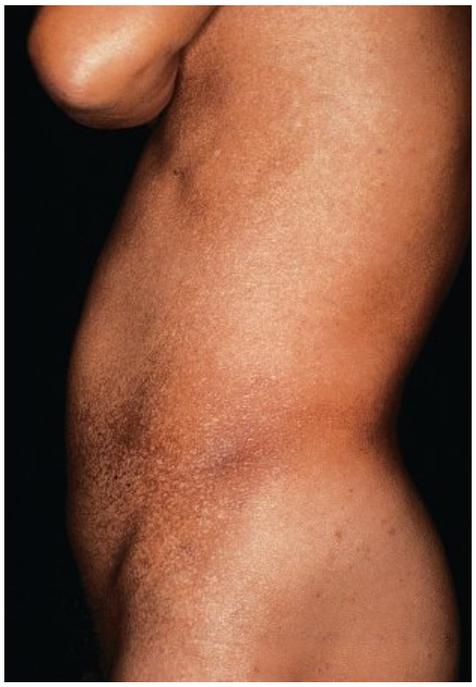


Fig. 67.29 Dyschromatosis universalis hereditaria. Both hypo- and hyperpigmentation were present in a widespread distribution. *With permission from Urabe K, Hori Y. Dyschromatosis. Semin Cutan Med Surg 1997;16:81–5.*

Introduction

Dyschromatosis symmetrica hereditaria (DSH) was first reported by Toyama in 1929. It is characterized by both hyper- and hypopigmented macules of varying size on the dorsal surfaces of the distal extremities. The vast majority of reports have come from Japan, China, and Korea, but DSH has also been described in European, Afro-Caribbean, and Indian patients[51]. The prevalence in Japan is ~1.5 per 100 000[52].

Pathogenesis

DSH has an autosomal dominant inheritance pattern with high penetrance. It is caused by heterozygous mutations in *ADAR (DSRAD)*, which encodes the RNA-specific adenosine deaminase[52–54]. Of note, biallelic *ADAR* mutations are one cause of Aicardi–Goutières syndrome (AGS), a type I interferonopathy presenting with encephalopathy and variable pernio-like skin lesions (see Table 45.7).

Clinical Features

Hyper- and hypopigmented macules arise in infancy or early childhood. The macules often increase in size and number until adolescence, when they stabilize; darkening after sun exposure may be observed. This dyschromatosis favors the distal extremities and is usually most marked on the dorsal aspects of the hands and feet (see Fig. 67.28); it spares the palms, soles, and mucous membranes. Spontaneous clearing has not been described. A few patients with dystonia and neurologic

DYSCHROMATOSES	
Disorder	**Key features**
Genetic disorders	
Dyschromatosis symmetrica hereditaria	Symmetrical dyschromatosis of distal extremities, especially dorsal aspects of hands and feet (see Fig. 67.28); palms, soles, and mucous membranes spared Usually presents by age 6 years Caused by heterozygous mutations in *ADAR*, which encodes RNA-specific adenosine deaminase Vast majority of patients are Japanese or Chinese (see text)
Dyschromatosis universalis hereditaria	Truncal or generalized hyper- and hypopigmented macules (see Fig. 67.29); can occur on palms and soles, but not mucous membranes Usually presents by age 6 years, often becoming apparent in the first year of life Subsets due to mutations in *ABCB6*, which encodes an ATP-binding cassette transporter protein, and SASH1 Most common in Japan (see text)
Xeroderma pigmentosum (XP)	Lentigines and hypopigmented macules on dorsal aspects of hands and feet, face, and other chronically sun-exposed sites (see Fig. 86.13) Actinic damage beginning in infancy and early childhood, with skin cancers often developing during the first decade of life Autosomal recessive disorder caused by defective nucleotide excision repair (complementation groups A–G) or error-free bypass (XP-variant) of UV-induced DNA damage
Dyskeratosis congenita	Reticulated hyperpigmentation can be admixed with macules of hypopigmentation; nail dystrophy and leukoplakia Predisposition to mucosal SCC and other malignancies Most common form is X-linked recessive (see Table 67.9 and text)
Epidermolysis bullosa simplex with mottled pigmentation	Acral blistering early in childhood, mottled pigmentation, punctate keratoses of the palms and soles, and dystrophic, thickened nails Typically due to a specific keratin 5 mutation (P25L; see Ch. 32)
Familial progressive hyper- and hypopigmentation (FPHH)	Generalized distribution (including face, palms, and soles) of hyper- and hypopigmented macules and patches of various sizes, with progressive development beginning in infancy; diffuse background hyperpigmentation accentuated with sun exposure Sparse lateral eyebrows, short stature Autosomal dominant due to mutations in the gene encoding KIT ligand
Wende–Bauckus/Pegum syndrome	At ~1 year of age, background hyperpigmentation (gray–brown) develops on the trunk > extremities Tiny white macules on the trunk with confluence in flexures
Ziprkowski–Margolis syndrome	Diffuse pigmentary dilution of the hair and skin, sparing the buttocks and genital region Later, multiple hyperpigmented macules appear, giving the skin a leopard-like appearance Congenital sensorineural deafness, heterochromia irides X-linked recessive inheritance
Chédiak–Higashi syndrome (CHS) and Griscelli syndrome (GS)	In addition to pigmentary dilution of the skin, patients may develop diffuse hyperpigmentation with superimposed guttate hypopigmentation in sun-exposed areas Silvery hair with clumps of melanin, bleeding diathesis (CHS), neurologic abnormalities (CHS, GS1), immunodeficiency (CHS, GS2) (see Ch. 66 and Table 60.5)

Table 67.11 Dyschromatoses.

Continued

DYSCHROMATOSES	
Disorder	**Key features**
Syndromes with ectodermal dysplasia	
Berlin syndrome	Generalized grayish-brown hyperpigmentation with superimposed guttate hypopigmented macules Sparse eyebrows with absent lateral aspect, delayed dentition/hypodontia, short stature, sexual underdevelopment in male patients, intellectual disability Described in one family (Iranians living in Israel; four affected siblings; consanguineous parents)
Lucky/Winter syndrome	Generalized hyperpigmentation with superimposed guttate hypopigmented macules most prominent in flexural sites Scant lightly pigmented hair, enamel hypoplasia (single central incisor in one patient), "digitalized" thumbs, short stature Likely autosomal dominant inheritance
Acromelanosis albo-punctata	Diffuse hyperpigmentation with superimposed guttate hypopigmentation affecting acral and flexural areas, with atrophic skin on the dorsal aspects of the hands and feet Keratotic follicular papules on the legs, pili torti, platonychia
Pigmentation defects, palmoplantar keratoderma, and cutaneous SCC	Hypo- and hyperpigmented macules on the trunk, face, and extremities develop during infancy/childhood Progressive alopecia, diffuse palmoplantar keratoderma, nail dystrophy, early loss of teeth, conjunctival telangiectasias, and cutaneous SCCs Autosomal recessive due to *SASH1* mutations (in 2 Moroccan siblings)
Exposures	
Arsenic	From systemic ingestion of inorganic arsenic Background of bronze hyperpigmentation with superimposed "raindrop"-like guttate hypopigmented macules Palmoplantar keratoses, Bowen disease, basal cell carcinoma, and SCC Increased risk of certain internal malignancies
Diphenylcyclopropenone (DPCP)	Used for topical immunotherapy for alopecia areata of the scalp Hyperpigmented patches with superimposed confetti-like hypopigmented macules occurring mainly on treated areas of the scalp, sometimes at remote untreated sites Described in four patients among 243 patients treated with DPCP
Monobenzyl ether of hydroquinone	Dyschromia with confetti-like hyper-, hypo- or depigmented macules occurring following topical application; typically used for depigmentation therapy in patients with severe vitiligo
Betel leaf (*Piper betle*)	Contact leukomelanosis on the face following application of betel leaves (used as a home remedy for hyperpigmentation) Initially described in Taiwanese patients
Photoleukomelanodermatitis of Kobori	Dyschromic drug eruption that occurs after ingestion of afloqualone, thiazides, or tetracyclines, followed by exposure to sunlight
Infections	
Secondary syphilis (necklace of Venus)	Background hyperpigmentation with superimposed white macules on neck (see Ch. 82)
Pinta	During late phases, copper-colored and slate-blue macules become admixed with depigmented macules and patches (see Ch. 74)
Other	
Dyschromic amyloidosis cutis	Generalized guttate leukoderma plus reticulated macules of hyperpigmentation (see Fig. 67.27), primarily in sun-exposed skin Onset before puberty; may have autosomal dominant inheritance Small foci of amyloid deposits in the papillary dermis
Kwashiorkor	Protein malnutrition, usually in an infant or young child Small hypopigmented macules in diaper area and on thighs, lower abdomen and back in addition to hyperpigmented areas "Flaky paint" dermatosis
Acquired brachial cutaneous dyschromatosis	Gray–brown patches with irregular borders on the extensor forearms Intermixed with the patches are hypopigmented macules and a variable number of telangiectasias Typically affects White women in the fifth to seventh decade of life and associated with chronic sun exposure

Table 67.11 Dyschromatoses. See Table 67.10 for Fanconi anemia. SASH1, SAM and SH3 domain-containing 1; SCC, squamous cell carcinoma.

deterioration associated with a particular *ADAR* mutation have been reported, and features of both DSH and AGS have been described in individuals with biallelic *ADAR* mutations.

Pathology

In the hyperpigmented macules, there is increased melanin within basal keratinocytes, while the hypopigmented macules demonstrate a decrease in the density of DOPA-positive melanocytes.

Differential Diagnosis

Reticulate acropigmentation of Kitamura lacks hypopigmented macules, while vitiligo lacks hyperpigmented macules. Patients with xeroderma pigmentosum also develop hyper- and hypopigmented macules during childhood, but the lesions are in a photodistribution that includes the face and upper trunk. In dyschromatosis universalis hereditaria (see below), the dyschromic lesions have a similar clinical appearance, but they may be present at birth in some patients and, more importantly, the distribution is primarily truncal (see Table 67.11).

Treatment

Current treatments are unsatisfactory. Strict sun avoidance may decrease the contrast between the hypo- and hyperpigmented macules[54].

DYSCHROMATOSIS UNIVERSALIS HEREDITARIA

Key features

- Hyperpigmented and hypopigmented macules in a generalized distribution, with onset in early childhood
- Most reported patients have been Japanese

Introduction and Pathogenesis

Dyschromatosis universalis hereditaria (DUH) is a rare disorder characterized by hypo- and hyperpigmented macules in a generalized distribution. Initially described in 1933, this condition is most common in Japan but has also been reported in patients from other parts of Asia and Europe. One autosomal dominant form of DUH is caused by heterozygous mutations in *ABCB6*, which encodes an ATP-binding cassette transporter protein that is expressed in keratinocytes and melanocytes[55]. Heterozygous mutations in *SASH1*, which encodes a SAM and SH3 domain-containing protein with several purported roles in melanogenesis, can result in either DUH or an autosomal dominant lentiginosis favoring sun-exposed sites[56]. In addition, biallelic *SASH1* mutations may produce a constellation of findings including palmoplantar keratoderma, alopecia, and cutaneous SCC as well as dyschromatosis (see Table 67.11). An autosomal recessive form of DUH has also been mapped to 12q21–q23.

Clinical Features

Over 80% of DUH patients develop dyschromia by 6 years of age, and ~20% have dyspigmentation at birth. Numerous hyperpigmented and hypopigmented macules of various sizes develop on the head, neck, extremities, and trunk (see Fig. 67.29). Hyperpigmented macules on the face can resemble ephelides or lentigines. The dyschromia may be accentuated in sun-exposed sites, especially in SASH1-related DUH; it can also involve the palms and soles as well as the dorsal aspects of the hands and feet, but spares the mucous membranes. There is no seasonal change or spontaneous regression with age[57]. Extracutaneous abnormalities reported in isolated cases of DUH include short stature and high-frequency deafness; abnormalities in erythrocytes, platelets and tryptophan metabolism; bilateral glaucoma and unilateral cataract; and seizures[58].

Pathology

A focal increase or decrease in the melanin content of the basal epidermal layer is seen in the hyperpigmented and hypopigmented areas, respectively[58].

Differential Diagnosis

Xeroderma pigmentosum may have similar dyspigmentation, but it is in a photodistribution and associated with premature actinic damage (see Ch. 86). Additional causes of dyschromatosis are outlined in Table 67.11.

Treatment

There is no satisfactory treatment.

ACQUIRED BRACHIAL CUTANEOUS DYSCHROMATOSIS

This acquired dyschromatosis was described in 2000[59] and primarily affects White women in the fifth to seventh decades of life. It is characterized by chronic, asymptomatic gray–brown patches with geographic borders on the dorsal aspect of the forearms[59]. Intermixed with the patches are hypopigmented macules and a variable number of telangiectasias. Affected individuals often have evidence of chronic sun exposure clinically (e.g. poikiloderma of Civatte) or histologically (e.g. solar elastosis).

Additional figures available in our eBook (see inside front cover for access code).

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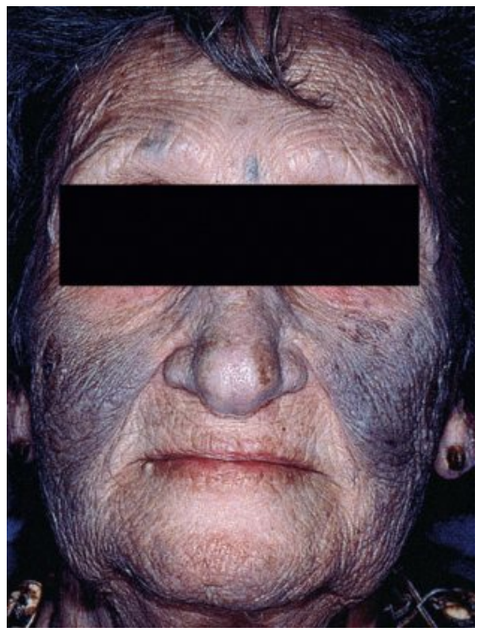
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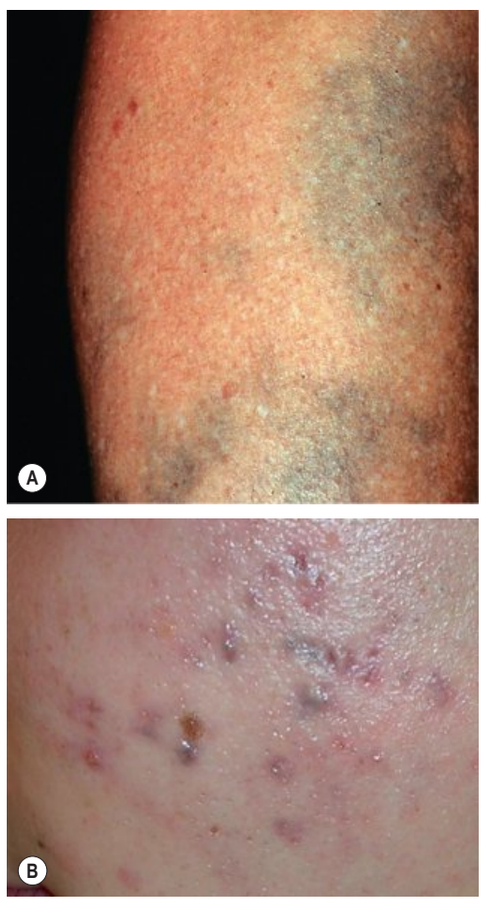
eFig. 67.1 Postinflammatory hyperpigmentation in a patient with pemphigus foliaceus and phototype IV skin.



eFig. 67.2 Malar melasma in a man. Note the irregular borders. *Courtesy Kalman Watsky, MD.*



eFig. 67.3 Blue–violet discoloration of previous leprosy lesions in a patient treated with clofazimine. *Courtesy Anne Burdick, MD.*



eFig. 67.4 Minocycline-induced discoloration. A Sometimes the discoloration is misdiagnosed as ecchymoses, but the subsequent color changes of green and yellow do not occur. **B** Blue–black pigmentation within acne scars and inflammatory papules. B, *Courtesy Richard Antaya, MD.*



eFig. 67.5 Minocycline-induced discoloration. Note the muddy gray–brown color and demarcation at Wallace's line. *Courtesy Edward Cowen, MD*.



eFig. 67.6 Linear epidermal hyperpigmentation due to phytophotodermatitis. *Courtesy Julie V. Schaffer*.



eFig. 67.7 Phytophotodermatitis. The patient was exposed to limes then sunlight while making guacamole dip. *Courtesy Kalman Watsky, MD*.



eFig. 67.8 Phytophotodermatitis. Linear hyperpigmented streaks in a child. The lesions do not follow the lines of Blaschko. *Courtesy Julie V. Schaffer, MD*.



eFig. 67.9 Linear postinflammatory hyperpigmentation on the forehead. The lesions were due to neurotic excoriations.



eFig. 67.10 Linear and whorled nevoid hypermelanosis. Light brown streaks along the lines of Blaschko. *Courtesy Julie V. Schaffer, MD.*



eFig. 67.12 Conradi–Hünermann–Happle syndrome. Linear hyperpigmentation along the lines of Blaschko. *Courtesy Julie V. Schaffer, MD.*



eFig. 67.11 Stage III incontinentia pigmenti in a 2-year-old infant. Note the characteristic gray–brown color, and the distribution along the lines of Blaschko.



eFig. 67.13 Linear hyperpigmentation due to atrophoderma of Moulin. Note the subtle depression of the lesions on the upper lateral thigh. *Courtesy Jean L. Bolognia, MD.*



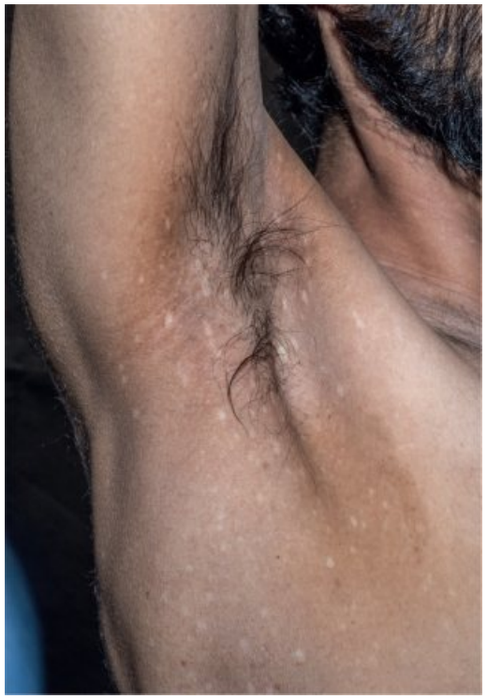
eFig. 67.14 Erythema ab igne. Reticulated hyperpigmentation on the lower back due to prolonged exposure to heat. Note the wide spacing of the net-like pattern.



eFig. 67.16 Dyskeratosis congenita. Longitudinal ridging, splitting, and early pterygium formation. *Courtesy Anthony Mancini, MD.*



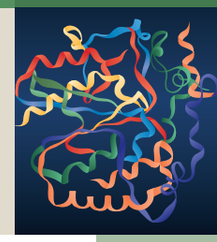
eFig. 67.15 Prurigo pigmentosa – clinical features. Eroded and crusted erythematous papules and plaques. A reticulated pattern is evident. *Courtesy Luis Requena, MD.*



eFig. 67.17 Fanconi anemia. Diffuse hyperpigmentation of the skin folds in addition to scattered hypopigmented macules. *Courtesy Edward Cowen, MD.*

Biology of Hair and Nails

68



Etienne C.E. Wang, David de Berker and Angela M. Christiano

Key features

- The pilosebaceous unit and nail apparatus are epidermal derivatives that produce two of the hardest epithelial structures in mammalian biology
- The hair follicle is the only continuously cycling organ in mammals, while the nail exhibits uninterrupted growth
- Hair and nails serve multiple functions, including protection, sensation, and social communication
- Hair shafts and nail plates largely consist of dead, terminally differentiated keratinocytes (trichocytes and onychocytes, respectively) whose durability is based on the presence of abundant keratin intermediate filaments
- The hair cycle includes phases of growth (anagen), regression (catagen), resting (telogen), and hair shaft shedding (exogen/teloptosis)
- The hair follicle is a site of immune privilege and a major reservoir for epithelial and melanocyte stem cells; immune privilege and stem cells within the nail unit are also becoming recognized
- The nail apparatus consists of the fully cornified nail plate, which is produced by the nail matrix, and other specialized epithelial tissues such as the nail bed and nail folds

PRINCIPLES OF ADNEXAL MORPHOGENESIS

Skin adnexa in mammals develop through evolutionarily conserved mechanisms. Similar processes lead to modifications of epithelial cells and proteins in order to form functional structures such as hairs, feathers, nails, glands, and teeth. In all cases, adnexa result from interactions between adjacent tissue layers, the ectoderm (epidermis) and underlying mesoderm (dermis) (Fig. 68.1). For example, the hair follicle (HF) first arises as a small epidermal bud and then, via reciprocal signaling involving the underlying dermis, progresses to form a complex, multi-cylindrical organ with associated sebaceous and apocrine glands (see Fig. 2.4). The developmental relationships among different adnexal structures is evidenced by the hair, nail, sweat gland, and tooth defects observed in ectodermal dysplasias (see Ch. 63).

The basic principles of adnexal development were defined by a series of classic tissue recombination experiments performed in the 1970s, which have served as the foundation for research in this field[1,2]. These experiments demonstrated that the dermal mesenchyme emits the initial "message" for the development of all types of skin adnexa (stage 0). The mesenchyme itself does not change morphologically but rather signals the overlying epithelium to thicken and form a placode (stage 1) (Fig. 68.2). The type of appendage that develops is determined within the epidermis, where positional and epigenetic cues dictate the ultimate phenotype[3]. Canonical β-catenin-dependent WNT (*w*ingless-type *int*egration site) signals are candidates for the dermal message, and it is thought that they precede other activators and regulators of adnexal development[4]. Recent advances in single-cell RNA sequencing and the study of increasingly smaller cellular subsets have confirmed the developmental trajectory of an early dermal condensate that drives appendageal morphogenesis[5,6].

BIOLOGY OF HAIR

Hair Follicle Morphogenesis

WNT signaling plays key roles in HF development. In mice, lack of WNT signaling through overexpression of the WNT inhibitor Dickkopf homolog 1 (DKK1) prevents HF formation[4], while overexpression of β-catenin in the epidermis (acting downstream of WNT; see Fig. 55.6) promotes conversion to a placode fate[7]. Loss-of-function mutations in *WNT10A*, which encodes an activator of WNT signaling, cause several forms of ectodermal dysplasia in humans, including odonto-onychodermal dysplasia and Schöpf–Schulz–Passarge syndrome (see Ch. 63). The spectrum of cutaneous findings that can result from *WNT10A* mutations includes hypotrichosis, nail dystrophy, palmoplantar keratoderma with eccrine syringofibroadenomatosis, and apocrine hidrocystomas[8]; in addition, *WNT10A* polymorphisms have been associated with hair shape, tooth morphology, and corneal thickness[9,10]. The APCDD1 (adenomatosis polyposis coli downregulated 1) protein normally inhibits WNT/β-catenin signaling by binding to WNT and low-density lipoprotein receptor-related proteins (LRPs) upstream of β-catenin. *APCDD1* mutations that lead to dysregulation of the WNT/β-catenin pathway result in hypotrichosis simplex characterized by hair shaft miniaturization (see Fig. 55.6)[11].

In normal mouse HF development, WNT and β-catenin activation occurs in the placode following the initial dermal signal. This induces transcription of the ectodysplasin A receptor gene (*Edar*), which mediates nuclear factor-κB (NF-κB) signaling[12]. Expression of EDAR within the primary follicle placode also suppresses inhibitory signals from the surrounding epidermis, which refines WNT/β-catenin expression within the placode. Competing gradients of WNT (activating) and DKK (inhibitory) signals within the epidermis modulate HF spacing, establishing regular intervals between follicles[13,14].

After determination of placode fate, reciprocal signaling between the mesenchyme and epithelium continue to drive HF morphogenesis through a complex interplay among secreted molecules (see Fig. 68.2). Fibroblast growth factor (FGF)-20 secreted by the placode promotes formation of a dermal condensate[15]. A second dermal signal follows,

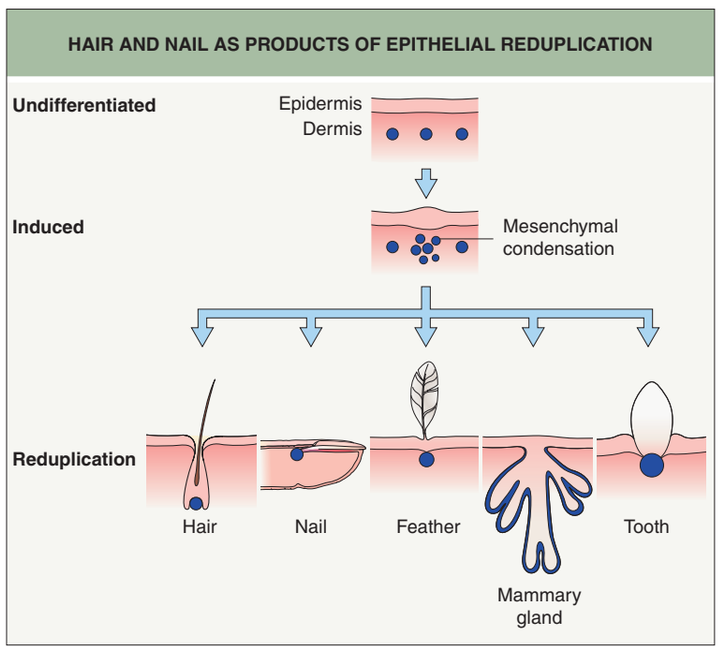


Fig. 68.1 Hair and nail as products of epithelial reduplication. *Reproduced with permission from Chuong C-M. Morphogenesis of epithelial appendages: variations on top of a common theme and implications in regeneration. In: Chuong C-M (ed). Molecular Basis of Epithelial Appendage Morphogenesis. Austin: R.G. Landes Company, 1998:3–13.*

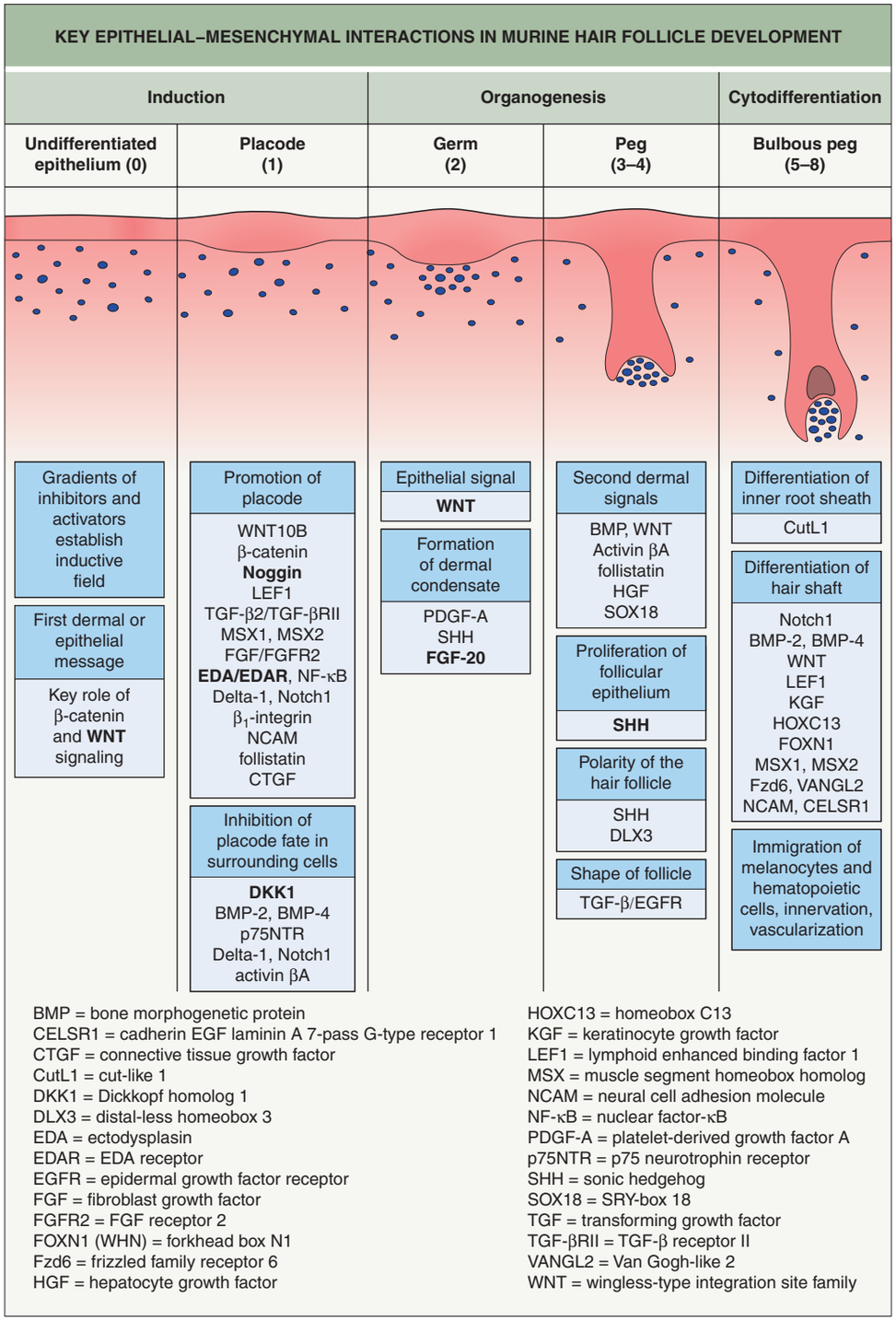


Fig. 68.2 Key epithelial–mesenchymal interactions in murine hair follicle development. The undifferentiated epithelium emits an as-yet unidentified initial signal affecting the WNT pathway, which leads to accumulation of β-catenin in the superficial dermis. Dermal cells respond with secretion of morphogens such as WNTs, ectodysplasin A (EDA), and fibroblast growth factors (FGFs) that lead to specification of the epidermal placode. The placode produces Dickkopf homolog (DKK) and bone morphogenic proteins (BMPs) that inhibit surrounding epithelial cells, thus refining the patterning. The placode matures into the primary hair germ, and its secretion of platelet-derived growth factor A (PDGF-A), sonic hedgehog (SHH), and FGF-20 promote condensation of the dermal cells. Signals from the dermal condensate include WNTs, SHH, and hepatocyte growth factor (HGF); this initiates downgrowth of the hair germ to form the peg, which envelopes the condensate and tightens the interaction interface. Subsequent cross-talk activates a host of morphogens that direct differentiation of the bulbous peg into concentric layers of keratinocytes that ultimately form the hair follicle. *Adapted from Millar SE. Molecular mechanisms regulating hair follicle development. J Invest Dermatol 2002;118:216–25.*

which induces proliferation of the epidermis and invasion of the dermis by a column of epithelial cells that forms the hair germ (stage 2), followed by the hair peg (stage 3–4) and subsequently the bulbous peg (stage 5–8) (see Fig. 68.2)[16]. WNT and EDAR signaling control the expression of sonic hedgehog (SHH), which drives downgrowth of the hair germ[17]. Primary cilia on dermal cells within the condensate coordinate SHH signaling. In mice that lack SHH or have abnormal cilia, the dermal condensate forms but proliferation and downgrowth of the epithelium are arrested[18,19]. Hemidesmosomal integrins also have a physical role in hair germ development, and mice with deficient β1 or β4 integrins have hair germs that cannot remodel their basement membrane and descend into the dermis[20,21].

During follicle development, the mesenchymal condensate is progressively engulfed by epidermal cells and becomes enclosed, thereby evolving into the dermal papilla. Although epithelial growth is initially downward, a switch to an upward differentiation program occurs in response to WNT and bone morphogenic protein (BMP) signaling from the dermal papilla. This gives rise to concentric layers of the hair shaft and inner root sheath. In human hair follicles, epithelial keratins 1, 10, 14, and 16 are expressed by 12 weeks' gestational age, with keratin 16 in proliferative regions such as the bulb; this is followed by keratin 20 expression. Epithelial cell fate depends upon the relative position of a matrix cell with respect to the dermal papilla[22]. An early effector of this signaling within the matrix is the distal-less homeobox 3 (DLX3) transcription factor, which directly regulates expression of hair keratin genes in the hair shaft and inner root sheath[23]. A dominant frameshift mutation in *DLX3* results in tricho-dento-osseous syndrome, a form of ectodermal dysplasia characterized by dystrophic hair, enamel hypoplasia, and thickening of skull and jaw bones[24]. Mutations in additional genes with key roles in hair follicle development underlie other ectodermal dysplasias as well as non-syndromic hair disorders (see Ch. 63 and Table 69.7).

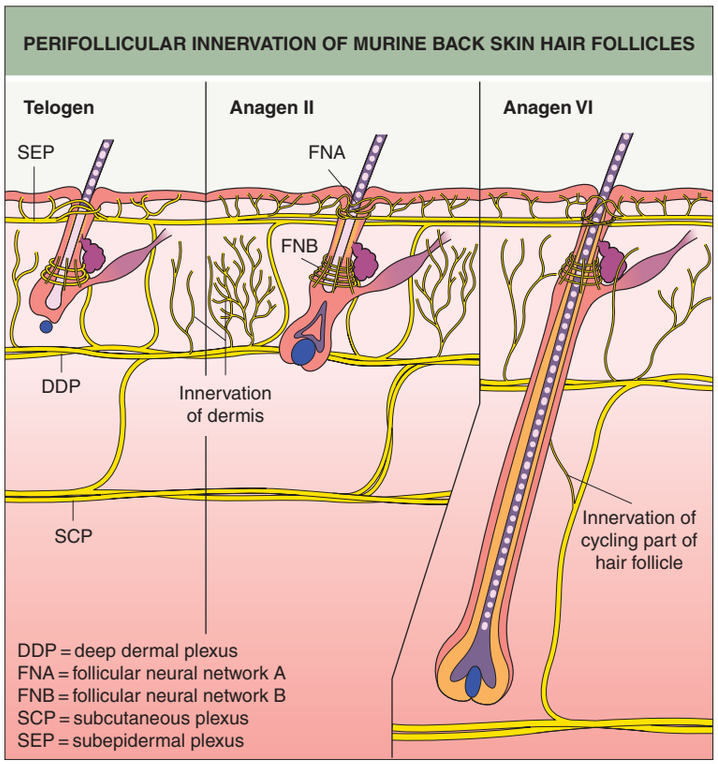


Fig. 68.3 Perifollicular innervation of murine back skin hair follicles. *Adapted from Paus R, Peters EM, Eichmüller S, Botchkarev VA. Neural mechanisms of hair growth control. J Invest Dermatol Symp Proc. 1997;2:61–8.*

Complex neural networks develop in conjunction with HF morphogenesis. Nerve fibers arrive in the skin first and are located at presumptive follicular sites, running parallel to a dense network of blood vessels (Fig. 68.3). Developing follicles become innervated around stage 5, with nerve fibers encircling the isthmus and bulge regions[25]. Neurotrophins released from the follicular epithelium regulate this innervation, and in turn the nerves may influence the stem cell niche of the HF[26]. Similarly, signaling proteins that promote angiogenesis, such as vascular endothelial growth factor (VEGF), are released from the epithelium and affect development of the vascular network surrounding HFs[27].

Hair follicle patterning

Individual mammals can produce different types of hairs that share basic architectural principles. In the dorsal skin of mice, HF development occurs in three successive waves: (1) large, straight, *primary guard* or *tylotrich* hairs, which comprise 1%–3% of total hairs and have two sebaceous glands, form on embryonic day 14.5; (2) *secondary awl* (straight, ~30% of the coat) and *auchene* (one bend, ~0.1% of the coat) hairs form on embryonic day 16.5; and (3) *tertiary zigzag* hairs, which have several bends and account for ~70% of the coat, form on embryonic day 18.5. The mouse coat therefore contains four distinct hair types, in addition to specialized hairs such as vibrissae (whiskers) and tail hairs[28]. EDAR is necessary for placode development in primary HFs[29] but not for induction of secondary HFs, which utilize signaling pathways that involve Noggin and SRY-box 18 (SOX18) expression within the dermal papillae[29–31].

In humans, hypohidrotic ectodermal dysplasia (HED) with abnormal morphogenesis of scalp hair, sweat glands, and teeth results from mutations in the genes encoding components of the EDAR/NF-κB signaling pathway, including EDAR, its ligand ectodysplasin A, and the downstream effector EDAR-associated death domain (EDARADD)[32] (see Fig. 63.15). In addition, a non-synonymous single nucleotide polymorphism (SNP) within *EDAR* is associated with increased hair thickness in Asian populations[33]. Deep deformations in the hair shaft were identified in Swedish patients with an autosomal dominant form of HED due to an *EDAR* mutation[34]. These clinical observations underscore the importance of the EDAR/NF-κB signaling pathway in human appendage development. Interestingly, mutations in human *SOX18* cause lymphedema and telangiectasias as well as hypotrichosis[35].

The hairs of the mouse dorsal coat have anterior–posterior polarity along the body axis, which contributes to formation of a sleek coat. SHH and neural cell adhesion molecule (NCAM) within the HF have an asymmetric distribution pattern, which is established by a conserved planar cell polarity (PCP) pathway during hair germ development[36]. PCP proteins VANGL2 (Van Gogh-like 2) and CELSR1 (cadherin epidermal growth factor laminin A seven-pass G-type receptor 1) respond to directional cues and are necessary for the correct polarization of follicles within the skin[36,37]. Mutations in *Vangl2* or the frizzled family receptor 6 (*Fzd6*) affect the early global alignment of HFs, resulting in germs that first grow vertically. Over time the follicles reorient themselves in competing patterns, producing characteristic whorls on the back of the mouse[38]. In *Fzd6*$^{-/-}$ mice, an additional mutation in Astrotactin2 (*Astn2*), which has roles in neuronal migration, leads to a 180-degree reorientation of the dorsal coat to a posterior–anterior polarity[39]. Hair whorls are frequently observed in mammals, such as on the occipital scalp in humans, between the eyes in horses and cattle, and on the upper chest in dogs[38]. Aberrant or displaced hair whorls are observed in a number of genetic disorders (omim.org).

Under physiologic conditions, human HF morphogenesis occurs only once. Lanugo, vellus, and terminal hairs have the same basic architecture (Table 68.1). The first "coat" is composed of fine, long, variably pigmented lanugo hair, which is shed in an anterior-to-posterior wave during the third trimester. A second coat of fine, shorter, unpigmented lanugo hair then grows in all areas except the scalp and is shed 3–4 months after birth; pigmented scalp hairs, which have variable lengths and diameters, are also shed postnatally in an anterior-to-posterior wave. Thereafter, the hair grows in an asynchronous "mosaic" pattern rather than waves. In prepubertal children, hair is terminal on the scalp, eyelashes, and eyebrows, while it is vellus on the face, trunk, and extremities. During puberty, vellus hairs in some sites become terminal hairs under the influence of androgens. Paradoxically, terminal hairs on the scalp exposed to the same androgens revert to miniaturized vellus-like hairs in androgenetic alopecia.

Congenital generalized hypertrichosis (Ambras syndrome) is characterized by a disruption in the patterning of hairs, with terminal hairs growing at sites that normally have vellus follicles[40]. A position effect that downregulates the expression of the trichorhinophalangeal syndrome I gene (*TRPS1*) was found to underlie this hypertrichosis phenotype in both humans and mice[41]. In addition, X-linked congenital generalized hypertrichosis in a Mexican family was associated with a position effect that decreased the expression of *FGF13*[42].

In most mammals, the hair pattern differs depending on the body site. While the ectoderm involved in skin and hair development is non-neural and relatively homogeneous, the mesenchyme has various origins which may explain this regionalization. The dorsal dermis is derived from the somitic dermomyotome, the ventral dermis has a somatopleural origin, and the craniofacial dermis arises from the neural crest[43,44]. The dermal progenitors at each of these sites are specified by different signaling pathways. Mice display regional differences in skin thickness as well as hair color and type. The postnatal identity of their skin is acquired by embryonic day 12.5, with the T-box 15 (TBX15) transcription factor appearing within dorsal skin to demarcate the dorsal–ventral boundary[45].

In humans, the effects of androgens on HFs depend upon the body site. Follicles in the frontal scalp are normally androgen-dependent, whereas occipital scalp follicles are hormonally insensitive and therefore less susceptible to androgenetic alopecia. When HFs from the occipital scalp are transplanted to the frontal scalp, they typically retain the pigmentary characteristics, androgen sensitivity, and growth rate of the donor site[46]. However, in other instances, transplanted hairs take on characteristics of the recipient site, such as scalp hairs moved into the eyebrow region. It remains to be established exactly which characteristics are more influenced by the recipient site versus the donor site following transplantation.

Postnatal hair follicle development

Although HF formation in general occurs prior to birth, adult mammalian skin retains the capacity for HF morphogenesis. In adult mouse and rabbit skin, WNT-dependent *de novo* HF formation occurs after wounding[47]; this is mediated by FGF-9 secreted by infiltrating γδ-T cells and wound

TRICHOLOGY TERMS	
Hair follicle (HF) cycle	Autonomous, rhythmic transformation of fully developed HFs through phases of growth, regression, and resting; controlled by the follicle itself by an as yet enigmatic "hair cycle clock", with modulation by numerous systemic/extrafollicular factors
Anagen	Growth stage of the HF cycle
Catagen	Involution of the lower two-thirds of the HF by massive keratinocyte apoptosis
Telogen	Resting phase of the HF cycle
Exogen	Phase of active hair shaft shedding (during anagen in rodents; most likely during the telogen to anagen transition in humans)
Kenogen	Telogen follicle with no club hair present
Hair bulb	Lowermost portion of the HF
Hair matrix	Rapidly proliferating keratinocytes that terminally differentiate to produce the hair shaft
Club hair/fiber	Fully keratinized proximal tip of hair shaft, formed during late catagen and telogen; brush-like appearance; characteristic of telogen follicles
Vellus hair (follicle)	Very short, non-pigmented, and usually non-medullated; absence of arrector pili muscle; tiny vellus follicles can have large sebaceous glands (face); undergo full hair cycle, yet much shorter than terminal hair
Terminal hair	Large, usually pigmented and medullated hair
Lanugo hair	Fine hair on the fetal body; shed *in utero* or during the first weeks of life
Vibrissae	Special sensory HFs found on the upper lips/snout region in non-human mammals, especially rodents; largest and most densely innervated HFs with special sinusoid blood supply; first HFs to develop
Tylotrich HF	Large sensory HFs interspersed within truncal skin of non-human mammals, most notably rodents; extra large, long hair shaft, typically associated with double sebaceous gland and an innervated epidermal Merkel cell complex (Pinkus' Haarscheibe); second type of HF to develop
Non-tylotrich pelage hair	Majority of all HFs in non-human mammals; last to develop
Effluvium	Process of excessive shedding of hair shafts
Alopecia	Result of abnormal hair loss
Hirsutism	Excessive vellus-to-terminal hair conversion in androgen-dependent areas in women
Miniaturization	Terminal-to-vellus hair conversion, e.g. on the balding scalp in androgenetic alopecia; these miniaturized follicles still have an arrector pili muscle, unlike true vellus hairs
Infundibulum of follicle	Region extending from the junction with the interfollicular epidermis to the opening of the sebaceous gland; displays cornification similar to that of the interfollicular epidermis
Isthmus of follicle	Region located between the opening of the sebaceous gland and the site of insertion of the arrector pili muscle; displays trichilemmal keratinization
Arrector pili muscle	Inserts at the level of the bulge; pulls up hair ("goose bumps")
Bulge	Segment of the outer root sheath located at the level of arrector pili muscle insertion; major seat of epithelial stem cells of the HF
Secondary hair germ	Additional seat of epithelial stem cells and site of melanocyte stem cells; located between club hair and dermal papilla in telogen HF
Dermal sheath	Special mesenchymal follicular sheath that is tightly attached to the HF basement membrane and is continuous with the follicular dermal papilla
Follicular dermal papilla (DP)	Onion-shaped, closely packed, specialized fibroblast population with inductive and morphogenic properties; hair cycle-dependent fibroblast trafficking occurs between the dermal sheath and DP; volume of DP determines size of hair bulb and, thus, hair shaft diameter
Inner root sheath (IRS)	Packages and guides the hair shaft; cornifies
Outer root sheath (ORS)	Merges distally into the epidermis and proximally into the hair bulb; provides slippage plane, nutrition, regulatory molecules, and stem cells
Follicle pigmentary unit	Melanin-producing HF melanocytes located above and around the upper one-third of the DP; transfer eu- or pheomelanosomes to differentiating HF keratinocytes in the precortical matrix; goes largely into apoptosis during each catagen phase, regenerated from melanocyte stem cells in hair germ (and possibly from non-melanogenic ORS melanocytes) during anagen

Table 68.1 Trichology terms. *Courtesy John P. Sundberg, DVM, PhD.*

fibroblasts[48]. WNT-dependent expression of FGFs may also play a role in human hair follicle regeneration[49]. It is therefore reasonable to consider possible therapeutic interventions that would initiate *de novo* HF formation on the human scalp[50]. Trans-species end-bulb formation and hair fiber growth has been demonstrated after implantation of intact human dermal papillae onto transected mouse whisker follicles[51]. In humans, allogeneic transplantation of tissue from the dermal sheath that surrounds the dermal papilla can induce new follicle formation in the recipient, with immune privilege providing protection from rejection[52]. In addition, cultured tooth mesenchymal papilla cells from humans and rats have been shown to induce hair fiber formation in an amputated follicle, highlighting the conservation of inductive signals among different adnexa[53].

Dermal papilla cells in rodents show much more inductive potency than their human counterparts. Rodent HF papilla cells can reprogram differentiated glabrous epidermis to produce a *de novo* HF, and they are also capable of initiating transdifferentiation of amnion or even adult corneal epithelium into epidermis complete with HFs[54,55]. Human dermal papilla cells lose their inductive properties quickly in a standard monolayer culture, which hampers the utilization of these cells for hair regeneration. However, dermal papilla cells grown in a three-dimensional spheroid culture have been shown to retain their ability to induce hair growth in glabrous skin, suggesting that cellular interactions are critical to maintenance of dermal papilla identity[56].

The Mature Hair Follicle: Cycling and Anatomy

Once the mature HF is generated during embryogenesis and early postnatal life, it begins to cycle and continues to do so throughout its lifetime. The phases of the hair cycle include active growth (anagen), regression (catagen), and rest (telogen) (Fig. 68.4A). As noted above, mouse follicles cycle in a synchronous wave along the anterior to posterior axis, while human follicles cycle in a mosaic pattern. HF cycling is an autonomous phenomenon that continues even when HF units are isolated from the skin and grown in culture[57]. Signaling pathways involved in HF morphogenesis, including those mediated by WNT and FGFs, also regulate the mature hair cycle[58]. The portion of

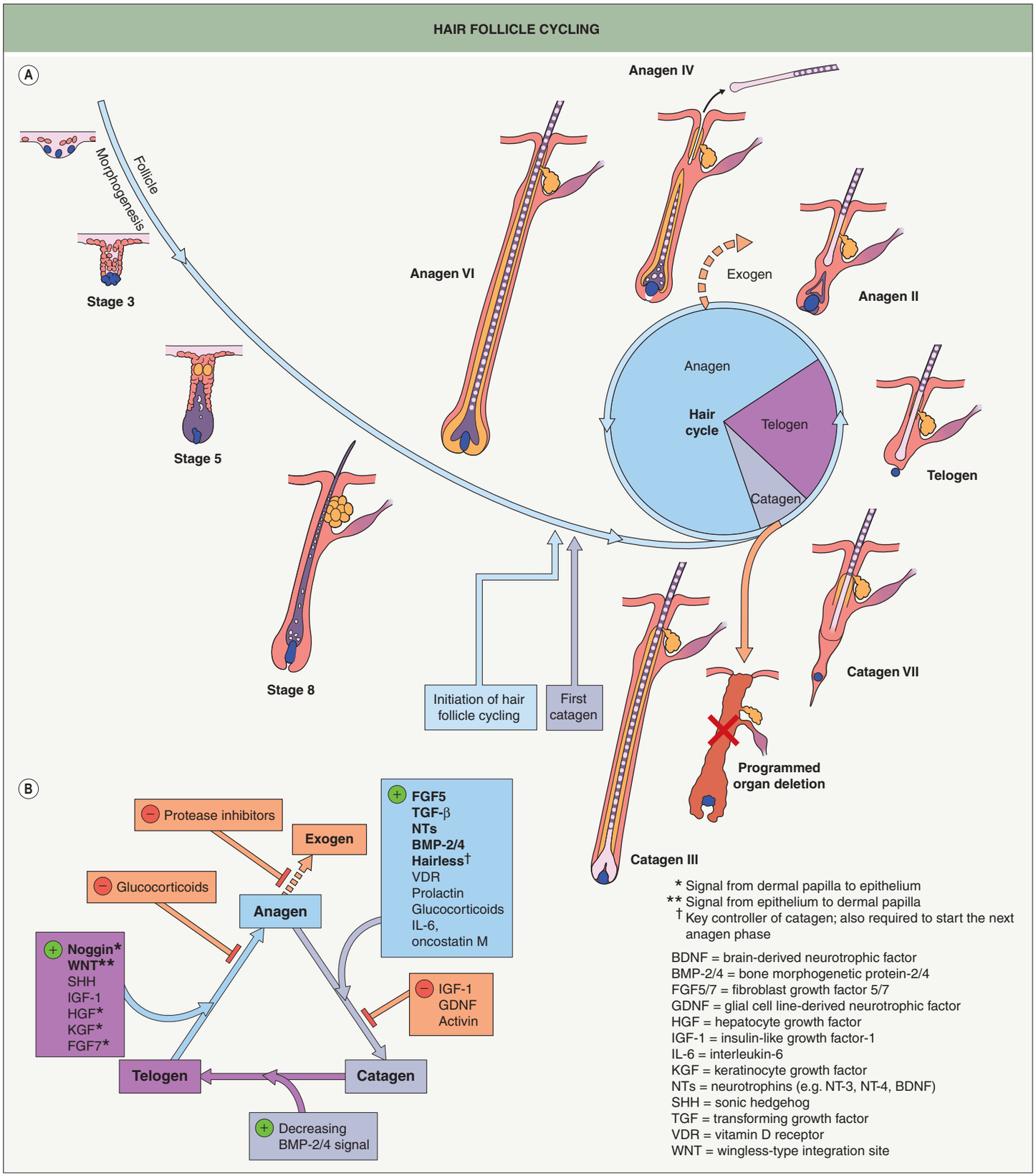


Fig. 68.4 Hair follicle cycling. A Model of hair follicle development and cycling. Although exogen is coupled to anagen in rodents, the timing of exogen in humans is less well characterized, and the club fiber is thought to usually be shed during the telogen to anagen transition. **B** Regulation of hair.

the follicle below the bulge undergoes distinct morphologic changes as it grows and regresses; in contrast, the upper region of the follicle including the sebaceous gland, isthmus, infundibulum, and hair canal remains permanent.

The process of cycling makes the HF a dynamic structure, enabling animals to have different hair lengths depending on the body site and to change their coats depending on the season for camouflage and insulation (Table 68.2). Coat changes involve two processes: (1) exogen – signals and structural changes culminating in hair shedding (teloptosis); and (2) initiation of new hair fiber growth[59]. "Kenogen" refers to a telogen follicle that has lost its club fiber but has not yet transitioned to anagen, representing the "true" resting phase of the hair cycle where metabolic activity is at a minimum.

Anagen

Anagen is the period of active hair fiber production, and its duration varies depending upon factors such as species and body site (Table 68.3). Anagen is divided into six substages, anagen I–VI; it lasts 1–3 weeks in mice and up to several years on the human scalp[60,61], explaining the longer lengths of human scalp hair. The start of anagen (anagen I), as observed in mouse skin, is associated with an increased size of the dermal papilla, due mainly to an influx of cells from the surrounding dermal sheath. Dermal sheath cells at the base of the follicle also contribute to dermal papilla regeneration after removal of the lower follicle[62,63]. The influx of cells at the start of anagen is accompanied by an increase in ECM material. This doubles the size of the dermal papilla[64], the width of which is directly proportional to the thickness of the hair shaft produced by the follicle. The degree of axial symmetry within the hair bulb determines the curvature of the final hair structure[65].

The dermal papilla provides signals to the surrounding matrix cells, whose position with respect to the dermal papilla specifies their fate, e.g. central cells become the medulla[22]. As the matrix cells begin to differentiate, they form precursor cells of the different follicle lineages. Migrating upwards, these cells undergo specialized programs of differentiation, expressing specific sets of keratins to form seven concentric epithelial lineages of the follicle, from the medulla to the companion layer (Figs. 68.5 and 68.6). In contrast, the outer root sheath (ORS), which is the outermost layer of the epidermal portion of the follicle, does not originate from upward growth of matrix cells, but rather directly from the bulge (see below)[66]. The growing HF ends up nestled in the subcutaneous fat by anagen VI. In the mouse, dermal adipocyte precursors secrete platelet-derived growth factor-A (PDGF-A), which acts on the dermal papilla to support anagen[67].

In rodents and rabbits, plucking telogen hairs can accelerate onset of the next anagen phase. The trauma of plucking causes release of chemokine C-C motif ligand 2 (CCL2) by the follicle, leading to recruitment of macrophages that secrete tumor necrosis factor (TNF), which promotes local follicles to enter anagen[68]. Osteopontin, which is produced by melanocytic nevi, also promotes anagen entry and stimulates hair growth[68a]. Other microenvironmental cues and "quorum-sensing" among HFs also likely play a role in hair cycle coordination.

FUNCTIONS OF HAIR AND NAILS
Functional properties of hair shafts
• Social and sexual communication • Camouflage • Protection against chemical and physical damage • Protection against insects • Provide sensory "antennae" • Insulation against heat loss, overheating, and desiccation • Removal from the skin surface of parasites, dirt, debris, and squames by the outward-moving hair shaft • Facilitation of sebum, apocrine sweat, and pheromone secretion • Organ of scavenging and excretion via the melanized hair shaft, which serves to deposit and extradite unwanted molecules • Hair shaft medulla can serve as a fiberoptic device for conversion of UV light into heat (polar bear)
Functional properties of pilosebaceous units
• Production, extrusion, containment, and mooring of pigmented hair shafts • Crucial stem cell reservoir, e.g. for keratinocytes and melanocytes • Reservoir for Langerhans cells • Highly sensitive tactile organs that sense hair shaft movements • Generate sebum, apocrine sweat, and pheromones
Functional properties of nails
• Social and sexual communication (color, shape, length) and aesthetic appearance • Protection of the distal phalanges of the digits from mechanical, chemical, and biological trauma • Contribute to the tactile discrimination and fine motor capacities of the fingertips • Provide the ability to scratch and groom • Rudimentary natural weapons • Contribute to pedal biomechanics essential for full motor functioning of the feet

Table 68.2 Functions of hair and nails. *Courtesy John P. Sundberg, DVM, PhD.*

Catagen

At the end of anagen, the follicle enters the regressive catagen phase, which is divided into eight substages (catagen I–VIII)[69]. Catagen lasts ~2 weeks in humans, regardless of the site and follicle type[61]. The initiation of catagen is characterized by a nearly 50% reduction in the volume of the dermal papilla due to loss of ECM and migration of cells into the surrounding dermal sheath, which acts as a repository that replenishes the dermal papilla in the subsequent anagen[70]. Melanocytes in the hair bulb also downregulate melanogenesis. Later, there is cessation of mitotic activity within the matrix cells of the bulb, and the remaining hair precursor cells at the base of the shaft differentiate to form a "club fiber".

The club fiber migrates up the follicle, and a germ capsule termed the trichilemmal sac forms around its base. This club fiber lacks pigmentation and is formed from cortical and cuticle cells only. The electron-dense, non-nucleated layer of trichilemmal keratin around its base has a characteristic "brush" structure that protrudes outwards and between surrounding ORS cells[71]. Abundant desmosomes between the trichilemmal keratin and surrounding tissue are thought to physically anchor the club fiber within its trichilemmal sac until it receives the signal for release[72].

As the club fiber moves up the follicle, the dermal papilla, which is initially still in the subcutaneous fat, becomes separated from the club by an epithelial strand that is surrounded by basement membrane (the glassy membrane)[73]. Apoptosis in the epithelial strand creates an "apoptotic force" that draws the dermal papilla up to just beneath the club fiber in the dermis, leaving behind a trailing dermal sheath called a fibrous streamer or stele[59]. FGF-5 produced by macrophage-like cells facilitates regression of human HFs[74], and *FGF5* mutations underlie familial trichomegaly characterized by abnormally long eyelashes[75]. Macrophages also participate in the clearance of cellular debris during catagen[76,77].

Loss-of-function mutations in the hairless gene (*HR*) can result in atrichia with papular lesions (APL)[78,79], a rare autosomal recessive disease characterized by complete hair loss early in life and later eruption of papular lesions. Hairless is a transcription factor that is required for apoptosis in the epithelial strand, which draws the dermal papilla up beneath the club fiber and secondary hair germ in a position to activate the next anagen phase. Thus, individuals with APL are born with hair, which never grows back after it is shed. Activating mutations in the upstream open reading frame of *HR* lead to another form of sparse hair, Marie Unna hypotrichosis[80]. Hairless interacts with the vitamin D receptor (VDR), which has ligand-independent functions in hair cycle control[81]. Patients with hereditary vitamin D-resistant rickets caused by *VDR* mutations present with alopecia that is not corrected by vitamin D supplementation[82].

Telogen

Telogen begins when the dermal papilla reaches the base of the permanent portion of the HF. The duration of telogen can be as short as 2 days in mice and as long as 3 months for human scalp hairs. The hair germ is derived from the bulge during the catagen-to-telogen transition and lies inferior to the bulge, separating the latter from the dermal papilla[83]. As in HF morphogenesis, epithelial–mesenchymal cross-talk is required to activate the new anagen phase. Anagen progression recapitulates the middle and later stages of HF development, and many factors that drive follicle morphogenesis (e.g. WNT, SHH, noggin) also play important roles in telogen-to-anagen transition (Fig. 68.4B). The

BASIC INFORMATION ON HUMAN HAIR FOLLICLES (HFs)	
Total number	~5 000 000 (mostly vellus)
Number of scalp HFs	~100 000 Blondes: + 20% Redheads: – 20%
Average density of hairs on the scalp*	Terminal + vellus: 1135/cm^2 (newborn) 615/cm^2 (20–30 years) 485/cm^2 (30–50 years) 435/cm^2 (70–80 years) African-Americans, Asians: lower density Terminal only: ~250/cm^2 Bald scalp (45–70 years): 330/cm^2 Highest density: cheek + forehead
Hair embryology	Development progresses at fixed intervals in cephalocaudal direction, first becoming visible in eyebrow, upper lip, and chin regions (9th week) At 16 weeks, hair shafts are formed in these regions HFs are formed in sequential waves of interspersed follicles
Hair cycle distribution for terminal scalp hair	Anagen: 85%–90% Telogen: 10%–15% Catagen: <1%
Duration of hair cycle phases	Anagen: 2–6 years Telogen: 2–3 weeks Catagen: 3 months } Terminal scalp hair
	There are substantial variations in anagen duration: Terminal mustache: 4–14 weeks Terminal on arms: 6–12 weeks Terminal on legs: 19–26 weeks Vellus: 6–12 weeks Premature anagen is induced by plucking of telogen hair shafts (depilation) Estrogens prolong anagen Thyroxine promotes growth, corticosteroids retard anagen onset
Number of lifetime cycles per scalp follicle	10–20
Physiologic hair shedding rate (scalp)	~100–200/day, with substantial interindividual and seasonal variations
Hair shaft production rate (scalp)	~0.35 mm/day, 1 cm/month Hair production is not influenced by cutting/shaving Estrogens reduce hair growth rate Androgens increase hair growth rate and hair diameter in androgen-dependent sites (e.g. beard)
Hair shaft diameter and length	Vellus: <0.03 mm; 1–2 mm Terminal: >0.06 mm; 1–50 cm Average diameter: Asian hair (circular): 120 microns Caucasian (elliptic): 50–90 microns
Hair shaft structures	Cuticle (outside), cortex, medulla (center) Cuticle maintains hair fiber integrity Cortex contains bulk of hair keratins and keratin-associated proteins Hair fiber strength is largely due to disulfide bonding Medulla consists of loosely connected trichocytes with large intercellular air spaces; provides insulation (animals)
Hair shaft pigmentation	Dark hair: predominance of eumelanin Blond/red hair: predominance of pheomelanin Melanosomes of hair cortex larger than those of epidermis
Hair graying (canities)	Generally commences in the third to fourth decade of life on the temples, spreading later to crown and occiput; by the age of 50 years, 50% of the population has at least 50% grey hair
Hair patterns	Pubic hair: horizontal (90% of women, 20% of men), acuminate (10% of women, 50% of men) Diffuse chest hair: normally grows only in men, after puberty until 6th decade Axillary: appears about 2 years after first pubic hairs, more sparse in Asians than White individuals; frequently absent in older individuals Trichoglyphics: single, clockwise parietal whirl present in 95% of individuals

*Data from Giacometti L. The anatomy of the human scalp. In: Montagna W (ed). Advances in Biology of Skin, Vol VI: Aging. Oxford: Pergamon Press, 1965:97–120.

Table 68.3 Basic information on human hair follicles (HFs).

bulge is relatively quiescent during telogen, traditionally referred to as the "resting" phase, due to inhibitory signals (e.g. FGF-18, BMP-6) from keratin 6-positive inner bulge cells[84]. The apparent dormancy of the HF during telogen may be an energy-efficient adaptation allowing for the maintenance of stem cells in preparation for the next anagen phase[85]. Consistent with this theory, mitochondrially localized myelin protein zero-like 3 (MPZL3) has recently been implicated in murine hair follicle cycling.[86]

The macro-environment surrounding the HF also takes part in regulating cycle transitions[87]. Immune cells surrounding the HF interact with the HF stem cell niche to control hair cycling. For example, in mice, TREM2$^+$ (triggering receptor expressed on myeloid

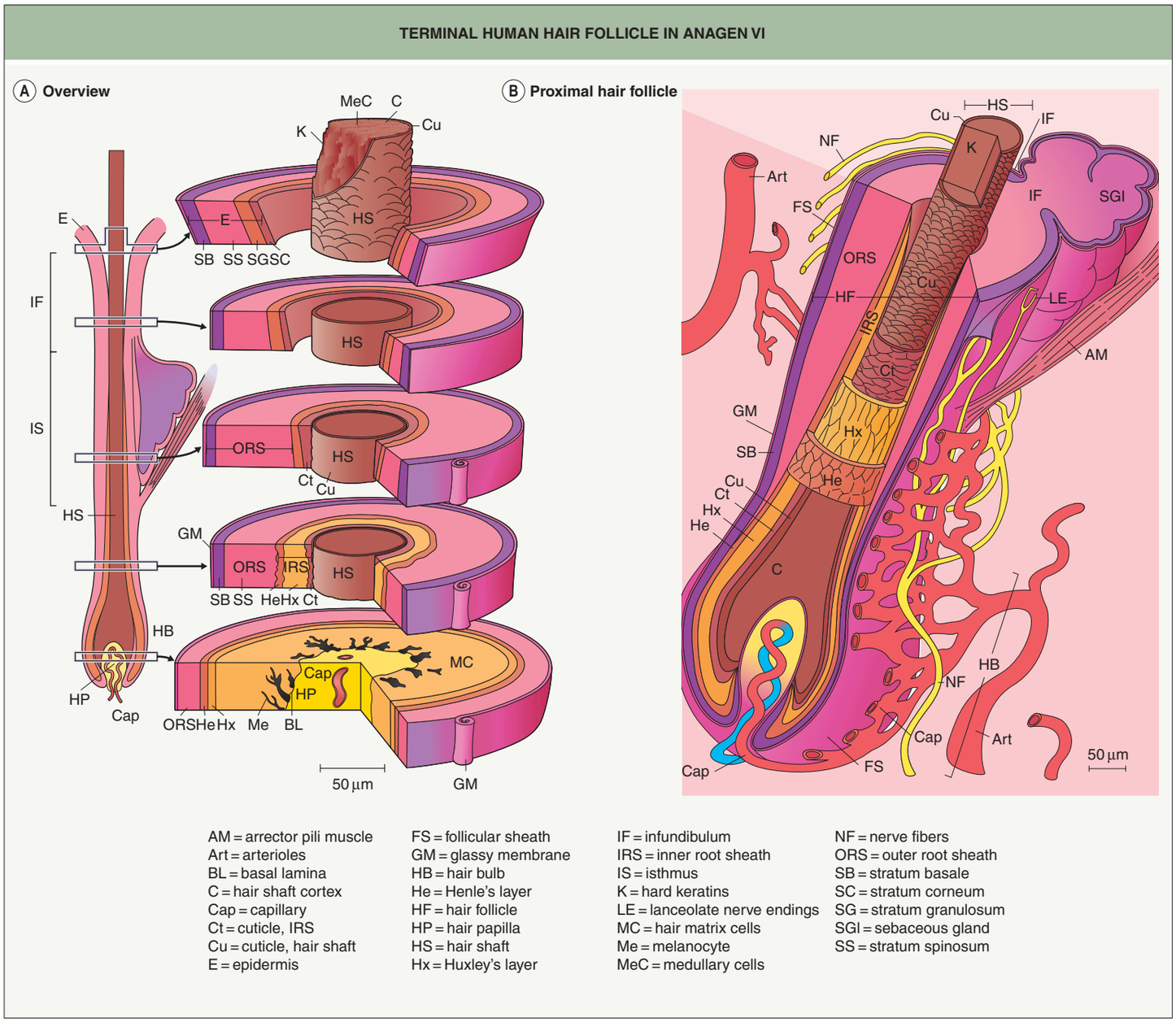


Fig. 68.5 Terminal human hair follicle in anagen VI. A Overview of the layers along the length of an anagen hair follicle. **B** Cross section of the longitudinal architecture of an anagen hair follicle.

cells 2) macrophages produce oncostatin M, which maintains the quiescence of HF stem cells and prevents anagen entry[88]. BMPs in the subcutaneous fat maintain HFs in a "refractory" telogen, and cessation of this inhibitory signal enables the follicle to progress to a "competent" telogen with a hair germ (biochemically distinct from the bulge) that is responsive to anagen-initiation signals and capable of entering a new anagen phase[83,89]. After secondary hair germ activation, the germ cells begin to contribute to the hair matrix and concentric layers of the follicle via an upward movement, while bulge cells generate the ORS through a downward movement[90]. In follicles with a longer anagen duration, the proliferative capacity of the matrix is not sufficient to sustain growth. The "stem cell trafficking theory" proposes that a continuous migration of precursor cells from the bulge down the ORS prevents exhaustion of the germinative matrix during anagen[91].

Exogen

The stimulus for entry into catagen, and hence the formation of a club hair, typically occurs several months before the hair is shed in humans[92]. "Exogen" represents the shedding of the club fiber (teloptosis) as well as the preceding signals and structural changes in the follicle[59]. Exogen is considered to be an active proteolytic event rather than a passive process where the club fiber is dislodged due solely to mechanical forces from the new growing fiber. A gradual decrease in the adhesion of the club fiber within its epithelial silo has been observed prior to its programmed release from the follicle[93].

Structure of the hair fiber

In response to signals from the dermal papilla, the matrix cells at the base of the follicle proliferate and differentiate during anagen, forming the layers of the follicle. The three central lineages – medulla, cortex, and hair cuticle – form the hair fiber, which fulfills the primary hair-producing function of the anagen follicle. Surrounding the hair fiber are the three concentric layers that compose the inner root sheath (IRS): the IRS cuticle, Huxley's layer, and Henle's layer. The IRS undergoes a complex program of differentiation during anagen, with Henle's layer terminally differentiating shortly after formation. The IRS cuticle differentiates further up the follicle, followed by Huxley's layer; all three layers undergo desmosomal remodeling during terminal differentiation[94]. The IRS forms a mechanically supportive tube around the hair fiber and is degraded by proteolytic enzymes at the level of the isthmus[95], allowing the hair shaft to enter the hair canal and emerge from the skin surface. Heparanase expressed in the IRS during anagen

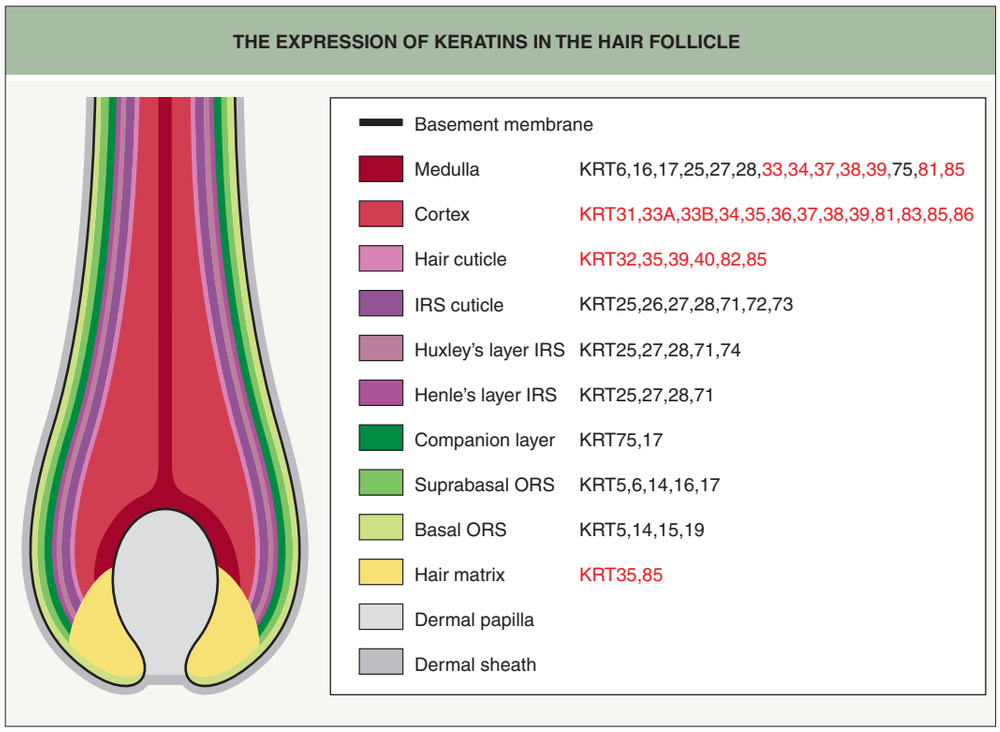


Fig. 68.6 The expression of keratins in the hair follicle. Hair keratins are in red font. KRT, keratin.

acts on heparin sulfate proteoglycans and controls IRS differentiation by influencing growth factor sequestration and diffusion[96].

The seventh concentric layer that originates from the matrix in line with the hair fiber and IRS is the companion layer, which is a single cell thick. Regarded as the "slippage plane" between the IRS and the surrounding ORS during anagen, the companion layer enables directional hair growth. It is attached to the IRS through "Flugelzellen" structures that extend from Huxley's layer through Henle's layer and link to the companion layer via numerous desmosomes[97,98]. A "barrel" of transversely oriented intermediate filaments on the inner side of the companion layer are thought to provide support for the inner root sheath, protecting it from the compressive forces of the expanding ORS[99].

Hair Keratins

The 54 functional keratin genes encode 28 type I and 26 type II keratins, which form heterodimeric pairs containing one keratin of each type[100]. There are 11 type I hair keratins, designated KRT31–KRT40, and six type II hair keratins, designated KRT81–KRT86 (see Table 56.2); the remainder are epithelial keratins[101,102]. Compared to epithelial keratins, hair keratins possess more sulfur in their head and tail domains, which allows them to form tight cross-links via disulfide bonds.

Different hair and epithelial keratins are expressed in the concentric layers of the HF, with hair keratins found primarily in the cortex and hair cuticle (see Fig. 56.6)[103]. Autosomal dominant monilethrix, which features fragile "beaded" hairs and follicular hyperkeratosis, is caused by mutations in the helix termination and initiation motifs of several type II hair keratins: KRT81, KRT86, and (less commonly) KRT83[104,105]. These keratins are highly expressed within the hair cortex and are critical to its development[104,105]. Mutations in the genes encoding KRT85 and KRT74 (see below) underlie autosomal recessive pure hair and nail ectodermal dysplasia. KRT85 is primarily expressed in the matrix of the follicle, which explains the total alopecia observed in these patients[106].

Some epithelial keratins exhibit HF specificity (see Fig. 68.6). The type I keratins KRT25, KRT27, and KRT28 and the type II keratin KRT71 are expressed within the IRS (cuticle, Huxley's layer, and Henle's layer). KRT74 is restricted to Huxley's layer, while KRT72 and KRT73 are found in the IRS cuticle[107]. Mutations in the genes encoding KRT71 and KRT74 can cause autosomal dominant woolly hair with or (for KRT74) without associated hypotrichosis[108,109], and a homozygous missense variant in *KRT25* has been implicated in autosomal recessive woolly hair[110].

The companion layer contains only one type II keratin, the epithelial KRT75, which is also expressed in the medulla of the hair shaft and the fungiform papillae of the tongue. Pseudofolliculitis barbae and loose anagen hair syndrome have possible links to defects in KRT75 in some patients[101]; KRT75 polymorphisms are also associated with reduced enamel hardness and increased risk of dental caries, highlighting the link between tooth and hair architecture[111]. The ORS expresses several keratins, including KRT5/KRT14, KRT6a/KRT16, and KRT6b/KRT17 (see Fig. 68.6). However, patients with pachyonychia congenita due to mutations in the latter keratin pairs only occasionally exhibit hair abnormalities such as pili torti (primarily with KRT17 defects)[112].

Desmosomes in the Hair Follicle

Desmosomes are specialized adhesive structures that couple neighboring cells together in a variety of tissues, with particular importance in epithelia and the myocardium[113]. Each desmosome is connected to the intermediate filament cytoskeletons of the interacting cells, which imparts resilience and resistance to mechanical stress (see Fig. 56.8). Desmogleins (Dsg1–4) and desmocollins (Dsc1–3) are desmosome-specific cadherins that interact in the intercellular space to couple the two halves of the desmosome; they are connected to intermediate filaments via the linker proteins plakoglobin, plakophilins (Pkp1–3), and desmoplakin. Mutations in genes encoding desmosomal components can result in diseases affecting: (1) the hair – woolly, fragile, and/or sparse; (2) the skin – palmoplantar keratoderma, fragility/blistering; and (3) the heart – cardiomyopathy. This leads to multisystem disorders such as Naxos disease, Carvajal syndrome, and skin fragility–ectodermal dysplasia syndrome (see Fig. 56.8 and Ch. 58).

All four desmogleins are found in the HF, with differentiation-specific expression patterns[114,115]. Dsg4 is the only desmosomal cadherin that is highly expressed in the hair shaft cortex, including the keratinizing zone in which hair keratins are abundant. Dsg4 is also present in the precortex, lower hair cuticle, upper IRS cuticle, and interfollicular epidermis (granular and cornified layers)[116]. Transcription factors that regulate the expression of both Dsg4 and hair keratins in differentiating trichocytes include LEF1 (lymphoid enhancer-binding factor), HOXC13 (homeobox C13), and FOXN1 (forkhead box N1)[117]. Dsg4 is a key mediator of keratinocyte adhesion in the HF, where it coordinates the transition from proliferation to differentiation[116]. Mutations in *DSG4* can cause autosomal recessive forms of localized hypotrichosis and monilethrix, with the pathomechanism involving a stress response due to accumulation of the mutant protein in the endoplasmic reticulum (ER)[118].

Although hair shedding and alopecia result when Dsg3 is disrupted in mice[119,120], similar hair phenotypes have not been identified in humans with Dsg3 defects. However, a homozygous mutation in *DSC3* has been reported to underlie hypotrichosis with recurrent skin "vesicles"[121]. In addition, mutations in *CDSN* which encodes corneodesmosin, a glycoprotein found in the IRS and modified desmosomes within the stratum corneum, can result in autosomal dominant hypotrichosis simplex of the scalp (see Fig. 56.8)[122]. *CDSN* mutations also cause autosomal recessive inflammatory peeling skin syndrome, reflecting the role of corneodesmosin proteolysis in desquamation[123].

Hair Follicle Stem Cells

Adult stem cells have the ability to self-renew and to regenerate tissues during homeostasis and wound repair. Given the dynamic remodeling seen with the cyclic regeneration of the HF, it has long been postulated that it contains one or more stem cell niche(s) (see Ch. 2). Studies in the 1990s showed that slow-cycling, label-retaining cells (characteristics of stem cells) are localized within the HF bulge area, which is named for the swelling evident at this site in rodents[66].

Although the bulge architecture in mice is not pronounced until 3 weeks after birth, slow-cycling bulge cells can be identified during early stages of murine HF morphogenesis by the marker SOX9[124]. During anagen in adult mouse skin, bulge stem cells express distinctive markers, including SOX9 as well as S100A4 and CD34. The molecular architecture of the bulge is not identical in mice and humans, as the human HF stem cell niche is not morphologically distinct. However, analysis of human anagen HFs have identified distinctive human bulge cells with clonogenic potential that express CD200 but, in contrast to bulge cells in mice, not CD34 (see Table 2.2)[125].

When murine follicles cycle through telogen, a secondary hair germ is formed below the bulge, just above the dermal papilla. Bulge cell progeny in this hair germ that had migrated out of the stem cell niche during the previous anagen are capable of returning and regaining stem cell characteristics[84]. Some markers are expressed in both the secondary hair germ and the bulge, including keratin 15 and (at low levels) SOX9[83] while others are only highly expressed in the former (e.g. P-cadherin, LEF1)[83]. Following wounding, bulge and hair germ cells can both contribute to the interfollicular epidermis[126]; however, this does not occur under homeostatic conditions. Cell populations that maintain the sebaceous glands and interfollicular epidermis in mice include a LGR6 (leucine protein G rich repeat coupled receptor 6)-positive population in the central isthmus[127] as well as leucine-rich repeats and LRIG1 (immunoglobulin-like domains 1)- and Blimp1-positive populations in the upper isthmus[128,129]. There is also an SCA1 (stem cell antigen-1)-positive cell population in the infundibulum that is thought to contribute to skin homeostasis[130].

The dermal papilla and dermal sheath represent a mesenchymal stem cell niche within the follicle. Under homeostatic conditions, dermal papilla cells rarely divide after formation of the initial condensate during morphogenesis, yet their gene expression profile is dynamic throughout development and the hair cycle. If removed from their niche, dermal papilla cells have the ability to differentiate into osteogenic, myogenic, adipogenic, and hematopoietic lineages[131–133]. In addition to their ability to transdifferentiate, a major function of dermal papilla cells is related to their inductive potential. Isolated and cultured dermal cells from adult follicles are capable of stimulating a range of committed epithelia to form follicles, inclusive of progenitor stem cells[55,134–136]. The potential of cultured human dermal papilla cells to induce *de novo* hair growth provides the basis for novel therapeutic approaches[56].

The Hair Follicle and the Immune System

The HF represents an immune privileged site, which is defined as a location in the body where foreign tissue grafts can survive for extended periods of time without immune rejection. Of note, other immune privileged sites include the anterior chamber of the eye, testis, brain, and placenta.

Initial evidence regarding the immune protection of the HF came from the classic "Billingham experiment" in 1971[137], in which skin from black guinea pigs was transplanted onto an immunologically incompatible strain of white guinea pigs. The grafted skin turned white, reflecting the expected immune response against the foreign epidermal melanocytes. However, pigmented hairs grew within the grafts, showing that the foreign HF melanocytes survived. Application of the contact allergen picryl chloride to mouse skin during early anagen results in an attenuated sensitization reaction compared to application during telogen[138], suggesting that the HF immune system is suppressed specifically during anagen. Features of the human anagen hair bulb that protect it from an immune response are summarized in Table 68.4.

The immune privilege of the HF was previously thought to be restricted to the matrix region during the anagen phase. However, evidence has accumulated that the bulge region has immune privilege during the entire hair cycle[139]. Since the bulge represents the HF stem cell niche, sustained immune privilege in this region may be essential for the survival of the follicle. Autoimmune attack leading to loss of the stem cells in the bulge results in cicatricial alopecia where regrowth is unlikely[140].

Two mechanisms can potentially underlie an immune reaction directed against the hair: (1) a primary attack of the immune system against the HF; or (2) a breakdown in HF immune privilege leading to a secondary attack by the immune system[141–143]. Since the hair matrix immune privilege is mainly restricted to the anagen phase[143], it has been postulated that an autoantigen from melanocytes, which are active during the anagen phase, could be responsible for initiating the immune response against the HF that occurs in alopecia areata. Indeed, antibodies against melanocyte-associated antigens have been found in patients with this condition[144,145].

The collapse of HF immune privilege is linked to upregulation of HF major histocompatibility complex (MHC) class I molecule expression, which allows presentation of autoantigens to the immune system[146]. In HFs affected by alopecia areata, there is increased expression of MICA (MHC class I polypeptide-related sequence A). $CD8^+$ T cells and natural killer (NK) cells accumulate around affected HFs and exhibit increased expression of the NKG2D activating receptor, but decreased expression of inhibitory receptors such as KIR3DL1 (killer cell

MECHANISMS CONTRIBUTING TO THE IMMUNE PRIVILEGE OF THE HAIR FOLLICLE

Mechanism of immune evasion	Function of the molecules affected
Downregulated expression of MHC class I, MICA, and β_2-microglobulin	Required for presentation of autoantigens to the immune system
Downregulated expression of MHC class II	Required for functioning of antigen-presenting cells
Upregulated expression of IL-10, transforming growth factor-β1 (TGF-β1), and α-melanocyte stimulating hormone (α-MSH)	Immunosuppressive actions
Increased production of Fas-ligand (FasL)	Induces apoptosis of activated T cells; known to be crucial for maintenance of immune privilege in the eye, brain, and fetus
Low expression of heterodimeric CD94/NKG2C and NKG2D receptors on NK cells and $CD8^+$ cytotoxic T cells as well as of the NKG2D ligand UL16 binding protein 3 (ULBP3)	These receptors activate NK cells and $CD8^+$ cytotoxic T cells upon ligand binding; NKG2D has been implicated in the immune attack on the hair follicle in alopecia areata
High expression of killer cell immunoglobulin-like receptors (KIRs) and heterodimeric CD94/NKG2A receptors on NK cells	These receptors inhibit NK cells
Increased production of indoleamine 2,3-dioxygenase (IDO)-1	Inhibits lymphocyte proliferation
Increased production of IK cytokine	Inhibits interferon-γ-induced expression of MHC class II antigens
Lack of lymphatic vessels around the hair follicle	Recruit immune cells

Table 68.4 Mechanisms contributing to the immune privilege of the hair follicle. IL, interleukin; MHC, major histocompatibility complex; MICA, MHC class I polypeptide-related sequence A; NK, natural killer.

immunoglobulin-like receptor three domains long cytoplasmic tail 1) and heterodimeric CD94/NKG2A[143,147]. ULBP3 (UL16 binding protein 3), a NKG2D ligand, is upregulated in the dermal sheath and papilla of HFs affected by alopecia areata[147]. These observations indicate that HFs in patients with alopecia areata lose their immune privilege and express danger signals in their outermost layer.

The pathogenesis of alopecia areata also involves downregulation of immunosuppressant molecules such as transforming growth factor (TGF)-β1, α-melanocyte stimulating hormone (MSH), indoleamine 2,3-dioxygenase (IDO)-1, and the IK cytokine that inhibits the functions of interferon (IFN)-γ[139,141,143]. IFN-γ plays a pivotal role by inducing the expression of MHC class II antigens, which are normally absent in the HF matrix and dermal sheath, thereby propagating the immune response and contributing to destruction of the hair follicle.

Genome-wide association studies (GWAS) in patients with alopecia areata have implicated genes that are involved in immune regulation, in particular the function of regulatory T cells, such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4), interleukin (ILs)-2 and -21, the IL-2 receptor A (CD25), ULBPs, and Eos (an Ikaros transcription factor), as well as genes expressed in the follicle (e.g. syntaxin 17, peroxiredoxin 5)[147,148]. Such studies have provided insights into potential therapeutic targets. For example, treatment with inhibitors of the Janus kinase (JAK) pathway, which is involved in signaling by many of the cytokines implicated in alopecia areata, can result in significant hair regrowth[149,150].

BIOLOGY OF NAILS

Like its phylogenetic ancestors (e.g. claws, hoofs), the nail protects the distal phalanges and contributes to a variety of motor and sensory functions (see Table 68.2). Two key aspects of nail biology are how nails grow and from what part of the nail apparatus they arise. The composition and appearance of the nails and the characteristics of the surrounding tissues are other important considerations, potentially representing signs of internal disease or environmental exposures[151,152]. An understanding of these aspects of the nail unit, in addition to its anatomy and development, can maximize the clinician's ability to assess, diagnose, and treat patients with nail disorders. However, our current knowledge of the regulation of nail development and growth on a molecular level is relatively poor, and acquisition of data has been hampered by the difficulty in obtaining nail-producing tissues and growing nails and/or nail matrix keratinocytes in culture. Tools such as mouse models given the substantial homology between murine claws and human nails, organ-culturing microdissected components of the human nail apparatus, and nail-equivalent *in vitro* systems will hopefully help to better elucidate the molecular mechanisms of nail biology.

Nail Unit Anatomy

An understanding of nail biology and disease requires knowledge of the local anatomy (Fig. 68.7)[153,154]. The nail plate is a hard, semitransparent, slightly convex sheet comprised of tightly packed corneocytes termed onychocytes. It contains "hard" hair-type keratins, which are embedded in a matrix of sulfur-rich, high-cysteine and high-glycine/tyrosine proteins (see below). The dermis of the nail apparatus is a fibrocollagenous network that is sandwiched between the nail plate and the underlying bone, lacking associated subcutaneous soft tissues or pilosebaceous units. As a result, bacterial infections in this region have a relatively high risk of spread to the bone, resulting in osteomyelitis of the distal phalanx.

The nail plate is surrounded on three edges by nail folds, one proximal and two lateral. The proximal nail fold, a double layer of skin overlying the proximal part of the nail, protects this area from trauma, solvents, and infectious agents that might otherwise alter nail shape and structure. The dorsal layer of the proximal nail fold is continuous with the skin of the digit, while the ventral layer is continuous with the nail matrix. The cuticle (eponychium) is a thin strip of cornified epithelium that adheres to the nail at the edge of the proximal nail fold and acts as a seal against ingress. Damage to the cuticle results in a predisposition to inflammation of the nail fold; conversely, inflammation of the nail folds disrupts normal maturation of the epithelium and cuticle formation. Nail-fold inflammation can also disturb the underlying matrix and alter nail plate production, most often manifesting as transverse ridging. The proximal nail fold may help to mold the emerging nail, forming a relatively thin structure that grows obliquely from its point of origin in the matrix.

The longitudinal axis of nail growth is also guided by the lateral nail folds, which compress the nail plate from each side and contribute to its transverse curvature. The lateral margins of the nail bed form deep

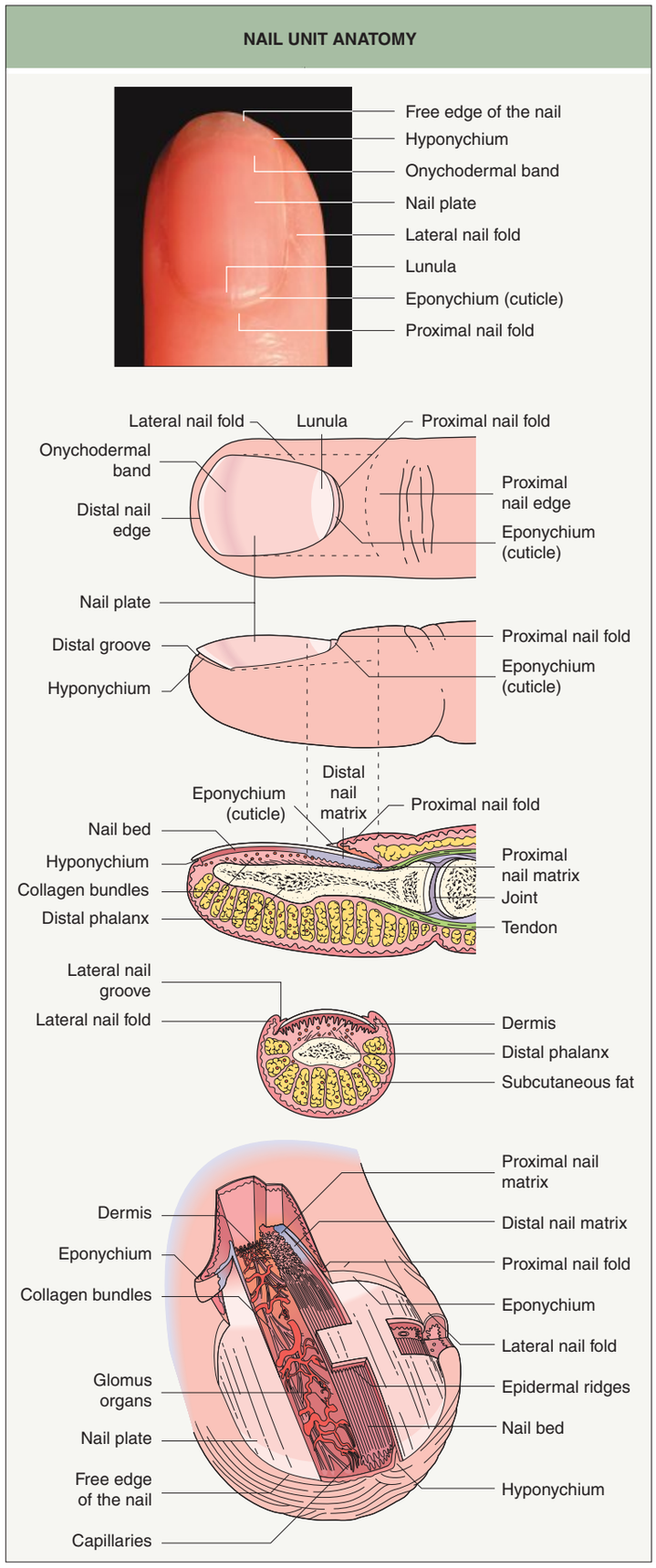


Fig. 68.7 Nail unit anatomy.

sulci that follow the curve of the distal phalanx and then fold back on themselves to produce the lateral nail folds. These sulci help to attach the nail to the soft tissues and, similar to the proximal nail fold and cuticle, provide a seal at the nail margin.

The structures bounded by the nail folds are the nail matrix proximally and the nail bed distally and medially. The half-moon-shaped lunula, which is most prominent on the thumb, demarcates the junction between the matrix and the nail bed. The lunula is less apparent, due in part to concealment by the proximal nail fold, with progression from the second to fifth finger. The lunulae of the toes are hidden by their thicker nail plates (especially for the great toes) and relatively prominent proximal nail folds, which may serve a protective function[153,154].

The nail plate is in continuity with the matrix from which it arises, while the nail bed represents its underlying support structure and extends from the distal margin of the lunula to the onychodermal band, a thin pinkish transverse strip proximal to the whitish onychocorneal band (see Fig. 68.7). A longitudinal pattern of rugose rete ridges in the nail bed increases the surface area of its attachment to the ventral aspect of the nail, which has corresponding ridges. This enhances adhesion between these surfaces and enables the free edge of the nail to be used as a levering tool without lifting the nail or causing pain. Histologically, both the nail bed and matrix normally lack a granular layer. The presence of a granular layer in these sites is a sign of pathology, such as the altered nail bed behavior associated with subungual hyperkeratosis.

The nail is in close proximity to the underlying distal phalanx, and BMPs are thought to have roles in the morphogenesis of both structures. When the distal phalanx and/or interphalangeal joint are affected by an inflammatory disease such as psoriasis, involvement of the nail matrix (and hence nail plate) often occurs. Congenital absence of part of the distal phalanx is typically accompanied by a small or otherwise altered nail (e.g. congenital onychodysplasia of the index fingers), further illustrating the relationship between these two structures[155]. In the neonatal period, digit tip regeneration can occur in humans after partial amputation. This appears to require the presence of a residual nail unit and to involve the expression of BMP-4 and the MSX1 (muscle segment homeobox 1) transcriptional repressor[156]. Overexpression of MSX1 and MSX2 is associated with increased regenerative capacity[157]. There appears to be a reciprocal interaction between nail and bone, with bone mesenchyme providing a scaffold for nail regrowth and the nail bed facilitating regeneration of underlying bone[158,159]. In later life, regeneration rarely, if ever, occurs upon partial amputation of the fingertip due to trauma or osteolysis in the setting of scleroderma, and secondary nail changes typically ensue.

Studies in adult mice suggest that LGR6-expressing nail stem cells in the proximal matrix are capable of WNT-dependent nail blastema formation, which enables digit tip regeneration[160,161]. Nerve-associated Schwann cell precursors that dedifferentiate and secrete growth factors such as oncostatin M and platelet-derived growth factor A promote expansion of the blastema and are required for murine digit regeneration[162]. The cytoskeletal protein flightless I (Flii) also enhances murine digit regeneration after amputation; although this is normally limited to distal third amputations, mice with overexpression of Flii can retain the proximal nail matrix and regenerate proximal amputations[163]. Outside of the nail unit Flii is associated with *inhibition* of epidermal stem cells and wound reepithelialization[164], suggesting that prevention of epithelialization may allow continued connective tissue proliferation and thereby enable the subepidermal repair required for greater digit regeneration. These observations in mice may help to develop therapies for human amputees in the future.

The vascular supply of the digit is through two dorsolateral and two ventrolateral arteries that lack an internal elastic lamina and have a tortuous morphology that helps them to withstand flexion and other movements. There is substantial communication between these vascular networks, particularly distally via plexuses in the proximal nail fold and digital pulp. This provides the digit with a blood supply of more than one origin and direction, which ensures continued flow in the event of trauma or a sustained grip that decreases supply from the ventral vessels. The pulp plexus is located within a recess produced by the gap between the ventral prominence of the distal phalanx and the rim of the distal interphalangeal joint[165].

In a cold environment, which leads to constriction of arterioles, arteriovenous anastomoses (Sucquet–Hoyer canals) within glomus bodies maintain sufficient blood supply to the distal digits. Glomus bodies are encapsulated oval structures containing modified smooth muscle cells that dilate upon exposure to the cold. These structures are most prominent in the subungual tissue, which represents the most common site of a glomus tumor, a benign proliferation of glomus cells[166] (see Ch. 114).

In the proximal nail fold, the dermal capillaries normally form a regular pattern of "hairpin" loops with a thin efferent limb and a more tortuous, thicker afferent limb. The organization of nail bed vessels is similar, although the hairpin turn is less evident. Dermatoscopic examination (capillaroscopy) of nail-fold vessels can help to assess a patient's acral microvascular status. The pattern and/or patency of the capillaries in the proximal nail fold and nail bed is often altered in patients with an autoimmune connective tissue disease (AI-CTD) or embolic disorder. The proximal nail folds of patients with lupus erythematosus typically show dilated, tortuous capillaries of normal density, whereas systemic sclerosis and dermatomyositis feature hemorrhages and decreased capillary density characterized by avascular areas alternating with dilated capillary loops. Acral infarction due to embolization (e.g. in the setting of endocarditis) can result in leakage of blood into the nail bed, referred to as splinter hemorrhages. These lesions can also develop secondary to trauma, AI-CTD, and psoriasis; the latter condition is associated with an increased number of papillary dermal vessels, disrupted nail integrity, and shearing forces between the nail plate and bed.

The nerve supply of the digit follows the pattern of the vascular supply, with two dorsal and two ventral branches that have some overlap distally in their sensory territories[154]. Since the fingertips have an important role in sensory perception, nerve endings that transmit pain (type I fibers), touch (Meissner and Pacinian bodies), and temperature are all abundant. The function of these nerve endings may be compromised by pressure due to relatively minor trauma and edema within the fascial envelope that encloses a finger or toe.

Nail Embryology

The nail primordium becomes evident at 8 weeks' gestational age as a transverse ridge on the distal dorsal surface of the digit (Fig. 68.8) (see Ch. 2). Over the next 4 weeks, the ridge takes a more proximal position and eventually invaginates beneath the emerging proximal nail fold. The outline of the nail unit is established by 16 weeks' gestational age, and the nail plate completely covers the nail bed during the fifth month.

The study of inherited nail diseases has provided clues regarding some of the processes that regulate the formation of the nail unit. An autosomal recessive form of anonychia congenita is caused by loss-of-function mutations in the gene encoding R-spondin 4 (RSPO4), which functions in the WNT signaling pathway[167]. Mouse studies have demonstrated expression of *Rspo4* in digit mesenchyme during embryogenesis, and it is thought to influence induction of the nail unit in the overlying epithelium. Human *WNT10A* mutations that alter β-catenin signaling can result in nail dystrophy as well as hypotrichosis, hypodontia, and palmoplantar keratoderma (see Ch. 63)[168]. In contrast, changes in claw formation have not been noted in *Wnt10* knock-out mice[169].

Nail–patella syndrome is another genetic disorder that has contributed to our understanding of nail development. The nail changes in this autosomal dominant condition include triangular lunulae and absent or hypoplastic nails, with most prominent involvement of the thumbnail and other radial digits; however, an individual nail is usually more severely affected on its ulnar side. Extracutaneous manifestations include hypoplastic patellae, iliac horns, nephropathy, and glaucoma. Nail–patella syndrome is caused by mutations in the gene encoding the LIM homeobox transcription factor 1β (LMX1B), which influences dorsoventral limb patterning[170,171]. In Clouston syndrome, a form of ectodermal dysplasia due to mutations in the gap junction β6 gene (*GJB6*) that encodes connexin 30, thickened nails with onycholysis occur in association with hypotrichosis and palmoplantar keratoderma (see Ch. 63)[172]. These genetic nail diseases illustrate the importance of communication between cells and tissues in the morphogenesis of the nails as well as other adnexal structures and organs. These messaging systems use the same code to initiate a variety of events in different tissues. Other genetic diseases affect the nails through alteration of their structural components, such as keratins or constituents of the basement membrane.

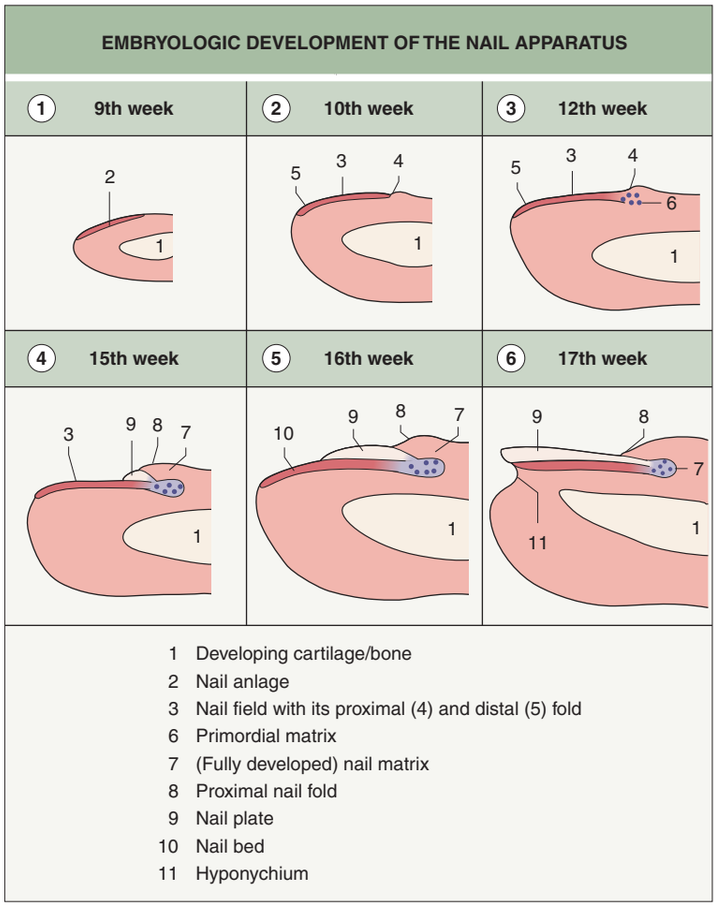


Fig. 68.8 Embryologic development of the nail apparatus.

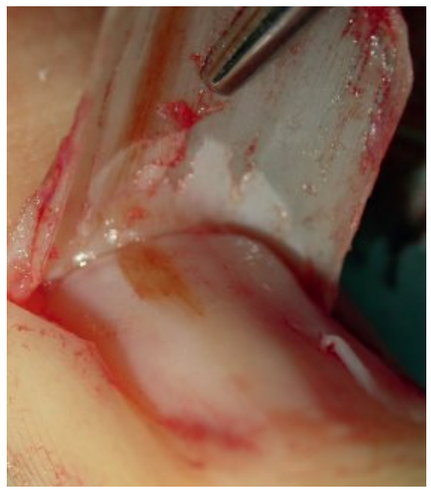


Fig. 68.9 Nail matrix biopsy to determine the etiology of longitudinal melanonychia. Note that the pigment in the nail extends to the proximal part of the matrix in the nail plate and (as seen when the nail is lifted) the matrix itself.

Nail Matrix

"Nail matrix" is a functional and anatomical term; although there is currently general consensus with regard to these definitions, disagreement about the precise functional role of the matrix (see below) can potentially lead to confusion about its exact anatomy.

Matrix anatomy

The anatomical boundaries of the classical matrix are visible during a surgical procedure in which the nail is avulsed and the proximal nail fold retracted (Fig. 68.9). This reveals two zones of tissues on which the nail rests, a proximal pale nail matrix and a distal pinker nail bed. Their arcuate junction is evident through the nail plate as the lunula (half moon). The most lateral portion of the matrix may be "buried" in the sulcus of the lateral nail fold (see Fig. 149.2); because this can be difficult to access surgically, procedures designed to remove the lateral part of the nail matrix sometimes leave behind a small piece of matrix that produces a detached spicule of nail (see Fig. 149.15). Proximally, the matrix extends to the point of flexure of the proximal nail fold, where the latter structure turns back over and protects the proximal margin of the nail (see Fig. 68.7). Compared to epidermal keratinocytes, those in the nail matrix are larger and have a higher rate of proliferation.

Matrix function

For more than 50 years, anatomists and clinical scientists have investigated the relationship between the matrix and production of the nail (Fig. 68.10). Early work by Lewis[173] used static histology of silver-stained longitudinal sections of the nail unit to delineate three layers that he postulated were derived from separate epithelial surfaces within the nail unit: (1) the ventral aspect of the proximal nail fold (upper nail plate); (2) the classical matrix as defined above (mid nail plate); and (3) the nail bed (lower nail plate). This led to the misconception that there are three areas of matrix – dorsal, ventral, and intermediate. Subsequent studies in squirrel monkeys, which have digits similar to those in humans, utilizing *in vivo* autoradiography provided evidence that most, if not all, of the nail plate is generated from the classical matrix[174]. In these experiments, systemic injection of tritiated thymidine was followed by amputations at different time points, demonstrating that the thymidine reached the nail plate via the matrix. Injection of radiolabeled glycine into the nail unit of human volunteers who then had nail biopsies also showed that the classical matrix is the main source of the nail plate[175].

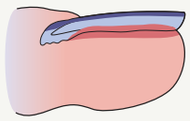
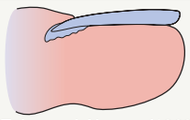
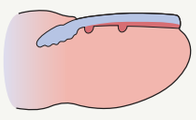
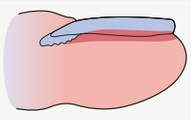
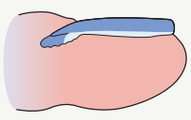
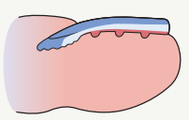
In the early 1990s, Johnson and colleagues[176] found that between the distal margin of the lunula and the end of the nail bed, the nail plate of the great toe increases in thickness by ~20%. They inferred from this observation that the nail bed contributed this proportion of the nail plate. Histologic assessment of great toe nail plates obtained via avulsion confirmed this increase in thickness but showed that the number of cells in the vertical axis of the nail plate did not increase from the proximal to distal nail bed. These results suggested that the nail plate thickens because of compaction due to distal-to-proximal compression rather than an active contribution from the underlying nail bed[177]. Walking while wearing shoes produces low-grade, repetitive trauma to the free edge of the great toenail, which would explain such an effect[177].

Immunohistochemical staining with proliferating cell nuclear antigen or Ki-67 demonstrates minimal proliferative activity in the nail bed but substantial activity in the matrix, further supporting that the matrix is the source of the nail plate[178]. The correlation between anatomy and function explains the different patterns of nail disease that result from pathology affecting the matrix versus the nail bed (see Table 71.1). It also accounts for the potential for permanent nail deformity following surgical intervention or biopsy of the matrix, but not for similar interventions involving the nail bed. Because the proximal half of the matrix produces ~80% of the nail plate, surgeries or biopsies in this area are more likely to produce nail dystrophy than those of the distal matrix. Onychocytes migrate upward and distally along an oblique axis during their maturation and differentiation; as a result, the proximal part of the matrix produces the dorsal portion of the nail plate, while the distal part of the matrix synthesizes the ventral portion of the nail plate. Abnormalities in the proximal matrix underlie clinical findings such as pitting and longitudinal ridging/splitting, whereas disruption of the distal matrix can cause true leukonychia. Interestingly, nail pitting can occur in association with alopecia areata, suggesting shared pathomechanisms.

Nail Stem Cells

Identification of label-retaining cells in the basal layer of the nail matrix has suggested that this represents the main source of nail stem cells[179], although other experimental approaches have suggested alternative nail stem cell niches[180]. In labeling studies, basal cells from the proximal nail matrix persisted longer than those from the distal matrix or nail bed[160]. Lineage tracing using HF stem cell markers (e.g. KRT15)

THEORIES ON THE ORIGIN OF THE NAIL PLATE

Origin of the nail plate	Evidence	Schematic, reference
Three portions of the nail matrix form three corresponding parts of the nail plate, which is characterized by a three-layer structure: Dorsal part = Proximal nail fold → Upper nail plate Inter-mediate part = Classical nail matrix → Intermediate nail plate Ventral part = Nail bed → Lower nail plate	Light microscopy and silver staining of human nails	 Lewis (1954)
Cells of the classical matrix are the origin of the whole nail plate	*In vivo* auto-radiography (with tritiated thymidine) in squirrel monkeys	 Zaias and Alvarez (1969)
Cells of the classical matrix produce nearly the total nail plate. Only a few cells of the nail bed in poorly defined locations take part in forming the nail plate	*In vivo* auto-radiography (with radiolabeled glycine) in human volunteers	 Norton (1971)
The regrowth of nail plates following traumatic avulsion of great toenails was investigated: approximately 20% of the nail plate's thickness was added when the nail grew over the nail bed, suggesting a nail bed contribution to the nail plate's growth	Changes in nail plate's thickness during nail growth in human volunteers	 Johnson et al. (1991,1993)
Cells of the proximal half of the matrix produce approximately 80% of the nail plate, whereas 1% or less of the nail plate is contributed by the nail bed. In psoriatic nails, the nail bed contribution may increase to over 25%	Immunohisto-chemical labeling in healthy human nails with antibodies to proliferating cell nuclear antigens and antigen Ki-67	 Healthy nail  Psoriatic nail de Berker and Angus (1996); de Berker et al. (1996)

Sites of origin and their contributions to the nail plate:

- Proximal matrix within nail fold (dorsal matrix)
- Nail bed
- Nail matrix
- Proximal half of nail matrix
- Distal half of nail matrix

Fig. 68.10 Theories on the origin of the nail plate. *Adapted fom Dawber RP, de Berker DA, Baran R. Science of the nail apparatus. In: Baran R, Dawber RP, de Berker DA, et al (eds). Diseases of the Nails and their Management. Oxford: Blackwell Science, 2001;1–47.*

identified a ring-like population of quiescent cells in the proximal nail fold that was harboring putative stem cells[181]. Much like the HF, the nail unit is likely to have more than one stem cell niche, each with distinct cellular dynamics and function.

Nail Unit Melanocytes

Melanocytes are found in the nail matrix but not in the normal nail bed. In general, foci of pigment in the nail bed that are separated from the nail folds and matrix are not melanocytic in origin[182], with possible exceptions including a metastatic melanoma and a partially amelanotic melanoma that is continuous with the matrix or nail fold. Nail matrix melanocytes are most abundant in the distal matrix and are found in suprabasal layers as well as the basal layer, which may reflect a distinct expression pattern of adhesion molecules (e.g. α_2, α_3, and β_1 integrins) that regulate interactions between melanocytes and keratinocytes[183].

The main distribution pattern of melanin in the nail plate is pigmented bands, referred to as longitudinal melanonychia, which vary in number, intensity, and width depending on their etiology (see Ch. 71). Multiple streaks of longitudinal melanonychia due to active nail matrix melanocytes are commonly found in individuals with darkly pigmented skin, sometimes as a result of trauma or inflammation affecting the matrix. In contrast, nail matrix melanocytes in individuals with lightly pigmented skin are normally quiescent; longitudinal melanonychia in such patients, especially an isolated band in an adult with no systemic or local causative factors, usually requires a nail matrix biopsy to exclude the possibility of melanoma (see Ch. 149). Inadequate biopsy specimens (e.g. too small, non-representative) can lead to a delay in diagnosis and less favorable prognosis[184].

The Nail Immune System

The nail unit, in particular the proximal matrix, represents a site of relative immune privilege, with reduced expression of MHC class I and II antigens and decreased numbers of antigen-presenting cells. Similar to the HF, the stem cell niche of the nail unit is believed to have immune privilege to ensure its preservation in the face of constant environmental exposure. Although the immune privilege may prevent over-reactivity to environmental antigens, it may also increase vulnerability to human papillomavirus infections and their potential oncogenic effects, which can result in periungual squamous cell carcinomas[185]. Collapse of immune privilege has been suggested to underlie lichen planus of the nail unit as well as lichen planopilaris of the scalp[140].

Nail Keratins

Multiple types of keratins are expressed in the nail apparatus (Fig. 68.11), and they account for 80% of the dry weight of the nail plate. The nail plate and matrix contain "hard" hair-type keratins with a large number of sulfur-containing amino acids that facilitate cross-linking between keratin molecules. This reduces the amount of water associated with these proteins and makes them more rugged and resistant to chemical destruction compared to "soft" epithelial keratins[186]. Keratin 15 in the proximal ventral aspect of the proximal nail fold may represent a marker of a keratinocyte stem cell population[181].

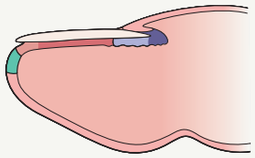
The pattern of keratin expression within the nail unit explains the involvement of this structure in several genodermatoses that are caused by keratin defects[187,188]. Pachyonychia congenita (PC) is an autosomal dominant disorder caused by mutations in the genes encoding keratins 6a, 6b, 6c, 16, or 17 (see Chs. 58 & 71). These keratins are expressed in the nail bed, HF, and sebaceous gland as well as palmoplantar, injured (e.g. ulcer margins), and hyperproliferative epidermis. PC features thickening of the nail plate, much of which represents compaction of dense subungual hyperkeratosis, together with painful palmoplantar keratoderma, follicular keratoses, and variable oral leukokeratosis and cysts (e.g. steatocystoma multiplex). Nail fragility as well as alopecia characterize the pure hair–nail ectodermal dysplasia that results from mutations in the gene for keratin 85. In these patients, keratin 85 lacks two cysteine residues, which may compromise nail integrity via diminished cross-linking of amino acids within keratins.

The nail bed does not express keratins 1 and 10[188], which characterize terminally differentiated stratified epithelia such as the epidermis. It has been postulated that the presence of the nail plate overlying the nail bed inhibits further differentiation of the latter structure. Indeed, if the nail plate is avulsed, the nail bed develops a cornified layer over the next 3 to 4 weeks.

Other Nail Plate Components

In addition to keratins, the nail plate contains structural proteins high in sulfur (with elevated cysteine content) or glycine and tyrosine

DISTRIBUTION OF KERATINS AND NON-KERATIN PROTEINS IN THE NAIL APPARATUS



Anatomical region	Keratins (key examples)		Non-keratin proteins
	Soft keratins	Hard keratins	
Nail plate	KRT14, KRT16, KRT17 KRT5, KRT6	KRT31–KRT34 KRT81–KRT84	Ultra-high-sulfur proteins, high-sulfur proteins, high-glycine/tyrosine proteins, trichohyalin
Proximal nail matrix	KRT10, KRT14, KRT15, KRT16, KRT17 KRT1, KRT5, KRT6	KRT31, KRT34 KRT81, KRT85, KRT86	Actin, involucrin, filaggrin*, trichohyalin*, plasminogen activator inhibitor type II, laminin
Distal nail matrix	KRT10, KRT14, KRT20 KRT1, KRT5	KRT31	
Nail bed	KRT14, KRT16, KRT17 KRT5, KRT6, KRT7		Trichohyalin, plasminogen activator inhibitor type II, laminin
Hyponychium	KRT10, KRT14 KRT1, KRT5		Laminin
Tip	KRT16, KRT17 KRT6		
Embryonic nail unit	KRT19		*detected in monkey nails

Fig. 68.11 Distribution of keratins and non-keratin proteins in the nail apparatus. *Adapted from Dawber RP, de Berker DA, Baran R. Science of the nail apparatus. In: Baran R, Dawber RP, de Berker DA, et al (eds). Diseases of the Nails and their Management. Oxford: Blackwell Science, 2001;1–47.*

THE NAIL APPARATUS: BASIC INFORMATION AND TERMINOLOGY	
Nail plate thickness	Toenails are usually thicker than fingernails Toenails: 1.4 mm in women, 1.65 mm in men Fingernails: 0.5 mm in women, 0.6 mm in men
Growth rate	Fingernails usually grow faster than toenails Fingernails: 2–3 mm/month Toenails: 1 mm/month Complete replacement of a nail requires 6 (fingernails) to 18 months (toenails)
Nail plate	Tightly packed cornified cells (onychocytes) arranged in a lamellar pattern; weakly eosin+, strongly acid-fast+; largest on the great toe, covering ~50% of this digit; fingernails have a longer longitudinal axis compared to the transverse axis, while toenails usually have a longer transverse axis
Nail matrix	Epithelium situated above the middle part of the distal phalanx of the digits; keratinizes without a granular layer and generates the nail plate; contains many melanocytes (up to 300/mm^2), predominantly in supra-basal layers
Nail bed	Thin epithelium consisting of 2–5 cell layers with abrupt keratinization and no granular layer; typically no melanocytes
Proximal nail fold	Epithelium with a granular layer; its dorsal part corresponds to the skin of the dorsum of the digit and contains sweat glands but is devoid of pilosebaceous units; densely innervated; the ventral part is thinner and connects with the nail matrix epithelium
Hyponychium	An epithelium equivalent to the volar skin containing granular and thick cornified layers
Nail pigmentation	Banded pigmentation (longitudinal melanonychia) is common in Asian and Black individuals (~75% by age 20 years, nearly 100% by age 50 years); relatively uncommon in White individuals

Table 68.5 The nail apparatus: basic information and terminology. *Courtesy John P. Sundberg, DVM, PhD.*

(see Fig. 68.11). Other molecules and elements within the nail plate include water (normally ~10%–15%, compared to ~15%–25% for the epidermis), lipids (primarily cholesterol), and minerals (e.g. iron, zinc, calcium). The nail plate is relatively porous and ~1000-fold more permeable to water than is the epidermis; as a result, nails can be rapidly dehydrated and hydrated. Low water content in nails leads to brittleness, while nails composed of >30% water are soft and opaque. Although calcium is present in the nail plate, it does not influence the hardness of the nail. Likewise, the white "flecks" that are commonly seen in the nail plate (especially in children) have nothing to do with calcium but rather reflect small disturbances in the compaction of onychocytes, usually related to trauma.

The nail can also contain markers of various metabolic processes and exposures to exogenous substances (e.g. drugs, environmental pollutants). Biomarkers in the nail plate include glycosylated keratin in patients with diabetes mellitus[189], high sodium levels in those with cystic fibrosis[190], and increased amounts of lipids in hyperlipidemic individuals[191]. Exogenous substances that are found in the nail plate in settings of systemic exposure due to environmental contamination include arsenic, lead, and other heavy metals[192,193]. Drugs taken for medical purposes or recreationally may also be present in the nail plate, depending on their binding properties and lipid solubility. Analysis of nicotine in the toenails can be used to track exposure to cigarette smoke via inhalation[194], and a range of narcotics can be identified in nail clippings, either within deposits beneath the free edge of the nail plate due to recent direct contact or incorporated into the nail plate via systemic exposure over previous months[195]. For neonates, it is possible to measure *in utero* exposure to some drugs using nail analysis[196].

Nail Growth

Nail growth is typically measured in the longitudinal axis (e.g. using a vernier caliper) from a defined reference point to the free edge or by monitoring the movement over time of a transverse groove made at the peak of the lunula (Table 68.5)[197]; the mass of nail produced in clippings over a fixed period can also be determined. When a systemic event or local trauma disrupts nail growth for a brief period, a transverse groove reflecting the contour of the proximal margin of the matrix appears and grows outward with the affected nail, allowing the timing of the inciting phenomenon to be estimated. This clinical sign is known as Beau's lines, named after the Parisian cardiologist Justin Beau, who described these bands in patients recovering from typhoid[198].

Multiple physiologic conditions, medical disorders and drug exposures can influence nail growth (Table 68.6). The appearance of decreased nail growth is occasionally explained by substantial thickening of the nail plate that deviates the axis of growth such that nail is accumulating upwards in the vertical axis as well as outward in the longitudinal axis. Examples include onychogryphosis and yellow nail syndrome[199] (see Ch. 71), which are both accompanied by retraction of the proximal nail fold that may normally have a role in molding and flattening the early nail. In these instances, measurement of nail bulk rather than length illustrates that the nails are actually growing, but in a different direction.

FACTORS THAT CAN INFLUENCE NAIL GROWTH		
Factor/condition	**Reduction of growth**	**Acceleration of growth**
Age	Elderly	Young
Time of day	Night	Day
Seasons	Winter	Summer
Anatomic location	Toes Thumb, little finger	Fingers Middle finger
Physiologic states		Pregnancy
Extracutaneous disorders	Fever Poor nutrition Denervation, immobilization Infections (e.g. mumps, tuberculosis)	Hyperthyroidism Arteriovenous shunting
Cutaneous disorders	Onychomycosis	Psoriasis, pityriasis rubra pilaris
Drugs	L-DOPA Methotrexate Azathioprine Acitretin	Itraconazole Acitretin (in psoriasis patients)

Table 68.6 Factors that can influence nail growth.

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Alopecias 69

Lidia Rudnicka and Catherine M. Stefanato

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INTRODUCTION

In this chapter, the major non-cicatricial alopecias will be reviewed first, followed by a discussion of cicatricial alopecias and then a review of structural hair shaft abnormalities. Chapter 68 reviews the structure and function of the hair follicle as well as regulation of the hair cycle. Table 69.1 outlines the information of importance in the evaluation of alopecias while Figs. 69.1 and 69.2 depict a clinical approach and the diagnostic tests that can be performed in addition to the clinical examination. The decision to perform trichoscopy, histopathology, hair shaft analysis, and blood tests is guided by the differential diagnosis.

NON-CICATRICIAL (NON-SCARRING) ALOPECIAS

Androgenetic Alopecia

Synonyms: ■ Male pattern and female pattern hair loss (MPHL and FPHL) ■ Female androgenetic alopecia (FAGA)

Key features

- Dihydrotestosterone (DHT) is a key hormone in the pathogenesis of androgenetic alopecia
- There is a conversion of terminal scalp hairs into miniaturized vellus hairs
- Treatment options include oral 5α-reductase inhibitors, topical minoxidil, and low-dose oral minoxidil

Introduction

Androgenetic alopecia (AGA) is an androgen-dependent disorder characterized by the conversion of terminal scalp hairs into miniaturized vellus hairs in a characteristic pattern. Both prevalence and severity increase with age, with up to 80% of men and 50% of women having evidence of AGA during their lifetime. Female androgenetic alopecia (FAGA) and male androgenetic alopecia share several pathogenetic, histopathologic, and trichoscopic features, but differ in their typical distribution patterns[1]. Onset can occur during adolescence, but pediatric androgenetic alopecia is rarely observed[2].

Pathogenesis

Genetic factors

In men, a polygenic basis for AGA is now generally accepted and is supported by the results of genome-wide association studies. Polymorphisms in the androgen receptor gene are thought to play a significant pathogenic role in men, but not in women. A second gene with potential importance in both men and women is *WNT10A* whose protein product is expressed in the follicular bulge during anagen. The WNT signaling pathway is known to play a critical role in hair follicle development (see Ch. 68), and loss-of-function mutations in *WNT10A* lead to several types of ectodermal dysplasia. Of note, polymorphisms in *APCDD1*, which encodes a WNT signaling inhibitor, have also been implicated in AGA. Lastly, FAGA has been associated with polymorphisms in *CYP19A1* and *ESR2*, whose protein products are an aromatase that converts C19 androgens to C18 estrogens and estrogen receptor 2, respectively[3,4].

Hormonal factors

Dihydrotestosterone (DHT) plays a central role in the pathogenesis of AGA, serving as a trigger for hair follicle miniaturization (see Fig. 157.1). The enzyme 5α-reductase, of which there are three isoenzymes (types I, II, and III), converts testosterone to DHT (see Fig. 69.10). The latter androgen may not directly miniaturize hair follicles, but rather serve as a co-mediator of hair sheath thickening, perifollicular fibrosis, and

CLINICAL APPROACH TO THE PATIENT WITH ALOPECIA
Historical information
• Increased hair shedding versus only reduction in hair density (the latter points to hair follicle miniaturization) • Shedding versus hair breakage • Expected hair length (allows identification of "hair that never grows") • Coexisting scalp symptoms (e.g. scaling, pruritus, burning, trichodynia [pain and/or paresthesias], tenderness) • Duration, including age of onset • Persistent versus intermittent with recurrent episodes of hair loss • Possible triggering factors (e.g. postpartum, medications or supplements, preceding high fever or severe illness, malnutrition, flare of systemic disease such as lupus erythematosus, significant emotional stress) • Review of symptoms to detect possible underlying systemic disease (e.g. thyroid dysfunction) • Family history of alopecia
Physical examination
• Diffuse versus patchy or patterned alopecia • Cicatricial versus non-cicatricial alopecia • Length and structure of hairs • Scalp changes (e.g. scaling, erythema, pustules, tenderness, drainage, scarring)
Diagnostic procedures
• Gentle hair pull test • Trichoscopy • Hair card test • Light microscopy of cut hair shafts (can include polarized light microscopy) • Trichogram (if telogen effluvium or loose anagen hair syndrome suspected) • Fungal culture and/or Wood's lamp examination; bacterial culture • Trichoscopy-guided biopsy for histopathology • Biopsy for direct immunofluorescence (discoid lupus versus lichen planopilaris, mucous membrane pemphigoid) • Blood tests (e.g. DHEA-S, free testosterone, TSH)
Treatment considerations
• Previous therapies, including duration and if used correctly • Psychological burden and impact on quality of life • Comorbidities and current medications (e.g. drug–drug interactions) or supplements (e.g. biotin's interference with avidin-based laboratory tests) • Expectations (e.g. halting progression, preventing relapse, degree of hair regrowth) • Commitment to long-term therapy • In women of childbearing age, discuss pregnancy plans and contraindicated medications

Table 69.1 Clinical approach to the patient with alopecia. TSH, thyroid stimulating hormone.

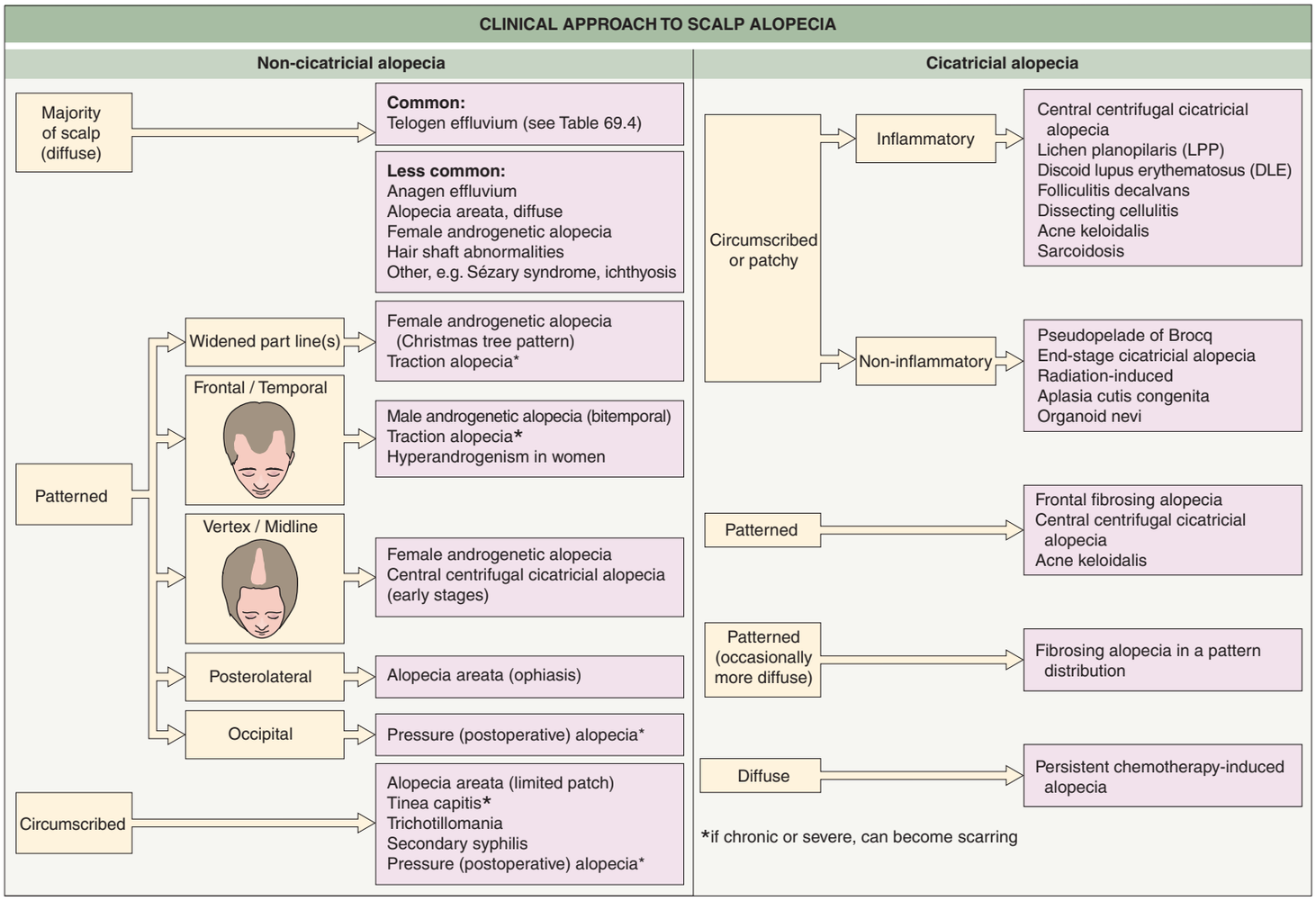


Fig. 69.1 Clinical approach to more common causes of scalp alopecia.

sometimes even calcification. These changes could then result in miniaturization via restriction of the follicle's growth space as well as its oxygen and nutrient supply[5].

In patients with AGA, 5α-reductase activity and DHT levels are increased in balding scalp skin when compared to non-balding scalp skin. Decreasing DHT levels in both the skin and the blood have been associated with a reversal of miniaturization in men with AGA. In women, a similar androgen-related pathophysiology has been postulated. However, most patients, both men and women, with AGA have normal circulating testosterone levels and signs and symptoms of systemic hyperandrogenism are unusual. Thus, AGA represents a local androgen-driven process.

Clinical features

In both men and women, the most common presentation is progressive non-synchronized hair miniaturization. The end stage of hair miniaturization is the development of vellus hairs. Because vellus hairs are short, thin, and hypopigmented, they are nearly invisible on clinical examination. Therefore, the "hair loss" in AGA represents "terminal hair loss" with retention of vellus hairs. However, prolonged disease eventually leads to follicular dropout.

The areas with the most pronounced hair miniaturization differ between men and women. In men, progressive recession of the frontotemporal hairline and diffuse thinning of the crown constitute the predominant sites of involvement (see Ch. 157). In women, the frontal hairline is usually preserved and hair loss favors the mid scalp, especially the frontal region; this can lead to a "Christmas tree" pattern of hair thinning (Fig. 69.3A). The degree to which there is widening of the central part line is also indicative of the severity of FAGA (Fig. 69.4). Occasionally, men may develop a female pattern of hair loss and vice versa[1,6]. A history of increased hair shedding may precede the clinical appearance of hair thinning.

The Hamilton and Norwood scales are most commonly used to grade and classify male AGA. They are depicted in Fig. 157.2. In female patients with AGA, the Ludwig grading system is often employed and consists of three major grades (see Fig. 157.3). The Sinclair scale represents another grading system for FAGA and it divides patients into five stages (Fig. 69.5; Table 69.2).

Diagnosis

In most men with AGA, the diagnosis is based upon clinical features and is relatively straightforward. However, additional evaluation can be helpful in women and this includes trichoscopy, i.e. dermoscopy of the hair and scalp (see Fig. 69.2)[7]. In AGA, there is heterogeneity of hair shaft thickness (Fig. 69.6) as well as a predominance of follicular units with only one terminal hair. Both findings are due to non-synchronized hair miniaturization (including within a single follicular unit). Sparse yellow dots, which represent empty hair follicles containing sebum and keratotic material, are also seen (Fig. 69.7)[8].

In the absence of signs or symptoms of hyperandrogenism, the authors do not perform screening laboratory tests[6]. However, some experts routinely order screening blood tests (e.g. serum DHEA-S, total and free testosterone; see Ch. 70) in women with AGA while others recommend detailed testing for possible androgen excess[9]. As there may be an increased risk of metabolic syndrome, cardiovascular disease, and prostate cancer in men with AGA, assessment and longitudinal evaluation for these disorders should be considered in the appropriate clinical setting[10].

In some patients, especially those with confusing clinical presentations, scalp biopsies may provide helpful information. Interpretation of the histopathologic findings requires an appreciation of the characteristic

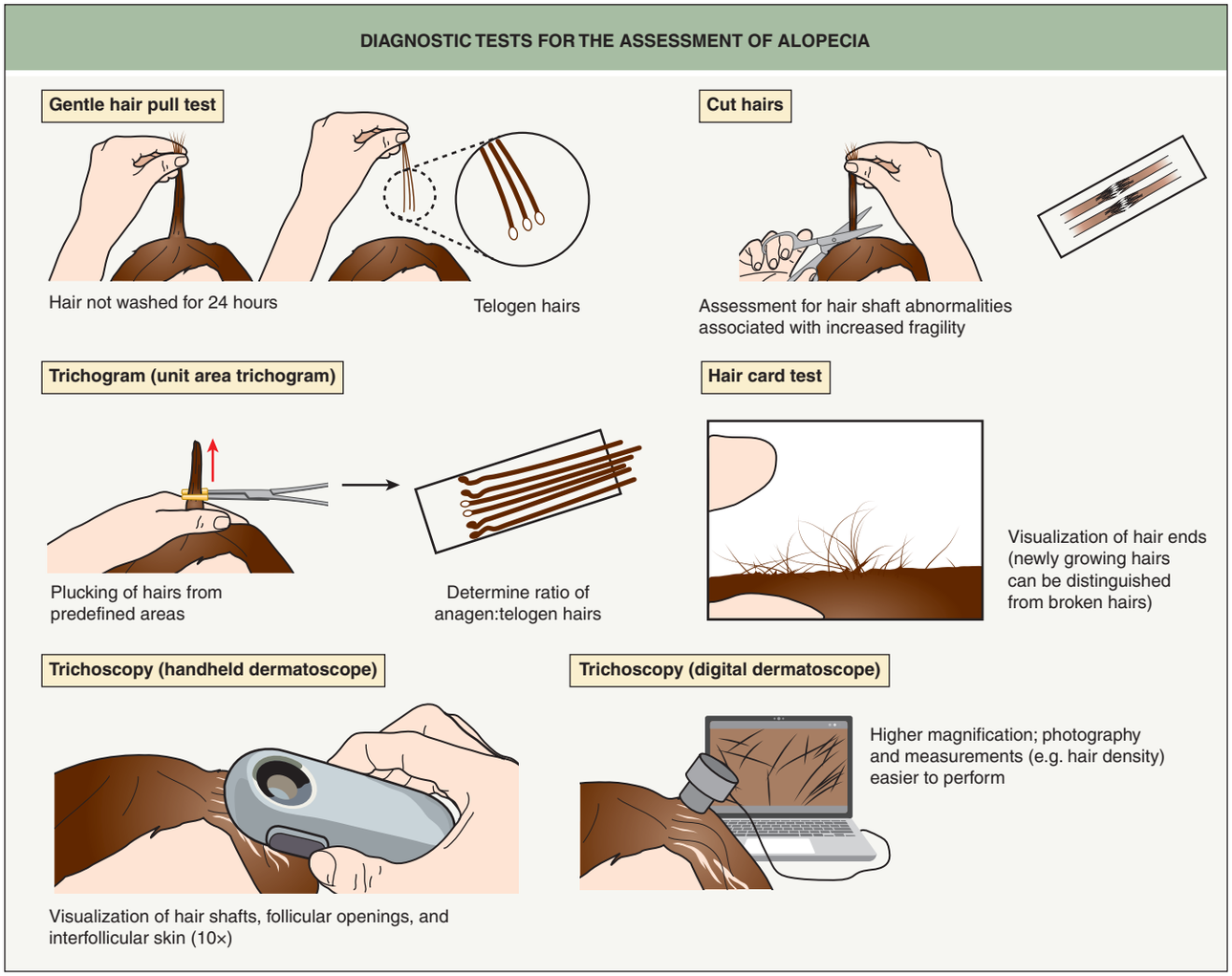


Fig. 69.2 Diagnostic tests for the assessment of alopecia. Additional investigations include fungal culture, Wood's lamp examination, scalp biopsy, polarized light microscopy of scalp hairs, and blood tests.

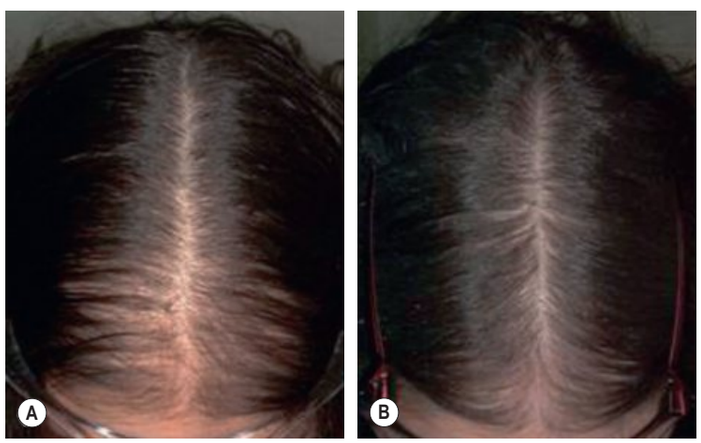


Fig. 69.3 Female androgenetic alopecia. A Prior to treatment. Note the greater hair loss anteriorly. **B** Obvious improvement following 5 years of therapy. Androgenetic alopecia may be at least partially reversible, when treated early. *Courtesy Rodney D. Sinclair, MD.*

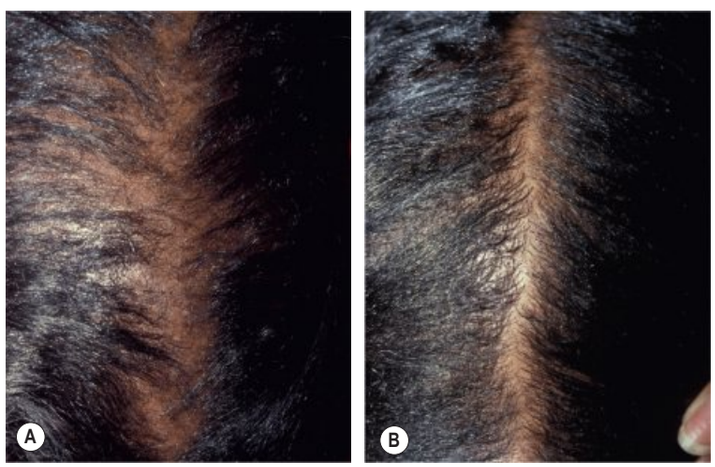


Fig. 69.4 Female androgenetic alopecia. Comparison of the part line on the top of the scalp (**A**) and the occiput (**B**). *Courtesy Leonard C. Sperling, MD.*

structures at different levels within the follicular unit (Fig. 69.8). With the movement towards horizontal sections, this has become even more essential. The characteristic histopathologic findings in AGA are outlined in Table 69.3 and illustrated in Fig. 69.9A,C, & D.

Differential diagnosis

The diagnosis of AGA in men is relatively straightforward unless it is coincidentally associated with other non-scarring hair diseases such as alopecia areata or telogen effluvium. Initial recognition of FAGA may coincide with a superimposed telogen effluvium. Early-onset or severe patterned hair loss in women should suggest the possibility of pathologic hyperandrogenism, and appropriate screening laboratory tests (e.g. total and free testosterone, DHEA-S, and 17 hydroxyprogesterone) should be performed (see Ch. 70). Senile (senescent) alopecia is age-related and is due to more synchronized hair follicle miniaturization than in AGA. While the two disorders share some

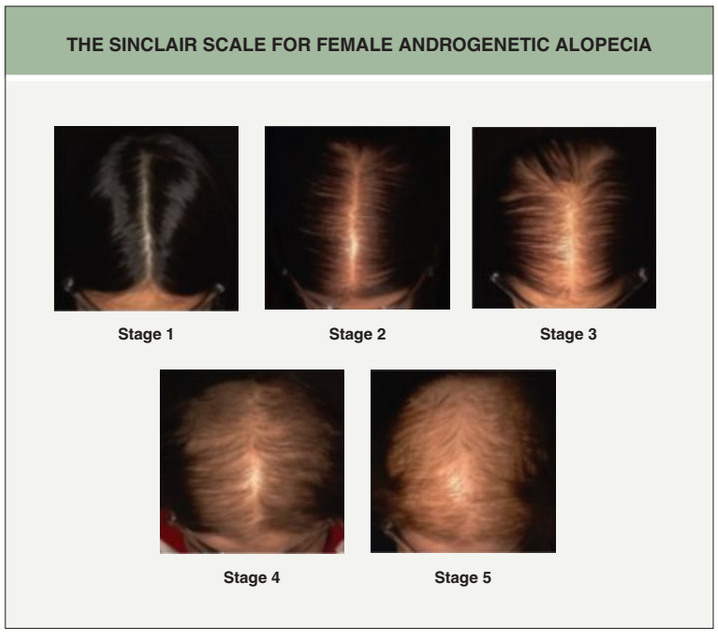


Fig. 69.5 The Sinclair scale for female androgenetic alopecia. Stage 1 – normal; Stage 2 – widening of the central part line; Stage 3 – widening of the part line with translucency of the hairs at its border; Stage 4 – development of a bald area anteriorly along the part line; and Stage 5 – advanced hair loss. *Courtesy Rodney D. Sinclair, MD.*

clinical and trichoscopic features, senile alopecia does not respond to antiandrogen therapies.

Treatment

Topical formulations of minoxidil (2% and 5%) have been approved by the US Food and Drug Administration (FDA) for the treatment of AGA in both men and women. Minoxidil-induced hair growth is commonly associated with shedding of telogen hairs and a paradoxical worsening of hair loss ~3 to 6 weeks following initiation of treatment. However, this resolves with continued treatment. Low-dose oral minoxidil is an off-label, but well documented treatment, for AGA. The optimal dose is currently being investigated, with recommended regimens ranging from 0.625 to 2.5 mg/day in women and 0.625 to 5 mg/day in men[11]. Side effects, including facial hypertrichosis, periorbital edema, lightheadness, and other potential cardiovascular effects, are reviewed in Chapter 157.

Oral finasteride, a type II 5α-reductase inhibitor (Fig. 69.10), is approved for AGA in men at a dose of 1 mg/day. It halts hair loss in 90% of men and partial hair regrowth occurs in ~65%. Continued use of the product is necessary to sustain these effects. Oral finasteride is not FDA-approved for women with AGA, but its efficacy and safety is well documented at a daily dose of 2.5–5 mg[12–14]. As there is some indirect evidence that finasteride may be teratogenic and DHT is required for development of male genitalia, adequate contraception is required for women of child-bearing age.

Possible finasteride side effects include reversible loss of libido, reduced volume of ejaculate fluid, and erectile dysfunction, which occurs in ~2% of men. There are reports of long-lasting sexual dysfunction (post-finasteride syndrome), but its incidence is unknown. While the overall incidence of prostatic carcinoma is *reduced* among elderly men who take finasteride 5 mg daily for benign prostatic hypertrophy, patients should be informed that this higher dose has been associated with an increased risk of the diagnosis of high-grade prostatic carcinoma[14]. It is uncertain if the latter represents overdiagnosis due to enhanced screening or whether it is predictive of an increased risk of metastasis and a higher mortality rate[15]. With regard to the effects of finasteride (1 mg/day) on lowering serum concentrations of prostate-specific antigen (PSA), the recommendation is to adjust the measured serum PSA concentrations upwards by 40%–50% for the purposes of prostate cancer screening[16].

EXAMPLES OF MOST COMMONLY USED ALOPECIA SCORING SYSTEMS

Scoring system	Number of grades or range of scores	Disorder
Ludwig grading system	1–3 (see Fig. 157.3)	Female androgenetic alopecia
Hamilton and Norwood classifications	I–VIII and I–VII (see Fig. 157.2)	Male androgenetic alopecia
Sinclair scale	5 (see Fig. 69.5)	Female androgenetic alopecia
Severity of Alopecia Tool (SALT)	0–100	Alopecia areata
Alopecia Areata Severity Index (AASI)	0–250	Alopecia areata
Alopecia Areata Predictive Score (AAPS)	6 (–4 to +2)* [trichoscopy-based]	Alopecia areata
Lichen Planopilaris Activity Index (LPPAI)	0–10	Based upon symptoms (30%), signs (scale, erythema; 30%), anagen pull test (25%), spreading (15%)
Frontal Fibrosing Alopecia Severity Score (FFASS)	0–25	Based upon cm of hairline recession, loss of eyebrows, perifollicular inflammation, symptoms (pruritus, pain)
Lee classification	9	Dissecting cellulitis; based upon presence/absence of intercommunicating sinus tracts and scarring plus number of involved regions
Melo classification	3 [trichoscopy-based]	Dissecting cellulitis

*Six point scoring system where points are added for upright regrowing hairs and pigtail hairs on trichoscopic exam (positive signs); points subtracted for exclamation hairs, tapered hairs, broken hairs, or black dots (negative signs; see Fig. 69.7). A final score of 1 or 2 is associated with treatment response, whereas scores of –1, –2, –3 or –4 indicate an unlikely response to treatment.

Table 69.2 Examples of most commonly used alopecia scoring systems. Additional scoring systems include: Ebling and Rook 5-stage classification, Savin's pictorial grading (9), and Olsen's classification (3) for female androgenetic alopecia and the alopecia barbae severity score (ALBAS; 0–100) for alopecia areata.



Fig. 69.6 Androgenetic alopecia – trichoscopic features. Full-thickness terminal hairs, intermediate hairs, thin hairs, and very thin (vellus) hairs are all observed simultaneously. This heterogeneity of hair shaft thickness is due to non-synchronized hair miniaturization.

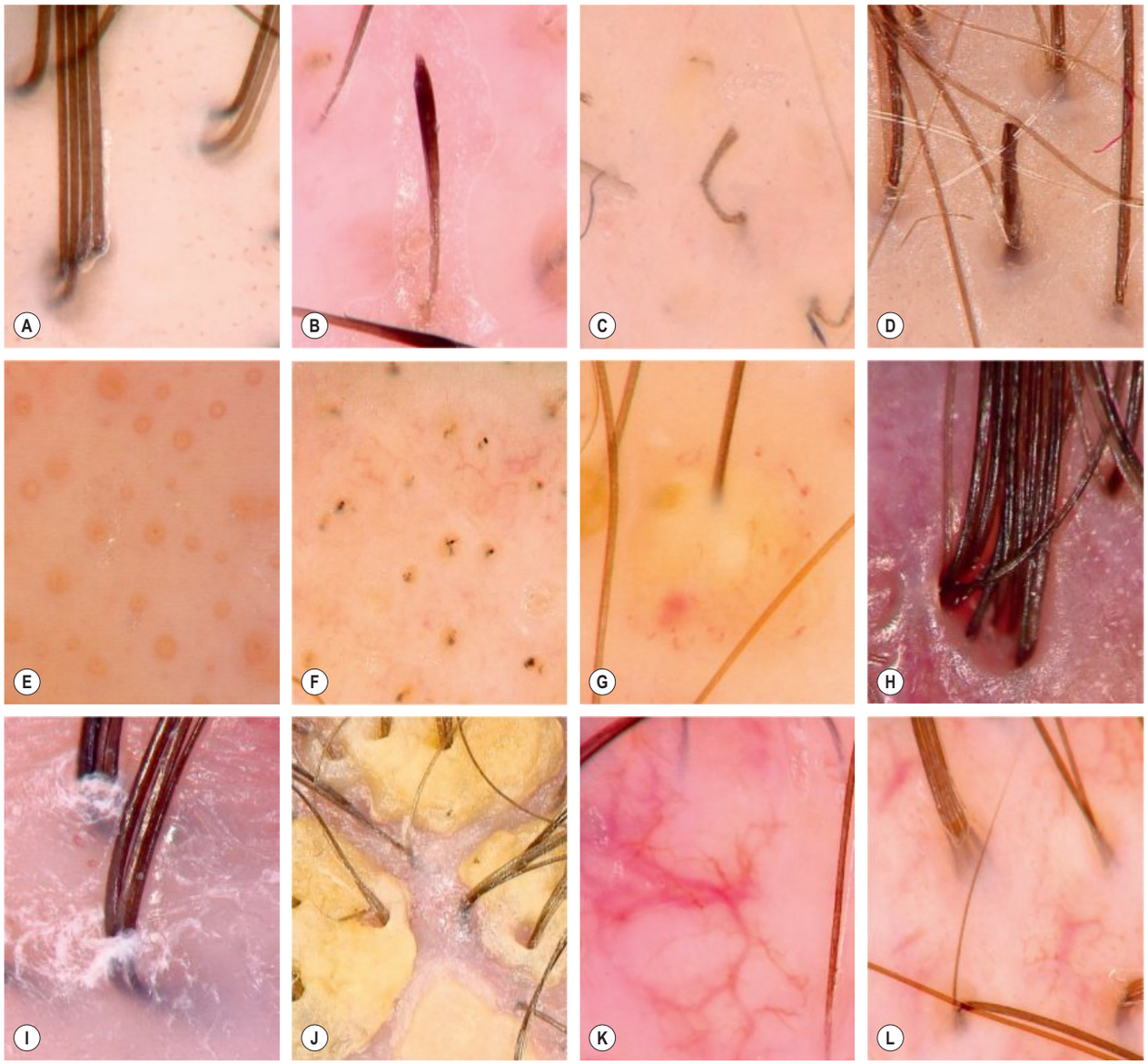


Fig. 69.7 Common trichoscopy findings. A Healthy hairs are uniform in color and shape throughout their length. The follicular units contain 1 to 4 hairs (average, 2.3). **B** Exclamation point hair – observed primarily in alopecia areata, trichotillomania, and chemotherapy-induced alopecia. **C** Comma hairs – tinea capitis. **D** Broken hair – trichotillomania, tinea capitis, and alopecia areata. **E** Yellow dots – alopecia areata and androgenetic alopecia. **F** Black dots – alopecia areata, tinea capitis, trichotillomania, and anagen effluvium. **G** Perifollicular pustule – folliculitis decalvans. **H** Hair tufts consisting of more than 5 hairs per follicular unit ("tufted folliculitis") – folliculitis decalvans. **I** Perifollicular scaling – lichen planopilaris, folliculitis decalvans, and frontal fibrosing alopecia. **J** Seropurulent exudate – dissecting cellulitis and tinea capitis. **K** Thick arborizing vessels and tortuous vessels – systemic lupus erythematosus. **L** Upright regrowing hair (healthy regrowing). Zigzag hairs can be seen in tinea capitis.

Oral dutasteride is more potent than finasteride due to its ability to inhibit 5α-reductase types I and II. It is not FDA-approved for AGA, but its efficacy is well documented at a dose of 0.5 mg/week to 0.5 mg/day[17]. In both men and women, the effectiveness of finasteride and dutasteride decreases with age. In a recent meta-analysis of oral therapies for male AGA, dutasteride (0.5 mg/day) was found to be most effective, followed by finasteride (5 mg/day) and then minoxidil (5 mg/day)[18]. Use of intralesional or topical dutasteride is currently under investigation, with topical 0.01% dutasteride solution plus microneedling leading to improvement. In a recent randomized controlled trial, topical 0.5% finasteride spray solution was shown to lead to a significant improvement in hair counts[19].

There are additional therapies that are based upon less rigorous evidence. For FAGA, these include spironolactone, cyproterone acetate plus ethinyl estradiol, and alfatradiol (17α-estradiol) (Fig. 69.3B; see Fig. 69.10)[20]. Use of low-level light therapy and platelet-rich plasma are reviewed in Chapter 157.

Hair transplantation remains a mainstay in the treatment of AGA and is combined with medical therapy for optimal results (see Ch. 157).

Telogen Effluvium

Key features

- Increased shedding of otherwise normal telogen hairs in response to an external or internal trigger (e.g. medication, high fever, malnutrition, systemic disease, significant emotional stress)
- A chronic form with no identifiable precipitating factor is observed in some women
- Laboratory evaluation is directed by history, physical examination, trichoscopy, and microscopic evaluation of plucked hairs (trichogram)

Introduction

Scalp hair grows longer than hair on other parts of the body because its anagen phase is longer. Unlike mammals that molt, hair cycling in humans is asynchronous such that shedding of each follicle is

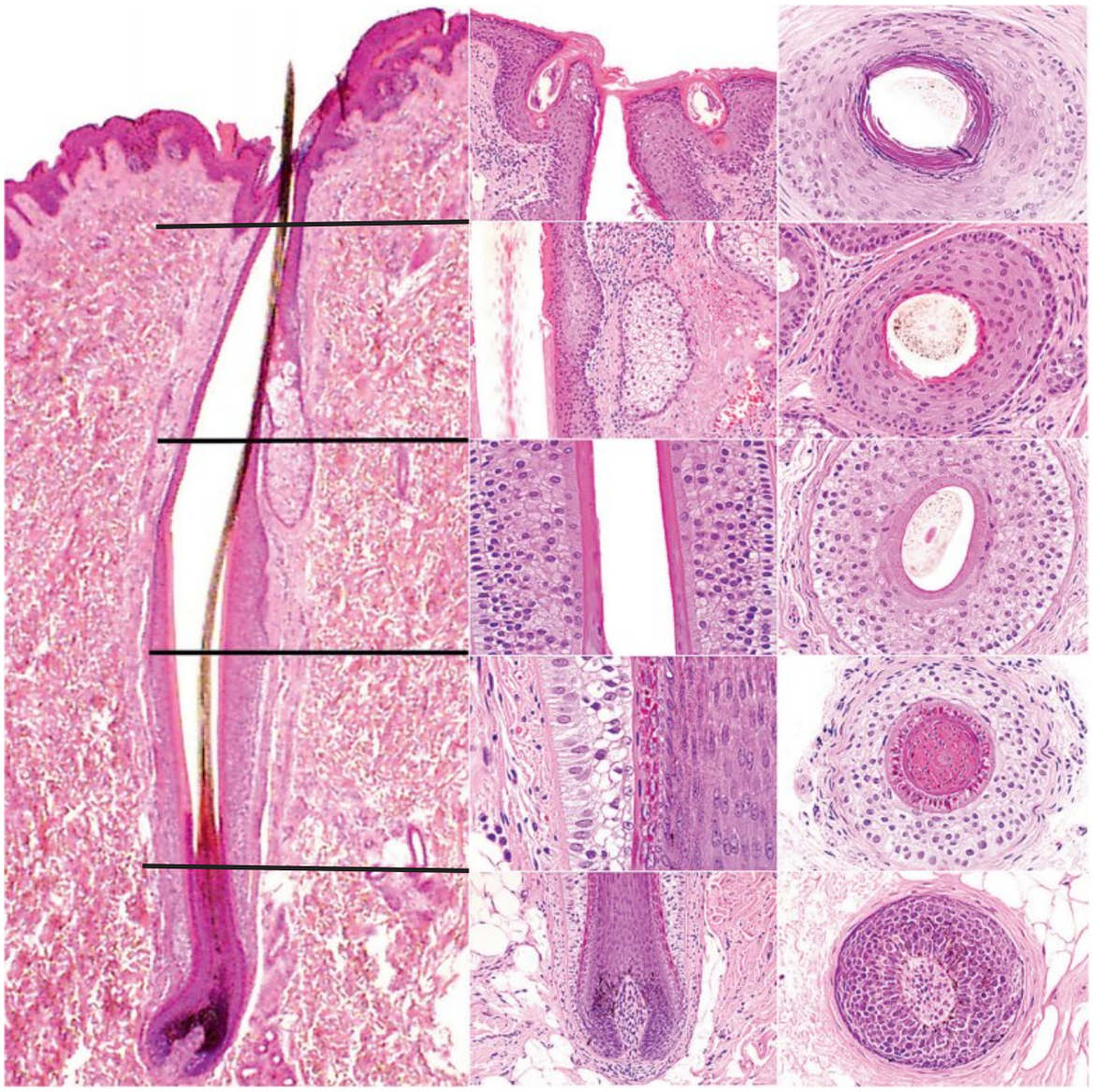


Fig. 69.8 Vertical and horizontal sections of a hair follicle cut at different levels (from bottom to top). *Bulb*: the hair bulb embraces the dermal papilla and is composed of matrical cells admixed with pigmented melanocytes; the nucleated hair shaft is surrounded by: (1) the early inner root sheath (IRS); (2) a paler outer root sheath (ORS); and (3) a dermal fibrous sheath in continuity with the dermal papilla. *Suprabulbar area*: the hair shaft is nucleated and is surrounded by (moving outwards): (1) the hair cuticle – a single layer of overlapping elongated cells; (2) the Huxley layer of the IRS – 3–4 layers of cuboidals cells with keratohyaline granules; (3) the Henle layer of the IRS – single layer of elongated cells; and (4) the pale ORS. *Subisthmus*: the IRS is completely keratinized, the hair shaft is no longer nucleated, and the ORS is less pale and more pink, resembling epidermis. *Isthmus*: upon entering the isthmus, abrupt disintegration of the keratinized IRS occurs and is replaced by tricholemmal keratinization by the ORS. *Infundibulum*: the epithelium has reached maturation and is identical to, and in continuity with, the epidermis.

independent of surrounding follicles. Consequently, a fairly uniform density of hair is maintained at all times.

In the normal scalp, there are ~100 000 hair follicles of which ~90% are in the *anagen* phase of the hair growth cycle; this phase typically lasts for 2–4 years. Hairs then enter the *catagen* phase (0.5%–1% of hair follicles), followed by a *telogen* phase (10% of hair follicles). The latter phase usually lasts for three months after which the hairs undergo conversion to *exogen* and are shed; daily ~50–200 hairs are shed (see Ch. 68)[21]. Internal or external factors that interfere with this normal hair cycle can trigger telogen effluvium. The most common disturbance is a shortened anagen phase.

Pathogenesis

Various external and internal factors may induce a simultaneous transition of a large number of hair follicles from anagen phase into telogen phase. This transition begins the hair shedding process which eventuates in clinically apparent hair loss (telogen effluvium) at the conclusion of the telogen phase, thus explaining its usual occurrence three months after the inciting cause. Potential triggers of telogen effluvium include pregnancy, medications, high fever, malnutrition, systemic diseases such as lupus erythematosus, and significant emotional stress as well as inflammatory scalp disorders (Table 69.4). Systemic infections represent an additional cause; for example, a quarter of individuals infected with SARS-CoV-2 experienced telogen effluvium within the following two months.

Although a wide range of medications have been reported to induce telogen effluvium, only a few have been proven. The severity of hair loss depends on the drug (see Table 69.4), its dosage, and patient susceptibility[8]. Lastly, a significant number of women have a chronic form of telogen effluvium that lacks any identifiable trigger[22].

Clinical features and diagnosis

Thinning and loss of terminal hairs involves the entire scalp and may also be noted on other hairy regions of the body. A trichogram will show an increased percentage of telogen hairs, with >20% diagnostic of telogen effluvium (Fig. 69.11)[23]. By trichoscopy, telogen effluvium is often a diagnosis of exclusion. An increased percentage of follicular units with only one hair is the most characteristic feature. During the regrowth phase, multiple short upright regrowing hairs can be seen.

When due to past events such as a severe illness or pregnancy, complete hair regrowth is expected. If the underlying etiology is an ongoing issue such as hypothyroidism, then the latter needs to be addressed first (see Table 69.4). While chronic telogen effluvium can continue for years or decades, it usually does not lead to baldness[24].

After a history (including medications and supplements) and physical examination have been performed and the triggering factor is still unclear, then thyroid function, complete blood count, metabolic panel, ESR, and serum ferritin level can be assessed. Serum ferritin levels should be at least 40 ng/dl, but the relationship of reduced iron stores to the hair loss still needs to be determined[24].

HISTOPATHOLOGIC FEATURES OF VARIOUS TYPES OF ALOPECIA
Androgenetic alopecia
• Normal *total* number of hair follicles when counted in the superficial dermis • Decreased number of hair follicles when counted at the dermal–subcutaneous fat junction ("miniaturization") • No significant inflammation • Increased fibrous "streamers" below miniaturized hairs • Slightly increased telogen count • Uninvolved scalp (e.g. occiput) appears normal
Telogen effluvium
• Normal *total* number of hairs • Normal number of terminal (large) hairs • Increase in the telogen count to >20% (>15% is suggestive); telogen count seldom exceeds 50%; >80% is inconsistent with telogen effluvium • Absence of inflammation and scarring
Alopecia areata
Early, progressive disease ("acute" and "subacute")
• Normal *total* number of hairs • Peribulbar mononuclear cell infiltrate (with occasional eosinophils), predominantly affecting terminal anagen and catagen hair bulbs • Occasional exocytosis of inflammatory cells into bulbar epithelium • Degenerative changes of hair matrix • Increased number of terminal catagen and telogen hairs • Increased number of miniaturized hairs • Trichomalacia and marked narrowing of hair shafts • Pigment casts
Longstanding and stable disease ("chronic")
• Majority of hairs in catagen or telogen phases • Diffuse miniaturization of hair follicles • Numerous miniaturized, "arrested", rapidly cycling hairs, referred to as *nanogen* hairs • Mild peribulbar mononuclear cell infiltrate around those nanogen hairs possessing anagen-like or catagen-like bulbs
Trichotillomania
• Follicles are normal size • Total number of hairs (both terminal and vellus) is normal • Incomplete, disrupted follicular anatomy • Increased number of terminal catagen and/or telogen hairs • Trichomalacia and pigment casts • No significant inflammation
Pressure (-induced) alopecia
• Early stage includes vascular thrombosis and inflammation within the dermis and superficial fat • Necrosis of the epidermis and eccrine coils when severe • In conjunction with alopecia, synchronized conversion of most or all of the terminal hair follicles to the catagen/telogen phase (*without* hair miniaturization) • Pigment casts, incontinent pigment within collapsed root sheaths, and trichomalacia (but not distorted follicular anatomy)
Traction alopecia
Early and progressive phases
• Increased number of telogen and catagen hair follicles • Occasional trichomalacia • No significant inflammation • Over time, drop-out of terminal hairs with retention of miniaturized hairs
Late phase
• Total number of terminal hairs is markedly reduced; residual vellus hair follicles • Distinct columns of connective tissue replace some follicles, leaving obvious "blank spaces" (follicular scars) • Sebaceous glands associated with the remaining hair follicles are still intact and sebaceous glands with arrector pili muscles persist in follicular units that seem to have lost all of their hair-producing epithelium • No significant perifollicular inflammation
Psoriasiform alopecia
• Psoriasiform epidermal changes may or may not be present • Marked increase in percentage of catagen/telogen hairs, associated with hair miniaturization • Occasional miniaturized follicle showing peribulbar chronic inflammation; plasma cells rare or absent • Marked atrophy of sebaceous glands
TNF inhibitor-induced psoriasiform alopecia
• Psoriasiform dermatitis often present • Increase in catagen/telogen hairs and miniaturization of hairs, similar to alopecia areata • Some peribulbar and superficial perivascular inflammation present, often with several eosinophils and plasma cells in the infiltrate

Table 69.3 Histopathologic features of various types of alopecia.

Continued

HISTOPATHOLOGIC FEATURES OF VARIOUS TYPES OF ALOPECIA
Lichen planopilaris
• Perifollicular band-like lymphoid cell infiltrate obscuring the interface between follicular epithelium and dermis; vacuolar alteration at the interface and hypergranulosis within affected infundibula is typical (sometimes with colloid or Civatte bodies) • Inflammation affects the *upper* portion of the follicle (infundibulum and isthmus) predominantly • Occasionally, interfollicular epidermal changes of lichen planus are found • Reduced or absent sebaceous glands • Over time, perifollicular fibrosis becomes prominent and the lymphocytic infiltrate seems to "back away" from the follicle • An artifactual cleft between epithelium and stroma is often found, with epithelium "floating" within the cleft (Max-Joseph spaces) • End-stages may show follicular "tufting" • Fragments of "naked" hair shafts in giant cells may be seen • Direct immunofluorescence shows colloid bodies (usually IgM) adjacent to the follicular epithelium and, when epidermis is involved, a linear "shaggy" band of fibrinogen is present
Central centrifugal cicatricial alopecia
• Premature desquamation of the inner root sheath in the subisthmic area • Eccentric epithelial atrophy (thinning) in the subisthmic area • Concentric lamellar fibroplasia (onion skin-like fibrosis) of affected follicles • Variably dense lymphocytic perifollicular inflammation, primarily at the level of the upper isthmus and lower infundibulum • Occasional fusion of infundibula (polytrichia) • In advanced lesions, total destruction of the follicular epithelium with retained hair shaft fragments and granulomatous inflammation • In pustular lesions ("folliculitis decalvans"), intrafollicular and perifollicular infiltrates rich in neutrophils and lymphocytes
Discoid lupus erythematosus
• Vacuolar interface alteration of the epidermis and follicular epithelium (the epidermis may be spared) • The interface change in follicles is usually vacuolar rather than lichenoid (less inflammation) • Reduced sebaceous glands • Follicular (and/or epidermal) basement membrane zone thickening present in late stages • Chronic inflammation with lymphocytes (often including plasma cells) of the eccrine sweat glands and arrector pili • Perineurial lymphoid cell infiltrate may be seen • Increased dermal mucin • Fragments of "naked" hair shafts in giant cells may be seen • Direct immunofluorescence typically shows granular deposits of IgG and C3 (less commonly IgM or IgA) at the dermal–epidermal junction and/or the junction of the follicular epithelium and dermis
Folliculitis decalvans
• Pustular neutrophilic folliculitis rich in lymphocytes and plasma cells • Early stages: perifollicular inflammation with mixed, predominantly neutrophilic, infiltrate; follicular neutrophilic abscesses • Rupture of the hair follicles with partly granulomatous inflammation • Fragments of "naked" hair shafts within giant cells may be seen • Gram-positive cocci often present • Late stages: perifollicular scarring with "tufting" and interfollicular dermal scarring
Acne keloidalis
• Perifollicular, chronic inflammation (lymphocytic and plasmacytic), most intense at the level of the isthmus and lower infundibulum • Lamellar fibroplasia, most marked at the level of the isthmus • Loss of sebaceous glands • Total follicular destruction in advanced disease
Dissecting cellulitis
• Moderately dense, perifollicular lymphocytic inflammation affecting the lower half of the dermis and extending down into the subcutaneous fat (early lesions) • Numerous intact and seemingly undamaged follicles in the upper dermis with intact sebaceous glands • Increased percentage of catagen/telogen hairs • Initially, lymphocytes dominate the infiltrate, but eventually neutrophils become more numerous, especially in longstanding, fluctuant lesions • Vascular proliferation accompanies the infiltrate as the disease evolves, and the deep dermis and subcutaneous fat begin to exhibit the histologic findings of granulation tissue • Eventually, chronic abscesses become lined with squamous epithelium derived from the overlying epidermis, and true sinus tracts are formed • When inflammation subsides, there is dense fibrosis of the dermis and the superficial fat with loss of follicles
"End-stage" cicatricial alopecia
• A decreased total number of hairs, especially terminal hairs • Loss of the sebaceous glands in zones of follicular loss • Residual, "naked" hair shafts within histiocytic giant cells surrounded by mild, granulomatous inflammation • Follicular streamers (stelae) without overlying follicles • Cylindrical columns of connective tissue representing the sites of former follicles

Table 69.3 Histopathologic features of various types of alopecia. See Fig. 69.7. Trichomalacia is characterized by pleated or twisted hair shafts within follicular infundibula.

For persistent cases of telogen effluvium, i.e. those lasting beyond 6 months, trichoscopy should be repeated and a trichoscopy-guided biopsy from the vertex area may be considered to exclude early AGA. The histopathologic findings in telogen effluvium are outlined in Table 69.3[25], with the ratio of terminal to vellus hairs at the level of the isthmus allowing for distinction from AGA[26]. That said, the coexistence of telogen effluvium and AGA is a common occurrence.

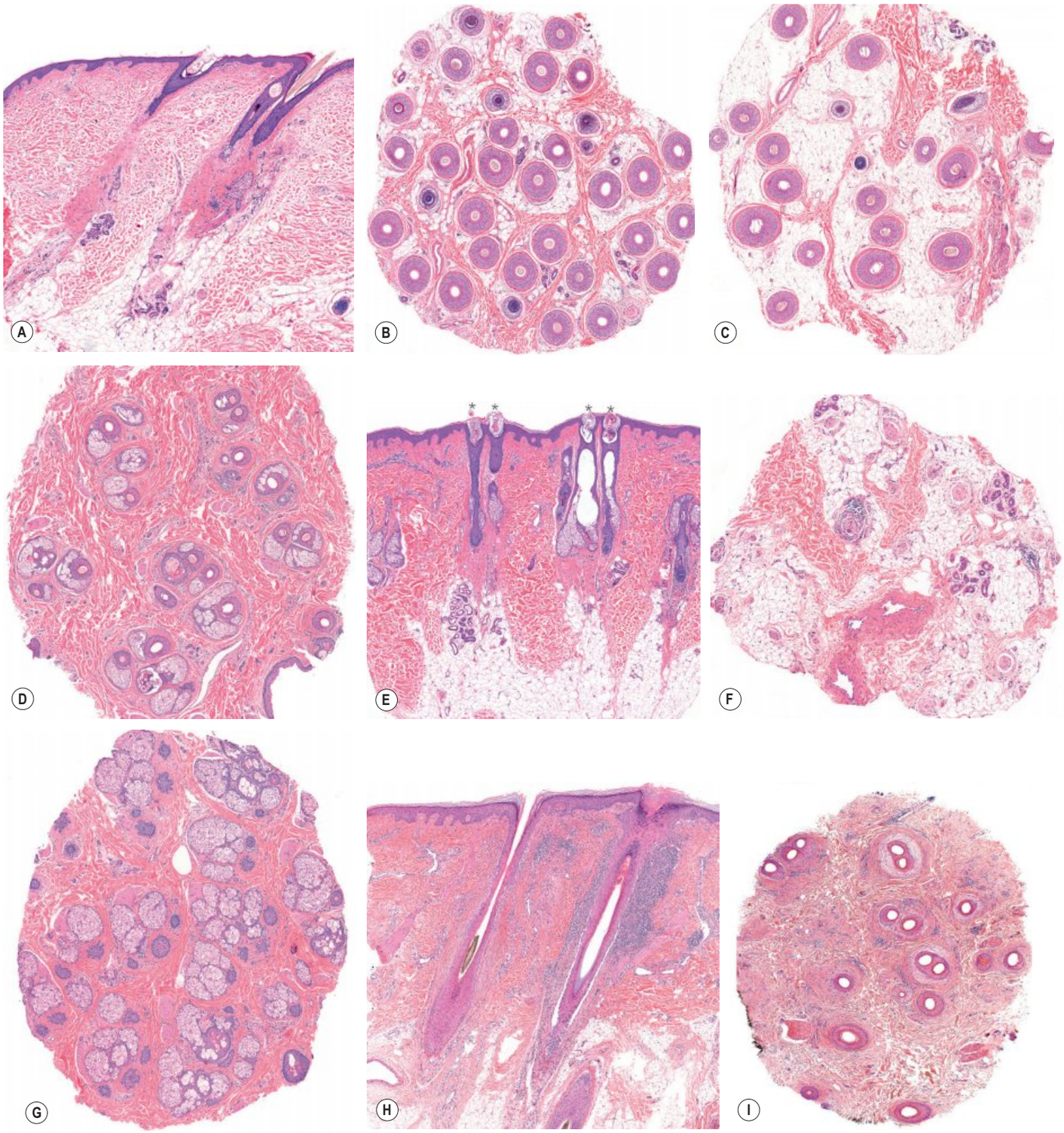


Fig. 69.9 Histopathologic features of androgenetic alopecia, alopecia areata, and lichen planopilaris. A *Androgenetic alopecia* with the characteristic miniaturization of hair follicles and fibrous streamers (vertical section). **B** Normal scalp (horizontal section). **C** *Androgenetic alopecia* with variation in hair follicle size (horizontal section; compare to B). **D** *Androgenetic alopecia* at the level of the isthmus with miniaturized vellus-like hair follicles and no significant inflammation (horizontal section). **E** *Alopecia areata* with miniaturized, vellus-like hair follicles, one of which has a peribulbar lymphocytic infiltrate (vertical section). A clue to the diagnosis is the dilatation of the follicular infundibula which corresponds to the yellow dots by trichoscopy (asterisks). **F** *Alopecia areata* with the characteristic peribulbar lymphocytic infiltrates (horizontal section). **G** *Alopecia areata* at the level of the isthmus demonstrating exclusively telogen follicles (horizontal section). **H** *Lichen planopilaris*. Focal hypergranulosis at the acrotrichium and a dense perifollicular lymphocytic infiltrate (vertical section). Note the Max-Joseph spaces between the hair follicle and the perifollicular sheath. **I** *Lichen planopilaris* at the level of the isthmus showing complete loss of sebaceous glands, perifollicular fibrosis, perifollicular lymphocytic infiltrate, and follicular tufting (horizontal section). *A–H, Courtesy Laila El Shabrawi-Caelen, MD.*

Treatment

With the exception of correcting underlying disorders or discontinuing (or substituting) medications outlined in Table 69.4, there is no well-documented treatment for telogen effluvium. Iron replacement in those with a serum ferritin level <40 ng/dl is recommended by many hair experts following determination of its etiology. Topical or low-dose oral minoxidil may be considered as an off-label, nonspecific hair growth-promoting agent[27] as can platelet-rich plasma injections.

Anagen Effluvium

Anagen effluvium develops when there is an abrupt and simultaneous inhibition of the mitotic activity of follicular matrix cells. Anagen follicles with the highest mitotic activity are most affected while those with less mitotic activity enter telogen phase. Within a few days to weeks, there is loss of actively growing anagen hairs. Of note, hair follicles in telogen phase are not affected. Chemotherapy is the most common cause but exposure to thallium, other heavy metals (e.g. arsenic, lead, bismuth), ionizing radiation, and severe nutritional deficiencies can lead to anagen effluvium[28]. Systemic medications used to treat skin diseases, such as methotrexate, azathioprine, and retinoids, are a rare cause of anagen effluvium. Anagen effluvium may be related to other hair disorders, e.g. alopecia areata.

The diagnosis is based on history and clinical appearance, with the abrupt loss of up to 90% of hair shafts a distinct finding. By trichoscopy, there are multiple black dots, terminal hairs with proximal hair thinning, and exclamation point hairs[29]. Some patients, especially those who receive taxanes and anthracyclines, can develop persistent chemotherapy-induced alopecia, which may improve with topical or low-dose oral minoxidil.

Treatment of anagen effluvium consists of discontinuation or avoidance of the causative factor. Scalp cooling during administration

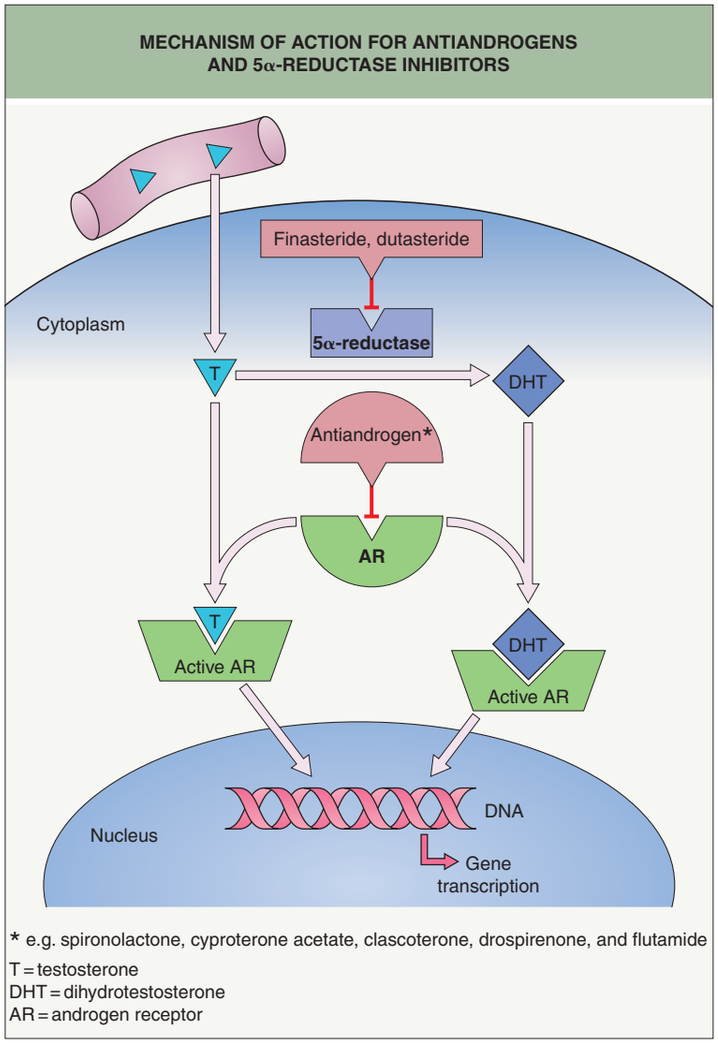


Fig. 69.10 Mechanism of action of antiandrogens and 5α-reductase inhibitors in androgenetic alopecia.

TRIGGERS OF TELOGEN EFFLUVIUM
• Shedding of the newborn (physiologic)
• Pregnancy
• High fever
• Severe infection (e.g. bacterial, viral) or illness
• Endocrinopathy (e.g. hyperthyroidism, hypothyroidism)
• Nutritional deficiencies (e.g. malnutrition, malabsorption, weight reduction diets, fad diets, post-bariatric surgery)
• Chronic systemic disease (e.g. AIDS, systemic lupus erythematosus)
• Major surgical procedure (general anesthesia)
• Acute or chronic blood loss, iron deficiency
• Medications
◦ discontinuation of oral contraceptives
◦ endocrine therapies (e.g. selective estrogen receptor modulators)
◦ retinoids (e.g. acitretin, isotretinoin) and vitamin A excess
◦ anticoagulants (especially heparin)
◦ antithyroid drugs (propylthiouracil, methimazole)
◦ lithium
◦ anticonvulsants (e.g. phenytoin, valproic acid, carbamazepine)
◦ interferon-α-2b
◦ β-blockers (e.g. propranolol, metoprolol, timolol)
◦ immunosuppressive drugs (e.g. methotrexate, azathioprine)
◦ nonsteroidal anti-inflammatory drugs (e.g. ibuprofen, ketoprofen)
◦ levodopa
◦ allopurinol
• Exposure to heavy metals (e.g. cadmium)*
• Severe, prolonged psychological stress
• Inflammatory scalp disorders (e.g. severe seborrheic dermatitis, psoriasis, allergic contact dermatitis)
*Also cause anagen effluvium.

Table 69.4 Triggers of telogen effluvium. There is also a chronic form of telogen effluvium for which there is no attributable cause or illness.

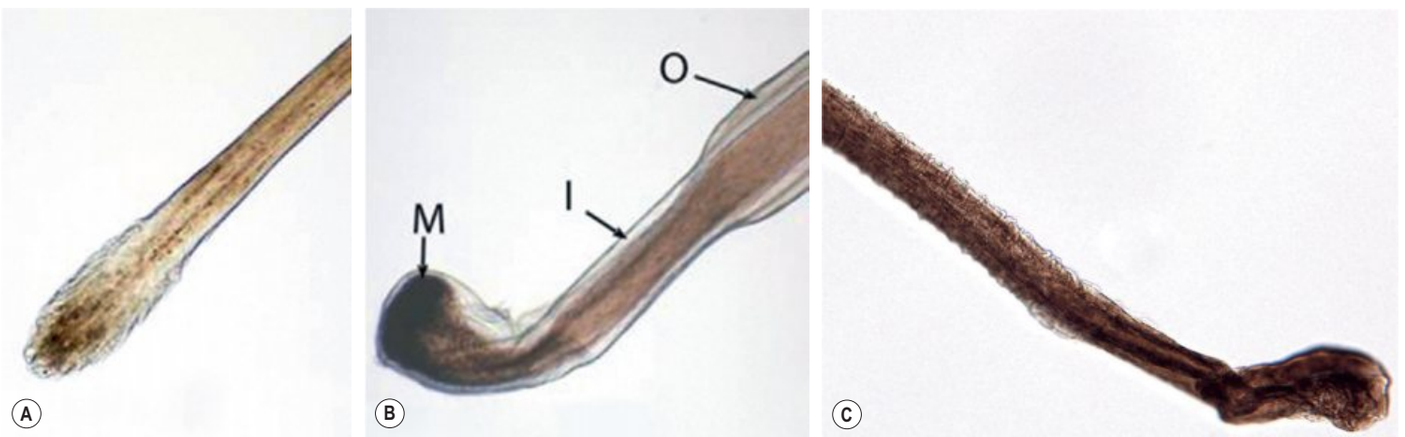


Fig. 69.11 Microscopic features of anagen and telogen hairs. A Telogen shaft showing a club-shaped bulb. **B** Anagen shaft with attached root sheaths, demonstrating a pigmented and distorted bulb. M, matrix; I, inner root sheath; O, outer root sheath. **C** Ruffled cuticle of loose anagen hair. *C, Courtesy Julie V. Schaffer, MD.*

of chemotherapy via cold caps or cooling systems has shown benefit in up 50% of patients, depending upon the chemotherapeutic regimen. To date, scalp cooling has been used primarily in breast cancer patients rather than in those with malignancies (e.g. hematologic) where there could be a theoretical reduction in chemotherapy efficacy.

Alopecia Areata

Key features

- Autoimmune disease characterized by chronic or episodic non-cicatricial hair loss
- Presents with hairless patches, most commonly on the scalp; may result in total hair loss
- Typical trichoscopic features are exclamation point hairs, black dots, and yellow dots
- Long-standing alopecia areata is associated with follicular dropout and may become irreversible

Introduction

Alopecia areata is an autoimmune disease, with genetic factors playing a role in disease susceptibility. It has a chronic relapsing course and although varying hair-bearing areas can be affected, the scalp and beard are the most common sites of involvement. The prevalence of alopecia areata in the population is ~0.1% to 0.2%, and the lifetime risk of developing alopecia areata is estimated to be ~2%[20].

Pathogenesis

The pathogenesis of alopecia areata is complex, with interactions involving immune, genetic, and environmental factors. It is an autoimmune T-cell mediated disease with a predominant Th1/IFN-γ response that leads to stimulation of $CD8^+NKG2D^+$ effector T cells. The latter infiltrate affected hair follicles, leading to upregulation of major histocompatibility complexes and subsequent loss of hair follicle immune privilege[30]. IL-15 is also upregulated in diseased hair follicles, activating IFN-γ-producing $CD8^+NKG2D^+$ cytotoxic T cells which then leads to a positive feedback loop that promotes additional IL-15 production. As a result, there is a continued autoimmune attack on hair follicles and a transition from anagen to catagen. IFN-γ and IL-15 are dependent on the JAK-STAT signaling pathway for the activation and proliferation of autoreactive T cells (see Fig. 128.11), providing an explanation for the therapeutic response to JAK inhibitors. Of note, follicular stem cells are not usually targeted, allowing for future hair regrowth via spontaneous remission or effective treatment.

For some patients, environmental factors such as viral infections, vaccines, medications, and stress have been implicated as possible triggers[30a]. From a genetic standpoint, alopecia areata is an example of a complex polygenic disease[30b,30c]. Genome-wide association studies have confirmed an association with particular HLA genes, with the HLA-DQB1*03 allele identified as an important susceptibility marker[30d,30e]. There is also a strong association with genes in the ULBP gene cluster (chromosome 6q25) which code for activating ligands of the NKG2D receptor[30f]. Patients with alopecia areata have an increased risk of other autoimmune diseases (e.g. thyroid disease, rheumatoid arthritis) and this may be due to a shared inherited autoimmune pathway. Indeed, several susceptibility loci linked to other autoimmune diseases have been identified in patients with alopecia areata, e.g. CTLA-4, IL-2/IL-21, IL-2RA[30g]. Lastly, both *PTPN22*, which encodes a lymphoid protein tyrosine phosphatase that normally suppresses T cell proliferation, and IL-1 cluster genes (IL-1RA) have been associated with severe forms of alopecia areata[30h].

Clinical features

Alopecia areata commonly presents as round or oval patches of non-scarring hair loss (patchy alopecia areata; Fig. 69.12A,B). Other presentations include alopecia totalis (loss of all scalp hair), alopecia universalis (loss of all scalp and body hair), ophiasis (band-like pattern of hair loss along the periphery of the temporal and occipital scalp), and alopecia involving the beard, eyebrows, or other hair-bearing sites (Fig. 69.12C–F). The reticular variant is characterized by recurrent patchy disease, in which the patient experiences hair loss in one area while at the same time undergoing spontaneous regrowth in other sites. An unusual variant is sisaipho (ophiasis inversus) in which the hair loss spares temporal and occipital areas. The rare diffuse variant of alopecia areata can present with widespread thinning or may primarily affect the vertex. Non-pigmented hairs may remain unaffected such that some patients with diffuse scalp involvement appear to develop rapid graying of the hair[20].

The hair loss in alopecia areata is generally reversible, but late-stage disease is characterized by progressive follicular drop-out. Prognosis worsens when alopecia areata persists beyond 5 years and hair loss can become irreversible when the alopecia persists for >10 years. However, irreversibility should not be assumed nor serve as a contraindication for a therapeutic trial[31]. The Alopecia Areata Predictive Score (AAPS) can be used to estimate the probability of hair regrowth based upon trichoscopy findings (see below)[32].

Alopecia areata, especially when severe, may be associated with nail involvement. The most common abnormality is nail pitting, often in a grid-like pattern (see Fig. 71.2). Other changes include trachyonychia (sandpaper-like roughness due to excessive longitudinal ridging; Fig. 69.12G), brittle nails, onycholysis, koilonychia, and rarely, onychomadesis[33].

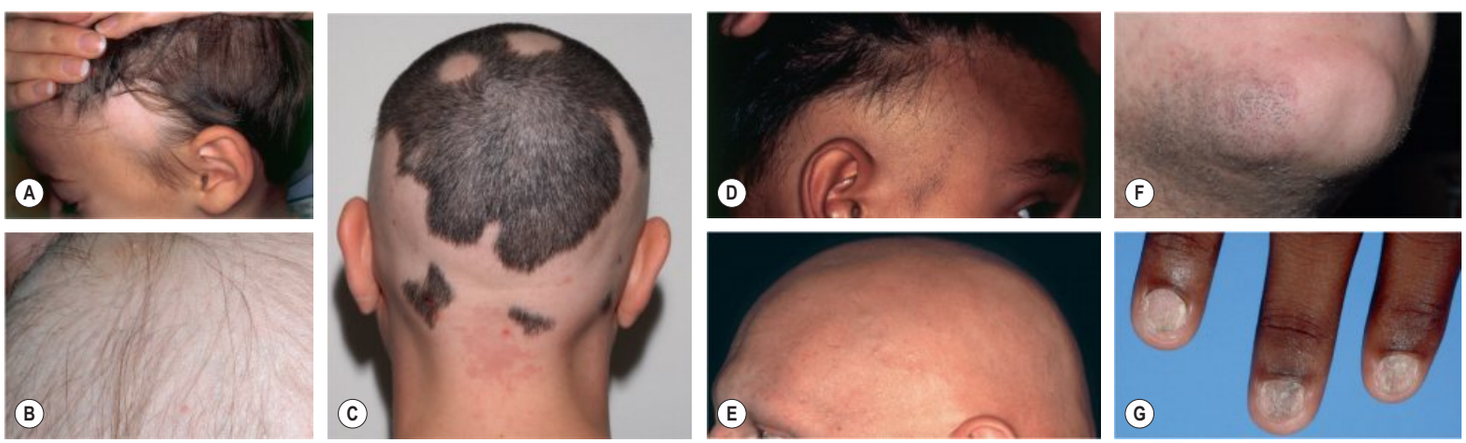


Fig. 69.12 Alopecia areata. A A circular patch of alopecia areata in a child. **B** Within a patch of alopecia areata, hair loss may be incomplete as telogen hairs remain; note the multiple exclamation point hairs. **C** Circular and confluent areas of alopecia, leading to an ophiasis pattern. There is an incidental nevus simplex. **D** Ophiasis with a band-like pattern of hair loss along the periphery of the temporal and occipital scalp. **E** Total alopecia of the scalp, eyebrows, and eyelashes in a patient with alopecia universalis. **F** Alopecia areata of the beard. **G** Trachyonychia, which is usually associated with severe alopecia areata. *B, G, Courtesy Julie V. Schaffer, MD; C, Courtesy Edward Cowen, MD; E, Courtesy Leonard C. Sperling, MD; F, Courtesy Rodney D. Sinclair, MD.*

In alopecia areata, the three most common trichoscopic findings are: (1) exclamation point hairs – proximal hair shaft thinning due to episodes of arrested mitotic activity within the germinal matrix; (2) black dots – when the exclamation point hairs break off, the residual dark hair shaft is visible in the follicular opening; and (3) yellow dots – empty hair follicles filled with keratotic material and sebum (Fig. 69.13; see Fig. 69.7B,E,F). The latter may be more subtle in prepubescent children. Tapered hairs represent very long exclamation point hairs and they indicate moderate disease activity. Pigtail (circle) and upright regrowing hairs indicate hair regrowth (see Fig. 69.7L)[34].

Comorbidities and associated disorders

Thyroid dysfunction, atopy, and systemic lupus erythematosus are the most common immune-mediated disorders associated with alopecia areata, with odds ratios of 4.4, 2.4, and 3.5, respectively[35,36]. Reported comorbidities include metabolic syndrome, depression, and anxiety. Patients with Down syndrome have an increased incidence of alopecia areata and the latter occurs in a third of individuals with the genodermatosis autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome. Some families with vitamin D-dependent rickets type II also develop alopecia areata.

Satoyoshi syndrome is a multisystem disorder in which patients can develop severe alopecia areata. Hair loss represents the syndrome's major criterion while intermittent painful muscle spasms, diarrhea, and anti-nuclear antibodies are the minor criteria (2 of 3 required for diagnosis[37]. Lastly, in a small study of patients with alopecia areata, gut dysbiosis was observed[38].

Differential diagnosis

Tinea capitis, trichotillomania, temporal triangular alopecia, traction alopecia, secondary syphilis, and loose anagen syndrome need to be considered in the differential diagnosis of alopecia areata as well as pressure-related alopecia, aplasia cutis, and "burnt-out" cicatricial alopecia. The diffuse variant may initially be confused with telogen effluvium and AGA. Usually, the history and clinical examination (including trichoscopy) is sufficient to distinguish between these conditions, but performing a scalp biopsy may prove useful for less distinctive presentations. The histopathologic features of alopecia areata are illustrated in Fig. 69.9E,F,G and are outlined in Table 69.3.

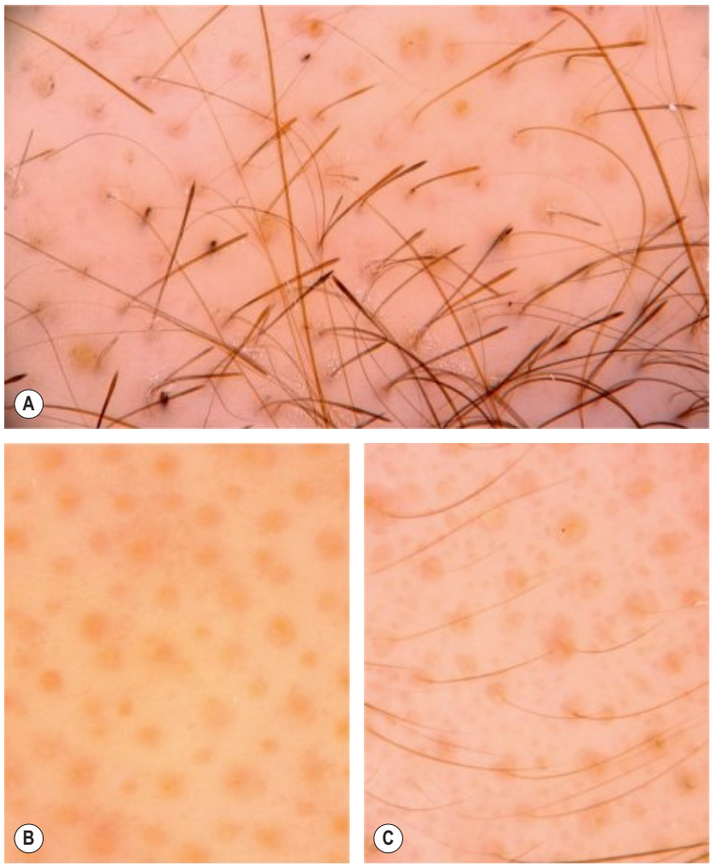


Fig. 69.13 Trichoscopy of alopecia areata. A Active disease with multiple exclamation point hairs and black dots; some yellow dots are also seen. **B** Chronic phase with only yellow dots. **C** Regrowth phase with thin hair shafts emerging from some of the yellow dots (eyebrow).

Treatment

Multiple off-label, variably successful topical, intralesional, and systemic therapies are available for the treatment of alopecia areata, with the therapeutic approach depending upon several factors such as age, extent of disease, and patient expectations. The FDA recently approved two oral JAK inhibitors for severe alopecia areata in adults (baricitinib) and for alopecia areata with extensive hair loss in individuals age 12 years and older (ritlecitinib). Most experts view a Severity of Alopecia Tool (SALT) score of >20 as an indication for systemic therapy[39].

Topical and intralesional

First-line topical therapy usually consists of an ultrapotent (class I) corticosteroid. Additional topical options include calcineurin inhibitors, minoxidil, anthralin, and especially for eyebrows, prostaglandin analogues (e.g. bimatoprost, latanoprost) and topical JAK inhibitors. Children with severe alopecia areata can be offered contact immunotherapy (e.g. diphenylcyclopropenone [diphencyprone], squaric acid dibutyl ester) before systemic therapy is considered. In all age groups, concurrent systemic immunosuppressants should be avoided as they can blunt the desired inflammatory response from contactants.

A solitary patch on the scalp is best treated with intralesional triamcinolone acetonide (2.5 to 5 mg/ml) every 3–4 weeks. Approximately 0.1 ml is injected into the mid to deep dermis, with injection sites at intervals of 1 cm apart. In an average adult, the recommended maximum dose administered during a single session is 10 to 20 mg[40].

Systemic

In adults and adolescents with severe disease, options include prednisone or prednisolone, Janus kinase (JAK) inhibitors, and cyclosporine; pulse corticosteroids (e.g. dexamethasone 0.1 mg/kg twice weekly, prednisolone 200 mg weekly, prednisolone 5 mg/kg [up to 300 mg] monthly) can also be considered in children as well as adults. When daily corticosteroids are administered for rapidly progressive disease, an initial dose of prednisolone is typically 0.4 to 0.6 mg/kg/day with a gradual taper over at least 12 weeks and a possible transition to a pulse regimen. Either cyclosporine (3 to 5 mg/kg/day) or methotrexate (15 to 20 mg weekly) may be used as a steroid-sparing agent or as monotherapy[40]. In younger patients, the methotrexate target dose is ~0.4 mg/kg/week[40]. For other steroid-sparing agents, including mycophenolate mofetil, azathioprine, dapsone, sulfasalazine, IL-17 inhibitors, apremilast and dupilumab, there are limited data regarding efficacy. The latter has been successful in patients who had concomitant atopic dermatitis.

Multiple more recent studies have demonstrated the effectiveness of oral JAK inhibitors (see Ch. 128), in particular baricitinib[41] and ritlecitinib[41a], which are now FDA-approved for the treatment of alopecia areata (see above), as well as tofacitinib and deuruxolitinib. However, maintenance therapy is necessary to avoid relapse. Topical JAK inhibitors (e.g. 2% tofacitinib, 1.5% ruxolitinib) are less effective than their oral counterparts, and use of JAK inhibitors in children (maximum daily dose of 0.625 mg [<20 kg] to 1.25 mg [20–40 kg]) is currently off-label. Irrespective of the preferred treatment, low-dose oral minoxidil can be employed as supplemental therapy.

Trichotillomania

Key features

- A body-focused repetitive behavior disorder characterized by hair pulling
- Varying lengths of hair are typically seen within areas of alopecia
- The most specific trichoscopic features are coiled hairs, flame hairs, and the v-sign
- A related disorder is trichotemnomania in which hairs are compulsively cut or shaved

Pathogenesis

Trichotillomania is defined by the American Psychiatric Association as one of the "obsessive–compulsive and related disorders" (see Ch. 7 for clinical criteria). However, individuals with trichotillomania represent a very heterogeneous group, varying from those with a mild habit to others who have an impulse-control disorder, personality disorder, or intellectual disability. Notably, many of the patients who have alopecia due to pulling their hair out do not fulfill the diagnostic criteria for psychiatric disorders.

Clinical features

Individuals with trichotillomania usually pluck scalp hair, resulting in patchy or full alopecia of the scalp (Fig. 69.14A). Some patients may also pluck from other hair-bearing regions such as the eyebrows, eyelashes, extremities, or pubic region. Patches of alopecia may have irregular shapes as well as erosions, crusts, and hairs of varying lengths. The clinical diagnosis can be supported by shaving a small area of involved scalp to demonstrate normal, dense regrowth as very short hair shafts are usually not plucked by the patient. The seven trichoscopy features with highest specificity for trichotillomania are: hook hairs; coiled hairs; the v-sign (two hairs broken at the same level in one follicle); hair powder; flame hairs (semi-transparent, wavy, cone-shaped hair residues); tulip hairs (short hairs with tulip flower-like ends); and trichoptilosis (Fig. 69.14B)[42]. Broken hairs and black dots are common, but nonspecific trichoscopic features. The histopathologic findings in trichotillomania are outlined in Table 69.3.

Treatment

No specific treatment approach has been established as effective in any large controlled study. Hypnosis, behavioral modification therapy, insight-oriented psychotherapy, and pharmacologic therapy have all been tried, but success rates are low. Habit reversal training is often used as a first-line non-pharmacologic treatment. If pharmacologic therapy is considered, N-acetylcysteine, clomipramine, or olanzapine can be tried. In preschool children, the hair pulling often resolves with no treatment[43].

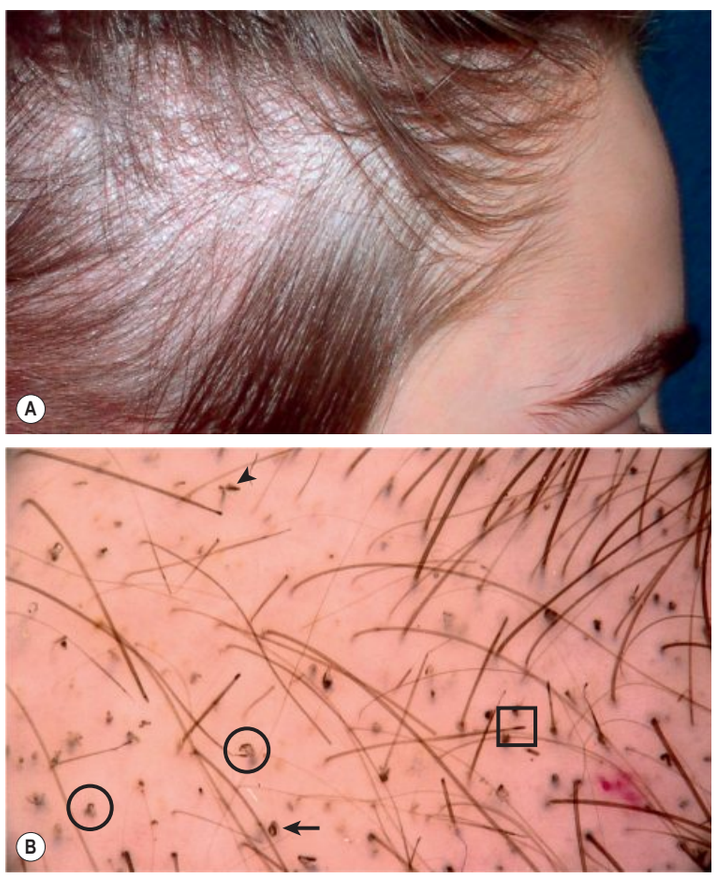


Fig. 69.14 Trichotillomania in a 14-year-old girl. A Decreased hair density in an irregularly shaped patch. **B** Trichoscopy shows multiple broken hairs of varying lengths ("irregularly irregular") and black dots. In addition, there are hook (circles), tulip (square), and coiled (arrow) hairs as well as the v-sign (arrowhead).

Pressure Alopecia (Pressure-Induced Alopecia)

Pressure alopecia usually develops following prolonged immobilization as occurs with a lengthy surgical procedure or hospitalization in an intensive care unit. Most commonly the patient is supine with the head fixed in one position on the operating table or bed and the pressure alopecia appears on the occiput. In theory, there is locally reduced microcirculation due to pressure. Although complete hair regrowth usually occurs, cases of permanent (i.e. cicatricial) hair loss have been reported[44]. Nonspecific findings are seen by trichoscopy. An analogous condition in newborns is the halo scalp ring which manifests as a self-resolving occipital band of alopecia. The ring is believed to be due to pressure from the maternal cervix during labor[45].

Temporal Triangular Alopecia

Temporal triangular alopecia (congenital triangular alopecia) presents as a hairless patch in the temporal region of the scalp (unilateral or bilateral). It may be present at birth or appear during the first decade of life. The alopecia is usually in the shape of a triangle, but oval and other shapes can be seen (Fig. 69.15). Trichoscopy shows very thin and vellus hairs within the entire patch. The alopecia is usually permanent[46].

Traction Alopecia

Traction alopecia results from repetitive and prolonged tension on scalp hairs. It usually develops from styling hair in cornrows, braids, dreadlocks, ponytails, or chignons. It may also be associated with other forms of tension, e.g. from hair extensions, and occasionally from wearing turbans. The hair loss is accentuated in areas with the greatest tension and is most commonly observed in the frontal and temporal areas (Fig. 69.16). In advanced traction alopecia, a "fringe sign" may be seen, i.e. a thin strip of retained hairs in the *original* frontotemporal hairline that is separated from the current hair-bearing margin by a 1- to 3-cm hairless band. Permanent damage to hair follicles and irreversible hair loss can occur in late-stage disease. The histopathologic findings are outlined in Table 69.3.

Trichoscopic features reflect the mechanical tension applied to the hairs, but without the chaotic arrangement that is typical of trichotillomania. A characteristic finding in traction alopecia is the Flambeau sign – perifollicular linear white tracks localized parallel to the emerging terminal hair. Vellus hairs are present in the frontal area, a feature which differentiates traction alopecia from frontal fibrosing alopecia. Hair casts and broken hairs are additional trichoscopic features of traction alopecia but they are nonspecific[47].



Fig. 69.15 Temporal triangular alopecia. The tip of the "lancet" points superiorly. *Courtesy Jean L. Bolognia, MD.*



Fig. 69.16 Traction alopecia. Favors the frontotemporal area in African-American women and is due to traumatic types of hair styling. The arrow points to the "fringe sign". *Courtesy Leonard C. Sperling, MD.*

In traction alopecia, the major therapeutic intervention is a switch to a looser hair style with less tension and avoidance of hair styles such as tight cornrows and heavy sewn-in extensions (see Table 69.6). Hair regrowth may be stimulated with topical or low-dose oral minoxidil; topical or intralesional corticosteroids as well as antibiotics (e.g. topical clindamycin, oral doxycycline) may have some efficacy. For late-stage disease with irreversible hair loss, hair restoration may be considered (see Ch. 157)[48].

Lipedematous Scalp and Lipedematous Alopecia

Lipedematous scalp is a disease of unknown etiology that is associated with local lymphatic dilatation and edematous thickening of the subcutis and dermis. Patients have a soft, "spongy" scalp and when pressed with a finger, a depression is seen. If associated with hair loss, then it is referred to as lipedematous alopecia. Hairs are usually sparse and short (~1–2 cm). By trichoscopy, multiple thin and vellus hairs as well as linear areas of erythema with fine arborizing vessels are seen.

The primary pathologic finding is an approximate doubling of scalp thickness as a result of expansion of the subcutaneous fat layer. If there is prominent alopecia, histopathologic changes include not only a thickened adipose layer, but also replacement of hair follicles with fibrous tracts without discernible inflammation. In case reports, partial hair regrowth has been described with topical clobetasol, intralesional triamcinolone, or mycophenolate mofetil[49,50].

Psoriatic Alopecia

The most common form of psoriatic alopecia is circumscribed and non-cicatricial. It occurs within psoriatic plaques and a specific finding is hair loss in tufts as thick psoriatic scales are shed from the scalp. Although clinically apparent psoriatic alopecia is rare, a decreased hair density is frequently observed histologically in scalp psoriasis along with an increased number of telogen hair follicles. The rapid development of severe psoriatic alopecia has been described as a paradoxical phenomenon in patients whose psoriasis has otherwise been successfully treated with TNF inhibitors (e.g. infliximab, adalimumab).

Only rarely will psoriasis of the scalp lead to a cicatricial alopecia. Trichoscopy of psoriatic cicatricial alopecia shows milky-red areas with no follicular openings (dots) in addition to vascular abnormalities typical for psoriasis, i.e. regularly distributed red dots or lace-like structures in a linear arrangement as well as bushy or glomerular structures.

Syphilitic Alopecia

Unless a chancre is located on the scalp, hair loss does not occur in primary syphilis. In secondary syphilis, the most typical presentation is a "moth-eaten" pattern of alopecia with multiple, small, ill-defined hairless patches primarily in the parieto-occipital region of the scalp. Hair loss may also occur in the eyebrows, beard, and other hair-bearing sites. Diffuse scalp alopecia, as in telogen effluvium, is less common. A third type of hair loss is seen within nodulo-ulcerative skin lesions of lues maligna; they heal with scarring, leading to secondary cicatricial alopecia. In tertiary syphilis, hair loss may occur within cutaneous gummas.

Non-Cicatricial Alopecia in Systemic Lupus Erythematosus

Non-cicatricial alopecia is a common presenting sign of systemic lupus erythematosus (SLE) and can accompany a flare of the disease. It is a criterion in both the SLICC (Systemic Lupus International Collaborating Clinics) and the EULAR/ACR criteria for SLE (see Tables 41.4 & 41.5). Three clinical forms have been described: (1) diffuse hair loss that resembles typical telogen effluvium; (2) focal hair loss that resembles alopecia areata; and (3) "lupus hairs"[51]. The latter represent short hair shafts that are brittle and fragile. They are occasionally observed in other autoimmune connective tissue diseases. The trichoscopic findings include thick, arborizing and tortuous, interfollicular blood vessels (see Fig. 69.7K), decreased hair density and shaft diameter, and hair shaft hypopigmentation; randomly distributed wavy hair shafts ("lupus hairs") are also seen[29].

Congenital Atrichia with Papular Lesions

Congenital atrichia with papular lesions is a rare autosomal recessive disorder in which there are multiple, widely distributed milia-like papules in addition to a complete absence of hair that is noted within a few months of birth. Patients have hair at birth but once it falls out it is not replaced. The alopecia is non-cicatricial but non-reversible and is due to mutations in the hairless gene (*HR*), which encodes a transcriptional corepressor of multiple nuclear receptors and Notched target genes. Histologically, there is replacement of the middle and lower portions of the hair follicle by keratinizing cysts.

CICATRICIAL (SCARRING) ALOPECIAS

Introduction

"Cicatricial" (or "scarring") alopecia implies that the follicular epithelium has been replaced by fibrotic tissue. The lack of hair follicles, in particular replacement of the follicular bulge region by collagen and other extracellular matrix proteins, results in irreversible hair loss. Cicatricial alopecia may be *primary* or *secondary*. In *primary* cicatricial alopecia, the follicle is destroyed by an inflammatory process which targets the follicular unit. In *secondary* cicatricial alopecia, the follicle is merely an "innocent bystander" in the disease process. Examples of secondary cicatricial alopecia include deep burns, radiation dermatitis, cutaneous malignancies, cutaneous sarcoidosis, morphea, necrobiosis lipoidica, and certain chronic infections such as cutaneous tuberculosis. The various forms of secondary cicatricial alopecia should have distinctive clinical and histologic features typical of the underlying disease.

Performing a scalp biopsy may be helpful not only in establishing a diagnosis but also in assessing the degree of inflammation and injury to the stem cell region. Specimens should be obtained at the hair-bearing margin (guided by trichoscopy), be at least 4 mm in diameter, and extend into the fat. If the central portion is sampled, only end-stage scarring with fibrosis will be seen. Ideally, two biopsies should be performed – one for vertical sectioning, the other for horizontal sectioning. The North American Hair Research Society proposed a classification for primary cicatricial alopecias and, despite some controversies, it remains the best available working classification[52].

Lichen Planopilaris

Several distinct entities are considered to be within the broader lichen planopilaris spectrum: (1) classic lichen planopilaris; (2) frontal fibrosing alopecia; and (3) Graham Little–Piccardi–Lasseur syndrome. Some authors also consider fibrosing alopecia in a pattern distribution (FAPD) a distinct entity within this spectrum.

Classic Lichen Planopilaris

Key features

- Chronic, progressive, inflammatory cicatricial alopecia
- Trichoscopy shows perifollicular scaling and areas with no hair follicle openings
- Histologically, there is a lymphocytic infiltrate involving the isthmus and infundibulum
- Treatment consists primarily of systemic immunosuppressive drugs

Pathophysiology

In lichen planopilaris, the infundibulo-isthmic (bulge) region of the hair follicle is targeted by an immune-mediated lymphocytic infiltrate. This folliculocentric inflammatory process leads to localized fibrosis and replacement of hair follicles by fibrous tracts. The factors which trigger this disease process remain unknown.

Clinical features and diagnosis

Lichen planopilaris occurs predominantly in White women with an onset of disease between 40 and 60 years of age. Lichen planopilaris in children is rare and is usually associated with a positive family history.

Hyperesthesia of the scalp may be a premonitory symptom. A burning sensation, pain, or pruritus is usually associated with active hair loss. During the early phase, one or more small (<1 cm) patches of cicatricial alopecia appear on the vertex or in the occipital region (Fig. 69.17A). In the hair-bearing margin, there is perifollicular erythema and hyperkeratosis (Fig. 69.17B). The patches of alopecia tend to increase in size and become confluent over time[53]. Occasionally "lonely hairs" may be present in the central portion of the lesions.

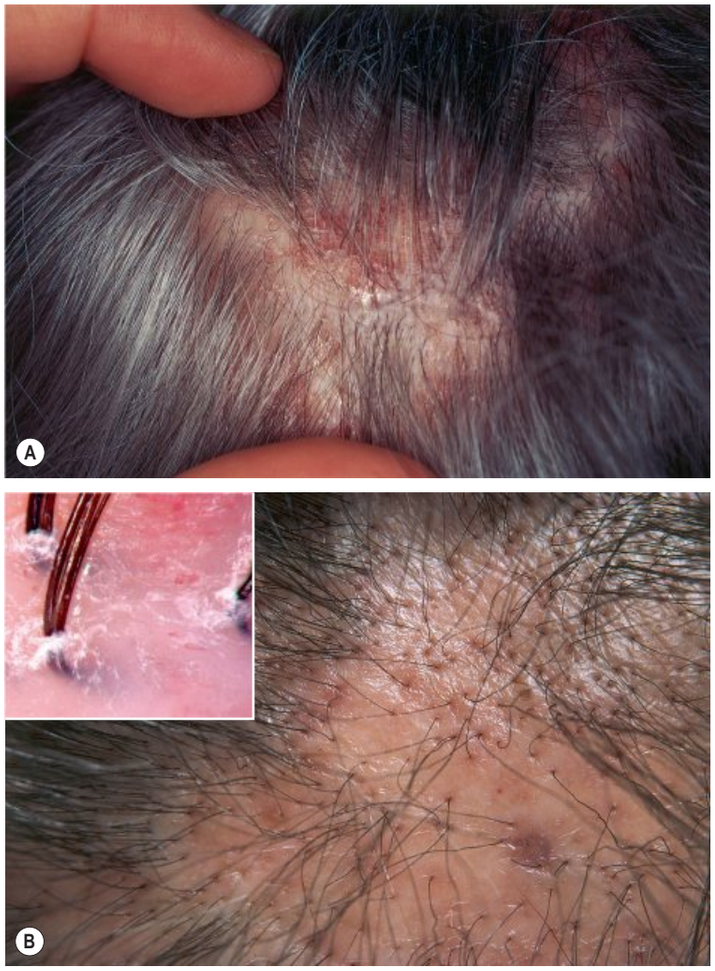


Fig. 69.17 Lichen planopilaris. A Patchy areas of alopecia with perifollicular erythema and scale at the active margins. **B** Later stage showing scarring with loss of follicular openings. By trichoscopy, there is perifollicular scaling and areas with no follicular openings (dots) due to loss of hair follicles (inset). *A, Courtesy Jean L. Bolognia, MD.*

Up to 15% of patients have coexisting mucosal lichen planus. Vulvovaginal–gingival–pilar lichen planus is a distinct entity that combines the vulvovaginal–gingival syndrome (see Ch. 11) with extensive and recalcitrant lichen planopilaris and circulating stratified epithelium-specific anti-nuclear antibodies (SES-ANA)[54].

Trichoscopy of lichen planopilaris shows perifollicular erythema and scaling, with the scales entangling hair shafts up to 2–3 mm above the scalp surface in a tubular fashion (Fig. 69.17B inset). Hair casts and elongated linear blood vessels may also be present. Late-stage disease is characterized by milky-red areas with no follicular openings[55]. The histopathologic features of lichen planopilaris are outlined in Table 69.3 and illustrated in Fig. 69.9H,I. Of note, perifollicular inflammation can be observed in areas with no clinically evident disease, raising the possibility that lichen planopilaris may be a generalized process that affects the entire scalp[56].

Treatment

The goal of treatment is to reduce pruritus and halt any further scarring. Recommended first-line treatments include hydroxychloroquine, doxycycline, and corticosteroids (intralesional or oral)[57]. Topically, potent corticosteroids and calcineurin inhibitors may be used as adjuvant therapy. Second-line therapeutic options include retinoids (acitretin and isotretinoin), mycophenolate mofetil, methotrexate, and cyclosporine[57] as well as JAK inhibitors, apremilast, and pioglitazone. Topical or low-dose oral minoxidil and 5α-reductase inhibitors may also be used as adjuvant therapy. While lichen planopilaris can burn out spontaneously, many patients have chronic progressive disease.

Frontal Fibrosing Alopecia

Key features

- Cicatricial alopecia with selective involvement of the hairline, most commonly frontotemporal
- Additional findings are a loss of eyebrows and facial papules
- Trichoscopy shows perifollicular scaling and "lonely hairs"
- Systemic immunosuppressants and 5α-reductase inhibitors may halt or slow progression of the disease

Pathogenesis

In frontal fibrosing alopecia (FFA), as in classic lichen planopilaris, the infundibulo-isthmic (bulge) region of the hair follicle is attacked by an immune-mediated inflammatory infiltrate; the latter has a predominance of $CD8^+$ T lymphocytes. The inciting factors that lead to this inflammation are unknown. Environmental exposures such as leave-on cosmetics, facial sunscreens, fragrances, haircare products, contact allergens, and diet have all been implicated as potential triggers in genetically predisposed patients, but to date there are no definitive associations.

Clinical features

Frontal fibrosing alopecia was first described by Kossard and colleagues in 1994[58]. It occurs primarily in perimenopausal women, but younger women and men may also be affected. A band-like recession of the frontotemporal hairline is typically seen, which usually progresses at a rate of ~0.3–1.5 mm per month[59]. The occipital and/or retro-auricular hairlines can also be involved[60].

Three clinical patterns of hair loss have been described: (1) linear – a clearly demarcated hairline is seen; (2) diffuse – there is a decrease in hair density in the frontal hairline; and (3) pseudo-fringe – a "fringe" of frontal hairs is isolated from the hairline by a hairless band (Fig. 69.18). In all three patterns, only full-thickness terminal hair shafts are visible within the involved hairline. Vellus hairs, which would be present in the "fringe" associated with traction alopecia, are not present because they are the first to disappear during the disease process. The skin is smooth, slightly atrophic, devoid of follicular openings, and lighter in color than the remaining skin of the forehead.

Additional clinical features of FFA include "lonely" hairs (Fig. 69.18A inset), lateral or complete eyebrow loss, partial loss of eyelashes,



Fig. 69.18 Frontal fibrosing alopecia. **A** Progressive hair loss along the anterior hairline with absence of solar lentigines (diffuse pattern). There are scattered "lonely" hairs (inset) and an eyebrow pencil has been used because of loss of eyebrow hairs. **B** Hypopigmented, atrophic band of cicatricial alopecia with a clearly demarcated, receded hairline (linear pattern) in addition to a "pseudo-fringe"; the latter is a fringe of hairs that marks the previous hair line. **C** Facial papules and loss of eyebrows; the patient also has rosacea. **D** By trichoscopy, discrete perifollicular scaling around remaining hairs and beige areas with no follicular openings (dots). *A, Courtesy Kalman Watsky, MD.*

prominent or depressed forehead veins, multiple facial papules (see Fig. 69.18C), and glabellar follicular red dots. The latter two findings are due to involvement of facial vellus hairs. In late-stage FFA, there may also be thinning of axillary, pubic, limb, and truncal hair[60]. Of note, classic lichen planus or lichen planus pigmentosus (especially in patients with darker skin phototypes) may accompany FFA. There are also rare reports of FFA coexisting with cutaneous lupus.

Treatment

Treatment options for FFA are similar to those described previously for lichen planopilaris. Of note, oral finasteride or dutasteride may be beneficial. Possible explanations for the efficacy of 5α-reductase inhibitors include an effect on coexisting androgenetic alopecia or inhibition of the conversion of terminal to vellus hair follicles, which would then lead to a reduction in the proportion of vellus hair follicles, the primary target in FFA.

Graham Little–Piccardi–Lasseur Syndrome

The Graham Little–Piccardi–Lasseur syndrome (Graham Little syndrome) was first described by Piccardi in 1913. The description by Ernst Graham Little (in a mutual patient with Lasseur) appeared in 1915 and was the inspiration for the eponym "Graham Little syndrome". The syndrome consists of a triad of lichen planopilaris of the scalp, non-cicatricial alopecia of the axilla and groin, and follicular lichen planus of the body (see Ch. 11).

Fibrosing Alopecia in a Pattern Distribution

Fibrosing alopecia in a pattern distribution (FAPD) is a more recently recognized type of cicatricial alopecia that has characteristics of both lichen planopilaris and AGA[61]. It is considered by many to be a subtype of lichen planopilaris. Although the etiology is not well understood, FAPD is thought to be due to an exaggerated inflammatory response to damaged hair follicles, perhaps triggered by AGA. It occurs primarily in androgen-dependent areas of the scalp in which there has been hair follicle miniaturization. Clinically and by trichoscopy, there is both perifollicular inflammation (e.g. erythema, scaling) and fibrosis with loss of follicular ostia. Sometimes FAPD is misdiagnosed as AGA plus seborrheic dermatitis, but histologic examination of early-stage sites of scalp inflammation can help confirm the diagnosis. Although there are no well-documented treatments, a combination of an anti-inflammatory drug (see Lichen Planopilaris, Treatment), antiandrogen medication (see AGA, Treatment), and hair growth-promoting agent (e.g. minoxidil) has been recommended.

Classic Pseudopelade (Pseudopelade of Brocq)

Classic pseudopelade is a non-inflammatory or minimally inflammatory form of cicatricial alopecia that most commonly affects middle-aged and older women. It most likely represents a distinct clinical entity that falls within the spectrum of lichen planopilaris. The hair loss usually begins on the vertex and is characterized by multiple, small (<2 cm), smooth, slightly depressed, asymptomatic hairless patches described as appearing like "footprints in the snow" (Fig. 69.19). Over time, these lesions can become confluent and form larger areas of alopecia. While pseudopelade is classified as a cicatricial alopecia (Table 69.5), there is debate as to whether the hair follicles undergo atrophy rather than being replaced by fibrotic tissue.

Pseudopelade is usually slowly progressive but in some patients may be self-limiting[62]. Treatment options are similar to those described previously for lichen planopilaris, with the caveat that immunosuppressive drugs are less likely to be effective in the absence of significant inflammatory infiltrates.

Central Centrifugal Cicatricial Alopecia

Key features

- Slowly progressive, symmetric cicatricial alopecia centered on the mid scalp or vertex
- Most often develops in Black women; in some patients has been associated with mutations in *PADI3*
- Treatment includes topical or intralesional corticosteroids, oral tetracyclines, and adjuvant immunosuppressive drugs



Fig. 69.19 Classic pseudopelade (pseudopelade of Brocq). Irregularly shaped areas of scarring alopecia along the midline. Despite no visible features of inflammation, the disease is usually progressive. Trichoscopy shows milky-red areas of cicatricial alopecia, sparse terminal hairs, and no features of inflammation (inset). *Courtesy Kalman Watsky, MD.*

THE NORTH AMERICAN HAIR RESEARCH SOCIETY PROPOSED WORKING CLASSIFICATION OF PRIMARY CICATRICIAL ALOPECIA WITH MINOR MODIFICATIONS
Lymphocytic
Lichen planopilaris (see Ch. 11) • Lichen planopilaris • Frontal fibrosing alopecia • Graham Little syndrome • Fibrosing alopecia in a pattern distribution (FAPD) Classic pseudopelade (pseudopelade of Brocq) Central centrifugal cicatricial alopecia Chronic cutaneous lupus erythematosus (discoid lupus erythematosus) (see Ch. 41) Alopecia mucinosa* (see Ch. 46) Keratosis follicularis spinulosa decalvans (see Ch. 38)
Neutrophilic
Folliculitis decalvans Dissecting cellulitis (perifolliculitis capitis abscedens et suffodiens)
Mixed
Acne keloidalis (see Ch. 38) Folliculitis (acne) necrotica Erosive pustular dermatosis (see Chs. 25 & 87)
Nonspecific (end-stage)
*Primary form not considered a classic form of cicatricial alopecia by some experts.

Table 69.5 The North American Hair Research Society proposed working classification of primary cicatricial alopecia with minor modifications[52].

Pathophysiology

Recent insights into the underlying pathophysiology of central centrifugal cicatricial alopecia (CCCA) include the discovery of mutations in *PADI3* in some patients. The latter encodes peptidyl arginine deiminase type III, which modulates hair structural proteins including filaggrin and trichohyalin via deimination. Perifollicular lymphocytic infiltrates also play a significant pathogenic role in that they induce premature desquamation of the inner root sheath which facilitates hair loss. In addition, hair styling practices that cause traction have been implicated as potential triggers as have infectious etiologies and autoimmunity, but they remain unproven.

Clinical features

The disease begins and remains most severe on the vertex and/or mid-scalp, expanding outward in a centrifugal manner (Fig. 69.20). Most patients note mild, episodic pruritus or tenderness in the involved areas. A few isolated hairs or tufts of hair may be stranded in the otherwise denuded central zone. Perifollicular pustules may also be present[63]. By trichoscopy, there is loss of follicular openings, mild perifollicular scaling, small hair tufts, and in darkly pigmented skin, fibrotic white dots.

Differential diagnosis

All conditions that can result in a progressive pattern of alopecia affecting the crown can mimic CCCA. These include AGA, lichen planopilaris, folliculitis decalvans, and even unusual cases of discoid lupus erythematosus. Other entities in the differential diagnosis are tinea capitis (kerion) and true bacterial infections of the scalp.

Treatment

Most authors suggest that the management should begin with reduction in chemical straightening and traction-producing hair styles as well as instituting healthy hair practices (Table 69.6). Corticosteroids (potent topical or intralesional triamcinolone) are usually employed as first-line treatment. Once stabilization is achieved, maintenance therapy can consist of less frequent application of a potent topical corticosteroid. Oral doxycycline or minocycline are frequently prescribed while other possible therapeutic options include low-dose oral minoxidil as well as hydroxychloroquine, thalidomide, cyclosporine, or mycophenolate mofetil. These systemic medications can be supplemented by topical minoxidil and calcineurin inhibitors. There are anecdotal reports of the use of oral JAK inhibitors.

Discoid Lupus Erythematosus

Synonym: ■ Chronic cutaneous lupus erythematosus, discoid form

Key features

- Early lesions are characterized by erythema, scaling, and dilated, plugged follicular ostia
- Inflammatory lesions are gradually replaced by cicatricial alopecia
- The diagnosis is based on clinical evaluation, trichoscopy, histopathology, and, if needed, direct immunofluorescence (DIF) of lesional skin
- Antimalarial drugs and intralesional corticosteroids represent first-line therapies

Introduction

Discoid lupus erythematosus (DLE) can be an isolated disease or it can occur in the setting of systemic lupus erythematosus (SLE). Among patients with skin disease only, the majority will have lesions limited to the head and neck region and most do not develop systemic disease (see Ch. 41). There is, however, an increased risk of SLE in those individuals who have lesions beyond the head and neck, i.e. disseminated DLE.

Clinical features

DLE is one of the four entities classified as chronic cutaneous LE (see Fig. 41.4), and the vast majority of patients are women. Early lesions are characterized by erythema, scaling, and dilated, plugged follicular ostia. Central hypopigmentation and peripheral hyperpigmentation are commonly seen in individuals with darker skin phototypes. The inflammatory lesions are gradually replaced by cicatricial alopecia, which develops in the central portion of the lesion and progresses outwards (Fig. 69.21)[1].

Diagnosis

By trichoscopy, there are large yellow dots, thick arborizing vessels, and fine scaling (Fig. 69.21 inset). Scattered dark-brown to bluish discoloration is seen in patients with darker skin phototypes. In late-stage disease, features are similar to those observed in other cicatricial alopecias, e.g. milky-red or white areas with no follicular openings (dots) (see Fig. 69.19 inset)[55].

The clinical diagnosis of DLE should be confirmed by histologic examination (see Table 69.3). If distinction from lichen planopilaris or other disorders in the differential diagnosis is not possible, DIF of the active peripheral edge of a lesion can be performed. It is recommended that application of topical corticosteroids be suspended for at least several days to proposed biopsy sites[64].

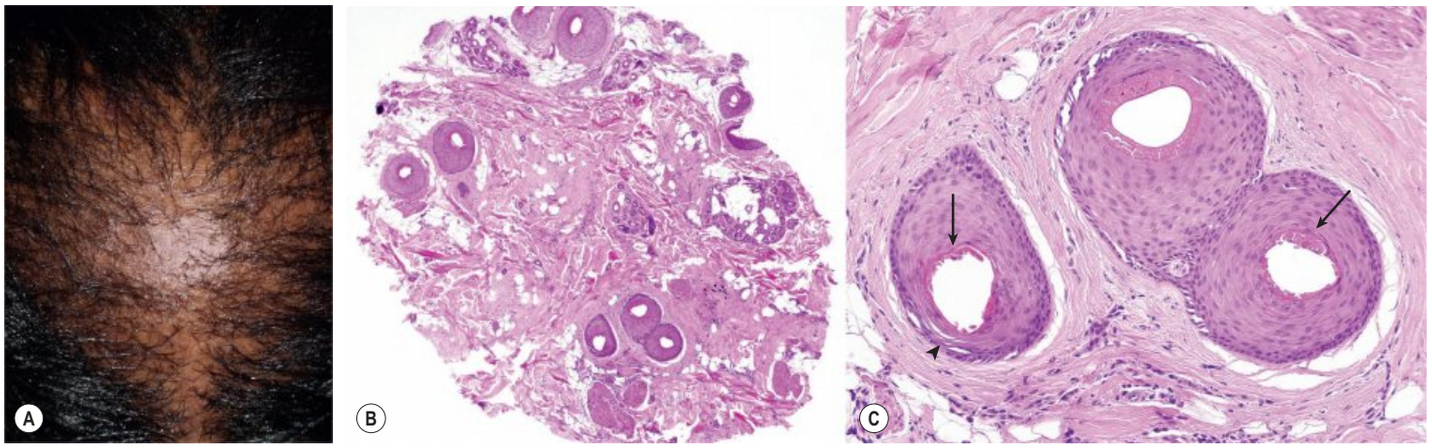


Fig. 69.20 Central centrifugal cicatricial alopecia in an African-American woman – clinical and histopathologic features. A Alopecia is most prominent on the crown and/or vertex. **B, C** Subisthmus horizontal section demonstrating scarring alopecia with reduction of terminal hair follicles and scant inflammatory cell infiltrate as well as premature desquamation of the inner root sheath (arrows) and eccentric thinning of the follicular epithelium (arrowhead) on higher magnification.
A, Courtesy Leonard C. Sperling, MD and Rodney D. Sinclair, MD.

HEALTHY HAIR PRACTICES AND TOPICAL THERAPIES FOR AFRO-TEXTURED HAIR

• Wash hair once a week or every other week
• Consider using a moisturizing, leave-in conditioner (e.g. with dimethicone, glycerin) after hair washing
• Use oil treatments (e.g. coconut oil, jojoba oil, avocado oil) or moisturizers (e.g. shea butter) on a regular basis
• Use caution with relaxers as these chemical straighteners remove fatty acids bound to the cuticle – limit use to every 2–3 months
• Use caution with thermal styling (e.g. ceramic combs, flat irons) – limit use to ~weekly*
• To limit traction alopecia, avoid tension from tight braids, cornrows, weaves, or extensions
  • crochet braids may have less tension
  • consider braids that have a higher hair base to width of braid ratio
  • weaves that are sewn into multiple corn rolls (parallel not perpendicular to frontal hairline) or a net overlying corn rolls may have less tension
  • change hairstyle every 2–3 months
• Topical therapies
  • oil-based topical corticosteroid (e.g. fluocinolone acetonide)
  • minoxidil solution (not foam) followed by moisturizer
  • zinc pyrithione or ciclopirox shampoo

*Blow dryer less damaging than flat iron.

Table 69.6 Healthy hair practices and topical therapies for Afro-textured hair.

Treatment

Photoprotection and avoidance of sun exposure are important preventive measures. Active, inflammatory discoid lesions usually respond to oral antimalarial drugs (e.g. hydroxychloroquine) and corticosteroids (topical, intralesional). Second-line therapies for antimalarial-resistant cutaneous disease, such as systemic retinoids, methotrexate, dapsone, mycophenolate mofetil, thalidomide, lenalidomide, and IVIg, are outlined in Table 41.11. Monoclonal antibodies, e.g. anifrolumab, litifilimab, daxdilimab, that inhibit production or actions of type I interferons and are usually prescribed for SLE can also improve associated mucocutaneous disease. There are scattered reports of JAK inhibitors and ustekinumab being effective in severe cases of recalcitrant DLE[65].

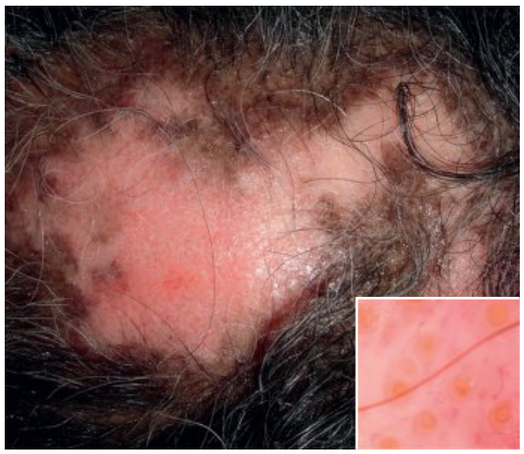


Fig. 69.21 Discoid lupus erythematosus. Coalescing areas of cicatricial alopecia in which there is obvious erythema. Central hypopigmentation is accompanied by peripheral hyperpigmentation. Trichoscopy shows follicular plugs (large yellow dots) and arborizing vessels (inset). *Courtesy Leonard C. Sperling, MD and Rodney D. Sinclair, MD.*

Follicular mucinosis

Synonym: ■ Alopecia mucinosa (clinical term)

Alopecia mucinosa is characterized histologically by the accumulation of mucin within the pilosebaceous unit. Patches, plaques, and papules commonly develop in the head and neck region. When the scalp is involved, well-defined areas of hair loss, usually 2–6 cm in diameter, can be seen; they are often accompanied by inflammation. Grouped erythematous follicular papules can also be observed within the hairless patches (see Fig. 46.15).

With the exception of urticaria-like follicular mucinosis in which there is no associated alopecia, patients with alopecia mucinosa are subdivided into primary and secondary forms (see Ch. 46). Primary disease favors children and adolescents and often resolves within 1–2 years, including hair regrowth. In adults, a greater number of lesions that are more persistent may be seen. However, excluding a secondary cause, in particular mycosis fungoides, is important in this latter group. In addition to primary alopecia mucinosa and an association with cutaneous lymphomas, deposition of mucin within hair follicles (follicular mucinosis) can be observed as an incidental finding in a number of disorders including eczematous dermatoses, SLE, and medications (e.g. imatinib). Trichoscopy shows multiple enlarged follicular openings filled with keratotic material.

In secondary follicular mucinosis, treatment focuses on the underlying disease, including phototherapy. Topical, intralesional, or oral corticosteroids may be used for primary disease, realizing that, especially in children and adolescents, the disease may resolve spontaneously[66]. Other treatment options include hydroxychloroquine, minocycline, dapsone, indomethacin, and isotretinoin.

Keratosis Follicularis Spinulosa Decalvans

Key features

- Rare X-linked recessive disorder within the spectrum of keratosis pilaris atrophicans
- Keratosis pilaris-like papules favor the scalp and face
- Follicular atrophy and scarring alopecia can follow resolution of papules

Keratosis follicularis spinulosa decalvans is a rare genodermatosis with an X-linked recessive (XLR) pattern of inheritance when due to mutations in *MBTPS2* (see Table 38.2). It is allelic with the XLR form of ichthyosis follicularis with atrichia and photophobia (IFAP) syndrome. The disease usually becomes apparent during infancy or early childhood and remains active through adolescence. Keratosis pilaris-like papules favor the face and scalp, but are sometimes more widespread. Additional findings include facial erythema, palmoplantar keratoderma, and keratitis (see Table 38.2). Hypotrichosis is often noted early on and progression of lesions leads to cicatricial alopecia of the scalp, eyebrows, and eyelashes.

Histologically, there is follicular hyperkeratosis and follicular destruction with a mixed lymphohistiocytic infiltrate as well as perifollicular and interfollicular fibrosis. In the one case described to date, trichoscopic findings (e.g. perifollicular scaling) were similar to those seen in lichen planopilaris. Oral medications, including isotretinoin, dapsone, and antibiotics, have been tried with varied results[67].

Folliculitis Decalvans

Key features

- Neutrophilic cicatricial alopecia
- It may possibly represent an altered immune response to the follicular microbiome
- When active, follicular pustules and hair tufts are the most characteristic findings
- The most common treatment is long-term oral antibiotics

Pathophysiology

Folliculitis decalvans is a neutrophilic primary cicatricial alopecia[68]. The presence of *Staphylococcus aureus* has been observed in 20%–75% of patients[44]. It has been suggested that folliculitis decalvans may result from an abnormal immune response to the follicular microbiome, with the inflammation leading to permanent follicular damage.

Clinical features

This disease typically affects young and middle-aged adults, predominantly men. The vertex and occipital area of the scalp are most often involved. During its early phase, there are recurrent follicular pustules; perifollicular erythema, scaling, erosions, and hemorrhagic crusts may also be seen. A hallmark of folliculitis decalvans is the presence of hair tufts (5–20 or more hairs in one follicular unit; Fig. 69.22), sometimes referred to as "tufted folliculitis". Although this is a characteristic finding in folliculitis decalvans, hair tufts also develop following repeated follicular injury in other inflammatory cicatricial alopecias (e.g. acne keloidalis, dissecting cellulitis). With progression, hairless patches develop that can coalesce to form large areas of cicatricial alopecia. In addition to hair tufts, active inflammation (e.g. erythema, follicular pustules, scaling, crusting) may be present at the margins of the alopecic lesions[69].

By trichoscopy, tufted hairs surrounded by perifollicular hyperplasia in a starburst pattern are seen. Previously described changes associated with inflammation may also be observed. The typical histopathologic features are outlined in Table 69.3. Occasionally, patients will have clinical features of both folliculitis decalvans and lichen planopilaris, either simultaneously or sequentially[70]. Of note, EGFR inhibitor-induced scarring alopecia can resemble folliculitis decalvans.

Treatment

In a recent analysis, a 10-week course of clindamycin plus rifampin led to the longest period of disease remission while doxycycline or azithromycin were associated with shorter remission times. Such courses of antibiotics may be repeated, if needed. Some authors prefer continuous treatment with antibiotics, either as monotherapy or in combination with immunosuppressive drugs. Isotretinoin may sometimes be effective, but its use in folliculitis decalvans remains controversial. There is a low level of evidence for other treatment options, including TNF inhibitors (e.g. adalimumab, infliximab), secukinumab, cyclosporine, apremilast, trimethoprim–sulfamethoxazole, JAK inhibitors, and photodynamic therapy. Topical corticosteroids and calcineurin inhibitors may be used as supplemental therapy.



Fig. 69.22 Folliculitis decalvans. Note the multiple hairs arising from a single inflamed follicular orifice ("tufted folliculitis") within the area of scarring alopecia. Trichoscopy shows hair tufts composed of multiple hairs and tubular perifollicular scaling (inset). *Courtesy Damon McClain, MD.*

Acne Keloidalis

Synonyms: ■ Acne keloidalis nuchae ■ Folliculitis keloidalis

Key features

- Persistent folliculitis on the nape of the neck with formation of keloid-like scars and cicatricial alopecia
- Most common in Black men, but can occur in women and White individuals
- Treatment options include intralesional triamcinolone, oral antibiotics (e.g. doxycycline), low-dose isotretinoin, and surgical excision

Pathophysiology

The etiology of acne keloidalis is still under investigation. It may be triggered by chronic follicular occlusion or trauma due to friction (e.g. rubbing from shirt collars or helmets), heat, humidity, or hair cutting practices. Other possible contributory factors include autoimmunity, infection, androgens, and medications (e.g. cyclosporine). Hypothetically, acute perifollicular inflammation leads to weakening of the follicular wall. Naked hair shafts then act as foreign bodies, with development of granulomatous inflammation and ultimately fibrosis[71].

Clinical features

Acne keloidalis typically affects young Black men and less often young Black women. It is significantly less common in White individuals. Papules, admixed with occasional pustules, appear in a band-like distribution on the posterior neck and lower occipital scalp (see Fig. 38.12). The initial papules are small (2–4 mm), smooth, and firm. Over time, they can coalesce to form larger, keloid-like, hairless plaques (see Fig. 38.13). Descriptions of trichoscopic features are limited, but include white halos around normal and dilated hair follicle openings, follicular ostia filled with keratin, and tufted hairs. The histopathologic findings are outlined in Table 69.3[106] and illustrated in Figure 38.14.

Treatment

Treatment options are discussed in detail in Chapter 38.

Dissecting Cellulitis

Synonym: ■ Perifolliculitis capitis abscedens et suffodiens

Key features

- Neutrophilic cicatricial alopecia
- May coexist with hidradenitis suppurativa, acne conglobata, and pilonidal sinus/cyst ("follicular occlusion tetrad")
- Scalp nodules appear first then develop into interconnecting, boggy, fluctuant, oval and linear ridges
- Isotretinoin and oral antibiotics are first-line therapies

Clinical features and diagnosis

Dissecting cellulitis is part of the "follicular occlusion triad" that includes hidradenitis suppurativa and acne conglobata (see Ch. 38) or "tetrad" that also includes pilonidal sinus/cyst. However, isolated scalp disease is often seen. Dissecting cellulitis most commonly affects young men, especially Black men. It occurs less commonly in White individuals and women.

Lesions begin as multiple, firm scalp nodules, most commonly on the mid and posterior vertex and the upper occiput (Fig. 69.23A). The hairless nodules rapidly develop into interconnecting, boggy, fluctuant, oval and linear ridges that eventually discharge purulent material (Fig. 69.23B). Over time the nodules become fibrotic, resulting in cicatricial alopecia. By trichoscopy, yellow structureless areas, 3D-shaped black dots, yellow dots, and dystrophic hair shafts are seen[55]. The histopathologic findings are listed in Table 69.3.

Treatment

Isotretinoin (0.5–1.5 mg/kg daily until 4 months after achieving a clinical remission) may be the most effective therapy, but this disease can prove difficult to treat. Additional therapeutic options include: antimicrobials (e.g. clindamycin, rifampin, ciprofloxacin, trimethoprim–sulfamethoxazole, metronidazole); TNF inhibitors (e.g. adalimumab, infliximab); other systemic retinoids (acitretin, alitretinoin); dapsone and colchicine. Corticosteroids (oral or intralesional) may be used to halt the inflammatory process. Some patients have been treated with laser therapy (e.g. 1064 nm Nd:YAG), photodynamic therapy, and external beam radiation therapy. Surgical therapy may be helpful in managing disfiguring, scarring, and recalcitrant disease.



Fig. 69.23 Dissecting cellulitis. A Earlier stage with multiple interconnected, inflammatory, alopecic nodules admixed with pustules and crusts. By trichoscopy, there are 3D ("bubble") black dots (inset). **B** Tender nodules with alopecia, draining sinuses, broad scarring, and linear scars. *B, Courtesy Jeffrey P. Callen, MD.*

Acne Necrotica

Synonyms: ■ Necrotizing lymphocytic folliculitis ■ Acne necrotica varioliformis

The etiology of this disease is unknown, but an altered immune reaction to microorganisms within the skin has been suggested. It primarily affects adults, with the face and scalp the most common sites of involvement followed by the neck and upper trunk. Acne necrotica can have a chronic or recurrent course lasting decades.

Lesions begin as umbilicated follicular vesicles or papulovesicles that then become pustular. Over time, hemorrhagic crusts develop and eventually varioliform scars. During a flare, the affected areas may be quite inflamed with significant erythema and numerous follicular lesions[72]. Based upon case reports and expert recommendations, long-term treatment with antibiotics (e.g. doxycycline) or isotretinoin is recommended combined with oral corticosteroids when needed.

Erosive Pustular Dermatosis of the Scalp

Erosive pustular dermatosis of the scalp is an inflammatory disease, and in some patients, it can lead to cicatricial alopecia. The disease occurs primarily on the central scalp in older adults within sites of significant photodamage (see Ch. 25). Less often lesions develop on the lower extremities in those with venous insufficiency or at sites of injury, including in neonates (see Table 34.1).

Clinically, there are erosions and they can be covered with thick keratotic crusts (see Fig. 87.24I). When the crusts are removed, purulent discharge may be present. On the scalp, the background skin is often atrophic and fragile with evidence of AGA, which represents a risk factor for the associated photodamage. Thus, unlike with other types of cicatricial alopecia, the inflammatory lesions are not limited to hair-bearing margins, but may involve the entire area of alopecia[73].

Trichoscopy shows follicular pustules, serous exudates, black crusts, follicular hyperkeratosis, and areas with an absence of follicular openings. In areas of skin atrophy, hair bulbs may be visible. Histologic findings during the early stage include laminated orthokeratosis and psoriasiform hyperplasia of the epidermis with mixed inflammatory infiltrates in the dermis. Late-stage disease is characterized by extensive fibrosis with atrophy, absence of sebaceous glands, and moderate mixed inflammatory infiltrates.

Multiple treatment options are outlined in Chapter 25.

Nonspecific (End-Stage) Cicatricial Alopecia

In patients with progressive cicatricial alopecia, "burnt-out" or "end-stage" disease presents with scalp fibrosis, which may be limited to

one or a few hairless patches or may involve the entire scalp. Clinically, no inflammation is apparent at this stage, and it is not possible to identify the preceding disease which led to the fibrosis. This clinical presentation should not be confused with the histopathologic pattern of "end-stage" disease; the latter can be seen when an older, inactive area is sampled even when there is active disease elsewhere on the scalp.

HAIR SHAFT ABNORMALITIES

Hair shaft abnormalities, both acquired and inherited (Table 69.7), are divided into two broad categories – those associated with increased hair fragility and those *not* associated with increased hair fragility (Fig. 69.24). The former group can lead to various degrees of alopecia while alteration of the clinical appearance of the hair (usually in the absence of alopecia) characterizes the latter group. The analysis of hair shaft abnormalities is best performed via trichoscopy (high magnification, if available) or light microscopy of cut hair shafts. Reflectance confocal microscopy and transmission or scanning electron microscopy are additional diagnostic modalities. When trichothiodystrophy is suspected, amino acid analysis can be performed to confirm low sulfur levels. Other than preventive hair care measures (e.g. conditioning, low tension hair styling), there are currently no specific treatments for inherited hair shaft abnormalities. Topical or low-dose oral minoxidil may stimulate hair regrowth but has no documented effect on hair shaft structure.

Hair Shaft Abnormalities Associated With Increased Hair Fragility

"Bubble hair"

This distinctive hair shaft abnormality is usually seen in young women with a localized area of uneven, fragile hairs. By trichoscopy or light microcopy, the hair shafts contain large irregularly spaced "bubbles" that expand and lead to thinning of the hair cortex (see Fig. 69.24F). Hair fractures occur at the site of larger bubbles.

Bubble hairs can develop when wet hair is exposed to hair care techniques that involve heat, including high-temperature hair dryers, hair straighteners or flat irons, and electric curlers. When wet, a hair shaft can expand up to 30% in diameter with retention of water within the shaft; exposure to heat can then lead to formation of expanding and destructive bubbles. Once the damaged hair is trimmed, the condition resolves completely with gentle hair styling[74].

Monilethrix

Synonym: ■ Beaded hair

In monilethrix, hair shafts have regular, periodic elliptical nodosities that alternate with shaft thinning and a tendency to fracture at the latter sites (see Fig. 69.24C). This disorder is usually inherited in an autosomal dominant fashion with variable expression and is due to heterozygous mutations in one of three hair cortex-specific keratin genes – *KRT86*, *KRT81*, or *KRT83*. There is also an autosomal recessive form due to mutations in *DSG4*, which encodes desmoglein 4.

Affected individuals usually have normal-appearing hair at birth, but within the first few months of life these fibers are replaced by short, fragile, brittle hair (Fig. 69.25). Patients may state "I have hair that never grows". The phenotype is variable, ranging from clinically normal hair to mild occipitotemporal hair loss to nearly total alopecia. Additional manifestations include keratotic follicular papules, primarily on the occiput, as well as syndactyly and nail (e.g. brittle, koilonychia), ocular (e.g. juvenile cataracts, decreased visual fields), and dental abnormalities[75].

By trichoscopy and light microscopy, there is variation in hair shaft thickness with uniformly spaced elliptical nodosities and intervening constrictions. Hairs are bent with a tendency to fracture at constriction sites[76]. Monilethrix-like hair shafts may be observed in other hair disorders, such as alopecia areata or chemotherapy-induced alopecia, but their clinical courses differ[29]. In pseudomonilethrix, there is irregular, square-shaped, flattening of hair shafts. Whether pseudomonilethrix is a true disease or an optical artifact is a matter of debate[29].

Pili torti

Pili torti is characterized by a flattening and 180° twisting of the hair shaft on its own axis (see Fig. 69.24G). The twists are typically narrow and occur in groups of three to ten twists, giving the hair shaft a spangled appearance. When *inherited*, pili torti can be an isolated abnormality or it may be a feature of other disorders, including Menkes disease (see Ch. 51), Björnstad syndrome, Bazex–Dupré–Christol syndrome, and several ectodermal dysplasias[29]. Hairs may be sparse or abnormal from birth or early childhood (early-onset, Ronchese type) or they may become brittle and fragile around puberty (late-onset, Beare type).

Acquired pili torti may be drug-induced (e.g. epidermal growth factor receptor inhibitors, retinoids), associated with perifollicular inflammation or fibrosis (e.g. cutaneous T cell lymphoma, cicatricial alopecia), or due to malnutrition[77]. The inherited form of pili torti can improve at puberty while resolution of the acquired form is dependent upon its etiology.

Trichorrhexis invaginata

Trichorrhexis invaginata ("bamboo hair") is a clinical feature of Netherton syndrome (see Ch. 57). This inherited disorder is due to pathogenic variants in *SPINK5*, which encodes a serine protease inhibitor, LEKTI. The hair abnormality usually becomes evident during infancy with the development of short, sparse, and very fragile hair. In scalp or eyebrow hairs, the breakage points consist of intussusceptions of the distal shaft ("ball") into the proximal shaft ("socket") due to defective cornification of the cortex (see Fig. 69.24B). Fracture of the shaft may leave the proximal shaft with a golf tee-shaped end.

Trichorrhexis nodosa

Trichorrhexis nodosa is the most common of all the structural hair abnormalities. It is characterized by hair shaft fractures in which the individual cortical cells and their fragments splay out, appearing like the ends of two brushes pushed into one another (see Fig. 69.24A). This abnormality is presumably caused by damage to the cuticular cells of the shaft and subsequently to the intercellular cement substance that normally binds cells together. Trichorrhexis nodosa may be congenital or acquired, with the congenital form occurring as an isolated finding (primary genetic) or in association with other inherited disorders, e.g. argininosuccinic aciduria, citrullinemia, trichohepatoenteric syndrome[78].

The acquired variant is most commonly caused by repeated trauma to the hair shaft. This can result from chemical relaxation, excessive heat (e.g. hair dryers, hair straighteners [flat irons, hot combs]), frequent brushing, or chronic scratching. Three clinical variants of acquired trichorrhexis nodosa have been described: (1) proximal – usually due to damage from chemicals and heat; (2) distal – due to cumulative cuticular damage; and (3) circumscribed – occurs in the scalp, moustache, or beard. Chronic use of masks may explain some cases of beard involvement. Trichorrhexis nodosa can also be seen in patients with other hair shaft abnormalities associated with increased hair fragility.

Trichothiodystrophy

Trichothiodystrophy is primarily an autosomal recessive disorder characterized by sulfur-deficient hair. By light microscopy and trichoscopy, hair shafts have transverse fractures (trichoschisis; see Fig. 69.24D) and alterations in their cuticles. Polarized light is required to visualize the alternating light and dark bands, i.e. the pathognomonic "tiger tail sign" (see Fig. 69.24E). Currently, based upon underlying genetic bases, there are nine types of trichothiodystrophy (TTD; www.omim.org). TTD1–3 have associated photosensitivity and are reviewed in Table 87.4 whereas TTD4–9 do not have photosensitivity, including X-linked recessive TTD5. The acronym PIBIDS has been used to describe possible findings in patients with TTD1–3: P (photosensitivity), I (ichthyosis), B (brittle hair), I (intellectual impairment with low IQ), D (decreased fertility), and S (short stature). Some patients may exhibit spasticity, tremors and ataxia, nail dystrophy, dental caries, cataracts, and bony and immune defects. The hair usually does not improve with age.

Hair Abnormalities Not Associated With Increased Hair Fragility

Acquired progressive kinking of the hair

The term encompasses acquired conditions characterized by curling of the scalp hair. It classically presents with curly, frizzy, and lusterless

INHERITED DISORDERS WITH HYPOTRICHOSIS AND/OR HAIR SHAFT ABNORMALITIES		
Disorder	**Mode of inheritance**	**Gene or gene product**
Alopecia, neurologic defects, and endocrinopathy syndrome	AR	RNA binding motif protein 23 (RBM23)
Argininosuccinic aciduria	AR	Argininosuccinate lyase
Atrichia with papular lesions	AR	Hairless (zinc finger transcription factor)
Bachmann-Bupp syndrome	AD	Ornithine decarboxylase
Björnstad syndrome	AR	BCS1-like (mitochondrial membrane protein)
Cartilage–hair hypoplasia (Ch. 60)	AR	RNA component of mitochondrial RNA-processing endoribonuclease
Giant axonal neuropathy 1 with curly hair	AR	Gigaxonin
Hypohidrotic ectodermal dysplasia (Ch. 63)	XLR	Ectodysplasin A
	AD	Ectodysplasin anhidrotic receptor gene or the EDAR-associated death domain gene
Hypotrichosis-lymphedema-telangiectasia	AR	SYR-box transcription factor 18
Hypotrichosis, Mari type	AR	Lipase H
Hypotrichosis, Marie Unna type,1	AD	5′ upstream open reading frame of *HR* (hairless) gene
Hypotrichosis simplex	AD	Adenomatosis polyposis down-regulated 1 gene
	AD	Small nucleotide RNP polypeptide E
	AD	Ribosomal protein L21
Hypotrichosis simplex of the scalp	AD	Corneodesmosin
Hypotrichosis with juvenile macular dystrophy	AR	Cadherin 3 (P cadherin)
Hypotrichosis with recurrent skin “vesicles”	AR	Desmocollin 3
Keratosis follicularis spinulosa decalvans (Ch. 38)	XLR	Membrane-bound transcription factor peptidase, site *2*
Ichthyosis, hystrix-like with deafness (Ch. 57)	AD	Connexin 26
Laron syndrome (pituitary dwarfism II)	AR	Growth hormone receptor
Localized autosomal recessive hypotrichosis	AR	Desmoglein 4
	AR	C3orf52 (cofactor for lipase H)
Menkes disease (Ch. 51)	XLR	Cu^{2+}-transporting P-type ATPase 7A
Monilethrix	AD	Keratin 81, Type II
	AD	Keratin 83, Type II
	AD	Keratin 86, Type II
	AR	Desmoglein 4
Netherton syndrome (Ch. 57)	AR	Serine protease inhibitor LEKTI
Pure hair nail ectodermal dysplasia (Ch. 63)	AD	Keratin 85
		Keratin 74
	AR	Homeobox C13
T cell immunodeficiency and congenital alopecia (Ch. 60)	AR	Forkhead box N1 (winged helix nude)
Trichothiodystrophy (TTD) (Chs. 57 & 87; TTD4-9 are non-photosensitive)	AR	XPB/TTD2; TFIIH subunit, DNA helicase (functions in nucleotide excision repair and as a basal transcription factor)
	AR	XPD/TTD1; TFIIH subunit, DNA helicase (functions in nucleotide excision repair and as a basal transcription factor)
	AR	General TFIIH, subunit 5 (TTD3; functions in nucleotide excision repair and as a basal transcription factor)
	AR XLR (TTD5)	TTD4: M-phase specific PLK1 interacting protein; TTD5: ring finger protein 113A; TTD6: general transcription factor IIE subunit 2; TTD7: threonyl-TRNA synthetase 1; TTD8: alanyl-TRNA synthetase 1; TTD9: methionyl-TRNA synthetase 1
Vitamin D-dependent rickets with alopecia	AR	Vitamin D receptor
Woolly hair	AR	Keratin 25
	AD	Keratin 74
Woolly hair with hypotrichosis	AD	Keratin 71
Woolly hair +/– hypotrichosis	AR	Lysophosphatidic acid receptor 6
	AR	Lipase H
Woolly hair in Naxos disease (Ch. 58)	AR	Plakoglobin
		Desmocollin 2
Woolly hair in Carvajal syndrome (Ch. 58)	AR > AD	Desmoplakin
Skin fragility/woolly hair syndrome (Ch. 32)	AR	Desmoplakin

Table 69.7 Inherited disorders with alopecia and/or hair shaft abnormalities. Hair and/or nail abnormalities can also be observed in patients with disorders of keratinization, epidermolysis bullosa, and ectodermal dysplasias (see Table 32.1). AD, autosomal dominant; AR, autosomal recessive; RNP, ribonucleoprotein; TFIIH, transcription factor IIH; XP, xeroderma pigmentosum; XLR, X-linked recessive.

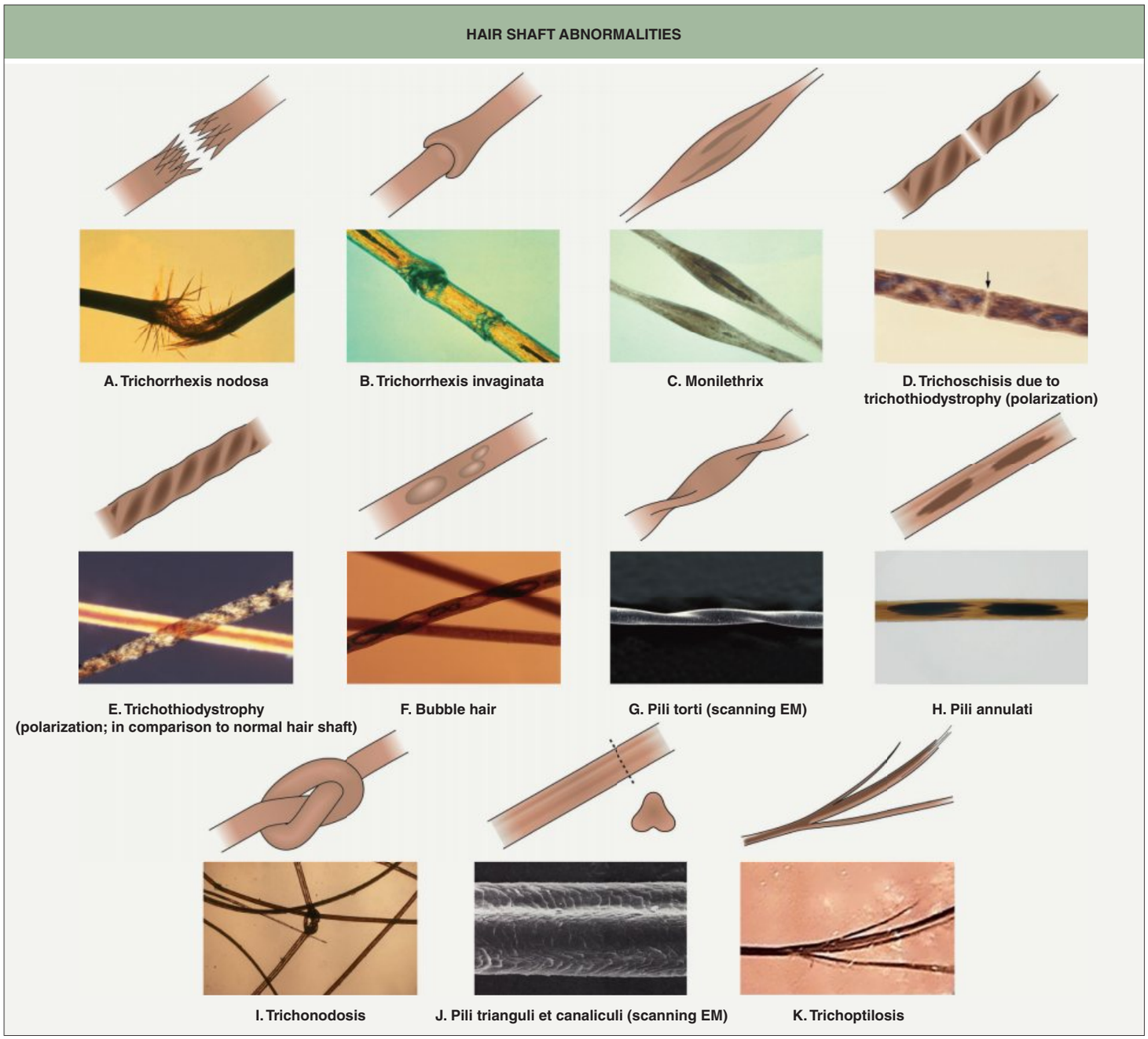


Fig. 69.24 Hair shaft abnormalities. EM, electron microscopy. *A, B, Courtesy Maria K. Hordinsky, MD; C–E, G, J, Courtesy Leonard C. Sperling, MD; F, Courtesy Jean L. Bolognia, MD.*

hair in the frontotemporal region or vertex of the scalp. There is often progression to AGA, but whether it is a harbinger of very early-onset AGA has been debated. Localized and diffuse forms of acquired hair kinking that are not associated with hair thinning have also been described.

Loose anagen hair syndrome

The classic presentation of loose anagen hair syndrome is a young girl with fairly short blond hair who has diffuse or patchy alopecia. There is no increase in hair fragility, but anagen hairs can be easily and painlessly pulled from the scalp. Because of the limited maximum hair length, patients may state "I have hair that never grows".

Microscopic examination reveals a ruffled proximal cuticle, absence of the root sheath, and a bent matrix (see Fig. 69.11C). Structural abnormalities that appear to disturb the normal supportive and anchoring functions of the inner root sheath are seen, presumably resulting in a loose attachment of the hair shaft to the anagen follicle. With trichoscopy, rectangular black granular structures are visible. Gradual improvement occurs with aging. In addition to telogen effluvium, alopecia areata, and trichotillomania, the differential diagnosis includes short anagen hair syndrome. The latter is seen primarily in children and is characterized by an increased number of telogen hairs, a shortened anagen phase with limited maximum hair length, and oftentimes a history of not requiring haircuts. If there is no improvement over time, some clinicians prescribe low-dose oral minoxidil (see Alopecia Areata, Treatment).

Pili annulati

Pili annulati (ringed hair) is characterized by hair shafts that have bright and dark bands when viewed by reflected light (see Fig. 69.24H). The bright bands are related to light scattered from periodically occurring clusters of abnormal, air-filled cavities within the hair. The condition may be sporadic or seen as an autosomal dominant trait. On microscopic examination of a hair mount, the air-filled cavities are seen as dark regions. By trichoscopy, there is alternating white and dark bands, with the former subtle, cloudy, and shorter than the remaining dark portions of the hair shaft. Approximately 20%–80% of the hairs are affected and the bands tend to disappear distally[29].



Fig. 69.25 Monilethrix. Fragility of the hair shafts leads to short broken hairs. Small perifollicular papules with scale are also present. By trichoscopy, the hair shafts have a beaded appearance (see Fig. 69.24C).

Pili bifurcati

This hair fiber anomaly is characterized by bifurcation of the hair fiber at multiple irregular intervals along the shaft, forming separate rami, which then again fuse. Each ramus has its own cuticle. As with other hair shaft disorders, the bifurcations may affect only a proportion of hairs and abnormal hairs may not be noticeable clinically.

Pili multigemini

The term pili multigemini is associated with multiple hair shafts arising from one papilla. Each hair fiber has its own inner root sheath, but all the fibers are surrounded by a common outer root sheath. Multigeminate hairs are usually found in the beard region, often in association with some perifollicular erythema. The differential diagnosis includes trichostasis spinulosa.

Uncombable hair (spun-glass hair)

This entity is also known as pili trianguli et canaliculi and refers to a rare hair abnormality in which hair has a "spun glass" appearance due to the reflection of light from variably oriented, flattened hair surfaces. Hair is characteristically stiff and difficult to comb. Abnormal keratinization of the internal root sheath is postulated to cause the irregularly shaped hair shafts, which have a triangular shape on cross-section and a longitudinal groove that is best seen by scanning electron microscopy (see Fig. 69.24J). Homozygous or compound heterozygous mutations have been identified in three genes that encode proteins involved in hair shaft formation – peptidylarginine deiminase 3 (*PADI3*), transglutaminase 3 (*TMG3*), and trichohyalin (*TCHH*).

Woolly hair

Human hair may at times develop a woolly appearance. The presence of woolly hair may be congenital and can be inherited as either an autosomal dominant or recessive trait. Some patients present with a circumscribed patch of woolly hair (woolly hair nevus). Microscopic examination may reveal elliptical cross-sections, axial twisting, and occasional trichorrhexis nodosa. With trichoscopy, hair shafts have a "crawling snake" appearance, with short wave cycles[79].

Wooly hair can be associated with several genetic disorders (see Table 69.7), including Naxos disease and Carvajal syndrome, which present with cardiomyopathy and either diffuse or striate palmoplantar keratoderma (PPK), respectively. It has also been observed in Noonan syndrome and cardio-facio-cutaneous syndrome. Kinky (but not truly woolly) hair is a feature of axonal neuropathy and tricho-dento-osseus-syndrome.

In Table 69.7, additional inherited disorders with alopecia are listed. Those genetic diseases associated with alopecia areata were discussed previously.

ALOPECIA OF SITES OTHER THAN THE SCALP

While alopecia of the scalp is the primary focus of this chapter, alopecia can occur in any hair-bearing site. Involvement of the eyebrows and/or eyelashes (madarosis) may be observed in alopecia areata, trichotillomania, and frontal fibrosing alopecia. Hypotrichosis of the lateral third of the eyebrows may serve as a clue to hypothyroidism or may be due to chronic rubbing or scratching.

Hair loss in the beard area is a common finding in patients with alopecia areata. Loss of body hair can develop in alopecia universalis and occasionally in patients with anagen effluvium. Non-scarring alopecia in the axillae and groin is a characteristic finding in Graham Little–Piccardi–Lasseur syndrome. Although the etiology is unknown, symmetric patches of alopecia on the anterolateral shins and thighs can also occur and are more obvious in men.

Acknowledgment

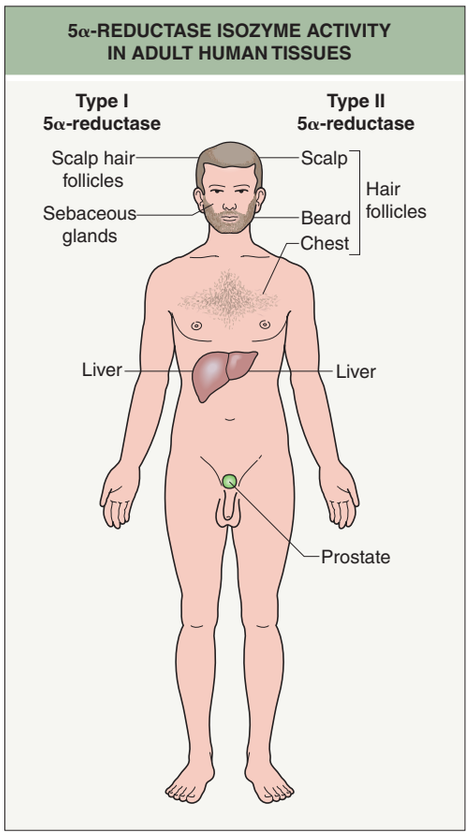
The authors wish to thank Leonard C. Sperling, MD, Rodney D. Sinclair, MD, and Laila El Shabrawi-Caelen, MD, for their valuable contributions to this chapter in the previous editions.

Additional figures and tables on Comorbidities and diseases associated with alopecia areata, Topical immunotherapy for alopecia areata, and DSM-5 diagnostic criteria for trichotillomania (hair-pulling disorder), available in our eBook (see inside front cover for access code).

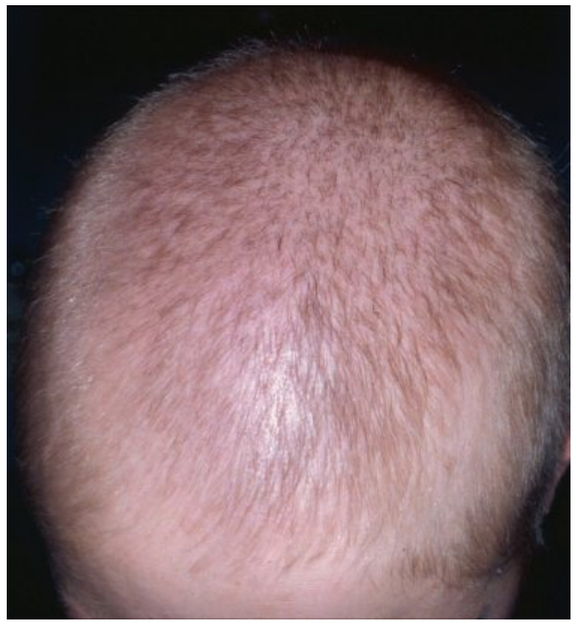
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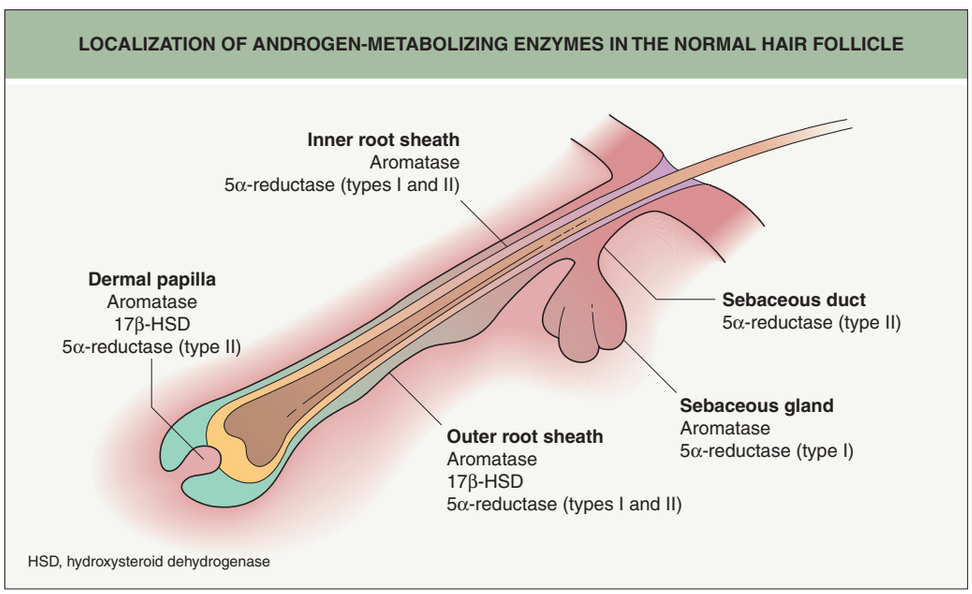
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eFig. 69.1 5α-reductase isoenzyme activity in adult human tissues. Type III 5α-reductase is found throughout the epidermis and dermis, but its functional role has not yet been elucidated.



eFig. 69.3 Alopecia areata – diffuse variant. *Courtesy Maria K. Hordinsky MD.*



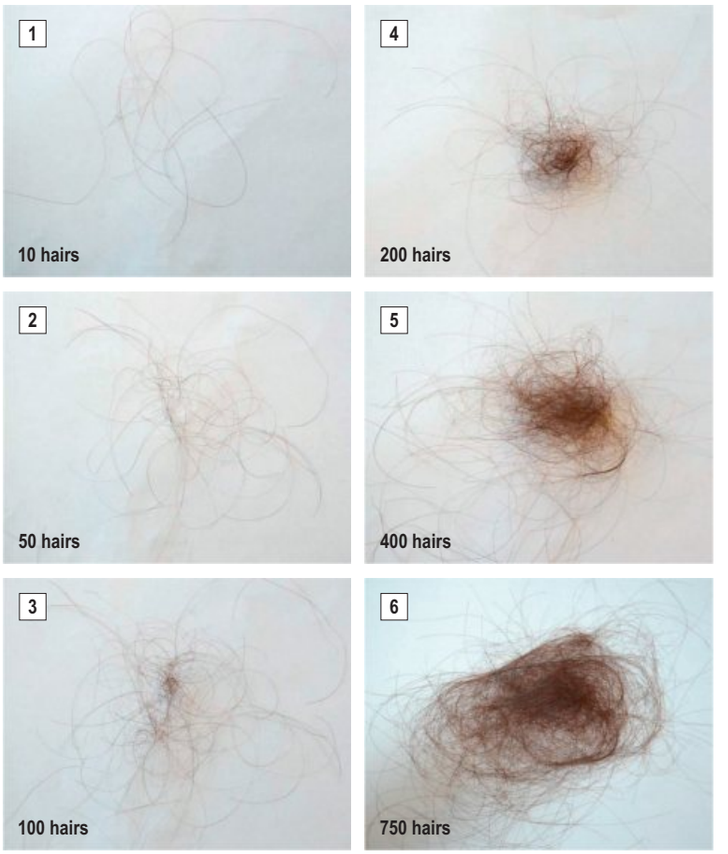
eFig. 69.2 Localization of androgen-metabolizing enzymes in the normal hair follicle. *Courtesy Maria K. Hordinsky, MD.*



eFig. 69.4 Alopecia areata. A Three circular areas of non-scarring alopecia. **B** Circular areas of non-scarring alopecia plus ophiasis. *Courtesy Julie V. Schaffer, MD.*



eFig. 69.5 Alopecia areata. Multiple circular areas of non-scarring alopecia that have become confluent. *Courtesy Eugene Mirrer, MD.*



eFig. 69.6 Visual shedding scale. The patient chooses the photograph that best correlates with the amount of daily hair shedding in the setting of daily washing. Grades 1–4 are considered normal while grades 5 and 6 reflect excessive shedding. *From Sinclair R. Hair shedding in women: how much is too much? Br J Dermatol 2015;173:846–8.*



eFig. 69.7 Temporal triangular alopecia. The tip of the "lancet" points superiorly. Occasionally, the lesion is located outside the temporal region, as seen here. *Courtesy Leonard C. Sperling, MD and Rodney D. Sinclair, MD.*



eFig. 69.9 Frontal fibrosing alopecia. Progressive hair loss along the frontotemporal hairline. Note eyebrow hair loss as well as the presence of isolated "lonely" hairs on the upper forehead. *Courtesy Rodney D. Sinclair, MD.*

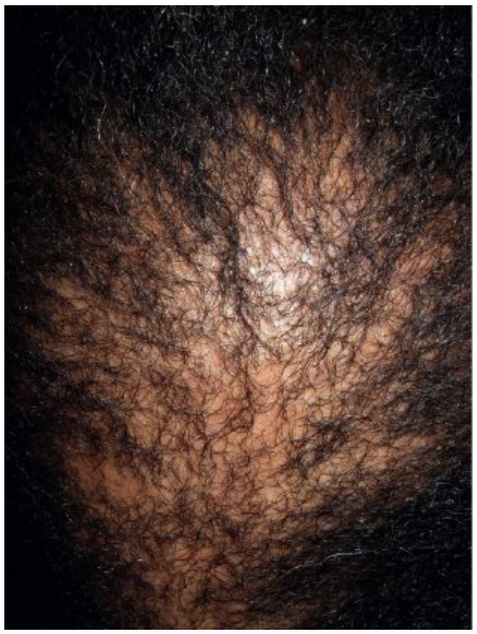




eFig. 69.8 Frontal fibrosing alopecia. A Progressive hair loss along the anterior hairline. Note the "lonely" hairs. **B** In addition to "lonely" hairs, there is an absence of solar lentigines and perifollicular rims of erythema. *Courtesy Kalman Watsky, MD.*



eFig. 69.10 Late-stage lichen planopilaris. Scarring alopecia with loss of follicular openings but with minimal inflammation. *Courtesy Rodney D. Sinclair, MD.*



eFig. 69.11 Central centrifugal cicatricial alopecia in an African-American woman. Alopecia is most prominent on the crown and/or vertex. *Courtesy Leonard C. Sperling, MD.*



eFig. 69.12 Central centrifugal cicatricial alopecia. Polytrichia, in which multiple hairs emerge from a single follicular opening, leads to tufting that resembles "baby doll hair" or a hair brush. *Courtesy Edward Cowen, MD.*



eFig. 69.13 Scarring alopecia due to discoid lupus erythematosus. There is still active inflammation present. *Courtesy Luis Requena, MD.*



eFig. 69.14 Late-stage discoid lupus erythematosus. When lesions become less inflamed (burnt out), they can mimic pseudopelade of Brocq. *Courtesy Leonard C. Sperling, MD.*



eFig. 69.15 Dissecting cellulitis of the scalp and acne keloidalis in an African-American man.



eFig. 69.16 Dissecting cellulitis of the scalp in an African-American man. The areas of alopecia vary in shape, from oval to linear. Interconnecting boggy and fluctuant nodules are accompanied by pustular drainage from sinuses and scarring. *Courtesy Joseph English, MD.*



eFig. 69.17 Dissecting cellulitis of the scalp. Scarring alopecia with fibrotic and fluctuant nodules on the scalp of a Black man who also had acne conglobata and hidradenitis suppurativa. There was marked improvement with isotretinoin. *Courtesy Jonathan S. Leventhal, MD.*



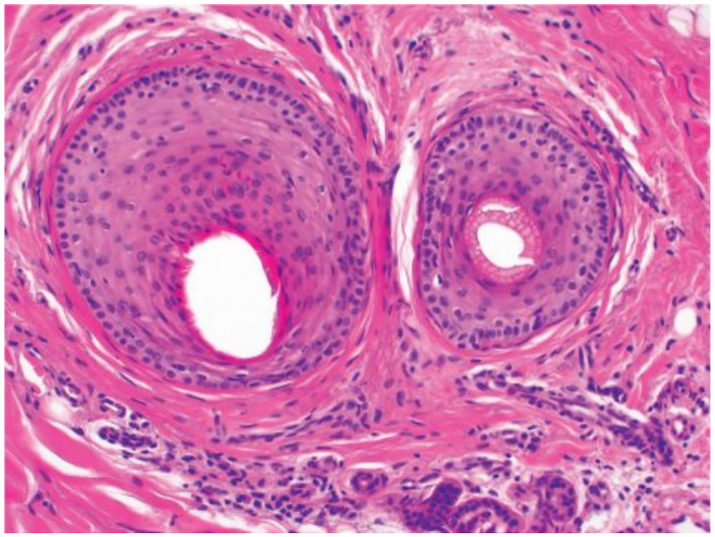
eFig. 69.19 Woolly hair nevus. Circumscribed area where scalp hair is wavier and has a woolly appearance.



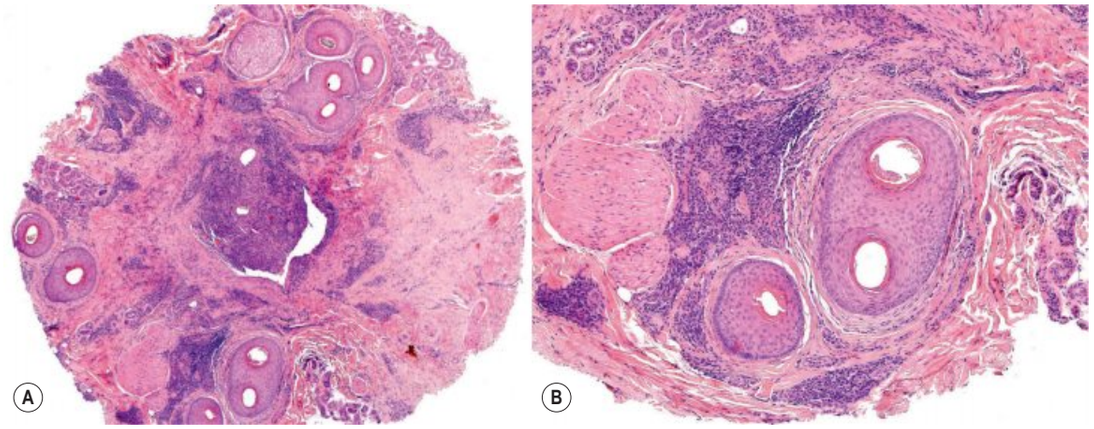
eFig. 69.18 Epidermal growth factor receptor inhibitor-induced scarring alopecia. *Courtesy Edward Cowen, MD.*



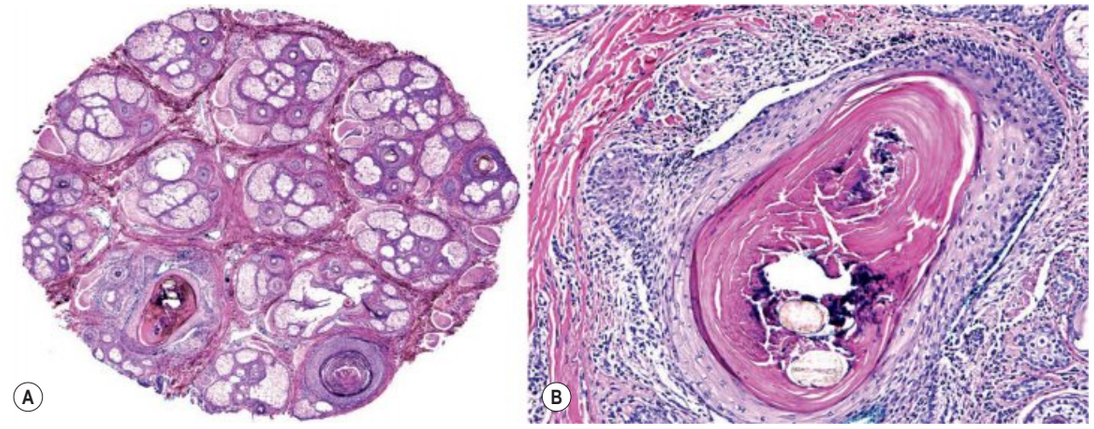
eFig. 69.20 "Tufted folliculitis" due to scarring alopecia. Note the multiple hairs arising from a single follicular orifice that is sometimes likened to doll's hair. *Courtesy Kalman Watsky, MD.*



eFig. 69.21 Central centrifugal cicatricial alopecia – histopathologic features. Subisthmus horizontal section showing premature desquamation of the inner root sheath and eccentric thinning of the follicular epithelium. *Courtesy Luis Requena, MD.*



eFig. 69.22 Folliculitis decalvans – histopathologic features. A Isthmus horizontal section showing a distinct reduction of hair follicles with loss of sebaceous glands, perifollicular and interfollicular mixed inflammatory cell infiltrate, and follicular "tufting". **B** Greater detail of perifollicular and interfollicular fibrosis and follicular "tufting".



eFig. 69.23 Folliculitis decalvans – histopathologic features. A Horizontal section demonstrating follicular "tufting" with perifollicular fibrosis and mixed inflammatory infiltrate. **B** Note two hair shafts with inflammation within one follicle. *Courtesy Luis Requena, MD.*



eFig. 69.24 Central centrifugal cicatricial alopecia – trichoscopy. Findings include loss of follicular openings, mild perifollicular scaling, and small hair tufts as well as fibrotic white dots in patients with darkly pigmented skin. *Courtesy Rodrigo Pirmez, MD.*

COMORBIDITIES AND DISEASES ASSOCIATED WITH ALOPECIA AREATA		
Comorbidity or associated disease	**Odds ratio (compared to general population)**	**Prevalence**
Atopic dermatitis	2.36	9.6%
Systemic lupus erythematosus	3.46	0.7%
Iron deficiency anemia	2.78	7.5%
Thyroid dysfunction (including subclinical hypothyroidism or subclinical hyperthyroidism)	4.36	12.5%
Metabolic syndrome	4.97	1.4%
Coronary artery disease	3.13	5.5%
Depression	2.27	18.9%
Anxiety	2.00	27.1%

eTable 69.1 Comorbidities and diseases associated with alopecia areata[35,36].

TOPICAL IMMUNOTHERAPY FOR ALOPECIA AREATA
Treatment protocol for diphencyprone (DPCP) or squaric acid dibutyl ester (SADBE)*

• Sensitize with a 2% solution in acetone applied to a 4×4 cm area on one side of the scalp
• After 1 week (2 weeks if the initial reaction is severe), a 0.001% solution is applied to all affected areas on the same side of the scalp
• Each week, DPCP or SADBE is applied to the same side of the scalp
  • The *concentration* is titrated according to the severity of the reaction the previous week, with a goal of maintaining a low-grade, tolerable degree of erythema, scaling, and pruritus for 24–36 hours after application
  • *Concentrations* are increased incrementally as follows: 0.001%, 0.01%, 0.025%, 0.05%, 0.1%, 0.25%, 0.5%, 1%, 2%
• Once hair growth is established, the other side is also treated
• Initial responses are usually seen after 12 weeks, and therapy is discontinued if there is no response by 24 weeks
• Frequency of treatment can be decreased in the presence of full regrowth

Additional information

• Acetone solutions should be applied using a generous amount of cotton at the end of a wooden stick†
• Following application:
  • The sensitizer is left on the scalp for 48 hours, then washed off
  • *Patients* should avoid touching the scalp for 6 hours
  • The *scalp* should be protected from light to avoid degradation of DPCP
• SADBE must be refrigerated
• Side effects include lymphadenopathy, severe or widespread eczematous reactions, and postinflammatory pigment alterations (particularly in patients with darkly pigmented skin)

Contraindications
• Pregnancy (although teratogenicity has not been established) • Malignancies and blood dyscrasias
*Both not FDA-approved. †Application by medical personnel is recommended.

eTable. 69.2 Topical immunotherapy for alopecia areata.

DSM-5 DIAGNOSTIC CRITERIA FOR TRICHOTILLOMANIA (HAIR-PULLING DISORDER)
A. Recurrent pulling out of one's hair, resulting in hair loss B. Repeated attempts to decrease or stop hair pulling C. The hair pulling causes clinically significant distress or impairment in social, occupational, or other important areas of functioning D. The hair pulling or hair loss is not attributable to another medical condition (e.g. a dermatological condition) E. The hair pulling is not better explained by the symptoms of another mental disorder (e.g. attempts to improve a perceived defect or flaw in appearance in body dysmorphic disorder)

eTable 69.3 DSM-5 diagnostic criteria for trichotillomania (hair-pulling disorder). It is DSM-5 disorder 312.39 (F63.3).

70 Hypertrichosis and Hirsutism

Rachel Reynolds, Kristen Corey and Francisco M. Camacho

Key features

- Hypertrichosis refers to excessive growth of hair anywhere on the body, whereas hirsutism represents excessive hair growth within androgen-dependent sites in girls and women
- Hypertrichosis may be generalized or localized, with etiologies ranging from genodermatoses to underlying hamartomas to repeated trauma
- Hirsutism is related to hormonal factors, in particular an increase in circulating androgen levels and/or enhanced sensitivity of hair follicles to androgens
- In women, the major sources of androgens are the adrenal glands and the ovaries; dysfunction of these organs must be considered when a patient presents with hirsutism
- Depending on its etiology, treatment of hirsutism may include oral contraceptives, antiandrogens, gonadotropin-releasing hormone agonists, glucocorticoids, and insulin-lowering agents, combined with topical medications and physical measures (e.g. laser hair removal)

HYPERTRICHOSIS

Introduction

Hypertrichosis describes the growth of excessive hair anywhere on the body. The term is frequently confused with hirsutism, which should only be applied to women with excessive growth of terminal hairs in androgen-dependent sites (i.e. a "male pattern") due to hyperandrogenemia or increased end-organ sensitivity to androgens[1–3]. Hypertrichosis can be classified based on its distribution (generalized versus localized), the age of onset (congenital or programmed from birth versus acquired), and the type of hair (lanugo or vellus versus terminal).

Clinical Features

Generalized hypertrichosis

In generalized hypertrichosis, there is lanugo hair, excess vellus hair, or terminal hair over much of the cutaneous surface, including an acquired transformation of terminal hair into lanugo hair (Fig. 70.1)[4]. Lanugo is the non-pigmented, non-medullated, fine hair that covers the fetus and can grow up to several centimeters in length; it is normally shed *in utero* at ~7–8 months' gestation or during the first few weeks of life and replaced by vellus hair on the body and terminal hair on the scalp. Some neonates, especially if born prematurely, transiently retain lanugo hairs diffusely and shed them during the first few weeks of life.

Congenital generalized hypertrichosis

A number of distinctive but rare genetic syndromes are associated with congenital generalized hypertrichosis (Table 70.1). While the majority of these disorders have extracutaneous manifestations such as gingival hyperplasia or facial dysmorphism, some have primarily hypertrichosis, including universal hypertrichosis. However, this latter entity is sometimes viewed as constitutional, i.e. simply exaggerated normal hairiness that may be familial. Genetic abnormalities associated with congenital generalized hypertrichosis lead to dysfunction of several proteins, ranging from those known to be involved in hair follicle development to membrane transporters (see Table 70.1).

The possibility of intrauterine exposure to medications (e.g. minoxidil) also needs to be considered in infants with congenital generalized hypertrichosis. The differential diagnosis also includes inherited disorders in which hypertrichosis can involve multiple sites and may appear early in life (Table 70.2).

Prepubertal hypertrichosis

Prepubertal hypertrichosis is a relatively common finding in otherwise healthy infants and children, most often occurring in individuals of Mediterranean or South Asian descent. Pigmented hair is present in a widespread, diffuse distribution and becomes more obvious during childhood. There is involvement of the face (especially the forehead, temples, and preauricular area), proximal extremities, and back; hairs in the latter location assume an "inverted fir tree" pattern. Bushy eyebrows and a low anterior hairline represent additional features.

The facial distribution pattern of prepubertal hypertrichosis can overlap with that of familial hirsutism (see below), and there may be a family history of excessive hairiness. Mildly elevated levels of total and free testosterone have been observed in a subset of girls with prepubertal hypertrichosis, while others have a normal androgen profile[12]. These findings suggest multiple etiologies for this clinical pattern of hypertrichosis, including androgen excess as well as an increased constitutional propensity for hair growth.

Acquired generalized hypertrichosis

Acquired generalized hypertrichosis is most often related to drug ingestion (Table 70.3). Drug-induced hypertrichosis is characterized by slow growth of terminal hair of medium thickness. The findings are most evident on the forehead, temples, flexor aspects of the extremities, and trunk. Drug-related hypertrichosis is usually reversible, and differs in distribution from drug-induced hirsutism.

Acquired generalized hypertrichosis can also represent a sign or consequence of a variety of systemic conditions, including disorders of the CNS (e.g. traumatic brain injuries), juvenile hypothyroidism, juvenile dermatomyositis, acromegaly (especially of the lower face), malnutrition (including anorexia nervosa), POEMS syndrome, and advanced HIV disease.

Acquired hypertrichosis lanuginosa

This is considered to be a paraneoplastic phenomenon as it is associated with internal malignancies, most often of the lung, colon, or breast. Occasionally, acquired hypertrichosis lanuginosa may precede the diagnosis of the neoplasm. In addition, it may be associated with other paraneoplastic dermatoses, such as acanthosis nigricans, palmoplantar keratoderma, the sign of Leser–Trélat, and acquired ichthyosis (see Ch. 53). The lanugo hair appears over the entire body within a short period of time, although in mild forms it may be localized to the face, leading to a "simian" appearance. Lanugo hair may even develop in areas of androgenetic alopecia.

Localized hypertrichosis

Most cases of localized hypertrichosis involve a switch from vellus to terminal hair in sites that do not usually bear terminal hair. Localized hypertrichosis can develop as a component of a hamartoma, as an isolated congenital lesion, as a manifestation of a systemic disease (inherited or acquired), or as a consequence of cutaneous trauma or inflammation.

Congenital localized hypertrichosis

Hamartomas, including those with delayed clinical presentation, and congenital abnormalities characterized by hypertrichosis of a specific anatomic site (Figs. 70.2 and 70.3; Tables 70.4 & 70.5) are included in this category.

Congenital melanocytic nevi and plexiform neurofibromas

Congenital melanocytic nevi often have associated hypertrichosis. The increased hair growth may be noted at birth, but often becomes

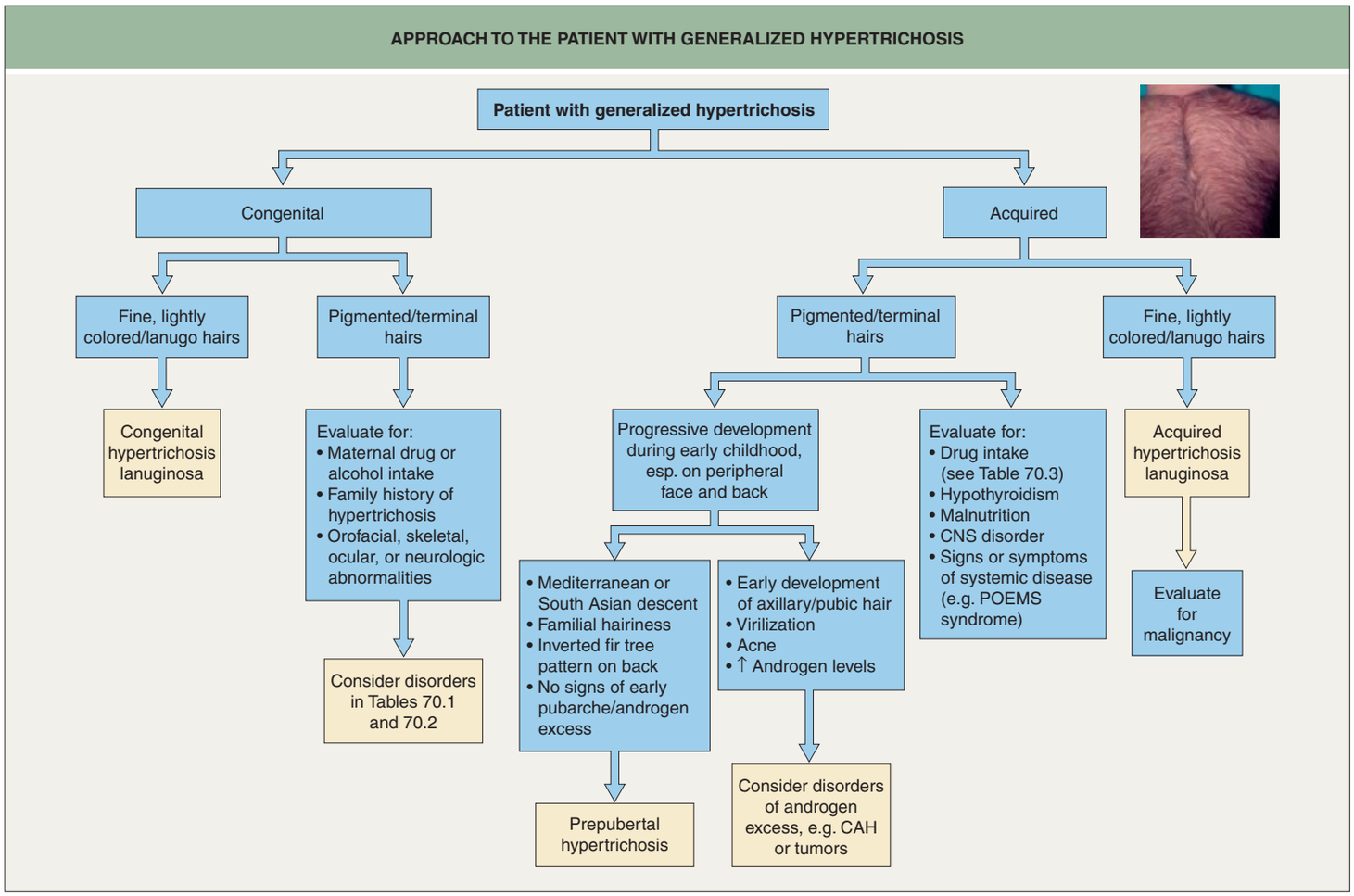


Fig. 70.1 Approach to the patient with generalized hypertrichosis. CAH, congenital adrenal hyperplasia; POEMS, *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal gammopathy, *s*kin lesions. The photograph is an example of universal hypertrichosis, which some authors view as simply exaggerated normal hairiness that may be familial.

more prominent during infancy or early childhood. Hypertrichosis can be seen in all sizes of congenital melanocytic nevi (see Ch. 112). A particularly dense growth of terminal hairs may accompany scalp nevi. Plexiform neurofibromas can also have associated hyperpigmentation and hypertrichosis.

Becker melanosis (nevus)

This is a hamartoma characterized by macular hyperpigmentation with irregular borders, most commonly located on the upper lateral trunk (anterior or posterior) (see Ch. 112). Some patients have associated hypertrichosis while others do not. The pigmentation usually arises during the first decade of life, whereas the hypertrichosis typically appears in the second decade (Fig. 70.5). Becker melanosis is most often diagnosed in boys and men. Postzygotic mutations in the *ACTB* gene encoding β-actin have been found to underlie Becker melanosis and associated anomalies (referred to as Becker nevus syndrome; see below) as well as smooth muscle hamartomas (see Ch. 117 and below)[15].

Occasionally, asymmetry of the extremities and hyperplasia or hypoplasia of the affected areas is evident, especially ipsilateral mammary hypoplasia in women or, less often, the Poland anomaly (unilateral chest wall hypoplasia and ipsilateral hand syndactyly). Rarely, there may be an association with genitourinary tract abnormalities (SNUB syndrome: supernumerary nipples, uropathies, Becker melanosis)[16]. Because of its benign nature, surgical removal of Becker melanosis is not recommended. Epilation can be performed by various techniques, but attempts at decreasing pigmentation via laser therapy are often not successful.

Smooth muscle hamartomas, which exist on a spectrum with Becker melanosis, may present as circumscribed hypertrichotic plaques with variable hyperpigmentation. A rare generalized form is characterized by extensive hypertrichosis and folding of the skin which has been reported under the term "Michelin tire baby" (see Table 97.7). Lastly, the hypertrichosis observed in the setting of hemimaxillofacial dysplasia (with facial asymmetry due to unilateral maxillary enlargement, gingival hyperplasia, and hypoplastic teeth) is often associated with Becker melanosis or smooth muscle hamartoma.

Other hamartomas and infantile tumors

Hypertrichosis can also overlie the following skin lesions: plaque-type blue nevus, neurocristic hamartoma, fibrous hamartoma of infancy, dermal dendrocyte hamartoma, eccrine angiomatous hamartoma, and tufted angioma.

Nevoid hypertrichosis

This is an uncommon congenital alteration characterized by the growth of terminal hairs in a circumscribed area. In general, there are no extracutaneous associations in *primary nevoid hypertrichosis*; the skin within the affected area is normally pigmented and there is no underlying hamartoma (Fig. 70.6). Table 70.4 outlines specific sites of localized hypertrichosis that can be familial. To date there is a report of one family with primary multifocal localized hypertrichosis[17]. Nevoid hypertrichosis has also been observed to follow the lines of Blaschko, as reported in female carriers of X-linked hypertrichosis (see Table 70.1).

Secondary nevoid hypertrichosis can be associated with lipodystrophy, hemihypertrophy, scoliosis, and abnormalities of the underlying vasculature. Nevoid hypertrichosis also occasionally occurs together with epidermal nevi or nevoid hypopigmentation, and it can represent a manifestation of Proteus and Happle–Tinschert syndromes.

Spinal dysraphism and the hair collar sign

Dysraphism is defined as an alteration of the formation of a fold or elevation which is constituted in the midline of the human body during

HEREDITARY DISORDERS CHARACTERIZED BY CONGENITAL GENERALIZED HYPERTRICHOSIS		
Disorder	**Inheritance (genetic basis/gene)**	**Other key features**
Increased hair is the major feature		
Congenital hypertrichosis lanuginosa	AD	• Fetal lanugo hair is not replaced by normal hair and continues to grow • Fine, downy, silvery-gray to blond lanugo hair that may be up to 10 cm in length • Involves entire body surface (except for the palms, soles, dorsal surface of distal phalanges, and prepuce) but hair may be shed over the first year of life • Occasional dental anomalies; rarely other associations (e.g. ear defects, glaucoma, pyloric stenosis, photophobia, ID)
Universal hypertrichosis	AD	• Thicker, longer hair most prominent on the back, proximal extremities and the frontal, temporal, and preauricular areas of the face* • Increases during infancy and tends to persist • Considered by some authors to be simply exaggerated normal hairiness that may be familial
Ambras syndrome (hypertrichosis universalis congenita, Ambras type; HTC1)[5,6]	AD (8q22–q24 breakpoints; position effect downregulates *TRPS1* expression)	• Fine, silky, lightly colored, long vellus hair involving the entire body but primarily the face, ears, and shoulders • Uniformly distributed on the face, including the nose • Persists for life • Minor facial dysmorphism, dental anomalies, supernumerary nipples
Generalized hypertrichosis with extracutaneous features		
X-linked hypertrichosis (congenital generalized hypertrichosis; HTC2)[7]	XLD (Xq27.1; palindrome-mediated interchromosomal insertion; position effect downregulates *FGF13* expression)	• Curly, shorter, dark hair most prominent on the face and upper body • Anteverted nostrils, prognathism; occasional dental anomalies, deafness • Female carriers may have nevoid hypertrichosis following lines of Blaschko
Congenital generalized hypertrichosis with or without gingival hyperplasia (HCT3)[8]	AD or AR (17q24.2–q24.3 microdeletion or microduplication [AD]; position effect downregulates *SOX9* expression; also *ABCA5* [AR])	• Dark terminal hairs on the peripheral face, central back, and extremities • In addition to gingival hyperplasia, coarse facies, ID, seizures
FHEIG syndrome	AD (*KCNK4*)	• *F*acial dysmorphism, *h*ypertrichosis, epilepsy, *I*D, *g*ingival overgrowth
Cantú syndrome (hypertrichotic osteochondrodysplasia)	AD (*ABCC9*)	• Coarse facies, osteochondrodysplasia, macrosomia at birth, cardiomegaly
Zimmermann–Laband syndrome	1: AD (*KCNH1*) 2: AD (*ATP6V1B2*) 3: AD (*KCNN3*)	• Gingival hyperplasia, coarse facies, hypoplastic nails and distal phalanges, joint hyperextensibility, splenomegaly, ID
Coffin–Siris syndrome†	1: AD (*ARID1B*) 2: AD (*ARID1A*) 3: AD (*SMARCB1*) 4: AD (*SMARCA4*) 5: AD (*SMARCE1*) 8: AD (*SMARCC2*) 9: AD (*SOX11*)	• Sparse scalp hair, coarse facies, hypoplastic fifth fingernails and toenails, GD, ID
Schinzel–Giedion midface retraction syndrome	AD (*SETBP1*)	• Midfacial vascular stain, midfacial retraction, hyperconvex nails, hypoplastic distal phalanges and dermatoglyphs, GU anomalies, GD, ID
Fontaine progeroid syndrome (includes Gorlin–Chaudry–Moss syndrome)	AD (*SLC25A24*)	• Craniofacial dysostosis with midfacial hypoplasia, hypoplastic distal phalanges, ocular and dental anomalies, genital hypoplasia, GD
Adducted thumbs syndrome	AR	• Arthrogryposis, craniosynostosis, myopathy
Barber–Say syndrome	AD (*TWIST2*)	• Lax skin, ectropion, macrostomia, coarse facies, hypoplastic nipples, GD

*This pattern of distribution is also observed in prepubertal hypertrichosis (see text).
†Protein products of mutated genes are subunits of the SWI/SNF complex.

Table 70.1 Hereditary disorders characterized by congenital generalized hypertrichosis. Autosomal recessive disorders presenting with congenital amaurosis or cataracts in addition to hypertrichosis have also been reported in individual families. ABC, ATP-binding cassette transporter; AD, autosomal dominant; AR, autosomal recessive; ARID, AT-rich interaction domain; ATP6V1B2, ATPase H^+ transporting V1 subunit B2; FGF, fibroblast growth factor; GD, growth delay; GU, genitourinary; HTC, hypertrichosis; ID, intellectual disability; KCN, potassium voltage-gated channel; SLC, solute carrier family; SMARC, SWI/SNF related, matrix associated, actin dependent regulator of chromatin; TRPS1, transcriptional repressor GATA binding 1/tricho-rhino-phalangeal syndrome 1 protein; TWIST, twist family BHLH transcription factor 2; XLD, X-linked dominant.

the union of two lateral portions. In spinal dysraphism, abnormal closure of the neural tube leads to defects in the vertebral column and/or spinal cord (see Ch. 64). Skin lesions marking a hidden vertebral defect are usually located in the dorsal midline. The faun tail is most often a sign of spina bifida occulta or diastematomyelia (split spinal cord), and is typically located in the lumbosacral region. In addition, a ring of hypertrichosis on the scalp, referred to as the hair collar sign, can surround membranous aplasia cutis or ectopic neural tissue, reflecting the origin of these midline lesions as incomplete neural tube defects.

Localized hypertrichosis in hereditary and acquired systemic diseases

There are multiple genetic diseases characterized by the presence of localized hypertrichosis as a major or secondary diagnostic feature (see Table 70.2). For example, hypertrichosis within sun-exposed areas is one of the signs of the porphyrias – in particular, porphyria cutanea tarda (Fig. 70.7) and hepatoerythropoietic porphyria. Likewise, the low frontal hairline and synophrys ("unibrow") in the Cornelia de Lange syndrome are important diagnostic features of that entity. Localized hypertrichosis

HEREDITARY DISEASES AND CONGENITAL SYNDROMES ASSOCIATED WITH REGIONAL HYPERTRICHOSIS		
Disorder	**Sites of hypertrichosis**	**Other key features**
Dysmorphic syndromes		
Cornelia de Lange syndrome	• Forehead, lateral face, shoulders, back • Low anterior hairline, synophrys, trichomegaly	• Distinctive facies, upper extremity anomalies, microcephaly, GD, ID, "growling cry" • AD (1,3,4): *NIPBL* > *SMC3*, *RAD21* • XLD (2,5): *SMC1A*, *HDAC8*
Rubinstein–Taybi syndrome	• Lateral face, shoulders, back • Thick eyebrows, trichomegaly	• Midfacial vascular stains, keloids, pilomatricomas • Broad thumbs/halluces, beaked nose, high-arched palate, short stature, ID • AD; *CREBBP* > *EP300*
KINSSHIP syndrome	• Extremities	• Horseshoe *ki*dney, *N*ievergelt/Savarirayan mesomelic dysplasia, *s*eizures, *h*ypertrichosis, *I*D, *p*ulmonary anomalies • AD (*AFF3*)
Disorders with primary cutaneous features		
Porphyrias	• Sun-exposed areas • Favors lateral face in PCT, HEP, VP • Face, trunk, extremities in CEP	• See Ch. 49
Lipodystrophy syndromes (e.g. Berardinelli–Seip syndrome, leprechaunism)	• Face, neck, extremities • Low hairline	• See Ch. 101
Superficial epidermolytic ichthyosis (SEI)*, erythrokeratodermia variabilis et progressiva (EKVP)	• Extremities (SEI); trunk and extremities (EKVP)	• See Ch. 57
Dystrophic epidermolysis bullosa*	• Areas of previous blistering	• See Ch. 32
Metabolic disorders		
Mucopolysaccharidoses†	• Trunk, extremities	• See Ch. 48
Congenital hypothyroidism	• Back, extremities	• See Ch. 46
Mitochondrial disorders		
Leigh syndrome due to *SURF1* mutations	• Forehead, extremities	• Progressive neurodegeneration
MELAS syndrome	• Lower extremities	• *M*itochondrial encephalopathy, *l*actic *a*cidosis, and stroke-like episodes
Intrauterine exposures‡		
Fetal hydantoin syndrome	• Face, back, extremities	• Gingival hyperplasia, coarse facies, hypoplastic nails and distal phalanges, GD
Fetal alcohol syndrome	• Face, back, extremities	• Midfacial hypoplasia, GD, CNS anomalies
Morpheaform or sclerodermoid disorders		
MONA (*m*ulticentric *o*steolysis, *n*odulosis, and *a*rthropathy; previously known as Winchester syndrome)	• Hypertrichosis and hyperpigmentation overlying areas of skin thickening	• Gingival hyperplasia, carpal/tarsal osteolysis, osteoporosis, coarse facies, GD • AR; *MMP2* (matrix metalloproteinase-2)
Histiocytosis-lymphadenopathy plus syndrome¶ (including H syndrome)[9–11]	• Lower trunk and lower extremities (in association with areas of *h*yperpigmentation & induration) • Histologic features in areas of induration include a polyclonal perivascular lymphohistiocytic infiltrate with numerous plasma cells in the dermis and subcutis	• Sensorineural *h*earing loss, short *h*eight, *h*eart anomalies, *h*epatosplenomegaly, scrotal masses, hypergonadotropic *h*ypogonadism, antibody-negative insulin-dependent diabetes mellitus, facial telangiectasias • AR; *SLC29A3* (encodes nucleoside transporter hENT3 which localizes to lysosomes and mitochondria)
Stiff skin syndrome	• Variable	• See Ch. 43
Linear melorheostosis (isolated melorheostosis)§	• Overlying affected skin and bone	• Hyperostosis ("candle wax" appearance) with overlying scleroderma • Isolated cases due to *LEMD3* mutations

*Hypertrichosis is an uncommon feature.
†Hypertrichosis may also be observed in other lysosomal storage diseases, e.g. Krabbe disease and GM1-gangliosidosis, as well as sialuria.
‡Also minoxidil and diazoxide.
¶Includes pigmented hypertrichosis with insulin-dependent diabetes mellitus (PHID) syndrome, sinus histiocytosis with massive lymphadenopathy (SHML), and Faisalabad histiocytosis as well as H syndrome.
§Hypertrichosis has also been described overlying linear scleroderma in the absence of melorheostosis.

Table 70.2 Hereditary diseases and congenital syndromes associated with regional hypertrichosis. Varying degrees of hypertrichosis (predominantly facial or generalized) have also been observed in children with chromosomal anomalies, e.g. partial trisomy of 1q, 3q, 4p, or 17q. Autosomal recessive palmoplantar keratoderma and exuberant curly scalp hair due to *FAM83G* mutations has also been reported. *NIPBL*, *SMC1A*, *SMC3*, and *RAD21* encode components of the cohesin complex. *RAD21* and *EP300* encode a histone acetyltransferase and a histone deacetylase, respectively. AD, autosomal dominant; *AFF3*, ALF transcription elongation factor 3; AR, autosomal recessive; CEP, congenital erythropoietic porphyria; GD, growth delay; HEP, hepatoerythropoietic porphyria; ID, intellectual disability; PCT, porphyria cutanea tarda; VP, variegate porphyria; XLD, X-linked dominant.

may also be observed in acquired systemic diseases, such as infrapatellar hypertrichosis in juvenile dermatomyositis or hypertrichosis overlying pretibial myxedema, indurated plaques of Rosai–Dorfman disease, and areas affected by the complex regional pain syndrome.

Acquired localized hypertrichosis

After repeated trauma, friction, irritation, or inflammation, the hair within affected areas of skin may become longer and thicker (e.g.

HYPERTRICHOSIS DUE TO DRUGS	
Antibiotics	
• Streptomycin	
Anticonvulsants	
• **Phenytoin**	
Anti-inflammatory drugs	
• Benoxaprofen	• Corticosteroids
Antiseptic agents	
• Hexachlorobenzene	
Chelators	
• Penicillamine	
Diuretics	
• Acetazolamide	
Immunosuppressives	
• **Cyclosporine**	• Mycophenolate mofetil
Psoralens	
• Methoxypsoralen	• Trimethylpsoralen
Vasodilators	
• Diazoxide • **Minoxidil**	• Prostaglandin E1
Other	
• Interferon-α • Fenoterol	• EGFR inhibitors (e.g. cetuximab, panitumumab, erlotinib, gefitinib) • IL-17 inhibitors (e.g. secukinumab, ixekizumab)

Table 70.3 Hypertrichosis due to drugs. Most common drugs are in **bold**. EGFR, epidermal growth factor receptor.



Fig. 70.2 Hypertrichosis cubiti. Multiple terminal hairs on both elbows in a child.



Fig. 70.3 Anterior cervical hypertrichosis. *Courtesy Harvey Lui, MD.*

HEREDITARY HYPERTRICHOSIS AFFECTING SPECIFIC ANATOMIC SITES			
Condition	**Inheritance**	**Onset**	**Other features**
Hypertrichosis cubiti (Fig. 70.2)	AD	Birth to early childhood	• Short stature* • Wiedemann–Steiner syndrome: short stature, facial dysmorphism, ID; *KMT2A*
Hairy palms and soles	AD	Birth	
Hypertrichosis of the auricle	AD†	Childhood or adolescence	• Primarily affects males
Hypertrichosis of the eyebrows	?	Adolescence	
Trichomegaly of the eyelashes	AR	Childhood	
Hypertrichosis of the nasal tip	?	Adolescence	• Primarily affects males
Anterior cervical hypertrichosis[13] (Fig. 70.3)	AD‡	Birth to early childhood	• Sensory and motor neuropathy, ID* • Hallux valgus*
Posterior cervical hypertrichosis	AD	Birth	• Kyphoscoliosis
Polythelia, including the hairy variant¶[,14]	AD§	Adolescence	• Urinary tract anomalies*

*Occasional finding.
†Shown not to be Y-linked in a cohort of Indian men; congenital hypertrichosis of the pinna can be seen in the offspring of diabetic mothers and in individuals with XYY syndrome.
‡Possible AR inheritance in a consanguineous family.
¶Tuft of hair along the "mammary line".
§Approximately 10% of cases are familial.

Table 70.4 Hereditary hypertrichosis affecting specific anatomic sites. Localized hypertrichosis as a sign of spinal dysraphism is discussed in Ch. 64. AD, autosomal dominant; AR, autosomal recessive; ID, intellectual disability; KMT2a, lysine-specific methyltransferase 2 A.

HYPERTRICHOSIS OF THE EYEBROWS AND EYELASHES
Synophrys ("unibrow")
• Isolated trait • Waardenburg syndrome (see Ch. 66) • Cornelia de Lange syndrome (see Table 70.2) • Zimmerman–Laband syndrome (see Table 70.1) • Mucopolysaccharidoses (see Ch. 48)
Inherited and/or congenital trichomegaly
• Trichomegaly due to *FGF5* mutations (AR) • Oliver–McFarlane syndrome* • Cornelia de Lange and Rubinstein–Taybi syndromes (see Table 70.2) • Congenital hypertrichosis lanuginosa and Ambras syndrome (see Table 70.1) • Cantú, Coffin–Siris, and Barber–Say syndromes (see Table 70.1) • Hermansky–Pudlak syndrome (see Ch. 66) • Kabuki and floating harbor syndromes† • Fetal alcohol syndrome (see Table 70.2)
Acquired trichomegaly
• HIV infection • Systemic medications: cyclosporine, EGFR inhibitors (e.g. cetuximab, gefitinib; Fig. 70.4), topiramate, tacrolimus, interferon-α • Ophthalmic medications: latanoprost, bimatoprost • Hypothyroidism • Porphyrias • Dermatomyositis, systemic lupus erythematosus • Malnutrition, anorexia nervosa
Distichiasis (double row of eyelashes)
• Lymphedema–distichiasis syndrome‡ • Setleis syndrome (double upper and absent lower lashes; see Ch. 64)
*Autosomal recessive (AR) disorder also featuring sparse scalp hair, intellectual disability, short stature, and retinal pigmentary degeneration. †Autosomal dominant (AD) disorders featuring distinctive facies, growth delay, and, in the former, intellectual disability. ‡AD condition due to FOXC2 mutations (see Ch. 104).

Table 70.5 Hypertrichosis of the eyebrows and eyelashes. EGFR, epidermal growth factor receptor.



Fig 70.4 Epidermal growth factor receptor inhibitor-induced trichomegaly. The eyelashes increased in both length and disorder after treatment with erlotinib. *Courtesy Edward Cowen, MD.*

hypertrichosis of the back in sack carriers, hypertrichosis of a fractured limb after the application of a plaster cast, hypertrichosis of the posterior neck in people who bear heavy weights; Fig. 70.8)[18]. Chronic rubbing or scratching can also lead to localized hypertrichosis. Transient localized hypertrichosis has been observed within vaccination sites and varicella scars as well as sites of wart removal and laser epilation[19]. In addition, hypertrichosis has been described overlying lipoatrophy following lupus panniculitis and within resolving lesions of psoriasis and morphea. Extractable hairs mimicking hypertrichosis are often evident within a pilonidal sinus (cyst), which is usually located within the gluteal cleft.



Fig. 70.5 Becker melanosis (nevus) on the mid back in a young man. In addition to hyperpigmentation, there is marked hypertrichosis. The degree of hypertrichosis can vary (see Ch. 112). When it is marked as in this patient, the clinical differential diagnosis includes congenital melanocytic nevus, especially when there is an underlying smooth muscle hamartoma.

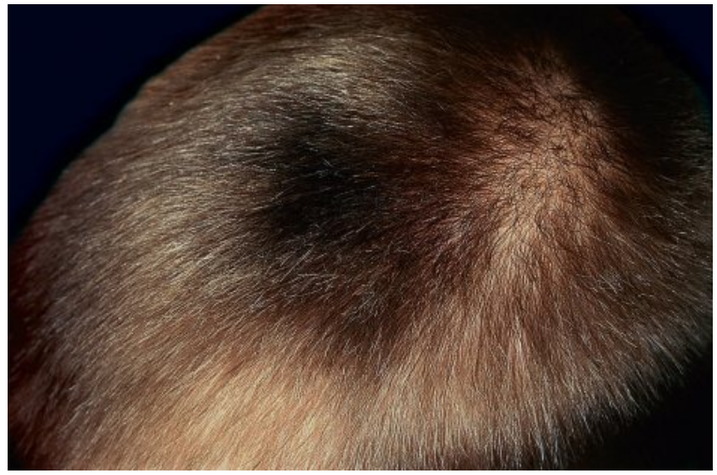


Fig. 70.6 Nevoid hypertrichosis (nevus pilosus) of the scalp in a young boy. There was no underlying melanocytic nevus or hyperpigmentation. *Courtesy Jean L. Bolognia, MD.*

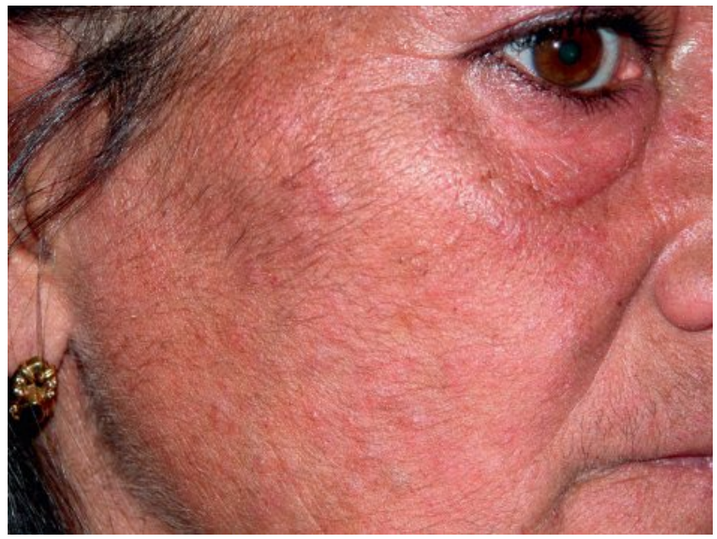


Fig. 70.7 Facial hypertrichosis in a woman due to porphyria cutanea tarda. *Courtesy Luis Requena, MD.*



Fig. 70.8 Acquired localized hypertrichosis. Hypertrichosis, hyperpigmentation, and epidermal hyperplasia at the site of friction.

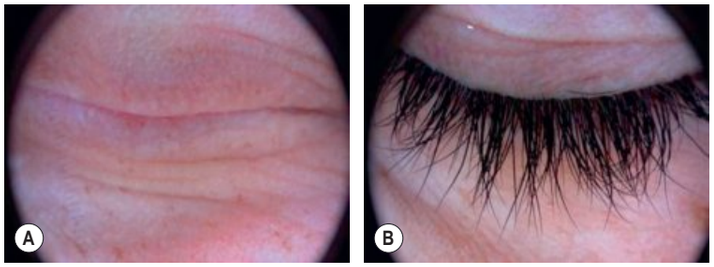


Fig. 70.9 Treatment of eyelash alopecia in a patient with alopecia universalis. A Prior to treatment. **B** Following daily application of topical latanoprost ophthalmic 0.005% solution for 6 months, there was regrowth of eyelashes.

Localized hypertrichosis has been reported after PUVA therapy. Sites of application of potent topical corticosteroids, tacrolimus, and creams containing mercury or iodine can also develop localized hypertrichosis, as can sites of repeated irritation from anthralin. Prostaglandin F-2α analogues (e.g. latanoprost, bimatoprost), which are topical agents used for the treatment of glaucoma, can induce trichomegaly of the eyelashes as well as brown iris pigmentation. The FDA has approved bimatoprost 0.03% solution for the stimulation of eyelash growth, and latanoprost has also been used off-label for this purpose (Fig. 70.9)[20].

Treatment

Methods available to treat hypertrichosis include chemical depilatory agents, electrolysis (see Ch. 140), and laser hair removal (see Ch. 137). Systems utilized for photoepilation include Nd:YAG, diode, and alexandrite lasers as well as intense pulsed light (IPL) sources (see Ch. 137). Barium sulfate depilatory creams have been shown to be especially effective, but they are odiferous and more irritating than calcium thioglycolate depilatory creams. Shaving and other physical methods (e.g. tweezing, waxing, threading, sugaring) may also be employed[21].

HIRSUTISM

Introduction

The term "*hirsutism*" is defined as excessive terminal hair growth in women that is within androgen-dependent sites (e.g. upper lip, chin, mid sternum, abdomen, back, buttocks; Fig. 70.10), representing a male distribution pattern. It reflects either hyperandrogenemia (an increase in circulating androgens) or an enhanced end-organ response to androgens[22–25]. Additional signs of hyperandrogenemia may include acne, a female pattern of androgenetic alopecia (see Ch. 69), irregular menstruation, and virilization. Virilization, which is uncommon and occurs with more severe hyperandrogenemia, also manifests with deepening of the voice, clitoromegaly, increased muscle mass, and male pattern hair loss (see Table 70.7).



Fig. 70.10 Idiopathic (constitutional) hirsutism. This patient had *s*eborrhea, *a*cne, *h*irsutism, and *a*lopecia, termed SAHA syndrome.

Epidemiology

Hirsutism, as defined by an abnormal score on the modified Ferriman and Gallwey scoring system (mFG; Fig. 70.11), affects ~5%–10% of women of reproductive age in the general population and rarely postmenopausal women[26,27]. In a study of North American women, 35% had terminal hairs on the linea alba, 17% in the periareolar area, 16% in the lumbosacral area, and 10% in the upper pubic triangle[23,24]. Androgen excess is present in >80% of premenopausal women with hirsutism, and ~70%–80% of these individuals have polycystic ovary syndrome (PCOS)[28]. Other women without hyperandrogenemia have idiopathic (constitutional) hirsutism, which tends to be relatively mild. Additional causes of hirsutism include drug intake, non-classic congenital adrenal hyperplasia, other endocrinopathies, and rarely androgen-secreting tumors (adrenal or ovarian; <0.3%) (Table 70.6). Women with rapid onset of hirsutism or signs of virilization are more likely to have an androgen-secreting tumor.

Classification

For clinical and therapeutic purposes, hirsutism can be classified according to the underlying causes (see Table 70.6)[23,24,29,30].

Clinical Features

Idiopathic (constitutional) hirsutism

Idiopathic (constitutional) hirsutism is a diagnosis of exclusion that is characterized by normal menses, normal ovaries on ultrasound, and no evidence of other causes. Androgen levels are usually normal but occasionally minimally elevated. Possible contributing factors include altered peripheral androgen activity and obesity[31], and this condition may be familial (Fig. 70.12). Approximately 5%–20% of all women with hirsutism and 50% of those with *mild* hirsutism have the idiopathic form[28]. Some women have acne and androgenetic alopecia as well as hirsutism, in association with slight increases in serum androgen levels (e.g. testosterone and dehydroepiandrosterone sulfate [DHEAS]). This constellation of findings has been referred to as *SAHA – s*eborrhea, *a*cne, *h*irsutism, and *a*ndrogenetic alopecia – *syndrome* (see Fig. 70.10)[32,33].

Ovarian hirsutism

Ovarian hirsutism can be of non-tumoral or tumoral origin. Non-tumoral etiologies include PCOS and ovarian hyperthecosis, with the former most common in premenopausal women and the latter typically occurring after menopause. A variety of benign or malignant ovarian tumors can also cause hirsutism, with malignant etiologies more likely to present with an abrupt onset of hirsutism, virilization, and markedly elevated testosterone levels.

Non-tumoral ovarian hirsutism

Polycystic ovary syndrome (PCOS)

This common syndrome, first described by Stein and Leventhal in 1935, affects ~5%–15% of women who are of reproductive age. It is

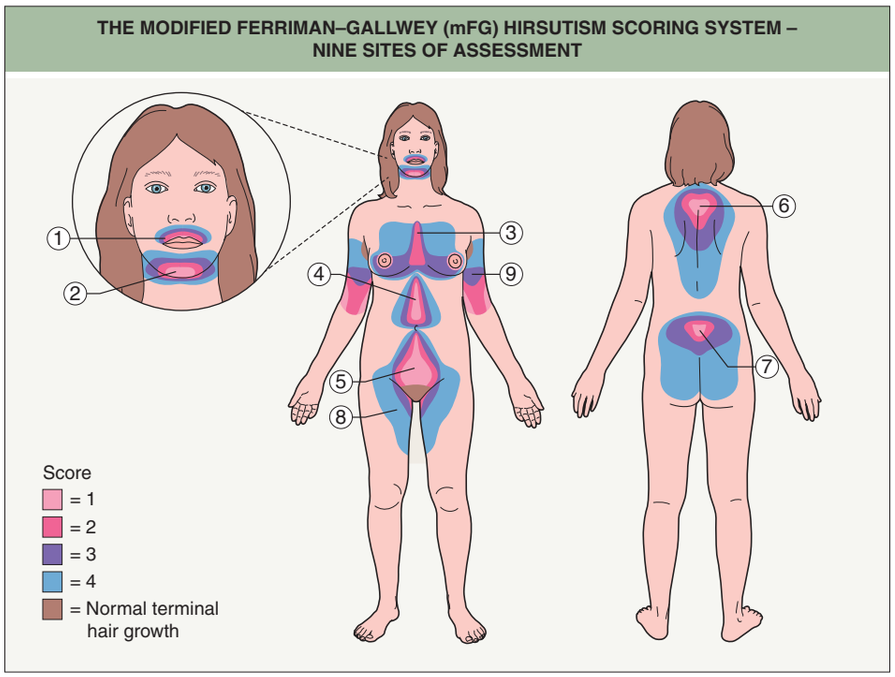


Fig. 70.11 The modified Ferriman–Gallwey (mFG) hirsutism scoring system – nine sites of assessment. The modified Ferriman and Gallwey score is based upon the sum of the values (graded from 0 to 4 points) for each of the nine body areas illustrated as follows: 0 points (no terminal hairs); 1 point (minimal terminal hairs); 2 points (hair growth is more than minimal but not yet that of a man); 3 points (hair growth is that of a man who is not very hairy); and 4 points (equivalent to a very hairy man). Total mFG scores that define hirsutism in reproductive-aged women vary depending upon race/ethnicity and are as follows: US and United Kingdom White or Black women, ≥8 (8–15 generally considered mild, 16–25 moderate, and >25 severe hirsutism); Mediterranean, Middle Eastern and Hispanic women, ≥9–10; South American women, ≥6; and Asian women, ranging from ≥2 for Han Chinese women to ≥7 for Southern Chinese women.

characterized by three major features (Rotterdam criteria): (1) oligo- or anovulatory cycles; (2) clinical or biochemical signs of hyperandrogenism (Fig. 70.13); and (3) ultrasonographic evidence of polycystic ovaries. Diagnosis requires two of these three criteria as well as exclusion of other causes of hirsutism (Fig. 70.14)[34]. Biochemically, there is typically a decrease in follicle-stimulating hormone (FSH) and an increase in luteinizing hormone (LH), as well as elevated serum levels of estrone and testosterone. Occasionally, serum prolactin levels are also increased.

After a normal menarche, patients develop persistent oligo- or amenorrhea that is frequently accompanied by infertility. Acne is present in 70% of patients and hirsutism in 90%. The associated hirsutism is usually lateral (i.e. on the breasts and lateral aspects of the face and neck) as well as on the central abdomen (see Fig. 70.13). Androgenetic alopecia in a female or male pattern is also commonly evident, but there are no signs of genital virilization. At least 50% of patients are obese, and some develop acanthosis nigricans and acrochordons in association with insulin resistance (see below). Patients with PCOS have large ovaries with a pearly gray surface, a thickened capsule and cysts with hyperplasia of the internal theca, but no signs of activity in the granulosa.

Women with PCOS have a higher prevalence of insulin resistance[35], dyslipidemia, hypertension, and obesity, which represent components of the "metabolic syndrome" that confers increased risk of atherosclerotic cardiovascular disease. Patients should be screened and followed for these conditions as well as non-alcoholic fatty liver disease (recently renamed metabolic dysfunction-associated steatotic liver disease), sleep apnea, endometrial cancer, and mood disorders, depending upon risk assessment (see Fig. 70.14)[34,36,37]. Although obesity, insulin resistance, and hyperandrogenemia are interconnected components of PCOS[37], it is important to note that insulin resistance also frequently occurs in non-obese patients with PCOS[38]. *HAIR-AN syndrome* characterized by hyperandrogenemia (*HA*), insulin resistance (*IR*), and acanthosis nigricans (*AN*) is now considered to represent a more severe subtype of PCOS that is more likely to result in type 2 diabetes, hypertension, and cardiovascular disease[39].

PCOS is oftentimes familial, but it is clearly a heterogeneous disorder. Attempts to identify its genetic basis have led to several possible candidate genes that could play a role in insulin resistance and androgen production, including those which encode cytochrome (CYP) 17, CYP 11A1, and insulin receptor substrate 1[37].

Ovarian hyperthecosis

This rare entity, which occurs primarily in postmenopausal women, is characterized by severe hyperandrogenism and insulin resistance. It results from differentiation of ovarian interstitial cells into steroidogenically active luteinized theca cells that overproduce testosterone. Women typically present with acne and hirsutism and are often virilized (Fig. 70.15). Serum testosterone levels are greatly elevated and result in increased peripheral estrogen production, which can increase the risk of endometrial carcinoma.

Tumoral ovarian hirsutism

Androgen-secreting ovarian tumors (e.g. Sertoli–Leydig cell, Leydig cell, steroid cell, and granulosa cell tumors) account for <5% of all ovarian neoplasms and can result in markedly elevated serum testosterone levels. Patients typically present with sudden onset and rapid progression of virilization in addition to hirsutism.

Adrenal hirsutism

Adrenal hirsutism can also be of non-tumoral or tumoral origin. The most frequent non-tumoral etiology is non-classic (mild) congenital adrenal hyperplasia. Androgen-secreting adrenal tumors are much less common and typically present in older women with abrupt onset and rapid progression of hirsutism and virilization[23–25].

Non-tumoral adrenal hirsutism – adrenal hyperplasias

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders caused by genetic defects in enzymes involved in adrenal hormone production (Fig. 70.16). The most common type (≥95%) is *21-hydroxylase deficiency (21-OHD)* due to *CYP21A2* mutations, which has a broad range of clinical manifestations depending on the underlying *CYP21A2* defect. The classic (severe) form of 21-OHD CAH occurs in ~1:15 000 live births worldwide, whereas the non-classic (milder) form has a prevalence of ~1:200 to 1:2000 and is more common in certain ethnic groups, including women of Ashkenazi Jewish, Middle Eastern, and Indian heritage[40–43]. Other rare forms of CAH include those caused by defects in 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase.

Classic CAH presents during the first 2 weeks of life with dehydration and electrolyte abnormalities (salt wasting) due to aldosterone as well as cortisol deficiency in ~75% of affected neonates. Female neonates with both salt-wasting and simple virilizing forms of classic CAH typically have ambiguous genitalia, while male neonates may manifest with subtle hyperpigmentation of the genitals, flexural areas, and palmoplantar creases. The US and many other countries have universal newborn screening programs for classic CAH based on detection of elevated levels of 17-hydroxyprogesterone, the preferred substrate for 21-hydroxylase[40,41]. As a result, affected neonates rarely present to a dermatologist[40,41].

CLASSIFICATION OF TYPES OF HIRSUTISM		
Type	**Notable lab abnormalities**	**Clinical findings/comments**
Idiopathic (constitutional) hirsutism		
Idiopathic hirsutism	Normal to slightly elevated serum androgen levels (testosterone, DHEAS)	• Normal ovaries on ultrasound • Normal menses • No identifiable cause • Idiopathic form often associated with obesity
Familial hirsutism (see Fig. 70.12)	Normal serum androgen levels	
Ovarian hirsutism		
Polycystic ovary syndrome (PCOS)	Normal to ↑ testosterone Normal DHEAS ↓ SHBG LH:FSH > 3	Defined by the presence of ≥2 of the following (see Fig. 70.14): • Chronic anovulation • Clinical or laboratory evidence of hyperandrogenism • Polycystic ovaries on ultrasound
Ovarian hyperthecosis	↑↑ testosterone Normal DHEAS	• Post- > premenopausal • Progressive severe hirsutism, virilization
Androgen-secreting ovarian tumor	↑↑ testosterone Normal DHEAS	• Rapid onset and progression of hirsutism, often with virilization • Post- > premenopausal
Adrenal hirsutism		
Classic (severe) congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency	↑↑ 17-OH progesterone ↑ androstenedione ↓ cortisol	• Presents during the neonatal period • Ambiguous genitalia in girls • May develop signs and symptoms of PCOS in adolescence if poorly controlled
Non-classic (mild) congenital adrenal hyperplasia (NCAH) due to 21-hydroxylase deficiency	↑17-OH progesterone Normal to slightly ↓ cortisol	• Clinical findings overlap with those of PCOS • Increased prevalence in certain ethnic groups (e.g. Ashkenazi Jews)
Androgen-secreting adrenal tumor	↑ to ↑↑ testosterone ↑↑ DHEAS ↑ cortisol ↓ ACTH	• Rapid onset and progression of hirsutism, often with virilization (carcinoma > adenoma)
Endocrinopathies that may be associated with hirsutism*		
Cushing syndrome	↑ to ↑↑ ACTH (pituitary adenoma or ectopic ACTH [e.g. small cell lung cancer, carcinoid tumor]) ↓ ACTH (adrenal tumor, adrenal primary nodular hyperplasia) ↑ DHEAS ↑ cortisol	• More rapid appearance when due to an adrenal carcinoma or malignancy • Acne, central obesity, moon facies, buffalo hump, striae distensae, hypertension, impaired glucose tolerance
Acromegaly	↑ growth hormone ↑ insulin-like growth factor 1 (IGF-1)	• Coarse facial features, macrognathia, enlarged hands and feet, deepened voice, hyperhidrosis
Hyperprolactinemia	↑↑ prolactin	• Amenorrhea, galactorrhea, infertility
Thyroid disorders	↓ SHBG (hypothyroidism) Abnormal TSH	• Menstrual dysfunction • Thyroid dysfunction
Insulin resistance disorders (obesity-related and genetic syndromes)	↑ insulin (fasting) ↑ triglycerides Hyperglycemia	• Severe insulin resistance, impaired glucose tolerance • Acanthosis nigricans, acrochordons, virilization • Amenorrhea, infertility • Often polycystic ovaries on ultrasound • Metabolic syndrome
Drug-induced hirsutism		
• Exogenous androgens (topical, oral, injections) (e.g. danazol, testosterone, DHEA) • Anabolic steroids • Corticotropin (ACTH) • Glucocorticoids • Metyrapone • Progestins • Valproic acid		• Also consider the use of topical androgens by a patient's partner
*Rarely present with isolated hirsutism.		

Table 70.6 Classification of types of hirsutism. More common entities are in **bold** font. Patients with liver disease can have a decrease in sex hormone binding globulin (SHBG), and a subsequent increase in free testosterone, which may exacerbate other causes of hirsutism. There is also conversion of androgens (e.g. Δ-4-androstenedione > testosterone) into estrogens in the ovaries and peripheral sites (adipose tissue, liver). In theory, a reduction in this conversion could lead to an increase in circulating androgens. ACTH, adrenocorticotropic hormone; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

Non-classic CAH (NCAH) presents postnatally, typically with onset during childhood or early adulthood; 17-hydroxyprogesterone levels are elevated but not high enough to be detected via newborn screening. Hirsutism represents the only manifestation in ~40%–60% of women with NCAH, which accounts for ~4% of all women with hirsutism. Premature pubarche is the most common presentation in children with NCAH, whereas female adolescents and women often develop acne, androgenic alopecia, irregular menses, and infertility as well as hirsutism.

Polycystic ovarian morphology may also be observed in NCAH; although virilization (Table 70.7) is more frequently evident in women with NCAH than in those with PCOS, measuring the serum 17-hydroxyprogesterone level is typically required to distinguish these two entities. Boys and men with NCAH less frequently seek medical attention for signs of androgen excess (e.g. early beard growth, large phallus)[40,41].

Tumoral adrenal hirsutism

Virilizing adrenal adenomas and carcinomas most often develop in postmenopausal women and may result in rapid onset and progression of hirsutism and virilization. Androgen-secreting carcinomas are more common than adenomas and typically produce both androgens and cortisol. Clinical findings may also include acne, androgenetic alopecia, amenorrhea, and features of Cushing syndrome (see below). Serum



Fig. 70.12 Familial hirsutism. Prolongation of the preauricular hair implantation line with terminal hairs of the lateral lower face and neck.

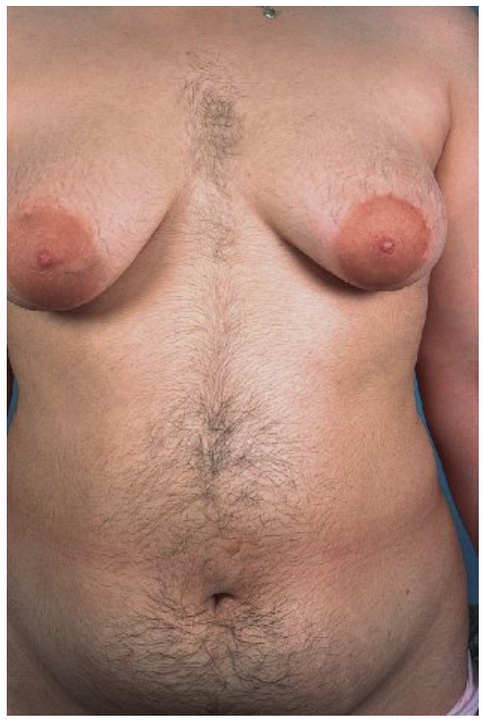


Fig. 70.13 Hirsutism in a young woman with polycystic ovary syndrome. Both lateral and central patterns are present.

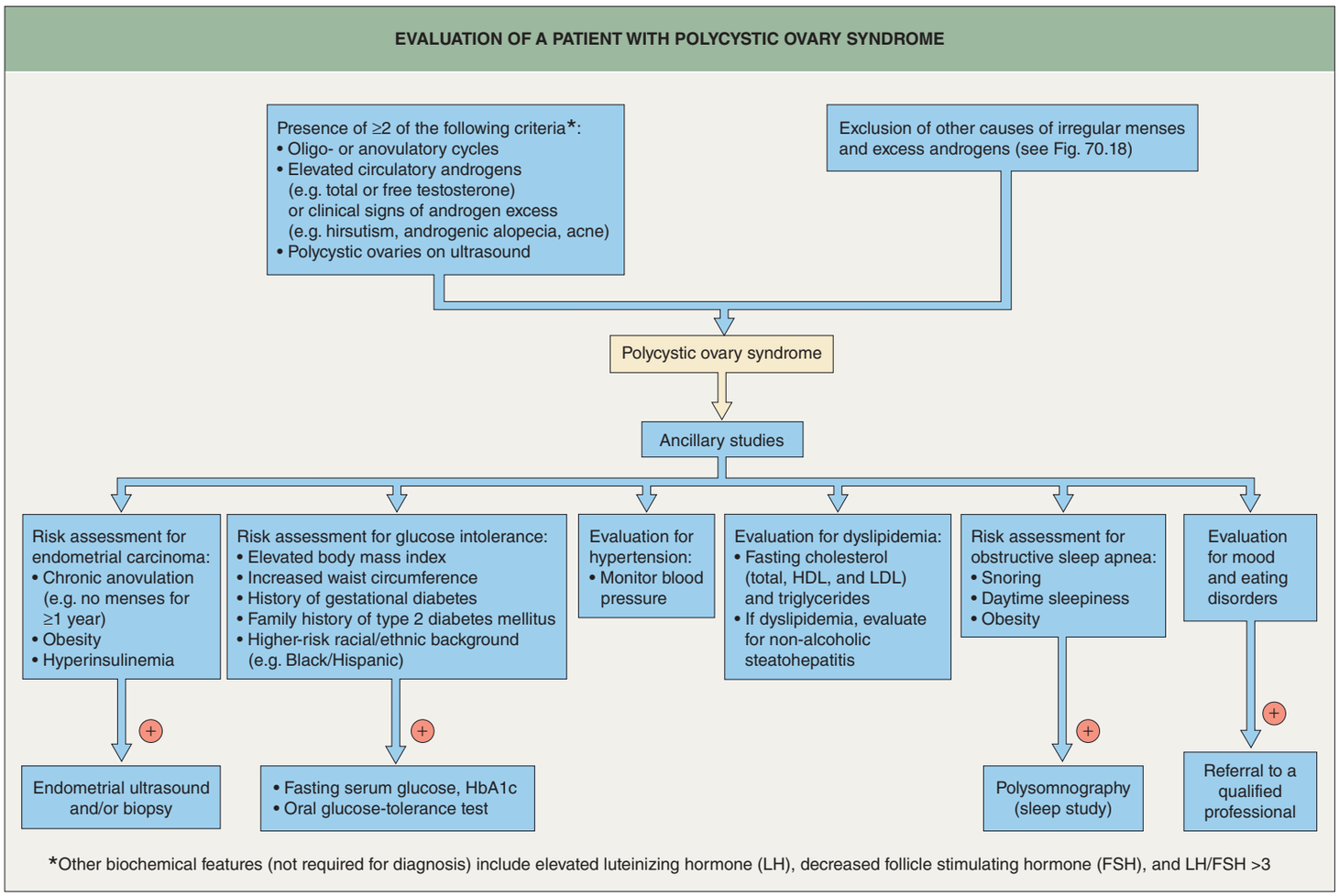


Fig. 70.14 Evaluation of a patient with polycystic ovary syndrome. Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein. *Adapted from Ehrman DA. Polycystic ovary syndrome. N Engl J Med 2005;352:1223–36.*

levels of testosterone and DHEAS levels are markedly elevated, and serum cortisol may also be increased.

Other endocrinopathies associated with hirsutism

Other endocrinopathies in which women may develop hirsutism together with disease-specific manifestations include Cushing syndrome, hyperprolactinemia, acromegaly, thyroid disorders, and insulin resistance disorders[28]. Pregnant women may also present with hirsutism as a result of ovarian and placental androgen production.

Hypercortisolism (Cushing syndrome)

Cushing syndrome may be associated with either high plasma ACTH levels (pituitary hyperproduction or "ectopic ACTH syndrome") or a nearly complete lack thereof (adrenal primary nodular hyperplasia, adrenal adenoma, or adrenal carcinoma). All patients have an increase in plasma cortisol, which is the cause of the major clinical features: central obesity with "moon facies" and "buffalo hump", hypertension, glucose intolerance, purple striae, and ecchymoses. Patients with adrenal hyperplasia (usually due to ACTH hyperstimulation by a pituitary adenoma) or adrenal adenomas typically have an insidious onset of symptoms, but with an adrenal carcinoma or ectopic ACTH production by a malignant tumor, manifestations appear more rapidly. If there is significant production of androgens, which is not the norm for adrenal adenomas, virilization with hirsutism will be present in addition to the typical manifestations of Cushing syndrome.

Hyperprolactinemia

Hirsutism represents a rare manifestation of hyperprolactinemia, which is most often caused by pituitary adenomas and drugs (e.g. dopamine antagonists). This etiology of hirsutism should be considered in women <50 years of age who present with galactorrhea together with oligomenorrhea, amenorrhea, or infertility ("amenorrhea–galactorrhea syndrome").

Acromegaly

Acromegaly results from excess secretion of growth hormone (GH), most commonly by a pituitary adenoma. The clinical features reflect elevated serum concentrations of both GH and insulin-like growth factor 1 (IGF-1), which is GH dependent. Long-term excess of GH



Fig. 70.15 Facial hirsutism due to ovarian hyperthecosis. *Courtesy Robert Hartman, MD.*

DIFFERENCES BETWEEN DEFEMINIZATION AND VIRILIZATION	
Defeminization	**Virilization**
• Acne • Female pattern hair loss • Menstrual alterations (e.g. oligomenorrhea) • Breast atrophy and loss of female body contours • Decreased rugosity of the vaginal columns • Infertility	• Hirsutism • Male pattern hair loss • Amenorrhea • Muscle mass increased • Clitoromegaly • Coarsening of the voice

Table 70.7 Differences between defeminization and virilization.

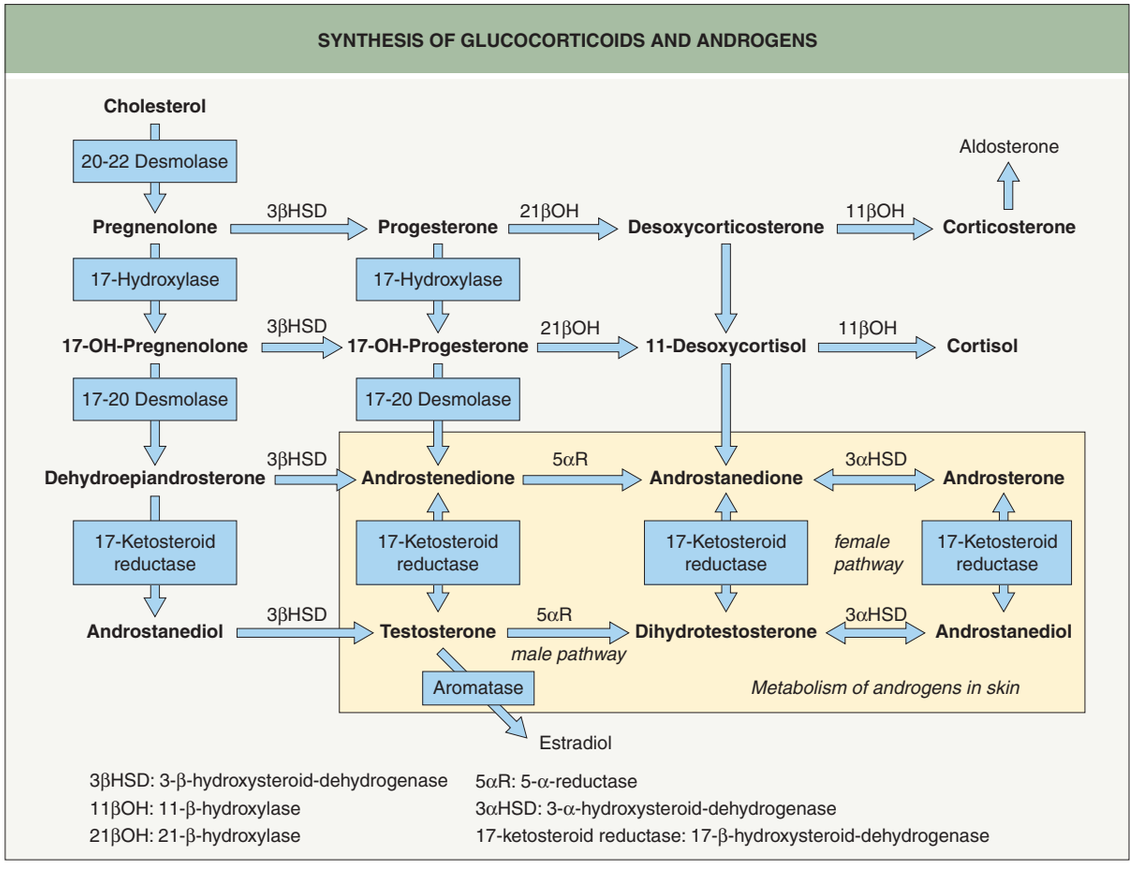


Fig. 70.16 Synthesis of glucocorticoids and androgens. The most common cause of congenital adrenal hyperplasia is 21-hydroxylase deficiency. This leads to an accumulation of 17-OH-progesterone.

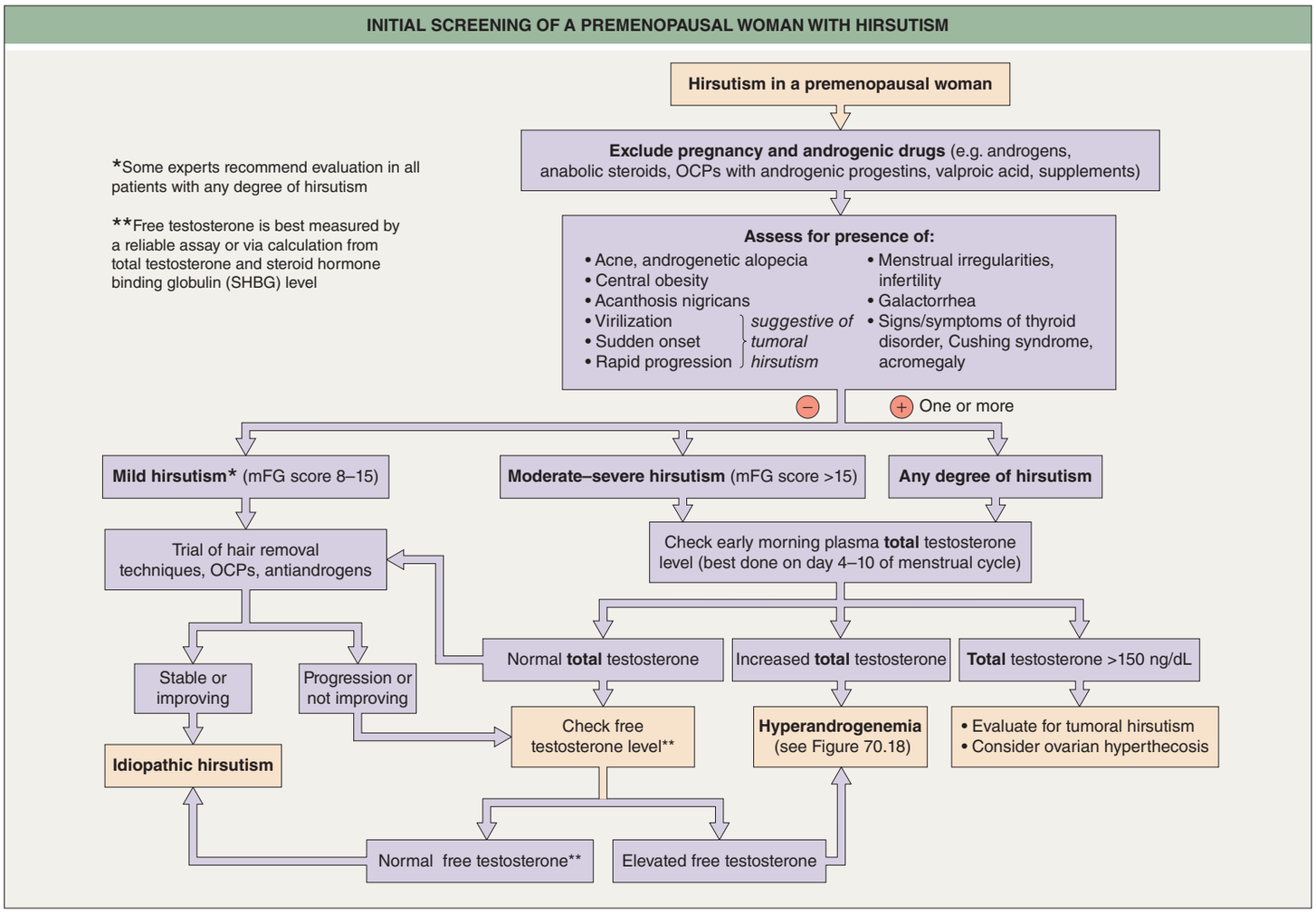


Fig. 70.17 Initial screening of a premenopausal woman with hirsutism. mFG, modified Ferriman and Gallwey; OCPs, oral contraceptives.

and IGF-1 results in overgrowth of many tissues and organs, including skin thickening as well as the classic findings of enlarged hands and feet, macrognathia, and macroglossia. Additional cutaneous manifestations can include hirsutism, hypertrichosis, hyperhidrosis, acanthosis nigricans, acrochordons, and cutis verticis gyrata.

Thyroid disorders

Thyroid dysfunction interferes with sex hormone metabolism and can result in irregular menstruation. Hypothyroidism can also cause cystic ovarian changes and decreased levels of sex hormone-binding globulin (SHBG), which increases the amount of free circulating testosterone.

Insulin-resistance disorders

Disorders of severe insulin resistance (e.g. obesity-related, insulin receptor mutations [*type A syndrome*], anti-insulin receptor antibodies [*type B syndrome*]) are often associated with hyperandrogenism, hirsutism, and even virilization[44,45]. Marked hyperinsulinemia results in ovarian hyperandrogenism, presumably via receptors for insulin and IGF-1 on ovarian theca cells. Insulin also decreases SHBG levels, thereby increasing the amount of free circulating testosterone. Ovaries often show a polycystic pattern on ultrasound.

Drug-induced hirsutism

Several drugs have been associated with the development of hirsutism (see Table 70.6). Identifying such culprit drugs and stopping them will typically result in reversal of the hirsutism.

Diagnosis

Hirsutism is a clinical diagnosis and a potential indicator of a hyperandrogenic disorder that may require treatment and have associated comorbidities such as metabolic syndrome or fertility issues. In a premenopausal woman with hirsutism, the mFG score (see Fig. 70.11) should be determined and assessment for associated findings initiated (Fig. 70.17). Additional evaluation of women with hyperandrogenemia for signs of PCOS are outlined in Figs. 70.18 and 70.14.

It is important to inquire about the age of onset (premenopausal vs postmenopausal), progression (rapid vs gradual), and emotional and psychosocial impact of the hirsutism. Patients should also be asked about their menstrual history (e.g. oligo- or amenorrhea), medications (see Table 70.6), comorbidities (e.g. insulin resistance disorders), ethnicity, and family history. Physical examination should determine if true hirsutism (versus hypertrichosis) is present as well as its severity (see Fig. 70.11). In addition, patients should be evaluated for additional findings of hyperandrogenism (e.g. acne, androgenic alopecia), virilization (see Table 70.7), acanthosis nigricans, central obesity, and manifestations of other endocrinopathies associated with hirsutism (see Table 70.6). An abrupt onset and rapid progression of hirsutism or the presence of virilization should raise suspicion for a more serious cause of androgen excess (e.g. an androgen-secreting tumor). Premenopausal women with hirsutism are most likely to have PCOS, idiopathic hirsutism or NCAH, whereas postmenopausal women with new onset hirsutism are more likely to have an androgen-secreting tumor or ovarian hyperthecosis.

In a *premenopausal* woman with hirsutism, serum total testosterone is recommended as the initial biochemical study[28]. Additional considerations include measuring the serum 17-hydroxyprogesterone level (e.g. in women at higher risk of NCAH based on ethnicity or family history) and transvaginal pelvic ultrasonography to assess for PCOS. Additional evaluation based upon these results and the clinical presentation are outlined in Figs. 70.17 and 70.18. Of note, in women taking an oral contraceptive (OCP) or spironolactone, the results of laboratory testing

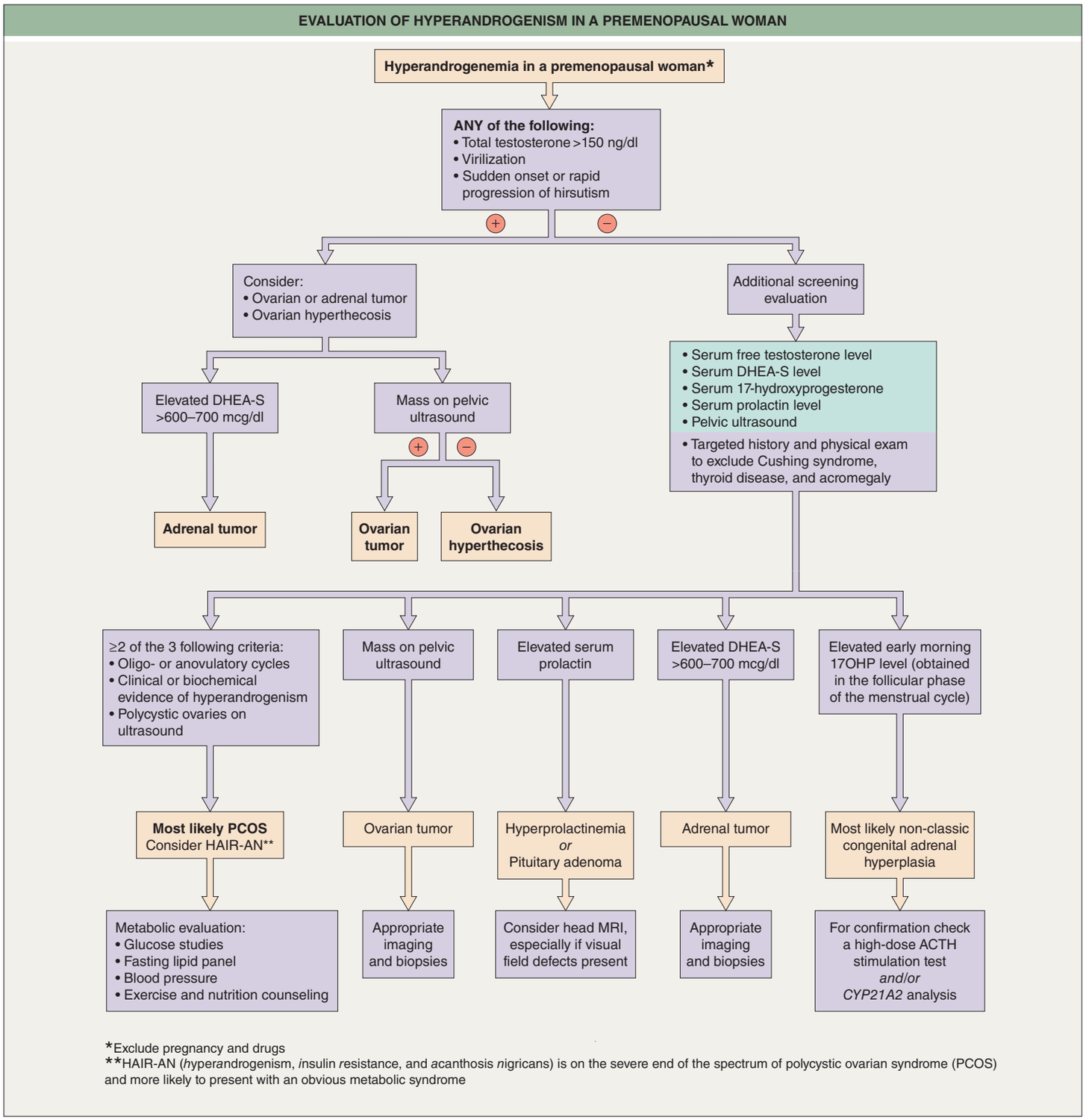


Fig. 70.18 Evaluation of hyperandrogenemia in a premenopausal woman.

will not be reliable. If an evaluation is desired, then discontinuation of the medications for at least 8–12 weeks is recommended.

The most useful biochemical tests to evaluate a *postmenopausal* woman with hirsutism are serum total testosterone and DHEAS levels. Serum total testosterone levels >150 ng/dl are suggestive of an androgen-secreting tumor, with higher testosterone levels typically associated with an ovarian source and DHEAS >700 mcg/dl suggestive of an adrenal source. Hyperandrogenism due to PCOS or NCAH can persist into menopause, and a serum 17-hydroxyprogesterone level should be considered if not evaluated previously. Other laboratory testing depends upon the presence of signs or symptoms suggestive of another endocrinopathy (see Table 70.6).

Treatment

The impact of hirsutism on a woman's quality of life should be assessed and regardless of the mFG score, treatment should be initiated if it is causing distress to the patient ("patient-important" hirsutism)[28]. Management of premenopausal and postmenopausal hirsutism involves a combination of systemic pharmacologic therapies (Table 70.8) and direct hair removal methods, both of which should be offered to women with "patient-important" hirsutism. Bilateral oophorectomy can be considered in the management of ovarian hyperthecosis. In the case of ovarian and adrenal tumors, surgical intervention is usually required.

TREATMENT OF HIRSUTISM AND HYPERANDROGENISM – SYSTEMIC AGENTS AND CLINICAL SCENARIOS		
Systemic agents		
Combined oral contraceptives (cOCPs)* • All cOCPs appear to have similar effectiveness for treating hirsutism • For women at higher risk for VTE (e.g. obesity, age ≥40 years), select a cOCP with the lowest effective dose of ethinyl estradiol (usually 20 mcg) and a low-risk progestin (e.g. norethindrone, norgestimate) **Antiandrogens**† • Spironolactone 100–200 mg/day (usually given in divided doses, twice daily; see Ch. 36) • Cyproterone acetate 50–100 mg/day (given on days 5–15 of menstrual cycle)‡ • Finasteride 2.5–5 mg/day • Bicalutamide 50 mg/day (occasional hepatotoxicity) • Flutamide (not recommended because of hepatotoxicity risk) **Gonadotropin-releasing hormone (GnRH) agonists** (risk of severe estrogen deficiency; *typically reserved for severe hirsutism [e.g. ovarian hyperthecosis] that is unresponsive to combined OCPs + antiandrogen therapy*) **Insulin-lowering agents** – metformin > thiazolidinediones (improve metabolic syndrome and reproductive function but not useful as monotherapy for hirsutism) **Glucocorticoids** – e.g. low-dose hydrocortisone, prednisone, or dexamethasone (*second-line treatment for NCAH*)		
Clinical scenarios and recommended treatment¶		
Premenopausal female	**First-line**§: cOCP **Second-line**: cOCP + spironolactone or cyproterone acetate‡	**Severe or refractory:** finasteride or GnRH agonist plus cOCP or other contraceptive method
Postmenopausal female	**First-line**: spironolactone or cyproterone acetate‡	
NCAH	**First-line:** cOCP ± spironolactone or cyproterone acetate‡ **Second-line or if seeking ovulation induction**: glucocorticoid	

*Avoid in women with a history of VTE, inherited thrombophilia, smoking (if age >35 years), migraine with aura, or an estrogen-dependent neoplasm.
†Because of teratogenicity, not recommended as monotherapy in sexually active women of reproductive age unless a reliable contraceptive method is used.
‡CPA is not available in the United States; ethinylestradiol 20–35 mg is also typically given on days 5–25 of the menstrual cycle in premenopausal women.
¶A waiting period of 6 months is recommended after initiating a treatment and before adding or changing medications.
§In patients with severe hirsutism causing emotional distress and/or previous history of treatment failure with combined OCP, consider first-line treatment with a cOCP + antiandrogen.

Table 70.8 Treatment of hirsutism and hyperandrogenism – systemic agents and clinical scenarios. For hirsute women with obesity, including those with polycystic ovary syndrome (PCOS), lifestyle changes (e.g. diet, exercise) are also recommended. NCAH, non-classic congenital adrenal hyperplasia; VTE, venous thromboembolism.

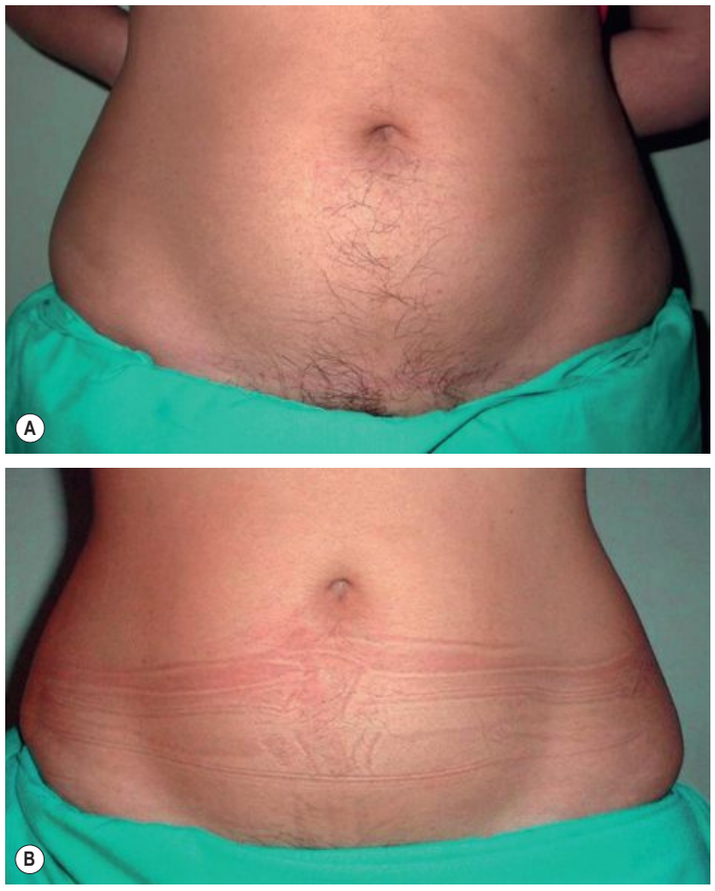


Fig. 70.19 Hirsutism before (A) and after treatment (B) with antiandrogen therapy. This patient had the SAHA (*s*eborrhea, *a*cne, *h*irsutism, and *a*lopecia) syndrome and achieved clinical improvement in hirsutism after one year of antiandrogen therapy.

Systemic therapy

The 2018 Endocrine Society clinical guidelines[28] recommend initial treatment with systemic pharmacologic therapy in *premenopausal* "patient-important" hirsutism that persists despite cosmetic measures. They suggest a combined estrogen–progesterone OCP as first-line treatment, as long as fertility is not immediately desired and there are no contraindications (e.g. history of venous thromboembolism [VTE], inherited thrombophilia, smoking if age >35 years, migraine with aura, estrogen-dependent neoplasm). Combined OCPs (cOCPs) suppress LH secretion and thus ovarian androgen production. They also stimulate the production of SHBG, which results in a decrease of circulating free androgen levels. The Endocrine Society guidelines do not recommend one cOCP over another for treating hirsutism based on a meta-analysis of effectiveness[28,46,47]. Although cOCPs containing antiandrogenic progestins (e.g. drospirenone, cyproterone acetate [not available in the US]) have been shown in some studies to lower mFG scores slightly more than other combined OCPs, the difference is not thought to be clinically important[46]. A cOCP containing the lowest effective dose of ethinyl estradiol (usually 20 mcg) and a low VTE-risk progestin (e.g. norgestimate, norethindrone) is recommended in women at higher risk for VTE (e.g. obesity, age ≥40 years)[28]. Although levonorgestrel is associated with a low VTE risk, this progestin is the most androgenic and may have adverse metabolic effects, making it less suitable for patients with PCOS[28].

If the clinical response is not achieved after 6 months of a cOCP, then an antiandrogen (e.g. spironolactone) can be added (see Ch. 36). A trial of at least 6 months is suggested before making dose adjustments or medication changes (Fig. 70.19)[28]. Antiandrogen monotherapy is not advised unless the patient is using adequate contraception, given the risk of impact on a developing fetus. If the hirsutism is severe or previous use of a cOCP has been unsuccessful, then initial therapy with both a cOCP and antiandrogen can be considered.

Additional systemic treatment options for hirsutism are summarized in Table 70.8. Flutamide and bicalutamide are nonsteroidal androgen receptor blockers that are approved for the treatment of prostate cancer. Although both of these agents have been utilized for the treatment of hirsutism, flutamide is not recommended for this indication because of its higher potential for hepatotoxicity. Insulin-lowering

medications (e.g. metformin) have not shown efficacy as monotherapy for hirsutism[28]. Management of PCOS comorbidities are outlined in Fig. 70.14. Lifestyle modifications (e.g. diet, exercise) are recommended for all hirsute women with obesity[28,31]. Lastly, for women with NCAH, glucocorticoids may be utilized to treat hirsutism that does not respond adequately to a cOCP ± antiandrogen or to induce ovulation.

In *postmenopausal* women with "patient-important" hirsutism and no evidence of an androgen-secreting tumor, treatment typically includes an antiandrogen plus direct hair removal methods (see Table 70.8).

Topical therapy

Topical antiandrogen therapy (e.g. canrenone [active metabolite of spironolactone], finasteride) is generally not recommended for treatment of hirsutism because of limited evidence of efficacy. A newer topical antiandrogen, clascoterone, has been approved for the treatment of acne but has yet to be studied for hirsutism.

Eflornithine HCL 13.9% cream is FDA-approved for the reduction of unwanted facial hair in women; it was discontinued by the original manufacturer in 2023. It irreversibly inhibits ornithine decarboxylase, an enzyme that catalyzes the rate-limiting step in follicular polyamine synthesis, which is necessary for hair growth. In a randomized vehicle-controlled study in 594 women, it was shown to reduce hair length and mass by ~25%[48]. Because eflornithine HCL slows hair growth rather than removes hair, it is best used and more effective in conjunction with other direct hair removal methods (e.g. laser or intense pulsed light [IPL])[49]. Results can take up to 8 weeks to become evident, and hair gradually returns to pretreatment levels upon discontinuation.

Direct hair removal methods

Direct hair removal methods can either remove a portion of the hair from above the skin's surface (depilation) or the entire hair shaft (epilation)[50]. Epilation methods may result in temporary or potentially permanent hair reduction. Each hair removal option has advantages and disadvantages[50].

Depilation methods include trimming, shaving, dermaplaning, and chemical depilatories. Shaving is easy and inexpensive but must be done frequently and can cause skin irritation. Contrary to popular belief, shaving does not change the texture, color, or growth rate of hair. It does, however, create a blunt tip upon regrowth that can give the illusion of thicker hair. Chemical depilatory agents, which dissolve the hair shafts via breakage of disulfide bonds, can be used for large areas but often cause skin irritation.

The results of epilation typically last longer than those of depilation. Tweezing, threading, waxing, and sugaring are effective temporary epilation techniques, but they are painful and often impractical for larger areas. Potentially permanent options include electrolysis and photoepilation utilizing a laser or IPL. Although effective, electrolysis is painful, time-consuming, and not practical for treating large areas (see Ch. 140). Photoepilation, which can treat larger areas in a shorter amount of time, represents the preferred option for long-term hair removal[27]. It utilizes pulses of light absorbed by melanin to destroy pigmented terminal hair follicles through thermal damage. Photoepilation systems include alexandrite, diode, and Nd:YAG lasers and various IPL sources, which are selected based upon the patient's skin and hair color (see Ch. 137). Clinical trials have shown ~40%–80% hair reduction, depending upon the device used and the number of treatments provided[51,52]. Photoepilation is ineffective for blond, white, or gray hairs and can be costly and painful, with potential side effects including pigmentary changes and rarely scarring or paradoxical hypertrichosis[19].

Additional figures and tables on Abraham's classification of hirsutism, and Methods to reduce unwanted hair, available in our eBook (see inside front cover for access code).

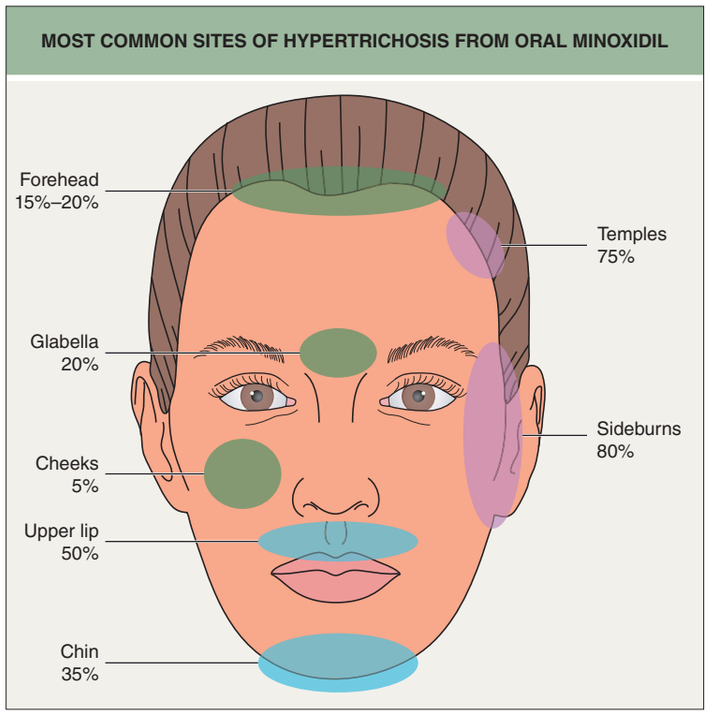
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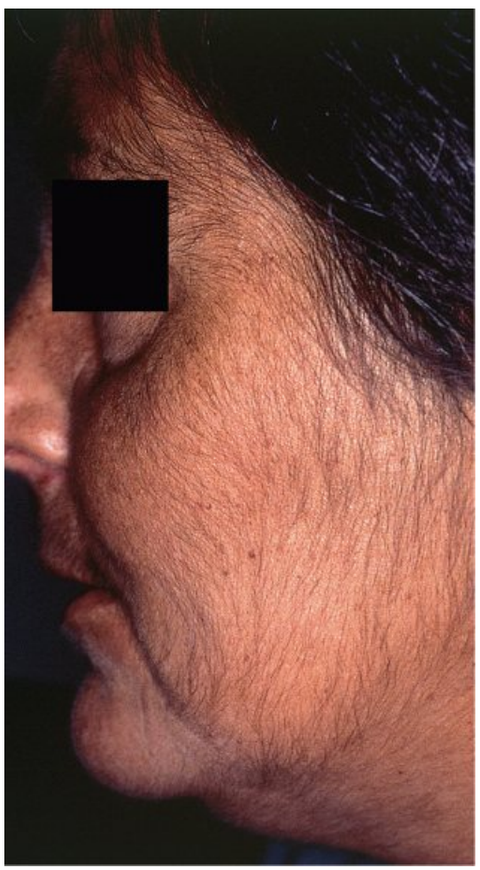
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eFig. 70.1 Becker melanosis (nevus). Both hyperpigmentation and hypertrichosis are present. *Courtesy Jean L. Bolognia, MD.*



eFig. 70.3 Most common sites of hypertrichosis from oral minoxidil.
Adapted from Jimenez-Cauhe J, Saceda-Corralo D, Rodrigues-Barata R, et al. Characterization and management of hypertrichosis induced by low-dose oral minoxidil in the treatment of hair loss. J Am Acad Dermatol 2021;84:222–3.



eFig. 70.2 Facial hypertrichosis in a woman due to porphyria cutanea tarda.

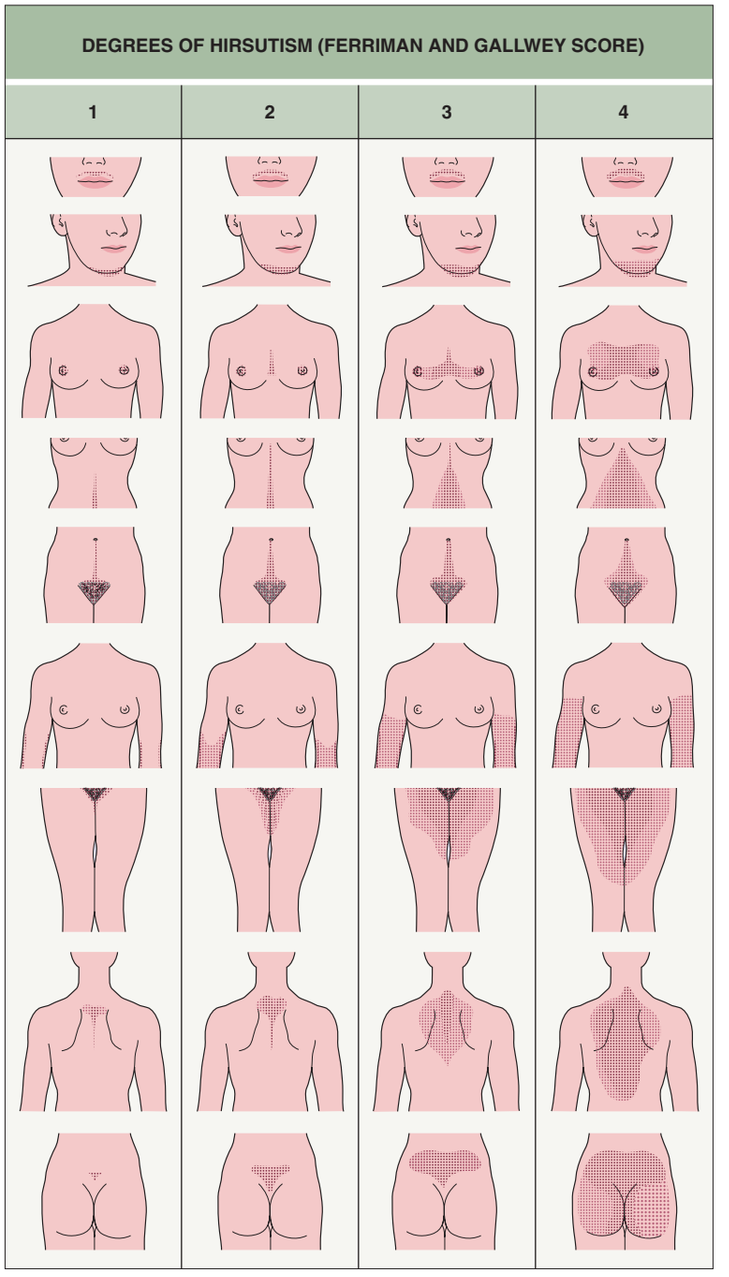


eFig. 70.4 Hypertrichosis secondary to oral minoxidil. *Courtesy Eugene Mirrer, MD.*





eFig. 70.5 "Pseudo"-hypertrichosis occurring in an umbilical pilonidal sinus (cyst). Localized "pseudo"-hypertrichosis can occur within a pilonidal sinus (cyst), usually located within the gluteal cleft and rarely elsewhere, e.g. umbilicus, as seen here (**A**). However, hairs are easily extracted (**B**). *Courtesy Karynne O. Duncan MD*.



eFig. 70.6 The modified Ferriman–Gallwey (mFG) hirsutism scoring system – nine sites of assessment. The modified Ferriman and Gallwey score is based upon the sum of the values (graded from 0 to 4 points) for each of the nine body areas illustrated as follows: 0 points (no terminal hairs); 1 point (minimal terminal hairs); 2 points (hair growth is more than minimal but not yet that of a man); 3 points (hair growth is that of a man who is not very hairy); and 4 points (equivalent to a very hairy man). Total mFG scores that define hirsutism in reproductive-aged women vary depending upon race/ethnicity and are as follows: US and United Kingdom White or Black women, ≥8 (scores between 8 and 15 generally considered mild, 16–25 moderate, and >25 severe hirsutism); Mediterranean, Middle Eastern and Hispanic women, >9–10; South American women, ≥6; and Asian women, ranging from ≥2 for Han Chinese women to ≥7 for Southern Chinese women.



eFig. 70.7 Acquired hypertrichosis lanuginosa. *Courtesy Jeffrey P. Callen, MD.*

ABRAHAM'S CLASSIFICATION OF HIRSUTISM	
Score	**Classification**
<8	Normal
8–16	Discrete
17–25	Moderate
>25	Important

eTable 70.1 Abraham's classification of hirsutism. Based on the Ferriman and Gallwey score.

METHODS TO REDUCE UNWANTED HAIR		
Camouflage	**Direct hair removal methods**	**Retardation of hair growth**
• Lightening of hair with bleaching product	***Depilation***	• Eflornithine HCL (13.9%) cream (best used in conjunction with other hair removal techniques); discontinued by the original manufacturer
	Chemical • Barium sulfate creams* • Calcium thioglycolate creams ***Mechanical*** • Trimming • Shaving • Dermaplaning	
	Epilation	
	• Tweezing • Waxing • Threading • Sugaring • Electrolysis† • Thermolysis† • Lasers (e.g. Nd:YAG, diode, alexandrite) or IPL	
*More effective than calcium thioglycolate but more irritating and odiferous. †Potential for permanent hair removal.		

eTable 70.2 Methods to reduce unwanted hair. The results of epilation typically last longer than those of depilation. Chemical depilatories work by dissolving hair shafts via breakage of disulfide bonds. IPL, intense pulsed light.

71 Nail Disorders

Antonella Tosti and Bianca Maria Piraccini

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ANATOMY

Key features

- Nail matrix → nail plate production
  proximal matrix → dorsal nail plate
  distal matrix (lunula) → ventral nail plate
- Proximal nail fold → nail matrix protection
- Nail bed and hyponychium → nail plate adhesion and distal detachment
- Nail growth rate: fingernails: 3 mm/month; toenails: 1 mm/month

The nail plate is a fully keratinized structure produced by the germinative epithelium of the nail matrix. As it grows, the nail plate emerges from the proximal nail fold and progresses distally, lying across and strictly adhering to the nail bed (Fig. 71.1). As the nail plate approaches the tip of the digit, it detaches from the underlying tissues, forming the hyponychium. Proximally and laterally, the nail plate is surrounded by the nail folds. The proximal nail fold consists of two layers of epithelium – a dorsal layer, which is the distal continuation of the skin of the dorsum of the digit, and a ventral layer, which is continuous with the nail matrix.

The nail matrix is responsible for the production of the nail plate and consists of an epithelium that keratinizes without the formation of a granular layer. Nail matrix keratinization occurs along an oblique axis, reflecting the upward and distal movement of cells during the process of maturation and differentiation[1]. For this reason, the proximal portion of the nail matrix produces the dorsal portion of the nail plate, while the distal matrix is responsible for the production of the ventral nail plate (see Fig. 149.2). The distal portion of the nail matrix is visible through the transparent nail plate as a white, distally convex half-moon known as the lunula. The matrix contains melanocytes that are normally quiescent; however, they may become activated and synthesize melanin, which is transferred to the surrounding keratinocytes. Distal migration of melanin-containing keratinocytes then gives rise to a hyperpigmented nail plate (melanonychia).

Nail plate production occurs continuously, proceeding from the 15th week of embryonic life until death. Under normal conditions, the mean growth rate of a fingernail is 3 mm/month and that of a toenail is 1 mm/month. Nail growth rate can be influenced by several factors, including age, systemic diseases, and medications.

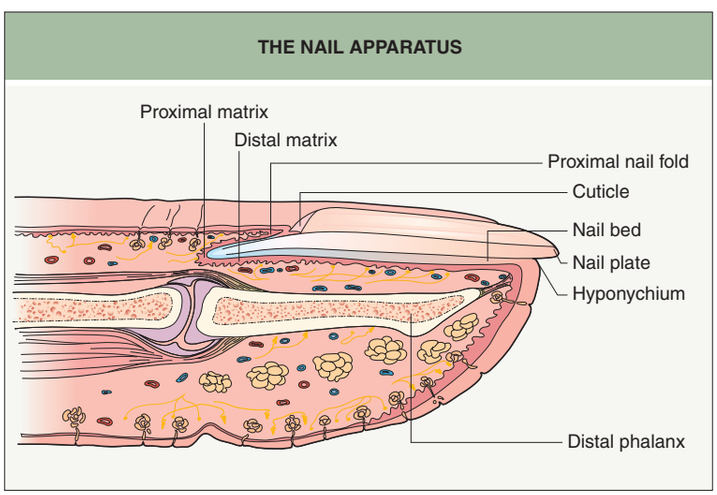


Fig. 71.1 Schematic drawing of the nail apparatus in longitudinal section. For additional details, see Figs. 149.1 & 149.2.

NAIL SIGNS

The clinical signs of various nail disorders depend upon the component of the nail apparatus that has been affected: nail plate alterations are due to matrix damage whereas nail plate detachment and/or uplifting arise from dysfunction of the hyponychium or nail bed (Table 71.1). Paronychia represents inflammation of the nail fold, which can lead to secondary matrix damage. The nail plate can develop a wide range of structural changes, from thickening to fissuring to atrophy, in addition to discoloration (Fig. 71.2).

Nail signs can be schematically divided into three major categories:

- signs due to abnormal nail matrix function
- signs due to nail bed disorders
- signs due to deposition of pigment within the nail plate.

Nail Signs Due to Abnormal Nail Matrix Function

Beau's lines

Key features

- Transverse depressions that are more evident in the central portion of the nail plate
- Most often due to trauma
- Involvement of multiple digits suggests a systemic cause

CORRELATION OF NAIL FINDINGS WITH ANATOMIC SITE OF NAIL DAMAGE	
Affected site	**Clinical manifestation**
Proximal matrix	Beau's lines Pitting Longitudinal ridging Longitudinal fissuring Trachyonychia
Distal matrix	True leukonychia
Proximal + distal matrix	Onychomadesis Koilonychia Nail plate thinning Onychauxis (nail plate hypertrophy or thickening)
Nail bed	Onycholysis Subungual hyperkeratosis Apparent leukonychia Splinter hemorrhages

Table 71.1 Correlation of nail findings with anatomic site of nail damage.

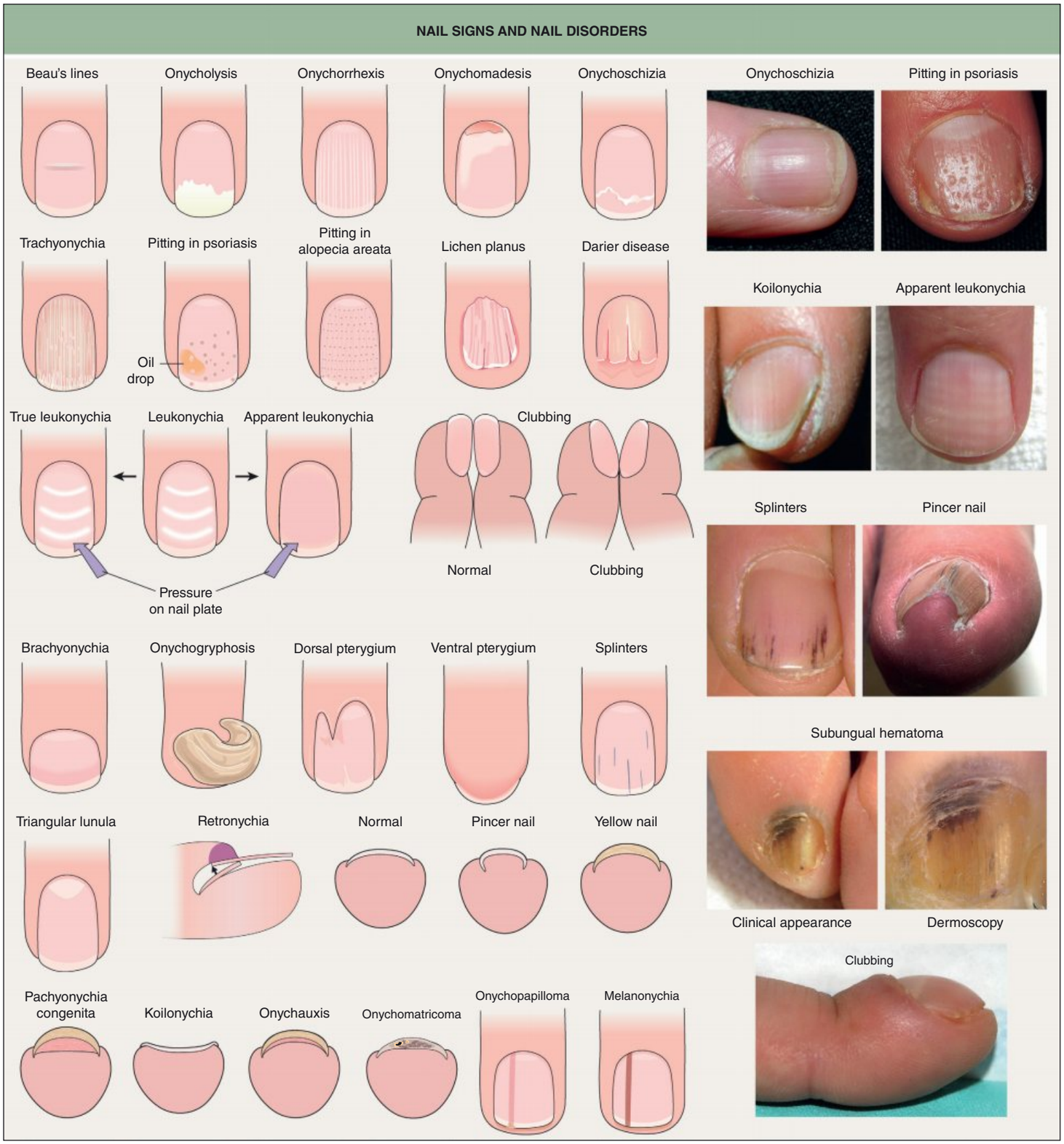


Fig. 71.2 Nail signs and nail disorders. In *apparent* leukonychia (e.g. Muehrcke's lines due to hypoalbuminemia and presumed secondary edema), the transverse white lines disappear with pressure, but not in *true* leukonychia (e.g. Mees' lines due to parakeratosis). Terry's nails and half-and-half nails are additional examples of apparent leukonychia. Dermoscopy of a subungual hematoma shows small red longitudinal splinter hemorrhages and dark purple pigmentation under the proximal nail fold and nail plate due to accumulated blood, with a typical fringed distal edge. *Photographs courtesy Jean L. Bolognia, MD; Leonard J. Swinyer, MD; Kalman Watsky, MD; and authors.*

First described by Beau in 1846, these transverse depressions of the nail plate surface result from a temporary interruption of the mitotic activity of the proximal nail matrix. The depth of the depression indicates the extent of the damage within the matrix; the width of the depression indicates the duration of the insult. Beau's lines migrate distally along with nail plate growth, with multiple lines indicating repeated damage (Fig. 71.3). Most commonly, Beau's lines are caused by mechanical trauma (e.g. manicures, onychotillomania) or dermatologic disease of the proximal nail fold (e.g. eczema, chronic paronychia). The presence of Beau's lines at the same level in all nails suggests a systemic cause (e.g. severe or febrile illness, cytotoxic drugs, erythroderma).



Fig. 71.3 Beau's lines. Multiple transverse depressions due to repeated traumatic insults to the proximal nail matrix from aggressive manicures. The depressions are more evident in the central portion of the nail plate.



Fig. 71.4 Onychomadesis of the fingernails following hand-foot-and-mouth disease due to coxsackievirus A6 infection.

Onychomadesis (nail shedding)

Key features

- Proximal detachment of the nail that is most often due to trauma
- Similar involvement of multiple digits suggests a systemic cause

The term *onychomadesis* describes the detachment of the nail plate from the proximal nail fold and is due to a severe insult that produces a complete arrest of nail matrix activity. Onychomadesis appears as a sulcus that replaces the proximal nail plate. The causes of onychomadesis include those that produce Beau's lines (see above)[2]. Retrospectively, it can indicate a previous infection, most typically hand-foot-and-mouth disease (Fig. 71.4), but also scarlet fever or Kawasaki disease. In addition, onychomadesis may appear in the setting of pemphigus vulgaris or Stevens–Johnson syndrome.

Pitting

Pitting describes the presence of punctate depressions of the nail plate surface that can have an irregular outline (see Fig. 71.2). Pits are due to foci of abnormal keratinization of the proximal nail matrix which result in clusters of parakeratotic cells within the dorsal nail plate. In the proximal plate, these clusters appear as nontransparent collections of scales. Over time, shedding of the parakeratotic cells leads to the appearance of pits. These pits migrate distally with nail growth.

Diseases that produce nail pitting include psoriasis, alopecia areata, and eczema. Fig. 71.2 demonstrates how patterns of the pits can differ. Psoriatic pits vary in size and depth and have an irregular distribution, whereas in patients with alopecia areata, the pits are small, superficial, and geometrically distributed.



Fig. 71.5 Trachyonychia (twenty-nail dystrophy). The nails appear to be sandpapered in a longitudinal direction.

Onychorrhexis

Onychorrhexis is characterized by longitudinal ridging and fissuring of the nail plate (see Fig. 71.2). The depth of the ridges can vary as can the extent of involvement, i.e. a portion versus the entire nail plate, and one or several nails may be involved. It is often associated with nail thinning, indicating damage to the nail matrix. Diseases commonly responsible for onychorrhexis include lichen planus (several nails), conditions that lead to impaired vascular supply, trauma, and tumors that compress the nail matrix (typically a single nail). The differential diagnosis includes the common phenomenon of increased longitudinal ridging of the nail plate that is age-related.

Trachyonychia (twenty-nail dystrophy, sandpapered nails)

Key features

- Nail roughness
- Associated with thinning, koilonychia, and cuticular hyperkeratosis
- Conditions that may cause trachyonychia include alopecia areata (common), lichen planus (uncommon), psoriasis (rare), and eczema (very rare)

Trachyonychia is a specific nail plate surface abnormality characterized by diffuse homogeneous roughness (Fig. 71.5)[3]. In most patients, the affected nails are opaque, lusterless, and rough; the nail plate surface has longitudinal ridging due to fine superficial striations distributed in a regular, parallel pattern (sandpapered nails). A less common variant, referred to as shiny trachyonychia, is characterized by multiple small punctate depressions distributed in a geometric pattern within parallel, longitudinal lines. Trachyonychia is a reflection of mild, diffuse damage to the proximal nail matrix by inflammatory disorders (see above). It can also be a presenting sign of systemic AL amyloidosis.

True leukonychia

Key features

- White opaque discoloration that is punctate, striate, or diffuse
- Punctate and striate leukonychia most often due to trauma to the distal nail matrix
- Needs to be distinguished from *apparent* leukonychia (nail bed discoloration that fades with pressure) and friable *pseudo-leukonychia* due to superficial white onychomycosis or nail fragility



Fig. 71.6 True leukonychia – diffuse variant. The nail plate is completely or almost completely opaque and white. It may be inherited due to mutations in *PLCD1*, *GJA1* (also keratoderma and hypotrichosis), or *GJB2* (also deafness, keratoderma and knuckle pads); the latter two genes encode connexins 43 and 26, respectively.

The nail plate has a normal surface but loses its transparency and looks white because of the presence of parakeratotic cells within its ventral portion. True leukonychia is caused by diseases that disturb distal nail matrix keratinization and it presents with three morphologic variants:

- **Punctate leukonychia**. The nail plate has small opaque white spots that move distally with nail growth and sometimes disappear before reaching the distal nail. It is caused by trauma and is most commonly observed in the fingernails of children.
- **Striate leukonychia**. The nail plate has one or more transverse, opaque white, parallel lines that migrate distally with nail growth. It is frequently observed in the fingernails of women, due to matrix trauma secondary to manicures. Striate leukonychia may also occur in great toenails as a consequence of trauma from shoes. It is also typical of Mees' lines, the white transverse bands seen in arsenic and thallium poisoning[4].
- **Diffuse leukonychia (porcelain nails, leukonychia totalis)**. The nail plate is completely or almost completely opaque and white (Fig. 71.6). Diffuse true leukonychia is rare and may result from mutations in *PLCD1* (encodes phosphoinositide-specific phospholipase C delta 1 subunit, a key enzyme in phosphoinositide metabolism expressed in the nail matrix) or *GJA1* (encodes connexin 43). Patients with *GJA1* mutations also have keratoderma and hypotrichosis. Bart–Pumphrey syndrome, in which patients have deafness, knuckle pads, and palmoplantar keratoderma in addition to leukonychia, is due to mutations in *GJB2* (encodes connexin 26; see Ch. 58).

Koilonychia (spoon nails)

The nail plate is thinned and depressed centrally with upward eversion of its lateral and distal edges, leading to a concave spoon-like shape (see Fig. 71.2). Koilonychia, especially of the 2nd–4th toes in young children (1–4 years of age), is physiologic and eventually resolves spontaneously. Isolated koilonychia is unusual and occurs in association with severe iron deficiency[5] or from contact with chemicals that damage the nail plate. More commonly, koilonychia accompanies other nail abnormalities (e.g. trachyonychia), including in the setting of inflammatory diseases such as lichen planus.

Nail Signs Due to Nail Bed Disorders

Onycholysis

The distal nail plate is detached from the nail bed and usually appears white because of the presence of air in the subungual space. If an exogenous pigment is present, the nail may appear yellow (fungi and exudate) to green–black (pyocyanin). In addition to environmental trauma, the nail bed disorders that most commonly produce onycholysis are psoriasis and onychomycosis (Fig. 71.7). Drug-induced onycholysis/photo-onycholysis involves several nails and may have associated subungual hemorrhage (e.g. taxanes)[6].

Subungual hyperkeratosis

The nail plate appears thickened due to an accumulation of subungual scales. Subungual hyperkeratosis results from excessive proliferation of the keratinocytes in the nail bed and hyponychium. It is commonly seen in inflammatory disorders such as psoriasis and contact dermatitis as well as in distal subungual onychomycosis.

Apparent leukonychia

Key features

- White discoloration that fades with pressure
- Nail plate transparency maintained
- Often due to drugs (e.g. chemotherapeutic agents) or systemic diseases (e.g. hypoalbuminemia)

The nails appear white because of abnormalities in the color of the nail bed and this is usually due to nail bed edema. Apparent leukonychia does *not* move distally with nail growth and the white discoloration fades with pressure (see Fig. 71.2). See section on Systemic Diseases for discussion of the three major forms.

Splinter hemorrhages

Splinter hemorrhages appear as one or more red–brown to purple–black, thin longitudinal lines, and they are most commonly seen in the distal portion of the nail (see Fig. 71.2). The shape of the subungual hemorrhages is due to the longitudinal orientation of nail bed capillaries. Onychoscopy allows better visualization of the hemorrhages which typically have a deep red to black color with peripheral fading.

The most common cause of splinter hemorrhages is trauma, followed by psoriasis, onychomycosis, and occasionally medications. Proximal splinters are rare and possible indicators of systemic diseases, including endocarditis (infectious and marantic), vasculitis (including septic vasculitis), trichinosis, and the antiphospholipid antibody syndrome.

Approximately 30% of patients with tuberous sclerosis complex have "red comets", i.e. short red longitudinal streaks of the nail with an enlarged distal end (see Fig. 61.17)[7]. They are partially blanchable and are thought to represent telangiectasias plus extravasated blood.

Nail Signs Due to Deposition of Pigment

Key features

- Exogenous → convex proximal border
- Endogenous → concave proximal border (distally convex)
- Subungual deposition → nail bed discoloration with a transparent nail plate

Causes of nail pigmentation include: (1) staining from external pigment; (2) pigment under the nail plate or in the nail bed dermis; and (3) deposition of pigment within the nail plate. Nail pigmentation from *external* staining typically follows the shape of the proximal nail fold. Common examples are yellow–brown nail discoloration due to nicotine in smokers or darkening of the nail plate due to hair dyes in hairdressers. *Subungual* deposition of pigment is often seen with *Pseudomonas* colonization, where the green discoloration of the nail results from the production of pyocyanin by the bacteria. Dermatophytes usually cause a yellow–white subungual color. Occasionally, there can be deposition of heavy metals or medications (e.g. minocycline) within the nail bed dermis. In melanonychia, the nail appears brown–black due to the incorporation of nail matrix-produced melanin into the *nail plate* itself (see below).

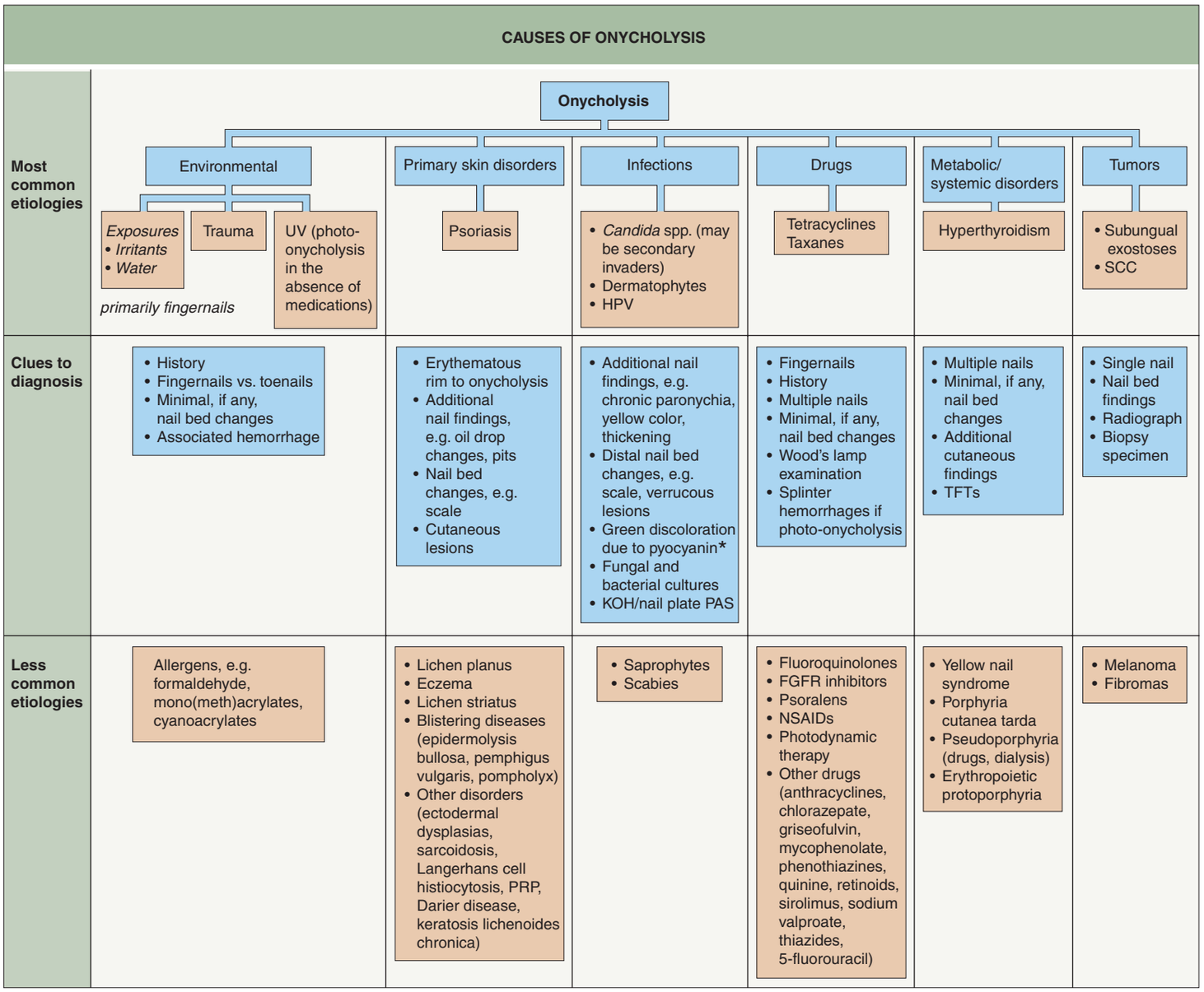


Fig. 71.7 Causes of onycholysis. *Due to secondary colonization with *Pseudomonas aeruginosa*. Serrated onycholysis is a characteristic finding in onychomycosis. FGFR, fibroblast growth factor receptor; HPV, human papillomavirus infection; NSAIDs, nonsteroidal anti-inflammatory drugs; PRP, pityriasis rubra pilaris; PAS, periodic acid Schiff (stain); SCC, squamous cell carcinoma; TFTs, thyroid function tests.

Longitudinal melanonychia

Key features

- Longitudinal brown to black band extending from the proximal nail fold to the distal margin
- Common in darkly pigmented individuals
- Single band may be a sign of melanocyte activation or proliferation (nevus, melanoma)
- Multiple bands point to physiologic, trauma/onychotillomania, drugs, or systemic disease

Longitudinal melanonychia results from melanin production by nail matrix melanocytes and is most commonly due to simple activation of these melanocytes. It can also result from melanocyte hyperplasia as is found in a lentigo, nevus, or melanoma[8]. Clinically, melanonychia presents as one or more longitudinal pigmented bands extending from the proximal nail fold to the distal margin (Fig. 71.8). The band of melanonychia can vary in color from light brown to black and the pigmentation may be homogeneous or variable. The width ranges from a few millimeters to the width of the whole nail. Melanonychia of several digits is usually due to melanocyte activation and is common in patients with darkly pigmented skin (Table 71.2). When melanonychia presents during adulthood in a single digit and there are no systemic or local causative factors, it is important to consider the possibility of nail melanoma. Fig. 71.9 outlines an approach to the patient with longitudinal melanonychia.

Dermoscopic criteria for benign and malignant nail melanocytic lesions have been proposed[9], but nail dermoscopy is not always feasible nor is it completely reliable in the evaluation of nail pigmentation[10]. For example, it cannot be performed when the nail is totally black or very thick such that the lines and borders appear blurred. Additionally, dermoscopic evaluation may give false results, as irregular lines may sometimes be seen with benign pigmentation, especially in children[11]. In addition, hyponychial brush pigmentation (distal fibrillar pattern) is seen in 25%–30% of pediatric patients with longitudinal melanonychia, especially if congenital or early-onset. Histopathologic examination, when clinically warranted, remains the gold standard for the evaluation of nail pigmentation. A detailed description of biopsy procedures for longitudinal melanonychia is found in Chapter 149.

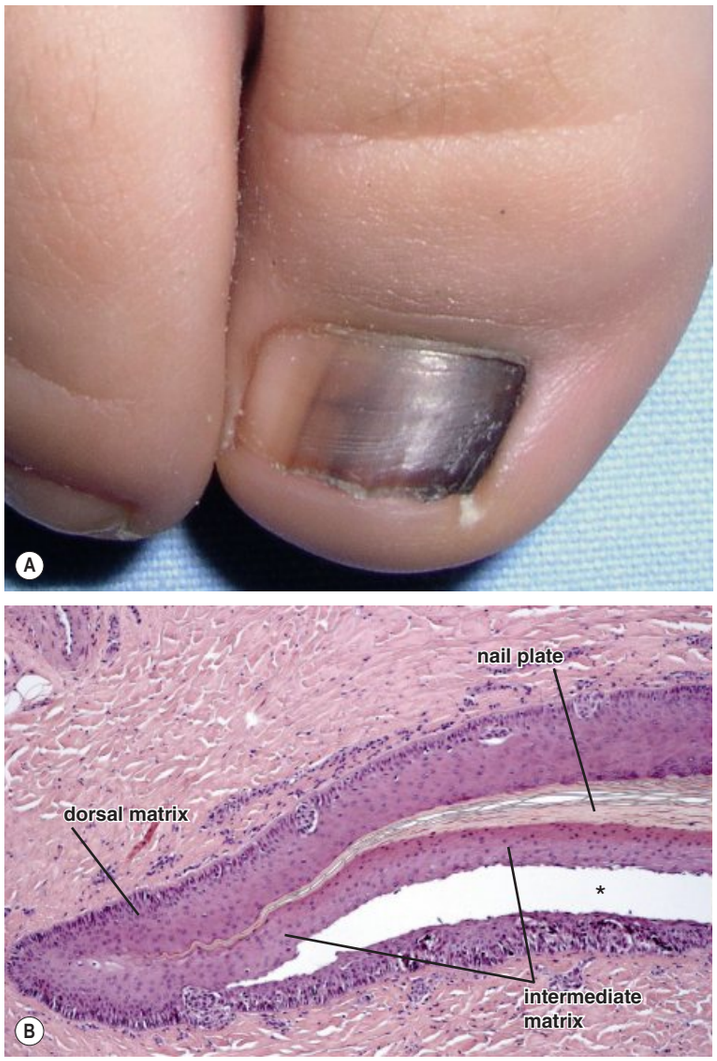


Fig. 71.8 Longitudinal melanonychia due to a congenital melanocytic nevus of the nail matrix. A The pigmentation involves approximately 75% of the nail plate and the color varies from light brown to black. **B** The biopsy specimen shows nests of melanocytes within the basal layer and lower portion of the nail matrix epithelium. The cleft (*) represents an artifact.

Green nail syndrome

The yellow–green to green–black nail plate discoloration is due to the production of the pigments pyocyanin and pyoverdin by *Pseudomonas aeruginosa* (see Ch. 74). This discoloration is most often present in the subungual space created by onycholysis and less often in the lateral nail plate in the setting of chronic paronychia. Predisposing factors include prolonged exposure to water, use of detergents and soaps, nail trauma, and other causes of onycholysis or paronychia. Not surprisingly, this disorder is seen in barbers, dishwashers, bakers, and medical personnel.

Pseudomonas colonization can be eliminated from the nail surface by applying a few drops of 2% sodium hypochlorite solution (or household chlorine bleach diluted 1 : 4 in water) and from the subungual space by soaking the affected digits in the same solution for 5 minutes per day for 20–30 days. The underlying nail disorder must also be addressed, e.g. clipping back the detached nail plate if there is onycholysis.

CONGENITAL AND HEREDITARY NAIL DISEASES

The congenital and hereditary nail diseases include a number of conditions in which nail abnormalities may be present at birth or develop during infancy. A delayed onset can also occur as in Darier disease. In some patients, the nail abnormalities are key features for the diagnosis of genetic syndromes, e.g. congenital anonychia due to mutations in the gene that encodes R-spondin 4 (*RSPO4*) or PLACK syndrome in which there is peeling skin, leukonychia, knuckle pads, and acral keratoses (Table 71.3).

CAUSES OF LONGITUDINAL MELANONYCHIA	
Melanocyte activation	Racial Trauma • manicure • nail biting/onychotillomania • friction, primarily in toenails Drugs • cancer chemotherapeutic agents • zidovudine (AZT) • psoralens Radiation Pregnancy Laugier–Hunziker syndrome Peutz–Jeghers syndrome Addison disease HIV infection Postinflammatory • lichen planus • pustular psoriasis, psoriasis • onychomycosis (*T. rubrum* and *Scytalidium* spp.) • cutaneous lupus erythematosus
Non-melanocytic tumors	Bowen disease Onychopapilloma Onychomatricoma
Melanocyte hyperplasia/ neoplasia	Nail matrix lentigo Nail matrix nevus Nail matrix melanoma

Table 71.2 Causes of longitudinal melanonychia.

Congenital Malalignment of the Great Toenails

Congenital malalignment of the great toenails is possibly caused by an abnormality in the ligament that connects the matrix to the periosteum of the distal phalanx. The nail plate of the hallux is laterally deviated with respect to the longitudinal axis of the distal phalanx. This results in nail matrix damage with Beau's lines and onychomadesis (Fig. 71.10). The nail plate is often thickened and transversely overcurved. Congenital malalignment of the great toenails is frequently bilateral and is the most common cause of ingrown toenails in children and adolescents.

Congenital Hypertrophy of the Lateral Fold of the Hallux

Hypertrophic lateral nail folds are usually present at birth. There is an overgrowth of the soft tissue of the internal portion of the lateral nail fold, resulting in a hypertrophic lip that partially covers the nail plate. This abnormal growth may deviate the nail laterally and/or cause nail embedding with an acute inflammatory reaction and pain. The abnormality is usually bilateral and may regress spontaneously after a few years[12].

Racquet Thumbs (Brachyonychia)

Racquet thumb is a common congenital malformation due to shortening of the distal phalanx. It is usually inherited as an autosomal dominant trait. The nail is shortened and abnormally wide (see Fig. 71.2). Racquet nails are usually an isolated finding and radiologic examination demonstrates a short distal phalanx.

Nail–Patella Syndrome (Oncho-Osteodysplasia; Fong Disease)

Nail–patella syndrome is an autosomal dominantly inherited condition due to mutations in *LMX1B*, which encodes a transcription factor that regulates collagen synthesis. The condition most frequently involves the thumb and may also involve the other fingers but to a lesser extent

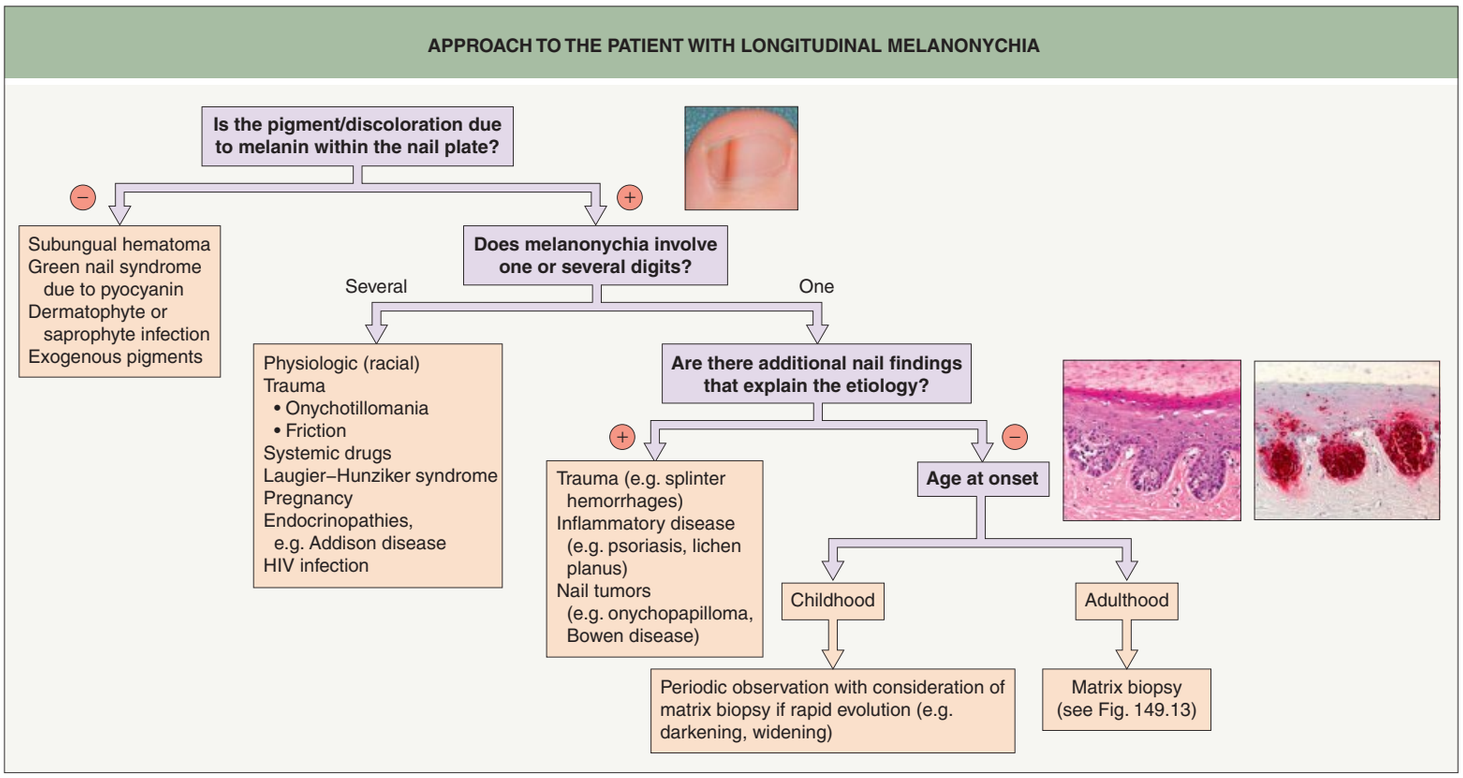


Fig. 71.9 Approach to the patient with longitudinal melanonychia. See Table 71.2 for a more extensive list of etiologies.

SELECTED HEREDITARY DISORDERS OF THE NAILS		
Disorder	**Mode of inheritance**	**Gene or gene product**
Anonychia congenita	AR	R-spondin family, member 4
Isolated AR nail dysplasia	AR	Frizzled 6
Isolated congenital nail clubbing	AR	Hydroxyprostaglandin dehydrogenase 15-(NAD)
Isolated toenail dystrophy	AD	Collagen VII, α1 chain
Leukonychia totalis	AD, AR	Phospholipase C delta 1 Connexin 43
Bart-Pumphrey syndrome	AD	Connexin 26
PLACK syndrome	AR	Calpastatin
Nail–patella syndrome	AD	LIM homeobox transcription factor 1β
Pachyonychia congenita-6a	AD	Keratin 6a
Pachyonychia congenita-16	AD	Keratin 16
Pachyonychia congenita-6b	AD	Keratin 6b
Pachyonychia congenita-17	AD	Keratin 17
Pachyonychia congenita-6c (mild nail involvement, limited to toenails)	AD	Keratin 6c
Tricho-rhino-phalangeal syndrome 1	AD	*TRPS1* (zinc finger protein)

Table 71.3 Selected hereditary disorders of the nails. Nail abnormalities can also be observed in patients with disorders of keratinization, ectodermal dysplasias, and epidermolysis bullosa. Pachydermoperiostosis is discussed in Ch. 98. PLACK, peeling skin, leukonychia, acral punctate keratoses, cheilitis, and knuckle pads.

(Fig. 71.11). The nails are absent or hypoplastic, and the dystrophy is usually more marked on the radial side of the digit. A triangle-shaped lunula is commonly observed. The nail changes are typically associated with bony abnormalities, including absent or hypoplastic



Fig. 71.10 Congenital malalignment of the great toenails. The longitudinal axis of the nail plate is deviated laterally. Note the Beau's lines and initial lateral ingrowing of the nail plate.

patellae, radial head dysplasia, and iliac crest exostoses ("horns"). In children, the diagnosis is best confirmed by the presence of iliac horns on pelvic X-ray.

Nephropathy develops in ~40% of patients. This leads to renal insufficiency in up to 8% of patients.

Epidermolysis Bullosa

Nail abnormalities are common in all forms of epidermolysis bullosa (EB), and nail involvement is one of the items scored to assess degree of severity of EB[13]. Repeated, trauma-induced blistering produces onycholysis with shortening and thickening of the nail due to nail bed scarring. Involvement of the matrix can result in nail thinning and atrophy as well as pterygium. Dystrophic or absent nails with periungual granulation tissue are characteristic of most subtypes of junctional EB and laryngo-onycho-cutaneous syndrome.



Fig. 71.11 Nail hypoplasia in nail–patella syndrome. There is hypoplasia of the nails of the first and second digits. This gradient of severity of nail involvement is characteristic. Note the triangular lunulae of the third and fourth fingernails.

Ectodermal Dysplasias

Nail abnormalities are an important sign in many of the ectodermal dysplasia syndromes, where they are associated with hair, teeth, and/or eccrine gland abnormalities (see Ch. 63). Most frequently, the nails are short and thickened with onycholysis. All the fingernails and toenails are usually affected.

Pachyonychia Congenita

Patients with pachyonychia congenita (PC) are currently classified on the basis of the mutated keratin gene (*KRT*). PC-K6a, PC-K6b, PC-K16, and PC-K17 are due to dominant-negative mutations in *KRT6a*, *KRT6b*, *KRT16*, and *KRT17*, respectively. *KRT6c* mutations can lead to both isolated palmoplantar keratoderma and PC (see Ch. 58).

Nail abnormalities are frequently present and in general are more marked in PC-K6a and PC-K16. However, the number of nails affected can vary and in some patients with specific mutations in PC-K16, the fingernails may be spared. The characteristic finding is a thickened nail with an increased transverse curvature due to severe nail bed hyperkeratosis (see Figs. 71.2 & 58.12). Affected nails are extremely hard and difficult to trim. Associated findings include hyperhidrosis, oral leukokeratosis, follicular hyperkeratosis, hoarseness, and palmoplantar keratoderma, with pain on ambulation. Multiple pilosebaceous cysts are observed most frequently in PC-K17. There are case reports of the successful use of EGFR inhibitors (e.g. oral erlotinib) that target the overactive EGFR signaling observed in pachyonychia congenita[13a].

Darier Disease (Follicular Dyskeratosis)

Key features

- Red and white longitudinal streaks
- V-shaped indentation (notching) of the distal margin
- Giant cells in the nail bed epithelium

Nail abnormalities of Darier disease are both common and diagnostic. The nail plate has multiple red and white longitudinal streaks (Fig. 71.12). Distally, wedge-shaped subungual hyperkeratosis and fissuring of the free margin of the nail plate are also seen (see Fig. 71.2). The latter occur in conjunction with the white and red bands. Similar nail abnormalities may be seen in patients with Hailey–Hailey disease.

A single, red longitudinal band (longitudinal erythronychia) with distal subungual hyperkeratosis is not sufficient for diagnosing Darier disease of the nails, since single bands may be due to a subungual benign tumor (e.g. onychopapilloma, glomus tumor) and, less often, Bowen disease[14].



Fig. 71.12 Darier disease. Longitudinal red and white streaks, fissuring, and V-shaped notching of the distal margin accompanied by focal subungual hyperkeratosis.

THE NAIL IN DERMATOLOGIC DISEASES

A number of skin diseases have associated nail abnormalities that often aid in establishing the proper diagnosis.

Psoriasis

Key features

- Several nails affected
- Diagnostic signs (usually fingernails): irregular pitting, "oil drop" sign (salmon patch), onycholysis with an erythematous border
- In toenails, psoriasis is usually clinically indistinguishable from onychomycosis
- Often associated with psoriatic arthropathy
- The Koebner phenomenon worsens nail symptoms

Nail abnormalities are present in up to 50% of patients with psoriasis and may be the only manifestation of the disease. Nail psoriasis is often associated with psoriatic arthritis and enthesitis[15]. Clinical findings that are diagnostic for nail psoriasis include irregular pitting, nail bed "oil drops", and onycholysis with an erythematous border. These signs are often seen together and are usually localized to the fingernails. Psoriatic pits are large, deep, and irregularly scattered within the nail plate (see Fig. 71.2); they may be covered by whitish, easily detachable scales. The "oil drop" sign (salmon patch) appears as an irregular area of yellow–orange discoloration visible through the nail plate (Fig. 71.13). Onycholysis surrounded by an erythematous border is also typical in nail psoriasis. Patients with psoriasis often have other nail abnormalities that are not diagnostic, as they are commonly seen in other conditions. These include splinter hemorrhages, subungual hyperkeratosis, nail plate thickening and crumbling, and paronychia.

Diseases that should be differentiated from nail psoriasis are listed in Table 71.4.

Treatment

Nail psoriasis usually does not respond to topical treatment and can be aggravated by sun exposure. Treatment measures are reviewed in Table 71.5.

Acrodermatitis Continua of Hallopeau (Hallopeau's Acrodermatitis, Dermatitis Repens)

In most patients, a single digit is involved. There are recurrent episodes of acute painful inflammation with pustules around and under the nail plate (Fig. 71.14). In addition, onycholysis as well as scaling of the nail bed and periungual skin may be seen[16]. Acrodermatitis continua of the



Fig. 71.13 Nail psoriasis. The nails show "oil drop" changes (salmon patches) and onycholysis with an erythematous border.

DIFFERENTIAL DIAGNOSIS OF NAIL PSORIASIS	
Disorder	**Comments**
Onychomycosis	• Psoriasis of the toenails may be difficult to distinguish from onychomycosis without mycologic or histologic examination of nail clippings
Idiopathic or traumatic onycholysis	• The area of onycholysis is not surrounded by erythema and there is an absence of subungual hyperkeratosis (see Fig. 71.7) • By dermoscopy, there is a linear proximal edge (in onychomycosis, this edge is ragged with spikes)
Alopecia areata	• Pits are small and geometrically distributed (see Fig. 71.2)
Acrokeratosis paraneoplastica (Bazex syndrome; paraneoplastic acrokeratosis)	• The psoriasiform eruption has a typical acral distribution with involvement of the nose and ears

Table 71.4 Differential diagnosis of nail psoriasis. Additional entities to consider are pityriasis rubra pilaris (may have subungual hyperkeratosis, onycholysis, splinter hemorrhages, longitudinal ridging) and lichen planus.

nail is, in most cases, not associated with cutaneous plaques of psoriasis vulgaris. Occasionally, proximal spread of the disease or acro-osteolysis of the distal phalanx occurs.

The differential diagnosis of acrodermatitis continua is outlined in Table 71.6. Of note, patients with palmoplantar or generalized pustular psoriasis may develop acute inflammation of multiple nails with pustule formation.

Treatment

- Topical: vitamin D_3 analogues (calcipotriene [calcipotriol], calcitriol), or the combination of calcipotriene plus a class I corticosteroid. Distal nail bed disease is most easily treated with a solution or lotion as the vehicle.
- Injection of corticosteroids into the proximal (matrix disease) or lateral nail folds (nail bed disease) of 1–4 digits.
- Systemic (severe cases): acitretin (0.3 mg/kg/day for 4–6 months), methotrexate (15 mg/week for 6–12 months), targeted immunomodulators ("biologics", e.g. ixekizumab)

Parakeratosis Pustulosa

Parakeratosis pustulosa is seen exclusively in children and is usually limited to one digit, most often the thumb or index finger. Nail changes, in particular distal onycholysis and subungual hyperkeratosis, are accompanied by psoriasiform lesions of the fingertip. The disease usually regresses spontaneously, but some children develop psoriasis.

THERAPEUTIC LADDER FOR NAIL PSORIASIS
Topical therapies
• Avoid trauma (3) • Clip onycholytic part of nail – nail bed psoriasis (3) • Topical vitamin D_3 analogues: calcipotriene (calcipotriol) – nail bed psoriasis (2) • Topical tazarotene* 0.1% gel – nail bed psoriasis (2) • Topical calcipotriene plus Class I corticosteroid ointment – nail bed psoriasis (2) • Topical tacrolimus 0.1% ointment – nail bed psoriasis (3)
Intralesional therapies
• Intralesional corticosteroid (e.g. 2.5–10 mg/ml triamcinolone acetonide in saline) – nail matrix psoriasis (1)
Systemic therapies

• Acitretin (0.2–0.4 mg/kg/day) – nail matrix and nail bed psoriasis (1)
• Methotrexate (15 mg once weekly) – if indicated for additional manifestations (2)
• Targeted immunomodulators – if indicated for additional manifestations (1):
  • IL-17 inhibitors (e.g. ixekizumab, secukinumab)
  • TNF inhibitors (e.g. etanercept, adalimumab, infliximab, certolizumab, golimumab)
  • IL-12/23 or -23 inhibitors (e.g. ustekinumab, guselkumab)
  • Janus kinase inhibitor (e.g. tofacitinib, deucravacitinib)
  • PDE-4 inhibitors (apremilast)
• Cyclosporine – if indicated for additional manifestations (2)

*May be used in combination with topical corticosteroids.

Table 71.5 Therapeutic ladder for nail psoriasis. If nail involvement is mild or affecting relatively few nails (≤3), quality of life is not significantly impacted, and psoriatic arthritis is absent, then topical therapies are typically first-line therapeutic options. Systemic therapies are best considered when nail involvement is more severe or numerous nails involved (>3), topical therapy has failed, quality of life is impaired, or psoriatic arthritis or other manifestations of psoriasis are present. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. *Based on Rigopoulos D, Baran R, Chiheb S, et al. Recommendations for the definition, evaluation, and treatment of nail psoriasis in adult patients with no or mild skin psoriasis. A dermatologist and nail expert group consensus. J Am Acad Dermatol 2019;81:228–40.*



Fig. 71.14 Acrodermatitis continua of Hallopeau. Recurrent pustular eruption of the nail bed and distal finger.

Treatment

Treatment includes topical corticosteroids and/or calcipotriene.

Lichen Planus

Nail abnormalities are present in ~10% of patients with lichen planus (see Fig. 11.15). However, nail lichen planus is most frequently seen in the absence of skin, scalp, or mucosal involvement. Clinical findings that are diagnostic include nail thinning, longitudinal ridging and fissuring, and dorsal pterygium (due to scarring) (Fig. 71.15)[17]. The combination of

DIFFERENTIAL DIAGNOSIS OF ACRODERMATITIS CONTINUA OF HALLOPEAU	
Disorder	**Comments**
Acute contact dermatitis	• Lesions are usually vesicular rather than pustular, with palmar and/or plantar involvement
Bacterial or viral paronychia	• A relapsing course is not typical of bacterial infection; relapses are seen in HSV infection, but the nail heals completely between episodes
Onychomycosis due to non-dermatophyte molds	• May be associated with periungual or subungual inflammation and a purulent discharge • Toenails are most commonly affected and the nail shows signs of fungal infection (e.g. onycholysis, subungual hyperkeratosis, yellow–orange discoloration of the nail plate) • KOH and fungal culture required for distinction
Parakeratosis pustulosa	• Favors young children (females > males) • Generally painless • Pustules are transient and appear early in course

Table 71.6 Differential diagnosis of acrodermatitis continua of Hallopeau.



Fig. 71.15 Nail lichen planus. Note the nail thinning, atrophy, and dorsal pterygium. The index finger has an "angel's wings" deformity.

fissuring plus atrophy can lead to a deformity likened to "angel's wings" and when the nail is viewed *en face* it has been likened to a "pup tent".

Several nails are usually affected. The presence of onychorrhexis and thinning indicates matrix involvement and the need for prompt treatment to avoid scarring. Dorsal pterygium results from adhesion of the proximal nail fold to the nail bed due to matrix destruction and disappearance of the nail plate. Nail bed lichen planus produces nonspecific nail changes such as onycholysis, nail thickening, and yellow discoloration. The toenails can present with abnormalities that resemble those seen in the yellow nail syndrome.

When isolated, this diagnosis may be difficult to establish, and histologic evaluation is required. The differential diagnosis of nail lichen planus is outlined in Table 71.7.

Treatment

Treatment with systemic corticosteroids may be required to avoid pterygium formation. Intralesional injections of corticosteroid (2.5–5 mg/ml triamcinolone acetonide in saline) may be utilized when the disease involves a few nails[18]. Additional treatments for lichen planus are outlined in Table 11.5.

Trachyonychia (Twenty-Nail Dystrophy, Sandpapered Nails)

In trachyonychia, there is nail plate roughness due primarily to excessive longitudinal ridging[3]. Several nails are usually affected, and in some patients, all the nails are dystrophic. Trachyonychia may be idiopathic or associated with an inflammatory skin disease, in particular alopecia areata (12% of children and 3% of adults with severe alopecia areata).

DIFFERENTIAL DIAGNOSIS OF NAIL LICHEN PLANUS	
Disorder	**Comments**
Systemic amyloidosis (AL)	• Thinning and fissuring are associated with splinter hemorrhages • Histologic examination demonstrates amyloid deposits within the nail matrix and nail bed dermis
Lichen striatus	• The lichenoid nail changes are restricted to one or two digits and often limited to one side of the nail plate
Dyskeratosis congenita	• Lichenoid nail changes are associated with oral leukoplakia and reticulated hyperpigmentation
Graft-versus-host disease	• Similar nail changes, but specific clinical setting and additional cutaneous manifestations
Nail pterygium due to bullous diseases	• The history differs and there are often associated cutaneous and/or mucosal lesions
Nail pterygium due to digital ischemia	• The digits are typically cold and there is a history of Raynaud phenomenon
Additional entities: psoriasis, onychomycosis, and yellow nail syndrome	

Table 71.7 Differential diagnosis of nail lichen planus.

In *opaque* trachyonychia, the nails appear lusterless and give the impression of having been sandpapered in a longitudinal direction, i.e. vertically striated (see Fig. 71.5). *Shiny* trachyonychia is less severe and the nails are rough because of multiple small punctate depressions distributed in a geometric pattern within parallel, longitudinal lines. The cuticles are often hyperkeratotic. Trachyonychia is fairly asymptomatic and patients or their parents primarily complain of brittleness and the cosmetic appearance. In addition to alopecia areata, trachyonychia is occasionally caused by several inflammatory diseases that mildly disturb nail matrix keratinization, including lichen planus, eczema, and psoriasis. A nail biopsy is not recommended because of the benign nature of the disease and the tendency for the majority of patients to spontaneously improve.

Systemic corticosteroids and systemic retinoids can improve associated trachyonychia when used to treat hair and cutaneous manifestations in patients with alopecia areata and psoriasis, respectively. Janus kinase inhibitors (e.g. tofacitinib, baricitinib) may also lead to improvement.

Alopecia Areata

Nail abnormalities are present in ~20% of adults and 50% of children with alopecia areata. Signs that are characteristic of nail alopecia areata include geometric pitting and trachyonychia. The pits are small, superficial, and regularly distributed in a geometric pattern (grid-like; see Fig. 71.2). Additional nail abnormalities observed in alopecia areata include punctate leukonychia, erythema of the lunula, and onychomadesis. Trachyonychia is more common in children and most frequently seen in male patients with alopecia totalis or universalis.

Eczema (Dermatitis)

Hand eczema is often associated with nail changes. In acute eczema, there are vesicles and erythema of the proximal nail fold and the hyponychium. Nail matrix damage produces irregular pitting and Beau's lines; onychomadesis can occur in severe cases. Chronic eczema frequently localizes to the hyponychium, resulting in subungual hyperkeratosis, onycholysis, and fissuring of the hyponychium. Chronic eczema of the proximal nail fold can lead to chronic paronychia. In atopic dermatitis, the nail plate frequently shows mild superficial abnormalities such as irregular pits and Beau's lines. Controlling the skin disease results in gradual improvement of the nails.

THE NAIL IN SYSTEMIC DISEASES

Abnormalities of the nails have been anecdotally reported in a number of systemic diseases, but most of these abnormalities are nonspecific. In this chapter, we will discuss only those nail changes that are useful in the diagnosis of systemic disorders.

SYSTEMIC CONDITIONS ASSOCIATED WITH CLUBBING	
Congenital/genetic	
Cardiovascular disorders	Congenital heart disease (usually cyanotic) Pulmonary arteriovenous malformations (often in the setting of hereditary hemorrhagic telangiectasia)
Bronchopulmonary disease	Cystic fibrosis
Other	Pachydermoperiostosis (primary hypertrophic osteoarthropathy; see Ch. 98)
Acquired	
Bronchopulmonary diseases	Neoplasms (primary or metastatic cancers, pleural tumors) Chronic infections (abscesses of the lungs, tuberculosis) Bronchiectasis Pulmonary fibrosis Sarcoidosis
Cardiovascular diseases	Aneurysm or dialysis fistula (unilateral clubbing) Congestive heart failure Bacterial endocarditis
Gastrointestinal diseases	Inflammatory bowel disease Carcinomas Infestations, e.g. amebiasis, ascariasis Liver disorders, e.g. chronic active hepatitis, cirrhosis
Infection	HIV infection Arterial graft sepsis (clubbing limited to perfused extremities)
Endocrine diseases	Thyroid disease (primarily hyperthyroidism)* Secondary hyperparathyroidism
Other	POEMS syndrome Laxative abuse Hemiplegia (unilateral) Trauma, median nerve injury (unidigital)

*Most often in the setting of thyroid acropachy (clubbing together with digital swelling and periosteal reaction) in patients with autoimmune thyroid disease.

Table 71.8 Systemic conditions associated with clubbing.

Clubbing (Watch-Glass Nails, Hippocratic Fingers, Drumstick Fingers)

First described by Hippocrates in the first century BCE, clubbing may be congenital or acquired. Acquired clubbing is uncommon and in 80% of patients is associated with pulmonary diseases.

Clubbing is caused by enlargement of the soft tissue of the distal digit, leading to a bulbous appearance. The nail plate is enlarged and excessively curved, with widening of the angle between the proximal nail fold and the nail plate to greater than 180° (Lovibond's sign; see Fig. 71.2). In hypertrophic osteoarthropathy, clubbing is associated with hypertrophy of the extremities and painful pseudoinflammatory joint disease. Systemic conditions associated with clubbing are outlined in Table 71.8.

Yellow Nail Syndrome

The yellow nail syndrome was first described by Samman and White in 1964. It is uncommon and its pathogenesis is still unknown. Linear nail growth is arrested or greatly reduced. The nails are thickened and transversely and longitudinally overcurved with disappearance of the cuticle. The nail color varies from pale yellow to dark yellow–green (Fig. 71.16). Onycholysis and onychomadesis are frequently seen. In most patients, all 20 nails are involved.

Characteristically, the nail abnormalities are associated with lymphedema and respiratory tract involvement, including chronic bronchitis, bronchiectasis, sinusitis, pleural effusions, and rarely malignancies. The diagnosis of yellow nail syndrome, however, requires only the presence of the typical nail changes.



Fig. 71.16 Yellow nail syndrome. Note the overcurvature of the nail, both transversely and longitudinally, and loss of the cuticle, in addition to the yellow discoloration.



Fig. 71.17 Muehrcke's nails in a patient undergoing chemotherapy. There are multiple parallel transverse white bands that will fade with pressure (apparent leukonychia). Note the associated melanonychia.

Treatment

Treatment is not effective in all cases and must be prescribed for several months[19]:

- vitamin E 1200 IU/day
- pulse itraconazole (200 mg twice daily for 1 week a month) or fluconazole (150 mg daily for 1 week a month)

There are case reports of improvement following treatment of a coexisting malignancy.

Apparent Leukonychia

In apparent leukonychia, there is white discoloration of the nail that fades with pressure and nail transparency is maintained. On the basis of the pattern of the nail discoloration, three different types of apparent leukonychia can be distinguished.

- **Muehrcke's nails** were described by Muehrcke in 1956 in patients with hypoalbuminemia (nephrotic syndrome). They are a very common finding in patients receiving combination chemotherapy. The nail has multiple transverse whitish bands, parallel to the lunula (Fig. 71.17).

- **Half-and-half nails**. First reported by Bean in 1963, half-and-half nails are detected in up to 25% of patients with chronic renal disease who are undergoing hemodialysis. The apparent leukonychia affects the proximal half of the nail. Half-and-half nails may also be seen in normal individuals.
- **Terry's nails** were described by Terry in 1954 as a common sign of liver cirrhosis, occurring in up to 80% of patients. The leukonychia affects the whole nail except for a 1- to 2-mm distal band. Terry's nails are also frequently seen in normal individuals.

Autoimmune Connective Tissue Disorders

Abnormalities in the proximal nail fold capillaries are frequently seen in three major autoimmune connective tissue disorders[20]. Roughness, hemorrhages, and necrosis of the cuticles are common in *dermatomyositis* and *systemic sclerosis*, where capillaroscopy shows reduced capillary density in which avascular areas alternate with dilated capillary loops. In *systemic lupus erythematosus*, capillaroscopy shows a normal capillary density with dilated tortuous capillaries. Ventral pterygium (pterygium inversus unguis) is characterized by the adhesion of the distal nail plate to the hyponychium, resulting in pain during nail trimming. Ventral pterygium is a distinctive sign of systemic sclerosis related to impaired peripheral perfusion. In systemic sclerosis, ischemic changes and bone resorption may result in a parrot beak nail with bending of the nail plate around the shortened fingertip (see Fig. 43.5).

HIV Infection

Onychomycoses are common in HIV-infected patients who are in clinical stages 2 to 4 (see Ch. 78). Dermatophytes are most commonly responsible, but *Candida* spp. and molds are also often isolated[21]. Although numerous nail abnormalities have been reported in association with AIDS[22], only a few clinical entities can be considered typical of this disease.

- **Proximal subungual onychomycosis** due to *Trichophyton rubrum*. This variety of onychomycosis is considered a marker of immunosuppression and at-risk populations include solid organ transplant recipients and those with untreated HIV infection. The proximal nail plate is opaque and white due to the presence of fungi in its ventral portion (see Ch. 77).
- ***Candida* onychomycosis**. *Candida* does not invade the nail plate of immunocompetent individuals, and the diagnosis of true *Candida* onychomycosis indicates immunosuppression, including that due to HIV infection, or chronic mucocutaneous candidiasis.
- **Longitudinal melanonychia**. Usually, several nails are involved, and it is often associated with cutaneous hyperpigmentation.
- **HPV-induced squamous cell carcinoma** (SCC). Longstanding periungual warts in HIV-infected patients should always raise the suspicion of SCC and be examined histologically. HPV type 16 has most commonly been detected in such lesions.

Drug-Induced Nail Abnormalities

Drug-induced nail changes usually involve several or all nails (Table 71.9). The pathogenesis is most often toxic in nature[23].

- Cancer chemotherapeutic agents, due to their cytotoxic properties, are the most frequent cause of nail changes (see Ch. 21). These include Beau's lines, onychomadesis, fragility, onycholysis, paronychia, and vascular complications, including subungual hemorrhages, hematomas, and ischemia. Painful onycholysis with subungual hemorrhages is typically seen with taxanes (e.g. paclitaxel, docetaxel). Chemotherapy can also induce multiple bands of longitudinal or transverse melanonychia as well as diffuse nail pigmentation and Muehrcke's nails (see Fig. 71.17).
- Paronychia associated with (pseudo)pyogenic granulomas is a side effect of epidermal growth factor receptor (EGFR) inhibitors. Nail changes appear from 1 to 3 months after starting treatment and disappear after interruption of treatment. Fibroblast growth factor receptor (FGFR) inhibitors can lead to severe onycholysis while brittle nails occur in patients receiving Bruton's tyrosine kinase (BTK) inhibitors.
- Oral retinoids are frequently responsible for nail abnormalities, in particular nail fragility, paronychia, onychocryptosis, and periungual pyogenic granulomas.

DRUG-INDUCED NAIL ABNORMALITIES	
Nail abnormality	**Responsible agents**
Beau's lines and onychomadesis	Chemotherapeutic agents
True leukonychia	Chemotherapeutic agents
Nail thinning and brittleness	Chemotherapeutic agents Retinoids
Onycholysis/photo-onycholysis (see Fig. 71.7)	Chemotherapeutic agents, particularly taxanes Fibroblast growth factor receptor inhibitors Tetracyclines Psoralens NSAIDs
Apparent leukonychia (e.g. Muehrcke's nails)	Chemotherapeutic agents
Melanonychia	Chemotherapeutic agents Psoralens Zidovudine (AZT)
Discoloration (non-melanin)	Minocycline Antimalarials Gold Silver
Paronychia and periungual pyogenic granulomas	Retinoids Antiretroviral drugs (e.g. indinavir, efavirenz, lamivudine) Epidermal growth factor receptor (EGFR) inhibitors (e.g. cetuximab, gefitinib, erlotinib, panitumumab) Methotrexate Capecitabine (prodrug of 5-fluorouracil) Sirolimus, everolimus
Ischemic changes	β-blockers Bleomycin
Splinter hemorrhages	Tyrosine kinase inhibitors and VEGF inhibitors
Pincer nails	β-blockers
Lunula discoloration	Tetracyclines (yellow), hydroxyurea (blue), AZT (blue), silver (blue–gray), lithium (brown–black)

Table 71.9 Drug-induced nail abnormalities. VEGF, vascular endothelial growth factor.



Fig. 71.18 Multiple periungual pyogenic granulomas in a patient taking indinavir.

- Antiretroviral drugs can cause nail pigmentation, paronychia, and pyogenic granulomas (Fig. 71.18).
- Although uncommon, photo-onycholysis is a characteristic side effect of tetracyclines, psoralens, and photodynamic therapy (see Fig. 71.7).
- Certain drugs (e.g. anticoagulants, anticonvulsants) taken during pregnancy may impair the development of the digits, leading to congenital nail hypoplasia.

INFECTIONS

Acute Paronychia

Key features

- Painful whitlow
- Recurrent when due to herpes simplex virus (HSV)
- Viral and bacterial cultures are mandatory

The affected digit becomes swollen, red, and painful and typically there is involvement of one of the nail folds. Compression of the nail fold may produce purulent drainage. Acute paronychia is most commonly due to bacteria, in particular *Staphylococcus aureus* or *Streptococcus pyogenes*, and it follows minor trauma to the nail. Recurrent episodes of acute paronychia in the same digit should raise the suspicion of an HSV infection. A Tzanck smear, along with PCR, direct immunofluorescence assay or viral culture, can confirm the diagnosis[24].

Treatment

Drainage of the abscess, followed by systemic or topical antibiotics or systemic antivirals when due to HSV.

Warts

Periungual warts are common in nail biters, in whom they are multiple and involve several nails (see Ch. 79). The warts appear as keratotic papules, and when localized to the proximal nail fold, they frequently produce periungual hyperkeratosis simulating a hyperkeratotic cuticle. For subclinical presentations, dermoscopy can aid in diagnosis[25]. Nail bed warts lead to uplifting of the nail plate with onycholysis and subungual hyperkeratosis. SCC can arise in or mimic a verruca; therefore, suspicious lesions must be further evaluated.

Treatment

Therapeutic options are outlined in Table 71.10.

Onychomycosis (Tinea Unguium)

See Chapter 77.

ENVIRONMENTAL NAIL DISORDERS

Brittle Nails (Fragility, Onychoschizia)

Brittle fingernails are very common and usually affect women[26]. Nail brittleness results from dehydration of the nail plate as a result of environmental factors such as frequent handwashing. In onychoschizia, there is lamellar exfoliation in which the distal nail plate splits horizontally into multiple layers (see Fig. 71.2). Other signs of nail brittleness include splitting, softening, onychorrhexis, and keratin degranulation. The latter occurs in persons who wear nail polish continuously; it is characterized by whitish discoloration and fragmentation of the superficial layers of the nail (Fig. 71.19).

Treatment

- Avoidance of water and chemical exposure.
- Biotin (2.5–5 mg/day). Inform the patient that biotin should be held for several days prior to having bloodwork done as it can interfere with tests that use biotin–streptavidin technology (e.g. TSH).
- Topical moisturizers and humectants, e.g. 12% lactic acid, 10% urea.

Chronic Paronychia

Chronic paronychia commonly involves the fingernails of adult women. Although the pathogenesis is still debated, there is accumulating evidence that the condition represents a contact reaction to irritants or allergens[27]. Occupational chronic paronychia is common in food handlers. Chronic paronychia is characterized clinically by longstanding inflammation of the proximal nail fold with erythema, edema, and absence of the cuticle. One or several fingernails are affected, in particular the thumb and second or third fingers of the dominant hand. Damage to the nail matrix results in nail plate surface abnormalities such as Beau's lines. *Pseudomonas* colonization of the brittle nail surface may induce a green discoloration. Recurrent, self-limited episodes of acute exacerbation are common.

Treatment

- Avoidance of water and chemical exposure.
- Topical corticosteroids and topical imidazoles, but not systemic antifungals.
- Topical antiseptics (e.g. 4% thymol in 95% ethanol).

Idiopathic Onycholysis

Idiopathic onycholysis frequently involves the fingernails as a consequence of repetitive water immersion and exposure to irritants (see Fig. 71.7). The affected nail is detached from the nail bed and usually appears white because of air in the subungual space. Secondary microbial colonization of the subungual space can lead to discoloration, e.g. green due to pyocyanin. An absence of subungual hyperkeratosis is characteristic.

Treatment

- Avoidance of water and chemical exposures.
- Clipping of the detached nail plate and topical antiseptics.

THERAPEUTIC LADDER FOR PERIUNGUAL WARTS ℞

- Keratolytics (2)
- Cryotherapy (2)
- Topical 0.7% cantharidin (2)
- Topical 5% imiquimod (2)
- Intralesional injection of *Candida*, *Trichophyton*, or mumps skin test antigens (1)
- Topical immunotherapy† (2)
- Topical (1%–3%) or intralesional (15 mg/ml) cidofovir (2)
- Intralesional bleomycin (2)
- Topical (5%) or intralesional 5-fluorouracil (2, 1)
- Laser: CO_2, Er:YAG, pulsed dye (2)
- Photodynamic therapy (2)
- Ablative CO_2 fractional laser followed by PDT* (2)

*With methyl 5-aminolevulinic acid and red light.
†For details, see Table 129.10.

Table 71.10 Therapeutic ladder for periungual warts. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. PDT, photodynamic therapy.



Fig. 71.19 Keratin degranulation of the fingernails due to prolonged wearing of nail lacquer. The distal nail plate is opaque and fragile due to multiple small areas of breakage on its surface.

NAIL CHANGES ASSOCIATED WITH A MANICURE OR PEDICURE	
Nail abnormality	**Etiology**
Beau's lines	Matrix damage from cuticle removal
True leukonychia (transverse)	Matrix damage from cuticle removal
Nail brittleness (onychorrhexis, onychoschizia, keratin granulation*)	Nail varnish solvents; electric drills
Nail brittleness (keratin granulation*)	Prolonged nail polish wearing
Distal onycholysis ("roller coaster")	Mechanical (nail tools utilized to clean the nail plate free edge)
Diffuse onycholysis	Mechanical (artificial nails acting as a lever)
Diffuse onycholysis	Chemical (acrylic nails, gel polish manicure)
Discoloration (yellow/orange)	Nail varnishes
Acute paronychia Chronic paronychia Periungual pyogenic granulomas Periungual warts	Periungual cuts from sharp instruments Contact allergy Constant cuticle removal Periungual wounds Mechanical trauma to the cuticle
Pterygium inversum unguis	Gel polish manicure
*Also referred to as superficial granulation.	

Table 71.11 Nail changes associated with a manicure or pedicure.

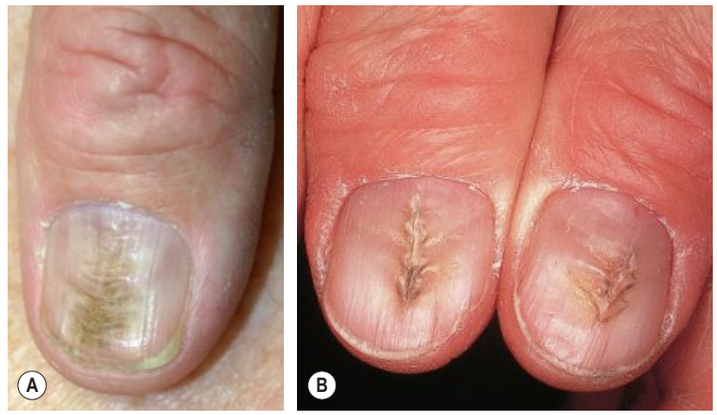


Fig. 71.20 Habit-tic deformity (A) and median canaliform dystrophy of Heller (B). A The multiple midline Beau's lines resemble a washboard. **B** A central longitudinal split with an inverted fir tree pattern. In both, deposits of exogenous pigments can be seen.



Fig. 71.21 Onychotillomania. In four of the nails, the nail plate is damaged or absent. The hemorrhagic crusts on the nail bed and proximal nail fold serve as a clue to the diagnosis.

TRAUMATIC NAIL ABNORMALITIES

Mechanical insults or exposure to chemicals can lead to nail injury. These may be accidental, self-induced, or due to attempts at adornment (e.g. manicures, pedicures; Table 71.11).

Onychotillomania

Key features

- Cuticle absent and proximal nail fold inflamed
- Nail plate surface abnormalities, e.g. midline transverse ridging
- Melanonychia
- Hemorrhages and crusts

Self-induced nail abnormalities are common, but often not recognized due to the wide range of nail signs and the difficulty in obtaining a correct clinical history.

- **Nail biting** may affect the nail plate and/or the proximal nail fold; the trauma often produces nail matrix damage with secondary nail plate abnormalities, including surface irregularities and longitudinal melanonychia.
- **Habit-tic deformity** affects the thumb and is due to the nervous habit of rubbing and pushing back the midportion of the cuticle of the thumb with the index finger. The nail plate of the thumb shows multiple midline Beau's lines that resemble a washboard (Fig. 71.20A). **Median canaliform dystrophy of Heller** (solenonychia) is considered a separate entity in which there is central longitudinal split with an inverted fir tree pattern (Fig. 71.20B); it is also probably caused by trauma.
- Nail destruction associated with psychiatric disorders. The clinical picture is variable, with nail plate destruction, hemorrhages, and periungual crusts and erosions (Fig. 71.21). Instruments (scissors, clippers, etc.) are often utilized to destroy the nails.

Treatment

- Topical preparations that taste unpleasant and bandages.
- Serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline), N-acetylcysteine.

Subungual Hematoma

Acute hematomas occur after trauma severe enough to damage subungual blood vessels, leading to accumulation of blood under the nail plate. Acute hematomas are typically associated with pain, and compression of the matrix may cause secondary nail plate dystrophy. An X-ray of the digit may be advisable to exclude a bone fracture. Repeated microtrauma or a bleeding diathesis can lead to asymptomatic small subungual hematomas of the nails that are incorporated within the ventral nail plate.

Subungual hematomas migrate distally with nail growth and this may be demonstrated by gently pushing back the cuticle. The color of subungual hematomas ranges from purple–red to black. Onychoscopy is useful for differentiating hematomas from melanin deposition (see Fig. 71.2)[28].

Treatment

Acute hematomas require prompt drainage of the blood by creating a hole through the nail plate.

Traumatic Toenail Abnormalities

Traumatic toenail abnormalities are most commonly seen in women who wear high-heeled pointed shoes, but can also be seen in athletes. They are often bilateral.

- Traumatic onycholysis of the hallux is the most common clinical presentation (Fig. 71.22). The onycholysis may be *distal*, where the detachment is caused by compression of the distal pulp by poorly fitting shoes, or *lateral*, when there is overlapping of the second toe onto the first. Clipping of the detached nail plate reveals a normal



Fig. 71.22 Traumatic onycholysis of the nail of the first toe. Age-related lateral deviation of the hallux (hallux valgus) plays a role. Although the two entities can coexist, it is often misdiagnosed as lateral onychomycosis.

nail bed. The differential diagnosis includes onychomycosis, but here the onycholysis is associated with subungual hyperkeratosis and the proximal margin of the detachment has a jagged edge by onychoscopy[29].

- Transverse leukonychia of the hallux results from repeated microtrauma by shoes to untrimmed, long, great toenails. Multiple bands of true leukonychia move distally with nail growth.
- Frictional melanonychia affects the toenails of the fourth and/or fifth digits of women. It is due to activation of nail matrix melanocytes by friction from shoes or from the adjacent digit. The bands may be multiple and black in color.
- Retronychia is caused by embedding of the nail into the proximal nail fold following trauma and may present with inflammation of the proximal nail fold.

Onychogryphosis

Onychogryphosis is common in elderly persons and almost exclusively affects the toenails, usually the hallux. The nail acquires a typical ram's horn shape due to asymmetric growth (see Fig. 71.2). The nail plate is thick, hard, and yellow–brown. Multiple transverse striations are often present. Nail hardness and self-neglect may lead to monstrous deformities.

Pincer Nails (Trumpet Nails)

Pincer nails are usually seen on the toes and may be hereditary or acquired; the latter is most commonly due to ill-fitting shoes. The nail plate displays an excessive transverse overcurvature, especially in its distal portion (see Fig. 71.2). This results in compression (pinching) of the distal nail bed and can be associated with severe pain. Subungual exostosis should be excluded by X-ray examination. Consider drug-induced pincer nails (e.g. from β-blockers) when several nails, including fingernails, are involved.

Treatment

Lateral chemical or surgical matricectomy is the treatment of choice for pincer nails (see Ch. 149).

Ingrown Toenails (Onychocryptosis)

Lateral ingrowing usually affects the hallux of young adults with congenital malalignment of the great toenails. Precipitating factors in all patients include improper or aggressive nail cutting and trauma. In addition, hyperhidrosis contributes to fragmentation of the distolateral edge. Penetration of nail plate spicules into the lateral nail fold epithelium causes painful inflammation. Chronic inflammation then leads to formation of granulation tissue that eventually undergoes epithelialization.

Distal embedding is a common complication of nail avulsion. The nail plate growth is blocked by the pulp, which forms a distal rim. Distal embedding can also occur in young infants but it resolves spontaneously.

Retronychia describes ingrowth of the proximal nail plate into the proximal nail fold, with one to three nail plates misaligned beneath the uppermost nail plate (see Fig. 71.2)[30]. There may be associated proximal nail fold erythema and swelling as well as proximal periungual pyogenic granulomas.

Treatment

- Prevention through patient education.
- Removal of the embedded spicule.
- Uplifting of the lateral nail plate with cotton, dental floss, slit tubes, or cotton casts.
- Granulation tissue may be reduced by topical antibiotics and topical corticosteroids or chemical cauterization (e.g. silver nitrate) or removed via curettage.
- Chemical (phenol, sodium hydroxide or trichloroacetic acid), laser, or excisional surgical removal of the lateral matrix is advisable in severe cases.
- In retronychia, surgical avulsion of the nail plate/s is necessary.

NAIL TUMORS

Nail surgery is discussed in Chapter 149.

Benign Tumors and Proliferations

Pyogenic granuloma (botryomycoma)

Pyogenic granulomas commonly appear within the nail apparatus, where they may be periungual or subungual and rarely under the proximal nail fold. While pyogenic granulomas of the nail unit often follow penetrating trauma, other common causes include ingrown toenails, systemic drugs (e.g. retinoids, EGFR inhibitors), peripheral nerve damage, and frictional onycholysis due to prolonged walking[31]. The tumor appears as a bleeding, friable, soft red nodule (see Fig. 71.18). When subungual, it is associated with onycholysis. The differential diagnosis includes amelanotic melanoma and treatment is surgical.

Fibromas/fibrokeratomas

Isolated periungual and subungual fibromas are not rare in the general population. Multiple lesions occur in 50% of patients with tuberous sclerosis complex (Koenen tumors). Periungual fibromas appear as pink or skin-colored, fusiform-shaped papules originating from the proximal nail fold (see Ch. 61). The fibroma may compress the nail matrix and produce a longitudinal groove in the nail plate. Subungual fibromas that grow underneath the nail plate produce longitudinal erythronychia or onycholysis. A fibrokeratoma is characterized by a hyperkeratotic tip and may be surrounded by a collarette of raised skin.

Subungual exostosis

Subungual exostoses, first described by Dupuytren in 1847, are benign bony proliferations associated with nail abnormalities. Subungual exostoses are commonly precipitated by trauma and usually seen on the great toe of young patients. An exostosis produces a hard, tender, subungual nodule that elevates the nail plate (Fig. 71.23A). The nodule may ulcerate or become hyperkeratotic. The diagnosis is confirmed by X-ray examination (Fig. 71.23B)[32] and the treatment is surgical.

Myxoid cyst (mucous cyst, digital mucous cyst)

Myxoid cysts are a common finding and favor middle-aged women (see Ch. 110). Typically located in the proximal nail fold of the fingernails, they appear as small, soft, skin-colored papulonodules that often spontaneously drain a viscous jelly-like fluid. Compression of the matrix produces nail plate depression and longitudinal grooves (Fig. 71.24). Occasionally, the cysts are subungual. These cysts are connected to the distal interphalangeal joint by a tract, and osteoarthritis of the distal joint is a frequent association[33].

Treatment

Possible treatments for myxoid cysts include sclerotherapy, cryosurgery, and intralesional corticosteroid injections. All of these procedures are

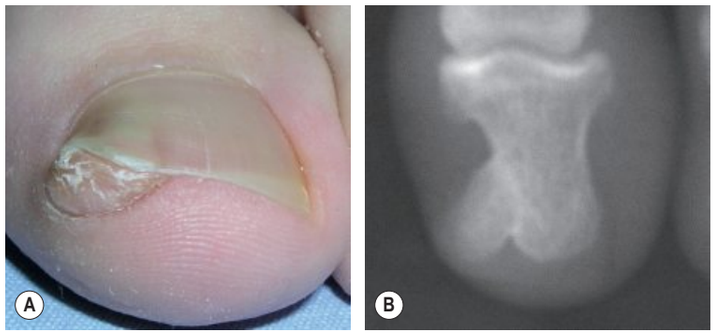


Fig. 71.23 Subungual exostosis. A Skin-colored subungual nodule elevating the nail plate. **B** Radiograph of the digit demonstrating the subungual bony proliferation.



Fig. 71.24 Myxoid cyst. The longitudinal nail groove is a result of the compression of the nail matrix by the cyst.

associated with a high frequency of relapses. Definitive cure of myxoid cysts requires a surgical procedure that includes ligation of the pedicle that connects the cyst to the joint.

Glomus tumor

A glomus tumor arises from the neuromyoarterial glomus cells of the nail bed dermis. It is typically associated with severe pain that radiates proximally and is often aggravated by physical (e.g. compression) or thermal stimuli (especially cold). Subjective symptoms typically exceed clinical signs. The tumor may not be clinically apparent or may appear as a red–bluish nail bed macule visible through the transparent nail plate (see Fig. 114.33). MRI allows the diagnosis (see Fig. 114.34).

Onychomatricoma

First described by Baran and Kint in 1992, onychomatricoma is an uncommon neoplasm that produces localized or diffuse thickening of the nail plate in which multiple longitudinal hollows contain the digitating tumor (Fig. 71.25). The affected nail is thickened and yellow–white in color, with transverse overcurvature and multiple splinter hemorrhages. In an *en face* view of the distal nail, multiple holes in the thickened free margin are typically seen (see Fig. 71.2).

Histologically, the tumor is characterized by multiple fibroepithelial projections that extend into the thickened nail plate. The tumor epithelium is identical to that of the normal nail matrix and keratinizes without a granular layer. Histopathologic examination of a simple nail clipping is sufficient for diagnosis[34].

Onychopapilloma

Onychopapilloma is a benign tumor that grows under the nail plate and has a thin filiform shape. It arises from the distal matrix/proximal



Fig. 71.25 Onychomatricoma of the left third fingernail. A longitudinal, thickened yellowish band is seen extending from the cuticle to the distal nail plate. Proximal splinter hemorrhages are also visible. Onychoscopy of the distal nail plate reveals the diagnostic finding of localized nail thickening with a honeycomb appearance (inset).



Fig. 71.26 Onychopapilloma of the left first fingernail. A thin longitudinal band of erythronychia is seen extending from the lunula. Onychoscopy reveals the crescent-shaped proximal origin of the erythronychia (lower inset) and a small subungual mass can be appreciated on the free edge of the nail (upper inset).

nail bed and extends to the distal nail margin. Small tumors produce thin longitudinal erythronychia while larger onychopapillomas induce thinning of the overlying nail plate and distal fissuring. Splinter hemorrhages are an associated finding. Examination of the free margin reveals a keratotic mass that adheres to the ventral nail plate (Fig. 71.26). Less often the tumor manifests as longitudinal leukonychia or melanonychia.

By dermoscopy, the origin (lunula) and the end (distal margin) of the thin red band can be appreciated, as can splinter hemorrhages and the distal keratotic mass. A nail clipping demonstrates a localized asymmetric keratotic thickening on the underside of the nail plate, corresponding to the location of the filiform tumor[35].

Melanocytic nevi of the nail matrix

Melanocytic nevi of the nail matrix are an uncommon cause of longitudinal melanonychia (see Table 71.2). They usually develop during childhood and often involve the fingers, especially the thumb[36,37]. Clinically, a band of melanonychia that is brown to black in color



Fig. 71.27 Bowen disease. The lateral portion of the nail plate is absent. The nail bed shows hyperkeratosis with scaling and fissuring of the epithelium.



Fig. 71.28 Amelanotic melanoma. Note the diffuse nail destruction and ulceration as well as swelling of the proximal nail fold. The tumor can resemble granulation tissue. *Courtesy Lorenzo Cerroni, MD.*

involves a portion of the nail or its entirety. The color, width, and pigment distribution may vary considerably and it is not unusual to observe fading or darkening of the pigmentation over time in an individual patient. Pigmentation of periungual tissues is also possible because nests of nevus cells can be present in the proximal nail fold or hyponychium. When dark brown or black in color, bands are often visible through the cuticle (pseudo-Hutchinson sign). The age at onset represents the most important clue to the diagnosis. Histologically, a lentigo or junctional nevus is usually seen (see Fig. 71.8B).

Treatment

Optimal management of nail matrix nevi is still debated. See Fig. 71.9 for an approach to longitudinal melanonychia, including in children.

Malignant Tumors

Malignant tumors of the nail are summarized below. For further details regarding these malignancies and their treatment, see Chapters 108 and 113.

Bowen disease (squamous cell carcinoma in situ)

Bowen disease of the nail is uncommon and is seen most often in middle-aged men. Fingers of the left hand are most commonly involved[38]. Clinically, it may be difficult to differentiate Bowen disease from warts. The affected digit shows periungual or subungual verrucous lesions with onycholysis and/or longitudinal melanonychia (Fig. 71.27). Predisposing factors include HPV infection and chronic X-ray exposure.

Keratoacanthoma

Keratoacanthoma of the nail is extremely rare and usually affects a single digit. It appears as a painful, subungual, keratotic nodule that grows rapidly over a period of weeks. Deep invasion with bone destruction frequently occurs and typically there is evidence of osteolysis on X-ray examination. A history of trauma is often reported. In contrast to cutaneous keratoacanthomas, keratoacanthomas of the nail do not regress spontaneously[39].

Squamous cell carcinoma

Squamous cell carcinoma (SCC) is the most common malignant tumor of the nail apparatus. It often affects the fingernails of middle-aged men. A number of studies have confirmed a causative role for HPV, usually HPV-16, in the development of this tumor. Clinically, it may present as slowly growing periungual or subungual verrucous mass or nodule that may ulcerate and bleed[40]. Compared to cutaneous SCC elsewhere, nail SCC tends to more quickly become invasive, but metastases are rare. Bone invasion occurs in <20% of patients and the osteolysis detected on X-ray examination is more often due to compression rather than true bone invasion.

Verrucous carcinoma (carcinoma cuniculatum, epithelioma cuniculatum)

Verrucous carcinoma is a rare, low-grade variant of SCC characterized by locally aggressive clinical behavior but low potential for metastasis. It rarely involves the nail apparatus. Clinically, the tumor appears as a rapidly growing verrucous nodule that often destroys the nail. Bone resorption is common.

Melanoma

Nail melanoma is rare, accounting for 0.7%–3.5% of all melanomas. It most frequently involves the thumb of middle-aged individuals, and patients often report a history of trauma. Diagnosis is often delayed, and in 25% of patients the tumor is amelanotic. Historically, the 5-year survival is only 15%. From a clinical standpoint, nail melanoma may have the following presentations:

- Longitudinal melanonychia[41]. Melanoma should be suspected when a single band arises during adulthood without another plausible explanation (see Fig. 71.9). The pigmented band is usually dark brown or black in color, with blurred margins and a width >3–4 mm. An ABCDEF "rule" has been proposed to aid in diagnosis[42]: A) **A**ge – peak incidence fifth to seventh decades with **A**fricans, **A**sians, and Native **A**mericans (more darkly pigmented individuals) accounting for up to one-third of all cases; B) **B**lack or **b**rown with band width of 3 mm or more; C) **C**hange in the nail or lack of improved change with treatment; D) **D**igit most commonly involved (thumb, great toe, index); E) **E**xtension of pigment onto the proximal or lateral nail fold (Hutchinson sign); and F) **F**amily or personal history of dysplastic nevus or melanoma. Except for criterion F, these represent validated clinical criteria.
  When longitudinal melanonychia is due to nail melanoma, dermoscopically the band typically has nonhomogeneous pigmentation, blurred borders, and nonparallel interrupted lines of different colors. However, for diagnosis, onychoscopy alone is not completely reliable, especially if the nails are thick or the bands are black. Moreover, sometimes the lines are regular in nail melanoma. Therefore, integration of the history, clinical appearance, and dermoscopic findings is required[9–11].
- Amelanotic nodule that ulcerates and bleeds, resembling a pyogenic granuloma (Fig. 71.28).

The presence of: (1) Hutchinson sign – pigmentation of periungual tissues due to radial spread of the tumor; or (2) micro-Hutchinson sign – pigmentation visible only by dermoscopy is a strongly suggestive clinical feature.

Additional figures and table on the ABCDEF rule for subungual melanoma, available in our eBook (see inside front cover for access code).

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eFig. 71.1 Onychomadesis after an episode of acute paronychia.



eFig. 71.2 Onychomadesis of the fingernails following hand-foot-and-mouth disease due to coxsackievirus A6 infection. *Courtesy Julie V. Schaffer, MD.*



eFig. 71.3 Trachyonychia (twenty-nail dystrophy). The nails appear to be sandpapered in a longitudinal direction.



eFig. 71.4 True leukonychia – diffuse variant. The nail plate is completely or almost completely opaque and white. It may be inherited due to mutations in *PLCD1*, *GJA1* (also keratoderma and hypotrichosis), or *GJB2* (also deafness, keratoderma and knuckle pads); the latter two genes encode connexins 43 and 26, respectively. *Courtesy Julie V. Schaffer, MD.*





eFig. 71.5 Congenital malalignment of the great toenails. A The longitudinal axis of the nail plate is deviated laterally. There is also onychomadesis of both great toenails and mild nail thickening with lateral ingrowing of the right great toenail. **B** The nail plates are thickened, yellow, and transversely overcurved as well as laterally deviated. *B, Courtesy Julie V. Schaffer, MD.*



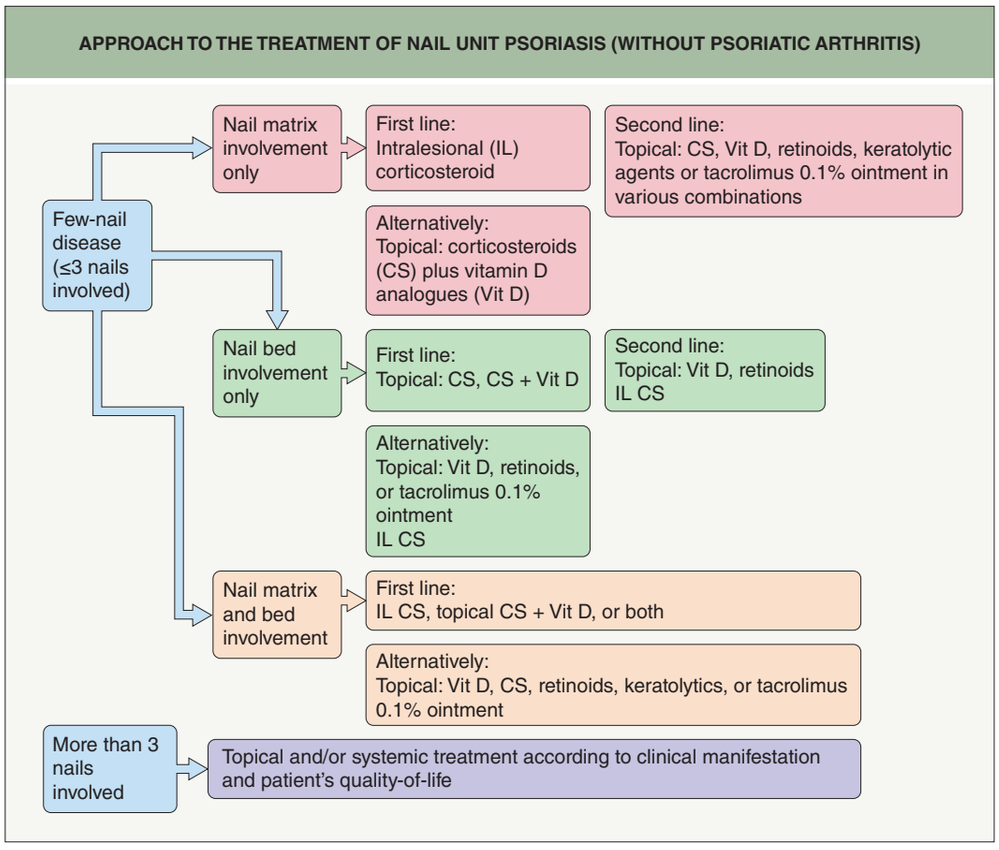
eFig. 71.6 Nail hypoplasia in nail–patella syndrome. Note more prominent involvement on the radial side of the digit.



eFig. 71.8 Darier disease. Longitudinal red and white streaks, fissuring, and V-shaped notching of the distal margin accompanied by focal subungual hyperkeratosis.



eFig. 71.7 Darier disease. V-shaped notching of the distal margin of the nail plate along with white longitudinal streaks.



eFig. 71.9 Approach to the treatment of nail unit psoriasis. *From Rigopoulos D, Baran R, Chiheb S, et al. Recommendations for the definition, evaluation, and treatment of nail psoriasis in adult patients with no or mild skin psoriasis. A dermatologist and nail expert group consensus. J Am Acad Dermatol 2019;81:228–40.*



eFig. 71.10 Nail lichen planus. Note the nail thinning with longitudinal ridging and fissuring.



eFig. 71.11 Clubbing in a patient with pachydermoperiostosis (primary hypertrophic osteoarthropathy). *Courtesy Dr D. Timaná and Dr J. Valverde, Hospital Docente de Trujillo.*

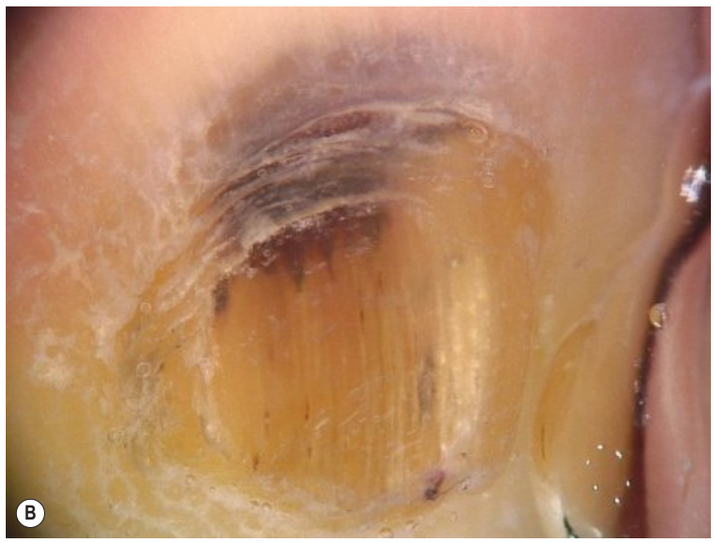


eFig. 71.12 Severe onycholysis in a patient receiving a fibroblast growth factor receptor inhibitor. *Courtesy Jean L. Bolognia, MD.*



eFig. 71.13 Acute paronychia. In addition to the erythema and purulent discharge, there is significant tenderness.





eFig. 71.14 Subungual hematoma. A Dark purple–black discoloration of the lateral portion of the proximal nail fold and nail plate of the fifth toe. **B** Dermoscopy shows small red longitudinal splinter hemorrhages and dark purple pigmentation under the proximal nail fold and nail plate due to accumulated blood, with a typical fringed distal edge.



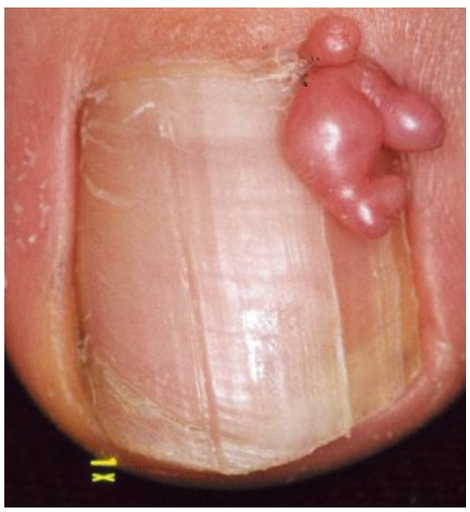


eFig. 71.15 Traumatic onycholysis of the nail of the first toe. A Clinical appearance – the whitish, crescent-shaped areas of nail plate detachment reflect the areas of trauma. **B** By dermoscopy, the proximal margin of the nail plate detachment has a linear shape.





eFig. 71.16 Onycholysis due to hallux erectus. A Involvement of both first toes. **B** Upward extension of the first toe. *Courtesy Bertrand Richert, MD, PhD.*



eFig. 71.17 Periungual fibroma producing a longitudinal groove due to matrix compression.



eFig. 71.18 Subungual exostosis. Subungual nodule elevating the nail plate.



eFig. 71.19 Onychomatricoma. The nail is thickened and overcurved with longitudinal yellow streaks. The distal border shows several holes.



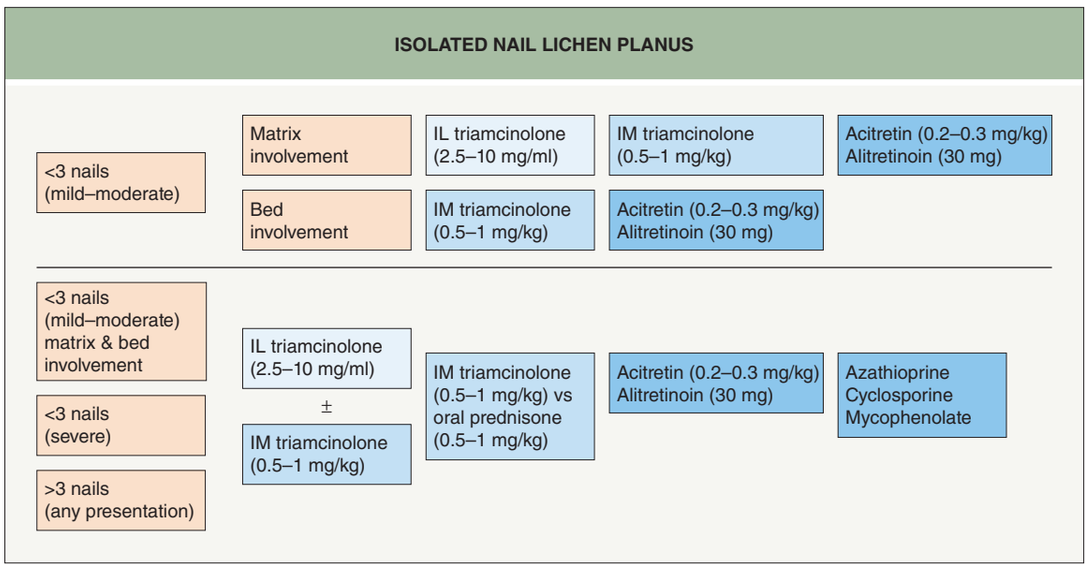
eFig. 71.21 Amelanotic melanoma. Note the diffuse nail destruction and ulceration.



eFig. 71.20 Onychopapilloma. Longitudinal erythronychia and leukonychia with focal hemorrhage and a subtle distal notch. The subungual tumor is best appreciated by viewing the nail *en face* at its distal free edge (inset). *Courtesy Harvey Lui, MD.*



eFig. 71.22 True leukonychia – striate and punctate. These changes are due to trauma.



eFig. 71.23 Isolated nail lichen planus. Dark blue shade: first-line therapy; medium blue shade: second-line therapy; pale blue shade: third-line therapy. IL, intralesional; IM, intramuscular. *Adapted from Tosti A, Starace M, Baran R, et al. Isolated nail lichen planus: An expert consensus on treatment of the classical form. J Am Acad Dermatol 2020;83:1717–23.*



eFig. 71.24 Trachyonychia. The nails have a sandpapered appearance. *Courtesy Kalman Watsky, MD.*

ABCDEF RULE FOR SUBUNGUAL MELANOMA	
Feature	**Rule**
A	**A**ge – peak incidence fifth to seventh decades with Africans, Asians and native Americans (dark-skinned races) accounting for up to one third of all cases
B	**B**lack or brown with band width of 3 mm or more
C	**C**hange in the nail or lack of improved change with treatment
D	**D**igit most commonly involved (thumb, great toe, index)
E	**E**xtension of pigment onto the proximal or lateral nail fold (Hutchinson sign)
F*	**F**amily or personal history of dysplastic nevus or melanoma
*This criterion has not been validated.	

eTable 71.1 ABCDEF rule for subungual melanoma. *Adapted from Levit EK, Kagen MH, Scher RK, et al. The ABC rule for clinical detection of subungual melanoma. J Am Acad Dermatol 2000;42:269–74.*

72 Oral Diseases

Maryam Jessri, Kristin K. McNamara and Nathaniel Treister

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Introduction

From both a clinical and histologic standpoint, the oral cavity is a diverse anatomic region reflecting its various functions and environmental interactions. Sites that are exposed to the friction of mastication, such as the hard palate and attached gingivae, are bound to the underlying periosteum and are referred to as *attached mucosa* or *keratinized mucosa* (Fig. 72.1). Histologically, these anatomic sites have prominent rete ridge formation and a thick layer of keratin. The dorsal tongue has the thickest epithelium within the oral cavity and its specialized functions include taste, mastication, and deglutition. The filiform, fungiform, foliate, and circumvallate papillae are distributed on the dorsal tongue, with pigmentation of the fungiform papillae a normal variant (Fig. 72.2A). All other oral mucosal sites, including the soft palate, labial mucosa, and floor of the mouth, are "unattached" and represent *non-keratinized mucosa*. Numerous salivary glands are present within the connective tissue (submucosa) beneath the non-keratinized mucosa. In the buccal mucosa, there are variable numbers of heterotopic sebaceous glands (Fordyce granules).

COMMON BENIGN CONDITIONS OF THE ORAL CAVITY

Fordyce Granules

Synonyms: ■ Ectopic sebaceous glands ■ Heterotopic or anomalous sebaceous glands ■ Fordyce spots

Key features

- Common variation of normal sebaceous glands
- Multiple yellowish papules of the buccal mucosa and vermilion zone of the upper lip

Introduction

Fordyce granules represent sebaceous glands that are present in the vermilion portion of the lips and the buccal mucosa. Although historically considered as ectopic, Fordyce granules are simply regarded as a variation of normal anatomy. "Free" sebaceous glands (see below) can also be found on the eyelids (meibomian glands), areolae (Montgomery tubercles), labia minora, and prepuce (Tyson glands).

Epidemiology

Fordyce granules are found in 70%–85% of the adult population, with no sex predilection[1]. They are uncommon in children and a surge in prevalence occurs around puberty followed by an incremental increase with age[2].

Clinical features

Fordyce granules characteristically present as multiple asymptomatic, yellow to yellow–white macules and papules. They usually measure 1–2 mm in diameter but may become confluent. The most common sites are the buccal mucosa bilaterally and the vermilion zone of the upper lip (Fig. 72.2B,C).

Pathology

Fordyce granules are similar to sebaceous glands found in the skin, but they are not associated with hair follicles, i.e. they are "free" sebaceous glands[1].

Treatment

Because Fordyce granules are a normal anatomical variant, no treatment is required. However, patients may express a cosmetic concern when lesions appear on the vermilion lip.

Geographic Tongue

Synonyms: ■ Benign migratory glossitis ■ Oral erythema migrans ■ Glossitis areata migrans ■ Stomatitis areata migrans ■ Erythema areata migrans ■ Benign migratory stomatitis

Key features

- Red, well-demarcated patches on the lateral and dorsal tongue with scalloped, thin white borders
- Psoriasiform mucositis of unknown etiology
- No treatment is generally necessary

Introduction

Geographic tongue is a benign inflammatory condition of unknown etiology that primarily affects the tongue and tends to recur.

Epidemiology

Geographic tongue affects 1%–3% of the general population, with no sex predilection[2]. In up to one-third of patients, concomitant fissured tongue has been observed. An increased incidence in atopic individuals has been reported as well as an association with psoriasis and reactive arthritis. In some patients, mutations in *IL36RN*, a causative gene for generalized pustular psoriasis, have been identified in tissue biopsies[3].

Clinical features

Geographic tongue typically presents on the dorsum of the tongue as one or multiple depapillated areas which gradually enlarge to form slightly atrophic patches with peripheral erythema and a yellowish-white serpiginous border (Fig. 72.3). In addition to migration, lesions often wax and wane and can involve other mucosal sites including the floor

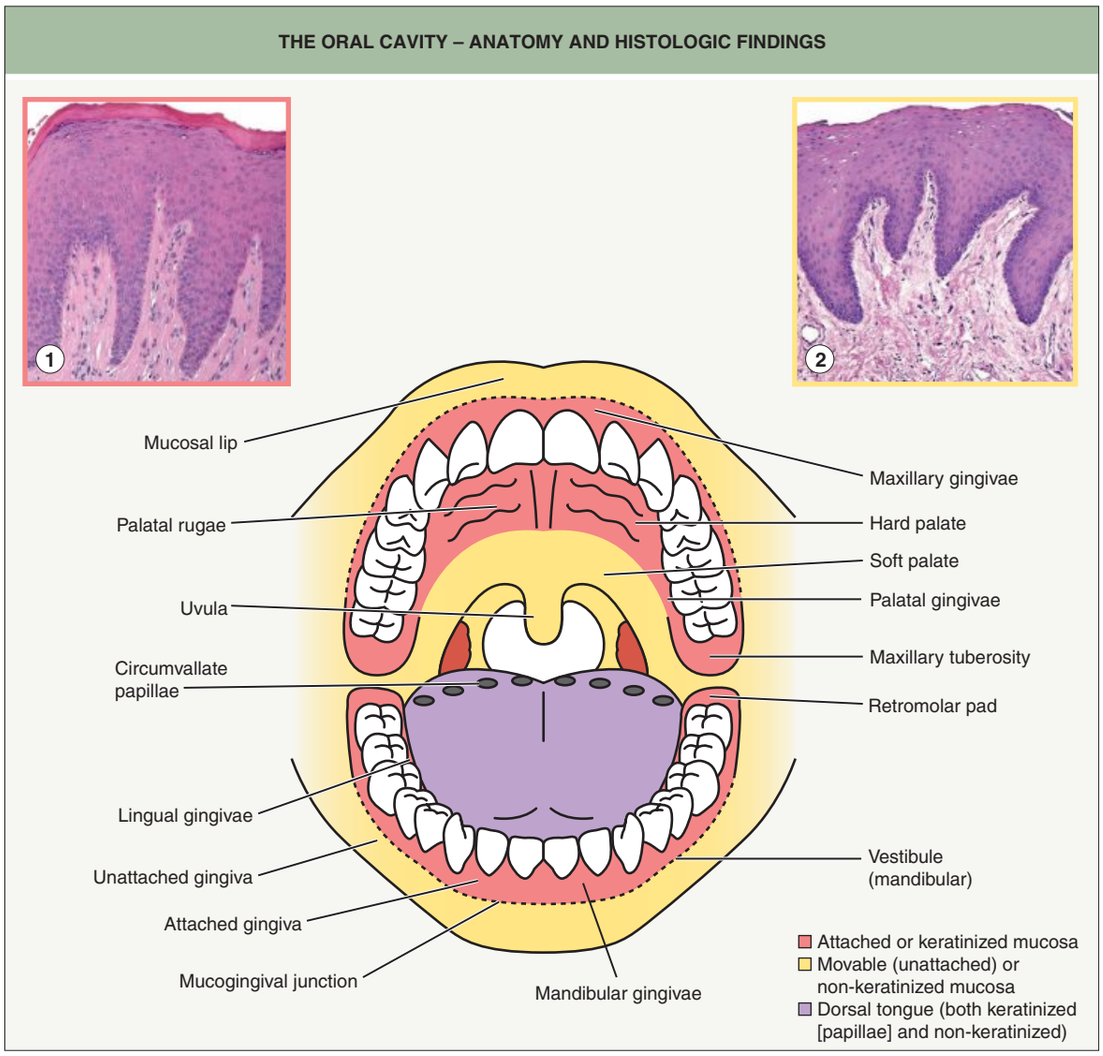


Fig. 72.1 The oral cavity – anatomy and histopathologic findings. Pink represents attached (keratinized) mucosa, yellow represents movable (non-keratinized) mucosa, and purple the dorsal tongue. Inset 1: Histologic features of the palate with prominent rete ridge formation, a granular layer, and orthohyperkeratosis; the attached gingivae have similar findings. Inset 2: Histologic features of the buccal mucosa with less pronounced rete ridges, minimal parakeratosis, and no orthokeratosis; the soft palate, labial mucosa, ventral tongue, and floor of mouth exhibit similar histologic features.

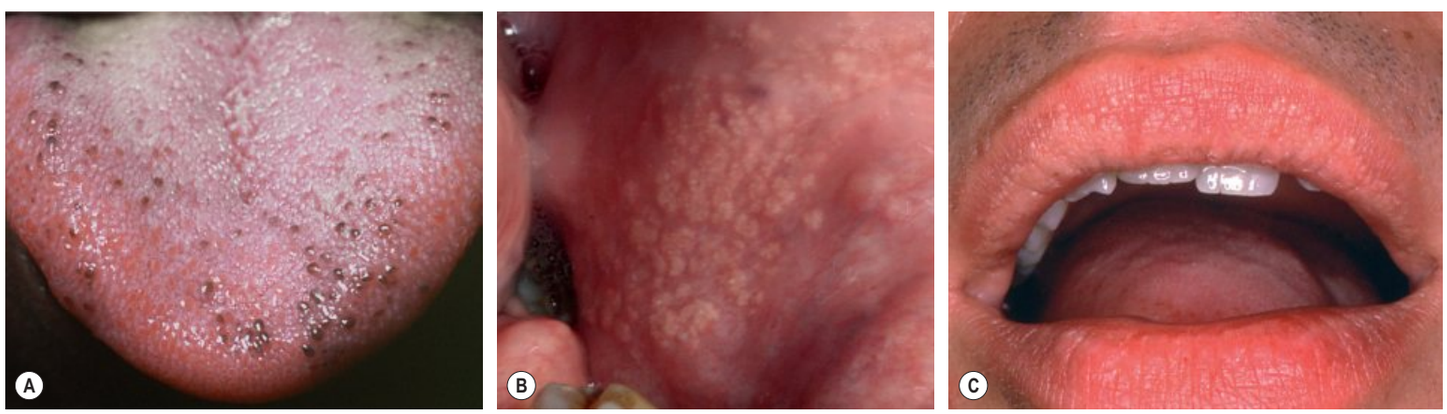


Fig. 72.2 Variations of normal anatomy – Fordyce granules and pigmented papillae of the tongue. A Multiple, tiny, brown papules representing pigmented fungiform papillae are seen on the tip and lateral aspects of the tongue; they represent a normal variant in individuals with darker skin phototypes. The more numerous keratotic projections represent normal filiform papillae. **B, C** Multiple yellowish 1–2 mm papules on the buccal mucosa and upper vermilion lip, representing "free" sebaceous glands.

of the mouth, buccal mucosa, and labial mucosa. Because geographic tongue is frequently asymptomatic, most patients are unaware of its existence. While generally an incidental finding during a routine oral examination[4], there may be associated symptoms such as a burning sensation or sensitivity to hot or spicy foods.

Pathology

Since the histopathologic features are similar to those of psoriasis, it is also referred to as "psoriasiform mucositis". At the edge of the lesion, there is a characteristic loss of the papillary surface morphology of the tongue, elongation of rete ridges, varying parakeratosis, and spongiosis, along with numerous, typically confluent, superficial intraepithelial neutrophilic microabscesses[2].

Treatment

When asymptomatic, geographic tongue requires no treatment other than assuring the patient that it represents a benign condition. If symptoms interfere with the patient's lifestyle, application of viscous



Fig. 72.3 Geographic tongue. Multiple depapillated areas which have gradually enlarged to form slightly atrophic patches with peripheral erythema and a yellowish-white serpiginous border. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*

lidocaine, diphenhydramine, or in more severe cases, topical corticosteroids may provide relief.

Fissured Tongue

Synonyms: ■ Scrotal tongue ■ Plicated tongue ■ Lingua plicata ■ Furrowed tongue

Introduction

Fissured tongue is a common, benign condition of unknown etiology that affects the dorsal tongue. It may occur in isolation or accompany another oral condition (e.g. geographic tongue) or a genetic syndrome (e.g. Down and Cowden syndromes, pachyonychia congenita). The etiology is unknown but there may be an hereditary component, either polygenic or autosomal dominant with incomplete penetrance. Lastly, fissured tongue is a clinical feature of Melkersson–Rosenthal syndrome (see below).

Epidemiology

Fissured tongue affects both sexes. The prevalence increases with age and ranges from 2%–30%, depending on the population studied[4]. There may be an increased incidence in patients with acromegaly.

Clinical features

Fissured tongue typically presents as multiple 2–5 mm deep grooves or furrows on the dorsal tongue (Fig. 72.4). These grooves may develop on the entire surface of the dorsal tongue, present as a central fissure with or without a smaller branching fissure, or affect just isolated areas of the dorsolateral tongue. Although most patients are asymptomatic, some may report mild soreness or burning.

Pathology

Histopathologic features include hyperplastic rete ridges, loss of keratin overlying filiform papillae, deep fissures accompanied by exocytosis of neutrophils and intraepithelial microabscesses, and mixed inflammation within the lamina propria.

Treatment

Fissured tongue is a benign condition requiring no treatment.

Hairy Tongue

Synonyms: ■ Coated tongue ■ Black hairy tongue ■ Lingua villosa nigra



Fig. 72.4 Fissured tongue. Numerous asymptomatic furrows and grooves on the dorsal tongue. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*

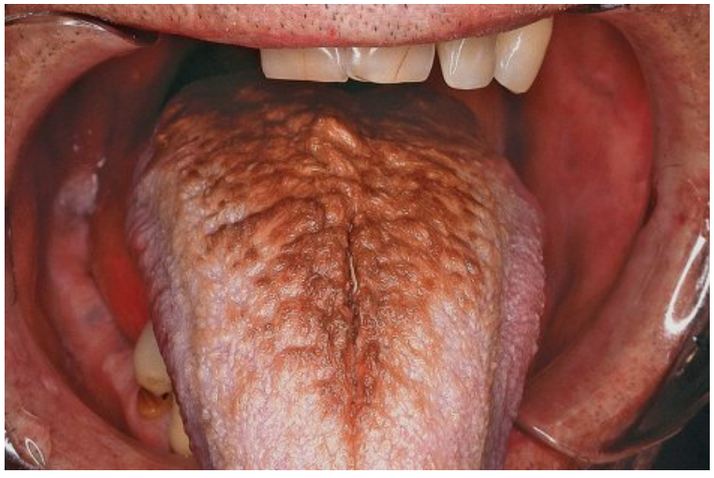


Fig. 72.5 Hairy tongue. The filiform papillae of the dorsal tongue have a marked accumulation of keratin, along with a brown discoloration. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*

Key features

- Retention of keratin on the tips of filiform papillae
- Not due to yeast infection
- Best managed using a tongue scraper

Introduction

Hairy tongue is a benign acquired condition that reflects a reduced rate of desquamation and subsequent accumulation of keratin over the filiform papillae. Predisposing factors include a reduction in food intake, dehydration, and adherence to a primarily soft or liquid diet as well as smoking, hyposalivation, poor oral hygiene, use of oxidizing mouthwashes, and frequent consumption of hot beverages.

Epidemiology

Hairy tongue affects both sexes, with a prevalence reported as 0.5%–5% of the population.

Clinical features

Hairy tongue is usually asymptomatic and favors the midportion of the dorsal tongue (Fig. 72.5). The elongated papillae are usually yellow to brown–black, although a wide range of colors may occur due to differential exogenous staining from food, tobacco, or chromogenic bacteria. Some patients complain of bad breath, a bad taste, or a gagging sensation. A distinctly different entity is pigmented papillae of the tongue, a normal variant in which multiple uniformly spaced, tiny brown papules (representing normal fungiform papillae) are seen on the tip and lateral aspects of the tongue in darkly pigmented individuals (see Fig. 72.2A). Pseudo-back hairy tongue refers to black discoloration of the tongue due to bismuth.

Pathology

Microscopic examination reveals pronounced accumulation of parakeratosis at the tips of otherwise normal filiform papillae. Often, bacteria can be seen colonizing the surface.

Treatment

Hairy tongue is usually a self-limiting condition requiring no treatment. Better hydration, a diet containing fresh fruits or vegetables and more coarse foods, cessation of habits such as smoking or using alcoholic mouth rinses, and gentle exfoliation of the tongue with a soft toothbrush or tongue scraper can lead to improvement. Anecdotally, consumption of fresh pineapple may be recommended due to its acidity and high content of fiber and bromelain (bromelin).

Central Papillary Atrophy

Synonyms: ■ Median rhomboid glossitis ■ Erythematous candidiasis

Key features

- Red, well-demarcated area in the midline of the posterior dorsal tongue
- Consistently associated with candidiasis
- Responds partially or completely to antifungal therapy

Introduction

Central papillary atrophy, also referred to as median rhomboid glossitis, was originally thought to be a developmental defect resulting from failure of the embryonic tuberculum impar to be covered by the lateral processes of the tongue. However, it is seen more often in adults than in children and there is a frequent association with chronic candidal infection.

Epidemiology

The lesion is seen in up to 1% of adults, with no sex predilection.

Clinical features

Central papillary atrophy appears as a variably symptomatic, well-demarcated, diamond- or oval-shaped area of erythema and atrophy in the midline of the dorsal tongue (Fig. 72.6), anterior to the circumvallate papillae. The surface may be smooth or lobulated. It may be the sole clinical finding or there may be other sites of involvement – the hard and soft palate (kissing lesions) and/or the angles of the mouth (angular cheilitis) – as a reflection of chronic multifocal candidiasis.

Pathology

In the setting of active infection, histopathologic features include loss of the filiform papillae and pseudohyphae of *Candida albicans* embedded within parakeratosis. The diagnosis is usually a clinical one, with confirmation via demonstration of pseudohyphae in a potassium hydroxide (KOH) preparation or a PAS-stained exfoliative cytologic preparation.



Fig. 72.6 Central papillary atrophy. On the dorsal tongue anterior to the circumvallate papillae, there is a well-demarcated, smooth area with loss of filiform papillae.

Treatment

Topical antifungals include nystatin rinses and pastilles, clotrimazole troches, and in some countries, miconazole gel and amphotericin lozenges (see Table 77.15). First-line systemic therapy consists primarily of oral fluconazole. Following appropriate anti-candidal therapy, the mucosal alterations normally resolve partially or completely. Recalcitrant disease may be due to persistence of risk factors or possibly drug resistance (see Ch. 77).

SYNDROMES OF THE HEAD AND NECK

Basal Cell Nevus Syndrome

Synonyms: ■ Nevoid basal cell carcinoma syndrome ■ Gorlin syndrome

Basal cell nevus syndrome (BCNS) is an autosomal dominant disorder due to *PTCH1*, or rarely *PTCH2* or *SUFU*, mutations (see Ch. 107). However, up to 50% of patients may have *de novo* mutations[5]. Major clinical criteria include multiple basal cell carcinomas (BCCs) and palmoplantar pits as well as skeletal anomalies and odontogenic keratocysts (OKCs) of the jaws (see Table 108.3). OKCs typically develop in the posterior body of the mandible and appear radiologically as radiolucent cystic lesions with well corticated borders. Careful and complete excision of OKCs is recommended as recurrences and significant complications may follow incomplete removal.

Gardner Syndrome

Synonym: ■ Familial colorectal polyposis

Gardner syndrome is a variant of *familial adenomatous polyposis*, an autosomal dominant disorder due to mutations in the adenomatous polyposis coli gene (*APC*). Up to 30% of patients may have *de novo* mutations. In addition to premalignant intestinal polyps, patients can develop desmoid or fibrous tumors of the skin and early-onset epidermoid cysts (see Ch. 63). Osteomas occur in the majority of patients and favor the mandible as well as other bones of the skull. Osteomas, along with bilateral CHRPE (*c*ongenital *h*ypertrophy of the *r*etinal *p*igment *e*pithelium), represent early manifestations of this syndrome. Screening, dental anomalies, and treatment recommendations are discussed in Chapter 63.

Multiple Endocrine Neoplasia Syndrome Type 2B

Synonyms: ■ Multiple endocrine neoplasia type 3 ■ Multiple mucosal neuroma syndrome

Multiple endocrine neoplasia syndrome type 2B (MEN 2B) is a rare autosomal dominant disorder due to missense mutations in the *RET* proto-oncogene. It is associated with early-onset medullary thyroid carcinoma, diffuse gastrointestinal ganglioneuromatosis, and pheochromocytomas (see Table 63.2)[6]. Multiple soft mucosal neuromas of the lips, anterior tongue, and eyelid margins may be present at birth or develop during early childhood thus serving as an important diagnostic finding (see Fig. 63.2). Of note, however, patients with PTEN hamartoma tumor syndrome also occasionally develop mucosal neuromas.

Analysis of the *RET* gene should be performed in patients with clinical evidence of the disease as well as in asymptomatic individuals with an affected parent. Based upon the specific *RET* mutation detected, the recommended age for prophylactic thyroidectomy varies from infancy to 10 years.

PERIODONTAL AND DENTAL DISEASE

Necrotizing Ulcerative Gingivitis

Synonyms: ■ Trench mouth ■ Acute necrotizing ulcerative gingivitis (becoming historic given lack of chronic form) ■ Necrotizing gingivostomatitis ■ Vincent infection ■ Fusospirochetal gingivitis

Key features

- Painful, hemorrhagic, necrotic gingivae with classic "punched-out" interdental papillae
- Mixed bacterial infection in susceptible hosts with predisposing risk factors
- Predisposing risk factors include immunosuppression, malnutrition, stress, smoking, and poor oral hygiene

Introduction

Necrotizing ulcerative gingivitis (NUG) is characterized by pain, bleeding, and necrosis of interdental gingival papillae. The infection is due to a mixed population of bacteria, including spirochetes (e.g. *Treponema*), *Prevotella intermedia*, *Fusobacterium* and *Selenomonas* spp., and *Porphyromonas gingivalis*.

Epidemiology

NUG affects <0.1% of the population, is primarily seen in young to middle-aged adults, and does not have a sex predilection. Predisposing factors include immunosuppression, malnutrition, poor oral hygiene, physical stress, and smoking.

Clinical features

NUG is characterized by inflamed, edematous, and hemorrhagic interdental papillae. However, unlike generalized severe gingivitis, the affected papillae in NUG have a blunted appearance with "punched-out", crater-like areas of necrosis and ulceration. Generally, patients present with halitosis, severe pain, spontaneous bleeding from the gingivae, and accumulation of necrotic debris on the teeth and gingival surfaces. Systemic signs and symptoms may include fever, malaise, and lymphadenopathy.

Pathology

The histopathologic features are nonspecific and include ulceration of the epithelium that is covered by fibrinous debris and a mixed inflammatory infiltrate in the lamina propria. Bacterial colonization is common but because the primary etiologic agents represent normal oral flora, bacterial culture results are not very helpful.

Treatment

The most appropriate therapy is provided by a periodontist and includes debridement of the necrotic tissue to reduce inflammation and microbial load as well as investigation of the underlying cause(s). Chlorhexidine oral rinses (0.12%) may reduce the bacterial load. Broad-spectrum antibiotics are prescribed, especially when there are systemic signs of infection.

Desquamative Gingivitis

Key features

- A clinical descriptor for oral manifestations of an underlying immune-mediated vesiculoerosive disease
- Characterized by diffusely smooth, red, and sometimes painful gingivae
- Histopathologic and immunofluorescence studies are required for appropriate diagnosis and subsequent treatment of the underlying condition

Introduction

Desquamative gingivitis is a nonspecific clinical term used to describe superficial sloughing of the gingival epithelium. It is nearly always a manifestation of a vesiculoerosive disease such as lichen planus (see Ch. 11), mucous membrane pemphigoid (see Ch. 30), or pemphigus vulgaris (see Ch. 29). Fig. 72.7 outlines the multiple causes of desquamative gingivitis.

Epidemiology

Desquamative gingivitis primarily affects women over the age of 40 years.

Clinical features

Desquamative gingivitis primarily affects the maxillary and mandibular gingivae, either focally or diffusely (see Fig. 72.1). Affected areas are friable, denuded, and erythematous with occasional ulceration (Fig. 72.8). The gingivae may be the sole site of involvement or the gingivitis may be accompanied by erosions elsewhere in the mouth, on the lips, or in other mucosal sites. Patients often report soreness and sensitivity and, depending on the severity, diet and maintaining oral hygiene may be adversely impacted. Intact vesicles of the gingivae are rarely seen.

Pathology

The specific histopathologic and immunopathologic features of desquamative gingivitis depend on the underlying vesiculoerosive disease. Diagnosis is established via an incisional biopsy processed for both routine histology and direct immunofluorescence (DIF)[7]. In addition, when indicated, indirect IF (IIF) testing or an enzyme-linked immunosorbent assay (ELISA) can be utilized to detect circulating autoantibodies (see Fig. 72.7).

Treatment

Once a diagnosis is established, appropriate treatment for the responsible condition can follow. Meticulous dental prophylaxis (cleaning), oral hygiene instructions, and longitudinal evaluation are recommended. Reducing bacterial plaque often decreases the severity of lesions and is an important adjunct to medical therapy[7].

Sequelae of Dental Caries

Key features

- Dental infections can spread beyond the periapical region of teeth
- Periapical abscess, osteomyelitis, cellulitis, intraoral dental sinus, and cutaneous sinus are potential sequelae
- Emergent cases require immediate treatment to avoid airway obstruction or possible sepsis

Introduction

Dental caries is due to a microbial process that causes localized destruction and loss of mineralized tissues. This may result in infection of the pulp with extension to the periapical region of the tooth. In immunocompromised hosts or with particularly virulent bacteria, there may be spread of the infection to bone and soft tissues or further localized destruction. The latter can lead to a cutaneous sinus of dental origin (Fig. 72.9).

Clinical features

Dental caries is defined as localized loss of the mineralized structure of the tooth (enamel, dentin, or cementum) due to an infectious process. It may present as any one or a combination of the following: cavitation of enamel, brown discoloration, whitened chalky appearance, or soft scrapable tooth structure. Sequelae from spread of the bacterial infection beyond the tooth structure vary from contained asymptomatic bone destruction to severe facial cellulitis.

A periapical abscess forms when there is a localized accumulation of inflammatory cells and bacterial debris in the periapical space of a non-vital tooth; the abscess may be acute or chronic and symptoms range from none to severe pain. When the infection erodes through cortical bone to create a path for drainage, a "sinus tract" or "parulis" forms. An *intraoral dental sinus tract* is characterized by a soft, non-tender, erythematous papule that develops on the alveolar process, typically in the same region as the apex of the offending non-vital tooth. If the infection tunnels through the skin, a *cutaneous sinus tract of dental origin* forms which can present as an ulceration, a fibrosed depression, or an erythematous, sometimes eroded, papule (see Fig. 72.9).

DIFFERENTIAL DIAGNOSIS OF DESQUAMATIVE GINGIVITIS



Differential diagnosis of desquamative gingivitis*

Lichen planus (LP) Lichenoid drug reaction Lupus erythematosus (LE) GVHD	Autoimmune bullous disorder – mucous membrane (cicatricial) pemphigoid, pemphigus vulgaris, paraneoplastic pemphigus (PNP) > EBA, BP, LABD	Erythema multiforme, fixed drug eruption	Chronic ulcerative stomatitis	Contact dermatitis, allergic or irritant	Lichenoid contact stomatitis, lichenoid foreign body gingivitis
• Lacy white plaques (e.g. Wickham striae) of oral &/or other mucosae • Correct clinical setting for LE or GVHD • Appropriate medication history	• Erosions, ulcers, & occasionally vesicles/ bullae of oral &/or other mucosae • Ragged ulcers → pemphigus; smooth but irregular ulcers → mucous membrane pemphigoid	• Erosions, ulcers, & occasionally vesicles/ bullae of oral &/or other mucosae** • Recurrent episodes	• Clinically, resembles oral erosive LP, but asymmetric distribution of lesions & striae less sharply defined	• Need to look for unusual causes (e.g. nail polish in nail biters, sucking on metal objects) • See Table 72.1	• Lesions may result from exposure to cinnamon flavoring agents in food, beverage, and oral hygiene products; embedded particles from dentifrices and dental restorative materials in foreign body gingivitis
H&E: interface-lichenoid inflammation; may be minimal in GVHD **DIF:** nonspecific, e.g. shaggy fibrinogen at BMZ in LP; granular IgG and/or IgM, C3 at BMZ in LE **IIF:** negative	**H&E:** (edge of erosion): acantholysis & intraepithelial (suprabasal) cleft versus subepithelial cleft; pleomorphic pattern in PNP† **DIF/IIF:** see Chs. 29 31	**H&E:** interface-lichenoid inflammation, apoptotic keratinocytes **DIF:** nonspecific **IIF:** negative	**H&E:** nonspecific, patchy interface mucositis **DIF:** staining of basal/ parabasal cell nuclei (necessary for diagnosis) **IIF:** positive – similar pattern to DIF	**H&E:** spongiosis, eosinophils in allergic form **DIF:** negative **IIF:** negative	**H&E:** interface-lichenoid inflammation **DIF:** nonspecific **IIF:** negative

*Some entities may have cutaneous lesions.

**Other mucosae (genital, ocular) – more so for erythema multiforme.

†The pleomorphic pattern in paraneoplastic pemphigus includes features of pemphigus and erythema multiforme as well as lichenoid inflammation.

Fig. 72.7 Differential diagnosis of desquamative gingivitis. If the gingivae are painful, hemorrhagic, and necrotic with punched-out interdental papillae, then necrotizing ulcerative gingivitis is the most likely clinical diagnosis. For presumed chronic ulcerative stomatitis, the detection of circulating anti-p63 antibodies via ELISA may assist in diagnosis. BP, bullous pemphigoid; BMZ, basement membrane zone; DIF, direct immunofluorescence (IF); EBA, epidermolysis bullosa acquisita; GVHD, graft-versus-host disease; IIF, indirect IF; LABD, linear IgA bullous dermatosis.



Fig. 72.8 Desquamative gingivitis due to oral erosive lichen planus. Erosions and prominent, fairly well-defined areas of erythema of the attached (keratinized) gingivae. Histopathologic examination plus DIF (and occasionally IIF or ELISA) are needed to establish the etiology (see Fig. 72.7).



Fig. 72.9 Cutaneous sinus of dental origin. A Dull pink papule and adjacent indentation on the jawline. **B** An ulceration in a similar location. These sinuses originated from periapical dental abscesses in the mandible that then channeled through the overlying skin to drain. They may be mistaken for a pyogenic granuloma, neoplasm, or cutaneous infection. *A, Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*

In addition to sinus tracts, cellulitis and occasionally osteomyelitis may develop and both usually have associated pain. Patients with cellulitis can also have fever, chills, and lymphadenopathy while a foul-smelling drainage may accompany osteomyelitis. There are two potential complications that represent a particular danger to patients and demand immediate attention. *Ludwig's angina* presents as swelling of the submandibular, submental, and sublingual spaces. Urgent attention is required for this form of cellulitis as it can rapidly spread to the retropharyngeal space, obstructing breathing, and even spread to the mediastinum. *Cavernous sinus thrombosis* due to a dental abscess may initially present as swelling of the canine space. Infraorbital, ocular, and eventually CNS involvement may develop.

Treatment

Treatment involves elimination of the focus of infection, which often requires incision and drainage, endodontic "root canal" therapy or extraction of the involved tooth, appropriate antibiotic therapy, and airway management, if necessary. Microbiological testing assists in the choice of antibiotics and allows exclusion of cervicofacial actinomycosis.

PHYSICAL AND CHEMICAL INJURIES

Fibroma

Synonyms: ■ Bite fibroma ■ Irritation or traumatic fibroma ■ Fibrous hyperplasia or nodule

Key features

- Smooth, pink, soft to rubbery nodule, typically on the buccal mucosa
- Asymptomatic unless persistently irritated or traumatized

Introduction

A fibroma is the most common "tumor" of the oral cavity. It most likely represents reactive hyperplasia of fibrous connective tissue in response to local trauma, including repeated biting.

Epidemiology

Fibromas most commonly occur during the fourth to sixth decades, with no sex predilection.

Clinical features

The typical lesion is a sessile, soft, smooth-surfaced papule or nodule similar in color to the surrounding normal mucosa. Depending on the location and extent of acute and chronic trauma, fibromas may be ulcerated or have a white keratotic surface. These papulonodules are usually <1.5 cm in diameter and are most commonly observed along the bite line of the buccal mucosa. However, they can also occur in other easily traumatized sites such as the lower labial mucosa and the anterolateral aspects of the tongue.

Pathology

Histologically, there is an unencapsulated mass of hyperplastic fibrous connective tissue with varying vascularity and minimal inflammation. The overlying epithelium may be ulcerated, atrophic, or hyperkeratotic secondary to friction or biting.

Treatment

Surgical excision is curative and histopathologic examination allows confirmation of the clinical diagnosis.

Contact Stomatitis

Key features

- Can be allergic or irritant
- Irritant contact stomatitis is the result of direct contact with a caustic agent
- Allergic contact stomatitis can be acute or chronic and has a range of signs and symptoms

Introduction

Contact stomatitis is a broad term that encompasses clinical findings secondary to exposure of the oral mucosa to a known contactant. It is subdivided into irritant contact stomatitis (ICS) and allergic contact stomatitis (ACS). As in the skin, the former results from direct mucosal injury by an irritant and when pronounced is referred to as a chemical burn; the latter is characterized by delayed type hypersensitivity to an allergen.

Epidemiology

Contact stomatitis may present at any age, but is more common in adults. While ICS does not have a sex predilection, ACS has a female predominance.

Clinical features

In mild ICS, erythema and textural changes of the mucosa may be seen. Direct placement of a caustic agent such as an aspirin or alendronate onto the mucosa can lead to more severe disease, with erythema appearing shortly after exposure. Depending on the duration of exposure and irritancy potential of the contactant, ICS may present as edema, sloughing of the epithelium, and even painful necrotic ulcers (Fig. 72.10)[8].

A wide range of allergens can induce ACS including flavorings such as cinnamon and peppermint in dentifrices, mouthwashes, and chewing gum and dental restorative materials (e.g. amalgam) (Fig. 72.11; Table 72.1). The clinical findings of acute ACS range from varying degrees of erythema with or without edema to superficial ulcerations and in rare cases, vesicle formation. In chronic ACS, sites of involvement may be erythematous, keratotic, or erosive and in some patients resemble lichen planus. The most common symptom of both ACS and ICS is burning within the mouth which may be generalized or limited to the affected area.

Pathology

The range of clinical presentations results in varying histopathologic findings. In ACS, epithelial spongiosis and submucosal inflammatory infiltrates that contain eosinophils and plasma cells can be seen. Ulcerations from ICS or ACS have coagulative necrosis of the epithelium with variable extension into the underlying connective tissue. In lichenoid contact stomatitis, e.g. due to contact with metals contained in dental amalgam, a lichenoid inflammatory reaction is seen that is indistinguishable from oral lichen planus. Metal particles within the lamina propria (particularly amalgam), if present, are a clue to lichenoid contact stomatitis.

Treatment

A thorough history may identify the responsible contactant and its elimination is often curative. In the case of ACS, patch testing can

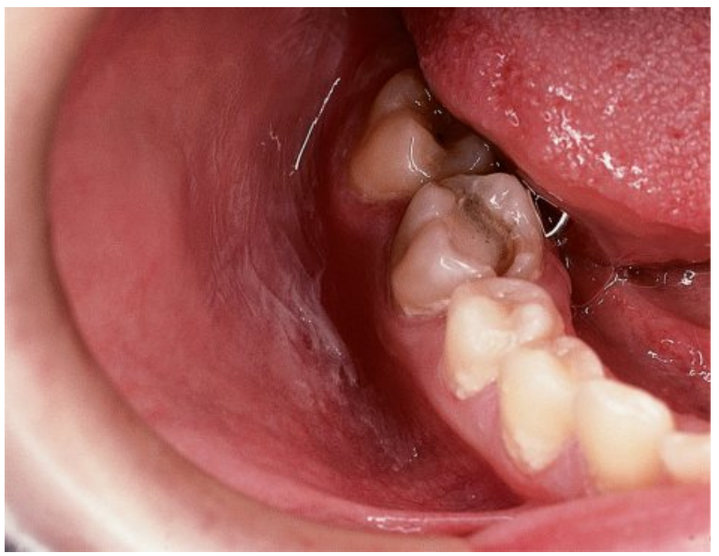


Fig. 72.10 Irritant contact stomatitis (aspirin burn). To relieve a toothache, this patient placed an aspirin in the mouth adjacent to the symptomatic tooth. Note the wrinkled white membrane that represents superficial epithelial necrosis.
Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.



Fig. 72.11 Allergic contact stomatitis from artificial cinnamon flavoring. Shaggy, white keratotic plaque of the left buccal mucosa caused by the use of artificial cinnamon-flavored gum. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*

POTENTIAL CAUSES OF CONTACT STOMATITIS OR CHEILITIS
Allergic
• **Flavorings**: cinnamon, mint, menthol, vanillin • **Fragrances**: *Myroxylon pereirae* (Balsam of Peru), cinnamic aldehyde • **Dental metals**: nickel, mercury, gold, palladium, copper, silver, cobalt, chromium, beryllium, tin, zinc • Dental adhesives: acrylic resin monomers, eugenol (combined with zinc oxide) • Topical anesthetics: benzocaine • Essential oils: clove, lemon, orange • For additional causes of allergic contact cheilitis, see Fig. 72.15
Irritant
• **Aspirin** • Dental chemicals: eugenol, peroxides, phenol, sodium hypochlorite • Chlorhexidine mouth rinse • Silver nitrate stick • Sodium lauryl sulfate and sodium pyrophosphate (in toothpaste)

Table 72.1 Potential causes of contact stomatitis or cheilitis. Most common offenders in **bold** (see Chs. 14 & 15). Contact lichenoid reactions also occur (e.g. metals, spices, acrylic resin monomers), and heat or traumatic injuries can lead to irritation.

identify the responsible allergen (see Ch. 14). Application of emollient pastes or topical anesthetics as a palliative measure may provide temporary relief.

Morsicatio Mucosae Oris

Synonyms: ■ Chronic bite keratosis
Variants: ■ Morsicatio buccarum (buccal mucosa) ■ Morsicatio labiorum (labial mucosa) ■ Morsicatio linguarum (tongue)

Key features

- Factitial habit
- Shaggy white lesions of the anterior buccal mucosa, lateral tongue, or lower labial mucosa
- No treatment indicated

Introduction

Morsicatio mucosae oris (MMO) is a benign condition that is due to repetitive chewing, biting, or nibbling of the oral mucosa[2].



Fig. 72.12 Cheek chewing (morsicatio buccarum) – clinical and histopathologic findings. Repetitive nibbling of the superficial layers of the epithelium resulted in these changes. Note that the characteristic shaggy, white lesion approximates the area where the upper and lower teeth meet. Inset: Oral epithelium exhibiting acanthosis and prominent parakeratosis, with a ragged surface architecture and superficial colonization by bacteria. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*

Epidemiology

MMO usually affects individuals during or after their fourth decade of life.

Clinical features

The most common site for MMO is the buccal mucosa followed in frequency by the ventrolateral tongue and lower labial mucosa. MMO classically presents as bilateral shaggy white lesions of the anterior buccal mucosa that approximate the area of chronic trauma (Fig. 72.12).

Pathology

Histopathologic findings are nonspecific and include acanthosis, marked parakeratosis, an irregular, shaggy surface of the epithelium with fissures and clefts, and varying degrees of vacuolization and spongiosis in the superficial portion of the epithelium (Fig. 72.12 inset). Surface colonization by bacteria is also a frequent feature.

Treatment

Because MMO is a benign condition, it requires no treatment.

Traumatic Ulcer

Key features

- Acute or chronic injury to the oral mucosa may cause a traumatic ulcer
- Commonly occurs on the tongue, lips, or buccal mucosa
- Simple traumatic ulcers are self-limiting and heal within a week following removal of the etiologic agent
- Traumatic ulcerative granuloma with stromal eosinophilia may mimic oral squamous cell carcinoma

Introduction

Acute or chronic mechanical injury, e.g. biting or trauma from sharp foods or objects such as the sharp edge of a fractured tooth, may result in laceration of the oral mucosa. Simple traumatic ulcers (STUs) usually heal within days. However, sometimes there is progression to a chronic variant which is referred to as traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) as well as eosinophilic ulceration, traumatic granuloma, and eosinophilic granuloma of the tongue. These ulcers may mimic oral squamous cell carcinoma (OSCC).

Epidemiology

TUGSE has a bimodal peak prevalence: (1) infants between 1 week and 1 year of age (Riga–Fede disease); and (2) adults. TUGSE is uncommon in older children and adolescents.

Clinical features

Traumatic ulcers most commonly affect the tongue, followed by the lips and buccal mucosa. An STU presents as a central ulcer with a variable degree of surrounding erythema and it heals within 7–10 days. TUGSE often presents as a central ulcer with a yellow fibrinous base whose border is rolled, white, and keratotic with mild erythema (Fig. 72.13). Because these ulcers may persist for months, they can mimic OSCC.

Riga–Fede disease is associated with neonatal teeth and most commonly involves the anterior ventral or dorsal surface of the tongue due to mandibular or maxillary incisors, respectively.

Pathology

In an STU, there is a sharply demarcated ulcer with overlying fibrin and neutrophils and a variable nonspecific inflammatory infiltrate at its base. The adjacent epithelium is normal or hyperplastic. TUGSEs are characterized by a dense, diffuse inflammatory response composed of eosinophils, lymphocytes, plasma cells, and pleomorphic mononuclear cells that extend deeply into the submucosal tissue and underlying striated muscle. Although $CD30^+$ cells are a common finding, TUGSE is not associated with EBV infection and should be distinguished from EBV^+ mucocutaneous ulcer.

Treatment

For STU, avoidance of injury or elimination of the obvious causative agent(s) is usually curative. Given the clinically suspicious presentation, TUGSEs often undergo incisional or excisional biopsy which may trigger healing. Application of topical corticosteroids can accelerate healing and provide symptomatic relief; however, some cases may require more aggressive therapy including intralesional corticosteroids or surgical excision.

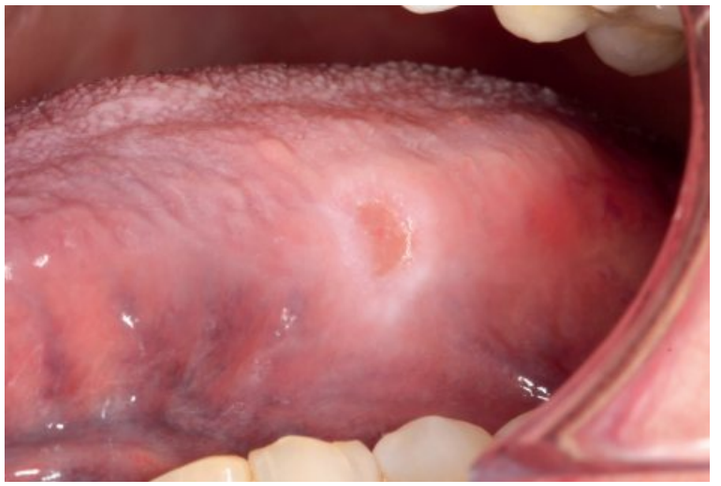


Fig. 72.13 Traumatic ulcer of the lateral tongue. The ulceration has a yellow fibrinous base with a blended white hyperkeratotic border. Compare this to the ulcerated leukoplakia with well-defined keratotic borders depicted in Fig. 72.21A and the exophytic, ulcerated mass depicted in Fig. 72.21B, which represent oral squamous cell carcinomas. *Courtesy Carl M. Allen, DDS, MSD, Charles Camisa, MD, and Kristin K. McNamara, DDS, MS.*

Drug-Related Gingival Hyperplasia

Synonyms: ■ Medication-related gingival hyperplasia ■ Drug-related gingival overgrowth ■ Drug-related gingival enlargement

Key features

- Enlargement of the gums occurs during the first year of drug administration
- Most commonly associated with phenytoin, nifedipine, and cyclosporine
- Severity correlates with patient susceptibility and level of oral hygiene

Introduction

Drug-related gingival hyperplasia is characterized by abnormal growth of the gingivae in response to a systemic medication. Multiple medications have been associated with gingival enlargement, in particular phenytoin, nifedipine, and cyclosporine (Table 72.2). Although a dose-dependent association is still controversial, the overgrowth definitely correlates with poor oral hygiene. Other causes of gingival hyperplasia are outlined in Table 72.2.

Epidemiology

The most common age for presentation depends upon the epidemiology of the condition being treated by the culprit medication. While drug-related gingival hyperplasia due to the use of phenytoin is more common in those under the age of 25, cases secondary to calcium channel blockers mainly occur in middle-aged or older adults.

Clinical features

Evidence of gingival hyperplasia can be noted as early as one month after drug initiation, with the interdental papillae the most common initial site of involvement. The hyperplasia may extend over part or all of the involved teeth. Although edentulous areas are usually spared, significant hyperplasia under poorly maintained dentures has been reported. The enlarged gingiva is usually normal in color, firm, and nodular or lobulated. However, associated inflammation can lead to a red, edematous, or friable appearance.



CAUSES OF GINGIVAL HYPERPLASIA (ENLARGEMENT, OVERGROWTH)



Systemic medications	
Common	
Anticonvulsants (**phenytoin**, phenobarbital, lamotrigine, vigabatrin, ethosuximide, topiramate, primidone, valproate)	
Calcium channel blocking agents (**nifedipine**, amlodipine, diltiazem, felodipine, verapamil)	
Cyclosporine*	
Uncommon	
Antibiotics (clarithromycin, erythromycin, trimethoprim-sulfamethoxazole [co-trimoxazole])	Sertraline
Lithium	Oral contraceptives, estrogens
Amphetamines	Vemurafenib
Additional causes	
• Local inflammatory factors – poor oral hygiene, periodontal disease • Hormone-related – pregnancy, acromegaly • Granulomatous disorders – primary orofacial granulomatosis (cheilitis granulomatosa), Crohn disease, sarcoidosis • Granulomatosis with polyangiitis (formerly Wegener granulomatosis) • Vitamin C deficiency (scurvy) • Gingival fibromatosis/multiple gingival fibromas – tuberous sclerosis complex, Cowden syndrome, hereditary gingival fibromatosis • Leukemia – acute monocytic leukemia, acute myelomonocytic leukemia > other types of myelogenous or lymphocytic leukemias • Other malignancies – Kaposi sarcoma; metastases, in particular carcinoma of the breast, prostate, colon, kidney, or lung • Deposition – primary systemic amyloidosis, infantile systemic hyalinosis, mucopolysaccharidoses, fucosidosis, Fabry disease	
*There is evidence that substitution of tacrolimus for cyclosporine may lead to resolution or reduce the risk of recurrence after surgical removal of the hyperplastic tissue.	

Table 72.2 Causes of gingival hyperplasia (enlargement, overgrowth). Most common drugs in **bold**.

Pathology

Microscopically, the redundant tissue is of normal composition or exhibits fibrovascular hyperplasia. When the specimen is clinically inflamed, there is increased vascularity and a chronic inflammatory cell infiltrate.

Treatment

A rigorous regimen of oral hygiene consisting of frequent professional cleaning and home plaque control utilizing chlorhexidine rinses is recommended. Discontinuation of the suspected offending drug or even substitution with another drug of the same class may result in cessation or some regression of the gingival hyperplasia. If discontinuation of the suspected medication does not lead to improvement, gingivectomy may be considered.

ALLERGIC AND IMMUNOLOGIC DISEASES

Recurrent Aphthous Stomatitis

Synonyms: ■ Recurrent oral aphthae ■ Aphthous ulcers ■ Canker sores
Variants: ■ Minor aphthae ■ Major aphthae ■ Herpetiform aphthae ■ Complex aphthosis

Key features

- The etiopathogenesis is unknown, but immunologic factors may play a role
- Although individual ulcers often heal spontaneously, topical corticosteroids and systemic medications can be used to address disease activity

Introduction

Recurrent aphthous stomatitis (RAS) is a relatively common ulcerative disorder of the oral cavity. While the etiology remains obscure, it is likely multifactorial and influenced by a host of predisposing factors. Although most commonly idiopathic, RAS can be associated with Behçet disease, inflammatory bowel disease, cyclic neutropenia, HIV infection, and possibly hematinic (iron, folate, or vitamin B_{12}) deficiencies (Table 72.3)[9]. Complex aphthosis is defined as nearly constant disease with ≥3 oral ulcers +/− genital ulcers and requires a search for an underlying disease or syndrome.

Epidemiology

RAS is a common disorder affecting >20% of the population. Idiopathic disease usually presents during the second or third decades of life, with severity and frequency diminishing with age.

Clinical features

Four clinical subtypes of RAS have been described: minor, major, herpetiform, and complex (severe). *Minor aphthae*, the most common form, are characterized by round to ovoid, shallow, painful ulcers that are usually <1 cm in diameter (Fig. 72.14). The ulcers are typically limited to the non-keratinized ("movable") oral mucosa, with common sites of involvement including the labial and buccal mucosa, floor of the mouth, ventral surface of the tongue, soft palate, and oropharyngeal mucosa. These lesions usually heal without scarring within 1–2 weeks.

Major aphthae are characterized by larger, deeper ulcers, typically >1 cm. They persist for up to 6 weeks and may heal with scarring. Lesions are associated with considerable oral pain and are sometimes accompanied by fever and malaise. *Herpetiform aphthae* are uncommon, consisting of multiple (>10) small, painful ulcers that resemble primary HSV infection. They are typically confined to non-keratinized mucosa and after coalescing can mimic major aphthae. In *complex aphthosis* (*severe aphthae*), there are continuous recurrences of minor aphthae (see definition above)[10,11].

Pathology

Histopathologic features are relatively nonspecific. They include an ulceration with overlying fibrin and neutrophils and an underlying inflammatory infiltrate. In most patients, however, the appearance and distribution of lesions allow for the diagnosis to be made clinically.

Treatment

The primary goals of therapy are promotion of healing, management of pain and nutrition, and prevention of recurrence[12]. Typically, analgesia and topical corticosteroids significantly reduce pain and time to healing. The frequency of episodes is often reduced following topical corticosteroid therapy. Patients with complex aphthosis may require systemic therapy (Table 72.4).

Behçet Disease

Synonym: ■ Behçet syndrome

Key features

- Recurrent oral and genital aphthae
- Anterior or posterior uveitis and/or retinal vasculitis
- Erythema nodosum-like and papulopustular lesions

Behçet disease is a rare chronic multisystem disorder that is more prevalent in individuals whose ancestry includes regions along the ancient Silk Route (see Ch. 26)[12,13]. Disease activity may be intermittent, with exacerbations and remissions of unpredictable duration

RECURRENT APHTHAE – ETIOLOGIES AND DIFFERENTIAL DIAGNOSIS
Etiologies
• Idiopathic (immune-mediated) • Related to an underlying systemic disorder: inflammatory bowel disease, celiac disease, systemic lupus erythematosus, HIV infection, Behçet disease, MAGIC syndrome (*m*outh *a*nd *g*enital ulcers with *i*nflamed *c*artilage), reactive arthritis*, cyclic neutropenia, PFAPA (*p*eriodic *f*ever, *a*phthous stomatitis, *p*haryngitis and *a*denitis) syndrome, certain hereditary periodic fever syndromes (e.g. HIDS, NOMID) • Medications (e.g. mTOR inhibitor) • Possibly related to an underlying nutritional disorder (controversial): vitamin B_{12}, folate, or iron deficiency
Differential diagnosis
• Recurrent erosions and ulcerations due to an inflammatory disorder, e.g. erythema multiforme, fixed drug eruption, contact stomatitis, autoimmune bullous disease – less pain at onset, less peripheral erythema • Recurrent herpes simplex viral infection – only involves keratinized mucosa (hard palate, attached gingiva) in immunocompetent hosts (see Fig. 72.1) • Trauma – less pain at onset, less peripheral erythema, more ragged edges
*Previously referred to as Reiter disease.

Table 72.3 Recurrent aphthae – etiologies and differential diagnosis. Potential triggers are stress and specific foods (e.g. nuts, citrus, or acidic foods). HIDS, hyperimmunoglobulinemia D with periodic fever syndrome; HIV, human immunodeficiency virus; NOMID, neonatal-onset multisystem inflammatory disease.



Fig. 72.14 Recurrent aphthous stomatitis. Adjacent minor aphthous ulcers arising in non-keratinized mucosa. The ulcerations are shallow with a creamy white surface and surrounded by an intensely red halo, a characteristic finding. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*

and frequency. Multiple oral aphthae are often the first sign of the disease and are present in the vast majority of patients[13].

Systemic manifestations, clinical criteria for the diagnosis of Behçet disease, and treatment options are outlined in Tables 25.12, 25.14 and 25.15, respectively.

Autoimmune Bullous Diseases

Multiple erosions or ulcerations occur in several autoimmune bullous diseases, most commonly pemphigus vulgaris, but also mucous membrane pemphigoid, paraneoplastic pemphigus, bullous pemphigoid, epidermolysis bullosa acquisita, and linear IgA bullous dermatosis (see Chs. 29–31). The differential diagnosis includes multiple fixed drug eruption, herpetic infections, *Mycoplasma pneumoniae*-induced rash and mucositis (MIRM), and hemorrhagic bullous angina. The latter is an idiopathic or trauma-induced disorder that presents with recurrent hemorrhagic bullae within the oral cavity (usually the soft palate).

THERAPEUTIC LADDER FOR COMPLEX APHTHOSIS
Local therapy (agents may be used in combination)
Local anesthetics (2) Topical doxycycline hyclate (1) Superpotent topical corticosteroids (1*/2) or corticosteroid inhalers (2) Intralesional corticosteroids (2) Topical tacrolimus (3) Silver nitrate (1)
Systemic therapy
Intermittent prednisone (e.g. 20–40 mg/day × 4–7 days, 25 mg/day then taper over 2 months; up to 3 cycles/year) (3,1) Colchicine (1†/2) Dapsone (1†/2) Combination of colchicine and dapsone (2) Apremilast (1†/2) Thalidomide (1) Montelukast (1) TNF inhibitors (e.g. etanercept, adalimumab, infliximab, golimumab) (3)
*Clobetasol propionate in an adhesive denture paste. †In patients with Behçet disease.

Table 72.4 Therapeutic ladder for complex aphthosis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. *Adapted from Letsinger JA, et al. J Am Acad Dermatol 2005;52:500–8, with permission.*

CHEILITIS

Key features

- A general term used to describe inflammation of the lips
- Depending on the underlying cause, the clinical presentation and treatment may vary

Introduction

Cheilitis is an umbrella term used to describe inflammation of the lips, which may involve both the vermilion zone and the perioral region. It is caused by a variety of internal and external factors, most commonly contact dermatitis (irritant > allergic) and chronic UV exposure (Fig. 72.15 & 72.16).

Eczematous cheilitis

Eczematous cheilitis can be due to atopic dermatitis as well as irritant and allergic contact dermatitis. A combination of these dermatitides is also commonly seen. It typically presents with xerosis, scaling, erythema, and fissuring of the lips. Burning and pruritus are common symptoms.

Irritant contact cheilitis often results from chronic lip licking (lip-licker's dermatitis) as well as from environmental factors such as cold, wind, and low humidity (see Fig. 72.16A). Additional causative factors include irritants in cosmetics, foods, and oral hygiene products (see Ch. 15). Typically, the upper and lower lips are involved, with frequent

DIFFERENTIAL DIAGNOSIS OF CHEILITIS*

Common	Less common	Less common
Actinic cheilitis Lower >> upper vermilion lip (Fig. 108.4) Background of photodamage History of AKs, BCC, SCC May have diffuse hyperkeratosis and/or discrete AKs	**Allergic contact dermatitis** Both upper and lower lip involved (Fig. 14.7) Allergens include: fragrances/flavorings (e.g. oral hygiene products, cosmetics), preservatives, sunscreens (Fig. 72.16B) > topical antibiotics (e.g. neomycin), metals (e.g. nickel; perioral > vermilion lips), propolis, topical corticosteroids	**Lichen planus, LE & GVHD** Lacy pattern on lips and oral mucosa (Fig. 72.16C) Oral and lip ulcerations (Fig. 72.16D–F) Lesions of lichen planus or GVHD elsewhere
Irritant contact dermatitis Both lower & upper lip involved Often extends onto cutaneous lip Lip licking most common cause (Fig. 72.16A)	**Candidal cheilitis** Predisposing factors: dentures/orthodontic appliances, inhaled/oral corticosteroids, diabetes mellitus, HIV infection, deep oral commissure grooves, drooling Scattered white plaques on vermilion lip (Fig. 77.22B) May have erosions Angular fissures and plaques (Fig. 77.22C) More likely to have oral thrush (Fig. 77.22A) When severe, can become verrucous	**Cheilitis granulomatosa** Diffuse enlargement of lip (Fig. 72.16G) Superimposed processes may lead to secondary changes May be associated with scrotal tongue and 7th nerve palsy in Melkersson–Rosenthal syndrome Sarcoidosis and Crohn disease are causes of secondary orofacial granulomatosis
Atopic dermatitis Atopic diathesis Lesions of atopic dermatitis elsewhere Xerosis Angular fissures (Fig. 12.14A)		**Other** Medications, in particular retinoids Nutritional deficiencies (see Table 51.2) Kawasaki disease, MIS-C Plasma cell cheilitis

*Often a combination, e.g. atopic dermatitis plus irritant contact dermatitis.

Fig. 72.15 Differential diagnosis of cheilitis. Uncommon causes include exfoliative cheilitis, cheilitis glandularis, and associations with other cutaneous disorders (e.g. cutaneous lupus erythematosus, actinic prurigo, lichen sclerosus), systemic disorders (e.g. Crohn disease, sarcoidosis, syphilis), and genetic disorders (e.g. Down syndrome, KID syndrome). AKs, actinic keratoses; BCC, basal cell carcinoma; GVHD, graft-versus-host disease; MIS-C, multisystem inflammatory syndrome in children; SCC, squamous cell carcinoma. *Courtesy Jean L. Bolognia, MD.*



Fig. 72.16 Different causes of cheilitis. A *Irritant contact dermatitis* due to lip licking with involvement of the vermilion and cutaneous lips as well as the perioral region. **B** *Allergic contact dermatitis* to oxybenzone with involvement of the upper and lower vermilion lips. **C** *Lichen planus* with a white lacy pattern of the lower lip and central upper lip. **D** Erosive *lichen planus* of the vermilion and mucosal lower lip. **E** Multiple jagged erosions limited to the lower vermilion lip in a patient with cutaneous *lupus erythematosus*. **F** Chronic *graft-versus-host disease* in which gray-white plaques are at the periphery of broad erosions. **G** Secondary *orofacial granulomatosis* characterized by diffuse enlargement of the lower > upper lip in an adolescent girl with Crohn disease. Note the coalescing tiny pink papules of the lower cutaneous lip and upper chin. *A, Courtesy Jeffrey P. Callen, MD; B, D, Courtesy Kalman Watsky, MD; C, F, G, Courtesy Julie V. Schaffer, MD; E, Courtesy Luis Requena, MD.*

extension onto the cutaneous lip. *Atopic* cheilitis occurs in individuals with atopic dermatitis or an atopic diathesis and characteristically presents with xerosis and angular fissures in addition to erythema and scaling (see Fig. 12.14A). A number of allergens (see Fig. 72.15) can lead to *allergic* contact cheilitis (see Fig. 72.16B)[14]. Women are more commonly affected than men, presumably due to greater exposure to lipsticks and cosmetics. Patients typically present with erythema, scaling, edema, fissuring, and superficial erosions on both the upper and lower lips, oftentimes with extension to the perioral cutaneous regions. In addition to careful history-taking, patch testing can assist in identifying culprit allergens (see Ch. 14).

Treatment involves removal and future avoidance of any known or suspected irritants or allergens. Simple emollients, such as white petrolatum, should be used frequently. Low- to mid-potency topical corticosteroids or topical calcineurin inhibitors can be applied twice daily for 2–3 weeks. Prolonged use of topical corticosteroids should be avoided, as it can exacerbate perioral dermatitis.

Actinic Cheilitis (see below)

Angular Cheilitis

In angular cheilitis (perlèche), there is inflammation of the skin and adjacent labial mucosa at the lateral commissures (angles or corners) of the mouth. Moist, macerated erythematous patches may be accompanied by erosions, angular fissures, and soreness (see Fig. 77.22C); oral thrush and candidal cheilitis may also be present. It is caused by excessive moisture that accumulates in the oral commissure grooves along with secondary infection with *Candida albicans*, and less commonly *Staphylococcus aureus*. It can occur at any age but is most often seen in older individuals with deep oral commissure grooves due to recession of the alveolar ridges, including those who are edentulous and wear dentures. In young children, excessive drooling and thumb sucking are common causes.

Diagnosis is usually made clinically, but in more difficult cases a lesional swab for bacterial and fungal culture can be obtained. Treatment involves addressing predisposing factors (e.g. poorly fitting dentures) as well as treating secondary fungal and bacterial infections. A topical antifungal cream (e.g. ketoconazole, clotrimazole) +/– topical mupirocin ointment applied twice a day for 1–3 weeks is often used, and oral thrush, if present, is treated. Maintenance therapy includes nighttime use of a barrier emollient such as white petrolatum or zinc oxide paste.

Drug-Induced Cheilitis

Several medications have been associated with cheilitis, most notably systemic retinoids, indinavir, sorafenib, and anticholinergic medications. Systemic retinoids routinely cause xerosis, peeling, and fissuring of the lips, and the effect is dose-dependent (see Fig. 126.8). Some implicated medications cause xerostomia with associated dryness of the lips. Management while on the medication includes liberal use of emollients (e.g. white petrolatum).

Exfoliative Cheilitis

In exfoliative cheilitis, there is persistent exfoliation of the vermilion lips, with scaling, desquamation, crusting, and hyperkeratosis. It is thought to be caused by chronic injury, most often from excessive licking, biting, picking, or sucking of the lips. It is most common in women under the age of 30 and many patients deny or are not aware of the habit. Exfoliative cheilitis is a diagnosis of exclusion. Topical emollients (e.g. white petrolatum), corticosteroids, and calcineurin inhibitors may be helpful in reducing symptoms, but psychiatric care to address underlying obsessive-compulsive tendencies or anxiety is often needed.

Plasma Cell Cheilitis

Plasma cell cheilitis is a rare disorder that typically presents as a well-circumscribed, eroded, erythematous plaque on the lower > upper lip. It is clinically and histologically similar to Zoon balanitis/vulvitis and the diagnosis is made upon histopathologic features. Treatment is difficult and often involves a trial of potent topical or intralesional corticosteroids.

Cheilitis Glandularis

Cheilitis glandularis is a rare condition characterized by inflammatory hyperplasia of the minor salivary glands of the lower lip and it may occur in association with actinic cheilitis. The secretory ducts of these hyperplastic salivary glands become dilated and inflamed and appear as pinpoint orifices from which a sticky mucous substance can be extracted. In mild cases, sunscreen and topical corticosteroids may be helpful, while in severe cases, vermilionectomy and dissection of the hyperplastic minor salivary glands has been described.

Orofacial Granulomatosis (OFG)

Key features

- Persistent non-tender swelling of the lip and/or face
- Non-caseating granulomatous inflammation
- Both primary (idiopathic) and secondary subtypes
- Primary OFG includes cheilitis granulomatosa and Melkersson–Rosenthal syndrome

Introduction

Orofacial granulomatosis (OFG) is a term introduced in 1985 to describe a spectrum of diseases characterized by non-necrotizing, non-infectious granulomatous inflammation of the face and mouth *in the absence of systemic disease*[15]. More recently, the term OFG has been used more loosely to describe a group of disorders characterized by non-caseating granulomatous inflammation involving the face and mouth including systemic disorders such as sarcoidosis and Crohn disease. In order to reconcile these different viewpoints, it is best to consider OFG as either *primary* (idiopathic) or *secondary*. *Primary* OFG would include cheilitis granulomatosa (CG) and Melkersson–Rosenthal syndrome (MRS). *Secondary* OFG would then include localized and systemic associations such as allergic contact dermatitis, foreign body reaction, sarcoidosis, and Crohn disease (see Fig. 72.16G).

Epidemiology

CG is rare and primarily occurs in young adults without sex predilection. The etiology is unknown and multiple factors have been implicated, including allergy to foods, additives or flavorings, genetic predisposition, and infection.

Clinical features

CG is a chronic process that initially can present as intermittent (hours to days) swelling of either the upper or lower lip mimicking angioedema. With progression, the episodes of swelling increase in duration and lead to persistent, often disfiguring swelling that may involve both lips and occasionally the face. Rarely, CG is associated with recurrent facial palsy and/or lingua plicata (fissured tongue), termed Melkersson–Rosenthal syndrome (MRS).

Diagnosis is made upon clinicopathologic correlation and exclusion of other entities, including angioedema (improves spontaneously in 24–48 hours), Crohn disease, sarcoidosis, foreign body reaction, allergic contact dermatitis, and infection (e.g. tuberculosis, Hansen disease [leprosy], histoplasmosis, cutaneous leishmaniasis).

Pathology

The most striking feature of OFG is the presence of non-necrotizing, epithelioid granulomas; in many cases the granulomas are sparse.

Treatment

Treatment of CG is difficult with a tendency for relapse and incomplete remission. Topical or intralesional corticosteroids are typically first-line therapy. Weekly (×3) intralesional triamcinolone injections (40 mg/ml) into the lips is one reported regimen[16]. Other anecdotal treatment options include systemic corticosteroids, oral antibiotics (e.g. minocycline, metronidazole, clofazimine), adalimumab, methotrexate, and dapsone[17]. Refractory cases have been managed surgically, with reduction cheiloplasty.

Granulomatosis with Polyangiitis (Formerly Wegener Granulomatosis)

Key features

- Necrotizing granulomatous vasculitis of the upper and lower respiratory tract and necrotizing glomerulonephritis
- Destructive ulcerated lesions of the oral and nasal cavity
- Pathognomonic friable "strawberry gums" may be seen
- Up to 90% of patients have anti-neutrophil cytoplasmic antibodies (ANCA)



Fig. 72.17 Granulomatosis with polyangiitis – strawberry gums. The affected areas of the gingiva are red–purple, micropapular and friable, with a resemblance to ripe strawberries. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*

Introduction

Granulomatosis with polyangiitis (GPA) is an uncommon necrotizing granulomatous disease of unknown etiology (see Ch. 24). Clinically, there is both limited GPA (without renal involvement) and generalized GPA (see Fig. 40.6).

Epidemiology

Although individuals with GPA include children and the elderly, middle-aged adults are most commonly affected; there is no sex predilection.

Clinical features

Because GPA commonly involves the nose, nasopharynx, and paranasal sinuses, patients can present with epistaxis, sinusitis, or nasal ulcerations and obstruction. Destruction of the nasal cartilage may result in perforation of the nasal septum and/or saddle nose deformity[18]. The most characteristic oral manifestation is erythematous, friable gingival hyperplasia that easily bleeds, referred to as *strawberry gingivitis* (Fig. 72.17)[19,20]. Oropharyngeal, lingual, or gingival ulcerations may also be seen and tend to occur later in the course of the disease.

Pathology

For the gingival hyperplasia, histopathologic findings include papillary hyperplasia, granulation tissue, and a focal giant cell reaction. Histopathologic features of the cutaneous lesions are reviewed in Chapter 24.

Treatment

The treatment of classic GPA includes systemic corticosteroids, pulse cyclophosphamide, and rituximab[21]; oral lesions typically respond to these regimens (see Table 24.10).

EPITHELIAL PATHOLOGY

Oral Leukoplakia and Proliferative Verrucous Leukoplakia

Key features

- Leukoplakia and proliferative verrucous leukoplakia represent *clinical* diagnoses
- Leukoplakia is the most common potentially malignant disorder of the oral cavity
- Biopsy is mandatory in order to assess the degree of dysplasia and to exclude invasive SCC

Introduction

The World Health Organization (WHO) defines *oral potentially malignant disorders* (OPMDs) as "clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in clinically normal oral mucosa"[22]. The major OPMDs are leukoplakia (including proliferative verrucous leukoplakia), erythroplakia, erythroleukoplakia, oral lichen planus and discoid lupus erythematous, oral submucous fibrosis, smokeless tobacco keratosis, palatal lesions associated with reverse smoking, chronic candidiasis, and actinic cheilitis.

Oral leukoplakia is defined as "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer"[23]. In addition to smoking, excessive alcohol intake, betel nut use, older age, and male sex represent risk factors. Individuals who are immunocompromised or have genetic syndromes such as dyskeratosis congenita or Fanconi anemia also have an increased risk of developing oral leukoplakia. Proliferative verrucous leukoplakia (PVL) was first described in 1985 as a subset of leukoplakia. While sharing some features with leukoplakia, the transformation rate of PVL is far higher such that many consider PVL a distinct entity warranting a separate classification.

Epidemiology

Oral leukoplakia is the most common OPMD. It has a male predominance with a peak incidence after 50 years of age. In contrast, PVL is more common in older women and the majority have few to none of the traditional risk factors for leukoplakia and OSCC.

Clinical features

Oral leukoplakia presents as a white plaque or patch and is usually asymptomatic. Although leukoplakia can involve any site within the oral cavity, the tongue, floor of the mouth, gingivae, and buccal mucosa are the most commonly affected sites (Fig. 72.18)[24]. Based upon clinical presentation, oral leukoplakia is classified as: (1) *homogenous leukoplakia* – well-demarcated white plaque or patch that is mainly smooth-surfaced with varying degrees of surface fissuring; and (2) *non-homogenous leukoplakia*. The latter has three subtypes: (a) *erythroleukoplakia* – varying amounts of erythema within a well-demarcated, mostly white plaque and a patchy or speckled pattern; (b) verrucous leukoplakia – a rough surface that at times appears leathery and most commonly occurs on the gingivae; and (c) nodular leukoplakia – nodular surface, at least focally.

PVL is characterized by the progressive development of white, often verrucous and fissured, patches and plaques in multiple non-contiguous sites or as a single large lesion. Although the seventh decade represents the average age at the time of diagnosis, many patients have had the condition for years. Dysplasia is regarded as the best predictor of transformation, but a meta-analysis found that only 12% of dysplastic lesions transformed to OSCC. That said, as many as 70% of patients with PVL eventually develop OSCC despite their lack of traditional risk factors and benign histopathologic features in early stages.



Fig 72.18 Leukoplakia. Non-homogenous, sharply demarcated white plaque involving the left ventrolateral tongue.

Pathology

The diagnosis of both leukoplakia and PVL is clinically based, i.e. independent of the presence or absence of dysplasia. Nonetheless, biopsies are routinely obtained due to concern regarding OSCC. Histopathologic features vary from only hyperkeratosis to dysplasia to frank OSCC. Major features of dysplasia include irregular, altered epithelial architecture with loss of basal cell polarity, as well as nuclear pleomorphism, dyskeratosis, hyperchromasia, and an increased number of mitoses with superficial and atypical mitotic figures[22]. Dysplasia is graded from mild to severe, depending on the portion of the involved epithelium (lower third or more). A band-like inflammatory infiltrate can be seen in the upper lamina propria (lichenoid dysplasia) and should be differentiated from oral lichen planus.

Differential diagnosis

Entities in the differential diagnosis include leukoedema, in which the white to gray–white discoloration disappears with stretching (Fig. 72.19), white sponge nevus due to mutations in *KRT4* and *KRT13*, the leukokeratosis seen in patients with pachyonychia congenita (see Ch. 58), and oral lichen planus. Oral white plaques can also be seen in hereditary benign intraepithelial dyskeratosis, a disorder that occurs primarily in Native Americans.

Treatment

A baseline incisional biopsy is considered the gold standard for management of leukoplakia and PVL. Although complete excision of the lesion (via scalpel, CO_2 laser, or cryosurgery) has been proposed as first-line therapy by some authors, removal of OPMDs has not been proven to prevent the onset of OSCC[25,26]. When possible, surgical removal of the entire lesion is performed to avoid sampling error and to exclude OSCC. Habit cessation (in particular tobacco use), longitudinal evaluation by an oral medicine specialist, and repeat biopsies as indicated are recommended for all patients.

Erythroplakia

Key features

- Erythroplakia is less common than leukoplakia but is also a clinical diagnosis
- High likelihood of dysplasia or invasive SCC at the time of diagnosis

Introduction

The WHO defines erythroplakia as "a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease"[22]. Similar to leukoplakia, erythroplakia is an OPMD that is strongly associated with traditional risk factors for OSCC. A diagnosis of erythroplakia is only established after exclusion of other red lesions of the oral cavity.

Epidemiology

A rare condition that most commonly affects middle-aged and elderly men with traditional OSCC risk factors.

Clinical features

Erythroplakia typically presents as an asymptomatic, rather sharply circumscribed, velvety red patch or thin plaque. The most commonly involved sites are the floor of the mouth, tongue, soft palate, and buccal mucosa.

Pathology

Advanced dysplasia (see leukoplakia above) or invasive OSCC is found in >90% of lesional biopsies. In addition to a lack of keratinization and atrophy of the epithelium, varying degrees of cellular and architectural findings consistent with OSCC (see below) or dysplasia (see leukoplakia above) are seen in these cases.

Treatment

A baseline biopsy should be performed, with treatment based upon the histopathologic diagnosis. Patients with OSCC are referred to head and neck surgeons or oncologists. When possible, complete surgical removal of dysplastic lesions is performed to avoid sampling error and to exclude OSCC. Habit cessation (in particular tobacco use), longitudinal evaluation by an oral medicine specialist, and repeat biopsies as indicated are recommended.

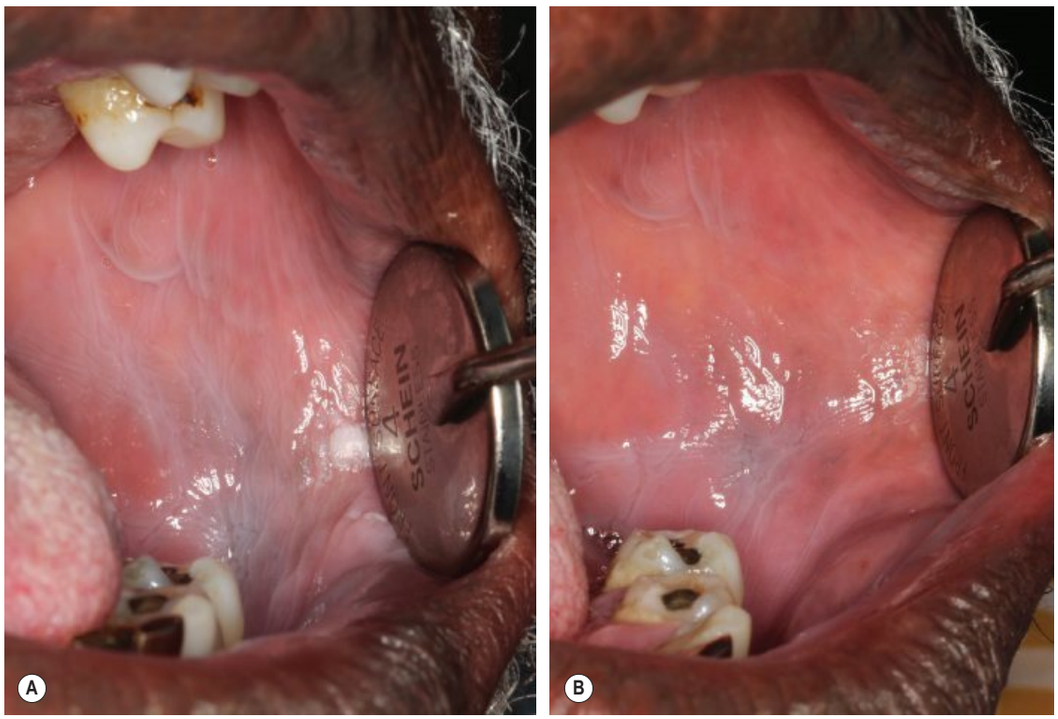


Fig 72.19 Leukoedema. A Diffuse grayish-white and wrinkled appearance of the left buccal mucosa. **B** These findings disappear when the cheek is stretched.

Nicotinic Stomatitis

Synonyms: ■ Nicotine stomatitis ■ Stomatitis nicotina

Key features

- Gray–white mucosa with umbilicated papules
- Caused by exposure of the palatal mucosa to intense heat from smoking, not nicotine

Introduction

Nicotinic stomatitis is most commonly observed in pipe, cigar, and reverse smokers. However, the resultant inflammation of the palatal mucosa is more closely linked to exposure to the intense heat from smoking rather than nicotine, as the name has erroneously implied. For example, identical lesions are observed in hot beverage drinkers[27]. The exact etiology in e-cigarette users is less clear and may be related to nicotine or other chemical compounds (e.g. strawberry flavoring) added to the liquid[28].

Epidemiology

Nicotinic stomatitis most frequently affects men in the fifth decade of life.

Clinical features

The palatal mucosa is thickened and has a diffuse gray or white discoloration. In addition, there are scattered 1–3 mm umbilicated papules with central red puncta which represent inflamed salivary gland orifices (Fig. 72.20). These changes are more prominent toward the posterior hard palate and anterior soft palate.

Pathology

The histopathologic features include hyperkeratosis, parakeratosis, acanthosis, and mild chronic sialodochitis, but the diagnosis is usually made on clinical grounds.

Treatment

Since habit cessation typically leads to resolution, it is necessary to exclude true leukoplakia or erythroplakia if any white or red plaque persists after habit cessation.



Fig. 72.20 Nicotinic stomatitis. Gray–white palatal mucosa with numerous umbilicated papules representing inflamed palatal salivary glands. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*

Actinic Cheilitis

Synonyms: ■ Actinic cheilosis ■ Solar cheilosis

Key features

- Primarily affects the vermilion zone of the lower lip in fair-skinned individuals
- Indicator of photodamage from cumulative sun exposure

Introduction

Actinic cheilitis is a common OPMD that has the same etiology as actinic keratoses (see Ch. 108). Given its relationship to chronic UV exposure, the vermilion zone of the lower lip is the primary mucosal site of involvement.

Epidemiology

Actinic cheilitis is most common in men over 40 years of age with skin phototypes I–II[29]. It reflects significant photodamage from cumulative exposure to UV irradiation.

Clinical features

Early features include loss of normal dermatoglyphics, atrophy, and blurring of the margin between the vermilion zone and the skin. Signs of progression to precancerous actinic cheilitis include scaling and roughness, sometimes in conjunction with leukoplakia (see Fig. 108.4). Although often localized initially, over time multifocal involvement is characteristic. Fissuring and erosions may also be present as the condition worsens. Some patients have concomitant cheilitis glandularis (see above).

Pathology

There is hyperkeratosis and variable thickness of the spinous layer as well as dysplasia of the lower part of the epithelium. Actinic cheilitis may be observed in contiguity with SCC *in situ* or invasive SCC.

Treatment

Actinic cheilitis frequently represents a "field change", and while worrisome clinical features may appear focal in nature, the photodamage and epithelial dysplasia are more extensive. Treatment options include topical 5-fluorouracil or imiquimod, photodynamic therapy, and cryosurgery. When severe or treatment-resistant, vermilionectomy with histopathologic examination is a therapeutic option. Any site suspicious for SCC should be biopsied, including prior to CO_2 laser ablation.

Oral Squamous Cell Carcinoma

Key features

- The most common malignancy of the oral cavity
- Develops primarily in middle-aged or elderly men
- Significant association with the use of tobacco and alcohol
- In contrast to oropharyngeal SCC, only a small percentage of oral SCCs are associated with HPV infection, particularly types 16 and 18
- Most common intraoral sites are the lateral and ventral surfaces of the tongue, floor of the mouth, and soft palate



Fig. 72.21 Squamous cell carcinoma. A Ulcerated leukoplakia of the ventrolateral tongue. **B** Ulcerated, indurated, exophytic mass involving the right lateral border of the tongue. Both are typical presentations for this tumor. *Courtesy Carl M. Allen, DDS, MSD, Charles Camisa, MD, and Kristin K. McNamara, DDS, MS.*

Introduction

SCC is the most common malignancy of the oral cavity, and may or may not be preceded by an OPMD. OSCC risk factors include tobacco use, excessive alcohol consumption, betel nut chewing (primarily in the Indian subcontinent and Southeast Asia), chronic immunosuppression, and genetic syndromes such as dyskeratosis congenita and Fanconi anemia. Human papillomavirus (HPV) infection, especially types 16 and 18, has been implicated in the etiopathogenesis of oropharyngeal SCC, with HPV-positive tumors associated with a more favorable outcome[30,31].

Epidemiology

OSCC accounts for >90% of all malignant neoplasms of the mouth. It is typically a disease of middle-aged or elderly men; however, an increasing incidence of oral SCC among women and younger patients has been noted. Globally, the overall age-adjusted incidence is 4 per 100 000 individuals, but there is marked variation depending upon geographic location[22,32]. For example, the Indian subcontinent has recorded an incidence as high as 22 per 100 000 and worldwide accounts for one-third of all OSCCs.

Clinical features

While any intraoral site may be affected, the most common locations are the lateral and ventral surfaces of the tongue, floor of the mouth, and soft palate. OSCC may present as an ulcer, a white plaque, an exophytic mass, or an endophytic process with varying degrees of induration (Fig. 72.21). The surface is typically irregular, rough, or granular. Early on lesions are often painless, but with disease progression and local invasion, patients may experience pain, paresthesia, dysphagia, dysphonia, or difficulty moving the tongue[33].

In comparison to cutaneous SCC, OSCC is significantly more aggressive and has a less favorable prognosis. The five-year survival rates for stage I or II disease approach 80%, while the 5-year survival rate for stages III and IV is <40%[34].

Pathology

OSCCs are histologically similar to those occurring elsewhere (see Ch. 108).

Treatment

Because treatment depends upon the clinical stage, computed tomography (CT), positron emission tomography (PET), and/or magnetic resonance imaging (MRI) may be required to determine the extent of local and distant disease. In general, smaller tumors (stages I and II) are surgically excised +/− sentinel lymph node biopsy or cervical lymph node dissection. For stages III and IV, various combinations of surgery, radiotherapy, chemotherapy, and immune checkpoint inhibitors are employed[35]. Patients have a 3%–7% annual risk of developing a second primary SCC of the upper aerodigestive tract after treatment of their original tumor[36].

Verrucous Carcinoma

Subtype/synonyms: ■ Oral verrucous carcinoma ■ Oral florid papillomatosis ■ Ackerman tumor

Key features

- Uncommon, low-grade variant of SCC
- Exophytic mass with a papillary or verrucous topography
- Characterized by slow, persistent growth

Introduction

Verrucous carcinoma is a rare, low-grade variant of SCC that may involve the oral, laryngeal, sinonasal, esophageal, or genital mucosa as well as the plantar surface of the foot (see Ch. 108). Oral verrucous carcinoma has been associated with the use of snuff and chewing tobacco. Although HPV-6, -11, -16, and -18 have sometimes been isolated from these tumors, the precise etiologic role of HPV remains unclear.

Epidemiology

Verrucous carcinoma typically affects men over 55 years of age.

Clinical features

The tumor location often corresponds to the site where intraoral tobacco has been chronically placed. Therefore, tumors most commonly develop in the mandibular vestibule, buccal mucosa, tongue, and gingiva. In populations where tobacco is placed under the tongue or in the maxillary vestibule, the floor of the mouth and hard palate are commonly affected.

Verrucous carcinoma presents as a slowly growing, exophytic, papillomatous, or warty proliferation with well-demarcated margins. The color depends on associated inflammation and degree of hyperkeratosis but is most often white. If left untreated, local destruction of underlying bone, muscle, and salivary glands may occur; metastases are rare.

Pathology

Histologically, there is hyperkeratosis, acanthosis, and a papillary or verrucous surface[37]. The epithelium is well differentiated, with minimal atypia and rare mitotic figures. A dense infiltrate of chronic inflammatory cells is frequently present in the superficial connective tissue. Multiple sections are recommended because up to 20% of verrucous carcinomas show foci of conventional OSCC (hybrid carcinoma).

Treatment

Compared to conventional OSCC, verrucous carcinoma has a better prognosis. The 5-year survival rate is 85%–90% with prognosis based upon stage at diagnosis. The treatment of choice is surgical excision[38]. Although cervical lymph node metastases are rare, sentinel lymph node biopsy can be performed. In contrast, hybrid carcinomas may metastasize and should be managed as conventional OSCC. Treatment failure has been attributed to extensive involvement, delayed diagnosis, comorbidities, and failure to identify hybrid carcinomas.

SALIVARY GLAND DISEASES

Mucocele

Synonyms: ■ Mucous cyst of oral mucosa ■ Mucous extravasation phenomenon

Key features

- Disruption of a minor salivary gland duct with resultant leakage of mucus into the submucosal tissue
- Fluid-filled, dome-shaped mucosal swelling ranging from a few millimeters to 1–2 cm
- Most commonly seen on the lower labial mucosa
- May require surgical excision

Introduction

Mucocele is a common disorder that results from disruption of a salivary gland duct and escape of mucus into the adjacent submucosal connective tissue (see Ch. 110). Although the term mucocele is sometimes used to describe both retention and extravasation mucoceles, these two conditions differ in location, etiology, and histopathology. The preferred term for a retention mucocele is salivary duct cyst. Herein, the term mucocele refers exclusively to extravasation mucocele.

Epidemiology

While the majority of mucoceles are detected in younger individuals (second through fourth decades), they can present at any age and are usually due to trauma. Patients with chronic oral GVHD can develop superficial mucoceles, primarily on the palate.

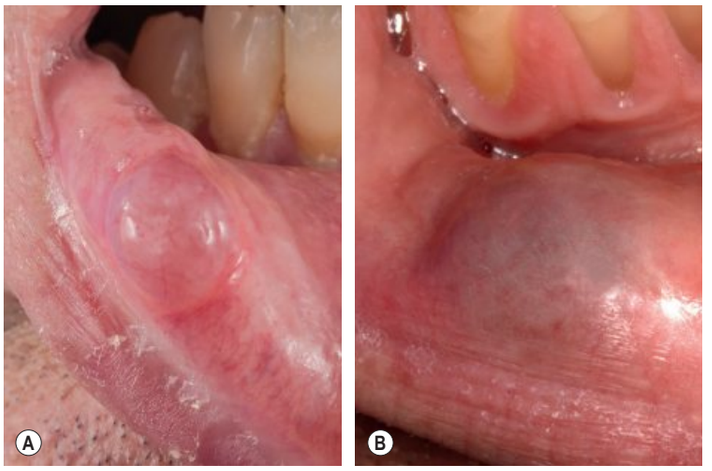


Fig. 72.22 Mucoceles of the mucosal lower lip. A Superficial mucocele that is translucent and has a vesicular appearance. **B** Slightly deeper mucocele presenting as a soft nodule with a bluish hue. This lateral location is commonly observed. *A, Courtesy Edward Cowen, MD.*

Clinical features

Mucoceles present as dome-shaped, mucosal swellings ranging from 1–2 mm to a few centimeters in size. Their color depends on the depth of the swelling relative to the surface mucosa, with very superficial lesions often appearing vesicular and slightly deeper mucoceles having a bluish tinge (Fig. 72.22); the deepest lesions have no discernible color change. In general, mucoceles are asymptomatic and undergo multiple cycles of swelling, rupturing, and then refilling. While the lower labial mucosa is the most common site of involvement, any oral mucosal area that contains minor salivary glands can potentially be affected[39]. In particular, mucoceles may develop on the ventral tongue, buccal mucosa, and posterior hard palate. A mucocele on the floor of the mouth and confined to sublingual tissues superior to the mylohyoid muscle is referred to as a *ranula*.

Pathology (see Ch. 110)

Treatment

While some mucoceles may resolve spontaneously, others require surgical excision. Other therapeutic modalities are outlined in Chapter 110.

Necrotizing Sialometaplasia

Key features

- Uncommon ulcerative process of the hard palate thought to be due to ischemia
- Frequently misdiagnosed as a malignancy, both clinically and histologically

Introduction

Necrotizing sialometaplasia is an uncommon, locally destructive disease that is most likely due to an interruption of the blood supply to salivary gland tissue, leading to ischemic necrosis[40]. While such a disruption in blood supply can follow local trauma, in most patients the cause of the ischemic injury is unknown. Very infrequently, a submucosal malignancy may occlude the palatal blood vessels[41,42].

Epidemiology

The condition is almost always seen in adults, with a slight male predominance.

Clinical features

The patient will typically report a sudden onset of swelling of the hard palate, in addition to localized pain, paresthesia, or anesthesia. Within 1–2 weeks, the ischemic tissue sloughs and the patient will often state that

"part of the roof of my mouth fell off". This leads to a well-demarcated ulcer with a smooth or minimally elevated border. By palpation, the ulcer has no underlying induration. A malignancy is often suspected clinically and therefore a biopsy is performed to exclude OSCC or a salivary gland tumor.

Pathology

Early on, acinar necrosis is seen, followed by squamous metaplasia of the salivary ducts, spillage of mucin into the surrounding connective tissue, and an associated inflammatory infiltrate. When present, preservation of the lobular architecture of the gland helps to distinguish necrotizing sialometaplasia from mucoepidermoid carcinoma and squamous cell carcinoma.

Treatment

Once a diagnosis of necrotizing sialometaplasia is established, additional treatment is not required. The condition resolves spontaneously within 5–6 weeks.

Sjögren Syndrome

Key features

- Autoimmune disorder characterized by keratoconjunctivitis sicca and xerostomia
- Primarily affects women

Introduction

Sjögren syndrome (SjS) is a chronic autoimmune connective tissue disease in which lacrimal and salivary gland dysfunction leads to dry eyes (keratoconjunctivitis sicca) and mouth (xerostomia) (see Ch. 45). While the etiology and pathogenesis of SjS remain unclear, patients do produce several autoantibodies, in particular anti-SSA/Ro and -SSB/La (see Ch. 40). Patients with SjS have a 40-fold increased risk of lymphoma, predominantly extranodal B cell non-Hodgkin type[43]. Diagnostic criteria for SjS are outlined in Table 40.4.

Epidemiology

SjS primarily affects women in their 50s and 60s.

Clinical features

Both the major and minor salivary glands may be involved, leading to reduced salivary production. Major gland involvement is clinically evident in fewer than one-half of affected patients, presenting as firm, diffuse, non-tender or slightly tender glandular enlargement that is usually bilateral.

Patients have variable degrees of ocular and oral dryness[44,45], usually with a gradual onset of symptoms. There may be changes in either quality (frothy) or quantity (reduced) of saliva and most patients have a lack of the usual pooling in the floor of the mouth. Affected patients may present with difficulty swallowing, dysgeusia, halitosis, dental caries along the gum line, difficulty wearing dentures, coated or hairy tongue, and oral candidiasis.

Pathology

An SjS diagnostic criterion is one or more foci of inflammatory cells (≥50 lymphocytes) in 4 mm^2 of minor salivary gland tissue (see Table 40.4)[45]. In major salivary glands, there are intraglandular infiltrates of lymphocytes as well as hyperplasia and metaplasia of salivary duct epithelia, forming the characteristic *epimyoepithelial islands*.

Treatment (see Table 40.5)

Salivary Gland Tumors

Key features

- Most commonly occur in the parotid gland
- Benign salivary gland tumors are more common than malignant tumors

THE DIFFERENTIAL DIAGNOSIS OF INTRAORAL TUMORS AND TUMOR-LIKE LESIONS	
Developmental lesions	

• Congenital inclusion cysts
  • Bohn nodules (alveolar ridge)
  • Epstein pearls (palate)
• Torus palatinus, torus mandibularis
• Lingual thyroid
	• Dermoid cyst
	• Enteric duplication cyst
	• Nasoalveolar (nasolabial) cyst
	• Lymphoepithelial cyst
	• Lymphatic/vascular malformation

Reactive/inflammatory conditions	
• Mucocele • Fibroma* • Oral melanoacanthoma • Eosinophilic ulcer	• Pyogenic granuloma • Peripheral giant cell granuloma • Necrotizing sialometaplasia • Nodular fasciitis
Benign salivary gland neoplasms	
• Pleomorphic adenoma • Lymphomatous papillary cystadenoma	• Monomorphic adenoma
Other benign neoplasms	
• Squamous papilloma • Infantile hemangioma • Angiomyoma • Myofibroma, hemangiopericytoma • Granular cell tumor† • Neurofibroma	• Schwannoma • Palisaded encapsulated neuroma • Melanotic neuroectodermal tumor of infancy • Ameloblastoma • Lipoma
Malignant salivary gland neoplasms	
• Mucoepidermoid carcinoma • Acinic cell carcinoma	• Adenoid cystic carcinoma
Other malignant neoplasms	
• Squamous cell carcinoma • Melanoma • Lymphoma^ • Kaposi sarcoma	• Rhabdomyosarcoma • Osteosarcoma • Fibrosarcoma • Liposarcoma
*Ossification may occur. †A congenital epulis represents a granular cell tumor of the alveolar ridge. ^Both B- and T-cell lymphomas can involve the mouth as can less common entities such as plasmacytomas and EBV^+ mucocutaneous ulcers.	

Table 72.5 The differential diagnosis of intraoral tumors and tumor-like lesions.

Introduction

Salivary gland tumors (SGTs) can occur in both minor and major salivary glands. They are considered primary epithelial neoplasms and there exists a wide array of distinct benign and malignant salivary gland tumors.

Epidemiology

The low incidence, ever-evolving classification, and disparities between old and new studies are some of the obstacles in estimating the true incidence of SGTs. Pleomorphic adenoma followed by lymphomatous papillary cystadenoma (Warthin tumor) are the most common benign SGTs and mucoepidermoid carcinoma followed by acinic cell carcinoma are the most common malignant SGTs (Table 72.5). SGTs account for <10% of head and neck tumors, with radiation, smoking, viral infections, and environmental exposures (e.g. nickel compounds) implicated in their development.

Clinical features

The parotid gland is the most frequent site of SGTs, and the majority (>70%) are benign. SGTs involving major glands present as a painless, rubbery to firm, slowly growing swelling. Less frequently, SGTs develop within submandibular, sublingual, or minor salivary glands. They can present as a painless submucosal mass or mucosal ulceration, most commonly of the posterior hard palate/anterior soft palate followed by the upper lip or buccal mucosa[46,47]. When malignant, SGTs occur most often in the sublingual gland followed by minor salivary glands.

Pathology

For a definitive diagnosis of SGT, histopathologic examination is required which demonstrates different features, depending upon the type of tumor. Ultrasound-guided fine needle biopsy may be performed prior to surgical intervention. For staging information, see https://cancer.net/cancer-types/salivary-gland-cancer/stages-and-grades.

Treatment

The treatment of benign SGTs consists of conservative surgical excision. Malignant tumors usually require more extensive surgery and postoperative radiation therapy.

ORAL MANIFESTATIONS OF HEMATOLOGIC/ONCOLOGIC DISEASE

Oral Mucositis

Key features

- Chemotherapy-induced oral mucositis usually develops in patients who have been treated with cytotoxic drugs and subsequently develop neutropenia
- Radiotherapy-induced oral mucositis most commonly occurs in patients treated for head and neck malignancies
- Erosions, ulcerations, and hemorrhagic crusting of the oral mucosa are seen
- Self-healing, but recurrent, in patients receiving multiple cycles of chemotherapy

Introduction

Oral mucositis (OM) is a common side effect of conventional chemotherapy, head and neck radiation therapy, immunotherapy, and targeted therapies (see Tables 21.15–21.18).

Epidemiology

A systematic review estimated the incidence of all grades of chemotherapy-associated OM to be 70%–87% in patients receiving myeloablative therapy prior to hematopoietic stem cell transplantation (HSCT) and 100% in patients who received radiation therapy for oral and oropharyngeal cancer[48]. Patients receiving conventional dose cytotoxic chemotherapy or targeted therapy are at a relatively lower risk for developing OM[49,50].

Clinical features

OM typically develops within a few days after conventional chemotherapy administration and within the second to third week of radiation therapy. While radiation-associated OM generally corresponds to the site of radiation, chemotherapy-induced OM characteristically involves non-keratinized surfaces (i.e. buccal mucosa, floor of the mouth, ventrolateral tongue, and soft palate). A white discoloration followed by atrophic mucosa with a loss of keratin are often the initial findings. The mucosa may also appear edematous, erythematous, and friable. Eventually a removable yellowish, fibrinopurulent membrane can form.

Oral side effects from immune checkpoint inhibitors (ICIs) may have a delayed onset and can present as lichenoid reactions with erythema, ulceration, reticulation, and hyperkeratosis. Oral erosions can also be seen in patients who develop ICI-associated erythema multiforme major, Stevens–Johnson syndrome, or bullous pemphigoid (see Table 21.18)[51,52]. Acute-onset salivary gland hypofunction has also been reported. In addition, patients receiving various classes of targeted anticancer therapies can have a range of oral side effects, including lichenoid, hyperkeratosis, and aphthous-like ulcers (see Table 21.16).

Regardless of the triggering therapy, OM is commonly associated with pain, burning, and discomfort. Xerostomia, dysgeusia, dysphagia, and difficulty speaking can occur and negatively impact patients' oral intake, oral hygiene, or quality of life. Patients with severe OM may require intravenous hydration and parenteral nutrition and, given their immunocompromised status, may develop secondary infections.

Treatment

OM typically resolves within 2–3 weeks post completion of chemotherapy or radiation therapy. Pain management with topical and systemic analgesics, nutritional support, and maintaining good oral hygiene represent standard treatments. Other interventions to reduce pain and discomfort include cryotherapy (placement of ice chips in the mouth) during bolus doses of chemotherapeutic agents, photobiomodulation, and mouthwashes that contain a topical anesthetic, Maalox®, and diphenhydramine[53,54]. Keratinocyte growth factor (palifermin) is FDA-approved for those receiving myeloablative therapy prior to HSCT but is not commonly used[55]. ICI-related lichenoid reactions may respond to topical or systemic corticosteroids.

Leukemia

Key features

- Associated intraoral findings include infections and gingival hemorrhage
- Gingival enlargement occurs most commonly with monocytic and myelomonocytic leukemias

Introduction

Approximately one-third of patients with acute and 10% with chronic leukemia develop one or more oral manifestations at some point during the course of their disease[56]. More commonly, they are infectious (e.g. herpes simplex, candidiasis) or inflammatory (e.g. GVHD) rather than neoplastic.

Clinical features

Patients often experience bruising or spontaneous and persistent hemorrhage due to thrombocytopenia. Leukopenia results in poor healing and an increased prevalence of bacterial and fungal infections while lymphopenia increases the risk of viral infections. The tissues may exhibit an overall pallor of anemia or ulcerative gingivitis. Diffuse, firm, non-tender gingival enlargement can result from infiltration of the gingival connective tissue by leukemic cells, primarily in patients with monocytic or myelomonocytic forms of leukemia.

Treatment

Multi-agent chemotherapy and allogeneic HSCT are most commonly used to treat acute leukemias. Leukemic infiltrates generally respond to therapeutic regimens for the underlying leukemia.

Lymphoma

Key features

- Non-Hodgkin lymphomas (NHLs) account for over 80% of lymphomas
- Relatively uncommon within the oral cavity, where it presents as extranodal disease

Introduction

Unlike Hodgkin lymphoma, up to 40% of NHLs may arise in extranodal sites, including the oral cavity. NHL is the second most common malignancy of the oral cavity, accounting for ~3.5% of all oral cavity malignancies. HIV-infected individuals appear to have a greater risk of developing oral NHL.

Clinical features

The head and neck region is the second most common extranodal site for NHL, after the gastrointestinal tract. The Waldeyer ring (oropharyngeal lymphoid ring that includes the tonsils) is the most commonly affected head and neck site, and the most common *intraoral* sites include the palate, buccal mucosa, tongue, and floor of the mouth. Lymphomas in these latter areas present as a soft to rubbery-firm, slowly growing, mucosa-colored to purplish swelling or mass. Ulceration may be present, mimicking OSCC, as well as overlying telangiectasias. Pain is usually not a prominent feature.

Pathology

NHLs of the oral cavity are primarily of the B cell type. However, involvement of the oral mucosa can be seen in patients with several types of cutaneous T cell lymphoma.

Treatment

Depending on type and stage, treatment options consist of chemotherapy, radiation therapy, targeted therapy (e.g. rituximab), chimeric antigen receptor therapy (CAR-T), and autologous or allogeneic HSCT.

Melanoma

Key features

- Oral mucosal melanomas are rare, constituting <1% of all melanomas
- Approximately one oral melanoma is detected annually per 10 million individuals in the US
- Predominantly affects men, with an average age of 55 years

Introduction

In contrast to cutaneous melanomas, *BRAF* mutations are present in <10% of oral melanomas while *c-KIT* (CD117) is overexpressed in a majority (~80%). The etiology of oral melanoma is unknown and UV exposure is not considered a risk factor. Oral mucosal melanomas account for <1% of all oral malignancies.

Clinical features

Oral melanoma can exhibit all the clinical features of cutaneous melanoma, including usually being painless. The preferred site is the hard palate, followed by the maxillary-attached gingiva. The differential diagnosis includes foreign body tattoo (Fig. 72.23), blue nevus, oral melanotic macule, physiologic pigmentation, drug-related pigmentation (Table 72.6), and melanoacanthoma. Occasionally these melanomas are amelanotic and then resemble erythroplakia, pyogenic granuloma, or OSCC.

Pathology

Histopathological features are similar to those of melanoma arising at other sites. PRAME positivity can be used to confirm the diagnosis and can assist in distinguishing melanoma from melanosis, although negativity may be rarely observed. For lesions devoid of melanin, the diagnosis may be confirmed by immunohistochemistry (e.g. SOX10; see Ch. 113). Of note, these mucosal melanomas are usually in a vertical growth phase at the time of diagnosis with the majority apparently having a minimal associated radial growth phase.

Treatment

The treatment of choice for oral melanoma is wide surgical excision with adequate negative margins[58]. Sentinel lymph node biopsy also provides useful prognostic information[59]. Targeted and immunotherapies may improve survival (see Ch. 113), but historically the overall 5-year survival rate for oral mucosal melanoma is only ~15%, with a median survival of <2 years.

ORAL MANIFESTATIONS OF SYSTEMIC DISEASE

Amyloidosis

Key features

- Systemic or localized deposition of fibrillar proteins
- May be primary or secondary
- Internally, most commonly affects the kidney and heart
- Amyloid deposits within the tongue can occur and may produce macroglossia

Introduction

In amyloidosis, there is extracellular deposition of pathologic insoluble fibrillar proteins (see Ch. 47). Systemic amyloidosis can be primary (e.g. associated with a plasma cell dyscrasia) or secondary (e.g. due to a chronic inflammatory disease). There are also inherited and age-related forms of amyloidosis.

Clinical features

Macroglossia, a classic feature observed in ~20% of patients with primary systemic amyloidosis, is characterized by firm enlargement of the tongue[60]. Scalloping of its edge can occur and sometimes secondary ulceration develops (see Fig. 47.8B). Translucent and hemorrhagic papules and plaques may also be seen on the tongue or in other oral mucosal sites (see Fig. 47.8A). Taste disturbances have been noted with or without macroglossia, and xerostomia can result from involvement of the salivary glands. Cutaneous and systemic features are discussed in Chapter 47.

DRUGS ASSOCIATED WITH ORAL MUCOSAL PIGMENTATION	
• Amlodipine	• Hydroxychloroquine
• Busulfan	• Hydroxyurea
• Capecitabine	• Imatinib mesylate
• Chloroquine	• Irinotecan
• Chlorpromazine	• Ketoconazole
• Clofazimine	• Minocycline
• Cyclophosphamide	• Phenolphthalein
• Doxorubicin	• Quinacrine
• Estrogen	• Quinidine
• 5-Fluorouracil	• Tetracycline
• Golimumab	• Zidovudine (AZT)

Table 72.6 Drugs associated with oral mucosal pigmentation[57].

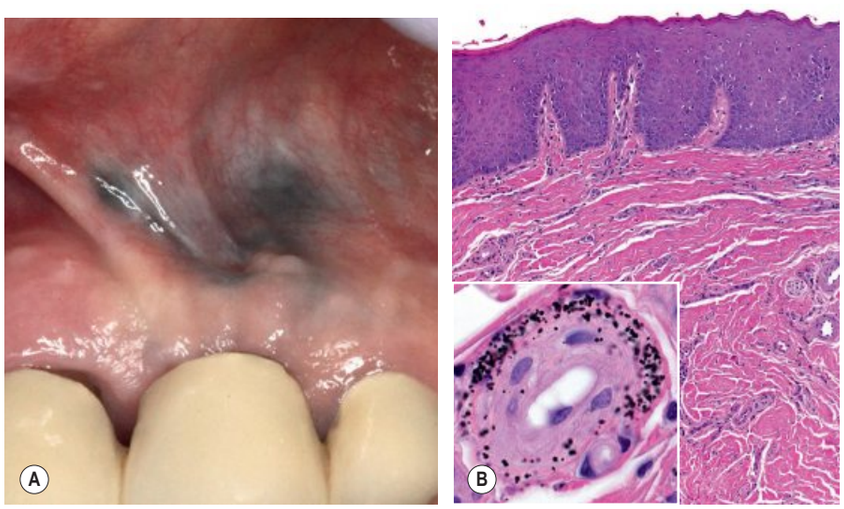


Fig. 72.23 Amalgam tattoo. Foreign body tattoos are the most common cause of acquired oral pigmentation, and most of them are due to iatrogenic implantation of dental amalgam. In this case (**A**), the amalgam was used to seal the apices of endodontically treated teeth, resulting in tattooing of the maxillary vestibule. **B** Histologically, darkly staining deposits are seen within the submucosa. Inset: black granular pigment within the secretory coil of a salivary gland. *A, Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD; B, Courtesy Lorenzo Cerroni, MD.*

Pernicious Anemia

Key features

- Most common cause of vitamin B_{12} deficiency
- Immunologically mediated condition with antibodies directed against intrinsic factor and parietal cells of the stomach
- Tongue may appear smooth and beefy red

Introduction

Pernicious anemia is an autoimmune disorder characterized by megaloblastic hematopoiesis and/or neuropathy due to vitamin B_{12} deficiency. It is associated with atrophic gastritis and the production of autoantibodies directed against intrinsic factor and gastric parietal cells. The malabsorption of vitamin B_{12} results from intrinsic factor deficiency. B_{12} deficiency also occurs post-gastrectomy, in vegetarians, and in individuals with tapeworm infections.

Epidemiology

Pernicious anemia is a relatively common disorder, occurring in up to 2% of adults over 60 years of age. The disease occurs 20 times more frequently in close relatives, suggesting a genetic predispostion[61].

Clinical features

Pernicious anemia typically has an insidious onset, with patients eventually presenting with symptoms of anemia. Peripheral neuropathies are frequently observed, along with CNS involvement that ranges from demyelination to axonal degeneration.

Oral manifestations consist primarily of glossitis and stomatitis[62], and these changes may occur in the absence of symptomatic anemia. Atrophic glossitis manifests as a smooth, "beefy-red" tongue, with patchy, ill-defined areas of erythema gradually evolving to more diffuse dorsal tongue involvement (Fig. 72.24). Some patients experience a generalized sore mouth or burning sensation. Taste disturbances have also been reported. The differential diagnosis of atrophic glossitis includes other nutritional deficiencies (e.g. folate, iron, niacin, riboflavin) and candidiasis.

Treatment

Vitamin B_{12} replacement often leads to rapid improvement of oral signs and symptoms.

Crohn Disease

Key features

- Chronic granulomatous disorder affecting any segment of the gastrointestinal tract from the oral cavity to the anus
- Most commonly affects the distal ileum and/or proximal colon
- Oral involvement is uncommon and usually presents as linear ulceration of the buccal vestibule, although persistent swelling of the labial or buccal mucosa may be seen

Introduction/epidemiology

Crohn disease represents an idiopathic chronic granulomatous disorder of the gastrointestinal tract. The condition has also been termed "regional enteritis", due to the alternating of affected areas with unaffected areas. Crohn disease is usually diagnosed before the age of 30 years, with peak prevalence in the second and third decades; a second diagnostic peak is composed of patients over 50 years of age. There is no significant sex predilection, but White individuals are affected more frequently than other ethnic groups[63] and there is familial clustering. Oral involvement occurs in 5%–15% of patients and it precedes gastrointestinal manifestations in up to 30% of those with disease in both sites.

Clinical features

Linear fissures and/or ulcers of the vestibule are the most common clinical presentation (Fig. 72.25). Patients may also present with persistent, firm, painless swelling of the labial or buccal mucosa. Thus, there is a resemblance to cheilitis granulomatosa, both clinically and histologically. Cobblestone lesions of the buccal mucosa and vestibule, oral aphthae, and pyostomatitis vegetans are additional findings. Sequelae include oral fibrosis and adhesions.

Pathology

Histologically, non-necrotizing epithelioid inflammation is seen in the submucosa.

Treatment

Oral lesions typically respond to systemic therapies for gastrointestinal disease (e.g. sulfasalazine, TNF inhibitors, corticosteroids), but topical and intralesional corticosteroids can be employed for oral manifestations.



Fig. 72.24 Pernicious anemia/candidiasis. Erythematous, atrophic tongue as a manifestation of pernicious anemia with a superimposed candidal infection. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*

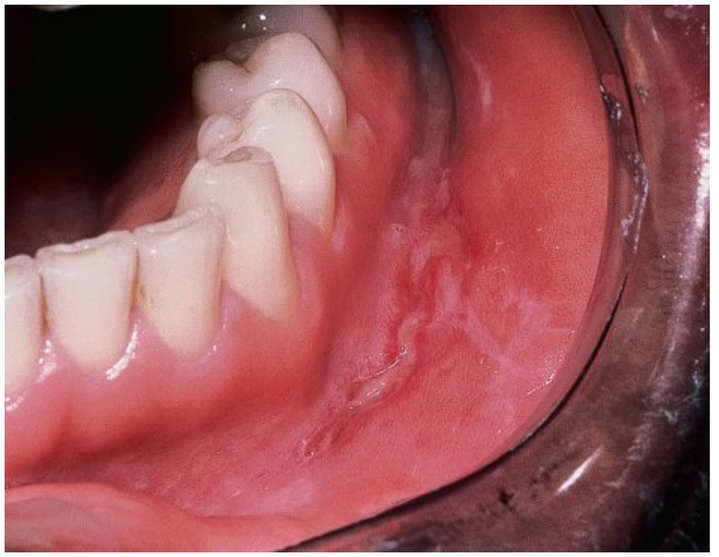


Fig. 72.25 Crohn disease. Linear ulceration of the mandibular vestibule: the classic oral manifestation of this disease. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*

Pyostomatitis Vegetans

Key features

- Typically associated with inflammatory bowel disease
- Multiple "snail-track" pustules superimposed upon diffuse mucosal erythema

Introduction

Pyostomatitis vegetans is a rare mucocutaneous disorder that is often associated with an underlying gastrointestinal disorder such as ulcerative colitis or, less commonly, Crohn disease. Pyostomatitis vegetans may represent an oral mucosal variant of pyoderma gangrenosum.

Epidemiology

Most commonly diagnosed in individuals 20 to 60 years of age, with men affected more frequently than women.

Clinical features

Pyostomatitis vegetans is characterized by multiple, tiny, creamy-yellow pustules within a background of diffuse intense erythema. The pustules are often arranged in a linear serpentine fashion and are described as having a "snail-track" appearance. The pustules are easily ruptured, leading to shallow erosions and ulcerations (see Fig. 26.9A). While any area of the oral cavity may be affected, the labial, gingival, and buccal mucosa are most commonly involved. The dorsum of the tongue is usually spared.

Pathology

Intraepithelial and/or subepithelial microabscesses containing numerous eosinophils as well as neutrophils are seen.

Treatment

Treatment focuses on controlling any underlying gastrointestinal disease with management of the latter often resulting in improvement of the oral lesions. Application of topical corticosteroids may also prove beneficial.

Oral Manifestations of HIV Infection

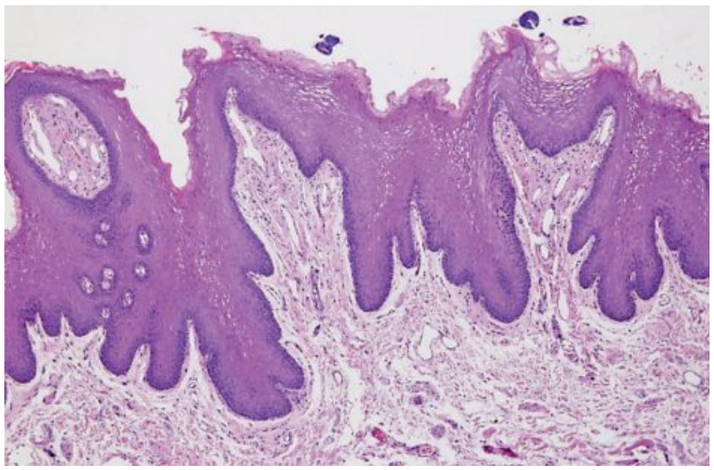
This subject is reviewed in Chapter 78.

Additional figures and tables on Topical care for oral inflammatory conditions, and Systemic diseases with oral manifestations, available in our eBook (see inside front cover for access code).

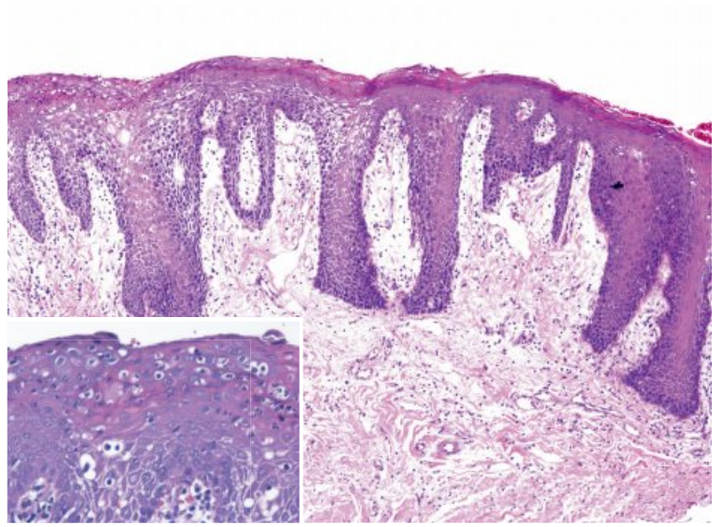
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eFig. 72.1 Dorsal tongue. Papillary surface architecture with parakeratosis and focal superficial bacterial colonization.



eFig. 72.2 Geographic tongue. Elongation of rete ridges with parakeratosis and variable neutrophilic infiltration. Inset shows collections of neutrophils (Munro abscesses) in the superficial spinous layers. This is called a psoriasiform mucositis because histopathologic features are similar to those of psoriasis.



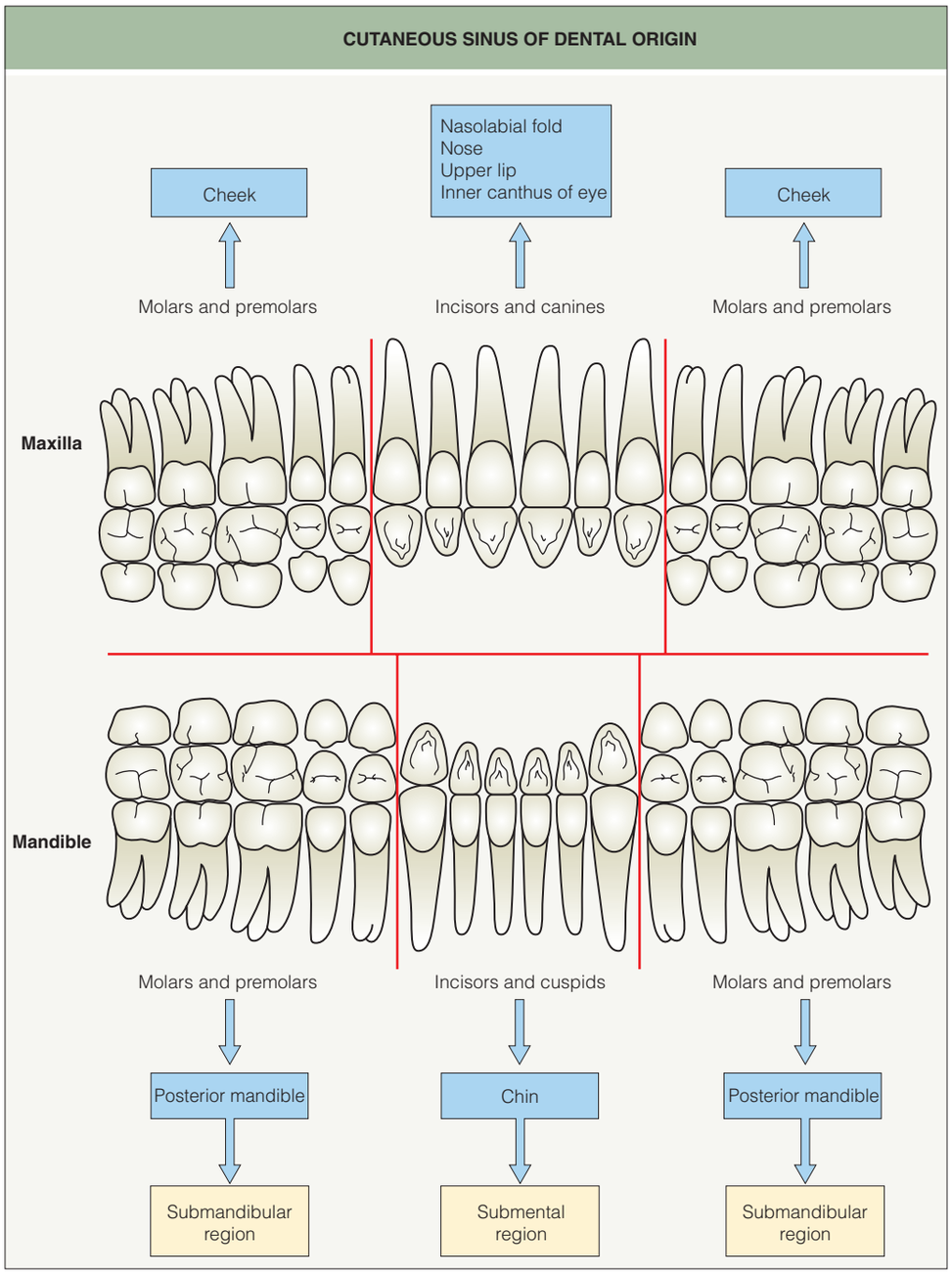
eFig. 72.3 Multiple endocrine neoplasia type 2B (MEN 2B). Enlarged lips and multiple neuromas of the tongue. *Courtesy Edward Cowen, MD.*



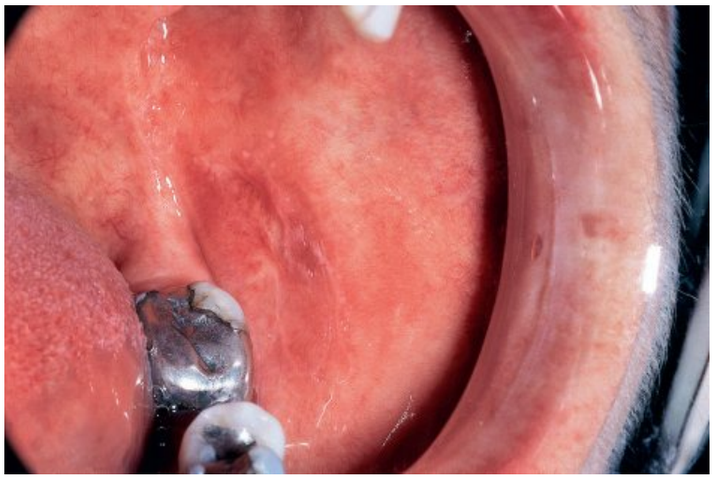
eFig. 72.4 Desquamative gingivitis. See Fig. 72.7 for evaluation to determine underling etiology. *Courtesy Luis Requena, MD.*



eFig. 72.5 Cutaneous sinus of dental origin. This sinus originated from a periapical dental abscess in the maxilla that then channeled through the overlying skin to drain. The pink–red papule may be mistaken for a pyogenic granuloma or a neoplasm, but note the associated indentation of the surrounding skin. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*



eFig. 72.6 Typical pathways and sites of extraoral drainage of dental sinuses. The majority of cutaneous sinus tracts are associated with mandibular teeth. *Adapted from Ciof GA, Terezhalmy GT, Parlette HL. Cutaneous draining sinus tract: an odontogenic etiology. J Am Acad Dermatol 1986;14:94–100, with permission from The American Academy of Dermatology, Inc.*



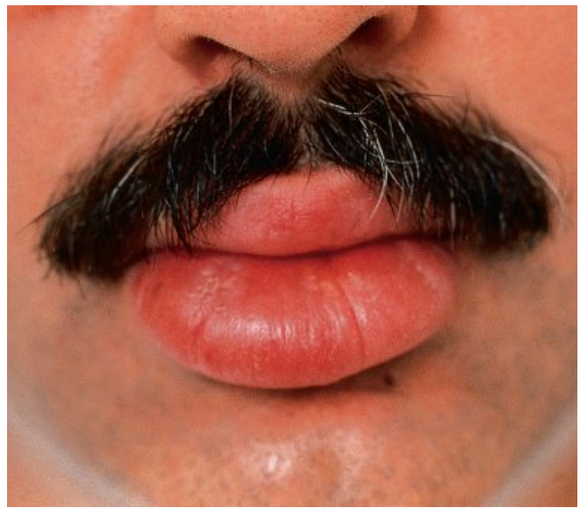
eFig. 72.7 Lichenoid contact stomatitis secondary to dental amalgam. Superficial erosions with radiating white striae are localized to the buccal mucosa adjacent to a large amalgam restoration. Of note, lichenoid amalgam reactions generally develop on movable mucosa in direct contact with surfaces of adjacent amalgam fillings (e.g. buccal mucosa, ventrolateral tongue). *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*



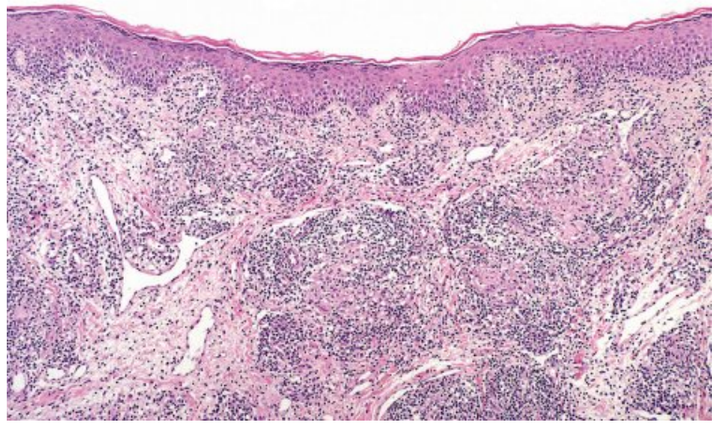
eFig. 72.8 Lichenoid contact stomatitis secondary to dental amalgam. Erythema and radiating hyperkeratosis of the left buccal mucosa and left ventrolateral surfaces of the tongue adjacent to large amalgam restorations in a patient with positive patch test results.



eFig. 72.9 Cheilitis glandularis. Inflammatory hyperplasia of the lower labial salivary glands may result from chronic irritation and can arise in association with actinic cheilitis. The secretory ducts of the salivary glands become dilated and inflamed and appear as pinpoint red mucosal macules. The clinical presentation varies from slight hypertrophy of the lower lip to nodular enlargement resulting in eversion. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*



eFig. 72.10 Cheilitis granulomatosa (primary orofacial granulomatosis). Slightly asymmetric swelling, predominantly of the lower lip. A biopsy specimen demonstrated non-caseating granulomas and causes of secondary orofacial granulomatosis were excluded (e.g. Crohn disease, sarcoidosis). Patients are sometimes misdiagnosed as having angioedema. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*



eFig. 72.11 Orofacial granulomatosis – histopathologic features. In the dermis, diffuse inflammatory infiltrate with several small epithelioid granulomas; the epidermis shows nonspecific changes represented by an interface dermatitis with a few necrotic keratinocytes.



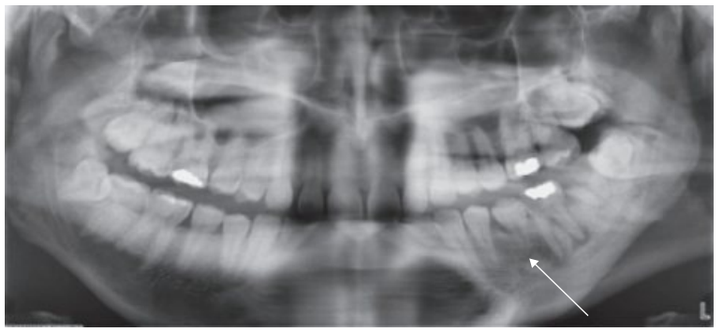
eFig. 72.12 Leukoplakia. Sharply demarcated, white plaque involving the ventral surface of the tongue and floor of the mouth. *Courtesy Carl M. Allen, DDS, MSD and Charles Camisa, MD.*



eFig. 72.13 Leukoedema. Diffuse grayish-white and wrinkled appearance of the left buccal mucosa. *Courtesy Carl M. Allen, DDS, MSD, Charles Camisa, MD, and Kristin K. McNamara, DDS, MS.*



eFig. 72.14 Crohn disease. Linear ulceration of the mandibular vestibule: the classic oral manifestation of this disease.



eFig. 72.15 Panorex dental x-ray in a patient with a dental sinus. There is periapical radiolucency in the left mandible at the site of the premolars and molars (arrow). *Courtesy Margaret Johnston, MD, and Jean Bolognia, MD.*

TOPICAL CARE FOR ORAL INFLAMMATORY CONDITIONS
Oral hygiene
• Soft toothbrush • Water pick, soft-tipped gum pick, or waxed tape-type dental floss to remove plaque • Non-alcohol-based mouthwash • Avoid trauma, e.g. biting cheeks, sharp/rough dental restorations/appliances • Rinses with baking soda +/– salt diluted with water (1 tsp of each in 4 cups of water)
Topical anesthetics for erosions/ulcers
• 2% viscous lidocaine (to surface of ulcers or as swish and spit) • "Magic mouthwash" with equal parts of: (1) 2% viscous lidocaine; (2) diphenhydramine 12.5 mg/5 ml; (3) magnesium and aluminum hydroxide plus sulcralfate (Maalox®) • Dyclonine lozenges
Topical anti-inflammatory medications
• Corticosteroids, e.g. clobetasol 0.05% gel/ointment, fluocinonide 0.05% gel/ointment, triamcinolone 0.1% paste (can be placed on gauze or in trays) • Dexamethasone elixir 0.5 mg/5 ml, swish and spit 5 ml BID–TID (leaving in mouth for 5 minutes)* • Corticosteroid inhaler • Tacrolimus 0.1% ointment • Tacrolimus 1 mg capsule dissolved in 0.5–1 L of water, swish and spit 5 ml BID (leaving in mouth for ≥2 minutes)*
Prevention of secondary infection†
• Clotrimazole 10 mg troches 4 times/day • Nystatin suspension (400,000–6000,000 units), swish and swallow 4 times/day • Chlorhexidine 0.12% oral rinse, swish and spit BID • Dilute hydrogen peroxide (one part 3% solution, 2 parts water), swish and spit BID
*Especially for patients with more widespread involvement. †Consider for patients with extensive oral erosion/ulceration, especially if using topical or systemic immunosuppressive agents.

eTable 72.1 Topical care for oral inflammatory conditions. *Courtesy Julie V. Schaffer, MD.*

SYSTEMIC DISEASES WITH ORAL MANIFESTATIONS	
Disease	**Characteristic oral findings**
Endocrinologic disorders	
Addison disease	Diffuse oral mucosal pigmentation
Diabetes mellitus	Severe periodontal disease, oral candidiasis, enlarged parotid glands
Genodermatoses	
Chronic mucocutaneous candidiasis/APECED syndrome	Thick white plaques due to candidiasis, enamel defects
Autosomal dominant (STAT3-deficient) hyper-IgE (Job) syndrome	Retention of primary teeth, candidiasis, high-arched palate
Cowden syndrome	Multiple mucosal-colored papules favoring the tongue, gingivae, lips, and buccal mucosa
Darier disease	Whitish papules and plaques favoring palate and gingivae
Dyskeratosis congenita	Leukoplakia may be premalignant or malignant and favors the tongue and buccal mucosa; may be preceded by bullae and erosions
Ectodermal dysplasias	Hypodontia, cone-shaped teeth, xerostomia
Epidermolysis bullosa	Fragility and vesicles/bullae; scarring results in reduced depth of the labial vestibule, microstomia, and ankyloglossia
Gardner syndrome	Osteomas of the maxilla and mandible, supernumerary and impacted teeth
Hereditary benign intraepithelial dyskeratosis	Diffuse thick white plaques favoring the buccal mucosa and labial mucosa
Hereditary hemorrhagic telangiectasia	Multiple red papules (AVMs) of the vermilion lip and oral mucosa; blanch with diascopy and can bleed
Incontinentia pigmenti	Hypodontia, cone-shaped and hypoplastic teeth, delayed dental eruption
Lipoid proteinosis	Diffuse infiltration or cobblestoned papules that favor the lips and tongue/frenulum, xerostomia
Multiple endocrine neoplasia type 2B	Mucosal neuromas favoring the lips and tongue
Basal cell nevus syndrome	Odontogenic keratocysts of the mandible > maxilla
Pachyonychia congenita	Thick white plaques favor the lateral and dorsal tongue
Peutz–Jeghers syndrome	Lentigines of the lips and oral mucosa
Tuberous sclerosis complex	Oral fibromas, dental enamel pits
White sponge nevus	Diffuse, bilateral, thick white plaques that favor the buccal mucosa
Xeroderma pigmentosum	Squamous cell carcinoma of the lower lip and tip of the tongue

eTable 72.2 Systemic diseases with oral manifestations.

Continued

SYSTEMIC DISEASES WITH ORAL MANIFESTATIONS	
Disease	**Characteristic oral findings**
Hematologic disorders	
Agranulocytosis	Necrotizing deep ulcerations that favor the gingivae, buccal mucosa, tongue, and palate
Aplastic anemia	Gingival hemorrhage plus petechiae, purpura, and ecchymoses due to thrombocytopenia, mucosal pallor, infections
Cyclic neutropenia	Recurrent episodes of oral ulcerations, especially of the gingivae, lips, tongue, and buccal mucosa
Extranodal NK/T cell lymphoma, nasal-type	Ulceration of the hard palate
Langerhans cell histiocytosis	Loosening of teeth, gingival erythema, ulcerations and bleeding, gingival papulonodules
Leukemia, especially (myelo)monocytic forms	Gingival hemorrhage, infections, gingival enlargement due to leukemic infiltration
Plasma cell dyscrasias, including multiple myeloma	In some patients with primary systemic amyloidosis, amyloid deposits can lead to macroglossia with scalloping of the tongue edge (due to dental impressions) as well as hemorrhagic papulonodules and ulcerations, xerostomia
Extramedullary plasmacytomas	Upper respiratory tract is common site; occasionally arise within oral cavity
Neutropenia	Infections, particularly bacterial, oral ulcerations
Non-Hodgkin lymphoma, including mycosis fungoides	Non-tender, boggy swellings favoring the buccal vestibule, posterior hard palate, or gingivae
Thrombocytopenia	Petechiae, purpura, ecchymoses, and spontaneous gingival hemorrhage
Immunologic disorders	
Behçet disease	Oral aphthous-like ulcers
Chronic ulcerative stomatitis	Oral erosions and ulcerations plus white striae
Systemic sclerosis, including CREST syndrome	Telangiectasias, microstomia, gingival recession, firm tongue, xerostomia
Erythema multiforme major, Stevens–Johnson syndrome	Oral erosions and ulcerations, hemorrhagic crusting of the vermilion zone of the lips
Graft-versus-host disease	White striae that resemble oral lichen planus, xerostomia, leukoplakia, mucocele
Lichen planus (LP) > lichenoid drug eruption or LP pemphigoides	Interlacing white lines (Wickham striae), oral erosions and ulcerations, desquamative gingivitis
Lupus erythematosus	White striae that resemble oral lichen planus, erythema, erosions, ulcerations; red and white plaques of the midline hard palate
Mucous membrane pemphigoid	Oral erosions and ulcerations, with vesicles or bullae occasionally seen, desquamative gingivitis
Paraneoplastic pemphigus	Oral ulcerations and hemorrhagic crusting of the vermilion zone of the lips
Pemphigus vulgaris	Ragged erosions and ulcerations, desquamative gingivitis
Sarcoidosis	Orofacial granulomatosis, xerostomia, salivary gland enlargement
Sjögren syndrome	Xerostomia
Granulomatosis with polyangiitis (Wegener granulomatosis)	Gingival hemorrhage with a friable micropapular surface (“strawberry gums”); non-healing ulcerations
Inflammatory bowel disease	
Crohn disease	Orofacial granulomatosis, linear ulcerations of buccal vestibule, aphthous-like ulcers, oral mucosal cobblestoning
Ulcerative colitis > Crohn disease	Pyostomatitis vegetans with oral pustules and erosions in a “snail-track” arrangement
Nutritional deficiencies	
Iron deficiency and B_{12} deficiency	Atrophic glossitis, stomatitis
Vitamin C deficiency (scurvy)	Gingival enlargement, hemorrhage, and erosions
Other	
Kawasaki disease	Cheilitis, diffuse oropharyngeal erythema, and strawberry tongue
MIS-C secondary to SARS-CoV-2 infection	Cheilitis, oral erosions, strawberry tongue

eTable 72.2 Systemic diseases with oral manifestations. AVM, arteriovenous malformation; CREST, calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias; MIS-C, multisystem inflammatory syndrome in children.

Anogenital (Non-venereal) Diseases 73

Susan M. Cooper

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INTRODUCTION

The diagnosis and management of skin diseases in the anogenital region may be complex. The juxtaposition of urinary, genital, and alimentary tracts gives rise to special considerations at this site (Fig. 73.1), and disease of any of these major systems may present with cutaneous manifestations. A number of systemic diseases such as Crohn disease and zinc deficiency preferentially affect the anogenital area. Local factors, including warmth, moisture, irritants, friction, and the effects of body fluids, are important in this region, contributing to skin problems.

Skin conditions may be more difficult to diagnose in the anogenital region than at other cutaneous sites, as the typical appearance of a particular skin disease may be lacking and there may be a hesitation to perform biopsies. Examination of the scalp, nails, mouth, and extragenital skin frequently assists in diagnosis. Special considerations apply to treatment, as the natural occlusion of this area may increase the percutaneous absorption of topical corticosteroids, with the potential for cutaneous atrophy and/or hypothalamic–pituitary–adrenal axis suppression. Warmth and moisture increase the risk of bacterial and yeast infections.

Only a limited number of symptoms in the anogenital area are possible, and pruritus and genital pain may be the presenting feature of a wide variety of diseases.

LICHEN SCLEROSUS

Synonyms: ■ Lichen sclerosus et atrophicus ■ Balanitis xerotica obliterans (men) ■ Kraurosis vulvae (women)

Key features

- Chronic inflammatory disease with a predilection for the anogenital region
- Pruritus is the most frequent symptom
- Major clinical signs are pallor, atrophy, fissures, and foci of hyperkeratosis
- Scarring may cause loss of the normal architecture of the vulva in women and phimosis in men

Introduction

Lichen sclerosus is a chronic inflammatory disease that preferentially affects the anogenital region, although any cutaneous site may be affected; 15%–20% of patients with genital lichen sclerosus will have extragenital disease. Symptoms may be longstanding as there is frequently a delay in diagnosis. Patients require long-term evaluation due to the risk of scarring and the risk of developing squamous cell carcinoma (SCC)[1].

Epidemiology

Lichen sclerosus is 6–10 times more prevalent in women than in men. The disorder may occur at any age, but the two peaks of onset are childhood and after menopause (or in the 4th or 5th decade in men). Although most studies have centered on White European patients, there are reports of lichen sclerosus occurring in Africans and Asians. Powell et al.[2] calculated a prevalence of 1 in 660 women and an annual incidence of 52/100 000 in postmenopausal women. The incidence of lichen sclerosus in boys may be underestimated; when foreskins of circumcised boys were examined, 14% were found to have the characteristic features of lichen sclerosus[3].

Etiology

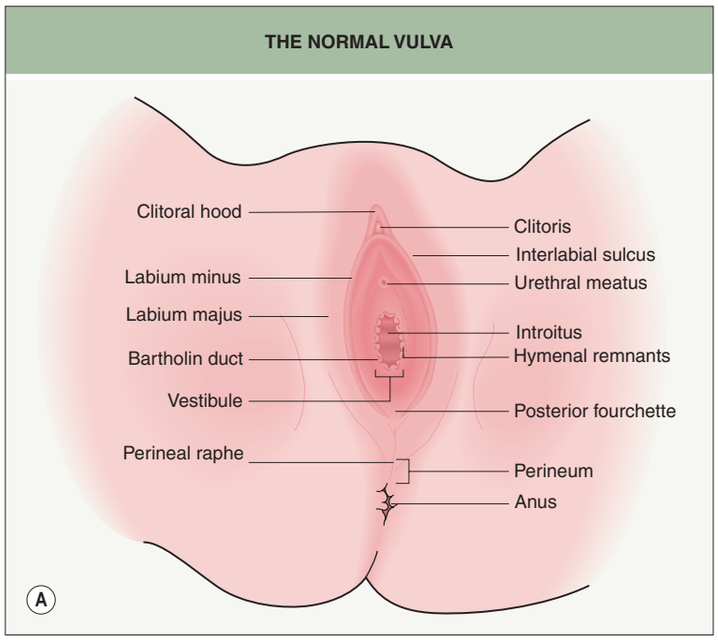
The cause of lichen sclerosus is unknown. In women, there is evidence to support an association with autoimmunity and heritability. Autoantibodies to extracellular matrix protein 1 (ECM1) are found in the majority of women with lichen sclerosus, but their role in pathogenesis is uncertain. A heritable risk is suggested by the occurrence of familial cases, as well as an association with HLA-DRB1*12 (and the related haplotype DRB1*12/DQB1*0301/04/09/010)[4] and autoimmune disorders such as thyroid disease[5]. However, in male patients, familial cases are uncommon, and HLA and autoimmune associations are rarely observed[6].

An infectious etiology has been proposed, but *Borrelia* or other spirochetal infection has not been confirmed in large studies. Local friction or rubbing may induce lesions of lichen sclerosus via the Koebner phenomenon, and some cases of early-onset lichen sclerosus may be associated with the antiandrogenic oral contraceptive pill. In men, chronic exposure of susceptible epithelium to urine due to naviculomeatal dysfunction (microurinary incontinence) has been proposed as causative[7]. Of note, lichen sclerosus of the penis does not occur in men circumcised at birth[6]. Whether urinary dysfunction plays a role in women and children is not known.

Clinical features

Both male and female patients may present with pruritus or soreness, but rarely are entirely asymptomatic[1,8]. Dyspareunia is frequently reported. Children with lichen sclerosus are more likely to present with urinary or bowel symptoms (e.g. constipation), purpura, or even hemorrhagic bullae, which may lead to a misdiagnosis of child abuse[8].

In women and girls, the characteristic clinical findings are vulvar hypopigmentation and thin, wrinkled, atrophic skin in a figure-of-eight distribution encircling the vulvar and perianal region (Fig. 73.2). Focal areas of hyperkeratosis, erosions, and fissures are frequently seen, with the perineum a common location for fissures. Additional cutaneous features that are helpful in identification are purpura (Fig. 73.3), telangiectasias, and rarely, hemorrhagic bullae. The hemorrhagic component can occasionally be so pronounced that it mimics a vascular lesion. Because lichen sclerosus is a scarring disease, architectural change is common (Fig. 73.4). Burying of the clitoris secondary to midline fusion or fusion of the labia minora to the labia majora may occur. In untreated or severe disease, there may be total loss of the labia minora



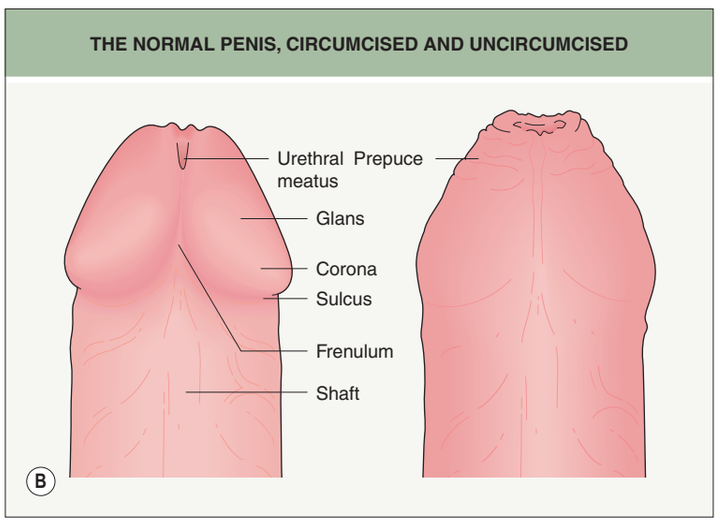


Fig. 73.1 Genital anatomy. A The normal vulva. **B** The normal penis, circumcised and uncircumcised.



Fig. 73.2 Anogenital lichen sclerosus in a girl. Hypopigmented, shiny skin in a figure-of-eight configuration with purpura, multiple erosions, and foci of hyperkeratosis. *Courtesy Julie V. Schaffer, MD.*



Fig. 73.3 Lichen sclerosus of the vulva with characteristic purpura. *Courtesy Kalman Watsky, MD.*

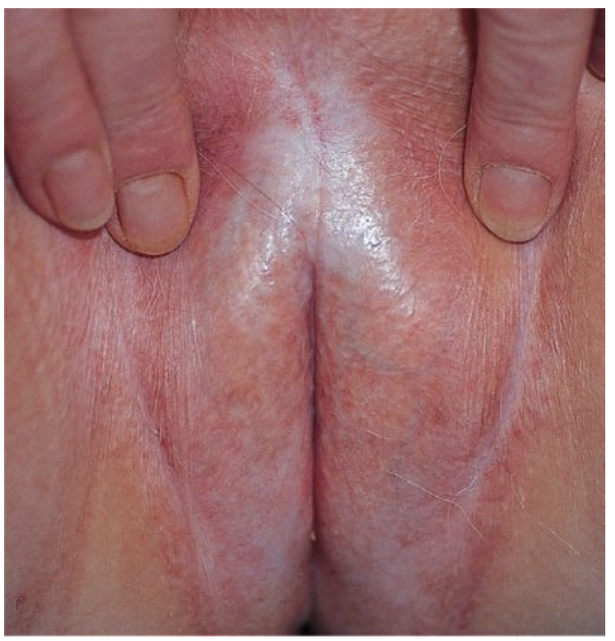


Fig. 73.4 Lichen sclerosus of the vulva. There is marked architectural change with loss of the labia minora and marked midline fusion.

and narrowing of the introitus. Darkly pigmented lentigines with an irregular outline may arise within areas of involvement.

Lichen sclerosus affects the glans penis and foreskin of men and, in contrast to women, involvement of the perianal region is uncommon. The disease usually presents with pruritus, pain, and dyspareunia[9]. Affected boys may have recurrent balanitis and a poor urinary stream, and circumcision is sometimes required. Men may report painful erections or erectile dysfunction as well as dysuria and spraying, dribbling, or poor flow of urine. Clinically, gray–white discoloration, purpura, and scarring can be seen (Fig. 73.5), leading to phimosis, paraphimosis, or constrictive posthitis. Additional architectural changes include coronal adhesions, reduced coronal sulcus and rim, and narrowing of the urethral meatus.

Extragenital lichen sclerosus favors the submammary region, as well as the shoulders, neck, and wrists, presenting as asymptomatic, hypopigmented, wrinkled patches with follicular plugging (see Ch. 44); occasionally, there are multiple guttate lesions. The diagnosis is established by a combination of the characteristic clinical and histologic findings.

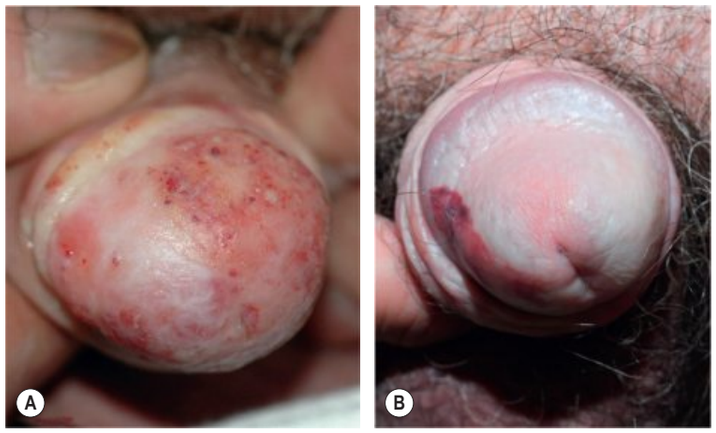


Fig. 73.5 Lichen sclerosus of the penis. A Erythematous and white plaque on the glans. **B** Shiny hypopigmented plaques of the glans in addition to purpura. *A, Courtesy Luis Requena, MD; B, Courtesy Kalman Watsky, MD.*

Pathology

The principal histologic findings are compact orthokeratosis, follicular plugging (in non-mucosal sites), a thinned epidermis, vacuolization of the basal layer, and hyalinization of the papillary dermis. A dense band-like lymphocytic infiltrate is often observed. Squamous hyperplasia may be present and may be associated with an increased risk of SCC. In bullous lichen sclerosus, there is extensive vacuolar degeneration of the basal layer with clefting and hemorrhage. Early on, the papillary dermis may be edematous and homogenous, but, with time, hyalinization and sclerosis are observed.

Histologic examination of the skin is recommended as it can be difficult to distinguish lichen sclerosus from mucous membrane (cicatricial) pemphigoid or erosive lichen planus on the basis of clinical appearance alone. Occasionally, despite marked clinical changes, the disease cannot be confirmed histologically and repeat biopsies over time may be needed to establish the diagnosis. Of note, in genital lesions, a dense band-like lymphoid infiltrate with several intraepithelial lymphocytes may be the only histopathologic finding, with hyalinization of the superficial collagen absent or only present focally. In lesions that have been treated with potent topical corticosteroids, ascertaining the diagnosis histologically may also prove challenging.

Differential diagnosis

Very mild or early disease may be confused with dermatitis. The presence of genital scarring necessitates the exclusion of other scarring disorders such as erosive lichen planus and mucous membrane pemphigoid. The absence of oral or vaginal mucosal involvement helps to distinguish lichen sclerosus from erosive lichen planus. In children, sexual abuse must be considered, as lichen sclerosus and sexual abuse are not mutually exclusive. Associated pruritus and topical therapies can lead to superimposed lichen simplex chronicus as well as allergic or irritant contact dermatitis. Histologically, the presence of a dense lymphoid infiltrate may be misdiagnosed as mycosis fungoides; the latter diagnosis, especially in the genital region, requires compelling evidence, particularly in children.

Treatment

The main aim of therapy is to bring the disease under control as quickly as possible with the fewest side effects. For induction treatment (after the diagnosis is established), a superpotent topical corticosteroid such as clobetasol propionate 0.05% ointment is prescribed until signs and symptoms improve, typically 1 to 3 months[1,9–13]. This alleviates symptoms in the majority of patients, often within weeks. Subsequently, the corticosteroid is tapered over 2–3 weeks and clinical remission maintained by limited (typically twice weekly) application of a higher potency corticosteroid or daily application of a lower potency topical corticosteroid. In some women, there is complete resolution of signs as well as symptoms, with the exception of scarring, which is irreversible[8]. Beyond preserving clinical remission, maintenance therapy has been associated with a reduced occurrence of SCC[12].

In the management of vulvar lichen sclerosus without secondary SCC, there is no longer a role for vulvectomy. For longstanding disease in which narrowing of the introitus has resulted in dyspareunia, surgical refashioning with division of adhesions may be helpful. Vaginal dilators may also be needed, in addition to psychosexual counseling to address the psychological distress that frequently accompanies lichen sclerosus.

In male patients, first-line therapy consists of potent topical corticosteroids, with cotton swab/bud application for meatal involvement[9]. Those with urinary symptoms should be evaluated by a urologist. If treatment does not lead to improvement or a tight phimosis is present, circumcision is often necessary.

Longitudinal evaluation is essential for patients with lichen sclerosus because both men and women are at increased risk of developing genital SCCs (estimates of the risk are 2%–6%)[9,11,12]. Women with childhood-onset lichen sclerosus may be particularly at risk of developing genital SCC, and notably the myth that childhood lichen sclerosus resolves at puberty has been debunked[14]. Women with lichen sclerosus may develop *differentiated* vulvar intraepithelial neoplasia (VIN), which has a higher risk of developing into invasive SCC when compared to high-grade squamous intraepithelial lesion (HSIL); the latter is an HPV-associated disease and was previously known as undifferentiated VIN. Men are at risk of penile intraepithelial neoplasia. Non-healing fissures, ulcers, or nodules must be examined histologically. Written educational material and patient support groups are very helpful. It is essential that patients who notice any features of malignancy seek prompt medical assessment.

The first- and second-line therapies for anogenital lichen sclerosus are outlined in Table 73.1.

MANAGEMENT OF ANOGENITAL LICHEN SCLEROSUS ℞

General

- Soap substitutes and regular use of emollients* (e.g. white petrolatum) (3,2)
- Apply white petrolatum prior to urinating, to minimize dysuria (2)
- Silk or cotton underwear
- Consider nighttime sedation, until pruritus controlled, to minimize scratching (3)
- Estrogen replacement (topical or systemic [if not contraindicated]) for postmenopausal women with atrophic vulvovaginal disease (2)
- Circumcision for phimosis or paraphimosis (2)
- Regular (at least yearly) examination for SCC

First-line

Induction

- Superpotent (Class I) topical corticosteroid* (e.g. clobetasol 0.05% ointment) applied once to twice daily until signs and symptoms resolve (typically 1–3 months) (1), then taper to maintenance

Maintenance†

- Superpotent (Class I) topical corticosteroid* twice weekly at bedtime (1)
  – *OR* –
- Potent (Class II, e.g. mometasone furoate 0.1% ointment) topical corticosteroid* twice weekly (1) – *OR* –
- Midpotency (Class V) topical corticosteroid* daily (2)
- Topical calcineurin inhibitors 2–3 times a week‡ (1)

Second-line

- Intralesional triamcinolone acetonide (e.g. 5–10 mg/cc monthly) (1)
- Oral retinoids (e.g. acitretin 10–50 mg/day for >6 months) (1)
- Methotrexate (2)
- Hydroxychloroquine (3)
- JAK inhibitors
- UVA1 (50 J/cm^2) (1)
- Photodynamic therapy (2)
- Fractional CO_2 laser (especially for hyperkeratotic plaques) (3)
- Circumcision, if unresponsive to medical treatment (3)
- Surgery to correct narrowing of introitus and reverse clitoral burying (3)

*Ointments are preferred over creams because they are less irritating.
†Ongoing maintenance, regardless of symptoms, has been shown to decrease the development of SCC.
‡Adding in tandem after topical corticosteroids rather than concurrently may reduce associated burning; some clinicians avoid chronic use because the long-term risk is unknown and there is an increased risk of secondary SCC in lichen sclerosus.

Table 73.1 Management of anogenital lichen sclerosus. Topical JAK inhibitors and dupilumab have been used for extragenital lichen sclerosus. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. SCC, squamous cell carcinoma.

LICHEN PLANUS

Synonyms: ■ Vulvovaginal gingival syndrome/vulvo-vaginal-gingival syndrome (erosive lichen planus in women) ■ Peno-gingival syndrome in men ■ Mucosal lichen planus

Key features

- Four distinct forms of genital lichen planus are observed: (1) papules or plaques in the setting of generalized cutaneous lichen planus; (2) erosive disease; (3) hypertrophic disease; and (4) lichen planopilaris
- Although cutaneous disease is often self-limiting, mucous membrane disease is more persistent
- The classic findings in cutaneous disease are violaceous, flat-topped papules and plaques; lacy white streaks typically occur on the genitalia as well as the oral mucosa
- Erosive lichen planus often involves multiple mucous membrane sites – in particular, the vulva, vagina, and oral mucosa

Introduction

Approximately 50% of women and 25% of men with cutaneous lichen planus have genital involvement. The classic violaceous papules and plaques typically affect the labia minora and majora or the mons pubis in women and the glans or shaft of the penis in men. Erosive lichen planus is a distinct subtype of the disease, characterized by severe, scarring erosive disease of the vestibule, introitus, vagina, and oral cavity[13,15]. Hypertrophic genital lichen planus and lichen planopilaris are the least frequent forms.

Epidemiology

Lichen planus is more common in women, generally presenting in the sixth decade. The exact prevalence is unknown, but it is likely that some cases of genital involvement in cutaneous lichen planus may be missed.

Etiology

Lichen planus probably represents T cell-mediated damage to epidermal cells that express altered self or foreign antigens on their surface, but the exact etiology is unknown (see Ch. 11). There is an autoimmune phenotype (see Lichen sclerosus above) in female patients with vulvar lichen planus and an association with autoimmune disease[5]. While some cases of lichen planus may be drug-induced, there are no definite associations with genital disease. Infectious triggers, particularly hepatitis C viral infection, may be associated with mucosal lichen planus in certain parts of the world such as the Mediterranean basin and Japan.

Clinical features

There are four distinct presentations of genital lichen planus[15,16], as follows:

- In *classic* lichen planus, the genital lesions are similar to those in other cutaneous sites, but lacy reticulation may be very prominent. Genital involvement is usually limited to the mons pubis and the labia majora and minora in women or the glans penis and shaft in men (see Fig. 11.4B). Penile plaques are frequently annular (Fig. 73.6A). Scarring is not a feature of classic lichen planus. Severe cutaneous pruritus is the usual presenting symptom, but genital lesions may be asymptomatic. Lesions are usually self-limited.
- *Erosive* lichen planus occurs much more frequently in women than in men. Pain and dyspareunia are the most common complaints. In female patients, extensive erosions occur around the vaginal orifice, edged by lacy white reticulations; similar lesions may also occur on the labia (Fig. 73.6B). Erosive lichen planus frequently leads to scarring, resulting in distortion of the vulvar architecture[13]. In severe cases, there may be complete obliteration of the vaginal canal and urinary retention. Vaginal involvement can present with a discharge, erythema and contact bleeding of the vaginal mucosa, and/or scarring with adhesions. Oral involvement is frequently observed, usually in the form of a desquamative gingivitis, but lacy white reticulations and erosions may also occur. Erosions limited to the perianal area alone have been described.
- In the *hypertrophic* form of lichen planus, hyperkeratotic white plaques on the vulva or shaft of the penis may be seen.
- In *lichen planopilaris*, follicular keratotic papules are limited to the hair-bearing labia majora and the mons pubis, but may also be seen on the scalp and trunk and in the axillae.

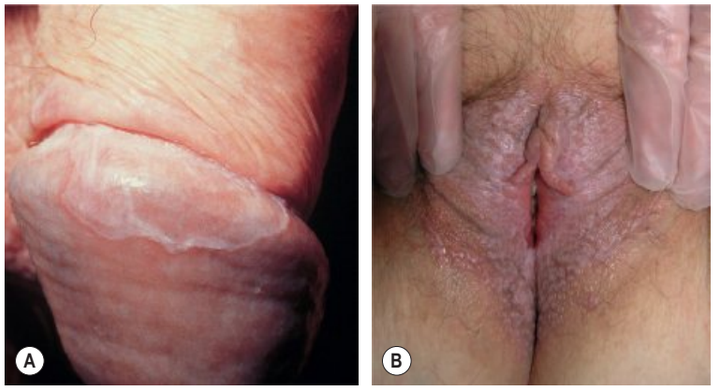


Fig. 73.6 Lichen planus. A An annular band is seen on the glans of the penis. This is a typical finding. **B** Erosive lichen planus of the vulva with fissures and an extensive white lacy pattern. *A, Courtesy R. Turner, MD.*

Pathology

The typical histologic findings are irregular epidermal acanthosis, accentuation of the granular layer, liquefactive degeneration of the basal layer, and a band-like dermal infiltrate of lymphocytes. It is more difficult to interpret biopsy specimens of mucous membranes, where these findings are more variable. Because there is loss of the epithelium in erosive disease, the specimen should include the edge of the erosion as well as the surrounding lacy reticulated skin. Despite this, it is sometimes difficult to unequivocally confirm the disease, but histologic evaluation can aid in excluding other disorders in the differential diagnosis.

Differential diagnosis

The principal entities in the differential diagnosis are lichen sclerosus; autoimmune bullous disease, including mucous membrane pemphigoid; Zoon (plasma cell) vulvitis; Behçet disease; graft-versus-host disease; and high-grade squamous intraepithelial lesion (HSIL; previously referred to as undifferentiated vulvar intraepithelial neoplasia) or SCC. Direct immunofluorescence may be necessary to exclude an autoimmune bullous disease. Orogenital ulceration raises the possibility of Behçet disease (see Ch. 26). For oral lesions, lupus erythematosus is in the differential diagnosis, but this would be unusual in the anogenital region. Early lichen planus may be confused with vulvar eczema and there may be superimposed lichen simplex chronicus. For hypertrophic disease, HSIL, SCC, and lichen simplex chronicus are the major entities in the differential diagnosis.

Treatment

The treatment of genital lichen planus is outlined in Table 73.2. Potent or moderately potent corticosteroid ointments will control most symptoms of classic genital lichen planus, as the disease is usually self-limiting. Hypertrophic disease may require intralesional corticosteroids.

The management of erosive lichen planus is more difficult, as the disease is often more persistent[15–17]. The majority of patients will respond to a 3-month course of topical clobetasol propionate 0.05% ointment (as described for lichen sclerosus) and thereafter can be maintained on moderately potent corticosteroids or twice weekly application of the potent corticosteroid. A combination of a moderately potent corticosteroid with a topical antifungal cream (e.g. econazole) may be as effective as more potent corticosteroids, particularly for maintenance therapy. For refractory disease, anecdotal case reports describe benefit from intralesional corticosteroid injections, topical calcineurin inhibitors, oral hydroxychloroquine, systemic immunosuppressants, and acitretin (see Table 73.2). Tricyclic antidepressants can be used to treat associated vulvodynia. Erosive vaginal disease requires

MANAGEMENT OF ANOGENITAL LICHEN PLANUS Rx
General
• Soap substitutes and regular use of emollients* (e.g. white petrolatum) (3) • Apply white petrolatum prior to urinating, to minimize dysuria (3) • Consider nighttime sedation, until pruritus controlled, to minimize scratching (3) • Estrogen replacement (topical or systemic [if not contraindicated]) for postmenopausal women with atrophic vulvovaginal disease (3)
First-line
Induction
• Superpotent (Class I) topical corticosteroid* (e.g. clobetasol 0.05% ointment) applied once to twice daily until signs (e.g. erosions) and symptoms resolve (1), then taper to maintenance • Intravaginal corticosteroids (*for vaginal disease*) nightly until controlled and then taper to maintenance (2); consider combining with weekly oral fluconazole (150–200 mg/week) for vulvovaginal candidiasis prophylaxis (3)
Maintenance
• Superpotent topical corticosteroid* (twice weekly) or combined moderately potent corticosteroid/antifungal/antibacterial preparations (3) • Intravaginal corticosteroids† (*for vaginal disease*) at bedtime, at minimum frequency needed for control ± weekly fluconazole (150–200 mg/week) for vulvovaginal candidiasis prophylaxis (3) • Regular use of vaginal dilators to prevent stenosis (3)
Second-line
• Topical calcineurin inhibitors (2) • Intralesional triamcinolone acetonide (e.g. 5–10 mg/cc monthly; hypertrophic disease, recalcitrant erosions) (3)
Recalcitrant or severe disease
• Prednisone (40–60 mg/day) – short course for rapid control and while initiating corticosteroid-sparing agent (2) • Hydroxychloroquine (2) • Systemic immunosuppressants (e.g. methotrexate (2), mycophenolate mofetil (2), azathioprine (3), TNF inhibitors (3)) • Acitretin (hypertrophic disease) (3) • Systemic antibiotics (tetracyclines ± nicotinamide) (3) • Photodynamic therapy (requires sedation) (1) • Surgery to correct narrowing of introitus and reverse clitoral burying in women or circumcision in men (3)
*Ointments are preferred over creams because they are less irritating. †Compounded vaginal suppositories that contain 200–300 mg of hydrocortisone acetate can be inserted nightly until control achieved, then frequency tapered.

Table 73.2 Management of anogenital lichen planus. Topical and oral JAK inhibitors as well as dupilumab have been used for extragenital lichen planus. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

intravaginal corticosteroids and regular use of vaginal dilators to prevent stenosis; surgery to lyse adhesions may be required.

Long-term evaluation of these patients is advised because of the risk of developing SCC[18]; the incidence of the latter has been estimated to be ~2.4%[16]. For further details on the treatment of lichen planus, including systemic agents for severe, refractory disease, see Chapter 11.

ZOON BALANITIS/VULVITIS

Synonyms: ■ Plasma cell balanitis/vulvitis ■ Vulvitis/balanitis circumscripta plasmacellularis ■ Zoon's erythroplasia

Key features

- Male predominance
- Erythematous, moist, speckled, discrete thin plaques
- Involvement of adjacent surfaces produces "kissing" lesions in men
- In men, cured by circumcision

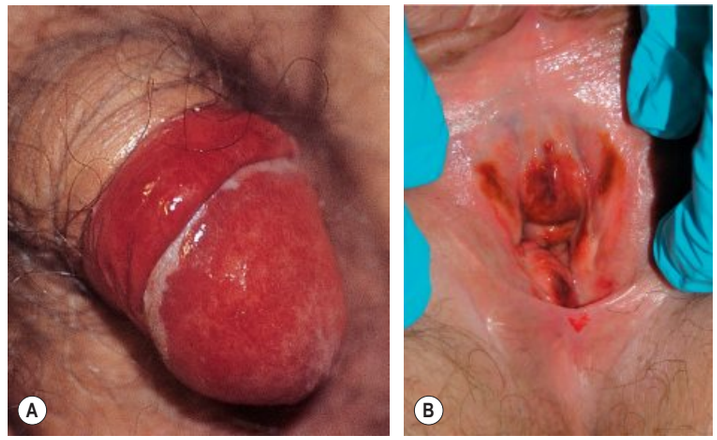


Fig. 73.7 Zoon balanitis and vulvitis. A There are moist red "kissing" lesions on adjacent surfaces of the glans and prepuce. **B** Light to dark red patches of the clitoris, vestibule, introitus, and labia.

Introduction

While most authorities believe this condition occurs in men, its existence as a separate entity in women has been questioned. This is because many of the clinical features in women are indistinguishable from those of erosive lichen planus, mucous membrane pemphigoid, or lupus erythematosus, and the lichenoid features histologically overlap with erosive lichen planus and lichen sclerosus.

Epidemiology

Zoon balanitis/vulvitis may occur at any age but is usually seen from the third decade onwards in uncircumcised men and in postmenopausal women.

Etiology

The etiology is unknown, but poor penile hygiene or chronic irritation from warmth or rubbing has been suggested. Zoon balanitis has not been observed in circumcised men. In women, the vulvitis may represent a reactive process secondary to trauma or reflect a postmenopausal hypoestrogenic state.

Clinical features

In men, the lesions on the glans penis may be asymptomatic or give rise to pruritus or dysuria. The lesions are erythematous, discrete, moist thin plaques with a "cayenne pepper" speckled appearance and a deep red to reddish-brown hue. "Kissing" lesions with involvement of adjacent, touching areas, e.g. around the urethral meatus, are a characteristic finding (Fig. 73.7A). Shallow erosions may resolve slowly, leaving a rusty color. In women, thin erythematous plaques similar to those in men may be seen anywhere on the vulva (Fig. 73.7B). Lesions may be asymptomatic or cause burning, dyspareunia, dysuria, pruritus, or pain.

Pathology

The typical histologic picture is a dense lichenoid infiltrate in the upper and mid dermis with a predominance of plasma cells. Additional features include "lozenge-shaped" keratinocytes, vascular proliferation, hemosiderin deposition, and erythrocyte extravasation.

Differential diagnosis

In order to establish the diagnosis, a biopsy is usually performed. The major disorder in the differential diagnosis is erosive lichen planus, but the possibility of cutaneous malignancy (e.g. SCC *in situ*, extramammary Paget disease) must be considered.

Treatment

In men, a circumcision will almost always cure the disease. Potent topical corticosteroids or topical calcineurin inhibitors may provide some symptomatic relief[19,20]. Vaginal estrogen may be helpful for some women.

EPITHELIAL DISORDERS OF THE ANOGENITAL REGION

Dermatitis

Key features

- Appearance ranges from mild erythema to marked lichenification
- Pruritus and soreness are the main complaints
- A mixed etiology is common
- Exogenous irritants and allergens must be sought

Introduction

Although anogenital dermatitis has traditionally been subdivided into endogenous dermatitis (e.g. seborrheic dermatitis, atopic dermatitis), lichen simplex chronicus, and exogenous dermatitis (e.g. allergic or irritant contact dermatitis), in practice it is often difficult to distinguish between subtypes. A mixed picture, in which endogenous dermatitis is worsened by exogenous irritants or allergens, is common. Lichen simplex chronicus may develop secondarily to other anogenital diseases such as candidiasis, psoriasis, and lichen sclerosus.

Pathogenesis

The majority of patients with vulvar dermatitis have an endogenous predisposition, having either an atopic background or seborrheic dermatitis. The anogenital area is susceptible to irritants, and allergic contact dermatitis is very prevalent in this site; the latter is usually due to topical medications or personal hygiene products. Psychological issues and local environmental problems such as heat, sweating, and over-cleansing may contribute.

Clinical features

The cutaneous features are varied, ranging from mild, usually poorly demarcated erythema to severe lichenification (Fig. 73.8). Symptoms include pruritus (Figs. 73.9 & 73.10), pain, and superficial dyspareunia in women. In lichen simplex chronicus, scratching or rubbing is associated with unremitting pruritus. Fissuring is common, especially perianally. The typical anogenital sites affected are the labia majora and the mons pubis in women, the crura and scrotum in men, and the perianal area in both sexes. Lichenification is most often seen on the scrotum in men and the labia majora in women. Signs of seborrheic dermatitis (e.g. a scaly scalp, greasy scaling and erythema of nasolabial folds and eyebrows), as well as erythema at other flexural sites such as the inframammary crease, intergluteal fold, and axilla, should be sought. Atopic dermatitis at other sites will usually be obvious from the history or examination. Any contribution from dermatographism can also been assessed.



Fig. 73.8 Vulvar dermatitis. Lichenification is prominent. The underlying diagnosis was atopic dermatitis.

Differential diagnosis

The key to making the diagnosis is a thorough dermatologic examination. The diagnosis is usually made on the basis of clinical appearance, but a skin biopsy can be helpful in excluding other diagnoses. For example, plaques of psoriasis are more well-circumscribed than those of dermatitis. Extramammary Paget disease should also be considered, but these lesions are also sharply demarcated and usually asymmetric. It is important to identify irritants and possible allergens through a careful history and possibly patch testing. In addition, bacterial and *Candida* cultures should be performed to exclude superimposed infection, which is common in the anogenital region. Early lesions of lichen sclerosus may be indistinguishable from dermatitis.

Treatment

The regular use of bland emollients and the substitution of an emollient for soap is recommended. Exacerbating factors, including stress, heat, excessive washing, use of premoistened personal hygiene wipes ("wet wipes"), and candidiasis, should be identified. A major therapeutic aim is reduction of pruritus and soreness. If the area is acutely inflamed, potent topical corticosteroids, often in combination with topical

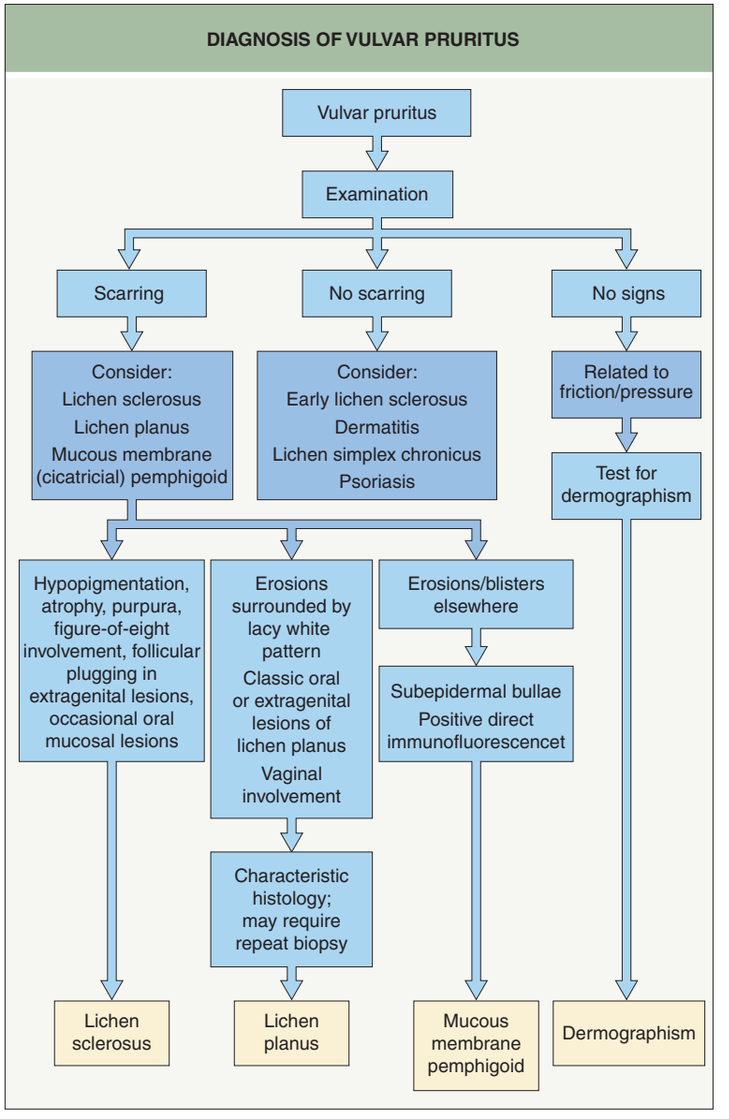


Fig. 73.9 Diagnosis of vulvar pruritus.

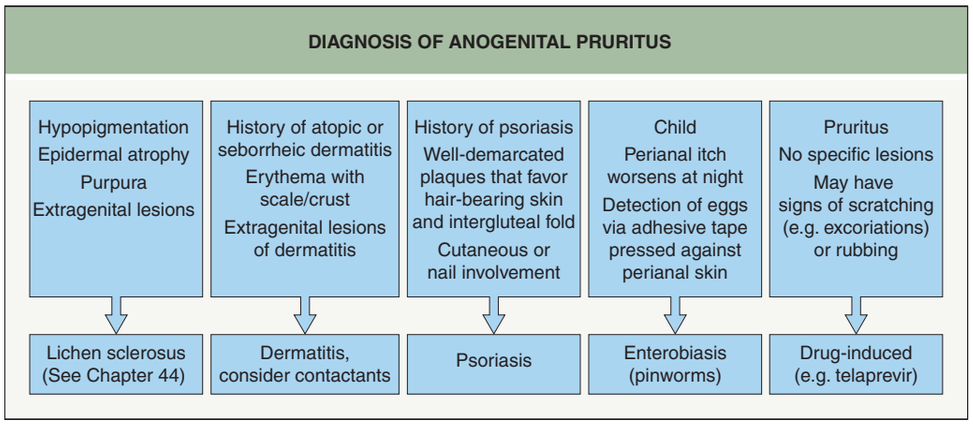


Fig. 73.10 Diagnosis of anogenital pruritus. Histologic evaluation may be required to confirm the clinical diagnosis (e.g. lichen sclerosus) or to exclude more unusual etiologies (e.g. extramammary Paget disease).

antifungal agents, topical antibacterial agents, and/or topical immunomodulators, are helpful. Over a period of a few weeks, the topical corticosteroid can be tapered to one that is less potent. When lichenification is present, it is especially important to break the itch–scratch cycle. Additional therapies include sedative antihistamines or tricyclic antidepressants, usually doxepin, at bedtime (see Ch. 6).

Contact Dermatitis

It is important to consider the possibility of contact dermatitis in any patient with dermatitis, a history of reactions to topical medications, or treatment-resistant disease. Contact dermatitis of the anogenital region may be irritant or allergic (see Chs. 14 & 15)[21]. Irritant contact dermatitis is seen in infants as diaper dermatitis and in older patients as a consequence of overzealous cleaning, urinary or fecal incontinence, or chronic diarrhea.

Allergic contact dermatitis is diagnosed by patch testing and can often arise as a treatment-related secondary condition. Topical medications are the most common cause of allergic contact dermatitis in the anogenital region[22]. Relevant allergens include preservatives, topical anesthetics, topical antibiotics, corticosteroids, fragrances, lanolin, and rubber chemicals. In perianal dermatitis, medications (topical, per anum), hemorrhoidal creams, and toilet wipes are common culprits. In addition to contact dermatitis, type I immediate hypersensitivity reactions to latex and seminal fluid may occur.

Psoriasis

Key features

- Erythematous well-defined plaques
- Evidence of psoriasis elsewhere on total body skin examination
- Intergluteal cleft frequently affected

Psoriasis of the anogenital region may appear quite different from psoriasis at other sites (see Ch. 8). The typical silvery scale is lost, as in other flexural sites such as the axillae and submammary region.

Clinical features

In women, erythematous, smooth, clearly demarcated plaques typically affect the labia majora and the mons pubis. Psoriasis is usually confined to the hair-bearing areas, so the labia minora are unaffected. Men may have circumscribed plaques on the glans penis and shaft of the penis (Fig. 73.11). Persistent, painful fissuring of the perianal area and the intergluteal cleft can be a severe problem in both sexes.

Differential diagnosis

Often the diagnosis is very straightforward, established from a combination of the clinical appearance in the genital region plus typical lesions elsewhere on the body or classic nail changes. Seborrheic dermatitis may be difficult to distinguish from psoriasis, and sometimes, clear features of both psoriasis and seborrheic dermatitis are seen in the same patient, where the term "sebopsoriasis" seems appropriate. The differential diagnosis includes tinea cruris (especially if there are pustules, an active border, extension of lesions onto the buttock or upper inner thigh, and/or concomitant tinea pedis or unguium), and erythrasma. In patients with reactive arthritis, lesions identical to those of psoriasis may be seen on the penis.



Fig. 73.11 Psoriasis of the penile shaft. Well-demarcated erythematous plaque with slight scale. Similar lesions can be seen in patients with reactive arthritis (formerly Reiter disease). *Courtesy Jean L. Bolognia, MD.*

Treatment

Unfortunately, topical therapy for anogenital psoriasis is not entirely satisfactory. Many topical agents suitable for use on the body, such as coal tar, anthralin, vitamin D derivatives, or retinoids, may be too irritating in flexural sites. Moderately potent topical corticosteroid–antibiotic–antifungal combinations remain the most useful therapy; however, in intertriginous sites, corticosteroid-induced atrophy remains a concern. Topical tacrolimus, pimecrolimus, or roflumilast may be helpful in such occluded sites. Some patients will improve when a systemic agent is used (e.g. methotrexate, cyclosporine, TNF inhibitors, systemic immunomodulators such as ixekizumab), usually for widespread disease.

RED SCROTUM SYNDROME/RED VULVA SYNDROME

The red scrotum syndrome (RSS) and red vulva syndrome (RVS) typically present in older individuals as persistent erythema of the scrotum or vulva with associated burning, pruritus, and/or pain. The precise etiology is unclear but possible contributing factors include rebound vasodilation resulting from prolonged use of topical corticosteroids and neurogenic inflammation[23]. Another theory is that it represents a form of localized erythromelalgia.

Because both RSS and RVS are diagnoses of exclusion, other entities including atopic, seborrheic or contact dermatitis, inverse psoriasis, superficial infections (e.g. tinea, candidiasis, erythrasma), fixed drug eruption, and extramammary Paget disease need to be considered. However, given the possible contribution of topical corticosteroids, RSS and RVS may be superimposed on another cutaneous disease. Treatment is challenging and includes the taper and then discontinuation of topical corticosteroids, thus attempting to avoid a rebound with more burning and erythema. This approach is similar to that employed in patients with steroid-induced rosacea. Based upon case reports, improvement has been observed with topical (e.g. timolol) and oral (carvedilol [6.25 mg three times weekly]) β-blockers[24], topical calcineurin inhibitors, oral doxycycline, and oral gabapentinoids (e.g. gabapentin, pregabalin).

PREMALIGNANT AND MALIGNANT LESIONS

Squamous Intraepithelial Neoplasia (Vulvar, Penile, Anal)

Synonyms: ■ Bowenoid papulosis ■ Bowen disease (squamous cell carcinoma *in situ*) ■ Erythroplasia of Queyrat

Key features

- High-grade squamous intraepithelial lesion (HSIL) of the vulva, previously known as usual type or undifferentiated vulvar intraepithelial neoplasia (uVIN), and most cases of PeIN (penile intraepithelial neoplasia), and AIN (anal intraepithelial neoplasia) are associated with human papillomaviruses
- Lichen sclerosus and lichen planus are predisposing factors for differentiated type VIN (dVIN)
- Despite treatment there is a high recurrence rate

Introduction

The term "squamous intraepithelial neoplasia" defines an intraepithelial change within anogenital epithelium that is premalignant. There have been several iterations of nomenclature but no universal agreement exists amongst all medical specialties. The International Society for the Study of Vulvovaginal Disease (ISSVD) divides vulvar squamous intraepithelial lesions (SIL) into: (1) high-grade squamous intraepithelial lesion (HSIL) – formerly referred to as usual type or undifferentiated vulvar intraepithelial neoplasia (uVIN); and (2) differentiated VIN (dVIN)[25]. The term for squamous intraepithelial neoplasia in men is penile intraepithelial neoplasia (PeIN), and for anal disease, anal intraepithelial neoplasia (AIN).

It is now recommended that the terms Bowen disease, erythroplasia of Queyrat, and Bowenoid papulosis not be used for lesions in the anogenital area. However, dermatologists still recognize a distinct clinical variant, Bowenoid papulosis, characterized by discrete papules in a younger age group and a tendency for spontaneous regression. Additionally, some authorities believe that erythroplasia of Queyrat and Bowen disease remain useful terms in men.

Epidemiology

It may occur at any age, but the incidence in young women is rising. Early evidence suggests that rates of HSIL may be falling in HPV-vaccinated populations.

Pathogenesis

Oncogenic human papillomaviruses, chiefly HPV types 16 and 18, are implicated in most cases of squamous intraepithelial neoplasia, especially HSIL, PeIN, and AIN. There is also an association with smoking and immunosuppression, including HIV infection. Lichen sclerosus and lichen planus are predisposing factors for dVIN.

Pathology

Intraepithelial neoplasia is characterized by nuclear hyperchromasia, disordered maturation of keratinocytes, and coarse nuclear chromatin. Multiple mitotic figures are usually visible above the basal layer.

Clinical features

The clinical presentation is varied. Erythematous well-demarcated plaques that look similar to plaques of Bowen disease in extragenital sites may occur on the vulva or the keratinized epithelium of the penis in men. Alternatively, warty white plaques, erosions, or hyperpigmented patches may be seen. Shiny erythematous plaques may occur on the glans and prepuce of the uncircumcised male (erythroplasia of Queyrat; Fig. 73.12). In patients with Bowenoid papulosis-type lesions, distinct red–brown papules are seen on the genitalia (Fig. 73.13A), which may extend to the inner thighs (Fig. 73.13B). Differentiated VIN usually presents as small ulcers or keratotic plaques.

Differential diagnosis

Intraepithelial neoplasia must be distinguished from inflammatory conditions such as lichen sclerosus, as well as condyloma acuminatum, Zoon balanitis/vulvitis, and cutaneous malignancies, in particular early invasive SCC.

Treatment

Treatment options depend on the site, the extent of disease, the age of the patient, and the type of intraepithelial neoplasia, but recurrence is a problem with all treatment modalities. In localized disease, a biopsy to establish the diagnosis, followed by local excision, is preferred, so long as the surgery is not too mutilating. In uncircumcised men, circumcision may reduce the risk of progression to invasion. Observation may be an option in selected cases if treatment is not feasible; however, if progression is observed, then surgical excision is necessary. Differentiated VIN associated with lichen sclerosus or lichen planus has a high risk of progression to invasive disease and must be excised. Cryosurgery is rarely indicated in the opinion of the author, as recurrence rates are very high; laser therapy also has a high recurrence rate. Topical imiquimod or fluorouracil may be helpful in some cases, especially when the disease is multifocal, although local side effects may limit their use. In some, but not all, patients, imiquimod



Fig. 73.12 Penile intraepithelial neoplasia. Persistent erythema not responding to topical corticosteroids. *Courtesy R. Turner, MD.*

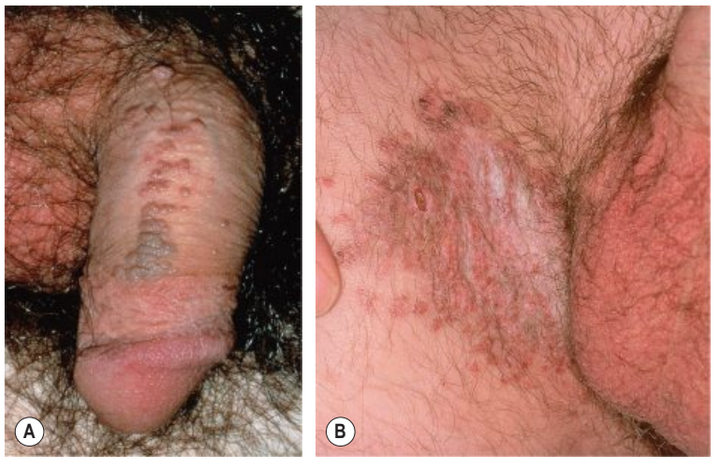


Fig. 73.13 Bowenoid papulosis variant of intraepithelial neoplasia. A Multiple red–brown to brown papules on the shaft of the penis. **B** Coalescence of red–brown to brown papules on the upper inner thigh. *B, Courtesy Robert Hartman, MD.*

can lead to histologic regression of disease and viral clearance[26,27]. In widespread disease, simple vulvectomy has been performed, but only after exhaustion of all other options.

Long-term evaluation is recommended and should include serial examinations and cervical and anal cytology, especially in the setting of HIV infection. Examination of sexual partners is advised.

Prevention

Vaccines are available to prevent infection with high-risk HPV subtypes (see Ch. 79). They are 97% effective in a population naive to these viruses at the time of the first vaccination. Cessation of cigarette smoking should be advised as this is a known risk factor for recurrence.

Pseudoepitheliomatous Keratotic and Micaceous Balanitis

This is a rare condition that occurs in elderly circumcised men[28]. Thick keratotic plaques develop on the glans penis. This condition may progress to verrucous carcinoma or SCC.

Invasive Squamous Cell Carcinomas

Key features

- Most common malignant tumor in the anogenital region
- Etiology is different from SCCs arising in actinically damaged skin

Epidemiology

Squamous cell carcinoma most frequently occurs in the elderly, although it may occur in young adults (see Ch. 108). The incidence of genital SCC in women is rising.

Pathogenesis

HPV infection and lichen sclerosus account for the majority of SCC of the anogenital region. HPV-associated tumors tend to arise in younger adults, while lichen sclerosus-related tumors occur in postmenopausal women and older men. Smoking and immunosuppression are also risk factors. SCC is very rare in circumcised men; the presence of a foreskin, which can lead to trapping of smegma and low-grade inflammation, may predispose to the development of carcinoma. SCC of the genital region is rarely due to cumulative UV light exposure, although there have been reports of SCC of the penis and scrotum in men who had received multiple PUVA treatments. Tar, chimney soot, asbestos, and petroleum products are known carcinogens in the case of scrotal SCC.

Clinical features

In men, the majority of lesions present as ulcers or plaques on the glans, the coronal sulcus, or the prepuce (Fig. 73.14). Ulcers often have a heaped-up edge. In the uncircumcised man, delay in diagnosis may occur because of associated phimosis masking the tumor. Although any area on the vulva may be involved, the labia are the most frequent sites. The clinical presentation varies from non-healing ulcers or fissures to nodules and plaques. Invasive anal carcinoma may arise from the anal margin or from within the lower anal canal.

Differential diagnosis

SCC must be distinguished from other tumors such as amelanotic melanoma or basal cell carcinoma. It is important to biopsy any suspicious lesion that develops in the anogenital region.

Treatment

Treatment is usually surgical, with the extent of surgery dependent on both the size and depth of invasion[29]. Microinvasive tumors (≤1 mm invasion and a maximum diameter of 2 cm) are removed via wide local excision. Sentinel lymph node biopsy is sometimes performed in patients with earlier stage SCC. For more advanced disease, inguinofemoral lymphadenectomy may be recommended. If the SCC arises within a background of lichen sclerosus, it is important to continue maintenance therapy with topical corticosteroids as this appears to reduce the recurrence rate of SCC[30].



Fig. 73.14 Invasive squamous cell carcinoma of the foreskin. This patient with psoriasis had received PUVA therapy without genital protection.

Anogenital Melanoma

Key features

- Rare tumor not related to UV exposure
- Delayed diagnosis is common resulting in greater depth of invasion
- Mucosal lentiginous melanoma is the most common histologic type
- Associated with a poor prognosis

Introduction

Although anogenital melanoma is a rare tumor, melanoma is the second most common primary malignant tumor of the vulva in women.

Epidemiology

Female genital tract melanomas account for <3% of melanomas diagnosed in women but ~20% of all mucosal melanomas[31]. Vulvar melanomas outnumber vaginal melanomas. Compared with cutaneous melanomas, vulvar and penile melanomas occur in an older population, typically in the seventh decade, although they may appear at any age. While the incidence of cutaneous melanoma is increasing, the incidence of urogenital tract melanoma in women is stable.

Pathogenesis

Melanoma is a multifactorial disease, but two of the major risk factors – sun exposure and melanocytic nevi – play a minimal (nevi) or no known (UV) role in anogenital melanoma. Current evidence suggests that the behavior of vulvar melanoma is similar to that of cutaneous melanoma and thus should be staged and initially managed in a similar manner. However, comparative genomic hybridization has shown a greater frequency of *KIT* mutations and fewer *BRAF* mutations in mucosal melanomas as compared to cutaneous melanomas (see Ch. 113)[32], and this does impact the choice of targeted therapy for metastatic disease. Tumor molecular profiling also includes other genes that have been detected in vulvovaginal melanomas (e.g. *NRAS*, *TP53*). Of note, 15% of patients with vulvar melanoma report a family history of cutaneous melanoma.

Clinical features

In women, melanomas may present with bleeding, pruritus, or a nodule. Amelanotic melanomas account for up to 10% of vulvovaginal melanomas. Tumors can arise throughout the genital tract, including the cervix and the vagina, as well as any site on the vulva. The labia minora, followed by the labia majora/clitoris, are the most common tumor sites. In men, a crusted nodule is the most frequent presentation, with most melanomas arising on the glans penis, although they may occur at any site, including the scrotum[33].

Because anogenital melanomas are often diagnosed at a more advanced stage, overall prognosis is significantly worse when compared

to more common cutaneous melanomas. Reported 5-year survival rates have varied from 5% to 25% for vulvovaginal melanomas, 10% for penile melanomas[31], and 5%–35% for anorectal melanomas[34]. Greater depth of invasion at the time of diagnosis may be due to a less noticeable location or the rich vascular and lymphatic network of the urogenital tract. Although these factors contribute to early spread and development of metastases, it remains to be determined whether anogenital melanomas are fundamentally more aggressive.

Pathology

On genital skin, mucosal lentiginous melanoma is the most frequent histologic type of melanoma. Nodular and superficial spreading melanomas occur less frequently. Mucosal lentiginous melanomas share some histologic features with cutaneous lentigo maligna melanomas. As with cutaneous melanoma, prognosis is determined by tumor thickness at presentation.

Differential diagnosis

For macular lesions, the major differential is mucosal melanosis. Palpable pigmented melanomas must be distinguished from atypical-appearing seborrheic keratoses, melanocytic nevi, or Bowenoid papulosis. Melanocytic nevi superimposed on lichen sclerosus may have an atypical clinical appearance and histopathologic features of a persistent nevus. Anorectal melanoma may initially be misdiagnosed as a hemorrhoid or adenomatous polyp.

Treatment

Due to the rarity of the tumor, there have been no randomized therapeutic trials. Vulvar and penile melanomas are staged and treated similarly to cutaneous melanoma. Surgical resection is the treatment of choice. Based upon recent consensus guidelines, the goal of surgical management of anogenital melanomas is to achieve microscopically clear (>1 mm) margins in the least radical fashion[34]. Lymphadenectomy is limited to clinically evident metastatic regional nodal disease, with sentinel lymph node biopsy recommended if it directs adjuvant treatment or clinical trial entry. Approximately one-third of patients have nodal disease at the time of presentation.

Immunotherapy (e.g. anti-CTLA-4 antibodies, anti-PD-1/PD-L1 antibodies) may improve survival rates and, depending upon the presence of specific mutations, targeted KIT or selective BRAF inhibitors may also be considered. Palliative radiotherapy has been tried for extensive local disease and can be considered in conjunction with immunotherapy.

Basal Cell Carcinoma

Basal cell carcinoma may occur in the anogenital area and is usually diagnosed clinically as SCC prior to biopsy or excision. Rarely, it has been reported to metastasize.

Genital Lymphoma

The anogenital region is a rare site of involvement for lymphoma. Several different types of lymphoma have been reported, including diffuse large B cell and other non-Hodgkin lymphomas. The usual presentation is that of a solid non-tender nodule. Plaques and tumors of mycosis fungoides (MF) can also be seen in this location, but MF *restricted* to the anogenital region should be seriously questioned and alternative diagnoses (e.g. pseudolymphomatous lichen sclerosus) considered.

Extramammary Paget Disease

Key features

- Rare intraepithelial adenocarcinoma
- May be primary (80%–90% of patients) or secondary to an underlying malignancy (10%–20% of patients)

Introduction

Extramammary Paget disease (EMPD) is a rare intraepithelial adenocarcinoma that develops primarily in apocrine-rich sites, with the vast majority arising in the anogenital region. Rarely EMPD occurs in the axillae or locations such as the eyelid, umbilicus, or external auditory canal. EMPD can either be *primary* (of cutaneous origin) or *secondary* (of non-cutaneous origin); the latter represents intraepithelial spread of neoplastic cells from an underlying internal malignancy. EMPD may become invasive and spread via the lymphatic system.

Epidemiology

Elderly White women most commonly develop this malignancy, but in Japan there is a male predominance.

Etiology and classification

The histogenesis of primary cutaneous EMPD has been long debated but appears in some patients to be of apocrine origin. Recurrent mutations in chromatin remodeling genes have recently been identified in both EMPD and mammary PD[35], along with the importance of the Msi1–mTOR pathway. Primary (type 1) EMPD can be divided into three subtypes: 1a – non-invasive; 1b – invasive; and 1c – associated with pagetoid spread from an underlying adnexal carcinoma. Secondary EMPD consists of either epidermotropic metastases or direct extension of a gastrointestinal tract (type 2) or urothelial tract (type 3) malignancy.

Clinical features

The vulva in women and the perianal region in men are the most commonly affected sites[36]. There may be associated pruritus or burning or the lesions may be asymptomatic. A slowly expanding, asymmetric erythematous plaque is typical, with a sharp demarcation between normal and involved skin (Fig. 73.15A–C). Scattered areas of white scale and erosion can give rise to a "strawberries and cream" appearance. Occasionally, lesions are pigmented.

Pathology

The diagnosis must be confirmed by histologic examination. Vacuolated pagetoid cells in the epidermis are distinctive (Fig. 73.15D), but immunohistochemical staining is necessary to exclude pagetoid melanoma and pagetoid Bowen disease, as well as to help differentiate between primary and secondary EMPD (Fig. 73.16)[37]. The diagnosis of primary EMPD requires a search for an underlying cutaneous adnexal carcinoma.

Differential diagnosis

EMPD is most often clinically misdiagnosed as psoriasis or dermatitis, leading to a delay in diagnosis. Histopathologically, the differential diagnosis consists primarily of melanoma and Bowen disease, but may include pagetoid dyskeratosis, clear cell papulosis, and Langerhans cell histiocytosis.

Evaluation

A thorough review of systems and complete physical examination, including lymph nodes, should be performed. Because the initial site of EMPD often correlates with the type of underlying malignancy, screening studies include the following: (1) perianal EMPD – upper and lower endoscopy +/– CT scan, cystoscopy, urine cytology, prostate-specific antigen (PSA, in men); (2) penoscrotal EMPD – colonoscopy, cystoscopy, PSA; and (3) vulvar EMPD – pelvic examination, Pap smear, colposcopy, cystoscopy, abdominal/pelvic CT scan. In women, breast examination and mammography are also recommended. Serum carcinoembryonic antigen (CEA) levels can be measured to monitor tumor status. Of note, the value of routine screening for primary intraepithelial (type 1a) EMPD has recently been questioned[38].

Treatment

It is important to distinguish between primary and secondary EMPD, and when possible determine if the malignancy is invasive (see Fig. 73.16). For localized disease in the anogenital region, wide local excision is usually performed. However, because of the multifocal nature of EMPD and the presence of clinically inapparent extension of disease, recurrences are very common. Mohs micrographic surgery often represents a preferred surgical option[37]. Additional treatment options include topical imiquimod, topical 5-fluorouracil, topical rapamycin, radiotherapy, photodynamic therapy, and CO_2 laser ablation, with



Fig. 73.15 Extramammary Paget disease. A Erythematous plaque with hydrated scale at the base of the scrotum. **B** Well-demarcated perianal plaque with both erosions and scale, giving rise to a "strawberries and cream" appearance. **C** Extensive, well-demarcated disease of the vulva with multiple foci of hydrated white scale. **D** Photomicrograph demonstrating pagetoid cells within the epidermis, both as single cells and in nests. *B, Courtesy Kalman Watsky, MD; D, Courtesy Lorenzo Cerroni, MD.*

combination therapy often employed. Long-term follow-up is recommended because invasive disease can occur.

DYSESTHETIC GENITAL PAIN SYNDROMES

The term "dysesthetic genital pain syndrome" encompasses a number of disorders in which the clinical appearance is normal despite the patient's experience of severe disabling pain (Fig. 73.17). Because these diagnoses require the absence of a clinically identifiable neurologic disorder (e.g. a radiculopathy), a neurologic examination is a prerequisite. Unmedullated C fibers transmit pain and touch, and it is now recognized that these nerve fibers can be remodeled after a stimulus has passed, explaining why perception of subsequent stimuli may be altered. Relatively minor inflammation or trauma, often unrecalled, may precipitate the onset of pain. The ISSVD has published a classification scheme for vulvar pain (Table 73.3)[39]. Of note, these pain disorders often have a profound effect on a patient's well-being and sexual functioning.

General Principles of Management

Simple measures, self-help, and patient education often lead to improvement. For more severe or long-standing symptoms, a multidisciplinary approach that includes physiotherapists, pain management specialists, psychologists, and psychosexual counselors is often required. The key interventions are patient education, pain modification (via local anesthetics, amitriptyline, gabapentinoids), physical therapy to address hypertonic pelvic floor muscles that can exacerbate pain, and psychological and psychosexual support[40].

Localized Vulvodynia (Vestibulodynia)

Key features

- Superficial dyspareunia
- Tenderness on localized pressure within the vulvar vestibule
- Occurs in young, sexually active women

Introduction

"Localized vulvodynia" is now the preferred term for this specific subtype of the vulvar pain syndrome, characterized by superficial dyspareunia and point tenderness within the vestibule, often at 5 and 7 o'clock.

Clinical features

This particular localized pain syndrome occurs in the young, premenopausal, sexually active woman whose main complaint is one of dyspareunia on penetration. Insertion of tampons may be impossible. The vulva looks entirely normal but there is pain when the vestibular area is pressed by a cotton-tipped applicator.

Differential diagnosis

Localized vulvodynia must be differentiated from other causes of vulvar pain (see Table 73.3). Hymenal and posterior vestibule fissures and herpes simplex viral infection must be excluded. Fungal culture should be obtained to eliminate *Candida* infection, and digital examination of the vagina is performed to exclude vaginismus. Sometimes these disorders can coexist.

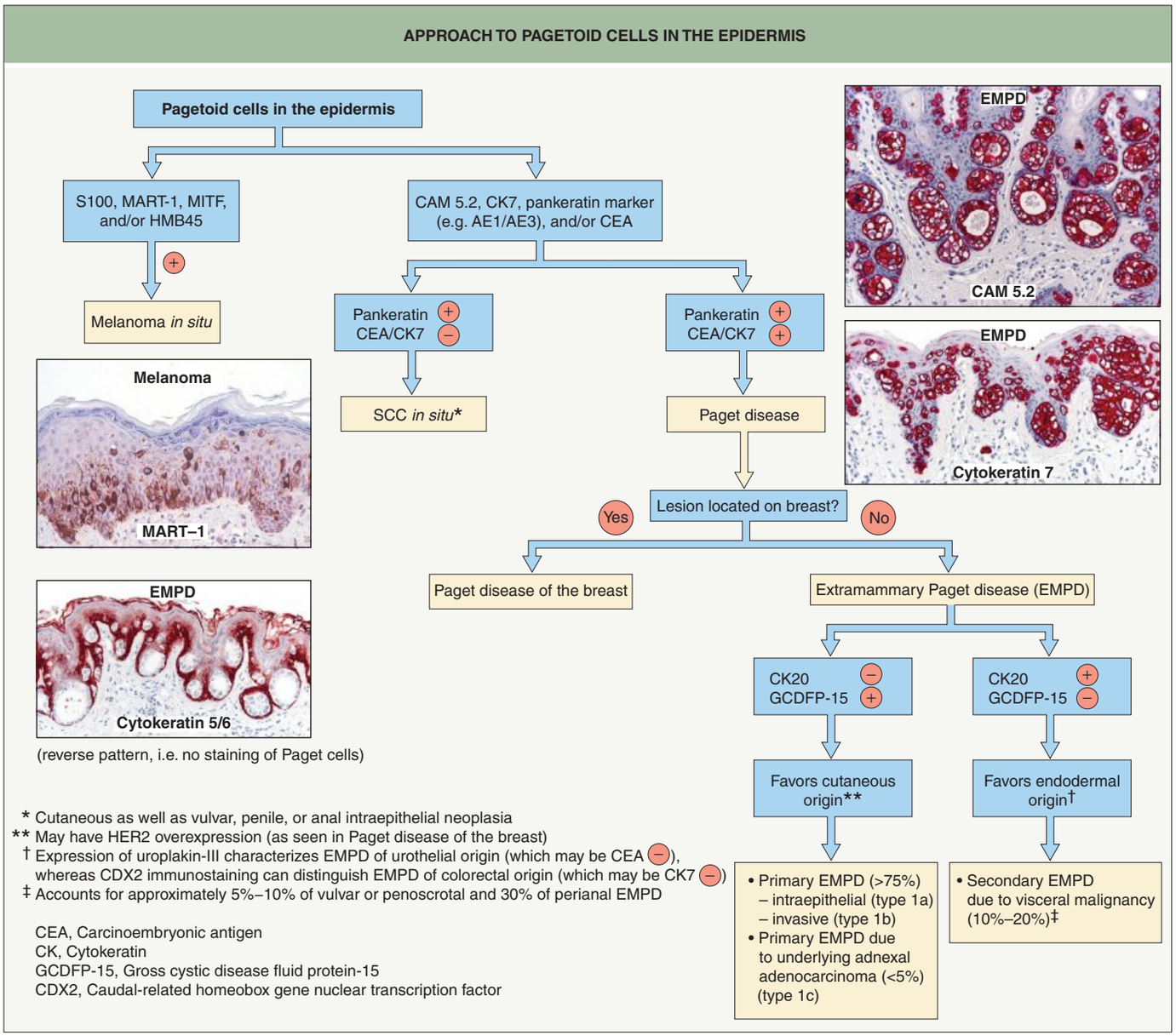


Fig. 73.16 Algorithm for the approach to pagetoid cells in the epidermis. The CAM 5.2 immunohistochemical stain is positive in >95% of Paget disease (mammary and extramammary) and approximately one-third of Bowen disease; it stains low-molecular-weight keratins. AE1 stains most subfamily A keratins (but not 12, 17, and 18) while AE3 stains subfamily B keratins. The differential diagnosis also includes pagetoid dyskeratosis (e.g. of the hand), Zuska disease, and clear cell papulosis.

Treatment

Topical local anesthetic agents (e.g. 5% lidocaine) applied before intercourse may be beneficial. Pelvic floor exercises, vaginal dilator training, and pelvic floor electromyography with biofeedback may prove useful. For a small number of women, surgery (e.g. modified vestibulectomy) might be helpful, but the role of surgery remains controversial[41].

Generalized Vulvodynia/Scrotodynia (Dysesthetic Vulvodynia/Scrotodynia)

Key features

- Burning and/or pain
- Clinical examination of vulva or scrotum is normal

Introduction

Persistent burning pain is characteristic and patients have often consulted many doctors before the correct diagnosis is made. Depression may be a feature of any chronic pain syndrome.

Scrotodynia is probably analogous to vulvodynia; however, there is less published on the subject[42]. Precipitating events include sexual activity, exercise, friction, and heat. Pain may also affect the penis.

Clinical features

Pain, often accompanied by a burning sensation, is felt over the entire vulva, scrotum, or penis, and it may extend down the thighs. The genital area may hurt even when nothing is touching it. Often, symptoms are worse on sitting or walking up stairs. Wearing of underwear may be impossible. On inspection, the scrotum or vulva looks entirely normal.

Differential diagnosis

Other causes of genital pain, e.g. infection (bacterial, viral, or fungal), lichen sclerosus, or lichen planus, must be excluded by examination before the diagnosis can be made. A potassium hydroxide (KOH) preparation and/or fungal culture to exclude candidiasis is essential. It is important to test for dermographism, as treatment with antihistamines may greatly benefit these patients.

Treatment

Treatment strategies are very similar to those for localized vulvodynia or scrotodynia (see above)[40]. Treatment with pain-modifying medications,

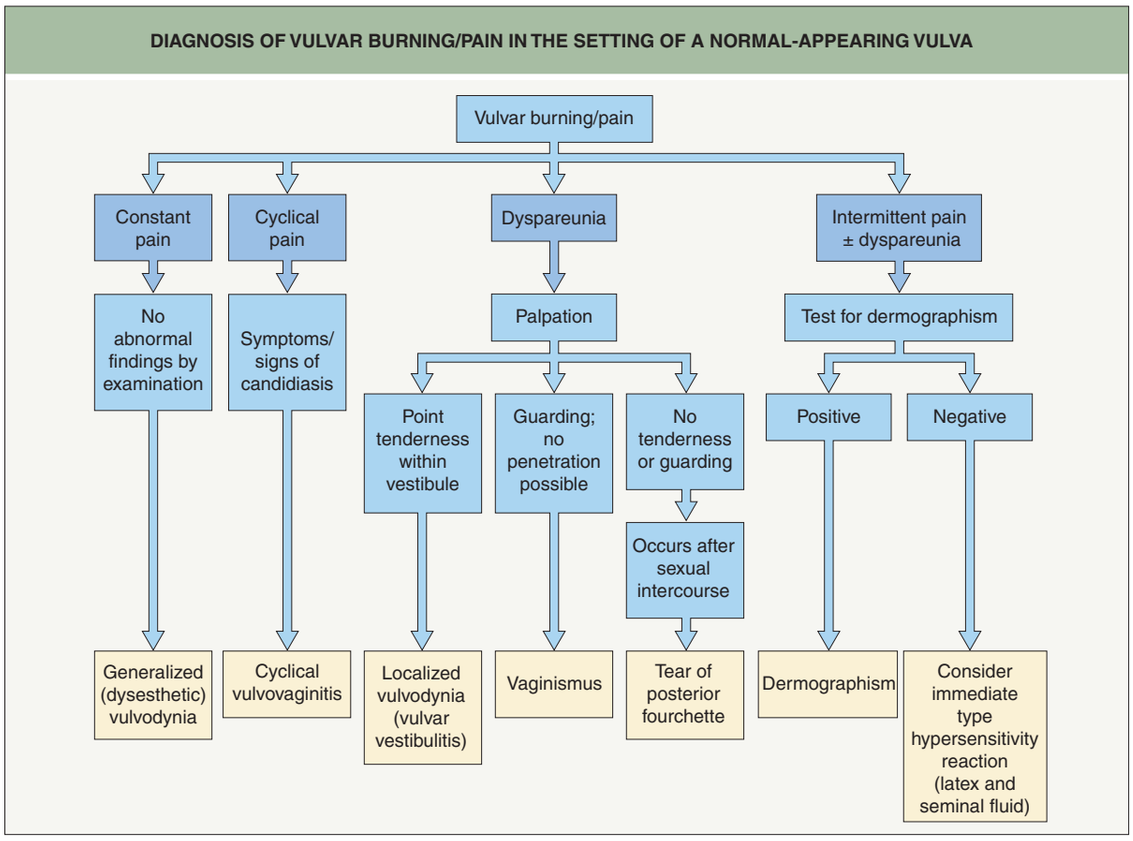


Fig. 73.17 Diagnosis of vulvar burning/pain in the setting of a normal-appearing vulva.

ISSVD TERMINOLOGY AND CLASSIFICATION OF PERSISTENT VULVAR PAIN
Vulvar pain caused by a specific disorder*
• Infectious (e.g. candidiasis, HSV infection) • Inflammatory (e.g. lichen planus, lichen sclerosus, immunobullous disorders) • Neoplastic (e.g. Paget disease, squamous cell carcinoma) • Neurologic (e.g. post-herpetic neuralgia, spinal nerve compression, neuroma) • Iatrogenic (e.g. postoperative, post-chemotherapy, post-radiation) • Trauma (e.g. cutting, obstetrical) • Hormonal deficiencies (e.g. genitourinary syndrome of menopause [vulvovaginal atrophy], lactational amenorrhea)
Vulvodynia†
Descriptors
• Localized (e.g. vestibulodynia, clitorodynia, hemivulvodynia) *or* generalized *or* mixed (localized and generalized) • Provoked (e.g. insertional, contact) *or* spontaneous *or* mixed (provoked and spontaneous) • Onset (primary or secondary) • Temporal pattern (intermittent, persistent, constant, immediate, delayed)
*Women may have both a specific disorder (e.g. lichen sclerosus) and vulvodynia. †Vulvar pain of more than 3 months' duration without clear identifiable cause; may have potential associated factors.

Table 73.3 International Society for the Study of Vulvovaginal Disease (ISSVD) terminology and classification of persistent vulvar pain (2015).

BENIGN LESIONS OF THE GENITALIA	
Common	
• Angiokeratomas • Bartholin cysts • Epidermoid cysts, milia • Fordyce spots • Melanocytic nevi	• Mucosal melanosis • Pearly penile papules • Urethral caruncle • Vestibular papillomatosis
Less common	
• Endometriosis • Fox–Fordyce disease • Hidradenoma papilliferum • Idiopathic calcinosis of the scrotum	• Papular acantholytic dyskeratosis* • Perineal pyramidal protrusion • Steatocystomas • Syringomas
*Somatic mutations in *ATP2A2* and *ATP2C1* detected.	

Table 73.4 Benign lesions of the genitalia. Papules can also be due to infections, e.g. mollusca contagiosa and condylomata acuminata. If a firm penile lesion is linear, consider sclerosing lymphangitis.

e.g. amitriptyline, gabapentin, is most likely to be beneficial in this disorder. Despite a variety of treatments, there remains a group that fails to respond.

Anal Pain

Anal pain may occur in both men and women and it shares many features with vulvodynia and scrotodynia. Associated depression is frequent.

BENIGN LESIONS

A wide variety of benign lesions can be found in the anogenital area (Table 73.4). Some of the more important lesions are discussed below.

Epidermoid Cysts

Epidermoid cysts are frequently encountered on the glabrous labia majora and scrotum, and may be multiple. They are yellow, vary in size, and may become inflamed. Treatment is by excision, but this is only necessary if the cyst is symptomatic.

Vestibular Papillomatosis

Papillomas within the vestibule are found in ~45% of premenopausal women and 10% of postmenopausal women. They are pink, asymptomatic, fine projections. Women should be reassured that the finding is normal.

SYSTEMIC DISEASES THAT MAY PRESENT IN THE ANOGENITAL REGION	
Systemic disease	**Clinical findings in the anogenital region**
Behçet disease	Recurrent aphthous ulcers (see text and Ch. 26)
Crohn disease	Recurrent abscesses, sinuses, and fistulas; linear (knife-cut) fissures; firm swelling of the labia or scrotum; firm anal "skin tags" (see Ch. 93)
Graft-versus-host disease	Fissures, erosions, ulcerations Can resemble anogenital lichen sclerosus or lichen planus Men: balanitis, phimosis Women: labial fusion, vaginal scarring with stenosis
Langerhans cell histiocytosis	Multiple red–brown papules and nodules, extending to thighs (usually children) Intertrigo-like erythema of the inguinal creases that may become erosive (see Ch. 91)
Neutrophilic dermatoses (e.g. Sweet syndrome)	Red to purple papules and nodules in association with fever
Zinc deficiency • Inherited • Acquired	Periorificial erythema, erosions, and crusting (see Ch. 51) Superimposed candidal infections

Table 73.5 Systemic diseases that may present in the anogenital region.

THE ANOGENITAL REGION AND SYSTEMIC DISEASE

There are a number of systemic disorders that may initially present in the anogenital region (Table 73.5). For example, Behçet disease is a rare multisystem inflammatory disorder in which recurrent oral aphthae are often accompanied by genital erosions or ulcers, in addition to arthritis, uveitis, neurologic disorders such as cranial nerve palsies and mono- and hemiparesis, arterial and venous thromboses, and pathergy (see Ch. 26). The disease is more prevalent in individuals from the Mediterranean basin, Japan, and Korea; it typically presents in young adults in their third or fourth decade of life. Recurrent flares and remissions are to be expected. Treatment options are outlined in Table 26.15.

INFECTIONS

Sexually transmitted infections (see Chs. 78 & 82) and condylomata acuminata (see Ch. 79) are described elsewhere, but miscellaneous infections that favor the anogenital region are discussed below.

Perianal Streptococcal Disease

The typical presentation is that of a 3- or 4-year-old boy with erythema and sometimes crusting of the perianal area[43] (see Ch. 74). Constipation is frequent because of discomfort. Similar findings may extend from the vaginal introitus onto the vulva in girls and less often around the urethral meatus in boys. The disease can be associated with guttate psoriasis and is frequently misdiagnosed as irritant dermatitis or candidiasis. Specimens for bacterial culture must be obtained. Group A β-hemolytic streptococci are responsible. Treatment is with oral penicillin, amoxicillin, or a first-generation cephalosporin.

Recurrent Toxin-Mediated Perineal Erythema

Recurrent toxin-mediated perineal erythema is an unusual condition that presents 2–3 days after a throat infection as a fine diffuse macular erythema of the perineal region[44]. Marked local edema may be present and the hands may be similarly affected. Desquamation follows the erythema and the condition can be recurrent. Streptococcal or staphylococcal pharyngitis is the most common cause and the erythema is toxin-mediated. Long-term prophylactic penicillin may be beneficial in some patients.

Kawasaki Disease

Kawasaki disease may be triggered by bacterial toxins or viral antigens, but the exact cause has not been elucidated. It is a disease of children. In up to two-thirds of cases, perineal erythema may be a presenting feature (see Ch. 81); additional findings include strawberry tongue, fissured lips, fever, and lymphadenopathy, followed by desquamation of the hands and feet. Coronary artery aneurysms may be life-threatening. Treatment is with aspirin and IVIg. Perineal erythema has also been observed in multisystem inflammatory syndrome in children (MIS-C) due to SARS-CoV-2 infection.

Fournier Gangrene

Fournier gangrene is a severe necrotizing infection of the external genitalia, perineum, or perianal area that occurs in patients with an underlying predisposition such as diabetes or immunosuppression[45] or who are receiving SGLT2 inhibitors. The infection is polymicrobial. Extensive surgical debridement with prolonged systemic antibiotics is necessary.

Erythrasma

Erythrasma is characterized by pigmented patches or thin plaques with fine scale that tend to occur in flexural areas, including the groin. Coral pink fluorescence under Wood's lamp examination is diagnostic. Distinction from dermatophytosis is usually possible clinically, as scaling is diffuse in erythrasma and there is no tendency toward central clearing.

Dermatophytosis

Chronic, slowly advancing, scaly erythematous lesions may be seen in the groin (tinea cruris) or the medial buttocks in addition to the upper thighs. Central clearing is often present and pustules may be seen; there is usually (if not always) concomitant tinea pedis and/or unguium. The diagnosis is made by microscopy and culture of skin scrapings.

Genital Candidiasis

Key features

- *Candida* spp. are normal commensals
- *Candida albicans* is responsible for 80%–90% of infections
- Underlying factors must be sought, e.g. diabetes, corticosteroids, systemic antibiotics
- In female patients usually seen during the reproductive years; occurs in infants but is uncommon in children or after menopause unless a risk factor is present

Introduction

It is important to confirm the infection by microscopy (KOH preparation) and culture because many genital skin problems in men and women are erroneously attributed to candidiasis.

Epidemiology

Candida spp. are normal commensals of the mucosal surfaces of the gastrointestinal and female genital tracts and may be found in small numbers in moist areas of skin[46]. There are at least 20 *Candida* spp. that can cause infections but evidence regarding their pathogenicity is conflicting. Resistance to imidazoles is an emerging problem.

Etiology

Candidiasis is more commonly seen in diabetics, especially when glycemic control is poor, and the immunosuppressed, as well as during treatment with systemic corticosteroids or broad-spectrum antibiotics. Candidiasis can be sexually transmitted and this is probably most important in recurrent infections. Polymorphisms in the mannose-binding lectin 2 gene (*MBL2*) have been implicated in some cases of severe recurrent candidiasis[47].

Clinical features

In men, balanitis, balanoposthitis, or rarely, widespread involvement of the perianal area, perineum, and groin is seen (see Ch. 77). Balanitis is more common in the uncircumcised man. The skin is erythematous and glazed with yellow pustules and erosions. In severe infections, edema may prevent retraction of the foreskin.

Women with candidiasis complain of pruritus and non-offensive vaginal discharge. Creamy white curds are visible on the vaginal walls, and there is vulvar erythema and sometimes fissuring. In severe cases swelling and pustules may be seen.

In both sexes, candidiasis may affect the perianal area with sheet-like erythema and fissuring. The inguinal–scrotal fold in men is a frequent site of involvement, and here, in addition to the erythema, the skin focally may appear white due to maceration of the accompanying scale. Satellite lesions, including pustules, are often seen.

In babies, candidiasis is a common cause of diaper dermatitis. There may be rapid spread of erythema and pustules that typically affect the skin creases, unlike the more common irritant dermatitis. Rarely, a nodular ulcerated variant may occur.

Differential diagnosis

Many inflammatory conditions of the genitalia are treated initially as a "yeast" infection. The presence of pseudohyphae alone is not sufficient to make the diagnosis; the appropriate clinical signs must also be present. Subcorneal pustules and erosions are also seen in impetigo, but this is excluded by a bacterial culture. In women, other causes of a vaginal discharge, including bacterial vaginosis, *Trichomonas* infection and desquamative inflammatory vaginitis, need to be considered. Some cases are mistakenly diagnosed as vulvar eczema.

Treatment

Topical polyene or imidazole antifungals may suffice in localized balanitis or intertrigo (see Ch. 127). The addition of a mild topical corticosteroid may help ameliorate symptoms. For vulvovaginal candidiasis, intravaginal imidazoles and single-dose oral fluconazole 150 mg are equally effective; in severe acute infections or in complicated infections (e.g. associated diabetes, immunocompromised state), these therapies should be repeated after 3 days. For non-*C. albicans* infections, nystatin pessaries or boric acid suppositories are recommended. Sexual partners only need treatment if they are symptomatic. An essential intervention is rectifying underlying causes such as uncontrolled diabetes.

Recurrent Candidiasis

Recurrent candidiasis is defined as more than four episodes of candidiasis per year. Precipitating factors must be identified, including hormone replacement therapy. Advice should be given on foreskin hygiene and keeping the perineal area cool with cotton underwear. In women, premenstrual exacerbations are typical. Possible regimens include oral fluconazole 150 mg weekly for 6 months or clotrimazole 500 mg vaginal tablet weekly for 6 months.

Schistosomiasis

Granulomatous lesions of the genitalia are primarily a manifestation of *Schistosoma haematobium* infection. Men may present with epididymitis, dysuria, or prostatitis and women with dyspareunia, dysmenorrhea, or contact bleeding.

EROSIVE GENITAL DISEASE

Erosions and ulcerations are seen in a wide variety of conditions (Table 73.6). Genital aphthae and HSV infections are common. Erosions may occur after scratching or rubbing or as a result of blister formation. To determine the cause of the erosions, it is essential to take a careful history and perform a full examination of the skin, including other mucosal surfaces. For example, a white lacy pattern on the buccal mucosa may suggest a diagnosis of lichen planus. Further investigations will be determined by the clinical appearance, but swabs for bacterial and fungal culture are often necessary. Biopsies of lesional skin for light microscopy and perilesional skin for direct immunofluorescence are indicated if an autoimmune blistering disorder is suspected.

CAUSES OF GENITAL EROSIONS AND ULCERATIONS
Lichen sclerosus
Erosive lichen planus
Genital aphthae/aphthosis*
Infection • Candidiasis • Herpes simplex or herpes zoster • Impetigo (*Staphylococcus*/*Streptococcus*) • Primary syphilis, chancroid • Epstein–Barr virus (EBV)†,‡, cytomegalovirus†, *Mycoplasma pneumoniae*†,¶ • Tuberculosis
Intraepithelial neoplasia
Squamous cell carcinoma and other malignancies
Trauma
Zoon balanitis/vulvitis
Acquired bullous diseases (see Table 73.7)
Drug reactions • Fixed drug eruption • Stevens–Johnson syndrome • Toxic erythema of chemotherapy • Other (e.g. penile/foscarnet, scrotal/multi-kinase inhibitors)
Inherited bullous diseases • Hailey–Hailey disease • Epidermolysis bullosa
Complex aphthosis – Behçet disease, inflammatory bowel disease
Crohn disease
Extramammary Paget disease
Langerhans cell histiocytosis
Pyoderma gangrenosum
Necrolytic migratory erythema, acrodermatitis enteropathica
Papular acantholytic dyskeratosis§
*Includes reactive non-sexually related acute genital ulcers which can be triggered by a variety of viral and bacterial infections. †Cause/trigger of reactive non-sexually related acute genital ulcers. ‡Primary EBV infection diagnosed via EBV IgM antibodies or PCR. ¶Trigger for *Mycoplasma*-induced rash and mucositis (MIRM)/reactive infectious mucocutaneous eruption (RIME). §Papules more common than erosions; it can occur in the setting of Hailey–Hailey disease or be associated with a somatic mutation in *ATP2C1* or *ATP2A2*.

Table 73.6 Causes of genital erosions and ulcerations. Infection-related disorders include erythema multiforme major, *Mycoplasma*-induced rash and mucositis (MIRM), and reactive non-sexually related acute genital ulcers.

Primarily in adolescent girls, reactive non-sexually related acute genital ulcers, sometimes referred to as Lipschutz ulcers, may be seen (Fig. 73.18). These ulcers can be large and deep and are triggered by a variety of viral or bacterial infections, including Epstein–Barr virus, *Mycoplasma*, cytomegalovirus, influenza, and streptococci. However, a cause is not always identified.

Acquired Autoimmune Bullous Diseases

Immunofluorescence (direct and indirect) is an essential investigation in suspected autoimmune bullous diseases as it may be very difficult to distinguish between the different blistering disorders on clinical grounds alone (Table 73.7)[48]. The most common autoimmune bullous diseases seen in the genital region are bullous pemphigoid, including the childhood variant[49], and mucous membrane pemphigoid. Unless blisters are seen or described, anogenital mucous membrane pemphigoid is often indistinguishable from erosive lichen planus; thus, histology and immunofluorescence are essential (Fig. 73.19). The extent and severity of the disease determine the treatment, which usually consists of a combination of topical and systemic anti-inflammatory and immunosuppressive agents. Great symptomatic relief can be gained from the use of potent topical corticosteroids, either as sole treatment in localized disease or as an adjunct to systemic treatment in widespread or more severe disease.



Fig. 73.18 Reactive non-sexually related acute genital ulcers associated with primary EBV infection. Extreme pain with urination required placement of a Foley catheter in this 13-year-old girl. EBV-related genital ulcers are often misdiagnosed as a genital herpes simplex viral infection. *Courtesy Julie V. Schaffer, MD.*



Fig. 73.19 Mucous membrane pemphigoid of the vulva. Ulcerations and scarring of the perianal area and perineum (positive direct immunofluorescence distinguished this from erosive lichen planus).

CLINICAL CHARACTERISTICS OF AUTOIMMUNE BULLOUS DISEASES THAT MAY PRESENT IN THE ANOGENITAL REGION			
Disease	**Age group**	**Clinical features**	**Chapter**
Bullous pemphigoid	Older adults; rare in children	Tense blisters that favor flexural sites, including the vulva in girls No scarring	Ch. 30
Mucous membrane (cicatricial) pemphigoid	Middle-aged and older adults	In the anogenital region, erosions and scarring but rarely blisters Involvement of oral and ocular mucosae	Ch. 30
Linear IgA bullous dermatosis	Children and adults	Trunk and limbs most common sites, but often face and genitalia in children Annular and polycyclic lesions composed of vesiculobullae	Ch. 31
Epidermolysis bullosa acquisita	Adults > children	Mechanobullous form with scarring more common than inflammatory form	Ch. 30
Pemphigus vulgaris	Peak age = 50–60 years	Initially mucosal involvement with primarily painful erosions Fragile cutaneous blisters and erosions may then develop	Ch. 29
Pemphigus vegetans	Peak age = 50–60 years	May have flexural accentuation, including inguinal	Ch. 29
Paraneoplastic pemphigus	Adults ≫ children	Erosive mucosal involvement that is severe & recalcitrant	Ch. 29

Table 73.7 Clinical characteristics of autoimmune bullous diseases that may present in the anogenital region.

Acquired Inflammatory Bullous Diseases

Erythema multiforme and Stevens–Johnson syndrome

Erythema multiforme (EM, primarily the major form) and Stevens–Johnson syndrome (SJS) may present as a bullous eruption in the genital region. In recurrent EM, HSV infection should be sought, remembering that there may be a delay of up to 2 weeks from infection to appearance of the lesions. In recurrent cases, a trial of prophylactic oral anti-HSV therapy may be indicated. Confluent dusky macular lesions point to SJS, in which drugs are the most common etiology. Prominent mucosal involvement also occurs in *Mycoplasma*-induced rash and mucositis (MIRM)/reactive infectious mucocutaneous eruption (RIME); see Ch. 20).

Fixed drug eruption

Recurrent erythematous or eroded plaques may occur on both skin and mucous membranes[50] (see Ch. 21). Often, cutaneous lesions are strikingly round, but this may not hold true in mucous membrane sites. The lesions recur in exactly the same site with each exposure to the drug. Bullous genital lesions frequently present as erosions. Common culprits are acetaminophen (paracetamol), tetracyclines, trimethoprim–sulfamethoxazole, and nonsteroidal anti-inflammatory drugs.

Inherited Bullous Disease

Hailey–Hailey disease

Patients with autosomal dominant Hailey–Hailey disease have recurrent involvement of flexural areas (see Ch. 59). Expanding erythematous plaques with superimposed erosions and sometimes vesicles and pustules are seen. In the inguinal creases, there is a particular tendency to form hypertrophic plaques. Secondary infection with bacteria, fungi, and HSV is a frequent problem and must be excluded in any exacerbation; for recurrent disease, suppressive therapy may be considered. Topical corticosteroids in combination with antifungal/antibacterial agents can ease symptoms. Low-dose naltrexone or CO_2 laser ablation may also prove helpful.

Additional figures and table on the 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) terminology of vulvar squamous intraepithelial lesions, available in our eBook (see inside front cover for access code).

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eFig. 73.1 Lichen sclerosus of the perianal region.



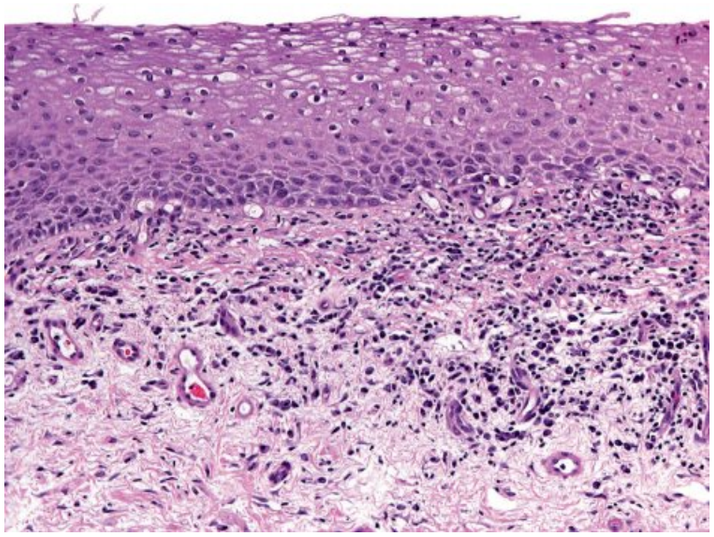
eFig. 73.3 Perianal lichen sclerosus. Well-demarcated ivory-white plaques with focal erosions and purpura. *Courtesy Julie V. Schaffer, MD.*



eFig. 73.2 Lichen sclerosus of the glans penis with extension onto the shaft. Note the hypopigmentation and purpura as well as scarring and ongoing inflammation. *Courtesy Kalman Watsky, MD.*



eFig. 73.4 Lichen planus of the penis. Multiple small, flat-topped, violaceous papules. *Courtesy Kalman Watsky, MD.*



eFig. 73.5 Zoon balanitis – histopathologic features. Lichenoid infiltrate in the upper dermis with a predominance of plasma cells. Additional features include increased dermal vascularization. Of note, plasma cells are commonly seen in mucosal biopsies, irrespective of the disorder. *Courtesy Lorenzo Cerroni, MD.*



eFig. 73.6 Lichen simplex chronicus of the scrotum. Note the increased skin markings with sparing of the scrotal raphe. *Courtesy Department of Dermatology, Medical University of Graz.*



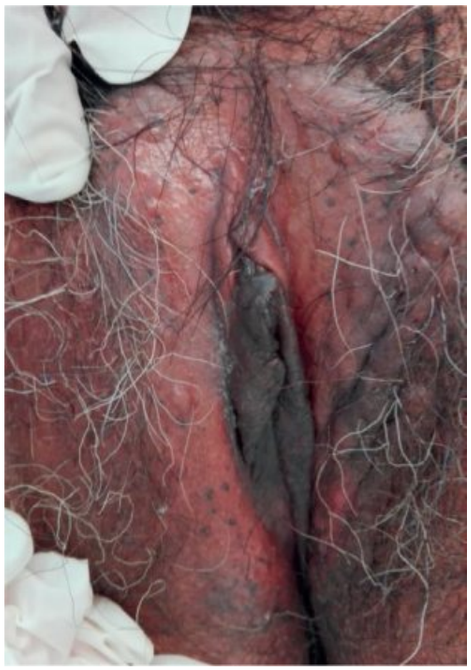
eFig. 73.7 Psoriasis involving the glans penis and distal finger. Thin pink plaques are seen with scale and erosions. *Courtesy Kalman Watsky, MD.*



eFig. 73.8 Extramammary Paget disease. Well-demarcated erythematous plaques of the labia majora and mons pubis. Erosions and white scale are also present. *Courtesy Kalman Watsky, MD.*



eFig. 73.9 Extranodal NK/T cell lymphoma, nasal type. Ulcerated indurated plaque involving the glans and distal shaft of the penis. *Courtesy Luis Requena, MD.*



eFig. 73.10 Vulvar syringomas. Multiple skin-colored papules on the labia majora in addition to mucosal melanosis. *Courtesy Diana Carolina Palacios Narváez, MD, and María Elisa Vega Memije, MD.*

2015 INTERNATIONAL SOCIETY FOR THE STUDY OF VULVOVAGINAL DISEASE TERMINOLOGY OF VULVAR SQUAMOUS INTRAEPITHELIAL LESIONS		
Vulvar lesion	**Other names**	**Comments**
Low-grade squamous intraepithelial lesion (LSIL)	Vulvar LSIL Flat condyloma HPV effect VIN 1 (historically)	• Often associated with low-risk HPV subtypes (e.g. 6, 11) • Negligible risk for malignant transformation to SCC
High-grade squamous intraepithelial lesion (HSIL)	Vulvar HSIL Usual type VIN (uVIN) Undifferentiated VIN VIN 2,3 (historically)	• Associated with high-risk HPV subtypes (e.g. 16, 18, 31) • ~20% risk of developing SCC
Differentiated VIN (dVIN)	VIN simplex type (historically)	• Associated with vulvar dermatoses, e.g. lichen sclerosus • ~30% risk of developing SCC

eTable 73.1 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) terminology of vulvar squamous intraepithelial lesions. HPV, human papillomavirus; SCC, squamous cell carcinoma; VIN, vulvar intraepithelial neoplasia.

Bacterial Diseases 74

R. Matthew McLarney, Lacy L. Sommer, Annette C. Reboli and Warren R. Heymann

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Key features

- Roughly 20% of outpatient dermatology visits are for bacterial skin infections
- Staphylococci and streptococci cause the majority of bacterial skin conditions, which range from common infections (e.g. impetigo) to multisystem disorders (e.g. toxic shock syndrome)
- Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a concern
- Various systemic diseases and immunodeficiency states predispose patients to bacterial skin infections that can be severe and refractory to treatment

THE CUTANEOUS MICROBIOTA

Hundreds of species of bacteria, along with fungi and viruses, collectively form a dynamic ecosystem known as the cutaneous microbiota (flora). The microbiota composition depends on the anatomic location – *Cutibacterium* (formerly *Propionibacterium*) spp. dominate in sebaceous sites, whereas *Staphylococcus* and *Corynebacterium* spp. thrive in moist skin folds (Fig. 74.1)[1,2]. Together these organisms help prevent skin infections by providing competition against pathogenic microbes and hydrolyzing lipids of sebum to produce free fatty acids, which are toxic to many pathogenic bacteria. The ecology of particular areas of the skin is determined by the availability of moisture, presence of sebaceous lipids, and gaseous environment. Disruption of the delicate balance between host and microorganisms can result in skin disorders or infection. The nomenclature of cutaneous bacterial infections reflects the site, depth, and extent of the infection as well as the organism involved.

GRAM-POSITIVE BACTERIA

STAPHYLOCOCCAL AND STREPTOCOCCAL SKIN INFECTIONS

Impetigo

Synonyms: ■ Bullous impetigo: pemphigus neonatorum ■ Impetigo contagiosa ■ Non-bullous impetigo: crusted impetigo ■ Staphylococcal impetigo ■ Streptococcal impetigo

Key features

- *Staphylococcus aureus* and, to a lesser degree, group A β-hemolytic streptococci are the major causes of impetigo
- Represents the most common bacterial skin infection in children
- Nasal carriers of *S. aureus* are at particular risk of developing impetigo
- Treatment decisions should consider resistance patterns of *S. aureus*

Introduction

Impetigo is a common, contagious, superficial skin infection that can present in non-bullous and bullous forms (Fig. 74.2). The most common pathogen in both non-bullous and bullous impetigo is *Staphylococcus aureus*. Group A β-hemolytic streptococcus (*Streptococcus pyogenes*) represents another important cause of non-bullous impetigo. Table 74.1 compares the clinical characteristics and complications of bullous and non-bullous impetigo.

Epidemiology

Impetigo occurs frequently in children, especially those <6 years of age, and it represents the most common bacterial skin infection in this group. Adults most commonly acquire impetigo through contact with infected children. Impetigo is extremely contagious, spreading rapidly via direct person-to-person contact or through fomites. In temperate climates, peak incidence is in the summer months. Predisposing factors include a warm ambient temperature, high humidity, poor hygiene, an atopic diathesis, scabies, skin trauma, and participation in contact sports[3]. Nasal, pharyngeal, axillary, and/or perineal colonization with *S. aureus* increases the risk for developing impetigo and other staphylococcal infections.

Pathogenesis

Non-bullous impetigo is usually caused by *S. aureus* or group A β-hemolytic streptococci. Infection typically occurs at sites of scratching (e.g. insect bites, atopic dermatitis), minor trauma (e.g. an abrasion, laceration, or burn) or other skin infections/infestations (e.g. pediculosis, scabies). Disruption of the skin barrier allows the bacteria to adhere, invade, and establish infection.

Bullous impetigo results from the local production of exfoliative toxins (ETA, ETB) by phage group II *S. aureus* at the site(s) of cutaneous infection; systemic elaboration of the same toxins is the cause of staphylococcal scalded skin syndrome (SSSS; see below). In both diseases, blister formation is mediated by exfoliative toxin binding to the desmosomal protein desmoglein 1 and cleaving its extracellular domain, thus leading to acantholysis within the epidermal granular layer. *S. aureus* can be cultured from fluid within the blisters of bullous impetigo, but

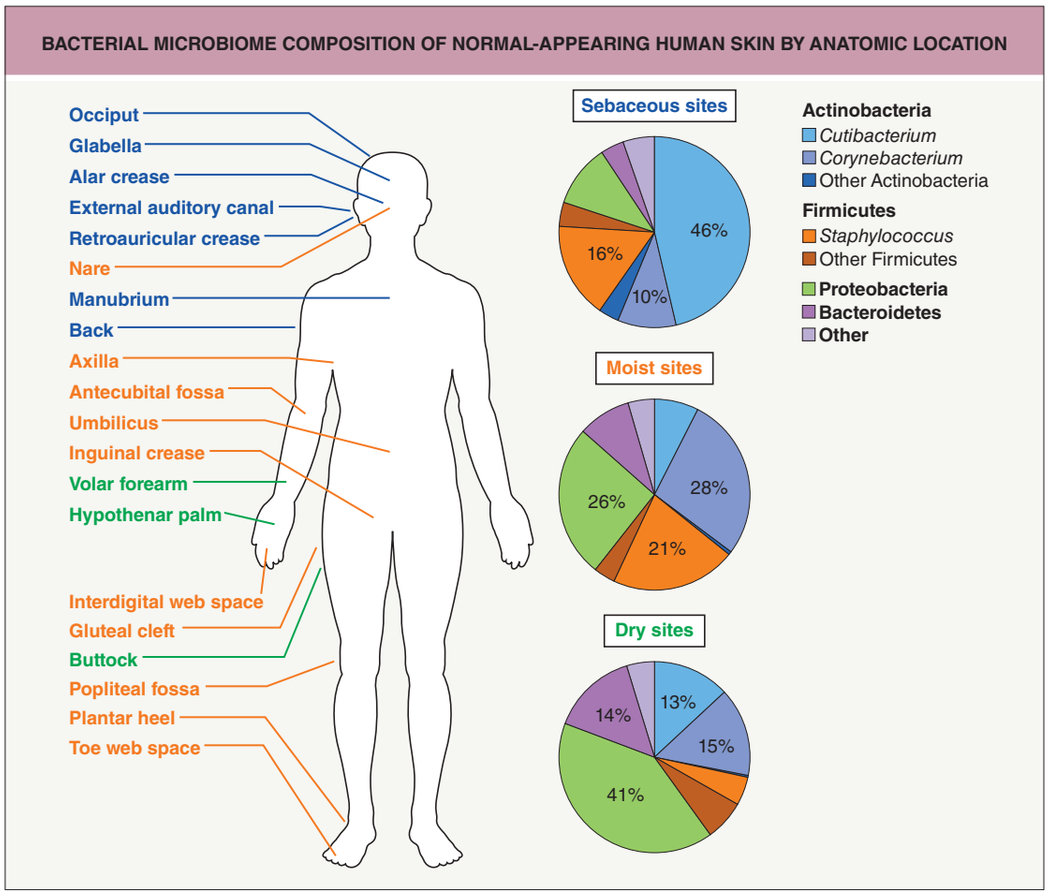


Fig. 74.1 Bacterial microbiome composition of normal-appearing human skin by anatomic location. *Adapted from Chen YE, Tsao H. The skin microbiome: Current perspective and future challenges. J Am Acad Dermatol 2013;69:143–55. Figure 3.*



Fig. 74.2 Staphylococcal impetigo. A Honey-colored crusts on the chin of a child with non-bullous impetigo. **B** Multiple small superficial erosions with crusting around the nares and on the chin in association with folliculitis in an adult. **C, D** Superficial round to oval erosions with central thin crusting and a peripheral collarette due to bullous impetigo in the axilla and on the neck. Note the small intact vesicles on the upper anterior neck (**D**). *A, Courtesy Julie V. Schaffer, MD; B, C, Courtesy Kalman Watsky, MD; D, Courtesy Lorenzo Cerroni, MD.*

CHARACTERISTIC FEATURES OF BULLOUS AND NON-BULLOUS IMPETIGO		
	Non-bullous impetigo	**Bullous impetigo**
Epidemiology	• 70% of all cases of impetigo • Children most often affected	• Less common • Often occurs in neonates (see Ch. 34) and children
Clinical lesions	• Early: single 2–4 mm erythematous macule that rapidly evolves into a short-lived vesicle or pustule • Late: superficial erosion with a typical "honey-colored" yellow crust and rapid direct extension of infection to surrounding skin	• Early: small vesicles enlarge into 1–2 cm superficial bullae • Late: flaccid, transparent bullae measuring up to 5 cm in diameter; after rupture there is a collarette of scale, but no thick crust; usually little surrounding erythema
Distribution	• Face (around the nose and mouth) and extremities	• Face, trunk, buttocks, perineum, axillae, and extremities
Associated findings	• Mild lymphadenopathy may be present	• Usually no systemic symptoms but can be associated with weakness, fever, and diarrhea
Clinical course	• Usually a benign, self-limited process • Usually resolves within 2 weeks without scarring if untreated	• Usually resolves in 3–6 weeks without scarring if not treated
Complications	• In 5% of cases, non-bullous impetigo caused by *Str. pyogenes* (M protein types 1, 4, 12, 49, 55, 57, 60) results in acute post-streptococcal glomerulonephritis (APSG)* • Risk of APSG is not altered by treatment with antibiotics • Impetigo has not been linked to a risk of rheumatic fever	• In infants/young children and adults with immunodeficiency or renal failure, exfoliative toxin may disseminate and cause staphylococcal scalded skin syndrome
*Associated with anti-DNase B and antistreptolysin O (ASO) antibodies.		

Table 74.1 Characteristic features of bullous and non-bullous impetigo.

not those of SSSS. Compared to non-bullous impetigo, the bullous form is more likely to develop on clinically intact skin, especially in intertriginous sites.

Clinical features

The clinical features of impetigo are outlined in Table 74.1[4,5].

Pathology

In *non-bullous impetigo*, small neutrophilic vesiculopustules are present within the epidermis. Spongiosis frequently underlies the pustule. The upper dermis contains an intense infiltrate of neutrophils and lymphocytes. Gram-positive cocci are present within the vesiculopustules.

In *bullous impetigo*, there is cleavage of the upper epidermis, typically within the granular layer. Acantholysis mimicking pemphigus foliaceus may be observed. Relatively few inflammatory cells are present within the blister cavity, and a neutrophilic infiltrate is often found in the upper dermis. Gram-positive cocci may be evident.

Diagnosis and differential diagnosis

The diagnosis of impetigo is usually made clinically; exudate from beneath the crust or fluid from intact bullae can be sent for culture to confirm the diagnosis and determine susceptibility to antibiotics. Leukocytosis is seen in approximately half of patients with impetigo and regional lymphadenopathy is common. The differential diagnosis of non-bullous and bullous impetigo is presented in Table 74.2.

Treatment

For healthy patients with a few superficial lesions and no systemic symptoms, topical mupirocin, retapamulin, ozenoxacin, or fusidic acid (not available in the US) are often equally (if not more) effective than oral antibiotics[6]. However, *S. aureus* can develop resistance to each of these agents[7]. Treatment should also include cleansing the affected area and removing crusts, which can be facilitated by wet dressings.

The extent of skin involvement, the presence of complications (e.g. cellulitis, lymphangitis, bacteremia), comorbid conditions (e.g. atopic dermatitis, varicella), the patient's immune status, and local drug-resistance patterns (e.g. the prevalence of community-associated methicillin-resistant *S. aureus* [CA-MRSA]) should be considered when deciding whether topical, oral, or intravenous therapy is the most appropriate treatment (Table 74.3). The risk of developing post-streptococcal glomerulonephritis following streptococcal impetigo is not affected by treatment and is greater with certain subtypes of group A β-hemolytic streptococci (see Table 74.1)[4,6,8]. In contrast to pharyngitis, a link between streptococcal pyoderma and acute rheumatic fever has not been established. Methods for "decolonizing" the nares and skin of patients with recurrent staphylococcal impetigo are discussed in the folliculitis section below.

DIFFERENTIAL DIAGNOSIS OF NON-BULLOUS AND BULLOUS IMPETIGO		
	Most common	**Less common**
Non-bullous impetigo	• Insect bites • Eczematous dermatoses • Herpes simplex viral infection • Candidiasis	• Inflammatory tinea corporis/faciei • Varicella • Scabies • Pediculosis • Pemphigus foliaceus
Bullous impetigo	• Bullous insect bite reactions • Thermal burns • Herpes simplex viral infection • Acute contact dermatitis (allergic or irritant)	• Autoimmune bullous dermatoses • Bullous erythema multiforme • Stevens–Johnson syndrome • Bullous mastocytosis

Table 74.2 Differential diagnosis of non-bullous and bullous impetigo.

Bacterial Folliculitis

Introduction

Bacterial folliculitis is a superficial or deep infection of the hair follicle. A furuncle develops when the entire follicle and surrounding tissue are involved (see below).

Epidemiology and pathogenesis

S. aureus is the most common infectious cause of folliculitis (see Ch. 38). Gram-negative folliculitis occasionally develops in acne vulgaris patients treated with prolonged courses of oral antibiotics. In addition, *Pseudomonas* or (less often) *Aeromonas* folliculitis can result from the use of improperly chlorinated hot tubs and swimming pools[9]. Predisposing factors for staphylococcal folliculitis include occlusion, maceration, and hyperhydration of the skin; shaving, plucking, or waxing hair; use of topical corticosteroids; hot and humid weather; atopic dermatitis; and diabetes mellitus.

Clinical features

Staphylococcal folliculitis most frequently involves the face (especially the beard area), scalp, chest, back, axillae, and buttocks (see Ch. 38). The appearance depends on the depth of follicular involvement. Superficial folliculitis (impetigo of Bockhart) presents with small (1–4 mm) pustules or crusted papules on an erythematous base. The lesions are frequently clustered and heal without scarring. Sycosis barbae, a type of deep folliculitis, appears as large erythematous papules, often with a central pustule and sometimes coalescing to form plaques studded with pustules and crusts. Bacterial folliculitis may be pruritic or tender (especially if there is deeper involvement)[10].

EMPIRIC TREATMENT OF CUTANEOUS STAPHYLOCOCCAL AND STREPTOCOCCAL INFECTIONS IN ADULTS	
Organism/situation	**Suggested antibiotics**
Streptococcal infection	• Dicloxacillin 500 mg PO four times a day • First generation cephalosporin (see below) • Nafcillin or oxacillin 1–2 g IV four times a day, if severe
Suspected MSSA infection • e.g. impetigo requiring systemic treatment or non-purulent cellulitis	• First-generation cephalosporin, e.g. cephalexin 250–500 mg PO three or four times a day • Dicloxacillin 250–500 mg PO four times a day
Suspected MRSA infection (see Table 74.4) • e.g. furuncles/abscesses, purulent cellulitis, or infections that failed to respond to treatment with an antistaphylococcal β-lactam	• Doxycycline 100 mg PO two times a day* • Trimethoprim–sulfamethoxazole 1 or 2 double-strength tablets PO twice a day* • Clindamycin 300–450 mg PO four times a day (although some MRSA strains are clindamycin-resistant)
	Other oral options • Minocycline* • Linezolid† or tedizolid‡,† • Delafloxacin†
	Intravenous options for severe disease • Vancomycin (first line) • Daptomycin‡ • Telavancin‡, oritavancin‡, or dalbavancin‡ • Ceftaroline‡
Penicillin-allergic patients	• Clindamycin (see above) • Clarithromycin 250 mg PO two times a day

Additional special considerations	• Furuncle/abscess: incision and drainage (without packing) is a key component of successful treatment
	• If recurrent infections, address carrier state:
	  • Mupirocin 2% nasal ointment twice a day for 5 days
	  • Mupirocin 2% cream to major body folds (e.g. axillae, groin, inframammary) and umbilicus twice a day for 5 days
	  • Wash body with chlorhexidine or dilute bleach¶ 2–3 times per week
	• Address fomites including sports equipment, keyboards, and remote controls
	• Consider close human contacts or pets as source of infection

*Does not provide coverage of group A streptococci; if coverage of the latter is desired, a β-lactam should also be prescribed. †Intravenous form also available. ‡Their cost-effective role in treatment of MRSA has not been established. ¶e.g. 0.5 cup of household bleach (6%–8.25% sodium hypochlorite) in a full 40-gallon bathtub, or 0.5–1 teaspoon per gallon in a spray bottle.	

Table 74.3 Empiric treatment of cutaneous staphylococcal and streptococcal infections in adults. Treatment duration is usually 5–14 days, depending on the severity and clinical response. Initial choice of antibiotic is dependent on known resistance patterns in a given community. Topical treatments for localized superficial infections (e.g. impetigo) include mupirocin 2% ointment/cream, retapamulin 1% ointment, ozenoxacin 1% cream, and fusidic acid 2% cream (not available in the US). The contents of pustules or exudate (e.g. underlying a crust) should be sent for culture and sensitivities prior to beginning therapy. Systemic quinolones (other than delafloxacin) and macrolides are not optimal, as staphylococcal resistance is common and may develop rapidly. IV, intravenously; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, orally.

Diagnosis and differential diagnosis

The diagnosis of bacterial folliculitis is usually made based on the clinical findings. Gram staining and bacterial cultures can help to identify the causative organisms, which is especially useful in severe, recurrent, or treatment-resistant cases. The differential diagnosis includes other forms of folliculitis (see Ch. 38), acne vulgaris, rosacea, chloracne, pseudofolliculitis barbae, and keratosis pilaris.

Treatment

Superficial staphylococcal folliculitis can be treated with antibacterial washes that contain chlorhexidine or sodium hypochlorite. Topical antibiotics such as mupirocin or clindamycin may also be used for 7–10 days to treat localized lesions. When staphylococcal folliculitis is widespread or recurrent, oral β-lactam antibiotics (e.g. a β-lactamase-resistant penicillin or first-generation cephalosporin), tetracyclines, trimethoprim–sulfamethoxazole (TMP-SMZ), macrolides, or linezolid (depending on local resistance patterns) can be prescribed (see Table 74.3).

The carrier state should be addressed in patients with recurrent staphylococcal folliculitis and their close contacts (see Table 74.3). Application of mupirocin 2% ointment twice daily to the nares for 5–10 days can be used to eradicate nasal carriage of *S. aureus*. Methods to decolonize the skin (e.g. axillae, umbilicus, perineum/groin, submammary area) include topical mupirocin, washes containing chlorhexidine, and dilute sodium hypochlorite baths (e.g. 0.5 cup household bleach [6%–8.25% sodium hypochlorite] in a full standard bathtub). However, mupirocin resistance has been increasing, especially among MRSA isolates[11]. Elimination of bacterial contamination of potential fomites such as keyboards, toys, and sports equipment (e.g. shoulder pads, wrestling mats) should also be considered, e.g. by using ethanol- or sodium hypochlorite-based disinfectants.

Abscesses, Furuncles, and Carbuncles

Introduction

Abscesses and furuncles (boils) are collections of pus that are "walled-off" from the surrounding tissues. Whereas an abscess can occur anywhere in or on the body, a furuncle, by definition, involves a hair follicle. A contiguous collection of furuncles is termed a carbuncle.

Epidemiology and pathogenesis

Furuncles most often occur in adolescents and young adults. *S. aureus* is usually the causative organism, although anaerobic bacteria are occasionally cultured from recurrent furuncles in the anogenital region. Predisposing factors include chronic *S. aureus* carriage, close personal contact with affected individuals (e.g. households, athletic activities), diabetes mellitus, obesity, poor hygiene, immunodeficiency syndromes (e.g. chronic granulomatous disease, hyperimmunoglobulin E syndrome), and hereditary sensory and autonomic neuropathy due to defects in nerve growth factor β or its high-affinity receptor (see Table 6.10)[12].

Clinical features

Abscesses are localized collections of pus that are usually inflamed. They can arise in any cutaneous site. Furuncles are acute, inflammatory abscesses of individual hair follicles and the surrounding tissue and, as such, occur only in hair-bearing skin. The most common locations are the face, neck, axillae, buttocks, thighs, and perineum. Sites prone to friction or minor trauma, such as the area under a belt, are also susceptible. Furuncles usually begin as firm, tender, red nodules that progressively enlarge, becoming painful and fluctuant (Fig. 74.3);

rupture results in decreased pain. Systemic symptoms are usually absent, although regional lymphadenopathy may develop. Furunculosis (multiple or recurrent furuncles) can be associated with chronic *S. aureus* carriage.

Carbuncles are collections of furuncles that extend deep into the subcutaneous tissue. The surface usually displays multiple draining sinus tracts and occasionally ulcerates. They usually occur in areas with thicker skin (e.g. nape of neck, back, thigh). Systemic symptoms are often present. Carbuncles are slow to heal and lead to scarring.

Pathology

Biopsy specimens reveal a dense neutrophilic infiltrate in the subcutaneous tissue. Furuncles are characterized by an acute, suppurative reaction involving the follicle below the infundibulum, as well as perifollicular necrosis with fibrinoid debris.



Fig. 74.3 Furuncles secondary to methicillin-resistant *Staphylococcus aureus*. Fluctuant erythematous nodules with a central pustule on the ankle (**A**) and finger (**B**). *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Frank Samarin, MD.*

Diagnosis and differential diagnosis

Diagnosis is based primarily on clinical appearance. Gram stains and cultures from the lesion support the diagnosis. Extensive furuncles and carbuncles can be associated with leukocytosis. A ruptured epidermoid or pilar cyst, hidradenitis suppurativa, "cold" abscesses in immunodeficiency syndromes (see Fig 60.8A), and cystic acne should be considered in the differential diagnosis.

Treatment

For simple furuncles, warm compresses may promote maturation, drainage, and resolution. Larger or deeper fluctuant lesions typically require incision and drainage. Systemic antibiotic therapy is recommended (in conjunction with incision and drainage if possible) in the following situations: (1) furuncles around the nose, in the external auditory canal, or in other locations where drainage is difficult (e.g. elsewhere on the face, hands, genitalia); (2) severe or extensive disease (e.g. multiple sites); (3) lesions with surrounding cellulitis/phlebitis or associated with signs/symptoms of systemic illness; (4) lesions not responding to local care; and (5) patients with concerning comorbidities or immunosuppression[13,14]. Given the high proportion of furuncles that are caused by MRSA, empiric coverage with antibiotics such as doxycycline, TMP-SMX, or (depending on local resistance patterns) clindamycin should be considered (see Table 74.3 and below). Large controlled studies found that administration of a systemic antibiotic (TMP-SMX or clindamycin) following incision and drainage of a solitary, uncomplicated cutaneous abscess increases the cure rate and decreases the likelihood of recurrence[15,16]. However, this benefit must be weighed against the potential for antibiotic side effects. Patients with recurrent furunculosis may benefit from eradication of *S. aureus* from the nares, axillae, umbilicus, and perineum (see Table 74.3).

Methicillin-Resistant *Staphylococcus aureus* Infection

Introduction

Methicillin resistance was first noted in isolates of *S. aureus* in 1961. Although initially associated with nosocomial infection (healthcare-associated [HA]-MRSA), community-associated (CA)-MRSA has become a growing problem among individuals without predisposing factors[17]. Table 74.4 compares CA- and HA-MRSA. In the US, rates of HA-MRSA infection have fallen in recent years while CA-MRSA rates have stayed relatively stable[18]. Although there is considerable regional variation, overall, MRSA represents the most common cause of purulent skin and soft tissue infections presenting

COMPARISON OF COMMUNITY-ASSOCIATED (CA) AND HEALTHCARE-ASSOCIATED (HA) METHICILLIN-RESISTANT *STAPHYLOCOCCAL AUREUS* (MRSA)

	CA-MRSA	HA-MRSA
Epidemiology	• Favors children and young adults	• Favors adults age >65 years
Risk factors	• Close interpersonal contact (e.g. athletes, military personnel, prison inmates, children attending daycare) • Men having sex with men • Injection drug use • Recent antibiotic use • Homelessness • HIV infection • Skin trauma (e.g. lacerations, abrasions, tattoos, body shaving/piercing) • Dermatologic conditions (e.g. atopic dermatitis*)	• Underlying comorbidities (e.g. diabetes mellitus) • Recent surgery or hospitalization (especially if prolonged or in an ICU) • Residence in a long-term care facility • Dialysis • Indwelling percutaneous medical devices and catheters • Chronic wounds
Typical sites/types of infection	• Skin and soft tissue, especially furuncles/abscesses or purulent cellulitis	• Skin and soft tissue, especially in surgical sites • Urinary tract • Respiratory tract • Bloodstream
Molecular characteristics	• SCC*mec* types IV and V • Panton–Valentine leucocidin (PVL) genes • USA300 or USA400 PFGE	• SCC*mec* types I–III • USA100 or USA200 PFGE
Antibiotic susceptibility	• Usually multiple agents	• Limited

*Increased risk of staphylococcal infections, but not generally in the proportion due to MRSA.

Table 74.4 Comparison of community-associated (CA) and healthcare-associated (HA) methicillin-resistant *Staphylococcal aureus* (MRSA). ICU, intensive care unit; PFGE, pulsed-field electrophoresis pattern.

to emergency departments in the United States[17,19]. MRSA also represents one of the ESKAPE pathogens that have emerged due to widespread overuse of antibiotics (Table 74.5); these organisms have become problematic sources of nosocomial infections, especially among burn victims.

Clinical features

Furunculosis is the most frequent manifestation of CA-MRSA infection (see Fig. 74.3). These lesions can evolve into large abscesses, cellulitis, or necrotic plaques which may be misdiagnosed as spider bites. Less often, impetigo, SSSS, and folliculitis are seen, and life-threatening complications such as septic shock, toxic shock syndrome, and necrotizing fasciitis occasionally develop.

Pathogenesis

Methicillin resistance is caused by the production of an altered penicillin-binding protein 2a (PBP2a) that has decreased affinity for β-lactam antibiotics. PBP2a is the protein product of the *mecA* gene, which is located within a specific mobile genetic element called the staphylococcal cassette chromosome *mec* (SCC*mec*). Acquisition of different SCC*mec* elements by *S. aureus* led to the emergence of HA-MRSA (usually SCC*mec* types I–III) and CA-MRSA (usually SCC*mec* types IV and V) strains; methicillin-resistant coagulase-negative staphylococci are thought to represent a reservoir of SCC*mec* for CA-MRSA. Many CA-MRSA strains also encode virulence factors such as Panton–Valentine leukocidin (PVL), a pore-forming cytotoxin that can cause destruction of leukocytes and tissue necrosis.

As a reflection of their distinct SCC*mec* elements, CA-MRSA and HA-MRSA have different patterns of antibiotic resistance. CA-MRSA is typically susceptible to multiple non-β-lactam antibiotics, whereas HA-MRSA is usually resistant to several antimicrobial classes, including aminoglycosides, macrolides, and clindamycin. However, some isolates of the USA300 clone, which currently causes most CA-MRSA skin infections in the US have developed resistance to macrolides, clindamycin, tetracycline (less often doxycycline), quinolones, and mupirocin[20].

Resistance to macrolides in staphylococci may result from: (1) active drug efflux via a pump encoded by the *msrA/msrB* gene (frequent in MRSA isolates); (2) synthesis of macrolide-inactivating enzymes; or (3) modification of the bacterial ribosome by the erythromycin ribosomal methylase encoded by *erm* genes, which produces cross-resistance to clindamycin[21]. Erythromycin stimulates expression of *erm*, which leads to clinically relevant resistance. If initial sensitivity testing shows resistance to erythromycin and susceptibility to clindamycin, resistance to clindamycin will still develop if *erm* is present, since bacterial variants with constitutive *erm* expression commonly arise and are selected for during clindamycin therapy. This "inducible resistance" can be assessed with the D-test (double-disk diffusion) (Fig. 74.4).

THE ESKAPE PATHOGENS
Enterococcus faecium
Staphylococcus aureus
Klebsiella pneumoniae
Acinetobacter baumannii
Pseudomonas aeruginosa
Enterobacter species

Table 74.5 The ESKAPE pathogens

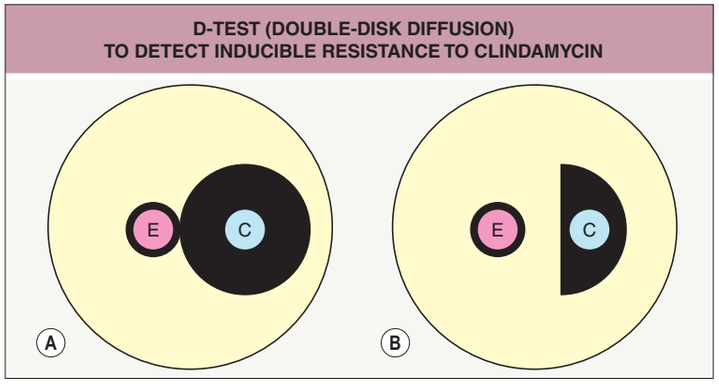


Fig. 74.4 D-test (double-disk diffusion) to detect inducible resistance to clindamycin. Erythromycin (E) and clindamycin (C) disks are placed 15–17 mm apart on an agar plate inoculated with the organism. Following incubation, the zones of inhibition around the disks are evaluated. If the zone around the clindamycin disk is circular in shape and of sufficient size (**A**), the organism is negative for inducible resistance. However, if the portion of the zone adjacent to the erythromycin disk is "flattened", producing a "D" shape (**B**), the organism is positive for inducible resistance to clindamycin.

Diagnosis and treatment

When *S. aureus* infection is suspected, culture and susceptibility testing should be performed, whenever feasible, to guide antibiotic selection. Prior to obtaining sensitivity results, empiric antibiotic therapy can be chosen based on the prevalence of MRSA and resistance patterns in a given community, as well as the severity of the infection (see Table 74.3). Vancomycin should be considered for patients with severe infections, especially in geographic regions where CA-MRSA is prevalent and in individuals with a history of MRSA colonization or injection drug use[17]. PCR-based (e.g. BD Max™ StaphSR) and bacteriophage-based (e.g. cobas® vivoDx) assays are also available for rapid detection of MRSA from nasal or potentially skin swab samples, but they do not provide other drug susceptibility information[22].

Blistering Distal Dactylitis

Blistering distal dactylitis is a localized infection of the volar fat pad of a finger or, less often, a toe, with occasional involvement of the nail fold or more proximal portion of the digit. Darkening of the skin is often observed for several days to a week before blister formation (Fig. 74.5). The infection most commonly occurs in children aged 2–16 years.

Group A beta-hemolytic streptococci or *S. aureus* are usually the causative organisms. Inoculation may follow local skin trauma or autoinoculation from nose picking[23]. The differential diagnosis includes herpetic whitlow, a thermal or chemical burn, acute paronychia, bullous impetigo, and frictional bullae.

Drainage and a 10-day course of an oral antistaphylococcal antibiotic are recommended. Although topical therapy with mupirocin has been described, systemic therapy can prevent development of new sites of infection as well as local extension.

Ecthyma

Ecthyma is a deep variant of non-bullous impetigo characterized by extension into the dermis to produce a shallow ulcer that heals with scarring (Fig. 74.6). It can be caused by a primary infection with group A beta-hemolytic streptococci or a streptococcal superinfection, e.g. of an excoriated insect bite. Outbreaks of ecthyma have occurred among infantry units where skin trauma, poor hygiene, and crowded living conditions facilitate disease spread[24]. Table 74.6 summarizes the clinical aspects and treatment of ecthyma[25].

Staphylococcal Scalded Skin Syndrome

Synonyms: ■ Ritter's disease ■ Pemphigus neonatorum



Fig. 74.5 Blistering distal dactylitis. Large vesiculopustule due to infection with group A *Streptococcus*. *Courtesy Julie V. Schaffer, MD.*



Fig. 74.6 Ecthyma. Ulceration with hemorrhagic crust on the wrist (**A**) and leg (**B**) due to infection with group A streptococci. *A, Courtesy Kalman Watsky, MD; B, Courtesy Michal Kidacki, MD, PhD.*

CLINICAL FEATURES OF ECTHYMA	
Clinical findings	• Usually fewer than 10 lesions, most commonly on the lower extremities • An initial vesiculopustule enlarges (0.5–3 cm in diameter) over several days, and develops a hemorrhagic crust • The ulcer has a "punched-out" appearance and a purulent, necrotic base • Lesions are slow to heal and produce scarring
Risk factors	• Young age (children), lymphedematous limbs, poor hygiene, neglect (including the elderly), immunosuppression, scratching (e.g. of insect bites), trauma
Complications	• Lesions are often contaminated with staphylococci • Systemic symptoms and bacteremia are rarely seen • Cellulitis and osteomyelitis are extremely infrequent
Diagnosis	• Clinical appearance • Culture of moist, purulent base; skin biopsy with deep-tissue Gram stain and culture occasionally required
Differential diagnosis	• Ecthyma gangrenosum • Ulcers due to vasculitis, vasculopathies, other causes (see Ch. 105)

Table 74.6 Clinical features of ecthyma. This deeper form of non-bullous impetigo is due to a group A streptococcal infection.

Introduction

Staphylococcal scalded skin syndrome (SSSS) is caused by hematogenous dissemination of the same exfoliative toxins that lead to bullous impetigo when produced locally. Cleavage of the epidermis through the granular layer results in the formation of tender, flaccid bullae[26].

Epidemiology

SSSS is primarily a disease of infants and young children, who have decreased renal toxin clearance (especially neonates) and/or a lack of toxin-neutralizing antibodies. Adults with predisposing conditions such as renal insufficiency, diabetes mellitus, substance abuse, and cancer are occasionally affected[27]. Outbreaks occurring in neonatal nurseries are usually secondary to asymptomatic carriage of a toxigenic strain of *S. aureus* by healthcare workers or parents. A male predominance exists, with a 2:1 male:female ratio in sporadic cases and 4:1 in epidemics.

Pathogenesis

Most cases of SSSS are caused by *S. aureus* phage group II types 55 and 71, which can be methicillin-sensitive or resistant. These organisms produce exfoliative (also known as epidermolytic) toxins (ETs). ETA (chromosomally encoded) and ETB (plasmid encoded) are serine proteases that bind and cleave desmoglein-1 (Dsg1). This causes splitting of the desmosomes, which leads to disruption of the epidermal layer and bulla formation. Dsg1 is targeted by autoantibodies in pemphigus foliaceus, which has identical histologic features to SSSS. Young children have a relatively low amount of Dsg1 and less renal clearance of ETs, contributing to their increased risk of SSSS, whereas adults are more likely to have anti-ET antibodies.

In contrast to bullous impetigo, where the effects of the ETs are limited to the site(s) of infection, in SSSS the toxin diffuses from the nidus of infection and spreads hematogenously to produce widespread effects. In children, the infectious focus is usually in the nasopharynx or conjunctivae, whereas staphylococcal pneumonia or bacteremia may be present in adults[28].

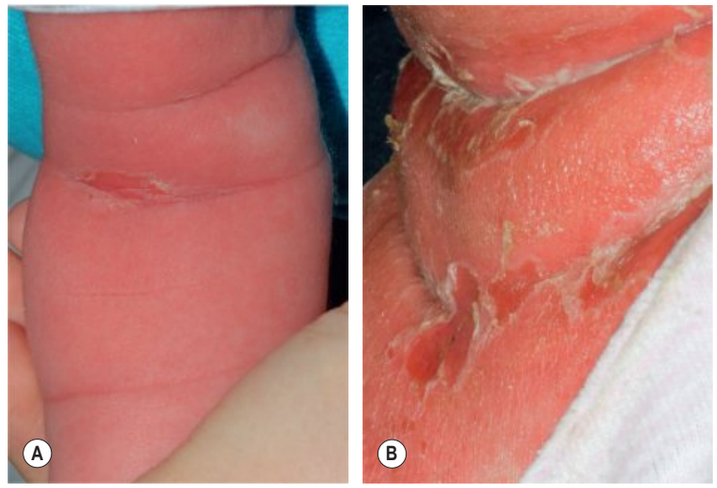


Fig. 74.7 Staphylococcal scalded skin syndrome. A Diffuse erythema with an early superficial erosion in the antecubital fossa. **B** More extensive involvement on the neck with a wrinkled appearance of the erythematous skin in addition to peeling and multiple erosions. *Courtesy Julie V. Schaffer, MD.*

Clinical features

There is often a prodrome of malaise, fever, irritability, and skin tenderness. The patient may have purulent rhinorrhea or conjunctivitis as a manifestation of the underlying staphylococcal infection. Erythema typically first appears on the head (accompanied by variable facial edema) and in intertriginous sites, often with generalization within 48 hours. The skin subsequently develops a wrinkled appearance owing to the formation of flaccid, sterile bullae within the superficial epidermis (Fig. 74.7). The Nikolsky sign is positive. Classically, the flexural areas are the first to exfoliate, leaving behind moist skin and thin, varnish-like crusting. Patients also demonstrate characteristic periorificial (e.g. perioral, periocular) crusting and radial fissuring (see Figs. 34.17 & 81.17). Intraoral lesions do not occur.

Scaling and desquamation continue for the next 3–5 days, followed by re-epithelialization without scarring. With proper treatment, SSSS resolves in 1–2 weeks, usually without sequelae. The mortality rate is ≤4% for children but may approach 50% in adults[29].

Pathology

Histologic examination shows a sharply demarcated zone of cleavage at or below the stratum granulosum. There are usually no inflammatory cells in the bullae. The upper dermis also lacks an inflammatory infiltrate, and no organisms are seen on Gram stain of biopsy specimens.

Diagnosis and differential diagnosis

SSSS is generally a clinical diagnosis. Although cultures taken from intact bullae are negative, *S. aureus* may be cultured from the conjunctiva, nasopharynx, perianal area, or pyogenic foci on the skin. Blood cultures are almost always negative in children but may be positive in adults. The leukocyte count can be elevated or normal. Examination of frozen sections is occasionally helpful in confirming the level of the split in the bullae. Slide latex agglutination, double immunodiffusion, or enzyme-linked immunosorbent assay (ELISA) tests can identify the toxins responsible for SSSS.

COMPARISON OF TOXIC EPIDERMAL NECROLYSIS AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME		
	TEN	**SSSS**
Cause	Usually drug-induced	Infection with toxin-producing *S. aureus*
Age	Primarily adults	Primarily infants and young children
Histology	Dermal–epidermal separation with epidermal necrosis; dermis has a variable inflammatory infiltrate	Granular layer split in epidermis; dermis lacks inflammatory infiltrate
Distribution of rash	Areas of sparing often present	Generalized with flexural accentuation
Mucous membranes	Involved, erosions	Uninvolved
Nikolsky sign	In some areas, difficult to elicit	Present in seemingly uninvolved skin
Face	Vermilion lip erosions and crusting	Perioral and periocular crusting and radial fissuring with mild facial swelling
Treatment	IVIg, cyclosporine, corticosteroids (short course), and TNF inhibitors Supportive care (similar to a burn victim)	Antibiotics (β-lactamase-resistant ± clindamycin) and supportive care

Table 74.7 Comparison of toxic epidermal necrolysis (TEN) and staphylococcal scalded skin syndrome (SSSS). Also see Fig. 81.17. *Adapted from Habif T. Clinical Dermatology: A Color Guide to Diagnosis and Therapy. New York: Mosby-Year Book, 1996: 256–7, 570–4.*

The differential diagnosis may include a drug reaction, a viral exanthem, sunburn, Kawasaki disease, extensive bullous impetigo, toxic shock syndrome, graft-versus-host disease (GVHD), and pemphigus foliaceus. Differentiation from toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) is outlined in Table 74.7 and Fig. 81.17, respectively.

Treatment

Patients with severe, generalized forms of SSSS require hospitalization and parenteral antibiotics (e.g. vancomycin). Oral treatment with a β-lactamase-resistant penicillin or first-generation cephalosporin for a minimum of 1 week is usually sufficient for milder disease, although SSSS is occasionally caused by MRSA. Clindamycin administration may help to reduce bacterial toxin production, but up to 50% of strains implicated in SSSS are clindamycin resistant, so monotherapy with this agent is not recommended[29]. Identification and decolonization of *S. aureus* carriers (see Table 74.3) are important, especially in hospital-acquired cases[26].

Toxic Shock Syndrome

Introduction

Toxic shock syndrome (TSS) is an acute multisystem disease caused by a *S. aureus* exotoxin (Table 74.8).

Epidemiology and pathogenesis

In the early 1980s, there was an outbreak of TSS in young women using highly absorbent tampons ("menstrual" TSS). The incidence of menstrual TSS then declined following changes in tampon manufacturing and use, and by the early 2000s it accounted for approximately half of TSS cases[30]. TSS can occur in patients who have undergone surgical procedures. In addition, it may develop in association with cutaneous pyodermas, postpartum infections, abscesses, burns, and infections associated with nasal packing or insulin pump infusion sites. Non-menstrual TSS affects both sexes equally.

TSS is due to infection or colonization with strains of *S. aureus* that produce toxic shock syndrome toxin-1 (TSST-1). This toxin is thought to act as a "superantigen" that binds to major histocompatibility complex (MHC) class II molecules of antigen-presenting cells (APCs) and the Vβ region of T cell receptors in a non-antigen-specific manner, which leads to massive release of cytokines and chemokines as well as clonal T cell expansion (see section on Streptococcal TSS)[28]. In addition to TSST-1, *S. aureus* can produce other superantigens, including at least 15 enterotoxins. The hyperinflammatory "cytokine storm" response to bacterial superantigens involves invariant natural killer T cells, mucosa-associated invariant T (MAIT) cells, and interleukin-17A-producing effector memory T cells[31,32]. Of note, the *neonatal TSS-like exanthematous disease* (see Ch. 10) occurs during the first week of life due to colonization with TSST-1-producing *S. aureus* (usually methicillin-resistant) and has a relatively mild course due to the relatively anergic state of T cells in newborns[33].

CASE DEFINITIONS FOR THE TOXIC SHOCK SYNDROMES
Toxic shock syndrome

• Fever: temperature >102°F (or >38.9°C)
• Rash: diffuse macular erythroderma
• Desquamation: 1–2 weeks after the onset of illness (especially palms and soles)
• Hypotension: systolic blood pressure <90 mmHg for adults (<5th percentile for children)
• Involvement of three or more of the following organ systems:
  • Gastrointestinal
  • Muscular
  • Central nervous
  • Renal
  • Hepatic
  • Mucous membranes (erythema)
  • Hematologic (platelets <100 000/mm^3)

• Negative results for the following tests (if done):
  • Blood and cerebrospinal fluid cultures (blood culture may be positive for *Staphylococcus aureus*)
  • Serologic tests for Rocky Mountain spotted fever, leptospirosis, measles

Streptococcal toxic shock syndrome
• Isolation of group A streptococci from a normally sterile site* (e.g. blood, cerebrospinal fluid, tissue biopsy, surgical wound) *or* • Isolation of group A streptococci from a non-sterile site† (e.g. throat, sputum, vagina, superficial skin lesion) *and* • Hypotension: systolic blood pressure <90 mmHg for adults (<5th percentile for children) *and*

• Two or more of the following signs:
  • Renal impairment
  • Coagulopathy (platelets <100 000/mm^3 or disseminated intravascular coagulation)
  • Liver impairment
  • Acute respiratory distress syndrome
  • Generalized erythematous macular rash ± desquamation
  • Soft tissue necrosis (e.g. necrotizing fasciitis, myositis, gangrene)

*Defined as a definite case. †Defined as a probable case, excluding any other possible etiology.

Table 74.8 Case definitions for the toxic shock syndromes. See https://ndc.services.cdc.gov/case-definitions/toxic-shock-syndrome-2011/ and https://ndc.services.cdc.gov/case-definitions/streptococcal-toxic-shock-syndrome-2010/ for details.

Clinical features

TSS is characterized by the sudden onset of high fever with myalgias, vomiting, diarrhea, headache, and pharyngitis. Rapid progression to hypotensive shock can occur, but the clinical spectrum ranges from mild to fulminant fatal disease. The dermatologic manifestations are more extensive and predictable in staphylococcal TSS than in streptococcal TSS (Table 74.9). Patients usually develop diffuse erythema

TOXIC SHOCK SYNDROMES		
	Staphylococcal	**Streptococcal**
Typical patient	Young (15–35 years) and healthy	Young (20–50 years) and healthy
Diffuse macular erythroderma	Very common	Less common
Vesicles and bullae	Rare	Uncommon (5%)
Localized extremity pain	Rare	Common
Soft tissue infection	Rare	Common
Hypotension	100%	100%
Renal impairment	Common	Common
Predisposing factors	Surgical packing, surgical meshes, abscesses, contraceptive sponge, tampon	Lacerations, bites, bruises, varicella
Positive blood cultures	<15%	>50%
Mortality	<3%	30%–60%

Table 74.9 Toxic shock syndromes (staphylococcal versus streptococcal).

or a scarlatiniform exanthem that starts on the trunk and spreads to the extremities (Fig. 74.8). Additional findings include erythema and edema of the palms, soles, and oral mucosa as well as a strawberry tongue, conjunctival hyperemia, and (with disease progression) generalized non-pitting edema. Desquamation of the hands and feet occurs 1–3 weeks after the onset of symptoms.

After recovery, Beau's lines and nail shedding can be seen. In severe cases, telogen effluvium may occur. With proper treatment, the majority of patients completely recover. However, complications include decreased renal function, prolonged weakness and fatigue, protracted myalgias, vocal cord paralysis, upper extremity paresthesias, carpal tunnel syndrome, arthralgias, amenorrhea, and gangrene.

Pathology

Biopsy specimens of the eruption show an infiltrate of neutrophils and lymphocytes in the superficial dermis. Papillary dermal edema as well as epidermal spongiosis and exocytosis may be noted. Hair follicles and eccrine sweat glands display similar findings.

Diagnosis and differential diagnosis

A high index of suspicion is required in order to make a timely diagnosis. Table 74.8 outlines the case definition of TSS. The possibility of streptococcal TSS (see Table 74.9 and below) should also be considered. TSS can have clinical overlap with Kawasaki disease, scarlet fever, SSSS, early TEN, Rocky Mountain spotted fever, and leptospirosis.

Treatment

Severe cases of TSS require intensive monitoring and supportive therapy. Hypotension can be treated with intravenous fluids and vasopressor agents. Foreign bodies (e.g. surgical mesh, nasal packing, tampons) that may represent a nidus of infection should be removed and abscesses drained. Beta-lactamase-resistant penicillins and first-generation cephalosporins are traditionally used to eradicate the toxin-producing staphylococci; although MRSA is responsible for only a small proportion of TSS cases, vancomycin or linezolid can be considered, depending upon local resistance patterns[30]. Some advocate using antibiotics that suppress protein (and thereby toxin) synthesis, such as clindamycin or linezolid. Administration of intravenous immunoglobulin (IVIg) may help to neutralize the toxin[34]. In severe cases of shock unresponsive to antibiotics, low-dose corticosteroids have been used[35].

Scarlet Fever

Synonym: ■ Scarlatina

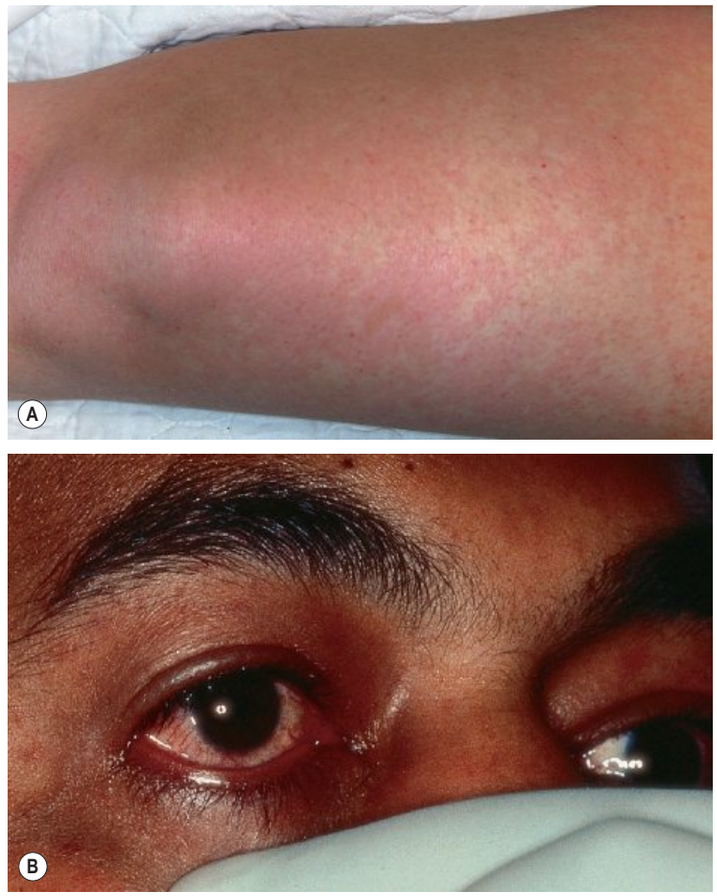


Fig. 74.8 Toxic shock syndrome due to *Staphylococcus aureus* infection. A Blotchy erythema is evident on the thigh. **B** Hyperemia of the conjunctiva is seen.

Introduction

Primarily a disease of children, scarlet fever was often fatal in the pre-antibiotic era. The erythematous exanthem and enanthem are due to toxins produced by group A β-hemolytic streptococci.

Epidemiology and pathogenesis

Scarlet fever is caused by streptococcal pyrogenic exotoxins (SPEs) types A, B, and C (also referred to as erythrogenic toxins), which are produced by group A streptococci and lead to immune activation. The majority of cases occur between 1 and 10 years of age; by the age of 10 years, 80% of the population has developed anti-SPE antibodies that prevent development of the eruption. Scarlet fever usually follows tonsillitis or pharyngitis and is most common during the late fall, winter, and spring in temperate climates. However, it occasionally develops as a complication of wound ("surgical scarlet fever"), post-burn, pelvic, or puerperal infections[36].

Clinical features

Scarlet fever is typically preceded by the sudden onset of a sore throat, headache, malaise, chills, anorexia, nausea, and high fevers. Patients, especially young children, may experience vomiting, abdominal pain, and seizures. The eruption begins 12–48 hours later as blanchable erythema on the neck, chest, and axillae. There is subsequent generalization (usually within 12 hours) and development of tiny superimposed papules with a sandpaper-like texture ("sunburn with goose pimples"). Pastia's lines (linear petechial streaks) are seen in the axillary, antecubital, and inguinal areas. The cheeks are flushed with circumoral pallor. The throat is red and edematous, developing an exudate after 3–4 days; palatal petechiae and tender cervical adenopathy are often evident. The tongue is initially white with bright red papillae, but later becomes beefy red ("strawberry tongue"). Desquamation occurs after 7–10 days, most prominently on the hands and feet (Fig. 74.9), and can last for 2–6 weeks. Possible complications of scarlet fever and the underlying streptococcal infection include otitis, mastoiditis, sinusitis, pneumonia, myocarditis, meningitis, arthritis, hepatitis, acute glomerulonephritis, and rheumatic fever[28].



Fig. 74.9 Desquamation of the foot following scarlet fever. *Courtesy Eugene Mirrer, MD.*

Pathology

Biopsy specimens reveal engorged capillaries and dilated lymphatics, most prominent around hair follicles. Dermal edema, perivascular neutrophilic infiltrates and small areas of hemorrhage represent additional findings. Spongiosis and parakeratosis are seen during the desquamative stage.

Diagnosis and differential diagnosis

Clinical diagnosis is usually not difficult. There is typically an elevated leukocyte count with a left shift. Eosinophilia of 10%–20% is often seen after 2–3 weeks of convalescence. Hemolytic anemia can occur, and mild albuminuria and hematuria may be present early in the disease. Nasal and/or throat cultures grow group A streptococci. Detection of antistreptolysin O (ASO) and anti-DNase B antibodies can also be useful in confirming the streptococcal infection.

The differential diagnosis of scarlet fever may include a drug eruption, a viral exanthem, TSS, early SSSS, Kawasaki disease, recurrent toxin-mediated perineal erythema, and infection with *Arcanobacterium haemolyticum*[37].

Treatment

As with other group A streptococcal infections, penicillin (or amoxicillin) is the drug of choice; a 10- to 14-day course is usually sufficient. A clinical response can be expected within 24–48 hours. Antibiotic treatment as long as 10 days after the onset of symptoms will prevent the development of rheumatic fever. In penicillin-allergic patients, a first-generation cephalosporin (if no history of an immediate-type reaction), clindamycin, azithromycin, or clarithromycin can be used; of note, some strains of group A streptococci are resistant to macrolides.

Streptococcal Toxic Shock Syndrome

Synonyms: ■ Streptococcal toxic shock-like syndrome ■ Toxic streptococcal syndrome

Introduction

Streptococcal TSS is a rapidly progressive, life-threatening illness caused by infection with toxin-producing group A and rarely group G streptococci[38].

Epidemiology and pathogenesis

Streptococcal TSS mainly affects healthy individuals between 20 and 50 years of age but can also occur in children (mean age, ~5 years)[39]. A disruption of the cutaneous barrier usually serves as the portal of bacterial entry. In contrast to the occult infections that predominate in staphylococcal TSS, many cases are associated with invasive soft tissue infections (e.g. necrotizing fasciitis) with virulent (e.g. M types 1 and 3) strains of group A streptococci, and the majority of patients are bacteremic[40]. Toxins that have been implicated include SPEs A, B, and C as well as the more potent streptococcal mitogenic exotoxin Z[41]. Streptolysin O may also act synergistically with SPE-A.

Similar to staphylococcal TSS, the clinical manifestations of streptococcal TSS result from massive cytokine release due to superantigen activity of bacterial exotoxins[41]. Superantigens bind directly (without intracellular processing) to MHC class II molecules on APCs (outside the antigen-presenting groove) and the Vβ region of the T cell receptor (Fig. 74.10), thereby stimulating T cells in a relatively nonspecific manner. A given superantigen–T cell interaction may lead to the activation of 5%–30% of the entire circulating T cell population, compared to ~0.01% for conventional antigens. This leads to production of huge amounts of cytokines, especially tumor necrosis factor (TNF), interleukin-1 (IL-1), and IL-6; there is also upregulation of Toll-like receptors (TLRs) 2 and 4, which augments deleterious effects of endotoxin from Gram-negative bacteria (e.g. those colonizing the gut) as well as streptococci, resulting in further elaboration of proinflammatory mediators. As a consequence, patients develop clinical manifestations such as fever, erythematous eruptions, vomiting, hypotension, and tissue injury in multiple organ systems[28]. The use of nonsteroidal anti-inflammatory drugs (NSAIDs), which lessen fever and other signs of infection, might delay the diagnosis and treatment of a streptococcal soft tissue infection, allowing TSS to occur[42].

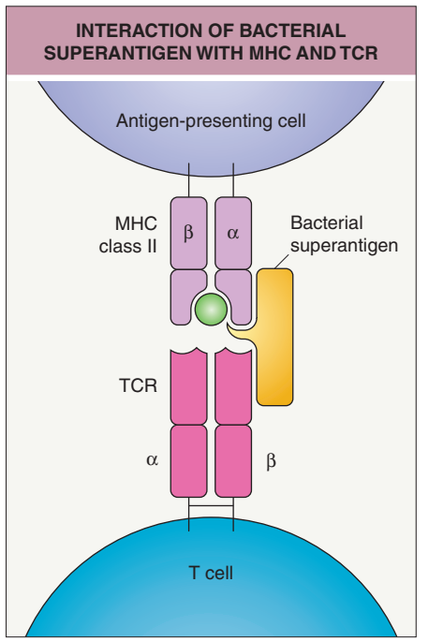


Fig. 74.10 Interaction of bacterial superantigen with the major histocompatibility complex (MHC) and the T cell receptor (TCR). *Adapted from Janeway CA, Travers P, Walport M, Shlomchik M. Immunobiology: The Immune System in Health and Disease, 6th edn. New York: Garland Science, 2004.*

Clinical features

Streptococcal TSS is defined as a group A streptococcal infection with an early onset of shock and organ failure (see Table 74.8). The most common initial symptom is severe local pain in an extremity. Although 50% of patients display signs of a soft tissue infection (e.g. swelling, tenderness, erythema), some present with only pain and no obvious physical findings. The development of a violaceous hue, bullae, or necrosis points to a deeper infection, such as necrotizing fasciitis or myositis, and portends a worse outcome.

The disease may begin insidiously with nonspecific flu-like symptoms, such as fever, chills, myalgias, and diarrhea. Symptoms of encephalopathy (e.g. confusion, altered consciousness) are commonly seen. A generalized blanching macular erythema is observed much less often than in staphylococcal TSS, but blistering is more likely to occur. Desquamation on the hands and feet eventually appears in 20% of patients. Shock and multiorgan failure usually develop 48–72 hours after the onset of symptoms. Complications of streptococcal TSS include renal failure, disseminated intravascular coagulation, and acute respiratory distress syndrome. The mortality rate for streptococcal TSS ranges from 30% to 60%.

Pathology

Biopsy specimens from skin lesions may show spongiosis, necrotic keratinocytes, subepidermal blister formation, and a neutrophilic and/or lymphocytic perivascular infiltrate in the dermis[43].

Diagnosis and differential diagnosis

Published criteria require isolation of group A streptococci from a sterile site for a "definite" diagnosis, combined with hypotension and clinical or laboratory abnormalities in two or more organ systems (see Table 74.8). Serum creatinine often rises early in the course, and creatine phosphokinase is elevated in the setting of necrotizing fasciitis or myonecrosis. The white blood cell count may be increased or normal with a substantial

left shift. Although staphylococcal and streptococcal TSSs share some common features, major differences exist (see Table 74.9).

Treatment

Most cases require intensive supportive therapy. Hypotension should be treated with aggressive intravenous fluid and vasopressors. Empiric broad-spectrum antibiotic coverage should be administered until infection with streptococci is confirmed. Clindamycin inhibits the production of bacterial toxins and is a component of first-line antimicrobial treatment (together with penicillin) for streptococcal TSS; linezolid also blocks toxin production, and administration of IVIg to neutralize toxins may be of benefit[44]. Early surgical intervention (e.g. drainage, debridement, fasciotomy, amputation) is crucial for necrotizing soft tissue infections and can be life-saving[14].

Erysipelas

Synonym: ▪ St Anthony's fire

Introduction

Erysipelas is a superficial variant of cellulitis caused primarily by group A streptococci that affects the dermis with prominent lymphatic involvement; in contrast, classic cellulitis is centered in the deep dermis and subcutaneous tissues[45].

Epidemiology and pathogenesis

Erysipelas is usually a disease of the very young, the aged, the debilitated, and those with lymphedema or chronic cutaneous ulcers. Women outnumber men, but boys are more commonly affected than girls in the pediatric age group. Erysipelas is usually caused by group A streptococci; groups G, B, C, and D streptococci are occasionally implicated. *S. aureus*, *Pneumococcus* spp., *Klebsiella pneumoniae*, *Yersinia enterocolitica*, *Campylobacter jejuni*, and *Haemophilus influenzae* type b can also cause an erysipelas-like infection[46].

Clinical features

After an incubation period of 2 to 5 days, there is an abrupt onset of fever, chills, malaise, and nausea. A few hours to a day later, a sharply marginated erythematous plaque with a ridge-like border develops and progressively enlarges. Clear demarcation from the surrounding skin is a characteristic feature (Fig. 74.11A,B). The plaque is hot, tense, indurated, and painful to palpation, with non-pitting edema and sometimes an associated burning sensation. Regional lymphadenopathy is usually present, with or without lymphangitis. Pustules, vesicles, bullae, and small areas of hemorrhagic necrosis may also form. Complications of erysipelas are uncommon and usually occur



Fig. 74.11 Cutaneous streptococcal infections. A, B Sharply demarcated erythema on the upper arm and chest (**A**) and buttocks (**B**) in two patients with erysipelas. **C** Streptococcal intertrigo presenting as a sharply demarcated, bright pink, moist plaque in the axilla of an infant. **D** Bright red erythema extending from the anal verge in a young boy with streptococcal perianal disease. *A, Courtesy Lorenzo Cerroni, MD; B, Courtesy Mary Stone, MD; C, D, Courtesy Julie V. Schaffer, MD.*

in patients with underlying disease[45]. When the infection resolves, desquamation and postinflammatory pigmentary changes may ensue.

Pathology

Biopsy specimens reveal diffuse edema and a neutrophilic infiltrate in the dermis. Dilation of the lymphatics, foci of suppurative necrosis, and dermal–epidermal separation are often seen. There is no primary necrotizing vasculitis, thrombosis, or leukocytoclasis.

Diagnosis and differential diagnosis

Diagnosis is based primarily on clinical findings. Laboratory evaluation shows an elevated leukocyte count with a left shift. Blood cultures are positive in ~5%–10% of cases. Although cultures from pustules or bullae may be helpful, the sensitivity of cultures of skin biopsy specimens is low, especially in immunocompetent hosts. Anti-DNase B and ASO titers are useful indicators of the streptococcal etiology. Direct immunofluorescence and latex agglutination tests can be used to detect streptococci within skin specimens.

The differential diagnosis of erysipelas includes other forms of cellulitis and soft tissue infections (e.g. erysipeloid, necrotizing fasciitis) as well as inflammatory causes of "pseudocellulitis" (Table 74.10).

Treatment

A 10- to 14-day course of penicillin is the treatment of choice for erysipelas caused by streptococci. Although macrolides (e.g. erythromycin) or clindamycin may be used in penicillin-allergic patients, some strains of *Str. pyogenes* are resistant to these agents. Erysipelas may recur in patients with abnormal local circulation (e.g. lymphedema), and penicillin prophylaxis is occasionally required[47]. The development of an effective vaccine against *Streptococcus* spp. could dramatically change the epidemiology of the infections caused by this microorganism[47].

Streptococcal Intertrigo

Intertrigo caused by group A streptococci is an under-recognized entity that usually affects infants and young children[48]. Infants are particularly vulnerable due to irritation and friction in moist, deep skin folds of the neck, axillae, antecubital and popliteal fossae, and inguinal region. Sharply demarcated, intensely erythematous patches or thin plaques are observed in an intertriginous site, often accompanied by a foul odor (Fig. 74.11C). In contrast to intertriginous candidiasis, satellite lesions are uncommon. Affected children occasionally exhibit irritability, low-grade fevers, and bacteremia. In genetically predisposed children, cutaneous streptococcal infection may trigger psoriasis[41]. Bacterial culture can confirm the diagnosis, which should be considered when simple intertrigo fails to respond to barrier creams and other measures to reduce friction and minimize moisture. A 10-day course of oral penicillin or amoxicillin is usually effective.

CAUSES OF "PSEUDOCELLULITIS"	
Infections and bites	**Other inflammatory disorders**
• Arthropod bite reactions (e.g. insect, spider) • Erythema migrans (see Fig. 74.15) • Herpes zoster • Toxin-mediated erythema (e.g. recurrent toxin-mediated perineal erythema)	• Allergic contact dermatitis (including airborne and dermal), stasis dermatitis • Phytophotodermatitis • Well syndrome • Panniculitis, e.g. lipodermatosclerosis, erythema nodosum • Bursitis • Thrombophlebitis • Angioedema • Interstitial granulomatous dermatitis, patch type granuloma annulare • Inflammatory morphea • Acute inflammatory edema
Neutrophilic dermatoses	**Metabolic disorders**
• Sweet syndrome, neutrophilic panniculitis • Familial Mediterranean fever, other autoinflammatory syndromes	• Gouty arthritis
Drug reactions	**Malignancy**
• Fixed drug eruptions (especially non-pigmenting) • Vaccine/injection site reactions • Toxic erythema of chemotherapy (e.g. due to gemcitabine), neutrophilic eccrine hidradenitis*	• Erysipeloid skin metastases (especially breast carcinoma)
*Occasionally develops prior to onset of leukemia or due to infection.	

Table 74.10 Causes of "pseudocellulitis".

Perianal and Vulvovaginal (Perineal) Streptococcal Infection

Synonyms: ■ Perianal – perianal streptococcal disease, perianal cellulitis, perianal streptococcal dermatitis ■ Vulvovaginal – perivaginal streptococcal disease, streptococcal vulvovaginitis

Perianal group A streptococcal infection presents as sharply demarcated, bright erythema extending 1–3 cm around the anal verge (Fig. 74.11D); similar findings can extend from the vaginal introitus onto the vulva in girls and, less often, around the urethral meatus in boys. Patients may complain of pruritus or irritation; painful defecation or dysuria; and blood-streaked stools or vaginal discharge. Systemic symptoms are generally absent. Children ages 2–7 years, especially boys (for perianal disease), are most commonly affected[49]. Perineal infection may be preceded by symptomatic pharyngitis and is frequently associated with a positive pharyngeal culture for group A streptococci even in asymptomatic patients; patients often have family members with a recent streptococcal infection. Assessment for perineal streptococcal infection should be performed in children with an outbreak of guttate psoriasis.

Other causes of perineal erythema or pruritus include contact dermatitis (irritant or allergic), *S. aureus* infection, candidiasis, seborrheic dermatitis, pinworm infestation, inflammatory bowel disease, lichen sclerosus, child abuse, and the early phase of Kawasaki disease. Perineal streptococcal infection can be diagnosed with skin culture or group A streptococcal rapid testing, although the latter is less specific. In a randomized controlled study, a 7-day course of cefuroxime was found to be more effective than a 10-day course of penicillin in the treatment of perianal streptococcal disease[50].

Cellulitis

Introduction

Cellulitis is an infection of the deep dermis and subcutaneous tissue that manifests as areas of erythema, swelling, warmth, and tenderness.

Epidemiology and pathogenesis

Cellulitis in immunocompetent adults is most often caused by group A streptococci or *S. aureus*, and the latter organism is the most frequent etiology in children. Cellulitis caused by *H. influenzae* is now rare due to routine vaccination against *H. influenzae* type B[51]. A mixture of Gram-positive cocci and Gram-negative aerobes and anaerobes is often implicated in cellulitis surrounding diabetic and decubitus ulcers[52]. Bacteria typically gain access to the dermis via a break in the skin barrier in immunocompetent individuals, but a bloodborne route is common in immunocompromised patients. Lymphedema, alcoholism, diabetes mellitus, injection drug use, and peripheral vascular disease are all risk factors for cellulitis. Recurrent bouts of cellulitis may result from damage to the lymphatic system, e.g. via prior lymph node dissection, saphenous vein harvest, or previous episodes of cellulitis.

Clinical features

Cellulitis is often preceded by systemic symptoms such as fever, chills, and malaise. The affected area displays all four of the cardinal signs of inflammation: rubor (erythema), calor (warmth), dolor (pain), and tumor (swelling). The borders are usually ill-defined and non-palpable. In severe infections, vesicles, bullae, pustules or necrotic tissue may be present (Fig. 74.12). Ascending lymphangitis and regional lymph node involvement may occur. In children, cellulitis most often affects the





Fig. 74.12 Bullous and necrotizing cellulitis. A Extensive soft tissue infection of the lower extremity due to group A streptococcal infection. **B** Edema and confluent bullae. **C** Multiple areas of necrotic crusting and focal purulence due to streptococcal cellulitis.

head and neck, whereas in adults it tends to involve the extremities. Cellulitis due to injection drug use typically affects the upper extremities, the usual sites of drug injection. Complications are uncommon but may include acute glomerulonephritis (if caused by a nephritogenic strain of *Streptococcus*), lymphadenitis, infectious endocarditis, and recurrences related to disrupted lymphatic damage.

Pathology

A mild or moderate inflammatory infiltrate composed of lymphocytes and neutrophils can be seen throughout the dermis, often extending into the subcutaneous fat (Fig. 74.13). Additional findings include edema, which occasionally leads to subepidermal bullae, and dilation of lymphatics and small blood vessels. With special stains, the causative organism may be identified.

Diagnosis and differential diagnosis

The diagnosis of cellulitis is usually clinical (Fig. 74.14). The leukocyte count is often normal or only slightly elevated. Blood cultures are almost always negative in immunocompetent hosts. An exception is *H. influenzae* cellulitis, where there is usually an increased leukocyte count with a left shift and positive blood cultures. Atypical organisms are more common in children and immunocompromised patients, and needle aspiration or skin biopsy may help to identify the infectious etiology. The differential diagnosis of lower extremity cellulitis includes deep vein thrombosis and inflammatory diseases such as stasis dermatitis, superficial thrombophlebitis, lipodermatosclerosis, and other

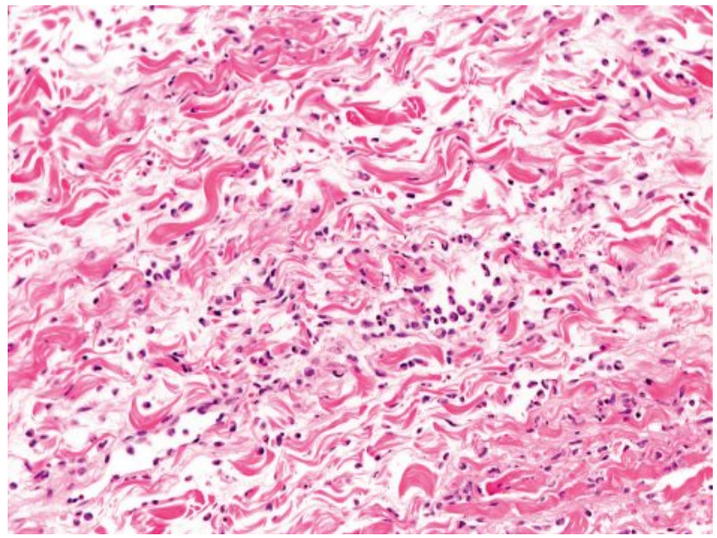


Fig. 74.13 Histopathology of cellulitis. Dermal edema and a neutrophilic infiltrate are evident. *Courtesy Lorenzo Cerroni, MD.*

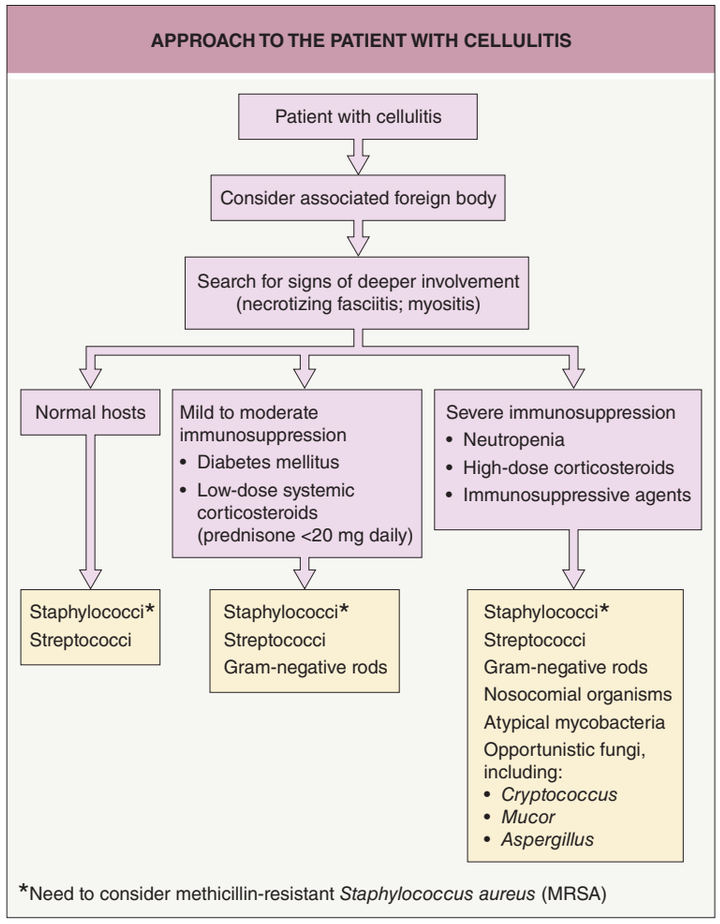


Fig. 74.14 Approach to the patient with cellulitis.

forms of panniculitis. While superficial thrombophlebitis often presents with redness and tenderness, the absence of a fever and the presence of a palpable cord aid in the diagnosis. Misdiagnosis of lipodermatosclerosis as cellulitis often leads to unnecessary hospitalizations. Additional causes of "pseudocellulitis" are listed in Table 74.10 and illustrated in Fig. 74.15. The ALT-70 score based on asymmetric involvement, leukocytosis, tachycardia, and older patient age aids in differentiating cellulitis from pseudocellulitis of the lower extremities up to 48 hours after presentation in the emergency department[53].



Fig. 74.15 Pseudocellulitis – clinical examples. A Erythema migrans with erosion following rupture of a central bulla. Inking of the skin reflects initial diagnosis of cellulitis. **B** Extravasation reaction following infusion of docetaxel. **C** Excessive limb swelling (ELS) following injection of multiple vaccines. This reaction does not preclude future immunizations. **D** Acute gout with abrupt onset of severe pain, warmth and erythema of the left great toe with difficulty in weight bearing. **E** Acute inflammatory edema with erythematous, edematous plaque sparing the inguinal fold. *A, Courtesy Kalman Watsky, MD; B, Courtesy Edward Cowen, MD; C, D, Courtesy Karynne O. Duncan, MD.*

Treatment

Treatment of cellulitis is typically targeted against group A streptococci and *S. aureus*, and a 5–10 day course of an oral antibiotic is appropriate for uncomplicated cases. Coverage for MRSA does not improve outcomes for non-purulent cellulitis[54]. For purulent cellulitis (e.g. presence of an abscess or pustules) or in patients with risk factors for MRSA, agents such as TMP-SMX, doxycycline, or clindamycin should be considered (see Tables 74.3 and 74.4). An agent with activity against both streptococcal and MRSA infections should be used when group A streptococcal infection is a possibility. Hospitalization and parenteral antibiotics may be necessary for patients with systemic manifestations (e.g. fever, tachycardia, tachypnea), facial involvement, significant comorbidities, or failure to respond to oral therapy. Broad spectrum antimicrobial coverage (e.g. vancomycin plus piperacillin/tazobactam, imipenem, or meropenem) should be provided for patients with severe non-purulent cellulitis and immunocompromised status, hypotension, or rapid progression[55]. Diabetic or decubitus ulcers complicated by cellulitis also require broad-spectrum coverage, such as piperacillin/tazobactam or, in penicillin-allergic patients, metronidazole plus ciprofloxacin. Adjunctive measures include immobilization and elevation of an affected extremity and the application of wet dressings to areas with bullae or exudate. NSAIDs may mask the signs and symptoms of deeper necrotizing infections and should be avoided when treating cellulitis.

Duration of therapy should be based on the clinical response. If signs and symptoms do not improve after 36–48 hours of treatment, then pseudocellulitis and atypical organisms should be considered. The clinical features and treatment of other types of cellulitis (e.g. *Erysipelothrix rhusiopathiae*, *Vibrio vulnificus*) are discussed below.

Preventive measures include regular foot examinations, treatment of tinea pedis and/or onychomycosis, and control of lymphedema. Compression therapy for lymphedema and prophylactic low-dose penicillin have both been shown to decrease the risk of recurrent lower extremity cellulitis; however, the protective effects diminish upon discontinuation of therapy[56,57].

Pyomyositis

Pyomyositis is a primary bacterial infection of the skeletal muscles that is caused by *S. aureus* in ~90% of cases. Other reported etiologies include: *Str. pyogenes*, *S. pneumoniae*, *Escherichia coli*, *Yersinia enterocolitica*, *Aeromonas*, *Fusobacterium*, and *H. influenzae* as well as mycobacteria and fungi; polymicrobial infections can also occur in immunocompromised patients. Once referred to as tropical myositis, pyomyositis also occurs in temperate climates. Predisposing factors include trauma, diabetes mellitus, HIV infection, injection drug use, and other forms of immunosuppression. Patients often present with a 1- to 2-week history of low-grade fevers, myalgias, and progressive firmness, pain, and enlargement of a deep soft tissue mass. Palpation of the affected area reveals "woody" induration. Muscle abscess formation occurs during the second stage of disease, and septicemia may follow.

MRI is the diagnostic modality of choice for early infection; ultrasound-guided aspiration may be helpful later in the course. Treatment of staphylococcal pyomyositis includes incision and drainage as well as appropriate intravenous antibiotics until clinical improvement is noted, followed by oral therapy[58].

Botryomycosis

Synonyms: ■ Granular bacteriosis ■ Bacterial pseudomycosis

Introduction

Botryomycosis was named for its characteristic groups of granules that resemble grapes. It is a rare, chronic, purulent and granulomatous bacterial infection that primarily affects the skin and is most often caused by *S. aureus*.

Epidemiology and pathogenesis

Botryomycosis is found worldwide, and over two-thirds of patients have only skin involvement. The disease affects all ages and has a slight male predominance. Although most often due to infection with *S. aureus*, it can also be caused by *Pseudomonas*, *Proteus*, *Moraxella*, *Serratia*, and *Corynebacteria* spp. Defects of cellular immunity, particularly low T lymphocyte counts, have been associated with the development of botryomycosis[59].

Clinical features

Botryomycosis presents as cutaneous and subcutaneous nodules, ulcers, or verrucous plaques. Multiple sinuses and fistulas may discharge purulent fluid or yellow granules composed of bacterial masses. Most patients have localized involvement of an extremity following trauma; disseminated cutaneous disease is rare[60]. The lesions may be pruritic or tender, and they may affect the underlying muscle or bone. Systemic symptoms are infrequent. Visceral botryomycosis, most often affecting the lungs, has been reported primarily in immunocompromised patients or following surgery[59].

Pathology

Biopsy specimens reveal a chronic inflammatory reaction with fibrosis and foreign body giant cells. The most distinctive feature is 1–3 mm granular bodies (grains) that represent bacteria, cells, and debris (Fig. 74.16). Grains have basophilic centers and a homogeneous, eosinophilic, hyaline periphery thought to be secondary to a host immunoglobulin response (Splendore–Hoeppli phenomenon). The granules stain with PAS, Gram, and Giemsa.

Diagnosis and differential diagnosis

When botryomycosis is suspected, bacterial, mycobacterial, and fungal cultures should be obtained and a skin biopsy performed for histopathologic examination as well as culture. Microscopic examination (fresh mount or 20% KOH) shows coarsely lobulated granules with club-like projections. Gram staining of crushed granules usually displays masses of staphylococci. The differential diagnosis of cutaneous botryomycosis includes mycetoma, actinomycosis, a ruptured epidermoid cyst, a staphylococcal abscess, orf, tuberculosis, and dimorphic fungal or atypical mycobacterial infections.

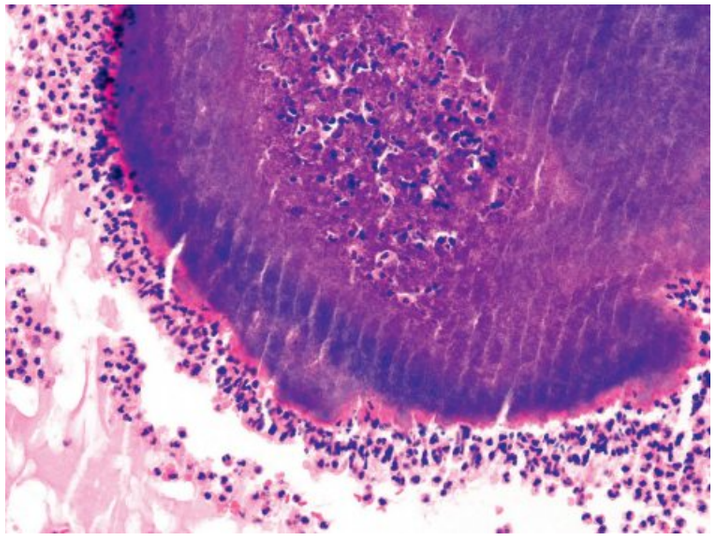


Fig. 74.16 Histopathology of botryomycosis. Note the basophilic center and eosinophilic, hyaline periphery of the granular body (grain). *Courtesy Luis Requena, MD.*

Treatment

Botryomycosis is typically treated surgically with debridement or excision in conjunction with antibiotic therapy. If possible, reducing immunosuppression may be of benefit.

Necrotizing Fasciitis

Synonyms: ■ Type 1 – polymicrobial necrotizing fasciitis ■ Type 2 – group A streptococcal necrotizing fasciitis ■ "Flesh-eating bacteria" syndrome ■ Fournier gangrene ■ Synergistic necrotizing cellulitis

Introduction

Necrotizing fasciitis is characterized by rapidly progressive necrosis of subcutaneous fat and fascia, which can be life-threatening without prompt recognition, aggressive surgical intervention, and immediate antibiotic therapy. It is classified into two major subtypes: (1) *type 1*, a polymicrobial infection including at least one anaerobe (e.g. *Bacterioides*, *Peptostreptococcus*) in addition to facultative anaerobes such as streptococci and Enterobacteriaceae; and (2) *type 2*, a monomicrobial infection, most often with group A streptococci. Some authors also distinguish *type 3* due to Gram-negative marine organisms (e.g. *Vibrio* and *Aeromonas* spp.) and *type 4* due to fungi (e.g. post trauma or in immunocompromised patients).

Epidemiology and pathogenesis

Approximately 700–1200 cases of necrotizing fasciitis are reported each year in the US. Risk factors include diabetes mellitus, immunosuppression, cardiac or peripheral vascular disease, renal failure, and therapy with medications such as sodium-glucose co-transporter 2 (SGLT2) inhibitors or bevacizumab[61], but it can also occur in young, previously healthy individuals. Necrotizing fasciitis may follow penetrating or blunt injury or develop in the absence of preceding trauma. Other predisposing factors include injection drug use, recent surgery, varicella, and decubitus or ischemic ulcers.

Mortality rates range from 20% to 60%. Higher mortality is associated with female sex, older age, malnutrition, greater extent of infection, delay to first debridement, an elevated serum creatinine or lactic acid level, disease due to group A streptococci, and a greater degree of organ dysfunction at the time of admission to hospital. Diabetes mellitus can also result in higher mortality, particularly if renal dysfunction or peripheral arterial disease is also present.

In children, necrotizing fasciitis is most commonly caused by group A streptococci. In adults, it often follows trauma or surgery and is due to a polymicrobial infection with bacteria such as streptococci, *S. aureus*, *Escherichia coli*, *Bacteroides*, and *Clostridium* spp. Less common pathogens include *V. vulnificus* (associated with sea water injuries; see below), *Aeromonas hydrophila* (associated with fresh water injuries; high mortality and amputation rates), *Pseudomonas aeruginosa*, and *H. influenzae* type B[62]. Opportunistic fungal infections, including zygomycosis, can cause necrotizing fasciitis in immunocompromised patients[63].

Clinical features

Infection begins with an area of exquisite tenderness, erythema, warmth, and swelling that does not respond to antibiotics. The skin appears shiny and tense. Initially, severe pain may be out of proportion to skin findings. The disease progresses at an alarming rate, with the skin changing from red and purple to a characteristic gray–blue color in ill-defined patches within 36 hours of onset (Fig. 74.17). Violaceous discoloration and/or hemorrhagic bullae may develop. Necrosis of the superficial fascia and fat produces a thin, watery, malodorous fluid. The area may later become anesthetic as cutaneous nerves are destroyed. The subcutaneous tissues may feel hard and "woody" on palpation. Patients can become extremely toxic, with fever, chills, malaise, leukocytosis, tachycardia, and shock. The most common site of involvement is the extremities, although the trunk is often affected in children. When necrotizing fasciitis involves the perineum and genitalia, it is referred to as Fournier gangrene, which is typically a polymicrobial infection[62,63].

Pathology

Gangrene of the subcutaneous tissues, with spread along fascial planes, is followed by involvement of the overlying skin. Fibrinoid necrosis is



Fig. 74.17 Necrotizing fasciitis. Tense, woody edema of the forearm with purple–gray areas of necrosis and bullae with watery discharge. Intravenous drug use was a predisposing factor. *Courtesy Luis Requena, MD.*

present in the media of vessels passing through the destroyed fascia, and fibrin thrombi are evident. The epidermis, dermis, and skin appendages in the area of gangrene undergo coagulation necrosis. Infiltration with neutrophils and mononuclear cells as well as numerous bacteria occurs in upper layers of the dermis.

Diagnosis and differential diagnosis

Early in the disease course, it is often difficult to differentiate necrotizing fasciitis from cellulitis. The presence of severe pain or anesthesia suggests a deeper component, and an MRI can delineate the depth of tissue involvement. Other clues that suggest necrotizing fasciitis rather than cellulitis include rapidly spreading tense edema, hemorrhagic bulla formation, grayish discoloration, foul-smelling discharge and an elevated creatine phosphokinase level. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score based on routinely performed laboratory tests has a high specificity but lower sensitivity, and thus should not be used to exclude necrotizing fasciitis[64]. Fig. 74.18 outlines an algorithm for assessing and treating suspected necrotizing fasciitis. Conditions that can mimic necrotizing fasciitis include trauma with hematoma formation, neutrophilic dermatoses, clostridial myonecrosis, pyomyositis, phlebitis, bursitis, and arthritis (see Fig. 25.7B).

Treatment

Extensive surgical debridement (fasciotomy) is the mainstay of effective treatment. Additional surgery may be necessary 24 hours later to ensure adequate debridement, and amputation is occasionally necessary. Empiric therapy should be initiated with broad-spectrum coverage against streptococci, staphylococci (including MRSA), Gram-negative bacilli and anaerobes – e.g. vancomycin plus piperacillin/tazobactam[14]. In a patient with true penicillin allergy, empiric therapy with ciprofloxacin plus metronidazole or clindamycin can be used. Coverage of *Pseudomonas* is particularly important for neutropenic patients. Once the microbial etiology has been determined, antibiotic coverage can be narrowed appropriately.

Hyperbaric oxygen therapy remains controversial, though it may be beneficial for a subset of patients with anaerobic Gram-negative necrotizing fasciitis; however, surgery and antimicrobial therapy should never be postponed. Although IVIg may be useful for patients with severe group A streptococcal infections, a randomized placebo-controlled trial failed to show benefit of IVIg administration in intensive care unit patients with necrotizing soft tissue infections[65]. Nutritional support is crucial for enhancing postoperative wound healing. Eventually, reconstructive surgery is often necessary[14].

Bacteremia/Septicemia

Staphylococcal septicemia may occur in the absence of any cutaneous or internal focus of infection. Immunocompromised states, erythroderma (especially secondary to Sézary syndrome), injection drug use, and the presence of central venous catheters or abnormal/prosthetic heart valves represent risk factors for Gram-positive bacteremia. A large percentage of patients with late-stage cutaneous T cell lymphoma eventually succumb

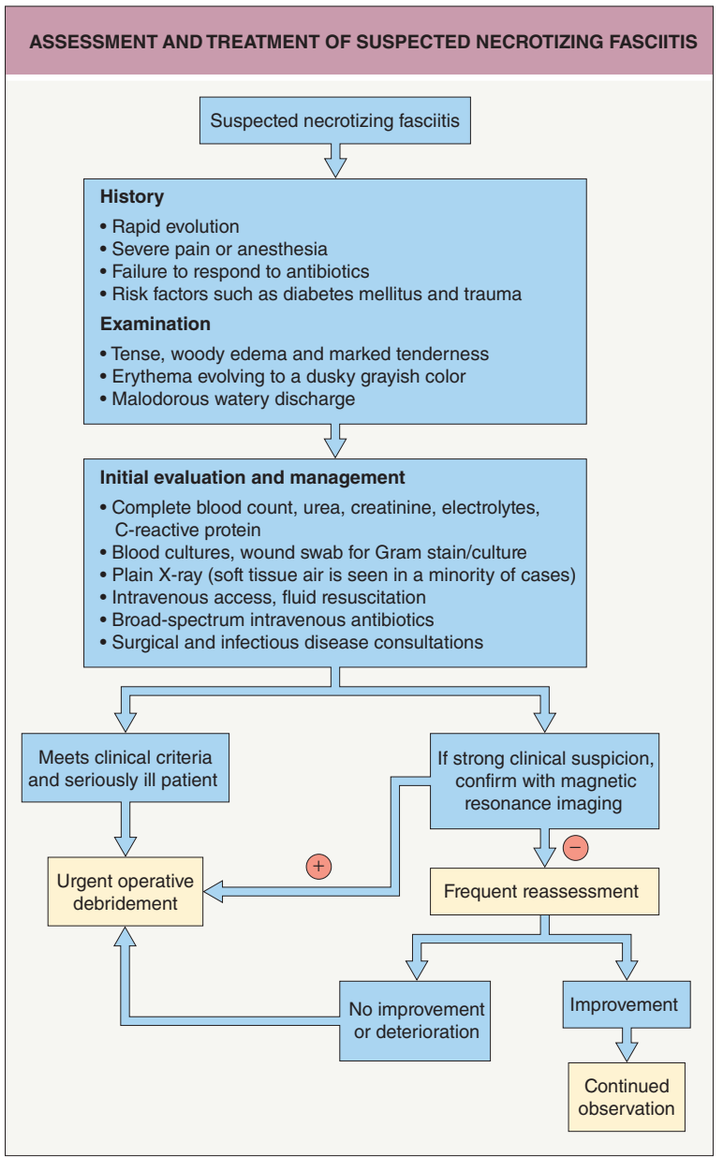


Fig. 74.18 Algorithm for assessment and treatment of suspected necrotizing fasciitis.

to septicemia, especially staphylococcal. The skin lesions of *S. aureus* septicemia are classically pustular petechiae, purulent purpura, and subcutaneous abscesses that probably represent hematogenous spread of the infection to the skin. Biopsy specimens show nonspecific inflammation, often with a positive Gram stain, and cultures grow *S. aureus*. When *S. aureus* bacteremia leads to endocarditis, a number of other characteristic skin signs may appear, including petechiae and splinter hemorrhages; Osler nodes resulting from immune complex deposition and small vessel vasculitis; and Janeway lesions that represent septic emboli with microabscess formation. Osler nodes are tender, erythematous papules and nodules with white centers that favor the finger pads and thenar/hypothenar eminences, whereas Janeway lesions are painless, small hemorrhagic macules or papules on the palms and soles (Fig. 74.19)[66]. Both staphylococcal bacteremia and endocarditis are treated with prolonged courses of intravenous antibiotics.

CLOSTRIDIAL SKIN INFECTIONS

Clostridia are spore-forming Gram-positive rods that are ubiquitous soil saprophytes and part of the normal intestinal flora. *Clostridium perfringens*, the most frequent cause of trauma-associated gas gangrene, is an obligate anaerobe and thus proliferates in hypoxic or ischemic tissue. *Clostridium septicum* is much more aerotolerant, requires a smaller infective dose, and is associated with spontaneous gas gangrene in patients with neutropenia or gastrointestinal malignancy[14].

C. perfringens produces two membrane-active toxins, alpha and theta (perfringolysin O), which have synergistic effects. Alpha toxin possesses biologic activity akin to phospholipase C and sphingomyelinase, while theta toxin disrupts endothelial cell integrity, impairs recruitment of phagocytes, and induces intravascular platelet aggregation, leading to reduced arteriolar blood flow. Impaired oxygen delivery then results in tissue hypoxia and anaerobic glycolysis of muscle tissues. Production of hydrogen sulfide and CO_2 accounts for the characteristic "gas" gangrene visualized on radiographic imaging. Local progression results in myonecrosis, whereas shock and multi-organ failure can occur when the toxins enter the systemic circulation.

The majority of cases of anaerobic cellulitis (a necrotizing subcutaneous infection) and myonecrosis (gas gangrene) are caused by clostridia. These diseases are compared and their treatment outlined in Table 74.11. Soft tissue crepitus, evidence of gas on plain films, or a foul-smelling brownish discharge ("dirty dishwater") should prompt the clinician to suspect a clostridial infection, especially following trauma or surgery in patients with diabetes mellitus and peripheral vascular disease[58].



Fig. 74.19 Palmar lesions due to staphylococcal endocarditis.

CORYNEBACTERIAL SKIN INFECTIONS

Corynebacteria are Gram-positive rods that account for nearly half of the cutaneous flora. A warm, moist local environment represents a risk factor for infection of the skin with non-diphtherial corynebacteria.

Erythrasma

Erythrasma is a superficial and often chronic skin infection caused by excessive proliferation of *Corynebacterium minutissimum* within the stratum corneum. The organism's growth is favored by moist, occluded intertriginous areas, including the groin, axillae, intergluteal fold, inframammary region, umbilicus, and web spaces between the toes. Other predisposing factors include a warm humid climate, poor hygiene, hyperhidrosis, obesity, diabetes mellitus, advanced age, and immunosuppression.

Lesions are pink to red, well-defined patches that are covered with fine scales and have associated wrinkling. With time, the red color fades to brown (Fig. 74.20A,C). The condition is asymptomatic or mildly pruritic. Interdigital erythrasma is the most common bacterial infection of the foot and the most frequent form of erythrasma. It presents as asymptomatic, chronic maceration with fissuring or scaling of interspaces. A "disciform" variant can occur in a more widespread distribution outside the usual intertriginous locations (Fig. 74.20D); this is occasionally the presenting manifestation of type 2 diabetes mellitus. Progression to cellulitis or bacteremia in immunocompromised patients has been reported.

When lesions are illuminated with a Wood's lamp, bright coral-red fluorescence appears as a result of porphyrin produced by the bacteria (Fig. 74.20B). Gram staining of the scale demonstrates Gram-positive filaments and rods, and *C. minutissimum* can be cultured on Tissue Culture Medium 199. The differential diagnosis of intertriginous erythrasma includes tinea, seborrheic dermatitis and cutaneous candidiasis, while interdigital erythrasma needs to be distinguished from tinea pedis and complex toe web infections[67].

Topical therapies include 20% aluminum chloride, clindamycin, erythromycin, mupirocin, fusidic acid, azole antifungals, and Whitfield ointment (salicylic and benzoic acids). Oral erythromycin, tetracyclines,

CLOSTRIDIAL ANAEROBIC CELLULITIS AND MYONECROSIS		
	Anaerobic cellulitis*	**Myonecrosis (gas gangrene)**
Risk factors (for both conditions)	Trauma (penetrating, "crush" injuries) or surgery, with improper/incomplete debridement or contamination of the wound Diabetes mellitus, peripheral vascular disease Injection drug use Colonic disease or malignancy (*C. septicum* myonecrosis)	
Organism†	*C. perfringens* > other anaerobic bacteria (e.g. *Bacteroides, Peptostreptococcus*, *Prevotella* spp.)	*C. perfringens* (~80%) > *C. novyi*, *C. septicum*
Incubation period	>3 days	12–24 hours
Course	Rapid	Very rapid
Exudate	Thin, dark gray–brown, foul-smelling ("dirty dishwater")	Thin, dark gray–brown, foul-smelling ("dirty dishwater")
Overlying skin changes	Minimal	Dark yellow to bronze discoloration, necrosis, bullae
Swelling	Minimal	Severe
Crepitus	Usually present (with abundant gas in subcutaneous tissues and along fascial planes)	Sometimes present
Pain	Absent or mild	Severe
Fever	Low-grade	Low-grade
Toxemia	Absent or mild	Present (e.g. tachycardia, hypotension, oliguria)
Bacteremia/laboratory findings	Usually absent/minimal	Bacteremia in ~15%; marked leukocytosis, hemolytic anemia
Treatment (for both conditions)	• Early, aggressive surgical debridement (repeated every 24–48 hours until clinical resolution) • The causative clostridial organisms are typically sensitive to penicillin; however, because the infections may be polymicrobial, broad-spectrum coverage (e.g. with clindamycin plus piperacillin–tazobactam or ticarcillin–clavulanate) is indicated until culture results are available • Adjunctive hyperbaric oxygen therapy	

*Can progress to myonecrosis.
†Infections may be polymicrobial, which can lead to overlap with necrotizing fasciitis.

Table 74.11 Clostridial anaerobic cellulitis and myonecrosis[139].



Fig. 74.20 Erythrasma. A Pink to brown scaly patches on the upper inner thighs. **B** Coral-red fluorescence upon illumination with a Wood's lamp. **C** Hyperpigmented plaques in the inguinal and periumbilical areas. **D** Well-demarcated, scaly, hyperpigmented plaque of disciform erythrasma. *A, B, Courtesy Louis A. Fragola, Jr, MD.*

or single-dose clarithromycin can be used for widespread or recalcitrant cases. Use of antibacterial soaps may help to prevent recurrences[68,69].

Pitted Keratolysis

Synonyms: ■ Keratolysis plantare sulcatum ■ Ringed keratolysis

Introduction

Pitted keratolysis is a non-inflammatory bacterial infection of palmoplantar skin.

Epidemiology and pathogenesis

Pitted keratolysis occurs worldwide in temperate and tropical climates. Hyperhidrosis, prolonged occlusion, and increased skin surface pH are predisposing factors. Most infections are caused by *Kytococcus sedentarius* (formerly *Micrococcus sedentarius*), but other bacteria such as *Dermatophilus congolensis*, *Corynebacterium* spp., and *Actinomyces* spp. have been implicated. *K. sedentarius* produces two serine proteases (K1 and K2) that degrade keratin in the stratum corneum. Sulfur-containing compounds released by the bacteria lead to a characteristic associated malodor.

Clinical features

Small (1–7 mm), crater-like depressions are present within the stratum corneum on weight-bearing regions of the soles (Fig. 74.21) and rarely the palms. These pits may coalesce into large craters or rings of craters. There is usually no associated erythema, and the condition may go unnoticed by the patient or result in bothersome malodor[70].

Pathology

Well-defined "pits" extend approximately two-thirds of the way into the stratum corneum. Gram, PAS, and Gomori methenamine silver stains reveal bacteria in the walls and at the bottom of the craters. No inflammation is observed.

Diagnosis and differential diagnosis

The diagnosis of pitted keratolysis is usually clinical. There is no fluorescence on examination with a Wood's light. The differential diagnosis includes plantar warts, tinea pedis, palmoplantar punctate keratoderma, pits of basal cell nevus syndrome, Darier disease, and circumscribed palmoplantar hypokeratosis (see Table 58.7).

Treatment

Topical benzoyl peroxide, erythromycin, clindamycin, mupirocin, tetracycline, chlorhexidine, and azole antifungals have all been reported to lead to a rapid resolution of pitted keratolysis. Aluminum chloride 20% solution, topical glycopyrrolate, or (in recalcitrant cases) botulinum toxin can be used to treat associated hyperhidrosis[71,72].

Trichomycosis Axillaris, Pubis, and Capitis

Synonym: ■ Trichobacteriosis axillaris, pubis, and capitis

Trichomycosis is a superficial corynebacterial infection that results in concretions on the shafts of axillary and less often pubic hairs; occasionally scalp hairs in infants are affected. The hair shafts develop adherent yellow, red, or black nodules or cylindrical sheaths that can be seen with the naked eye (Fig. 74.22). There is a characteristic odor, and the sweat occasionally takes on a red color and stains clothing. However, like pitted keratolysis, the condition frequently goes unnoticed. Wood's lamp examination reveals a pale yellow fluorescence, and Gram staining of the concretions shows Gram-positive rods. The differential diagnosis includes white piedra, black piedra, nits, and hair casts (see Ch. 77). Shaving the affected hair provides an instant cure, and use of antimicrobial cleansers can prevent recurrences. Additional treatment options include benzoyl peroxide and topical erythromycin or clindamycin[73].

Cutaneous Diphtheria

Cutaneous diphtheria can be caused by both toxigenic (i.e. capable of producing systemic disease) and non-toxigenic strains of *Corynebacterium diphtheriae* and *Corynebacterium ulcerans*. It is endemic in some tropical countries and in several urban poor populations, e.g. in Vancouver, Latvia, Russia, and Ukraine[74], where it is spread by person-to-person contact in a highly contagious manner. *C. ulcerans* can also be transmitted by domestic animals. Development





Fig. 74.21 Pitted keratolysis of the plantar surface of the foot. Multiple small (**A**) and larger coalescing (**B**) craters with decreased stratum corneum that favor pressure points on the plantar surface. *Courtesy Kalman Watsky, MD.*



Fig. 74.22 Trichomycosis axillaris. Cylindrical sheaths and beading of the axillary hairs. A yellow color is seen most commonly.



Fig. 74.23 Ecthyma diphthericum. Punched-out ulcer with a black eschar on the upper lip. *Courtesy Joyce Rico, MD.*

of cutaneous diphtheria in non-endemic regions is typically related to travel, and European outbreaks have occurred in refugees from East Africa and the Middle East.

For children living in endemic regions, cutaneous diphtheria represents a form of immunization, as toxin is absorbed slowly from skin lesions and induces high levels of antibodies. In addition to children, elderly and immunocompromised individuals are most commonly affected, with predisposing factors including poor hygiene, injection drug use, and skin trauma. Vaccination prevents toxin-mediated manifestations but not bacterial infection or transmission.

Cutaneous diphtheria most commonly presents as an ulcer (*ecthyma diphthericum*) with a punched-out appearance and variable gray "pseudomembranous" eschar (Fig. 74.23). Acral sites are favored, and a pustule or crusted dermatitis may also be observed. Lesions are commonly co-infected with *S. aureus* or *Str. pyogenes*. Local lymphadenopathy and toxin-mediated complications, such as myocarditis and polyneuritis, are rare.

Gram stain of ulcer exudate and culture on specialized media can establish the diagnosis. The lab should be notified in suspected cases, as *Corynebacteria* otherwise may be reported as normal skin flora[75]. Toxigenicity can be assessed utilizing a modified Elek immunoprecipitation test, a rapid enzyme immunoassay, or PCR-based methods. Treatment includes a 10-day course of oral antibiotics, with erythromycin and penicillin representing first-line agents; additional measures include thorough cleansing of the wound site, application of a topical antibiotic, and (for toxigenic strains) intravenous diphtheria antitoxin. Contacts should be screened and asymptomatic carriers treated.

OTHER GRAM-POSITIVE SKIN INFECTIONS

Cutaneous Anthrax

Introduction and epidemiology

The name *Bacillus anthracis* is derived from the Greek word for coal, *anthrakis*, reflecting the black, coal-like eschars. *B. anthracis* is an aerobic, sporulating, Gram-positive rod measuring 1–1.5×3–5 microns. The bacterium causes disease in humans via three routes: inhalation, ingestion, and cutaneous inoculation. While the latter produces the least severe form of anthrax, it accounts for ~95% of infections. Anthrax is primarily a disease of animals (e.g. sheep, cows, horses, goats) that is endemic in parts of Africa and the Middle East. Most human cases are due to occupational exposure to infected animals or their carcasses, including hides and wool ("woolsorter's disease"). Two thousand cases are reported annually worldwide, with <10 per year in the US.

History

The fifth and sixth plagues of Egypt that are described in the book of Exodus are thought to have been anthrax. *B. anthracis* was the first bacterium proven to be the etiologic agent of a specific disease,

independently demonstrated by Dr. Robert Koch and Dr. Louis Pasteur. Anthrax was first used as a biologic weapon during World War I. Accidental release of anthrax from a biologic weapons complex in the Soviet Union in 1979 resulted in 68 fatalities. In 2001, anthrax spores were sent through the US mail as a terrorist weapon, resulting in 22 cases of inhalational or cutaneous anthrax and 5 fatalities[76].

Pathogenesis

Anthrax spores are environmentally hardy and can survive for decades in the soil. Full virulence requires the presence of an antiphagocytic capsule and three toxin components (protective antigen, lethal factor, and edema factor) that combine to form both lethal toxin and edema toxin. Edema toxin impairs neutrophil function and affects water homeostasis, leading to edema; lethal toxin causes release of TNF and IL-1β[77].

Clinical features

The clinical features of cutaneous anthrax are outlined in Table 74.12. Additional key points include the following:

- The lack of pain despite a necrotic eschar helps to differentiate cutaneous anthrax from the bite of a brown recluse spider.
- A pustular primary lesion is unlikely to be cutaneous anthrax, although "cloudy" vesicles may form a "pearly wreath" around the eschar. The term "malignant pustule", which is often attributed to anthrax, is therefore a misnomer.
- Vesicles may discharge serosanguineous fluid containing numerous organisms, which are evident on Gram stain.
- Lymphangitis and painful lymphadenopathy with systemic symptoms (fever, malaise, headache) occur rarely.
- Antibiotic therapy does not alter the progression from vesicle to ulcer to eschar, as the process is toxin-mediated.
- Multiple lesions, when present, tend to cluster in the same area of the body.
- Palpebral anthrax manifests with eyelid swelling and necrosis, often resulting in cicatricial ectropion[78].

Pathology

Spongiosis, papillary dermal edema, and a superficial and deep inflammatory infiltrate with abundant neutrophils are observed. Substantial hemorrhage is often evident, and the inflammatory infiltrate may involve nerves. Extensive ulceration and coagulative necrosis can be seen in older lesions. Elongated Gram-positive bacilli are present, often in small clusters. Spores grow readily on all routine culture media at 37°C, with a "jointed bamboo-rod" cellular appearance and a unique "curled-hair" colonial morphology.

Diagnosis and differential diagnosis

Gram staining of exudate or touch preparations can aid in rapid diagnosis. The organism grows in culture within 6–24 hours; however, antibiotic administration for more than 24 hours prevents the recovery of pathogens in culture.

Laboratory personnel must be alerted to the possibility of anthrax to ensure that the *Bacillus* isolate is not assumed to be *B. cereus* and that further speciation is performed. Definitive diagnosis of anthrax requires specific testing such as detection of lethal factor, PCR-based analysis, and immunohistochemical staining. Serologic assays can become positive as early as 10 days after onset of symptoms, with peak titers at 40 days.

The differential diagnosis includes cutaneous infection with *Bacillus megaterium*, a brown recluse spider bite, the eschar of several rickettsial diseases, cellulitis, ecthyma gangrenosum, orf, milker's nodule, opportunistic bacterial and fungal infections, and entities in the ulceroglandular category (e.g. tularemia; see below)[79].

CUTANEOUS ANTHRAX – CLINICAL CHARACTERISTICS
• Incubation period averages 7 days (range 1–12 days)
• Purpuric macule or papule develops in an exposed area (e.g. forearm, neck, chest, finger); the papule may resemble an insect bite and can be pruritic
• Within 48 hours of the lesion's appearance, a vesicle (1–3 mm) forms with surrounding non-pitting edema
• The central vesicle ulcerates and small vesicles may form around the ulcer
• The lesion becomes hemorrhagic and depressed, and a *painless*, black necrotic eschar forms centrally with an increase in the surrounding erythema and edema
• The eschar dries, loosens, and sloughs over the next 1–2 weeks, with no permanent scar

Table 74.12 Cutaneous anthrax – clinical characteristics. *Adapted from Carucci JA, McGovern TW, Norton SA, et al. Cutaneous anthrax management algorithm. J Am Acad Dermatol 2002;47:766–9.*

Treatment

Without antibiotic treatment, mortality from cutaneous anthrax may be as high as 20% (usually from septicemia), but that number falls to almost zero with proper antimicrobial therapy. Although antibiotics do not alter the evolution of the cutaneous lesions (which are toxin-mediated), the likelihood of systemic illness is reduced. When cutaneous anthrax is associated with a concomitant inhalational exposure, the Centers for Disease Control and Prevention (CDC) recommend antibiotic therapy for at least 60 days, compared to a 7- to 10-day course for a purely cutaneous exposure to an animal-based source. Quinolones and doxycycline are first-line agents, with clindamycin and (if susceptible) penicillin or amoxicillin as alternatives[77].

An anthrax vaccine, consisting of an inactivated cell-free filtrate of a non-encapsulated, attenuated strain of *B. anthracis*, is available. The recommended five-dose pre-exposure series includes administration at 0, 1, 6, 12, and 18 months, followed by yearly boosters. For post-exposure prophylaxis, three vaccine doses can be given at 0, 2, and 4 weeks together with antimicrobial treatment. Raxibacumab and obiltoxaximab are recombinant human immunoglobulin monoclonal antibodies targeting the *B. anthracis* protective antigen. Either of these antibodies or polyclonal anthrax immune globulin may be administered as a single intravenous infusion (in conjunction with antibiotics) for the treatment and post-exposure prophylaxis of inhalational anthrax.

Bacillus cereus Infection

Bacillus cereus is a large Gram-positive rod best known for causing food poisoning. However, it can produce primary cutaneous disease in immunocompetent and immunosuppressed patients as well as pneumonia, meningitis, and necrotizing fasciitis in immunocompromised individuals. An outbreak of skin infections in neonates due to contamination of equipment used during delivery has been reported[80]. Skin infection typically presents as a single necrotic bulla, which may occur in association with high fevers and negative blood cultures in neutropenic individuals. Vancomycin is considered the drug of choice, but quinolones and imipenem may also be used.

Erysipeloid

Synonyms: ■ Diamond skin disease ■ Erysipeloid of Rosenbach (localized cutaneous form) ■ Pseudoerysipelas

Erysipeloid is an acute cutaneous infection caused by *Erysipelothrix rhusiopathiae* (formerly *insidiosa*), a Gram-positive, non-motile, smooth or curved bacillus. It is caused by traumatic inoculation of the organism into the skin, which most often occurs in fishermen or persons who prepare meat, poultry, or fish. It has also been reported following animal bites[81]. There are two types of erysipeloid, localized and generalized, and they usually occur within 1 week of inoculation. The *localized form* is characterized by an erythematous to violaceous area of non-suppurative cellulitis (Fig. 74.24), which can be pruritic or painful. Hemorrhagic vesicles may develop. Although the classic finding is involvement of the finger webs with sparing of the terminal phalanges, other sites may be affected. Constitutional symptoms are unusual in localized erysipeloid, which is typically a self-limited condition. However, the *generalized form* presents with fever and arthralgias in addition to widespread cutaneous lesions. The latter range from perifollicular papules to erythematous plaques to macular purpura and necrosis. Complications can include bacteremia, endocarditis, septic arthritis, and cerebral and other visceral abscesses. The organism is often difficult to culture, and PCR-based assays can help to establish the diagnosis[82]. Erysipelas, cellulitis, spider bites, and fixed drug eruptions may simulate localized erysipeloid (see

Table 74.10). Most patients with untreated localized disease recover spontaneously. Penicillin is the drug of choice; erythromycin, cephalosporins, clindamycin, linezolid, and quinolones are alternatives. The best means of prevention is using gloves when preparing fish or meat.

Listeriosis

Listeria monocytogenes is a motile Gram-positive bacillus that represents a common veterinary (e.g. cattle, sheep) and zoonotic pathogen. Infection is usually acquired by eating contaminated food (e.g. soft cheeses, ice cream). Listeriosis primarily affects the elderly, pregnant women, and immunocompromised individuals. Manifestations include meningitis and gastroenteritis accompanied by fever, myalgias, and bacteremia. Pregnant women are at risk of miscarriage, stillbirth, and premature delivery. Neonatal septicemia and meningitis due to vertical transmission can occur and may be associated with disseminated vesiculopustules, purpura, or granulomatous papules and nodules (*"granulomatosis infantiseptica"*)[83]. Primary cutaneous listeriosis can present as grouped papulopustules, an abscess, or cellulitis. Transmission may occur via skin exposure to bovine products of conception in veterinarians and farmers, but this has decreased in recent years due to safer occupational practices[83]. In otherwise healthy individuals, primary cutaneous listeriosis may be self-limited. The first-line treatment for listeriosis is ampicillin, and TMP-SMX represents an alternative; *L. monocytogenes* is resistant to cephalosporins.



Fig. 74.24 Erysipeloid. Erythema and edema with vesicle formation on the hand and fifth digit.

GRAM-NEGATIVE BACTERIA

Table 74.13 outlines selected Gram-negative infections that present with systemic symptoms (e.g. fever) and skin findings.

NEISSERIA MENINGITIDIS

Acute and Chronic Meningococcemia

Introduction

Meningococcemia is characterized by fever and a petechial eruption, and it has acute and chronic forms. The causative organism, *Neisseria meningitidis*, is an aerobic Gram-negative diplococcus.

Epidemiology and pathogenesis

Meningococcal infections occur worldwide and affect primarily infants (6 months to 1 year), adolescents, and young adults. There is a male predominance, with a male : female ratio of 3–4 : 1. Most cases develop in the winter and spring. Risk factors include HIV infection and asplenia; deficiencies in complement component C3 (which may be associated with partial lipodystrophy), terminal complement components (C5–C9), properdin, factor D or H, and immunoglobulins (see Ch. 60)[84]; and treatment with terminal complement inhibitors (e.g. eculizumab, ravulizumab) and potentially TNF inhibitors. In addition, there is evidence that patients with low TNF production, high IL-10 or plasminogen activator inhibitor 1 production, or homozygosity of certain alleles at the IL-1 locus are at increased risk of a fatal outcome[85,86].

Thirteen clinically significant *N. meningitidis* serogroups are distinguished by their capsular polysaccharide virulence factors. Serogroups A, B, C, X, Y, and W-135 are most often implicated in human disease. Proliferation of *N. meningitidis* in contact with host cells increases the production of a bacterial transferase that adds phosphoglycerol onto its type IV pili; this modification results in bacterial detachment and

UNCOMMON GRAM-NEGATIVE INFECTIONS THAT PRESENT WITH FEVER AND SKIN FINDINGS

Infection	Common organism(s)	Transmission/other factors	Skin findings and other characteristic features
Infection with *Vibrio vulnificus*	*Vibrio vulnificus*	See Table 74.16	• Hemorrhagic bullae with cellulitis
Tularemia	*Francisella tularensis*	Infected rabbits; deer fly or tick (e.g. *Amblyomma americanum*) as vector	• Ulcers associated with lymphadenopathy • May show sporotrichoid pattern
Glanders	*Burkholderia mallei*	Direct contact with infected animals (horses, mules, donkeys)	• Nodule, pustule, or vesicle surrounded by erythema • Sporotrichoid pattern
Plague	*Yersinia pestis*	Contaminated food or water; fleas can be the vector	• Bubonic form due to inoculation: pustule or ulcer with painful regional lymphadenopathy; may have a sporotrichoid pattern • Septicemic form: emboli can present as vesicles, petechiae/purpura, or abscesses
Melioidosis	*Burkholderia pseudomallei*	Contact with contaminated soil or water; ingestion or inhalation; sexual intercourse; fleas can be the vector	• Abscesses, granulomatous lesions, purpura, pustules, urticaria, ecthyma gangrenosum
Rat-bite fever (Haverhill fever)	*Streptobacillus moniliformis* > *Spirillum minus*	Close contact with infected rodents or contaminated food, water, or raw milk (Haverhill fever)	• Acral palmoplantar eruption of macules, papules, petechiae, vesicles, pustules, and/or crusts • Migratory polyarthritis mimicking rheumatoid arthritis in 50% of patients
Brucellosis	*Brucella abortus*	Consumption of unpasteurized milk products	• Malodorous perspiration • Erythema nodosum • Vasculitis
Typhoid fever	*Salmonella typhi*	Contact with infected persons	• Rose spots: 2–8 mm pink, blanching papules, often in clusters of 5–15 on the anterior trunk • Erythema multiforme, Sweet syndrome, hemorrhagic bullae, pustules

Table 74.13 Uncommon Gram-negative infections that present with fever and skin findings. Next-generation sequencing assays are available to detect microbial cell-free DNA from >1000 infectious organisms in a peripheral blood sample, which may help to diagnose systemic infections with cutaneous manifestations.

migration across the epithelium, a prerequisite for dissemination and invasive disease[87]. The bacteria elaborate an endotoxin that triggers inflammatory processes leading to shock, multi-organ failure, and purpura fulminans.

The only known reservoir is the human nasopharynx. Rates of asymptomatic carriage in the US range from 5% to 15%[88]. Transmission is by the respiratory route, with an incubation period of 2–10 days. Active or passive exposure to tobacco smoke, as well as concurrent viral infection of the upper respiratory tract, disrupts the integrity of the respiratory mucosa, thereby increasing the risk of invasive meningococcal disease.

Clinical features

Infection with *N. meningitidis* most often results in an asymptomatic carrier state, which leads to lifelong immunity against that subgroup. Upper respiratory symptoms as well as bacteremia without sepsis may also occur. When acute meningococcemia develops, one-third to one-half of patients present with a petechial eruption, typically in association with a fever, chills, myalgias, and headache. Retiform purpura and ischemic necrosis may follow (Fig. 74.25). Bullous hemorrhagic lesions occasionally arise, most commonly on the trunk and lower extremities. In a minority of patients, only a transient, blanchable morbilliform eruption is seen. Hypotension, meningitis, meningoencephalitis, pneumonia, arthritis, pericarditis, myocarditis, and progression to disseminated intravascular coagulation (DIC) can develop.

Chronic meningococcemia comprises less than 5% of invasive meningococcal disease cases and is defined by blood cultures positive for *N. meningitidis* and symptom duration >7 days, without either meningitis or shock. Typical symptoms include recurrent fevers, migratory arthralgias, and the development of polymorphous erythematous macules and papules 12–24 hours after the onset of fevers. The skin lesions may develop into tender nodules with indistinct borders. Petechiae, retiform purpura, pustules, and erythema multiforme-like lesions have also been described. The fever and rash of chronic meningococcemia tend to resolve concurrently and then recur within 2–10 days[89].

Pathology

Biopsy specimens from patients with acute meningococcemia show leukocytoclastic vasculitis and thrombosis; organisms can be visualized with Gram stain in 70% of cases. In chronic meningococcemia, a perivascular infiltrate composed of lymphocytes and a few neutrophils can be appreciated; leukocytoclastic vasculitis may be seen in petechial lesions, and Gram or silver staining is often negative.

Diagnosis and differential diagnosis

The initial diagnosis is often clinical. Time is of the essence in diagnosing patients with meningococcemia and initiating treatment, as rapid decompensation occurs in acute infections. Culture of *N. meningitidis* from the skin or a normally sterile body fluid (e.g. blood, cerebrospinal fluid [CSF], synovial fluid) can establish the diagnosis; however, the sensitivity may be low, especially after administration of antibiotics. Latex agglutination tests that detect group A, B, C, Y, and W-135 antigens in the CSF and urine have good specificity but low sensitivity. PCR-based assays are also specific and have better sensitivity, which may be higher in skin biopsy specimens than blood or CSF samples, but bacterial culture is still necessary for susceptibility testing[90].



Fig. 74.25 Acute meningococcemia. Purpura with irregular outline and central gunmetal gray color. *Courtesy Kalman Watsky, MD.*

Acute meningococcemia must be differentiated from enteroviral infections (which can present with meningitis and a petechial exanthem), Rocky Mountain spotted fever, septic vasculitis due to acute bacteremia and endocarditis, TSS, purpura fulminans, leptospirosis, and various non-infectious vasculitides. The differential diagnosis of chronic meningococcemia includes bacterial endocarditis, Sweet syndrome, Henoch–Schönlein purpura, rat-bite fever, erythema multiforme, and chronic gonococcemia. The rash and arthralgias associated with chronic meningococcemia must not be confused with inflammatory diseases, as administration of corticosteroids or other immunosuppressive medications could provoke progression of the infection.

Treatment

While early institution of appropriate therapy for acute meningococcemia is essential, if possible, blood and CSF samples should be obtained prior to antibiotic administration. A third-generation cephalosporin is the recommended treatment for suspected (e.g. Gram stain with Gram-negative diplococci) or culture-proven acute meningococcemia prior to obtaining susceptibility results. Chloramphenicol and quinolones are alternatives in patients with a history of immediate-type hypersensitivity to penicillins, although quinolone-resistant strains have been reported[91]. Chronic meningococcemia is treated with similar antibiotics. All close contacts should receive prophylactic treatment with ciprofloxacin, rifampin, or ceftriaxone. Experimental therapies that have been tried in small numbers of patients include activated protein C, anti-endotoxin monoclonal antibodies, tissue plasminogen activator, antithrombin III infusion, topical nitroglycerin, plasmapheresis, and extracorporeal membrane oxygenation[92]. To date, these interventions have not proven to be effective in decreasing mortality.

Several meningococcal vaccines are approved for use in the US: three quadrivalent vaccines effective against serogroups A, C, W, and Y; a bivalent vaccine effective against serogroups C and Y plus *H. influenzae* type b; and two monovalent vaccines effective against serogroup B. The duration of immunity for these vaccines is ~3–5 years. A quadrivalent conjugated vaccine is routinely given to children at age 11–12 years with a booster at age 16 years; this vaccine is also administered to other individuals at high risk for infection, such as college students living in dormitories and military recruits, as well as patients ≥2 months of age at increased risk of severe meningococcal infection due to conditions such as complement deficiencies and asplenia. The monovalent serogroup B vaccine is recommended for patients ≥10 years of age in the latter high-risk group; in addition, it is offered to teens, preferably at age 16–18 years.

PSEUDOMONAS AERUGINOSA

Pseudomonas aeruginosa is a ubiquitous Gram-negative, strictly aerobic, motile bacillus. It is widely distributed in the soil and on plants, growing especially well in aqueous environments. This organism has relatively low virulence and usually requires a local anatomic or immunologic defect to cause disease. Primary cutaneous infection with *P. aeruginosa* can occur in otherwise healthy individuals in areas exposed to high levels of moisture in conjunction with skin barrier disruption; these infections have a very good prognosis. In contrast, cutaneous manifestations of *Pseudomonas* sepsis in immunocompromised individuals are associated with a grave prognosis.

Green Nail Syndrome

In green nail syndrome (chloronychia), green–blue to green–black discoloration of the nail develops due to pyocyanin, a blue–green pigment produced by *P. aeruginosa* (Fig. 74.26). There is typically associated distal onycholysis and sometimes proximal chronic paronychia. Predisposing factors include frequent or prolonged exposure to water, excessive use of detergents and soaps, nail trauma, onychomycosis[93], and other causes of onycholysis (see Ch. 71). The diagnosis of green nail syndrome is usually clinical; if necessary, it can be confirmed by Gram stain and culture of exudate and nail fragments. The differential diagnosis includes a subungual hematoma, melanocytic nevus, melanoma, and *Aspergillus* infection. Treatment involves avoidance of

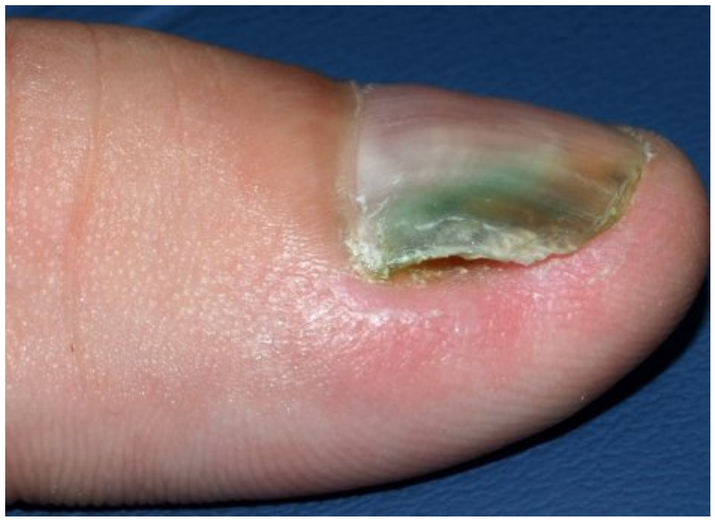


Fig. 74.26 Green nail syndrome. Blue–green discoloration of the nail due to pyocyanin produced by *Pseudomonas aeruginosa*. Note the associated onycholysis. *Courtesy Julie V. Schaffer, MD.*



Fig. 74.27 Superficial infection of the skin with *Pseudomonas*. Note the maceration, erosions, and moth-eaten appearance of the skin. *Courtesy Kalman Watsky, MD.*

predisposing factors, clipping the nail, and topical application of 2% sodium hypochlorite (household bleach diluted 1:4; see Ch. 71), a quinolone, or aminoglycoside (e.g. tobramycin) solution for 1–4 months. Treatment of coexistent onychomycosis may help prevent recurrence. In refractory cases, removal of the affected nail may be required.

Pseudomonal Pyoderma and Blastomycosis-Like Pyoderma

Pseudomonal pyoderma is a superficial infection of the skin with *P. aeruginosa*. Features include a blue–green purulence, a "grape juice-like" or "mousy" odor, and a moth-eaten appearance of the skin. The borders are often macerated and eroded (Fig. 74.27). Pseudomonal pyoderma can complicate burns, decubitus ulcers, and other chronic cutaneous ulcers. Pseudomonal pyoderma often plays a role in Gram-negative toe web infections and in "infectious eczematoid dermatitis" on the hands and feet or in the anogenital region[94].

Blastomycosis-like pyoderma is a rare reactive condition that occurs in the setting of a long-standing localized infection, presenting as large verrucous plaques with multiple pustules and elevated borders. Histologic examination reveals pseudoepitheliomatous hyperplasia with intraepidermal abscess formation; fungi are not seen, and fungal cultures are negative. This condition usually occurs in immunocompromised patients, and other bacteria (e.g. *S. aureus*) have also been implicated.

Treatment of these conditions includes systemic antipseudomonal antibiotics, topical antimicrobial and drying agents, and debridement of the hyperkeratotic rim in web space infections. Additional treatment options for blastomycosis-like pyoderma include acitretin, saturated solution of potassium iodide, surgical excision, electrodesiccation and curettage, and ablative laser therapy[95].

Otitis Externa and Necrotizing (Malignant) Otitis Externa

P. aeruginosa colonizes 1%–2% of normal ear canals. However, pseudomonal infection can result in otitis externa ("swimmer's ear"). Predisposing factors include eczema and psoriasis of the ear, swimming, mechanical trauma, hearing-aid use, and ear irrigation. In this condition, the external auditory canal is swollen and macerated with a green, purulent discharge. The tympanic membrane is uninvolved, and manipulation of the pinna results in extreme pain. An exudative dermatitis of the external ear and retroauricular area may also be present. Treatment includes removal of canal debris, antibiotic eardrops (preferably those that cover *S. aureus* co-infection), and possibly the instillation of a cotton wick. Oral therapy is only occasionally required, but recurrences can occur[96].

Necrotizing (malignant) otitis externa refers to infection that progresses to affect the temporal bone and adjacent structures. It is seen most often in elderly diabetic patients and those with HIV infection or other immunodeficiencies. Manifestations include severe pain, persistent drainage, and granulation tissue within the ear canal. Local lymphadenopathy and parotid swelling may be present. Deeper invasion can result in osteomyelitis of the skull, nerve palsies, mastoiditis, sepsis, and sigmoid sinus thrombosis. Treatment includes extended courses of intravenous antipseudomonal penicillins or cephalosporins as well as oral ciprofloxacin; surgical intervention may be required.

Auricular chondritis secondary to *Pseudomonas* spp. has been associated with piercing of the cartilaginous portion of the pinna[97].

Pseudomonal Folliculitis

Pseudomonal folliculitis ("hot tub folliculitis") is associated with the use of whirlpools, hot tubs, and (less often) swimming pools with low chlorine levels; transmission from fomites such as nylon bath towels and rubber gloves has also been reported. Erythematous, edematous perifollicular papules and papulopustules arise 8–48 hours after exposure and resolve spontaneously in 7–14 days (see Ch. 38). The lesions frequently occur in sites covered by bathing suits, and the face and neck are usually spared. Associated symptoms (which do not reflect systemic spread of *P. aeruginosa*) may include pruritus, painful eyes, earaches, a sore throat, headache, fever, painful swollen breasts, malaise, rhinorrhea, nausea, vomiting, and abdominal pain.

The diagnosis can be confirmed by isolation of *P. aeruginosa*, especially serotype O-11, from lesions. The differential diagnosis includes other forms of folliculitis (e.g. due to *S. aureus*) and papular urticaria. Treatment is generally not indicated in immunocompetent hosts, as it is usually a self-limited process. Warm compresses with 2% acetic acid and application of topical polymyxin B or gentamicin may be of benefit. In the case of widespread eruptions, recurrences, an immunosuppressed host, or associated systemic symptoms, an oral quinolone can be used[98].

Pseudomonas Hot-Foot Syndrome

Pseudomonas hot-foot syndrome occurs after swimming or wading in pool water that contains high concentrations of *P. aeruginosa*. The soles may be diffusely erythematous, and extremely painful, red-to-purple, 1–2 cm nodules develop on weight-bearing surfaces (Fig. 74.28); palmar involvement occasionally occurs. Systemic symptoms are uncommon.



Fig. 74.28 Pseudomonas hot-foot syndrome. Tender erythematous nodules on the heel. *Courtesy Justin J. Green, MD.*

Histologic examination of the nodules shows perivascular and periecrine neutrophilic infiltrates with microabscess formation. The condition is self-limiting and requires only symptomatic treatment. Idiopathic palmoplantar hidradenitis (see Ch. 39) has identical clinical features and may be pathogenically related to pseudomonas hot-foot syndrome. Additional diagnostic considerations may include pernio, symmetric lividities, and erythema nodosum[99].

Ecthyma Gangrenosum

Ecthyma gangrenosum represents an infectious vasculitis that causes skin necrosis. The most common clinical scenario is *Pseudomonas* bacteremia in a neutropenic patient. However, it may also occur in previously healthy individuals, sometimes as the initial presentation of immunodeficiency (e.g. X-linked agammaglobulinemia in young boys; see Ch. 60). Clinically identical lesions can result from other bacteria (e.g. *E. coli, Klebsiella pneumoniae, Aeromonas, Stenotrophomonas, Citrobacter, S. aureus)* or fungi (*Candida, Mucor, Fusarium, Scytalidium, Aspergillus*). Although ecthyma gangrenosum usually occurs in the setting of bacteremia (or fungemia), a localized anogenital form without identifiable bacteremia has also been described.

Lesions are usually few in number and begin as erythematous or purpuric macules, most commonly located in the anogenital area or on the lower extremities. They then evolve into hemorrhagic vesicles or bullae, which rupture and become necrotic ulcers with a central black eschar. The surrounding tissue is erythematous and tender (Fig. 74.29).

Histologic examination shows a necrotizing hemorrhagic vasculitis, and Gram-negative rods or other causative organisms can be seen in the medial and adventitial walls of deeper vessels. The intima is characteristically spared. Multiple lesions, prolonged neutropenia, and a delay in antibiotic treatment portend a poor prognosis. Once the diagnosis is suspected, biopsy and tissue culture of a skin lesion (as well as blood and urine cultures) should be performed, followed by prompt initiation of intravenous therapy (e.g. with an aminoglycoside and an antipseudomonal penicillin). Surgical debridement is often necessary[100]. Ecthyma gangrenosum in a previously healthy patient should prompt a search for an underlying immunocompromised state.

BARTONELLA

Bartonella are small, pleomorphic, facultative intracellular Gram-negative bacilli (closely related to *Brucella*) that are capable of infecting erythrocytes and endothelial cells. Although there are >30 known species of *Bartonella*, *B. henselae* (cat scratch disease), *B. quintana* (trench fever), and *B. bacilliformis* (Carrion disease) represent the three major human pathogens. Both *B. henselae* and *B. quintana* also cause bacillary angiomatosis and endocarditis. Transmission occurs via close contact between animals and humans, arthropod vectors, and possibly blood transfusions. Depending on factors such as the immune status of the infected individual, a particular *Bartonella* species can cause either acute or chronic infection and manifestations ranging from vascular proliferation to suppuration[101,102]. There is no therapeutic regimen that guarantees eradication of *Bartonella*.



Fig. 74.29 Ecthyma gangrenosum. Embolic lesion of *Pseudomonas aeruginosa* on the chest. Note the necrotic center and inflammatory border.

Bartonellosis

Synonyms: ■ Carrion disease ■ Oroya fever ■ Verruga peruana

Introduction

Bartonellosis is a potentially life-threatening biphasic infection caused by *Bartonella bacilliformis*. Two distinct clinical forms may occur independently or sequentially: (1) Oroya fever, an acute febrile disease with associated hemolytic anemia and transient immunodeficiency; and (2) verruga peruana (Peruvian wart), a chronic disease characterized by cutaneous vasoproliferative lesions.

History

The biphasic nature of bartonellosis was first described in 1540 by Miguel de Steta. In 1885, a Peruvian medical student, Daniel Carrion, died of complications of Oroya fever after inoculating himself with blood derived from a lesion of verruga peruana, proving a common causality for the two disease states[103].

Epidemiology and pathogenesis

The disease is transmitted by the bite of female Phlebotomine sand flies (*Lutzomyia verrucarum*). It occurs in mountain valleys of Peru, Ecuador, and southwestern Colombia, where the vector resides. There is no racial, sex, or age predilection, but the disease tends to be milder in children than in adults. The incubation period varies between 3 and 14 weeks.

Clinical features

The onset of *Oroya fever* is often sudden, with dyspnea, weakness, pallor, tachycardia, fever, thirst, anorexia, arthralgias, and headache. A precipitous drop in hemoglobin may occur secondary to invasion of erythrocytes, and hyperbilirubinemia and hemoglobinuria can result. After the initial septicemia, a variable degree of immunodeficiency ensues. During this phase, a third of patients develop secondary bacterial infections; when death occurs, it is often secondary to an enteropathic bacterial infection, especially *Salmonella enterica*. Lymphadenopathy, splenomegaly, and megaloblastic hyperplasia of the bone marrow are seen in severe cases. Patients with Oroya fever usually require 8–10 weeks for full recovery.

Most patients who recover from Oroya fever develop cutaneous nodules during or after their convalescent period, but *verruga peruana* can also appear in previously asymptomatic individuals and in those

treated with antibiotics for acute infection. Bright red papules and nodules measuring 2 mm to several centimeters in diameter appear within small erythematous patches. Lesions may be sessile or pedunculated and are usually located on the head and extremities. Hemorrhage, ulceration, and secondary bacterial infection can occur. In the absence of complications, lesions usually heal without scarring but may recur and serve as a reservoir for further transmission[104].

Pathology

The histologic features of verruga peruana vary and can resemble those of a pyogenic granuloma or Kaposi sarcoma. Masses of intracytoplasmic *Bartonella* organisms (Rocha–Lima inclusions) are present within swollen endothelial cells as well as in red blood cells; the bacilli are also found extracellularly. Thrombosis and occlusion of vessels occurs.

Diagnosis and differential diagnosis

The presence of organisms within red blood cells or within the cytoplasm of endothelial cells is diagnostic. *B. bacilliformis* can be isolated from blood cultures; immunologic testing (e.g. ELISA, immunoblot) and PCR-based assays for blood or tissue samples are also available[105]. The differential diagnosis of verruga peruana includes multiple pyogenic granulomas, bacillary angiomatosis, warts, molluscum contagiosum, and yaws.

Treatment

Table 74.14 outlines the treatment recommendations for bartonellosis.

Cat Scratch Disease

Synonyms: ■ Cat scratch fever ■ Subacute regional lymphadenitis ■ Inoculation lymphoreticulosis ■ English–Wear infection

Introduction

Cat scratch disease (CSD) is caused by infection with *Bartonella henselae*. In immunocompetent hosts, it is a benign, self-limited illness characterized by tender regional lymphadenitis that lasts for weeks to months. Over 90% of patients report a recent scratch and/or bite from a cat.

Epidemiology and pathogenesis

CSD occurs worldwide, and ~12 500 cases are diagnosed annually in the US[106]. Exposure to cats is the primary factor for CSD. Although flea-vectored transmission to humans has not been documented, it could explain some cases in which there is no history of exposure to cats.

Clinical features

CSD is a common cause of persistent lymphadenopathy (>3–4 weeks) in children and adolescents. Lymphadenopathy usually presents 2–4 weeks after a scratch and can last 2–6 months, or even longer if fibrosis occurs. A single, large (1–10 cm), tender, mobile lymph node, with erythema and swelling of the overlying skin, is most often noted in the axilla. Suppuration occurs in only 10%–25% of patients. A skin lesion (e.g. a red or crusted pustule) develops at the inoculation site in most patients. Other skin findings can include a morbilliform eruption, erythema multiforme, granuloma annulare, and erythema nodosum[107].

Although most patients are otherwise well, the lymphadenopathy can be accompanied by fevers, malaise, fatigue, weakness, and headaches. Additional manifestations such as encephalopathy, hepatic granulomas, osteomyelitis, and pulmonary involvement develop in up to 15% of patients. The oculoglandular syndrome of Parinaud – unilateral conjunctivitis and ipsilateral preauricular lymphadenopathy – occurs in ~5% of individuals with CSD. Immunosuppressed patients (e.g. those with HIV infection) are prone to a more severe and complicated disease course.

Pathology

Affected lymph nodes display central necrosis surrounded by histiocytic and epithelioid cells with an inner palisading layer. Giant cells with a peripheral zone of lymphoid cells are also evident. The primary skin lesion can show similar changes, albeit less well developed. The Warthin–Starry silver stain demonstrates bacilli within areas of necrosis.

Diagnosis and differential diagnosis

For patients who present with regional adenopathy and a history of a recent cat scratch, the diagnosis is usually made clinically. A sensitive and specific assay for *B. henselae* antibodies is available, and antibody titers are usually high during the first few weeks after the onset of lymphadenopathy; PCR-based testing can also be performed. Culture is difficult and not routinely recommended. Other causes of lymphadenopathy such as infections (bacterial, fungal, or viral), reactive hyperplasia, drug reactions, or malignancy can be excluded by fine-needle aspiration histology or biopsy and culture of lymph node tissue.

Treatment

Table 74.14 outlines current recommendations for the treatment of CSD.

Bacillary Angiomatosis

Synonyms: ■ Epithelioid angiomatosis ■ Disseminated cat scratch disease

Introduction

Bacillary angiomatosis is caused by infection with *B. henselae* or *B. quintana*. Vascular proliferation is the predominant feature of this condition, which most often affects HIV-infected individuals.

History

The disorder was first described in 1983 as subcutaneous vascular proliferations in individuals with AIDS. Electron microscopy and Warthin–Starry-stained sections of the lesions revealed small bacilli. In 1989, LeBoit and colleagues coined the name "bacillary angiomatosis" and proposed histologic criteria for the disorder. In the early 1990s, *Rochalimaea quintana* and *R. henselae* (subsequently reclassified in the genus *Bartonella*) were recognized as the causes of bacillary angiomatosis (see Table 74.14).

Epidemiology and pathogenesis

Bacillary angiomatosis is an uncommon disease that is most often seen in HIV-infected patients when their $CD4^+$ count is <200 cells/mcl (see Ch. 78). Fortunately, with the advent of effective antiretroviral therapy (ART), the prevalence of bacillary angiomatosis has decreased substantially. The associated vascular proliferation may reflect aberrant vascular endothelial growth factor (VEGF) signaling in endothelial cells[108]. Only 20% of patients with bacillary angiomatosis due to *B. henselae* report a preceding cat scratch or bite, compared to 90% of those with CSD.

Clinical features

Cutaneous lesions of bacillary angiomatosis may present as superficial angiomatous papules and nodules, violaceous lichenoid plaques, or deep subcutaneous nodules. The papules and nodules resemble pyogenic granulomas (Fig. 74.30A) and may be smooth-surfaced, pedunculated, or surrounded by a collarette of scale. These lesions may display central umbilication, crusting, or ulceration. Subcutaneous nodules are often several centimeters in diameter and skin-colored; overlying erosions or ulcerations may develop. Less commonly, bacillary angiomatosis presents as a cellulitic erythematous plaque that can involve the underlying bone. The host immune status largely determines the number and distribution of the lesions. Immunocompetent patients may have a single lesion at the site of inoculation, whereas the entire cutaneous surface can be affected in those who are severely immunocompromised.

Extracutaneous bacillary angiomatosis may occur with or without cutaneous disease and can affect any organ. Bacillary peliosis hepatis caused by *B. henselae* (but not *B. quintana*) presents with nausea, vomiting, diarrhea, abdominal pain, hepatosplenomegaly, and elevated liver enzymes. Bacillary peliosis splenis may lead to pancytopenia and require splenectomy. Patients can also present with malaise and night sweats.

Pathology

Biopsy specimens reveal lobular proliferations of capillaries and venules, plump and protuberant endothelial cells, and a marked neutrophilic infiltrate with evidence of leukocytoclasis throughout the interstitium

MAJOR HUMAN DISEASES CAUSED BY *BARTONELLA* SPECIES AND THEIR TREATMENT				
Species	**Disease**	**Vector**	**Reservoir/host**	**Epidemiology**
B. bacilliformis	Bartonellosis (Carrion disease, Oroya fever, verruga peruana)	Phlebotomine sand fly (*Lutzomyia verrucarum*)	Human	• Andean mountain valley regions of Peru, Ecuador, and southwestern Colombia (altitudes of 2500–8000 feet) • More common in immunologically naive tourists and transient workers • Milder in children
B. henselae	Cat scratch disease	Cat flea (*Ctenocephalides felis*)	Cat	• Primarily seen in young people (<18 years) in the fall and winter • Immunocompetent > immunocompromised
	Bacillary angiomatosis			• Immunocompromised (e.g. common in HIV)
	Bacillary peliosis hepatis			• Immunocompromised
	Bacteremia (chronic afebrile)		*(Cat exposure not a risk factor in bacteremia)*	• Immunocompetent or immunocompromised
	Endocarditis			• Late complication of chronic bacteremia
B. quintana	Trench fever "Five day fever" "Urban trench fever" "Quintan fever"	Human body louse (*Pediculosis humanus*)	Human	• First reported in troops, now seen with homelessness and poor hygiene ("urban trench fever")
	Bacillary angiomatosis			• Immunocompromised (e.g. common in HIV)
	Bacteremia (chronic afebrile)			• Immunocompetent or immunocompromised
	Endocarditis			• Late complication of chronic bacteremia
*Gray baby syndrome can develop in premature neonates who receive chloramphenicol.				

Table 74.14 Major human diseases caused by *Bartonella* species and their treatment. Fever and splenomegaly due to bacteremia with *Bartonella rochalimae* (a recently recognized species) has also been described.

(Fig. 74.30B). In H&E-stained sections, interstitial clumps of bacilli appear as purplish granular material. Bacteria can be readily identified with a Warthin–Starry stain (see Fig. 74.30B, inset).

Diagnosis and differential diagnosis

PCR-based assays are a rapid and sensitive method to identify *Bartonella* from tissue specimens. Culture of *B. henselae* or *B. quintana* on chocolate or supplemented agar may take 20 to 40 days. Testing to detect antibodies against *B. henselae* (but not *B. quintana*) is sensitive and specific.

The clinical differential diagnosis includes pyogenic granulomas, Kaposi sarcoma, cherry angiomas, angiokeratomas, verruga peruana, and a disseminated non-tuberculous mycobacterial infection. Histologically, bacillary angiomatosis can be confused with verruga peruana, Kaposi sarcoma, pyogenic granuloma, and angiosarcoma.

Treatment

Cutaneous lesions begin to improve within 1 week of appropriate antibiotic therapy and resolve completely within 4 weeks. At least 3 months of treatment is recommended, as therapeutic failures and relapses can occur with shorter courses. Immunosuppressed patients with disease relapses may require maintenance therapy. Surgical excision of solitary cutaneous lesions, although effective, is usually not necessary. Table 74.14 outlines treatment recommendations for bacillary angiomatosis.

OTHER GRAM-NEGATIVE SKIN INFECTIONS

Brucellosis

Synonyms: ■ Undulant fever ■ Malta fever ■ Bang disease

Brucellosis is a chronic granulomatous disease caused by *Brucella*, a genus of Gram-negative coccobacilli. It is the most common zoonosis worldwide, with >500 000 cases annually. Endemic regions include the Middle East, Mediterranean basin, Central Asia, and Indian subcontinent. Transmission occurs through the consumption of contaminated unpasteurized milk products (commonly raw goat's milk and cheese), direct contact with infected animal parts, or inhalation of aerosolized particles. Infection is rare in the US (~100 cases per year) and is primarily an occupational disease of farmers, laboratory personnel, butchers, and veterinarians. Children tend to have a more benign course, with fewer complications and better response to treatment, whereas pregnant women with brucellosis have a substantial risk of miscarriage[109].

Brucellosis demonstrates substantial clinical variability (Fig. 74.31). Acute disease is characterized by fevers, chills, headache, arthralgias, myalgias, back pain, and hepatosplenomegaly. Additional manifestations can include peripheral arthritis, spondylitis, epididymo-orchitis, endocarditis, and depression. Malodorous perspiration is highly characteristic. Skin lesions occur in <10% of patients, most often presenting as a disseminated eruption of violaceous papulonodules. Other cutaneous manifestations of brucellosis include erythema nodosum-like lesions, extensive purpura, and morbilliform eruptions. Endocarditis represents the major cause of death.

Acute brucellosis may mimic mononucleosis, influenza, malaria, typhoid fever, typhus, tularemia, tuberculosis, or sarcoidosis. The chronic form can be confused with rheumatologic, neurologic, or psychosomatic conditions. Multidrug regimens are recommended for brucellosis, with six weeks of doxycycline plus streptomycin, gentamicin, or rifampin representing a first-line treatment regimen; quinolones and TMP-SMX are other possible components of combination therapy. There is some concern regarding the use of rifampin in areas with a high prevalence of tuberculosis, as resistance may develop[110].

Recommended treatment	First-line	Second-line	Notes
• Oroya fever	• Chloramphenicol* plus β-lactam antibiotic • Quinolone (norfloxacin, ciprofloxacin) [>6 years of age, non-pregnant]	• Amoxicillin–clavulanate or ceftriaxone (first-line in children and pregnant women) • Trimethoprim–sulfamethoxazole • Macrolide • Doxycycline	• Successful treatment does not eliminate risk for developing verruga peruana • Adjunctive treatment needed with chloramphenicol, as treatment failures have been seen with monotherapy • Death occurs in ~40% of untreated individuals
• Verruga peruana	• Azithromycin	• Rifampin • Ciprofloxacin • Streptomycin [traditional]	• Only 5% of patients recall an acute febrile illness • Disappearance of skin lesions within 1 month with treatment
• Mild to moderate, uncomplicated	• Supportive care • Needle aspiration of painful suppurative lymph nodes • Azithromycin (antibiotic treatment is optional)	• Clarithromycin • Rifampin	• Azithromycin shown to decrease lymph node volume but not effective in preventing dissemination or complications
• Severe, complicated	• Doxycycline *plus* rifampin	• Azithromycin or trimethoprim–sulfamethoxazole, *plus* rifampin	• Severe disease includes retinitis, encephalopathy, visceral spread
• Mild, uncomplicated bacillary angiomatosis	• Doxycycline • Erythromycin	• Azithromycin • Clarithromycin	• Jarish–Herxheimer-like reaction may occur • Treatment failures seen with quinolones, trimethoprim–sulfamethoxazole, narrow-spectrum cephalosporins • Use of IV antibiotics recommended for GI intolerance or poor absorption states • Doxycycline *plus* rifampin recommended for CNS disease because of better CNS penetration
• Severe, complicated bacillary angiomatosis	• Doxycycline *plus* gentamicin	• Doxycycline *plus* rifampin • Azithromycin *plus* gentamicin	

Glanders

Glanders is principally a disease of horses, mules, and donkeys that is caused by *Burkholderia mallei* (formerly *Pseudomonas mallei*), a non-motile, strictly aerobic, facultative intracellular, Gram-negative bacillus. Human disease occurs chiefly in those with direct contact with infected animals and laboratory personnel. A naturally occurring human case has not been reported in the US since 1934, but infections still occur in East Asia, South America, Eastern Europe, North Africa, and the Middle East. Use of *B. mallei* as a biological weapon has been documented. Tissue damage results from production of exotoxins, including pyocyanin (interferes with electron transfer), lecithinase (causes cell lysis), collagenase, lipase, and hemolysin.

Glanders has four clinical forms – septicemic, localized, pulmonary, and chronic. Acute *septicemic* glanders is characterized by malaise, anorexia, chills, fever, diarrhea, and joint pains. Patients may have flushing, cyanosis, a disseminated pustular eruption, cellulitis, lymphangitis, erythroderma, and/or jaundice. Multi-organ failure ensues, and the mortality rate is ~50% (>90% without treatment).

In the *localized* form, a nodule, pustule, or vesicle surrounded by hemorrhagic edema appears at the inoculation site after approximately 1 to 5 days. The superficial portion of the lesion sloughs, producing an ulcer with a gray–brown base. Glanders may also involve the nose and cause ulceration or perforation of the nasal septum or palate.

Chronic glanders features malaise, myalgias, and often fevers. Painful subcutaneous and intramuscular abscesses may appear at any site and can ulcerate, drain, or extend into joints, periosteum, and bone. Multiple subcutaneous and intramuscular nodules ("farcy buds") appear along the draining lymphatics, and the term "farcy pipes" refers to the firm cords that result from lymphatic involvement.

Glanders should be considered when localized cutaneous abscesses and secondary lesions appear in the path of lymphatic drainage (see Table 77.17). Definitive diagnosis requires isolation of *B. mallei*, but serological, PCR-based, and indirect hemagglutination assays are also available[111]. For localized disease, a 60- to 150-day course of oral amoxicillin/clavulanate, doxycycline, or TMP-SMX can be prescribed; the regimens recommended for melioidosis represent another option (see below). Alternatives include ciprofloxacin, streptomycin, and gentamicin.

Melioidosis

Synonym: ▪ Whitmore disease

Melioidosis is caused by *Burkholderia pseudomallei*, a mobile, obligately aerobic, intracellular, non-spore-forming bacillus found in soil and water. The name melioidosis is derived from the Greek words *melis*, meaning "donkey distemper", and *eidos*, meaning "resembles glanders". Melioidosis is endemic in Southeast Asia and northern Australia, but it also occurs in Africa, the Middle East, and Central and South America. *B. pseudomallei* has been identified in the environment along the Gulf Coast of the US, with two reports of local transmission of melioidosis in Texas; contaminated imported products (e.g. aromatherapy spray from India) have also been implicated in melioidosis outbreaks in the US[112]. Infection develops via direct contact of abraded or lacerated skin with contaminated soil or water as well as through ingestion, inhalation, or sexual intercourse. Cases peak during the rainy season, likely due to aerosolization of bacteria. It is more common in adults with underlying medical conditions, especially diabetes mellitus, alcohol use, chronic lung disease, and chronic kidney disease.

Acute melioidosis can produce localized cutaneous infections, genitourinary infections, pneumonia, or septicemia. *Subacute* melioidosis, primarily a pulmonary disease, is frequently confused with tuberculosis. *Chronic* melioidosis is characterized by abscesses and granulomas in

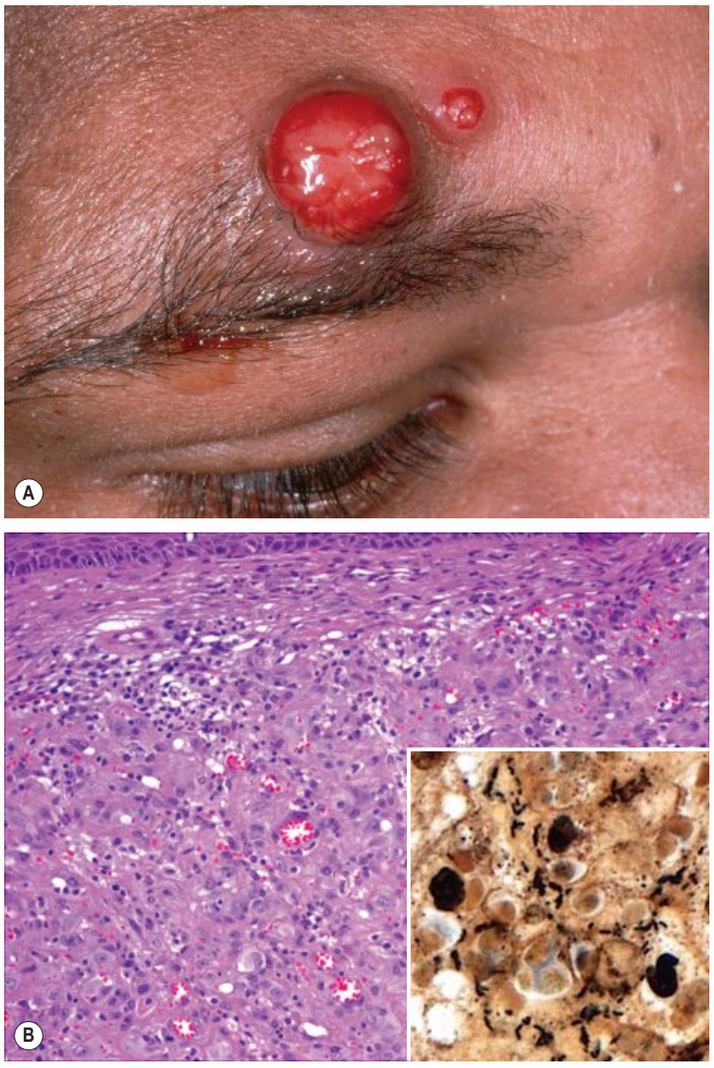


Fig. 74.30 Bacillary angiomatosis. A Bright red nodule and papule on the forehead. **B** Histologically, a dermal proliferation of vessels with plump endothelial cells is evident and scattered neutrophils are present in the accompanying infiltrate. Bacilli (in this case *Bartonella henselae*) are identified with the Warthin–Starry stain (inset). *B, Courtesy James Patterson, MD.*

multiple sites. Cutaneous manifestations may include cellulitis, subcutaneous abscesses, granulomatous lesions, ecthyma gangrenosum, purpura, pustules, Sweet syndrome, and urticaria.

Bacterial culture represents the standard for diagnosis of melioidosis, but the sensitivity is as low as 60%. Multiplex PCR-based assays are more sensitive as well as species-specific[113]. Both complement-fixing and agglutinating antibodies appear within 4 to 6 weeks after infection, but serologic testing alone is inadequate in endemic regions[114].

Treatment of melioidosis is difficult, and susceptibility testing should be performed. Current guidelines recommend an initial intensive phase with intravenous administration of ceftazidime or a carbapenem for at least 10–14 days, followed by an eradication phase with oral TMP-SMX or amoxicillin/clavulanate for ≥3 months. Of note, *B. pseudomallei* has shown resistance to quinolones, macrolides, and aminoglycosides. Melioidosis-associated sepsis has a mortality rate of 50%–90%; however, intensive supportive care lowers this to ~20%. Melioidosis has a relapse rate of ~10%, and *B. pseudomallei* can remain latent in the body for decades.

Because *B. mallei* and *B. pseudomallei* represent potential agents of bioterrorism, attempts are underway to develop vaccines for these infections.

Cutaneous Malacoplakia (Malakoplakia)

Cutaneous malacoplakia, from the Greek *malakos* ("soft") and *plakia* ("plaque"), is a chronic infectious condition that is characterized by granulomatous inflammation with distinctive macrophages that are unable to kill bacteria effectively. It occurs primarily in immunocompromised hosts, including solid organ (especially kidney) transplant recipients, people living with HIV, and children with primary immunodeficiencies[115]. Malacoplakia is most commonly due to *E. coli*, although *Pseudomonas, Proteus, Klebsiella, Staphylococcus, Shigella, Enterococcus, Rhodococcus*, and *Mycobacterium* spp. have also been implicated.

Malacoplakia most often affects the genitourinary tract but rarely involves the skin. Cutaneous lesions usually develop in the perianal region and can present as ulcerations, abscesses with multiple draining sinuses, yellow-to-pink soft papules, and erythematous indurated nodules.

Histologic examination of involved tissue shows highly characteristic findings. *Michaelis–Gutmann bodies* are intracytoplasmic laminated concretions that represent accumulations of calcified, iron-containing phagolysosomes; they stain with PAS, von Kossa, Perls', and Giemsa stains. The presence of such concretions is noted in other conditions by different names (e.g. Schaumann bodies in sarcoidosis) and thus not pathognomonic for malacoplakia. *Von Hansemann cells* are large macrophages that contain Michaelis–Gutmann bodies and stain positively for CD68, lysozyme, and alpha-1 antitrypsin. The histopathologic differential diagnosis may include sarcoidosis, infectious granulomas, Langerhans cell histiocytosis, granular cell tumor, and fibrous histiocytoma.

The treatment of malacoplakia is difficult. Localized disease may be amenable to surgical excision. Prolonged courses of antibiotics such as quinolones, TMP-SMX, penicillins, and clofazimine may be of benefit. Ascorbic acid and bethanechol chloride can be employed to improve macrophage function. In severe cases, reducing the dosage of immunosuppressive therapy (if possible) may be of benefit. Lesions may spontaneously regress after ~6 months but can also be recalcitrant to therapy[116].

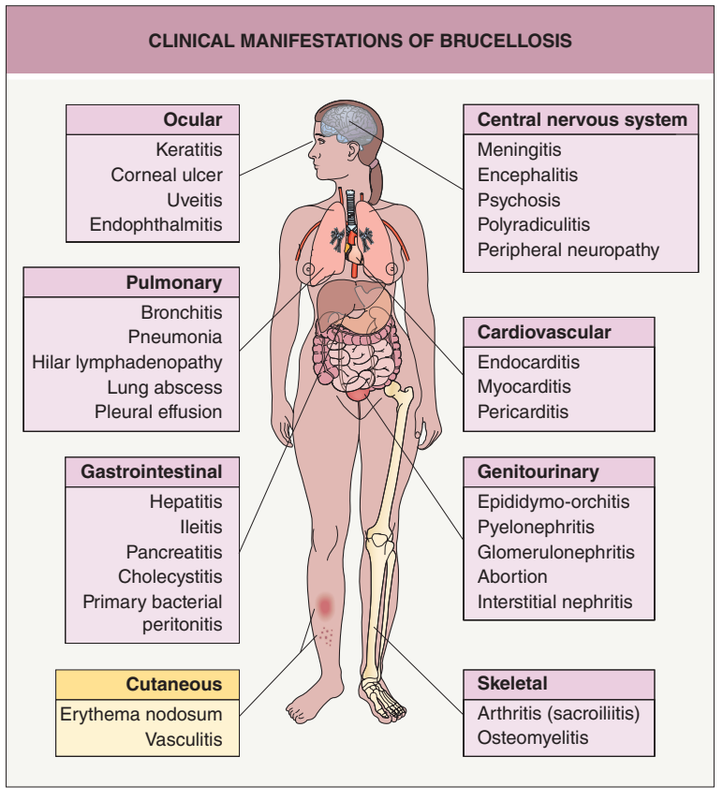


Fig. 74.31 Clinical manifestations of brucellosis. *With permission from Slack MPE. Gram-negative coccobacilli. In: Armstrong D, Powderly WG (eds). Infectious Diseases. Edinburgh: Mosby, 2004.*

Tularemia

Synonyms: ■ Deer fly fever ■ Rabbit fever ■ Pahvant Valley plague

Tularemia is a bacterial infection caused by *Francisella tularensis*, a Gram-negative, non-motile coccobacillus. First described in 1911 as a plague-like illness, there were ~2100 cases reported in the US from 2011 to 2020. Transmission to humans may occur via direct contact with mucous membranes or eroded skin, ingestion of contaminated food or water, inhalation of infectious particles, or bites from ticks or deer flies. Rodents and rabbits are the main reservoirs of disease, which may also affect domestic cats and sheep[117].

Tularemia occurs in six clinical forms according to the mode of transmission – ulceroglandular, glandular, oculoglandular, oropharyngeal/gastrointestinal, typhoidal/septicemic, and pneumonic (Fig. 74.32). Ulceroglandular tularemia is the most common form and is characterized by lymphadenopathy and an erythematous, indurated, punched-out ulcer at the site of cutaneous exposure that may last for weeks. Regional lymph nodes can become fluctuant and suppurate. Occasionally, ulceration or lymphadenopathy occurs in isolation. Other rare cutaneous manifestations include buboes, a morbilliform or vesicular eruption, erythema nodosum, and erythema multiforme.

Because of concern regarding the potential use of *F. tularensis* as a biologic weapon, tularemia is a reportable disease in the US. Diagnostic methods include direct fluorescent antibody testing (available in designated reference laboratories), immunohistochemical staining of tissue samples, and PCR-based assays. Attempts to culture *F. tularensis* are usually not made due to its high infectivity, risk to laboratory workers, and inability to grow on most media. The differential diagnosis of ulceroglandular tularemia includes other ulceroglandular entities (e.g. bubonic plague, tuberculous chancre, rat-bite fever, glanders), anthrax, soft tissue infections (i.e. *Staphylococcus*, *Streptococcus*, *Pasteurella multocida*), and infectious causes of a sporotrichoid pattern (see Ch. 77).

Treatment recommendations include a 10-day course of streptomycin (the classic first-line agent), gentamicin, or ciprofloxacin; a 14- to 21-day course of doxycycline is another option that results in a higher risk of relapse. A Jarisch–Herxheimer-like reaction may occur following the initiation of therapy. There are ongoing efforts to develop a safe and effective vaccine.

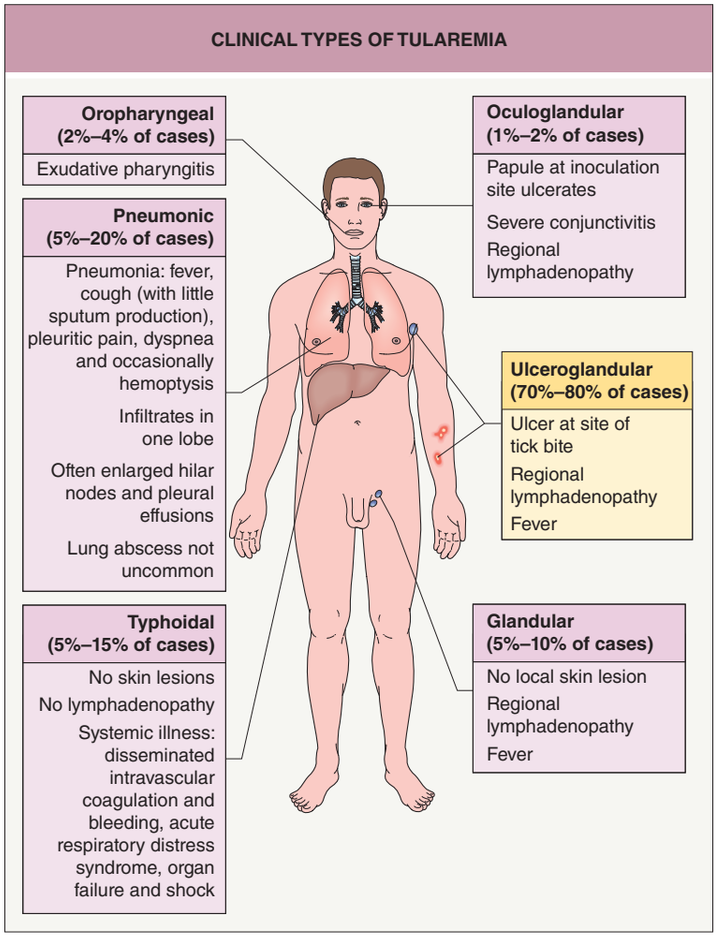


Fig. 74.32 Clinical types of tularemia. *Adapted with permission from Slack MPE. Gram-negative coccobacilli. In: Armstrong D, Powderly WG (eds). Infectious Diseases. Edinburgh: Mosby, 2004.*

Haemophilus influenzae Cellulitis

Haemophilus influenzae is a Gram-negative coccobacillus that can cause facial cellulitis with a violaceous hue in infants and young children (usually 6–24 months of age) following an upper respiratory tract infection. It favors the buccal and periorbital areas and is often associated with high fevers, an increased leukocyte count with a left shift, and positive blood cultures. If diagnosis is delayed, systemic spread may lead to meningitis. Routine vaccination of children against *H. influenzae* type b has greatly reduced the incidence of this form of cellulitis[51]. However, *H. influenzae* type f and non-typeable (unencapsulated) strains have been reported to cause cellulitis of the extremities in patients immunized to *H. influenzae* type b. First-line therapy for severe *H. influenzae* infections is a third-generation cephalosporin; selection of empiric antibiotic therapy for cellulitis is discussed above.

Rhinoscleroma

Rhinoscleroma is a slowly progressive, chronic granulomatous infection involving the nose and upper respiratory tract. It is caused by *Klebsiella rhinoscleromatis*, a short, immotile Gram-negative coccobacillus that is a subspecies of *Klebsiella pneumoniae*. Endemic foci exist in Central Europe, Egypt, India, Indonesia, Mexico, Central America, and tropical Africa. Rhinoscleroma is acquired via inhalation of contaminated droplets. Ineffective macrophage killing of *K. rhinoscleromatis* results in large, vacuolated, non-lipidized histiocytes with intracellular bacteria (Mikulicz cells)[118]. Clinical features, diagnostic techniques, the differential diagnosis, and treatment recommendations are outlined in Table 74.15. Recurrence after treatment is common. Histologic findings mimicking Rosai–Dorfman disease have been observed in cutaneous lesions and lymph nodes of patients with rhinoscleroma[119].

Salmonellosis

Salmonellosis refers to the spectrum of infections caused by Gram-negative aerobic bacilli in the genus *Salmonella*. Resultant forms of enteric fever include typhoid fever due to *S. typhi* and paratyphoid fever due to *S. paratyphi*. *S. typhi* is spread via direct contact with persons who have typhoid fever or are chronic carriers. In contrast, paratyphoid fever is most commonly acquired from inadequately cooked poultry or eggs as well as other contaminated food products or water, resulting in gastroenteritis.

Typhoid fever is characterized by fever, headache, malaise, myalgias, cough, sore throat, nausea, vomiting, and diarrhea or constipation. The characteristic cutaneous sign, "rose spots", are pink, blanching, slightly elevated papules that measure 2–8 mm and are usually found on the anterior trunk in groups of 5–15 lesions. They occur in up to 30% of patients with typhoid fever and less often in non-typhoidal enteric fever. Rose spots often occur in crops during the second to fourth weeks of the illness, and *Salmonella* spp. can usually be cultured from these lesions. Other cutaneous manifestations of salmonellosis include erythema multiforme, Sweet syndrome, hemorrhagic bullae, pustular dermatitis, and a generalized erythematous eruption known as erythema typhosum. Hemophagocytic lymphohistiocytosis represents a rare complication of salmonellosis[120].

A history of travel to endemic areas (e.g. Southeast Asia, Africa), persistence of fevers, and positive cultures aid in distinguishing typhoid fever from influenza and other viral infections. Culture of *Salmonella* spp. from the bone marrow is the most sensitive diagnostic procedure but is rarely used in clinical practice. Blood cultures are less sensitive and PCR-based detection is limited by the low concentrations of microbial DNA in clinical samples. Since the late 1980s, *S. typhi* has developed resistance to the drugs that were previously used as first-line treatments (e.g. chloramphenicol, TMP-SMX, and ampicillin). Current treatment options include azithromycin, carbapenems, and (depending on resistance patterns) quinolones and third-generation cephalosporins[121]. Typhoid conjugate vaccines are available and are recommended for travelers to endemic areas.

RHINOSCLEROMA – CLINICAL FEATURES, DIFFERENTIAL DIAGNOSIS, AND TREATMENT	
Risk factors	• Poor hygiene, poor nutrition, and living in overcrowded conditions
Stage one: rhinitic/catarrhal; lasts weeks-months	• Nonspecific rhinitis • Purulent rhinorrhea and crusting • Nasal obstruction
Stage two: granulomatous/ infiltrative; lasts months–years	• Granulomatous nodules form in the nose, pharynx, and larynx • Dysphonia, anosmia, and anesthesia of soft palate may occur • Epistaxis, deformity of the nose, destruction of the nasal cartilage (Hebra nose) • Mikulicz cells readily identified on histopathology
Stage three: sclerotic/cicatricial	• Nodules replaced by fibrous tissues with resultant extensive scarring and stenosis often requiring surgical intervention (e.g. tracheotomy, reconstruction of the airway)

Diagnosis	• Presence of Mikulicz cells and Russell bodies on routine histology
	  • *Mikulicz cells*: large, vacuolated, non-lipidized histiocytes with intracellular bacteria
	  • *Russell bodies*: plasma cells with aggregates of condensed immunoglobulins
	• PAS, Giemsa, silver, and Gram stains are reliable
	• Immunoperoxidase studies are sensitive and specific
	• Cultures are positive in only ~50% of cases
	• "Crypt-like" irregularities of the trachea can be seen on computed tomography

Differential diagnosis (see Table 45.3)	• Mucocutaneous (New World) leishmaniasis, paracoccidioidomycosis (and other dimorphic fungal infections), rhinosporidiosis, leprosy, yaws, tertiary syphilis, nasal tuberculosis, sarcoidosis, granulomatosis with polyangiitis, nasal T cell/natural killer cell lymphoma, basal cell and squamous cell carcinoma, extranodal Rosai–Dorfman disease
Treatment	• Antimicrobial therapy for 6 months or until nasal biopsy is negative; tetracycline is first-line therapy along with surgical correction of obstructed airway • Rifampin and ciprofloxacin are alternative antibiotics • Sclerotic lesions respond to ciprofloxacin • Bacterial superinfection is common, requiring treatment with clindamycin or a third-generation cephalosporin

Table 74.15 Rhinoscleroma – clinical features, differential diagnosis, and treatment.

Rat-Bite Fever

Synonyms: ■ Haverhill fever ■ Sodoku ■ Erythema arthriticum epidemicum

Rat-bite fever is most often due to infection with *Streptobacillus moniliformis* in North America and *Spirillum minus* in Asia, where it is known as sodoku. Infection results in an acute illness characterized by fever, arthritis, and a rash. While the disorder is usually caused by a bite (rat-bite fever), it can also occur from close contact with rodents or ingestion of contaminated food, water, or raw milk (Haverhill fever).

The incidence of rat-bite fever is highest in urban areas with poor sanitation resulting in a large rat population, but it can also occur from exposure to pet rats or laboratory rats. Approximately half of cases are in children. Erythema, edema, abscess formation, ulceration, and secondary infection may develop at the site of the bite. Regional lymphadenopathy is common. Paroxysms of fever interspersed with afebrile periods as well as headaches, nausea, vomiting, and myalgias may occur. In infants and children, weight loss and diarrhea can be significant. One of the hallmarks of the disease is a migratory polyarthritis that occurs in 50% of patients and may mimic rheumatoid arthritis. At 2 to 4 days following the onset of fever and arthritis, most patients with rat-bite fever develop an acrally distributed eruption involving the palms and soles. Erythematous macules and papules, petechiae, vesicles, pustules, and crusts may be seen.

Rat-bite fever can be diagnosed by culturing *Streptobacillus moniliformis* from blood, synovial fluid, or abscess aspirates, which requires an environment free of sodium polyanethol sulfonate[122]; *Spirillum minus* does not grow in culture. PCR-based assays may also be utilized. The triad of fever, arthritis/arthralgias, and a rash can be caused by a variety of infectious diseases, including viral infections (e.g. enteroviruses, EBV, parvovirus B19), Rocky Mountain spotted fever, acute or chronic meningococcemia, acute rheumatic fever, and secondary syphilis. Non-infectious causes include Still disease, systemic lupus erythematosus, serum sickness-like drug reactions, and Sweet, Schnitzler, and periodic fever syndromes.

Penicillin is the drug of choice for rat-bite fever and is usually administered for a week, although patients with septicemia may require up to 6 weeks of parenteral therapy. Ceftriaxone, tetracyclines, and streptomycin represent additional options; erythromycin and clindamycin have also been used, but studies of their efficacy are lacking. Although most infections resolve spontaneously within 2 weeks, 10%–15% of untreated cases are fatal.

Plague

Plague is caused by *Yersinia pestis*, a Gram-negative, rounded, bipolar bacillus transmitted predominantly by fleas (Fig. 74.33). Peru, Democratic Republic of the Congo, and Madagascar are currently the most plague-endemic countries. There are typically <10 cases reported yearly in the US, with most occurring in two regions: (1) northern New Mexico, northern Arizona and southern Colorado; and (2) California, southern Oregon and far western Nevada.

Three clinical forms of plague are recognized – bubonic, septicemic, and pneumonic. The symptoms of *bubonic* plague are variable. Constitutional symptoms range from absent to severe. In approximately 10% of patients, the inoculation wound develops into a pustule or ulcer. This is followed by painful regional lymphadenopathy (bubo); suppuration and discharge from the lymph nodes may occur. In *septicemic* plague, vesicles, carbuncles, petechiae, and purpura may be seen. Necrotic lesions and hemorrhage from the nasopharynx or gastrointestinal tract have also been described. In *pneumonic* plague, the patient develops acute pneumonitis. Apathy, delirium, coma, and seizures occur in seriously ill patients. Bubonic plague may simulate tularemia, rat-bite fever, sporotrichosis, tuberculosis, streptococcal ecthyma, syphilis, or lymphogranuloma venereum. Septicemic plague must be differentiated from typhus, typhoid fever, tularemia, malaria, and other bacteremias. *Y. pestis* produces a virulence factor that reduces pyrin activity, explaining why individuals with familial Mediterranean fever (*MEFV*) gene variants that result in increased pyrin activity demonstrate resistance to plague[123].

Untreated bubonic plague has a 40%–60% fatality rate, while untreated septicemic or pneumonic plague is nearly always fatal. Streptomycin and other aminoglycosides (e.g. gentamicin) are first-line treatments for plague. Doxycycline and quinolones may be used when oral therapy is acceptable. Chloramphenicol (which attains high concentrations in the cerebrospinal fluid) is the drug of choice for plague meningitis or endophthalmitis. Postexposure prophylaxis with doxycycline or ciprofloxacin, if taken within 6 days, is effective in preventing disease. Live vaccines are utilized for prevention of plague in some parts of the world, but they have poor safety profiles. There are ongoing efforts to develop a safe and effective *Y. pestis* vaccine.

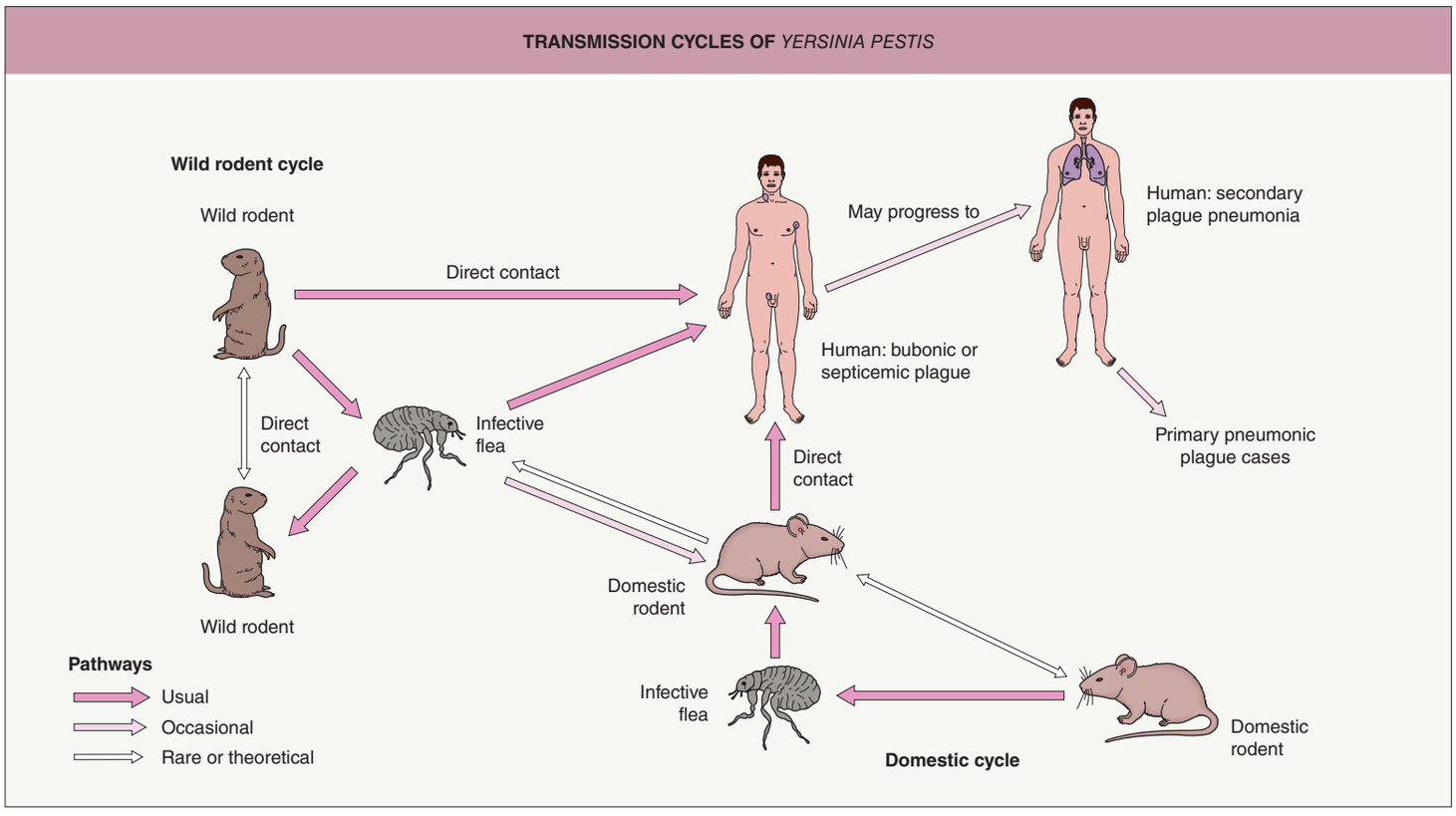


Fig. 74.33 Transmission cycles of *Yersinia pestis*. *With permission from Dennis DT, Gage KL. Plague. In: Armstrong D, Powderly WG (eds). Infectious Diseases. Edinburgh: Mosby, 2004.*

RISK FACTORS FOR *VIBRIO VULNIFICUS* INFECTION
Acquisition of infection
Cutaneous exposure to contaminated seawater and/or shellfish
• Exposure to warm coastal salt water • Handling shellfish • New injury to the skin or a pre-existing wound predisposes to a primary cutaneous infection, which can lead to cellulitis, necrotizing fasciitis, and/or septicemia in susceptible hosts (see below)
Consumption of contaminated raw/undercooked seafood
• Raw oysters, clams, crabs, and other shellfish • Leads to an acute gastrointestinal illness in immunocompetent individuals and septicemia in susceptible hosts (see below)
Underlying medical conditions that predispose to severe infections
Liver disease

• Hemochromatosis or iron overload in the setting of thalassemia
  • *V. vulnificus* is ferrophilic and requires higher levels of iron than other pathogens
  • Patients have decreased hepcidin antibacterial activity
• Alcoholic cirrhosis or chronic hepatitis

Diabetes mellitus
• Peripheral neuropathy predisposes to cutaneous wounds that serve as a portal of entry
Gastrointestinal disease
• Peptic ulcer disease   • Antacid use may lead to increased survival of *V. vulnificus* • Gastrointestinal surgery
Immunosuppression
• HIV infection • Leukemia or lymphoma • Treatment with corticosteroids, chemotherapy, and other immunosuppressive agents
Chronic kidney disease

Table 74.16 Risk factors for *Vibrio vulnificus* infection. Infections are most common in men >40 years of age.

Vibrio vulnificus Infection

The genus *Vibrio* constitutes a group of Gram-negative anaerobic bacteria, among which *V. vulnificus* is the most common cause of cutaneous disease. *V. vulnificus* infections occur most commonly in men over 40 years of age who have chronic liver disease, diabetes mellitus, or immunosuppression plus a history of exposure to warm seawater or raw/undercooked seafood. "*Vibrio* season" traditionally lasts from May to October in the US, but climate change has elongated this to the later fall and expanded the bacterium's geographic range[124]. Additional risk factors are listed in Table 74.16.

The clinical presentation of *V. vulnificus* septicemia includes fever, chills, nausea, vomiting, diarrhea, abdominal cramps, and hypotension. Skin lesions develop in 75% of these patients, with progression from erythematous and purpuric macules to vesicles and hemorrhagic bullae (Fig. 74.34) and then to necrotic ulcers in a manner reminiscent of purpura fulminans. Wounds acquired in or contaminated by seawater can also lead to *Vibrio* cellulitis that is erythematous, edematous, and painful, typically with rapid evolution to hemorrhagic bullae. Progression to necrotizing fasciitis or myositis occasionally occurs. First-line treatment is doxycycline (oral or intravenous) plus a third-generation cephalosporin (intravenous or intramuscular). Necrotic lesions may require surgical debridement[125].

EHRLICHIOSIS AND ANAPLASMOSIS

These infections are discussed in Chapter 76.

SPIROCHETES

BORRELIA BURGDORFERI

Lyme Disease

Synonym: ■ Lyme borreliosis

Lyme disease is a multisystem disorder with prominent skin findings that is caused by *Borrelia* species of spirochetes. Although found



Fig. 74.34 Hemorrhagic bullae of the leg secondary to *Vibrio vulnificus* infection.

worldwide, it has a particularly high incidence in North America and Europe, representing the most common tick-borne disease in the US. Lyme disease can occur year-round, but most cases present in the summer. If diagnosed in its early stages, it is a completely curable illness.

The species of *Ixodes* tick vector differs depending on the geographic region, e.g. *I. pacificus* in the western US, *I. scapularis* (also called *I. dammini*) in the eastern US and Great Lakes region, *I. ricinus* in Europe, and *I. persulcatus* in Asia. *B. burgdorferi* is the predominant etiologic organism in the US, whereas *B. garinii* and *B. afzelii* are the predominant causes of Lyme disease in Europe[126]. This may explain the occurrence of borrelial lymphocytoma and acrodermatitis chronica atrophicans in Europe, but not the US. Once the spirochete is in the midgut of the tick vector after feeding on an infected host (e.g. white-tailed deer), it produces outer surface protein C, which enables it to traverse the midgut epithelium, enter the hemocoel, and make its way to the salivary glands. *B. burgdorferi* is ultimately transmitted to humans via the tick's saliva. The rate of transmission is extremely low during the first 48 hours of tick attachment[127].

Chapter 19 describes the clinical features and treatment of Lyme disease, in particular erythema migrans (see Fig. 74.15), and Table 74.17 outlines the extracutaneous manifestations of Lyme disease. The next sections discuss borrelial lymphocytoma and acrodermatitis chronica atrophicans.

Borrelial Lymphocytoma

Synonyms: ■ Lymphadenosis benigna cutis ■ Lymphocytoma cutis ■ Cutaneous lymphoid hyperplasia ■ Spiegler–Fendt lymphoid hyperplasia, pseudolymphoma of Spiegler and Fendt, sarcoidosis of Spiegler and Fendt

Lymphocytoma is a benign, reactive form of lymphoid hyperplasia that can be attributed to various stimuli, including *Borrelia* infection. Borrelial lymphocytoma usually appears during the early disseminated stage of Lyme disease (see Ch. 19). Because it is caused by *B. afzelii* and *B. garinii*, neither of which is found in North America, borrelial lymphocytoma is virtually never seen in those who have not traveled outside of the US. However, it occurs in approximately 1% of patients with Lyme disease in Europe, with a predilection for children.

The formation of a lymphocytoma following a tick bite was first reported in 1950, but it was not until 1986 that *Borrelia* was cultured from such a lesion. A firm, bluish-red, occasionally tender nodule or plaque appears most commonly on the earlobes in children and the nipple/areola in adults, less often developing on the genitalia, trunk, or extremities. It may be associated with regional lymphadenopathy or concomitant erythema migrans.

MAJOR EXTRACUTANEOUS FEATURES OF LYME DISEASE	
General	Fever, malaise, headache, regional lymphadenopathy, non-productive cough
Eyes	Conjunctivitis, keratitis, iritis, episcleritis, retrobulbar neuritis
Neurologic	Meningitis, encephalitis, Guillain–Barré syndrome, Bell's palsy, psychiatric syndromes, optic atrophy, ataxia
Cardiac	Heart block, arrhythmias, pericarditis, myocarditis, cardiomyopathy, congestive heart failure
Rheumatologic	Arthralgias, tendinitis, oligoarthritis, bone calcifications and cysts
Genitourinary	Orchitis, softening of the testes, proteinuria, microhematuria

Table 74.17 Major extracutaneous features of Lyme disease.

Histologically, the epidermis is normal and separated from the dermal infiltrate by a Grenz zone. The dense dermal infiltrate of lymphocytes forms a pattern that closely resembles the architecture of a lymphoid follicle. The histologic differential diagnosis includes an arthropod bite reaction and cutaneous lymphoma, with the presence of Bcl-2 protein within follicular cells and monoclonality by PCR favoring the latter (see Ch. 119). Of note, *B. burgdorferi*-associated B cell lymphomas have rarely been described[128]. Borrelial lymphocytoma responds to the antibiotics used for Lyme disease (see Ch. 19).

Acrodermatitis Chronica Atrophicans

Synonym: ■ Herxheimer disease

Acrodermatitis chronica atrophicans (ACA) is a cutaneous manifestation of chronic Lyme disease. First described in Europe in 1883 by Buchwald as "idiopathic atrophy", it is most commonly due to an infection with *B. afzelii*, although it has also been associated with *B. burgdorferi* and *B. garinii*. As a result, it is extremely rare in the Americas but is seen in up to 10% of patients with Lyme disease in Europe.

ACA occurs months to years after the initial infection, predominantly in women 40–70 years of age, and appears to be associated with persistence of *Borrelia* organisms in the skin. It is a biphasic disorder consisting of an early, easily treatable, inflammatory stage and a late, treatment-resistant, atrophic stage. Initially, erythematous to violaceous plaques and nodules develop on the acral portion of the extremities, often insidiously. The skin is frequently doughy and swollen. This early stage follows a waxing and waning course for weeks to years. In the late stage, the skin has a glistening ("cigarette-paper") appearance with prominent blood vessels (Fig. 74.35). Fibrous nodules may form on extensor surfaces (ulnar or tibial bands). Hypopigmentation, hyperpigmentation, pain, pruritus, hyperesthesia, paresthesias, and scaling may also be present. Rarely, the condition may be complicated by the development of basal cell or squamous cell carcinoma.

In biopsy specimens of early lesions, a dermal perivascular lymphocytic infiltrate with plasma cells, telangiectatic endothelial-lined spaces, and mild epidermal atrophy are seen. Histologic examination of late lesions shows an atrophic epidermis and an interstitial lymphocytic infiltrate with plasma cells and occasional histiocytes and mast cells. The dermis may be attenuated, with periadnexal fibrosis. *Borrelia* DNA may be detected by PCR in skin biopsy specimens. The differential diagnosis may include eczematous dermatitis (e.g. due to stasis), cold injury, atrophy secondary to chronic use of potent topical corticosteroids, severe photodamage, and, in the case of fibrotic lesions, scars, morphea, and fibromatoses[129].

NON-VENEREAL (ENDEMIC) TREPONEMATOSES

Yaws, pinta, and bejel (endemic syphilis) are caused by organisms that are morphologically and antigenically identical to the causative organism of venereal syphilis, *Treponema pallidum* (see Ch. 82). All three diseases have chronic relapsing courses with major dermatologic



Fig. 74.35 Acrodermatitis chronica atrophicans. The acral skin is atrophic, shiny, and wrinkled, with prominent superficial veins.



Fig. 74.36 Cutaneous yaws on the knee of an adolescent from Indonesia. *Courtesy Peter Ehrnstrom, MD.*

manifestations. The primary route of transmission is person-to-person via skin, mucous membrane, or possibly fomite contact. With the exception of pinta, children are most often affected.

The diagnosis of yaws, pinta, and bejel is based primarily upon clinical features. The same serologic assays used for venereal syphilis can be used to diagnose the endemic treponematoses, but a positive test does not differentiate among the four diseases. Treponemal tests (e.g. TPHA, FTA-ABS, MHA-TP) are specific for treponemal infections (see Ch. 82) and may remain positive for life, regardless of treatment. The non-treponemal tests (e.g. VDRL, RPR) may indicate a current or recent infection, or a biologic false-positive result (in 1%–3% of the population). The vast majority of false-positive sera have antibody titers of <1 : 4. The quantitative non-treponemal tests are particularly useful in the evaluation of patients following therapy; a fourfold decrease in antibody titers indicates successful treatment, while a fourfold rise indicates reinfection or relapse. Diagnosis can also be made through darkfield examination of exudates from lesions.

For over 50 years the primary treatment for patients with endemic treponematoses was benzathine penicillin, given as a single intramuscular dose of 1.2 million units in individuals ≥10 years of age and 0.6 million units in children <10 years of age. A single high dose of oral azithromycin (30 mg/kg, maximum 2 g) was shown to be non-inferior to benzathine penicillin for the treatment of active and latent yaws. Due to the ease of administration and safe use in patients with penicillin allergy, azithromycin is now recommended as the first-line treatment for yaws by the WHO, with goals of mass treatment and disease eradication (see below)[130,131]. To date, no formal trials have studied azithromycin efficacy for pinta and bejel.

Yaws

Synonyms: ■ Pian (French) ■ Frambösie (German) ■ Buba (Spanish) ■ Parangi (Malay)

Yaws is a three-stage infection caused by *T. pallidum* subspecies *pertenue* and represents the most common and severe endemic treponematosis. It occurs in tropical climates, most often in the Pacific islands, Southeast Asia, and Africa. Yaws most commonly involves the lower extremities of children <15 years of age (Fig. 74.36). A "mother yaw", the main lesion of the *primary* stage, occurs at the site of inoculation within 10 days to 3 months. It begins as an erythematous, infiltrated, painless papule that over time enlarges peripherally to become 1–5 cm in diameter, then ulcerates and develops an amber-yellow crust. The lesion is rich in treponemes and eventually heals spontaneously over 3 to 6 months.

"Daughter yaws", the lesions of *secondary* yaws, are smaller and more widespread than the primary lesion. They usually occur adjacent to body orifices, such as the nose and mouth, and can expand or ulcerate. Both types of lesions are highly infectious. Patients may then enter a latent phase with reactive serology but absent clinical findings. Only 10% of patients progress to the final stage, during which abscesses form, become necrotic, and ulcerate. The ulcers may coalesce into serpiginous tracts, which heal with significant scarring and produce crippling deformities. Yaws can also cause periostitis, dactylitis, and osteitis, with the latter potentially leading to curvature of the tibia ("saber shins").

Histologic examination of early yaws lesions demonstrates spongiosis, acanthosis, and papillomatosis. A moderate to dense dermal inflammatory infiltrate composed mostly of plasma cells and lymphocytes can be seen. Silver stains easily identify treponemes in specimens. Clinically, the skin lesions of yaws can resemble venereal syphilis, chancroid, eczema, psoriasis, verrucae, calluses, scabies, tungiasis, sarcoidosis, and vitamin deficiencies[132].

Renewed eradication efforts against yaws began in 2012, and in 2016 India was the first country to be declared free of yaws by the WHO. However, the emergence of azithromycin-resistant yaws in Papua New Guinea threatens eradication efforts[133].

Pinta

Pinta affects the skin exclusively and is caused by an infection with *T. carateum*. The disease is found only in the western hemisphere (Central and South America) in semiarid, warm climates. All ages are equally affected. The *primary* lesions occur 7 days to 2 months after inoculation, most often on the lower extremities. They begin as tiny macules or papules surrounded by an erythematous halo. Over a period of months, they develop into poorly defined, erythematous, infiltrated plaques that measure 10–12 cm in diameter. *Secondary* lesions ("pintids") start as small, scaly papules, subsequently enlarging and coalescing into psoriasiform plaques. They are initially red but later become slate-blue, brown, gray, and black. The primary and secondary lesions are highly infectious. *Tertiary* pinta is characterized by symmetric depigmented, vitiligo-like lesions, which may be atrophic or hyperkeratotic and are not considered to be infectious.

Biopsy specimens of primary and secondary lesions reveal moderate acanthosis, slight spongiosis, and a superficial dermal inflammatory infiltrate consisting of lymphocytes, plasma cells, and neutrophils around dilated blood vessels. Some lesions show lichenoid changes, with hyperkeratosis, hypergranulosis, and vacuolar degeneration of the basal layer. The depigmented lesions of late pinta have epidermal atrophy and a complete absence of melanin. Except for longstanding, late depigmented lesions, treponemes can be visualized in biopsy specimens with silver stains. Early pinta is difficult to differentiate from venereal syphilis, yaws, and bejel. The early lesions can also be confused with eczema, psoriasis, leprosy, lichen planus, lupus erythematosus, and tinea corporis. The lesions of late pinta are frequently mistaken for vitiligo[132].

Bejel

Synonym: ■ Endemic syphilis

Bejel is caused by an infection with *T. pallidum* subspecies *endemicum*. Most cases are seen in the arid, warm climates of North and West Africa and the Arabian Peninsula. Children <15 years of age are most

commonly affected. Bejel is usually acquired via skin-to-skin or oral contact but can be transmitted sexually. In contrast to yaws and pinta, a *primary* lesion is rarely noticed. It usually consists of an inconspicuous small papule or ulcer in the oropharynx or on the nipples of breastfeeding women. *Secondary* bejel may present with findings similar to venereal syphilis, such as patches on mucous membranes, split papules, angular stomatitis, non-pruritic papular skin eruptions, and generalized lymphadenopathy. Condylomata lata are also frequently present. During the secondary stage, some patients experience osteoperiostitis of the long bones, which can cause nocturnal leg pain.

Six months to several years after inoculation, some patients develop the *tertiary* stage of bejel. Gumma formation may lead to gross mutilation of the skin, mucous membranes, muscle, cartilage, and bone. Without treatment, disfiguring lesions of the palate and nasal septum may occur, leading to difficulty in articulation and swallowing. The eyes and bones can also be severely affected in late-stage bejel.

The histologic picture closely resembles that of venereal syphilis. In the early stages, biopsy specimens demonstrate a perivascular dermal infiltrate of mostly plasma cells and lymphocytes. Oral lesions may resemble venereal syphilis, aphthosis, perlèche, vitamin deficiencies, and primary herpes simplex viral infection. The mutilating nasopharyngeal lesions of bejel can be mistaken for tertiary venereal syphilis, leprosy, rhinoscleroma, mucocutaneous leishmaniasis, paracoccidioidomycosis, and tuberculosis (see Tables 45.3 & 74.15)[132].

LEPTOSPIROSIS

Synonyms: ■ Fort Bragg fever ■ Pretibial fever ■ Weil's disease

Leptospirosis is a worldwide zoonosis caused by spirochetes in the genus *Leptospira*. It is transmitted via contact of non-intact skin or mucous membranes with urine or other body fluids (with the exception of saliva) from infected mammals, either directly or from drinking or swimming in contaminated water. Veterinarians, farmers, slaughterhouse or sewer workers, and recreational water sport participants are most often affected. Leptospirosis occurs in an anicteric form (~90% of cases) and a more severe icteric form (~10% of cases). After an incubation period of 7–12 days, an initial "septicemic" stage of fevers, chills, and myalgias lasting 3–7 days is followed by an "immune" stage (during which serologic tests are positive) that can result in meningitis, uveitis, and renal, hepatic, and/or pulmonary dysfunction. Cutaneous manifestations include erythematous macules, papules, patches, and/or plaques in a widespread distribution or (especially with *L. interrogans* serovar Autumnalis) localized to the shins, as well as petechiae and purpura secondary to vascular involvement. Although most cases are self-limited, antibiotics may decrease the duration of illness and reduce shedding of organisms in the urine. Oral doxycycline, amoxicillin, or azithromycin and (for more severe disease) intravenous penicillin or third-generation cephalosporins have been used[134].

BACTERIA PREVIOUSLY CLASSIFIED AS FUNGI

ACTINOMYCOSIS

Introduction

Actinomycosis is a subacute or chronic bacterial infection characterized by suppurating abscesses, granulomatous inflammation, and sinus formation. *Actinomyces israelii*, an anaerobic or microaerophilic Gram-positive, non-acid-fast actinomycete, is the most common causative organism. Cervicofacial (accounting for two-thirds of infections), pulmonary/thoracic, gastrointestinal, and pelvic forms exist.

Epidemiology and pathogenesis

Actinomycosis is seen worldwide, and men are affected more often than women. Humans are the only known reservoir for *Actinomyces* spp. *A. israelii* is part of the normal flora of the oral cavity and is also found in the gastrointestinal and female genital tracts. *Actinomyces* spp. are not considered particularly pathogenic, and their virulence is enhanced by co-infection with other organisms. In actinomycotic mycetoma, species of *Actinomyces* other than *A. israelii* are usually responsible for the formation of sulfur granules (see Ch. 77).



Fig. 74.37 Cervicofacial actinomycosis or "lumpy jaw". Soft tissue swelling and draining erythematous nodules are seen. The discharge contained sulfur granules. *Courtesy Joyce Rico, MD.*

Clinical features

In patients with *cervicofacial* actinomycosis ("lumpy jaw"), there is usually a history of poor dental hygiene, dental disease, or a previous orofacial injury or dental procedure. Additional risk factors include chronic tonsillitis and radiation therapy. An initial bluish swelling in the mandibular area progresses to brawny erythematous nodules, which become indurated (Fig. 74.37). Further progression leads to development of sinus tracts which drain purulent material with characteristic yellow "sulfur granules" that represent clumps of bacteria. Fever, pain, and leukocytosis may develop. Lymphadenopathy is usually absent. Once actinomycosis may spread via direct extension or hematogenous dissemination. Destruction of surrounding bony structures can result in facial deformity, and central nervous system involvement may lead to brain abscesses[135].

Pulmonary actinomycosis (15%–20% of patients) occurs after bacteria gain access to the lung through the aspiration of infected oral material. Pulmonary cavities are usually seen at the bases of the lungs. Extension to the pleura and chest wall may occur, and pleurocutaneous fistulas can develop. *Gastrointestinal* actinomycosis is usually preceded by trauma or inflammatory disease but may occur spontaneously. Granulomatous lesions involving the bowel can eventually extend to the abdominal wall, producing an erythematous mass with draining sinus tracts. *Pelvic* actinomycosis in women is often associated with intrauterine contraceptive devices. Actinomycosis may also involve the musculoskeletal system, gastrointestinal tract, and heart.

Pathology

An intense neutrophilic infiltrate is followed by the development of granulomatous inflammation with giant cells. Histiocytes, plasma cells, and epithelioid cells can be seen at the periphery of the abscess, while granules representing microcolonies of *Actinomyces* are seen centrally. Histologically these "sulfur granules" have a basophilic center and acidophilic periphery; they measure up to 30 microns in diameter.

Diagnosis and differential diagnosis

Microscopic examination of purulent material should be performed to detect the sulfur granules that are characteristic of actinomycosis (or actinomycotic mycetoma). They are composed of Gram-positive, branching filaments that fragment into diphtheroid forms and coccobacilli; acid-fast staining is negative. *Actinomyces* grows slowly, so cultures should be held for ≥2 weeks. Cervicofacial actinomycosis may resemble symbiotic anaerobic (e.g. *Eikenella corrodens*) and aerobic bacterial infections, scrofuloderma, dimorphic fungal infections, dental sinus tracts, and even neoplasms[136].

Treatment

The drug of choice for actinomycosis is penicillin G or ampicillin. Deep-seated, chronic infections should be treated with 2–6 weeks of intravenous therapy followed by 3–12 months of oral penicillin. For acute infections, 2–3 weeks of oral penicillin plus incision and drainage and surgical excision of sinus tracts is sufficient. Doxycycline, minocycline, and clindamycin are acceptable alternatives for penicillin-allergic patients. Imipenem has been shown to be effective in treatment-resistant cases. In order to avoid relapse, therapy should be extended beyond the resolution of symptoms[137].

NOCARDIOSIS

Introduction

Nocardiosis is caused by various species of *Nocardia*, a filamentous, Gram-positive, acid-fast organism. *Nocardia* is recognized as an opportunistic pathogen in immunocompromised individuals, causing disseminated or systemic disease; in contrast, cutaneous nocardiosis commonly occurs in immunocompetent hosts.

Epidemiology and pathogenesis

Nocardiosis has a worldwide distribution and affects all age groups. Men are affected more often than women, and children may be more prone to developing lymphocutaneous disease[138]. *Nocardia* spp. are ubiquitous in the soil. Localized trauma (e.g. puncture wounds), occupational exposures (e.g. farmers, gardeners), and immunodeficiency are risk factors for contracting nocardiosis.

Clinical features

The three major forms of primary cutaneous nocardiosis are: (1) mycetoma (see Ch. 77); (2) lymphocutaneous nocardiosis; (3) superficial cutaneous nocardiosis. Secondary skin infection may also develop after hematogenous dissemination, often from a pulmonary source. Table 74.18 details the various clinical presentations of *Nocardia* infection.

Pathology

Histologically, an intense neutrophilic infiltrate with abscess formation is seen. Sulfur granules are observed in *Nocardia* mycetoma but are absent in other forms of cutaneous nocardiosis. Organisms are not visible in routinely stained sections but appear as branching filaments on Gram stain. *Nocardia* also stains with methenamine silver and acid-fast stains.

Diagnosis and differential diagnosis

Nocardia grows easily on all common laboratory media. However, growth is slow, so cultures should be held for ≥2 weeks. Nocardiosis should be suspected in patients with sporotrichoid lesions or trauma-associated superficial cutaneous infections that do not respond to routine treatment. It should also be considered in patients at risk for opportunistic infections.

FOUR MAJOR CLINICAL FORMS OF CUTANEOUS NOCARDIOSIS	
Primary	
Actinomycotic mycetoma	• Half of all cases of actinomycotic mycetoma are due to *Nocardia* species* • Traumatic inoculation causes a painless nodule that enlarges, suppurates, and drains via sinus tracts • Purulent discharge contains sulfur granules • The foot is the usual site of involvement • May involve underlying muscle and bone
Lymphocutaneous	• Occurs days to weeks after trauma • Appears as a crusted pustule or abscess resistant to antibiotics • Ascending lymphatic streaks, a sporotrichoid pattern of papulonodules, and tender palpable lymph nodes may be seen
Superficial cutaneous	• Traumatic implantation of foreign objects (including soil and gravel) into the skin, which may result in pustules, abscesses, cellulitis, and ulcers • The diagnosis is based on a high index of suspicion, lack of response to routine antibiotic treatment, and laboratory results
Secondary	
Pulmonary/systemic	• Subcutaneous abscesses of the chest wall • Pustules, nodules, cutaneous fistulae • Almost universally fatal if left untreated • Most commonly caused by *Nocardia asteroides*

*In Mexico and Central and South America, *N. brasiliensis* is the etiology of 90% of actinomycotic mycetomas, whereas in the United States, most mycetomas are caused by true fungi.

Table 74.18 Four major clinical forms of cutaneous nocardiosis.

Treatment

Sulfonamides are the drugs of choice for nocardiosis. Minocycline is an effective alternative for sulfonamide-allergic patients, and linezolid may be added in resistant cases. For subcutaneous abscesses, surgical treatment is often required. Local forms of nocardiosis should be treated for 6–12 weeks, whereas immunocompromised patients and those with disseminated disease require 3–12 months of antimicrobial therapy.

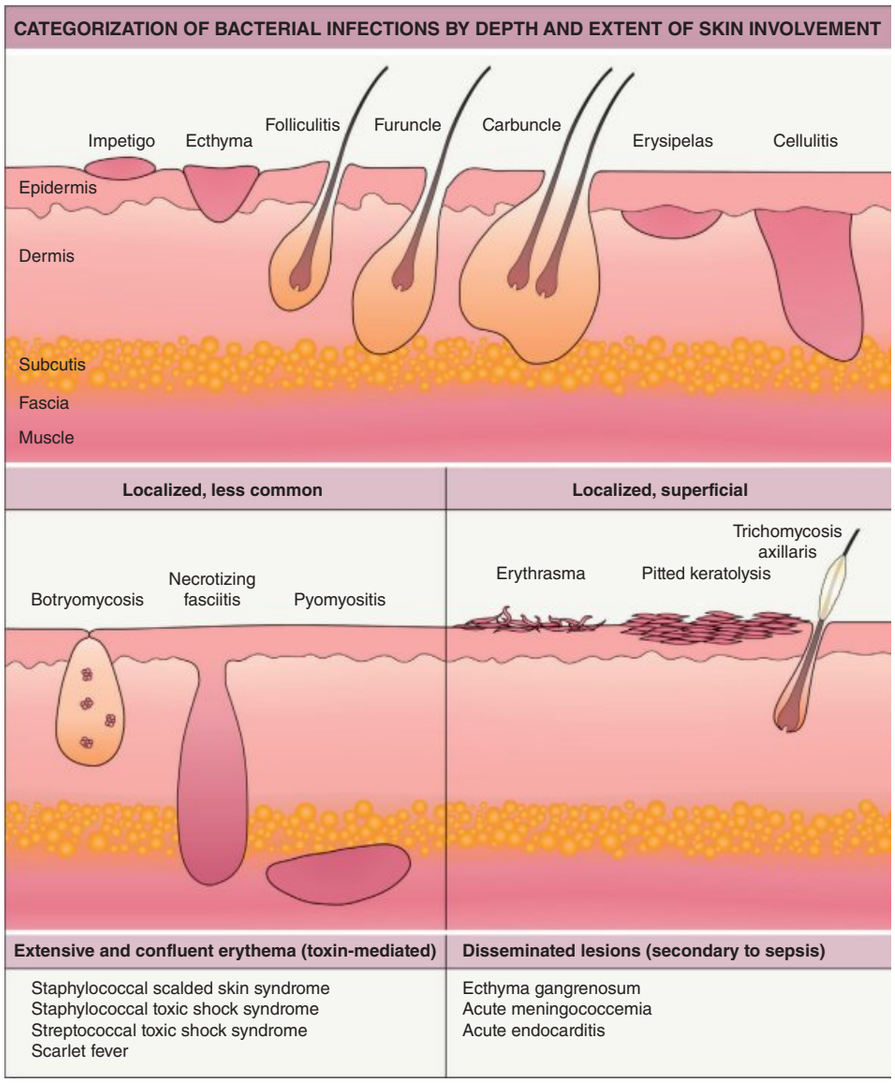
Additional tables and figures available in our eBook (see inside front cover for access code).

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eFig. 74.1 Categorization of bacterial infections by depth and extent of skin involvement. *With permission from Bolognia J, Schaffer J, Duncan K, Ko C. Dermatology Essentials. Philadelphia: Saunders, 2014.*



eFig. 74.2 Impetigo. Superficial erosions with honey-colored crusting. *Courtesy Julie V. Schaffer, MD.*



eFig. 74.3 Erosions due to bullous impetigo in the diaper area. *Courtesy Julie V. Schaffer, MD.*



eFig. 74.4 Bullous impetigo. Multiple superficial erosions with collarettes on the lateral aspect of the trunk. *Courtesy Julie V. Schaffer, MD.*



eFig. 74.5 Bullous impetigo. Small vesiculopustules and superficial erosions with a peripheral collarette in the axilla. *Courtesy Lorenzo Cerroni, MD.*



eFig. 74.6 Staphylococcal impetigo. A Superficial bullae and dry erosion on the nose due to bullous impetigo. **B** Small erosions with slight crusting on the neck and chin. **C** Thick scale-crust on the cheek. *B, Courtesy Kalman Watsky, MD.*



eFig. 74.7 Acute paronychia due to *Staphylococcus aureus*. A collection of pus with surrounding erythema is seen.



eFig. 74.9 Palmar lesions due to staphylococcal endocarditis. *Courtesy Lorenzo Cerroni, MD.*



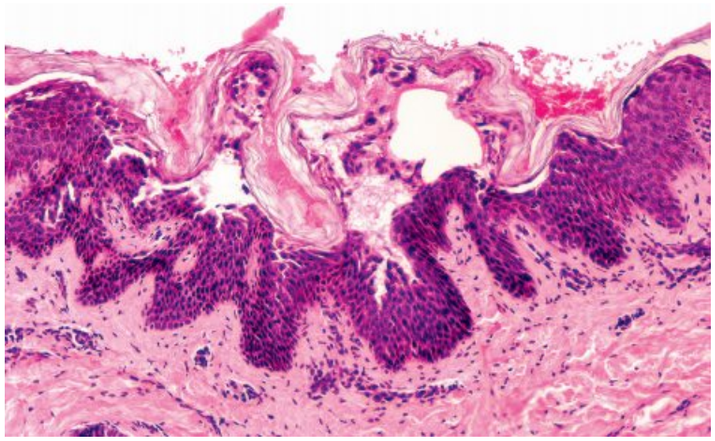
eFig. 74.8 Bacterial abscess. Erythematous, edematous tender plaque with central pustule. In an otherwise healthy individual with no systemic symptoms, initial management includes incision and drainage plus consideration of empiric oral antibiotic coverage for methicillin-resistant *Staphylococcus aureus*. *Courtesy Karynne O. Duncan, MD.*



eFig. 74.10 Blistering distal dactylitis. Large vesiculopustule due to infection with group A *Streptococcus*. *Courtesy Elizabeth Tkachenko, MD.*



eFig. 74.11 Ecthyma due to infection with group A streptococci (*Streptococcus pyogenes*). Isolated erythematous plaque with central ulceration and overlying hemorrhagic crust. *Courtesy Karynne O. Duncan, MD.*



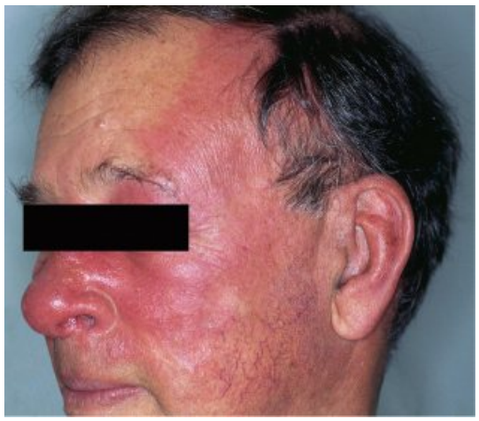
eFig. 74.13 Histopathology of staphylococcal scalded skin syndrome. Note the zone of cleavage at the stratum granulosum. *Courtesy Luis Requena, MD.*



eFig. 74.14 Desquamation of the hand following scarlet fever. *Courtesy Eugene Mirrer, MD.*



eFig. 74.12 Staphylococcal scalded skin syndrome in a young child. A Diffuse, tender erythema with accentuation on the neck. Note the flaccid vesicles, skin wrinkling, and superficial erosion. **B** Later development of extensive superficial sloughing of the skin. *Courtesy Julie V. Schaffer, MD.*



eFig. 74.15 Erysipelas. Sharply demarcated erythema of the face, most clearly demarcated on the forehead. *Courtesy Kalman Watsky, MD.*



eFig. 74.16 Erythema migrans as possible "pseudocellulitis". Expanding erythematous plaque on the neck that could be mistaken for cellulitis.



eFig. 74.17 Extravasation reaction following infusion of enfortumab that may be misdiagnosed as bullous bacterial cellulitis ("pseudocellulitis"). *Courtesy Katherine Ligtenburg, MD.*



eFig. 74.18 Necrotizing fasciitis. Necrosis of the subcutaneous fat and fascia of the inner aspect of the upper arm in an elderly patient with diabetes mellitus. Note the watery discharge. *Courtesy Jean L. Bolognia, MD.*



eFig. 74.19 Necrotizing fasciitis due to Group A β-hemolytic *Streptococcus*. **A** Cluster of dusky plaques on the shin. **B** Extent of necrosis after debridement. *Courtesy Edward Cowen, MD.*



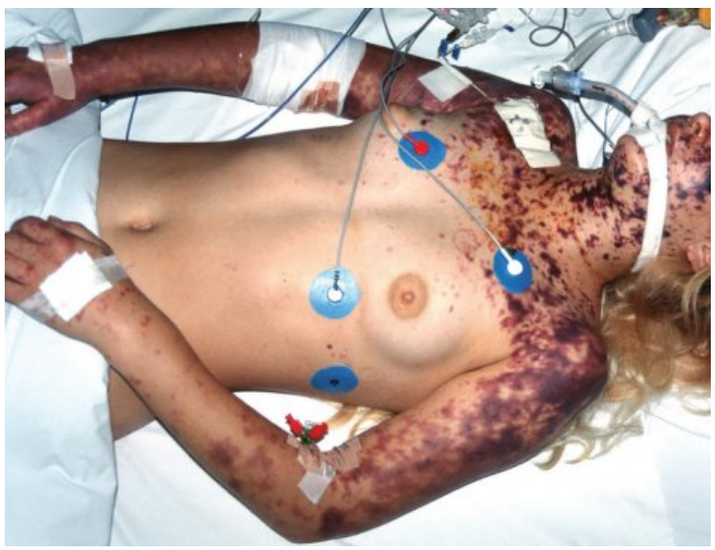
eFig. 74.20 Necrotizing fasciitis in a patient with HIV infection.



eFig. 74.21 Cutaneous anthrax. The ulcerations have black eschars and are surrounded by edema. *Courtesy Regional Dermatology Training Centre, Moshi, Tanzania.*



eFig. 74.22 Chronic meningococcemia. Multiple erythematous crusted papules and nodules on the arm.



eFig. 74.23 Retiform purpura due to disseminated intravascular coagulation in the setting of meningococcal sepsis. *Courtesy Lorenzo Cerroni, MD.*



eFig 74.24 Superficial infection of the skin with *Pseudomonas aeruginosa*. Note the macerated border, erosions, and the moth-eaten appearance of the skin. *Courtesy Kalman Watsky, MD.*



eFig. 74.25 Erythema migrans. Expanding erythematous plaque with central vesiculation. *Courtesy Oscar Colegio, MD.*



eFig. 74.27 Cervicofacial actinomycosis or "lumpy jaw" with soft tissue swelling and draining ulcerated nodules. The discharge contained sulfur granules. *Courtesy Peter Ehrnstrom MD.*





eFig. 74.26 Acrodermatitis chronica atrophicans. *Courtesy Lorenzo Cerroni, MD.*



eFig. 74.28 Tray utilized to perform a sterile biopsy for tissue culture. *Courtesy Jean L. Bolognia, MD.*

ALT-70 CELLULITIS PREDICTIVE MODEL – CALCULATION OF THE ALT-70 SCORE		
Criterion	**Definition**	**Score**
Asymmetry	Unilateral lower extremity involvement	3
Leukocytosis	White blood cell count ≥10 000/mcl	1
Tachycardia	Heart rate ≥90 bpm	1
Age	≥70 years	2
Total score: 0–2: favors pseudocellulitis 3–4: may benefit from dermatology consultation ≥5: favors cellulitis		

eTable 74.1 The ALT-70 cellulitis prediction model – calculation of the ALT-70 score. This represents a prospectively validated clinical decision support tool that incorporates objective clinical and laboratory measures to distinguish between lower extremity cellulitis and "pseudocellulitis" at the time of presentation in the emergency department and up to 48 hours later[53]. bpm, beats per minute.

THE LABORATORY RISK INDICATOR FOR NECROTIZING FASCIITIS (LRINEC) SCORE		
Parameter	**Range**	**Score**
Hgb	>13.5 g/dl	0
	11–13.5 g/dl	1
	<11 g/dl	2
WBC	$<15 \times 10^3$/mcl	0
	$15–25 \times 10^3$/mcl	1
	$>25 \times 10^3$/mcl	2
Sodium	<135 mEq/l	2
Creatinine	>1.6 mg/dl	2
Glucose	>180 mg/dl	1
C-reactive protein	≥150 mg/l	4
Total score: ≤5: <50% risk of necrotizing fasciitis (low)* 6–7: raises suspicion of necrotizing fasciitis (intermediate) ≥8: strongly predictive of necrotizing fasciitis; >75% risk (high)		
*Clinical suspicion for necrotizing fasciitis should overrule a low LRINEC score in order to avoid delay in evaluation and management.		

eTable 74.2 The laboratory risk indicator for necrotizing fasciitis (LRINEC) score. The LRINEC tool was devised to identify and distinguish early cases of necrotizing fasciitis from other soft tissue infections using laboratory parameters[64]. Although initially found to have a high specificity and negative predictive value, subsequent studies showed a relatively low sensitivity. Hgb, hemoglobin; WBC, white blood cell count.

75 Mycobacterial Infections

Marcia Ramos-e-Silva, Maria Cristina Ribeiro de Castro and Maria Teresa Ochoa

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In 1896, the name "mycobacteria" was given to a large group of bacteria that produce filamentous pellicles similar to molds when grown in liquid media. These organisms are thin, slightly curved to straight, non-motile and non-spore-forming, with a waxy coating that makes them resistant to most stains. Mycobacteria are also acid-fast, which means they are not readily decolorized by acid after staining[1–3]. Of the >170 species in the genus *Mycobacterium*, a number of them may or may not be pathogenic depending on the immunologic state of the host[2,4], whereas *M. leprae* and *M. tuberculosis* are virulent and constitute an important world health problem. Research on Hansen disease (leprosy) has been greatly hampered by the inability to culture the organism, which has the longest doubling time of all known bacteria, but the discovery of the genomic sequence of *M. leprae* in 2001 was a significant advancement[5].

Although the classic mycobacterioses – Hansen disease and tuberculosis – have been known since antiquity, over the past few decades there has been a worldwide explosion in the incidence of mycobacterial infections. Several factors have played a role in this increase, including the emergence of resistant strains of *M. tuberculosis* and a rise in the number of immunocompromised hosts, including those with AIDS[3]. In Table 75.1, the different species of mycobacteria that are associated with cutaneous disease are outlined utilizing Runyon's classification scheme[1,3,6].

This chapter addresses the mycobacterial species that are of greatest interest to dermatologists: *M. leprae, M. tuberculosis*, and non-tuberculous mycobacteria that cause cutaneous infections.

HANSEN DISEASE (LEPROSY)

Key features

- Chronic infectious disease caused by *Mycobacterium leprae* or *M. lepromatosis*, intracytoplasmic bacteria that parasitize macrophages and Schwann cells
- Slowly progressive condition characterized by granulomas and neurotropism, with a predilection for the skin as well as peripheral nerves
- The primary skin lesion is erythematous or hypopigmented, and it is often anesthetic
- Based upon the clinicopathologic findings, which reflect the degree/type of immunity, Hansen disease is divided into two major forms – lepromatous with a predominantly Th2 response and tuberculoid with a predominantly Th1 response
- In the lepromatous form of Hansen disease, multiple organisms are present in the dermis, whereas in the tuberculoid form, there are only a few organisms

Introduction

Hansen disease is a chronic infectious disease that is caused by *Mycobacterium leprae* or *M. lepromatosis* and has a predilection for the skin and nerves[7,8]. It is divided into two major forms depending upon the degree and type of immunity – lepromatous with a predominantly Th2 response and tuberculoid with a predominantly Th1 response. Hansen disease is classified by the World Health Organization (WHO) as a "neglected tropical disease" that represents a public health concern in a number of low-income countries. Once worldwide in distribution, Hansen disease is now seen primarily in tropical and subtropical regions of Asia, Africa, and Central and South America (Fig. 75.1). Early diagnosis and prompt therapy are key components in the strategy to control this chronic infectious disease[9].

History

The first written descriptions of leprosy may date back to as early as 600 BCE in India, and to 200 BCE in China and Japan. Many of the cases mentioned in the Bible may actually have been psoriasis, vitiligo, or other skin disorders rather than leprosy. The earliest scientific evidence of leprosy has come from an Egyptian skeleton and two Coptic mummies from the second century BCE and the fifth century CE, respectively. One theory was that leprosy was brought from India to the Mediterranean basin by Alexander the Great's soldiers between 327 and 326 BCE and then spread throughout the Greek and Roman Empires. Recent studies utilizing comparative genomics have shown that all extant cases of leprosy are attributable to a single clone, and the disease appears to have originated in the Near East or eastern Africa[10]. During the Middle Ages, leprosy reached epidemic proportions in Europe and then spread to the New World via the wave of exploration in the late fifteenth and sixteenth centuries[11]. Independent of geographic location, the afflicted have frequently been ostracized by their communities and families.

During the nineteenth century, Danielssen and Boeck provided the first modern description of leprosy, and in the 1870s, a third Norwegian, Gerhard Henrik Armauer Hansen, identified *M. leprae*. The term Hansen disease is commonly used nowadays and may help to decrease the stigma associated with this infection. Mitsuda created the skin test for leprosy in 1919[12], and the value of sulfones in the treatment of leprosy was reported in 1942[13]. In 1966, Ridley and Jopling suggested a classification of leprosy based on the immunologic status of the patient (see below)[14].

Epidemiology

In the early 1980s, 11–15 million people worldwide were estimated to have Hansen disease. Introduction of multidrug therapy (MDT) has substantially reduced the number of affected individuals. The number of new cases per year decreased from >500 000 in 2003 to <150 000 in 2021, with only ~130 000 patients requiring treatment remaining worldwide[15,16]. However, the incidence remains relatively high among patients <15 years of age. The goal of the WHO is a prevalence rate of <1 case per 10 000 persons, which has been achieved in all but a few countries[17]. In 2021, Brazil (especially western Amazonia), India, and Indonesia accounted for ~75% of new cases, with other countries that have high infection rates located primarily in Southeast Asia and Africa (see Fig. 75.1). In the US, ~150–200 new cases are reported yearly. Recent evidence suggests that Hansen disease may be endemic in Florida[17a].

Although men and women are equally affected, the lepromatous form of Hansen disease is seen more often in men than in women (~1.5 : 1). Hansen disease affects all races and ages, with the highest incidences in individuals 10–15 and 30–60 years of age[18]. Key factors in the acquisition of Hansen disease are close contact of a susceptible person (e.g. based on genetic predisposition; see below) with a contagious individual (e.g. with multibacillary disease). The risk of acquiring the disease from household contacts is 25%, emphasizing the public health importance of domicile control[19]. The incubation period varies widely, from months to >30 years, but it is usually 4–10 years[18]. *M. leprae* is spread

predominantly by patients with multibacillary disease via nasal and oral droplets and much less often from eroded skin[12,20].

Although Hansen disease primarily affects humans, it can be found in nine-banded armadillos (southern US from Texas to Florida, Brazil) and red squirrels (British Isles)[9,21]. In one study, ~40% of patients with Hansen disease from the southeastern US were infected with one of two *M. leprae* genotypes associated with wild armadillos, suggesting that Hansen disease represents a zoonosis in this region[22].

MYCOBACTERIA THAT CAUSE CUTANEOUS DISEASE		
Group and pigment	**Rate of growth**	**Pathogens**
Slow growers		
Photochromogens*	2–3 weeks	*M. kansasii, M. marinum, M. simiae*
Scotochromogens†	2–3 weeks	*M. scrofulaceum, M. szulgai, M. gordonae, M. xenopi*
Nonchromogens‡	2–3 weeks	*M. tuberculosis, M. avium, M. intracellulare, M. ulcerans, M. haemophilum, M. malmoense, M. terrae, M. genavense, M. bovis*¶, *M. nonchromogenicum*
Rapid growers	3–5 days	*M. fortuitum, M. chelonae, M. smegmatis, M. abscessus*§, *M. immunogenum, M. goodii, M. wolinskyi, M. cosmeticum, M. mucogenicum, M. mageritense*
Non-cultured (to date)		*M. leprae*

*Capable of yellow pigment formation upon exposure to light.
†Capable of yellow pigment production without light exposure.
‡Incapable of pigment production.
¶Including bacillus Calmette–Guérin.
§Including *M. abscessus* subsp. *massiliense* and *M. abscessus* subsp. *bolletii*.

Table 75.1 Mycobacteria that cause cutaneous disease. Modified classification of Runyon[1,3,6].

Pathogenesis

M. leprae and *M. lepromatosis* are very small, slightly curved rods that are characteristically acid-fast. They are obligate intracellular microorganisms with a predilection for macrophages and Schwann cells. The major sites of involvement are the peripheral nerves, skin, mucous membranes, bones, and viscera (e.g. testes, liver). In animal models, these bacilli grow best at a temperature of 27–33°C, and they thus prefer cooler regions of the body (e.g. nose, testicles, ear lobes) as well as regions where the peripheral nerves are close to the skin[18,23].

The fact that the majority of exposed individuals do not develop disease implies that there is variability in susceptibility/resistance, depending upon genetic and environmental factors. For example, susceptibility and the type of immune response appear to correlate with specific HLA types, such that individuals with HLA-DR2 and HLA-DR3 are more likely to develop the tuberculoid form and those with HLA-DQ1 the lepromatous form[18].

Polymorphisms in the genes that encode interleukin (IL)-6, 10, 12, and 17A/F; tumor necrosis factor (TNF); lymphotoxin-α (a low-producing allele linked to early-onset Hansen disease); and the IL-23 receptor, vitamin D receptor (VDR), and Toll-like receptors (TLRs) 1 and 2 have been shown to be related to either overall Hansen disease susceptibility or the particular form of Hansen disease that develops[24–27]. The genetic factors implicated vary in different populations. For example, in Vietnamese and Brazilian populations, variants in the shared regulatory region of the *PRKN* (encoding Parkin, an E3 ubiquitin protein ligase) and *PACRG* genes have been associated with susceptibility to Hansen disease[28]. Genome-wide association studies in Chinese populations have linked variants in genes encoding proteins in the NOD2 (nucleotide-binding oligomerization domain containing 2) pathway with susceptibility to Hansen disease, especially the multibacillary form[29]. The NOD2 pathway, along with the VDR, TLRs, and Parkin, play key roles in the innate immune response, as do several additional proteins encoded by genes associated with Hansen disease, e.g. *MBL* (mannose-binding lectin), *MRC1* (mannose receptor C-type 1), *SLC11A1* (solute carrier family 11 member 1), and *KIR* (killer cell immunoglobulin-like receptor). TLRs, NOD2, and MRC1 have been associated with modulation of autophagy, whereas Parkin and LRRK2 (leucine rich repeat kinase 2) have roles in the regulation of host cell apoptosis.

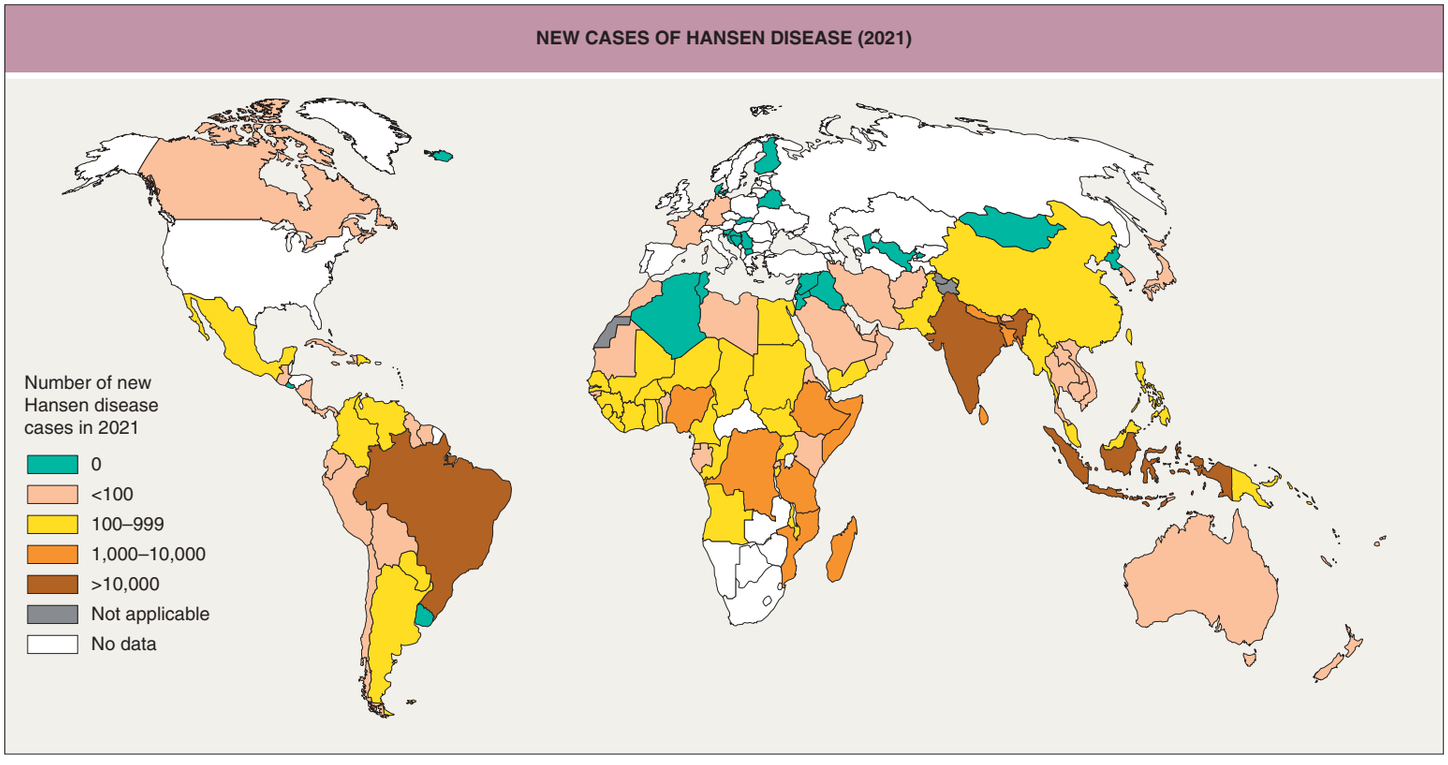


Fig. 75.1 New cases of Hansen disease, 2021. The World Health Organization (WHO) has achieved its goal of a prevalence rate of less than 1 case per 10 000 persons in all but a few countries. Over half of cases in the US are from seven states – Florida, Louisiana, Texas, California, New York, Hawaii, and Georgia. *Reproduced from the World Health Organization, https://apps.who.int/neglected_diseases/ntddata/leprosy/leprosy.html*

Presentations of Hansen disease exist on a clinical–immunologic spectrum. At one end, patients with the *tuberculoid* form of Hansen disease have specific cell-mediated immunity (CMI), as reflected in a positive lepromin test (Mitsuda reaction; see below). At the other end, patients with the *lepromatous* form of Hansen disease have a negative lepromin test and minimal CMI, while humoral immunity is increased (Fig. 75.2)[9]. For example, serum levels of antibodies against phenolic glycolipid-1 (PGL-1), an *M. leprae*-specific antigen, are highest in patients with the lepromatous form[30].

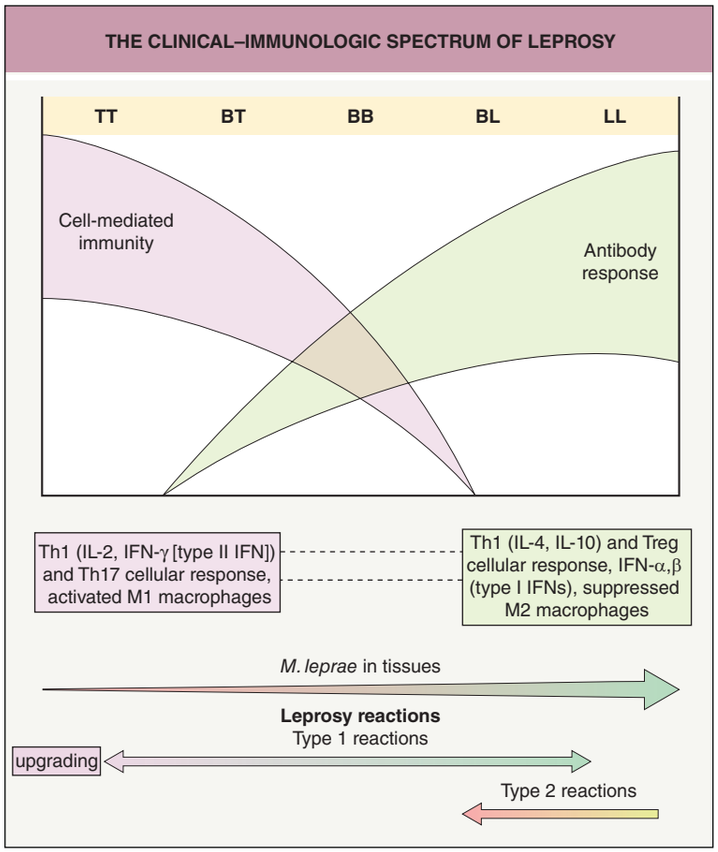


Fig. 75.2 The clinical–immunologic spectrum of Hansen disease. This reflects the underlying host immunity as measured by the T lymphocyte and antibody responses to *Mycobacterium leprae*. TT, tuberculoid leprosy; BT, borderline tuberculoid leprosy; BB, mid-borderline leprosy; BL, borderline lepromatous leprosy; LL, lepromatous leprosy; IFN, interferon; IL, interleukin. *Adapted from Britton WJ. Leprosy. In Cohen J, Powderly WG (eds). Infectious Diseases. London: Mosby, 2003. With permission of Elsevier.*

Macrophages play an important role in the body's attempt to eliminate *M. leprae*, activating a type I interferon (IFN) response and producing IL-1, TNF, and IL-12. Patients with the *tuberculoid* form maintain this inflammatory response and an effective CMI. They display a Th1 $CD4^+$ T cell response that produces IL-2, IFN-γ (type II IFN), and lymphotoxin-α in addition to involvement of $CD8^+$ cytotoxic T cells, γ/δ T cells, CD1a-restricted T cells, and Th17 cells. In patients with the *lepromatous* form, a predominantly Th2 response leads to the release of different cytokines – IL-4, IL-5, IL-10, and IL-13; these cytokines suppress macrophage activity[23,31]. $CD4^+$ regulatory T cells, $CD8^+$ suppressor T cells, and type I IFNs predominate in these patients[32]. The cell wall of *M. leprae* contains lipid complexes, including PGL-1, which may suppress T cell responses and IFN-γ production as well as the organism's invasion of Schwann cells in a laminin-2-dependent pathway[23,33,34].

$CD4^+$ T cells that express the antimicrobial protein granulysin have been detected at a sixfold greater frequency in tuberculoid as compared to lepromatous skin lesions[35]. Tuberculoid lesions also have stronger expression of TLR2 and TLR1, activation of which can induce differentiation of macrophages and dendritic cells. $CD1b^+$ dendritic cells, which promote T cell activation and secretion of proinflammatory cytokines, were not detected in lesions from patients with the lepromatous form of Hansen disease[36]; instead, these lesions had upregulation of genes belonging to the leukocyte immunoglobulin-like receptor (LIR) family. LIR-7 has been shown to suppress innate host defense by several mechanisms, including blocking antimicrobial activity triggered by TLRs[37].

Clinical Features

There is a wide spectrum of clinical findings in Hansen disease, and several classification schemes have been utilized. The Ridley and Jopling classification is based on an immunopathologic spectrum (Table 75.2; see Fig. 75.2), with lepromatous (LL) at the end with the least effective immune response, tuberculoid (TT) at the end with strong CMI, and three types of borderline leprosy in between: borderline lepromatous (BL), borderline–borderline (BB, in the middle), and borderline tuberculoid (BT) (Fig. 75.3)[12,14,18].

In addition, the WHO created an operational system to facilitate the classification and treatment of Hansen disease in endemic areas. Per the WHO, the diagnosis of Hansen disease is based on the presence of at least one of the following cardinal features: (1) anesthesia in a hypopigmented or erythematous skin lesion; (2) enlarged peripheral nerve with associated loss of sensation and/or weakness; and (3) the presence of acid-fast bacilli in a slit-skin smear or biopsy. The current WHO classification system (revised in 2017) divides Hansen disease into two main groups: (1) *paucibacillary leprosy* – one to five skin lesions, without demonstrated presence of bacilli in a slit-skin smear or biopsy when assessed; and (2) *multibacillary leprosy* – more than five skin lesions, nerve involvement (pure neuritis or with any number of skin lesions),

CLASSIFICATION OF HANSEN DISEASE						
Clinical findings	**LL**	**BL**	**BB**	**BT**	**TT**	**I**
Type of lesions	Macules, papules, nodules, diffuse infiltration	Macules, papules, annular plaques, infiltration	Annular plaques with a "Swiss cheese" appearance; dome-shaped, punched-out lesions	Infiltrated plaques, often larger than those of TT	Erythematous or hypopigmented patch or plaque with raised border	Macules, often hypopigmented
Number of lesions	Numerous	Many	Many	Single, usually with satellite lesions, to 5	One or few (≤5)	One or few
Distribution	Symmetric	Tendency to symmetry	Usually symmetric	Asymmetric	Localized, asymmetric	Variable
Definition	Vague, difficult to distinguish normal versus affected skin	Ill-defined borders	Well-defined inner border, less defined outer border	Compared to TT, less defined borders	Well-defined, sharp borders	Not always defined
Sensation	Not affected	Diminished	Diminished	Absent	Absent	Impaired
Bacilli in skin lesions	Many (globi)	Many	Many	Few (1+), if any, detected	None detected	Usually none detected

Table 75.2 Classification of Hansen disease. LL, lepromatous leprosy; BL, borderline LL; BB, mid-borderline leprosy; BT, borderline TT; TT, tuberculoid leprosy; I, indeterminate. *Adapted from A Guide to Leprosy Control, 2nd ed. Geneva: World Health Organization, 1988:27–8.*

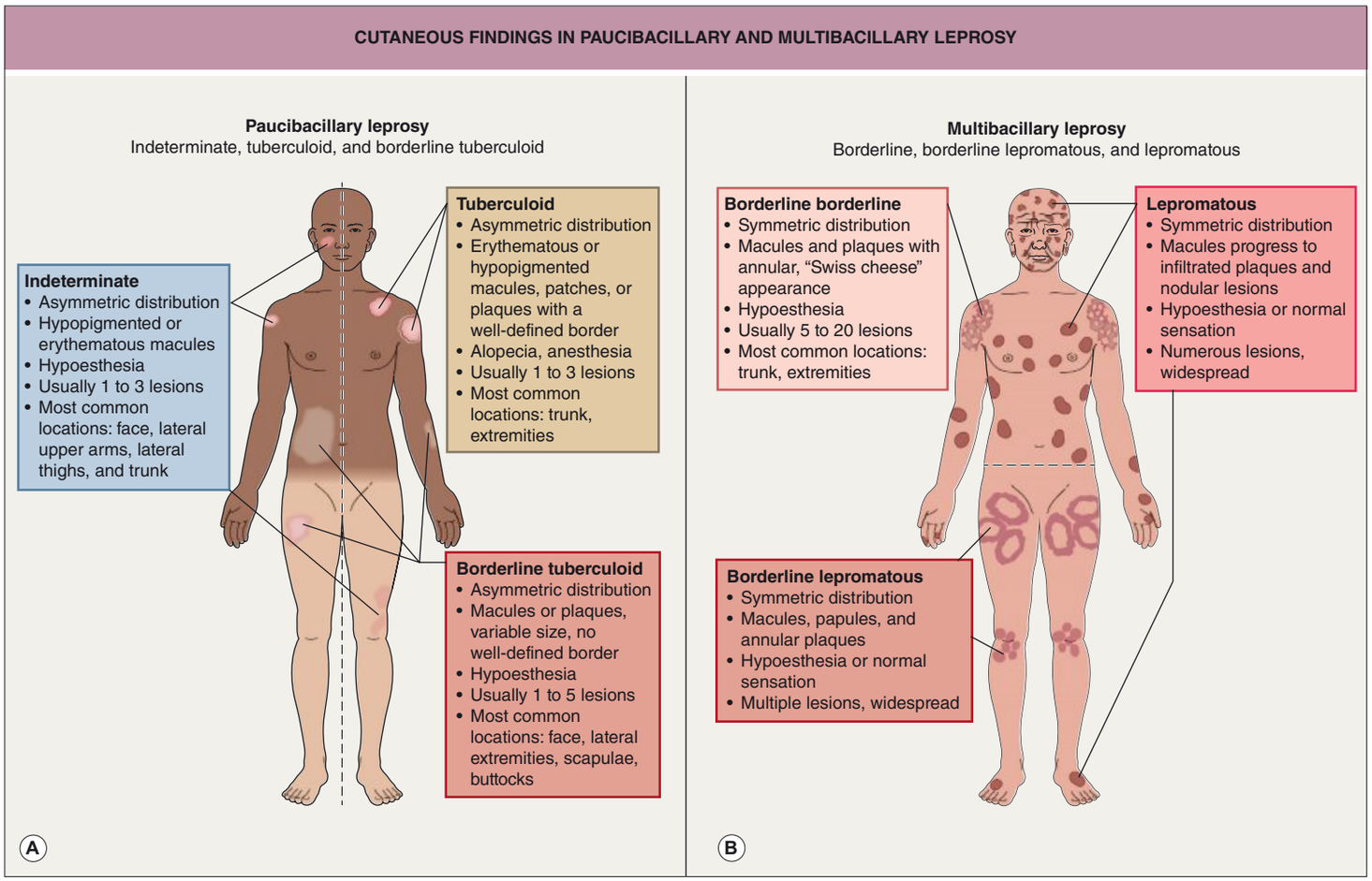


Fig. 75.3 Cutaneous findings in paucibacillary and multibacillary leprosy. A Paucibacillary disease – indeterminate, tuberculoid, and borderline tuberculoid. **B** Multibacillary disease – borderline, borderline lepromatous, and lepromatous.

or the presence of bacilli in a slit-skin smear or biopsy (with any number of skin lesions)[38]. This classification is commonly employed worldwide.

Certain peripheral nerves are more commonly affected, based primarily upon their more superficial location. Palpation of these nerves is an integral component of the physical examination of a patient with Hansen disease (Fig. 75.4). The clinician should determine whether there is a decrease in sensation to pain, temperature, and/or touch. This is in addition to inspection for neuropathic changes (e.g. muscle atrophy, flexion contractures of the fourth and fifth fingers), vasomotor alterations, and secretory disturbances (e.g. dry skin and eyes)[12,18].

The *lepromatous* form of Hansen disease, the form with the least cellular immunity and greatest number of bacilli, is characterized initially by multiple, poorly defined, erythematous macules, papules, nodules, and plaques (Fig. 75.5A). Lesions are widespread and usually symmetric in distribution. The most common sites of involvement are the face, buttocks, and extremities. Infiltration of the skin of the forehead can lead to leonine facies (Fig. 75.5B). Additional signs and late sequelae include madarosis, saddle nose, infiltration of both earlobes, and acquired ichthyosis on the lower extremities (Fig. 75.6). Anesthesia in a stocking or glove distribution may develop, often together with enlarged peripheral nerves and neuropathic changes. Ocular manifestations such as lagophthalmos (inability to completely close the eyes) and corneal and conjunctival anesthesia due to involvement of branches of the facial and trigeminal nerves, respectively, are sometimes present in severe cases[18].

Histoid leprosy is a clinically distinct form of multibacillary disease that some authors classify as a variant of the lepromatous form. It is characterized by the development of dermatofibroma-like papules and nodules. *Lucio leprosy* is a non-nodular, diffuse form of lepromatous leprosy most commonly seen in Mexico and Central America that results from *M. lepromatosis* infection[39].

Borderline leprosy, as its name implies, has features that are intermediate between the two ends of the spectrum. The severity of the cutaneous and peripheral nervous system manifestations depends upon whether the patient is "leaning" towards the lepromatous pole (BL) or the tuberculoid pole (BT; see Table 75.2). BT cutaneous lesions are usually asymmetric and are typically larger in size with less defined borders than those of the tuberculoid form (see Fig. 75.3A). Affected areas are hypoesthetic and have decreased sweating. BB leprosy characteristically presents with annular plaques that can have a "Swiss cheese" appearance (Fig. 75.7; see Fig. 75.3B). The cutaneous lesions of BL leprosy are more numerous and symmetric, with variable morphologies.

The *tuberculoid* form of Hansen disease usually presents with a few patches or plaques that have sharply demarcated, slightly raised borders. The color of these lesions ranges from erythematous to hypopigmented, with the latter especially common in patients with darkly pigmented skin (Fig. 75.8). Lesional alopecia and anesthesia or hypesthesia can represent clues to the diagnosis. Unilateral neuropathic changes, especially of the extremities (e.g. digital resorption), may be seen[14]. Occasionally, only neural involvement is present ("pure neuritic [neural] leprosy").

The development of reactions complicates the course of Hansen disease in ~30%–50% of patients, especially during treatment (see Fig. 75.2). These are characterized by acute inflammation that appears suddenly before, during, or after treatment (Fig. 75.9 & 75.10). *Type 1 reactions* can affect patients with any form of Hansen disease (except for the early indeterminate form), but there is a predilection for borderline categories. *Type 2 reactions* most often occur in lepromatous or BL leprosy. In addition to the administration of antimicrobial drugs, the most frequent triggers for reactions are pregnancy, other infections, and mental distress. The immunopathogenesis, clinical manifestations, and treatment of the two major types of inflammatory reactions are outlined in Table 75.3[40].

Type 1 (reversal) reactions are due to a change in the immunologic state of the patient and are often associated with neuritis. When there is an increase in cell-mediated immunity, this is referred to as an "upgrading" reaction (see Fig. 75.10A). *Type 2 reactions* are due to the formation of immune complexes in association with neutrophil recruitment[41].

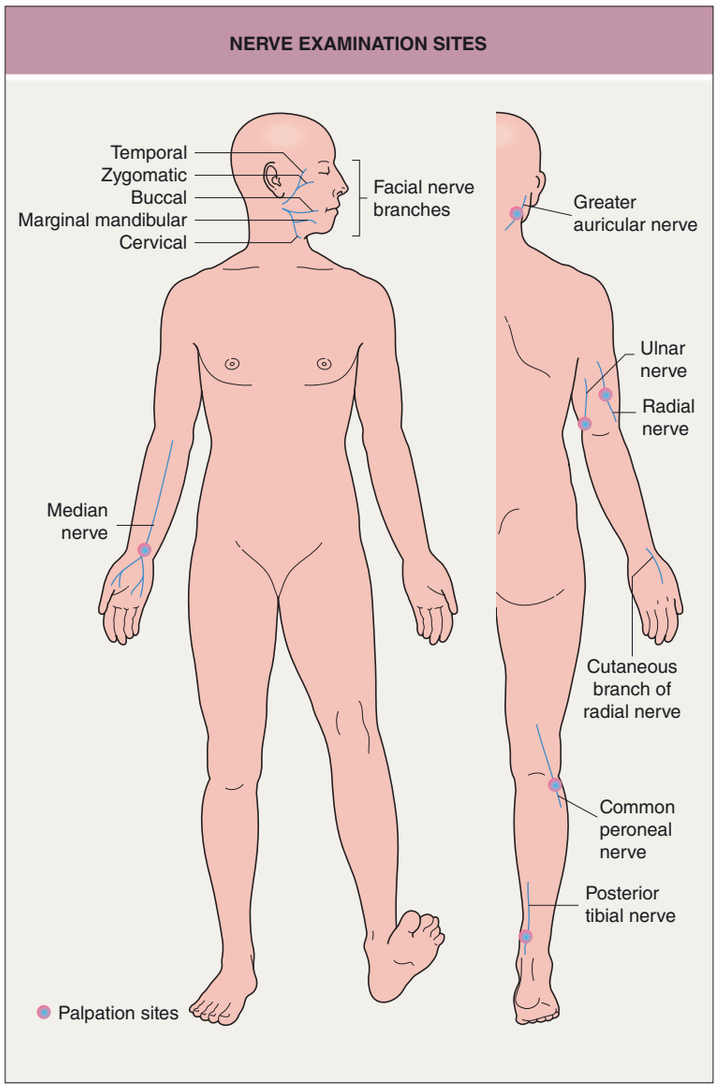


Fig. 75.4 Nerve examination sites.

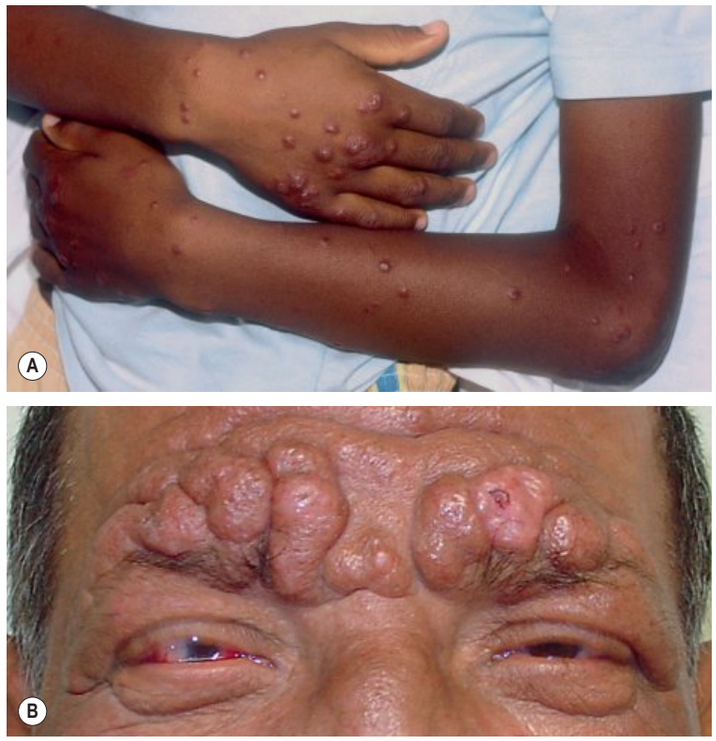


Fig. 75.5 Lepromatous form of Hansen disease. A Numerous erythematous papules and nodules on the forearms and hands. **B** Infiltrated nodules coalescing on the forehead with leonine facies and madarosis. Note the ocular involvement.

A type 2 reaction can result in cutaneous and systemic small vessel vasculitis (e.g. erythema nodosum leprosum; see Fig. 75.10B,C)[12,18,23]. Patients with the diffuse form of lepromatous leprosy, who are usually from Central or South America, may develop the *Lucio phenomenon*, a reactional state characterized by thrombosis associated with antiphospholipid antibodies in addition to a vasculopathy and/or necrotizing cutaneous small vessel vasculitis (Fig. 75.10D). On a worldwide basis, Hansen disease is a common cause of cutaneous vasculitis, especially in low-income countries[42].

Pathology and Laboratory Evaluation

There are three basic histopathologic patterns observed in Hansen disease: lepromatous, tuberculoid, and borderline. In the *lepromatous* pattern, an infiltrate may be seen in the dermis, subcutis, lymph nodes, abdominal organs (e.g. kidney, liver), testicles, and bone marrow. The infiltrate contains Virchow cells, which are macrophages with numerous bacilli as well as lipid droplets in their cytoplasm. In H&E-stained sections, these cells have a foamy appearance. The bacilli in Hansen disease can be detected by a Fite–Faraco stain (more sensitive) or Ziehl–Neelsen stain, both of which stain the bacilli a bright red color. For lesions in which bacilli are usually scant, it is recommended that at least six sections be examined before declaring them negative[12].

A band of normal-appearing dermis (Unna band or Grenz zone) separates the epidermis from the dermal infiltrate, which is composed of plasma cells and a few lymphocytes in addition to foamy macrophages containing globi (clumps of bacilli) (Fig. 75.11). Following successful therapy, the organisms fragment and become granular. Cutaneous nerves demonstrate lamination of the perineurium, producing an onion-skin appearance. In the histoid variant, a well-circumscribed proliferation of spindle cells contains numerous bacilli, which typically line up along the long axis of the cell.

In the *tuberculoid* pattern of Hansen disease, a dermal granulomatous infiltrate is seen and may have a linear pattern following the course of a nerve (Fig. 75.12). Epithelioid cells and Langhans giant cells are surrounded by lymphocytes. The cutaneous nerves are edematous, and organisms are absent or rare, even with special stains. Inflammation and fragmentation of nerve fibers in the tuberculoid form differentiate it from sarcoidosis and other granulomatous disorders.

The *borderline* pattern contains histologic features of both the lepromatous form (e.g. Virchow cells) and tuberculoid form (e.g. granulomas). Predominance of the former versus the latter is dependent upon whether the patient has the BL, BB, or BT form of borderline leprosy.

Indeterminate Hansen disease is usually difficult to diagnose histologically. Only a patchy infiltrate of lymphocytes or histiocytes around blood vessels or appendages is seen[9]. There are no granulomas or Virchow cells[12], and organisms are usually absent.

When Hansen disease is suspected, the diagnosis can be confirmed by finding bacilli in a biopsy or a slit-skin smear. Samples for the slit-skin smear may be obtained from the earlobes, elbows, knees, and cutaneous lesions. To avoid bleeding, a fold of skin is firmly squeezed between the finger and thumb of the examiner or with forceps, and a small incision is made with a scalpel blade. The liquid obtained is smeared onto a slide and allowed to dry. The smear is usually stained by the Fite–Faraco method and a search is made for red rods (against a blue background) at 100× with oil immersion[9]. Organisms are found in 100% of patients with the lepromatous form, 75% of those with borderline leprosy, and only 5% of those with the tuberculoid form. A biopsy specimen of the skin lesions should be obtained, especially in patients with suspected tuberculoid leprosy (see above). Where available, fluorescent microscopy with auramine rhodamine staining has been shown to be more sensitive than the Fite–Faraco method for detecting organisms in skin biopsy specimens[43].

PCR can be utilized to amplify genes that encode antigenic proteins (e.g. 36 kDa proline-rich antigen, Ag85B, 16 s) as well as *M. leprae*- or *M. lepromatosis*-specific repetitive repeat sequences (RLEP region). Molecular methods (e.g. analyzing RLEP region) can distinguish *M. leprae* from *M. lepromatosis* and are particularly helpful in

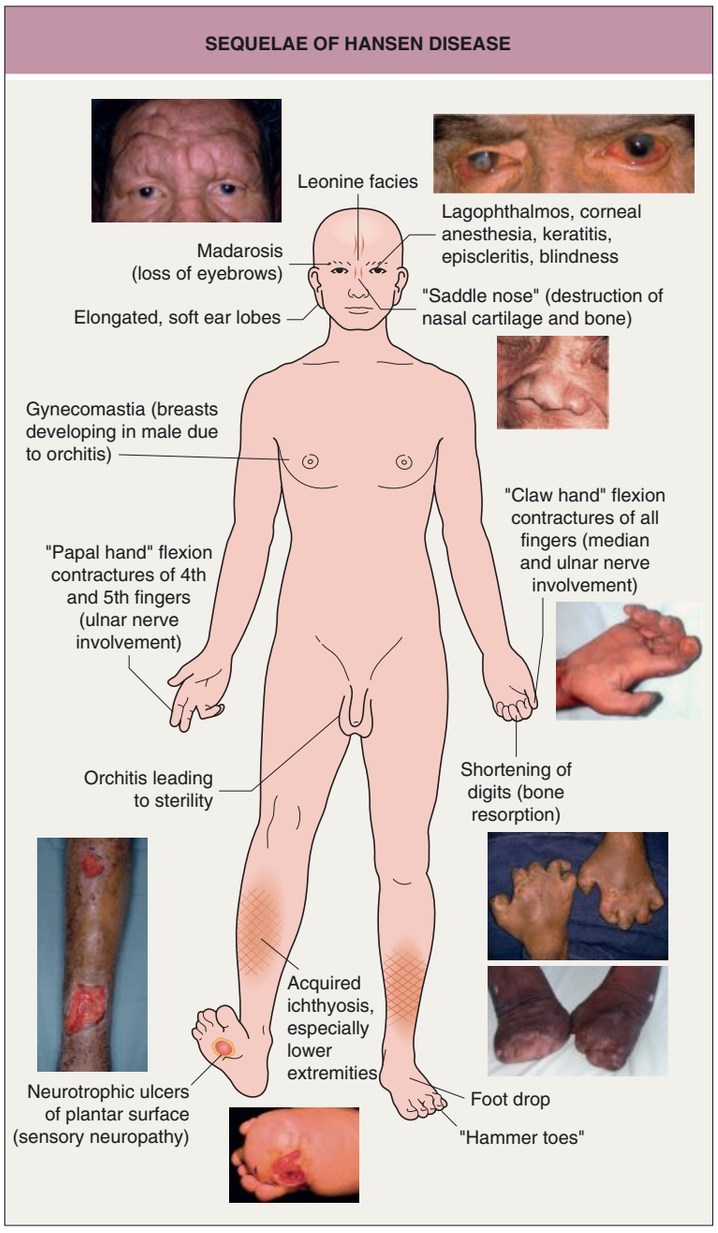


Fig. 75.6 Sequelae of Hansen disease. *Insets, Courtesy Louis A. Fragola, Jr, MD and Joyce Rico, MD.*

paucibacillary and pure neuritic leprosy[44]. PCR can also be performed on slit-skin smears and fresh, frozen[45], or paraffin-embedded skin biopsy specimens (Table 75.4). In a study utilizing RLEP real-time PCR, *M. leprae* DNA was detected in 38 (75%) of 51 paraffin-embedded skin biopsy specimens from patients with paucibacillary leprosy[46,47]. In addition, immunohistochemical staining of biopsy specimens for the PGL-1 antigen may prove helpful in paucibacillary disease.

Serologic assays for anti-PGL antibodies are only sensitive for the diagnosis of multibacillary disease. However, measurement of these antibodies can help to classify patients, monitor the response to treatment, and predict leprosy reactions[48]. Serum levels of anti-PGL-1 IgG and IgM antibodies are highest in lepromatous disease and lowest (or absent) in BT or tuberculoid disease, therefore representing a marker of mycobacterial "load". Elevation of anti-PGL-1 IgM antibody levels is also associated with reactions and impairment of nerve function[30].

The lepromin (Mitsuda) test consists of an intradermal injection of 0.1 ml of a suspension of heat-killed *M. leprae*. The response is positive when a nodule forms at the site of injection 3 to 4 weeks later, indicating that the patient can mount a specific cell-mediated response to the bacilli. The test provides prognostic, but not diagnostic, information. It is positive in TT and BT leprosy[9].

Lastly, Hansen disease, especially LL and BL, is one of the causes of biologically false-positive anti-nuclear antibodies (ANA) or rheumatoid

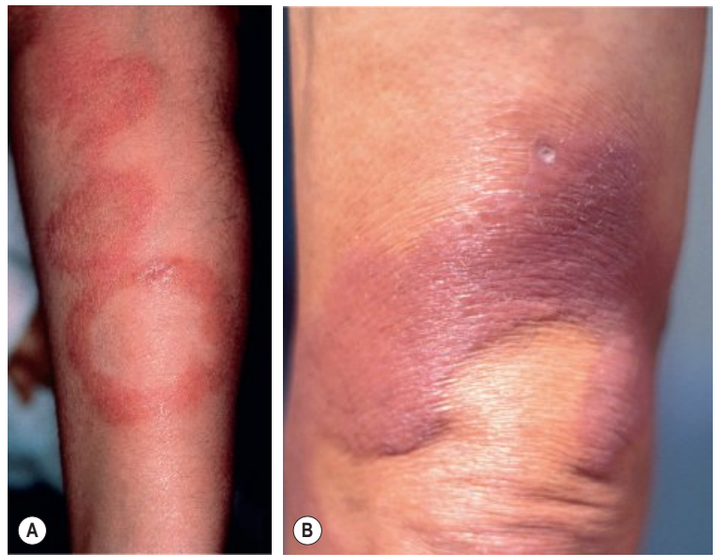


Fig. 75.7 Borderline borderline leprosy. Erythematous plaques with central clearing leading to annular (**A**) and arcuate (**B**) lesions. Note the ill-defined outer borders and well-demarcated inner borders.

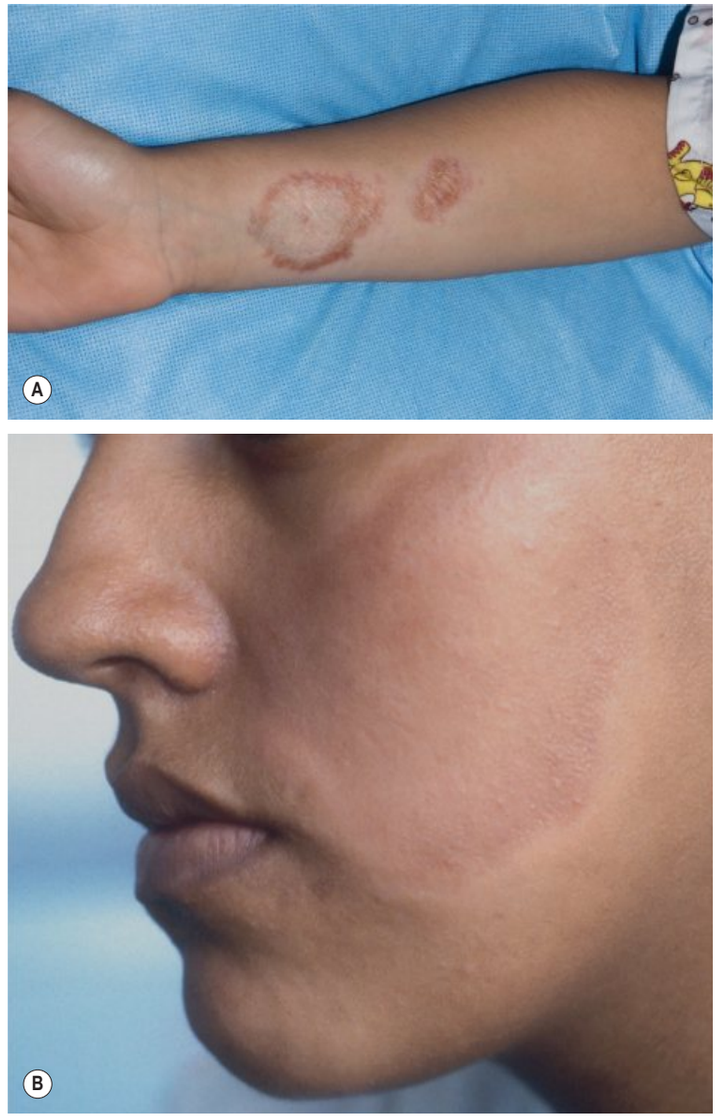


Fig. 75.8 Tuberculoid form of Hansen disease. A Two plaques on the forearm of a child that have dull pink–brown raised borders and central atrophy with hypopigmentation. **B** Large annular lesion on the cheek with a red–brown color and rim of hypopigmentation. *A, Courtesy Edward Cowen, MD.*

factor as well as Venereal Disease Research Laboratory (VDRL) and fluorescent treponemal antibody absorption (FTA-ABS) assays for syphilis (see Ch. 82).

An important goal in the management of Hansen disease is the prevention of disability. The WHO divides Hansen disease-related disability into three categories: grade 0, normal protective sensation; grade 1, loss of protective sensation of hands, feet, or eyes; and grade 2, visible deformities including ulcers, claw hand, foot drop, bone resorption, and lagophthalmos. Early detection of neuropathy is critical to prevent disability, but unfortunately the diagnosis of Hansen disease is often delayed for 1–2 years[48a]. Methods to detect nerve damage range from simple tests such as light touch with a cotton swab or monofilament to techniques such as nerve conductive studies, high resolution ultrasound, and MRI[48b].

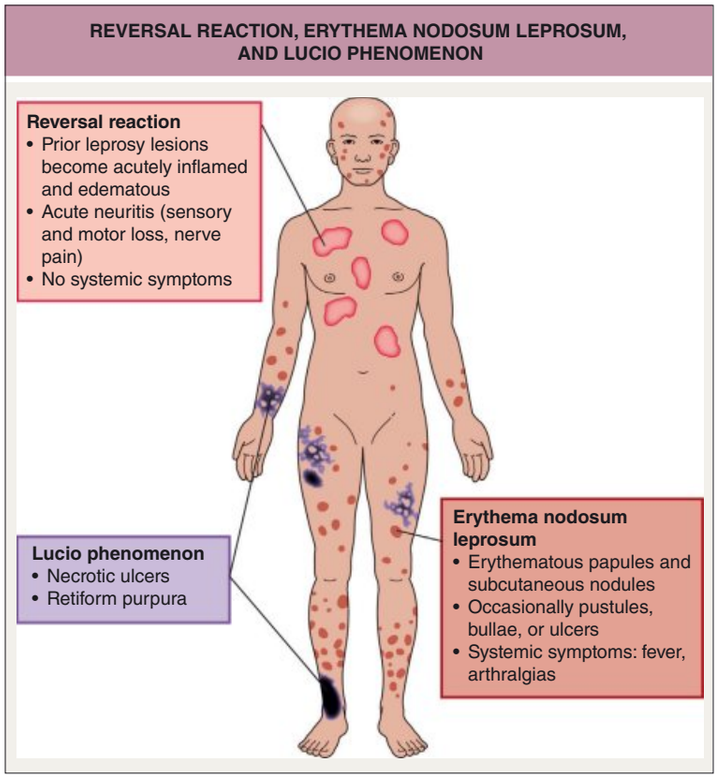


Fig. 75.9 Leprosy reactions – reversal reaction (type 1), erythema nodosum leprosum (type 2), and Lucio phenomenon.

TWO MAJOR TYPES OF LEPROSY REACTIONAL STATES		
	Type 1 – reversal reaction	**Type 2 – erythema nodosum leprosum**
Immune mechanism	Delayed-type hypersensitivity reaction with a Th1 cytokine pattern	Excessive humoral immunity with a Th2 cytokine pattern and formation of immune complexes; may be accompanied by increased cell-mediated immunity and neutrophils
Leprosy category	Borderline (BT, BB, BL) or tuberculoid with immunologic recovery (upgrading)	Lepromatous and BL > BB; especially patients with a high bacterial index
Clinical characteristics	• Increased inflammation in established skin lesions; in severe form, swelling and ulceration of facial lesions • Acute nerve pain or tenderness (neuritis) and loss of function • Recent (<6 month history) or progressive neurologic impairment in the absence of painful nerves • "Hot" abscess of nerve*	• New papular or nodular skin lesions • Fever, myalgias, malaise • Severe joint swelling and pain • Iridocyclitis • Lymphadenitis • Hepatosplenomegaly • Orchitis • Glomerulonephritis • Mild disease – low-grade fever, few ENL lesions of extremities, no internal organ involvement • Severe disease – high fever, numerous recurrent ENL nodules which can be pustular or ulcerative, internal organ involvement
Treatment	Prednisone: 40 mg per day tapered over 12 to 36 weeks, depending upon whether paucibacillary vs multibacillary and specific protocol†	Thalidomide: for severe disease, 400 mg po daily then taper to 300 mg po daily once reaction under control followed by taper to the lowest dose without a flare; latter dose then continued 2–3 months

*As opposed to "cold" abscess of nerve in TT leprosy.
†e.g. International Federation of Anti-Leprosy Associations (ILEP) protocol (https://ilepfederation.org/wp-content/uploads/2020/02/LG2.pdf)

Table 75.3 Two major types of leprosy reactional states[12,23,40]. Secondary amyloidosis may occur in patients with type 2 reactional states.

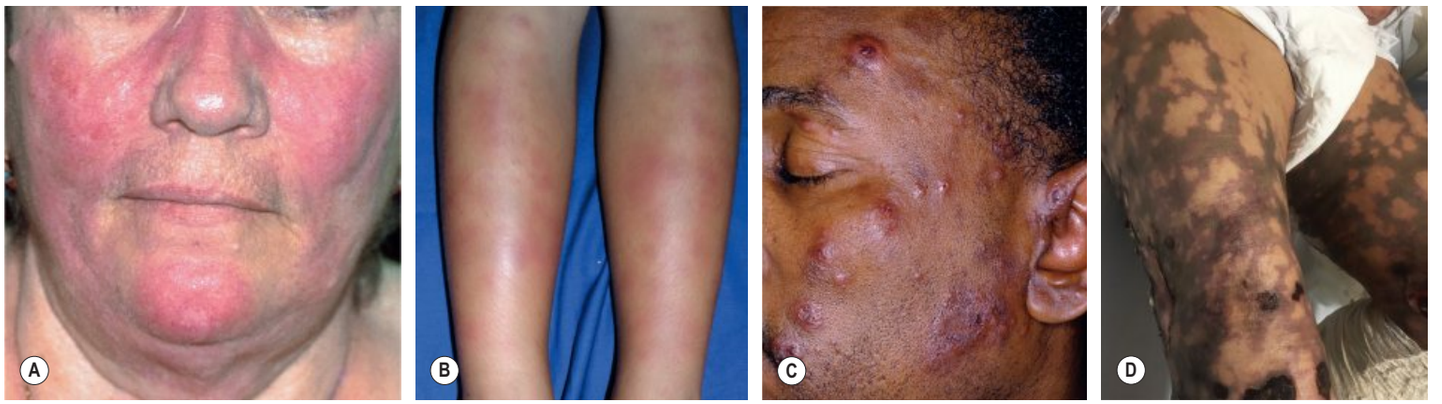


Fig. 75.10 Leprosy reactions. A Type 1 "upgrading" reaction with lupus erythematosus-like facial involvement in a "butterfly" distribution with marked inflammation. **B** Erythema nodosum leprosum, a type 2 reaction, presenting with erythematous nodules on the legs. **C** Type 2 reaction presenting with red facial papulonodules due to immune complex-mediated small vessel vasculitis in patients with the lepromatous form of Hansen disease. **D** Lucio phenomenon presenting with retiform purpura and necrotic ulcers. *C, Courtesy Louis A. Fragola, Jr, MD; D, Courtesy Carlos G. Wambier, MD, PhD.*

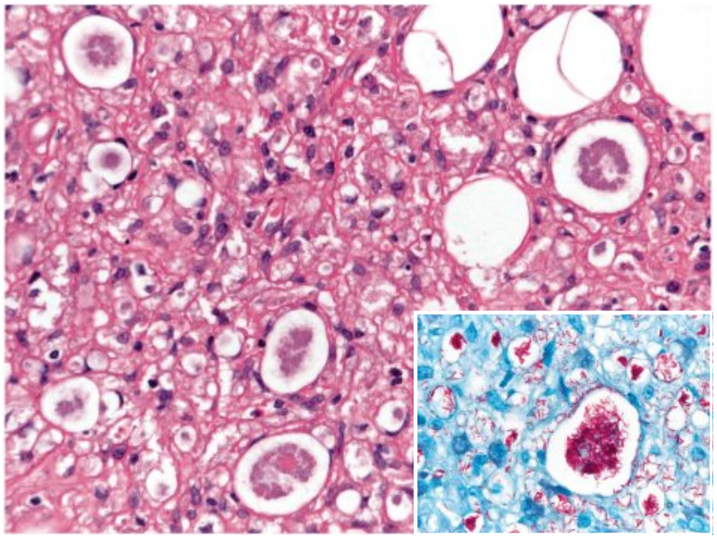


Fig. 75.11 Lepromatous form of Hansen disease. Diffuse dermal infiltrate of foamy histiocytes; note the globi which represent clumping of mycobacteria. Fite–Faraco stain highlighting the numerous bacilli as well as globi (inset). *Courtesy Lorenzo Cerroni, MD.*

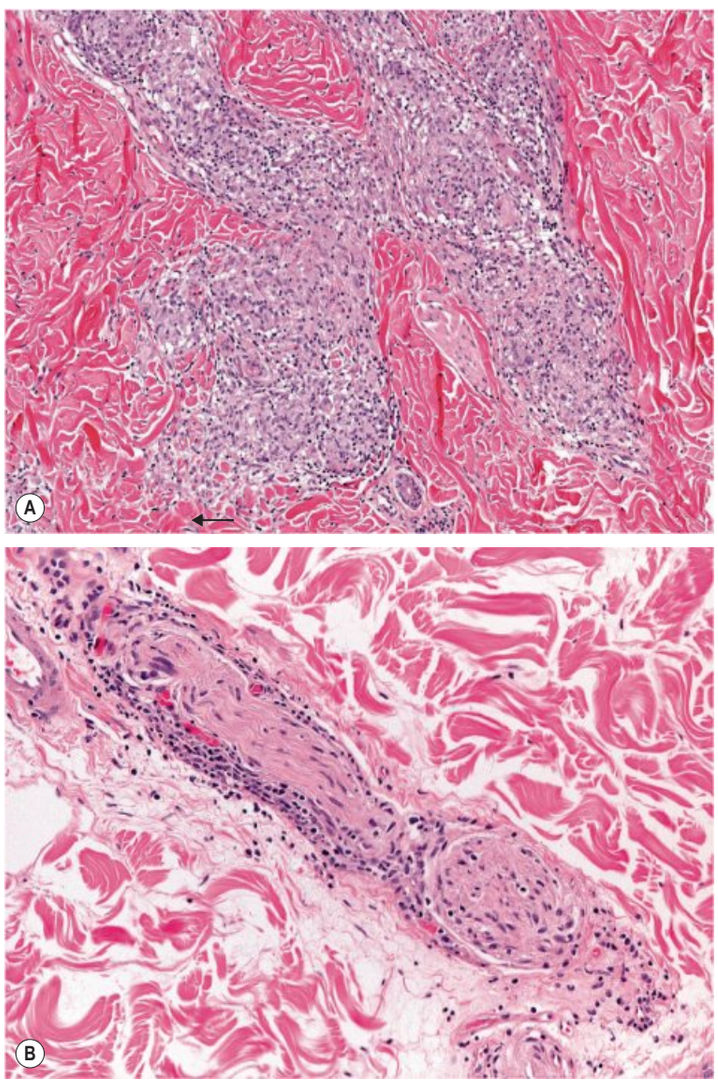


Fig. 75.12 Tuberculoid form of Hansen disease. A Granulomatous nodular infiltrate within the dermis. **B** Nerve involvement characterized by a sparse perineural infiltrate with lymphocytes and histiocytes. *Courtesy Lorenzo Cerroni, MD.*

PCR TESTING FOR *MYCOBACTERIA LEPRAE* AND *M. LEPROMATOSIS*	
Skin biopsy specimen	**Comments**
• 4–5 mm punch biopsy that includes subcutaneous fat	• Ensures that involved nerves, often within the deep dermis, are included
• Preferred site of biopsy is active margin of lesion	
• Formalin-fixed, paraffin-embedded tissue block – *or* – tissue within formalin*	• Testing *cannot* be performed on tissue sections on a slide
• Drug resistance can also be assessed	
*Requires expedited delivery to avoid prolonged exposure to formalin.	

Table 75.4 PCR testing for *Mycobacteria leprae* and *M. lepromatosis*. In addition to PCR, secondary histopathologic review is performed. This evaluation is provided free-of-charge to patients and submitting facilities within the USA and its territories by the National Hansen's Disease Program in Baton Rouge, LA (consultation request form is available online at www.hrsa.gov/sites/default/files/hrsa/hansens-disease/skin-biopsy-protocol-form.pdf).

Differential Diagnosis

Skin diseases that may be confused with the different cutaneous presentations of Hansen disease are outlined in Table 75.5.

Treatment

Safety, effectiveness, and ease of administration represent key considerations in multidrug therapy for Hansen disease. The WHO 2018 guidelines recommend a three-drug regimen consisting of rifampin (rifampicin), dapsone, and clofazimine for all patients with Hansen disease, with a treatment duration of 6 months for paucibacillary (PB) disease and 12 months for multibacillary (MB) disease (Table 75.6)[38]. This change from only two drugs (rifampin and dapsone) for PB disease in the previous WHO guidelines was based on better outcomes with three drugs as well as simplification of treatment (e.g. only one type of blister pack) and reducing the impact of misclassification of MB as PB disease. Of note, Chinese patients with a HLA-B*13-01 polymorphism are at high risk of hypersensitivity to dapsone[49].

In the US, the National Hansen Disease Program recommends a longer duration of treatment (1 year for PB, 2 years for MB), with no clofazimine for PB disease and the option of daily (rather than monthly) rifampin administration[50]. For patients with PB disease, therapy with *r*ifampin, *o*floxacin, and *m*inocycline ("ROM scheme"), including a single dose for individuals with a single lesion, has also produced good results[51,52].

Multidrug therapy is extremely effective. Importantly, after the first dose, the patient is no longer infectious to others. Granular or beaded bacilli may be found in biopsy specimens following initiation of treatment but are considered to be non-viable. Hansen disease relapses are rare in the setting of recommended therapy/treatment regimens, affecting <5% of patients over a 5–10 year follow-up period. In a study of 1932 patients from endemic countries with MB disease, molecular evidence of resistance to rifampin, dapsone, and/or ofloxacin was present in 8% of cases[53]. Antimicrobial resistance to rifampin and dapsone is due primarily to mutations in *rpoB* (encodes DNA-directed RNA polymerase β subunit) and *folp1* (encodes dihydropteroate synthase), respectively.

Alternative antibiotics such as minocycline, clarithromycin, and ofloxacin can be used when there is resistance to or intolerance of first-line agents (see Table 75.6). Drugs that may play a significant role in the treatment of Hansen disease in the future include other quinolones (e.g. moxifloxacin) and ansamycins[54–56]. Rifapentine (a rifampin derivative) has higher peak serum concentrations, a longer serum half-life, and more bactericidal activity against *M. leprae* than rifampin. In addition, moxifloxacin appears to be more bactericidal than ofloxacin. Thus, the combination of rifapentine, moxifloxacin, and minocycline (PMM) may be superior to rifampin, ofloxacin, and minocycline (ROM)[56].

For the two major inflammatory reactions, additional medications are often required. Oral prednisone is used for type 1 (reversal) reactions, while thalidomide is the principal therapy for type 2 reactions (erythema nodosum leprosum; see Table 75.3). Systemic corticosteroids are also recommended for the Lucio phenomenon. Although thalidomide

CLINICAL DIFFERENTIAL DIAGNOSIS OF HANSEN DISEASE	
Hypopigmented lesions	• Mycosis fungoides, including the hypopigmented variant • Sarcoidosis, but the hypopigmented variant is usually more papulonodular • Postinflammatory hypopigmentation, pityriasis alba • Tinea versicolor
Circinate (annular) plaques	• Mycosis fungoides and other forms of cutaneous lymphoma • Sarcoidosis • Psoriasis • Reactive granulomatous dermatitis • Granuloma annulare, erythema annulare centrifugum • Tinea corporis
Infiltrated plaques/ nodules	• Lymphoma • Sarcoidosis • Other infections (e.g. dimorphic fungal infection, tuberculosis, leishmaniasis, syphilis) • For DDx of leonine facies, see Table 46.5
Neurologic findings	• Peripheral neuropathy due to other disorders (e.g. diabetes mellitus, Guillain–Barré syndrome, nutritional deficiencies, Lyme disease, syringomyelia)
Deforming acral features	• Systemic sclerosis • Tabes dorsalis • Dupuytren contracture
Type 1 reaction	• Acute cutaneous lupus erythematosus • Cellulitis and pseudocellulitis • Drug reaction • Misdiagnosis as worsening of disease
Type 2 reaction	• Sweet syndrome • Medium-vessel vasculitis • Panniculitides, e.g. erythema nodosum*, lupus panniculitis • Infections, including other mycobacterial, bacterial, dimorphic fungal, and other opportunistic fungal
*Lesions favor the shins, erythema nodosum leprosum lesions are widespread.	

Table 75.5 Clinical differential diagnosis of Hansen disease.

remains the treatment of choice for type 2 reactions, teratogenicity is a major limitation and it is unavailable in many countries where Hansen disease is endemic. Lenalidomide and pomalidomide are thalidomide analogues with different side-effect profiles (e.g. more myelosuppression, less neuropathy), with potential utility in the treatment of type 2 reactions. Cyclosporine and methotrexate have been used in both type 1 and type 2 reactions, and additional drugs with possible benefit for type 2 reactions include phosphodiesterase 4 inhibitors (e.g. apremilast), TNF inhibitors, high-dose clofazimine, chloroquine, and pentoxifylline[56–58].

Although Hansen disease is now considered a curable disease with a good prognosis and excellent survival rate, it can still be incapacitating and stigmatizing. It is very important to make the diagnosis as soon as possible and to examine contacts, since early treatment prevents disability. The WHO 2018 guidelines recommended chemoprophylaxis with a single dose of rifampin to adults and children ≥2 years of age in contact with Hansen disease patients[38]. However, concerns about cost-effectiveness, stigma, and drug resistance have prevented implementation[59]. A single dose of rifapentine has also been shown to prevent Hansen disease in household contacts[59a]. Recognition of Hansen disease in its initial phases by healthcare professionals as well as the general population in endemic countries is essential in order to reduce the impact of this disease[9].

CUTANEOUS TUBERCULOSIS

Key features

- Infection of the skin due to *Mycobacterium tuberculosis*, an acid- and alcohol-fast bacillus
- A resurgence of tuberculosis (TB) in the late 1980s and early 1990s resulted from the HIV epidemic, emergence of resistant strains of *M. tuberculosis*, and a decline in TB control efforts
- Exogenous exposure produces primarily the tuberculous chancre and TB verrucosa cutis
- Endogenous infection can lead to scrofuloderma, miliary TB, and lupus vulgaris
- Tuberculids include a papulonecrotic eruption, lichen scrofulosorum, and erythema induratum

WHO 2018 GUIDELINES FOR THE TREATMENT OF HANSEN DISEASE				
Recommended first-line regimen				
Age group	***Drug***	***Dosage and frequency***	***Duration***	
			MB	***PB***
Adult	Rifampin	600 mg monthly	12 months	6 months
	Clofazimine	300 mg monthly + 50 mg daily		
	Dapsone	100 mg daily		
Children ages 10–14 years and weight ≥40 kg	Rifampin	450 mg monthly	12 months	6 months
	Clofazimine	150 mg monthly + 50 mg every other day		
	Dapsone	50 mg daily		
Children age <10 years or weight <40 kg	Rifampin	10 mg/kg monthly	12 months	6 months
	Clofazimine	100 mg monthly + 50 mg twice weekly		
	Dapsone	2 mg/kg daily		
Recommended regimens for drug-resistant disease (adult doses)				
Resistance type	Treatment for first 6 months (daily)		Treatment for next 18 months (daily)	
Rifampin resistance	Ofloxacin 400 mg* + minocycline 100 mg + clofazimine 50 mg		Ofloxacin 400 mg* – *or* – minocycline 100 mg + clofazimine 50 mg	
	Ofloxacin 400 mg* + clarithromycin 500 mg + clofazimine 50 mg		Ofloxacin 400 mg* + clofazimine 50 mg	
Rifampin and ofloxacin resistance	Clarithromycin 500 mg + minocycline 100 mg + clofazimine 50 mg		Clarithromycin 500 mg – *or* – minocycline 100 mg + clofazimine 50 mg	
*Ofloxacin 400 mg can be replaced by levofloxacin 500 mg or moxifloxacin 400 mg.				

Table 75.6 WHO 2018 guidelines for the treatment of Hansen disease[38]. Rifampicin is another name for rifampin. MB, multibacillary; PB, paucibacillary. *Adapted from World Health Organization. Guidelines for the diagnosis, treatment and prevention of leprosy. Table 3. https://apps.who.int/iris/bitstream/handle/10665/274127/9789290226383-eng.pdf?ua=.*

Introduction

Tuberculosis (TB) has affected humans since prehistoric times. There was, however, a worldwide explosion in its incidence in the late 1980s and early 1990s, and consequently a resurgence of cutaneous TB[2,60–63]. This phenomenon has been attributed to the HIV epidemic, the emergence of resistant strains of *Mycobacterium tuberculosis*, increased use of immunosuppressive therapies, more migration of people around the world, and a decline in TB control efforts[61,62], superimposed on the pre-existing factors of poverty and malnutrition.

History

There are paleopathologic findings that suggest there were *M. tuberculosis* infections as early as 3700 BCE in Egypt, and 2500–1500 BCE in Europe. Utilizing PCR, *M. tuberculosis* DNA was detected in mummified remains from ancient times. In 1826, Laennec first reported cutaneous TB in the form of a "prosector's wart". Rokitansky and Virchow subsequently described the histologic features of cutaneous TB in detail. The discovery of *M. tuberculosis* by Koch in 1882 and the advances in descriptive pathology during the nineteenth century helped establish cutaneous TB as part of the spectrum of this infectious disease[62,63].

Epidemiology

M. tuberculosis is not particularly virulent, as only 5% to 10% of infections lead to clinical disease in immunocompetent hosts. This bacterium has a worldwide distribution (Fig. 75.13), with >6 million people newly diagnosed with TB in 2021[64]. Cutaneous involvement is relatively uncommon, accounting for ~1%–2% of extracutaneous manifestations of TB[65]. The incidence of cutaneous TB parallels that of pulmonary TB and is therefore higher in low-income countries and impoverished populations. HIV infection, immunosuppressive therapies (especially TNF inhibitors; see Ch. 128), and innate defects of the IL-12/IFN-γ axis (see Ch. 60) place individuals at greater risk for the development and reactivation of TB.

Pathogenesis

M. tuberculosis is the predominant etiologic agent of cutaneous TB. Occasionally, *M. bovis* and bacille Calmette–Guérin (BCG), an attenuated strain of *M. bovis*, may produce skin lesions[61].

M. tuberculosis is a non-motile, aerobic, non-spore-forming, filamentous rod. It is an acid- and alcohol-fast bacillus that has a waxy coating with a high lipid content, which makes the organism resistant to degradation after phagocytosis[66]. *M. tuberculosis* produces multiple proteins involved in immune system invasion, allowing it to survive inside phagocytic cells[67].

M. tuberculosis disseminates primarily via inhalation of aerosolized droplets of saliva from individuals with active disease; transmission by ingestion or inoculation can also occur[66]. Intact skin provides an effective protective barrier against invasion of the organism, but a break in the mucocutaneous barrier can facilitate entrance[68]. Untreated infected individuals who do not have underlying medical problems have a 5% to 10% lifetime risk of progression to active TB; this risk increases substantially with immunosuppression, e.g. due to HIV infection or treatment with medications such as TNF inhibitors.

Studies using a model of zebrafish infected with *M. marinum* have demonstrated that granulomas, which are classically considered as host-protective structures formed to control infection, actually contribute to early bacterial growth and facilitate spread of infection[69] (Fig. 75.14). Mycobacteria induce granuloma formation by releasing the early secreted antigenic target 6 (ESAT-6) protein, which stimulates neighboring epithelial cells to produce matrix metalloproteinase-9 (MMP-9). MMP-9 enhances recruitment of macrophages that contribute to bacterial proliferation and spread as well as maturation of the nascent granuloma[70]. Increased production of other MMPs (e.g. MMP-1, MMP-3) has been shown to drive tissue destruction in TB[71]. Eventually, development of adaptive immunity results in the curtailment, but not eradication, of bacterial growth by $CD4^+$ and $CD8^+$ effector T cells. The mature granuloma therefore represents an equilibrium between mycobacterial growth and the host immune response, and MMPs represent potential targets for antimycobacterial therapy.

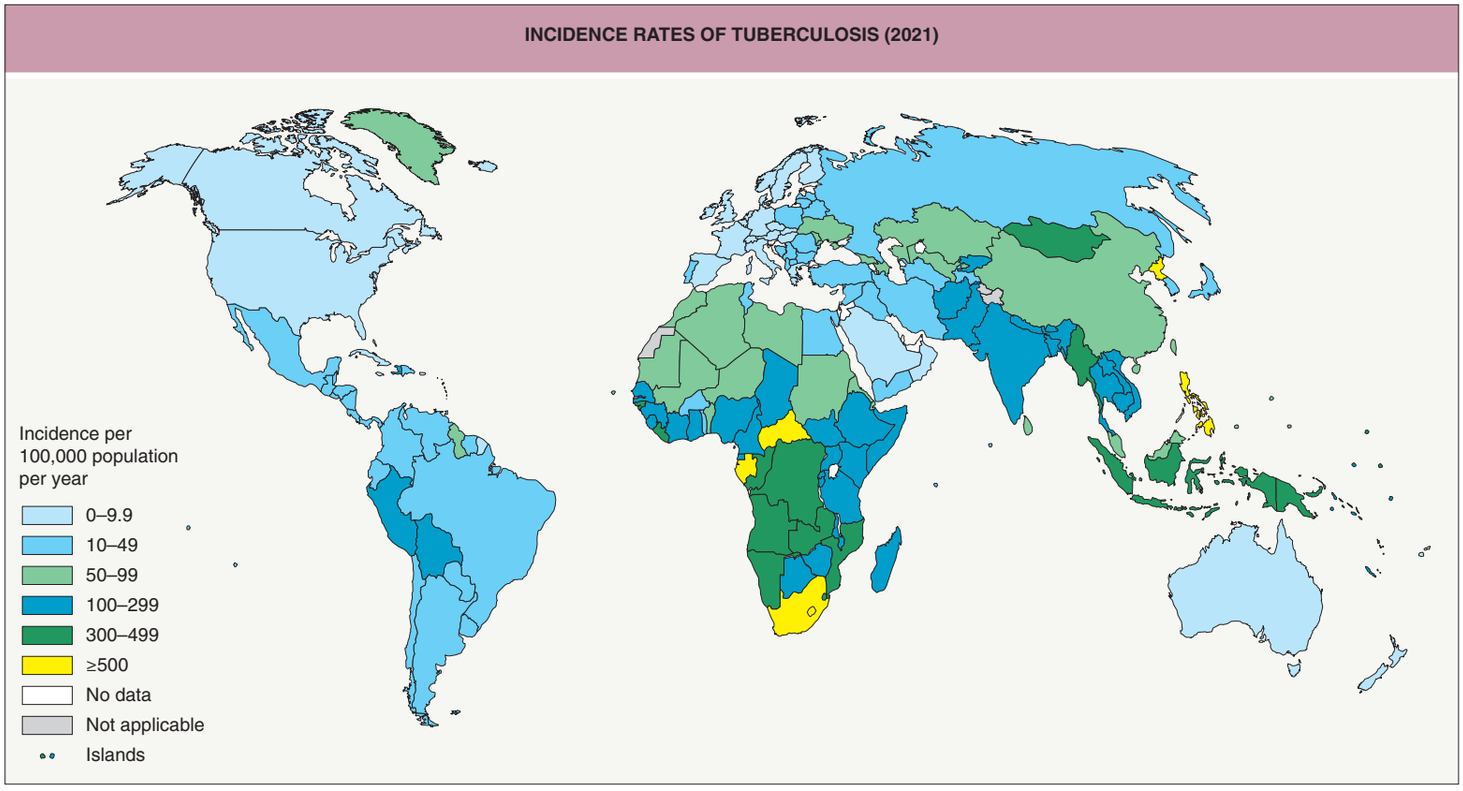


Fig. 75.13 Tuberculosis incidence rates, 2021. *Reproduced from the Global Tuberculosis Report 2022. Geneva: World Health Organization, 2022. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-1-tb-incidence*

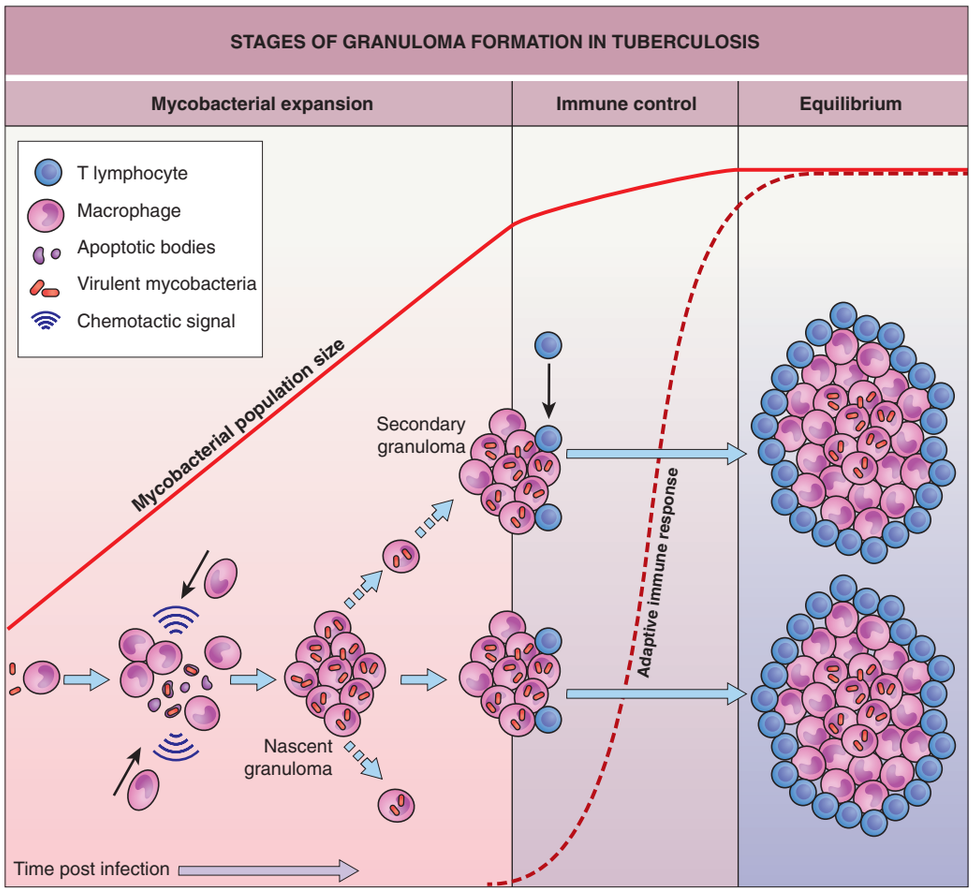


Fig. 75.14 Stages of granuloma formation in tuberculosis. The initial stage of tuberculosis is characterized by expansion of the mycobacterial population in the absence of adaptive immunity. Mycobacterial multiplication and spread are facilitated by the formation of the nascent granuloma. Infected macrophages undergo apoptosis and recruit additional macrophages, which phagocytose remnants of infected cells and their mycobacterial contents. Some of these newly infected macrophages then seed secondary granuloma formation. When adaptive immunity eventually occurs, $CD4^+$ and $CD8^+$ effector T cells curtail mycobacterial growth. Although this controls the infection, it is not eradicated. The mature granuloma therefore represents an equilibrium between mycobacterial proliferation and the host response. *Adapted with permission from Bold TB, Ernst JD. Who benefits from granulomas, mycobacteria or host? Cell 2009;136:18–19.*

The interaction of T cells and mycobacterial antigens, which are displayed on the surface of antigen-presenting cells, induces the liberation of interferons and other cytokines. These substances promote the activation and expression of MHC class II on antigen-presenting cells as well as the IL-2 receptor on T cells. During the initial sensitization, memory T cells are generated and remain for decades in lymphoid organs and the circulation[61]. In mice, the intracellular pathogen resistance 1 gene (*Ipr1*) within the supersusceptibility to tuberculosis 1 (sst1) locus encodes a protein that mediates innate immunity to *M. tuberculosis* and other intracellular organisms. Ipr1 is expressed in macrophages and limits the multiplication of *M. tuberculosis* within these cells[72]. IFN-γ-induced nitric oxide production also contributes to defense against *M. tuberculosis* by modulating macrophage responses (e.g. via activation of hypoxia inducible factor-1α) and repressing a neutrophil recruitment cascade that promotes bacterial replication[73].

The sensitization status of the host to mycobacterial antigens (e.g. previously infected versus never exposed), the degree of cell-mediated immunity of the host, the route of infection, and the pathogenicity of the infective strain of mycobacteria determine the resulting infection (Table 75.7). In immunocompromised hosts, cell-mediated immunity is impaired; as a consequence, there may be reactivation of quiescent disease[61,68].

Clinical Features and Pathology

Cutaneous TB has a wide variety of clinical presentations[3,61,63,66,74]. Direct inoculation of *M. tuberculosis* from an exogenous source can lead to tuberculous chancre, TB verrucosa cutis, and occasionally, lupus vulgaris. Skin involvement due to endogenous infection may appear as scrofuloderma, acute miliary TB, a tuberculous gumma, orificial TB, and lupus vulgaris (see Table 75.7). In addition, there are cutaneous tuberculids, which represent immune reactions against *M. tuberculosis* or its antigens.

Cutaneous tuberculosis

A *tuberculous chancre* develops 2 to 4 weeks after the inoculation of *M. tuberculosis* into the skin of an individual without a history of TB. It is a painless, firm, red–brown papulonodule that slowly enlarges, eventually eroding to form a sharply demarcated ulcer[3,61,66]. Frequently there is spread to draining lymphatics and regional lymph nodes[61]; the combination of the latter with a tuberculous chancre is analogous to the Ghon complex in the lung[61,66]. The skin lesion usually heals spontaneously within 3 to 12 months, leaving an atrophic scar and calcified regional lymph nodes. The tuberculous chancre may occasionally evolve into verrucous plaques, scrofuloderma-like lesions, or lupus vulgaris[63,66].

Tuberculosis verrucosa cutis results from exogenous inoculation of *M. tuberculosis* at sites prone to trauma in previously infected individuals[3,66]. The lesion begins as a small, asymptomatic, indurated wart-like papule with a subtle inflammatory rim (Fig. 75.15). It gradually enlarges, often in a serpiginous manner, to form a firm reddish–brown verrucous plaque. The center of the lesion may become fluctuant, with pus and keratinaceous debris expressed by slight pressure[3,63,66]. After several years, the plaque can heal spontaneously[61].

Scrofuloderma begins as a firm, deep-seated, subcutaneous nodule that has accumulated inflammatory material and necrotic tissue, best characterized as a "cold abscess". The suppurative nodule later becomes fluctuant and drains, with ulceration and sinus tract formation (Fig. 75.16). Because of the drainage, the bacilli secondarily infect the overlying dermis. The borders of the ulcers are often blue, the margins are undermined, and the base is covered with soft granulation tissue. Multiple ulcers can appear. After healing, keloids and retracted tethered scars develop at the sites of infection. The original focus of TB is usually underlying lymph nodes or bones, but it may be joints or the epididymis[3,61,63,75].

Orificial tuberculosis usually results from autoinoculation of *M. tuberculosis*, although occasionally it has an exogenous origin. Affected individuals typically have advanced systemic TB in the setting of impaired cell-mediated immunity (CMI). The mucosal or cutaneous lesions occur within or adjacent to a natural orifice that is draining an active tuberculous infection, primarily pulmonary, intestinal, or anogenital. The most common location is the mouth, especially the tongue. The initial lesion is an edematous red papule that ulcerates (Fig. 75.17) and develops undermined edges. The ulcers are painful, recalcitrant to treatment, and do not tend to heal spontaneously[3,66].

CLINICAL PRESENTATIONS OF CUTANEOUS TUBERCULOSIS							
	Tuberculous chancre	**Tuberculosis verrucosa cutis**	**Scrofuloderma**	**Orificial tuberculosis**	**Lupus vulgaris**	**Acute miliary tuberculosis**	**Tuberculous gumma**
Synonyms	Primary inoculation tuberculosis, cutaneous primary complex	Warty tuberculosis, prosector's wart, lupus verrucosus	Tuberculosis cutis colliquativa	Acute tuberculous ulcer, tuberculosis cutis orificialis	Tuberculosis luposa	Tuberculosis cutis disseminata, tuberculosis cutis acuta generalisata	Metastatic tuberculous ulcer, metastatic tuberculous abscess
Incidence	Rare except in Asia; 1%–2% of cutaneous tuberculosis	Most common form of cutaneous tuberculosis (e.g. ~40% of cases in Hong Kong)	Common in immigrants from developing countries	Rare	Low: 10%–15% of cutaneous tuberculosis; women affected 2–3 times more often than men	Rare; infants and young children, seldom adolescents or adults	Children with low socioeconomic status or immunocompromised hosts
Transmission	Inoculation into skin and/or mucosa of previously uninfected person, i.e. with no specific immunity	Inoculation into skin and/or mucosa of previously infected person with moderate or high immunity	Contiguous involvement of skin overlying a focus of tuberculosis, usually in lymph node or bone. Also reported after BCG vaccination	Autoinoculation of mucosa or skin adjacent to a natural orifice draining an active internal tuberculous infection	Direct extension; hematogenous or lymphatic spread from a tuberculous focus; reinfection; BCG vaccination	Hematogenous dissemination from primary lung focus in patient with low immunity; may follow viral infection	Acute hematogenous dissemination from a primary focus during periods of bacillemia and lowered resistance
Tuberculin skin test	Early: negative Later: positive	Positive	Usually positive	Variable, often negative	Usually positive	Usually negative	Usually negative
Histopathology	• Acute: nonspecific neutrophilic inflammation with necrosis; bacilli • Later: granulomatous inflammation with central caseation, epithelioid and Langhans giant cells; disappearance of bacilli	Acute inflammation in the epidermis, pseudoepitheliomatous hyperplasia, microabscesses in upper dermis, sparse granulomatous foci; occasionally bacilli present	Tuberculous granulation tissue and caseation necrosis in the deeper dermis; bacilli can be isolated from pus	Nonspecific inflammatory infiltrate and necrosis, some tubercles with caseation deep in dermis; bacilli easily found	Well-developed tubercles with scant caseation, nonspecific inflammatory infiltrate; no visible bacilli	Necrosis, nonspecific inflammatory infiltrate surrounded by macrophages, sometimes developing into small abscesses; abundant bacilli	Massive necrosis and abscess formation; large number of bacilli
Diagnosis	Histology and culture PCR IGRA*	Culture PCR IGRA	Culture PCR IGRA	Histology and culture PCR Presence of another focus of TB IGRA*	Histology and culture PCR IGRA	Smear, histology and culture; PCR Presence of another focus of TB IGRA*	Culture and histology PCR IGRA*
Differential diagnosis	Other pyogenic ulcers and chronic chancriform lesions, including the following: sporotrichosis, dimorphic or opportunistic fungal infections, *M. marinum* infection, nocardiosis, tularemia, syphilis, cat scratch disease	Warts, verrucous fungal infections (e.g. chromomycosis), tertiary syphilis, hypertrophic lichen planus	Dimorphic or opportunistic fungal infections, non-tuberculous mycobacterial infections, syphilitic gumma, actinomycosis, chronic bacterial osteomyelitis, adenitis with drainage, hidradenitis suppurativa, severe acne conglobata	Painful ulcerative diseases that affect orifices and perioricial skin: HSV, recurrent aphthous stomatitis, pemphigus, histoplasmosis	Sarcoidosis, discoid lupus erythematosus, dimorphic fungal infections, leishmaniasis, tertiary syphilis, squamous cell carcinoma	Varicella, enteroviral exanthems, rickettsialpox, PLEVA	Panniculitis, dimorphic or opportunistic fungal infection, syphilitic gumma, hidradenitis suppurativa

*May have an indeterminate result early in the disease course or in immunocompromised patients.

Table 75.7 Clinical presentations of cutaneous tuberculosis. BCG, bacille Calmette–Guérin; IGRA, interferon-γ release assay (e.g. QuantiFERON® TB Gold Plus, T-SPOT®.TB; see Table 75.8); PLEVA, pityriasis lichenoides et varioliformis acuta.

Lupus vulgaris is a form of cutaneous TB that occurs in previously sensitized individuals who have a strongly positive delayed-type hypersensitivity reaction to tuberculin due to intact CMI. It can develop secondarily from TB verrucosa cutis or scrofuloderma as well as from other endogenous and exogenous sources; lupus vulgaris also occasionally arises following BCG inoculation. The typical lesion is a red–brown plaque composed of papulonodules with an "apple-jelly" color on diascopy (Fig. 75.18). As the plaque expands, central scarring often develops. This can lead to substantial tissue destruction over a period of years. Clinical presentations of lupus vulgaris include: (1) plaque-type; (2) ulcerative or mutilating; (3) vegetating; (4) tumor-like; and (5) papulonodular. The head and neck region is the most commonly affected site, in particular the nose, cheeks, and ear lobes[3,63,66]. Mucosa, especially oral, can also be involved.



Fig. 75.15 Tuberculosis verrucosa cutis. A wart-like papule at the site of exogenous inoculation in a patient with immunity against *M. tuberculosis*.



Fig. 75.16 Scrofuloderma. Plaques and nodules with central ulceration as well as resultant scarring with retraction.

The initial lesions of *miliary tuberculosis* are pinhead-sized, bluish-red papules capped by minute vesicles. The vesicles develop a tiny central umbilication followed by crusting. When the papules heal, they leave a residual white scar with a brownish rim[3,61,66]. The cutaneous lesions are the result of mycobacteremia, and the primary focus is often in the lungs.

A *tuberculous gumma* is also due to mycobacteremia with cutaneous seeding. It can present as either a firm subcutaneous nodule that slowly softens or an ill-defined fluctuant swelling. The overlying skin gradually breaks down to form an undermined ulcer, often with sinus tract formation. The extremities are more often affected than the trunk[3].

A skin biopsy of early lesions of cutaneous tuberculosis typically shows a mixed infiltrate that includes lymphocytes, neutrophils, and plasma cells. This is followed after a few weeks by granulomatous inflammation (tuberculoid granulomas; see Fig. 0.26A), sometimes with central caseation. Acid-fast bacilli are usually abundant in early lesions, but are difficult to find when granulomas develop.

Tuberculids

The tuberculids represent a group of disorders that classically were associated with systemic TB. They are considered immune reactions within the skin due to hematogenous dissemination of *M. tuberculosis* or its antigens from a primary source, in an individual with strong antituberculous CMI. Often beginning as an immune complex-mediated reaction, they evolve into a granulomatous inflammatory response.

There is an ongoing debate as to the pathogenesis of tuberculids[3,63,74]. Arguments in favor of an association with *M. tuberculosis* include a positive tuberculin skin reaction in affected patients; detection by PCR of *M. tuberculosis* DNA within lesions of erythema induratum, lichen scrofulosorum, and papulonecrotic tuberculid; and improvement with antituberculous therapy. In addition, many skin lesions demonstrate granulomatous



Fig. 75.17 Orificial tuberculosis. A non-healing ulcer of the nasal mucosa. *Courtesy Louis A. Fragola, Jr, MD.*

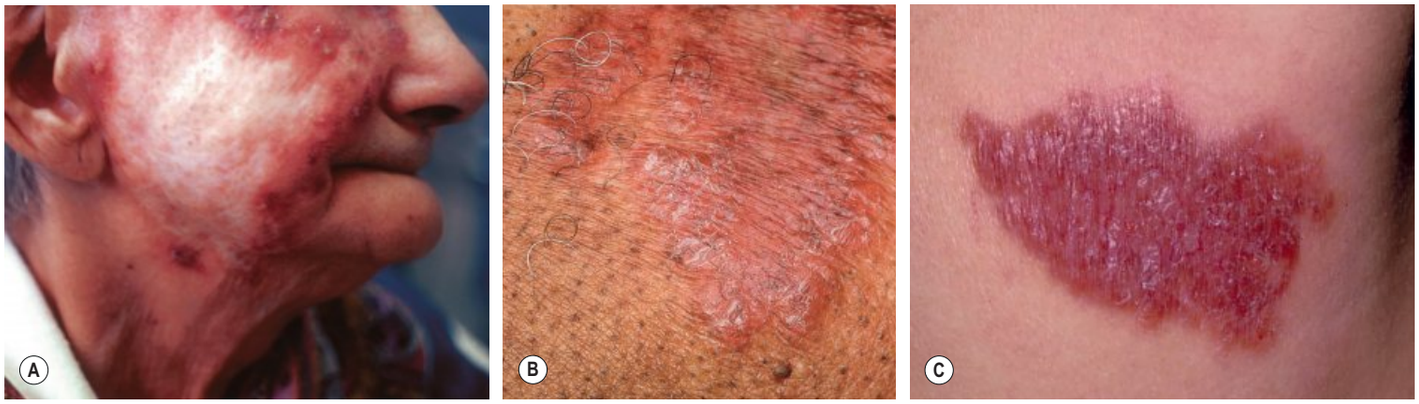


Fig. 75.18 Lupus vulgaris. A Annular granulomatous plaque with central scarring. **B** Coalescing pink–brown papules. **C** Red–brown plaque on the neck. *C, Courtesy Eugene Mirrer, MD.*

inflammation. However, there are multiple alternative causes of granulomatous inflammation and an active focus of TB is usually not found in patients with tuberculids; only a positive tuberculin test or IFN-γ release assay reflecting past exposure to TB is a consistent finding. The argument that corticosteroids can improve these eruptions is not a particularly strong one against an association, since other infectious diseases, e.g. viral hepatitis, can improve with such therapy and one would expect an antigen-driven inflammatory process to respond to corticosteroids. Although a positive PCR is not absolute proof of pathogenesis, in the setting of appropriate controls, it provides strong evidence in favor of an association.

Papulonecrotic tuberculid is seen most frequently in children and young adults. It presents with dusky red papules or papulopustules that are widely distributed in a somewhat symmetric pattern and favor the extensor aspects of the extremities and buttocks (Fig. 75.19). Individual lesions may have central necrosis and are usually asymptomatic; occasionally there is associated pruritus. Usually there is spontaneous healing of individual lesions, often with scar formation. Multiple cyclic eruptions are characteristic, even after antimycobacterial therapy. PCR for mycobacterial DNA and the tuberculin test are positive[3,63]. Histologically, there is evidence of leukocytoclastic or granulomatous vasculitis and wedge-shaped necrosis in the dermis. The history and clinical appearance aid in the diagnosis, which is bolstered by the histologic findings. The differential diagnosis often includes pityriasis lichenoides et varioliformis acuta (PLEVA) and small vessel vasculitis.

The early lesions of *lichen scrofulosorum*, a rare disorder, are firm, typically perifollicular, pink or yellow–brown, tiny flat-topped papules with variable scale. These asymptomatic papules are grouped in clusters, predominantly on the trunk. Lesions may persist for months and then disappear without scarring. Although it is seen in all age groups, children with nodal or skeletal TB are most frequently affected. This type of tuberculid has also been reported after BCG vaccination and can be triggered by tuberculin testing in highly reactive patients. Histologic examination demonstrates superficial granulomas around hair follicles and sweat ducts, with little or no caseation necrosis. No bacilli are found; however, PCR testing has demonstrated *M. tuberculosis* DNA within lesions. The clinical differential diagnosis includes lichen nitidus, lichen planus, and other lichenoid dermatoses (see Ch. 11) as well as "id" reactions, Blau syndrome, sarcoidosis, and secondary syphilis[3,63,74].

Erythema induratum (*nodular vasculitis*) is a form of lobular panniculitis associated with *M. tuberculosis* infection in a subset of affected individuals, especially in countries with a high prevalence of TB (see Ch. 100). The term *erythema induratum of Bazin* is reserved for cases related to *M. tuberculosis*. Both immune complex deposition, which may play a role in the vasculitic component, and a delayed-type hypersensitivity reaction to mycobacterial antigens are thought to be involved in the pathogenesis[74]. Women are most commonly affected (80%–90% of patients), with peaks in incidence during early adolescence and around menopause.

Symptoms often begin after exposure to low temperatures. Typically, subcutaneous nodules appear on the calves of both legs; they may involute or break down, creating irregular deep ulcers with undermined bluish borders. Healing results in atrophic hyperpigmented scars. Histologically, there is a lobular panniculitis with or without septal involvement. A neutrophilic vasculitis with mural thickening of subcutaneous arteries and veins and perivascular cuffing is often evident. Fat necrosis and granulomas can sometimes be observed. Bacilli are absent and caseation is rare[3,63].

Other entities such as erythema nodosum, lupus miliaris disseminatus faciei, granulomatous rosacea, and lichenoid tuberculid were formerly considered tuberculids, but are no longer included in this category[74].



Fig. 75.19 Papulonecrotic tuberculid. Erythematous papules and papulopustules on the heel.

BCG inoculation

BCG vaccination is performed with attenuated *M. bovis*. By increasing the degree of protection against *M. tuberculosis* infection, this vaccine has reduced the worldwide incidence of TB considerably. It can, however, cause complications, which include localized or generalized tuberculids, lupus vulgaris, scrofuloderma, and other nonspecific reactions such as fever, local inflammation, subcutaneous abscesses with or without ulceration, severe regional lymphadenitis, osteitis, and tuberculous foci in distant organs (Fig. 75.20). Rarely, it leads to a disseminated or even fatal infection, especially in individuals with a primary immunodeficiency affecting the IL-12/IFN-γ axis (e.g. Mendelian susceptibility to mycobacterial disease, hypohidrotic ectodermal dysplasia with immunodeficiency; see Ch. 60)[74]. Injections of methanol extraction residue (MER) of BCG have been used as adjuvant immunotherapy in patients with melanoma and can also result in nodules and subcutaneous abscesses (Fig. 75.21).

Diagnosis

In addition to the use of tuberculin skin tests, *M. tuberculosis* infection can be diagnosed with IFN-γ release assays (IGRAs; e.g. QuantiFERON® TB Gold Plus, T-SPOT®.TB)[76,77]. These assays determine whether exposure to recombinant peptides from *M. tuberculosis* (ESAT-6,



Fig. 75.20 Site of a BCG vaccination. Enlarging granulomatous plaque (BCGitis).



Fig. 75.21 Complication of injection of methanol extraction residue (MER) of BCG. Nodules, some of which have ulcerated, arranged in a linear "lymphatic" pattern in a patient with a high-risk extremity melanoma who had received an injection of MER of BCG as adjuvant immunotherapy.

culture filtrate protein [CFP]-10, ± TB7.7) stimulates IFN-γ production by T cells within patient blood samples. In general, IGRAs have similar sensitivity (~80%–85%, less in immunocompromised individuals) and greater specificity compared to tuberculin skin tests[76]. Current guidelines from the US Centers for Disease Control and Prevention (CDC) and National TB Controllers Association state that IGRAs may be used in place of a tuberculin skin test in all situations where the latter would be employed, with a general preference for IGRAs in patients ≥2–5 years of age with a low or intermediate risk of disease progression[76–78]. Advantages and disadvantages of these methods of TB detection as well as situations where one type of test would be preferred are listed in Table 75.8. Of note, these tests are negative in a subset of individuals with active TB disease and should not be used to exclude TB in patients with clinical evidence of infection.

Methods to detect *M. tuberculosis* in samples of respiratory secretions and infected tissues such as the skin include staining for acid-fast bacteria, culture, and PCR-based assays. The latter have variable sensitivities but are rapid and specific for organisms in the *M. tuberculosis* complex (which includes BCG). The Xpert MTB/RIF® is an automated, fast, semi-quantitative PCR method that simultaneously detects organisms in the *M. tuberculosis* complex and resistance to rifampin (rifampicin) in liquid clinical samples (e.g. sputum, lymph node aspirate) over a period of two hours. Genotyping methods based on spacer oligonucleotides (spoligotyping), mycobacterial interspersed repetitive unit-variable number tandem repeats (MIRU-VNTRs), and restriction fragment-length polymorphisms (RFLPs) can separate *M. tuberculosis* from non-tuberculous mycobacteria and detect mutants associated with drug resistance[67].

ADVANTAGES AND DISADVANTAGES OF IFN-γ RELEASE ASSAYS AND TUBERCULIN SKIN TESTING		
	Tuberculin skin test	**IFN-γ release assays**
Advantages	• Does not require a laboratory • Relatively low cost	• Requires a single patient visit • Results can be available within 24 hours • Prior BCG vaccination does not cause a false-positive result • Does not boost responses measured by subsequent tests
Disadvantages	• Requires two patient visits • Results are not available for 48 hours • Prior BCG vaccination can cause a false-positive result • May boost responses in subsequent tests • Infections with non-tuberculous mycobacteria may lead to a false-positive result	• Requires laboratory processing within 16 hours (for QuantiFERON® TB Gold Plus) or 8–30 hours (for T-SPOT®.TB; the latter if using T-cell Xtend®) • Relatively high cost • Infections with some non-tuberculous mycobacteria (e.g. *M. kansasii*, *M. szulgai*, *M. marinum*) may lead to a false-positive result
Situations where preferable	• Children <2–5 years of age	• Patient groups that historically have low rates of returning for a second visit (e.g. homeless persons, drug users) • Individuals who have received BCG

Table 75.8 Advantages and disadvantages of interferon-γ (IFN-γ) release assays and tuberculin skin testing. Both types of tests may be negative in patients with early active tuberculosis. Indeterminate IFN-γ release assay results due to failure of the internal positive control (i.e. a "low mitogen" response) are more common in immunocompromised individuals, young children, and older adults. Indeterminate results due to inappropriately high IFN-γ levels in the negative control ("high nil") can also occur. Testing with a second method after an initial negative test may be useful when the risk of infection/progression is high or when there is clinical suspicion of active tuberculosis. The QuantiFERON® TB Gold Plus test directly measures IFN-γ levels, whereas the T-SPOT®.TB test determines the number of IFN-γ-producing T cells; both use a peripheral blood sample. BCG, bacille Calmette–Guérin.

Treatment

Medications used to treat cutaneous forms of TB are the same as those for systemic TB (Table 75.9 & Fig. 75.22). Administration of appropriate therapy also assists in preventing bacterial resistance and reducing transmission of *M. tuberculosis*. In addition to the increase in *multidrug-resistant TB* that accompanied the resurgence of this disease in the late 1980s and early 1990s, *extensively drug-resistant TB* strains that are even more difficult to treat have also emerged in all regions of the world (Table 75.10). For latent TB infection, recommended regimens include isoniazid plus rifapentine weekly for 3 months, isoniazid plus rifampin daily for 3 months, and rifampin daily for 4 months[79].

In addition to "repurposing" existing antibiotics (e.g. quinolones, amoxicillin with clavulanate, linezolid, clarithromycin) for use in patients with extensively drug-resistant TB, novel drugs have been developed. *Bedaquiline*, a diarylquinoline that inhibits mycobacterial ATP synthase, was FDA-approved in 2012 as a part of combination therapy for multidrug-resistant TB. Although bedaquiline was found to increase the rate of sputum culture conversion, this drug can lead to QT prolongation and more deaths were observed when compared to the placebo group[80]. Pre-screening electrocardiography is recommended, and an initial 8-week course of bedaquiline plus linezolid for rifampin-sensitive TB was recently reported as noninferior to standard therapy, notably with limited toxic effects[81]. *Pretomanid*, a nitroimidazole, was FDA-approved in 2019 to treat extensively drug-resistant TB in combination with bedaqualine and linezolid. *Delamanid*, a dihydro-nitroimidazooxazole derivative that inhibits synthesis of the mycolic acid component of mycobacterial cell walls, was approved in Europe in 2014 for treatment of multidrug-resistant TB[82]. The antidiabetic drug metformin may have an adjunctive role in TB treatment by increasing reactive oxygen species production, enhancing specific immune responses, improving the efficacy of conventional anti-TB drugs, and decreasing detrimental inflammation[83].

The development of new TB vaccines with effective adjuvants represents a priority of the WHO[84]. Sequential administration of BCG and a recombinant modified vaccinia virus Ankara (MVA) expressing antigen 85A can induce robust antimycobacterial immunity[85]. Several TB subunit and virus-vectored vaccines are currently being evaluated in clinical trials[84,86,87]. Vaccines found to have efficacy in controlled studies include the adjuvanted protein subunit vaccine M72/AS01E (~50% efficacy after 3 years), a non-tuberculous *Mycobacterium*-derived inactivated whole-cell vaccine, an adenovirus-vectored vaccine containing three *M. tuberculosis* antigens (85A, 85B, and TB10.4), and the recombinant "next-generation" BCG vaccine VPM1002[88,89].

Although the production of nitric oxide by macrophages is known to help control infection by *M. tuberculosis*, the organisms can persist within these cells. Proper function of the mycobacterial proteosome appears to play an important defensive role, and, in the future, inhibition of proteosome function could provide a novel therapeutic approach[90].

NON-TUBERCULOUS MYCOBACTERIOSES

Synonyms: ■ Atypical mycobacterioses ■ Mycobacteria other than tuberculosis (MOTT) ■ Environmental mycobacterioses ■ Anonymous mycobacterioses ■ Opportunistic mycobacterioses

Key features

- Over a dozen species of mycobacteria, found in the natural environment and transmitted via inoculation into the skin, can produce cutaneous disease
- Clinical presentations include pustules, keratotic plaques and nodules (with or without suppuration), a sporotrichoid (lymphocutaneous) pattern, and ulcers with draining sinuses
- Disseminated infections usually occur in immunocompromised hosts
- Although suggested by a history of exposure, the diagnosis rests on isolation or identification of the responsible organism

CLASSES, ACTIVITIES AND CROSS-RESISTANCES OF THE ANTITUBERCULOUS AGENTS			
Agent	**Class of compound**	**Spectrum of activity**	**Cross-resistance to other antituberculous agents**
First-line agents			
Rifampin	Antibiotic	Broad	Other rifamycins
Isoniazid	Synthetic	Tubercle bacilli	None
Pyrazinamide	Synthetic	Tubercle bacilli	None
Ethambutol	Synthetic	Tubercle bacilli	None
Rifapentine	Antibiotic	Broad	Other rifamycins
Rifabutin	Antibiotic	Broad	Other rifamycins
Second-line agents			
Kanamycin, amikacin, streptomycin	Aminoglycoside antibiotics	Broad	Other aminoglycosides, viomycin, capreomycin
Capreomycin, viomycin	Tuberactinomycin antibiotics	Tubercle bacilli	Aminoglycosides
Levofloxacin, ofloxacin, moxifloxacin	Quinolone antibiotics	Broad	None
Ethionamide, prothionamide	Thioamides	Tubercle bacilli	Thiacetazone
Cycloserine, terizidone	Synthetic	Broad	None
para-Aminosalicylic acid	Synthetic	Tubercle bacilli	None
Third-line agents			
Clofazimine	Riminophenazine antileprotic	Mycobacteria	None
Amoxicillin/clavulonate	β-lactam antibiotic/β-lactamase inhibitor	Broad	None
Linezolid	Oxazolindinone antibiotic	Broad	None
Imipenem	β-lactam antibiotic	Broad	None
Thiacetazone	Synthetic	Tubercle bacilli	Ethionamide, prothionamide
Clarithromycin	Macrolide antibiotic	Broad	None
Bedaquiline	Diarylquinoline antibiotic	Broad	None
Delamanid	Dihydro-nitro-imidazooxazole	Mycobacteria	None
Pretomanid	Nitroimidazole	Mycobacteria	None

Table 75.9 Classes, activities, and cross-resistances of the antituberculous agents. Agents that are active against *M. tuberculosis* may also show activity against some other species of mycobacteria. Strains of *M. bovis* are naturally resistant to pyrazinamide. There are only limited data on other activities of capreomycin and viomycin. *Adapted from Grange JM, Zumla A. Antituberculosis agents. In Cohen J, Powderly WG (eds). Infectious Diseases. London: Mosby, 2003. With permission from Elsevier.*

Introduction

Non-tuberculous ("atypical") mycobacteria (NTM) were first isolated in 1931 by Pinners, who also discovered that these organisms were different from *M. tuberculosis* – they were not virulent in the guinea pig model, and they responded poorly to antituberculous therapy[91]. Their importance as human pathogens, however, was not appreciated until the 1950s[92].

These environmental mycobacteria are found in water, wet soil, house dust, dairy products, cold-blooded animals, vegetation, and human feces. NTM are transmitted by inhalation, ingestion, or percutaneous penetration, which can result in pulmonary, lymph node, or skin disease[6,91]. The type of disease depends on the species of mycobacteria, the route and degree of exposure, and the immune status of the host[1]. Individuals with innate defects of the IL-12/IFN-γ axis (≥10 genes implicated; e.g. *STAT1*, *ISG15* [IFN-stimulated gene 15]), GATA2 deficiency, and anti-IFN-γ antibodies are predisposed to severe and disseminated infections with NTM[93] (see Ch. 60).

The incidence of infections by NTM appears to be increasing due to factors such as greater use of immunosuppressive medications and more frequent surgical procedures as well as improved detection via PCR-based techniques[93]. Although these infections should be considered in patients with indolent ulcers, nodules, or plaques, especially in the setting of immunosuppression, they are often misdiagnosed because of their nonspecific or sometimes subtle clinical presentations, combined with inadequate biopsy and culture techniques[91]. The ability of some NTM to survive sterilization procedures and to even contaminate antiseptic solutions can lead to infections in surgical patients. These infections have been described in association with cutaneous surgical procedures (e.g. laser resurfacing, botulinum toxin injections, hair transplantation, liposuction), other surgical procedures (e.g. cardiothoracic, ocular, breast reconstruction), and acupuncture, body piercing, and tattooing[94–97].

Antibiotic susceptibility and therefore selection of therapy depends on the NTM species (Table 75.11)[91,98–104]. Empiric treatment with clarithromycin can be initiated while awaiting culture and sensitivity results in patients with clinical presentations suggestive of cutaneous NTM infection[105]. However, multiplex PCR-based assays (e.g. targeting 16S rRNA and hsp65) are available to more rapidly identify NTM species of clinical importance and help direct therapy[106,107].

In 1954, Runyon proposed the first classification system for NTM based upon rate of growth *in vitro* and pigment production following exposure to light (see Table 75.1). Due to advances in genomic analysis, at least 200 species of mycobacteria are now recognized[107]. Selected NTM of dermatologic interest will be discussed in this chapter.

Mycobacterium ulcerans

Synonyms: ■ Buruli ulcer ■ Bairnsdale ulcer ■ Searle's ulcer

Introduction and history

M. ulcerans is a slow-growing, acid-fast bacillus that characteristically infects the skin and subcutaneous tissues, producing indolent ulcers. After Hansen disease and tuberculosis, the "Buruli ulcer" is the third most common mycobacteriosis worldwide in immunocompetent hosts, and it is classified as a neglected tropical disease by the WHO. In 1897, Cook first described patients with huge cutaneous ulcers from the Buruli county of Uganda. It was not until the late 1940s, in Australia, that the agent was isolated and characterized by MacCallum and colleagues[1].

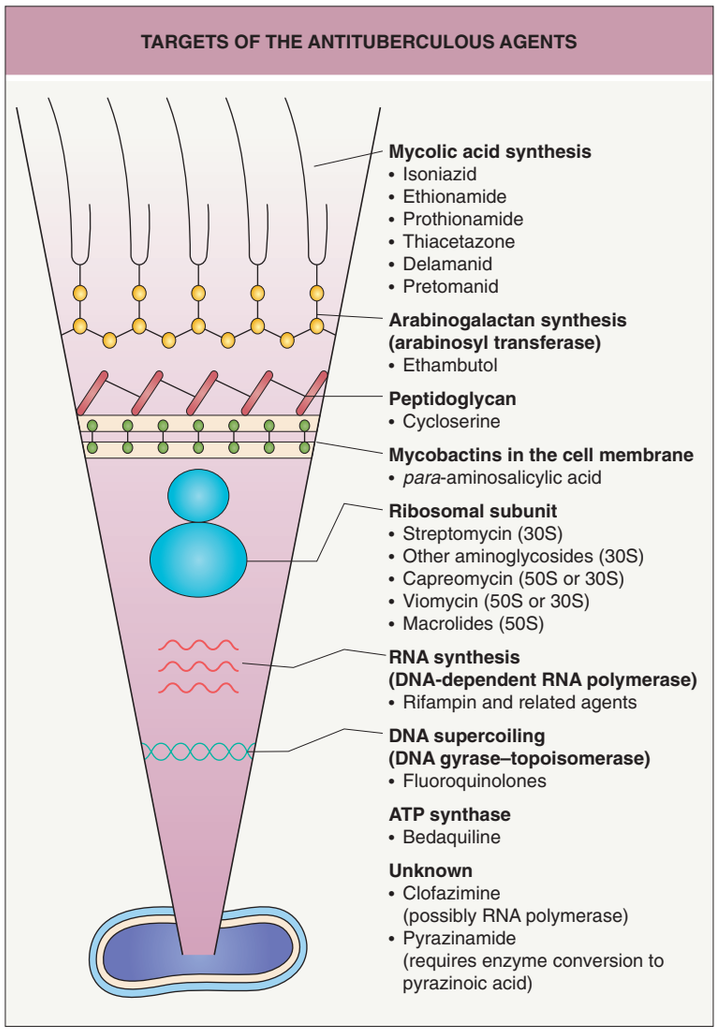


Fig. 75.22 Targets of the antituberculous agents. *Adapted from Grange JM, Zumla A. Antituberculous agents. In: Cohen J, Powderly WG (eds). Infectious Diseases. London: Mosby, 2003. With permission from Elsevier.*

Epidemiology

M. ulcerans infections have been reported in >30 countries worldwide, with primary endemic foci near freshwater wetlands in tropical and subtropical countries. Although the exact mode of transmission is not known, exposure to water or mud from rivers, ponds, or swamps is thought to play a role. The organism is harbored by snails, fish, and water insects, and it can be isolated from aquatic plants. In Australia, koalas and opossums are naturally infected.

Agricultural activities and consequent deforestation have contributed to increases in the incidence of *M. ulcerans* infections, especially in West Africa. Focal outbreaks have followed floods and human migrations, and HIV co-infection has been associated with more rapid progression into severe ulcerative stages[65,108]. The countries most affected are in Central Africa (e.g. Uganda, Democratic Republic of the Congo) and West Africa (e.g. Ivory Coast, Ghana, Benin). Japan, Southeast Asian countries, and Australia have major foci of infection, and there have been a few reports from South America and Mexico.

M. ulcerans is typically introduced into the skin by minor trauma, and the disease is rarely transmitted from patient to patient. Children under 15 years of age are most commonly affected in West Africa, but infection can occur in all age groups[92].

Pathogenesis

After inoculation into the skin, *M. ulcerans* organisms proliferate and form abundant clumps of extracellular acid-fast bacilli. The organisms

MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS
Multidrug-resistant tuberculosis (MDR-TB)
• Resistant to isoniazid and rifampin, the two most effective first-line drugs • Estimated to account for ~3% of all new TB cases worldwide in 2021, but ~20% of individuals previously treated for TB
Extensively drug-resistant tuberculosis (XDR-TB)
• Resistant to isoniazid and rifampin • Resistant to quinolones, the most effective second-line drugs • Resistant to at least one of three injectable second-line drugs: amikacin, kanamycin, or capreomycin • Estimated to account for 10% of cases of MDR-TB

Table 75.10 Multidrug-resistant and extensively drug-resistant tuberculosis.

TREATMENT OF NON-TUBERCULOUS ("ATYPICAL") MYCOBACTERIAL INFECTIONS		
Agent	**Local**	**Systemic medications: alone or combined**
M. ulcerans	For ulcers, surgical excision; local heat (40°C); hyperbaric oxygen	Rifampin plus clarithromycin, streptomycin, or a quinolone (e.g. moxifloxacin, ciprofloxacin) for 8 weeks; other drugs occasionally used in combination therapy include ethambutol, amikacin, and azithromycin
M. marinum		Clarithromycin, minocycline > doxycycline*, rifampin, ethambutol, trimethoprim–sulfamethoxazole; two agents for serious infections (e.g. clarithromycin + rifampin or ethambutol)
M. kansasii		Isoniazid (or clarithromycin) + rifampin + ethambutol ± pyridoxine; other options (depending on susceptibilities) include azithromycin, moxifloxacin, streptomycin and sulfamethoxazole
M. fortuitum	Surgical excision	Ciprofloxacin, ofloxacin, clarithromycin†, trimethoprim–sulfamethoxazole, minocycline, amikacin, meropenem, linezolid, doxycycline; at least two agents for serious infections
M. chelonae	Surgical excision	Clarithromycin; for severe infections, combine clarithromycin with linezolid, imipenem, tobramycin, amikacin, doxycycline, and/or ciprofloxacin (often resistant to latter two agents)
M. abscessus	Surgical excision	Clarithromycin or azithromycin + (for serious infections) amikacin, cefoxitin or imipenem
M. avium complex		Azithromycin (or clarithromycin) + ethambutol ± rifampin or rifabutin; second-line medications include streptomycin, amikacin, clofazimine, linezolid, bedaquiline
M. haemophilum	Surgical excision	Clarithromycin + rifampin (or rifamycin, rifabutin) ± ciprofloxacin or amikacin
M. scrofulaceum	Surgical excision	Isoniazid + rifampin, clarithromycin

*Resistance to tetracyclines has been reported.
†Often have inducible resistance to macrolides.

Table 75.11 Treatment of non-tuberculous ("atypical") mycobacterial infections[91,92,98–104]. Therapy for 3 to 6 months or more is often required. If clinical suspicion is high for a non-tuberculous mycobacterial infection, empiric treatment with clarithromycin can be considered while waiting for culture and sensitivity results.

are found at the base of the ulcer and within adjacent necrotic subcutaneous tissue as well as in surrounding normal-appearing skin.

M. ulcerans produces mycolactone, a macrolide exotoxin produced by polyketide synthases that are encoded by the virulence plasmid pMUM. Mycolactone is able to: (1) decrease inflammation via inhibition of protein translocation into the endoplasmic reticulum (ER), leading to suppression of cytokine/chemokine production, dendritic cell function, and L-selectin-mediated lymphocyte homing; (2) promote cell death via anoikis by disrupting actin dynamics through hyperactivation of the Wiskott–Aldrich syndrome protein (WASP); and (3) inhibit pain perception by binding to angiotensin II type 2 receptors on neurons, leading to potassium-dependent hyperpolarization[109]. These effects explain the severe tissue destruction with minimal pain and inflammation observed in Buruli ulcers, and different geographical lineages of *M. ulcerans* produce forms of mycolactone with varying virulence[109]. In addition, mycolactone itself represents a potential diagnostic/prognostic biomarker and therapeutic target.

Clinical features

The initial lesion is usually a single, asymptomatic, firm, non-tender, mobile subcutaneous nodule that measures 1 to 2 cm in diameter. After 1 or 2 months, the nodule becomes fluctuant and ulcerates. The resultant painless ulcer has a deep necrotic base with undermined edges, and often expands to 15 cm or more in diameter. Most lesions are on the extremities, especially the leg. There is little to no regional lymphadenopathy or systemic manifestations, although edema can develop in adjacent tissues. Without treatment, ulcers may remain small and heal as depressed scars, or they may spread rapidly over large areas of skin causing extensive scarring and deformity. Structures such as the eye, breast, or genitalia are sometimes severely damaged. Underlying bone can become involved, and progressive osteomyelitis may require amputation[92].

The WHO divides *M. ulcerans* disease into three categories of severity: (1) single lesion <5 cm in diameter; (2) single lesion (± ulceration) or area of edema 5–15 cm in diameter; (3) lesion >15 cm in diameter, multiple lesions, osteomyelitis, or joint involvement.

Pathology

Histologically, mature lesions show extensive necrosis with destruction of nerves, appendages, and blood vessels[1,92]. There are few inflammatory cells in active lesions, but a granulomatous response may develop during healing. Many acid-fast bacilli can be seen in characteristic clumps, particularly in the center of the lesion[92].

Diagnosis and differential diagnosis

Clumps of acid-fast bacilli are typically seen with Ziehl–Neelsen staining of smears and biopsy specimens from the necrotic ulcer base or undermined ulcer edge. *M. ulcerans* can be cultured, but visible growth often requires 6 to 8 weeks of incubation at 32°C[92]. PCR-based detection of the *M. ulcerans*-specific insertion sequence 2404 (IS2404), which is highly sensitive and specific, has become the gold standard for Buruli ulcer diagnosis. Additional diagnostic tests that are under development include the loop-mediated isothermal amplification (LAMP) test, thin-layer chromatography for the detection of mycolactone, and antigen detection assays[108]. In a series of 70 patients with Buruli ulcers, a modified PCR assay had a sensitivity of 98%, while the sensitivities of direct smear, culture, and histology were 42%, 49%, and 82%, respectively[110].

The differential diagnosis depends upon the stage of disease. During the initial phase, when a subcutaneous nodule is present, *M. ulcerans* infection must be differentiated clinically from other forms of panniculitis (infectious and non-infectious; see Ch. 100), cysts, nodular fasciitis, foreign body granulomas, and other granulomatous diseases. During the ulcerative phase, considerations may include fungal infections, pyoderma gangrenosum, suppurative panniculitis, and other causes of chronic ulcers (see Ch. 105)[1].

Treatment

Antibiotic therapy can be effective when used alone or in combination with surgery (debridement or more extensive procedures [see below]). Treatment with oral rifampin (10 mg/kg daily) plus clarithromycin (7.5 mg/kg twice daily or 15 mg/kg extended release daily) is now recommended as first-line treatment by the WHO. A randomized controlled trial demonstrated that 8 weeks of this regimen was not inferior to and better tolerated than the same oral rifampin dose plus intramuscular streptomycin (15 mg/kg) daily in patients with a single lesion ≤10 cm in diameter[111]. Other antibiotic protocols (e.g. in Australia) utilize rifampin plus moxifloxacin or ciprofloxacin for 6–8 weeks[112,113]. Of note, ~10%–20% of patients with Buruli ulcers (especially those associated with a high bacterial load) experience a paradoxical reaction upon initiation of antibiotic therapy, with temporary worsening of ulceration (peak at 6–8 weeks) and subsequent healing[114].

While surgical excision represents the traditional treatment of choice for ulcers (see Table 75.11), this is obviously easier to accomplish when the ulcers are small, as large ulcers often require skin grafts or, rarely, amputation[1,92]. Continuous local heating to 40°C by circulating water jackets promotes healing, even without excision[72], and hyperbaric oxygen may also be useful[1,3]. Physical therapy is important when the patient is at risk for contractures. There is no effective prophylaxis, but vaccination with BCG may lead to limited, relatively short-lived protection.

Mycobacterium marinum

Synonyms: ■ Fish tank granuloma ■ Swimming pool granuloma ■ Infection by *M. balnei*

Introduction and history

M. marinum is a free-living organism that causes disease in freshwater and saltwater fish and sporadically in humans. The latter results from exposure to contaminated water when there are breaks in the skin barrier[99]. *M. marinum* was first isolated from saltwater fish in the Philadelphia Aquarium in 1926 by Aronso[1,3]. The first report of human disease was in 1951, when the agent was found in granulomatous skin lesions of individuals who swam in a contaminated swimming pool[3]. There is scientific interest in *M. marinum* because of its phylogenetic similarity to *M. tuberculosis*[115].

Epidemiology and pathogenesis

M. marinum is found in aquatic environments, including fresh, salt, and brackish water. When cleaning fish tanks at home or in the workplace (e.g. restaurants, fish markets), trauma to the hands may result in exposure to *M. marinum*. The infection can also affect swimming pool bathers, as this organism seems to be rather resistant to chlorine[1].

Cutaneous infection with *M. marinum* requires a portal of entry, e.g. abraded or traumatized skin[1]. The incubation period is typically 2 to 3 weeks, but it can range from 1 week to 2 months[1]. In several case series of skin infections due to NTM from higher-income countries, *M. marinum* was the most common species identified[104,105].

Clinical features

The initial lesion is a single bluish-red inflammatory nodule or pustule at the site of inoculation, which is often on an upper extremity (Fig. 75.23A). It then forms a crusted ulcer, suppurative abscess, or verrucous nodule[1,3]. Multiple lesions can develop along the course of the draining lymphatics, i.e. sporotrichoid (lymphocutaneous) spread (Fig. 75.23B; see Table 77.17). Among the NTM, *M. marinum* is the most common cause of this pattern. Occasionally, deeper infections are complicated by tenosynovitis, septic arthritis, or rarely, osteomyelitis. As with other NTM, atypical or disseminated lesions can occur in immunocompromised hosts, including those treated with TNF inhibitors (Fig. 75.23C).

Pathology

The histologic features, as in other mycobacterial infections, range from acute and chronic inflammation to well-formed tuberculoid granulomas. Fibrinoid changes and caseation necrosis can occur[3]. In immunocompetent individuals, organisms are often difficult to find.

Diagnosis and differential diagnosis

The clinical features combined with a history of trauma in a wet environment or exposure to fish tanks suggests the possibility of *M. marinum* infection. The diagnosis is confirmed by culture, which is positive in 70% to 80% of cases[99]. When this infection is suspected,

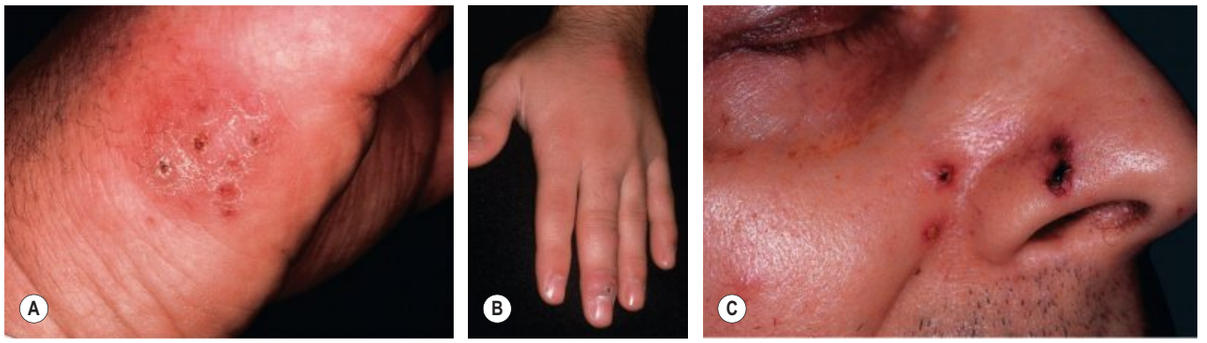


Fig. 75.23 *Mycobacterium marinum* infections. A range of presentations, including an erythematous plaque with scale-crust at the inoculation site on the lateral hand (**A**), a sporotrichoid pattern with the inoculation site on the distal third finger (**B**), and disseminated necrotic lesions on the face of an immunocompromised patient (**C**).

the laboratory should be notified in advance and care must be taken to provide proper culture conditions. *M. marinum* grows best at 31°C, in contrast to the optimal incubation temperature of 37°C for many other mycobacteria[99]; growth becomes evident after a mean of ~3 weeks, and identification of the species and its antimicrobial susceptibility pattern often requires 2 months[104]. PCR can also be performed to enable a rapid diagnosis.

Infection due to *M. marinum* should be differentiated from sporotrichosis and the entities outlined in Table 77.17 as well as tuberculosis verrucosa cutis. It is not associated with marked regional lymphadenitis.

Treatment

M. marinum is usually sensitive to the antimicrobial drugs listed in Table 75.11[91]; however, sensitivity testing should be requested as part of the laboratory evaluation[99]. Based on usual *in vitro* susceptibility patterns and clinical responsiveness, initial empiric treatment with clarithromycin (pending culture and sensitivity results) has been recommended when there is suspicion of an *M. marinum* infection[104]. A general approach is to treat with two agents (e.g. clarithromycin plus ethambutol or rifampin) until 1–2 months after resolution of clinical findings, often for a total of 3–4 months[104]; a single agent is an option for milder disease, and longer-term treatment may be necessary in immunosuppressed patients[115].

Mycobacterium kansasii

Introduction and history

M. kansasii most often causes lung disease, which can be clinically and radiologically indistinguishable from tuberculosis. There is also evidence that infection with this organism provides increased immunity against tuberculosis[92].

M. kansasii was first reported in 1953 as the "yellow bacillus". This characteristic pigmentation is due to the deposition of β-carotene crystals after exposure to light[1].

Epidemiology and pathogenesis

This organism is found throughout the world, but it is more prevalent in temperate zones within the US, South America, China, and Europe. It has been isolated from cattle and swine, but the natural reservoir may be water. Middle-class, middle-aged White men living in urban areas are most commonly affected[3,92]. Cutaneous infection is usually acquired via minor trauma such as puncture wounds[74].

Clinical features

Verrucous plaques, ulcers, and nodules are observed, and the lesions may be arranged in a lymphocutaneous (sporotrichoid) pattern. The majority of patients with cutaneous involvement have some alteration in immune status[1,3,92]. Papulonecrotic lesions and cellulitis are less common presentations[3]. Iijima and Sasaki[116] divided cutaneous mycobacteriosis due to *M. kansasii* into three types: (1) primary cutaneous chronic granulomatous; (2) primary cutaneous pyogenic; and (3) disseminated acute pyogenic, which occurs primarily in immunocompromised individuals.

Pathology

Histologic features are as variable as the clinical presentations. Typical tuberculoid granulomas may be seen, or a dense neutrophilic infiltrate may be evident, with or without abscess formation and epidermal necrosis[92]. In some patients, the findings are indistinguishable from those of *M. tuberculosis* infection[1].

Diagnosis and differential diagnosis

M. kansasii can be isolated from lesional skin biopsy specimens, and the laboratory should be advised to provide appropriate culture conditions to detect slow-growing mycobacteria[1,92]. The rarity of diagnosis of primary cutaneous *M. kansasii* infections may reflect failure to grow the organisms in culture as well as difficulties in phenotyping. PCR analysis may circumvent these potential problems because of its higher sensitivity and specificity[117].

Table 75.7 and the *M. ulcerans* section above outline the differential diagnosis of verrucous plaques and ulcers, respectively. Sporotrichosis and other NTM infections need to be considered when there is a sporotrichoid pattern (see Table 77.17). A combination of histologic examination, special stains, and culture for bacteria and fungi usually distinguishes these entities, but PCR may be required.

Treatment

A combination of antituberculous medications should be used (see Table 75.11), especially for disseminated infections. Because resistance to rifampin and other drugs may occur, sensitivity testing should be performed to optimize therapy[1,3,92].

Mycobacterium fortuitum, Mycobacterium chelonae, and *Mycobacterium abscessus*

Synonyms: ■ *M. chelonei* = *M. chelonae* ■ Turtle tubercle bacillus

Introduction and history

These rapidly growing mycobacteria are members of either the *M. fortuitum* group or the *M. chelonae/M. abscessus* complex[118]. Although the individual organisms can be distinguished on the basis of their DNA and serologic analyses, they result in infections with similar clinical features[3].

In 1903, Friedmann[68] isolated *M. chelonae*. Two subspecies (*chelonae* and *abscessus*) were initially identified, but *M. abscessus* was reclassified as a separate species in 1992[1]. Costa-Cruz used the name *M. fortuitum* in 1938 for what he believed to be a new species isolated from a skin abscess that occurred after an injection[1,119]. The *M. fortuitum* group currently includes the following additional species reported to cause human infections – *M. alvei*, *M. boenickei*, *M. conceptionense*, *M. farcinogenes*, *M. houstonense*, *M. neworleansense*, *M. peregrinum*, *M. porcinum*, *M. senegalense*, *M. septicum*, *M. setense*. The *M. chelonae/M. abscessus* complex now consists of *M. chelonae*, *M. abscessus* subsp. abscessus, *M. abscessus* subsp. bolletii, *M. abscessus* subsp. massiliense, *M. immunogenum*, and *M. salmoniphilum*[118,120].

Epidemiology and pathogenesis

The organisms exist as saprophytes, and they are found in water, soil, dust, and animals. Cutaneous infections are uncommon, and immunocompromised patients are more susceptible to severe disease caused by these species of mycobacteria[91,121].

Infections typically occur following trauma, surgery, or other procedures, including contact with contaminated medical instruments (e.g. liposuction, mesotherapy), placement of implants (e.g. prosthetic



Fig. 75.24 *Mycobacterium fortuitum* infection. Multiple eroded papulonodules and plaques within a background of erythema on the foot in a patient with an undefined immunodeficiency. *Courtesy Edward Cowen, MD.*

breast implants), and tattoo ink or acupuncture needles[96,97,122]. A post-injection abscess is another frequent presentation[3], e.g. after injection of botulinum toxin, dermal filler, phosphatidylcholine/deoxycholate, or vaccines. Furunculosis of the lower extremities has also been observed following footbaths in nail salon customers[95]. Less often, cutaneous infection is the result of dissemination from an endogenous source[91].

Clinical features

This group of mycobacteria can produce a variety of clinical diseases, including non-cavitary pneumonia, keratitis, endocarditis, lymphadenitis, osteomyelitis, and skin infections. The cutaneous manifestations range from cellulitis, abscesses, and papulopustules to sinuses and ulcers with extensive subcutaneous necrosis and serosanguineous or purulent discharge (Fig. 75.24 & 75.25A)[91]. However, the most common presentation is multiple erythematous subcutaneous nodules, frequently occurring on the distal limbs or in a sporotrichoid pattern (see Fig. 75.24)[3,119,121].

Pathology

The presence of both neutrophilic microabscesses and granuloma formation with foreign body-type giant cells is characteristic (Fig. 75.25B)[1]. Necrosis may occur[3].

Diagnosis and differential diagnosis

Culture of biopsy material must be performed. When an abscess is present, a biopsy specimen that includes the wall is preferred, rather than aspiration of pus. The organisms grow on routine bacterial culture media, such as 5% sheep blood agar or chocolate agar, within 7 days. Molecular methods utilizing PCR, gene sequencing, and matrix-assisted laser desorption ionization–time of flight mass spectrometry are available to identify these NTM[118,120].

Infection with these organisms should be considered in patients with therapy-resistant or "cold" abscesses. It can also be confused with foreign body reactions, subcutaneous mycoses, or osteomyelitis[3].

Treatment

Treatment is dependent on the type and extent of the lesions[1]. These organisms are resistant to antituberculous drugs, but nearly all *M. chelonae* and ~80% of *M. fortuitum* isolates are sensitive to clarithromycin. Excision and debridement may be required for abscesses and ulcers. Recommended antibiotics, either alone or in combination, are listed in Table 75.11[3,91,98]; prolonged courses may be required. Successful treatment of refractory pulmonary and disseminated *M. abscessus* infections by intravenous administration of engineered bacteriophages has been reported in patients with advanced cystic fibrosis lung disease[123].

Mycobacterium avium Complex (MAC)

Synonyms: ■ *M. avium* ■ *M. avium-intracellulare* (MAI) ■ *M. intracellulare*

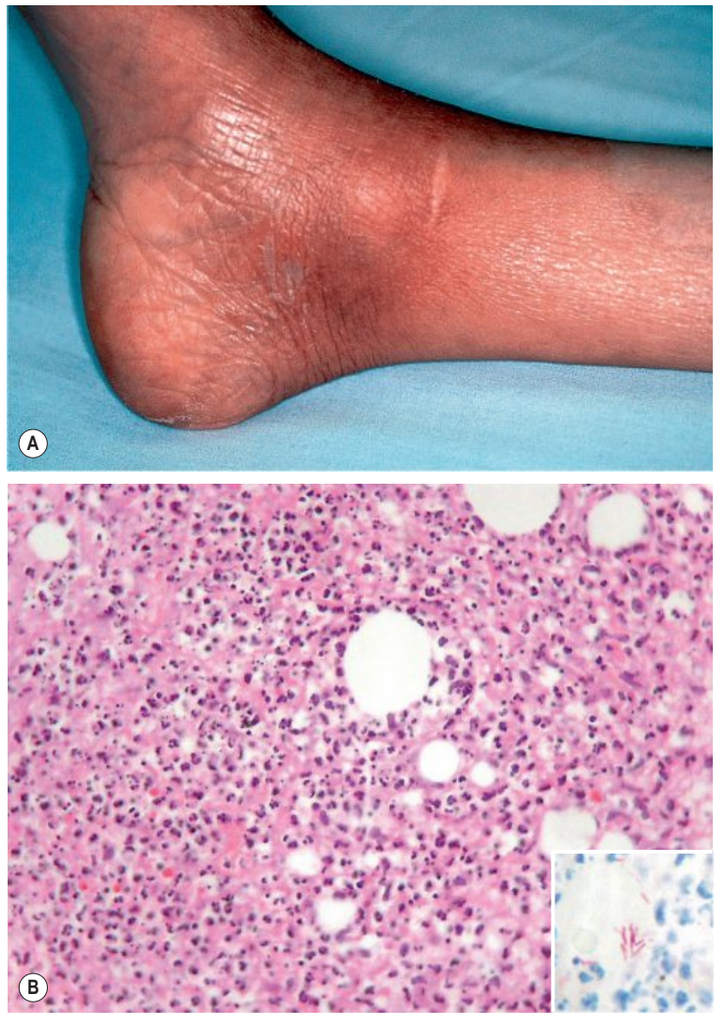


Fig. 75.25 *Mycobacterium chelonae* infection. A This immunosuppressed patient presented with an area of warmth and mild erythema on the ankle. **B** Mixed diffuse inflammatory infiltrate with granuloma formation. Curved acid-fast bacilli are seen with Fite staining (inset).

Introduction

In the 1980s, two closely related pathogens, *M. avium* and *M. intracellulare*, were designated as *M. avium-intracellulare* (MAI). Currently, the term *M. avium* complex (MAC) is utilized for these organisms as well as a growing number of additional species, including the emerging pathogen *M. chimaera* and others that have rarely been identified in human infections (*M. arosiense, M. bouchedurhonense, M. colombiense, M. marseillense, M. timonense, M. vulneris, M. yongonense*)[124].

MAC organisms are facultative pathogens that only occasionally produced human disease prior to the HIV epidemic[91], when these mycobacteria produced disseminated disease in 15%–40% of patients with AIDS[91].

Epidemiology and pathogenesis

MAC organisms are found in the environment, including fresh and salt water, soil, dairy products, and domestic animals[3,91]. They may be transmitted via inhalation into the lungs, or via water and food into the gastrointestinal tract, without person-to-person transmission[1]. As many as 30% of samples of normal human feces yield isolates of MAC[1,3].

Chronic pulmonary infection is the most common clinical manifestation of MAC infection in those who are not co-infected with HIV, followed in frequency by cervical and inguinal lymphadenitis and osteomyelitis. Lymphadenitis more frequently occurs in children. Cutaneous lesions may be primary after a traumatic inoculation, which is rare, or secondary to a disseminated infection in an immunocompromised host[3,91].

Clinical features

In patients with AIDS, there is often disseminated disease characterized by nonspecific symptoms such as fever, night sweats, weight loss, bone pain, hepatosplenomegaly, and lymphadenopathy. Serum alkaline phosphatase levels may be elevated[1]. Skin involvement is unusual and most often presents with papulopustules and multiple purulent leg ulcers[1]. Nodules with abscess formation (Fig. 75.26), panniculitis, sinus tracts, folliculitis, and granulomatous plaques may also be seen[3,91]. A papulonecrotic tuberculid-like eruption due to disseminated MAC infection has been reported in patients with AIDS[91].

Pathology

Macrophages may contain large numbers of bacilli without necrosis, and spindle cell transformation of macrophages with formation of a histoid-like lesion (as in Hansen disease) can occur[42]. The histologic features can resemble those of the lepromatous form of Hansen disease (see above) or a spindle cell neoplasm (mycobacterial spindle cell pseudotumor).

Diagnosis and differential diagnosis

In disseminated disease, the diagnosis is often established by culture of the blood or from bone marrow or liver biopsies[3]. Depending on the site(s) of involvement, cultures can also be performed on sputum or biopsies of skin and lymph nodes[99]; in addition, highly sensitive and specific PCR analysis is available.

The differential diagnosis includes pyoderma, folliculitis, other causes of panniculitis and ulcers, dimorphic fungal infections, the lepromatous form of Hansen disease, cutaneous tuberculosis, and a spindle cell neoplasm.



Fig. 75.26 *Mycobacterium avium* complex infections. A Papules and nodules on the neck in a patient with interferon gamma receptor deficiency. **B** Sporotrichoid (lymphocutaneous) pattern of the coalescing nodules with abscess formation in an immunocompromised patient. *A, Courtesy Edward Cowen, MD.*

Treatment

Table 75.11 provides a list of the medications that have been used alone or in combination[1,3] to treat MAC infections. Immunocompetent patients should continue treatment until culture-negative for at least one year, whereas antimicrobial therapy should be continued for life in immunocompromised individuals with disseminated infection[3,124,125].

Mycobacterium haemophilum

Introduction

M. haemophilum is a short, slightly curved rod that occurs singly or in a cord-like arrangement. It is a fastidious organism that requires ferric ions to grow, provided as hemin, hematin, hemoglobin, or ferric ammonium citrate. In initial studies, growth was only observed with the addition of hemolyzed sheep erythrocytes; as a consequence, the organism was given the name *M. haemophilum*[92,100].

Epidemiology and pathogenesis

M. haemophilum infection occurs primarily in immunocompromised hosts, including people living with HIV, organ transplant recipients, and individuals receiving immunosuppressive medications[126]. However, this organism can also cause cervical lymphadenitis in healthy children, and cutaneous infections following tattooing (including permanent make-up) and acupuncture have been reported. The majority of affected individuals are from cities located near the ocean, the Mediterranean Sea, or the Great Lakes of North America[92,100].The natural habitat of *M. haemophilum* has not yet been identified, although water reservoirs are suspected[92,100]. *M. leprae* and *M. haemophilum* are phylogenetically related, which may explain why some individuals infected with *M. haemophilum* experience immune reconstitution events analogous to leprosy reactions (see above)[65].

Clinical features

This bacillus can produce several different types of cutaneous lesions[92]. Immunosuppressed adults typically present with one or more bluish-red tender pustules, papulonodules, or plaques, which evolve into abscesses and/or ulcers[92,102,126]. Lesions are usually located on the extremities, often overlying joints. *M. haemophilum* can also cause contiguous septic arthritis, osteomyelitis, and pneumonia. In immunocompetent individuals, cutaneous inoculation can lead to papulonodules and pustules. Immunocompetent children infected by this organism frequently have isolated cervical, submandibular, or perihilar lymphadenitis[100].

Pathology

A mixed reaction with both suppurative and granulomatous inflammation is commonly seen, but other cases have a nonspecific pattern. The bacilli are sometimes found aggregated in globi, resembling those seen in the lepromatous form of Hansen disease[92,100].

Diagnosis and differential diagnosis

The diagnosis is established by culture of the bacillus from tissue or synovial fluid; in some patients, blood cultures are positive. However, this organism requires a special environment to grow, with a source of iron and a temperature between 30°C and 32°C[92,100]. Due to these stringent requirements, it may not be isolated using routine techniques[1]. Highly sensitive and specific PCR analysis is also available.

In immunocompetent children with cervical or submandibular lymphadenitis, the possibility of MAC infection should be considered[100], along with the more common causes of lymphadenitis (e.g. EBV, CMV). The differential diagnosis of the cutaneous lesions is similar to that for infections with other NTM (see above, *M. fortuitum* and MAC).

Treatment

M. haemophilum is often resistant to antituberculous drugs, except for the rifamycins, such as rifampin and rifabutin. The combination of rifampin and clarithromycin (± amikacin) has been used successfully (see Table 75.11). The duration of therapy should be at least 6–24 months, with longer courses in immunosuppressed patients. Surgical excision is also an option when the disease is localized, e.g. adenitis in an immunocompetent child[92,100].

Mycobacterium scrofulaceum

Introduction

M. scrofulaceum was formerly grouped with MAC in a complex called MAIS (*M. avium-intracellulare-scrofulaceum*) but was separated due to its distinct clinical manifestations. *M. scrofulaceum* produces self-limited disease, particularly lymphadenitis, while MAC typically causes chronic lung disease and, less often, osteomyelitis. *M. scrofulaceum* may also cause cervical lymphadenitis with sinus formation clinically indistinguishable from scrofuloderma[74].

Epidemiology and pathogenesis

This organism is most prevalent in the southeastern US. It is widely distributed and has been isolated from raw milk, other dairy products, oysters, soil, and water[100]. Bacilli can be found in environments with: a warm temperature; low pH and dissolved oxygen level; and high soluble zinc, humic acid, and fulvic acid levels. It has also been found on the skin of healthy people and in cutaneous lesions of Hansen disease[101].

In general, infection by *M. scrofulaceum* affects children and occurs via inhalation or ingestion. Focal infection of lymph nodes due to contamination during surgical procedures may also occur. Cutaneous disease in a campground worker with corticosteroid-treated systemic lupus erythematosus and no history of preceding trauma was thought to result from subclinical bacteremia[100,101].

Clinical features

M. scrofulaceum may cause pulmonary disease and local lymphadenitis, primarily in the submandibular and submaxillary regions. It is usually a benign, self-limited condition with no systemic symptoms except for mild neck pain. The involved lymph nodes slowly enlarge over several weeks, and eventually ulceration and drainage occur with fistula formation. This organism can also produce skin lesions in a sporotrichoid pattern, but it rarely causes disseminated infection[100]. Primary cutaneous disease due to inoculation of *M. scrofulaceum* is unusual[100].

Pathology

In the lymph nodes, widespread abscess formation is the typical finding; histiocytes and granulomas may be inconspicuous. It may be difficult to differentiate *M. scrofulaceum* lymphadenitis from that due to *M. tuberculosis*[74] when there are tuberculoid granulomas with central necrosis and abscess formation. The bacilli are found within involved lymph nodes[100]. In the skin, abscess formation is typically seen.

Diagnosis and differential diagnosis

In addition to histologic examination, culture of sputum, skin, or involved lymph nodes helps to confirm the diagnosis. The infection should be distinguished from other causes of cervical lymphadenopathy (see *M. haemophilum*), particularly infection with *M. tuberculosis*[100]. However, *M. tuberculosis* usually affects tonsillar and anterior cervical nodes, while *M. scrofulaceum* typically affects submandibular and submaxillary nodes. When lesions have a sporotrichoid pattern, *M. marinum* infections and other non-tuberculous mycobacterioses should be considered (see Table 77.17)[101].

Treatment

The treatment of choice is total excision of the involved lymph nodes[74,100] because, in general, antibiotic therapy is unsatisfactory. However, promising results have been reported with isoniazid plus rifampin[101]. Successful treatment with clarithromycin has also been described (see Table 75.11)[100].

Additional figures and a table on Drug regimens for pulmonary tuberculosis, available in our eBook (see inside front cover for access code).

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eFig. 75.1 Lepromatous form of Hansen disease. Numerous nodules on the forearms. *Courtesy Louis A. Fragola, Jr, MD.*



eFig. 75.3 Tuberculoid form of Hansen disease. Plaque with slightly elevated, erythematous border and central hypopigmentation.





eFig. 75.2 Lepromatous form of Hansen disease. A, B Diffuse infiltration with leonine facies and madarosis. *A, Courtesy Louis A. Fragola, Jr, MD.*



eFig. 75.4 Borderline tuberculoid leprosy. Thick brown plaque on the arm with central clearing. *Courtesy Edward Cowen, MD.*



eFig. 75.5 Type 1 leprosy reaction. "Upgrading" reaction in a patient with borderline lepromatous disease characterized by marked inflammation of a facial plaque.



eFig. 75.6 Leprosy reactions. Erythema nodosum leprosum (type 2 reaction) with the appearance of multiple red papulonodules in a patient with the lepromatous form of Hansen disease.







eFig. 75.7 Erythema nodosum leprosum. A–C Erythematous papules, plaques, and nodules on the extremities. *Courtesy Louis A. Fragola, Jr, MD.*



eFig. 75.8 Lucio phenomenon. Note the retiform purpura and necrotic ulcers. *Courtesy Carlos G. Wambier, MD, PhD.*



eFig. 75.9 Nerve enlargement (arrow) in a patient with the lepromatous form of Hansen disease.



eFig. 75.10 Tuberculous mastitis. Grouped ulcerated nodules, draining sinuses, and scarring are seen. The lesions resolved following treatment with rifampin, isoniazid, ethambutol, and pyrazinamide. *Courtesy Karen Martínez-Vargas, MD, Dennise Vázquez-González, MD, and Griselda Montes de Oca-Sánchez, MD.*



eFig. 75.11 Tuberculosis presenting with an ulcer on the tongue.



eFig. 75.12 Scrofuloderma. Ulceration with involvement of the underlying bone.



eFig. 75.13 Buruli ulcer. There is an undermined indurated border. *Courtesy Francisco Bravo, MD.*



eFig. 75.14 *Mycobacterium fortuitum* infection. Suppurative lymphadenitis due to an inoculation chancre on the foot. *From Azulay RD, Neves RG, Estrella RR, et al. Complexo primário cutáneo-ganglionar por Mycobacterium fortuitum. AMB Rev Assoc Med Bras 1974;20:177–81. Courtesy Rubem Azulay, MD.*

DRUG REGIMENS FOR CULTURE-POSITIVE PULMONARY TUBERCULOSIS (TB) CAUSED BY DRUG-SUSCEPTIBLE ORGANISMS						
Regimen	**Intensive phase**		**Continuation phase**		**Range of total doses**	**Comments**[¶,§]
	Drugs*	**Interval and doses† (minimal duration)**	**Drugs**	**Interval and doses‡,¶ (minimal duration)**		
1	INH RIF PZA EMB	7 days/week for 56 doses (8 wk) or 5 days/week for 40 doses (8 wk)	INH RIF	7 days per week for 126 doses (18 wk) or 5 days per week for 90 doses (18 wk)	182–130	Preferred regimen for patients with newly diagnosed pulmonary TB
2	INH RIF PZA EMB	7 days/week for 56 doses (8 wk) or 5 days/week for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during the continuation phase is difficult to achieve
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use with caution in patients with HIV and/or cavitary disease. A missed dose can lead to treatment failure, relapse, and acquired drug resistance
4	INH RIF PZA EMB	7 days/week for 14 doses (2 wk) then twice weekly for 12 doses (6 wk)[§]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use in HIV-infected patients or individuals with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior
5	RPT MOX INH PZA[‖]	7 days/wk for 56 doses (8 wk)	RPT MOX INH	7 days/wk for 63 doses (9 wk)	119	Patients ≥12 years of age and weighing ≥40 kg with pulmonary TB

*Other drug combinations may be appropriate in certain circumstances.
†DOT should be used when drugs are administered <7 days/week.
‡Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.
¶Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (e.g. pregnant women; breastfeeding infants; individuals with HIV infection, diabetes, alcoholism, malnutrition, chronic renal failure, or advanced age). The pyridoxine dose should be increased to 100 mg/day in patients with peripheral neuropathy.
§Alternatively, some US TB control programs have administered intensive-phase regimens 5 days/week for 15 doses (3 weeks), and then twice weekly for 12 doses.
‖Pyrazinamide weight-based dosing: 1000 mg if 40–54 kg, 1500 mg if 55–75 kg, 2000 mg if >75 kg.

eTable 75.1 Treatment regimens for culture-positive pulmonary tuberculosis (TB) caused by drug-susceptible organisms. The effectiveness of the regimen decreases from regimen 1 to 4. With the exception of 17 weeks for regimen 5, the total duration of therapy is 26 weeks; however, the total number of doses varies. Among patients with extrapulmonary tuberculosis, regimen 1 is generally recommended as initial therapy unless the organisms are known or strongly suspected of being resistant to the first-line drugs. Doses of medications (maximum dose) when given *daily*: INH, isoniazid 5 mg/kg (300 mg); RIF, rifampin 10 mg/kg (600 mg); RPT, rifapentine 1200 mg; MOX, moxifloxacin 400 mg; PZA, pyrazinamide 35 mg/kg (2000 mg); EMB, ethambutol 20 mg/kg (1600 mg). DOT, Directly Observed Therapy. *From Nahid P, Dorman SE, Alipanah N, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis 2016;63:853–67.*

PROTOCOL FOR SUBMITTING SPECIMENS FOR EVALUATION OF HANSEN'S DISEASE

Submit the completed consultation request form (below) along with the biopsy sample to the National Hansen's Disease Program (NHDP).
Please clearly specify which tests should be performed by checking the appropriate boxes below (test(s) to be ordered).
Please include a copy of any related biopsy reports or clinical photos. Please send blocks with a cold pack.

The following are the requirements needed to send a biopsy for evaluation:

1. A biopsy collected with a 4 - 5 mm punch. The specimen should be deep enough to include subcutaneous fat. This depth is important because the most prominently involved nerves will most often be found in the deep dermis. As a general rule, the biopsy should be taken from an active margin of a lesion.

2. After initial fixation in 10% neutral buffered formalin (for best PCR results tissue should not remain in formalin for more than 24 hours), process tissue into a paraffin block.
   ***Initial pathology review should also be conducted prior to submitting the case to NHDP.**
   *If using an auto embedder, specimen should be re-embedded prior to sending to avoid plastic cage.

3. Slides of unstained sections - 5 unstained slides are also required for staining & histology review at NHDP.

4. Stained slides may also be submitted for histological review -- **H&E & Fite stains only.**

5. If tissue cannot be processed into a paraffin block, place specimen in 10% neutral buffered formalin, and submit for processing at the NHDP. Expedited shipping methods should be used to avoid prolonged exposure to formalin. Packages are only received during weekdays with the exception of federal holidays.
   Please note:** pathology services are conducted on a first come, first serve basis and subject to current workload/pathologist availability. Obtaining initial pathology review before sending is ***strongly recommended.

PCR TESTING--
The clinical laboratory is able to conduct PCR testing on the same formalin fixed specimen submitted for histological evaluation. Testing is limited to the identification of M. leprae and M. lepromatosis.

Requirements for PCR testing:
1. Paraffin block – required for PCR testing.
   a. If tissue is too small, PCR may not be feasible and another biopsy may be required.
   b. Please send blocks with a cold pack to prevent damage/melting during warmer months.
   c. If auto embedded, specimen will need to be re-embedded prior to sending to avoid plastic cage.

2. Formalin fixed samples may also be submitted for PCR testing if tissue cannot be processed into a block.

Reporting:
Our lab is accredited through the Joint Commission and is CLIA certified separately from the NHDP clinic. As a result, we operate as a stand-alone entity; as with any other laboratory, we are unable to release lab results to any provider/practice other than those listed on the submission paperwork. For clinical consultation purposes, please make sure to check the appropriate box below, granting the NHDP Clinic access to this report as well.

Please send specimens to the following location:
National Hansen's Disease Program
Attn: Clinical Lab (Nurah Al-Ahmed)
9181 Interline Ave.
Baton Rouge, LA 70809
Clinical Laboratory Phone: 225-756-3733; Fax: 225-756-3734; E-mail:NAL-AHMED@hrsa.gov

eTable 75.2 US protocol and request form for submitting specimens for evaluation of Hansen disease.

DEPARTMENT OF HEALTH & HUMAN SERVICES
NATIONAL HANSEN'S DISEASE PROGRAM
9181 Interline Ave. Baton Rouge, LA 70809
1-800-642-2477 https://www.hrsa.gov/hansens-disease

PATHOLOGY CONSULATION REQUEST FORM

Date: _____

Submitting Provider/Pathologist Information:

Pathologist Name: _____
Phone No: _____
Fax No: _____
Email: _____

TREATING Provider Information:

Physician Name: _____
Phone No: _____
Fax No: _____
Email: _____

Our lab is accredited through the Joint Commission and is CLIA certified separately from the NHDP clinic. As a result, we operate as a stand-alone entity; as with any other laboratory, we are unable to release lab results to any provider/practice other than those listed on the submission paperwork. For clinical consultation purposes, please make sure to check the appropriate box, granting the NHDP Clinic access to this report as well. ☐ **Checked box indicates report can be released to the NHDP Clinic**

Test(s) to be ordered: ☐ **PCR** ☐ **Histological Review (H&E and Fite Stain)**

Return Materials to: _____

Patient Information:

Name (Last): _____ Name (First):_____DOB:_____ Age:_____
Sex:_____ Country of Birth:_____ Race: _____
Accession #:_____ Collection Date:_____ Biopsy Site:_____

Brief History: (please check all that apply)

1. Number of lesions: ☐ 5 or LESS lesions ☐ MORE than 5 lesions
2. Does patient experience decreased sensation around biopsy site? ☐ Yes ☐ No
3. Was this condition ever previously treated? ☐ Yes ☐ No If Yes, where? _____
4. Please list any medications given for this condition_____
5. Additional Information:

Mail Pathology Materials To:

National Hansen's Disease Program
Attn: Clinical Lab-Nurah Al-Ahmed
9181 Interline Avenue
Baton Rouge, LA 70809
Phone: 225-756-3733/Fax: 225- 756-3734
***Please include a copy of this form, as well as the biopsy report with submission.

NHDP FORM 199 REV JUN 2022
PATHOLOGY REQUEST FORM

eTable 75.2 US protocol and request form for submitting specimens for evaluation of Hansen disease. *Courtesy National Hansen's Disease Program, US Department of Health and Human Services, Baton Rouge, Louisiana; www.hrsa.gov/sites/default/files/hrsa/hansens-disease/skin-biopsy-protocol-form.pdf.*

Rickettsial Diseases 76

Lucas S. Blanton and David H. Walker

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Spotted Fever and Typhus Group Rickettsial Infections *1333*
Scrub Typhus *1340*
Human Ehrlichioses *1340*
Human Granulocytic Anaplasmosis *1341*
Q Fever *1341*

Key features

- Rickettsiae are small, obligately intracellular, Gram-negative bacteria that reside within an arthropod host (tick, flea, louse, or mite) during part of their life cycle
- The arthropod vector transmits the rickettsiae in its saliva or feces during feeding
- The major vertebrate target cells of *Rickettsia* (endothelium), *Orientia* (endothelium), *Ehrlichia* (monocytes or neutrophils), *Anaplasma* (neutrophils), and *Coxiella* (macrophages) determine to a large degree the pathogenesis of the disease
- In most spotted fever rickettsioses and scrub typhus, an eschar at the site of the vector's inoculation of organisms is an important physical sign
- A rash is the diagnostically critical clinical manifestation of Rocky Mountain spotted fever, other spotted fevers, murine typhus, and louse-borne typhus
- One of the most common rickettsial diseases in travelers is African tick bite fever

INTRODUCTION

Members of the order Rickettsiales are small, obligately intracellular, Gram-negative bacteria that reside within an arthropod host for at least part of their life cycle[1]. At least 30 bacterial species belonging to six genera (*Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia, and Neoehrlichia*) as well as the related *Coxiella* genus in the order Legionellales are known agents of human diseases (Table 76.1). Cutaneous manifestations vary from nearly always present in some spotted fevers and typhus to rare in others, such as human granulocytic anaplasmosis and Q fever (Table 76.2). Clinical recognition of a rash is frequently the event that leads to appropriate antimicrobial treatment for life-threatening Rocky Mountain spotted fever (RMSF) and other rickettsioses.

SPOTTED FEVER AND TYPHUS GROUP RICKETTSIAL INFECTIONS

History

Epidemic typhus was described by Fracastorius in Italy in 1546; RMSF, by Maxey in Idaho in 1899; and boutonneuse fever by Conor in Tunisia in 1910. A rickettsial agent was first identified in 1906 in the Bitterroot Valley of western Montana by Howard Ricketts, who also recognized its transmission by ticks. In 1916, S. Burt Wolbach visualized this agent, later named *Rickettsia rickettsii*, within endothelial cells. Charles Nicolle discovered in 1909 that lice transmit epidemic typhus, which was subsequently found to be caused by *Rickettsia prowazekii*. Epidemic louse-borne typhus influenced the outcome of most European wars after 1500, including Napoleon's failed Russian invasion in 1812 and World War I, during and after which typhus affected 25 million persons and caused 3 million deaths in Russia. In 1934, recrudescent typhus (Brill–Zinsser disease) was determined to be caused by reactivation of latent *R. prowazekii* infection. Endemic or murine typhus was shown during the 1930s to have a rat reservoir and flea vector.

Epidemiology

Spotted fever group rickettsiae (SFGR) are maintained in nature principally via transmission of the bacteria in infected ova from one generation of tick, mite, or flea to the next (see Table 76.1; Fig. 76.1). During feeding, infected arthropods instill saliva containing rickettsiae into their host's skin. Thus, the seasonal and geographic distribution of each disease (Fig. 76.2) depends upon the range and the host-seeking activity

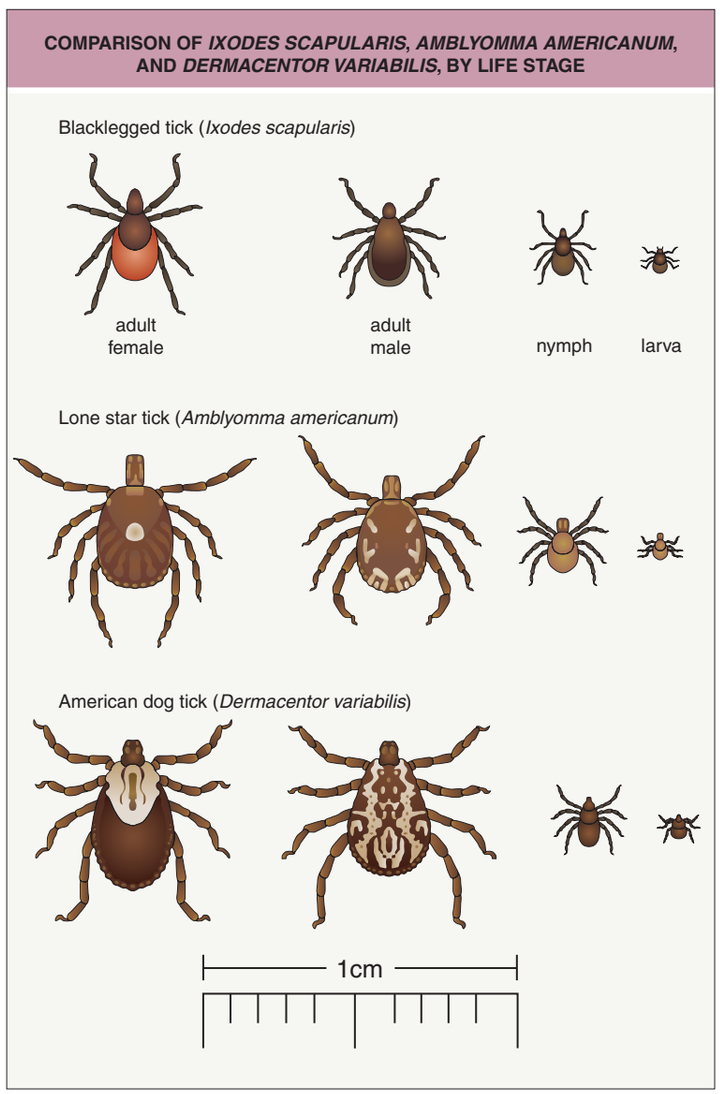


Fig. 76.1 Comparison of *Ixodes scapularis* (blacklegged tick), *Amblyomma americanum* (lone star tick), and *Dermacentor variabilis* (American dog tick), by life stage. *From Chapman AS, et al. MMWR Recomm Rep 2006;55:1–27.*

EPIDEMIOLOGY OF RICKETTSIAL AND RELATED INFECTIONS			
Agent	**Disease**	**Transmission**	**Geographic distribution**
Rickettsia rickettsii	Rocky Mountain spotted fever, Brazilian spotted fever	**Bite of tick:**	
		Dermacentor variabilis (Fig. 76.1)	Eastern two-thirds > Pacific Coast of US
		D. andersoni	Rocky Mountain states
		Rhipicephalus sanguineus	Southwestern US; northern Mexico
		Amblyomma cajennense complex, *A. aureolatum*	Mexico; Central and South America
Rickettsia akari	Rickettsialpox	**Bite of mouse mite**:	
		Liponyssoides sanguineus	North America; Eurasia
Rickettsia conorii (4 subspecies)	Boutonneuse fever (Mediterranean spotted fever), Indian and Israeli tick typhus, Astrakhan spotted fever	**Bite of tick**:	
		Rhipicephalus sanguineus	Southern Europe; Africa; western and southern Asia
		Rh. pumilio	Southern Russia
Rickettsia sibirica	North Asian and Siberian tick typhus, lymphangitis-associated rickettsiosis	**Bite of tick**:	
		Dermacentor nuttallii, D. silvarum, Haemaphysalis concinna, Hyalomma asiaticum, others	Eurasia and Africa
Rickettsia heilongjiangensis	Far Eastern spotted fever	**Bite of tick:**	
		Haemaphysalis species, D. silvarum, others	Eastern Russia, China, Thailand, Japan
Rickettsia australis	Queensland tick typhus	**Bite of tick**:	
		Ixodes cornuatus, I. holocyclus, I. tasmani	Eastern Australia
Rickettsia honei	Flinders Island spotted fever	**Bite of tick**:	
		Bothriocroton hydrosauri, others	Australia and Nepal (Flinders Island is located between Tasmania and mainland Australia)
Rickettsia japonica	Japanese spotted fever	**Bite of tick**:	
		Haemaphysalis flava, H. longicornis, Ixodes ovatus, Dermacentor taiwanensis	Japan and eastern Asia
Rickettsia massiliae	*Rickettsia massiliae* rickettsiosis	**Bite of tick:**	
		Rhipicephalus species, others	Europe, South America, Africa, Asia
Rickettsia felis	Flea-borne spotted fever	**By flea:**	
		e.g. *Ctenocephalides felis*	Worldwide
Rickettsia africae	African tick bite fever	**Bite of tick:**	
		Amblyomma hebraeum	Southern Africa
		A. variegatum	Central, eastern, and western Africa; Caribbean islands
Rickettsia parkeri	*Rickettsia parkeri* rickettsiosis (maculatum disease, American tick bite fever)	**Bite of tick:**	
		Amblyomma maculatum, A. americanum, Dermacentor parumapertus	North America
		A. triste, A. tigrinum, A. ovale	South America
Rickettsia philipii (364D)	Pacific Coast tick fever	**Bite of tick:**	
		Dermacentor occidentalis	California
Rickettsia aeschlimannii	*Rickettsia aeschlimannii* infection	**Bite of tick**:	
		Haemaphysalis concinna, Hyalomma marginatum, Rhipicephalus turanicus, others	Africa, Asia, Europe
Rickettsia slovaca, Rickettsia raoultii, or *Candidatus* Rickettsia rioja	Tick-borne lymphadenopathy, Dermacentor-borne necrosis and lymphadenopathy (DEBONEL)	**Bite of tick** (usually on the scalp):	
		Dermacentor marginatus, D. reticularis, others	Europe
Rickettsia prowazekii	Epidemic louse-borne typhus	**Feces of human body louse** (*Pediculus humanus* var. *corporis*)	South America; Africa; Eurasia
	Brill–Zinsser disease	**None (recrudescence of latent infection)**	
	Flying squirrel typhus	**Contact with flying squirrel** (*Glaucomys volans*) and its fleas and lice	North America
Rickettsia typhi	Murine (endemic) typhus	**Feces of fleas**:	
		Xenopsylla cheopis	Worldwide
		Ctenocephalides felis	North America

Table 76.1 Epidemiology of rickettsial and related infections.

EPIDEMIOLOGY OF RICKETTSIAL AND RELATED INFECTIONS			
Agent	**Disease**	**Transmission**	**Geographic distribution**
*Orientia tsutsugamushi**	Scrub typhus	**Bite of larval trombiculid mites**:	
		L. deliense, L. fletcheri, L. scutellare, L. arenicola	Southern and eastern Asia; islands of the southwestern Pacific and Indian Oceans; northern Australia
		e.g. *L. pallidum*	Japan; Korea; Russian Far East
		e.g. *L. scutellare*	China; Malaysia
		e.g. *L. deliense, L. fletcheri, L. arenicola*	Tropical regions
Ehrlichia chaffeensis	Human monocytic ehrlichiosis	**Bite of tick**:	
		Amblyomma americanum (Fig. 76.1), *Dermacentor variabilis*	Southeastern and South Central US
Ehrlichia muris eauclairensis	Ehrlichiosis (due to *Ehrlichia muris eauclairensis*)	**Bite of tick:**	
		Ixodes scapularis	Upper midwestern US
Ehrlichia ewingii	Ehrlichiosis (due to *Ehrlichia ewingii*)	**Bite of tick:**	
		Amblyomma americanum	Southeastern and South Central US
Anaplasma phagocytophilum	Human granulocytic anaplasmosis	**Bite of tick:**	
		Ixodes scapularis (Fig. 76.1)	Northern US
		I. pacificus	Far western US
		I. ricinus, I. persulcatus	Eurasia
Candidatus Neoehrlichia mikurensis	Neoehrlichiosis†	**Bite of tick:**	
		Ixodes ricinus	Europe
		Ixodes persulcatus	East Asia
Neorickettsia sennetsu	Sennetsu fever‡	**Ingestion** of infected trematode-infested raw fish or fish paste	East Asia
Coxiella burnetii	Q fever	**Aerosol** of infected products of parturition of ruminants (e.g. sheep, cattle, goats), cats, and other animals¶	Worldwide

*More recently identified causes of scrub typhus include *Orientia chuto* (Dubai, Africa) and *Candidatus* Orientia chiloensis (Chile).
†Febrile illness that may be associated with thrombosis, thrombophlebitis, and arteritis; described primarily in immunocompromised patients with a hematologic malignancy or autoimmune disease.
‡Mononucleosis-like syndrome characterized by fever, malaise, and generalized lymphadenopathy.
¶Less common means of transmission include ingestion of contaminated dairy products and tick bites (e.g. *Dermacentor* spp.).

Table 76.1 Epidemiology of rickettsial and related infections. Additional agents that have been implicated in infections with eschar and/or rash include *Rickettsia monacensis* (Europe) and *Candidatus* Rickettsia tarasevichiae (China). *Rickettsia helvetica* transmitted by *Ixodes ricinus* in Europe can also lead to "aneruptive fever" that lacks cutaneous involvement.

of the particular vector. For example, RMSF usually occurs during tick season, from late spring until the end of summer[2].

Typhus group rickettsiae are deposited on the host's skin in the feces of feeding human body lice (*R. prowazekii*) or fleas (*R. typhi*). The organisms are subsequently scratched into the skin, rubbed into mucous membranes, or inhaled. Humans who recover from louse-borne typhus remain latently infected and years later may develop recrudescent illness (Brill–Zinsser disease) and associated rickettsemia. Such individuals can infect feeding lice, which may then spread the disease to another person and ignite an epidemic. In addition, a zoonotic cycle of *R. prowazekii* is maintained in flying squirrels and their fleas and lice. *R. typhi* is maintained in natural cycles, classically in rats and oriental rat fleas as well as in opossums and cat fleas. Murine (endemic) typhus caused by *R. typhi* is prevalent in tropical and subtropical coastal regions worldwide, representing an increasingly recognized cause of febrile illness in travelers[3].

Pathogenesis

After entry into the dermis, rickettsiae spread throughout the body via the bloodstream. They attach to vascular endothelial cells by outer membrane protein B and, in the case of SFGR, also via outer membrane protein A. The organisms enter the cells by induced phagocytosis and then escape from the phagosome into the cytosol, where they obtain amino acids, nucleotides, and other building blocks for growth from the host cell and divide by binary fission. SFGR move intra- and intercellularly by stimulating propulsion via the host cell's actin, resulting

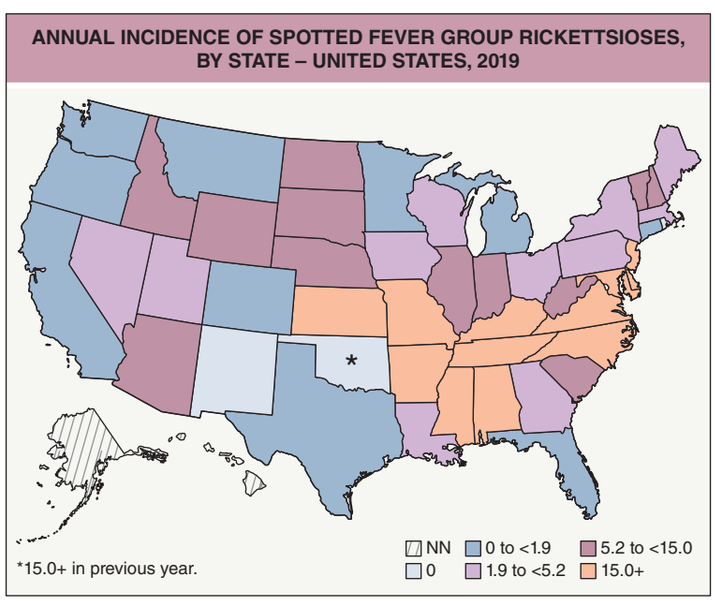


Fig. 76.2 Annual incidence (per million persons) of spotted fever group rickettsioses, by state – United States, 2019. Because serologic tests cannot reliably distinguish among spotted fever group *Rickettsia* species, since 2010 CDC reporting has combined them in a category that includes Rocky Mountain spotted fever (RMSF), *Rickettsia parkeri* rickettsiosis, Pacific Coast tick fever, and rickettsialpox. NN, not notifiable. *Courtesy US Centers for Disease Control and Prevention, cdc.gov/rmsf/stats/index.html.*

DERMATOLOGIC MANIFESTATIONS OF RICKETTSIAL INFECTIONS				
Disease	**Rash incidence (%)**	**Appearance of rash after onset of illness**	**Characteristics**	**Eschar (%)**
Rocky Mountain spotted fever, Brazilian spotted fever	90	3–5 days	Early macules, later papules; petechiae in 50% of patients; retiform purpura in severe disease	<1
Rickettsialpox	100	2–3 days	Early macules and papules; later papulovesicles and crusts	90
Boutonneuse fever and related conditions	95	3–5 days	Early macules, later papules	50
North Asian tick typhus and related conditions	100	4–5 days	Macules and papules	75
Far Eastern spotted fever	90	3–4 days	Macules and papules	90
Queensland tick typhus	90	2–6 days	Macules, papules, and vesicles	75
Flinders Island spotted fever	85	A few days	Early macules and papules, later (in some patients) petechiae	50
Japanese spotted fever	100	A few days	Early macules, later (in some patients) petechiae	90
Rickettsia massiliae rickettsiosis	75	Not reported	Macules and papules	100
Flea-borne spotted fever	80	A few days	Macules and papules; occasionally pustules	15–20
African tick bite fever	50	2–5 days	Generally relatively few lesions; macules, often vesicles	90, often multiple
Rickettsia parkeri rickettsiosis	80	2–4 days	Macules, papules, often vesicles	100
Pacific Coast tick fever	15	Not reported	Macules in region of eschar (one patient)	100
R. aeschlimannii infection	50	Not known	Macules and papules	100
Tick-borne lymphadenopathy	5	Not reported	Macules and papules	100
Epidemic louse-borne typhus	50–100	4–5 days	Early macules, later papules; petechiae	None
Brill–Zinsser disease	50	4–6 days	Macules and papules	None
Flying squirrel typhus	65	2–8 days	Macules and papules	None
Murine (endemic) typhus	50	5 days	Early macules, later papules	None
Scrub typhus	50	4–6 days	Early macules, later papules	60–90
Human monocytic ehrlichiosis	40	Median, 5 days	Macules, papules, occasionally petechiae	None
Ehrlichia muris eauclairensis ehrlichiosis	10	Not reported	Not reported	None
Human granulocytic anaplasmosis	≤5	Not reported	Erythematous rash on neck/chest; petechiae or purpura	None
Neoehrlichiosis	Rare	Not reported	Erythematous macules, erythema nodosum	None
Sennetsu fever	Rare	Not reported	Diffuse erythema, petechiae	None
Q fever	Rare	Associated with chronic infection	Macules, papules, palpable purpura; rarely erythema nodosum	None

Table 76.2 Dermatologic manifestations of rickettsial and related infections. To date, skin findings have not been described in patients with *Ehrlichia ewingii* ehrlichiosis.

in a contiguous network of infected endothelial cells that represent the source of the vascular-based disease manifestations, including skin lesions. Whereas SFGR injure the host endothelium by stimulating these cells to produce toxic reactive oxygen species, typhus group rickettsiae replicate within the infected endothelial cells until they burst[4].

The major pathophysiologic effect of rickettsial infection is increased vascular permeability, which can result in edema, hypovolemia, and hypotension. Although endothelial cells of the microcirculation are infected in every organ, the critical target organs in life-threatening infections are the lung and brain. A fatal outcome can result if increased vascular permeability leads to non-cardiogenic pulmonary edema, acute respiratory distress syndrome (ARDS), and meningoencephalitis[2].

As the infection progresses, macrophages and lymphocytes infiltrate the walls of affected vessels and act as effector cells, secreting cytokines such as interferon-γ and tumor necrosis factor. Infected endothelial cells and macrophages themselves are activated by cytokines, resulting in killing of intracellular rickettsiae by mechanisms involving nitric oxide, reactive oxygen species, and tryptophan starvation (via enzymatic degradation of this amino acid). Recruited cytotoxic T cells are critical to the apoptotic elimination of infected endothelial cells, which occurs through perforin-dependent pathways. A combination of rickettsicidal mechanisms and killing of infected endothelial cells ultimately leads to clearance of the infection. Antibodies to rickettsiae play a role in the prevention of reinfection[4].

Clinical Features

Clinical course and systemic features

Rickettsial infections typically begin with fever (>102°F [39°C]) in two-thirds of patients during the first 3 days of the illness and in 90% thereafter, accompanied by a severe headache and myalgias. Nausea, vomiting, abdominal pain, and abdominal tenderness are also frequent early symptoms. When a rash develops, it usually appears on day 3–6 of the illness (see below and Table 76.2). Cough (related to pneumonitis and/or pulmonary edema) and confusion or lethargy (related to encephalitis) may represent additional symptoms. Patients often have thrombocytopenia, although full-blown disseminated intravascular coagulation is rare, and hyponatremia frequently occurs secondary to increased antidiuretic hormone secretion in response to hypovolemia. Additional laboratory findings may include anemia, elevated liver enzymes, and abnormal renal function tests. As the clinical course progresses, hypotension, acute kidney injury, respiratory failure, and coma may develop[5].

Severe rickettsioses continue to cause death due to misdiagnosis and/or *delayed initiation* of antirickettsial treatment, with approximate mortality rates as follows: 4% for RMSF and louse-borne typhus; 2.5% for boutonneuse fever; and 0.5% for murine typhus[3]. If *not treated* with an appropriate antimicrobial agent, ~25% and 15% of patients with RMSF and louse-borne typhus, respectively, will die[2,6]. The case fatality rate is higher with older age, male sex, and comorbidities.



Fig. 76.3 Rocky Mountain spotted fever. The cutaneous lesions often appear first on the wrists and ankles. *Courtesy Philippe Berbis, MD.*



Fig. 76.4 Rocky Mountain spotted fever. Petechiae on the palms and soles often develop relatively late in the disease course. *Courtesy Ronald P. Rapini, MD.*



Fig. 76.5 Rocky Mountain spotted fever. Petechiae are present within erythematous papules and plaques on the buttocks. Some of the lesions have a retiform pattern.



Fig. 76.6 Rocky Mountain spotted fever. Retiform purpura on the distal lower extremity in a patient with more severe disease.

Shared cutaneous features

In many types of spotted fevers other than RMSF (see Table 76.2), an eschar consisting of central dermal and epidermal necrosis (typically 0.5–2 cm in diameter) surrounded by a zone of erythema appears during the incubation period (usually 4–10 days prior to onset of the illness) (see Figs. 76.7 and 76.8A). This represents the site of inoculation of rickettsiae by the tick or mite[7,8]. The rash typically begins as erythematous macules around the wrists and ankles (spotted fevers) (Fig. 76.3) or axillae (typhus fevers). The exanthem evolves during the course of the illness, with lesions eventually appearing on most of the body, often with relative sparing of the face. Macules and papules develop on the palms and soles in approximately half of the patients with spotted fevers, often relatively late in the disease course (Fig. 76.4). Macules reflect vasodilation related to infection of endothelial cells in the dermal microcirculation. As perivascular edema develops secondary to leakage of fluid from damaged blood vessels, macules become papules. When endothelial cell destruction leads to more severe vascular injury, petechiae appear within the lesions (Fig. 76.5), which can coalesce and become purpuric (Fig. 76.6). Cutaneous necrosis, including gangrene of the digits, extremities, ears or prepuce, occurs in ~5% of patients with RMSF and occasionally in epidemic typhus; this is due to more severe infection of the microcirculation in acral sites, which are cooler and therefore more favorable for rickettsial growth.

Features of specific diseases

RMSF usually follows the classic clinical course described above. After an incubation period of 2–14 (mean, 7) days following the tick bite (which ~40% of patients do not recall), affected individuals present with fever, myalgias, headache, and in >50% of patients, gastrointestinal symptoms. The rash typically appears 3–5 days after onset of the illness as subtle erythematous macules on the wrists and ankles, which is followed by centripetal spread to the trunk, formation of papular lesions, and eventual development of petechiae (~50% of patients). However, cutaneous findings are absent in 10%–15% of patients and may be difficult to recognize in darkly pigmented skin.

R. parkeri and *R. africae*, closely related strains of SFGR, cause two similar infections, ***R. parkeri rickettsiosis*** and ***African tick bite fever***, respectively. The former is endemic in the south central and southeastern US (the range of *A. maculatum*, the Gulf Coast tick; see Table 76.1 & Fig. 76.12B) as well as in South America, while the latter is endemic in sub-Saharan Africa and represents the rickettsial disease with the highest incidence among all international travelers returning to the US or other countries worldwide[9,10]. Patients with these conditions typically present with mild constitutional symptoms (e.g. fever, headache, myalgias), one or more eschars (Fig. 76.7), and tender lymphadenopathy in the region draining the eschar(s). In 50%–80% of affected individuals, usually 2–4 days after disease onset, a rash develops on



Fig. 76.7 African tick bite fever. Eschar at the tick bite site.

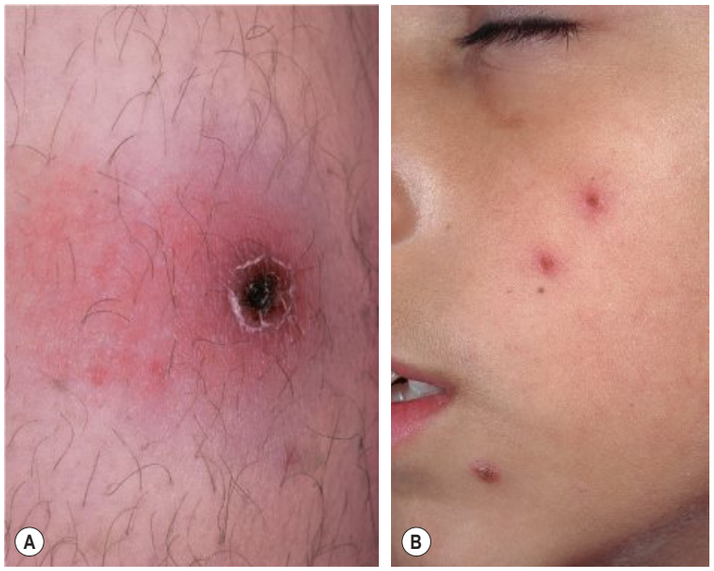


Fig. 76.8 Rickettsialpox. A Eschar at the site of the mite bite. **B** Scattered papules with hemorrhagic crusts.

the trunk and extremities, sometimes involving the palms and soles. The eruption may be relatively sparse and often features small central vesicles or pustules within erythematous macules and papules. No deaths have been reported for either type of infection. Despite the substantial difference in severity, it is likely that many *R. parkeri* infections are misdiagnosed as RMSF owing to serologic cross-reactivity with *R. rickettsii*[10].

Rickettsialpox occurs primarily in urban areas, especially in the northeastern US, and is transmitted by mites that parasitize house mice. A papulovesicle arises within 48 hours at the site of a mite bite and eventuates in an eschar with surrounding erythema and induration (Fig. 76.8A). Constitutional symptoms (e.g. fever, headache, myalgias) begin 1 to 2 weeks later, followed in 2 to 3 days by a cutaneous eruption that often involves the face (Fig. 76.8B) as well as the trunk and extremities, in no particular sequence. Approximately 20–40 skin lesions typically develop, evolving from erythematous macules and papules to papulovesicles to hemorrhagic crusts. The palms and soles are occasionally affected, and an enanthem characterized by small erosions on the tongue, palate, and pharynx may occur[3].

Pathology

Rickettsial infection is multifocal, which is reflected in the scattered distribution of cutaneous lesions. Randomly obtained tissue samples are unlikely to contain the classic finding of a lymphocytic vasculitis with extravasation of erythrocytes (Fig. 76.9), which is typically present in the center of a petechial macule or papule. The early finding of perivascular edema is difficult to identify histopathologically because of formalin-associated tissue shrinkage. Small fibrin thrombi are

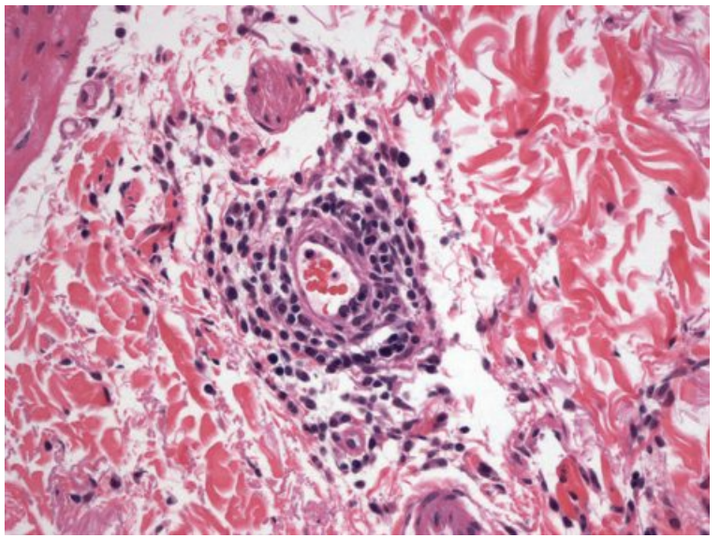


Fig. 76.9 Histologic findings in Rocky Mountain spotted fever. Typical lymphohistiocytic vasculitis involving a dermal blood vessel. *Courtesy James W. Patterson, MD.*

evident in a minority of cases. Later in the disease course, leukocytoclastic vasculitis can be detected histopathologically in the skin and other organs. Eschars reflect coagulative necrosis of the epidermis. Skin lesions of rickettsialpox show subepidermal edema associated with a mild vasculitis and dense lymphohistiocytic infiltrate. Fibrin thrombi may be observed.

Diagnosis and Differential Diagnosis

The diagnosis of rickettsiosis is based on disease signs and symptoms as well as potential arthropod exposure (Fig. 76.10)[11]. It is essential to begin empiric treatment with effective antirickettsial agents based on clinical suspicion rather than awaiting laboratory confirmation. Indeed, serologic diagnosis is usually retrospective, because antibodies do not develop until day 7 of the illness or later. Serologic confirmation requires seroconversion or a 4-fold increase between acute and convalescent antibody titers[12]. Previous exposure to non- or mildly pathogenic cross-reacting SFGR (e.g. *Rickettsia amblyommatis* within *Amblyomma americanum* [lone star] ticks) can make interpretation of single serologic specimens difficult[12,13].

Circulating rickettsiae are generally too few early in the illness to be detected in the blood by PCR-based assays, whereas PCR analysis of fresh and even formalin-fixed skin biopsy specimens is more sensitive[14] (see Fig. 76.10). Rickettsiae can also be identified by immunofluorescence or immunohistochemistry in a biopsy specimen of an eschar or a maculopapular lesion (Fig. 76.11), especially if the latter is petechial.

Prior to the onset of the rash, the differential diagnosis may include a wide variety of viral infections, ehrlichiosis, and typhoid fever. Patients with prominent nausea and vomiting are often suspected to have viral or bacterial enterocolitis. Abdominal pain and tenderness can suggest an acute surgical abdomen, which has led to exploratory laparotomies. Cough and crackles on auscultation due to pulmonary edema may lead to suspicion of bacterial or viral pneumonia. Neurologic signs and cerebrospinal fluid pleocytosis can suggest viral or bacterial meningoencephalitis, while jaundice and elevated hepatic enzymes may prompt the consideration of viral hepatitis or leptospirosis.

When the cutaneous eruption initially develops, the differential diagnosis may include a viral exanthem, a drug eruption, ehrlichiosis, Kawasaki disease, and early secondary syphilis. Exanthems due to enteroviruses, Epstein–Barr virus, parvovirus B19, adenovirus, dengue fever, and measles may have a petechial component (see Fig. 81.2). When petechial and/or purpuric lesions become more prominent, meningococcemia, small vessel vasculitis, disseminated gonococcal infection, and viral hemorrhagic fevers (e.g. dengue; see Table 81.7) may also be considered. In patients with thrombocytopenia, immune thrombocytopenic purpura or thrombotic thrombocytopenic purpura represent additional possibilities. The differential diagnosis for rickettsialpox and other rickettsial eruptions with a vesicular component

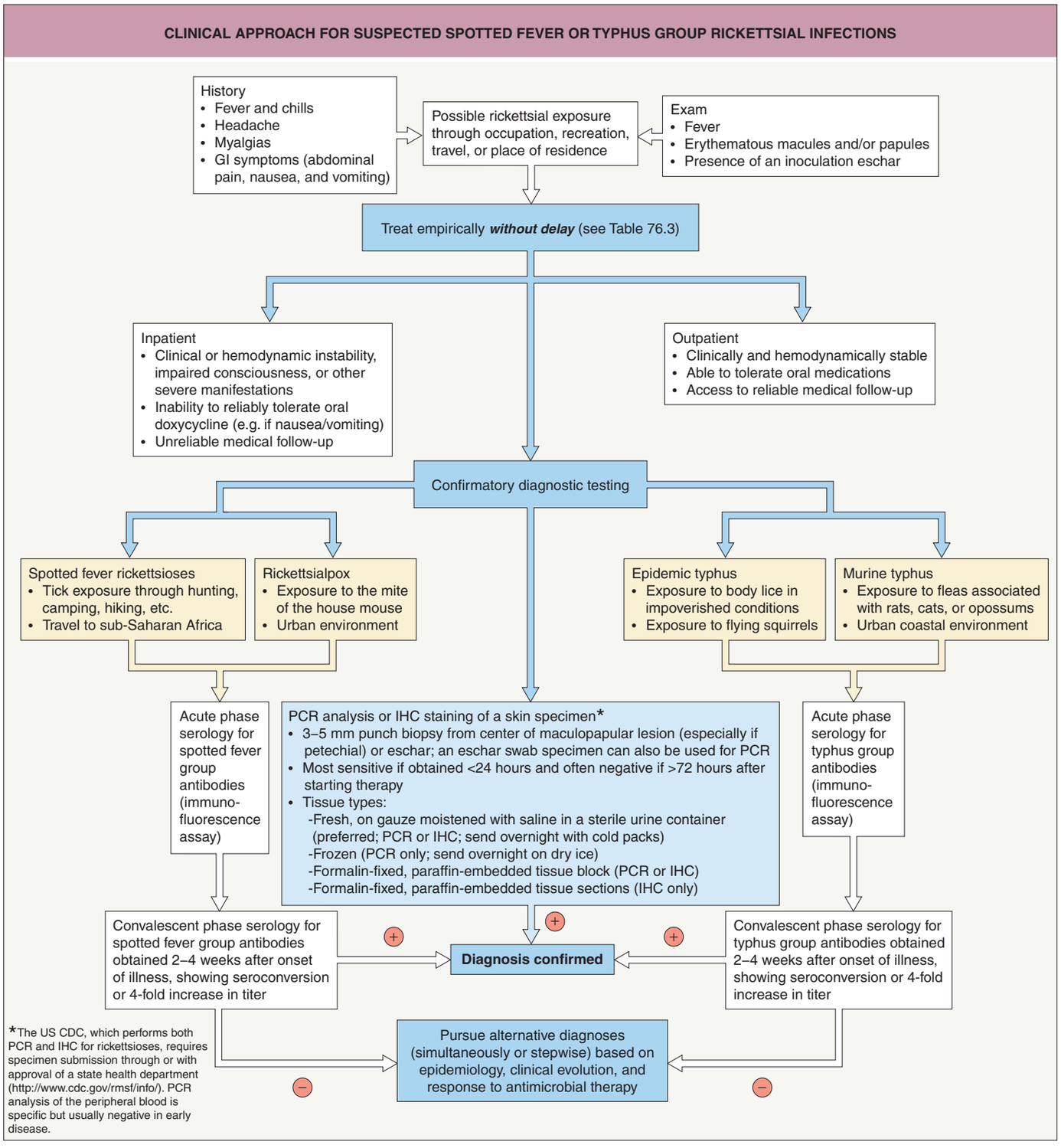


Fig. 76.10 Clinical approach for suspected spotted fever or typhus group rickettsial infections. IHC, immunohistochemical.

may include vesicular viral exanthems (e.g. due to coxsackieviruses), varicella, disseminated HSV infection, pityriasis lichenoides et varioliformis acuta (PLEVA), drug eruptions, bullous insect bite reactions, and scabies. Cutaneous necrosis resembling an eschar can be seen in spider bites, ecthyma gangrenosum (typically in immunocompromised hosts), cutaneous anthrax, *Bacillus cereus* infection, cutaneous diphtheria, tularemia, scrub typhus (see below), and primary syphilis.

Treatment

The drug of choice for rickettsial infections in nearly all patients, including young children, is doxycycline[11] (Table 76.3). Chloramphenicol is a less effective alternative, having a higher rate of fatal outcomes; in the US, oral chloramphenicol is not available and the intravenous form is difficult to obtain. Although older tetracyclines may lead to adverse effects in pregnant women and the developing fetus, doxycycline appears to be relatively safe and represents the best treatment option for severe rickettsioses (e.g. RMSF) during pregnancy[11].

Mild cases of boutonneuse fever in children have been treated with azithromycin or clarithromycin with an outcome equivalent to treatment with chloramphenicol. These antibiotics may also represent therapeutic options for mild rickettsioses during pregnancy[15]. Although fluoroquinolones have been used successfully to treat patients with boutonneuse fever, worse outcomes have been noted in those with

severe disease[16]. Fluoroquinolone or azithromycin therapy also results in delayed defervescence as compared to tetracyclines in murine typhus[3,17]. Therefore, treatment of severe rickettsial infection with macrolides or fluoroquinolones is not recommended.

SCRUB TYPHUS

Scrub typhus was described in association with red mites in China in CE 313. *Orientia tsutsugamushi* was discovered in Japan by Nagayo and Ogata in the 1920s and early 1930s. There are >70 strains of *O. tsutsugamushi*, which differs from *Rickettsia* spp. in its cell wall proteins and ultrastructure as well as by lacking lipopolysaccharide. *O. tsutsugamushi* is maintained in nature via transovarial transmission by its vector, trombiculid mites (see Table 76.1). Eggs laid by infected mites hatch with the emergence of infected larvae (chiggers) that feed on rats.

Approximately one million cases of scrub typhus occur annually, primarily affecting rural populations in Asia (from Afghanistan to Japan) and northern Australia[18]. In addition, novel *Orientia* spp. have been implicated in scrub typhus occurring in Dubai and Africa (*O. chuto*) as well as Chile (*Candidatus* O. chiloensis)[19–21]. Immunity is strain-specific and transient, resulting in reinfections. The severity of the illness is age-dependent and varies geographically.

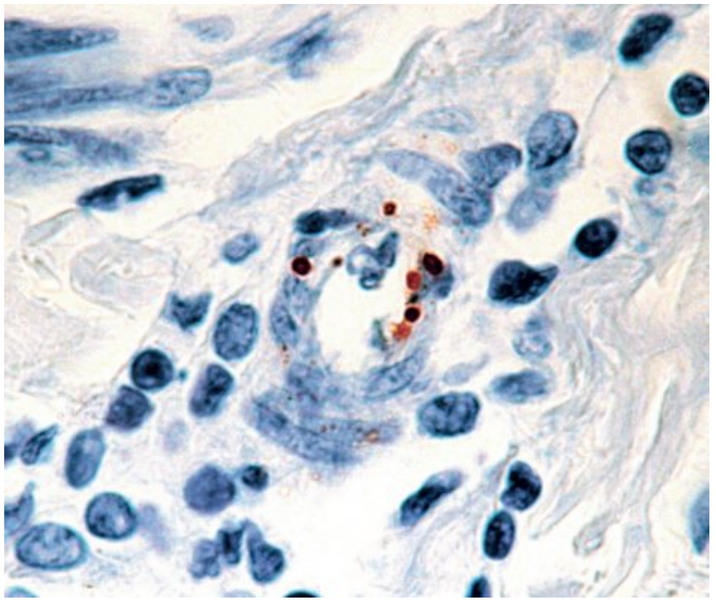


Fig. 76.11 Immunohistochemical detection of spotted fever rickettsiae. Organisms within the endothelium of a dermal blood vessel are highlighted by brown staining.

A cutaneous eschar forms at the site of chigger feeding in 60%–90% of primary infections. This is followed by regional lymphadenopathy, fever, and headache; generalized lymphadenopathy, conjunctival hyperemia, and hearing loss may also develop[18]. A rash occurs in approximately half of patients, usually appearing as erythematous macules on the trunk 4–6 days after disease onset. Lesions then become papular, with subsequent centrifugal spread. Interstitial pneumonia occurs frequently, presenting with cough, tachypnea, and radiographic infiltrates; meningoencephalitis is a less common manifestation[22]. In severe cases, ARDS, acute kidney injury, and hypotensive shock may develop.

Tetracyclines, particularly doxycycline, are generally the first-line treatment for scrub typhus. Azithromycin has similar efficacy and represents an option for pregnant women and children, whereas chloramphenicol is less effective[15]. However, reduced responsiveness of *O. tsutsugamushi* infections to doxycycline and chloramphenicol treatment has been reported in northern Thailand[23,24], and patients there have been treated successfully with azithromycin or rifampin.

HUMAN EHRLICHIOSES

Ehrlichial infections have been well known to veterinarians for >75 years, but human infection was not recognized until 1987, when an organism eventually identified as *Ehrlichia chaffeensis* was implicated as the etiologic agent of human monocytic ehrlichiosis (HME)[25]. In 1999, *E. ewingii* was found to cause human infections (most often in immunosuppressed patients) with clinical manifestations similar to HME[26]. *Ehrlichia* spp. are obligately intracellular, Gram-negative bacteria that target monocytes/macrophages (*E. chaffeensis*) or neutrophils (*E. ewingii*), within which they reside as a cytoplasmic microcolony that is occasionally visible in a peripheral blood smear. Both agents are maintained in a zoonotic cycle involving persistently infected white-tailed deer as the major reservoir and *Amblyomma americanum* as the primary vector (see Table 76.1). These ticks were originally found primarily in the south central and southeastern US, but their geographic distribution has expanded into the upper midwestern and northeastern states, overlapping with that of *Ixodes scapularis* (Fig. 76.12A)[25]. Trends of increasing temperatures with climate change are predicted to continue to shift the ranges of tick species northward[27]. *Ehrlichia muris eauclairensis*, transmitted by *Ixodes scapularis*, causes a human infection similar to HME in the upper midwestern US[28].

HME is a serious infectious disease with a ~3% case fatality rate. Its incidence is likely underestimated due to the lack of specific clinical findings[29]. Patients with HME and *Ehrlichia ewingii* ehrlichiosis typically present with fever, headache, and myalgias; common laboratory abnormalities include thrombocytopenia, leukopenia, and elevated transaminases. Progression to ARDS, meningoencephalitis, and toxic shock syndrome-like manifestations can occur. In addition, overwhelming ehrlichial infection may develop in immunocompromised hosts, such as those with HIV infection and organ transplant recipients[29,30].

TREATMENT OF RICKETTSIAL AND RELATED DISEASES

	Medication	Adult dose	Pediatric dose	Treatment duration
• First choice for virtually all rickettsial infections in children and adults*	Doxycycline	100 mg po or iv twice daily	2.2 mg/kg (max. 100 mg) po or iv twice daily	Until ≥3 days after defervescence, for a minimum total course of 5–7 days
• Alternative for non-life-threatening HME or HGA in pregnant women • Alternative for scrub typhus	Rifampin	300 mg po twice daily	10 mg/kg (max. 300 mg) twice daily	Until ≥3 days after defervescence, for a minimum total course of 7–10 days
• First choice for scrub typhus in pregnant women and potentially children • Alternative for mild rickettsioses (e.g. early boutonneuse fever) during pregnancy or in children	Azithromycin†	500 mg po daily	10 mg/kg po daily	3 days

*Other tetracyclines are also effective for rickettsial infection, but doxycycline is preferred during pregnancy, as older tetracyclines have been associated with adverse effects in this population (e.g. maternal pancreatitis, hepatitis, bone abnormalities in the developing fetus).
†Clarithromycin may also be considered.

Table 76.3 Treatment of rickettsial and related diseases. Empiric treatment with an appropriate agent should be initiated immediately when a diagnosis of Rocky Mountain spotted fever (RMSF), human monocytic ehrlichiosis (HME), human granulocytic anaplasmosis (HGA), or another potentially severe rickettsiosis is suspected clinically. Use of chloramphenicol in pregnant women is no longer recommended due to an increased likelihood of death in severe rickettsioses (e.g. RMSF) and potential risks including aplastic anemia and (when used in the late third trimester) gray baby syndrome. iv, intravenously; po, orally.

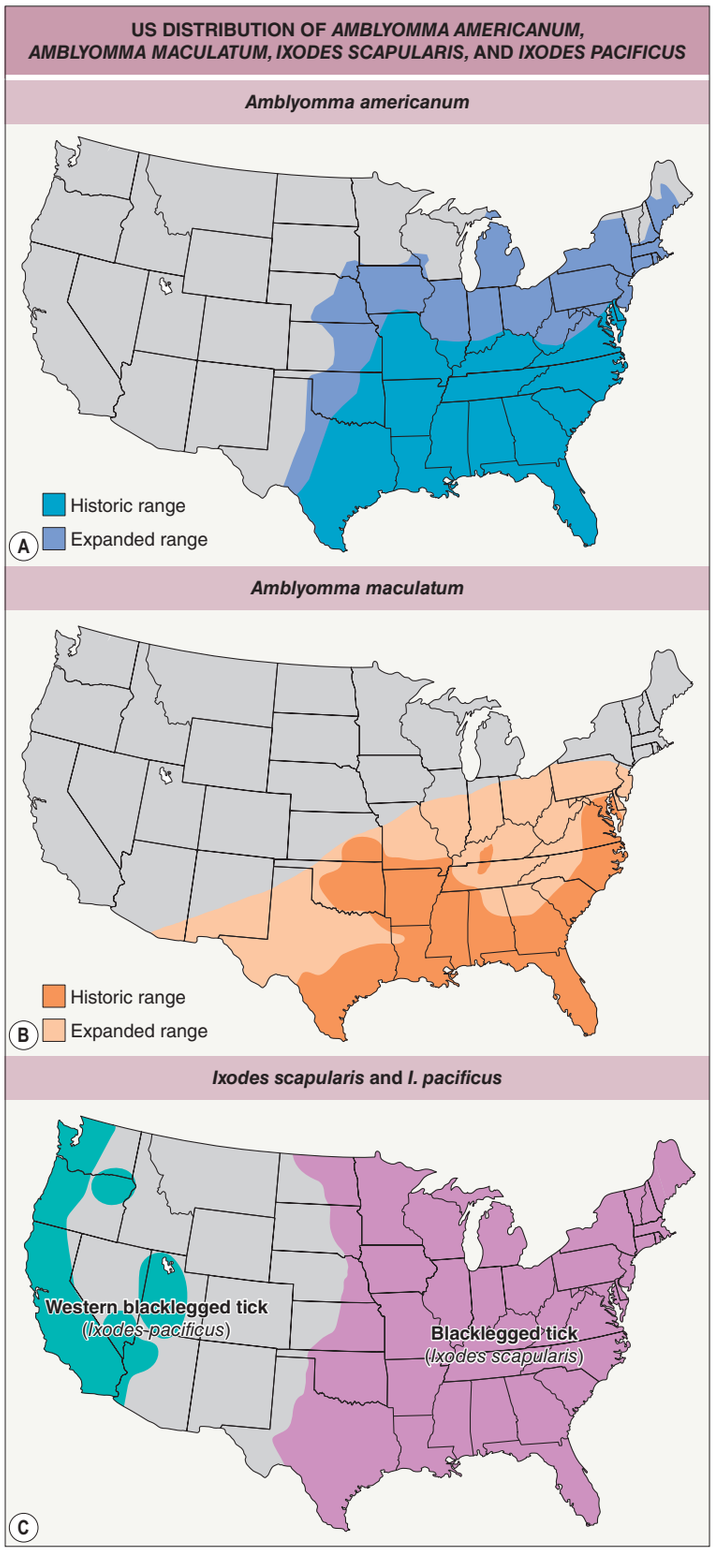


Fig. 76.12 US distribution of *Amblyomma americanum, A. maculatum, Ixodes scapularis*, and *I. pacificus*. *Amblyomma americanum* (**A**) and *A. maculatum* (Gulf Coast tick; **B**); both have original as well as extended distributions, with the latter in a second shade. **C** *Ixodes scapularis* and *I. pacificus*.

CUTANEOUS MANIFESTATIONS OF HUMAN MONOCYTIC EHRLICHIOSIS
Macular or maculopapular exanthematous eruptions
Mottled or diffuse macular erythema (transient or persistent)
Petechiae (favor the palms, soles, trunk, and palate)
Vesicles
Edema (especially of hands, feet, and scrotum)
Purpuric papules (with histologic evidence of vasculitis)
Nodules secondary to polyarteritis nodosa
Ulceration (reported on the penis)

Table 76.4 Cutaneous manifestations of human monocytic ehrlichiosis. Several types of lesions may be present simultaneously or sequentially in an individual patient.

Approximately 30%–40% of patients with HME have cutaneous manifestations, which develop a median of 5 days after the onset of the illness and may be more common in children[31]. Macular, maculopapular, and petechial eruptions involving the trunk and extremities are most often observed, but the morphology and distribution of skin lesions can vary considerably[31,32] (Table 76.4). *Ehrlichia ewingii* ehrlichiosis has not been reported to have cutaneous manifestations[26]. The differential diagnosis of ehrlichioses is similar to that of rickettsioses (see above).

Since *Ehrlichia* spp. and *Anaplasma phagocytophilum* are found within circulating monocytes or neutrophils, PCR-based assays of peripheral blood samples have greater sensitivity than for rickettsial infections[33]. However, empiric treatment should be initiated based on clinical suspicion rather than awaiting laboratory confirmation. Doxycycline is the drug of choice. *In vitro* evidence suggests that chloramphenicol is not an effective therapy for these infections.

HUMAN GRANULOCYTIC ANAPLASMOSIS

Anaplasma phagocytophilum, previously referred to as the "human granulocytic ehrlichiosis (HGE) agent", is an obligately intracellular bacterium (closely related to *Ehrlichia* spp.) that causes human granulocytic anaplasmosis (HGA; formerly known as HGE). HGA occurs in the same geographic distribution as Lyme disease (and babesiosis) owing to their transmission by the same *Ixodes* spp. tick vectors (see Table 76.1 & Fig. 76.12C). The clinical features of HGA are similar to those of HME, but HGA has a lower case fatality rate (0.5%–1%), often presents with peripheral neuropathy (but rarely meningoencephalitis), and seldom (≤5% of patients) has dermatologic manifestations other than petechiae or purpura related to thrombocytopenia[34]. Interestingly, Sweet syndrome has been described in association with HGA. As for HME, the first-line treatment is doxycycline.

Q FEVER

Coxiella burnetii are obligately intracellular bacteria categorized in the order Legionellales. Although they reside within several tick species, these organisms are transmitted to humans primarily by inhalation of aerosols generated from the placenta and birth fluids of infected animals (see Table 76.1)[35]. The bacteria target macrophages, where they thrive in acidic phagolysosomes, and their resistance to heat, desiccation, and disinfectants allows them to survive in the environment.

Acute disease typically presents as a nonspecific febrile illness, with atypical pneumonia or granulomatous hepatitis occurring occasionally. Chronic Q fever most often manifests as "culture-negative" endocarditis affecting a previously damaged heart valve. Cutaneous manifestations of Q fever are rare (see Table 76.2). A truncal maculopapular rash, an urticarial eruption, erythema nodosum, palpable purpura, palatal petechiae, and vasculitis (reported in association with mixed cryoglobulinemia) have been described.

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77 Fungal Diseases

Boni E. Elewski, Lauren C. Hughey, Katherine Marchiony Hunt and Roderick J. Hay

Key features

- Cutaneous fungal infections are broadly divided into two groups: (1) those that are limited to the stratum corneum, hair, and nails; and (2) those that involve the dermis and subcutaneous tissues
- Superficial fungal infections of the skin are most often due to dermatophytes and *Candida* spp.
- "Subcutaneous" mycoses are often the result of implantation, while systemic or "deep" mycoses of the skin usually represent hematogenous spread or extension from underlying structures
- In the immunocompromised host, opportunistic fungi, e.g. *Aspergillus* and *Mucor* spp., can lead to both cutaneous and systemic infections

This chapter reviews common cutaneous fungal infections, and they are subdivided into three major groups: (1) "superficial"; (2) "subcutaneous"; and (3) "deep" or systemic (Table 77.1).

SUPERFICIAL MYCOSES

Introduction

Superficial mycoses are due to fungi that only invade fully keratinized tissues, i.e. stratum corneum, hair, and nails. They can be further subdivided into those that induce minimal, if any, inflammatory response, e.g. tinea (pityriasis) versicolor, and those that lead to more substantial cutaneous inflammation, e.g. dermatophytoses (Table 77.2).

Non-inflammatory Superficial Mycoses

Synonyms: ■ Tinea nigra: tinea nigra palmaris et plantaris, superficial phaeohyphomycosis ■ Piedra: molestia de Beigel, trichomycosis nodularis ■ Tinea versicolor: pityriasis versicolor, dermatomycosis furfuracea, tinea flava

History

In 1846, Eichstedt first noted the disease known today as tinea (pityriasis) versicolor. Over the ensuing 150 years, *Malassezia furfur* (previously known as *Pityrosporum ovale* and *P. orbiculare*) came to be recognized as the causative microbe. More recently, however, studies have pointed to *M. globosa* as a major causative organism[1]. In 1865, Beigel first described piedra after isolating a fungus, which was likely actually a contaminant, from a wig. Tinea nigra was first described in the 1890s by Cerqueira, who named it "keratomycosis nigricans palmaris"[2].

Epidemiology

Tinea nigra and piedra most often occur in tropical climates of Central and South America, Africa and Asia, but also occasionally develop in the southeastern US. While any age, ethnicity, or sex may be affected, the typical patient is a young adult. *Trichosporon* spp., which were previously collectively known as *T. beigelii*, cause white piedra and can also lead to disseminated trichosporonosis in immunocompromised individuals (see Table 77.2)[3].

Malassezia spp. are found worldwide (Table 77.3). In fact, they are part of the normal flora (microbiota) of human skin (predominantly *M. sympodialis*, *M. globosa*, and *M. restricta*). Although tinea versicolor occurs most frequently in tropical climates with high ambient temperatures and high humidity, it is also common in temperate climates. No racial or sex differences have been observed. Tinea versicolor favors adolescents and young adults but can occur at any age. *Malassezia* requires oil to grow, accounting for its predilection for sebum-rich areas of the skin. *Malassezia* has been implicated in several other skin diseases, including seborrheic dermatitis and a variant of atopic dermatitis that primarily involves the head and neck. Neonatal cephalic pustulosis (neonatal acne) may also be associated with *Malassezia* spp., particularly *M. sympodialis*[4] (see Ch. 34).

Pathogenesis

Hortaea werneckii (formerly *Exophiala werneckii*) and *Piedraia hortae* are both environmental pathogens. *H. werneckii* (tinea nigra) can be found in soil, sewage, and even shower stalls under humid conditions. The source of exposure to *P. hortae* (black piedra) is thought to be the soil. There is no known transmission of these organisms from human to human. *Trichosporon* spp. (white piedra) are also acquired from the environment; in addition, they are occasionally part of the normal flora of the mucous membranes and skin, particularly inguinal and axillary areas[5].

Malassezia spp. normally live on human skin in amounts too minute to be detectable on potassium hydroxide (KOH) examination of stratum corneum[6]. Tinea versicolor occurs when the round yeast form transforms to the mycelial form. Factors that can promote this conversion include high ambient temperatures and humidity, oily skin, excessive sweating, immunodeficiency, poor nutrition, pregnancy, and corticosteroid use. Because this yeast is lipophilic, application of oils (especially organic products such as olive oil) to the skin may also encourage its growth. Risk factors for *Malassezia (Pityrosporum)* folliculitis include chronic antibiotic use, immunosuppression, and local occlusion.

Clinical features

Piedra

"Piedra" means "stone", reflecting the fungal elements' adherence to one another to form nodules along the hair shaft. Piedra is a superficial infection that begins under the cuticle of the hair and extends outward, which can lead to weakening and breakage of the hair. As the nodules enlarge, they can even envelope the hair shaft (Fig. 77.1). The two major forms – black piedra and white piedra – are distinguished by their clinical appearance and findings on microscopic examination (Table 77.4).

Patients with black piedra develop asymptomatic brown to black nodules along the hair shaft. White piedra manifests with soft, less adherent nodules that are typically white but may also be red, green, or light brown in color. In addition to white piedra, *Trichosporon* spp., especially *T. asahii*, can cause trichosporonosis in immunocompromised patients. This serious systemic infection presents with fungemia, fever, pulmonary infiltrates, and skin lesions. The latter are typically papulovesicular and purpuric, often with central necrosis; another potential finding is creamy white plaques resembling the *in vitro* fungal colonies. *Trichosporon* endocarditis, usually involving prosthetic valves, can also occur.

Tinea nigra

After a 10- to 15-day incubation period, tinea nigra most commonly presents as a single, sharply marginated, brown to gray–green macule or patch that can be velvety or have mild scale (Fig. 77.2). There are usually no associated symptoms (e.g. pruritus), and no predisposing factors have been identified. Although most frequently seen on the palms, tinea nigra can also appear on the soles, neck, and trunk. Palmoplantar lesions are said to resemble acquired acral melanocytic nevi, but the former are usually larger, lighter in color, and lack the linear striations

of acral nevi. The advancing border of a tinea nigra lesion may also be more darkly pigmented than its center. While the disease tends to be chronic, recurrence after effective treatment is infrequent except in the case of re-exposure.

Tinea (pityriasis) versicolor

Patients usually present with multiple oval-to-round macules, patches, or thin plaques with mild, fine scale. Demonstration of this associated scale may require scratching or stretching the skin surface. The lesions are often confluent centrally within areas of involvement, which may be extensive. Seborrheic regions, in particular the upper trunk and shoulders, are the favored sites. Less frequently, lesions are seen on the face (especially in children), scalp, antecubital fossae, submammary region, and groin. Involvement of flexural areas is sometimes referred to as "inverse" tinea versicolor.

CLASSIFICATION OF CUTANEOUS MYCOSES	
Superficial	Involve stratum corneum, hair, or nails
Subcutaneous	Involve dermis or subcutaneous tissue Often due to implantation
Systemic ("deep")	Involve dermis or subcutaneous tissue
"True" pathogens	Skin involvement usually reflects hematogenous spread or extension from underlying structures
Opportunistic	Primary or secondary skin lesions in immuno-compromised hosts

Table 77.1 Classification of cutaneous mycoses.

SUPERFICIAL MYCOSES OF THE SKIN		
	Cutaneous disorder	**Pathogen(s)**
Minimal, if any, inflammation	Tinea (pityriasis) versicolor	*Malassezia furfur*, *M. globosa*
	Tinea nigra	*Hortaea werneckii*
	Black piedra	*Piedraia hortae*
	White piedra	*Trichosporon* spp.*, e.g. *T. ovoides* (especially of scalp hair), *T. inkin* (especially of pubic hair), *T. cutaneum, T. loubieri*
Inflammatory response common	Tinea capitis, barbae, faciei, corporis, cruris, manuum, pedis	*Trichophyton*, *Microsporum*, *Epidermophyton* spp.
	Cutaneous candidiasis	*Candida albicans*, other *Candida* spp.

*Formerly known as *Trichosporon beigelii*, which has been reclassified into ~50 species, at least 16 of which have clinical relevance. Invasive or disseminated trichosporonosis typically occurs in immunocompromised patients (e.g. individuals with hematologic malignancies, organ transplant recipients) and is most often caused by *T. asahii*, followed by *T. mucoides* and *T. asteroides*; in some patients, the same species is isolated from the groin. *Trichosporon* spp. may also occasionally cause onychomycosis and hypersensitivity pneumonitis.

Table 77.2 Superficial mycoses of the skin.

The most common colors are brown (hyperpigmented; Fig. 77.3A) and whitish-tan (hypopigmented; Fig. 77.3B); occasionally there is mild inflammation leading to a pink color (Fig. 77.3C). Hypopigmentation may be secondary to either reduced tanning or inhibition of melanin production by dicarboxylic acids that result from metabolism of skin surface lipids by the yeast. In general, tinea versicolor is asymptomatic and the major concern is its appearance.

Malassezia (Pityrosporum) folliculitis

This condition is most commonly seen in young women and is characterized by pruritic, monomorphic follicular papules and pustules on the upper trunk, arms, neck, and face (especially on the forehead and along the hairline). It is due to excessive growth of *M. furfur* and *M. globosa* within the hair follicle, with resulting inflammation due to yeast products as well as free fatty acids generated by fungal lipases. Only yeast forms are observed, i.e. no hyphal forms as in tinea versicolor.

Pathology and fungal culture

For black and white piedra, cut hair shafts are placed in KOH and a "crush preparation" is examined microscopically. In a black piedra nodule, dematiaceous hyphae are seen around an organized cluster of asci, each of which contains eight ascospores. The ascospores represent the sexual phase of *P. hortae*. *P. hortae* grows very slowly when cultured and yields a green to black colony with a velvety texture (asexual phase)[7].

KOH preparation of a crushed white piedra nodule reveals non-dematiaceous hyphae, blastoconidia and arthroconidia, representing the asexual state (Fig. 77.4). When cultured, *Trichosporon* spp. grow rapidly, forming moist, cream-colored, yeast-like colonies that

DIFFERENT SPECIES OF *MALASSEZIA* AND COMMON CLINICAL PRESENTATIONS	
Species of *Malassezia*	**Common clinical presentations**
M. furfur	Tinea (pityriasis) versicolor, seborrheic dermatitis, folliculitis, neonatal cephalic pustulosis, blepharitis, and systemic infections in neonates receiving intravenous fat emulsions
M. globosa	Seborrheic dermatitis, tinea versicolor, folliculitis, neonatal cephalic pustulosis
M. sympodialis	Tinea versicolor, neonatal cephalic pustulosis*
M. pachydermatis	Often isolated from domestic and wild animals; has occasionally been implicated in cases of systemic infection in humans; may play a role in chronic dermatitis and otitis externa
M. restricta	Seborrheic dermatitis, tinea versicolor
M. slooffiae	Uncommon isolate
M. obtusa	Uncommon isolate

*Most commonly isolated species in this disorder.

Table 77.3 Different species *of Malassezia* and common clinical presentations.

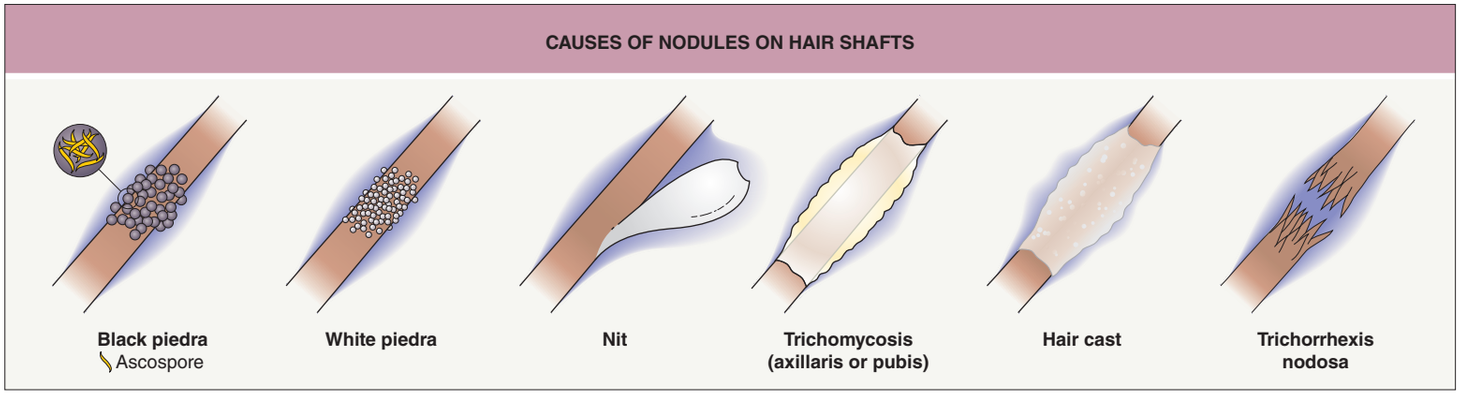


Fig. 77.1 Causes of nodules on hair shafts.

COMPARISON OF BLACK AND WHITE PIEDRA		
	White piedra	**Black piedra**
Nodule color	White (occasionally red, green, or light brown)	Brown to black
Nodule firmness	Soft	Hard
Nodule adherence to the hair shaft	Loose	Firm
Typical anatomic location	Face, axillae, and pubic region (occasionally scalp)	Scalp and face (occasionally pubic region)
Favored climate	Tropical	Tropical
Causative organism	*Trichosporon* spp.*, e.g. *T. ovoides, T. inkin*	*Piedraia hortae*
KOH examination of "crush prep" of cut hair shafts	Non-dematiaceous hyphae with blastoconidia and arthroconidia	Dematiaceous hyphae with asci and ascospores†
Culture on Sabouraud's agar	Moist, cream-colored, yeast-like colonies‡	Slow-growing, dark green to dark brown–black colonies
Treatment	Clip affected hairs, wash with antifungal shampoo	Clip affected hairs, wash with antifungal shampoo

*See Table 77.2 for the revised subdivision of the *Trichosporon* genus.
†Sexual reproduction
‡Growth inhibited by cycloheximide.

Table 77.4 Comparison of black and white piedra. *From reference 98.*

resemble "butter cream frosting". On Mycosel® agar, these organisms are inhibited by the presence of cycloheximide. When *Trichosporon* spp. are isolated from skin and nail specimens, correlation with clinical findings is necessary to determine the medical significance.

Biopsies of tinea versicolor and tinea nigra are usually not performed, as KOH examination of associated scale is typically diagnostic. In tinea versicolor, both hyphal and yeast forms are seen; although likened to "spaghetti and meatballs", the findings more closely resemble "ziti and meatballs" (Fig. 77.5A). In tinea nigra, KOH examination reveals septate pigmented hyphae. Dermoscopy of tinea nigra also shows curvilinear brown strands representing pigmented hyphae. When biopsy specimens



Fig. 77.2 Tinea nigra. Single, sharply demarcated brown macule on the finger. *Courtesy Frank Samarin, MD.*

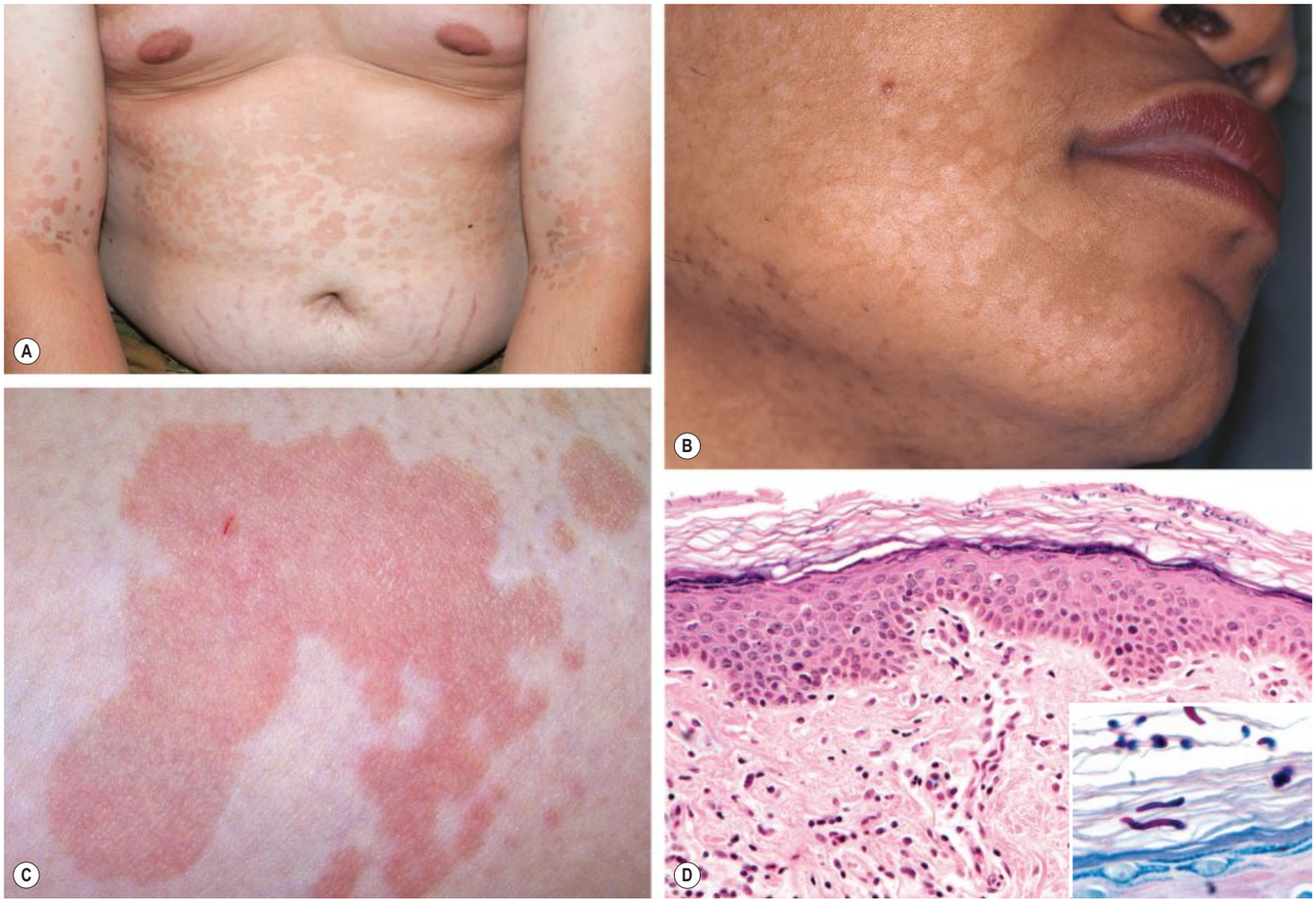


Fig. 77.3 Tinea (pityriasis) versicolor. A Hyperpigmented variant with confluence on the lower chest. **B** Hypopigmented variant on the face. **C** Coalescing pink lesions with fine scale. **D** Yeast and short hyphal forms in the stratum corneum highlighted by a PAS stain (inset). *A, B, Courtesy Kalman Watsky, MD; D, Courtesy Lorenzo Cerroni, MD.*

are obtained, similar findings are observed within the stratum corneum (Fig. 77.3D). In KOH examination of expressed follicular contents or biopsy specimens of *Malassezia (Pityrosporum)* folliculitis, only yeast forms are seen. Cultures of *H. werneckii* first appear as pasty, green–black colonies with a yeast-like appearance, and after approximately 2 weeks become a fuzzy, dematiaceous (dark in color) mold. Culture of *Malassezia* is generally not required; if necessary, the plate must be overlaid with sterile oil because of the organism's lipophilic nature.

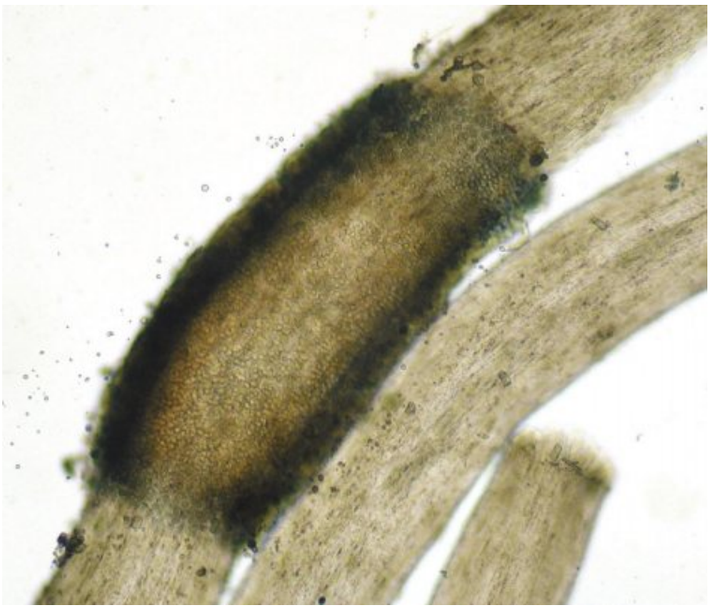


Fig. 77.4 White piedra. Potassium hydroxide preparation of a nodule on a hair shaft composed of arthroconidia and blastoconidia.

Differential diagnosis

Piedra is generally diagnosed by clinical and microscopic inspection of a hair shaft and must be distinguished from pediculosis (nits), hair casts, trichorrhexis nodosa, trichomycosis axillaris (see Fig. 77.1), and the scales of psoriasis and eczema. Unlike eczema and psoriasis, the scalp typically appears normal in piedra.

In most patients, the diagnosis of tinea nigra is made clinically and confirmed via KOH examination and/or fungal culture. Occasionally, tinea nigra could be confused with melanocytic nevi (see above), a fixed drug eruption, postinflammatory hyperpigmentation, or staining from chemicals, pigments, and dyes. Cutaneous melanoma has even been clinically misdiagnosed as tinea nigra.

Clinical examination is often sufficient to recognize tinea versicolor. However, pityriasis alba or other forms of postinflammatory hypopigmentation, vitiligo, seborrheic dermatitis, pityriasis rosea, tinea corporis, and secondary syphilis may be diagnostic considerations. Progressive macular hypomelanosis, which presents as non-scaly hypopigmented macules on the trunk of young adults and may be caused by *Cutibacterium* (formerly *Propionibacterium*) *acnes*, is often misdiagnosed as residual hypopigmentation related to tinea versicolor. Wood light examination revealing bright yellow fluorescence and then direct microscopy of scales can confirm the diagnosis of tinea versicolor. *Malassezia (Pityrosporum)* folliculitis must be differentiated from other causes of folliculitis (see Table 38.1), in particular itching folliculitis, as well as acne vulgaris.

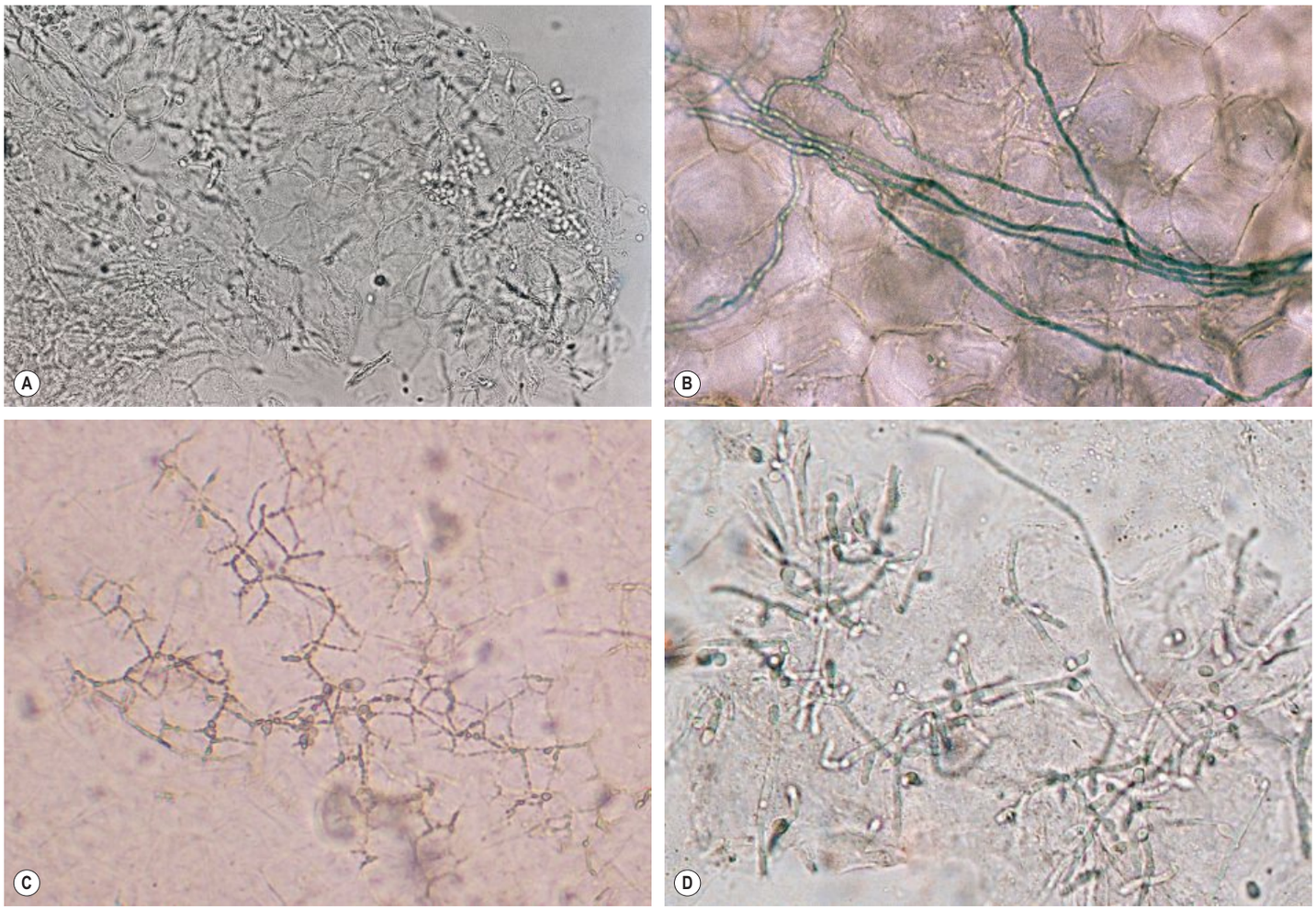


Fig. 77.5 Potassium hydroxide preparations. A Superficial skin scrapings from tinea (pityriasis) versicolor demonstrating clusters of yeast and short mycelial forms. **B** A dermatophyte, in this case *Trichophyton tonsurans*, demonstrating branching hyphae (chlorazol black stain). Note that the hyphae cross multiple squamous cells. **C** "Mosaic" pattern of cell walls that should not be misinterpreted as hyphae. **D** Yeast and pseudohyphae of candidiasis. *A, Courtesy Ronald P. Rapini, MD; C, Courtesy Louis A. Fragola, Jr, MD; D, Courtesy Frank Samarin, MD.*

Treatment

Clipping hairs with adherent nodules as well as shampooing the affected hairs with 2% ketoconazole shampoo is usually an effective treatment for piedra (see Table 77.4). Oral terbinafine may also be of therapeutic benefit. For treatment of tinea nigra, topical keratolytic agents such as Whitfield ointment (typically 6% benzoic acid plus 3% salicylic acid)[8] are effective, as are topical azole or allylamine antifungal medications. Several weeks of therapy may be required to prevent recurrence. Systemic therapy is generally not indicated, and griseofulvin is not effective.

Tinea versicolor usually responds to topical antifungal therapy, but oral treatment with fluconazole or itraconazole can be considered when there is more extensive involvement[9,10] (Table 77.5; see Ch. 127). Residual pigmentary changes often require weeks to months to resolve. The rate of recurrence of tinea versicolor is very high, especially in hot humid climates, and maintenance therapy may be helpful (see Table 77.5). The treatment of *Malassezia (Pityrosporum)* folliculitis is reviewed in Chapter 38.

Dermatophytoses

Synonyms: ■ Tinea corporis: ringworm, tinea circinata, tinea glabrosa ■ Tinea cruris: ringworm of the groin, eczema marginatum, jock itch, gym itch ■ Tinea barbae: tinea sycosis, barber's itch, ringworm of the beard ■ Tinea capitis: ringworm of the scalp/hair, tinea tonsurans, herpes tonsurans ■ Tinea pedis: ringworm of the foot, athlete's foot ■ Tinea unguium: ringworm of the nail, dermatophytic onychomycosis

Introduction

Dermatophytoses are fungal infections caused by three genera of fungi that have the unique ability to invade and multiply within keratinized tissue (hair, skin, and nails). These fungi, collectively called "dermatophytes", are alike in their physiology, morphology, and pathogenicity. The three genera are *Microsporum*, *Trichophyton*, and *Epidermophyton*; species within these genera that do not invade keratinized tissue in animals or humans are not considered as dermatophytes. In naming clinical infections due to dermatophytes, "tinea" precedes the Latin name for the involved body site, e.g. "tinea pedis" refers to a dermatophyte infection of the foot. Overall, ten species of dermatophytes are commonly isolated and an additional 20 are occasionally identified (Table 77.6)[11].

TREATMENT OF TINEA (PITYRIASIS) VERSICOLOR	

Initial therapy (often combination)	*Topical**
	• Antifungal shampoo applied as a body cleanser for 10–15 minutes before rinsing, twice weekly for 2–4 weeks
	  • Selenium sulfide shampoo, 1% (OTC) or 2.5%
	  • Ketoconazole shampoo, 1% (OTC) or 2%
	  • Ciclopirox olamine shampoo, 1%
	  • Zinc pyrithione shampoo
	• Antifungal cream applied several hand-widths beyond clinically visible lesions, daily to twice daily for 2 weeks
	  • Imidazole, e.g. ketoconazole 2% cream
	  • Ciclopirox olamine 0.77% cream, gel, or lotion
	Oral†
	• Fluconazole: 200 mg po daily × 5–7 days‡; 200–300 mg weekly × 2–3 weeks; or 400 mg once
	• Itraconazole: 200 mg po daily × 5–7 days

Maintenance therapy to prevent recurrence	• Treat previously affected sites with topical imidazole daily for 2 weeks prior to anticipated sun exposure • Apply antifungal shampoo (see above) 1–2 times weekly

*Treatment of all the skin from the neck down to the knees may lead to higher success rates.
†Although there are few comparative studies of oral antifungal medications, cure rates of 98%–100% have been reported in several randomized controlled trials of itraconazole 200 mg daily × 5 days and an open-label study of fluconazole 300 mg weekly × 2 weeks.
‡Based upon authors' personal experience.

Table 77.5 Treatment of tinea (pityriasis) versicolor. Oral ketoconazole is no longer indicated for treatment of superficial fungal infections due to risks of severe hepatotoxicity, QT prolongation, and serious drug interactions.

History

Dermatophyte infections have been described since ancient times. In 1910, Sabouraud published a categorization scheme that is currently employed in which dermatophytes are classified by genera. A revised and simplified nomenclature system was proposed in 2017[12].

Epidemiology

Some dermatophytes are restricted geographically, while others are found worldwide. *Trichophyton rubrum*, for example, is the most common dermatophyte and has a global distribution, while *T. concentricum* is endemic to certain parts of the South Pacific and South America. Human travel and migration, coupled with antifungal therapy and the development of drug resistance, have brought about significant changes in the geographic distribution of dermatophytes. Terbinafine-resistant *T. indotineae* (formerly *T. mentagrophytes var. VIII*), which was recognized in 2020, emerged in India with subsequent global spread[12a,12b]. One theory for its emergence is the misuse of potent topical corticosteroids in settings where they are available without a prescription. In general, dermatophyte infections are more common in tropical environments. Other important epidemiologic factors include socioeconomic status, occupation, air conditioning, and the use of footwear.

In general, dermatophytoses occur most frequently in postpubertal hosts. One major exception is tinea capitis (dermatophytosis of the scalp), which occurs primarily in children. Risk factors for the development of a dermatophyte infection during childhood include household exposure to tinea capitis or tinea pedis; environmental factors such as contaminated hats, brushes, and barber instruments; and (especially for tinea unguium) Down syndrome. Individuals with chronic mucocutaneous candidiasis, common variable immunodeficiency, or HIV infection have a propensity to develop severe, chronic, or recurrent dermatophytoses (see Chs. 60 & 78). Men more frequently have tinea pedis, tinea cruris, and tinea unguium than women.

Pathogenesis

Transmission of dermatophytes to humans occurs via three major sources, each resulting in infections with characteristic features (Table 77.7). While dermatophytes are not especially virulent and typically invade only the outer, cornified layers of the skin, they can be responsible for considerable morbidity. The first stage of infection involves contact with and adherence of the infectious elements of the fungus (arthroconidia) to the skin. The ability of certain fungi to adhere to a particular host arises from a variety of microbial mechanisms and host factors[2].

Dermatophytes, unlike most other fungi, produce keratinases (enzymes that break down keratin), which allow invasion of the fungi into the stratum corneum. Mannans in the cell walls of dermatophytes have immuno-inhibitory effects. In *T. rubrum*, the mannans may also decrease epidermal proliferation, thereby reducing the likelihood of the fungus being sloughed off prior to invasion. This mechanism is thought to contribute to the chronicity of infections caused by *T. rubrum*[13]. However, host factors such as protease inhibitors may limit the extent of invasion. If invasion is successful, disease occurs.

The severity of clinical disease is also affected by several host factors. Sebum has an inhibitory effect on dermatophytes, and the degree of disease activity may be related to the number and activity of sebaceous glands in a particular body region. Breaks in the skin barrier or macerated skin encourage dermatophyte invasion, and increased susceptibility related to immunologic factors may be inherited. Once dermatophytes invade and begin to proliferate in the skin, several mechanisms aid in limiting the infection to keratinized tissue. These include the preference of dermatophytes for the cooler temperature at the skin's surface, serum factors that inhibit dermatophyte growth (e.g. β-globulins, ferritin, other metal chelators), and the host immune response[2]. Further invasion or dissemination is extremely unusual (see below). Other conditions influencing dermatophyte infections include skin disorders that affect cutaneous barrier function, such as ichthyoses.

Clinical features

Tinea corporis

Tinea corporis is a dermatophyte infection of the skin of the trunk and extremities, excluding the hair, nails, palms, soles, and groin. The infection is generally restricted to the stratum corneum and most commonly affects exposed skin. Any dermatophyte can potentially

DERMATOPHYTES ISOLATED WORLDWIDE		
		Thallus (macroscopic) appearance* and/or microscopic findings
Most common		
Trichophyton	*mentagrophytes* (previously *mentagrophytes* var. *mentagrophytes*)	Granular front, buff reverse; pencil-shaped macroconidia, clusters of round microconidia, spiral hyphae
	interdigitale (previously *mentagrophytes* var. *interdigitale*)	Downy front, buff reverse; see above
	indotineae (previously *mentagrophytes* var. *VIII*)	Suede-like white front, yellow-brown reverse; cigar and club-shaped septate, thin-walled macroconidia; spiral and pyriform microconidia
	rubrum	White wooly front, venous blood reverse; pencil-shaped macroconidia, teardrop-shaped microconidia
	tonsurans	Granular front, mahogany reverse; pencil-shaped macroconidia, microconidia of varying sizes
	verrucosum	Convoluted, cream to gray, compact; chains of chlamydospores at 37°C
	violaceum	Creamy, waxy, becomes violet
Microsporum	*canis*	White wooly front, orange reverse; multi-celled, spindle-shaped macroconidia with thick walls and rough surface
	ferrugineum	Folded red–orange (rust-colored) front
	gypseum	Cinnamon–tan granular front; multi-celled, cucumber-shaped macroconidia with thin walls
Epidermophyton	*floccosum*	Khaki green, suede to granular; beaver tail-shaped macroconidia; no microconidia
Less common		
Trichophyton	*ajelloi*	Powdery surface, resembles *Microsporum* spp.
	concentricum	Glabrous colonies; antler-like hyphae
	equinum	Club-shaped macroconidia
	gourvilii	Waxy, pink to red front
	megninii	Pink, felt-like front with red reverse
	schoenleinii	Glabrous; antler- and nailhead-like hyphae; rat-tail-like macroconidia (media often fissured)
	simii	Club-shaped macroconidia in clusters
	soudanense	Yellow to apricot front with fringed border
	terrestre	Cream to yellow granular surface
	yaoundei	Glabrous, chocolate-brown front
Microsporum	*amazonicum*	Multi-celled, spindle-shaped, macroconidia with large inclusions
	audouinii	Flat, tan front with salmon reverse; pectinate (comb-like) hyphae
	cookei	Oval, thick-walled macroconidia
	equinum	One- to four-celled macroconidia resembling *M. canis*
	fulvum	Bullet-shaped macroconidia with spiral hyphae
	gallinae	Diffusable pink–red pigment
	nanum	Two-celled macroconidia
	persicolor	Pink to red front and reverse, resembles *T. mentagrophytes*
	praecox	Powdery front with yellow–orange reverse
	racemosum	Cream-colored powdery front
	vanbreuseghemii	Largest macroconidia

*On Sabouraud's agar.

Table 77.6 Dermatophytes isolated worldwide. *Adapted from reference 99.*

TYPES OF DERMATOPHYTES BASED ON MODE OF TRANSMISSION		
Category	**Mode of transmission**	**Typical clinical features**
Anthropophilic	Human to human	Mild to non-inflammatory, chronic
Zoophilic	Animal to human	Intense inflammation (pustules and vesicles possible), acute
Geophilic	Soil to human or animal	Moderate inflammation

Table 77.7 Types of dermatophytes based on mode of transmission.

cause tinea corporis, but *T. rubrum* is the most common pathogen worldwide, followed by *T. mentagrophytes* (Table 77.8).

Tinea corporis can result from human-to-human (including autoinoculation, e.g. from tinea capitis or pedis), animal-to-human (often transmitted by domestic animals), or soil-to-human spread (see Table 77.7). Sources include occupational or recreational exposure (e.g. military housing, gymnasiums, locker rooms, outdoor activities, wrestling) and contact with contaminated clothing or furniture[14].

There are multiple clinical presentations of tinea corporis, and they can mimic other dermatologic conditions (Table 77.9). As with most dermatophyte infections, the extent of inflammation depends on the causative pathogen and the immune response of the host. Because hair follicles serve as reservoirs for infection, hairier areas of the body may be more resistant to treatment.

The typical incubation period is 1 to 3 weeks. Infection spreads centrifugally from the point of skin invasion with central clearing of the fungus, typically resulting in annular lesions of varying sizes (Fig. 77.6A–D). Arcuate, circinate, concentric, and oval lesions can also develop (Fig. 77.6D–F). Although scale is usually present, it may be

lessened or absent if topical corticosteroids have been used (tinea "incognito") (Fig. 77.7). Pustules within the active border are suggestive of tinea (see Fig. 77.6E). Lesions are occasionally vesicular, granulomatous, or verrucous (Fig. 77.6G). Associated symptoms may include pruritus and burning.

Tinea profunda, nodular perifolliculitis (including Majocchi granuloma), and tinea imbricata represent clinical variants of tinea corporis[15]. *Tinea profunda* results from an excessive inflammatory response to a dermatophyte, analogous to a kerion on the scalp. It may have a granulomatous or verrucous appearance and be mistaken for cutaneous tuberculosis or a dimorphic fungal infection. *Nodular perifolliculitis*, usually caused by *T. rubrum*, is characterized by follicular papulopustules or granulomatous nodules that result from a deep dermatophyte folliculitis with disruption of the follicular wall (Fig. 77.8). This variant is most commonly seen in women who have tinea pedis or onychomycosis and shave their legs, and it can also occur in the setting of immunosuppression. The lesions may be extensive or even vegetating, and a prolonged granulomatous reaction (as described by Majocchi) can develop.

Tinea imbricata is a dermatophytosis caused by the anthropophilic dermatophyte *T. concentricum*. It causes chronic infections in an equatorial band encompassing the South Pacific, Asia, and Central and South America. The clinical presentation consists of concentric annular rings resembling erythema gyratum repens.

COMMON DERMATOPHYTES THAT CAUSE TINEA CORPORIS	
Dermatophyte	**Clinical features**
Anthropophilic	
Trichophyton rubrum	Commonly harbored by hair follicles; may produce concentric rings; can recur; causative organism in nodular perifolliculitis (Majocchi granuloma) and most common cause of tinea corporis
T. tonsurans	Commonly seen in adults who care for children with tinea capitis caused by this organism
Epidermophyton floccosum	Generally restricted to groin, feet; responsible for eczema marginatum
T. concentricum	Responsible for tinea imbricata; infections typically chronic
T. interdigitale (previously *T. mentagrophytes* var. *interdigitale*)	Causes interdigital tinea pedis, tinea cruris, and onychomycosis
T. indotineae (previously *T. mentagrophytes* var. *VIII*)	Terbinafine resistance leading to large annular lesions in a widespread distribution
Zoophilic	
T. mentagrophytes (previously *T. mentagrophytes* var. *mentagrophytes*)	May be associated with dermatophytid reaction; causes inflammatory tinea pedis and tinea barbae; associated with exposure to small mammals
Microsporum canis	Associated with pet exposure (cat or dog)
T. verrucosum	May mimic bacterial furunculosis; associated with exposure to cattle
T. benhamiae	Typically associated with exposure to a pet guinea pig; tinea faciei is also a common presentation
Geophilic	
M. gypseum	Frequently associated with outdoor/occupational exposure; lesions may be inflammatory or bullous

Table 77.8 Common dermatophytes that cause tinea corporis.

Tinea cruris

Tinea cruris is a dermatophyte infection of the inguinal region, in particular the inner aspects of the upper thighs (Fig. 77.9) and crural folds, with occasional extension onto the abdomen and buttocks. The three most common causative agents are *Epidermophyton floccosum*, *T. rubrum*, and *T. mentagrophytes* (Table 77.10).

This condition is more often seen in men than in women, since the scrotum provides a warm and moist environment that encourages fungal growth and men are more likely to have tinea pedis and onychomycosis as a source of dermatophytes. Other predisposing factors include obesity and excessive perspiration. Tinea cruris is frequently associated with tinea pedis because clothing that is brought over the feet is contaminated and then comes in contact with skin in the groin region.

The initial sign of infection is usually an area of erythema and pruritus in the fold between the scrotum and the inner thigh. Characteristic lesions are sharply demarcated with a raised, erythematous, scaly advancing border that may contain pustules or even vesicles. Lesions can initially be circinate and then become serpiginous. The disease may remain unilateral or become bilateral.

The duration of infection depends on the causative pathogen. Infections with *T. rubrum* and many other anthropophilic species tend to be chronic, sometimes with leathery and lichenified lesions. In contrast, the zoophilic form of *T. mentagrophytes* (previously *T. mentagrophytes* var. *mentagrophytes*) and other animal-acquired strains often cause acute infections with a prominent inflammatory component that may include pustules and vesicles (see Table 77.10). The scrotum itself is generally spared in tinea cruris. If the scrotum is involved or there are erosions or satellite pustules, cutaneous candidiasis should be considered. Measures to prevent recurrences of tinea cruris include wearing loose clothing, drying thoroughly after bathing, using topical powders, weight reduction (if obese), laundering contaminated clothing and linens, and treating concomitant tinea pedis.

Tinea manuum

Dermatophyte infections on the dorsal aspect of the hand have a clinical presentation similar to tinea corporis. However, dermatophyte infection of the palm and interdigital spaces has distinct characteristics and is referred to as tinea manuum. The reason for the two different clinical

DIFFERENTIAL DIAGNOSES OF DERMATOPHYTE INFECTIONS				
Tinea corporis	**Tinea cruris**	**Tinea faciei**	**Tinea capitis**	**Tinea pedis**
Dermatitis • Nummular eczema • Atopic • Stasis • Contact • Seborrheic (petaloid) Tinea versicolor Pityriasis rosea Parapsoriasis Erythema annulare centrifugum Annular psoriasis Subacute lupus erythematosus Granuloma annulare Impetigo	Cutaneous candidiasis Intertrigo • Seborrheic dermatitis • Psoriasis Erythrasma Contact dermatitis Lichen simplex chronicus Parapsoriasis/mycosis fungoides Hailey–Hailey disease Langerhans cell histiocytosis	Dermatitis • Seborrheic • Perioral • Contact Rosacea Lupus erythematosus Acne vulgaris Annular psoriasis (children)	Seborrheic dermatitis Alopecia areata Trichotillomania Psoriasis If pustules: • Pyoderma • Folliculitis If scarring: • Lichen planus • Discoid lupus erythematosus • Folliculitis decalvans • Central centrifugal cicatricial alopecia	Dermatitis • Dyshidrotic • Contact Psoriasis • Vulgaris • Pustular Juvenile plantar dermatosis Secondary syphilis If interdigital: • Erythrasma • Bacterial infection, e.g. GNR

Table 77.9 Differential diagnoses of dermatophyte infections. A kerion is sometimes misdiagnosed as an abscess. GNR, Gram-negative rods.

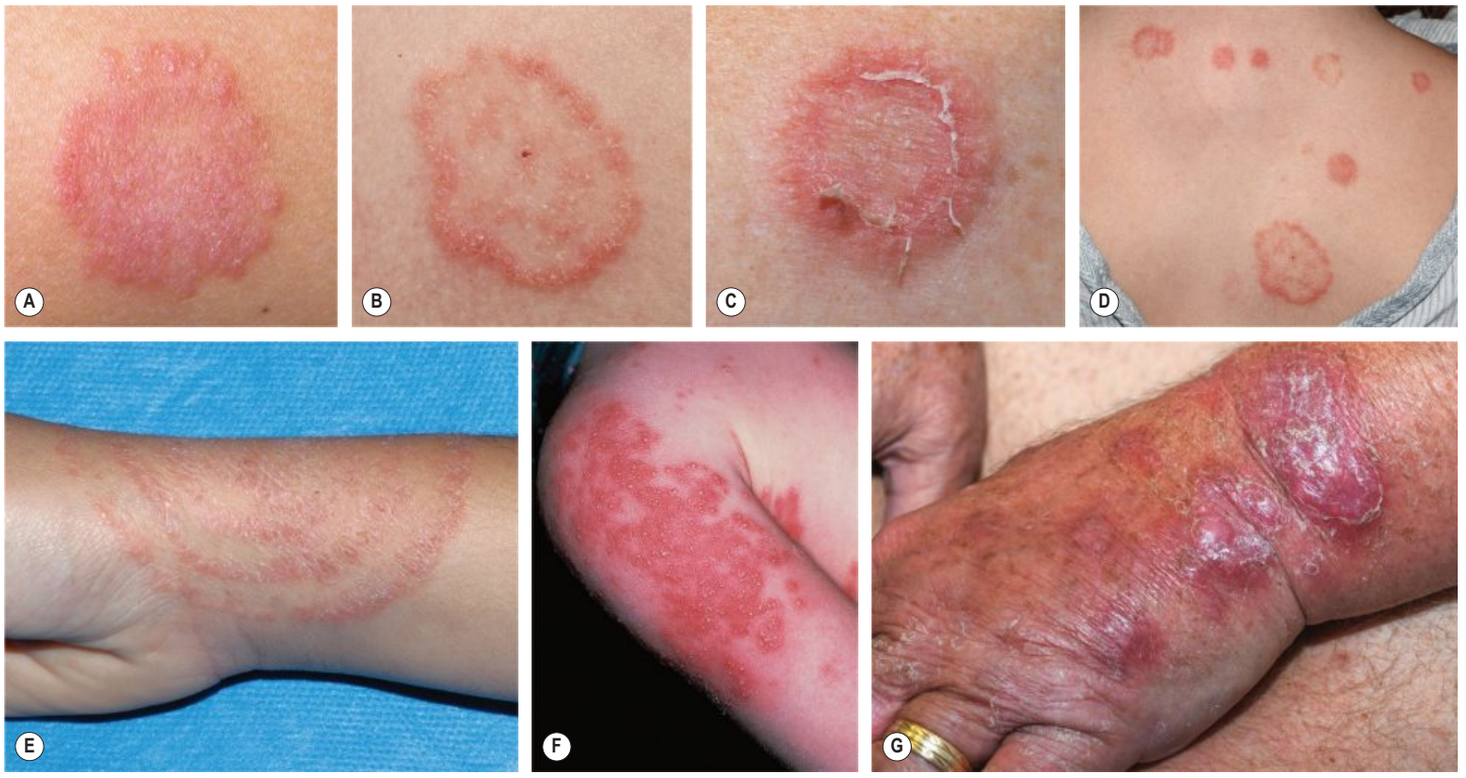


Fig. 77.6 Tinea corporis. A There is a subtle annular configuration with a border composed of individual, slightly scaly papules. **B** Classic annular lesion with a scaly raised border and central clearing. **C** Annular lesion with trailing scale reminiscent of erythema annulare centrifugum. **D** Multiple annular and circinate lesions of various sizes on the upper back. **E** Scaly concentric rings on the arm. **F** Pustules within multiple figurate lesions on the upper arm. **G** Inflammatory nodules on the dorsal hand and a thick granulomatous plaque on the distal forearm (tinea profunda). There is associated scale, including on the digits, and a few of the papulonodules are follicular (Majocchi granuloma). *B, D, Courtesy Julie V. Schaffer, MD; C, G Courtesy Kalman Watsky, MD.*



Fig. 77.7 Tinea incognito. Use of potent topical corticosteroids for the presumed diagnosis of dermatitis is a common clinical scenario. Numerous hyphae are usually seen on KOH examination. *Courtesy Louis A. Fragola, Jr, MD.*



Fig. 77.8 Nodular perifolliculitis (Majocchi granuloma). Perifollicular inflammation and follicular pustules on the leg due to *Trichophyton rubrum*. A few of the lowermost papules have a granulomatous appearance. *Courtesy Kalman Watsky, MD.*

pictures is thought to be related to the lack of sebaceous glands on the palms. The typical causative organisms are the same as those for tinea pedis and tinea cruris: *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*. Infections with *Neoscytalidium dimidiatum* and *N. hyalinum*, two non-dermatophyte fungi, can have a tinea manuum-like appearance.

Moccasin-type tinea pedis is often present in patients with tinea manuum, and the two share clinical features such as chronicity and hyperkeratosis. Tinea manuum is usually non-inflammatory and often unilateral ("two feet and one hand syndrome") (Fig. 77.10; see Fig. 77.16A); there is hyperkeratosis of the palms and digits, including within creases, that fails to respond to emollients[16]. Tinea unguium of the involved hand can serve as a clue to the diagnosis, but infection of all the fingernails is uncommon. Other presentations include exfoliative, vesicular, and papular variants. The differential diagnosis may include psoriasis, irritant or allergic contact dermatitis, dyshidrosis, and a "dermatophytid" reaction.

Tinea barbae

Tinea barbae is a dermatophytosis that involves the bearded areas of the face and neck in men. Because the disease is often acquired from animals, the causative organisms are typically zoophilic dermatophytes, namely



Fig. 77.9 Tinea cruris. A thin, "broken-up" erythematous plaque with an arciform papular border on the upper inner thigh.





Fig. 77.10 Tinea manuum. A Diffuse scaling of the palm of one hand, with accentuation in the creases. **B** Multiple collarettes of scale reminiscent of keratolysis exfoliativa on one palm.

TINEA CRURIS: COMMON CAUSATIVE PATHOGENS	
Dermatophyte	**Clinical features**
Trichophyton rubrum	• Most common cause of tinea cruris • Infection tends to be chronic • Fungus not viable in scale (e.g. on furniture, rugs, linens) for long periods of time • Frequent extension to buttocks, waist, and thighs
Epidermophyton floccosum	• Commonly associated with "epidemics" of tinea cruris in locker rooms or dormitories • Infection is acute (rarely chronic) • Arthroconidia are viable in scale (e.g. on furniture, rugs, linens) for long periods of time • Infection rarely extends beyond groin region • Causative agent of "eczema marginatum" (well-demarcated borders with multiple small vesicles or, sometimes, vesiculopustules)
T. mentagrophytes (previously *T. mentagrophytes* var. *mentagrophytes*)	• Infection tends to be more severe and acute, with intense inflammation and pustule formation • May rapidly spread to the trunk and lower extremities, causing a severe inflammatory condition • Often acquired from animal dander

Table 77.10 Tinea cruris: common causative pathogens.

T. mentagrophytes and *T. verrucosum*. Infection with *Microsporum canis* or *T. rubrum* is uncommon. In some geographic regions, other anthropophilic dermatophytes (*T. schoenleinii, T. violaceum*, and *T. megninii*) are endemic and cause tinea barbae. With the increased use of disposable razors and disinfectants, the incidence of tinea due to contaminated razors in barbershops has been dramatically reduced.

Since zoophilic organisms are the most common culprit and affected areas often have a large number of terminal hair follicles, the clinical presentation tends to be severe, with intense inflammation and multiple follicular pustules. Abscesses, sinus tracts, bacterial superinfection, and kerion-like boggy plaques can develop. Patients may have constitutional symptoms such as malaise as well as lymphadenopathy and even scarring alopecia. A second type of tinea barbae is superficial, less inflammatory, and similar to tinea corporis; *T. rubrum* is usually the causative agent in this variant (Fig. 77.11). Alopecia may be present in the center of the lesion, but it is reversible. Other conditions that can mimic tinea barbae include bacterial folliculitis, viral infections (herpes simplex or zoster), acne vulgaris, cervicofacial actinomycosis, and a dental sinus tract. Spontaneous resolution may occur if all of the infected hairs fall out.



Fig. 77.11 Superficial form of tinea barbae due to *Trichophyton rubrum*. Several follicular pustules are evident. *Courtesy Jean L. Bolognia, MD.*

Tinea faciei

While some dermatophyte infections of the face have classic features (e.g. scale, annular configuration, pustules in the border), others can be more difficult to diagnose clinically and require a high index of suspicion (Fig. 77.12, see Table 77.9).

Tinea capitis

Tinea capitis is a common dermatophyte infection of the scalp in children (Fig. 77.13), whereas adult infection occurs infrequently. The causative pathogens are members of only two genera: *Trichophyton* and *Microsporum*. *T. tonsurans* is currently the most common cause



Fig. 77.12 Tinea faciei. A Erythema and scale on the nose and philtrum of a young child. The location and lack of central clearing may lead to the misdiagnosis of dermatitis with secondary impetiginization. **B** Child with pink papules, a few tiny pustules, and thin annular and arcuate scaly plaques in a perinasal and perioral distribution. These clinical findings could be mistaken for periorificial dermatitis. **C** Hyperpigmented lesions with subtle arcuate and annular configurations in a woman with darkly pigmented skin. There is minimal scale following the use of topical corticosteroids ("tinea incognito"). The clue to the application of topical corticosteroids is the relative hypopigmentation as compared with the more medial cheek. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Antonio Torrelo, MD; C, Courtesy Kalman Watsky, MD.*

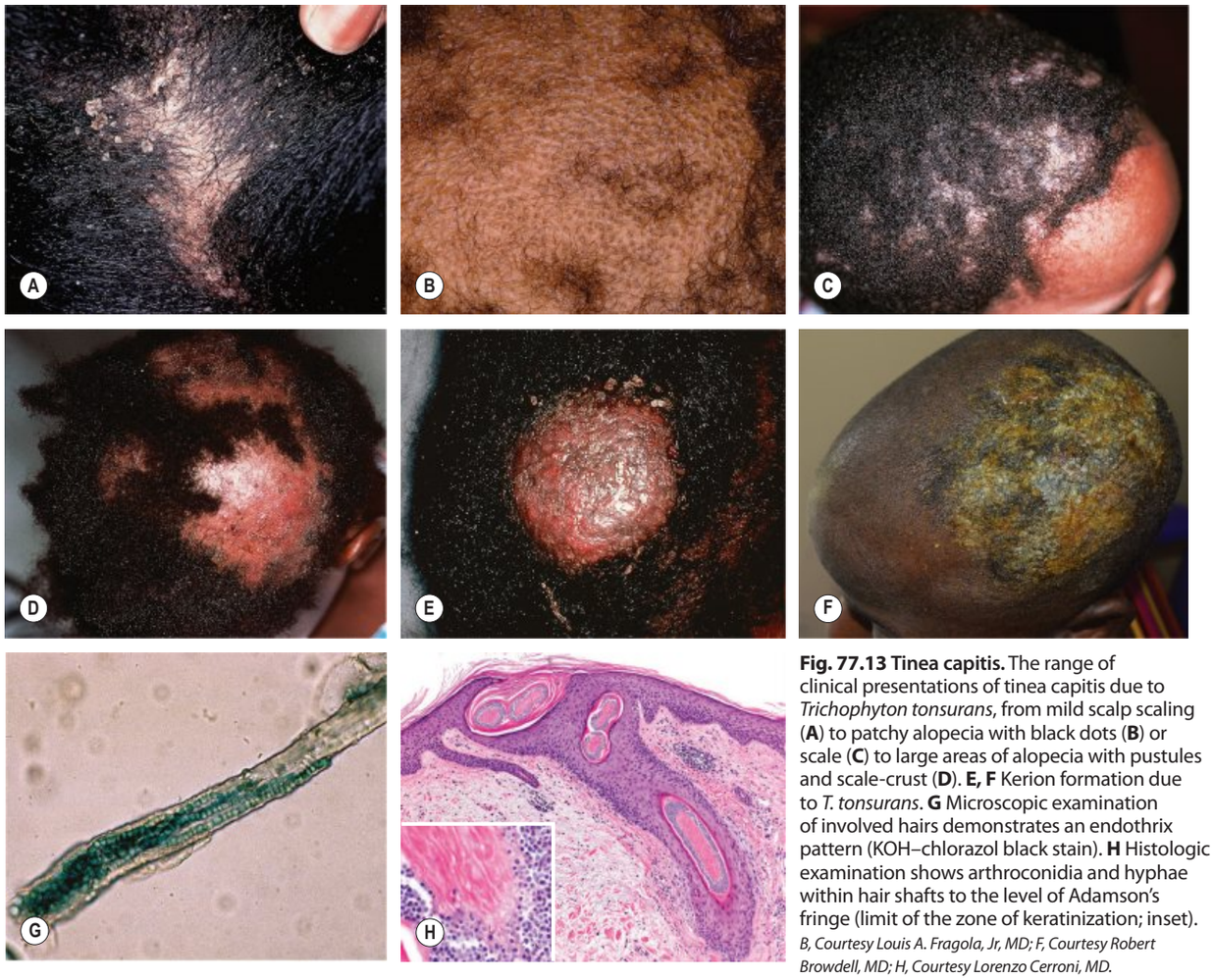


Fig. 77.13 Tinea capitis. The range of clinical presentations of tinea capitis due to *Trichophyton tonsurans*, from mild scalp scaling (**A**) to patchy alopecia with black dots (**B**) or scale (**C**) to large areas of alopecia with pustules and scale-crust (**D**). **E, F** Kerion formation due to *T. tonsurans*. **G** Microscopic examination of involved hairs demonstrates an endothrix pattern (KOH–chlorazol black stain). **H** Histologic examination shows arthroconidia and hyphae within hair shafts to the level of Adamson's fringe (limit of the zone of keratinization; inset). *B, Courtesy Louis A. Fragola, Jr, MD; F, Courtesy Robert Browdell, MD; H, Courtesy Lorenzo Cerroni, MD.*

of tinea capitis in the US (accounting for >90% of cases), with a predilection for individuals with Afro-textured hair[17], and *M. canis* is the second most frequent etiology. Globally, there is significant variation in the epidemiology of tinea capitis. While *M. canis* is a common cause in many countries, *T. tonsurans* has emerged as a major agent in Europe and elsewhere. The incidence of tinea capitis due to *T. violaceum*, which is endemic in Africa, has also recently increased in some areas of the US and Europe (especially western and Mediterranean regions), likely reflecting immigration patterns. The anthropophilic dermatophyte *M. audouinii*, which was once common and then subsequently diminished secondary to social and therapeutic advances, has more recently reappeared in Europe and may also potentially re-emerge in the US.

Different clinical presentations arise from the various causative organisms. For example, *T. tonsurans* causes an endothrix infection (see below), which classically results in "black dot" tinea capitis due to hair breakage near the scalp. In contrast, *M. audouinii* is an ectothrix form of tinea capitis that typically presents with dry, scaly patches of alopecia ("gray patch" tinea capitis). Both the pathogenicity of the culprit organism and the host immune response are factors that determine the severity of disease. Tinea capitis can range from non-inflammatory scaling that resembles seborrheic dermatitis (especially with *T. tonsurans*; Fig. 77.13A) to a severe pustular reaction with alopecia, known as a kerion. Alopecia with or without obvious scale is the most common presentation of tinea capitis (Fig. 77.13B–D). The alopecia may occur in discrete patches or involve the entire scalp. Use of dermoscopy can highlight "comma", "corkscrew", and dystrophic broken hairs that represent clues to the diagnosis of tinea capitis (see Ch. 69)[18]. Many patients have posterior cervical and posterior auricular lymphadenopathy, which is helpful in differentiating tinea capitis from less inflammatory causes of alopecia, such as alopecia areata.

A kerion results from advanced disease coupled with an exaggerated host response that leads to boggy, purulent plaques with abscess formation and associated alopecia (Fig. 77.13E,F). Some patients may even become systemically ill with extensive lymphadenopathy. The hair in the affected area usually returns, but the longer the infection persists, the more likely the alopecia will be permanent. If a kerion is misdiagnosed as a bacterial abscess and treated with antibiotics following incision and drainage, the infection will likely worsen, thereby increasing the likelihood of scarring alopecia.

The "carrier state" of *T. tonsurans* refers to a clinical situation in which there are no obvious signs or symptoms of a scalp infection, yet a positive fungal culture is obtained. Although also seen in children, this typically occurs in adults who have been exposed to infected children. The carriers shed the fungus and are considered contagious[19]. Consequently, some experts advocate treating all carriers with oral or topical antifungals.

For those dermatophytes that invade hair, three patterns of invasion exist: endothrix, ectothrix, and favus (Fig. 77.14):

- The *endothrix pattern* results from infection with anthropophilic fungi in the genus *Trichophyton* and is characterized by non-fluorescent arthroconidia within the hair shaft (Fig. 77.13G). The clinical presentation varies from scaling to "black dots" with patchy alopecia to kerion formation. *T. tonsurans* and *T. violaceum* are important causes of endothrix infection.
- The *ectothrix pattern* occurs when arthroconidia are formed from fragmented hyphae outside the hair shaft (see Fig. 77.14). Cuticle destruction ensues. Ectothrix infection can be fluorescent (*Microsporum*) or non-fluorescent (*Microsporum* and *Trichophyton*), as determined by Wood's lamp examination. Clinical features vary from patchy, scaly alopecia with little inflammation that may mimic alopecia areata to kerion formation.
- *Favus* is the most severe form of dermatophyte hair infection and is most frequently caused by *T. schoenleinii*. Hyphae and air spaces are observed within the hair shaft, and a bluish-white fluorescence by Wood's light examination is typically seen. Favus presents as thick, yellow crusts composed of hyphae and skin debris ("scutula"). Scarring alopecia may develop in chronic infections (Fig. 77.15).



Fig. 77.15 Favus due to *Trichophyton schoenleinii*. Scarring alopecia with erosions and several scutula on the occipital scalp. The latter represent masses of keratin plus fungi. *Courtesy Israel Dvoretzky, MD.*

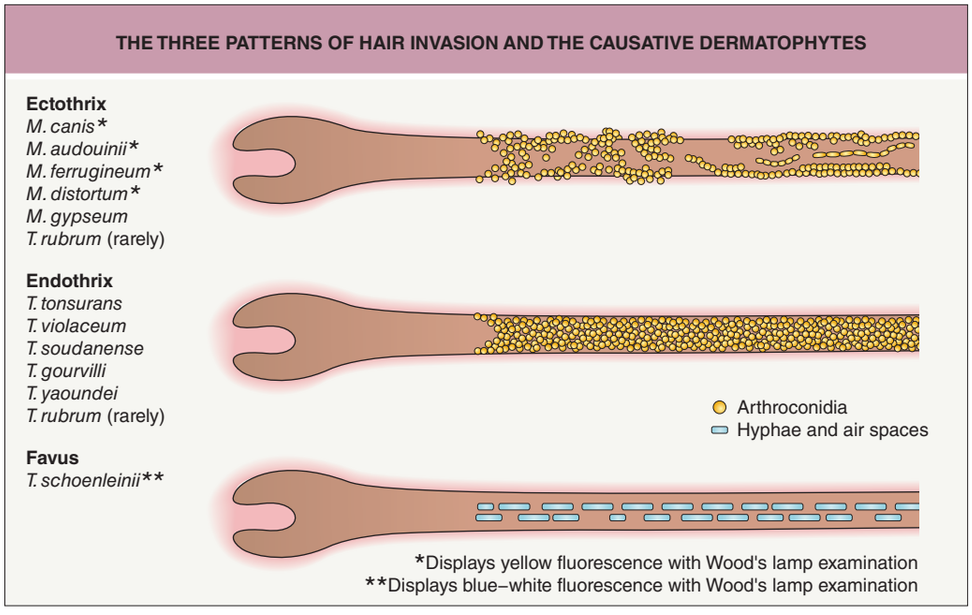


Fig. 77.14 The three patterns of hair invasion and the causative dermatophytes.

There are many scalp and hair disorders that lead to scaling or alopecia (scarring and non-scarring) that are not due to fungal infections (see Table 77.9). However, one should always consider and exclude a fungal infection (especially in children), because the treatment is typically quite simple and effective, and chronic untreated tinea capitis can lead to scarring alopecia. Oral therapy is required, as the drug must penetrate the hair follicle to be effective. Preventative measures are also important in the management of tinea capitis. Because the disease is contagious, all individuals residing with the infected patient should be examined for signs of tinea capitis and appropriately treated. Chronicity may develop if a child is continually re-exposed from untreated family members. Appropriate adjunctive treatment for household contacts as well as the patient includes regular (e.g. every other day) use of an antifungal shampoo, such as 2% ketoconazole or 2.5% selenium sulfide, until the patient is free of disease. Although routine screening in schools is difficult, screening children who have two or more infected classmates may be beneficial[20]. Combs, brushes, and headwear used by the patient should be disinfected or preferably discarded.

Tinea pedis

Tinea pedis is a dermatophyte infection of the soles and interdigital web spaces of the feet. Infection of the dorsal aspect of the foot is considered tinea corporis. The feet are the most common location for dermatophyte infections, and the majority of the US adult population has experienced tinea pedis. This condition is more common in adults than children and is found around the world, affecting both sexes. The lack of sebaceous glands and the moist environment created by occlusive shoes are important factors in the development of tinea pedis[21]. In fact, tinea pedis is uncommon in populations that do not wear shoes. However, the fungus may be acquired from going barefoot (locker rooms, gyms, public facilities).

The dermatophytes that are typically responsible for tinea pedis are *T. rubrum*, *T. interdigitale* (previously *T. mentagrophytes* var. *interdigitale)*, *T. mentagrophytes*, *E. floccosum*, and *T. tonsurans* (in children). Non-dermatophyte pathogens that produce clinical findings identical with tinea pedis include *Neoscytalidium dimidiatum* and *N. hyalinum* (moccasin and interdigital types) and, occasionally, *Candida* spp. (interdigital type). There are four major clinical types of tinea pedis, as outlined in Table 77.11: moccasin (Fig. 77.16A), interdigital (Fig. 77.16B), inflammatory (Fig. 77.16C), and ulcerative. Each type has different associated morbidities and complications that can affect diagnostic considerations and therapeutic options. These include bacterial superinfection (the "dermatophytosis complex"), dermatophytid reactions, cellulitis (especially in patients who have venous hypertension, harvested saphenous veins, and chronic edema), and

THE FOUR MAJOR TYPES OF "TINEA PEDIS" CAUSED BY DERMATOPHYTES AND NON-DERMATOPHYTES

Type	Causative organism	Clinical features	Treatment considerations
Moccasin	*Trichophyton rubrum* *Epidermophyton floccosum* *Neoscytalidium hyalinum* *N. dimidiatum*	Diffuse hyperkeratosis, erythema scaling and fissures on one or both plantar surfaces; frequently chronic and difficult to cure*; occasionally associated with immune deficiency	Topical antifungal plus product with urea or lactic acid; may require oral antifungal therapy
Interdigital	*T. interdigitale* (previously *mentagrophytes* var. *interdigitale*) *T. rubrum* *E. floccosum* *N. hyalinum* *N. dimidiatum* *Candida* spp. *Fusarium* spp.	Most common type; erythema, scaling, fissures and maceration in the web spaces; the two lateral web spaces are most commonly affected; "dermatophytosis complex" (fungal infection followed by bacterial invasion†) can develop; pruritus common; may extend to dorsum and sole of foot	Topical antifungal; may require topical or oral antibiotic if superimposed bacterial infection
Inflammatory (vesicular)	*T. mentagrophytes* (previously *T. mentagrophytes* var. *mentagrophytes*)	Vesicles and bullae on the medial foot; often associated with a dermatophytid reaction‡	Topical antifungal usually sufficient
Ulcerative	*T. rubrum* *T. interdigitale* (previously *T. mentagrophytes* var. *interdigitale*) *E. floccosum*	Typically an exacerbation of interdigital tinea pedis; ulcers and erosions in the web spaces; commonly secondarily infected with bacteria; seen in immunocompromised and diabetic patients	Topical antifungal; may require topical or oral antibiotics if secondary bacterial infection (common)

Dermatophytes Non-dermatophytes

*Because of the thickness of stratum corneum on plantar surfaces and the inability of *T. rubrum* to elicit a sufficient immune response to eliminate the fungus[22].
†Often *Pseudomonas*, *Proteus* spp., or *Staphylococcus aureus*.
‡Reaction to fungal elements presenting as a dyshidrotic-like eruption on the fingers and palms (culture negative for fungus).

Table 77.11 The four major types of "tinea pedis" caused by dermatophytes and non-dermatophytes.

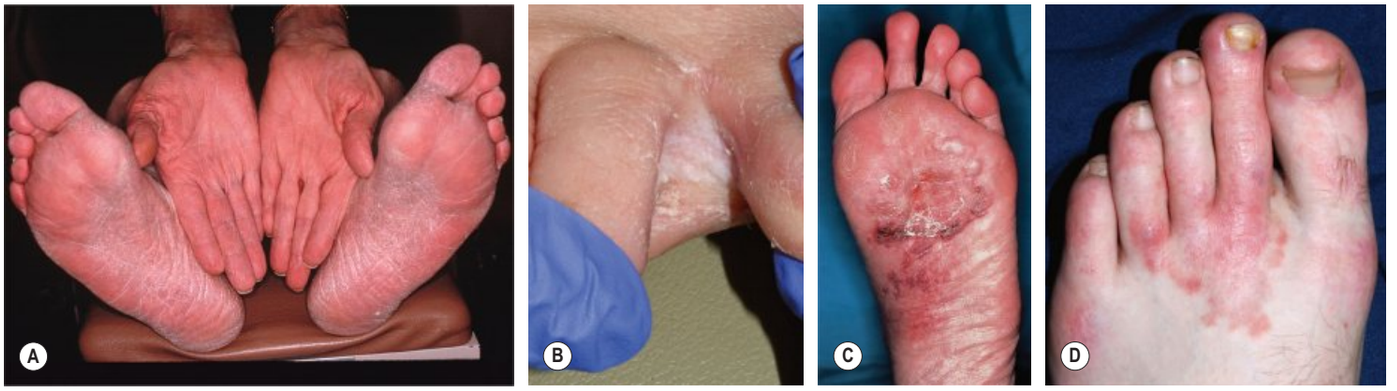


Fig. 77.16 Tinea pedis A Diffuse scaling on both feet (moccasin type) as well as on the right hand, representing "one hand–two feet" tinea. B Maceration and scaling between the fourth and fifth toes in the interdigital form. **C** Erythema, scale-crust, and bullae in the inflammatory form. **D** Extension of tinea pedis onto the dorsal foot in a serpiginous configuration of erythema and papules. Scale is minimal due to the patient's use of a potent topical corticosteroid for presumed dermatitis. *B, D, Courtesy Julie V. Schaffer, MD.*

even osteomyelitis leading to amputation in diabetics. Other conditions that can mimic tinea pedis are listed in Table 77.9. KOH examination and culture easily differentiate the moccasin and inflammatory forms of tinea pedis from these entities[22]. Erythrasma can be diagnosed with Wood's light examination because of its "coral red" fluorescence. Oral antifungal therapy should be considered in diabetics, immunocompromised patients, and those with moccasin-type tinea pedis. Finally, other dermatophyte infections often occur together with tinea pedis – in particular, tinea cruris, onychomycosis, and tinea manuum – and these sites should be examined (Fig. 77.17).



Fig. 77.17 Extensive tinea corporis emanating from tinea manuum and tinea pedis. Note the confluent involvement, serpiginous scaly borders, and associated tinea unguium of the toenails and one fingernail.

Tinea unguium (dermatophytic onychomycosis)

Onychomycosis is a term used to encompass all fungal infections of the nail and includes those due to dermatophytes as well as non-dermatophytes. It is divided into three patterns based upon the point of fungal entry into the nail unit:

- *distal/lateral subungual*, with invasion via the hyponychium (most common; Fig. 77.18A–C)
- *superficial white*, with direct penetration into (and usually confinement to) the dorsal surface of the nail plate (often due to *T. interdigitale*; Fig. 77.18D)
- *proximal subungual*, with invasion under the proximal nail fold (frequently in immunocompromised hosts)
- *mixed pattern*, with ≥2 of the above patterns in the same nail.

Onychomycosis can be challenging to manage due to difficulties in diagnosis, the requirement for long treatment periods, potential side effects of systemic medications, and frequent recurrences. Although many consider onychomycosis solely as an annoyance, patients with the condition often complain of discomfort and pain associated with trimming the nails, running, and other activities such as dancing. In addition, serious complications such as cellulitis can result from onychomycosis, especially in patients who are diabetic or immunocompromised. Infections with non-dermatophytes such as *Fusarium* spp. (see below) are of particular concern in the latter group.

Tinea unguium refers specifically to dermatophyte infection of the nail unit. It occurs worldwide, affects men more often than women, and is frequently associated with chronic tinea pedis. Trauma and other nail disorders represent predisposing factors. Although all dermatophytes can cause tinea unguium, *Microsporum* spp. do so very rarely. The most common causative pathogens are *T. rubrum*, *T. interdigitale*, *T. tonsurans* (in children), and *E. floccosum*.

Toenail infections are considerably more common than fingernail infections, and only rarely does fingernail onychomycosis occur without concurrent toenail infection. A single nail may be involved, but more frequently, multiple nails on one or both hands or feet are affected. In the *distal/lateral subungual type*, invasion of the hyponychial region leads to hyperkeratosis of the nail bed. With further progression of infection, there



Fig. 77.18 Tinea unguium. Onycholysis, yellowing, crumbling and thickening of the fingernails (**A**), thumb nails (**B**), and toenails (**C**) in the distal/lateral subungual variant. **D** White discoloration of the toenail in the superficial white variant. **E** Hyphae within a formalin-fixed, PAS-stained nail plate. *A, D Courtesy Jean L. Bolognia, MD; B, Courtesy Louis A. Fragola, Jr, MD; E, Courtesy Mary Stone, MD.*

is yellowing and thickening of the distal nail plate as well as onycholysis (see Fig. 77.18A–C), which provides an ideal environment for further proximal invasion and growth of the dermatophyte. Eventually, the entire nail bed and plate may become involved (total dystrophic pattern).

The clinical appearance of the *superficial white type* of onychomycosis can vary based on host factors (e.g. immunosuppression) and the causative organism. Discrete white patches are seen in the classic form due to *T. interdigitale* (see Fig. 77.18D). However, transverse striate bands, origination from the proximal nail fold (which may overlap with the proximal subungual type if there is also invasion under the nail fold), and deeper invasion of the nail plate can also occur. These variants are more likely to be caused by *T. rubrum*, with more invasive forms observed in healthy children as well as people living with HIV; deep invasion of the nail plate can also result from non-dermatophyte molds such as *Fusarium* spp.[23].

Although nail dystrophy can be the result of trauma, psoriasis, inherited disorders, and other conditions (see Ch. 71), an estimated 50% or more of cases are due to onychomycosis. Dermatophytes account for ~90% of cases of onychomycosis, and the remainder are due to yeasts or non-dermatophyte molds (Table 77.12). *Candida* spp. are often found in association with chronic paronychia (see Ch. 71), and infection of the nail may occur in this setting. The fingernails are usually affected, with ridging, yellow discoloration, and onycholysis. *Candida* spp. are a relatively common cause of onychomycosis in children less than 3 years of age, and nail involvement also represents a manifestation of chronic mucocutaneous candidiasis (see Ch. 60).

NON-DERMATOPHYTE MOLDS THAT CAN CAUSE ONYCHOMYCOSIS

Fungus	Key features
Fusarium spp.	Superficial white pattern*
Aspergillus spp.	Superficial white pattern*
Acremonium	Superficial white pattern*
Scopulariopsis brevicaulis	Lateral yellow–brown discoloration KOH of nail reveals lemon-shaped conidia and atypical hyphae
Neoscytalidium hyalinum	Distal and lateral nail invasion†
Neoscytalidium dimidiatum	Distal and lateral nail invasion†

*Deeper invasion of the nail plate can also occur.
†May also be associated with paronychia or tinea pedis.

Table 77.12 Non-dermatophyte molds that can cause onychomycosis.

Pathology

Tinea pedis, manuum, faciei, cruris, and corporis are usually diagnosed via KOH examination (see Fig. 77.5B) and occasionally with fungal cultures. The chlorazol black E stain can help to highlight fungal elements in KOH preparations. Use of calcofluor, a fluorescent stain specific for the chitin in the fungal cell wall, and examination with a fluorescent microscope can also demonstrate fungi (apple-green fluorescence). PCR-based assays for dermatophytes are also commercially available.

If biopsies are performed of cutaneous dermatophyte infections, hyphae are seen within the stratum corneum; the fungi are made more apparent by PAS or silver stains. In dermatophytoses affecting glabrous skin, spongiosis, parakeratosis, and pustules are often seen. In onychomycosis, hyphae and arthroconidia may be visible in the nail plate and nail bed with PAS staining, and little to no inflammation is generally present[2]. Histologic examination of formalin-fixed, PAS-stained nail plates is a quick and reliable method for diagnosing onychomycosis (Fig. 77.18E), with a sensitivity of 80% to >95%, compared with 35%–60% for culture alone[24]. Biopsy specimens of tinea capitis, Majocchi granuloma, and tinea barbae can demonstrate hyphae or arthroconidia within hair shafts and are usually done if the diagnosis is suspected but KOH examination and culture are negative. However, false-negative results are a potential problem and tissue should also be sent for culture.

Differential diagnosis

Careful clinical examination is the first and most important step in diagnosing dermatophyte infections. Because many other conditions can mimic dermatophytoses (see Table 77.9), KOH examination and/or culture are often necessary to confirm the diagnosis. Guidelines for proper specimen collection are outlined in Fig. 77.19. Because all dermatophytes have hyaline hyphae, they essentially look the same in KOH preparations. When identification of the particular species will provide helpful information or culture is needed to confirm the diagnosis, the specimen is cultured at 25–30°C (and in some instances also at 37°C) for 2 to 4 weeks.

Colonial morphology, microscopic examination of conidia (the asexual propagules formed *de novo* by the fungus), noting the growth rate/requirements, and biochemical tests allow precise identification of the dermatophyte. The presence or absence of microconidia (usually small and unicellular) and macroconidia (usually larger and multicellular) and the typical features of each (e.g. shape, cell wall texture) remain fairly consistent among genera (Fig. 77.20). Other distinguishing microscopic features include the identification of arthroconidia (infective fungal elements) and chlamydoconidia. Sometimes, conidia may not be present in culture ("sterile" organism), and the hyphal patterns (spiral,

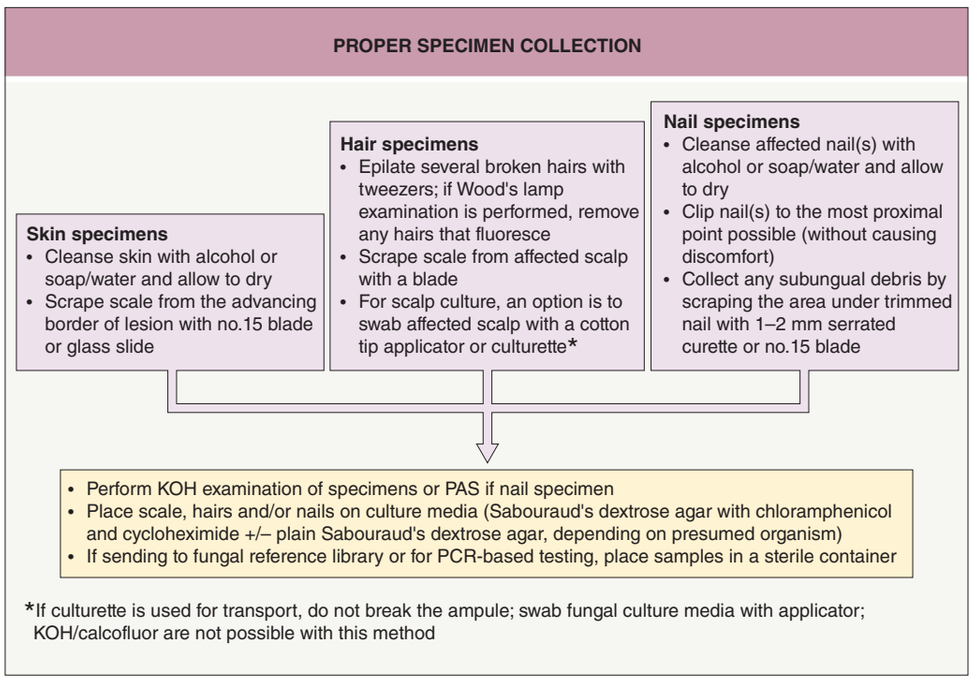


Fig. 77.19 Proper specimen collection. Proper collection of skin, hair, and nails is important. Following these simple guidelines will help the clinician to achieve the most accurate diagnosis. *Courtesy Judy Warner.*

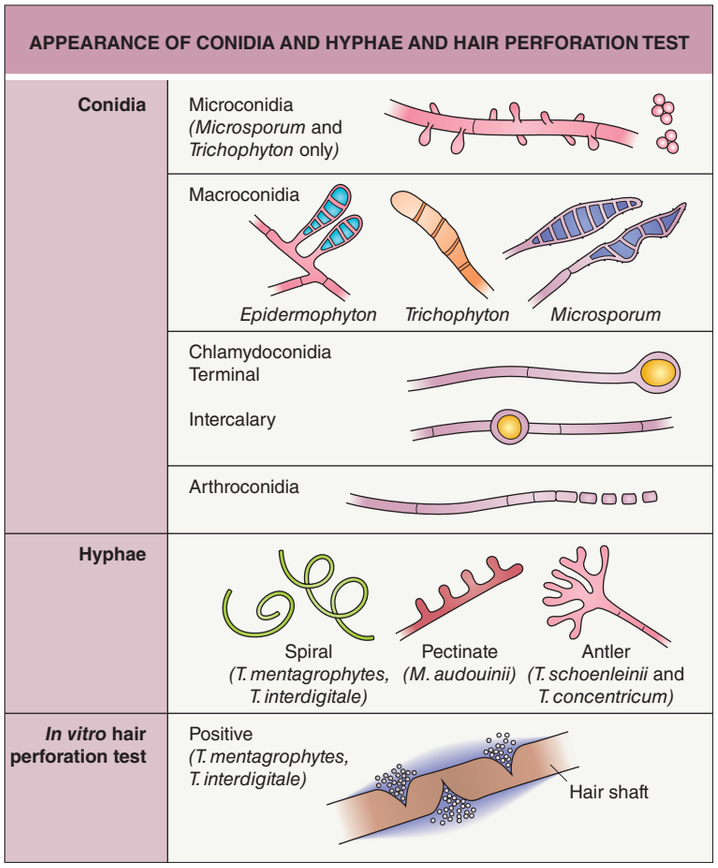


Fig. 77.20 Microscopic appearance of various forms of conidia and hyphae and the *in vitro* hair perforation test.

pectinate, antler, racquet, and nodular bodies) may be important in identification of the organism. The color, texture, and topography of the colony are features that are typical of, or even unique to, a particular species (see Table 77.6).

Dermatophytes are able to grow on media containing cycloheximide (e.g. Mycosel®, DTM [dermatophyte test medium]). However, some clinically relevant non-dermatophyte fungi do not, including *Scopulariopsis brevicaulis*, *Aspergillus* spp., *Cryptococcus neoformans*, *Candida tropicalis*, *Pseudallescheria boydii/Scedosporium apiospermum*, and *Trichosporon* spp.[25]. These can potentially be missed if specimens, in particular from nails, are grown only on cycloheximide-containing media[26].

Treatment

Topical antifungals are the first-line treatment for many patients with uncomplicated, localized cutaneous dermatophyte infections such as tinea corporis, tinea cruris, and tinea pedis (see Ch. 127). The major potential adverse reaction is irritant (or, occasionally, allergic) contact dermatitis, usually from alcohols or other components in the vehicle[27]. Systemic antifungal therapy, although associated with both a higher incidence of side effects including potentially severe adverse reactions and the potential for drug–drug interactions, is typically required to cure tinea manuum, capitis, and unguium. Suggested regimens are presented in Table 77.13[28]. In general, oral treatment is also needed for infections involving extensive areas of skin, in hairy sites other than the scalp (e.g. tinea barbae), or associated with excessive inflammatory reactions. The adjunctive use of topical products containing glycolic acid, lactic acid, or urea may help to reduce the amount of hyperkeratosis in infections such as tinea manuum and pedis.

Treatment of tinea unguium deserves special consideration. Oral antifungal therapy is usually required to achieve a complete cure (see Table 77.13), with the occasional exception of classic superficial white onychomycosis. Topical therapies that have been FDA-approved for mild to moderate onychomycosis have combined clinical and mycologic cure rates after daily application for 48 weeks ranging from 6%–10% for tavaborole 5% and ciclopirox olamine 8% solutions to 15%–20% for efinaconazole 10% solution. Although mycologic cure rates of up to 80% (or higher with prolonged therapy) have been reported with oral antifungal drugs (terbinafine, itraconazole, and fluconazole), the combined clinical and mycologic cure rates are lower, i.e. ~20%–40% after 12 weeks for toenails. Recurrent disease is common, especially in the toenails and when the degree of involvement is severe (Table 77.14)[7,29]. Preventive measures include breathable footwear and socks, antifungal or absorbent powders, frequent nail clipping, and avoiding re-exposure (e.g. not going barefoot in locker rooms). Old shoes often harbor large numbers of infectious organisms and should be discarded or treated with disinfectants or antifungal powders.

Combination therapy consisting of a topical corticosteroid plus topical antifungal has been advocated by some clinicians for the treatment of dermatophyte infections. While a reduction in inflammation can be seen, the negative effects of high-potency corticosteroids on immune defenses coupled with restrictions on treatment duration to avoid side effects such as striae lead to an unacceptable failure rate[30]. Dermatophyte resistance to antifungal therapy has emerged as a public health concern, especially with regard to squalene epoxidase mutations that lead to terbinafine resistance (see Fig. 127.9). Species affected include *T. rubrum* in the US as well as the recently recognized *T. indotineae* (*T. mentagrophytes* internal transcribed spacer [ITS] genotype VIII) that has resulted in an epidemic of resistant dermatophytosis in India, with subsequent global spread[31]. This highlights the importance of confirmatory testing and antifungal stewardship, including limiting the use of combination topical corticosteroid-antifungal products and reserving agents such as posaconazole and voriconazole for more severe infections[32].

Invasive dermatophytosis

Rarely, dermatophytes proliferate within the dermis. Invasion or dissemination of dermatophytes typically occurs in the setting of a chronic dermatophyte infection (most commonly *T. rubrum*) in an individual with a primary immunodeficiency such as CARD9 deficiency (see Ch. 60) or iatrogenic immunosuppression[33]. Hematogenous spread can lead to an acute onset of ulcerating or draining dermal and subcutaneous nodules. A more indolent process can also occur and most often presents as tender nodules on the extremities (Fig. 77.21). Currently, the recommended treatment is surgical excision (if localized) and systemic terbinafine, itraconazole, or posaconazole[34,35].

Mucocutaneous *Candida* Infections

Mucocutaneous candidiasis has a wide spectrum of clinical presentations. Early descriptions of oral candidiasis (thrush) were made by Hippocrates. In the 1940s, the association between oral antibiotic use and candidal infections was recognized. Oral candidiasis often presents as thrush, with the *pseudomembranous* form characterized by a white exudate resembling cottage cheese (Fig. 77.22A,B) and the *chronic atrophic* form by a patch of erythema; it can also lead to a *chronic hyperplastic* form with adherent white plaques or *glossitis* with painful atrophy of the dorsal tongue. Other presentations include denture stomatitis, angular cheilitis (perlèche) (Fig. 77.22C), vulvovaginitis, and balanitis (see Ch. 73). Predisposing factors for mucocutaneous candidiasis include diabetes mellitus, xerostomia, occlusion, hyperhidrosis, the use of corticosteroids or broad-spectrum antibiotics, and immunosuppression, including HIV infection[36]. In the case of angular cheilitis, deep grooves due to overlap of the skin at the angles of the mouth, which is common in edentulous and older patients, is a key contributing factor, along with the use of orthodontic appliances, drooling, atopic dermatitis, and (occasionally) iron or vitamin deficiencies (e.g. B_2).

Cutaneous *Candida* infections present with markedly erythematous, sometimes erosive, patches that are often accompanied by satellite papules and pustules (Fig. 77.22D–F). The most common sites of involvement are intertriginous zones (e.g. submammary, beneath pannus, inguinal creases, intergluteal fold) and the scrotum, as well as the diaper area in infants. Candidiasis is sometimes superimposed on intertriginous seborrheic dermatitis or psoriasis. *Candida* can also infect periungual areas (e.g. in the setting of chronic paronychia), nails (see Tinea unguium above), and the web space between the third and fourth fingers (erosio interdigitalis blastomycetica; Fig. 77.22G), especially in individuals whose hands are frequently exposed to water.

SUGGESTED SYSTEMIC REGIMENS FOR DERMATOPHYTOSES				
	Fluconazole	**Griseofulvin**	**Itraconazole***	**Terbinafine**
Tinea pedis (moccasin type)/ tinea manuum (adults)	150–450 mg/week × 4–6 weeks[28]	750–1000 mg/day (microsize) or 500–750 mg/day (ultramicrosize) × 4 weeks	200–400 mg/day × 1 week	250 mg/day × 2 weeks
Tinea pedis (moccasin type)/ tinea manuum (children)	6 mg/kg/week × 4–6 weeks	15–20 mg/kg/day (microsize suspension) × 4 weeks	3–5 mg/kg/day (maximum 400 mg) × 1 week	Daily dosing as for tinea capitis (see below) × 2 weeks
Tinea unguium (adults)	Toenail ± fingernail involvement:			
	150–450 mg/week until nails are clear[28]	1–2 g/day (microsize) or 750 mg/day (ultramicrosize) until nails are normal†	200 mg/day × 12 weeks or 200 mg BID × 1 week/month for 3–4 consecutive months	250 mg/day × 12 weeks
	Fingernail involvement only:			
	150–450 mg/week until nails are clear[28]	1–2 g/day (microsize) or 750 mg/day (ultramicrosize) until nails are normal†	200 mg/day × 6 weeks or 200 mg BID × 1 week/month for 2 consecutive months	250 mg/day × 6 weeks
Tinea unguium (children)	6 mg/kg/week × 3–4 months (fingernails) or 5–7 months (toenails), or until nails are clear	20 mg/kg/day (microsize suspension) until nails are normal†	5 mg/kg/day (<20 kg), 100 mg/day (20–40 kg), 200 mg/day (40–50 kg), or 200 mg BID (>50 kg) × 1 week/month for 2 (fingernails) or 3 (toenails) consecutive months	Daily dosing as for tinea capitis (see below) × 6 weeks (fingernails) or 12 weeks (toenails)
Tinea corporis (extensive, adults)	150–200 mg/week × 2–4 weeks	500–1000 mg/day (microsize) or 375–500 mg/day (ultramicrosize) × 2–4 weeks‡	200 mg/day × 1 week‡	250 mg/day × 1 week‡
Tinea corporis (extensive, children)	6 mg/kg/week × 2–4 weeks	15–20 mg/kg/day (microsize suspension) × 2–4 weeks	3–5 mg/kg/day (maximum 200 mg) × 1 week	Daily dosing as for tinea capitis (see below) × 1 week
Tinea capitis (adults)¶	6 mg/kg/day × 3–6 weeks	10–15 mg/kg/day (ultramicrosize; usually maximum 750 mg/day) × 6–8 weeks	5 mg/kg/day (maximum 400 mg) × 4–8 weeks	250 mg/day × 3–4 weeks§
Tinea capitis (children)¶	6 mg/kg/day × 3–6 weeks	20–25 mg/kg/day (microsize suspension) × 6–8 weeks	5 mg/kg/day (maximum 500 mg) × 4–8 weeks	62.5 mg/day (<20 kg), 125 mg/day (20–40 kg), or 250 mg/day (>40 kg) × 3–4 weeks§

*Not approved in US for use in children.
†No longer commonly used for this indication.
‡For patients with Majocchi granuloma, treatment is continued for 1–6 months depending on the disease severity and clinical response.
¶Combined with 2.5% selenium sulfide shampoo or ketoconazole 2% shampoo; "id" reaction should not be confused with a medication allergy.
§Not recommended for *Microsporum canis*, unless given at double-dose.

Table 77.13 Suggested systemic regimens for dermatophytoses. BID, twice daily.

INDICATORS OF MORE SEVERE ONYCHOMYCOSIS WITH A POOR RESPONSE TO TREATMENT	
Nail factors	• Subungual hyperkeratosis >2 mm thick* • Significant lateral involvement • Dermatophytoma† • >50% involvement of nail bed • Slow nail growth rate • Total dystrophic onychomycosis • Matrix involvement
Patient factors	• Immunosuppression • Peripheral arterial disease • Poorly controlled diabetes mellitus

*Measurement of nail plate plus nail bed.
†Streak or patch representing a subungual pocket of densely packed hyphae; removal prior to initiating antifungal therapy can be helpful.

Table 77.14 Indicators of more severe onychomycosis with a poor response to treatment. *Adapted from reference 29.*



Fig. 77.21 Invasive dermatophytosis due to *Trichophyton rubrum* in an immunocompromised host. *Courtesy Evelyn Lilly, MD.*

Mucocutaneous candidiasis is most commonly due to *C. albicans*, followed by *C. tropicalis*. The diagnosis is established by the presence of budding yeast and pseudohyphae on KOH examination (see Fig. 77.5D) and by a positive fungal culture. *C. albicans* and *C. stellatoidea* can be distinguished by their ability to form chlamydoconidia on cornmeal-Tween 80 agar. Identifying and removing predisposing factors is very important in the management of mucocutaneous candidiasis. Treatment with topical nystatin or azole antifungals is often effective[37,38]. When oral therapy is required for more extensive involvement, options include fluconazole and itraconazole (see Ch. 127). Treatment regimens for various forms of mucocutaneous candidiasis are outlined in Table 77.15.

Chronic mucocutaneous candidiasis

This is discussed in detail in Chapter 60. Chronic mucocutaneous candidiasis is not a single entity but rather a clinical manifestation of

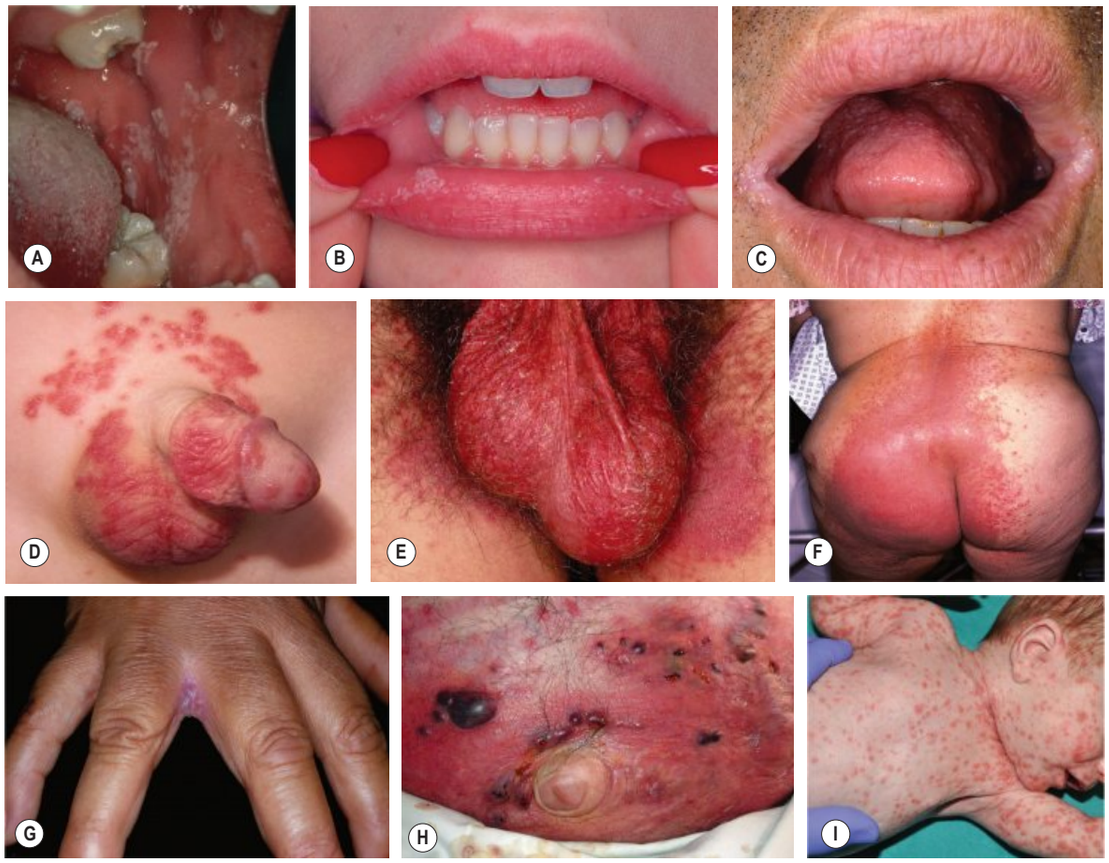


Fig. 77.22 Mucocutaneous candidiasis. A Thrush with "cottage cheese"-like exudate on the buccal mucosa in a man with AIDS. **B** Thrush and candidal cheilitis. **C** Angular cheilitis (perlèche). **D** Candidiasis of the suprapubic area and penis in a young boy. Note the collarettes of scale on the coalescing, brightly erythematous papules. **E** Candidiasis of the scrotum and medial thighs with beefy red erythema, scale, and satellite papules. **F** This infection occurred in a hospitalized patient with diabetes mellitus who was receiving broad-spectrum antibiotics. Note the multiple satellite lesions. **G** Erosive interdigital candidiasis (erosio interdigitalis blastomycetica) in the classic location between the third and fourth fingers. **H** Dermal candidiasis in an immunosuppressed patient. **I** Early-onset cutaneous candidiasis in a term neonate. Widespread pink papules, some of which have collarettes of white scale, admixed with small pustules. This typically results from intrauterine acquisition and may be present at birth or appear during the first six days of life. *B, D Courtesy Louis A. Fragola, Jr, MD; C, Courtesy Kalman Watsky, MD; E, G, Courtesy Eugene Mirrer, MD; I, Courtesy Antonio Torrelo, MD.*

a number of disorders, including primary immunodeficiencies. Patients have defects in the T helper 17 (Th17) response that prevent effective handling of *Candida* organisms, leading to chronic, recalcitrant infections of the skin (including granulomatous lesions), nails, and mucosae. Some patients have associated autoimmune endocrinopathies as well as alopecia areata and vitiligo. Therapy involves oral fluconazole and itraconazole (see Table 77.15).

Erosive Papulonodular Dermatosis: Granuloma Gluteale Infantum/Adultorum and Perianal Pseudoverrucous Papules/Nodules (see Ch. 15)

Granuloma gluteale infantum/adultorum and perianal pseudoverrucous papules/nodules are reactive conditions that occur in the setting of chronic, severe irritant contact dermatitis in the anogenital region of either infants with chronic diarrhea or children and adults with encopresis or urinary incontinence[39]. They exist within the spectrum of erosive papulonodular dermatosis, which also includes *Jacquet erosive dermatitis*, a variant with prominent punched-out erosions[40]. Erythematous to violaceous nodules and plaques, often ovoid in shape and sometimes eroded, develop on the vulva, lower buttocks, perianal region, and occasionally scrotum (Fig. 77.23). In addition to chronic irritation (e.g. from frequent loose stools), contributing factors may include candidal infection (in the past viewed as the key factor), occlusion, and topical corticosteroid use. Histologically, epidermal hyperplasia, a variably dense mixed inflammatory infiltrate in the dermis, and vascular proliferation are typically observed. Although barrier creams and topical antifungal agents may have some benefit, the condition tends to persist until the irritant trigger is eliminated (see Fig 15.6).

SUBCUTANEOUS MYCOSES

The "subcutaneous" mycoses are due to a large and diverse group of organisms that cause disease when implanted or otherwise introduced into the dermis or subcutis. Chromoblastomycosis, mycetoma, sporotrichosis, and lobomycosis are discussed in detail in this section; the first three have been designated as neglected tropical diseases (NTDs) by the World Health Organization (WHO).

Another chronic subcutaneous fungal infection is basidiobolomycosis, which is caused by *Basidiobolus ranarum*. Although this organism is an environmental saprophyte that is found worldwide, the associated infection occurs most commonly in children living in tropical and subtropical climates. The most common portal of entry is the skin, typically after arthropod bites or minor trauma. Clinically, the disease manifests as a solitary, painless, indurated subcutaneous nodule or swelling of the thigh or buttock. The classic treatment is saturated solution of potassium iodide (SSKI; see Ch. 100), although successful results have been reported with oral azole antifungals and trimethoprim–sulfamethoxazole. Surgical excision is not recommended. A related organism, *Conidiobolus coronatus*, causes an infection that has similar clinical features but typically affects the face, especially the nasal region.

Although not a true fungal disease, protothecosis is treated with antifungal agents. *Prototheca* (usually *P. wickerhamii*) is a genus of achlorophyllic algae that can be introduced into the skin via trauma, often in the setting of exposure to contaminated water. Common clinical presentations include solitary cutaneous plaques (sometimes eczematous), nodules or ulcers, as well as olecranon bursitis. The extremities are the most frequent sites of involvement. Although immunocompetent patients typically have chronic, stable disease, patients who are immunocompromised can have widespread involvement, including algemia. Protothecosis is difficult to treat; surgical excision and systemic antifungals (e.g. amphotericin B) are more effective in immunocompetent hosts.

Skin and soft tissue infections with *Pythium insidiosum*, an aquatic oomycete, may present as progressive necrotic plaques in previously healthy children and adults as well as immunocompromised individuals[41]. Pythiosis typically develops on the lower extremities or in the periocular area following exposure to stagnant water. It most often occurs in Thailand and India but has been reported worldwide, including in the southern US. These organisms resemble filamentous fungi but are more closely related to diatoms and algae. Treatment is difficult and includes surgical debridement together with antifungal and antibacterial agents.

TREATMENT OF MUCOCUTANEOUS *CANDIDA* INFECTIONS	
Type of infection	**Treatment regimen (adult doses unless otherwise indicated)**
Oropharyngeal candidiasis	**Nystatin*** 100 000 units/ml suspension: • Children and adults – 4–6 ml swish and swallow four times daily • Infants – 2 ml (1 ml inside each cheek) four times daily **Clotrimazole*** 10 mg troche five times daily **Fluconazole**† 200 mg po on day 1, then 100–200 mg po daily • Continue treatment for 7–14 days after clinical resolution
Esophageal candidiasis	**Fluconazole*** 200–400 mg po on day 1, then 100–400 mg daily **Itraconazole** 200 mg po daily **Voriconazole** 200 mg po or iv BID **Posaconazole** 400 mg po BID **Caspofungin** 50 mg po iv daily Continue treatment for 7–14 days following resolution of symptoms, for a minimum of 21 days total
Candidal vulvovaginitis‡	**Fluconazole*** 150 mg po single dose or (for severe disease or an immunosuppressed patient) three doses at 3-day intervals **Ibrexafungerp** 300 mg po, two doses 12 hours apart **Butoconazole** 2% vaginal cream, 5 g daily for 1–3 days **Clotrimazole***,¶ • 1% vaginal cream (or other topical formulation), 5 g daily for 7–14 days • Vaginal suppositories: 100 mg daily for 7 days or 200 mg daily for 3 days **Miconazole***,¶ • 2% cream, 5 g daily for 7 days • Vaginal suppositories: 100 mg daily for 7 days, 200 mg daily for 3 days, or 1200 mg single dose **Tioconazole*** 6.5% cream, 5 g single dose **Terconazole*** • 0.4% or 0.8% cream, 5 g daily for 7 or 3 days, respectively • 80 mg vaginal suppository daily for 3 days **Nystatin** 100 000 units vaginal suppository daily for 14 days *For suppression in patients with recurrent infections:* **Fluconazole** 150 mg weekly for 6 months **Oteseconazole** 600 mg po on day 1, 450 mg on day 2, then 150 mg weekly for 11 weeks (beginning on day 14) **Ibrexafungerp** 300 mg po monthly for 6 months **Clotrimazole** vaginal suppository, 200 mg twice weekly or 500 mg weekly for 6 months
Chronic mucocutaneous candidiasis	**Fluconazole** • *Eradication:* 400–800 mg po daily for 4–6 months • *Suppressive therapy*: 200 mg po daily
Candidal intertrigo or balanitis‡	Topical **imidazole** (see Table 127.12) or **ciclopirox** cream or lotion twice daily for 1–2 weeks or until resolved§ *Systemic agents for recalcitrant or severe cases:* **Fluconazole** • 50 to 100 mg po daily for 14 days • 150 mg po weekly for 2–4 weeks **Itraconazole** 200 mg po twice daily for 14 days

*Recommended as first-line treatment for immunocompetent individuals.
†Recommended as first-line treatment for people living with HIV (or other immunosuppressed individuals) who have moderate to severe disease, recurrent infection, or a CD4 count of <200 cells/mcl.
‡In cases of recurrent vulvovaginitis, treatment of the patient's sexual partner is controversial; in contrast, for recurrent balanitis, eradication of *Candida* from the sexual partner's genital tract is generally recommended.
¶Preferred treatments (with 7-day regimens) for pregnant patients.
§After clinical resolution, topical treatments may be continued twice weekly to prevent recurrence.

Table 77.15 Treatment of mucocutaneous *Candida* infections. Candidal onychomycosis can be treated with the oral fluconazole or itraconazole regimens described for tinea unguium in Table 77.13. See Table 127.17 for pediatric dosing of fluconazole. BID, twice daily; iv, intravenously; po, orally.

Chromoblastomycosis

Synonyms: ■ Chromomycosis ■ Cladosporiosis ■ Verrucous dermatitis ■ Phaeosporotrichosis ■ Pedroso disease ■ Fonseca disease

Introduction

Chromoblastomycosis presents as a "verrucous dermatosis" and is caused by several genera of dematiaceous (pigmented) fungi. Typically chronic in nature, an expanding verrucous plaque on the lower, or occasionally upper, extremity is the classic presentation. Two fungi, *Fonsecaea pedrosoi* and *Cladophialophora carrionii*, are responsible for most cases; less common causes include *Fonsecaea compacta, Fonsecaea monophora, Phialophora verrucosa*, and *Rhinocladiella aquaspersa*. The clinical presentation and colonial morphologies of each of these fungi are very similar, and differentiation is based on microscopic and conidial characteristics.

History

Pedroso first recognized chromoblastomycosis in 1911. Four years later, Medlar and Lane reported the first case in the US (in Boston)[42]. There has been confusion over the proper naming of this condition. At one point, chromoblastomycosis was thought to be closely related to blastomycosis; however, cellular division does not occur via budding ("blasto-") but rather via internal septation, hence the preference for the term "chromomycosis". Nonetheless, some authors have argued that the latter is also confusing, because it has the same meaning as phaeohyphomycosis (see below), and so they prefer the term "chromoblastomycosis".

Epidemiology and pathogenesis

Chromoblastomycosis is an NTD that is most commonly found in tropical and subtropical climates and occasionally in temperate zones such as the US, Europe, and Canada. Farmers, miners, and others working in rural areas are at increased risk. Men 20–60 years of age are most often affected, probably due to increased occupational exposure, which accounts for up to 90% of cases[43].

The fungi responsible for causing chromoblastomycosis are found in the soil and in decaying plants and wood. The disease is typically contracted from trauma to the lower extremities, including from not wearing shoes. As a result, the organism is introduced into the dermis or subcutis via implantation.

Clinical features

The disease usually presents as a papule or nodule on the leg, which progresses to form a verrucous or granulomatous plaque (Fig. 77.24). The lesion may appear annular as the central portion resolves with scarring. Several lesions may coalesce to form a multinodular mass, or multiple lesions may exist as discrete islands scattered within unaffected skin. It is thought that autoinoculation from scratching may be responsible for the spread of infection. Typically, only one extremity is affected. A subcutaneous nodule or mass is occasionally the presenting lesion. There are usually no constitutional symptoms.

Pathology

Pseudoepitheliomatous hyperplasia, intraepidermal abscesses, and suppurative and granulomatous inflammation within the dermis are the typical histologic findings (Fig. 77.24C). Pathognomonic round, pigmented "Medlar bodies" or sclerotic bodies, which are 6 to 12 microns in diameter and said to resemble "copper pennies", are present in the dermis, both extracellularly and within giant cells[2]. Organisms can also be detected via PCR of tissue samples.



Fig. 77.23 Granuloma gluteale infantum. Coalescing moist, pink papules on the vulva and suprapubic area of an infant. *Courtesy Julie V. Schaffer, MD.*

Differential diagnosis

Although characteristic reddish brown to black dots may be evident using dermoscopy, a biopsy is indicated to exclude other infectious diseases characterized by granulomatous lesions associated with scarring, such as cutaneous tuberculosis, tertiary syphilis, blastomycosis, and leishmaniasis. Mycetoma is another implantation mycosis that commonly affects the lower extremity, but edema, draining sinuses, and grains point to this diagnosis. If a biopsy is not feasible, a KOH examination of scrapings from a pigmented portion of the lesion can be performed. The presence of Medlar bodies is diagnostic (excluding other entities such as blastomycosis), but hyphae may also be seen. Culture growth at 25–30°C is slow and the different genera produce similar colonial morphologies. The major differences between genera are the microscopic features, in particular the type of conidia produced in culture. The three major types are:

- Cladophialophora-like (long branching side chains with shield cells at branch points)
- Phialophora-like (conidia resemble overflowing buds in a vase)
- Rhinocladiella-like (overall configuration similar to a mascara brush).

Treatment

Therapeutic options are limited. Some authors have advocated heat therapy based on evidence that the causative organisms will not grow at high temperatures. For small lesions, surgical excision can be attempted together with systemic antifungal treatment. 5-Flucytosine combined with either intravenous amphotericin B or an oral triazole has been reported to be efficacious. Itraconazole alone (200–400 mg/day) administered for at least 6 months may have cure rates of up to 80%–90%[44]. Successful treatment with voriconazole or posaconazole has also been described. In a small series, oral terbinafine (500 mg/day) given for at least 7 months was effective[45]. Other treatment considerations include cryosurgery and the addition of antibiotics if the lesion is secondarily infected.

Mycetoma

Synonyms: ■ Madura foot ■ Maduromycosis

Introduction

Mycetoma, often referred to as "Madura foot", is a Greek term for "fungal tumor". Due to implantation, it is a granulomatous infection of dermal and subcutaneous tissue that may extend to muscle or even bone. Mycetoma is differentiated from other mycoses by its characteristic draining sinuses containing grains (sclerotia, sulfur granules) and local edema. Two subtypes exist: (1) actinomycotic mycetoma – caused by filamentous aerobic and anaerobic organisms, e.g. *Nocardia brasiliensis*, *Actinomadura madurae*; and (2) eumycotic mycetoma – caused by true fungi. *Botryomycosis* caused by true bacteria (e.g. *Staphylococcus aureus*, *Pseudomonas* spp.) is also associated with grains, as is actinomycosis (see Ch. 74)[46].



Fig. 77.24 Chromoblastomycosis. Annular and figurate plaques due to central clearing and scarring with a verrucous surface on the arm (**A**) and a more granulomatous appearance on the leg (**B**). **C** Brown-colored sclerotic body (inset) within a mixed granulomatous and neutrophilic dermal infiltrate. *C, Courtesy C. Massone, MD.*

History and epidemiology

Dr. John Gill provided the first formal description of mycetoma in 1842, in Madura (India), hence the name "Madura foot"[47]. Mycetoma, now classified as an NTD, is endemic to tropical and subtropical climates. Actinomycotic mycetoma is more prevalent in Mexico, while eumycotic mycetoma is more common in other areas including Africa. The typical patient is a man between 20 and 50 years of age.

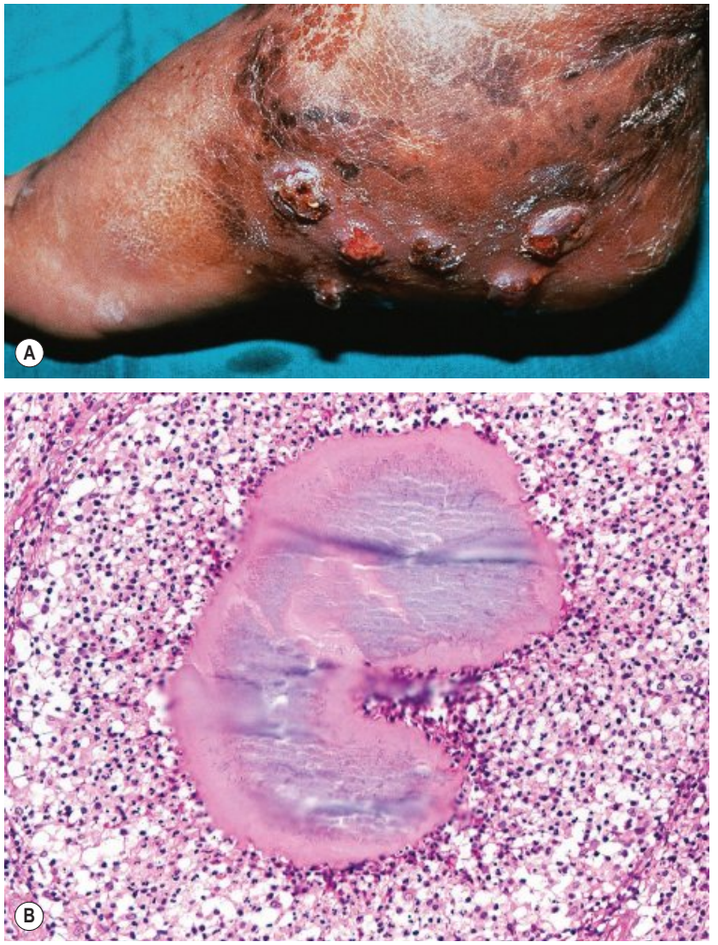


Fig. 77.25 Mycetoma (Madura foot). A Note the soft tissue swelling of the foot as well as multiple nodules with pustular discharge. **B** Histology of a grain, which represents tightly packed colonies of fungal organisms. *B, Courtesy Lorenzo Cerroni, MD.*

Pathogenesis

In most cases, causative organisms are acquired from the soil via direct inoculation into the skin, leading to a dermal and subcutaneous fungal infection. Deeper invasion to muscle or bone can subsequently occur. This process may occur rapidly or over many years. Sometimes, multiple sites of involvement appear in the vicinity of the original lesion, likely due to multiple injuries rather than contiguous spread of disease. Lack of protective footwear, malnutrition, and exposed cuts and abrasions are risk factors for infection.

Clinical features

The foot is the most common site of infection, followed by the hand, trunk, and scalp. Involvement is typically unilateral and begins as a painless papule. Once the subcutaneous tissues are infected, there is swelling and eventual formation of purulent draining sinuses (Fig. 77.25A). The drainage contains the characteristic grains, which represent compact masses of fungal colonies and vary in size from minute to half a centimeter in diameter. Invasion of deeper tissues then ensues, and sometimes cavities are formed within involved bone. Surprisingly, this disease is generally asymptomatic. All subtypes can have a similar clinical presentation.

Pathology

Pseudoepitheliomatous hyperplasia is a common histologic finding that accompanies suppurative and granulomatous inflammation of the dermis and subcutis as well as fibrosis. The characteristic grains represent tightly packed colonies of organisms (Fig. 77.25B). Estimation of the diameter of the filaments comprising the grain as compared to the size of the nuclei of surrounding inflammatory cells allows a distinction between eumycotic (thicker filaments) and actinomycotic (thin, fine filaments) mycetomas. Special stains, e.g. methenamine silver, Brown–Brenn, can aid in distinguishing the subtype (see Ch. 0).

Differential diagnosis

To establish the diagnosis of mycetoma, both the history and clinical appearance are important considerations followed by laboratory evaluation. In addition to noting the color of the grains (Table 77.16), KOH examination, Gram stain, and culture (bacterial and fungal) of exudate from a sinus tract and/or tissue should be performed. Molecular techniques such as PCR-based assays can also be utilized to identify organisms. Mycetoma has to be differentiated from botryomycosis and actinomycosis, which are also associated with grain formation (see Ch. 74).

COLORS OF GRAINS AND GEOGRAPHIC DISTRIBUTION OF EUMYCOTIC AND ACTINOMYCOTIC MYCETOMAS

Pathogen		Grain color	Geographic distribution
Eumycotic	*Madurella mycetomatis* also *M.sudanensis, M fahalii*	Black	Sudan, Africa, Central and South America; Caribbean, Middle East, Asia
	Trematosphaeria grisea	Black	North, Central and South America; Africa, Asia
	Plenodomus senegalensis	Black	Africa, Asia
	*Scedosporium apiospermum**	White	North, Central and South America; Africa, Oceania, Asia, Europe
	Acremonium and *Sarocladium* spp.	White	North, Central and South America; Asia, Europe, Oceania
Actinomycotic	*Nocardia brasiliensis*†	White	Worldwide (all *Nocardia* spp.)
	Nocardia asteroides‡	White	
	Nocardia caviae	Yellow–white	
	Actinomadura madurae	Yellow or white	Worldwide
	Actinomadura pelletieri	Red	North and South America, Africa, India
	Streptomyces somaliensis	Brown or yellow	Africa (arid regions)
	Actinomyces israelii¶	Yellow–white	Worldwide

*Most common cause in the US.
†Most common cause in Mexico.
‡Rare.
¶Very rare cause of mycetoma; usually causes actinomycosis (e.g. cervicofacial, thoracic and abdominal), which also has draining sinuses and grains.

Table 77.16 Colors of grains and geographic distribution of eumycotic and actinomycotic mycetomas. Grains can also be seen in botryomycosis and actinomycosis (see Ch. 74).

Treatment

For the best outcome, eumycotic mycetoma must be diagnosed early and surgically excised (including a large margin of normal surrounding tissue) before the underlying bone becomes involved. Systemic antifungal therapy is administered before and after excision. Depending upon the particular fungus, itraconazole, voriconazole, posaconazole, and terbinafine have been used to treat eumycotic mycetomas[48]. The medical treatment of actinomycotic mycetoma typically consists of streptomycin or amikacin plus either trimethoprim–sulfamethoxazole or dapsone; therapy is continued for months to years. Other useful drugs include moxifloxacin and imipenem.

Sporotrichosis

Synonym: ■ Rose gardener's disease

Introduction

Sporotrichosis is a subcutaneous mycosis caused by dimorphic organisms of the genus *Sporothrix* (e.g. *S. schenckii*, *S. braziliensis*, *S. globose*, *S. mexicana)*[49]. A gardener being pricked by a contaminated rose thorn is a classic vignette for the acquisition of sporotrichosis. Although various clinical presentations are possible, the most common one is a lymphocutaneous or "sporotrichoid" pattern, which refers to the primary inoculation site plus spread of the infection along the lymphatics in a nodular pattern.

Epidemiology

Sporothrix is present in the soil throughout the world. However, sporotrichosis is endemic to Mexico, Central America, and South America as well as other areas such as South Africa. In these locations, exposure to the organism typically occurs in individuals who work outdoors. In temperate climates, such as in the US and Canada, the disease most often develops in gardeners, especially those growing orchids and roses. All age groups can be affected, but it is more common in adults. In the past several decades, the incidence of sporotrichosis in the Rio de Janeiro region of Brazil has increased >100-fold due to transmission of *S. brasiliensis* by infected cats, which (in contrast to humans) harbor large numbers of organisms in cutaneous ulcers[50]. This epidemic has spread to other areas of Brazil and adjacent countries such as Argentina, with recent reports outside of South America (e.g. in the United Kingdom).

Pathogenesis

Sporotrichosis is most commonly acquired from cutaneous inoculation, especially by vegetation such as thorns and wood. With the exception of *S. brasiliensis* from cats, animal-to-human transmission is rare. Multiple inoculations may occur simultaneously, not to be confused with spread of a single primary lesion. The presentation and course of sporotrichosis depends on the host immune response as well as the size and virulence of the inoculum. In naive hosts, involvement of regional lymphatics ensues. However, in some patients, especially those with a prior history of exposure to *Sporothrix*, lymphatic spread does not occur and a "fixed" ulcer[51] or granulomatous plaque develops at the site of inoculation; the latter is often seen on the face, especially in children living in endemic areas.

Extensive cutaneous disease with or without systemic involvement is also possible, especially in an immunocompromised host. Cases of inhaled sporotrichosis have been reported with systemic and cutaneous dissemination, similar to disseminated histoplasmosis and other dimorphic fungal infections.

Clinical features

The initial presentation of sporotrichosis is a single papule at a site of injury, most commonly on the hand, appearing several weeks after inoculation. The lesion then becomes eroded or ulcerated with purulent drainage, but it is generally not painful. Additional lesions appear weeks later, typically developing as dermal and subcutaneous nodules and ulcers along the path of lymphatic drainage (often up the arm; Fig. 77.26). This is the well-known "sporotrichoid" pattern. The involved lymphatic vessels may become fibrosed[52]. Lesions of "fixed" cutaneous sporotrichosis can have a granulomatous appearance, often with ulceration, while disseminated lesions typically present as subcutaneous nodules. Reactive conditions such as erythema multiforme and erythema nodusum have been reported in patients with sporotrichosis, especially that due to *S. brasiliensis*.

Pathology

Histologically, suppurative and granulomatous inflammation is found in the dermis and subcutis. The causative organisms are rarely evident; staining with fluorescent-labeled antibodies may aid in recognition of the sparse cigar-shaped yeast forms. Asteroid bodies are often seen. When numerous fungi are present (e.g. in an immunocompromised host), budding yeast and cigar-shaped organisms can often be visualized with PAS (Fig. 77.26D) or silver stains.

Differential diagnosis

When there is a sporotrichoid pattern, the major entity to be excluded is an atypical mycobacterial infection, in particular with *M. marinum*; less common causes are outlined in Table 77.17. As organisms are not typically seen by KOH or histopathologic examination, culture (of pus or tissue) is often required to definitively diagnose sporotrichosis; a nested PCR assay can also be used to detect organisms in clinical samples[53]. *Sporothrix* spp. are dimorphic fungi (see below), and whether a hyphal or yeast form develops depends on the temperature. Growth is rapid at 25°C, revealing a glabrous white to brown mold that becomes firm, wrinkled, and more darkly pigmented over time. Microscopically, delicate conidia are clustered at the ends of conidiophores (specialized



Fig. 77.26 Lymphocutaneous (sporotrichoid) pattern. A An eroded nodule on the thumb representing the primary lesion with a secondary lesion along the lymphatics due to sporotrichosis. **B** Ulcerated nodule on the extensor forearm with multiple more proximal nodules due to nocardiosis in a patient with lymphoma who was receiving systemic corticosteroids. **C** Granulomatous plaques with evidence of upward spread along the lymphatics. **D** Multiple yeast forms of *Sporothrix schenckii* in the dermis; note that many of the organisms have the characteristic cigar shape. *B, Courtesy Jean L. Bolognia, MD; C, Courtesy Luis Requena, MD; D, Courtesy Ronald P. Rapini, MD.*

hyphae); single, thick-walled pigmented conidia can also arise from hyphae. At 37°C, on enriched glucose-containing media, there are slow-growing, whitish, pasty, yeast-like colonies. On microscopic examination of the latter, cigar-shaped budding yeasts are seen. Full speciation depends on molecular studies[49]. The differential diagnosis of fixed plaque sporotrichosis and disseminated lesions is broad and includes other granulomatous disorders, both infectious and inflammatory.

Treatment

Topical therapy is not effective. Oral saturated solution of potassium iodide (SSKI) has been used with success. Although neither fungistatic nor fungicidal, SSKI is thought to affect the host's immune reaction to the organism. Its cost is low, but it has a bitter taste as well as potential side effects including iododerma, gastrointestinal upset, and thyroid suppression (see Ch. 100). Based upon multicenter, non-randomized trials and case series, the Mycoses Study Group of the Infectious Diseases Society of America has recommended itraconazole (100–200 mg/day) for 3–6 months as the treatment of choice for lymphocutaneous or fixed cutaneous sporotrichosis[54]. The drug is generally safe and well tolerated, and the relapse rate is low. Amphotericin B may be indicated in severe or disseminated disease.

Lobomycosis

Synonyms: ■ Keloidal blastomycosis ■ Lacaziosis ■ Lobo's disease

Lobomycosis is a chronic fungal infection characterized by cutaneous nodules that resemble keloids. The causative organism, *Lacazia loboi* (previously known as *Loboa loboi*)[55], is closely related to *Paracoccidioides brasiliensis* and has never been cultured *in vitro*[56]. Lobomycosis occurs in Central and South America and has been linked to contact with dolphins and a marine environment as well as soil and vegetation in rural areas. Infection typically occurs after minor trauma and most often affects men[57].

Lobomycosis presents as firm, keloid-like nodules that may be pruritic or asymptomatic. It favors the distal extremities, ears (especially the helices), and face but can also affect the trunk (Fig. 77.27A,B). The lesions enlarge slowly over years, forming broad, multinodular plaques that may have a smooth surface or (occasionally) a verrucous appearance and ulceration. Histologic evaluation shows highly characteristic chains of thick-walled, yeast-like cells (known as "brass knuckles") with intercellular bridges (Fig. 77.27C); PAS or silver stains highlight these organisms, which can also be identified in scrapings from the surface of skin lesions[58]. Additional findings include a dermal granulomatous infiltrate and either atrophy or pseudoepitheliomatous hyperplasia of the epidermis. Treatment with surgical excision or cryosurgery is employed if feasible, since antifungal medications are typically ineffective. However, posaconazole or clofazimine plus itraconazole may be of benefit for patients with widespread disease[59,60].

INFECTIOUS CAUSES OF A LYMPHOCUTANEOUS ("SPOROTRICHOID") PATTERN
Most common
Atypical mycobacteria, especially *M. marinum*, but also other species (e.g. *M. chelonae*, *M. kansasii*)
Sporotrichosis (Fig. 77.26A)
Unusual
Nocardiosis (Fig. 77.26B)
Pyogenic bacteria (e.g. *Staphylococcus aureus*, *Streptococcus pyogenes*)
Pseudallescheria boydii/Scedosporium apiospermum
Rare (in high-income countries)
Leishmaniasis
Tularemia*
Tuberculosis*
Dimorphic fungi (other than *Sporothrix* spp.)
Opportunistic fungi in immunocompromised hosts (e.g. *Fusarium*, *Alternaria* spp.)
Glanders (*Burkholderia mallei*)*
Cat scratch disease*
Anthrax
Cowpox
Acanthamoeba spp.
*Often ulceroglandular.

Table 77.17 Infectious causes of a lymphocutaneous ("sporotrichoid") pattern. There are also non-infectious causes such as lymphoma, Langerhans cell histiocytosis, and in-transit metastases. In addition, perineural spread of leprosy can mimic a lymphocutaneous pattern.

SYSTEMIC MYCOSES

This section reviews systemic infections caused by opportunistic as well as true fungal pathogens. The true pathogens are generally dimorphic and cause infection in hosts with normal immune status, while opportunistic pathogens, which are generally less virulent, take advantage of the immunocompromised state.

True Pathogens

Introduction

The systemic mycoses due to true pathogens include histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis. They are caused by dimorphic fungi, meaning the organisms can exist in two forms – as molds (with septate hyphae and conidia) in nature and as other forms (usually yeasts) in living tissue and (with the exception of *Coccidioides* spp.) at 37°C. Each pathogen has certain geographic preferences (Fig. 77.28; see below). Acquisition of disease is typically through inhalation of the causative fungi, leading to pulmonary symptoms and pneumonitis. The vast majority of infections resolve spontaneously, and patients are left with strong, specific immunity. Disseminated histoplasmosis and coccidioidomycosis may occur in people living with HIV, as can disseminated infections with *S. schenckii* (dimorphic) and *Talaromyces (Penicillium) marneffei* (talaromycosis; dimorphic and opportunistic)[61]. *Emergomyces* spp. are dimorphic fungal pathogens that were initially described in South Africa (*E. africanus*; formerly *Emmonsia pasteuriana*) and subsequently reported in Europe, Asia, and the Americas (*E. canadensis, E. europaeus, R. orientalis, E. pasteurianus*)[62,63]. Disseminated infection in immunocompromised patients (e.g. those with HIV infection) can present with multiple crusted papules/nodules or ulcers, with parasitized macrophages similar to histoplasmosis and penicilliosis evident histologically[62,63] (Table 77.18).

Histoplasmosis

Synonyms: ■ Darling's disease ■ Cave disease ■ Ohio valley disease ■ Reticuloendotheliosis



Fig. 77.27 Lobomycosis. A, B Multinodular pinkish-brown plaques with a keloid-like appearance on the helix and back. **C** Spherical organisms with doubly refractile walls are seen within the dermis. Chain formation is commonly observed (inset; methenamine silver stain). *A, B, Courtesy Regina Carneiro, MD and Caroline Brandao, MD; C, Courtesy C. Massone, MD.*

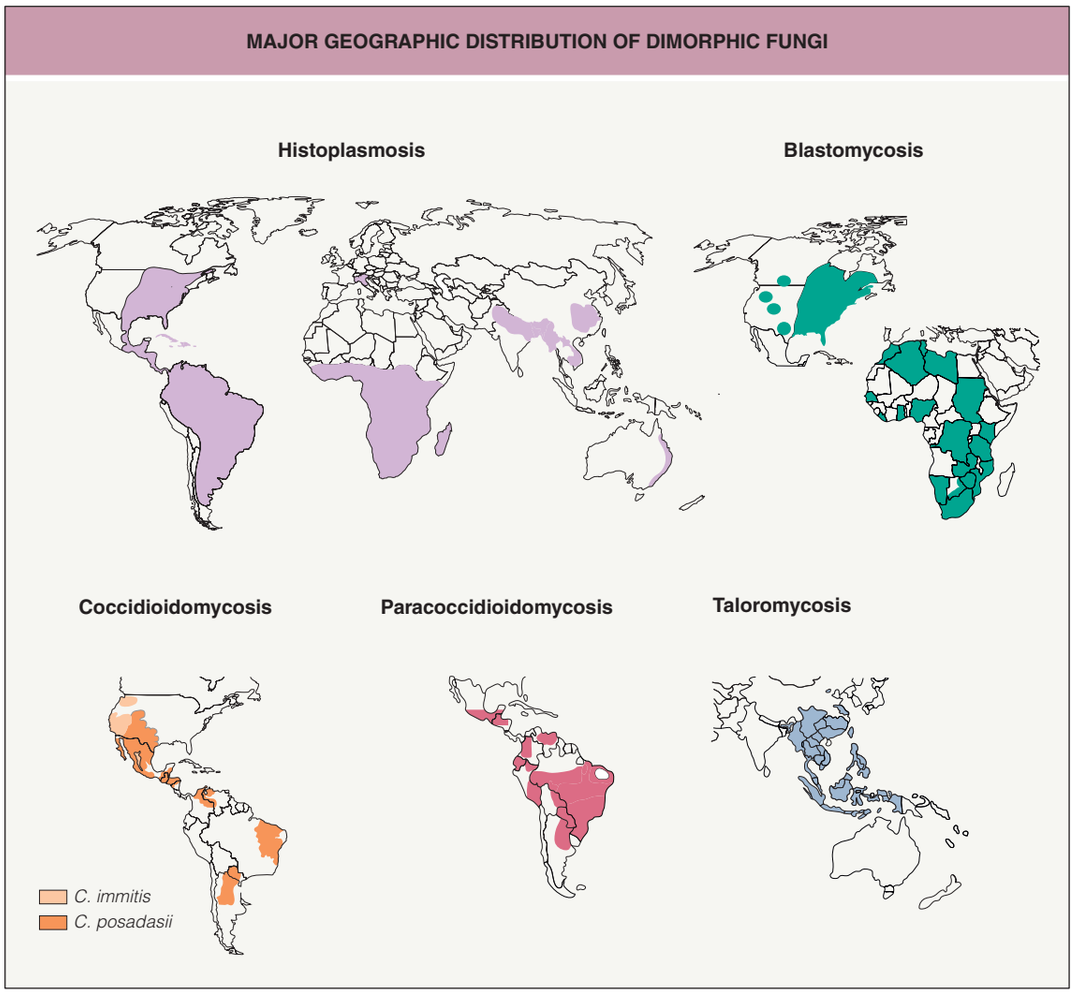


Fig. 77.28 Major geographic distribution of dimorphic fungi. Histoplasmosis has a worldwide distribution, with cases reported outside of these areas, and blastomycosis has also been reported in India and the Middle East. In addition, emergomycosis due to several dimorphic fungal species (*Emergomyces africanus, E. canadensis, E. europaeus, R. orientalis, E. pasteurianus*) has been reported in Africa, Europe, Asia, and the Americas.

DIFFERENTIAL DIAGNOSIS OF PARASITIZED MACROPHAGES		
Disease	**Organism**	**Key features**
Rhinoscleroma	*Klebsiella rhinoscleromatis*	Russell bodies (dilated endoplasmic reticulum cisternae containing aggregated immunoglobulins; form within plasma cells); Mikulicz cell (large histiocyte containing organisms)
Granuloma inguinale	*Calymmatobacterium granulomatis*	"Donovanosis"; Donovan bodies (vacuoles containing bacilli within macrophages)
Histoplasmosis	*Histoplasma capsulatum*	Yeast within cytoplasm of macrophages; surrounded by clear halo
Leishmaniasis	*Leishmania* spp.	Non-encapsulated organism; contains nucleus and paranucleus (kinetoplast)
Talaromycosis	*Talaromyces (Penicillium) marneffei*	Small yeast within macrophages; resembles histoplasmosis
Emergomycosis	*Emergomyces* spp. (include the former *Emmonsia pasteuriana*)	Small yeast within macrophages

Table 77.18 Differential diagnosis of parasitized macrophages. *Adapted from reference 2.*

Introduction

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum* var. *capsulatum*[64].

Epidemiology

H. capsulatum is found in the soil in warm, moist climates, particularly the Mississippi, Ohio, and St Lawrence river valleys in the US and Canada. Between 80% and 90% of persons from endemic areas may exhibit positive histoplasmin skin testing[65]. Birds, fowl, and bats are significant reservoirs for histoplasmosis. Because the feces of these animals contain the organisms, the areas in which they live can harbor infectious fungal spores. Caves, schoolyards, construction sites, unoccupied buildings, and chicken coops tend to be high-risk areas. *H. capsulatum* var. *capsulatum* is also endemic along river basins in some areas of Africa, India, Southeast Asia, and Australia.

Pathogenesis

Histoplasmosis is caused either by inhalation of *H. capsulatum* or, rarely, by direct cutaneous inoculation of the fungus. Immunocompetent hosts can acquire the disease, but immunocompromised hosts have a higher risk of dissemination. Clinical presentations include acute and chronic pulmonary histoplasmosis, disseminated histoplasmosis, and primary cutaneous histoplasmosis. In disseminated histoplasmosis, the most common sites of involvement (after the lung) are the spleen, lymph nodes, bone marrow, and liver; calcifications within the lymph nodes, lungs, and spleen can serve as evidence of prior infection. Cutaneous manifestations most commonly result from disseminated disease. Severe disseminated histoplasmosis has been reported in individuals with impaired interferon-γ responses due to mutations in *IFNGR1* or *STAT1*, which encode interferon-γ receptor 1 and signal transducer and activator of transcription 1, respectively (see Ch. 60).

Clinical features
The skin lesions of histoplasmosis are nonspecific, making the diagnosis virtually impossible with physical examination alone. When chronic disseminated histoplasmosis occurs in immunocompetent hosts, the most common mucocutaneous finding is oral ulcers but occasionally nodules and vegetative plaques are also seen. Disseminated histoplasmosis in immunocompromised hosts (including people living with HIV) can present with mucocutaneous erosions or ulcers as well as multiple erythematous papules or nodules with scale or crust (Fig. 77.29A,B). In African histoplasmosis, a variant caused by *H. capsulatum* var. *duboisii*, most patients present with mucocutaneous, subcutaneous, and bone lesions.

Pathology
Microscopic examination of biopsy specimens demonstrates characteristic intracellular yeast forms surrounded by a rim of clearing (Fig. 77.29C). Histiocytes and giant cells are the host cells in histoplasmosis, which is in the differential diagnosis of "parasitized macrophages" (see Table 77.18). For easier identification of the fungi, tissue may be stained with PAS or methenamine silver (Fig. 77.29D).

Differential diagnosis
Because cutaneous histoplasmosis has a wide spectrum of clinical presentations, the diagnosis usually rests on histologic examination and culture of involved skin tissue. To evaluate for disseminated disease, bone marrow (sensitivity 70%–90%) and blood should be cultured at 25°C and 37°C, with plates held for up to a month. At 25°C, characteristic tuberculate macroconidia develop. Additional diagnostic tests include cultures of sputum and body fluids, polysaccharide antigen testing of blood and urine (useful in detecting disseminated disease), histoplasmin skin testing (indicated only in non-endemic areas), and serologic assays to measure antibody responses (complement fixation, immunodiffusion). Highly sensitive and specific PCR-based assays can be used to identify histoplasmosis in blood and tissue[66,67]. Diseases in the differential diagnosis include other dimorphic fungal infections (e.g. paracoccidioidomycosis), mucocutaneous tuberculosis, major aphthae, and oral squamous cell carcinoma. For primary cutaneous histoplasmosis, entities in Table 77.17 should be considered.

Treatment
In primary, self-limited, asymptomatic histoplasmosis, treatment may not be necessary. However, in symptomatic or disseminated disease, systemic antifungal therapy is required. Amphotericin B, given intravenously and titrated up to 1 mg/kg/day, is currently the most effective therapy and should be used initially for severe disease, followed by itraconazole. In immunocompetent hosts with mild to moderate, stable disease, itraconazole (200–400 mg/day) is the treatment of choice[68]. HIV-infected patients with disseminated histoplasmosis require lifelong maintenance therapy with itraconazole after initial treatment with amphotericin B (if required for severe disease). Successful treatment with voriconazole, posaconazole, and isavuconazole have also been described[69,70], but ketoconazole is no longer routinely used.

Blastomycosis

Synonyms: ■ North American blastomycosis ■ Gilchrist's disease

Introduction
Blastomyces dermatitidis is a dimorphic fungus and the most common causative agent of blastomycosis. Additional species that have more recently been associated with blastomycosis include *B. gilchristii*, *B. helicus* (formerly *Emmonsia helica*), *B. emzantsi*, and *B. percursus*[70–72].

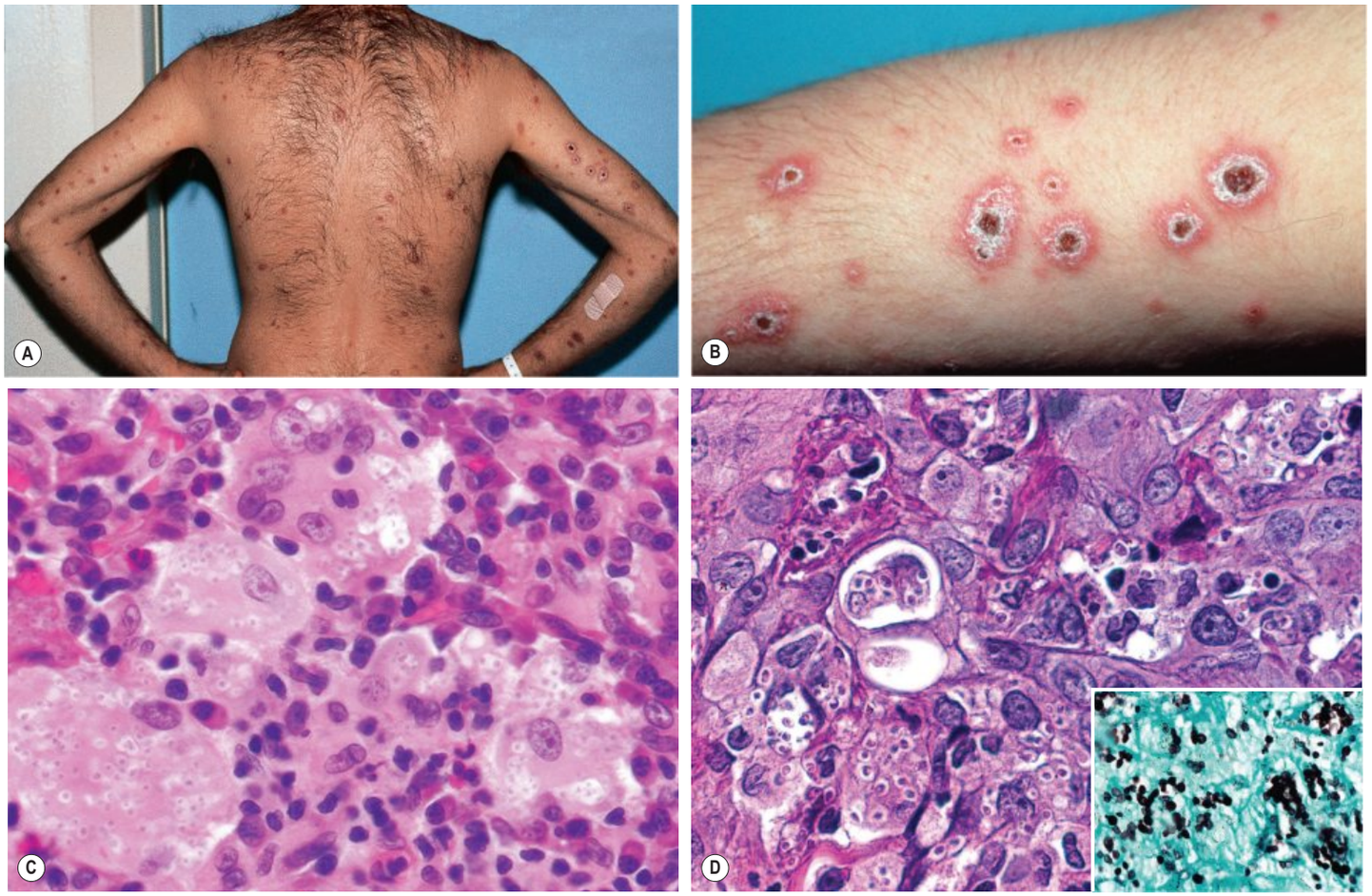


Fig. 77.29 Histoplasmosis. A, B Disseminated papules and nodules with scale-crust in a patient with AIDS. **C** Numerous yeasts within giant cells as well as dermal macrophages. **D** The organisms are highlighted with a methenamine silver stain (inset). *C, Courtesy Jennifer McNiff, MD; D, Courtesy C. Massone, MD.*

Epidemiology
Blastomycosis due to *B. dermatitidis* is endemic to North America, particularly the Mississippi and Ohio river valleys, Great Lakes region, and southeastern states; within this region, especially in the northern US and Canada, blastomycosis is also occasionally caused by *B. gilchristii*[72]. While all ages and sexes can be affected, adult men are most likely to develop systemic infection, and children are more likely to develop acute pulmonary blastomycosis rather than chronic or cutaneous disease. The soil is an important source of infection, making those who have occupations with frequent outdoor exposure at higher risk than the remainder of the population. Disseminated disease due to *B. helicus* in immunocompromised hosts has been reported in the Western US and Canada[72]. Blastomycosis also rarely occurs in other areas of the world, including Africa, India, and the Middle East; recent investigations suggest that *B. emzantsi* and *B. percusus* underlie most disease in these regions[69,72].

Pathogenesis
The lungs are typically the first site of infection, via inhalation of organisms. In contrast to infections with other dimorphic fungi, secondary cutaneous dissemination is a common occurrence and may even be the first sign of disease. Cutaneous manifestations are sometimes seen in the absence of overt pulmonary disease. Primary cutaneous blastomycosis is uncommon and results from direct inoculation of the skin from trauma, such as in the laboratory.

Clinical features
The most common cutaneous findings are papulopustules and well-demarcated verrucous plaques with scale-crust and pustules within their borders (Fig. 77.30A,B). Central ulceration can occur, and more advanced disease may have an appearance similar to pyoderma gangrenosum. The number of lesions can vary from one to several, and they tend to occur on exposed skin. Healing begins centrally and is followed by cribriform scarring. Mucous membrane involvement is occasionally observed.

Pulmonary infection is subclinical in up to 50% of patients with inhalation blastomycosis. Bone involvement may occur and presents as osteomyelitis with rare extension to muscle; genitourinary disease is uncommon.

Pathology
Histologic examination of skin lesions demonstrates pseudoepitheliomatous hyperplasia, suppurative and granulomatous inflammation, and round yeast forms with characteristic broad-based budding and thick, double-contoured walls. This budding pattern helps to differentiate blastomycosis from other fungal infections. Methenamine silver and PAS staining allow better visualization of the fungi within giant cells and neutrophilic abscesses (Fig. 77.30D). Similar budding yeast forms can be seen in sputum samples.

Differential diagnosis
Cutaneous blastomycosis must be differentiated from other cutaneous infections (e.g. verrucae, folliculitis, nocardiosis, tuberculosis, chromoblastomycosis, those due to other dimorphic fungi), inflammatory dermatoses (e.g. pyoderma gangrenosum, halogenoderma, sarcoidosis) and neoplasms (e.g. squamous cell carcinoma). Lesions of blastomycosis-like pyoderma, an exaggerated vegetative response to a prolonged primary or secondary bacterial infection, can also resemble cutaneous blastomycosis. Current or past residence in an area in which blastomycosis is endemic is a helpful clue.

Identification of characteristic broad-based budding yeast forms in pus by KOH or calcofluor examination is diagnostic of blastomycosis. Either skin tissue or pus should be cultured at both 37°C and 25°C. The former temperature allows identification of the budding yeast form, while the characteristic colonial morphology with white spikes (coremia) is observed at 25°C. Other tests such as blastomycin skin testing and complement fixation testing are not usually helpful, but PCR-based assays are available[73].

Treatment
Blastomycosis, like histoplasmosis, requires systemic treatment with amphotericin B (given at the same doses) when severe or progressive. In mild to moderate non-CNS disease, itraconazole (200–400 mg/day) is the treatment of choice[74]. Fluconazole (400–800 mg/day), voriconazole (especially following amphotericin B for CNS disease), posaconazole, and isavuconazole are alternative medications[69,75]; ketoconazole is no longer routinely used. Occasionally, surgical treatment is indicated.

Coccidioidomycosis

Synonyms: ■ Valley fever ■ Desert rheumatism ■ San Joaquin valley fever ■ California disease

Introduction
Coccidioidomycosis is caused by two dimorphic and highly virulent pathogens that are closely related, *Coccidioides immitis* and *C. posadasii*[76].

Epidemiology
Coccidioidomycosis occurs predominantly in the summer and fall in the southwestern US, northern Mexico, and Central and South America; *C. immitis* is found primarily in California and *C. posadasii* elsewhere within these regions. The arthroconidia of *Coccidioides* spp. are inhaled via dust particles. Primary infection of the respiratory tract shows no sex or age preference, but disseminated disease is more common in Mexicans (5×), African-Americans (25×) and Filipinos (175×). Immunosuppressed states (e.g. HIV infection) and pregnancy also predispose to dissemination; White women are most likely to have more limited disease.



Fig. 77.30 Blastomycosis. A Facial plaque with scale-crust and a border with a granulomatous appearance. **B** Well-demarcated plaques with erosions, central scarring, and black crusting. **C** Verrucous plaque with focal crusting on the medial thigh. **D** Budding yeast forms in the dermis, several of which are within a giant cell (PAS stain). Note the single, broad-based budding (arrow). *A, Courtesy Louis A. Fragola, Jr, MD; B, Courtesy Paul Lucky, MD; C, Courtesy Elizabeth Ergen, MD; D, Courtesy Mary Stone, MD.*

Pathogenesis

C. immitis and C. posadasii are thought to be the most virulent of all fungi[76]. Infectious arthroconidia are inhaled and cause pulmonary infection in the vast majority of people living in endemic areas. The infection is asymptomatic in ~60% of affected individuals, while the remainder develop flu-like symptoms several weeks after exposure[77]. Dissemination to the skin and other organs can occur and depends on host factors (see above). Of note, similar to histoplasmosis, severe disseminated disease has been associated with an impaired interferon-γ response due to mutations in *IFNGR1* or *STAT1* (see Ch. 60). Rarely, primary cutaneous coccidioidomycosis results from direct inoculation of the organism into the skin.

Clinical features

Symptomatic primary inhalation coccidioidomycosis typically presents as a flu-like syndrome with fatigue, anorexia, fever, cough, and pleuritic chest pain. The cutaneous manifestations can occur alone or in combination with the above symptoms and are grouped into four patterns:

- papules, pustules, plaques, abscesses, and sinus tracts favoring the face (Fig. 77.31A,B)
- ulcerations
- toxic erythema presenting as a diffuse macular eruption early in the disease course and sometimes mimicking contact dermatitis
- hypersensitivity reactions such as erythema multiforme and erythema nodosum.

In people living with HIV, the papules may resemble molluscum contagiosum. Bone and meningeal involvement can also occur, presenting as osteomyelitis and meningitis, respectively.

Pathology

Biopsy specimens of specific lesions (types 1 and 2 above) reveal characteristic endospore-containing spherules that measure 30–60 microns when mature (Fig. 77.31C). PAS and methenamine silver stains are helpful in identifying immature spherules. A suppurative granulomatous reaction with histiocytes, lymphocytes, and giant cells typically surrounds the spherules and released endospores.

Differential diagnosis

Coccidioidomycosis can be diagnosed via direct examination (with KOH or calcofluor) and culture of infected tissue, pus, or body fluids. Histologically, larger sporangia (up to 300 microns in diameter) containing numerous endospores can also be seen in mucosal polyps due to *Rhinosporidium seeberi*. When cultured at 25°C or 37°C, *Coccidioides* spp. proliferate quickly (within days) and yield white to tan-brown colonies with varying morphology. Microscopically, septate hyphae that form thick-walled, barrel-shaped arthroconidia are seen at both temperatures. These arthroconidia alternate with thin-walled, vacant cells, which rupture and release the infectious arthroconidia when mature (Fig. 77.32). The infectious hyphal forms produced in culture should be examined with extreme caution, as the examiner is at risk for contracting the disease.

Serologic testing and exoantigen testing are useful in making the diagnosis of coccidioidomycosis. PCR-based assays are also available and *in situ* hybridization has been described[73,78].

Treatment

As in the other dimorphic fungal infections, systemic antifungal therapy is required for severe or disseminated disease. Amphotericin B is the most effective medication, and the intravenous dose for severe disease is 1.0–1.5 mg/kg per day (higher dose for patients with AIDS). The chronic nature of disseminated disease requires prolonged therapy with itraconazole (400 mg/day) or, in the case of meningitis, fluconazole. Voriconazole, posaconazole, and isavuconazole, which have *in vitro* activity against coccidioidomycosis equal or superior to that of itraconazole, have been used successfully (alone or in combination with liposomal amphotericin B) to treat disseminated disease[69]. Ketoconazole is no longer routinely used. Successful use of targeted immunomodulation with dupilumab and interferon-γ in addition to antifungal therapy in a child with refractory disseminated coccidioidomycosis associated with increased interleukin-4 and reduced interferon-γ has been reported[79].

Paracoccidioidomycosis

Synonyms: ■ South American blastomycosis ■ Brazilian blastomycosis

Introduction and epidemiology

Paracoccidioidomycosis is caused by the dimorphic fungus *Paracoccidioides brasiliensis*. It is endemic to the Central and South American countries of Brazil, Argentina, Venezuela, Ecuador, and Colombia.

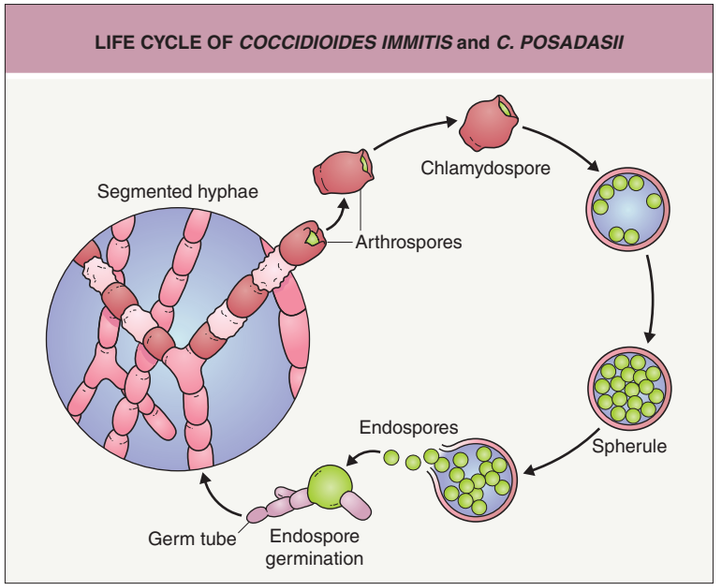


Fig. 77.32 Life cycle of *Coccidioides immitis* and *C. posadasii*.



Fig. 77.31 Coccidioidomycosis. Moist erythematous plaque on the face (**A**) and multiple papules and suppurative nodules on the arm (**B**) in two patients living in the southwestern US. **C** An endospore-containing spherule within a giant cell. *C, Courtesy Jennifer McNiff, MD.*

Pathogenesis
P. brasiliensis is a dimorphic saprophyte that is found in the soil. In most cases, infection occurs via inhalation of the conidia from the environment. Pulmonary disease ensues and can be followed by dissemination to the skin, mucous membranes, gastrointestinal tract, spleen, adrenal glands, and lymph nodes.

Clinical features
Paracoccidioidomycosis has several different clinical presentations with varying prognoses. In many patients, the primary pulmonary disease is subclinical to mild. When progressive disseminated disease occurs, mucocutaneous involvement is commonly seen. Lesions are often painful and ulcerative or verrucous; they are typically found on the face and in the nasal and oral mucosae (Fig. 77.33A,B). The ulcerations are referred to as "moriform stomatitis". Lymphatic spread may occur, resulting in cervical lymphadenopathy.

Another clinical presentation is that of primary mucocutaneous paracoccidioidomycosis. This frequently has an intraoral and perioral distribution due to trauma from chewing contaminated sticks and leaves. Granulomatous lesions are typically seen. Primary cutaneous paracoccidioidomycosis can also occur via direct inoculation of the skin, resulting in the development of a verrucous papule or plaque or cutaneous ulceration.

Pathology
The histologic features of paracoccidioidomycosis resemble those of blastomycosis (see above). Pseudoepitheliomatous hyperplasia is accompanied by suppurative and granulomatous inflammation. Yeast forms are found within and outside of giant cells. Large, thick-walled organisms with multiple narrow-based buds may be seen, leading to an outline that resembles a "mariner's wheel" (Fig. 77.33C).

Differential diagnosis
The differential diagnosis includes mucocutaneous leishmaniasis, granulomatosis with polyangiitis, NK cell lymphoma, and syphilis (endemic and epidemic) (see Table 45.3). Microscopic examination and culture of the organism are essential for diagnosing paracoccidioidomycosis. KOH or calcofluor examination of an appropriate specimen (sputum, dermal scraping, or pus) may reveal round to ovoid cells with narrow-based buds, which are also seen when the organism is cultured at 37°C.

Treatment
There are several effective treatment options for paracoccidioidomycosis, including amphotericin B, systemic azoles, and sulfonamides. Prolonged therapy is generally required. In disseminated disease, systemic therapy with amphotericin B or an azole antifungal is indicated. Itraconazole is a preferred treatment because it provides reasonable efficacy and side-effect profile, as well as low potential for recurrent disease. Treatment with voriconazole or isavuconazole can also be effective. Attempts to modulate the immune system via peptides derived from the *P. brasiliensis* 43 kDa glycoprotein have been described[80].



Fig. 77.33 Paracoccidioidomycosis. Ulcerated plaques on the palate (**A**) and verrucous granulomatous red–brown plaques with crusting involving the perioral region and upper lip (**B**). **C** Dermal histiocytic infiltrate and yeast forms with multiple small, narrow-based buds. The organisms are highlighted with a methenamine silver stain (inset). *A, B, Courtesy Marcia Ramos-e-Silva, MD, PhD; C, Courtesy C. Massone, MD.*

Opportunistic Pathogens

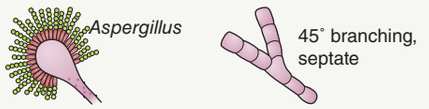
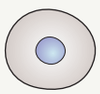
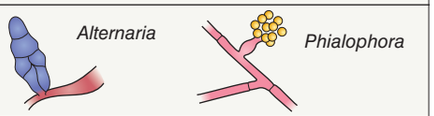
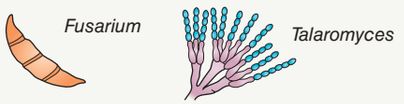
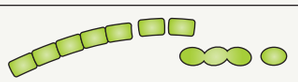
Introduction
Opportunistic mycotic infections may occur in individuals with primary or secondary immunodeficiencies. Worldwide, disseminated candidiasis and aspergillosis are the two most common systemic mycoses in neutropenic patients. Less commonly, mucormycosis, phaeohyphomycosis (due to pigmented fungi; see below), and hyalohyphomycosis (due to non-pigmented [hyaline] fungi; most often fusariosis) are seen (Fig. 77.34). Disseminated histoplasmosis, coccidioidomycosis, cryptococcosis, and talaromycosis are the systemic mycoses seen most commonly in the setting of HIV infection[61]. Opportunistic pathogens are less virulent than true pathogens and impart no specific protective immunity to those infected.

History
Aspergillosis was among the first mycoses recognized, with the initial report of a human case by Sluyter in 1847. In 1855, Kurchenmeister isolated *Mucor* from the lung and described zygomycosis. Benham distinguished cryptococcosis from blastomycosis in the 1930s. *Fusarium* emerged as an opportunistic pathogen in neutropenic oncology patients in the 1990s.

Epidemiology
With the exception of several dimorphic fungi, opportunistic fungal infections occur worldwide and have no geographic predilection. The causative pathogens are commonly found in the environment. For example, *Aspergillus* spp., *Fusarium* spp., and Mucormycetes are soil saprophytes found in decaying vegetation[81]. *Cryptococcus neoformans* can be isolated from avian (especially pigeon) droppings. *T. marneffei* is endemic to Southeast Asia and China, where the reservoir is thought to be in bamboo rats, but imported infections have been reported in the US. Lastly, *Candida* spp. commonly colonize the skin and gastrointestinal tract[1].

Overall, the incidence of opportunistic mycoses increased in conjunction with the greater use of immunosuppressive therapy and the HIV pandemic. In fact, some opportunistic mycoses are considered to be AIDS-defining diseases (see Ch. 78). Notably, the incidence of disseminated candidiasis and aspergillosis has fallen with the use of prophylactic voriconazole in high-risk oncology patients (e.g. neutropenic patients with hematologic malignancies, hematopoietic stem cell transplant

CUTANEOUS FEATURES OF COMMON OPPORTUNISTIC MYCOSES

Mycosis	Common cutaneous presentations	Microscopic appearance
Systemic candidiasis† • *Candida albicans* • *C. tropicalis* (frequent skin lesions) • *C. glabrata, C. krusei* (intrinsic fluconazole resistance)	Firm erythematous papules and nodules, often with a pale center (but possibly hemorrhagic); ecthyma gangrenosum-like lesions	
Aspergillosis† • *Aspergillus flavus* and *fumigatus*	Necrotic papulonodules, subcutaneous nodules (secondary cutaneous); may be associated with an intravenous catheter site (primary cutaneous); disseminated disease usually results from primary pulmonary involvement; galactomannan (more specific, lower sensitivity) and 1,3β-D-glucan (less specific for aspergillosis) serum assays can be used to screen high-risk patients	
Mucormycosis† • *Mucor* • *Rhizopus* • *Lichtheimia* (formerly *Absidia*)	Ecthyma gangrenosum-like lesions, cellulitis, facial edema (commonly unilateral due to contiguous spread of sino-orbital disease), necrotic papulonodules, plaques, large hemorrhagic crusts on the face; may be associated with an intravenous catheter site (primary cutaneous)	
Cryptococcosis** • *Cryptococcus*	Ulceration, cellulitis, molluscum contagiosum-like lesions; assays to detect cryptococcal antigens in blood or CSF are available	
Phaeohyphomycosis* • *Alternaria* • *Exophiala* • *Phialophora*	Subcutaneous cysts, ulcerated plaques, hemorrhagic pustules, necrotic papulonodules	
Hyalohyphomycosis* • *Fusarium* • *Talaromyces (Penicillium)*** • *Paecilomyces*	Umbilicated or necrotic papules, pustules, abscesses, cellulitis, subcutaneous nodules; *Fusarium* infection can be associated with a periungual focus	
Trichosporonosis • *Trichosporon* spp.	Papulovesicles, purpuric papules, necrotic papulonodules	

* Less common
** Especially in the setting of AIDS
† With the use of prophylactic voriconazole, posaconazole, and isavuconazole in high-risk oncology patients (e.g. neutropenic patients with hematologic malignancies, hematopoietic stem cell transplant recipients), the incidences of disseminated candidiasis, systemic aspergillosis, and mucormycosis (posaconazole and isavuconazole) have declined in these individuals

Fig. 77.34 Cutaneous features of common opportunistic mycoses. While the lesions of opportunistic fungal infections seem nonspecific, certain presentations may be more likely associated with a particular species.

recipients). However, voriconazole lacks activity against Mucormycetes, which are covered by newer antifungals (e.g. posaconazole, isavuconazole).

Pathogenesis

Aspergillosis is an opportunistic mycosis that is caused by fungi in the genus *Aspergillus*, most often *A. fumigatus* and *A. flavus*. Burns, sites of trauma, surgical wounds, intravenous catheters (Fig. 77.35A), and macerated skin underlying occlusive dressings typically serve as portals of entry in primary cutaneous aspergillosis[82]. The risk of dissemination is significant in immunocompromised individuals. In *secondary* cutaneous aspergillosis (a more common form), the conidia are inhaled, producing a primary lung infection that is followed by dissemination to the skin. Immunosuppression – particularly neutropenia plus chronic use of corticosteroids and sometimes late-stage AIDS – is a major risk factor for the development of invasive or disseminated aspergillosis.

Fungi in the subphylum Mucoromycotina, class Mucormycetes (also known as Mucoromycetes; formerly Zygomycetes), and order Mucorales cause mucormycosis, which was previously called zygomycosis. The genera most commonly responsible are *Rhizopus, Mucor, Rhizomucor*, and *Lichtheimia* (formerly *Absidia*)[83]. Risk factors include poorly controlled diabetes mellitus as well as other forms of immunosuppression, especially when associated with neutropenia. *Primary* infections can be rhino-orbito-cerebral, pulmonary, or gastrointestinal as well as cutaneous via direct inoculation of the skin in settings similar to those of primary cutaneous aspergillosis; hematogenous dissemination may occur in immunocompromised hosts. Skin lesions that arise from contiguous spread (e.g. from the sinuses) or hematogenous dissemination are referred to as *secondary* cutaneous mucormycosis. Aspergillosis and mucormycosis are both characterized by necrotic skin lesions due to the angioinvasive nature of these organisms. Rapidly progressive mucormycosis with a mortality rate of up to ~30% has been described in association with SARS-CoV-2 infection, most often rhino-orbital(-cerebral) disease in patients with diabetes mellitus who recently received systemic corticosteroids[84].

Cryptococcus neoformans represents the predominant pathogen in cryptococcosis, which is known for producing meningitis in immunocompromised patients. In contrast, symptomatic infections with the *C. gattii* complex more commonly develop in otherwise healthy individuals and have led to outbreaks of life-threatening pneumonia in the Pacific Northwest[85]. Both of these organisms, which are present in the soil and bird droppings (pigeons for *C. neoformans*), result in a primary pulmonary infection via inhalation. Subsequent dissemination to the CNS, bone, and skin may occur, especially with *C. neoformans* infections in people living with HIV and other immunocompromised hosts. Resultant skin disease is referred to as *secondary* cutaneous cryptococcosis. *Primary* cutaneous cryptococcosis can also occur, but the diagnosis is made after a systemic evaluation has been performed. The use of antiretroviral therapy (ART) in people living with HIV has led to a dramatic decrease in the incidence of cryptococcosis.

Yeasts belonging to the genus *Candida* are responsible for candidiasis, which can present as a mucocutaneous condition (see above) or, in immunocompromised hosts, a disseminated infection that often originates from the gastrointestinal tract. The ability of *Candida* to



Fig. 77.35 Clinical findings of opportunistic fungal infections in immunocompromised hosts. Primary cutaneous aspergillosis characterized by hyperpigmented plaques with brown–black scale-crusts at the site of intravenous catheters on the arm (**A**); firm pink papulonodule due to disseminated candidiasis (**B**); erythematous papulonodules with central purpura, vesiculation and/or crusting in a leukemic patient with disseminated fusariosis (**C**); hemorrhagic vesicle representing a *Fusarium solani* septic embolus in a patient with acute lymphoblastic leukemia (**D**); necrotic hemorrhagic bulla due to embolus of *Aspergillus flavus* (**E**); cellulitis with large areas of necrosis due to *Rhizopus* (**F**) and cryptococcosis (**G**); cryptococcal cellulitis mimicking bacterial cellulitis (**H**); disseminated cryptococcosis presenting with crusted lesion(s) resembling molluscum contagiosum (**I**) and a basal cell carcinoma (**J**); cryptococcal cellulitis (**K**); numerous papules and nodules with central umbilication and crusting in disseminated *Talaromyces (Penicillium) marneffei* infection (**L**). *D, Courtesy Edward Cowen, MD; H, Courtesy Catherine Baker, MD; L, Courtesy Evangeline Handog, MD and the Dermatology Department, Research Institute for Tropical Medicine.*

exist in the form of pseudohyphae in tissue and blastoconidia in the bloodstream allows for adaptation and evasion of host defenses[86]. Neutropenia, especially in patients who have received prolonged courses of corticosteroids, sets the stage for disseminated candidiasis; patients are usually also receiving broad-spectrum antibiotics. *C. albicans* is the most common species, but *C. tropicalis* is often implicated in fungemia in patients with leukemia. *C. auris* has been detected in ~50 countries, with increased frequency since the SARS-CoV-2 pandemic and a tendency to colonize the skin, medical equipment, and other surfaces. This organism presents a global health threat due to multidrug resistance, high transmissibility, and challenges in laboratory identification, with a mortality rate of ~20%–60% for invasive infection[87].

Hyalohyphomycosis includes infections with *Fusarium, Talaromyces*, and *Paecilomyces* spp. (see Fig. 77.34). These molds are found in the soil and throughout the environment and can cause disseminated infections in immunocompromised hosts. Disseminated infections with *Fusarium*, an angioinvasive organism, most often affect neutropenic oncology patients and may originate from a periungual focus (e.g. paronychia, onychomycosis). *Talaromyces marneffei* is a dimorphic fungus, and people living with HIV are particularly at risk.

Clinical features

All of the opportunistic mycoses can present with several different types of cutaneous lesions (see Fig. 77.34). Skin findings range from firm papules (Fig. 77. 35B) and purpuric or necrotic papulonodules (Fig. 77.35C) to hemorrhagic bullae (Fig. 77.35D,E) and ulcers. Subcutaneous nodules and cellulitis, often with areas of necrosis, can also be seen (Fig. 77.35F,G,H,K).

In disseminated aspergillosis, the CNS, kidneys, and heart (in addition to the lungs) are often involved in severe widespread disease. The prognosis is poor but improves when the patient is no longer neutropenic or corticosteroids are discontinued. Secondary cutaneous mucormycosis due to an underlying sinus infection may initially present with subtle unilateral facial swelling and mild erythema, while advanced disease is characterized by large areas of necrosis covered by a thick hemorrhagic crust.

Secondary cutaneous cryptococcosis is associated with a poor overall prognosis, with a mortality rate of up to 80% if left untreated[88]. Findings range from papulonodules to cellulitis and panniculitis to necrotic ulcers and abscesses (Fig. 77.35H,K); they may also resemble lesions of molluscum contagiosum, herpes viral infections, or basal cell carcinoma (Fig. 77.35I,J)[89]. Approximately 15% of patients with systemic cryptococcosis have skin lesions, and no predictable body distribution has been identified[90].

Cutaneous lesions of disseminated candidiasis frequently present as firm pink papules or nodules (see Fig. 77.35B) on the trunk and extremities. The lesions often have a pale center but may be purpuric in patients with thrombocytopenia. Other presentations include ecthyma gangrenosum-like lesions (hemorrhagic bulla followed by a necrotic eschar; see Fig. 77.22H), pustules, abscesses, and purpura (in thrombocytopenic patients). While *C. albicans* is the most commonly associated species, *C. tropicalis* is more likely to produce cutaneous lesions. Systemic sites of involvement include the liver, spleen, muscle, kidney, retina, and heart valves. A sepsis-like syndrome may occur, with tachycardia, hypotension, dyspnea, and high fevers.

Like histoplasmosis, *T. marneffei* typically infects the liver, spleen, and lymph nodes. The skin may be involved with umbilicated papules that resemble molluscum contagiosum, necrotic nodules, and acneiform lesions. The most common sites are the face (particularly the forehead), arms, and trunk (Fig. 77.35L). When mucosal surfaces are involved, ulcers and papules are seen; prominent lymphadenopathy is often present.

Skin lesions develop in ~75% of patients with disseminated fusariosis, typically presenting as targetoid erythematous, ecthyma gangrenosum-like, or purpuric nodular lesions in a widespread, scattered distribution (see Fig. 77.35C). Affected individuals often have high fevers and severe myalgias.

Pathology

Histologic examination of lesions of cutaneous aspergillosis demonstrates 45° dichotomous branching of hyaline, septate hyphae that are best demonstrated with methenamine silver or PAS staining (Fig. 77.36A). Suppurative and granulomatous inflammation and/or necrosis may be observed.

In mucormycosis, there are highly characteristic broad, non-septate hyphae that have 90° branching and have been likened to ribbons (Fig. 77.36B). PAS staining may be helpful. Suppuration and necrosis, as well as blood vessel invasion by the fungi, are often seen.

Histologic findings in cryptococcosis are described as either gelatinous with numerous organisms and little inflammation, or granulomatous with fewer organisms, more inflammation, and little necrosis. While a PAS stain highlights the central yeast forms (Fig. 77.36C), mucicarmine or Alcian blue is used to visualize the characteristic capsule. India ink preparations, e.g. of CSF or dermal scrapings, also demonstrate the presence of the capsule. The wider the capsule and the more severe the immunocompromised state, the less the inflammation. Of note, cryptococcoid Sweet syndrome can mimic cryptococcosis both clinically and histologically, with cytoplasmic vacuolization of inflammatory cells resembling the capsule of *Cryptococcus* organisms and acellular basophilic bodies mimicking the yeast itself.

In disseminated candidiasis, budding yeast and pseudohyphae are seen in the dermis, rather than in the stratum corneum as in mucocutaneous candidiasis.

T. marneffei has microscopic characteristics similar to histoplasmosis. The small organisms are numerous and found within macrophages and giant cells (see Table 77.18). The histologic findings of fusariosis are similar to those of aspergillosis, with acute-branching, septate hyphae, angioinvasion, necrosis, and a variable granulomatous infiltrate.

Differential diagnosis

Microscopic examination of dermal scrapings (using KOH or calcofluor), histologic analysis, and culture of skin tissue are used to diagnose opportunistic fungal infections. The former studies are important considering that many of these organisms can also represent culture contaminants[91]. The clinical differential diagnosis ranges from folliculitis and molluscum contagiosum to cellulitis and ecthyma gangrenosum due to a disseminated bacterial infection. When there are necrotic eschars, the possibility of herpes zoster or vasculitis may be raised (see Fig. 77.34).

Macroscopically, cultures of *Aspergillus flavus* and *A. fumigatus* have been likened to "south sea islands" because the central portion is khaki

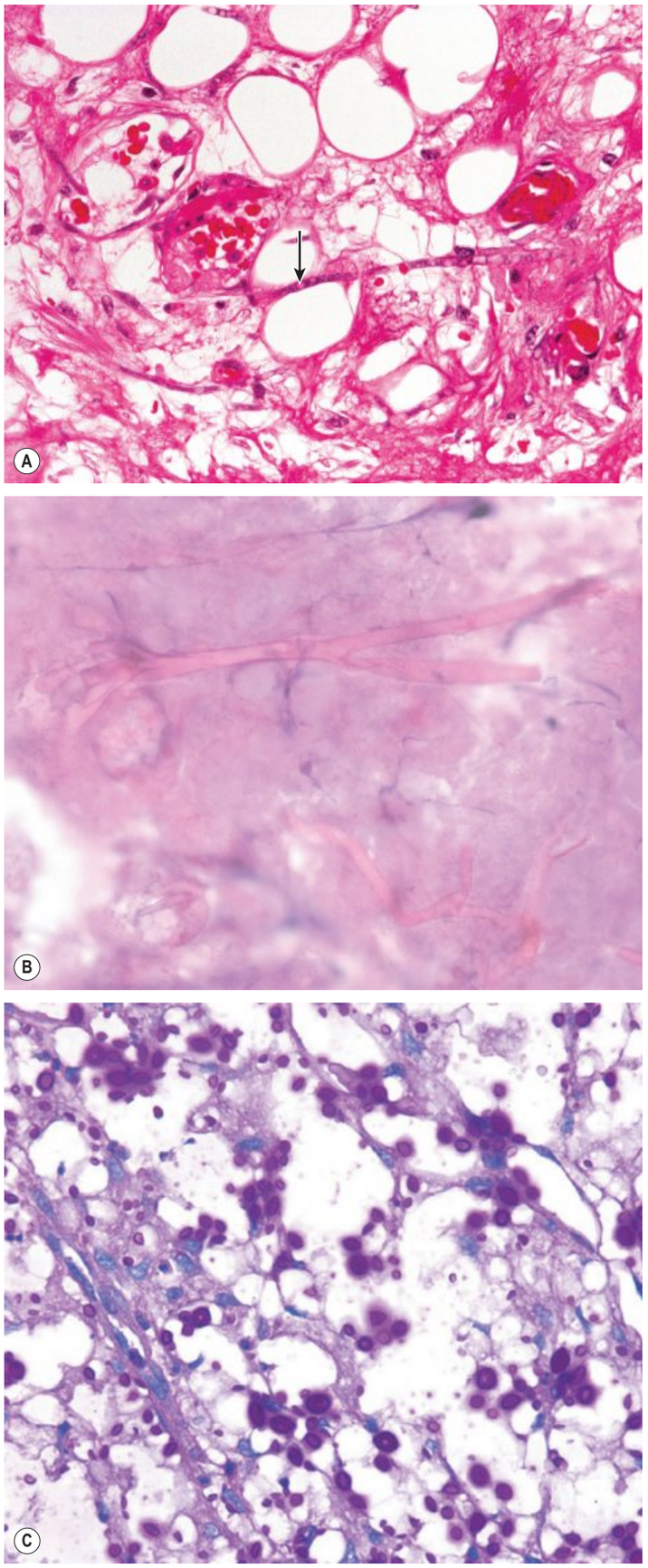


Fig. 77.36 Histologic findings of opportunistic fungal infections in immunocompromised hosts. A Septate hyphae (arrow) within necrotic skin from a patient with disseminated aspergillosis. **B** Ribbon-like, non-septate *Rhizopus* hyphae in a "touch" preparation of dermal scrapings from the base of a necrotic bulla. **C** Numerous dermal yeast forms with gelatinous capsules in secondary cutaneous cryptococcosis (PAS stain). *A, Courtesy Lorenzo Cerroni, MD; B, Courtesy Jean L. Bolognia, MD; C, Courtesy Athanasia Syrengelas, MD, PhD.*

green (*flavus*) or blue–green (*fumigatus*) with a rim of white to yellow color. Microscopically, spherical "heads" with conidia forming on the exterior are seen. In zygomycoses, culture reveals fast-growing "woolly" colonies in most instances. Microscopically, rhizoids, round sporangia, and sporangiospores (asexual spores formed within sporangia) are seen (see Fig. 77.34)[51]. Culture of *Cryptococcus neoformans* yields a cream-colored colony that is similar in appearance to *Candida* colonies. On birdseed agar, the *C. neoformans* colony becomes brown. Because *T. marneffei* is a dimorphic fungus, at 25°C the mold form is seen with a diffusible red pigment, and at 37°C the colony appears as a yeast.

Antibodies against the capsule can be detected in cryptococcosis, and high titers herald a poor prognosis. Serum assays for components of the fungal cell wall, such as 1,3 β-D-glucan (detects a variety of fungi, including *Aspergillus* and *Fusarium*) and galactomannan (relatively specific for *Aspergillus* but somewhat less sensitive), have been used to screen high-risk patients for early evidence of an invasive fungal infection. PCR-based assays have also become available for detection of many opportunistic fungi (especially *Aspergillus*)[92,93].

Treatment

Prevention of opportunistic mycoses in high-risk patients can be aided by reduced exposure to environments such as construction sites and the use of ventilation systems. Prophylaxis with systemic antifungals (e.g. fluconazole, posaconazole, voriconazole, isavuconazole) is commonly administered to patients receiving myelosuppressive chemotherapy and to hematopoietic stem cell transplant recipients, both before and during periods of neutropenia. Even in the absence of neutropenia, individuals on chronic high-dose systemic corticosteroids (e.g. with chronic GVHD) are at significant risk for opportunistic fungal infections and represent another group now receiving prophylaxis. In the past, a febrile neutropenic patient unresponsive to systemic broad-spectrum antibiotics was empirically begun on amphotericin B. Nowadays, that patient might receive voriconazole, posaconazole, isavuconazole, or one of the echinocandins (e.g. caspofungin; Table 77.19; see Ch. 127). Of note, voriconazole is a triazole that has activity against *Aspergillus* and *Fusarium* as well as *Candida* (but not Mucormycetes); it causes photosensitivity associated with an increased risk of squamous cell carcinoma and melanoma and, like itraconazole, drug–drug interactions due to inhibition of cytochrome P450. Posaconazole and isavuconazole, triazoles with a similar range of activity (except for less *Fusarium* coverage with isavuconazole) that also cover Mucormycetes, are used for both treatment and prophylaxis of opportunistic fungal infections.

Once an opportunistic mycosis is diagnosed, prompt treatment is essential. Primary cutaneous infections with opportunistic molds, if localized, can be surgically excised, followed by administration of oral antifungals. Disseminated infections carry a poor prognosis and are frequently fatal, particularly when treatment is delayed or ineffective. Amphotericin B (including lipid formulations) had been the standard treatment for several decades. However, voriconazole has proven superior for invasive fungal infections due to *Aspergillus*, and, in the case of disseminated candidiasis, caspofungin can also be administered[94] (see Ch. 127). For systemic infections due to other opportunistic fungi, amphotericin B is sometimes still employed, but voriconazole has activity against *Fusarium*, while posaconazole has activity against both *Fusarium* and Mucormycetes and isavuconazole is approved for the treatment of invasive mucormycosis.

In addition to amphotericin B and several triazoles, terbinafine may have activity against *T. marneffei*, which has a high mortality rate if inadequately treated. Unfortunately, recurrence is likely unless treatment is continued indefinitely[95].

Phaeohyphomycosis

Introduction and history

Phaeohyphomycosis refers to infections with a group of dematiaceous fungi (i.e. pigmented due to melanin in the cell wall) that produce distinct brown to black hyphae in tissue rather than Medlar bodies or grains (see chromoblastomycosis and eumycotic mycetoma above). Although systemic disease can occur, particularly spread to the CNS from a primary lung source, this section will focus on the other three forms of phaeohyphomycosis – superficial, cutaneous, and subcutaneous.

Ajello and colleagues coined the term "phaeohyphomycosis" in 1974. Initially, the list of causative pathogens was limited, but it is now extensive and continues to lengthen[11].

Epidemiology

Because phaeohyphomycosis encompasses infections caused by many fungi, the epidemiology is complex. All age groups and both sexes may be affected. There may be a slightly higher incidence in men due to increased environmental and occupational exposure. The culprit fungi in phaeohyphomycosis are found in plants and soil, making individuals with certain occupations, activities, and cultural habits (such as not wearing protective footwear) at higher risk of infection.

Pathogenesis

Superficial phaeohyphomycosis includes tinea nigra and black piedra (see above), while cutaneous phaeohyphomycosis includes infections of the hands, feet, and nails that mimic tinea infections in the same locations (e.g. *N. hyalinum*, *N. dimidiatum*; see Table 77.11). Trauma is typically the cause of subcutaneous phaeohyphomycosis. Both immunocompetent and immunocompromised hosts may acquire this disease. The immune status of the patient has a significant effect on the severity and the likelihood for disseminated disease; *Cladophialophora bantiana* is most commonly associated with CNS disease[88]. Secondary cutaneous phaeohyphomycosis occurs when dematiaceous fungi spread from other sites to the skin.

Clinical features

The clinical presentation of cutaneous phaeohyphomycosis is similar to that of dermatophyte infections of the hands, feet, or nails. Subcutaneous phaeohyphomycosis most commonly presents as a nodule or plaque in regions of the body that are prone to trauma (Fig. 77.37A). The course is usually chronic, with slowly progressive disease. Clinical manifestations of disseminated disease include nonspecific skin lesions (papules, plaques, nodules) and signs of cerebral involvement.

TREATMENT OF OPPORTUNISTIC MYCOSES

	Aspergillosis	Mucormycosis	Cryptococcosis	Candidiasis	*T. marneffei* infection	Fusariosis	Forms of administration
Amphotericin B	+	+	+	+	+	+	iv
Itraconazole (200–400 mg/day)	+	–	+	+	+	–	po, iv
Fluconazole	–	–	+	+	–	–	po, iv
Voriconazole	+	–	+	+	+	+	po, iv
Posaconazole	+	+	+	+	+	+	po
Isavuconazole	+	+	+	+	–	–	po, iv
Caspofungin	+	–	–	+	–	–	iv
Micafungin	+	–	–	+	–	–	iv
Anidulafungin	+	–	–	+	–	–	iv

Table 77.19 Treatment of opportunistic mycoses. Appropriate selection of therapy for opportunistic infections is essential, given the likelihood of rapid, widespread dissemination and high mortality rates[67]. iv, intravenously; po, orally.



Fig. 77.37 Phaeohyphomycosis – clinical and histopathologic findings. **A** Purpuric plaque with central necrosis and surrounding erythema in a patient with subcutaneous phaeohyphomycosis due to *Exerohilum rostratum*. **B** PAS-positive hyphae with focal pigmentation within a phaeohyphomycotic cyst. *B, Courtesy Luis Requena, MD.*

Pathology

Histologic examination of cutaneous and subcutaneous phaeohyphomycosis reveals pigmented hyphae in the stratum corneum and dermis/subcutis, respectively (Fig. 77.37B). In the latter, there are cyst-like abscesses that can have a fibrous capsule, hence the term "phaeomycotic cysts". Occasionally, implanted material (e.g. a splinter) may also be observed.

Differential diagnosis

For the subcutaneous and systemic forms, the differential diagnosis may include a foreign body granuloma, cutaneous leishmaniasis, chromoblastomycosis, and dimorphic fungal infections. KOH examination (superficial and cutaneous types), culture (all types), and histopathology (usually just subcutaneous and systemic types) allow the diagnosis to be made. Determination of genera and species requires fungal culture, but histopathology is useful in determining the extent of invasion and in differentiating causative pathogens from contaminants in culture specimens. *Exophiala jeanselmei* and *E. dermatitidis* are the organisms most commonly isolated from subcutaneous phaeohyphomycosis.

Treatment

Subcutaneous disease is surgically excised, if possible[96]; complete surgical excision is usually curative. Systemic disease due to dematiaceous fungi continues to be a therapeutic dilemma, as it is difficult to eliminate with oral antifungals alone. Nevertheless, itraconazole, given at a dose of 200 mg twice daily for a prolonged course (>12 months), has some efficacy for the non-surgical treatment of phaeohyphomycosis. Close follow-up is required and includes repeat cultures and histologic analyses of affected sites. Additional treatments for systemic disease include voriconazole, posaconazole, amphotericin B, and flucytosine.

Pneumocystis

In the past, *Pneumocystis jirovecii* (formerly referred to as *Pneumocystis carinii*) was classified as a protozoan. Currently, it is considered to be a fungus, based on genetic and biochemical analyses. This opportunistic infection occurs in individuals who are immunocompromised, including those with AIDS. The lungs are the most common site of infection (pneumonia), but, on occasion (<3% of patients), there is dissemination to other sites such as the liver, spleen, and lymph nodes.

Cutaneous involvement is rare and is characterized by erythematous or skin-colored, non-tender papules or nodules[97]; there may be associated ulceration. The external ear (including the auditory canal) represents the most commonly reported site of involvement. Histologically, a diffuse infiltrate of foamy cells is seen within the dermis. Special stains (e.g. methenamine silver, Giemsa, Steiner) can be used to highlight the organisms, as can monoclonal antibodies; detection of *P. jirovecii* is also possible via PCR.

The most common treatment for pneumocystosis is trimethoprim–sulfamethoxazole (TMP-SMX). Additional therapies include parenteral pentamidine and oral atovaquone. Prophylaxis in the setting of immunosuppression usually consists of oral TMP-SMX or, less often, aerosolized pentamidine, oral dapsone, or oral atovaquone. Prophylaxis is important for dermatologic patients receiving systemic corticosteroids combined with immunosuppressive agents such as azathioprine and cyclophosphamide.

Additional figures available in our eBook (see inside front cover for access code).

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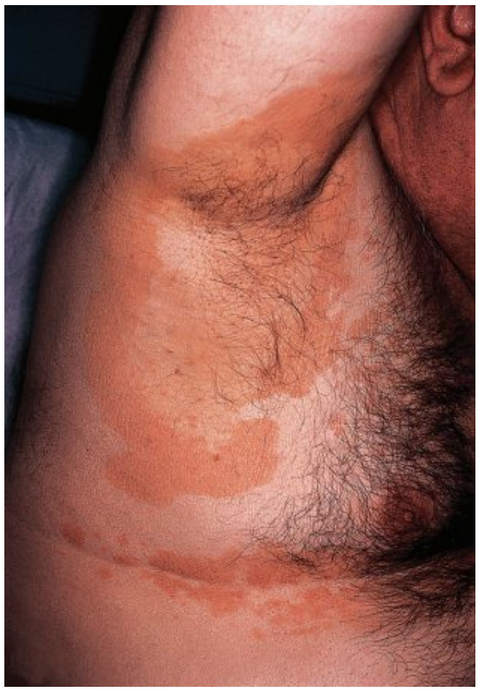
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eFig. 77.1 Tinea nigra. Two sharply demarcated brown macules on the palm.



eFig. 77.3 Tinea versicolor. Pink to pink–orange thin plaques that are discrete on the abdomen and antecubital fossa and confluent on the chest. *Courtesy Kalman Watsky, MD.*



eFig. 77.2 Hyperpigmented variant of tinea versicolor. *Courtesy Kalman Watsky, MD.*



eFig. 77.4 Tinea versicolor with follicular accentuation. Hyperpigmented, shiny 2–3 mm bland follicular papules with inducible scale. *Courtesy Robert Brodell, MD.*





eFig. 77.5 Interdigital tinea pedis. Whitish maceration between the toes.
A, Courtesy Jean L. Bolognia, MD; B, Courtesy Robert Brodell, MD.



eFig. 77.6 Tinea pedis. Note the elevated scaly border. *Courtesy Elizabeth Ergen, MD.*



eFig. 77.7 Tinea manuum. Diffuse scaling of the palms with accentuation in the creases. *Courtesy Kalman Watsky, MD.*



eFig. 77.8 Tinea cruris with extension onto the lower abdomen. *Courtesy Kalman Watsky, MD.*



eFig. 77.9 Tinea cruris. Note the polycyclic and arcuate raised border. *Courtesy Julie V. Schaffer, MD.*



eFig. 77.11 Tinea "incognito" due to use of topical corticosteroids. Note the discontinuous concentric rings with variable scaling. *Courtesy Julie V. Schaffer, MD.*



eFig. 77.10 Tinea incognito. Use of potent topical corticosteroids for the presumed diagnosis of dermatitis is a common clinical scenario. Numerous hyphae are usually seen on KOH examination. *Courtesy Kalman Watsky, MD.*



eFig. 77.12 Tinea corporis. Large, expanding area with multiple annular and serpiginous lesions. *Courtesy Antonio Torrelo, MD.*



eFig. 77.13 Tinea corporis. Almost confluent involvement on the neck with well-demarcated, scaly borders.



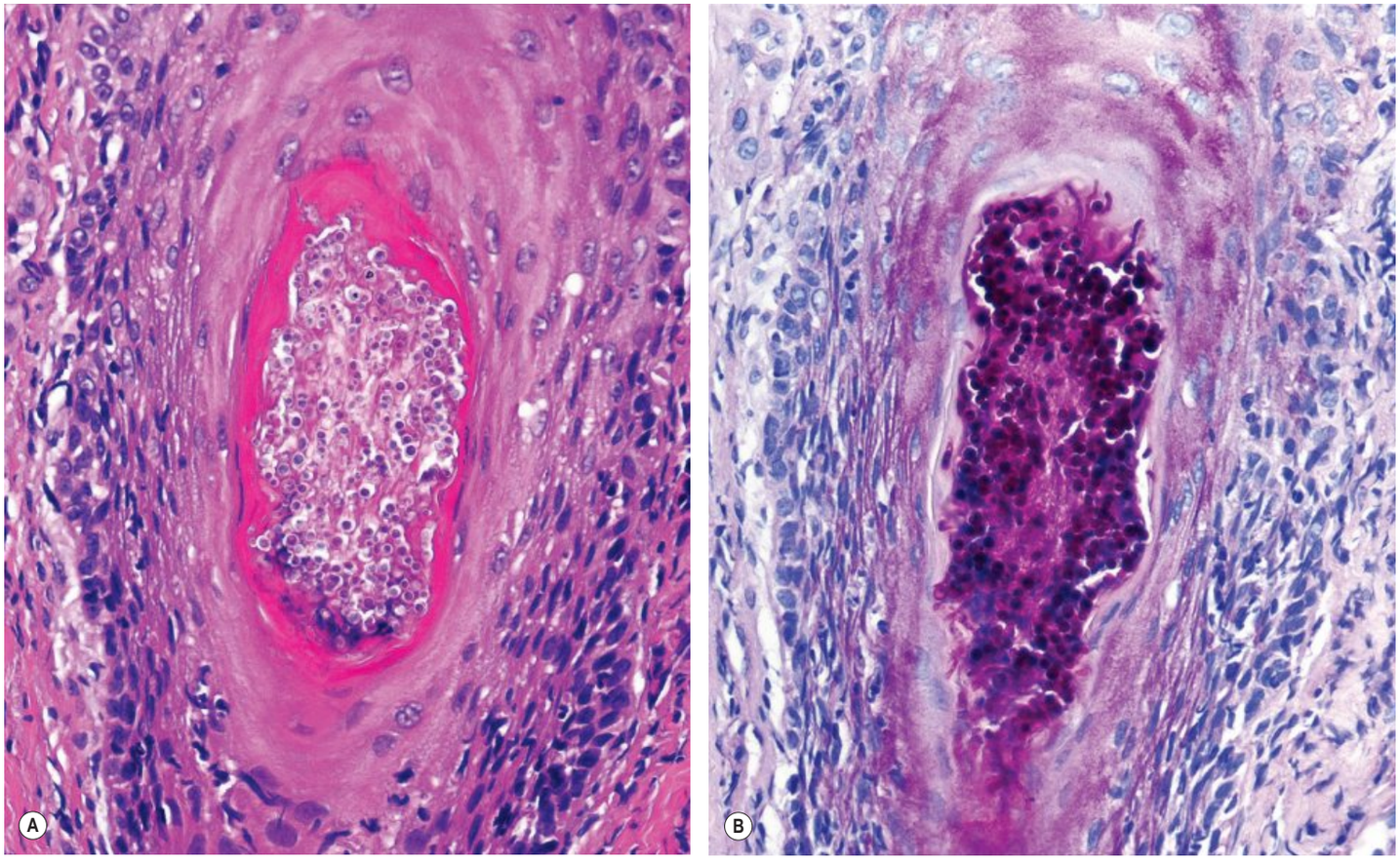
eFig. 77.14 Nodular perifolliculitis (Majocchi granuloma). Perifollicular inflammation and pustules on the arm due to *Trichophyton rubrum*.



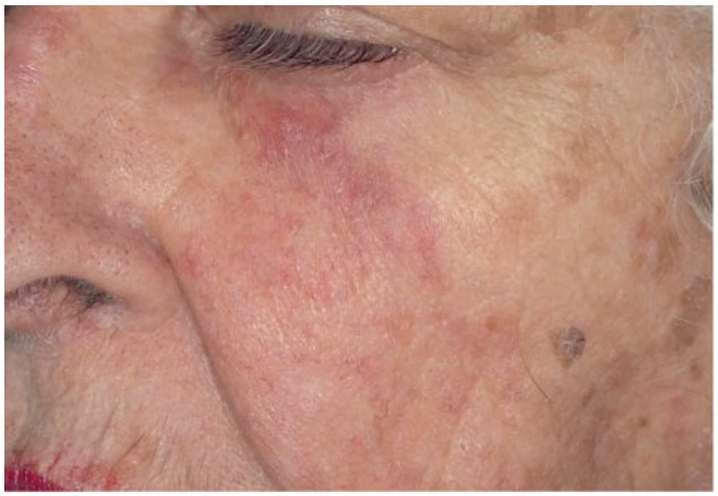
eFig. 77.15 Nodular perifolliculitis (Majocchi granuloma). Perifollicular inflammation and pustules on the buttocks due to *Trichophyton rubrum*.



eFig. 77.17 Tinea cruris and corporis. *Courtesy Kalman Watsky, MD.*



eFig. 77.16 Nodular perifolliculitis (Majocchi granuloma) – histopathologic features. A Hematoxylin and eosin stain. **B** Periodic acid Schiff (PAS) stain. *Courtesy Luis Requena, MD.*



eFig. 77.18 Tinea faciei. Serpiginous lesion with minimal scale on the upper cheek of an older woman. *Courtesy Jean L. Bolognia, MD*



eFig. 77.21 Tinea faciei. The clues to the diagnosis include the pustule on the right cheek and the scale within the active border on the nose. *Courtesy Kalman Watsky, MD*.



eFig. 77.19 Tinea faciei. Annular and arcuate plaques on the cheek and around the mouth of a child. *Courtesy Antonio Torrelo, MD*.



eFig. 77.22 Tinea capitis due to *Trichophyton tonsurans* resembling seborrheic dermatitis. *Courtesy Julie V. Schaffer, MD*.



eFig. 77.20 Tinea faciei. Large annular plaque with pustules in a young child. *Courtesy Antonio Torrelo, MD*.



eFig. 77.23 Tinea unguium, distal/lateral subungual variant.



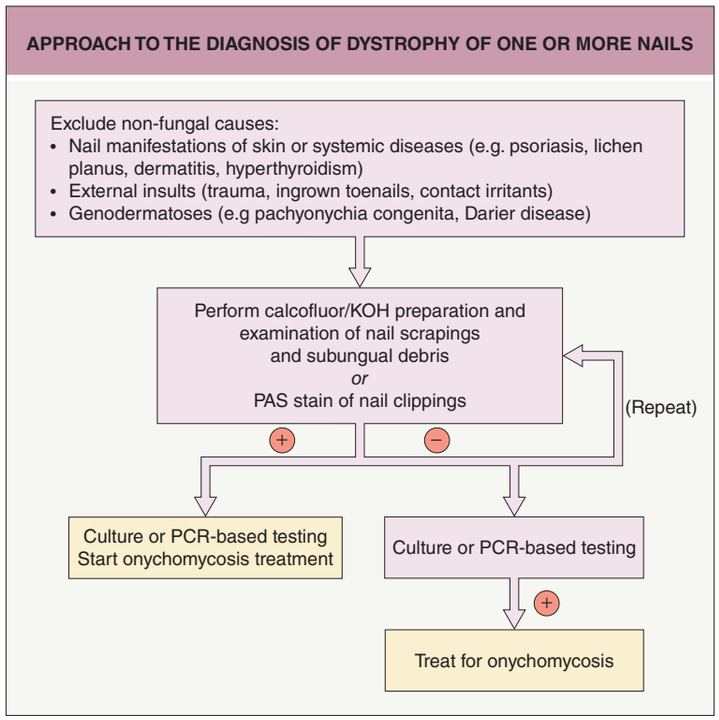
eFig. 77.24 Tinea unguium, white proximal subungual variant.



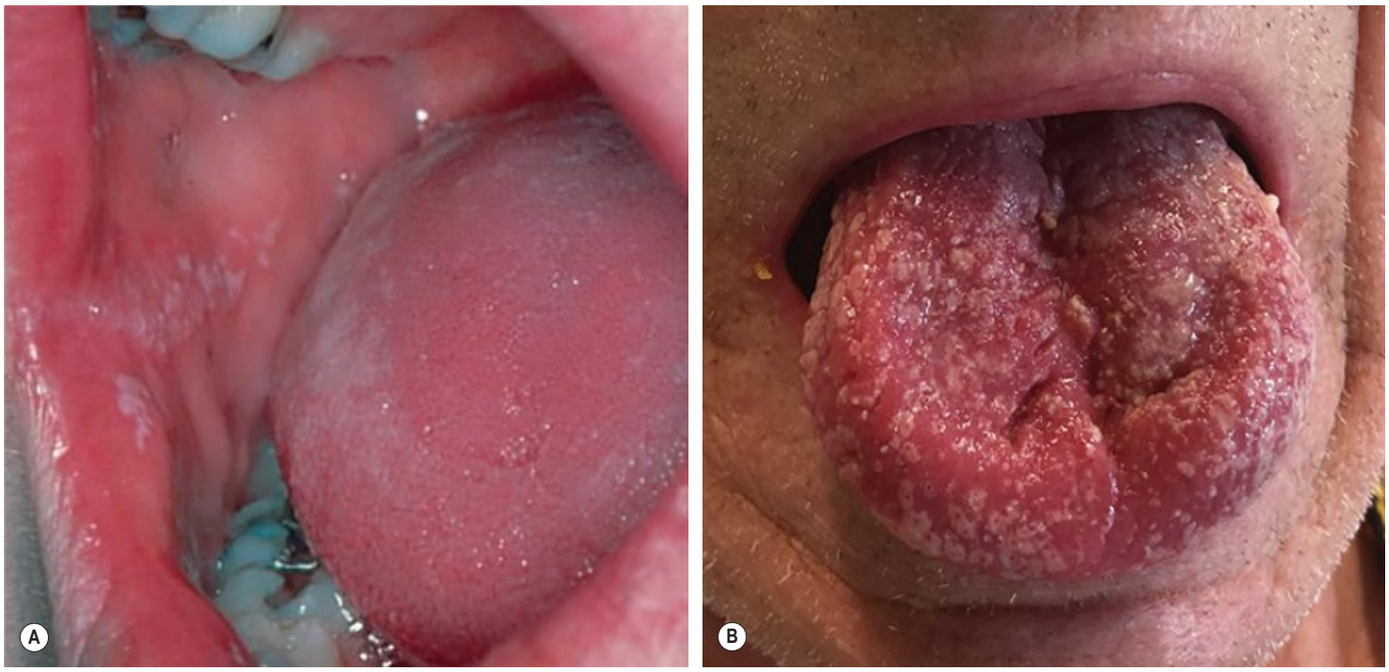
eFig. 77.25 Tinea unguium, striate form of superficial white variant.



eFig. 77.26 Tinea unguium and nodular perifolliculitis in immunosuppressed patient.



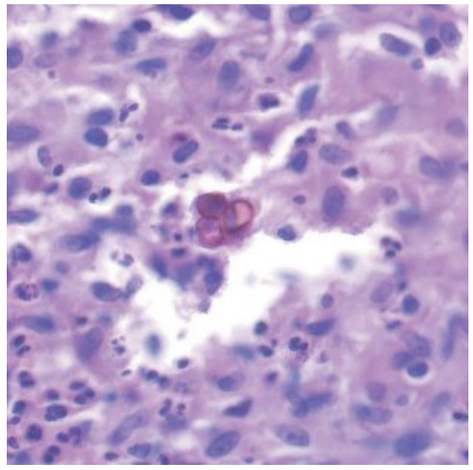
eFig. 77.27 Approach to the diagnosis of dystrophy of one or more nails. An organized approach is essential in correctly and efficiently diagnosing onychomycosis.



eFig. 77.28 Mucocutaneous candidiasis. A Thrush with "cottage cheese"-like exudate on the buccal mucosa. **B** Candidal glossitis. *A, Courtesy Judit Stenn, MD; B, Courtesy Kalman Watsky, MD.*



eFig. 77.29 Candidiasis in the diaper area. Involvement of the inguinal crease with satellite papules and extension onto the scrotum. *Courtesy Julie V. Schaffer, MD.*



eFig. 77.30 Chromoblastomycosis. Brown-colored sclerotic body within a mixed granulomatous and neutrophilic dermal infiltrate. *Courtesy Jennifer McNiff, MD.*



eFig. 77.31 Mucormycosis. Erythematous papulonodule with central necrosis due to *Mucor circinelloides*. *Courtesy Julie V. Schaffer, MD.*



eFig. 77.32 Mucormycosis. Purpuric nodule with central necrosis.



eFig. 77.33 Disseminated cryptococcosis presenting as crusted molluscum contagiosum-like lesions. *Courtesy Athanasia Syrengelas, MD PhD.*



eFig. 77.34 Cryptococcal cellulitis with areas of necrosis. *Courtesy Kalman Watsky, MD.*



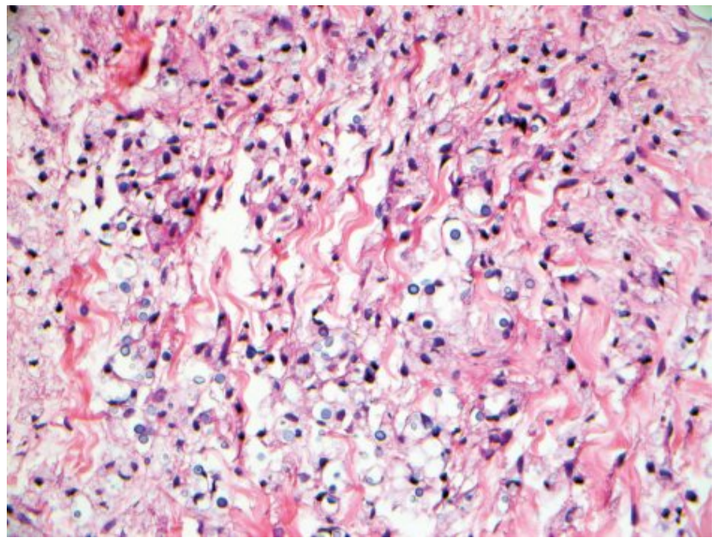
eFig. 77.35 Disseminated cryptococcosis presenting as purpuric papules.



eFig. 77.36 Erosive cryptococcal cellulitis.



eFig. 77.37 Disseminated *Talaromyces (Penicillium) marneffei* infection. The papules and nodules exhibit central umbilication and crusting. *Courtesy Evangeline Handog, MD and the Dermatology Department, Research Institute for Tropical Medicine.*



eFig. 77.39 Histologic findings of cryptococcosis. Numerous yeast forms with gelatinous capsules in the subcutis.



eFig. 77.38 Mycetoma. *Courtesy Regional Training Center.*

78 Cutaneous Manifestations of HIV Infection

Roy K.W. Chan, Martin T.W. Chio and Hong Yi Koh

Key features

- A broad spectrum of infectious, inflammatory, and neoplastic skin conditions may occur in the setting of HIV-induced immune dysfunction
- The cutaneous findings often correlate with immune status, and knowing the viral load and $CD4^+$ T cell count can help to generate a more focused differential diagnosis
- The possibility of HIV infection should be considered when patients present with severe, unusual, and treatment-resistant skin conditions; examples include giant molluscum contagiosum, extensive seborrheic dermatitis, and refractory herpes simplex virus infection
- Following initiation of antiretroviral therapy (ART), skin disorders such as herpes zoster and *Mycobacterium avium* complex infection may become clinically apparent or worsen when the immune status improves, a phenomenon known as the immune reconstitution inflammatory syndrome (IRIS)
- Although ART has led to a reduction in the frequency of severe opportunistic infections and skin conditions associated with advanced HIV disease, e.g. Kaposi sarcoma, other dermatologic problems have become more common, e.g. lipodystrophy, neoplasia related to human papillomavirus infection
- The medications used in ART can lead to drug eruptions, and HLA testing prior to initiating therapy may help predict the likelihood of a severe cutaneous adverse reaction

INTRODUCTION

Mucocutaneous disorders not only provide important clues to the diagnosis of HIV disease and significantly impact quality of life, but they also serve as markers of progression and possible associated systemic disease. In addition, relapse of skin diseases can be associated with failure or discontinuation of antiretroviral therapy (ART). The World Health Organization (WHO) clinical staging of HIV-related disease is shown in Table 78.1, and conditions that typically develop at different $CD4^+$ T cell counts are presented in Table 78.2. Effective ART has transformed HIV disease from a progressive, fatal disorder to a chronic condition requiring maintenance therapy. As a result, cutaneous disorders associated with severe immunosuppression, such as Kaposi sarcoma and serious opportunistic infections, are observed less frequently. However, with longer survival, other diseases have become more common (e.g. anal intraepithelial neoplasia), and ART itself has led to dermatologic challenges, including drug reactions, lipodystrophy, and immune reconstitution inflammatory syndrome (IRIS). In low-income countries where ART may not be readily available, opportunistic infections are still a common cause of morbidity and mortality. Approximately 80%–95% of people living with HIV develop at least one skin disorder, and dermatologists worldwide continue to play important roles in their care.

HISTORY

In 1981, reports of *Pneumocystis jirovecii* (formerly *carinii*) pneumonia, Kaposi sarcoma, and chronic ulcerative herpes simplex virus (HSV) infections in homosexual men in association with reduced cell-mediated immunity were first published. Soon thereafter, the underlying condition was termed acquired immune deficiency syndrome (AIDS), with descriptions of other associated opportunistic infections as well as additional affected populations, including hemophiliacs/blood transfusion recipients, intravenous drug users, sexual partners of persons with the disease, infants, and heterosexual Haitians. The causative T-lymphotropic retrovirus was identified in 1983 and named the human immunodeficiency virus (HIV); homology to an African zoonosis originating from non-human primates was demonstrated.

Identification of blood-borne, sexual, and mother-to-child transmission of HIV led to universal precautions for the handling of blood and body fluids as well as specific protocols for delivery and breast-feeding. The first effective therapy against HIV, the nucleoside reverse transcriptase inhibitor zidovudine (AZT), was FDA-approved in 1987. Highly active antiretroviral therapy (HAART; now referred to as ART), which utilizes several agents to suppress viral replication and thereby delay clinical progression, was introduced in 1996. The latter has led to a substantial reduction in HIV-related morbidity and mortality.

EPIDEMIOLOGY

Approximately 85 million people have been diagnosed with HIV disease since the start of the pandemic, and HIV/AIDS continues to be a major worldwide public health challenge in the 21st century. HIV/AIDS disproportionately affects resource-poor countries and *key populations* which include sex workers, individuals who inject drugs, gay men, other men who have sex with men (MSM), transgender people, and prisoners. Globally in 2021, 38 million people were estimated to be living with HIV, with the majority (~21 million) in Eastern and Southern Africa (Fig. 78.1). The proportion of people with HIV who are receiving ART has risen dramatically, from <3% in 2000 to 75% in 2021[1], and the number of yearly AIDS-related deaths worldwide decreased from a peak of 2 million in 2005 to ~650 000 in 2021. Globally, ~1.5 million people were newly diagnosed with HIV in 2021, representing a decline of almost 50% from 2.9 million in 2000.

Although the annual number of new HIV diagnoses in sub-Saharan Africa has been decreasing since 2010, the HIV pandemic still most severely affects this region, which accounted for two-thirds of all people living with HIV and ~60% of new HIV diagnoses in 2021. Of note, the HIV transmission rate has recently increased in Eastern Europe, Central Asia, the Middle East, North Africa, and Latin America[1,2]. In 2021, key populations and their sexual partners accounted for 70% of new HIV disease globally, ranging from 46% in Eastern and Southern Africa to >95% in Europe, Asia, the Pacific, the Middle East, North Africa, and North America. Risk factors for HIV transmission include high viral load, condomless receptive anal intercourse, lack of circumcision, and the presence of other sexually transmitted infections.

PATHOGENESIS

AIDS is caused by HIV-1 and much less often HIV-2. Both are enveloped, single-stranded RNA lentiviruses in the Retroviridae family. They are zoonotic and originated from simian immunodeficiency viruses (SIVs) that infect African primates: HIV-1 from chimpanzees and HIV-2 from sooty mangabeys. HIV-1 has four distinct lineages, each resulting from an independent cross-species transmission event; group M is responsible for ~99% of pandemic HIV disease, while groups N, O, and P are restricted to West Africa. HIV-2 is also largely restricted to West Africa, where its overall prevalence is declining. Compared with HIV-1, HIV-2 is less transmissible and virulent, resulting in lower viral loads and infrequent progression to AIDS. HIV exhibits substantial genetic variability due to the error-prone nature of its reverse transcriptase as well as very rapid virus replication in infected individuals.

During HIV-1 infection, the viral envelope proteins gp120 and gp41 initially interact with the CD4 molecule followed by a second interaction with a chemokine receptor, usually CCR5 or CXCR4 (Fig. 78.2).

WHO CLINICAL STAGING OF HIV/AIDS IN THE SETTING OF CONFIRMED HIV INFECTION		
All ages	**Adults and adolescents**	**Children**
Clinical stage 1 – asymptomatic; immunologic correlate*: ≥500 CD4⁺ cells/mm³		
• Asymptomatic • Persistent generalized lymphadenopathy		
Clinical stage 2 – mild; immunologic correlate*: 350–499 CD4⁺ cells/mm³		
• **Herpes zoster** • **Fungal nail infection** • **Pruritic papular eruptions†** • **Angular cheilitis** • **Recurrent oral ulcerations** • Recurrent/chronic upper respiratory tract infections (sinusitis, otitis media/otorrhea, tonsillitis, pharyngitis)	• **Seborrheic dermatitis** • Moderate unexplained weight loss (<10% of body weight)	• **Extensive warts** • **Extensive molluscum contagiosum** • **Linear gingival erythema** • Unexplained persistent parotid enlargement • Unexplained persistent hepatosplenomegaly
Clinical stage 3 – advanced; immunologic correlate*: 200–349 CD4⁺ cells/mm³		
• **Persistent oral candidiasis (after first 6–8 weeks of life)** • **Oral hairy leukoplakia** • **Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis** • Unexplained chronic diarrhea (>1 month in adults, >2 weeks in children) • Unexplained persistent fever (≥37.6°C intermittent or constant, for >1 month) • Pulmonary tuberculosis (current) • Unexplained anemia (<8 g/dL), neutropenia (<0.5 × 10^9/L) or chronic thrombocytopenia (<50 × 10^9/L)	• Unexplained severe weight loss (>10% of body weight) • Severe bacterial infections such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia	• Unexplained moderate malnutrition or wasting not adequately responding to standard therapy • Recurrent severe bacterial pneumonia • Symptomatic lymphoid interstitial pneumonitis • Lymph node tuberculosis • Chronic HIV-associated lung disease including bronchiectasis
Clinical stage 4 – severe/AIDS-defining conditions; immunologic correlate*: <200 CD4⁺ cells/mm³		
• **Chronic herpes simplex infection (orolabial, genital, or anorectal of >1 month's duration or visceral at any site)** • **Kaposi sarcoma** • **Extrapulmonary cryptococcosis including meningitis** • **Disseminated endemic mycosis (coccidioidomycosis or histoplasmosis)** • **Disseminated non-tuberculous mycobacterial infection** • Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy (HIV wasting syndrome) • Cytomegalovirus infection (retinitis or infection of other organs; onset at age >1 month) • HIV encephalopathy • Progressive multifocal leukoencephalopathy • Extrapulmonary tuberculosis • Candidiasis of the esophagus, trachea, bronchi, or lungs • *Pneumocystis* pneumonia • Central nervous system toxoplasmosis (onset at age >1 month) • Chronic cryptosporidiosis (with diarrhea) • Chronic isosporiasis • Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy • Cerebral or B cell non-Hodgkin lymphoma, or other HIV-associated solid tumor	• **Atypical disseminated leishmaniasis** • Recurrent severe bacterial pneumonia • Recurrent non-typhoidal *Salmonella* bacteremia • Invasive cervical carcinoma	• Recurrent severe bacterial infections such as empyema, pyomyositis, bone or joint infection, or meningitis (but excluding pneumonia)

*In individuals ≥6 years of age; corresponding counts in children <6 years of age are available at https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm?s_cid=rr6303a1_e.
†In the literature, <200 CD4⁺ cells/mm³.

Table 78.1 World Health Organization (WHO) Clinical Staging of HIV/AIDS in the setting of confirmed HIV infection. Conditions with mucocutaneous manifestations are in **bold**.

These receptors are found on activated CD4⁺ T cells, monocyte-macrophages, and dendritic cells. CXCR5 is the predominant fusion cofactor in most HIV transmissions; however, CD4-independent infection of renal cells and astrocytes gives rise to chronic renal disease and neurocognitive disorders. Following binding, changes in conformation induce fusion of the viral envelope with the plasma membrane, and the virus particle is thereby internalized. The RNA genome is transcribed by a reverse transcriptase enzyme that produces a DNA copy of the HIV RNA. This viral DNA copy is spliced into the host DNA through the action of an integrase enzyme. Transcription of viral DNA into RNA yields genomic material for new viral particles or it can be translated into viral proteins. Cleavage of the latter into structural components of the virus is accomplished by proteases. Intact viruses are then produced and host cells are destroyed.

Infection by the transmitted/founder virus is followed by a rapid increase in HIV replication (Fig. 78.3). After ~6 months, the viral load falls to a set point that is determined by the host's innate natural killer (NK) cell response plus an adaptive immune response by CD8⁺ cells and neutralizing antibodies. The initial antibody response develops within 1–3 months after transmission and is strain-specific. This antibody response drives viral escape, and virus mutants become resistant to neutralization in 80% of patients. However, in 20% of patients, variants of the transmitted/founder virus evolve and induce antibodies with considerable neutralization breadth. CD8⁺ cytotoxic T cells directed against HIV begin to function within 10 days of exposure, correlating with the reduction in viremia during the acute retroviral syndrome; these cells also help to control the HIV throughout the disease course.

Initial infection results in a reduction in circulating CD4⁺ T cells, which is followed by a recovery to nearly normal levels and a subsequent slow fall of about 50 to 100 cells/mm³ per year (see Fig. 78.3). In contrast, the CD4⁺ T cells residing within the gastrointestinal tract are rapidly depleted early on. The progressive depletion of CD4⁺ T cells is the result of killing by direct infection, bystander effects of syncytia formation, chronic immune activation, lymphoid tissue damage, and senescence.

The marked chronic immune activation that characterizes HIV disease is thought to be related to low-grade HIV replication, immune responses

GENERAL CORRELATIONS OF $CD4^+$ CELL COUNT WITH SPECIFIC HIV-ASSOCIATED DISORDERS				
System	**≥500 $CD4^+$ cells/mm^3**	**<500 $CD4^+$ cells/mm^3**	**<250 $CD4^+$ cells/mm^3**	**<50 $CD4^+$ cells/mm^3**
Dermatologic	Acute retroviral syndrome Vaginal candidiasis	Oropharyngeal candidiasis (thrush) Herpes zoster Oral hairy leukoplakia Seborrheic dermatitis, moderate to severe Psoriasis, severe or refractory Eruptive atypical melanocytic nevi and melanoma Kaposi sarcoma	Eosinophilic folliculitis Papular pruritic eruption Mollusca, extensive in adults Bacillary angiomatosis Miliary/extrapulmonary tuberculosis HSV infection, disseminated Cryptococcosis, disseminated Histoplasmosis, disseminated Coccidioidomycosis, disseminated Botryomycosis Non-Hodgkin lymphoma Keratinocyte carcinoma	Large, non-healing mucocutaneous HSV infections (e.g. perianal) Giant mollusca Perianal ulcers due to CMV Aspergillosis Acquired ichthyosis *Mycobacterium avium* complex infections Major aphthae
Respiratory	Bacterial pneumonia and sinusitis	Pneumococcal pneumonia Pulmonary tuberculosis Lymphocytic interstitial pneumonia (pediatric)	*Pneumocystis jirovecii* pneumonia	*Pseudomonas* spp. pneumonia
Nervous	Aseptic meningitis Guillain–Barré syndrome	Mononeuritis multiplex	HIV-associated dementia Cerebral toxoplasmosis Peripheral neuropathy Progressive multifocal leukoencephalopathy	Primary CNS lymphoma
Hematologic	Persistent generalized lymphadenopathy	Anemia Idiopathic thrombocytopenic purpura	Non-Hodgkin lymphoma	
Other	Myopathy	Cryptosporidiosis Cervical/anal intraepithelial neoplasia	Esophageal candidiasis Wasting Microsporidiosis Vacuolar myelopathy Cardiomyopathy Invasive cervical cancer Invasive anal cancer	Cryptosporidiosis, refractory CMV retinitis, extraocular systemic CMV infection

Table 78.2 General correlations of $CD4^+$ cell count with specific HIV-associated disorders. In general, these conditions occur at increased frequency and severity at lower $CD4^+$ T cell counts. CMV, cytomegalovirus; HSV, herpes simplex virus.

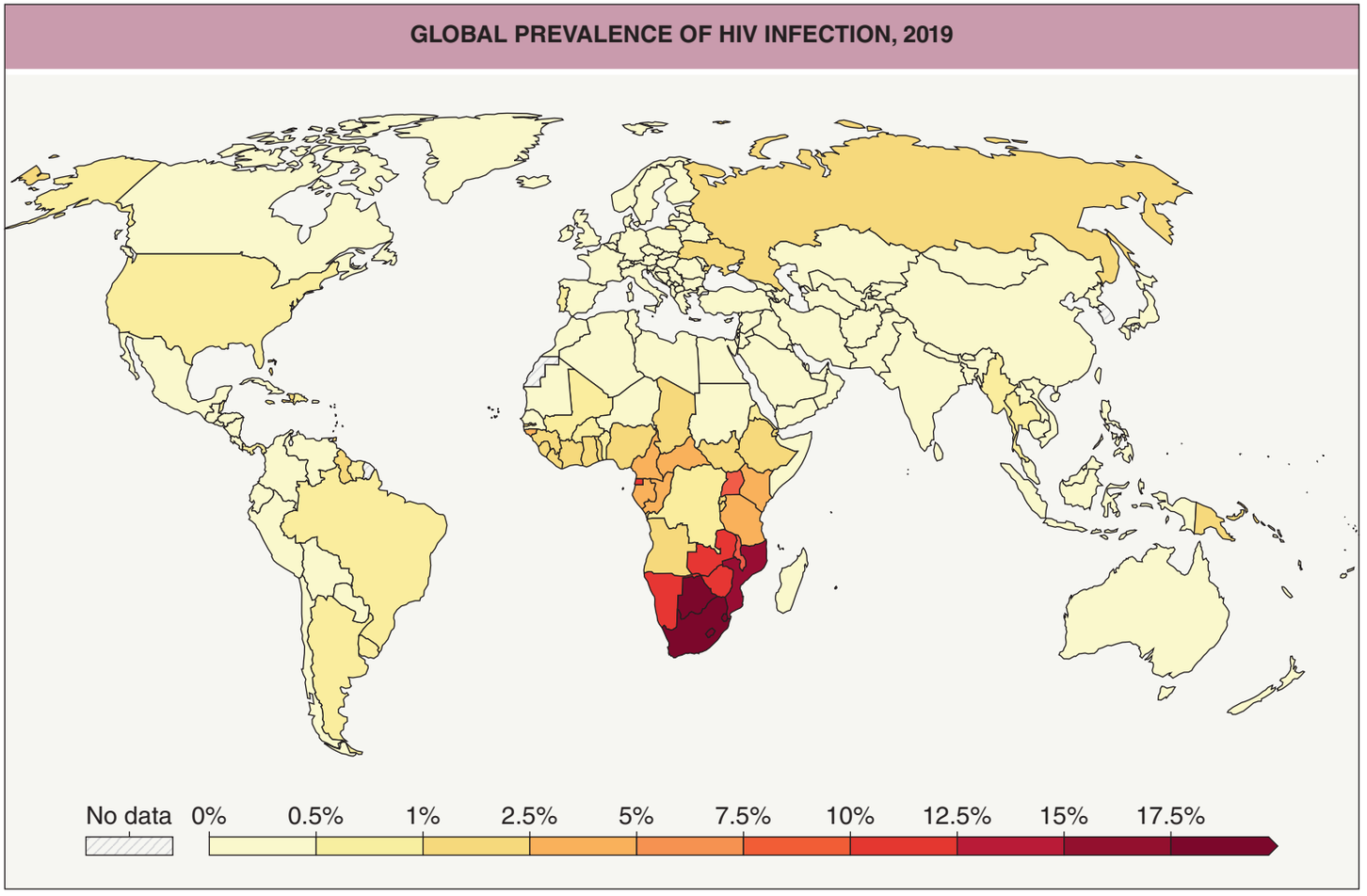


Fig. 78.1 Global prevalence of HIV infection, 2019. The worldwide estimate of the number of people living with HIV was 38.4 million in 2021, representing an overall prevalence of almost 0.5%. *From the Institute for Health Metrics and Evaluation (IHME) 2019 Global Burden of Disease.*

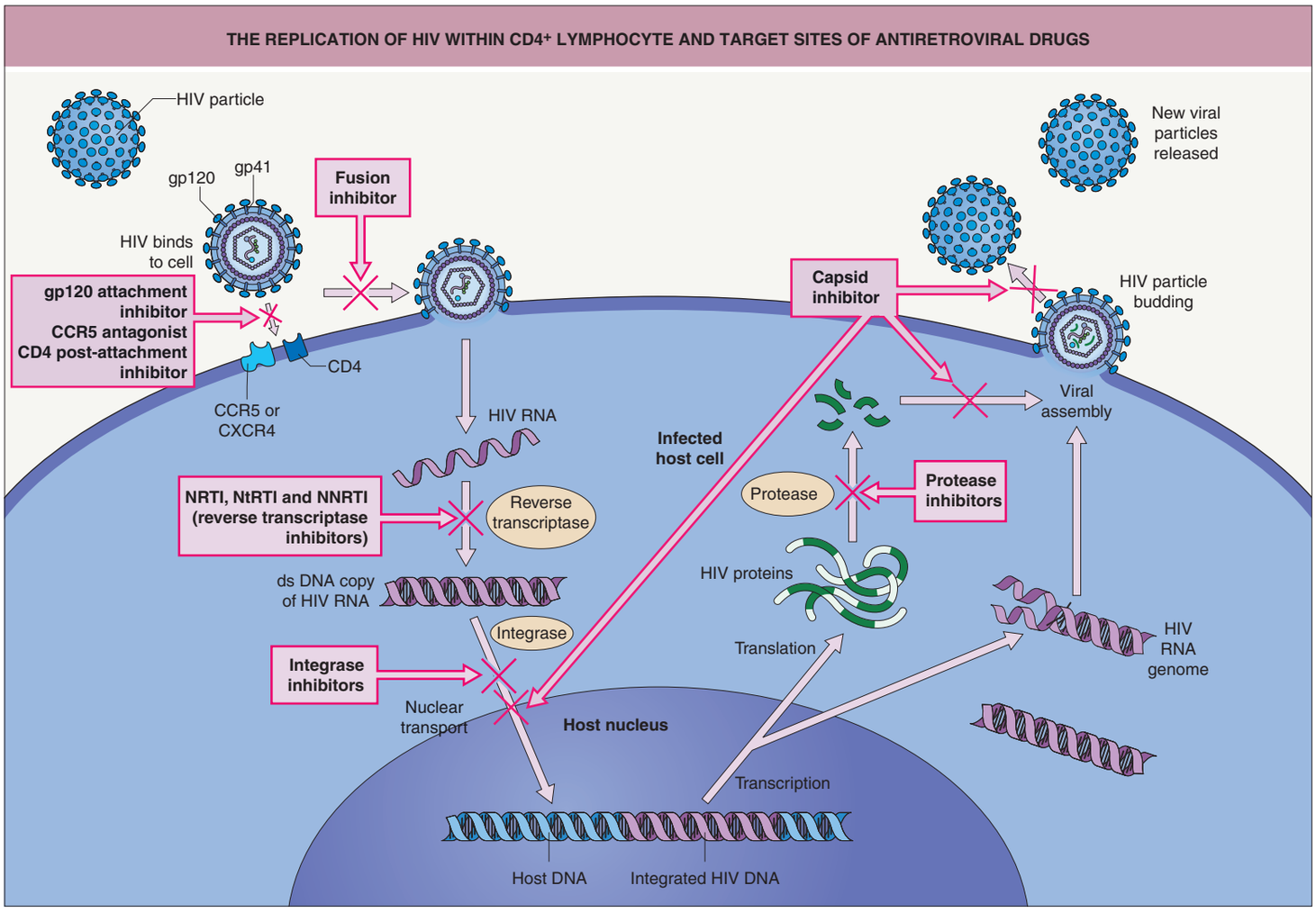


Fig. 78.2 Replication of HIV within CD4⁺ lymphocyte and target sites of antiretroviral drugs. CCR5, CC-chemokine receptor 5; NRTI, nucleoside reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor. Information on FDA-approved antiretroviral drugs is available at https://hivinfo.nih.gov/understanding-hiv/fact-sheets/fda-approved-hiv-medicines

to HIV, reactivated infections, loss of mucosal integrity with consequent microbial translocation, and increased production of proinflammatory molecules. In patients receiving ART, increased levels of markers of inflammation have been associated with higher mortality rates and risk of cancer as well as cardiovascular, neurologic, and liver disease.

In a person living with HIV, AIDS is defined by a $CD4^+$ cell count of $<200/mm^3$ or <14% $CD4^+$ T cells and/or the presence of an AIDS-defining condition (see Table 78.1). The natural history of HIV disease varies considerably, with the rate of decline in $CD4^+$ T cells correlating with viral burden. In the absence of treatment, the median time for progression to AIDS is ~10 years. However, ~10%–15% of untreated patients, historically referred to as "long-term non-progressors", live with HIV for ≥8 years with no symptoms and $CD4^+$ T cell counts of $>500\,cells/mm^3$; in addition, <0.5% of patients are "elite controllers" with no evidence of viremia even without ART. The ability of ART to suppress viral replication and enable reconstitution of $CD4^+$ T cells has an immense impact on the disease course. Immune reactivation due to ART can result in a variety of inflammatory sequelae referred to as IRIS, ranging from unmasking or paradoxical "worsening" of infections or neoplasms to exacerbations of inflammatory disorders (see below).

HIV-RELATED INFECTIOUS SKIN CONDITIONS

In addition to the primary HIV exanthem, HIV-positive individuals often develop cutaneous viral, bacterial, and fungal infections as well as infestations. Patients who acquired HIV via sexual contact should also be tested for other sexually transmitted infections (see Ch. 82); the converse is also true. The presence of erosions and ulceration in the anogenital region due to conditions such as syphilis and herpes simplex virus infections can also increase the risk of HIV transmission.

Viral Infections

Primary HIV exanthem (acute retroviral syndrome)

Primary HIV infection refers to the initial disease phase, when HIV-1 RNA, DNA, and/or p24 antigen are present in the plasma prior to the development of HIV-1 antibodies. Initially, up to 80% of patients develop an "acute retroviral syndrome" resembling influenza or infectious mononucleosis. Symptoms develop 2–6 weeks after HIV exposure and often include fever, headache, myalgia/arthralgia, pharyngitis, lymphadenopathy, and night sweats. A morbilliform exanthem also occurs in 40%–80% of patients; it lasts 4–5 days and is typically generalized, with the most prominent involvement on the face and trunk. Oral and genital ulcers are occasionally present. Symptoms are self-limited and resolve in a few days to weeks, with a median duration of 14 days. The initial phase of rapid HIV-1 replication causes a temporary fall in $CD4^+$ cell counts, occasionally to an extent that gives rise to opportunistic infections.

Greater severity and longer duration of the acute retroviral syndrome is associated with a higher viral load set point and more rapid disease progression. Early initiation of ART during primary HIV infection may delay disease progression.

Herpes simplex virus (HSV) infection

Relatively immunocompetent people living with HIV usually have typical, self-limited HSV disease. As immunity wanes, the frequency of HSV recurrences increases and lesions take longer to heal, potentially evolving into chronic, extensive, deep, and painful ulcers that favor the perianal region, genitalia, and tongue (Fig. 78.4). Atypical presentations of HSV infection include folliculitis, verrucous plaques, and hypertrophic anogenital masses simulating neoplasia. Infection may become

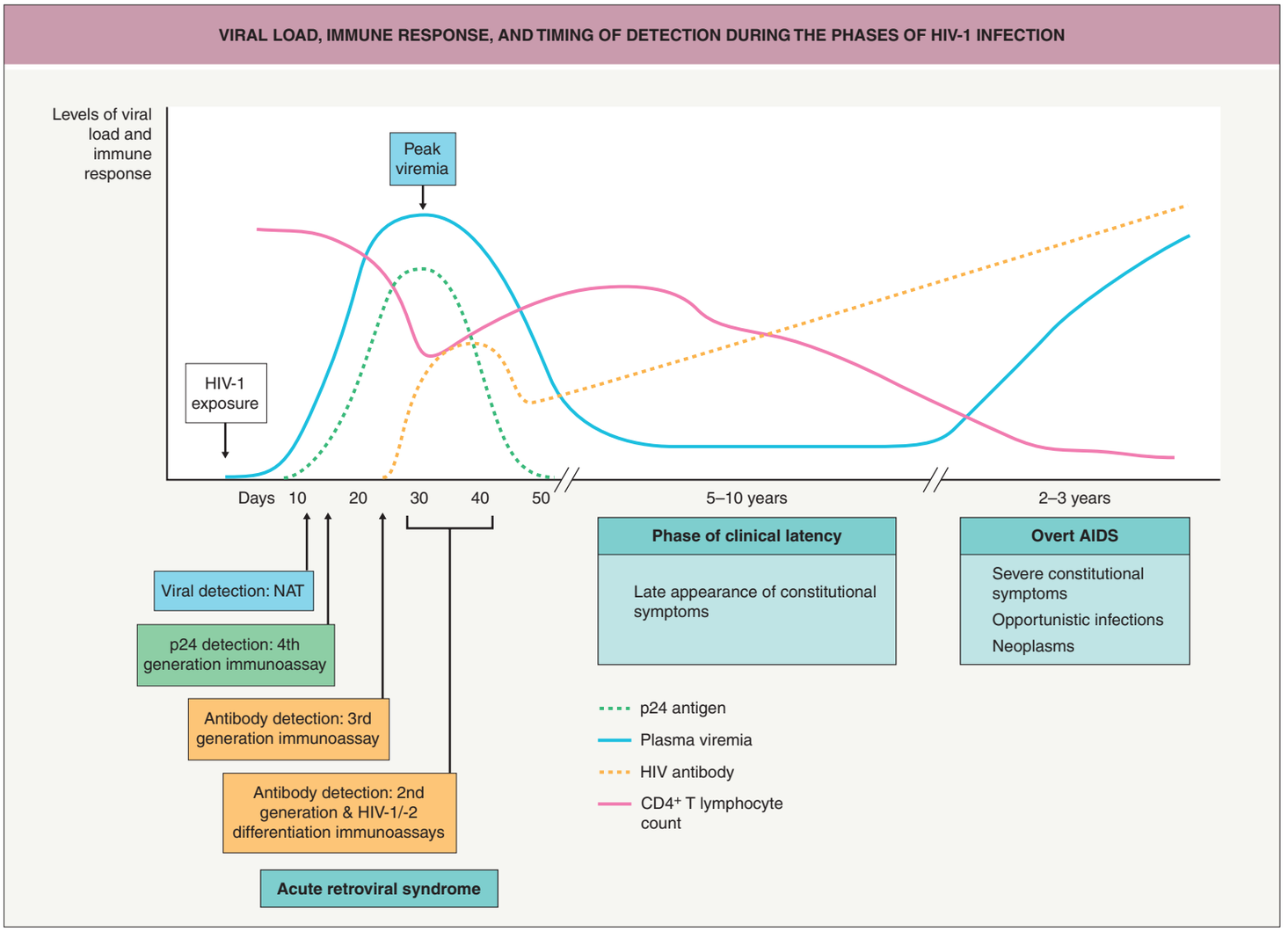


Fig. 78.3 Viral load, immune response, and timing of detection during the phases of HIV-1 infection. After HIV-1 exposure, initial virus replication and spread occur in the lymphoid organs, and systemic dissemination of HIV-1 is reflected by the peak of plasma viremia. A clinical syndrome of varying severity is associated with this phase of primary HIV-1 infection in up to 80% of HIV-1-infected persons. Downregulation of viremia during the transition from the primary to the early chronic phase coincides with the appearance of HIV-1-specific cytotoxic T lymphocytes and with the progressive resolution of the clinical syndrome. The long phase of clinical latency is associated with active virus replication, particularly in the lymphoid tissue. During the clinically latent period, $CD4^+$ T lymphocyte counts slowly decrease, as does the HIV-1-specific immune response. When $CD4^+$ T lymphocyte counts decrease below 200 cells/ml (i.e. when overt AIDS occurs), the clinical picture is characterized by severe constitutional symptoms and by the possible development of opportunistic infections and/or neoplasms. *Adapted from Bart PA, Pantaleo G. The immunopathogenesis of HIV-1 infection. In: Cohen J, Powderly WG. Infectious Diseases. Edinburgh: Mosby, 2004:1236.*



Fig. 78.4 Chronic ulcerative herpes simplex virus infection in a patient with HIV. Slowly enlarging ulcers on the buttocks and perianal area have a scalloped border.

disseminated or occur at unusual sites such as the non-keratinized (unattached) mucosa of the oropharynx (see Fig. 72.1) and the esophagus.

The ulcer edge should be scraped for HSV PCR (most sensitive), direct fluorescent antibody assay (DFA), and/or viral culture and, if negative, a skin biopsy performed; a Tzanck smear has low sensitivity. Higher doses and longer courses of antiviral medications are typically required, with continuation until all mucocutaneous lesions are healed. Resistance to acyclovir, usually due to reduced viral thymidine kinase activity, occurs more commonly in immunosuppressed (~5%) compared to immunocompetent (~1%) hosts. Alternative agents that do not rely on thymidine kinase include foscarnet, cidofovir, and imiquimod. Of note, HSV-2 infection increases the risk of HIV acquisition and promotes HIV-1 replication[3].

Varicella and herpes zoster

In people living with HIV, varicella tends to have new lesion formation over a longer period of time, a higher lesion count, and (particularly in adults) complications such as pneumonitis, hepatitis, and encephalitis. Lesions that persist as slowly healing ulcers have been reported.

People living with HIV have a 7- to 15-fold higher incidence of herpes zoster compared to the general population[4]. Of children living with HIV who develop varicella, herpes zoster or a disseminated eruption reminiscent of varicella occurs in ~50% within 2 years. In addition to classic dermatomal eruptions, HIV-associated herpes zoster can present

as chronic non-healing ulcers, hyperkeratotic verrucous plaques, and multidermatomal or disseminated skin lesions; potential complications include bacterial superinfection, systemic involvement, and multiple recurrences. The recombinant Shingrix® vaccine is recommended for the prevention of herpes zoster in immunocompromised adults, including those with HIV disease (see Ch. 80)[5].

People living with HIV who do not have VZV immunity should receive varicella–zoster immune globulin within 10 days of exposure to VZV. Antiviral treatment of VZV infection in patients should be continued until clinical resolution occurs (see Ch. 80); acyclovir resistance is possible. Of note, patients treated with ART may experience paradoxical worsening of herpes zoster when their CD4$^+$ T cell counts rise (see IRIS below).

Molluscum contagiosum

Molluscum contagiosum (MC) commonly occurs and tends to be more persistent in individuals with significantly reduced CD4$^+$ T cell counts. In addition to the typical presentation of small umbilicated papules (Fig. 78.5), people living with HIV can develop larger (>1 cm), coalescent, verrucous, and widespread lesions. The clinical differential diagnosis may include basal cell carcinoma (BCC) and cutaneous lesions of cryptococcosis, histoplasmosis, or other dimorphic fungal infections. Dermoscopic evaluation, microscopic examination following curettage of lesional contents, or biopsy can help to confirm the diagnosis. In addition to curettage and other destructive modalities, topical and intravenous cidofovir have been used successfully for refractory MC in patients with HIV disease. MC may resolve spontaneously after initiation of ART but can also present as a manifestation of IRIS.

Human papillomavirus (HPV) infections

The spectrum of mucocutaneous lesions due to HPV infection ranges from common warts and condylomata acuminata to squamous intraepithelial neoplasia and carcinoma. The prevalence of HPV infection is higher in people living with HIV than in the general population and correlates with decreasing CD4$^+$ T cell counts. People living with HIV have reduced HPV clearance, more treatment-resistant mucocutaneous lesions, and accelerated development of HPV-associated carcinoma. Skin lesions are often multiple, coalescent, and extensive (Fig. 78.6). There is evidence for synergistic interactions between HIV and HPV infections, suggesting that HPV vaccination may help control both infections at the population level in high prevalence settings[6].

Acquired epidermodysplasia verruciformis (AEDV) is characterized by hypopigmented to pink tinea versicolor-like lesions and numerous flat-topped papules that are due to HPV-5, -8, and other β HPV types. People living with HIV may develop squamous cell carcinomas (SCCs) in association with AEDV and other cutaneous warts, e.g. digital lesions due to high-risk HPV types, as well as anogenital warts.

Compared to the general population, women living with HIV have a 3-fold increase in the incidence of cervical intraepithelial neoplasia (CIN) as well as higher rates of high-grade CIN[7]. Anal HPV is present in >90% of MSM with HIV disease, and most have at least one high-risk HPV type. MSM with HIV disease also have an up to 50% prevalence of high-grade anal intraepithelial neoplasia (AIN) and a 30- to 50-fold higher risk of anal cancer than does the general population[8]; a 5-fold increased risk of penile cancer has also been documented[9]. Monitoring should include serial physical examinations of the anogenital area, colposcopy/proctoscopy, cervical/anal HPV determination and cytology, and histologic examination when indicated.

ART has not shown a demonstrable effect on the occurrence or clearance of cutaneous or anogenital warts. Enlargement or inflammation of pre-existing warts and an eruption of new warts can occur in the setting of IRIS. Some studies have shown a protective effect of ART on the development and progression of CIN and AIN. However, compared to the pre-ART era, incidence rates of cervical and anal cancers have not decreased[7]. This is likely due to the longer life expectancy afforded by ART.

The choice of therapy for anogenital warts depends upon their size, number, and location. Options include destructive modalities such as cryotherapy, electrosurgery, laser therapy and surgical excision, in addition to patient-applied topical therapies including imiquimod and podophyllotoxin (see Ch. 79). Immunosuppressed patients require more treatment sessions to achieve clearance and have frequent recurrences. The threshold for biopsy should be low, and several sites may need to be sampled to exclude SCC. HPV vaccines are immunogenic and well-tolerated in people with HIV disease.

Oral hairy leukoplakia due to Epstein–Barr virus (EBV) infection

Oral hairy leukoplakia (OHL) results from Epstein–Barr virus (EBV) infection of the oral mucosa and typically presents as hyperkeratotic, corrugated white plaques with hair-like projections on the lateral aspect of the tongue (Fig. 78.7). It can occur at any stage of HIV disease but is more prevalent in men and those with CD4$^+$ T cell counts below 200/mm^3. It represents a predictor of rapid disease progression if ART is not initiated[10]. OHL can also occur in patients with other forms of immunosuppression, such as organ transplant recipients. Although treatment is usually not necessary, topical or oral antiherpetic antiviral medications and topical podophyllin, tretinoin, or gentian violet may be of benefit; however, recurrence is common. OHL may also regress with ART.

Cytomegalovirus (CMV) infections

Reactivation of CMV is associated with CD4$^+$ T cell counts that are <100/mm^3, and it remains a significant cause of morbidity and mortality in patients with AIDS. Retinitis, esophagitis, and colitis represent common clinical manifestations, and mucosal ulcers may occur in the setting of disseminated disease. Cutaneous presentations are uncommon and include ulcers favoring the anogenital area (Fig. 78.8), verrucous or hyperpigmented plaques, prurigo nodularis-like lesions,

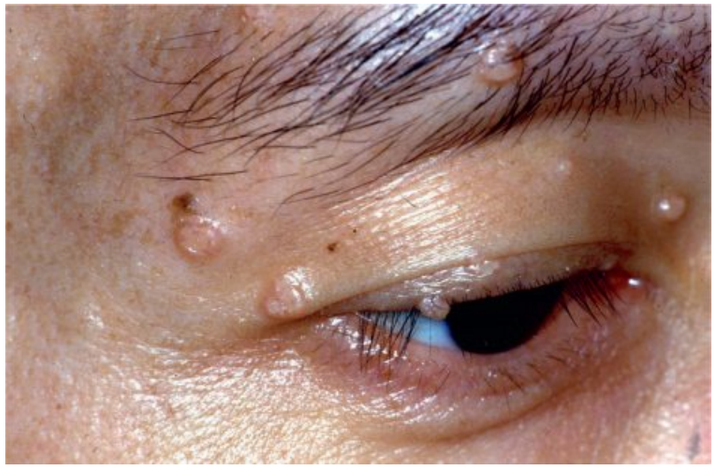


Fig. 78.5 Molluscum contagiosum. Multiple facial lesions are commonly seen in people living with HIV and less likely to resolve spontaneously. Disseminated fungal infections may present with molluscum contagiosum-like lesions and should be excluded.



Fig. 78.6 Extensive perianal condylomata acuminata. This 65-year-old man was receiving antiretroviral therapy and had a CD4$^+$ T cell count of 240/mm^3.



Fig. 78.7 Oral hairy leukoplakia. A Shaggy white keratotic plaques along the lateral aspect of the tongue. A corrugated pattern is often seen. **B** Histologic findings include irregular parakeratosis, acanthosis, and focal balloon cell change of the epithelium. The inset shows positive staining for Epstein–Barr virus-encoded RNA (EBER) in the nuclei of affected keratinocytes. *A, Courtesy Charles Camisa, MD; B, Courtesy Lorenzo Cerroni, MD; Inset, Courtesy Luis Requena, MD.*

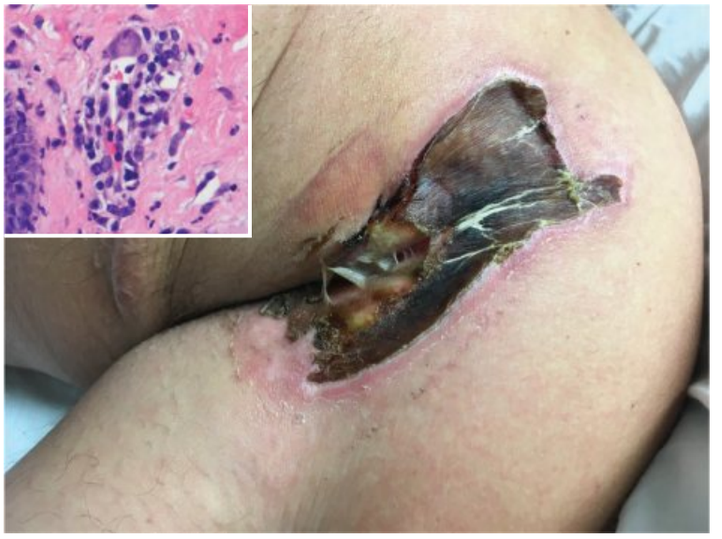


Fig. 78.8 Disseminated CMV infection with cutaneous involvement in a patient with newly diagnosed HIV infection. Well-demarcated ulceration with a thick eschar, pink rim, and associated brachial plexopathy. The HIV viral load was 6.6 million copies and CMV viral load was 14.5 million copies. Inset, histopathologic evaluation showed endothelial cell with "owl's eye" intracytoplasmic inclusions. *Courtesy Katherine Hunt, MD; Inset, Courtesy Peter Pavlidackey, MD.*

purpuric papules, vesicles, and morbilliform eruptions. Histologically, characteristic cytomegalic intranuclear inclusion bodies are seen within endothelial cells in the dermis of lesional skin (see Fig. 78.8 inset and Fig. 80.23). Ulcerative lesions are often co-infected with HSV or VZV, and because CMV can also be detected in non-lesional skin, its pathogenic role has been questioned. Specific treatments include oral valganciclovir and intravenous ganciclovir, foscarnet, and cidofovir.

Bacterial Infections

People living with HIV are at increased risk for the development of recurrent and potentially severe cutaneous bacterial infections, which can be localized or widespread and sometimes have unusual clinical appearances. In addition to diminished antibody- and cell-mediated immune responses, predisposing factors include skin barrier impairment from excoriations or other cutaneous infections, indwelling catheters, and malnutrition. In addition to the entities discussed below, cutaneous bacterial infections that can occur in association with HIV disease include necrotizing fasciitis, nocardiosis, malacoplakia, pseudomonal "hot tub" folliculitis, "malignant" otitis externa, and ecthyma gangrenosum.

Staphylococcus aureus *infections*

Staphylococcus aureus is the most common bacterial pathogen in individuals with HIV disease. Cutaneous presentations include impetigo, folliculitis, furunculosis, wound infections, cellulitis, and rarely botryomycosis. Compared with the general population, people living with HIV have a higher prevalence of methicillin-resistant *S. aureus* (MRSA) colonization of the skin and a 6- to 18-fold higher incidence of MRSA skin/soft tissue infections; they also have more frequent recurrences[11]. The lower extremities, buttocks, and scrotum are commonly affected, and risk factors include a low $CD4^+$ T cell count, prior MRSA infection, incarceration, illicit drug use, and recent antibiotic treatment or hospitalization. Use of intranasal mupirocin ointment and chlorhexidine washes can temporarily eradicate colonization but may not reduce infection rates.

Bacillary angiomatosis

Bacillary angiomatosis is a rare condition that is characterized by vascular proliferation and is due to the Gram-negative bacilli *Bartonella henselae* and *B. quintana*. It occurs in individuals with HIV disease who are severely immunocompromised, usually with $CD4^+$ T cell counts $<100/mm^3$. Bacillary angiomatosis favors the skin and subcutaneous tissues, although virtually any internal organ can be affected. Patients typically present with a single to numerous, firm, red or violaceous papules and nodules; these lesions may be painful, ulcerate, or bleed profusely after trauma. Large subcutaneous nodules of bacillary angiomatosis may also ulcerate. Disseminated infection is associated with systemic symptoms such as fever, night sweats, and weight loss.

The differential diagnosis may include Kaposi sarcoma, pyogenic granulomas, and non-tuberculous mycobacterial infections. Histologically, a lobular proliferation of capillaries and venules with large, protuberant endothelial cells is seen, surrounded by a neutrophilic infiltrate. Lesional bacilli can be visualized with a Warthin–Starry stain or identified via PCR-based assays; serologic testing for anti-*Bartonella* antibodies may assist in diagnosis. Treatment consists of doxycycline or macrolides. The median time to complete response is ~1 month, and 3–4 months of therapy is recommended to prevent relapse[12].

Mycobacterial infections

A diverse clinical spectrum of tuberculous and non-tuberculous mycobacterial skin infections can develop in people living with HIV. Cutaneous findings include erythematous to violaceous papules and nodules as well as ulcers, acneiform eruptions, abscesses, and verrucous plaques (Fig. 78.9); a sporotrichoid (lymphocutaneous) distribution pattern is sometimes seen. The risk of infection increases with progressive immunosuppression, and the classic histologic finding of caseating granulomas may be absent in patients with markedly diminished cell-mediated immunity.

Syphilis

Rates of syphilis have risen over the past decade, with possible factors including riskier sexual behaviors (due in part to the introduction of PrEP) as well as potential impediment of innate and acquired immunity to *Treponema pallidum* by ART[5,13]. In addition to classic papulosquamous lesions of secondary syphilis, people with HIV disease may



Fig. 78.9 *Mycobacterium haemophilum* infection. This 54-year-old man with HIV and a $CD4^+$ T cell count of 350/mm^3 presented with a 4-month history of slowly enlarging, thick plaques on his arms and legs. The lesions resolved over 6 months with treatment including ciprofloxacin, clarithromycin, and ethambutol.



Fig. 78.10 Secondary syphilis presenting as lues maligna. This man with HIV had a fever, headache, arthralgias, and myalgias together with this widespread eruption of pustules and crusted papulonodules.

present with multiple primary chancres, concomitant lesions of primary and secondary syphilis, palmoplantar keratoderma, annular plaques, and lues maligna. The latter, which is also known as malignant or ulceronodular syphilis, is a severe form of secondary syphilis (see Ch. 82). A prodrome of fever, arthralgia/myalgia, headache, and photophobia precedes the appearance of papules, pustules, and necrotic nodules with ulceration and crusting (Fig. 78.10); lesions are symmetrically distributed, with frequent involvement of the palms and sometimes the oral mucosa. Individuals with HIV disease have a higher likelihood, earlier onset, and greater severity of neurosyphilis. The standard stage-specific treatment regimens for syphilis are recommended, but with longer monitoring.

Fungal and Related Infections

In people living with HIV, clinical presentations of cutaneous fungal infections range from localized tinea corporis to widespread papulonodules due to disseminated dimorphic fungal infections.

Candidiasis

Candidiasis is the most common fungal disease in those living with HIV, and its incidence and severity are both increased in the setting of lower $CD4^+$ T cell counts. Oropharyngeal candidiasis is often the first clinical manifestation of HIV disease. Additional presentations include angular cheilitis, chronic paronychia, and onychodystrophy, as well as intertriginous, refractory vaginal, esophageal, and disseminated candidiasis. Continuous or intermittent use of systemic antifungal medications can prevent recurrences of candidiasis (see Ch. 127), but it increases the likelihood of infections with resistant *Candida albicans* as well as non-*C. albicans Candida* (NCAC) spp. that are intrinsically less sensitive to antifungal medications[14].

Dermatophytoses

Dermatophytosis in people living with HIV may be more widespread, atypical in appearance (e.g. less erythema, non-annular morphology), and refractory to treatment. Tinea pedis may extend onto the dorsum of the feet or give rise to chronic hyperkeratotic plaques, which may be bilateral on the palms and soles[15]. Nodular perifolliculitis (including Majocchi granuloma) can present with follicular papulopustules or deep granulomatous nodules. Proximal subungual onychomycosis is seen more frequently in immunocompromised patients and should prompt HIV testing. Of note, some azole antifungals (e.g. itraconazole) interact with antiretroviral medications (see Ch. 131). Use of absorbent powders and topical antifungal agents can help to prevent recurrences.

Systemic fungal infections

Individuals with HIV disease are predisposed to the development of disseminated cryptococcosis and dimorphic fungal infections, including histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, talaromycosis, emergomycosis, and sporotrichosis (see Ch. 77).

Cryptococcus neoformans is an encapsulated yeast that is found worldwide in bird droppings and contaminated soil. Patients with $CD4^+$ T cell counts $<100/mm^3$ are particularly susceptible, and pulmonary or central nervous system disease may be the initial presentation of AIDS. Cutaneous lesions occur in 10%–20% of patients with disseminated cryptococcosis and often appear as molluscum contagiosum-like umbilicated papules, nodules, and pustules that preferentially affect the head and neck (Fig. 78.11). Violaceous nodules and ulcerations may also be seen on the palate and tongue[16]. The yeast's polysaccharide capsule can be highlighted using the mucicarmine stain or India ink; detection of cryptococcal antigen in the serum or CSF can also be utilized for diagnosis.

Cutaneous findings in disseminated dimorphic fungal infections can include papulopustules, crusted or molluscum-like umbilicated papules, nodules, necrotic lesions, verrucous plaques, and ulcers. These may occur on the face, trunk, and extremities; oral or nasal ulcers can also be seen, especially with histoplasmosis and paracoccidioidomycosis. Intravenous amphotericin B is the first-line therapy for most of the severe, disseminated fungal infections, although azoles have a role as adjunctive and maintenance therapy. Treatment is often prolonged and difficult, with frequent relapses.

Because the differential diagnosis of widespread skin lesions in febrile patients with HIV disease includes disseminated bacterial, mycobacterial and fungal infections, a representative skin lesion should be biopsied and tissue sent for culture and/or PCR.

Pneumocystis jirovecii *infections*

P. jirovecii (formerly *P. carinii*) is currently categorized as a fungus rather than a protozoan. *Pneumocystis* pneumonia (PCP) is one of the most common opportunistic infections in those living with HIV. Extrapulmonary *P. jirovecii* infection is uncommon and most often involves the lymph nodes, liver, spleen, and bone marrow. Cutaneous involvement is very rare and may present as friable erythematous papulonodules of the external ear, molluscum contagiosum-like papules, and bluish or necrotic plaques. Treatment for extrapulmonary *P. jirovecii* infection includes intravenous trimethoprim–sulfamethoxazole (TMP-SMX), clindamycin–primaquine, or pentamidine. Patients with a previous *P. jirovecii* infection or $CD4^+$ T cell counts $<200/mm^3$ should receive prophylaxis with TMP-SMX, atovaquone, dapsone, or aerosolized pentamidine.

Other fungal and related infections

Cutaneous aspergillosis may be due to direct inoculation at sites of wounds and indwelling catheters, or arise from hematogenous dissemination. Clinical findings include fluctuant papulonodules, deep



Fig. 78.11 Disseminated cryptococcosis in the setting of AIDS. **A** Several ulcers with rolled borders. **B** Numerous molluscum contagiosum-like lesions. Microscopic examination and culture of either dermal scrapings or a biopsy specimen confirm the diagnosis.



Fig. 78.12 Crusted scabies in the setting of HIV infection. Crusted and keratotic plaque on the elbow that is teeming with mites.

abscesses, non-healing ulcers, and plaques with a purulent, verrucous or annular appearance[17]. Disseminated infections with *Fusarium*, *Pseudallescheria/Scedosporium*, and fungi in the order Mucorales (mucormycosis) can also occur. Protothecosis results from infection by the achlorophyllous algae *Prototheca*, usually after trauma or contact with contaminated water. Cutaneous lesions range from erythematous papulonodules and vesiculopustules to plaques and chronic ulcers.

Parasitic Infections

Leishmaniasis

Leishmaniasis is caused by at least 20 species of intracellular protozoans of the genus *Leishmania*. It is typically transmitted by sandflies with only occasional spread via contaminated needles. HIV-associated leishmaniasis occurs in both endemic and non-endemic regions of the world, with endemic areas including portions of the Mediterranean basin, Middle East, South Asia, East Africa, and Central/South America (see Fig. 83.1). HIV enhances the severity of leishmaniasis by inducing a shift from a protective Th1-type immune response to a Th2-type reaction pattern[18]. Cutaneous findings range from solitary ulcers in exposed areas to atypical diffuse induration of the skin, eroded erythematous plaques, extensive hyperpigmented macules and papules, and necrotic genital ulcers. Mucocutaneous leishmaniasis may result in disfiguring ulcerations of the lips, palate, and nose. The diagnosis of leishmaniasis can be established via microscopy, culture, or PCR of lesional tissue.

Leishmaniasis in people living with HIV has a higher rate of therapeutic failure, relapse, and associated mortality. Amphotericin B is recommended as first-line therapy, and lipid-based formulations are preferred due to their reduced systemic toxicity (particularly nephrotoxicity). Pentavalent antimonials do not represent first-line therapy in those co-infected with HIV and *Leishmania* due to a high incidence of side effects (e.g. pancreatitis, arrhythmias), treatment failure, and mortality[19]. Oral miltefosine is well-tolerated but less effective in the setting of HIV infection. Early initiation of ART is recommended, as it contributes to higher survival rates and lower relapse rates.

Strongyloidiasis

Strongyloides stercoralis is a soil-transmitted intestinal helminth with a worldwide distribution, although it most commonly leads to infection in tropical and subtropical regions. Autoinfection due to penetration of the intestinal mucosa can cause hyperinfection and disseminated strongyloidiasis, both of which are more common in patients with impaired cell-mediated immunity (see Ch. 83). People living with HIV have twice the risk of *S. stercoralis* infection compared to the general population, but not necessarily higher rates of hyperinfection or disseminated strongyloidiasis.

Cutaneous manifestations of strongyloidiasis include urticaria and larva currens – urticarial serpiginous tracks from larval penetration and migration through the dermis, often beginning in the perianal area. Disseminated strongyloidiasis produces rapidly progressing petechial and purpuric eruptions on the abdomen and proximal limbs ("thumbprint" purpura), and eosinophilia is common. Larvae are generally absent in skin biopsies of larva currens, but in disseminated disease they may be observed in the dermis in association with vascular damage. Ivermectin and albendazole have replaced thiabendazole as first-line treatment because of greater efficacy and tolerability. Mortality is high (up to 80%) with hyperinfection or disseminated disease.

Acanthamebiasis

Acanthamoeba are free-living amoebae present in the environment and secretions of healthy individuals. Infection occurs in people living with HIV who have CD4$^+$ T cell counts <250/mm^3[3,20]. The skin may be the initial portal of entry or a site of hematogenous dissemination. Cutaneous lesions include papules, pustules, ulcers, and indurated bluish or erythematous cellulitic plaques, which may or may not be painful. Trophozoites are scant and difficult to detect in routinely stained histologic sections. Optimal treatment is not well-defined and includes combinations of miltefosine with antifungal and antibacterial agents.

Ectoparasitic Infestations and Insect Bites

Scabies

The *Sarcoptes scabiei* var. *hominis* mite is the most common cause of ectoparasitic infestation in people living with HIV. In relatively immunocompetent hosts, scabies often has a classic presentation with extremely pruritic crusted papules, vesicles, and burrows favoring the interdigital web spaces of the hands, wrists, ankles, axillae, nipples/areolae (for women), waist, and groin (see Ch. 84). With progressive immunosuppression, especially when CD4$^+$ T cell counts fall below 200/mm^3, more severe forms develop, including generalized papules and crusted scabies. The latter presents with thick, hyperkeratotic, grayish-white plaques with characteristic granular, sand-like scales (Fig. 78.12). These lesions may be generalized or localized and can be surprisingly non-pruritic despite the high mite burden, numbering thousands per gram of skin. While the head and neck are usually spared in immunocompetent adults with scabies, these areas are commonly affected in those living with HIV, which may lead to the misdiagnosis of seborrheic dermatitis. Scabies can also resemble drug eruptions, eczema, and psoriasis. A high index of suspicion is necessary as delayed diagnosis may lead to major outbreaks in health care facilities.

Definitive diagnosis can be based on dermoscopy or identification of mites, eggs, or fecal pellets (scybala) on potassium hydroxide (KOH) or

mineral oil mounts of skin scrapings. PCR-based detection of *S. scabiei* DNA from skin scales has also been described[21]. Patients with classic scabies should receive standard therapy, such as topical permethrin 5% cream. Because treatment failure is more likely with crusted scabies, a combined regimen including topical permethrin and repeated doses of oral ivermectin is recommended; keratolytic agents can facilitate removal of scale. Scabies infestation may be complicated by bacterial superinfection and fatal septicemia in immunocompromised hosts.

Demodicosis

Demodicosis due to *Demodex folliculorum* and *D. brevis* can occur in the setting of HIV disease. Patients present with itchy or "burning" facial erythema in conjunction with papules, pustules, and scaling of the cheeks, perioral area, and neck. The differential diagnosis includes rosacea, acne vulgaris, eosinophilic folliculitis, and other pruritic papular eruptions associated with HIV disease (see below). Demodicosis can also flare as a manifestation of IRIS. Microscopic examination of skin scrapings placed in mineral oil or KOH solution demonstrates multiple *Demodex* mites. Treatment options include topical ivermectin, permethrin, or sulfur preparations as well as oral ivermectin or metronidazole[22].

Insect bite reactions

Exaggerated reactions to insect bites can occur in patients with HIV disease, attributable to immune dysregulation and hypereosinophilia[23]. Patients present with pruritic or painful erythematous, edematous papules and plaques that may blister (see Ch. 33). Occasionally, they are associated with constitutional symptoms such as fevers and malaise. The differential diagnosis often includes non-infectious papular pruritic disorders associated with HIV disease.

NON-INFECTIOUS HIV-RELATED DERMATOSES

While some non-infectious skin disorders specifically affect people living with HIV, others simply occur more frequently or have enhanced severity and unusual morphologies (Table 78.3). Such presentations should alert the clinician to consider the possibility of HIV as an underlying risk factor.

Papulosquamous and Eczematous Disorders

Seborrheic dermatitis

Seborrheic dermatitis affects ~30%–50% of people living with HIV, compared to <10% of the general population, and it can be seen in all stages of HIV disease. An acute onset or sudden flare of extensive or severe seborrheic dermatitis should raise the possibility of HIV infection. Atypical presentations include a papular component, exuberant facial plaques, involvement of non-seborrheic areas, and even erythroderma. Because particular histopathologic findings such as confluent parakeratosis, necrotic keratinocytes, plasma cells, and exocytosis can be seen, the term "seborrheic-like dermatitis of AIDS" has been proposed[24,25]. HIV-associated seborrheic dermatitis can prove more resistant to conventional therapies, including those targeting *Malassezia* spp.

Psoriasis

Although the prevalence of psoriasis is similar in people living with HIV as in the general population, HIV-associated psoriasis is characterized by greater disease severity, frequent exacerbations, atypical presentations, resistance to treatment, and a higher frequency of psoriatic arthritis[24]. While plaque psoriasis is still the most common subtype (Fig. 78.13), there is a greater likelihood of inverse, guttate, and erythrodermic psoriasis as well as rupioid lesions characterized by thick, lamellated, concentric scale-crust. A hallmark of HIV-associated psoriasis is multiple morphologic subtypes in the same patient. An acute change in the pattern of pre-existing psoriasis or new onset of psoriasis with atypical features should prompt consideration of HIV infection[26].

For HIV-associated psoriasis that is not responding to topical medications, therapeutic options include phototherapy (e.g. narrowband UVB), acitretin, and ART[27,28]. The latter has been reported to result in marked improvement or clearance of psoriasis, although worsening of psoriasis may occur as a manifestation of IRIS. Data on the use of targeted immune modulators is limited, and these agents should be reserved for individuals with refractory skin disease receiving concomitant ART, along with monitoring of the CD4$^+$ T cell count and viral load. Inhibitors of TNF, IL-(12/)23, and IL-17 as well as apremilast have been used successfully in this patient population, with less risk of opportunistic infections than traditional immunosuppressive agents (e.g. methotrexate, cyclosporine)[27].

MUCOCUTANEOUS DISORDERS ASSOCIATED WITH HIV INFECTION
Inflammatory disorders
When severe, recalcitrant, or of sudden onset, consider HIV infection
• Seborrheic dermatitis (e.g. face, scalp) • Psoriasis • Reactive arthritis
Alone raises the possibility of HIV infection
• Eosinophilic folliculitis* • Papular pruritic eruption • Pityriasis rubra pilaris type VI, with follicular spines ± acne conglobata
Infectious diseases and infestations*
When severe and/or recalcitrant, consider HIV infection
• Human papilloma virus infections (warts), including acquired epidermodysplasia verruciformis-like lesions • Molluscum contagiosum – numerous, coalescent, and/or giant-sized, especially in adults • Dermatophyte infections
Alone raises the possibility of HIV infection
• Syphilis and other sexually transmitted infections (e.g. chancroid) • Bacillary angiomatosis • Botryomycosis ("grains" within the dermis composed of *Staphylococcus*, *Pseudomonas*) • Disseminated mycobacterial infections (tuberculous and non-tuberculous) • Chronic oral and anogenital herpes simplex or disseminated HSV • Herpes zoster, especially if multi-dermatomal, disseminated, verrucous or chronic, but can have classic presentation • Oral hairy leukoplakia • Anogenital and oral ulcers, verrucous plaques, or morbilliform eruption due to CMV • Kaposi sarcoma • Oropharyngeal candidiasis • Proximal subungual onychomycosis • Disseminated cryptococcosis • Disseminated dimorphic fungal infections (e.g. coccidioidomycosis, histoplasmosis, talaromycosis) • Crusted scabies • *Demodex* folliculitis • Disseminated or necrotic cutaneous leishmaniasis
Other
• Xerosis and acquired ichthyosis • Major aphthae; acute necrotizing ulcerative stomatitis with gingivitis • Porphyria cutanea tarda (often in association with hepatitis C) • Facial hyperpigmentation, idiopathic or due to photolichenoid drug eruption • Linear telangiectasias of the chest • Trichomegaly of the eyelashes and change in texture of scalp hair (e.g. curly → fine and straight) • Cutaneous lesions of non-Hodgkin lymphoma • Anal intraepithelial neoplasia/anal carcinoma; keratinocyte carcinomas • Acral persistent papular mucinosis; atypical variants of granuloma annulare
*Particularly when there is no known cause of immunosuppression.

Table 78.3 Mucocutaneous disorders associated with HIV infection.

Reactive arthritis

In patients with HIV disease, the typical presentation of reactive arthritis is oligoarthritis involving lower extremity joints plus enthesitis and mucocutaneous features such as keratoderma blenorrhagicum and circinate balanitis. HLA-B27 is present in 80%–90% of White individuals but absent in nearly all Black individuals with HIV-associated reactive arthritis[29]. Acitretin, sulfasalazine, and institution of ART are preferred over immunosuppressive therapies. Reactive arthritis can also be a manifestation of IRIS.



Fig. 78.13 Severe psoriasis in a patient with AIDS. Both sudden acute exacerbations and treatment resistance can be observed.

Other eczematous and papulosquamous dermatoses

Xerosis, atopic dermatitis, prurigo nodularis, and pruritus are common in people living with HIV, with a prevalence of up to ~40%[5]. This may reflect an HIV-induced shift to a predominantly Th2 cytokine profile, which can lead to disruption of the skin barrier. Higher rates of pruritus and atopy are associated with lower $CD4^+$ T cell counts. Acquired ichthyosis can also be seen; it typically begins on the lower extremities and may become generalized. HIV-associated pityriasis rubra pilaris (type VI PRP) is characterized by a variable association with acne conglobata, hidradenitis suppurativa, and lichen spinulosus, which together are often referred to as the HIV-associated follicular syndrome[30]. Patients may progress to erythroderma, with ensuing secondary infection and death reported.

Non-Infectious Pruritic Papular Disorders

Pruritic papular disorders are among the most common cutaneous manifestations of HIV disease. The severe pruritus and stigmatizing appearance of these eruptions can result in significant morbidity. Possible explanations include: (1) a shift towards a Th2 cytokine profile, with associated eosinophilia and increased levels of IgE and interleukins 4 and 5; (2) hypersensitivity to drugs or parasites; (3) circulating pruritogens associated with systemic disorders such as hepatobiliary or renal disease and lymphoma; and (4) HIV-related neural irritation and autonomic dysfunction, with reduced sweat and sebaceous gland secretion.

The differential diagnosis for pruritic papules is extensive. An evaluation should include the patient's current immune status, use of prescribed or recreational drugs, travel history, and other exposures. Infections, infestations (e.g. scabies), drug reactions, and pruritus due to systemic disorders should be excluded. Because atypical presentations are common in this group of patients, laboratory investigations and histologic evaluation may be necessary.

Pruritic papular eruption

The pruritic papular eruption (PPE) of HIV is characterized by severe pruritus and skin-colored to erythematous, non-follicular papules that are distributed symmetrically on the extremities and trunk (Fig. 78.14A). Excoriations, prurigo simplex, prurigo nodularis, and postinflammatory hyperpigmentation are additional findings. PPE is thought to represent a hypersensitivity reaction to arthropod antigens, an explanation supported by the higher prevalence in tropical countries and a predilection for the extremities. Histologically, there is a wedge-shaped perivascular and interstitial infiltrate of lymphocytes and eosinophils, similar to the features found in an arthropod bite reaction. Of note, some authors believe that PPE represents a spectrum of pruritic disorders that also includes eosinophilic folliculitis. Multiple treatments have been tried with limited success, including topical corticosteroids, antihistamines, oral antibiotics, and antiscabetic regimens. UVB phototherapy (broadband or narrowband) and ART may be of benefit in ameliorating the pruritus[31].

Eosinophilic folliculitis

Eosinophilic folliculitis is characterized by intensely pruritic, erythematous, follicular-based papules that are often excoriated; rarely, intact pustules are present. Lesions favor the scalp, face, neck, and upper trunk (Fig. 78.14B; see Ch. 38). Eosinophilic folliculitis usually develops in patients with advanced HIV disease and $CD4^+$ T cell counts <250–300/mm^3. Cultures are negative and there may be peripheral eosinophilia. An exaggerated reaction to *Malassezia*, *Demodex*, or other organisms normally present within the follicular infundibula is the proposed pathomechanism.



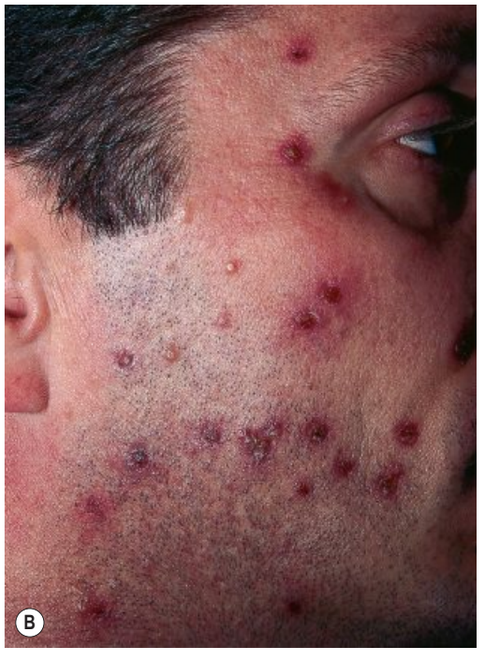


Fig. 78.14 Pruritic papular disorders. **A** The HIV-associated pruritic papular eruption is characterized by extremely itchy erythematous papules with a predilection for the limbs. This condition is thought to represent a hypersensitivity reaction to arthropod antigens. **B** Eosinophilic folliculitis with excoriated papules due to associated pruritus; lesions favor the head and upper trunk.

HIV-associated eosinophilic folliculitis, also referred to as immunosuppression-associated eosinophilic pustular folliculitis, can be distinguished from classic eosinophilic pustular folliculitis (Ofuji disease) by the intractable itch, lack of circinate lesions or palmoplantar involvement, and failure to respond to indomethacin. Although ART may lead to improvement of HIV-associated eosinophilic folliculitis, exacerbations can also occur as a manifestation of IRIS. Therapeutic options include: topical corticosteroids, tacrolimus and permethrin; oral antibiotics, itraconazole, dapsone and retinoids; and UVB phototherapy. However, the response is variable as HIV-associated eosinophilic folliculitis can prove difficult to treat.

Hair and Nail Disorders

A variety of hair and nail disorders can affect people living with HIV. Causes of hair loss range from telogen effluvium triggered by systemic infections to localized alopecia due to secondary syphilis or tinea capitis to side effects of antiretroviral drugs (e.g. emtricitabine/rilpivirine/tenofovir, indinavir, didanosine). Trichomegaly of the eyelashes, which reflects a prolonged anagen phase, has also been reported in association with HIV infection, including those treated with zidovudine and interferon-α[32,33]. Hair shaft alterations include straightening, curling, and becoming

softer/silkier or dull/lusterless. Sudden greying of the hair is thought to result from an autoimmune process targeting follicular melanocytes[34].

In one prospective study, nail changes were observed in two-thirds of individuals with HIV disease[35]. The most common finding was onychomycosis, with distal/lateral subungual and total dystrophic onychomycosis observed more frequently than the immunosuppression-associated proximal subungual variant. Additional reported nail changes include onychoschizia, onycholysis, leukonychia (including total leukonychia), Beau's lines, clubbing, koilonychia, and longitudinal melanonychia. Patients taking zidovudine may develop longitudinal and less often transverse or diffuse melanonychia (Fig. 78.15), and protease inhibitors (PIs) can cause paronychia or excessive periungual granulation tissue (see Ch. 71). Periungual erythema, fibromas, and SCC have also been reported.

Vasculitis

A broad spectrum of vasculitides, from cutaneous small vessel vasculitis to polyarteritis nodosa (PAN), has been observed in people living with HIV. Possible pathomechanisms include: (1) immune-complex deposition; (2) direct invasion of vessel walls by HIV; (3) co-infection with hepatitis B or C virus resulting in PAN or mixed cryoglobulinemia, respectively; and (4) opportunistic infections with cytomegalovirus, *Toxoplasma gondii*, *Pneumocystis jirovecii*, and mycobacteria[36]. Occasionally, a PAN-like vasculitis with peripheral neuropathy and digital ischemia occurs without concurrent hepatitis B virus infection. Erythema elevatum diutinum has been reported in patients with $CD4^+$ T cell counts $<300/mm^3$, and a Kawasaki-like syndrome has been described in both children and adults. Behçet disease has also been observed in the setting of acute HIV infection.

If corticosteroids and other immunosuppressive medications are required for HIV-associated vasculitis, they should be administered together with ART. ART alone may be beneficial but can also precipitate vasculitis as a manifestation of drug hypersensitivity or IRIS.

Photosensitivity Reactions

UV light hypersensitivity

People living with HIV may develop photosensitive dermatoses including chronic actinic dermatitis, porphyria cutanea tarda, photosensitive granuloma annulare, and photodistributed hyperpigmentation or depigmentation[37]. Photolichenoid eruptions can result from commonly prescribed medications such as TMP-SMX, dapsone, and NSAIDs (Fig. 78.16). Photosensitization is also a potential side effect of antiretroviral medications, e.g. efavirenz, tenofovir, saquinavir.

Porphyria cutanea tarda (PCT)

Acquired PCT can occur in patients with HIV disease, more often in men than women. This disruption in porphyrin metabolism could possibly be triggered by HIV-related impairment of cytochrome P450 enzymes, estrogen excess due to altered steroid hormone metabolism, co-infection with hepatitis B or C virus, alcohol intake, increased hepatic iron due to ineffective hematopoiesis, or direct hepatic damage by HIV[38].

Chronic actinic dermatitis

Chronic actinic dermatitis can be an initial manifestation of HIV disease. Pruritic eczematous lesions favor chronically sun-exposed areas (see Ch. 87). Most patients have a decreased minimal erythema dose (MED) to UVB ± UVA and visible light, and $CD4^+$ T cell counts are often $<200/mm^3$[3,39].

Metabolic Changes

HIV/ART-associated lipodystrophy and weight gain

In patients receiving ART, HIV/ART-associated lipodystrophy is a common finding. Patients may develop peripheral fat loss (lipoatrophy) or central fat gain (lipohypertrophy) or both (see Ch. 101). The underlying mechanisms of fat alteration are incompletely understood and involve a complex interplay between the virus, adipose immune system, and ART[40]. Lipodystrophy can be accompanied by metabolic abnormalities such as hyperlipidemia, insulin resistance, and diabetes mellitus. The reported prevalence ranges from 10% to 80%, with most patients developing the lipodystrophy within months to 2 years of ART initiation. Lipoatrophy and lipohypertrophy are recognized as distinct entities with separate pathogenic mechanisms.

Lipoatrophy is characterized by loss of subcutaneous fat, principally in the face, limbs and buttocks, without concomitant loss of lean muscle. The face looks "skeletal" due to loss of the buccal and/or temporal fat pads. Lipoatrophy is primarily a side effect of nucleoside reverse transcriptase inhibitors (NRTIs), especially earlier generation inhibitors such as stavudine. Proposed pathomechanisms include mitochondrial toxicity, impairment of adipogenesis and adipocyte differentiation, and increased lipolysis. Other risk factors include age >40–50 years, male sex, lower percentage of body fat, lower $CD4^+$ T cell count (<100 cells/mm^3), and higher plasma HIV-1 RNA levels ($>10^5$ copies/ml) at ART initiation.

Lipohypertrophy consists of fat accumulation in the abdominal visceral compartment, dorsocervical region ("buffalo hump"), and breasts. It has been attributed primarily to PIs and NRTIs. Hypothesized pathomechanisms include mitochondrial toxicity, dysregulation of fatty acid metabolism, changes in intra-abdominal glucocorticoid signaling, and alterations in growth hormone secretion. Additional risk factors include older age, female sex, elevated baseline triglycerides, higher percentage of baseline body fat, and longer duration of therapy. Lipohypertrophy represents one component of a broader condition of ectopic lipid deposition which can also involve the liver, epicardial tissue, and skeletal muscle.

Both weight and generalized fat gain are commonly observed following ART initiation, in part attributable to improved health and a concomitant gain in lean mass. However, weight gain is especially pronounced with



Fig. 78.15 Zidovudine-associated melanonychia. Patients receiving zidovudine may develop longitudinal streaks, horizontal bands, and diffuse hyperpigmentation.

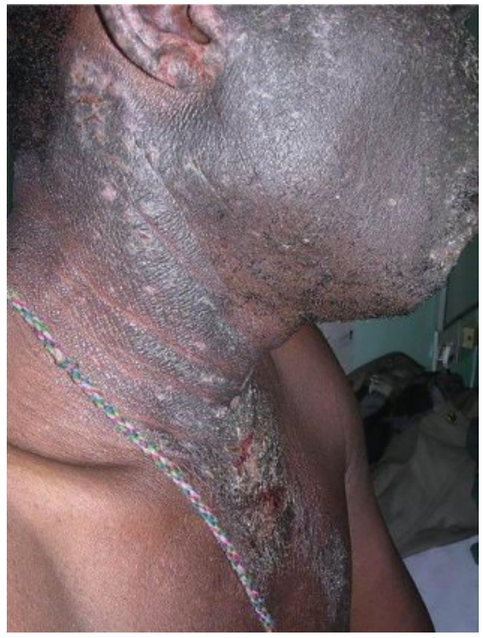


Fig. 78.16 Photolichenoid eruption in a patient with HIV. *Courtesy Ncoza Dlova, MD.*

integrase strand transfer inhibitors (INSTIs) and tenofovir alafenamide. The cause is unclear and may include effects on appetite or energy regulation.

The clinical implications of lipodystrophy include psychosocial distress, stigmatization, reduced adherence to ART, and increased risk for cardiovascular disease. Management includes a balanced diet with regular exercise and lipid- or glucose-lowering medications such as metformin[40]. Tesamorelin, an analogue of growth hormone-releasing hormone, is FDA-approved for treatment of abdominal obesity in individuals with HIV disease, but effects are not sustained after cessation of therapy and long-term safety data are lacking. Modest improvement in lipoatrophy and hyperlipidemia often occurs upon switching from thymidine analogue NRTIs to alternative agents, but substitution of other agents for PIs has had inconsistent effects in reversing lipohypertrophy.

Injectable fillers such as poly-L-lactic acid and calcium hydroxylapatite are FDA-approved for treatment of HIV/ART-associated lipoatrophy, and autologous fat transfer represents another option. Excess fat may be removed via surgery or liposuction, although reaccumulation typically occurs. In small series, bariatric surgery has been reported to lead to improvement. The incidence of lipodystrophy is expected to decrease further with the widespread use of newer ART regimens, although fat alterations can persist for years in patients who received older ART medications.

Malnutrition

The causes of malnutrition in people living with HIV include: (1) reduced food intake due to poor appetite, nausea, or dysphagia related to oral/esophageal candidiasis; (2) diarrhea secondary to infection, medications, or malignancy; (3) malabsorption; and (4) psychosocial issues[41]. Patients can develop the cutaneous manifestations of kwashiorkor, zinc deficiency, and other vitamin and mineral deficiencies. Nutritional replacement is critical, as malnutrition is associated with lower $CD4^+$ T cell counts and an increased risk of opportunistic infections.

Miscellaneous Dermatoses

Primary cutaneous mucinoses have been linked to HIV, especially localized papular variants of lichen myxedematosus in men with advanced HIV disease[42]. *Granuloma annulare* may present with generalized lesions or other atypical distribution patterns (e.g. a photodistribution). Both remission after ART and worsening as a manifestation of IRIS have been described[43]. *Major aphthae* presenting as large, painful, destructive oral lesions can also occur in people with HIV disease. Infective or neoplastic processes should be excluded, and severe cases may require treatment with systemic corticosteroids, thalidomide, or ART[44]. *Linear telangiectasias* on the chest have been reported in individuals with HIV infection, mostly in MSM[45].

HIV-RELATED CUTANEOUS NEOPLASMS

Factors that may contribute to the development of cutaneous malignancies in those with HIV disease include immunosuppression, co-infection with oncogenic viruses, and environmental exposures (e.g. UV radiation). In addition, HIV could potentially have direct effects such as activation of proto-oncogenes, alteration of cell cycle regulation, and inhibition of tumor suppressor genes[46].

Kaposi Sarcoma (KS)

HIV-associated KS is an aggressive vascular tumor that, like other types of KS (see Ch. 114), is caused by human herpesvirus type 8 (HHV-8). The latter can be transmitted by semen and saliva. Since the introduction of ART, there has been a marked decrease in the incidence, morbidity, and mortality of HIV-associated KS[47].

KS typically presents as red–purplish patches, papules, plaques, and nodules. The lesions can ulcerate and have a predilection for the face, upper body, oral cavity, and genitalia (Fig. 78.17). Oval lesions may align along the skin cleavage lines of the trunk (see Fig. 78.17D). Lymph node involvement can result in lymphedema, and the lungs and gastrointestinal tract are often affected.

The management of KS depends on the stage of HIV disease, the extent and sites of involvement, and medical comorbidities. ART is often an effective treatment for KS and represents a reasonable initial monotherapy for limited disease. However, flares of KS can also occur as a manifestation of IRIS following initiation of ART[48].

HIV-associated KS may respond to local destruction (e.g. cryotherapy), topical alitretinoin (9-cis-retinoic acid) gel, superficial radiotherapy/electron beam, photodynamic therapy, or intralesional vinblastine. Systemic therapies include liposomal doxorubicin or daunorubicin, paclitaxel, sirolimus, pomalidomide, interferon-α, and tyrosine kinase inhibitors (e.g. pazopanib) (see Ch. 114).

Keratinocyte Carcinomas and Melanoma

Compared to the general population, people living with HIV have a 2- to 3-fold increased risk of keratinocyte carcinomas[49]. The tumors tend to appear at a younger age and are more often multifocal and located on the trunk or extremities. In a Danish nationwide cohort study, the relative risks of BCC and SCC in people living with HIV compared to the general population were 1.8 and 5.4, respectively[50]. A low $CD4^+$ T cell count confers an increased risk of initial and subsequent primary SCCs[50,51]. These cutaneous SCCs also have a higher risk of recurrence and metastasis[48], but BCCs do not behave more aggressively. In general, BCCs and SCCs in patients with HIV disease should be managed in a traditional manner (see Ch. 108), with consideration of individual comorbidities.

Melanomas in people living with HIV are often multiple, frequently metastasize, and are associated with a poor prognosis[52]. Of note, HIV infection also increases the risk of developing Merkel cell carcinoma and sebaceous carcinoma[53].

Lymphomas

Cutaneous lymphomas may develop in people living with HIV[48,54], often in the setting of significant immune suppression. Clinically, pink to violaceous papules and nodules are seen; the lesions often ulcerate and may simulate panniculitis. HIV-associated lymphomas are most often B cell non-Hodgkin type and high or intermediate grade. They are typically in more advanced stages, and there is often involvement of the CNS, gastrointestinal tract, and/or skin at the time of presentation[55]. Approximately half of non-Hodgkin lymphomas in patients with HIV disease are associated with EBV infection.

Since the introduction of ART, a decrease in incidence and improved survival have been observed for all types of lymphoma. A prior diagnosis of AIDS and bone marrow involvement are associated with an unfavorable prognosis[56].

Cutaneous T cell lymphoma, in particular mycosis fungoides, as well as T cell lymphoproliferative disorders that may mimic mycosis fungoides clinically can also occur, albeit much less frequently than B cell lymphomas. The possibility of adult T cell leukemia/lymphoma caused by human T cell leukemia/lymphotropic virus type 1 (HTLV-1) should be considered and excluded.

Other Cutaneous Neoplasms

Eruptive atypical nevi have been described in people living with HIV. Cutaneous smooth muscle tumors, including leiomyomas and leiomyosarcoma, occur more frequently in children with HIV disease and may be associated with EBV infection.

DIFFERENTIAL DIAGNOSIS AND DIAGNOSIS

Differential Diagnosis of HIV-Associated Skin Conditions

The wide variety of infectious, inflammatory, and neoplastic disorders of the skin that may develop in the setting of HIV infection can have overlapping clinical features. Cutaneous eruptions range from classic forms to bizarre variants that present a diagnostic challenge. In particular, disseminated fungal infections and adverse drug reactions (see below) may be life-threatening and require early intervention with systemic antifungal agents or withdrawal of the offending medication.

The spectrum of cutaneous diseases tends to correlate with the immune status of the patient. An association between HIV-related disease incidence and the $CD4^+$ T cell count has been established (see Tables 78.1 & 78.2), and this allows for a more focused differential diagnosis. In general, disseminated and extensive disease occurs more frequently in the setting of lower $CD4^+$ T cell counts.

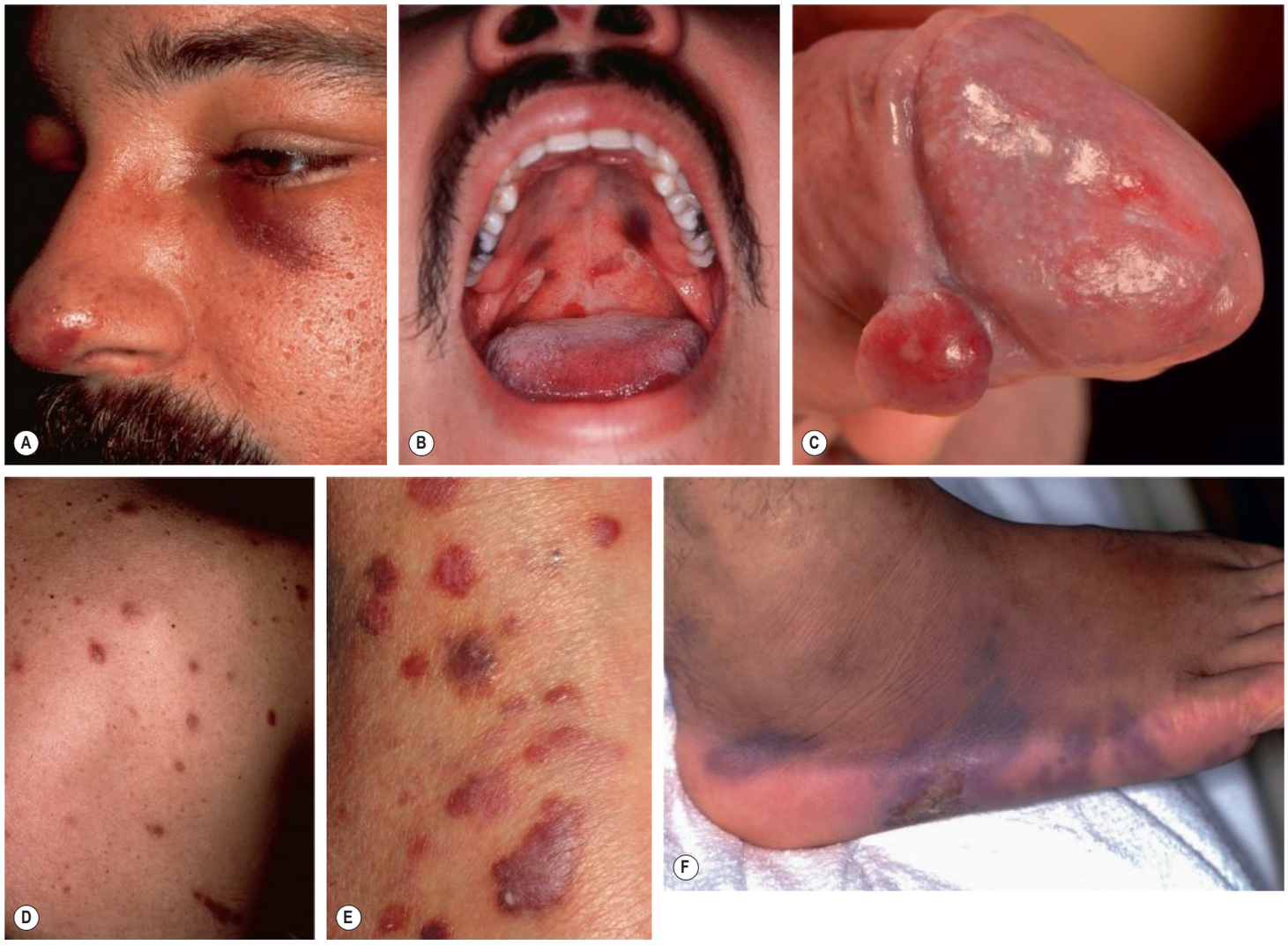


Fig. 78.17 HIV-associated Kaposi sarcoma. Violaceous to red–purple papules, nodules, and plaques on the face (**A**), palate (**B**), penis (**C**), back (**D**), leg (**E**), and foot (**F**). Oral candidiasis is also seen (**B**). Some of the elongated lesions on the trunk follow the skin cleavage lines (**D**), and early ulceration is evident on the foot (**F**). *F, Courtesy Thomas Horn, MD.*

Diagnosis of HIV-associated skin conditions

Diagnosis of cutaneous disorders in people living with HIV is based on the clinical appearance coupled with confirmatory studies such as scrapings, cultures, biopsies, and serologic or PCR-based assays. Patients often have mixed infections or combined infectious–neoplastic or inflammatory–neoplastic lesions (Fig. 78.18). Other factors such as age, sex, and anatomic distribution assist in narrowing the differential diagnosis (see Table 78.3).

Laboratory Diagnosis of HIV Infection

Since 1989, the diagnostic algorithm for HIV infection has included initial screening with a sensitive immunoassay, followed by confirmation with a more specific HIV antibody test, traditionally either a Western blot or indirect immunofluorescence assay (IFA). HIV seroconversion usually occurs ~4 weeks after initial infection, but the seronegative "window" period can last up to 3 months. Current fourth-generation HIV screening assays shorten this window via simultaneous assessment for anti-HIV IgM and IgG antibodies and the p24 capsid antigen, which can be detected as early as 15 days after infection (Table 78.4; see Fig. 78.3). The 2014 US Centers for Disease Control and Prevention (CDC) guidelines for the laboratory detection of HIV infection recommend fourth-generation screening with confirmation by an immunoassay that differentiates between HIV-1 and HIV-2 antibodies[57]. Although the screening tests have high sensitivities, the confirmatory tests are unable to detect recent infections; if the screening test is positive and the confirmatory test is negative or indeterminate, a nucleic acid test (NAT) for HIV-1 RNA can be performed[57].



Fig. 78.18 Oral herpes simplex virus infection and oral candidiasis. This combined infection was in an otherwise healthy young man who proved to be HIV-positive.

ANTIRETROVIRAL THERAPY (ART)

Antiretroviral Medications for Treatment and Prevention

There are >30 FDA-approved drugs in nine mechanistic classes that block HIV replication at various steps in its lifecycle (see Fig. 78.2). A list of FDA-approved antiretroviral medications is available at https://hivinfo.nih.gov/understanding-hiv/fact-sheets/fda-approved-hiv-medicines. Current ART regimens are more effective and better tolerated than those utilized in the past. Regimens that are less likely to lead to the emergence of HIV resistance, even when treatment adherence is not optimal, are favored.

LABORATORY TESTS FOR HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION		
Test	**Target of detection**	**Median "window" period from infection to positive test (days)**
Nucleic acid tests (NATs)		
Quantitative for HIV-1 viral load assessment	RNA (≥20–40 copies/ml)	6–10
Qualitative for HIV-1 diagnosis*	RNA (≥100 copies/ml)	10–12
Screening tests		
4th generation HIV-1/2 antigen/antibody EIA*	IgM, IgG, p24 antigen	16–18; 19–20 for rapid test†
3rd generation HIV-1/2 antibody EIA*	IgM, IgG	22–24; 26–32 for rapid test†
Supplemental/confirmatory tests		
HIV-1/2 antibody differentiation EIA*	IgG	32–36
HIV-1 Western blot	IgG	35–40
HIV-1 EIA	IgG	40+

*Currently recommended by the CDC for HIV diagnosis; the qualitative NAT is used when the screening test is positive but the confirmatory test is negative or indeterminate; tests that discriminate between HIV-1 and HIV-2 infection have been referred to as "5th generation".
†Results available in ≤30 minutes, so suitable for point-of-care use.

Table 78.4 Laboratory tests for human immunodeficiency virus (HIV) infection. The FDA-approved OraQuick® In-Home HIV Test provides results in 20 minutes from oral fluid, which has lower antibody levels than blood. Mail-in HIV tests that involve sending a finger-prick blood sample to a laboratory and receiving results as early as the next day are also available. EIA, enzyme-linked immunoassay; IFA, indirect immunofluorescence assay; NAT, nucleic acid test.
Data from Delaney KP, Hanson DL, Masciotra S, et al. Time until emergence of HIV test reactivity following infection with HIV-1: implications for interpreting test results and retesting after exposure. Clin Infect Dis 2017;64:53–9.

ART is recommended for all people with HIV who have a detectable viral load, regardless of the CD4+ T cell count[58]. Treatment should be initiated as soon as possible after HIV diagnosis in order to increase linkage to care and decrease time to viral suppression. The advantages of early HIV treatment include decreased morbidity and mortality as well as reduced HIV transmission.

The preferred first-line therapy in treatment-naive patients consists of an integrase strand transfer inhibitor (INSTI; also known as an integrase inhibitor) combined with dual nucleoside reverse transcriptase inhibitors (NRTIs); a two-drug regimen (INSTI + NRTI) is also an option in patients without hepatitis B co-infection[58–61]. Dual NRTIs plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI) represent alternative regimens. Multiple antiretroviral drugs are often combined into a single pill in order to reduce pill burden, and intramuscular injection of two long-acting agents (INSTI + NNRTI) every 1–2 months is an option for adults who are virologically suppressed on a stable ART regimen with no resistance to these agents or history of treatment failure. In the setting of virologic failure, subsequent medication changes are guided by resistance testing[59–61].

Over the past decade, effective strategies for preventing HIV transmission and acquisition have been described. In randomized controlled trials, the use of antiretroviral medications was shown to reduce the risk of HIV transmission from an infected person by ≥96%[62,63]. Pre-exposure prophylaxis (PrEP) consists of antiretroviral medications taken daily or on demand by HIV-negative individuals who are at risk of acquiring HIV; intramuscular injection of a long-acting INSTI every 2 months is also available[64,64a]. In MSM and persons who inject drugs, PrEP has been shown to reduce the risk of HIV acquisition by 50%–85%[65–67]. Of course, central to the effectiveness of this strategy is compliance. In women at risk for acquiring HIV, consistent use of a vaginal ring that continuously releases dapivirine and is inserted monthly led to a 75% reduction in HIV transmission. In addition, male circumcision reduced the risk of men acquiring HIV via insertive vaginal sex by ~60%[68–70]. Lastly, consistent and correct use of condoms remains a cornerstone in the drive to prevent transmission and acquisition of HIV.



Fig. 78.19 Exacerbation of leprosy due to immune reconstitution inflammatory syndrome following institution of ART therapy. *Courtesy Beatriz Trope, MD, PhD.*

CUTANEOUS DISEASES THAT CAN "FLARE" DUE TO THE IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME
Infections
Mycobacterium tuberculosis
Mycobacterium leprae
Mycobacterium avium complex and other species
Herpes simplex virus 1 and 2
Varicella–zoster virus
EBV (e.g. oral hairy leukoplakia)
Cytomegalovirus
Human papillomavirus
Molluscum contagiosum virus
Candida spp.
Dermatophytes
Cryptococcus spp.
Histoplasma capsulatum, Talaromyces (Penicillium) marneffei
Demodex, Malassezia spp. (e.g. folliculitis)
Leishmania spp.
Inflammatory disorders
Psoriasis, seborrheic dermatitis
Pityriasis rubra pilaris
Granuloma annulare
Sarcoidosis
Foreign body reactions (granulomatous)
Eosinophilic folliculitis
Acne vulgaris, rosacea
Papular pruritic eruption
Lupus erythematosus (systemic, discoid, tumid), relapsing polychondritis
Alopecia areata
Dyshidrotic eczema
Mid-dermal elastolysis
Neoplasms
Kaposi sarcoma
Non-Hodgkin lymphoma
Multiple eruptive dermatofibromas

Table 78.5 Cutaneous diseases that can "flare" due to the immune reconstitution inflammatory syndrome (IRIS).

Immune Reconstitution Inflammatory Syndrome (IRIS)

The rapid improvement in immunologic status that follows institution of ART can paradoxically result in clinical exacerbations of infectious, neoplastic, and inflammatory diseases in a subgroup of patients with HIV (Fig. 78.19)[71,72]. This phenomenon is known as *immune reconstitution inflammatory syndrome* (IRIS). It occurs in ~15% of patients 1 week to 3 months after initiation of ART, with a higher risk in those with low CD4+ T cell counts (<50/mm^3) prior to therapy[73]. The overall mortality of IRIS is ~5%, but it is as high as 20% in patients with cryptococcal meningitis. Distinguishing IRIS-associated flares of inflammation from active opportunistic infections or drug reactions may be difficult. Cutaneous diseases that can be exacerbated in the setting of IRIS are listed in Table 78.5.

Drug–Drug Interactions

Knowledge of potential drug interactions is necessary to prevent adverse reactions and therapeutic failures. The human cytochrome P450 system metabolizes a number of drugs used to treat HIV disease and associated complications. Cytochrome P450 3A4 inhibitors, which include most of the PIs and delavirdine, impair drug metabolism, leading to accumulation of drugs that share the same metabolic pathway (see Ch. 131). Cytochrome P450 3A4 mixed inducers/inhibitors and inducers (e.g. efavirenz and nevirapine, respectively) may accelerate clearance of other medications, thereby necessitating dose adjustments. Cytochrome P450-independent interactions include: (1) an increase in intracellular drug levels and toxicity of didanosine when used in combination with ribavirin and/or tenofovir[74]; and (2) a decrease in atazanavir concentration when coadministered with tenofovir[75].

Drug Eruptions

Adverse drug reactions (ADR) are common in people living with HIV. Underlying risk factors include genetic predisposition as well as immune dysregulation and alterations in drug metabolism[76]. Because these patients typically take multiple medications, identification of the causal agent or combination of agents is often a complex and frustrating process (see Ch. 21). Morbilliform eruptions are the most common presentation of drug hypersensitivity, and the incidence is significantly higher in people with HIV disease than in the general population. Patients may also present with urticaria, pruritus, vasculitis, exfoliative erythroderma, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). The major cutaneous side effects of antiretroviral medications are outlined in Table 78.6[77,78].

CUTANEOUS SIDE EFFECTS OF ANTIRETROVIRAL THERAPY (ART)

Type of skin reaction	NRTIs/NtRTIs	NNRTIs	Protease inhibitors	Integrase inhibitors	CCR5 inhibitors	Fusion inhibitors
Injection site reaction						
Morbilliform eruption	Emtricitabine*, Abacavir†	Nevirapine > etravirine, efavirenz	Atazanavir, fosamprenavir‡ > darunavir‡, tipranavir‡ > lopinavir			
DRESS (DIHS)	**Abacavir†**	**Etravirine, efavirenz**, **Nevirapine**	Atazanavir, darunavir‡, fosamprenavir‡, tipranavir‡, lopinavir	Raltegravir†	Rare	Rare
SJS/TEN	Rare	Rare, Nevirapine > efavirenz, etravirine	Rare	Rare		
Lipodystrophy (also insulin resistance and elevated TTGs)	d4T, ddI	Efavirenz				
Paronychia, excessive periungual granulation tissue	Lamivudine		Indinavir			
Xerosis			Indinavir			
Hyperpigmentation of skin and nails	AZT, emtricitabine (palmoplantar)					

*Palmoplantar eruption.
†Associated with HLA-B*5701 (abacavir) and HLA-B*5301 (raltegravir) alleles.
‡Sulfonamide-like structure and should be used cautiously in patients with sulfonamide allergy.

Table 78.6 Cutaneous side effects of antiretroviral therapy (ART). In general, patients with HIV infection have an increased risk of developing drug-induced morbilliform eruptions and toxic epidermal necrolysis, e.g. to sulfonamides. Rashes, including morbilliform eruptions, have also been described in patients treated with CD4 post-attachment and gp120 attachment inhibitors, and injection site reactions are common in patients receiving the capsid inhibitor lenacapavir. **Bold** = most common; dark-colored cells = common; light-colored cells = less common. A whole cell that lacks specific drug names refers to that class of drugs, whereas in subdivided cells, refers to the remainder of that class of drugs. AZT, zidovudine; CCR5, CC-chemokine receptor 5; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs/NtRTIs, nucleoside/nucleotide reverse transcriptase inhibitors; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; TTGs, triglycerides.



Fig. 78.20 Morbilliform drug eruption due to trimethoprim–sulfamethoxazole (TMP-SMX). This young man with HIV developed a widespread eruption of blanchable erythematous macules and papules 8 days after starting TMP-SMX. Note the coalescence on the upper trunk.

In people with HIV infection, trimethoprim–sulfamethoxazole (TMP-SMX) is the most common cause of a cutaneous drug reaction. Often taken for prophylaxis or treatment of *Pneumocystis jirovecii* pneumonia or toxoplasmosis, intravenously administered TMP-SMX leads to an exanthematous eruption and fever (typically 8–12 days after initiating therapy) in 50%–60% of patients (Fig. 78.20). This occurrence rate is 10 times that observed in the general population[79]. Additional side effects of TMP-SMX include fixed drug eruption, SJS, and TEN.

Close observation is often sufficient since most cutaneous drug eruptions spontaneously regress, especially the morbilliform type. However, if systemic signs such as fever develop or epidermal detachment is observed, the suspected offending agent(s) should be withdrawn immediately as this may herald a more serious, possibly life-threatening, complication. With some drugs such as zidovudine, sulfonamides, and dapsone, patients may be successfully desensitized after an adverse drug reaction. Drug rechallenge should be done under controlled circumstances. Rechallenge is contraindicated for abacavir and is not recommended for NNRTIs.

CONCLUSIONS

The number and variety of manifestations of HIV disease are greater in the skin than in any other organ. Cutaneous complications are a source of significant morbidity and may also be stigmatizing. Although ART has decreased the incidence of several HIV-associated skin conditions, other disorders such as IRIS, drug reactions, metabolic disturbances, HPV infections, and SCCs are still commonly observed. In fact, they may even be increasing in incidence due to prolonged survival of people living with HIV. By recognizing the spectrum of HIV-associated skin conditions and performing appropriate diagnostic tests, treatment can be administered in a timely fashion and outcomes optimized.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 78.1 Hypertrophic herpes simplex virus (HSV) infection. This unusual presentation of HSV is mainly reported in people with HIV. Treatment entails prolonged courses of antiviral medication or surgery. Biopsy may be required to exclude neoplasia.



eFig. 78.2 Herpes simplex virus (HSV) infection of the pinna. This patient presented with a chronic, non-healing ulcer due to HSV type 2. Antiviral medication was continued until full clinical resolution occurred.



eFig. 78.3 Chronic herpes zoster in a patient with HIV. *Courtesy Regional Dermatology Training Centre, Moshi, Tanzania.*



eFig. 78.4 Molluscum contagiosum. Large lesions with coalescence in a patient with HIV.



eFig. 78.5 Oral hairy leukoplakia. Irregular white plaques on the sides of the tongue due to EBV. These lesions have no malignant potential and treatment is optional.



eFig. 78.6 Necrotizing fasciitis in a patient with HIV.



eFig. 78.7 Disseminated histoplasmosis. Multiple umbilicated papules and ulcers with rolled borders. Diagnosis is via histology with fungal stains and culture. Patients are usually severely immunosuppressed.



eFig. 78.8 Psoriasis. This patient with HIV has extensive severe skin and nail psoriasis. Note the swelling of the right middle finger and left thumb. Arthritis is more common in HIV-associated psoriasis.



eFig. 78.9 Cutaneous vasculitis. Drug-induced and infective (e.g. due to hepatitis C) causes of vasculitis should be excluded in patients with HIV. Corticosteroids and other immunosuppressive therapies should be used with caution.



eFig. 78.10 Granuloma annulare in a patient with HIV. *Courtesy Kalman Watsky, MD.*



eFig. 78.11 Major aphthous ulcers in patients with HIV. Oral aphthous ulcers are often large, painful, and persistent in patients with HIV infection. Infectious and neoplastic processes should be excluded. Severe cases may require thalidomide.

79 Human Papillomaviruses

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Synonyms: ■ Verrucae vulgares (singular: verruca vulgaris) – common warts ■ Verrucae palmares et plantares – hand and foot warts ■ Verrucae planae – flat warts, plane warts ■ Condylomata acuminata (singular: condyloma acuminatum) – genital warts ■ Condylomata plana – flat cervical condylomas, plane condylomas ■ Squamous intraepithelial lesion (SIL) – cervical intraepithelial neoplasia (CIN); vulvar (VIN); vaginal (VaIN); penile (PIN or PeIN); anal (AIN) ■ Buschke–Löwenstein tumor – giant condylomata acuminata, condylomata acuminata gigantea ■ Florid oral papillomatosis – Ackerman tumor ■ Papillomatosis cutis carcinoides – Gottron tumor ■ Focal epithelial hyperplasia – Heck disease

Key features

- Human papillomaviruses (HPVs) comprise a large group of more than 200 genotypes that infect the epithelia of skin or mucosa and most commonly cause benign papillomas or warts
- Epidermodysplasia verruciformis (EV) is an inherited disease characterized by generalized flat warts or pityriasis versicolor-like macules, caused by chronic infection with HPV types in the genus β; patients often develop squamous cell carcinomas (SCCs) in sun-exposed areas
- EV-associated HPV types are also detected in skin cancers and normal skin. These viruses are activated by UV exposure, immunosuppression, and specific host genetic background (EV)
- Anogenital HPV is a highly prevalent, sexually transmitted infection (STI) seen predominantly in young adults. Condylomata acuminata or benign anogenital warts are typically caused by HPV-6 or -11, which are considered to be low-risk types
- Persistent infection with high-risk HPV types, predominantly HPV-16 and -18, is the major cause of cervical and anal cancers, a subset of vaginal, vulvar, penile, and oropharyngeal cancers, and rarely digital SCCs
- Patients with cellular immunodeficiencies are at higher risk for persistent HPV infection and progressive disease
- No effective specific antiviral treatment for warts exists, and most therapies focus on destruction of visible lesions or induction of a cellular immune response
- Highly effective prophylactic HPV vaccines based on virus-like particles (VLPs) have been licensed for the prevention of genital warts and/or HPV-associated anogenital cancers

INTRODUCTION

Papillomaviruses are a large group of DNA viruses that are widely distributed in animals and humans, most commonly inducing benign papillomas or warts[1]. Recurrent skin and anogenital warts may be disfiguring, impose a considerable psychological burden, and are a frequent cause of medical office visits. A subset of human papillomaviruses (HPVs) designated as high-risk types, most often HPV-16 and -18, is now recognized as the primary etiologic agent for: cervical cancer and its precursor lesions; a subset of malignancies at other anogenital sites and in the upper aerodigestive tract; and, rarely, squamous cell cancer (SCC) of the digits. In contrast, infection with the common cutaneous HPV types 1, 2, 4, 27, 57, etc. is not thought to have any oncogenic potential[1]. In immunocompromised patients, HPV infections tend to persist and result in an increased risk of anogenital neoplasias. The high prevalence of genital HPV infection in sexually active young adults is a major concern, as effective antiviral treatments do not exist. More than two decades ago, prophylactic vaccines based on virus-like particles (VLPs) that prevent transmission in animal models of papillomavirus infection were developed[2–4]. Human vaccine studies subsequently demonstrated safety and nearly complete (>90%) efficacy in preventing vaccine type-restricted genital HPV infection and the development of associated neoplasias[5–7].

History

An infectious etiology for human warts had long been suspected[1], and experimental transmission of common warts with a cell-free extract was demonstrated over 100 years ago[8]. The descriptions of cottontail rabbit papillomavirus (CRPV) in 1933 and the rare genodermatosis *epidermodysplasia verruciformis* (EV) demonstrated the oncogenic potential of papillomaviruses. Following the cloning of the first papillomavirus genome in the late 1970s, the plurality of human and animal papillomaviruses became evident[9]. Based on genome sequencing, HPV types can be grouped into phylogenetic trees with a remarkable relationship to biologic behavior, e.g. mucosal and cutaneous types, high-risk and low-risk genital HPV, and EV-associated HPV[9]. Today, the genomes of more than 200 HPV types have been fully characterized and additional partial DNA sequences have been obtained, indicating the existence of at least 200 HPV genotypes[10]. In 1976, zur Hausen proposed an association between papillomaviruses and cervical cancer[11], and subsequent molecular studies led to the recognition of a subset of HPV types in a high proportion of cervical carcinomas. The identification of biologic differences between "high-risk" and "low-risk" mucosal HPV confirmed that infection with oncogenic HPV was the main cause of cervical cancer and its precursor lesions[12].

EPIDEMIOLOGY

Cutaneous warts are caused by a small group of specific HPV types, with a prevalence of up to 30% in primary schoolchildren and a decline thereafter with increasing age[13–15]. Patients living in larger households often report an infected cohabitant, supporting the concept of person-to-person transmission. The majority of warts will regress spontaneously within 1–2 years. After clearance occurs, reinfection with the same HPV type appears to be uncommon, suggesting that protective type-restricted immunity may develop.

Genital infection with HPV occurs most commonly by intimate contact, while infection of non-genital skin may occur via direct skin-to-skin contact or indirectly through contaminated surfaces and objects (e.g. swimming pool, gymnasium). Basal keratinocytes, which serve as the primary targets for HPV infection, are exposed to the virus through minor abrasions, and infection is promoted by maceration. Autoinoculation of virus from the lesion to adjacent skin is observed frequently, especially for digital or flat warts. Using sensitive polymerase chain reaction (PCR)-based detection, normal-appearing skin surrounding HPV-associated lesions and even skin of healthy volunteers may contain HPV DNA. These observations help to explain the high recurrence rate of warts (e.g. 20%–50% for genital condylomata) and the observation that treatment may not prevent further transmission of the virus. Papillomaviruses are resistant to heat and desiccation due to the absence of a viral envelope, and even laser fumes may contain infectious virions[16].

Genital warts in prepubertal children are uncommon and their diagnosis raises special concerns. Although viral transmission may occur during delivery, from close family contacts, or by autoinoculation

from skin warts, the possibility that these lesions may have been caused by sexual abuse should always be carefully considered (see below)[17].

In the US, HPV infection of the lower anogenital tract was the most common sexually transmitted infection (STI)[18–21], with a historical overall prevalence of ~40% in those ages 19–59 years[18]. However, following the introduction of the quadrivalent HPV vaccine, the prevalence of HPV types 6, 11, 16, and 18 in cervicovaginal specimens decreased in women ages 14–19 years, declining from 11.5% in the prevaccine era (2003–2006) to 5% in the years 2007–2010[19]. Behavioral risk factors include sexual intercourse at an early age and the number of lifetime sexual partners[9]. Circumcised men are less likely to carry and transmit HPV infection. In men who have sex with men (MSM), anal HPV infection is very prevalent (up to 75%). The public health impact of genital HPV infection is evidenced by the high number of initial visits to physicians' offices for treatment of genital warts and the frequency of consequences such as abnormal Pap smears and cervical neoplasia. In the US, the estimated prevalence of sexually acquired HPV infection is 42 million people and the estimated annual cost burden of genital HPV infection is $6 billion, making it the second most costly STI after HIV infection[20].

Most genital papillomavirus infections resolve spontaneously, whereupon HPV DNA becomes undetectable by PCR. The median duration of high-risk HPV infections in women is 8 months and persistence is found in 30% after 1 year and in 9% after 2 years[9]. Persistent cervical infection with a high-risk HPV type is required for the development of cervical intraepithelial neoplasia (CIN) and carcinoma. HPV-16 is detected in ~50% of cervical cancers and high-grade CIN. Together, HPV-16, -18, -31, -33, -45, -52, and -58 have been identified in ~90% of cervical cancers[9], and all are targeted in the nine-valent HPV vaccine.

Worldwide, an estimated 570 000 cases of cervical cancer were diagnosed in 2018, resulting in about 310 000 deaths[22]. The disease occurs predominantly in low-income countries that lack effective cervical screening programs. In the US, prevention and early detection programs have reduced the incidence rate of cervical cancer by ~75%, to 8 per 100 000 women per year. According to the American Cancer Society, an estimated 14 500 new cases of cervical cancer occurred in 2021, resulting in ~4300 deaths. Although high-risk oncogenic HPV types account for most of the observed risk for developing cervical cancer, smoking, cervical inflammation, parity, and oral contraceptive use have been proposed as cofactors[9]. While there is little evidence for hematogenous spread of HPV, ~60% of patients with anogenital infections develop low-titer, type-restricted antibodies during the course of infection[23]. Titers tend to decrease slowly and may persist for years after viral clearance.

Immune suppression in HIV-infected patients and organ transplant recipients results in HPV infections that are more frequent, persistent, and likely to progress to intraepithelial neoplasia, with $CD4^+$ T cell depletion and HIV viral load being important risk factors. In studies analyzing anal swabs, up to 93% of HIV-seropositive MSM were positive for HPV DNA, compared to 60% of HIV-negative MSM[24]. HPV-associated anal intraepithelial neoplasia (AIN), a likely anal cancer precursor, is found in up to a third of HIV-infected MSM, compared to 20% of HIV-negative MSM. Antiretroviral therapy has shown no or only a modest beneficial effect on the incidence and progression of AIN or CIN. Similarly, organ transplant recipients are at an increased risk for developing warts and genital neoplasias[25]. They also have a higher incidence of premalignant and malignant skin neoplasias, e.g. actinic keratoses, Bowen disease, and SCCs, especially in sun-exposed areas.

Cutaneous tumors from organ transplant recipients as well as "healthy skin" and plucked hairs from immunocompetent patients often contain DNA from β HPV types (see below)[9,25]. Only in patients with EV and immunocompromised hosts do β HPV infections result in highly active viral replication with cytopathic effects and clinical lesions[25]. In skin swab samples, children from 1 month to 4 years of age have a high prevalence (from 50% to 70%) of HPV DNA[26], indicating that normal-appearing human skin is colonized with a multiplicity of β HPV types very early in life, most likely through close skin-to-skin contact. Beta HPV DNA has also been detected in psoriatic lesions[27] and skin cancers from PUVA-treated patients; however, highly sensitive PCR-based methods were required for detection and viral gene transcription has not been reported.

Recurrent respiratory papillomatosis (RRP) is characterized by exophytic lesions of the airways. It occurs in juvenile- and adult-onset forms and is usually caused by HPV-6 and -11. Despite its low incidence of 0.4–1.2 per 100 000[18], RRP is the most common benign tumor of the larynx. It is believed that in childhood-onset RRP, vertical HPV transmission from mother to child occurs by aspiration during delivery through an infected birth canal[28]. Although treatment should be considered in pregnant women with condylomata in order to reduce viral load, there is insufficient evidence to support cesarean section to prevent development of RRP in the offspring. Adult-onset RRP more likely results from genital-to-oral transmission.

PATHOGENESIS

Papillomavirus Evolution

Historically, papillomaviruses were grouped together with polyomaviruses, but their fundamentally different biology and genetic organization resulted in their reclassification as a separate family in 2000[10]. The National Center for Biotechnology Information (NCBI) nucleotide sequence database (www.ncbi.nlm.nih.gov) and the Karolinska Institutet International HPV Reference Center (www.hpvcenter.se) currently list more than 200 different HPV types as well as numerous incompletely characterized putative newer HPV types. By definition, a novel type has more than 10% dissimilarity from any previously characterized type in the DNA sequences of three HPV genes (E6, E7, and L1). Dissimilarity of 2%–10% is defined as a subtype, and <2% as a variant[10].

By comparing DNA sequences in conserved portions of the papillomavirus genomes across different types, a phylogenetic tree establishing the degree of relatedness among these types has been generated[10]. Two general, the α- and β-papillomaviruses, encompass almost all known HPV types, with the genus α containing mucosal and cutaneous HPV types that are pathogenic in normal hosts and the genus β containing the types associated with EV; γ, μ, and ν genera contain additional cutaneous types. Within each genus, HPV types are grouped according to sequence homology into species, which often share similar biologic and pathologic properties (e.g. HPV-16 and -31). Present models postulate that HPVs co-evolved with our human ancestors and novel HPV types or variants were generated through either genetic drift or natural selection via adoption of specialized ecologic niches. Genetic recombination between HPV types does not occur.

Virology

Papillomaviruses are non-enveloped, double-stranded DNA viruses ~55–60 nm in diameter[9]. The spherical capsid is composed of two virally encoded proteins: the major structural protein L1 and the minor structural protein L2. During virion assembly within cells, L1 proteins form pentamers called capsomeres, and 72 capsomeres multimerize to form the viral capsid with an icosahedral symmetry arranged on a $T = 7$ surface lattice. The capsid surrounds the viral DNA, thereby protecting it from degradation, and it also enables the virus to bind efficiently to target cells. Packaged viral DNA is associated with L2 and cellular histones, forming a mini chromosome. In contrast, the early (E) viral proteins are not incorporated into infectious virions.

When expressed in cell culture, the L1 major capsid proteins of papillomaviruses self-assemble into VLPs that are morphologically similar to native virions (Fig. 79.1)[3]. Papillomavirus VLPs display type-restricted and neutralization epitopes that are used to detect serum antibodies and as the basis for prophylactic vaccines (see below)[4,29].

The HPV genome, ~8 kilobases (kb) in length, is composed of three domains: the upstream regulatory region (URR), the early region, and the late region (Fig. 79.2). The URR, ~1 kb in length, lacks open reading frames (ORFs) and contains the origin of replication and many of the control elements for transcription and replication. The early region, ~4 kb in length, contains the ORFs for genes expressed early in the papillomavirus life cycle. The late region, ~3 kb in length, encodes the capsid proteins (see above)[9].

Papillomavirus Life Cycle

The papillomaviruses are highly species-specific, and productive infection has not been observed outside natural host tissue. The papillomavirus life cycle is completed only in fully differentiated squamous epithelia. This has impeded its study in monolayer tissue culture cells, where late gene expression and virion production do not occur. Only

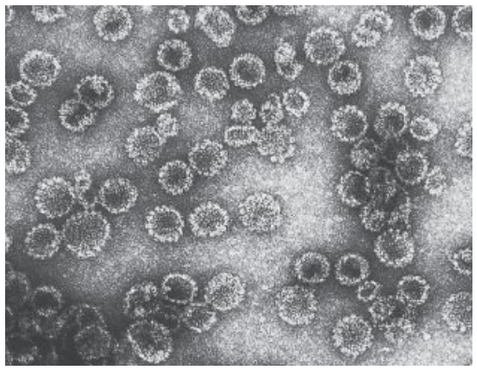


Fig. 79.1 Transmission electron photomicrograph of purified HPV-16 virus-like particles (VLPs). A prophylactic vaccine that contains HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58 VLPs has been approved for the prevention of anogenital warts and cancers. Following expression in cell culture, the L1 capsid protein self-assembles into VLPs (empty capsids ~50 nm in diameter devoid of HPV DNA) that display type-restricted and neutralization surface epitopes similar to native virions. *Courtesy Saeed Shafti-Keramat.*

a small number of HPV types have been successfully propagated in mouse xenograft or raft culture systems, and limited amounts of infectious virions have been generated[9].

Productive infection and induction of hyperproliferation are initiated when the virus enters proliferating basal epithelial cells (Fig. 79.3). This layer of cells is not normally accessible to the virus because of the mechanical barrier provided by the overlying differentiated cell layers. Therefore, it is likely that infection requires an abrasion or other trauma to the epithelium to expose the basal cells to the virus. Our knowledge about early steps of infection such as viral entry and uncoating is limited. The receptor(s) that mediate virus binding to epithelial cells have not been definitively identified, but binding appears to depend on the L1 major capsid protein, and cell surface and/or basement membrane heparan sulfate is necessary for efficient infection *in vitro*[30,31]. The amino terminus of the L2 minor capsid protein is then cleaved by furin (a proprotein convertase), which exposes both a cross-neutralization epitope on L2 and a binding site (thought to be on L1) that facilitates viral entry via a putative secondary receptor on keratinocytes[31,32]. Upon infection, the covalently closed circular DNA genome becomes established as a low-copy autonomous replicon in the nuclei of basal cells, thereby creating a long-term reservoir of viral DNA.

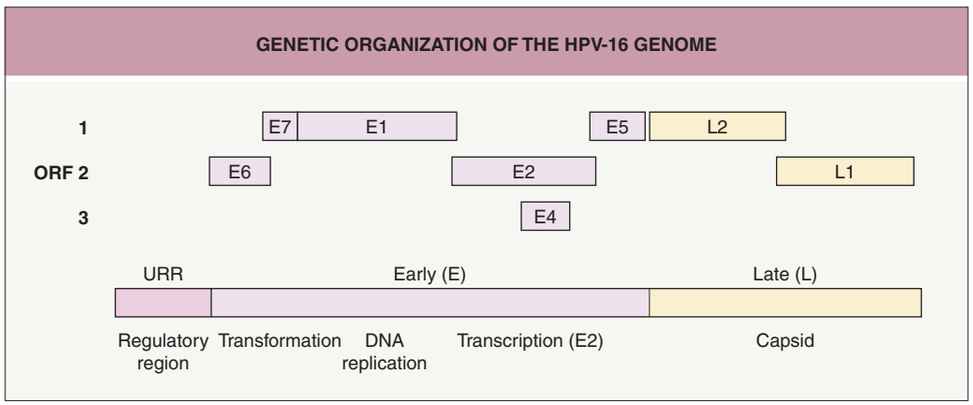


Fig. 79.2 Genetic organization of the HPV-16 genome. This is a linearized map of the 7.9 kb circular double-stranded genome. All open reading frames (ORFs) reside on one strand. Early (E) and late (L) regions are indicated. The upstream regulatory region (URR) contains the origin of replication and control elements for transcription and replication.

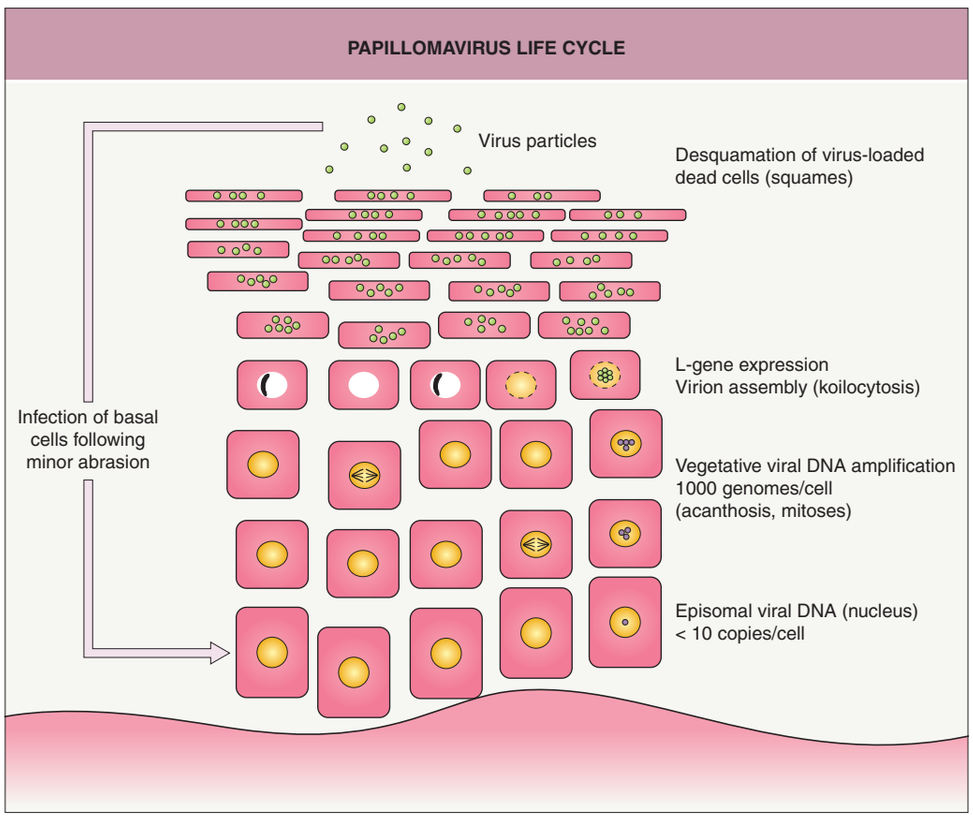


Fig. 79.3 The papillomavirus life cycle. The figure depicts a productive (virion-producing) benign wart. *Adapted from Orth G. Epidermodysplasia verruciformis. In: Salzman NP, Howley PM (eds). The Papovaviridae: Volume 2 The Papillomaviruses. New York: Plenum Press; 1987:199–243.*

The program of viral gene expression is intimately linked to the differentiation state of the infected cells. The E genes are transcribed at low levels in the basal cell layer and spinous layer. The first genes to be expressed following infection are the E1 and E2 genes, which are responsible for controlling the transcription of other viral genes and replication of the viral genome. HPVs do not encode the enzymes required for transcription or replication of viral DNA. Consequently, HPV is entirely dependent on the co-opting of cellular machinery for these functions. One major effect of HPV proteins E5, E6, and E7 is that the epidermal cell cycle, which is normally blocked for cells that are suprabasal, continues so that HPV genome copy number can be amplified to high levels during vegetative viral replication for assembly into virions (see Fig. 79.3). The E6 and E7 proteins of the high-risk mucosal HPV types act as viral oncoproteins, but no such functions are associated with the corresponding proteins of the low-risk mucosal and EV types[9]. There is limited understanding of possible differences between oncogenic (e.g. HPV-5, -8) and the non-oncogenic β HPV types.

In combination with other cellular proteins, E6 from high-risk mucosal HPV causes the ubiquitin-mediated degradation of the cellular protein p53. Elevated levels of p53 arrest cells in the G1 phase of the cell cycle or induce apoptotic cell death, so that E6-facilitated destruction of p53 removes a brake on suprabasal cell cycling. One of the principal effects of high-risk mucosal HPV E7 is to bind to the underphosphorylated form of RB (the retinoblastoma tumor suppressor protein). A physiologic role of underphosphorylated RB is to bind to and inhibit the function of the E2F transcription factor (see Fig. 107.4). When HPV E7 binds RB, E2F is liberated from this inhibition and is thereby able to induce the expression of genes required for DNA replication. Both E6 and E7 are multifunctional proteins, and while their effects on p53 and RB are critical ones, additional targets are also important to the oncogenic potential of the virus. These include activation of telomerase by E6, binding of histone deacetylases by E7, and synergistic effects of both proteins that lead to centrosome abnormalities and chromosomal instability[9].

The genes for the virion structural proteins, i.e. the late (or L) genes, are expressed in the terminally differentiated superficial layers of the epithelium. The more superficial epithelial layers also have higher levels of expression of E1 and E2 and amplification of viral DNA. The amplified genomes are encapsulated by the L1 and L2 capsid proteins to generate infectious virions, and virus particles are observed in the granular layer of the epithelium and above. Virus assembly is not believed to lyse the cells; instead, the virus is shed with the cornified layer as cells slough from the epithelial surface (see Fig. 79.3). E4 proteins are hypothesized to disrupt the intracellular filamentous network of keratinocytes, which may facilitate virus release from the corneocytes[9].

Host Immune Response

Persistent papillomavirus infections are common, indicating that HPVs have evolved mechanisms to evade immune surveillance. There is no viremic phase during the life cycle, so a systemic immune response is avoided. In addition, low levels of viral proteins are expressed in the basal and spinous cell layers of the epidermis, where they would be most likely to be recognized by Langerhans cells and infiltrating lymphocytes. Only in the more immunologically privileged terminally differentiated layers is there extensive production of virion proteins, with shedding of infectious virus exclusively from the external epithelial surface[9]. Despite the relative success of papillomaviruses in evading immune responses, up to two-thirds of cutaneous warts spontaneously regress within 2 years, and lesions of multifocal infections often regress concomitantly. There is also an increased prevalence of warts in patients with suppressed cell-mediated immunity. In contrast, patients with underlying defects in humoral immunity do not seem to be predisposed to HPV infections, suggesting a primary role of cell-mediated responses.

Although low amounts of virion capsid proteins are produced in the lower epidermal cell layers, serum antibodies specific to conformational virion epitopes of high-risk HPV-16 can be detected in more than half of women with low-grade or asymptomatic genital HPV-16 infections[33]. It is unknown if these antibodies play a role in limiting reinfection with the same type from autoinoculation or from an infected sexual partner.

Latent HPV infections are defined as persistence of HPV DNA in clinically and cytologically normal epithelium. However, it is difficult to distinguish true viral latency from persistent infection with a low level of DNA replication. The mechanisms by which HPV enters into and is activated out of latency are unknown[9].

Oncogenic Potential of HPV

Different HPV types have markedly different oncogenic potentials. The vast majority of cervical cancers, for example, contain the sequences of one of five HPV types: 16, 18, 31, 33, or 45[34]. In contrast, infection with HPV-6 or -11 occurs commonly in benign or low-grade intraepithelial lesions but is very rarely associated with the development of anogenital malignancies. HPV-5 and -8 DNA sequences are frequently detected in SCCs associated with EV.

Progression of HPV-associated cervical lesions to invasive cancer typically requires several decades. Both persistent HPV infection and the accumulation of additional genetic mutations are required in the current model of multistage carcinogenesis[9]. Integration of the viral genome randomly into the host DNA is a common event, invariably leading to loss of E1 and E2 expression. In HPV-16 and -18, E2 functions to repress the transcription of E6 and E7 genes. Therefore, integration is thought to increase expression of E6 and E7, which are selectively retained and expressed at elevated levels in carcinomas, suggesting a critical role for oncogenic progression (see above)[9].

Differences in the activities of E6 and E7 genes between oncogenic and non-oncogenic HPV types principally account for the different risk of progression. E6 and E7 proteins derived from high-risk HPV types (e.g. 16 and 18) degrade p53 and interact with RB (respectively) with greater efficiency than do E6 and E7 proteins from low-risk types (e.g. 6 and 11)[9]. Degradation of p53 by E6, which eliminates from infected cells the principal "guardian of the genome" (the protein responsible for cell cycle arrest in the presence of damage to cellular DNA), can lead to the accumulation of genetic mutations in infected cells. Thus, carcinogenic progression appears to be promoted or facilitated by increased E6 and E7 expression as well as by activity of external carcinogens, resulting in genomic instability[9].

CLINICAL FEATURES

Cutaneous and mucosal HPV types form two distinct groups that infect either skin or mucosa. However, viral tropism is not absolute, as DNA of skin types may be found in genital or oral warts, and in rare cases, mucosal types may be associated with skin lesions. Clinical manifestations depend on the HPV type involved, the anatomic location, and the immune status of the host (Table 79.1).

Cutaneous Infections

Cutaneous HPV types comprise a small group of viruses that infect the skin and induce common warts (Latin *verrucae vulgares*; singular *verruca vulgaris*), palmar and plantar warts (*verrucae palmares et plantares*), mosaic warts, flat warts (*verrucae planae*), and butcher's warts (see Table 79.1). In general, classification of warts is based on morphology, histology, and anatomic location.

Common warts are hyperkeratotic, exophytic, dome-shaped papules or plaques that are typically associated with HPV-1, -2, -4, -27, or -57. These warts are most frequently located on the fingers and dorsal surfaces of the hands (Fig. 79.4 & 79.5) or in other sites prone to trauma such as the knees or elbows, but they may occur anywhere on the skin surface. Involvement of the proximal nail fold and/or ablative therapy at that location may destroy the matrix, resulting in onychodystrophy (see Fig. 79.5). Characteristic features of common warts are punctate black dots representing hemorrhage into the stratum corneum (Fig. 79.6). Autoinoculation by scratching may cause a linear arrangement of warts. Slender, exophytic filiform warts can also develop, especially in periorificial locations on the face (Fig. 79.7). Numerous verrucae can be observed in immunocompromised patients and rarely they are eruptive when the immunosuppression is drug-induced.

Palmar and plantar warts appear as thick, endophytic papules on the palms, soles, and lateral aspects of the hands and feet, with gently sloping sides and a central depression resembling an anthill (hence the term *myrmecia*, meaning anthill). On the soles, these are often painful from pressure when walking, due to their deep inward growth (Fig. 79.8). Plantar warts that coalesce into large plaques are referred to as *mosaic warts* (see Fig. 79.8). Extensive chronic verrucosis that

CLINICAL MANIFESTATIONS AND ASSOCIATED HUMAN PAPILLOMAVIRUS (HPV) TYPES		
	Frequently detected	**Less frequently detected**
Skin lesions		
• Common, palmar, plantar, myrmecial and mosaic warts	1, 2, 4, 27, 57	29, 41, 60, 63, 65
• Flat warts	3, 10	28, 29
• Butcher's warts	7	1, 2, 3, 4, 10, 28
• Digital squamous cell carcinoma and Bowen disease	16	26, 31, 33, 34, 35, 51, 52, 56, 73
• Epidermodysplasia verruciformis (EV)	3, **5**, **8**	**9**, **12**, **14**, **15**, **17**, **19–25**, **36–38**, **47**, **49**, 50, etc.
• EV – squamous cell carcinoma	**5**, **8**	**14**, **17**, **20**, **47**
• Digital papillary adenocarcinoma	42	
Mucosal lesions		
• Condylomata acuminata	6, 11	40, 42*–44, 54, 61, 70, 72, 81
• High-grade intraepithelial neoplasias (including cervical condylomata plana, bowenoid papulosis, erythroplasia of Queyrat) and invasive cancer	16	18, 26*, 31, 33, 35, 39, 45, 51, 52, 53*, 56, 58, 59, 62, 66*, 68, 73, 82
• Buschke–Löwenstein tumor	6, 11	
• Recurrent respiratory papillomatosis, conjunctival papillomas	6, 11	
• Heck disease (focal epithelial hyperplasia)	13, 32	

*Probably carcinogenic[34].

Table 79.1 Clinical manifestations and associated human papillomavirus (HPV) types. HPV types in the genus β are in **bold**.



Fig. 79.4 Verrucae vulgares (common warts). *Courtesy A. Geusau, MD.*

is notoriously resistant to therapy has been observed in immunocompromised individuals, and, at times, in patients with no apparent immune dysfunction (Fig. 79.9). Inclusion warts of the sole are plantar cysts from which HPV types 4, 60, 63, and 65 have been isolated[35]. In studies from Europe, HPV-1 and the closely related types HPV-2, -27, and -57 caused the majority of palmoplantar warts, and they occurred most commonly in patients 6–10 years of age[36,37]. Although a higher incidence of HPV-2-related warts was reported in atopic children, other investigators have failed to find such an association.

Flat warts are skin-colored or pinkish to brown, relatively smooth-surfaced, slightly elevated, flat-topped papules that are most commonly located on the dorsal hands, arms, or face, often in a linear array (Fig. 79.10). They are usually caused by HPV-3 or -10, and less often by HPV-28 and -29.

Butcher's warts, which earn their name from their occurrence in meat- (or fish-) processing professionals, appear as extensive verrucous papules or cauliflower-like lesions on the dorsal, palmar, or periungual aspects of the hands and fingers. These warts are associated with HPV-7 not animal papillomaviruses.





Fig. 79.5 Periungual common warts. Destruction of the nail matrix and bed can lead to partial (**A**) or complete (**B**) absence of the nail plate. Bowen disease may be considered in the differential diagnosis, especially for a single, recalcitrant digital wart.



Fig. 79.6 Verrucae plantares (plantar warts). The photo was taken after shaving of the hyperkeratotic surface; the black dots represent hemorrhage into the stratum corneum.

Epidermodysplasia verruciformis (EV), first described in 1922 by Lewandowski and Lutz, is a rare genetic disease. It is characterized by a particular susceptibility to cutaneous infections with HPV types in the genus β (see above), which do not produce clinical lesions in immunocompetent individuals[38]. The disease usually manifests in childhood with highly polymorphic, widespread lesions. About two-dozen specific HPV types have been described in EV patients, a subset of which (mainly types 5 and 8) is also detected in EV-associated skin cancers. EV typically has an autosomal recessive pattern of inheritance and is caused by truncating mutations in two genes, *TMC6 (EVER1)* and



Fig. 79.7 Multiple filiform warts on the lower face.



Fig. 79.8 Myrmecial wart. The wart at the base of the distal phalanx of the hallux is painful due to deep endophytic growth; in addition, there are confluent plaques of superficial warts (mosaic warts).



Fig. 79.9 Extensive and chronic verrucosis of the soles in a patient with hepatic cirrhosis due to alcoholism. HPV-27 DNA was isolated from the lesions.

TMC8 (EVER2), that encode transmembrane proteins localized to the endoplasmic reticulum[39]. These proteins form a complex that interacts with the zinc transporter 1 (ZnT1) and affects intracellular zinc distribution, down-regulating zinc-associated transcription factors[40]. Inhibition of ZnT1-TMC6/8 function by the HPV E5 protein is thought to facilitate viral infection; β HPV types lack E5, but they become pathogenic in EV patients with TMC6/8 defects[40].

Patients with EV present with widespread, discrete, or confluent papules that resemble flat warts (Fig. 79.11A); scaly, pinkish, or hypopigmented guttate macules and thin plaques that resemble pityriasis versicolor represent another characteristic finding (Figs. 79.11B & 79.12). In an individual patient with EV, warts that appear clinically distinct often contain different HPV types, and each skin lesion usually contains several HPV types. Actinic keratoses usually arise after the age of 30 years and slowly transform into invasive SCCs in approximately half of EV patients. These tumors have low metastatic potential and develop primarily in sun-exposed areas such as the forehead, ears, and hands, implicating UV irradiation as an important co-carcinogen. Patients with EV should be educated about the importance of minimizing sun exposure, and family members should be screened for the presence of similar lesions.

It may be difficult to differentiate flat warts from EV-associated lesions based on histology alone (see below), but the presence of lesional β HPV DNA (e.g. HPV-5, -8, etc.) can establish the diagnosis in an otherwise healthy individual. Beta HPV types can also induce a sporadic EV-like eruption in immunosuppressed patients, including transplant recipients and those with AIDS or a lymphoma. Of note, efflorescence of HIV-associated acquired EV has been observed following the second dose of the quadrivalent HPV vaccine.

In addition, β HPV sequences have been isolated from the normal skin of healthy individuals by highly sensitive DNA detection methods, indicating that the general population acts as the reservoir for these HPV types. There is increasing epidemiologic and biologic evidence that β HPV types may play an adjunct role in the initiation, but not maintenance, of SCCs in immunosuppressed patients[41].

WHIM syndrome is a rare, autosomal dominant primary immunodeficiency disorder characterized by HPV-induced *w*arts (cutaneous and genital), *h*ypogammaglobulinemia, recurrent bacterial *i*nfections, and neutropenia due to *m*yelokathexis (retention of mature neutrophils in the bone marrow) (see Ch. 60). It is caused by mutations in the gene encoding the chemokine CXC receptor 4 (CXCR4), which result in impaired leukocyte trafficking and homing[42].

Several other primary immunodeficiencies are associated with severe HPV infection including DOCK8 deficiency, GATA2 deficiency (MonoMAC), hyper IgM syndrome, and idiopathic $CD4^+$ lymphopenia (see Table 60.1)[43].

Mucosal Infections

More than 40 HPV types preferentially infect the mucosa of the anogenital and upper aerodigestive tracts. Subclinical infections are much more common than visible warts. Application of 5% acetic acid (aceto-whitening) may aid in the identification of subclinical lesions as white areas.

Condylomata acuminata (singular: *condyloma acuminatum*), or anogenital warts, are found on the external genitalia and the perineum, perianally, or in adjacent areas such as the inguinal fold and mons pubis. Lesions may extend into the vagina, urethra, or anal canal (but rarely beyond the dentate line). Condylomata are typically discrete, sessile, smooth-surfaced exophytic papillomas or acuminate warts and may be skin-colored, brown, or whitish (especially when macerated in moist areas) (Fig. 79.13). They lack the thick cuirass of horny scale present on cutaneous warts and frequently measure one to several millimeters in diameter. Condylomata may also present as pedunculated or broad-based papillomas up to several centimeters in diameter or as large confluent plaques (Fig. 79.14). *Condylomata plana*, or flat cervical warts, may be difficult to recognize without aceto-whitening and the use of a (magnifying) colposcope. High-grade intraepithelial neoplasias are usually caused by high-risk types, mainly HPV-16, -18 and -31, whereas low-grade lesions may contain low-risk as well as high-risk HPV types.

Bowenoid papulosis manifests as multiple red–brown papules or confluent plaques on the external genitalia, on the perineum, or perianally (Fig. 79.15 & 79.16; see Fig. 73.13). These lesions primarily



Fig. 79.10 Verrucae planae (flat warts). Multiple skin-colored or pink (**A, B**) to brown (**C**) smooth-surfaced, flat-topped papules. (**D**) Thin pink papules and plaques that are well demarcated and have more scale than the patients in A-C. These lesions are typically caused by HPV-3 or -10. *B, Courtesy Kalman Watsky, MD; C, Courtesy Julie V. Schaffer, MD.*



Fig. 79.11 Epidermodysplasia verruciformis (EV). A Confluent scaly papules and plaques resembling flat warts. **B** Numerous hypopigmented and light pink, flat-topped papules, some of which are in a linear array, in acquired HIV-associated EV. *B, Courtesy Ncoza Dlova, MD.*



Fig. 79.12 Epidermodysplasia verruciformis. Generalized erythematous macules and plaques are seen in the same patient as shown in Fig. 79.11A. Lesions tested positive for HPV-8 and -36.

affect young adults and may clinically resemble genital warts, but histologically represent a high-grade squamous intraepithelial lesion (HSIL) or SCC *in situ*[44]. *Erythroplasia of Queyrat* is a distinct clinical entity, presenting as a well-demarcated, velvety erythematous plaque on the glabrous skin of the penis, vulva, or perianal region that histologically is an HSIL (Fig. 79.17). A biopsy is warranted for pigmented, erosive, bleeding, and/or therapy-resistant genital lesions to exclude malignancy. *Bowenoid papulosis* and *erythroplasia of Queyrat* contain high-risk HPV types, predominantly HPV-16, and may thus represent a precursor lesion of vulvar, penile, or perianal cancer. As noted above, these entities can represent variants of SCC *in situ*.

Buschke–Löwenstein tumor (giant condylomata acuminata), *oral florid papillomatosis of Ackerman* (oropharyngeal), *epithelioma cuniculatum* (plantar), and *papillomatosis cutis carcinoides of Gottron* (cutaneous) are types of "low-grade-malignant" verrucous carcinomas that have been associated with HPV infection. Verrucous carcinomas



Fig. 79.13 Condylomata acuminata. Verrucous lesions on the glans and in the sulcus, with a few small papules on the shaft of the penis and distal glans. Note the acuminate topography, i.e. the tapering to a point. *Courtesy Lorenzo Cerroni, MD.*





Fig. 79.14 Condylomata acuminata. A Confluent lesions forming hyperpigmented plaques in the perineal region and along the inguinal fold. A depigmented scar is seen at the site of prior treatment with liquid nitrogen. **B** Large, exophytic, broad-based or pedunculated papillomas in a healthy 15-year-old boy. The differential diagnosis includes Buschke-Löwenstein tumor.



Fig. 79.15 Bowenoid papulosis of the vulva with histopathologic features of vulvar intraepithelial neoplasia (VIN). Extensive red–brown or whitish papules and plaques containing high-risk mucosal HPV in an HIV-positive patient. Analogous high-grade squamous intraepithelial lesions (HSIL) were present perianally (AIN) and on the cervix (CIN).



Fig. 79.16 Bowenoid papulosis of the anus positive for high-risk mucosal HPV in a man who had sex with men. Histology revealed high-grade anal intraepithelial neoplasia (AIN), not invasive SCC. However, continued monitoring is indicated.

are locally invasive and destructive but rarely metastasize[45] (see Ch. 108). Buschke–Löwenstein tumor is a rare neoplasm of the anorectal area and external genitalia associated with the low-risk HPV types 6 or 11 that usually cause condylomata acuminata. The basis for the difference in biologic behavior between these two entities has not been established. In rare cases, pre-existing anogenital condylomata may progress into large exophytic cauliflower-like tumor masses that infiltrate deeply into underlying tissues and form fistulas and abscesses (Fig. 79.18). The histology of the Buschke–Löwenstein tumor may appear remarkably benign and resemble that of condylomata acuminata (Fig. 79.19), but its architecture is more irregular, the epithelium is more hyperplastic, and the pattern of growth is at least focally infiltrative. Focal frank malignant transformation can occur spontaneously or following X-irradiation. High-resolution imaging and a large biopsy are essential for identifying the extent of the infiltration and foci of SCC. Radical surgery may cure the disease, but recurrences are frequent, resulting in a high morbidity rate.

Oral warts appear as small, soft, pink or white, slightly elevated papules and plaques on the buccal, gingival, or labial mucosa (Fig. 79.20),



Fig. 79.17 Erythroplasia of Queyrat. A well-demarcated velvety plaque of the prepuce positive for high-risk HPV; histology revealed high-grade penile intraepithelial neoplasia (PIN).



Fig. 79.18 Giant condylomata acuminata (Buschke–Löwenstein tumor). Cauliflower-like, deeply infiltrating giant condylomata acuminata in an older woman.

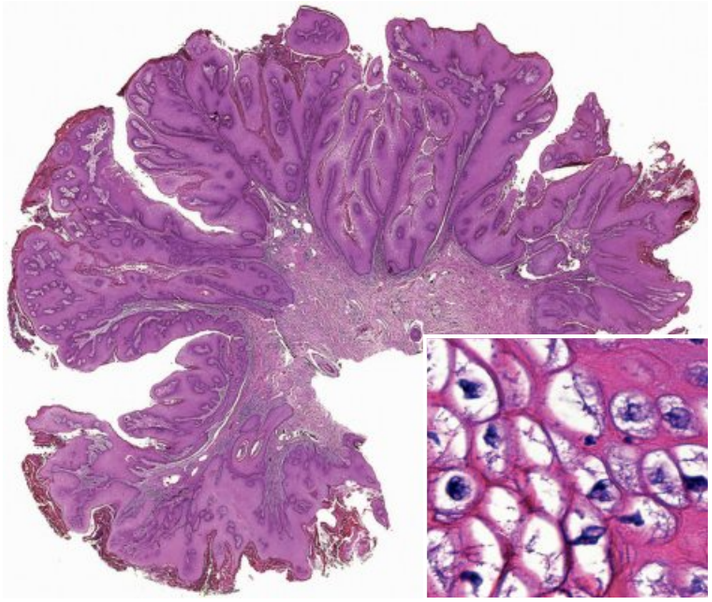


Fig. 79.19 Buschke–Löwenstein tumor – histopathologic features. Exophytic lesion with a papillomatous surface and marked, irregular epithelial hyperplasia without cellular atypia as well as the characteristic downward extension of bulbous rete ridges. Note vacuolated keratinocytes (inset). *Courtesy Luis Requena, MD.*



Fig. 79.20 Oral warts. Papillomas of the labial mucosa in a 6-year-old child.

the tongue, or the hard palate. Oral condylomata are associated with HPV types 6 and 11 and may result from digital or oral–genital sexual transmissions. In HIV-positive patients, oral papillomas are frequently detected and may contain unusual HPV types such as 7, 71, 72, and 73. In *focal epithelial hyperplasia*, or *Heck disease*, multiple circumscribed papules resembling flat warts or condylomata are found on the gingival, buccal, or labial mucosa. This disorder is rare in White individuals but relatively common in children who are native South Americans, native Greenlanders, or from South African communities. It is associated exclusively with HPV-13 or -32.

HPV (especially type 16) is a causative agent in about 25% of head and neck cancers, including the majority of oropharyngeal cancers that arise from the base of tongue and palatine tonsils. HPV-positive oropharyngeal cancers can develop irrespective of exposure to tobacco[46]. Although poorly differentiated histopathologically, they appear to have a better prognosis than HPV-negative oropharyngeal cancers whose primary risk factor is tobacco ± alcohol use[47].

In *oral florid papillomatosis*, multiple, confluent warty lesions are found in the oral cavity or the nasal sinuses. They are associated with HPV-6, -11, -16, and/or -18 in approximately half of cases. The development of these lesions is believed to be promoted by smoking, X-irradiation, and chronic inflammation. Patients with oral papillomas need frequent examinations and repeated biopsies for early diagnosis of progression to verrucous carcinoma.

In *recurrent respiratory papillomatosis* (RRP), there are benign exophytic laryngeal papillomas caused by HPV-6 and -11[28]. Patients classically present with a triad of hoarseness, stridor, and respiratory distress. Papillomas arise most often at the transition zones between the squamous and cilia-bearing epithelia of the larynx and subglottis, but they may rarely extend to the distal trachea, the bronchi, or even the bronchoalveoli. Malignant transformation of laryngeal papillomas into SCCs in patients with long-lasting disease has been reported, and exogenous factors such as X-irradiation, smoking, chemical toxins, or chemotherapy have been implicated as co-carcinogens.

PATHOLOGY

The histopathologic changes induced by HPV infection are variable, reflecting the myriad clinical presentations and different anatomic sites. In productive HPV infections, a common motif in epithelial cells

is the presence of cytoplasmic vacuoles isolating the nucleus from the cytoplasmic membrane. Cells with this distinctive vacuolization are referred to as koilocytotic (hollow) cells, and the presence of koilocytosis is a useful feature that distinguishes verrucae from other types of papillomas[48].

Common and Deep Palmoplantar Warts

Common warts are well circumscribed from the surrounding skin and characteristically have steeply sloping "church spire" papillomatosis heaped with ortho- and parakeratosis (Fig. 79.21). Parakeratosis is most commonly observed directly overlying the summits of the papillomatosis and is often accompanied by small intracorneal hemorrhages. There is also marked acanthosis and the rete ridges are elongated. In palmoplantar warts, the lateral edges of the wart bow inward to create a cup-shaped invagination below the papillomatosis. Higher-power examination reveals hypergranulosis and condensed coarse cytoplasmic keratohyalin-like granules of variable size and shape within the granular layer, along with vacuolization of cells on top of, or sometimes between, the papillae. Koilocytosis is typically observed in or immediately below the granular layer. The papillary dermis underlying the elongated rete ridges has minimal pathologic changes; increased vascularity can be observed.

Flat Warts

The characteristic features of flat warts include orthokeratosis alternating with parakeratosis, acanthosis, no or minimal papillomatosis, a uniformly thickened granular layer, and vacuolization of cells in the granular and upper spinous layers (termed "bird's eyes")[48].

Some patients with flat warts develop clinically evident inflammation around these warts, which may precede their spontaneous involution. Characteristic histologic features of regressing flat warts include parakeratosis, spongiosis, exocytosis of mononuclear cells into the lower epidermis, and (occasionally) satellite cell necrosis. By immunohistochemistry, T helper cells predominate and HLA-DR antigen, a marker of immune activation, is detected on the surface of the infiltrating lymphocytes and on some keratinocytes. Many of these changes can also be observed in regressing condylomata, suggesting that wart regression is mediated, at least in part, by a delayed-type hypersensitivity-like cellular immune response directed against keratinocytes expressing wart antigens[49].

Epidermodysplasia Verruciformis

In patients with EV, the flat warts and pityriasis versicolor-like lesions exhibit orthokeratosis with a basket-weave appearance, parakeratosis, and acanthosis. Under higher power, some cells within the hyperplastic spinous layer have characteristic cytopathic changes. These cells are large with perinuclear halos and a cytoplasm that has blue–gray pallor and contains keratohyaline granules of various sizes and shapes (Fig. 79.22). Keratinocytic dysplasia and actinic keratoses may be evident, especially in biopsies of lesions from sun-exposed areas[48]. Because the histologic picture is nonspecific, it may be difficult to differentiate typical flat warts from EV-associated lesions based on histology alone.

Anogenital Warts

The most consistent histologic features seen in condylomata include epidermal hyperplasia, parakeratosis, koilocytosis, and papillomatosis. The papillomatosis is more gently rounded than is seen in common warts. The upper portions of the epithelia of mucosal surfaces normally have some degree of cytoplasmic vacuolization, so its detection is specific for condylomata acuminata only if present within the deeper portions of the spinous layer[48]. Mitotic figures may be evident, and prior treatment with podophyllotoxin (which interferes with microtubule formation in cells undergoing mitosis) can induce the appearance of atypical mitoses that could potentially lead to misdiagnosis as SCC.

Giant Condylomata of Buschke–Löwenstein

The histology of the Buschke–Löwenstein tumor shares many features with condylomata acuminata, but there is more evident irregular epithelial hyperplasia, with marked downward extension of characteristically bulbous rete ridges, and less vacuolization of epidermal cells (see Fig. 79.19). Mitotic figures are rarely detectable, and, when present, are normal. While usually associated with extension into and destruction of local tissue, metastases to local lymph nodes from foci of SCC arising in these tumors have been reported[45].

Squamous Intraepithelial Neoplasias

Persistent infection with high-risk HPV types can lead to intraepithelial neoplasia that may progress to invasive carcinoma. The precancerous lesions represent a continuum of morphologic changes with indistinct boundaries. In CIN grade I, nuclear enlargement and hyperchromasia is observed in the lower epithelial layers; these changes may be accompanied by cytoplasmic halos (koilocytotic atypia). The next stage (CIN II) shows progressive atypia in all layers of the epithelium, with abnormal differentiation of the keratinizing cell layers. The atypical cells have an increased nuclear–cytoplasmic ratio, variability of nuclear size, and an increased number of mitotic figures, including abnormal mitoses and hyperchromasia. In CIN III, the epithelium is totally replaced by immature, atypical cells

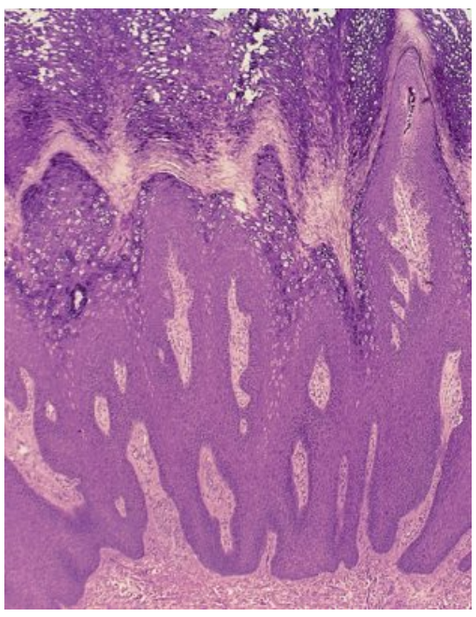


Fig. 79.21 Verruca vulgaris – histopathologic features. Note the characteristic features of "church spire" papillomatosis heaped with ortho- and parakeratosis, acanthosis, hypergranulosis, and koilocytosis. *Courtesy R. Tyler, MD.*

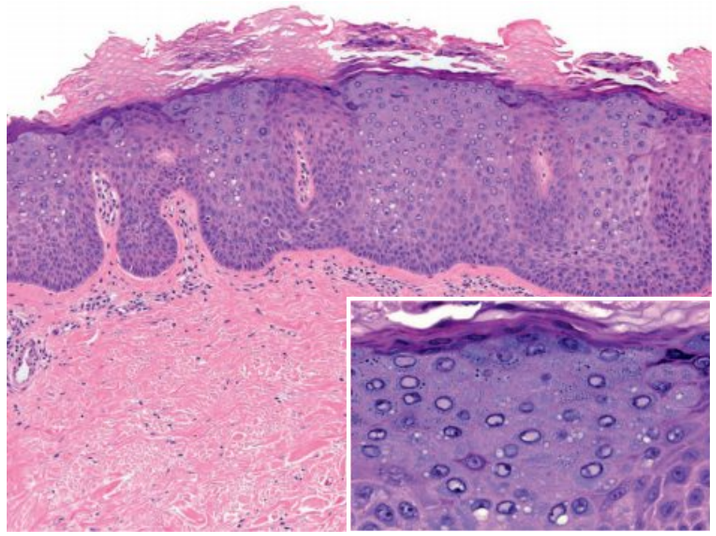


Fig. 79.22 Epidermodysplasia verruciformis – histopathologic features. Orthokeratosis alternating with parakeratosis and acanthosis are present. Note the cells with blue–gray, granular cytoplasm in the mid to upper epidermis (inset). *Courtesy Lorenzo Cerroni, MD.*

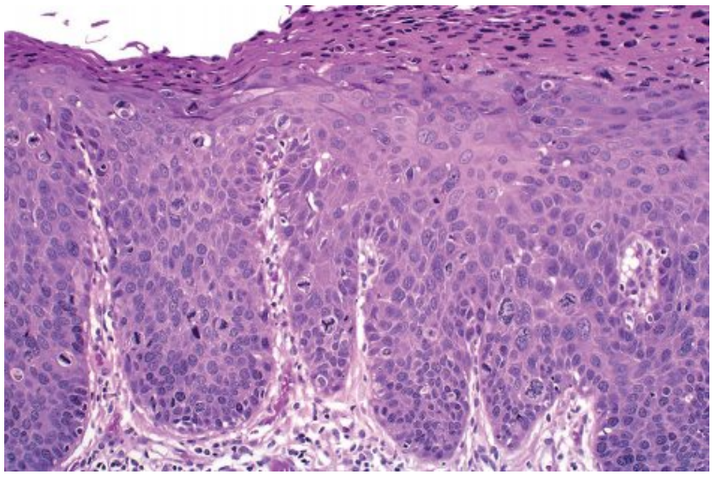


Fig. 79.23 Vulvar intraepithelial neoplasia (VIN) – histopathologic features. Note the characteristic features of abnormal keratinocyte maturation, nuclear pleomorphism, and dyskeratosis. Koilocytosis, due to cytoplasmic vacuoles that isolate the nucleus from the cytoplasmic membrane, can be observed in or immediately below the granular layer. Some pathologists refer to these intraepithelial neoplasias as SCC *in situ*. *Courtesy R. Tyler, MD.*

with a lack of surface differentiation. The analogous lesions of the vulva, vagina, penis, and anus are termed VIN (vulvar intraepithelial neoplasia; Fig. 79.23), VaIN (vaginal intraepithelial neoplasia), PIN or PeIN (penile intraepithelial neoplasia), and AIN (anal intraepithelial neoplasia), respectively. Clinically, these may appear as erythematous or whitish plaques (erythroplasia, leukoplakia) or red–brown papules (bowenoid papulosis) (see Figs. 79.15–79.17). Terminology of these lesions remains a matter of debate, and many pathologists refer to these "intraepithelial neoplasias" as "SCC *in situ*".

DIFFERENTIAL DIAGNOSIS

The diagnosis of cutaneous and genital warts is straightforward if typical clinical features are present. Occasionally, various other diagnoses have to be considered and a biopsy may be required for confirmation and to identify dysplastic lesions. Immunohistochemistry with antibodies directed against cross-reacting epitopes of papillomavirus capsid proteins allows the detection of virions in palmoplantar warts, which are highly productive infections, but has limited sensitivity in genital warts and dysplasias. There is no routine infectivity assay available to detect virions in clinical samples, and diagnostic tests are therefore based on the molecular detection of papillomavirus DNA. Commercially available tests that utilize nucleic acid hybridization (e.g. *digene* Hybrid Capture® 2 [HC2] HPV DNA Test; Amplicor® HPV and Linear Array® HPV Genotyping Test, Roche [not available in the US]) can identify low-risk versus high-risk mucosal HPV types in clinical samples with high sensitivity and specificity. In routinely processed histologic sections, RNA *in situ* hybridization can also be performed utilizing pooled high-risk versus low-risk HPV subtypes. In addition, PCR-based techniques can detect a broad range of genital and skin HPV types[50,51]. Development of circulating antibodies against the L1 major capsid protein is common following infection with genital HPV types, and ELISAs using L1 VLPs as the antigen have been useful in epidemiologic studies[33]. However, due to low antibody titers and variable intervals between infection and seroconversion, this assay is not used for diagnosis in individual patients.

Common, Flat, and Palmoplantar Warts

Seborrheic keratoses (SKs), actinic keratoses (AKs), cutaneous horns (which can arise from warts as well as AKs, SCCs, SKs, and other neoplasms; see Ch. 109), keratoacanthomas, other SCCs, tricholemmomas, Spitz nevi, and amelanotic melanomas may resemble *common warts*, and even tuberculosis verrucosa cutis or a plaque of psoriasis, hypertrophic lichen planus, hypertrophic lupus erythematosus, or pseudoepitheliomatous tattoo reaction can have a warty clinical appearance. On the distal or lateral finger or periungually, a wart-like or erythematous, well-demarcated plaque may occasionally represent Bowen disease and harbor high-risk HPV types, e.g. 16 or 18. Similarly, amelanotic melanoma can masquerade as a persistent periungual or plantar wart and should be clinically suspected if erosion or subtle pigmentation is present. The differential diagnosis of *flat warts* may include acrokeratosis verruciformis, Gottron papules of dermatomyositis (distinguished by their localization over the knuckles), lichen nitidus, lichen planus, and lichenoid keratoses. Although lesions of both lichen planus and flat warts can have a linear array, the presence of Wickham striae points to the former diagnosis. Plantar clavi (corns) are often misdiagnosed as warts, although verruca can be differentiated by the presence of punctate black dots rather than a glassy appearance; in addition, paring of the keratotic wart surface leads to capillary bleeding from the superficially located dermal papillae. Punctate palmoplantar keratoderma, punctate porokeratosis, arsenical keratoses, poromas, and eccrine poromatosis can mimic plantar warts.

In patients with cellular immunodeficiencies, including organ transplant recipients and those with AIDS or hematologic malignancies, the number as well as incidence of cutaneous and genital warts is increased. Warts that appear at less common sites such as the face and the neck need to be differentiated from mollusca contagiosa. In immunosuppressed patients, macular and flat warts may resemble EV, but the clinical setting and absence of a family history can aid in establishing the correct diagnosis. Other heritable immunodeficiencies that predispose affected individuals to the development of warts include WHIM syndrome (see above), idiopathic $CD4^+$ lymphopenia, DOCK8 deficiency, hyper IgM syndrome, PI3Kδ syndrome, and GATA2 deficiency (MonoMAC) (see Ch. 60 & Table 60.1)[43].

Anogenital Lesions

Condylomata acuminata are rarely confused with condylomata lata of secondary syphilis, but serologic testing for syphilis (and, as indicated, other STIs) is recommended in patients with genital warts, and dark-field examination for spirochetes may be considered. Mollusca contagiosa preferentially involve the mons pubis and can be distinguished by their umbilication, with dermoscopy revealing a multilobular, yellow–white central structure surrounded by a "crown" of vessels. In men, pearly penile papules are normal anatomic structures consisting of several rows of discrete, monomorphic, dome-shaped, 1 to 2 mm papules circumferentially around the corona and/or sulcus of the glans penis (see Ch. 116). An analogous picture exists in women, called vestibular papillomatosis, with tiny, uniformly shaped, finger-like projections at the introitus and on the labia minora. Sebaceous glands of the prepuce and labia majora appear as white–gray to yellow, small papules with a regular array. Epidermoid cysts, steatocystomas, or angiokeratomas of the scrotum seldom pose diagnostic problems. Occasionally, verrucous herpetic infections may mimic genital warts.

Detection of subclinical genital HPV infection is facilitated by soaking with 5% acetic acid for 3 to 5 minutes; this leads to whitening ("aceto-whitening") of lesions, and the use of a colposcope for magnification will further increase diagnostic accuracy. However, aceto-whitening is not specific for HPV-induced lesions and is also observed in infectious or inflammatory conditions such as *Candida* vulvitis or balanoposthitis, psoriasis, lichen planus, and eczematous dermatitis.

Bowenoid papulosis consists of red–brown papules or confluent, sometimes leukoplakia-like plaques that may be difficult to distinguish from condylomata (see Fig. 79.15 & 79.16 and Ch. 73). *Erythroplasia of Queyrat* is a well-defined, velvety, erythematous plaque of the glans or vulva that must be differentiated from erosive lichen planus and Zoon balanitis. *Bowen disease* can present as a solitary patch or plaque, sometimes scaly, of the vulva or penis, most often in older individuals. *Extramammary Paget disease* appears as a well-defined red plaque in the groin or pubic region or on the vulva, penile root, or perianal skin, with distinctive histopathologic features (see Ch. 73).

Vulvar carcinomas are etiologically heterogeneous. Carcinomas with basaloid or warty histology are related to HPV infection, whereas keratinizing squamous carcinomas are not[52]. Basaloid and warty vulvar carcinomas typically arise in younger women, are found adjacent to vulvar intraepithelial neoplasia (VIN; also referred to as high-grade squamous intraepithelial lesion [HSIL]), and are associated with risk factors related to sexual practices. Close to 90% of high-grade VIN/HSIL and basaloid and warty vulvar carcinomas contain high-risk HPV DNA



Fig. 79.24 Invasive squamous cell carcinoma of the penis. It developed over more than a decade from a papular lesion of the prepuce. HPV-16 and -51 DNAs were detected by RT-PCR.

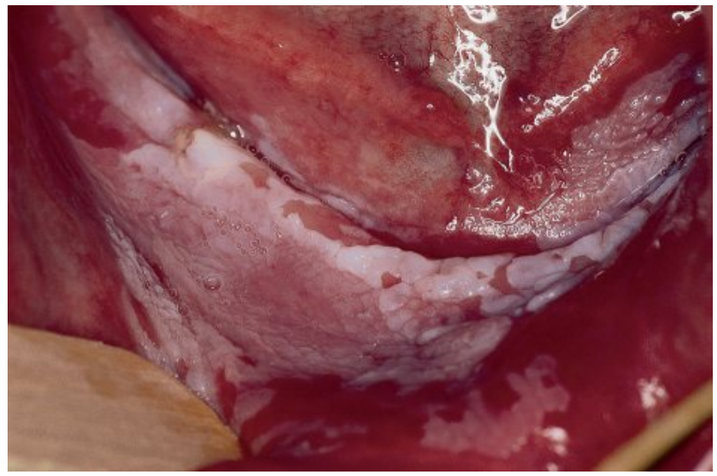


Fig. 79.25 Proliferative verrucous leukoplakia of the oral cavity. The lesions have focally progressed to invasive squamous cell carcinoma; HPV DNA was not detectable by PCR.

(most often HPV-16, but also HPV-31 and -33), suggesting a common etiology. In contrast, the more common keratinizing vulvar carcinomas in older women, which typically arise adjacent to lichen sclerosus and differentiated VIN, infrequently contain HPV DNA and thus are regarded as a distinct entity[53].

Although there is heterogeneity in anal SCC[53,54], in both sexes, the vast majority of anal cancers are attributable to HPV infection. Cancers of the anal canal that are positive for high-risk HPV (mostly HPV-16, but also HPV-18, -31, -33) tend to occur in younger men (especially MSM) and women with high-risk sexual behaviors, have basaloid histology, and arise adjacent to AIN. In contrast, HPV-negative anal cancers usually affect older men, are well keratinized, and arise from perianal skin without AIN. Heterogeneous etiology has also been described for penile cancer (Fig. 79.24), analogous to that observed for vulvar and anal SCCs[53]. Immunosuppression and a history of HPV-associated malignancy are notable risk factors for the development of a (second) anogenital cancer attributable to HPV.

Anogenital warts in children may give rise to suspicion of sexual abuse (see Ch. 90). Findings that make non-abusive transmission of HPV more likely include age <3 years, wart location somewhat distant from the anus or vulva, genital condylomata in the mother, and an absence of signs of physical abuse or of other sexually transmitted infections[17].

Giant condyloma acuminatum, or Buschke–Löwenstein tumor, is clinically suspected by its size and the presence of fistulas or abscesses (see Fig. 79.18). Histologic findings may be bland, and distinction from large benign genital warts can therefore be difficult at an early stage (see Fig. 79.19)[45,55]. However, high-resolution imaging reveals the extent of infiltration, and a large biopsy with serial sectioning may detect locally destructive growth and, rarely, transformed foci of SCC.

Oral Warts

Oral warts or condylomata may resemble the papules of focal epithelial hyperplasia (Heck disease); the latter is very rare in White individuals. A distinct oral condition with the descriptive name "proliferative verrucous leukoplakia" is clinically similar to oral florid papillomatosis but does not contain HPV DNA and has a high risk of progression to oral SCC (Fig. 79.25)[56]. Additional diagnostic considerations may include leukoedema (grayish-white translucent plaques, sometimes with a "moth-eaten" appearance, that favor the buccal mucosa and may become less evident upon stretching), white sponge nevus, and hereditary benign epithelial dyskeratosis.

MANAGEMENT OF ANOGENITAL WARTS WITH GRADING OF RECOMMENDATIONS
Patient-applied therapy (avoiding non-involved skin)
• Podophyllotoxin 0.5% solution, 0.5% gel, 0.15% cream* [BID for 3 days then discontinue for 4 days, up to 4 treatment cycles; ≤10 cm^2] (1) • Imiquimod 5% cream [6–10 hours 3 times/week, up to 16 weeks] (1) • Imiquimod 3.75% cream [once daily, up to 8 weeks] (1) • Sinecatechins 10%* or 15% ointment [TID, up to 16 weeks] (1)†
In-office therapies
• Cryotherapy (liquid nitrogen spray, cryoprobe) (1) • Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution (1) • Electrosurgery (1) • Scissor or shave excision, curettage (1) • Laser vaporization (CO_2, PDL, Nd:YAG) (2) • Surgical excision (3)
Other considerations
When external anal or perianal warts are present, the possibility of intra-anal warts should be excluded, e.g. by anoscopy
*Not FDA-approved; available outside the USA. †Might weaken condoms and vaginal diaphragms.

Table 79.2 Management of anogenital warts with grading of recommendations. Based upon cases series, additional therapies include 5-fluorouracil 5% cream, topical (1%–3%) or intralesional (15 mg/ml) cidofovir, and photodynamic therapy. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports[58,83]. PDL, pulsed dye laser. BID, twice daily; TID, three times daily.

THERAPY

General Considerations

There is currently no specific antiviral therapy available to cure HPV infection. Existing modalities focus primarily on the destruction or removal of visible lesions or induction of cytotoxicity against infected cells (Table 79.2). Because of the benign and self-limited nature of warts, treatments that cause scarring should be avoided. There is no evidence that aggressive treatment results in a better long-term outcome, and temporary interruption of therapy is an option. Common warts often regress spontaneously in children and therefore may not require treatment. A simplified algorithm for the approach to treatment of cutaneous warts is presented in Fig. 79.26.

Genital warts may be disfiguring and pose a significant psychological burden. HPV infection is typically widespread and multifocal throughout the anogenital tract, and subclinical lesions are often present. Thus, regardless of the applied therapeutic modality, reported recurrence rates are high (25%–65%) and it is unproven whether treatment reduces

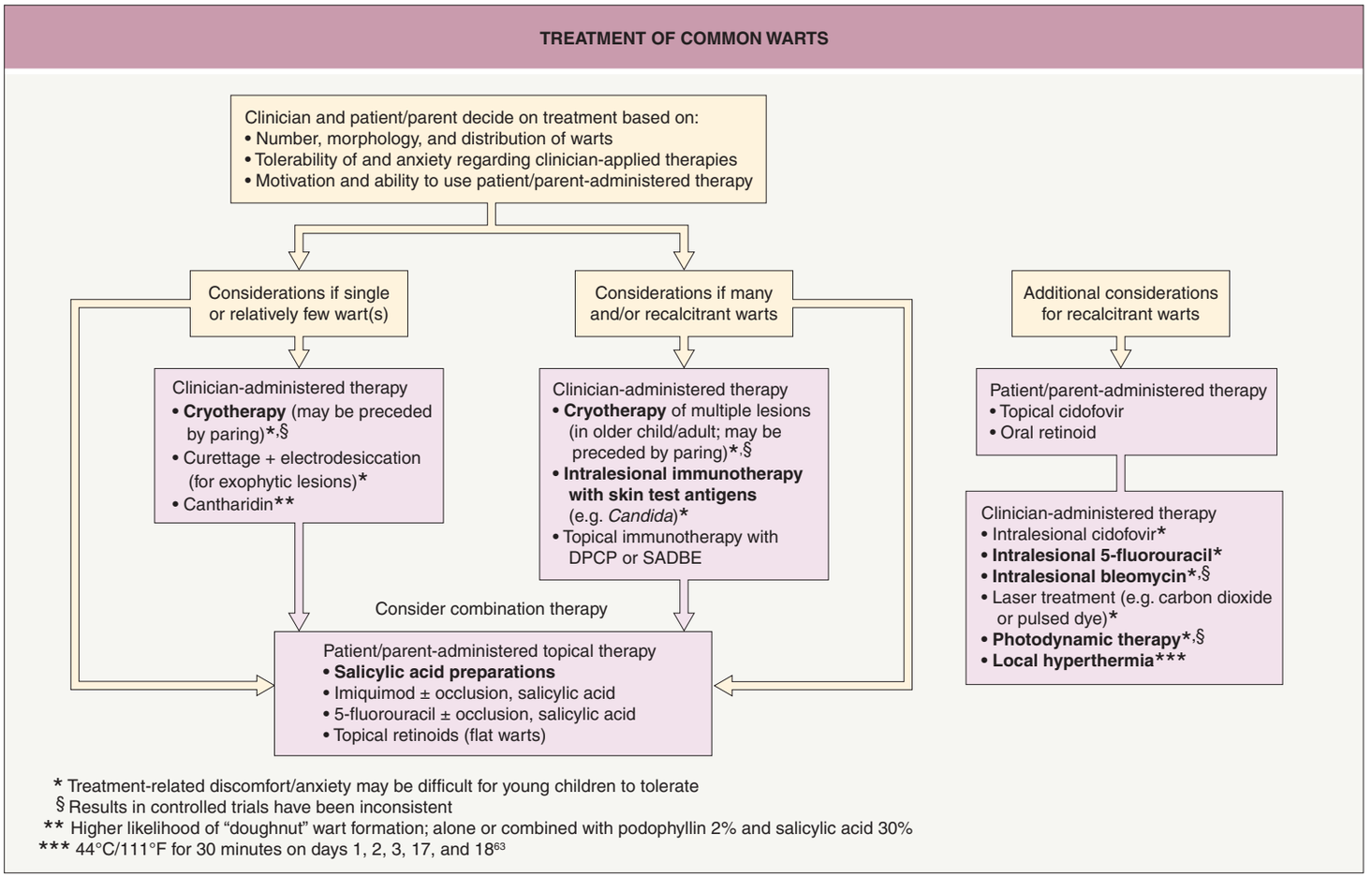


Fig. 79.26 Treatment of common warts. Therapies found to be effective in controlled trials are in **bold**. While still employed by some clinicians, three double-blind, placebo-controlled trials failed to confirm efficacy of cimetidine therapy for recalcitrant common warts. Topically, cidofovir is incorporated into an ointment, cream, or gel base at 1%–3% and intralesional cidofovir is diluted to 15 mg/ml saline. DPCP, diphenylcyclopropenone; SADBE, squaric acid dibutyl ester.

transmission rates to new sexual partners. Limiting the number of partners remains the mainstay of decreasing transmission. Condom use may also be helpful, and it has promoted regression of flat penile lesions and CIN as well as clearance of HPV in couples infected with the same HPV type[57]. Treatment is time-consuming, uncomfortable, and limited to visible warts and intraepithelial neoplasias with a high risk of progression. A simplified treatment algorithm is shown in Fig. 79.27. Current therapies for genital warts are summarized in Table 79.2 and include destructive, antiproliferative, and immunomodulatory modalities[58,59].

Local Destructive Therapy

Recommended destructive or ablative therapies for *genital warts* include cryotherapy, trichloroacetic acid (TCA) or bichloroacetic acid (BCA), electrosurgery, scissor or shave excision, curettage, laser vaporization, or excisional surgery. When anesthesia is required, topical application or injection of a local agent is usually sufficient (see Ch. 143), although general anesthesia may be indicated for surgical debulking of large lesions and occasionally in children. Ablative laser therapy is also useful for vaginal, vulvar, or anal intraepithelial neoplasias. Precautions should be taken to avoid inhalation of virus particles in the aerosol plume when laser or electrosurgical procedures are performed. Application of TCA 80%–90% solution is a commonly utilized office-applied therapy that results in local tissue destruction. Although scarring may occur following dermal injury, TCA has the advantage of a complete lack of systemic toxicity and it can be used during pregnancy.

Cryotherapy with liquid nitrogen is inexpensive, effective, safe during pregnancy, and usually does not require anesthesia; as a result, it is often used as a first-line in-office therapy for genital warts followed by patient-applied podophyllotoxin or imiquimod (see Table 79.2). Liquid nitrogen is applied with a cotton swab, spray gun, or closed system cryoprobe (see Ch. 138). Two freeze–thaw cycles, the extent of which is visually controlled, lead to wart necrosis and sometimes blistering. Multiple treatment sessions result in remission rates of 75% to 85%, with recurrences in 20%–40% of patients.

Cutaneous warts may be treated by daily application of salicylic acid/lactic acid/collodion (1:1:4), if possible with occlusion and after removing the thickened stratum corneum, or other salicylic acid preparations for 3–4 months; this results in regression in two-thirds of patients. Application of petrolatum to the surrounding normal skin protects against the corrosive effect of the concentrated acid. Weight pressure causes deep inward growth of plantar warts (myrmecia), and the resulting pain can be reduced by repeated shaving of the hyperkeratotic surface to a level at which capillary bleeding occurs. Cryotherapy with liquid nitrogen (see above) may be utilized for persistent or recurrent verrucae, including periungual lesions, with cure rates similar to or better than salicylic acid preparations in randomized controlled studies[60–64]. Other in-office or at-home freezing products (e.g. those containing dimethyl ether and propane) are less effective. Either cryotherapy that does not include a rim of surrounding skin or topical application of the blistering agent cantharidin (0.7% or 1%) may produce a "doughnut wart" due to clearance in the center but not at the periphery of the lesion. Additional destructive modalities include curettage or scissor excision (especially for filiform warts and other exophytic lesions), electrosurgery (see Ch. 140), and laser treatment (e.g. with CO_2, Nd:YAG, or pulsed dye lasers). Combination therapy with the application of topical agents following destruction may reduce the rate of recurrence.

Topical and Intralesional Cytotoxic Therapy

Podophyllin is a crude resin extract from the roots of the May apple *Podophyllum peltatum* (North America) or *Podophyllum emodi*

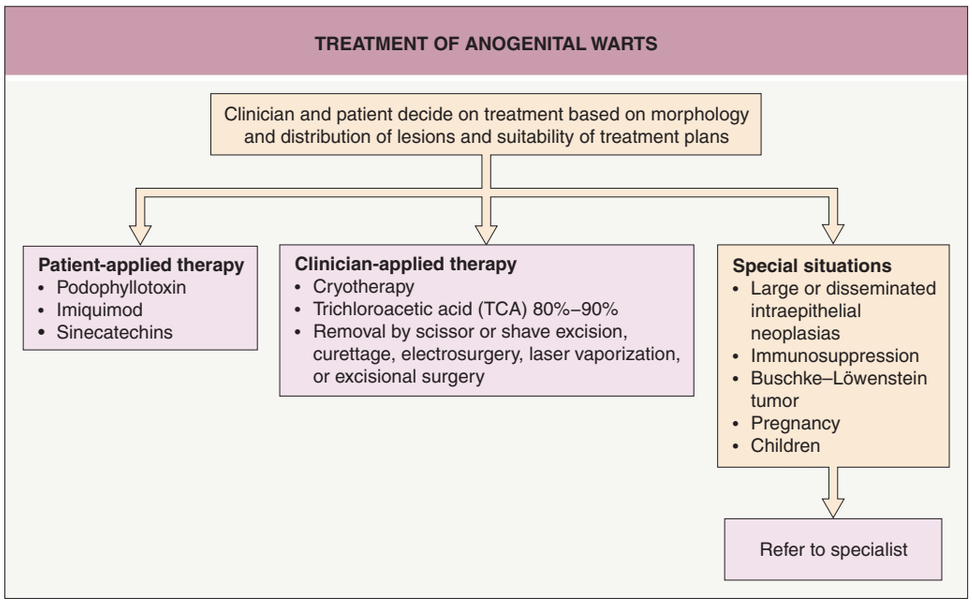


Fig. 79.27 Treatment of anogenital warts. See Table 79.2 for details of patient-applied therapies. TCA, trichloroacetic acid.

(Far East) that has been used since the early 1940s for the treatment of genital warts. Systemic toxicity can occur when applied in large volumes, and death, intrauterine demise, and teratogenicity have been reported. Because of low efficacy and potential toxicity, podophyllin use is no longer recommended[57]. Podophyllotoxin has been identified as the most active constituent of podophyllin. A regimen of patient self-applied podophyllotoxin 0.5% solution or gel twice a day for 3 days repeated in weekly cycles was shown to be effective and without evidence of systemic absorption and toxicity (see Table 79.2). Erythema and erosions are the most common side effects. In a recent network meta-analysis, podophyllotoxin 0.5% solution was significantly more efficacious than imiquimod 5% cream in clearing genital warts in non-immunocompromised patients, but the former had more adverse side effects[65]. Both podophyllin and podophyllotoxin are contraindicated during pregnancy.

Warts of the urethral meatus and urethra are difficult to manage, and stenosis and stricture due to therapy are potentially serious complications. 5-Fluorouracil (5-FU) 5% cream can be applied twice a week to treat intraurethral condylomata or, as an alternative to destructive treatments, intraepithelial neoplasias of the external genitalia. However, its use in the genital area is limited by inflammatory side effects. Successful treatment of cutaneous warts with 5-FU 5% cream applied daily under occlusion or together with salicylic acid has also been described in children and adults[66], and effective therapy with intralesional 5-FU has been reported.

Intralesional bleomycin is occasionally used to treat recalcitrant cutaneous warts, but injections are painful and may result in excessive cutaneous necrosis.

Topical Immunomodifiers

Imiquimod is an imidazoquinoline compound with immunomodulatory activities that has been approved by the US Food and Drug Administration (FDA) for the topical treatment of condylomata acuminata. Imiquimod has been shown to interact with Toll-like receptors 7 and (to a lesser degree) 8, resulting in activation of cytokine secretion from monocytes/macrophages (including interferon-α, interleukin-12, and tumor necrosis factor) as well as stimulation of antigen-presenting dendritic cells (see Ch. 128).

In an initial randomized, double-blind, placebo-controlled clinical trial, complete clearance of *genital warts* occurred in 50% of patients treated with imiquimod 5% cream compared to 11% of those treated with vehicle control; recurrence rates were low (<15%) in both groups[67]. Response rates were higher for warts on mucosal sites (i.e. female and uncircumcised male patients) than for lesions on the penile shaft or suprapubic area, suggesting the importance of crossing the stratum corneum barrier for effective treatment. Later studies confirmed the therapeutic effect of imiquimod for anogenital warts and documented that this treatment resulted in a reduction of viral load, presumably due to activation of cellular immune responses. A direct comparison of imiquimod and cryotherapy for genital warts found an earlier response with imiquimod, slightly higher efficacy with cryotherapy, and similar recurrence rates[68]. In clinical practice, destruction of genital warts by the physician, followed by patient-applied imiquimod (often requiring several cycles) is favorable over either modality alone[69]. Imiquimod has also been incorporated into suppositories and applied via anal tampons to prevent recurrence of anal condylomata following surgical ablation, or as primary treatment for anal condylomata and AIN in order to avoid the risk of scarring and stenosis of the anal canal associated with surgical procedures[70].

Therapeutic efficacy of imiquimod 5% cream has also been described for *persistent cutaneous warts*. In a controlled study (right versus left comparison) involving 14 immunosuppressed patients with recalcitrant warts on their hands and/or feet, a 36% response rate was observed for warts treated with imiquimod (three times weekly for 8 weeks, daily for 8 weeks, then daily with occlusion for 8 weeks) compared to 7% for untreated warts[71]. Improvement of common and flat warts with imiquimod therapy (daily application; ± occlusion for common warts) has also been reported in uncontrolled studies in immunocompetent patients[72]. Occlusion and/or concurrent use of salicylic acid or cryotherapy may increase imiquimod's penetration through the stratum corneum, which is especially important in acral sites.

Side effects of imiquimod include application site reactions (inflammation, erosion) that may require treatment-free periods. Imiquimod therapy is often more costly than other treatment options.

Sinecatechins 15% ointment, which contains green tea leaf-derived catechins thought to have immunostimulatory and antiproliferative properties, is approved as a topical treatment for anogenital warts. In randomized double-blind clinical studies, application of this product three times daily for up to 16 weeks led to complete clearance of anogenital warts in ~55% of patients (with frequent local irritation), compared to 35% of those treated with a vehicle control[73].

Systemic Immunomodifiers

Interferons have been used topically, intralesionally, and systemically for genital warts in controlled trials and have failed to demonstrate consistent efficacy. Systemic therapy, which is expensive and causes dose-related toxic side effects, is therefore not recommended for routine clinical use. However, interferons may be helpful as an adjunct or salvage therapy in selected patients[55]. More recently, low-dose pomalidomide was reported to clear or improve HPV-associated anal HSIL.

Immunotherapy

Increasing evidence that cellular immune responses play a critical role in wart clearance has inspired the development of topical and intralesional

immunotherapy regimens for patients with multiple and/or recalcitrant warts. In a large uncontrolled study[74], 154 children and adults with recalcitrant palmoplantar warts underwent successful topical sensitization with 2% diphenylcyclopropenone (DPCP) followed by at least six applications of 0.5%–4% DPCP to their warts at 3-week intervals. An 88% complete clearance rate was observed after an average of 6 months, with only local side effects (pruritus, blistering, eczematous reactions). Similar clearance rates have been reported for other contact sensitizers such as squaric acid dibutyl ester (SADBE), with application frequencies ranging from daily to monthly (often twice weekly), and regression of distant untreated warts has also been described.

Intralesional injection of *Candida*, *Trichophyton*, and/or mumps skin test antigens represents another approach to immunotherapy for warts in immunocompetent adults and children. In a randomized controlled clinical trial, a significantly higher clearance rate for treated as well as distant untreated common warts was observed in patients receiving intralesional antigen as compared to placebo at 3-week intervals for a total of up to five treatments (60% versus 22%, and 41% versus 19%, respectively)[75]. Effective treatment of flat warts and anogenital warts with topical and intralesional immunotherapy has also been described.

Antiviral Agents

Cidofovir is an acyclic nucleoside phosphonate with broad-spectrum activity against DNA viruses, including HSV and molluscum contagiosum, and it is approved for the systemic treatment of cytomegalovirus retinitis in AIDS patients. Although limited by the potential for renal toxicity, systemic treatment with cidofovir has shown efficacy in patients with HPV-associated lesions, including extensive cutaneous warts and severe RRP with pulmonary involvement. Intralesional injection of cidofovir (15 mg/ml saline) and topical application of 1%–3% cidofovir incorporated into an ointment, cream, or gel base have been successfully used in multiple case series of immunocompetent or immunosuppressed (e.g. HIV-infected) patients with cutaneous warts, condylomata acuminata, intraepithelial neoplasias, or RRP[76,77].

Retinoids

The effects of retinoids on keratinocyte differentiation and proliferation may lead to inhibition of HPV replication and assembly. Reduction in the bulk of extensive cutaneous or genital warts with oral retinoid therapy (e.g. acitretin, isotretinoin) has been reported in immunocompetent and immunosuppressed patients[78,79]. Successful treatment of flat warts with topical tretinoin or tazarotene has also been described.

Anti-PD-1/PD-L1 Antibodies

The aggressive nature of HPV-associated carcinomas is in part due to their ability to evade immunosurveillance via the expression of immune checkpoint molecules such as programmed cell death-ligand 1 (PD-L1), which interacts with its receptor (PD-1) on tumor-specific T cells and limits the latter's antitumor activity (Fig. 128.9)[80]. Increased levels of PD-L1 have been found in HPV-related cervical and head and neck SCCs and may play a critical role in the growth, progression, and metastases of these tumors. For example, expression of PD-L1 has been reported in 35%–95% of cervical carcinomas[81]. In several clinical trials of cervical or head and neck SCCs treated with anti-PD-1/PD-L1 antibodies, increased objective response rates and progression-free survival were observed when patients were stratified for HPV status and PD-L1 expression[82]. As a result, the FDA approved pembrolizumab in combination with chemotherapy for persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1. Pembrolizumab is also approved as a single agent for metastatic or unresectable recurrent head and neck SCCs that express PD-L1.

Special Considerations, Including Intraepithelial Neoplasias and Pregnancy

Early diagnosis of Buschke–Löwenstein tumor and other verrucous carcinomas is important to allow wide excision with clear resection margins. Surgery is the only established treatment that may cure the disease, although recurrence rates are high and the tumor can ultimately result in death. Cytotoxic chemotherapy and injections of interferon-α have led to remissions or cure in individual patients[45,55]. Whether anti-PD-1/PD-L1 antibodies could play a therapeutic role remains to be determined.

In transplant recipients and HIV-infected patients, skin and genital warts tend to resist standard treatment modalities. A surgical approach followed by non-invasive treatment of recurrent warts may be appropriate. In placebo-controlled studies, local application of imiquimod reduced genital wart area by more than 50% in 38% of HIV-infected patients. Imiquimod cream has also been used for VIN while imiquimod incorporated into suppositories or applied via anal tampons has been used for AIN, supporting a role for cellular immune enhancement for treatment of HPV-induced neoplasia.

During *pregnancy*, genital warts can increase in size and destructive procedures including surgery, cryotherapy, TCA application, and laser treatments are appropriate for removing lesions, which may theoretically reduce the risk for the newborn to acquire RRP[28]. However, this assumption is not proven and the presence of condylomata is not an indication for delivery by cesarean section. Podophyllin and podophyllotoxin are teratogenic and thus must not be used in pregnant women.

The treatment of intraepithelial neoplasias (bowenoid papulosis, erythroplasia of Queyrat, Bowen disease) is generally more aggressive than that of benign condylomata[83]. Prior to therapy, an aiming biopsy (e.g. colposcopically directed) is always required to exclude (micro) invasion histologically. For patients with bowenoid papulosis and erythroplasia who are younger than 45 years of age, superficial destruction of lesions (e.g. with cryotherapy or laser vaporization) may be appropriate to avoid mutilation[84]. In immunocompetent patients less than 35 years of age, bowenoid papulosis is regarded as a benign and self-limited disease[85]. Nevertheless, prolonged observation appears mandatory to detect recurrences.

HPV VACCINES

Three decades ago, recombinant DNA technology was used to generate a prophylactic subunit vaccine that consists of the L1 major capsid protein, which self-assembles into empty capsids designated as virus-like particles (VLPs) (see Fig. 79.1)[3]. VLPs resemble native virions morphologically and immunologically, and they carry neutralization epitopes on their surface. However, as a safety advantage, VLPs do not contain potentially oncogenic viral DNA and cannot replicate. Systemic immunizations with VLPs induce high-titer, long-lasting, and type-restricted neutralizing antibodies[4,86].

Prophylactic vaccinations in several animal models of papillomavirus infection were spectacularly successful in preventing natural or experimental infection of skin and mucosa[2,87]. In phase I/II human trials, systemic immunizations with VLP-based vaccines were non-toxic and highly immunogenic, inducing robust neutralizing antibody responses[86]. Based on these promising results, large-scale prophylactic vaccination trials were conducted to evaluate the safety and efficacy of two agents in preventing genital HPV infection and associated lesions in young women: (1) a quadrivalent vaccine of HPV-6, -11, -16, -18 VLPs (Gardasil®; Merck); and (2) a bivalent vaccine of HPV-16, -18 VLPs (Cervarix®; GlaxoSmithKline). Study endpoints were detection of HPV DNA and the development of dysplasias (squamous intraepithelial lesions) or (for the quadrivalent vaccine) anogenital warts. These studies showed near-complete protection (>90% vaccine efficacy) that was type-restricted against vaccine-type HPV infection. In addition, there was 100% protection in preventing genital warts as well as low- and high-grade CIN, VaIN, and VIN that were associated with the vaccine HPV types (for at least 10 years)[5–7,88,89]. The quadrivalent vaccine was also found to be nearly 90% effective in preventing both genital warts caused by HPV types 6 and 11 in young men and AIN. While post-marketing evaluation of the duration of efficacy of the vaccines is ongoing, trial results have demonstrated stabilized antibody titers for at least 10 years after vaccination, suggesting induction of a strong B cell memory response. Also, in studies where girls and boys between the ages of 10 and 15 years were vaccinated, more than 99% have seroconverted, and they developed antibody titers that were even higher than those in women 16 to 23 years of age[90].

Because these first two commercial HPV vaccines contain HPV-16 and -18 VLPs, they induce protection against the two high-risk HPV types that together account for ~70% of cervical cancers and high-grade CIN. Of note, they may offer limited cross-protection against closely related HPV-31, -33, and -45. More recently, the 9-valent vaccine

(Gardasil®9) was licensed which contains VLPs for HPV-6 and -11 as well as high-risk HPV types 16, 18, 31, 33, 45, 52, and 58[91]. Together, these seven high-risk HPV types have been identified in ~90% of cervical cancers[9,21]. Because it is not 100%, vaccinated women should continue to have Pap smears performed.

The three HPV vaccines that have been introduced worldwide over the past fifteen years are aimed at achieving universal vaccination of children and adolescents, ideally at 11 or 12 years of age. This would be prior to the onset of sexual activity and when the strongest immune response is generated, with the CDC recommending "catch-up" shots for those ages 13–26 years. Four years after implementing a national quadrivalent HPV vaccine program in Australia that was aimed at girls and young women and resulted in 70% coverage, genital warts nearly disappeared in women and heterosexual men <21 years of age[21]. In addition, high-grade cervical lesions significantly declined[92], with both outcomes demonstrating vaccine effectiveness at the population level.

The 9-valent vaccine is FDA-approved for females and males ages 9 to 45 years to prevent anogenital warts as well as cervical, vulvar and vaginal cancers, anal cancer, and HPV-related head and neck cancers. Of note, both the bivalent and quadrivalent vaccines have been removed from the US market due to low demand, but are available in other countries. The CDC views vaccination of inadequately vaccinated adults 27 to 45 years of age as optional as a greater percentage of these individuals have already been exposed to HPV.

Because the HPV vaccines have no therapeutic efficacy against preexisting infection or disease, the benefit of vaccinating older patients is considerably smaller. To date, there are no randomized, placebo-controlled trials demonstrating therapeutic efficacy of licensed HPV vaccines in the treatment of genital, cutaneous, or laryngeal warts. Although vaccinating males (e.g. with Gardasil®) is less cost-efficient than vaccinating females, this intervention likely increases vaccine efficiency in the population as a whole due to herd immunity[4,86]. Vaccination is also expected to lead to a drastic reduction in anal dysplasia and cancer (particularly in MSM) as well as an estimated one-third reduction in the incidence of oropharyngeal cancer. In 2020, the WHO launched a 90-70-90 strategy for the global elimination of cervical cancer via the vaccination of 90% of girls by age 15 years, screening 70% of women by 35 years of age and again by 45 years of age, and treating 90% of women with cervical precancer or cancer.

Currently, HPV vaccines are approved for use as either two- or three-dose regimens according to age. However, questions remain regarding the duration of vaccine efficacy and cross-protection with two doses (or even one dose) as compared to three doses. To date, several hundred million doses of HPV vaccines have been administered with retention of a good safety profile. There is also no indication of replacement by non-vaccine-targeted HPV types. The information gained from ongoing studies will aid in answering additional questions, including: duration of protection (when to boost if at all); possible longer-term benefit of preventing re-infection; utility of (pseudovirion) surrogate assays for neutralizing antibodies; and correlates of protection.

As an alternative approach for generating broader-spectrum vaccines, genetic engineering has been employed to develop L1 VLPs that also express type-common epitopes of the minor capsid protein L2 (e.g. the highly conserved "RG1" peptide of HPV-16 L2 that contains a cross-neutralization epitope), which can induce cross-protective immunity to a variety of mucosal and even cutaneous HPV types[93–95]. In a preclinical genital challenge animal model, vaccination with HPV16 RG1-VLP provided broad protection against virtually all high-risk mucosal HPVs, in addition to inducing cross-neutralization against low-risk mucosal types, common cutaneous types (HPV-2, -27, -57, -3), and oncogenic β types (HPV-5, -8)[96]. As part of the US National Cancer Institute PREVENT program, a phase I first-in-human trial of a RG1-VLP vaccine candidate is planned. Such monovalent VLP vaccines may become a cost-effective alternative strategy for implementing national HPV vaccination programs, especially in low-income countries that cannot afford multivalent HPV vaccines or cytology (Pap) screening, yet carry >80% of the worldwide burden of cervical cancer[97,98].

Successful experiments in animals have encouraged efforts to develop *therapeutic* vaccines against HPV infections. Most papillomavirus infections are self-limited, and it is generally agreed that a cellular immune response (albeit poorly understood) is required for clearance of infection. Cell-mediated immunity to L1 or L2 is unlikely to exhibit therapeutic efficacy, as capsid proteins are expressed neither in basal cells that harbor HPV DNA nor in progressed lesions that do not produce virions. Candidate rejection antigens are the E6 and E7 oncoproteins, which are selectively retained and expressed in cervical dysplasia and cancer, and E1 or E2 proteins, which are required to maintain the viral genome as an episome. Multiple strategies have been employed, including vaccinations with papillomavirus proteins fused to or combined with immunostimulants or dendritic cells in addition to attenuated viral or DNA expression vectors[99].

Chimeric VLPs have been engineered to incorporate an early protein such as E7 into an L1 or L1/L2 capsid. The induction of cytotoxic T-lymphocyte responses to the E7 oncoprotein, in addition to antibodies directed against the L1 capsid protein, provides both therapeutic and prophylactic benefit in mouse tumor models[100]. These strategies may prove effective in low-grade dysplasia or condylomata that have a high likelihood of spontaneous regression. However, mechanisms of immune evasion such as down-regulation of MHC type I expression may diminish the success of therapeutic vaccines and, thus, favor their application as an adjunct to established ablative therapies. Also, safety issues associated with live attenuated or DNA vectors and with vaccines containing E6 or E7 oncoproteins are complex[86,101].

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 79.1 Ring wart of the distal finger following cryotherapy.



eFig. 79.2 Extensive and chronic verrucosis of the sole causing pain when walking. HPV-2a was isolated from the lesions of this otherwise immunocompetent and healthy patient.

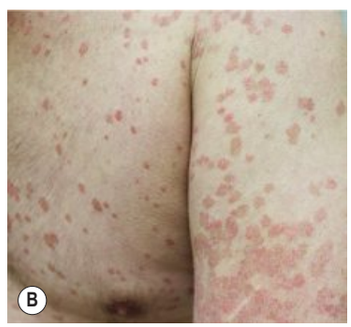


eFig. 79.3 Extensive periungual common warts in a patient with lymphoma.



eFig. 79.4 Verrucae vulgares in a patient with autosomal recessive hyperimmunoglobulin E syndrome (AR-HIES) due to DOCK8 deficiency. *Courtesy Edward Cowen, MD.*





eFig. 79.5 Hyper IgM syndrome. A, B Confluent verrucae on the hands; the verrucae on the trunk and arms have a pityriasis (tinea) versicolor-like appearance. *Courtesy Jonathan S. Leventhal, MD.*



eFig. 79.6 Penile condylomata acuminata (genital warts). Both sessile and exophytic warts are present.



eFig. 79.7 Extensive and treatment-resistant condylomata acuminata of the penis in a renal transplant recipient.



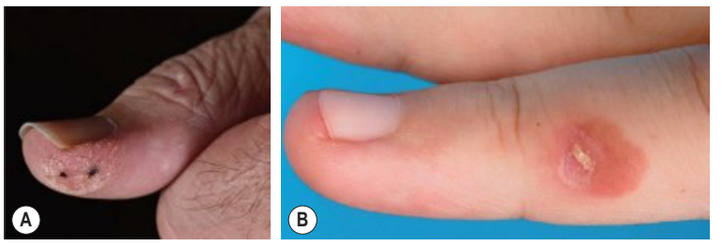
eFig. 79.8 Condylomata acuminata. Perianal papillomas that are macerated due to moisture from occlusion.



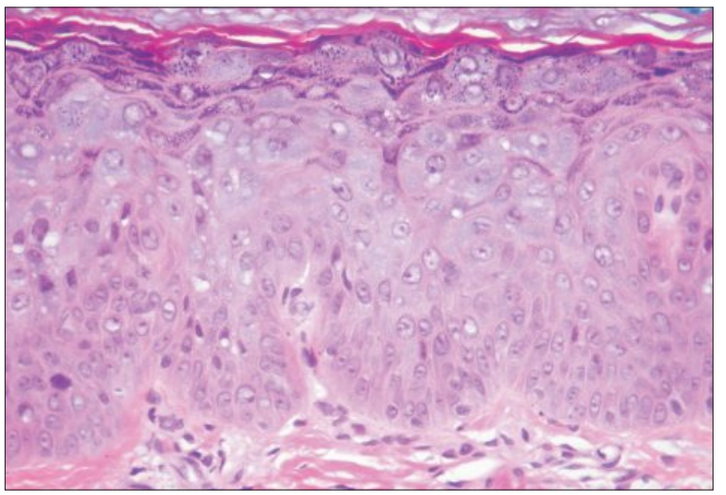
eFig. 79.9 Perianal condylomata acuminata. *Courtesy Kalman Watsky, MD.*



eFig. 79.10 Verrucous carcinoma (papillomatosis cutis carcinoides of Gottron). Large well-demarcated tumor of the shin with histologic features of a highly differentiated squamous cell carcinoma.



eFig. 79.11 Squamous cell carcinoma in situ (Bowen disease) of the finger. Periungual verrucous plaque (**A**) and well-demarcated, erythematous plaque with scale (**B**). Both harbored high-risk HPV DNA.



eFig. 79.12 Histology of epidermodysplasia verruciformis. Note the cells with blue–gray cytoplasm in the mid to upper epidermis. *Courtesy Mary S. Stone, MD.*



eFig. 79.13 Epidermal nevi that were misdiagnosed as condylomata acuminata. *Courtesy Kalman Watsky, MD.*

80 Human Herpesviruses

Joseph Jebain, Alfredo Siller Jr. and Stephen K. Tyring

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The human herpesviruses (HHVs) are categorized into three groups: alpha, beta, and gamma herpesvirinae (Table 80.1). Each virus contains a core of linear double-stranded DNA, an icosahedral capsid 100–110 nm in diameter, and an envelope with glycoprotein spikes on its surface. The pathogenesis of herpesvirus infections follows the sequence of primary infection, latency, and reactivation. The eight human herpesviruses are discussed in this chapter and include the following: herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella–zoster virus (VZV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus types 6–8 (HHV-6–8).

HERPES SIMPLEX VIRUSES (HSV-1 AND HSV-2)

Synonyms/clinical variants: ■ Herpes – herpes simplex ■ Herpes labialis – cold sore, fever blister, herpes febrilis ■ Herpes gladiatorum – scrum pox ■ Herpetic whitlow ■ Genital herpes – herpes progenitalis

Key features

- Herpes simplex viruses produce primary and recurrent vesicular eruptions that favor the orolabial and genital regions
- The use of sensitive and specific serologic markers has provided insights into the epidemiology of HSV infections
- Antiviral therapy significantly influences the course and spectrum of HSV disease

Introduction

HSV-1 and HSV-2 are ubiquitous pathogens that produce primarily orolabial and genital infections. Worldwide, genital herpes is one of the most common sexually transmitted infections. The use of sensitive and specific serologic markers has enabled the epidemiology of HSV infections to be deciphered, while antiviral therapy has allowed clinicians to control the course and extent of HSV disease. Prevention of HSV infections via molecularly derived vaccines remains an important goal.

History

Herpetic lesions have been described since antiquity, including by the noted physicians Hippocrates and Galen. The word "herpes" was first defined by Greek scholars as "to creep or crawl" in reference to the spreading nature of the skin lesions. The association between orolabial herpetic lesions and genital infection was first recognized during the late eighteenth century. However, better understanding of the pathogenesis of herpes infections did not occur until the twentieth century. Lipschitz was the first to suggest antigenic differences between the two HSV types, but it was not until 1968 that Nahmias and Dowdle demonstrated that HSV-1 was more frequently associated with orolabial and HSV-2 with genital infections[1]. In the past several decades, there have been critical insights into the pathogenesis of HSV infections as well as advances in their diagnosis, treatment, and prevention.

Epidemiology

Herpes simplex viruses have a worldwide distribution. Their interaction with human hosts has the following components: (1) *primary infection* – initial HSV infection, without pre-existing antibodies to HSV-1 or HSV-2; (2) *non-primary initial infection* – infection with one HSV type in an individual with pre-existing antibodies to the other HSV type; (3) *latency* – virus in sensory ganglia; and (4) *reactivation* – recurrent infection with asymptomatic viral shedding or clinical manifestations (recrudescence). Primary, non-primary initial, and recurrent infections can each be symptomatic or asymptomatic. It is estimated that approximately one-third of the world's population has experienced a symptomatic HSV infection.

In children <10 years of age, ~80%–90% of herpetic infections are caused by HSV-1. Analyses on a worldwide basis have demonstrated HSV-1 antibodies in 50%–90% of individuals 20–40 years old. Although HSV-2 remains the major cause of recurrent genital herpes infections (70%–90% overall)[2], the proportion due to HSV-1 has been increasing in the US, Canada, and the UK. In these countries, HSV-1 now accounts for the majority of genital herpes infections in young adults, especially college students[3,4]. Recurrences of genital herpes are less common with HSV-1, which lacks HSV-2's specific tropism for genital epithelium.

In the Centers for Disease Control and Prevention (CDC)'s 2015–2016 National Health and Nutrition Examination Survey (NHANES)[5], the seroprevalence of HSV-2 among individuals 14–49 years of age in the US was 12% overall, with higher rates in women (16%, versus 8% in men) and Black individuals (35%). Of note, ~80% of those with positive serology never had a previous diagnosis of genital HSV infection. Other factors associated with acquisition of genital herpes include an age of 15–30 years (period of greatest sexual activity), an increased number of sexual partners, lower levels of income and education, and HIV-positivity; conversely, genital HSV-2 infection also increases the risk of acquiring and transmitting HIV infection[3].

Pathogenesis

Transmission of HSV can occur during asymptomatic periods of viral shedding. HSV-1 is spread primarily through direct contact with contaminated saliva or other infected secretions, while HSV-2 is spread primarily by sexual contact. Virus replicates at the mucocutaneous site of infection and then travels by retrograde axonal flow to the dorsal root ganglia, where it establishes latency until reactivation. Latency enables the virus to exist in a relatively non-infectious state for varying periods of time in its host. HSV-1 can induce intracellular accumulation of CD1d molecules in antigen-presenting cells, providing a possible explanation for how the virus evades detection and establishes latency. Normally, CD1d molecules are transported to the cell surface, where they present lipids and stimulate natural killer T cells, thus promoting an immune response[6]. HSV's mechanisms to evade the immune system also include downregulation of various immunologic cells and cytokines (Table 80.2).

The goals of the early host immune response against HSV are to limit viral replication and recruit other inflammatory cells. Toll-like receptors are critical to the first line of innate immune defense against HSV, and their functions include priming $CD8^+$ T cells. HSV-specific memory $CD8^+$ T cells, which are selectively activated and retained in

THE EIGHT HUMAN HERPESVIRUSES, THEIR CLASSIFICATION AND DIFFERENTIAL DIAGNOSES				
Human herpesvirus	**Classification**	**Predominant cell type infected**		**Differential diagnosis**
		Lytic infection	**Latent infection**	
Herpes simplex virus type 1 (HSV-1) (HHV-1)	Alphaherpesvirinae	Epithelial cells	Neurons	Orolabial herpes: aphthous stomatitis, erythema multiforme major, Stevens–Johnson syndrome, herpangina, pharyngitis (e.g. due to EBV), oral candidiasis, mucositis secondary to chemotherapy
Herpes simplex virus type 2 (HSV-2) (HHV-2)	Alphaherpesvirinae	Epithelial cells	Neurons	Genital herpes: trauma, chancre (primary syphilis), aphthae, reactive non-sexually related acute genital ulcers associated with infection (e.g. EBV, CMV, *Mycoplasma*, influenza, SARS-CoV-2), CMV-related ulcers (AIDS), chancroid, granuloma inguinale, lymphogranuloma venereum
Varicella–zoster virus (VZV) (HHV-3)	Alphaherpesvirinae	Epithelial cells	Neurons	Varicella: vesicular viral exanthem (e.g. coxsackievirus A6), rickettsialpox, mpox, disseminated HSV, PLEVA, insect bites, drug eruption, scabies, smallpox
				Herpes zoster: zosteriform HSV, contact dermatitis, phytophotodermatitis, bullous impetigo, cellulitis
Epstein–Barr virus (EBV) (HHV-4)	Gammaherpesvirinae	B cells, epithelial cells	B cells	Group A streptococcal infection, acute viral hepatitis, drug reaction with eosinophilia and systemic symptoms (DRESS), toxoplasmosis, lymphoma; primary CMV, HHV-6, and HIV infections
				For genital ulcers: see genital herpes
Cytomegalovirus (CMV) (HHV-5)	Betaherpesvirinae	Lymphocytes, macrophages, endothelial cells	Lymphocytes, macrophages	EBV-induced infectious mononucleosis, toxoplasmosis, viral hepatitis, lymphoma
				For genital ulcers: see genital herpes
Human herpesvirus 6 (HHV-6)	Betaherpesvirinae	$CD4^+$ T cells	Lymphocytes, monocytes	Viral exanthems (e.g. measles, rubella; enterovirus, adenovirus, EBV, and parvovirus infections), scarlet fever, Rocky Mountain spotted fever, Kawasaki disease
Human herpesvirus 7 (HHV-7)	Betaherpesvirinae	T cells	T cells	Similar to HHV-6
Human herpesvirus 8 (HHV-8)	Gammaherpesvirinae	Lymphocytes	Lymphocytes, endothelial cells	Acroangiodermatitis (pseudo-KS), bacillary angiomatosis, ecchymosis, hemangioma, angiosarcoma, pyogenic granuloma, pseudolymphoma/lymphoma, dermatofibroma

Table 80.1 The eight human herpesviruses, their classification and differential diagnoses. KS, Kaposi sarcoma; PLEVA, pityriasis lichenoides et varioliformis acuta.

latently infected sensory ganglia, have important roles in controlling the infection and preventing symptomatic recurrences (see Table 80.2).

HSV can be reactivated either spontaneously or by a trigger such as emotional stress, ultraviolet light, fever, menstruation, immunosuppression, surgical or dental procedures, and other local tissue damage. Typically, reactivation produces vesicular lesions localized to the skin. However, viremia followed by widespread internal organ involvement can occur in immunocompromised hosts.

Clinical Features

HSV infections have a wide range of clinical presentations, and asymptomatic infection is very common. In primary infections, symptoms typically occur within 3 to 7 days after exposure. A prodrome of tender lymphadenopathy, malaise, anorexia, and fever often occurs before the onset of mucocutaneous lesions, which may be preceded by localized pain, tenderness, burning, and tingling. Painful, grouped vesicles appear on an erythematous base and may become umbilicated, followed by progression to pustules, erosions, and/or ulcerations with a characteristic scalloped border. Crusting of lesions and resolution of symptoms typically occurs within 2 to 6 weeks. A similar prodrome can precede recurrent lesions, but these are often fewer in number, with decreased severity and duration compared to those of a primary infection.

The majority of primary orolabial infections are asymptomatic. Symptomatic infections often present as gingivostomatitis in children or as pharyngitis and a mononucleosis-like syndrome in young adults. The mouth and lips are the most common sites of involvement (Fig. 80.1A,B), with oral lesions typically appearing on the buccal mucosa and gingivae. Edema and painful oropharyngeal ulcerations can lead to dysphagia and drooling.

Among individuals with latent HSV-1 infection, 20%–40% develop recurrent herpes labialis due to reactivation. Recurrent lesions appear most often on the vermilion border of the lip (Fig. 80.1C). Less common sites are perioral skin, nasal mucosa, cheek, and attached oral mucosa overlying bone (e.g. gingiva, hard palate) (Fig. 80.2). In immunocompromised hosts, recurrent herpes infections can involve intraoral movable mucosa not overlying bone (see Fig. 72.1).

Primary and non-primary initial genital herpes infections are frequently asymptomatic but (especially with the former) can also present as an excruciatingly painful, erosive balanitis, vulvitis, or vaginitis. In women, lesions often also involve the cervix, buttocks, and perineum and may be associated with inguinal adenopathy and dysuria (Fig. 80.3). Genital lesions in men typically occur on the glans or shaft of the penis, and the buttocks are occasionally affected. Systemic complaints and complications are more common in women. Extragenital lesions, urinary retention, and aseptic meningitis occur in 20%, 10%–15%, and 10% of affected women, respectively[7]. In contrast, aseptic meningitis is a rare complication of primary genital herpes infection in men. The presence of more extensive local involvement, regional lymphadenopathy, and fever generally distinguishes primary herpes infection from recurrent disease.

Genital HSV infections can result in both subclinical viral shedding and clinically evident recurrences, which are often relatively mild; recurrences occur more frequently with HSV-2 than HSV-1. Usually, a limited number of vesicles reappear on the genitalia or buttocks (Fig. 80.4), with resolution within 7–10 days, compared to ~20 days for primary infections[7]. Complications are uncommon. The frequency of recurrences correlates directly with the severity of the primary infection and tends to decrease over the next several years. The time interval between recurrences varies greatly, with individuals having an average of four to seven outbreaks annually. Surprisingly, although the majority of individuals with HSV-2 seropositivity report no history of genital herpes infection, symptomatic infection is eventually diagnosed in 50% of this group of patients.

Other Clinical Presentations of HSV Infection

HSV infection can occur anywhere on the skin or mucous membranes. The clinical settings and manifestations of other cutaneous and

INTERACTION OF HERPES SIMPLEX VIRUSES WITH THE IMMUNE SYSTEM: HOST RESPONSES AND VIRAL EVASION MECHANISMS
Host immune responses to HSV infection
Innate immunity

• HSV is detected by Toll-like receptors (TLRs; see Ch. 4) on epithelial cells, antigen-presenting cells (APCs), plasmacytoid dendritic cells (DCs), and NK cells
  • TLR2 on the cell surface interacts with a viral surface glycoprotein* and leads to proinflammatory cytokine production (via NF-κB activation), including IL-1β, IL-6, IL-8, IL-12, TNF, and MCP-1
  • TLR3 on endosomes interacts with double-stranded RNA (which accumulates in HSV-infected cells) and leads to IFN-β and IFN-λ production†
  • TLR9 on endosomes interacts with viral genomic DNA (unmethylated CpG sequences) and leads to IFN-α production via NF-κB activation
• HSV is also recognized by intracellular nucleic acid sensors (e.g. IFN-γ-inducible protein 16) that detect HSV DNA and stimulate type I IFN (IFN-α and -β) production
• Type I IFNs increase expression of IFN-stimulated genes; their effects include inhibiting translation/promoting degradation of viral mRNA, inducing DC maturation, and, in part through stimulation of IL-15 production, promoting NK cell survival and proliferation
• NK cells release IFN-γ and destroy virus-infected cells, e.g. via release of perforin and granzyme B
• $CD8^+$ T cells are primed in a process that requires TLR3 signaling by $CD8\alpha^+$ DCs
• Collectively, these responses limit HSV replication, promote host cell apoptosis, and recruit and activate DCs, other APCs, neutrophils, and other leukocytes of both innate and adaptive lineages
• Evidence is emerging that innate immune defenses also have a role in the control of latent HSV infections

Adaptive immunity
• $CD4^+$ T cells are recruited to the site of infection and activated by DCs • $CD4^+$ T cells release IFN-γ, which induces secretion of chemokines (e.g. CXCL9 and CXCL10 by epithelial cells) that recruit cytotoxic $CD8^+$ T cells • $CD8^+$ T cells, which also release IFN-γ, kill infected cells through perforin and Fas-mediated pathways, clearing the active infection • Following the priming and contraction phases of the T cell response, virus-specific $CD8^+$ T cells accumulate (referred to as memory inflation) and provide immunosurveillance; viral latency and periodic restimulation by subclinical HSV reactivation maintain this pool of cells • B cells are recruited to the site of infection and activated by $CD4^+$ T cells to produce antibodies • Regulatory T cells are present, but their exact role in preventing excessive immune responses versus diminishing the efficiency of viral clearance has not been determined
HSV's mechanisms of immune evasion
• HSV inhibits signaling through TLRs, e.g. the HSV-1 ICP0 protein reduces TLR2 signaling • The HSV *v*irion *h*ost *s*hut-off (VHS) protein degrades mRNA; it prevents DC activation by a TLR-independent pathway • HSV decreases cell surface expression of CD1d by APCs; this prevents presentation of lipid antigens that stimulate NK cells • HSV decreases langerin expression by and increases apoptosis of Langerhans cells • The HSV ICP47 protein binds to TAP and blocks loading of peptides onto MHC class I molecules; "empty" MHC class I molecules are degraded by the proteasome • The HSV-1 glycoprotein B manipulates the MHC class II processing pathway by hijacking HLA-DR from its normal transport route to the cell surface • The HSV-1 glycoprotein C blocks complement activation, and glycoprotein E functions as an IgG Fc receptor that can block host responses such as antibody-dependent cellular cytotoxicity • The HSV protein tristetraprolin destabilizes mRNA and can target proinflammatory cytokines such as TNF • HSV can block cytokine effects by other mechanisms, e.g. inducing expression of *s*uppressor *o*f *c*ytokine *s*ignaling-*1* (SOCS-1) in keratinocytes and thereby abrogating the effects of IFN-γ • HSV can induce expression of Fas ligand on the surface of monocytes/macrophages, causing apoptosis of interacting T cells and NK cells
*Viral envelope fusion with the host cell membrane during entry leaves viral proteins on the cell surface. †Mutations in the genes encoding TLR3 or proteins required for TLR3 signaling (e.g. *UNC-93B*, *TRAF3*) lead to particular susceptibility to HSV encephalitis, and polymorphisms in the gene encoding IFN-λ3 (IL-28b) have been associated with increased risk of recurrent orolabial herpes simplex.

Table 80.2 Interaction of herpes simplex viruses (HSV) with the immune system: host responses and viral evasion mechanisms. HLA, human leukocyte antigen; ICP, infected cell polypeptide; IFN, interferon; IL, interleukin; MCP-1, monocyte chemotactic peptide 1; MHC, major histocompatibility complex; NK, natural killer; TAP, transporter associated with antigen processing; TRAF3, tumor necrosis factor (TNF) receptor-associated factor 3.

extracutaneous presentations of HSV infection, including those in immunocompromised individuals and neonates[8–17], are summarized in Table 80.3 (Figs. 80.5–80.9).

Diagnosis and Pathology

Multiple laboratory tests are available to diagnose HSV infection, including viral culture, direct fluorescent antibody (DFA) assays, molecular techniques, and serology. Identification of HSV by viral culture usually requires 2–5 days. In addition to being the preferred method for identifying HSV in the cerebrospinal fluid, PCR is now commonly used as a more rapid, sensitive, and specific method for detecting HSV DNA in specimens from the skin and other organs.

For prevalence or incidence studies and to establish serostatus, the Western blot represents the gold standard for serologic assays; it is 99% sensitive and specific for HSV antibodies. In addition, several commercially available serologic tests can reliably identify patients who have been infected with HSV and are able to distinguish HSV-1 antibodies from HSV-2 antibodies by utilizing type-specific G-1 and G-2 glycoproteins, respectively. However, the sensitivity and specificity of these commercial assays do vary depending on the setting. The mean time to seroconversion following initial infection is 3–4 weeks[18].

A Tzanck smear of scrapings from early lesions, in particular the base/edges of a freshly unroofed vesicle, reveals multinucleated epithelial giant cells in ~60%–75% of HSV outbreaks (Fig. 80.10). In routinely stained biopsy specimens as well as Tzanck smears, HSV-1 cannot be differentiated from HSV-2. Enlarged, slate-gray keratinocyte nuclei with margination of chromatin represent an early histologic finding. This is followed by intraepidermal vesiculation associated with ballooning degeneration of keratinocytes, which is most prominent at the vesicle base (Fig. 80.11). These swollen, pale keratinocytes often fuse to form multinucleated giant cells and may contain eosinophilic intranuclear inclusion bodies surrounded by an artifactual cleft (Cowdry type A inclusions). Ballooning degeneration can affect adnexal structures as well as the interfollicular epidermis. A variably dense dermal infiltrate of lymphocytes, neutrophils, and eosinophils is observed, with a tendency to be milder in recurrent disease. Vascular changes may include areas of hemorrhagic necrosis and perivascular cuffing. Epidermal necrosis is sometimes extensive, especially in the setting of disseminated skin lesions.

Differential Diagnosis

Orolabial herpes can sometimes be confused with aphthous stomatitis, erythema multiforme major or Stevens–Johnson syndrome, herpangina



Fig. 80.1 Orolabial herpes simplex virus (HSV) infections. A Primary herpes gingivostomatitis due to HSV-1 in a child. Note the coalescing lesions with scalloped borders. **B** Primary versus non-primary initial HSV-2 infection in a teenager. There are grouped vesicles on an erythematous base; note the scalloped borders. **C** Recurrent herpes labialis (cold sore, fever blister). **D** Extensive HSV gingivostomatitis in a woman who was not immunosuppressed. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Jean L. Bolognia, MD; D, Courtesy Kalman Watsky, MD.*



Fig. 80.2 Recurrent herpes simplex virus type 1 infection on the cheek. Occasionally, such lesions are misdiagnosed as cellulitis or bullous impetigo. *Courtesy Kalman Watsky, MD.*



Fig. 80.3 Primary genital herpes. Grouped vesicles and erosions in the gluteal cleft. *Courtesy Kalman Watsky, MD.*

and other coxsackievirus infections, pharyngitis (e.g. due to EBV), oral candidiasis, Behçet disease, and chemotherapy-induced mucositis (see Table 80.1). Oral aphthae typically present as a single or few lesion(s) on the buccal mucosa without associated vesicles. Erythema multiforme major (most often triggered by HSV) and Stevens–Johnson syndrome can usually be distinguished from HSV by the presence of characteristic cutaneous as well as other mucosal lesions. In herpangina, the posterior pharynx is more commonly involved, unlike in HSV infection, which favors the anterior portion of the mouth. Oral lesions of hand-foot-and-mouth disease are generally accompanied by vesicles that favor acral and (especially with coxsackievirus A6) perioral areas. Exudative tonsillitis,



Fig. 80.4 Recurrent genital herpes. **A–C** Intact grouped vesicles and/or vesiculopustules with an erythematous base on the penis (**A**), medial buttock (**B**), and above the gluteal cleft (**C**). The buttocks represent a common location in women. **D** Ulcers with subtly scalloped borders on the penis. *A, C, Courtesy Kalman Watsky, MD; B, Courtesy Louis A. Fragola, Jr, MD; D, Courtesy Edward Cowen, MD.*

diffuse hyperemia of the oropharynx, and petechiae on the hard and soft palate are common manifestations of EBV-induced mononucleosis. Although a white, curd-like coating of the tongue, buccal mucosa, and pharynx is the most common presentation of oral candidiasis, there is also an erythematous form of the disease. In Behçet disease, oral aphthae are recurrent and patients have additional manifestations such as genital aphthae, uveitis, and papulopustular or erythema nodosum-like skin lesions[19]. In immunocompromised hosts, the possibility of coexisting infections must be considered.

Trauma, syphilitic chancres, chancroid, mpox, and lymphogranuloma venereum are considerations in the differential diagnosis of genital herpes (see Ch. 82). The syphilitic chancre is usually a single lesion that is neither painful nor recurrent. Chancroid often manifests as several tender ulcers with a yellowish-gray exudate overlying a base of granulation tissue, while lymphogranuloma venereum presents with a transient papule, herpetiform vesicle, erosion, or ulcer; both conditions typically result in tender inguinal lymphadenopathy. Reactive non-sexually related acute genital ulcers (e.g. associated with EBV, CMV, or *Mycoplasma* infection) and other genital aphthae can be difficult to distinguish from herpetic lesions without viral culture, DFA, or PCR. Additional entities in the differential diagnosis of genital erosions are listed in Table 73.6.

Treatment and Prevention

FDA-approved antiviral agents for treatment of recurrent episodes of orolabial herpes in immunocompetent persons include valacyclovir 2 g twice daily for 1 day, a single 1.5-g dose of famciclovir, and the topical treatments listed in Table 80.4. Randomized controlled trials have shown that these therapies have modest benefits, decreasing the duration of mucocutaneous lesions, viral shedding, and pain[20–23]; efficacy is maximized when treatment is started at the first sign or symptom of a recurrence. Both valacyclovir and famciclovir have also been shown to reduce the frequency of orofacial herpes outbreaks after laser resurfacing.

For treatment of primary and recurrent genital herpes, oral antivirals are the agents of choice (see Table 80.4). With initiation within 24–48 hours of onset, acyclovir, famciclovir, and valacyclovir reduce the duration of viral shedding, pain, and time to healing for first-episode and recurrent genital herpes. Intravenous acyclovir is indicated for neonatal HSV infection, severe infections in immunocompromised hosts, severe eczema herpeticum, and patients with systemic complications. In immunocompromised patients, it is important to treat with oral or intravenous antivirals until the cutaneous lesions are completely healed. Systemic antiviral agents need to be dose-adjusted for patients with impaired renal function (Table 80.5).

Chronic suppressive therapy with oral antiviral agents is usually reserved for patients with six or more outbreaks per year (see Table 80.4), although clinicians often exercise more lenient criteria for initiation of therapy for individuals with severe or problematic outbreaks, an insufficient prodrome to benefit from episodic therapy, or immunosuppression. In addition to decreasing the frequency of symptomatic outbreaks or even eliminating them, suppressive therapy decreases asymptomatic viral shedding by 95% and can thereby reduce transmission of genital herpes to a susceptible partner[24]. Daily suppressive therapy, together with consistent condom use and avoidance of sexual activity during recurrences, is therefore also recommended for individuals with genital herpes who have a seronegative partner.

OTHER CLINICAL PRESENTATIONS OF HERPES SIMPLEX VIRUS INFECTIONS		
Form of infection	**Clinical settings and HSV type(s)**	**Cutaneous and/or extracutaneous findings**
Predominantly mucocutaneous		
Eczema herpeticum (Kaposi varicelliform eruption)	• Affects infants/children > adults with atopic dermatitis (Fig. 80.5); risk is associated with mutations in the gene encoding filaggrin • A similar presentation can occur in patients with an impaired skin barrier due to other conditions such as burns, irritant contact dermatitis, pemphigus (foliaceus, vulgaris), Darier disease, Hailey–Hailey disease, mycosis fungoides, Sézary syndrome, ichthyoses, and rarely Grover disease and pityriasis rubra pilaris with acantholysis, as well as following ablative laser procedures or application of topical 5-fluorouracil • Usually due to HSV-1	• Rapid, widespread cutaneous dissemination of HSV infection in areas of dermatitis/skin barrier disruption • Monomorphic, discrete, 2–3 mm punched-out erosions with hemorrhagic crusts (see Fig. 80.5) are evident more often than intact vesicles • May have fevers, malaise, and lymphadenopathy • Occasionally complicated by bacterial superinfections (e.g. *Staphylococcus aureus*, group A streptococci) or systemic dissemination of HSV infection • Differential diagnosis includes "eczema coxsackium" due to coxsackievirus A6 infection and streptococcal infection and eczema vaccinatum
Herpetic whitlow	• Often in young children, usually due to HSV-1 (Fig. 80.6A) • Increasing frequency in adolescents/adults (Fig. 80.6B,C) secondary to digital–genital contact, usually due to HSV-2 • Historically in dental and medical personnel who did not use gloves	• Pain, swelling, and clustered vesicles on a digit (Fig. 80.6); appearance of vesicles may be delayed • Recurrences in the same location can be a clue to the diagnosis • Often misdiagnosed as blistering dactylitis or paronychia
Herpes gladiatorum	• Participation in contact sports such as wrestling (Fig. 80.7) • Usually due to HSV-1	• Distribution reflects sites of contact with another athlete's skin lesions and is sometimes widespread
Herpes simplex folliculitis	• Shaving with a blade razor (e.g. *herpetic sycosis* in a man's beard area) • Usually due to HSV-1 • HIV-positive or otherwise immunocompromised individuals	• Rapid development of follicular vesicles and pustules • See Table 38.1
Severe/chronic HSV infections	• Immunocompromised patients, e.g. hematopoietic stem cell or solid organ transplant recipients, individuals with HIV infection or leukemia/lymphoma	• Most common presentation is chronic, enlarging ulcerations (Fig. 80.8A,B) • Cutaneous lesions may affect multiple sites or be disseminated • Skin findings are often atypical, i.e. verrucous, exophytic, or pustular lesions • Recurrences can involve oral mucosa, including the tongue (Fig. 80.8C) and movable areas that do not overlie bone • Involvement of the respiratory tract, esophagus, and remainder of the gastrointestinal tract may also occur
Predominantly extracutaneous		
Ocular HSV infection	• Often due to HSV-2 in newborns (see below) • Usually due to HSV-1 in children and adults	• Primary infection: unilateral or bilateral keratoconjunctivitis with eyelid edema, tearing, photophobia, chemosis, and preauricular lymphadenopathy • Branching dendritic lesions of the cornea represent a pathognomonic finding • Recurrent episodes are common and typically unilateral • Complications include corneal ulceration and scarring, globe rupture, and blindness
Herpes encephalitis	• Most common cause of fatal sporadic viral encephalitis in the US • Associated with mutations in the genes encoding Toll-like receptor 3 or UNC-93B, which impair interferon-based cellular antiviral responses (see Table 80.2) • Usually due to HSV-1 • Natalizumab, an anti-α4 integrin monoclonal antibody used for the treatment of multiple sclerosis and Crohn disease, increases the risk of encephalitis and meningitis due to HSV and VZV	• Manifestations can include fever, altered mental status, bizarre behavior, and localized neurologic findings • The temporal lobe is often involved • Mortality ≥70% without treatment; residual neurologic defects in most survivors • Herpes labialis may be a coincidental finding
Proctitis	• Most common in men who have sex with men	• Manifestations include diarrhea, anal pain, and a feeling of rectal fullness
Cutaneous and extracutaneous		
Neonatal HSV infection	• Occurs in ~1:10 000 newborns in the US[8,9], usually resulting from exposure to HSV during a vaginal delivery • Risk of transmission is highest (30%–50%) for women who acquire a genital HSV infection (which is often asymptomatic) near the time of delivery • Risk of transmission is low (<1%–3%) for women with recurrent genital herpes • Due to HSV-2 or HSV-1; the latter accounts for 30%–50% of cases	• Onset from birth to 2 weeks of age, but usually ≥5 days of age • Localized (favoring the scalp and trunk; Fig. 80.9) or disseminated cutaneous lesions; involvement of the oral mucosa, eye, CNS, and multiple internal organs can occur • Vesicles may progress to bullae and erosions (see Ch. 34) • Encephalitis can present with lethargy, irritability, poor feeding, temperature instability, seizures, and a bulging fontanelle • For CNS or disseminated disease, mortality is >50% without treatment and ~15% with treatment; many survivors have neurologic deficits

Table 80.3 Other clinical presentations of herpes simplex virus (HSV) infections.



Fig. 80.5 Eczema herpeticum. A Monomorphic, punched-out erosions with a scalloped border in this infant with a history of facial atopic dermatitis. **B** Monomorphic, small hemorrhagic crusts and erosions coalescing in the popliteal fossae, an area of pre-existing atopic dermatitis. *A, Courtesy Julie V. Schaffer, MD; B, Courtesy Kalman Watsky, MD.*



Fig. 80.6 Herpetic whitlow. A Coalescing vesicles and erosions on the distal finger of a child. **B** An edematous erythematous plaque with relatively subtle central vesicle formation on the thumb of a child. **C** Grouped vesicles on the toe of an adult. Herpetic whitlow is sometimes misdiagnosed as cellulitis or blistering distal dactylitis, or, depending on the distribution, paronychia. *C, Courtesy Louis A. Fragola, Jr, MD.*

The emergence of acyclovir-resistant HSV is an increasing concern for immunocompromised individuals. Foscarnet is the only antiviral drug approved by the FDA for treatment of acyclovir-resistant HSV (see Fig. 127.11). Cidofovir is another antiviral agent that has shown efficacy in the treatment of acyclovir-resistant HSV. The use of foscarnet or *systemic* cidofovir is limited by potentially severe renal toxicity and the requirement for intravenous administration. Although not FDA-approved, compounded *topical* cidofovir has been advocated by the CDC as a "user-friendly", albeit expensive, alternative treatment[25].

Individuals co-infected with HIV and HSV have more severe outbreaks and more frequent viral shedding than those without HIV infection. When added to the medical regimen of HIV-infected patients, antiherpetic suppressive therapy appears to allow the co-infected person to respond better to antiretroviral therapy and to reduce genital and plasma HIV-1 RNA levels, but it does not seem to decrease the risk of HIV-1 transmission[26]. Oral acyclovir, famciclovir, and valacyclovir can be used for genital and orolabial HSV in the setting of HIV infection if there is no evidence of acyclovir resistance.

There is significant interest in prevention of HSV disease. Between 70% and 80% of HSV is transmitted during periods of asymptomatic viral shedding. Sexual abstinence is the only method for absolute prevention of genital herpes, which can be transmitted even with the use of condoms[27]. In addition to antiviral therapy, patient education regarding prevention of genital herpes transmission is essential.

There is currently no licensed vaccine available for HSV, although several vaccines are under development and evaluation for prevention of HSV infection and recurrences. GEN-003, a therapeutic vaccine under investigation for genital HSV-2 infection, was found in phase I/II clinical trials to reduce the rates of outbreaks and asymptomatic viral shedding[28]. In randomized controlled studies, adults with a history of genital herpes due to HSV-2 who received the helicase-primase inhibitor pritelivir had significantly decreased HSV shedding and fewer days with genital lesions than those who received placebo or valacyclovir[29]. There is currently an ongoing trial of the use of oral pritelivir for acyclovir-resistant mucocutaneous HSV infections in immunocompromised hosts.

VARICELLA–ZOSTER VIRUS (VZV; HHV-3)

Synonyms/clinical forms: ■ Varicella – chickenpox ■ Herpes zoster – shingles

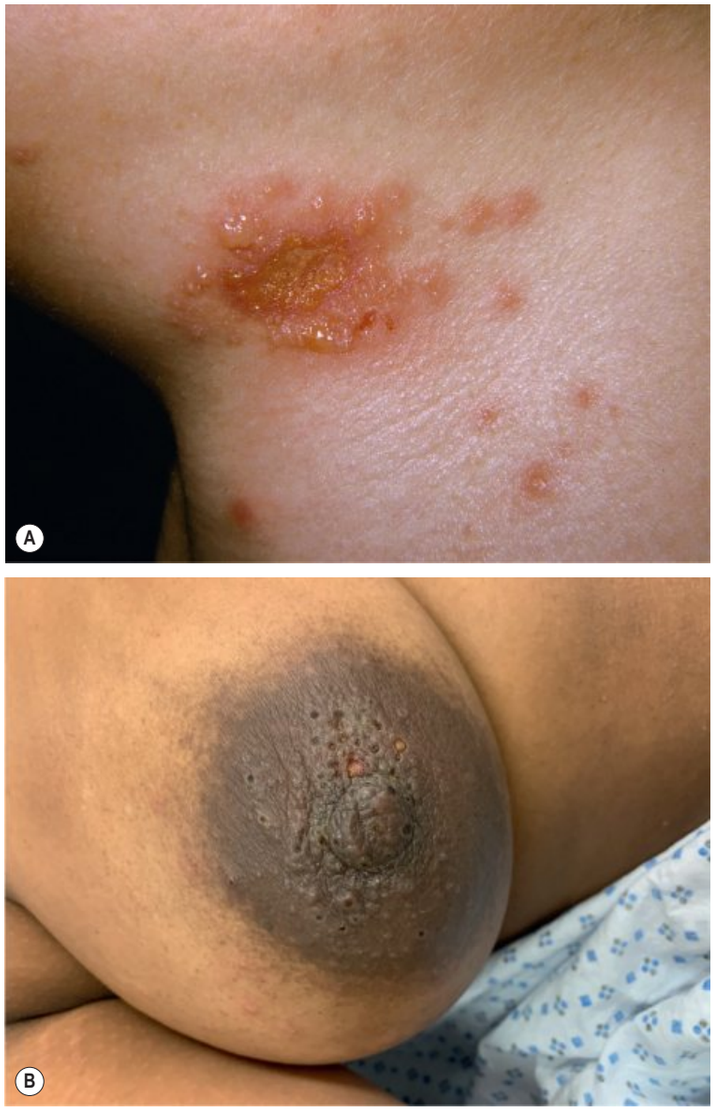


Fig. 80.7 Herpes simplex infections in less common locations. A Herpes gladiatorum presenting as grouped vesicles and erosions on the neck of a high-school wrestler. **B** Small vesicles and punched-out erosions clustered on the nipple and areola. *A, Courtesy Louis A. Fragola, Jr, MD; B, Courtesy Kalman Watsky, MD.*

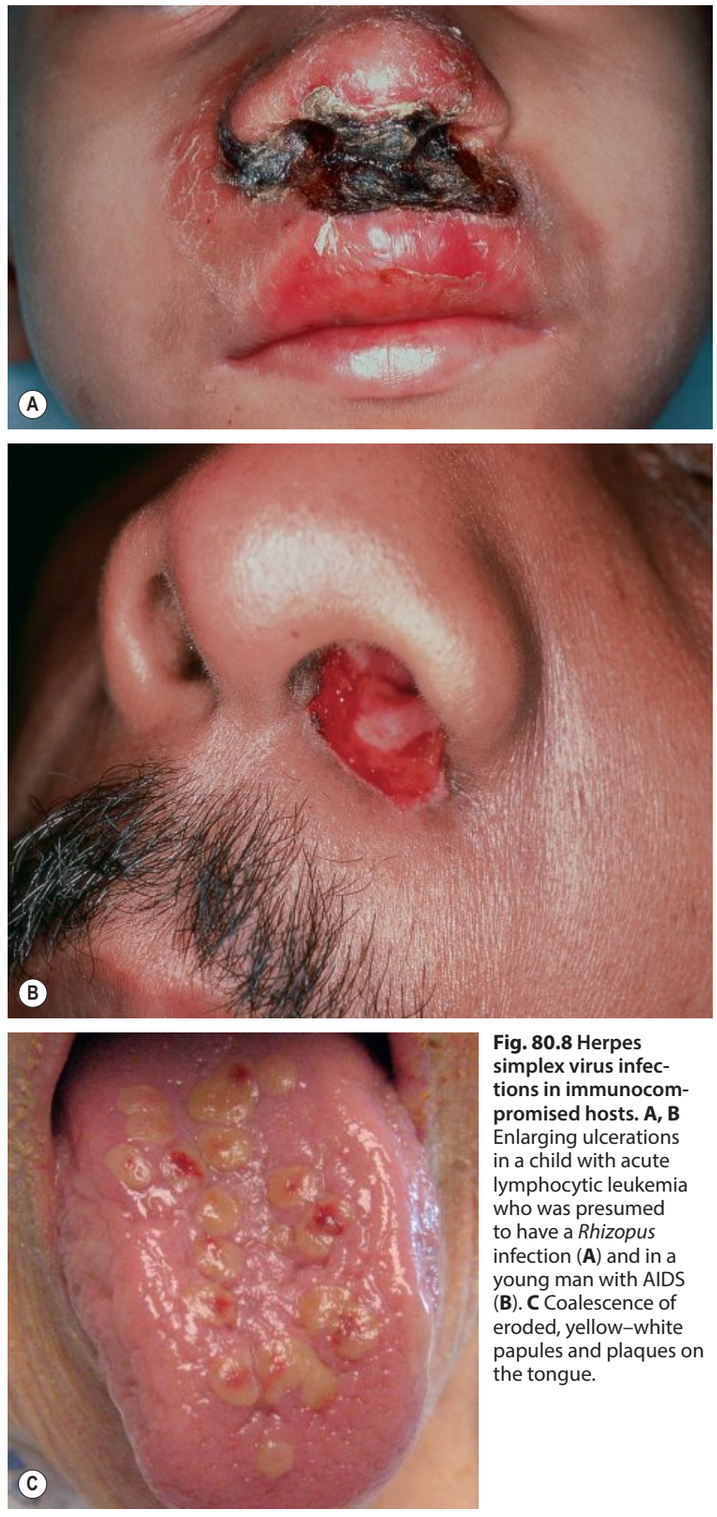


Fig. 80.8 Herpes simplex virus infections in immunocompromised hosts. A, B Enlarging ulcerations in a child with acute lymphocytic leukemia who was presumed to have a *Rhizopus* infection (**A**) and in a young man with AIDS (**B**). **C** Coalescence of eroded, yellow–white papules and plaques on the tongue.

Key features

- VZV is the etiologic agent of varicella (chickenpox) and herpes zoster (shingles)
- VZV has a high morbidity and mortality rate in immunocompromised hosts
- Antiviral treatment as well as vaccination can reduce or eliminate serious disease-associated sequelae and decrease the incidence of VZV infection

Introduction

VZV is the etiology of varicella (chickenpox) and herpes zoster (shingles). Varicella is usually symptomatic, and before the advent of the varicella vaccine, it occurred in 90% of children in the US by the time they reached 10 years of age. Herpes zoster represents reactivation of latent VZV infection and develops in ~20% of healthy adults and 50% of immunocompromised persons, with substantial morbidity and mortality in the latter group. Early initiation of antiviral treatment can reduce or eliminate serious sequelae of VZV infections.

History

Heberden first distinguished chickenpox from smallpox in 1767. The term "chickenpox" is thought to come from either the French word "chiche-pois" for chickpea (referring to the size of the vesicles) or the Old English word "gigan" meaning "to itch". The relationship between varicella and herpes zoster was first recognized in 1888, when von Bokay described the development of varicella in children following exposure to those with herpes zoster infection. Kundratitz (1922) and Bruusgaard (1932) more convincingly demonstrated the association between the two diseases by the development of varicella in susceptible children who had been inoculated with vesicle fluid from patients with herpes zoster. This was followed by the identification of the same virus in both diseases, confirming that their etiologies were identical.



Fig. 80.9 Neonatal herpes. Grouped papulovesicles with an erythematous base on the chest. Note the scalloped borders in areas of coalescence. *Courtesy Frank Samarin, MD.*

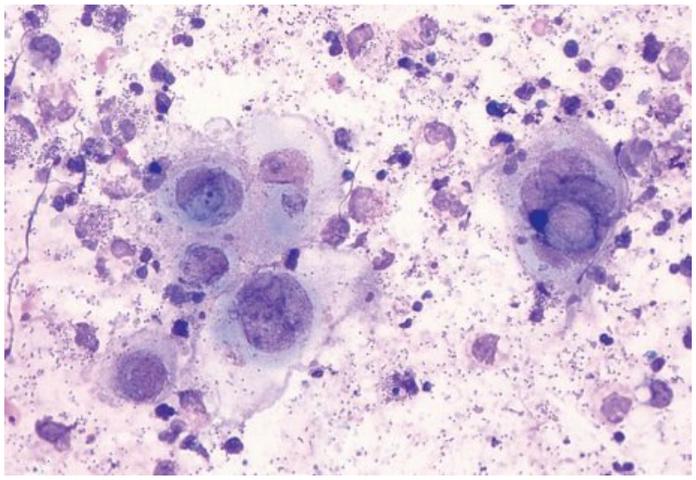


Fig. 80.10 Tzanck smear. Note the multinucleated epithelial giant cells from a patient with herpes simplex viral infection. *Courtesy Louis A. Fragola, Jr, MD.*

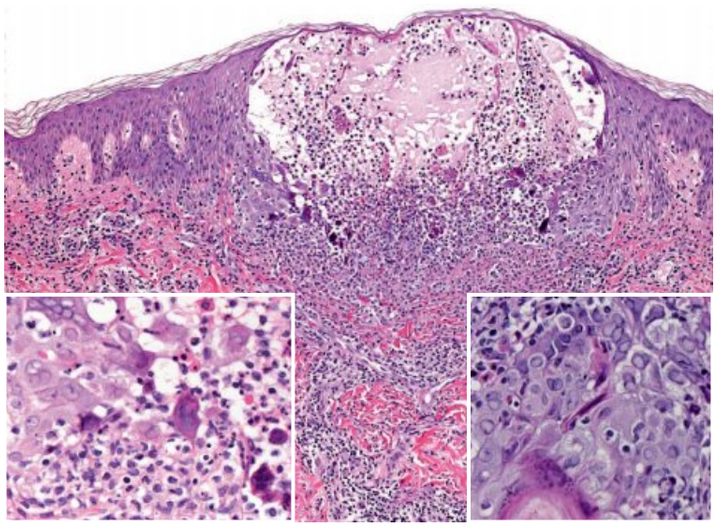


Fig. 80.11 Histology of herpes simplex viral infection. Intraepidermal vesicle with ballooning degeneration of keratinocytes and multinucleated giant cells; the latter arise from the fusion of infected keratinocytes. Note the steel-gray nuclei with margination of chromatin and inclusions (insets). *Courtesy Lorenzo Cerroni, MD.*

Epidemiology

VZV has a worldwide distribution and 98% of the adult population is seropositive. In the pre-vaccine era, 90% of children <10 years of age developed varicella and ~4 million cases occurred annually in the US, with large outbreaks during the winter and spring. Since the introduction of the varicella vaccine in 1995, the overall incidence of varicella has decreased by ~85%, with evidence of herd immunity. The age of peak incidence also shifted from 5–9 years to 10–14 years, and a higher rate of breakthrough varicella among immunized children in the latter age group led to the addition of a second varicella vaccine dose to the routine childhood immunization schedule in 2006[30].

Although the incidence and severity of herpes zoster increase substantially in middle to late adulthood, it can occur at any age and is more common in younger persons who had a varicella infection within the first year of life. Overall, individuals with a history of varicella have a 20% lifetime chance of developing zoster. The annual incidence of herpes zoster in the US and Europe is classically 2.5/1000 persons between ages 20 and 50 years, 5/1000 between ages 51 and 79 years, and 10/1000 in those >80 years of age. However, there is evidence that exposure to varicella can protect seropositive adults from the development of zoster, and it has been postulated that widespread vaccination against varicella could reduce this immune boosting effect and increase the incidence of zoster. Whether this hypothetical increase will be counterbalanced by zoster vaccination remains to be determined. Other risk factors for herpes zoster include mental and physical stress, a family history of zoster, use of JAK inhibitors or proteasome inhibitors (e.g. bortezomib, carfilzomib), and an immunocompromised state, especially when due to HIV infection and allogeneic hematopoietic stem cell transplantation (HSCT)[31,32].

Pathogenesis

Airborne droplets are the usual route of transmission of varicella, although direct contact with vesicular fluid is another mode of spread, and the incubation period is 11–20 days. Varicella is extremely contagious, and 80%–90% of susceptible household contacts develop a clinically evident infection. The affected individual is infectious from 1–2 days before skin lesions appear until all the vesicles have crusted.

During varicella infection, primary viremia occurs after an initial 2–4 days of viral replication within regional lymph nodes. A cycle of viral replication in the liver, spleen, and other organs is then followed by a secondary viremia, which seeds the entire body 14–16 days postexposure. During this period, the virus enters the epidermis by invading capillary endothelial cells. VZV subsequently travels from mucocutaneous lesions to dorsal root ganglion cells, where it remains latent until reactivation at a later time.

Herpes zoster appears upon reactivation of latent VZV, which may occur spontaneously or be induced by stress, fever, radiation therapy, local trauma, or immunosuppression. During a herpes zoster outbreak, the virus continues to replicate in the affected dorsal root ganglion and produces a painful ganglionitis. Neuronal inflammation and necrosis can result in a severe neuralgia that intensifies as the virus spreads down the sensory nerve. Fluid from herpes zoster vesicles can transmit VZV to seronegative individuals, leading to varicella but not herpes zoster. The transmission rate to susceptible household contacts is ~15% for zoster, compared to 80%–90% for varicella.

Clinical Features

Varicella

A prodrome of mild fever, malaise, and myalgia may occur, especially in adults. This is followed by an eruption of pruritic, erythematous macules and papules, which starts on the scalp and face, and then spreads to the trunk and extremities (Fig. 80.12). Lesions rapidly evolve over ~12 hours into 1–3 mm clear vesicles surrounded by narrow red halos ("dew drops on a rose petal"). The number of vesicles varies from only a few to several hundred, and there is often involvement of the oral mucosa (see Fig. 80.12D). Sparing of the distal and lower extremities is common. Older vesicles evolve to form pustules and crusts, with individual lesions healing within 7–10 days. The presence of lesions in all stages of development is a hallmark of varicella.

The disease course is usually self-limited and benign in healthy children. However, prior to introduction of the varicella vaccine, complications resulted in 11 000 hospitalizations annually in the US. Secondary bacterial infection of the skin with subsequent scarring is the most common complication. CNS sequelae are uncommon (<1 per 1000 cases) and may include encephalitis and acute cerebellar ataxia; Reye syndrome which consists of encephalitis plus fatty liver is now

ANTIVIRAL THERAPY FOR HERPES SIMPLEX VIRUS AND VARICELLA–ZOSTER VIRUS	
Disease context	**Drug and dosage**
Herpes simplex infections	
Orolabial herpes* (recurrence)	*Topical* Docosanol: 5×/d until healed Penciclovir: 1% cream applied q2 h while awake × 4 days Acyclovir: 5% ointment applied q3 h or 6 times/day × 7–10 days Acyclovir + hydrocortisone: 5%/1% cream applied 5×/d × 5 days Acyclovir mucoadhesive tablet: 50 mg single application in the canine fossa on the side affected *Oral** Acyclovir†: 400 mg po TID × 7–10 days Famciclovir: 1.5 g po × 1 dose Valacyclovir: 2 g po BID × 1 day
Genital herpes (first episode)	Acyclovir: 200 mg po 5×/d × 10 days or 400 mg po TID × 10 days Famciclovir: 250 mg po TID × 10 days Valacyclovir: 1 g po BID × 10 days
Genital herpes (recurrence)	Acyclovir: 400 mg po TID × 5 days or 800 mg po BID × 5 days or 800 mg po TID × 2 days Famciclovir: 1 g po BID × 1 day or 500 mg po × 1 dose then 250 mg po BID × 2 days or 125 mg po BID × 5 days Valacyclovir: 500 mg po BID × 3 days or 1 g po daily × 5 days
Chronic suppression	Acyclovir: 400 mg po BID Famciclovir: 250 mg po BID Valacyclovir: 500 mg po daily for <10 outbreaks/year or 1 g po daily for ≥10 outbreaks/year
Neonatal	Acyclovir: 20 mg/kg iv q8 h × 14–21 days
Immunocompromised	*Recommend use until all mucocutaneous lesions are healed* Acyclovir: 400 mg po 5×/d or 5 mg/kg (if age ≥12 y) to 10 mg/kg (if age <12 y) iv q8 h Famciclovir†: 500 mg po BID Valacyclovir†: 1 g po BID
Eczema herpeticum/Kaposi varicelliform eruption†	*Recommend use for 10–14 days or (especially if immunocompromised) until all mucocutaneous lesions are healed* Acyclovir: 15 mg/kg (400 mg max) po 3–5×/d or, if severe, 5 mg/kg (if age ≥12 y) to 10 mg/kg (if age <12 y) iv q8 h Famciclovir: 500 mg po BID Valacyclovir: 1 g po BID
Genital herpes, recurrent in the setting of HIV infection	*Recommend use until all mucocutaneous lesions are healed* Acyclovir†: 400 mg po TID Famciclovir: 500 mg po BID Valacyclovir†: 1 g po BID
Chronic suppression in the setting of HIV infection	Acyclovir†: 400–800 mg po BID–TID Famciclovir†: 250–500 mg po BID Valacyclovir: 500 mg po BID
Acyclovir-resistant HSV in immunocompromised patients	Foscarnet: 40 mg/kg iv q8–12 h × 2–3 weeks (or until all lesions are healed) Cidofovir: 1% cream or gel daily × 2–3 weeks or (for severe disease) 5 mg/kg iv weekly × 2 weeks then every other week (together with probenecid)
Varicella–zoster virus infections	
Varicella	Acyclovir: 20 mg/kg (800 mg max) po 4×/d × 5 days Valacyclovir‡: 20 mg/kg (1 g max) po TID × 5 days
Herpes zoster	Acyclovir: 800 mg po 5×/d × 7–10 days Famciclovir: 500 mg po TID × 7 days Valacyclovir: 1 g po TID × 7 days
Immunocompromised patient or disseminated disease	Acyclovir: 10 mg/kg (500 mg/m^2) iv q8 h × 7–10 days *or until cropping has ceased* (depending on the setting, consider continuing until lesions are healed)

*Indications for and efficacy of antiviral treatment for initial episodes of orolabial herpes in immunocompetent adults have not been defined, but the regimens used for initial genital episodes can be considered in individuals with severe disease; acyclovir 15 mg/kg (200 mg max) po 5×/d × 7 days (initiated within 3 days of disease onset) has been shown to be beneficial in young children with primary herpes gingivostomatitis.
†Not specifically FDA-approved for this indication.
‡FDA-approved for ages 2–17 years; pharmacies can compound valacyclovir tablets into an oral suspension (25 or 50 mg/ml).

Table 80.4 Antiviral therapy for herpes simplex virus and varicella–zoster virus. Topical antiviral agents should be applied using a finger with intact skin. BID, twice daily; d, day; h, hours; iv, intravenously; po, orally; q, every; TID, three times daily.

rare due to avoidance of aspirin in children with varicella. Varicella in adolescents and adults is often more severe than in children, with an increased number of skin lesions (see Fig. 80.12A) and more frequent development of pneumonia, which has a 10%–30% mortality rate if untreated[33]. Occasional complications include thrombocytopenia, hepatitis, glomerulonephritis, optic neuritis, keratitis, arthritis, myocarditis, pancreatitis, orchitis, and vasculitis.

Maternal varicella during the first 20 weeks of pregnancy is associated with an ~2% risk of *congenital* varicella syndrome (varicella embryopathy). Possible congenital defects include a low birth weight, cutaneous scarring, ocular abnormalities, cortical atrophy, psychomotor retardation, and hypoplastic limbs. Children whose mothers had varicella during pregnancy may also develop zoster early in life without ever having extrauterine varicella. Severe *neonatal* varicella, in which amelioration by maternal antibodies is lacking, can occur when maternal varicella develops between 5 days before and 2 days after delivery.

In immunocompromised individuals, varicella may lead to severe complications and even death. These patients frequently have a more extensive and atypical cutaneous eruption, often with hemorrhagic or purpuric lesions[10]. Involvement of the lungs, liver, and CNS is common.

DOSE REDUCTIONS FOR ACYCLOVIR, VALACYCLOVIR, AND FAMCICLOVIR IN PATIENTS WITH RENAL DISEASE						
Indication	**Acyclovir**		**Valacyclovir**		**Famciclovir**	
	Creatinine clearance (ml/min)	**Adjusted dose**	**Creatinine clearance (ml/min)**	**Adjusted dose**	**Creatinine clearance (ml/min)**	**Adjusted dose**
Primary genital herpes simplex	<10	200 mg po BID	10–29	1 g daily	20–39	125 mg BID
			<10	500 mg daily	<20	125 mg daily
Recurrent genital herpes simplex			<30	500 mg daily	40–59	500 mg BID × 1 day
					20–39	500 mg once
					<20	250 mg once
Chronic suppression of herpes simplex			<30	500 mg q48 h or daily	20–39	125 mg BID
					<20	125 mg daily
Recurrent orolabial herpes simplex	<10	200 mg po BID*	30–49	1 g BID × 1 day	40–59	750 mg once
			10–29	500 mg BID × 1 day	20–39	500 mg once
			<10	500 mg once	<20	250 mg once
Herpes zoster	10–25	800 mg po TID	30–49	1 g BID	40–59	500 mg BID
	<10	800 mg po BID	10–29	1 g daily	20–39	500 mg daily
			<10	500 mg daily	<20	250 mg daily
Immunocompromised patients with mucocutaneous herpes simplex; for iv acyclovir, also herpes encephalitis and disseminated zoster	25–50	5–10 mg/kg iv q12 h				
	10–24	5–10 mg/kg iv q24 h	10–29	1 g daily*	20–39	500 mg daily*
	<10	2.5–5 mg/kg iv q24 h	<10	500 mg daily*	<20	250 mg daily*

*Not specifically FDA-approved for this indication.

Table 80.5 Dose reductions for acyclovir, valacyclovir, and famciclovir in patients with renal disease. In hemodialysis patients, the medication should be administered after dialysis. BID, twice daily; h, hours; iv, intravenously; po, orally; q, every; TID, three times daily.

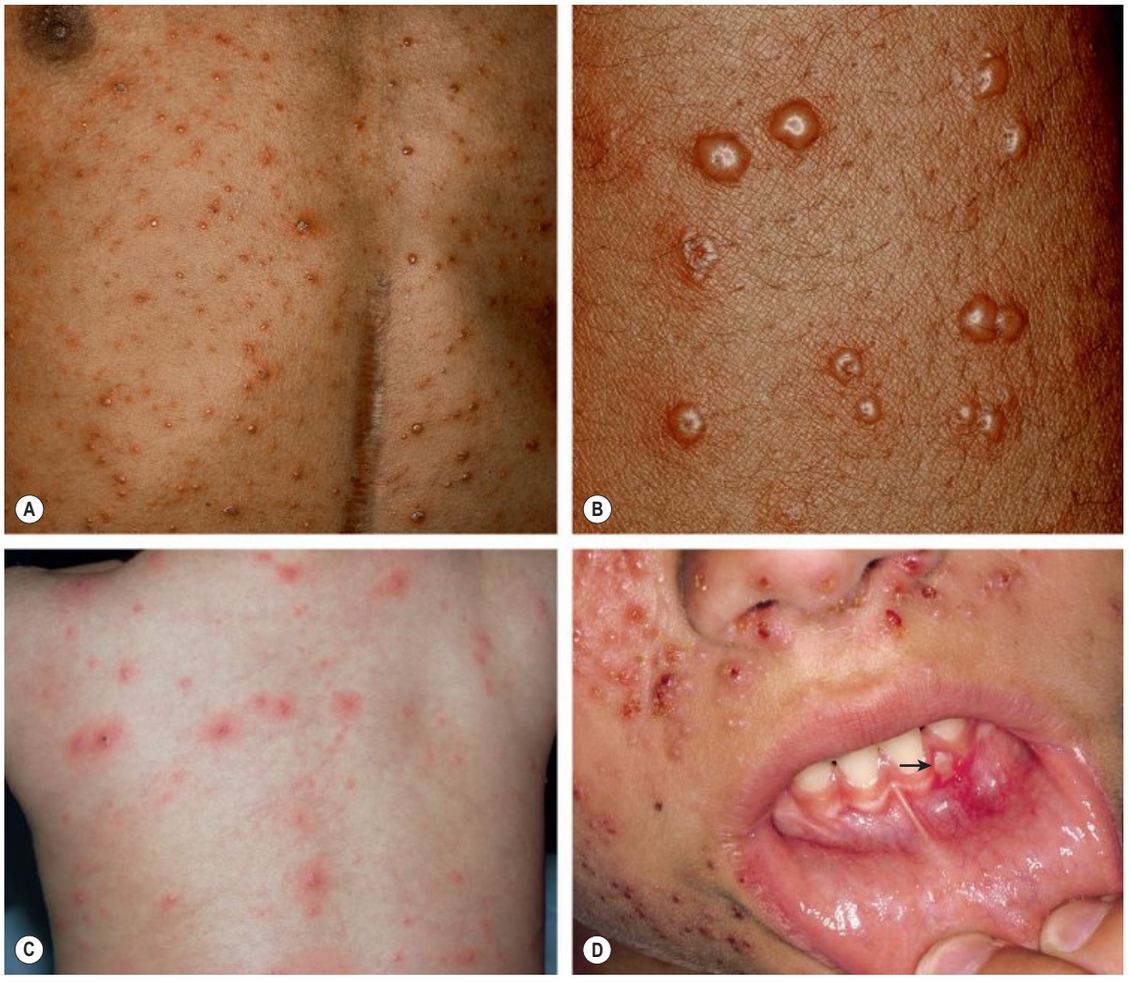


Fig. 80.12 Varicella. A–C Lesions in different stages of evolution, including vesicles, pustules, and hemorrhagic crusts. Vesicles often develop central umbilication. **D** Oral lesions can also occur (arrow). *A, B, Courtesy Robert Hartman, MD; C, Courtesy Julie V. Schaffer, MD; D, Courtesy Judit Stenn, MD.*

Herpes zoster

Reactivation of VZV may occur at any time after the development of varicella. In >90% of patients, herpes zoster begins with a prodrome of pruritus, tingling, tenderness, hyperesthesia, and/or intense pain, which can mimic a myocardial infarction, surgical abdomen, or toothache. These symptoms occasionally occur without subsequent skin lesions, a phenomenon referred to as "zoster sine herpete". However, most patients develop a painful eruption of grouped vesicles on an erythematous base in a dermatomal distribution (Figs. 80.13–80.15); the lesions can involve more than one contiguous dermatome and occasionally cross the midline. Edematous papules and plaques may precede the appearance of vesicles, and progression to pustules or bullae can occur (see Fig. 80.14). Any cutaneous site may be affected, with the trunk representing the most common location, followed by the face. VZV DNA can often be detected in the peripheral blood and saliva of patients with herpes zoster, even after initiation of antiviral treatment[34,35].

Herpes zoster usually resolves without sequelae in immunocompetent children and young adults. However, the pain, cutaneous lesions, and complications of herpes zoster become more severe with increasing age and immune compromise. The most common complication is postherpetic neuralgia, which is characterized by dysesthetic pain (e.g. burning or stabbing sensation, allodynia) that persists after the skin lesions have healed. This affects 10%–20% of all herpes zoster patients and increases in both incidence and severity with age[36]. Complications of herpes zoster related to the dermatome that is affected are presented in Table 80.6. Other complications can include secondary bacterial infection, scarring, meningoencephalitis, pneumonitis, and hepatitis. Cutaneous disorders that can develop within sites of previous herpes zoster, including granulomatous (Fig. 80.16) and pseudolymphomatous lesions, are listed in Table 80.7.

In immunocompromised individuals, herpes zoster may be more severe and can have unusual clinical presentations, e.g. persistent crusted, verrucous lesions in HIV-infected patients (Fig. 80.17) or postherpetic hyperhidrosis[10,37]. Disseminated cutaneous disease, defined as more than 20 vesicles outside the area of primary or adjacent dermatomes, and/or visceral involvement occurs in ~10% of immunocompromised persons with zoster (Fig. 80.18)[38].

Diagnosis and Pathology

A clinical diagnosis can usually be made based upon the history, including previous varicella or vaccine administration, and physical examination. A Tzanck smear, PCR, or DFA can assist in quickly confirming the diagnosis (see above and Fig. 80.10). The latter two (but not the Tzanck smear) can differentiate between HSV and VZV. Varicella and herpes zoster have the same histologic findings as HSV infections (see above and Fig. 80.11), but immunohistochemical staining can distinguish between the two viruses. Exclusive involvement of the hair follicles may be observed in herpes zoster, but not in HSV infection.

Additional laboratory tests include viral culture and serology. Viral culture is a very specific test; however, it is not very sensitive and results may not be available for >1 week. Serologic assays are diagnostic of VZV if the convalescent serum has at least a fourfold increase in the VZV titer relative to the acute serum. As a result, serology is only useful in retrospect.

Differential Diagnosis

The differential diagnosis of varicella may include vesicular viral exanthems (e.g. due to coxsackieviruses), disseminated HSV infection, pityriasis lichenoides et varioliformis acuta (PLEVA), rickettsialpox, drug eruptions, bullous insect bite reactions, and even scabies. Although no longer naturally occurring, smallpox also presents with a widespread vesicular eruption; its distinct clinical features are reviewed in Chapter 81. For herpes zoster, diagnostic considerations

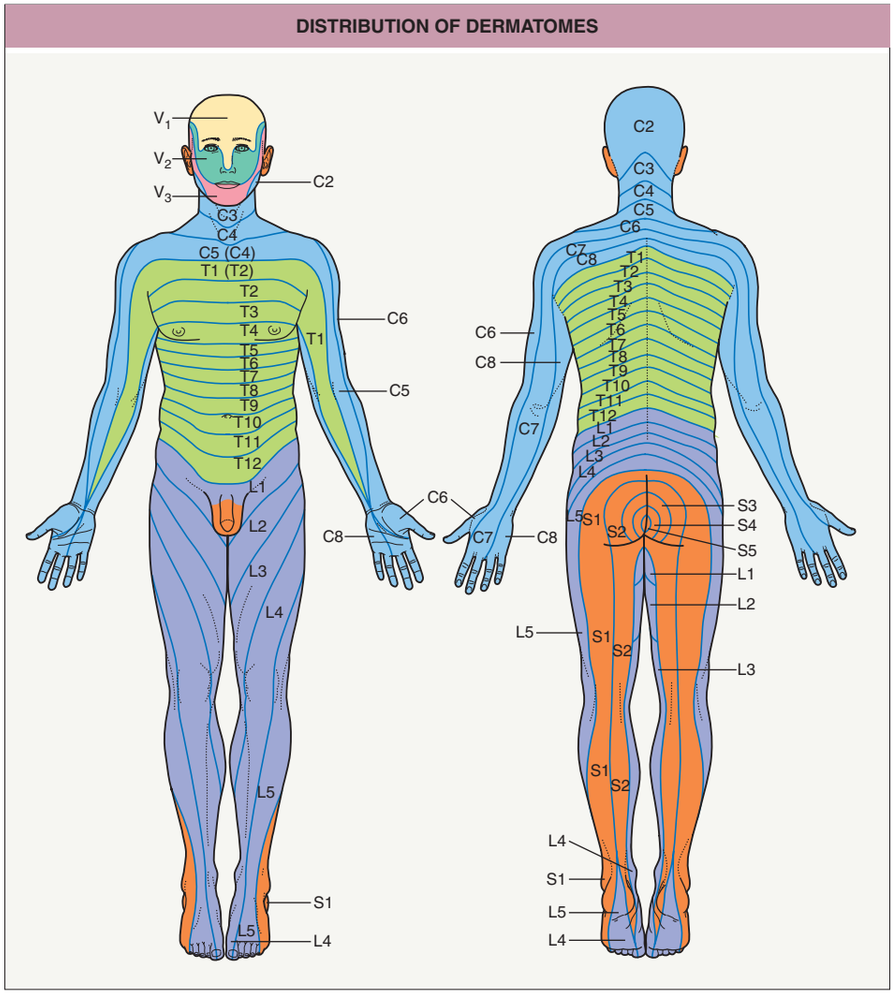


Fig. 80.13 Distribution of dermatomes.



Fig. 80.14 Herpes zoster. A–C Erythematous, edematous plaques with early vesicle formation. Note the perifollicular accentuation (**B**). **D, E** Later stages of evolution with prominent pustule formation (**D**) and a dusky purple color associated with older vesicles (**E**). **F** Bullous variant on the flexor arm. *B, Courtesy Jean L. Bolognia, MD; D, Courtesy Louis A. Fragola, Jr, MD.*

may include zosteriform HSV infections (which often recur in the same site), bacterial skin infections (e.g. cellulitis, bullous impetigo), contact dermatitis, and phytophotodermatitis. The entities listed above can usually be differentiated from VZV infections based on the history and clinical presentation, but laboratory studies and histologic evaluation are sometimes needed.

Treatment and Prevention

Varicella

Varicella in immunocompetent children can be treated symptomatically with antipyretics (e.g. acetaminophen), antihistamines, calamine lotion, and tepid baths. If started within 24–72 hours after the onset of the cutaneous eruption, acyclovir has been shown to decrease the duration and severity of varicella[39]. Oral acyclovir and valacyclovir are FDA-approved for the treatment of varicella in children (2–17 years of age) while acyclovir is approved for adults (see Table 80.4). These antiviral agents are recommended for varicella in healthy adolescents and adults as well as in children with chronic cutaneous or pulmonary disorders and in those receiving chronic salicylate therapy, inhaled corticosteroids, or intermittent oral corticosteroids. However, routine antiviral therapy is not recommended for otherwise healthy children with varicella due to the self-limited disease course and modest benefits of treatment[40]. Intravenous acyclovir is indicated for varicella in immunocompromised patients, including those receiving chronic systemic corticosteroids, due to their increased risk of more severe disease and complications[39].

Administration of varicella zoster immune globulin (125 U/10 kg, 625 U maximum) intramuscularly within 96 hours of varicella exposure is recommended to provide passive prophylaxis to nonimmune immunocompromised individuals and pregnant women as well as high-risk neonates (see above)[41]. Protection lasts for ~3 weeks. Another option for postexposure varicella prophylaxis in these patient groups is administration of intravenous immunoglobulin (IVIg; ≥400 mg/kg), which contains high levels of varicella-specific IgG[42]. Prophylactic oral acyclovir administration with usual varicella dosing (see Table 80.4) for 1 week, starting 7–10 days after exposure, can also be considered. Lastly, postexposure varicella vaccination (within 72–120 hours) may prevent or modify disease in nonimmune individuals who are ≥12 months of age, immunocompetent, and eligible to receive this live attenuated vaccine (see below).

Approved by the FDA in 1995, the live attenuated VZV vaccine (Oka strain; Varivax®) is highly efficacious, with seroprotection rates of ~85% after one dose and ≥99% after two doses in healthy children. Two doses of the vaccine, routinely given at ages 12–15 months and 4–6 years, are recommended to improve protection and counteract waning vaccine-induced immunity (see below). Studies indicate that one dose of the vaccine is 70%–90% effective in preventing infection and 95%–100% effective in preventing severe disease, and recipients of two doses are more than threefold less likely to develop breakthrough varicella than those who received one dose. The incidence and severity of both varicella (usually due to wild-type VZV) and zoster (most often due to the attenuated Oka strain) (Fig. 80.19) are decreased in vaccine recipients compared to unimmunized children. However, in a report based on surveillance of 350 000 subjects who received one vaccine



Fig. 80.15 Facial herpes zoster. **A** Clustered vesicles in a linear array within the distribution of V_1. **B** In the distribution of V_3, grouped pustules on the left side of the chin and hemorrhagic crusting of the lower lip, with one lesion extending past the midline. This could be mistaken for an acneiform eruption or impetigo. **C** In the same patient, erosions are present on the left side of the tongue. The anterior two-thirds of the tongue is innervated by the facial nerve (VII; taste) as well as V_3 (sensory); see Table 80.6 for details of Ramsay Hunt syndrome. **D** Focal hemorrhagic crusting with scalloped borders arising in an erythematous patch on the forehead within the V_1 distribution. Note the periorbital edema. *Courtesy Kalman Watsky, MD.*

CLINICAL FINDINGS RELATED TO THE DERMATOME INVOLVED IN HERPES ZOSTER		
Dermatome/nerve involved	**Cutaneous findings**	**Extracutaneous findings**
Ophthalmic division of the trigeminal nerve (V_1; ~10%–15% of zoster patients)	*Hutchinson's sign* refers to increased risk of ocular involvement if skin lesions are in the distribution of the nasociliary branch, which supplies the nasal tip, dorsum, and root of the nose, and medial canthus as well as the cornea	• ~50% of patients have ocular involvement, which can include conjunctivitis, (epi)scleritis, keratitis, uveitis, acute retinal necrosis, and optic neuritis • May lead to ocular scarring and visual loss
Geniculate ganglion of the facial nerve – *Ramsay Hunt syndrome*	Lesions affecting the external auditory canal, tympanic membrane, anterior two-thirds of the tongue, and/or hard palate	• Ear pain • Facial nerve paralysis (peripheral) • Loss of taste in anterior two-thirds of the tongue • Dry mouth and eyes • If the vestibulocochlear nerve is also affected: tinnitus, hearing loss, and/or vertigo
Cervical dermatome	Lesions in cervical dermatome	• Peripheral motor neuropathy of the arm, which may result in muscle atrophy with gradual recovery of strength • Diaphragmatic weakness (C3–5)
Thoracic dermatome	Lesions in thoracic dermatome	• Abdominal muscle weakness or paralysis • Abdominal wall pseudohernia presenting as asymptomatic bulging of the anterolateral abdomen
Lumbar or sacral dermatome	Lesions in lumbar or sacral dermatome	• Peripheral motor neuropathy of the leg, which may result in muscle atrophy with gradual recovery of strength • Bowel or bladder dysfunction

Table 80.6 Clinical findings related to the dermatome involved in herpes zoster.

dose, loss of vaccine-induced immunity over time was observed, e.g. within 1 year of vaccination, there were 1.6 cases of varicella per 1000 person-years versus 58.2 per 1000 person-years at 9 years post-vaccination[43]. Because this is a live viral vaccine, administration is contraindicated during pregnancy and in individuals with immunosuppression due to hematologic malignancies, HIV infection (if $CD4^+$ T cells are <15% or <200 cells/mcl), other T cell immunodeficiencies, or systemic immunosuppressive therapy such as TNF inhibitors or prednisone (≥20 mg daily for ≥2 weeks, or ≥2 mg/kg daily when weight <10 kg).

Herpes zoster

For herpes zoster, beginning antiviral treatment within 72 hours of the development of skin lesions is optimal, but initiation up to 7 days after onset also appears to be beneficial. Acyclovir, famciclovir, and valacyclovir are all FDA-approved for the treatment of herpes zoster in immunocompetent individuals and result in decreased severity and duration of both skin lesions and pain (see Table 80.4). In controlled studies of immunocompetent individuals >50 years of age with acute herpes zoster, famciclovir and valacyclovir were equally effective (and



Fig. 80.16 Granulomatous dermatitis in the site of previous herpes zoster. Pink papules and plaques developed several weeks after an episode of herpes zoster in the same dermatomes. A sharp midline demarcation was observed on the back. Histologically, a granulomatous dermatitis was present within the dermis and focally a perineural distribution pattern was seen. *Courtesy Rebecca Vaughn, MD.*

CUTANEOUS DISORDERS THAT CAN DEVELOP WITHIN SITES OF HERPES ZOSTER
Acneiform – comedones, furunculosis, "acneiform eruption", rosacea (trigeminal distribution)
Dermatitis and urticaria – contact dermatitis (allergic and irritant), chronic localized urticaria
Granulomatous – granuloma annulare (including perforating variant), granulomatous dermatitis (sarcoidal, tuberculoid, unclassified, periadnexal, perineural; see Fig. 80.16), granulomatous vasculitis, lichenoid and granulomatous dermatitis*
Infiltrative – pseudolymphoma†, xanthomatous, Rosai–Dorfman disease
Malignancies, hematologic – leukemia (especially CLL), lymphoma cutis‡
Malignancies, other – Kaposi sarcoma (HIV-associated form), angiosarcoma, solid-organ metastases
Papulosquamous – psoriasis, lichen planus, lichenoid GVHD*
Sclerosing – lichen sclerosus, morphea, hypertrophic scars/keloids
Ulcerative – trophic syndrome (trigeminal, cervical)
Miscellaneous – acquired perforating disorder (acquired perforating collagenosis), nodular solar degeneration, tinea, bullous pemphigoid
*"Giant cell lichenoid dermatitis" has also been described within herpes zoster scars in an allogeneic bone marrow transplant recipient.
†In patients with chronic lymphocytic leukemia, a diagnosis of "pseudolymphoma" should be made only if leukemia cutis has been excluded.
‡Some solid organ metastases may show a zosteriform arrangement of the lesions without history of previous herpes zoster.

Table 80.7 Cutaneous disorders that can develop within sites of herpes zoster. The phenomenon of a new, unrelated disease appearing in the same location as a previously healed disease is referred to as the *Wolf isotopic response*. This list does not include routine scarring and acute complications such as bacterial infections. CLL, chronic lymphocytic leukemia.

similar or superior to acyclovir) at reducing the frequency and duration of postherpetic neuralgia[44]. Intravenous acyclovir is indicated for the treatment of zoster in immunocompromised patients as well as those with serious complications. Amenamevir, a helicase-primase inhibitor that is approved in Japan, was found to be non-inferior to valacyclovir in treatment of adults with zoster.

Multiple treatments are available for patients who develop postherpetic neuralgia. Low-dose tricyclic antidepressants have demonstrated considerable efficacy and appear to act by a mechanism independent from their antidepressant effects. In a randomized, controlled, multicenter trial, gabapentin (up to 3600 mg/day) was found to be effective in the treatment of pain and sleep interference associated with



Fig. 80.17 Chronic verrucous zoster in an HIV-infected patient.





Fig. 80.18 Disseminated varicella zoster viral infection. A Multiple violet–black papules on the feet. **B** Widely distributed necrotizing vesicles and bullae, some of which have formed large clusters, in a patient with lymphoma. Patients with disseminated cutaneous skin lesions should be evaluated for possible visceral involvement (e.g. hepatic, pulmonary, CNS), especially if they are immunocompromised. *B, Courtesy Edward Cowen, MD.*



Fig. 80.19 Herpes zoster following varicella vaccination. This healthy 3-year-old boy developed an eruption of erythematous papulovesicles in the C5 and C6 dermatomes of the right arm. He had received the varicella vaccine in the right shoulder at age 12 months, and several erythematous, edematous papulonodules had appeared in the region of the injection 2 weeks later. *Courtesy Julie V. Schaffer, MD.*

postherpetic neuralgia[45]. Combined treatment with nortriptyline and gabapentin reduced pain more than either agent alone in another randomized controlled trial[46]. In one open study, the use of gabapentin together with valacyclovir during acute herpes zoster was more effective in preventing postherpetic neuralgia than treatment with valacyclovir alone in historical controls; this regimen is recommended for patients with acute herpes zoster presenting with moderate to severe pain[47,48]. Although treatment with prednisone in addition to acyclovir can reduce acute pain in patients with herpes zoster, several controlled trials have failed to demonstrate a difference in the incidence or severity of postherpetic neuralgia with this combination compared to acyclovir monotherapy[49]. An 8% capsaicin patch was found to reduce the pain of postherpetic neuralgia for up to 12 weeks after a 1-hour application[50]. Other treatments used for postherpetic neuralgia include analgesics, EMLA cream, lidocaine patches, narcotic analgesics, pregabalin, nerve blocks, and biofeedback. Although some evidence suggests that patients receiving TNF inhibitors for various immune-mediated diseases may have a slightly higher incidence of herpes zoster, development of postherpetic neuralgia in these patients appears to be uncommon[51,52].

Because reactivation of VZV is linked with states of decreased cell-mediated immunity, the varicella vaccine was studied as a method of prophylaxis for herpes zoster. A large trial utilizing a 14-fold more concentrated version of the varicella vaccine in almost 40 000 adults ≥60 years of age showed a 51% reduction in the incidence of herpes zoster and 67% decrease in the likelihood of postherpetic neuralgia in vaccine recipients[53]. The FDA approved this live attenuated vaccine (Zostavax®) for immunocompetent adults ≥50 years of age in 2006, and the Advisory Committee on Immunization Practices (ACIP) recommended a single dose of Zostavax® for the prevention of herpes zoster in immunocompetent individuals ≥60 years of age[54]. However, multiple subsequent studies found that immunity induced against zoster by this vaccine was relatively short-lived, with a decrease in efficacy to <35% by year 6 after administration[55–58]. Considering its limited effectiveness as well as reports of necrotizing retinitis in immunocompromised vaccine recipients, Zostavax® is no longer available in the US.

In phase III studies, a recombinant subunit vaccine containing VZV glycoprotein E and the $AS01_B$ adjuvant system (HZ/su) administered in two doses two months apart reduced the likelihood of herpes zoster ~97% and postherpetic neuralgia ~90% in adults ≥50 years of age[59]. Efficacy of this vaccine was unaffected by advancing age and persisted for >3 years. In 2017, the FDA approved this recombinant zoster vaccine (Shingrix®) as a two-dose regimen, with the ACIP also recommending its use for the prevention of herpes zoster in immunocompetent adults ≥50 years of age (2–6 months between doses) and those ≥18 years of age who are or will be immunocompromised (1–6 months between doses)[60,61]. Vaccination is recommended regardless of whether or not the individual has a history of varicella, herpes zoster, or administration of a live attenuated VZV vaccine[60].

EPSTEIN–BARR VIRUS (HHV-4)

Synonym: ■ Infectious mononucleosis – glandular fever

Key features

- EBV is responsible for a variety of clinical diseases, most notably infectious mononucleosis; it is also associated with lymphoproliferative disorders and lymphomas
- Knowledge of EBV-specific serologies and other laboratory tests for EBV is essential for the clinician

Introduction and History

EBV is a ubiquitous human herpesvirus (HHV-4) that is responsible for a broad spectrum of clinical diseases, including infectious mononucleosis, oral hairy leukoplakia (see Ch. 78), hydroa vacciniforme (see Ch. 87), and a variety of lymphoproliferative disorders, lymphomas (B and T cell), and other malignancies (Table 80.8). It replicates well in B lymphocytes and can lead to their immortalization. EBV was named after its two discoverers, who found this herpesvirus in an African Burkitt lymphoma in 1964. In 1968, a link between infectious mononucleosis and EBV was established. Since then, various clinical disorders have been associated with EBV and are classified based on the type of cell infected and state of viral infection.

Epidemiology

In high-income countries, the prevalence of EBV infection in the general population approaches 95% by early adulthood. Peaks of incidence occur in individuals 1 to 6 and 14 to 20 years of age. Approximately 60%–80% of young children in low-income countries are seropositive for EBV, compared to ≤50% in the US. Most children with primary EBV infection have either no symptoms or a mild, nonspecific febrile illness. In contrast, ~50% of adolescents and young adults with primary EBV infection develop infectious mononucleosis. In the US, EBV is commonly associated with B cell lymphomas (~20%) and lymphoproliferative disorders (polyclonal and monoclonal) in immunocompromised patients. Worldwide, EBV is also implicated in Burkitt lymphoma (particularly the African-endemic form) and nasopharyngeal carcinoma (primarily in Asia) (see Table 80.8).

Pathogenesis

EBV is transmitted primarily through infectious saliva and occasionally via blood transfusion, although its presence in genital secretions and breast milk has been reported[62,63]. The virus preferentially infects human mucosal epithelial cells and B lymphocytes, with primary infection originating within the oropharyngeal epithelium. Infectious mononucleosis results from active viral replication, which is subsequently terminated by the host immune response.

After infectious mononucleosis resolves, circulating B lymphocytes can become latently infected with EBV as the virus enters cells by specifically binding to cell surface complement receptors CR2 or CD21. As the B lymphocyte divides, expression of the EBV nuclear antigen-1 gene (*EBNA-1*) is essential for replication of EBV DNA. Furthermore, the EBNA-1 protein and the virally encoded latent membrane protein-2 (LMP-2) are important in establishment of EBV latency within B lymphocytes and evasion from the cellular immune system[64]. In the presence

EBV-ASSOCIATED DISORDERS
Infectious mononucleosis
Gianotti–Crosti syndrome
Genital ulcers*
Periodontal disease
Oral hairy leukoplakia
Hydroa vacciniforme and related conditions due to chronic active EBV infection in childhood†
• Classic hydroa vacciniforme
• Hydroa vacciniforme-like lymphoproliferative disorder‡
• Severe hypersensitivity to mosquito bites‡
Lymphadenitis, including Kikuchi disease
Lymphoproliferative disorders and lymphomas
• Post-transplant lymphoproliferative disorder/lymphoma
• Methotrexate-associated lymphoproliferative disorder (usually in patients with rheumatoid arthritis)
• Systemic EBV$^+$ T cell lymphoma of childhood
• EBV$^+$ mucocutaneous ulcer
• X-linked lymphoproliferative syndrome
• EBV$^+$ hemophagocytic lymphohistiocytosis
• Lymphomatoid granulomatosis
• Burkitt lymphoma, endemic ≫ sporadic
• Extranodal NK/T cell lymphoma, nasal type
• EBV$^+$ diffuse large B cell lymphoma, NOS
• Angioimmunoblastic T cell lymphoma
• Other non-Hodgkin lymphomas (including T cell), particularly in HIV-infected patients
• Hodgkin lymphoma
Other malignancies
• Nasopharyngeal carcinoma
• Gastric carcinoma
• Leiomyosarcoma
Smooth muscle tumors

*There may or may not be evidence of EBV within the ulcer; reactive non-sexually related acute genital ulcers (Lipschütz ulcers) can be triggered by EBV and other infections (e.g. cytomegalovirus, influenza, *Mycoplasma pneumoniae*), most often in adolescent girls; this is thought to represent a form of aphthosis, which may be recurrent and associated with a history of oral aphthous ulcers.
†May progress to T or NK cell lymphoma or hemophagocytic lymphohistiocytosis; most often affects East Asian and Latin American children.
‡Present with bullous, necrotic, and ulcerative skin lesions together with fever, lymphadenopathy, hepatosplenomegaly and (with mosquito bite hypersensitivity) natural killer (NK)-cell lymphocytosis.

Table 80.8 EBV-associated disorders. Other skin conditions that are only occasionally associated with EBV include erythema nodosum, urticaria, erythema multiforme, erythema annulare centrifugum, drug reaction with eosinophilia and systemic symptoms (DRESS), small vessel vasculitis, granuloma annulare-like eruptions, and pityriasis lichenoides. NOS, not otherwise specified.



Fig. 80.20 Reactive non-sexually related acute genital ulceration associated with primary EBV infection. EBV-related genital ulcers, which are most common in adolescent girls, are often misdiagnosed as genital herpes simplex infection and in some patients represent a variant of aphthosis (see Table 80.8).



Fig. 80.21 Ampicillin-induced eruption in a patient with infectious mononucleosis due to EBV infection. Erythematous macules and papules have become confluent on the upper trunk.

of a normally functioning immune system, cell-mediated immune responses toward EBV antigens generally prevent the transformation and immortalization of B lymphocytes. However, in patients with deficient cell-mediated immunity, B lymphocytes can become immortalized and give rise to EBV-induced lymphoproliferative disorders.

Cell-mediated immunity to EBV infection is persistent and protects against developing infectious mononucleosis upon re-exposure to different types and strains of EBV later in life. The humoral immune response, although it generates antibodies to a variety of EBV antigens, does not appear to be protective. Latent virus in EBV-infected B lymphocytes can subsequently reinfect the oropharyngeal epithelium, resulting in periodic EBV reactivation and viral shedding for the lifetime of the host. However, reactivation of EBV is less common compared to other herpesviruses.

Clinical Features

EBV-induced infectious mononucleosis most commonly occurs in adolescents and young adults 15–25 years of age. After an incubation period of 30–50 days, the clinical triad of pharyngitis, fever lasting up to 10 days, and lymphadenopathy (especially cervical) occurs in >80% of patients. An initial prodrome of headache, malaise, and fatigue often precedes onset of the triad. The absence of cervical lymphadenopathy and fatigue makes the diagnosis unlikely. Splenomegaly is found in >50% of patients and can be accompanied by hepatomegaly. Other clinical findings may include exudative pharyngitis (often gray–white), anorexia, nausea, vomiting, cough, and arthralgias.

EBV infection can have a variety of dermatologic manifestations. A faint, nonspecific erythematous exanthem has been reported in up to 70% of hospitalized patients and ~10% of all patients with infectious mononucleosis[65]. The exanthem typically develops on day 4–6 of the illness and may last up to 1 week. It can be morbilliform, urticarial, scarlatiniform, vesicular, erythema multiforme-like, purpuric, or petechial in nature, usually beginning on the trunk and proximal upper extremities with later extension to the face and forearms. Eyelid petechiae, periorbital edema, and petechiae at the junction of the hard and soft palate may also be observed. Resolution of the illness usually occurs after 2 to 3 weeks, although symptoms of fatigue and malaise may last longer.

Painful genital ulcers, often measuring >1 cm, occasionally develop in patients (especially adolescent girls) with primary EBV infection (Fig. 80.20); PCR or *in situ* hybridization has confirmed the presence of lesional EBV in some cases[66]. Cutaneous conditions that are occasionally associated with primary EBV infection include Gianotti–Crosti syndrome (see Ch. 81), erythema nodosum, urticaria, acrocyanosis, erythema multiforme, erythema annulare centrifugum, and pityriasis lichenoides.

Administration of ampicillin or amoxicillin, and less commonly penicillin or cephalosporins, to patients with infectious mononucleosis, frequently (up to 90% with the former agents) leads to the development of a "hypersensitivity" skin reaction. This usually develops 7–10 days following institution of the antibiotic. Typically, a pruritic, pink to copper-colored, scarlatiniform or morbilliform eruption develops on extensor surfaces and pressure points and then becomes confluent as it spreads onto the trunk and extremities (Fig. 80.21). Desquamation

occurs 1 week later. The mechanism of this enhanced immune response to aminopenicillins in the setting of EBV infection is not well understood. In the absence of a pre-existing allergy, such reactions do not generally preclude the use of this class of antibiotics after the infectious mononucleosis resolves.

EBV-induced infectious mononucleosis can have serious complications. Splenic rupture occurs in 0.2% of affected adults, usually after trauma. Significant enlargement of oropharyngeal lymphoid tissue can lead to airway compromise. Other potential complications include hepatitis, thrombocytopenia, hemolytic anemia, glomerulonephritis, and CNS disturbances.

Diagnosis and Pathology

Laboratory findings in patients with infectious mononucleosis include mild to moderately elevated hepatic transaminase levels, mild thrombocytopenia, and an absolute and relative lymphocytosis (up to 50 000 cells/dl) with 20%–40% atypical lymphocytes. Atypical lymphocytosis is not pathognomonic for EBV infection, as a variety of infectious agents and drugs can also cause this phenomenon. Diagnosis is usually made by a positive monospot test, a simple slide test that detects IgM heterophile antibodies, or by increased titers of heterophile antibodies; the latter reach a titer of >1 : 40 in ~90% of young adults infected with EBV. Heterophile antibodies are capable of agglutinating sheep, horse, or bovine erythrocytes, and they typically become detectable 1 week to 1 month after the onset of symptoms and persist for 3 to 18 months.

Because heterophile antibody titers are positive in only a minority of young children with a primary EBV infection, EBV-specific serologies are often necessary to establish the diagnosis in this age group. Titers of at least three different antibodies should be assessed to determine the stage of EBV infection, allowing differentiation between an acute primary, past/latent, and reactivated infection (Table 80.9)[65].

PCR-based assays to detect EBV DNA in peripheral blood or tissue samples are also available. Markedly elevated peripheral blood levels are found in patients with infectious mononucleosis and in immunodeficient individuals with EBV-associated lymphoproliferative disorders. Of note, lower levels of EBV DNA can also be detected in the peripheral blood of healthy individuals with a latent EBV infection. *In situ* hybridization for EBV-encoded small RNA (EBER) represents a widely available, sensitive, and specific method to detect EBV-infected cells in the skin and other tissues. This assay can be performed on paraffin-embedded specimens, and EBER-positive cells are prominent in EBV-related dermatoses (e.g. T cells in hydroa vacciniforme; see Fig. 87.11) and malignancies, but absent in inflammatory dermatoses and lymphomas that are not related to EBV infection.

Primary EBV infection is not associated with any pathognomonic histologic findings. Features are similar to those observed with other viral exanthems, i.e. slight spongiosis, parakeratosis, and a perivascular lymphocytic infiltrate. Additional findings may include focal keratinocyte necrosis, mild ballooning degeneration, and, rarely, multinucleated keratinocytes, but less prominent than with HSV and VZV infection. Aminopenicillin-induced eruptions in the setting of infectious mononucleosis often demonstrate vacuolar interface changes and spongiosis in association with a denser dermal inflammatory infiltrate. Biopsies of involved lymph nodes typically show reactive lymphoid hyperplasia.

Differential Diagnosis

The differential diagnosis of EBV-induced infectious mononucleosis includes drug reaction with eosinophilia and systemic symptoms (DRESS, see Ch. 21 and HHV-6 section below), which is often associated by reactivation of herpesviruses including EBV as well as HHV-6. DRESS is distinguished by exposure to an implicated drug in addition to features such as eosinophilia and marked facial edema. Group A streptococcal infection, acute viral hepatitis, toxoplasmosis, lymphoma, and primary CMV, HHV-6, and HIV infections may represent additional diagnostic considerations. A combination of history, physical examination, and laboratory studies can differentiate among these diseases.

Treatment

In most cases of infectious mononucleosis, the disease is self-limited and treatment is supportive. Acyclovir can inhibit EBV replication; however, in controlled studies where primary EBV infection was treated with acyclovir or acyclovir combined with systemic corticosteroids, there was no effect on clinical outcome[67]. In one study of healthy individuals with a past/latent EBV infection, the administration of valacyclovir for 1 year reduced the number of EBV-infected B cells in the peripheral blood compared to an untreated control group[68]. Due to their multiple side effects, corticosteroids are reserved for only complicated cases of infectious mononucleosis associated with hemolytic anemia, severe thrombocytopenia, liver failure, or lymphadenopathy resulting in airway compromise[69]. In patients with EBV-associated lymphoproliferative disorders, reduction of immunosuppression can lead to spontaneous resolution, especially when the disorder is polyclonal.

CYTOMEGALOVIRUS (HHV-5)

Key features

- CMV is the leading infectious cause of congenital deafness and intellectual disability (TORCH syndrome) as well as the leading cause of blindness (due to retinitis) in AIDS patients
- Neonates and immunocompromised hosts are at risk for severe clinical infections

Introduction

CMV is endemic in all parts of the world, and it is the most common cause of intrauterine infection in humans. In immunocompetent hosts, 95% of infections are asymptomatic or subclinical. Neonates and immunocompromised individuals, especially individuals with AIDS, allogeneic HSCT recipients, and patients receiving alemtuzumab, are at risk for severe clinical manifestations of CMV infection.

History

In 1881, Ribbert first observed "protozoan-like cells" in the organs of a stillborn baby with presumed congenital syphilis. Before the discovery of a viral etiology, the disease was initially called "cytomegalic inclusion

EBV SEROLOGIES					
Antibody	**Timing of appearance**	**Timing of disappearance**	**Acute primary infection**	**Past/latent infection**	**Reactivated (RA)/chronic active (CA)* infection**
VCA IgM	Prior to onset of symptoms	Usually within 3 months	Positive	Negative	Negative in RA/variable in CA
VCA IgG	With onset of symptoms	Persists for life	Positive	Positive	Positive
EA IgG†	With onset of symptoms	Usually within 3–6 months; positive if active infection‡	Positive	Negative‡	Positive
EBNA IgG	1–6 months after onset of symptoms, upon establishment of latency	Persists for life	Negative	Positive	Positive in RA/variable in CA

*Associated with hemophagocytic lymphohistiocytosis, lymphoproliferative disorders, and lymphomas.
†Not usually included in routine serologic testing.
‡Persists following resolution of infection in ~20% of healthy individuals.

Table 80.9 EBV serologies. EA, early antigen; EBNA, EBV nuclear antigen; VCA, viral capsid antigen.

disease" based on the characteristic enlarged cells (cytomegalia) and intranuclear inclusions. In 1956, human CMV was independently isolated *in vitro* by three groups of investigators led by Weller, Rowe, and Smith. Originally known as the "salivary gland virus" or "salivary inclusion disease virus", CMV was given its current name by Weller and his colleagues in 1960[70].

Epidemiology

The prevalence of CMV infection is inversely proportional to socioeconomic status. For example, 80%–100% of the African population is CMV-seropositive compared with 60%–70% of the US and Western European populations. The increased seroprevalence in low-income countries is thought to be due to crowded living conditions, poor hygiene, and greater numbers of individuals caring for an infant. Age-related prevalence studies in the US have shown highest risks of CMV acquisition during early childhood, adolescence, and the reproductive years.

CMV seropositivity is especially high among toddlers in day care centers, and transmission from young children to their mothers has been described[71]. In adults, CMV infections are often contracted through sexual contact. Blood transfusions carry a 3%–4% risk of CMV infection per transfusion unit[72]. To decrease this risk, leukocyte-depleted blood can be used in immunosuppressed patients.

Solid organ transplant and HSCT recipients, other individuals receiving immunosuppressive agents, and those infected with HIV are at increased risk of disseminated CMV infection. More recently introduced treatments such as CAR-T cellular therapy and bispecific T cell engager therapy also put patients at risk for CMV infections. CMV represents a source of significant morbidity (e.g. retinitis, colitis) and mortality in patients with AIDS. In the US, congenital CMV infection occurs in ~0.5% of all neonates[73].

Pathogenesis

Transmission of CMV is via body fluids, including saliva, blood, urine, semen, breast milk, and cervical and vaginal secretions, as well as in transplanted organs and rarely hematopoietic stem cells. CMV can also be spread indirectly by contaminated fomites, such as toys. Transplacental transmission of CMV to the fetus is more likely in the setting of a primary infection in the mother, with 40% of fetuses becoming infected, compared to <1% in recurrent cases.

CMV has an estimated incubation period of 4–8 weeks, followed by viremia via infected blood leukocytes and spread to various organs. It is a cytotoxic virus that causes cell enlargement (cytomegaly) and nuclear condensation (inclusion). In immunocompetent hosts, the virus induces high levels of specific anti-CMV $CD4^+$ and $CD8^+$ T cells[74]. CMV infection may be either primary or recurrent, and the latter can result from either viral reactivation or reinfection with a different antigenic type.

Following primary infection, CMV persists in a latent state for the life of the host and rarely causes disease. In immunocompromised individuals, however, reactivation of latent virus can lead to recurrent infection characterized by persistent viral replication, viremia, and dissemination to distant organs. Cell injury and tissue destruction contribute to organ damage by directly altering cellular function and producing an inflammatory response.

The organ infected depends on the age of the host. Infection in healthy children and adults often involves the lymphoid tissues, while fetal and neonatal infection commonly affects the salivary glands and neurons. Infection in immunocompromised individuals frequently involves the retina and lungs as well as the liver and gastrointestinal tract.

Clinical Features

More than 90% of primary CMV infections are subclinical, although a "mononucleosis-like syndrome" similar to that seen with EBV occasionally develops in immunocompetent persons (Table 80.10). This syndrome has also been described in both immunocompetent and immunocompromised individuals after a blood transfusion. Infected patients develop non-exudative pharyngitis in addition to fever, malaise, myalgias, lymphadenopathy, and hepatosplenomegaly. Atypical lymphocytosis and elevated liver enzymes may also occur. An exanthem, which can be morbilliform, urticarial, petechial or purpuric, develops in a small percentage of patients. As with infectious mononucleosis, the administration of ampicillin or related drugs during this symptomatic period leads to a cutaneous eruption in 80%–100% of individuals. Although the clinical course of CMV-induced mononucleosis is self-limited, rare complications include hemolytic anemia, thrombocytopenia, granulomatous hepatitis, Guillain–Barré syndrome, meningoencephalitis, myocarditis, interstitial pneumonia, arthritis, and gastrointestinal and genitourinary manifestations.

Congenital CMV infection is the leading infectious cause of deafness and intellectual disability in the US. Approximately 5%–10% of infected neonates have symptoms at birth, presenting with jaundice, hepatosplenomegaly, intrauterine growth retardation, thrombocytopenia, chorioretinitis, seizures, and/or intracranial calcifications. Cutaneous manifestations include purpuric papules and nodules of dermal hematopoiesis which are sometimes referred to as "blueberry muffin" lesions (Fig. 80.22; see Ch. 121), in addition to petechiae, purpura, and vesicles. Another 10%–15% of children are born with asymptomatic CMV infection and later develop sequelae, most often sensorineural hearing loss. Perinatal CMV infection is often asymptomatic; however, a limited number of infected infants develop pneumonitis, lymphadenopathy, or hepatosplenomegaly[75].

CUTANEOUS MANIFESTATIONS OF CMV INFECTIONS
Immunocompetent host
Mononucleosis-like syndrome
• Maculopapular/morbilliform eruption • Petechiae and purpura • Ampicillin-induced eruption • Urticaria • Erythema nodosum
Congenital infections
• "Blueberry muffin" lesions (extramedullary hematopoiesis; see Ch. 121) • Petechiae and purpura • Vesicles
Immunocompromised host
Cutaneous vasculitis Maculopapular/morbilliform eruption Petechiae and purpura Ulcers (most often genital, perianal, or oral) Vesicles Verrucous plaques Nodules and hyperpigmented plaques

Table 80.10 Cutaneous manifestations of CMV infections. CMV infection can also trigger reactive non-sexually related acute genital ulcers (see Table 80.8).



Fig. 80.22 TORCH syndrome due to cytomegalovirus. Multiple purpuric papules of dermal hematopoiesis. *Courtesy Mary S. Stone, MD.*

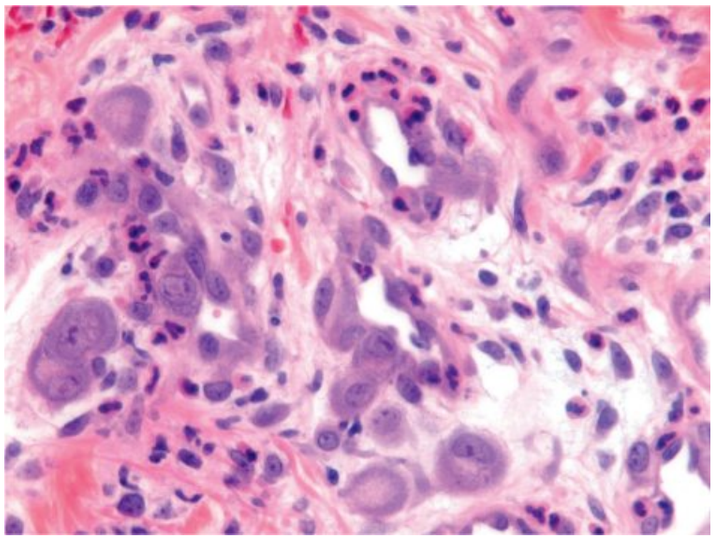


Fig. 80.23 Histology of cytomegalovirus (CMV) infection. Enlarged endothelial cells with a prominent intranuclear inclusion are typical of CMV infection. *Courtesy Angela Galan, MD.*

In AIDS patients, CMV may cause chronic ulcers of the perineum or extremities, chorioretinitis, esophagitis, colitis, and pneumonitis, as well as endocrine, bone marrow, CNS, and renal abnormalities. Cutaneous manifestations can range from vesicles to nodules to verrucous plaques. In recipients of solid organ transplants and HSCTs, gastrointestinal involvement and less often interstitial pneumonia are the most serious manifestations of CMV infection.

Diagnosis and Pathology

Culture of CMV in human fibroblasts is the traditional diagnostic "gold standard", but this takes several days to weeks. Detection of CMV in tissue cultures within 24–48 hours is possible with the shell vial assay, in which monoclonal antibodies specific for early CMV antigens are employed. In addition to CMV-specific serologies, assays that detect CMV antigens (e.g. pp65) within leukocytes or CMV DNA via PCR (necessary in neutropenic patients) are commonly employed to identify and monitor viremia and systemic infection[76]. CMV retinitis in patients with AIDS is diagnosed by ophthalmologic examination.

Like other viral exanthems, the histologic features of the acute exanthem of CMV infection include mild spongiosis and a sparse perivascular lymphocytic infiltrate in the upper dermis. Epidermal changes are minimal since CMV does not infect keratinocytes. However, it does infect endothelial cells, which can have an "owl's eye" appearance that is pathognomonic for CMV infection. The cells are enlarged two- to threefold and contain purplish, crystalline intranuclear inclusion bodies surrounded by a clear halo (Fig. 80.23). These cytomegalic cells are most likely to be evident in ulcers, and vascular dilatation is another common finding. CMV vasculitis, a manifestation of disseminated disease, is characterized by marked endothelial swelling and inflammation.

Differential Diagnosis

The clinical differential diagnosis of the mononucleosis-like syndrome of CMV infection includes EBV-induced infectious mononucleosis, which is generally more severe and often associated with exudative pharyngitis. Other diagnostic considerations may include DRESS, which may also be associated with reactivation of CMV (see HHV-6 section below), as well as toxoplasmosis, viral hepatitis, GVHD, and lymphoma. A high index of suspicion is necessary to diagnose CMV-induced ulcers and atypical cutaneous manifestations in immunocompromised patients.

Treatment and Prevention

Management is targeted at prevention plus prophylactic antiviral treatment in susceptible immunocompromised individuals as well as antiviral treatment in those who are symptomatic. Treatment of CMV-induced mononucleosis in immunocompetent individuals, however, is only supportive.

TREATMENT FOR CMV INFECTIONS IN IMMUNOCOMPROMISED PATIENTS		
Medication	**Route**	**Major side effects**
Ganciclovir	iv, intravitreal implant or injection	Bone marrow suppression, GI symptoms > renal insufficiency, neuropathy
Valganciclovir	po	
Maribavir	po	GI symptoms, taste disturbance, drug-drug interactions (e.g. cyclosporine, other CYP3A4 substrates/inducers)
Letermovir†	po, iv	GI symptoms, peripheral edema, cardiac adverse events, drug-drug interactions (e.g. cyclosporine, statins, pimozide, ergot alkaloids)
Cidofovir	iv*, intravitreal injection	Renal toxicity
Foscarnet	iv, intravitreal injection	Renal toxicity
Fomivirsen	Intravitreal injection	

*Initially given weekly for 2 weeks for AIDS-related CMV retinitis.
†FDA-approved for primary prophylaxis in CMV-seropositive adult allogeneic hematopoietic stem cell transplant recipients.

Table 80.11 Treatment options for CMV infections in immunocompromised patients. iv, intravenous; po, orally.

As a preventive measure, hematopoietic stem cells and other tissues from CMV-seronegative donors are used preferentially for transplantation in seronegative recipients. Letermovir, an inhibitor of the CMV terminase complex, is currently FDA-approved for prophylactic administration in adult CMV-seropositive allogeneic HSCT recipients. Usually administered for at least 100 days, letermovir reduces the risk of clinically significant CMV infection and non-relapse mortality in this patient population[77,78]. While letermovir lacks the myelosuppression associated with ganciclovir, it does not have activity against HSV-1 and -2. Pre-emptive management consisting of following blood CMV DNA levels and initiating first-line therapies if they increase represents another strategy in transplant recipients.

The first-line agents for treatment of CMV infections in immunocompromised patients are intravenous ganciclovir or oral valganciclovir; intravitreal injections/implants of ganciclovir are used for localized retinitis. When patients fail to respond to these medications or develop significant side effects, maribavir, foscarnet, and cidofovir are additional options[79] (Table 80.11). Maribavir, an inhibitor of the CMV UL97 protein kinase, was recently FDA-approved for post-transplant CMV infections that fail to respond to other medications. In general, relapse is common after discontinuation of antiviral agents. Treatment with CMV-specific T cell adoptive transfer is being studied in immunocompromised individuals but is not readily available.

There is ongoing investigation of several CMV vaccines, including those utilizing a replication defective whole-virus, adjuvanted subunits, virus-like particles, viral vectors, and mRNA encoding vaccine antigens.

HUMAN HERPESVIRUS TYPE 6 (HHV-6)

Synonym: ■ Roseola infantum – exanthem subitum, sixth disease

Key features

- HHV-6 is the cause of exanthem subitum (roseola infantum), a common febrile disease of early childhood
- Although HHV-6 infection is usually a benign condition without long-term consequences, it can be life-threatening if reactivated in the setting of immunosuppression
- HHV-6 and other herpesviruses (e.g. EBV, CMV, HHV-7) have been implicated in the pathogenesis of DRESS syndrome

Introduction

HHV-6 is the etiologic agent of exanthem subitum (roseola infantum), one of the most common viral exanthems in infants and young children. Although HHV-6 infection usually is a benign disease without long-term sequelae, the virus remains latent and can be life-threatening if reactivated in the setting of immunosuppression.

History

Zahorsky distinguished exanthem subitum from other exanthems in 1910 and is credited for its first description. In 1988, Yamanishi and colleagues used serologic methods to confirm that HHV-6 caused exanthem subitum[80]. A subsequent study discovered two distinct variants of the virus: HHV-6A and HHV-6B, each with different biologic, immunologic, and genetic characteristics. Variant B is primarily the cause of exanthem subitum, while the pathogenic role of variant A is unclear, except that it is identified more frequently in patients with Hashimoto disease.

Epidemiology

HHV-6 is found worldwide. Infection is most common in young children, occurring between the ages of 6 months and 3 years in 95% of cases, with a peak incidence between 6 and 12 months of age. Boys and girls are equally affected. Seroprevalence studies have shown that maternal IgG against HHV-6 is transferred to 70%–97% of fetuses. The level of these maternal antibodies in infants wanes by 6 months of age, and subsequent primary infections result in a peak HHV-6 seroprevalence of 90%–100% at 3 to 4 years of age. Antibody levels then decline again, with a prevalence of 65% to 95% in adults[81]. Despite the high seroprevalence, only 30% of children develop clinical manifestations of exanthem subitum. Infections occur throughout the year but are most common in the spring.

Pathogenesis

HHV-6 has a tropism for $CD4^+$ T lymphocytes, but it can infect a variety of other cells, including neurons. Transmission is typically through infected saliva, although HHV-6 DNA has been isolated from the cervix and may cause perinatal infection. After primary HHV-6 infection, the virus establishes lifelong latency in $CD4^+$ T lymphocytes, with the potential for reactivation. Immunosuppressed patients are at particular risk for HHV-6 reactivation, sometimes with severe consequences[82]. In HSCT recipients, asymptomatic HHV-6 reactivation is more common with alternative donors (e.g. cord blood, haploidentical) than with matched donors, but symptomatic disease (e.g. encephalitis) is unusual. HHV-6 also has the ability to integrate its genome into the telomeres of infected cells; as a result of this occurring in the germline, ~1% of the general population has inherited chromosomally-integrated HHV-6A/B present in all the cells of the body.

The effects of HHV-6 in HIV-infected individuals are unclear. *In vitro* studies have described both increased and decreased replication of HIV-1 in cells co-infected with HHV-6 and HIV-1. To date, there is no definitive evidence that HHV-6 influences HIV-1 disease progression[80,83].

Patients with acute myelogenous leukemia and lymphoproliferative malignancies including Hodgkin lymphoma, follicular large cell lymphoma, Burkitt lymphoma, and angioimmunoblastic T cell lymphoma have higher HHV-6 antibody titers than healthy individuals, as do patients with systemic lupus erythematosus, multiple sclerosis, and myalgic myoencephalitis/chronic fatigue syndrome. Of note, HHV-6 DNA has been demonstrated in lesions of Rosai–Dorfman disease[84], and HHV-6 has been postulated to have a possible role in the pathogenesis of pityriasis rosea (together with HHV-7; see below). HHV-6 and other herpesviruses (e.g. EBV, CMV, HHV-7) have been implicated in the pathogenesis of DRESS syndrome (see Ch. 21). It has been postulated that drug-related immunosuppression or induction of viral replication leads to viral reactivation, which stimulates a cellular immune response directed against herpesviruses and likely cross-reacting with the drug.

Clinical Features

The classic clinical manifestations of exanthem subitum occur in ~30% of those with primary HHV-6 infections. The incubation period ranges from 5 to 15 days, but it is most often 9–10 days. Typically, an otherwise well-appearing infant presents with a high fever (102–105°F; 38.9–40.6°C) that lasts for 3–5 days, followed by a cutaneous eruption as the fever begins to subside. The fever may be intermittent and tends to peak in the early evening. The cutaneous eruption usually lasts for 24–48 hours and may develop before the temperature returns to normal or up to 2 days afterwards. The lesions are discrete, circular or elliptical, "rose-red" macules and papules that are 2–5 mm in diameter and occasionally surrounded by a white halo. The cutaneous eruption commonly affects the trunk (Fig. 80.24), proximal extremities, neck, and less often the face; its appearance can be very similar to rubella or rubeola. An enanthem of red papules on the soft palate (Nagayama's spots) may also be seen, and ulcers on the uvula and at the palatoglossal junction represent a characteristic finding. Eyelid edema, mild upper respiratory symptoms, injection of the tympanic membranes, cervical or occipital lymphadenopathy, and a bulging anterior fontanelle may also be evident.

The most common complication of exanthem subitum is febrile seizures, which occur in 10%–15% of affected infants and children. Infection with or reactivation of HHV-6 in immunocompromised patients can lead to fever and a cutaneous eruption as well as more serious consequences such as hepatitis, pneumonitis, bone marrow suppression, encephalitis, and transplanted tissue rejection[80].

Diagnosis and Pathology

In healthy individuals, HHV-6 infection is typically diagnosed clinically. Serology may be helpful in ambiguous situations. The presence of IgM antibodies indicates primary infection, but this assay is not reliable for the detection of reactivation. A fourfold increase in IgG in paired samples from the acute and convalescent phases of the disease can give retrospective confirmation of HHV-6 reactivation.

Other diagnostic tools include PCR-based assays and viral culture. PCR detection of cell-free HHV-6 DNA in serum or plasma has diagnostic utility. However, qualitative PCR using cellular specimens (e.g. peripheral blood mononuclear cells) cannot reliably distinguish between latent and active infection.

Histopathologically, exanthem subitum shows nonspecific changes such as spongiosis of the epidermis with spongiform vesicles and exocytosis of lymphocytes. A sparse inflammatory infiltrate is found in the superficial dermis, and papillary dermal edema is often evident. Nuclear basophilic inclusions can be found within perivascular lymphocytes in the cutaneous eruptions that may occur in immunocompromised patients.



Fig. 80.24 Exanthem subitum (roseola infantum). Small pink–red macules and papules developed on the trunk and neck of this 9-month-old boy during defervescence of a high fever that had lasted for 5 days. *Courtesy Julie V. Schaffer, MD.*

Differential Diagnosis

The differential diagnosis of exanthem subitum is primarily other viral exanthems such as rubeola, rubella, and enterovirus, adenovirus, EBV, and parvovirus infections. Other considerations may include scarlet fever, Rocky Mountain spotted fever, and Kawasaki disease (see Ch. 81).

Treatment

Although HHV-6 infection is usually self-limited, serious complications can occur in immunocompromised patients. At present, there are no approved compounds or vaccines exclusively for the treatment of HHV-6. However, some studies have shown that phosphonoacetic acid, foscarnet, ganciclovir, brincidofovir, and artesunate may inhibit HHV-6. There are reports of successful treatment of serious infections with foscarnet and ganciclovir, and *post hoc* analysis of a randomized, placebo-controlled trial found that brincidofovir reduced the frequency of HHV-6 reactivation in HSCT recipients. A multivirus specific T-cell therapy, posoleucel, has orphan drug designation for infections with HHV-6 as well as EBV, CMV, adenovirus, BK virus, and JC virus in allogeneic HSCT recipients.

HUMAN HERPESVIRUS TYPE 7 (HHV-7)

Key feature

- HHV-7 is a lymphotropic virus that has been linked to reactivation of HHV-6 in some patients with exanthem subitum

HHV-7 is a ubiquitous lymphotropic herpesvirus that was first isolated by Frenkel et al.[85] in 1990. More than 95% of adults are seropositive[86]. Infections with HHV-7 mainly occur during the first 5 years of life, with a peak at 1–2 years of age, and then typically remain latent. Transmission via saliva is most likely, since HHV-7 is only known to replicate in human salivary glands; however, HHV-7 has also been found in cervical secretions.

Little is understood about the pathogenesis of HHV-7, but it has been shown to utilize the CD4 receptor for entry into cells. HHV-7 downregulates the expression of CD4 molecules on lymphocytes and may downregulate the infectivity of HIV, since both viruses compete for the same receptor.

The virus grows best in cord blood lymphocytes and has a limited range of host tissues compared to that of HHV-6, although HHV-7 antigen has been found in human lungs, mammary glands, and skin. Compared to HHV-6, HHV-7 is less cytopathic, associates more with cells, and grows more slowly in culture. Significant homology exists between the two viruses and limited antigenic cross-reactivity has been demonstrated between HHV-7 and HHV-6A (but not HHV-6B)[82]. However, HHV-7 is serologically distinct from HHV-6, and immunity to HHV-7 is not conferred with HHV-6 antibodies (or vice versa).

HHV-7 has not been clearly established as a causative factor for clinical disease, although it has been linked to several conditions, including DRESS (see above and Ch. 21). A subset of exanthem subitum has been associated with reactivation of HHV-6 (particularly variant B) in conjunction with primary infection with HHV-7. The cutaneous eruption associated with HHV-7-induced exanthem subitum is lighter in color and presents later in the disease course than that of primary HHV-6 infection[87]. Neurologic complications, such as febrile seizures and acute hemiplegia, have also been reported with HHV-7-induced exanthem subitum. Several studies have suggested that HHV-7 may be a cofactor for symptomatic CMV infection in renal transplant recipients[88,89].

HHV-7 and pityriasis rosea (PR) were first associated when HHV-7 DNA was detected via PCR in blood monocytes, plasma, and lesional skin from 12 patients with PR, but not in the plasma or skin of controls[90]. Although some subsequent studies were unable to isolate HHV-7 DNA from PR lesions, others supported a role for HHV-7, and possibly HHV-6, in PR[91].

Methods to detect HHV-7 infection include serologic tests, PCR, viral culture, and immunohistochemical staining. The differential diagnosis is similar to that of exanthem subitum. Currently, there is no available treatment for HHV-7 infection.

HUMAN HERPESVIRUS TYPE 8 (HHV-8)

Synonyms: ■ Kaposi sarcoma-associated herpesvirus (KSHV) ■ Kaposi sarcoma herpesvirus (KSHV)

Key features

- HHV-8 is a latent virus found in virtually all lesions of all types of Kaposi sarcoma (KS) worldwide
- The seroprevalence of HHV-8 corresponds to the incidence rates of KS and varies by geographic location
- Clinical features of primary infection with HHV-8 have not yet been clearly identified, and its associated diseases are postulated to be a result of viral reactivation

Introduction

HHV-8, also called Kaposi sarcoma herpesvirus (KSHV), is a latent virus found in all types of Kaposi sarcoma (KS) worldwide. KS is discussed in more detail in Chapter 114.

History

In 1994, the association of KS and HHV-8 was recognized when herpes-like DNA sequences were identified in KS lesions from an AIDS patient. Associations of HHV-8 with Castleman disease, body cavity-based lymphomas, and other lymphoproliferative disorders were subsequently noted.

Epidemiology

HHV-8 is found in all types of KS worldwide, including: (1) *classic KS* – favors older men of Mediterranean or Ashkenazi Jewish descent; (2) *African-endemic KS* – affects primarily men and young children; (3) *iatrogenic immunosuppression-associated KS* – most often occurs in solid organ transplant recipients; (4) *AIDS-related epidemic KS* – occurs mainly in men who have sex with men (MSM); and (5) the recently described *nonepidemic KS in HIV-seronegative MSM* – favors middle-aged individuals[92–94] (see Table 114.3).

Seroprevalence of HHV-8 varies geographically, ranging from <5% in North America and Northern Europe to ~10%–20% in Southern Europe and 30%–80% in Africa[92]. In North America and Europe, HHV-8 antibodies are present in ~30% of HIV-1-infected MSM[95].

Pathogenesis

The mechanisms of HHV-8 transmission are not fully understood. Receptive anal intercourse appears to increase the likelihood of transmission, as the seroprevalence of HHV-8 is higher in MSM than in HIV-infected women. The number of same-sex male partners and the presence of HIV infection may be other risk factors[80]. There is evidence that exposure to saliva via close non-sexual contact or sexual practices represents another route of HHV-8 transmission. In areas in Africa where HHV-8 is endemic, seroprevalence is high in young children, and some but not all studies have found that this is associated with mother-to-child horizontal transmission; vertical transmission is uncommon[96,97]. HIV-infected infants have a significantly increased risk of HHV-8 infection[97]. HHV-8 transmission by blood transfusion has also been demonstrated[98].

HHV-8 can infect the endothelial cells of both lymphatic and blood vessels and induce transcriptional reprogramming, providing an explanation for the mixed lymphatic/blood vascular phenotype (see Ch. 114). In addition, HHV-8 is involved in the development of several lymphoproliferative disorders, including primary effusion lymphoma (also associated with EBV infection), multicentric Castleman disease, HHV-8-positive diffuse large B cell lymphoma, germinotropic lymphoproliferative disorder, and HHV-8 inflammatory cytokine syndrome[99,100].



Fig. 80.25 Classic Kaposi sarcoma. Red–violet plaques on the toes with associated hyperkeratosis. *Courtesy Lorenzo Cerroni, MD.*

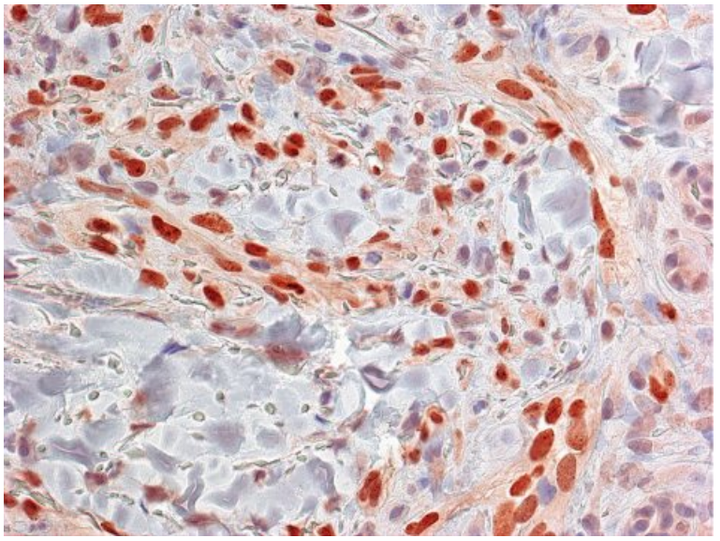


Fig. 80.26 Kaposi sarcoma. Immunohistochemical staining utilizing antibodies against a latency-associated nuclear antigen (LANA-1) demonstrates the presence of HHV-8. *Courtesy Shawn Cowper, MD.*

Clinical Features

Clinical manifestations of primary infection with HHV-8 have not yet been clearly identified. The five KS types have somewhat different presentations and clinical courses (see Ch. 114), although all typically feature red, brown, or violaceous papules, plaques, and nodules (Fig. 80.25). Edema is often present in all types, although less prominent in *nonepidemic KS in MSM*[92]. *Classic KS* favors the lower legs and can become hyperkeratotic or eczematous; it tends to be slowly progressive. *AIDS-related KS* typically presents as more widely distributed lesions, with frequent involvement of the trunk, central face, oral mucosa, and internal organs (e.g. lungs, gastrointestinal tract; see Ch. 78). Flares of KS may occur as a manifestation of IRIS (immune reconstitution inflammatory syndrome). *Immunosuppression-associated KS* can have an aggressive course but may improve or resolve upon reduction or removal of immunosuppressive therapy. Another option is substitution of sirolimus for calcineurin inhibitors as sirolimus inhibits the HHV-8 lytic replication cycle and has antineoplastic and antiangiogenic as well as immunosuppressive effects. The course of *African-endemic KS* ranges from indolent or locally aggressive disease to a fulminant lymphadenopathic pediatric variant. *Nonepidemic KS in MSM* typically has an indolent course similar to that of *classic KS*, although associated lymphoproliferative disease has been reported[101].

Diagnosis and Pathology

The diagnosis of KS is confirmed by a skin biopsy of a suspected lesion (see Ch. 114). Serology for HHV-8 is not required, but immunohistochemical staining for latency-associated nuclear antigen (LANA-1) can demonstrate the presence of HHV-8 within biopsy specimens of KS (Fig. 80.26).

Treatment

The treatment of KS is reviewed in Chapter 114.

CONCLUSION

The eight human herpesviruses are associated with a wide spectrum of clinical features. Expansion in the number of immunocompromised patients has led to significant increases in the diversity and severity of clinical presentations of human herpesvirus infections. Thus, it is imperative to be aware of the various manifestations of these viral infections and to perform appropriate diagnostic tests. The clinician must also be aware of the indications, contraindications, dosages, and limitations of antiviral agents. Currently, the only licensed vaccines that exist for human herpesvirus are the varicella and varicella zoster vaccines. Therefore, public health measures remain critical for controlling the spread of these viruses. It is anticipated that better diagnostic tests, antiviral drugs, and vaccines for human herpesviruses will become available in the future.

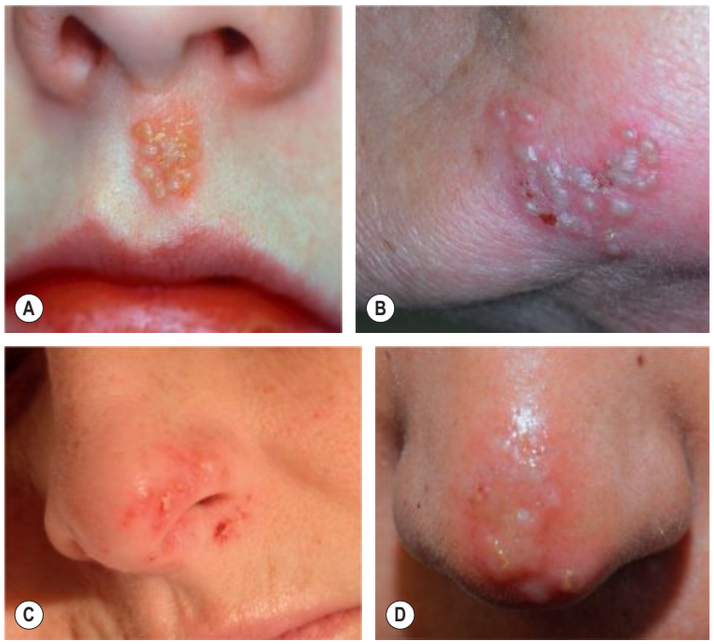
Additional figures and table on Recommendations of the Advisory Committee on Immunization Practices for administration of the varicella vaccine, available in our eBook (see inside front cover for access code).

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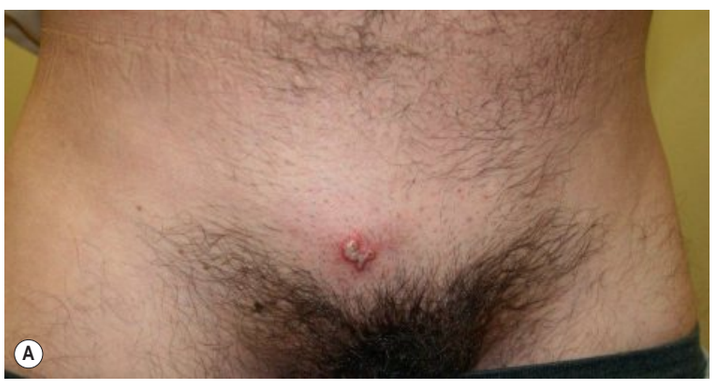


eFig. 80.1 Recurrent facial herpes simplex viral infection. A Grouped vesicles of the upper cutaneous lip. **B** Cluster of vesiculopustules with an erythematous base on the mandible. **C** Grouped pustules with an erythematous base on the nose in a solid organ transplant recipient. There are also clustered hemorrhagic crusts. **D** Coalescence of vesicles on the nose leading to a scalloped border. Note the inflammatory rim. *B, D, Courtesy Kalman Watsky, MD; C, Courtesy Noor Kibbi, MD.*



eFig. 80.3 Recurrent genital herpes simplex viral infection. Intact grouped vesicles on the penis. Note the genital wart at the base of the penis. *Courtesy Louis A. Fragola, Jr, MD.*

eFig. 80.2 Primary genital herpes. A Grouped vesicles on an erythematous base. **B** In addition to 1- to 2-mm hemorrhagic crusts, there are perifollicular vesiculopustules.







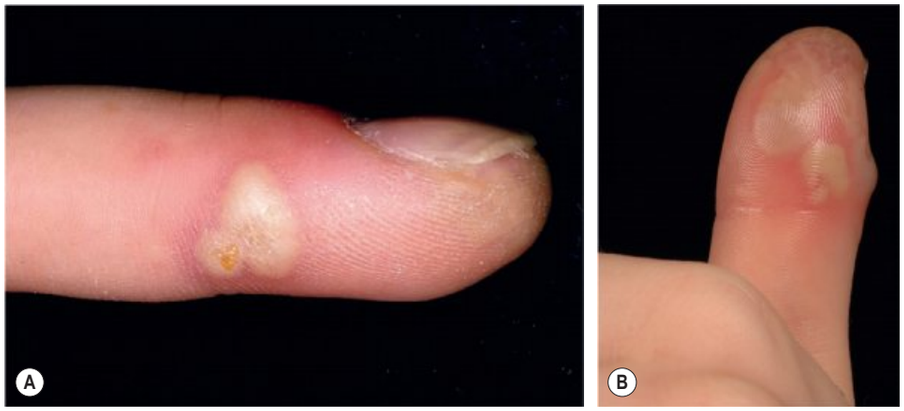
eFig. 80.4 Herpes simplex viral infection involving the penis and scrotum. Multiple monomorphic erosions. *Courtesy Louis A. Fragola, Jr, MD.*



eFig. 80.5 Recurrent herpes simplex viral infection on the penis. Grouped monomorphic ulcerations, some of which have healed. *Courtesy Louis A. Fragola, Jr, MD.*



eFig. 80.6 Recurrent genital herpes on the penis. Note the scalloped borders of the healing ulcerations. *Courtesy Joseph L. Jorizzo, MD.*



eFig. 80.7 Herpetic whitlow. Vesiculopustules with an erythematous base on the finger of a child (**A**) and on the distal thumb (**B**). *B, Courtesy Thomas Schwarz, MD.*



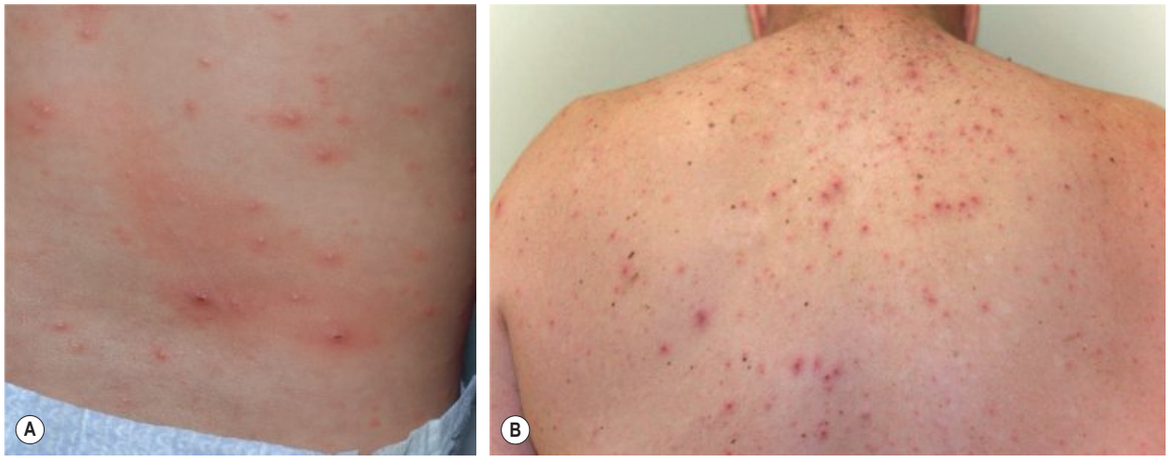
eFig. 80.8 Eczema herpeticum of a major skin fold. Papules with a central crust or dell are seen at the periphery of the confluent plaque. *Courtesy Ian W. Tattersall, MD, PhD.*



eFig. 80.9 Eczema herpeticum of the face. A background of dermatitis is present with superimposed monomorphous crusts and a few vesicles. The initial lesion was recurrent labial HSV. *Courtesy Kalman Watsky, MD.*



eFig. 80.10 Eczema herpeticum of the groin. Note the clusters of monomorphic vesicles and hemorrhagic crusts.



eFig. 80.11 Varicella. A, B Note the lesions in different stages of evolution. *A, Courtesy Julie V. Schaffer, MD.*



eFig. 80.12 Varicella. Numerous papulovesicles, some of which have a central dell or crust, and multiple hemorrhagic crusts on an erythematous base. *Courtesy Judit Stenn, MD.*



eFig. 80.13 Varicella. A, B Eruption of erythematous papulovesicles, several of which have developed central hemorrhagic crusts, reflecting lesions in different stages of evolution. Note the multiple edematous pink flares. *Courtesy Kalman Watsky, MD.*



eFig. 80.14 Varicella in a patient with HIV infection. Eruption of erythematous papulovesicles, several of which have developed central hemorrhagic crusts, reflecting lesions in different stages of evolution. Round ulcerations represent sites scraped for VZV PCR and Tzanck smear.



eFig. 80.15 Entities in the differential diagnosis of varicella. A, B Coxsackievirus A6 infection presenting as vesicles and papulovesicles on the hand and edematous crusted papules on the leg. *Courtesy Julie V. Schaffer, MD.*



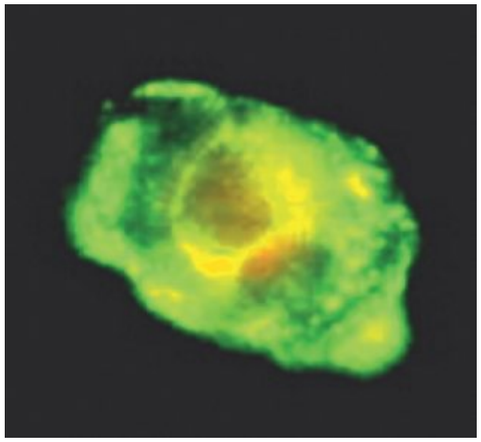
eFig. 80.16 Herpes zoster. Multidermatomal distribution of clustered vesicles, some of which have become hemorrhagic, arising on an inflammatory base. *Courtesy Edward Cowen, MD.*



eFig. 80.17 Herpes zoster. A Multiple clusters of papulovesicles on the inner knee within the L3 dermatome. **B** Grouped vesicles on an erythematous base within the C7 dermatome on the arm. **C** Clusters of papulovesicles within the C8 dermatome on the wrist. **D** Grouped vesicles as well as edematous papules and plaques within the distribution of the maxillary division of the trigeminal nerve (V_2). *Courtesy Kalman Watsky, MD.*



eFig. 80.18 Herpes zoster. Close-up of a cluster of vesicles on an erythematous base. *Courtesy Kalman Watsky, MD.*



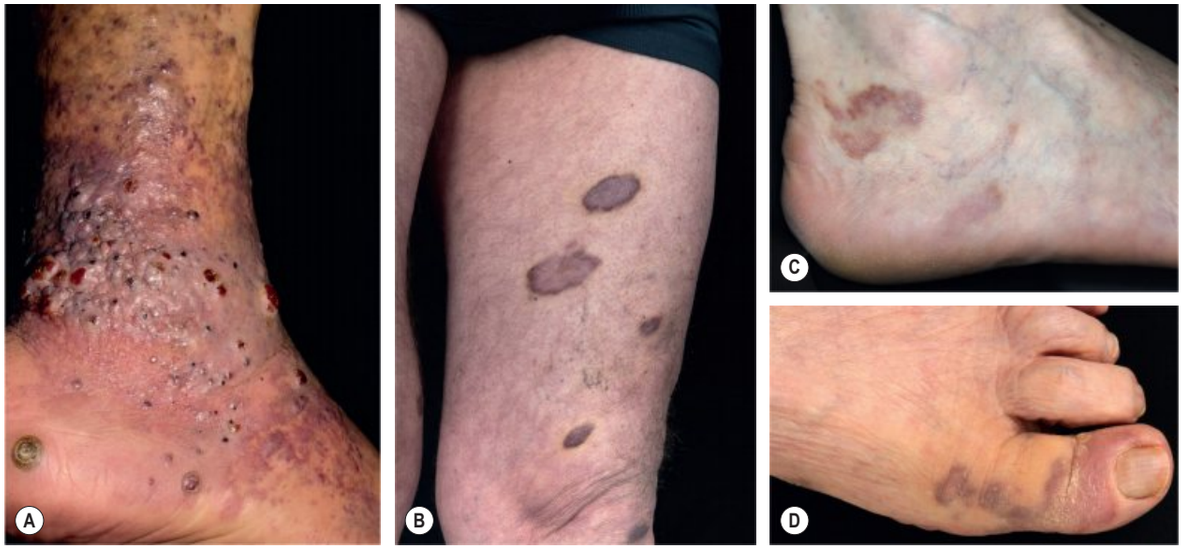
eFig. 80.20 Direct fluorescent antibody assay. A keratinocyte that is infected with herpes simplex virus fluoresces green. This assay can also detect the presence of varicella–zoster virus and has a rapid turnaround time. *Courtesy Marie L. Landry, MD.*



eFig. 80.19 Herpes zoster surrounded by circular purpura due to cupping. Cupping was performed to relieve the pain that preceded the appearance of the cutaneous lesions of herpes zoster. *Courtesy Kalman Watsky, MD.*



eFig. 80.21 Ophthalmic zoster (V_1). Note the sharp midline demarcation of erythema and crusts on the forehead as well as contralateral periorbital edema.



eFig. 80.22 Classic Kaposi sarcoma. A Multiple red–violet plaques and nodules with hemorrhagic crusting on the ankle and foot. **B** Multiple red–violet annular plaques on the thigh. **C** Subtle reddish-brown annular plaque on the ankle. **D** Coalescing red–violet papules and plaques with focal hyperkeratosis on the great toe. *A, Courtesy Joyce Rico, MD. B–D, Courtesy Lorenzo Cerroni, MD.*





eFig. 80.23 Cutaneous ulcers associated with disseminated cytomegalovirus (CMV) infection in immunocompromised patients. A Well-demarcated ulceration with a thick eschar, pink rim, and associated brachial plexopathy. HIV viral load was 6.6 million copies and CMV viral load was 14.5 million copies. **B** Ulcerations in different stages of healing. *A, Courtesy Katherine Hunt, MD.*

RECOMMENDATIONS OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES FOR ADMINISTRATION OF THE VARICELLA VACCINE

Category	Varicella vaccine administration

Routine childhood vaccination	• 2 doses
	  • First at age 12–15 months
	  • Second at age 4–6 years*

Individuals ≥13 years of age without evidence of varicella immunity, especially: • Students, teachers, residents/staff in institutional settings • Healthcare providers • If household contacts are immunocompromised or children • Postpartum/non-pregnant women of childbearing age • International travelers	• 2 doses, 4–8 weeks apart

Second dose catch-up vaccination for individuals >6 years of age who received 1 dose previously	• 1 additional dose
	  • ≥3 months after previous dose if <13 years old
	  • ≥4 weeks after previous dose if ≥13 years old

HIV-infected individuals: • 1–8 years of age with $CD4^+$ T cell percentage ≥15% • >8 years of age with $CD4^+$ T cell count ≥200 cells/mcl	• 2 doses, 3 months apart

Postexposure vaccination in individuals who received 1 dose previously	• 1 additional dose, ideally within 3–5 days, if:
	  • ≥3 months after previous dose for those <13 years old
	  • ≥4 weeks after previous dose for those ≥13 years old

Postexposure vaccination in individuals ≥1 year of age without evidence of varicella immunity	• Administer first dose within 3–5 days
Contraindications	
• Allergy to vaccine components • Immunocompromised states including: hematologic malignancies, HIV infection with $CD4^+$ T cell percentage <15% or count <200 cells/mcl, other T cell immunodeficiencies, systemic immunosuppressive therapy (e.g. tumor necrosis factor [TNF] inhibitors; prednisone ≥2 mg/kg/day or, if weight >10 kg, ≥20 mg/day for ≥2 weeks) • Pregnancy	

*May be given earlier provided that the interval between the two doses is ≥3 months.

eTable 80.1 Recommendations of the Advisory Committee on Immunization Practices for administration of the varicella vaccine. Varicella vaccination is generally required for entry to child care centers, schools, colleges, and other educational institutions. Skin lesions directly related to the attenuated virus (usually ≤5 papules or papulovesicles; localized to the area of injection in half of cases) develop in 5%–10% of vaccinated individuals, usually 5–25 days after immunization.

Other Viral Diseases 81

Anthony J. Mancini, Ayelet Shani-Adir and Robert Sidbury

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INTRODUCTION

Viral infections are frequently associated with cutaneous manifestations, especially in children, in whom they are the most common cause of exanthems. An exanthem is defined as a skin eruption occurring as a sign of a general disease. Viral exanthems may present with distinctive cutaneous features or in an entirely nonspecific fashion, and at times they may pose a significant diagnostic challenge, even to the most astute clinician[1]. While dermatologists are most likely to be consulted for atypical or less widely recognized exanthems, a solid working knowledge of the classic disorders, whether common (e.g. roseola) or rare in high-income countries (e.g. measles), is essential[2].

This chapter describes classic childhood and less common exanthems; eruptions associated with poxvirus and polyomavirus infections; and the cutaneous manifestations of hepatitis A, B, and C viral as well as SARS-CoV-2 infections. Kawasaki disease, which features a polymorphic exanthem together with other mucocutaneous findings and systemic manifestations that can mimic a viral syndrome, is also discussed. In contrast to the symptomatic management of most viral exanthems, prompt recognition and initiation of therapy for Kawasaki disease is necessary to prevent potentially life-threatening systemic complications. Herpesvirus infections, including infectious mononucleosis, are covered in Chapter 80. Structural features and sizes of major types of viruses that infect humans are shown in Fig. 81.1.

Nonspecific viral exanthems are the most common type of exanthem seen in children. These eruptions lack distinctive features such as specific lesional morphologies, distribution patterns, natural histories, or enanthems (eruption on the mucous membranes). They most often present with blanchable erythematous papules and macules in a widespread distribution on the trunk and extremities, and less often the face. Associated symptoms such as a low-grade fever, myalgias, headache, rhinorrhea, or gastrointestinal complaints may be present. Although multiple infectious agents can cause such exanthems, the most common etiologies in children are the non-polio enteroviruses (see below) in the summer/fall and respiratory viruses such as adenovirus and parainfluenza virus in the winter. Nonspecific exanthems tend to be self-limited, with spontaneous resolution within 1 week, and supportive therapy is usually sufficient. While identification of the exact etiologic agent would be desirable, in many instances it is neither necessary nor clinically feasible. Fig. 81.2 outlines the clinical features to be considered when evaluating the patient with a morbilliform ("maculopapular" or "measles-like") viral exanthem, highlighting similar and different aspects of various etiologies. Diagnostic considerations in patients presenting with fever and a "rash" are listed in Fig. 0.11.

ENTEROVIRUS INFECTIONS

Key features

- Most common in summer and fall
- Exanthems include erythematous, vesicular, and petechial types
- Meningitis and encephalitis possible

Introduction

The enteroviruses, a subgroup of the picornavirus family, cause a wide array of illnesses associated with exanthems. The non-polio enteroviruses include echoviruses and coxsackievirus types A and B, with >100 genetically distinct types that infect humans. These viruses consist of a single-stranded RNA genome with an unenveloped capsid.

Epidemiology

Enteroviral infections occur worldwide and are usually transmitted human-to-human via fecal–oral or respiratory routes, usually with a 3- to 6-day incubation period. They can also be spread from mother to infant in the peripartum period. Exposure to virus in fecally contaminated water in swimming pools or via ingestion of oysters may be responsible for some infections. Clinical attack rates are highest in young children, and infections occur more frequently in lower socioeconomic groups. In temperate climates, infections are most common in the summer and fall. However, coxsackievirus A6 outbreaks frequently affect adults and can occur in the winter.

Pathogenesis

Enteroviruses infect epithelial surfaces of the pharynx and lower alimentary tract. They then replicate in lymphoid tissues and disseminate via an initial minor viremia. Subsequently, replication may occur at multiple anatomic sites, including the CNS, heart, liver, adrenals, respiratory tract, skin, and mucous membranes[3]. This replication correlates with the appearance of clinical symptoms. A major viremia occurs during the period of viral multiplication in the secondary infection sites.

Clinical Features and Differential Diagnosis

Fig. 81.3 depicts the potential clinical manifestations of an enteroviral infection.

The most distinctive exanthematous illness due to enteroviruses is *hand-foot-and-mouth disease* (HFMD). This disorder is characterized by a vesicular eruption on the palms and soles (Fig. 81.4A) in conjunction with an erosive stomatitis. The dorsal aspect of the hands and feet may be involved as well as the buttocks and perineum; oral

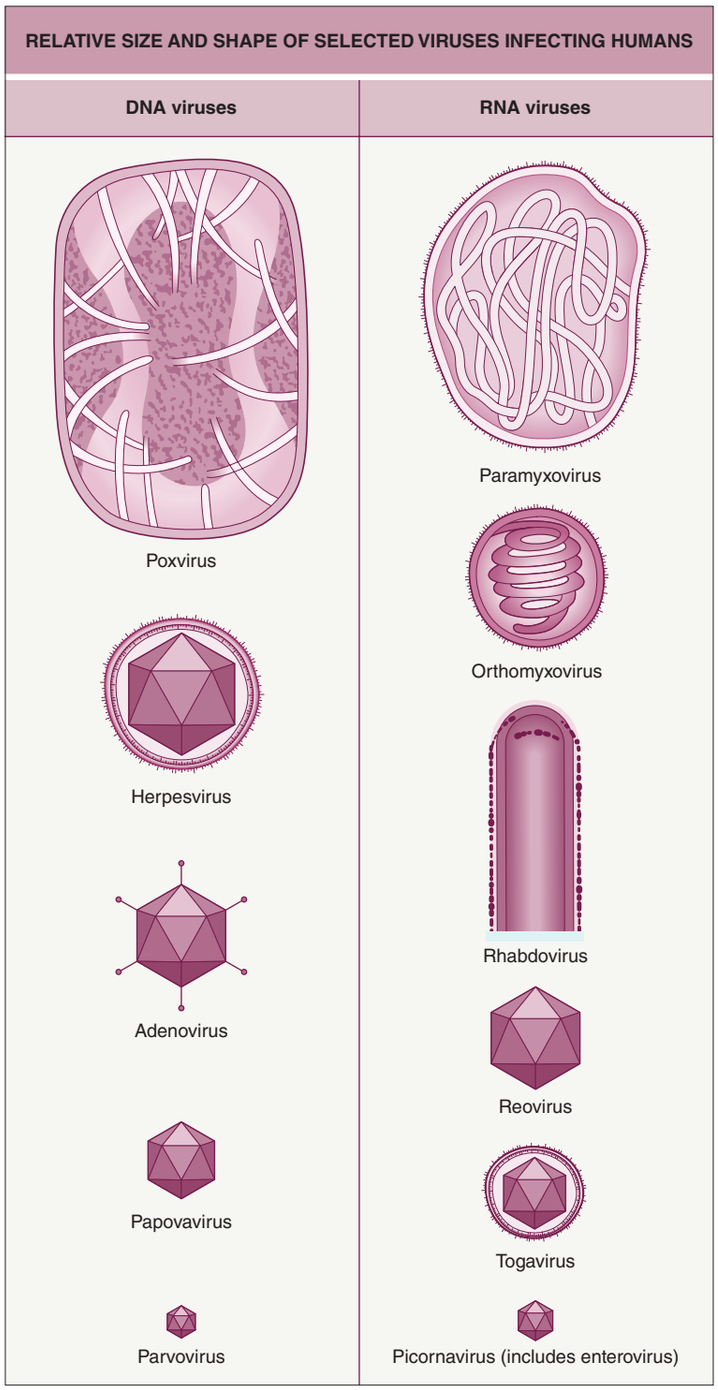


Fig. 81.1 Relative size and shape of selected viruses infecting humans. *Adapted from Hsiung's Diagnostic Virology, Yale University Press, 1994.*

lesions are most common on the tongue, buccal mucosa, palate, uvula, and anterior tonsillar pillars. Onychomadesis occasionally occurs 1–2 months after HFMD as a consequence of temporary nail matrix arrest related to the viral infection[4].

Patients with HFMD often present with fever and malaise, and they may have a mild prodrome prior to the onset of the exanthem. Numerous coxsackievirus serotypes have been implicated, most commonly type A16; in addition, type A10 represents a major cause of outbreaks in Europe and Asia. Although HFMD generally runs a benign and self-limited course, since 1998 there have been multiple epidemics of severe enterovirus 71 infection, primarily in the Asia-Pacific region, which have resulted in cardiopulmonary and neurologic complications and even deaths in affected young children[5].

Globally beginning in 2008 and since 2011 in the US, coxsackievirus A6 (CVA6) has emerged as a major cause of both outbreaks and sporadic cases of severe and atypical HFMD[6]. This variant is characterized by more widespread vesicular, papulovesicular, and sometimes bullous or petechial eruptions that frequently involve the perioral area, arms, legs, and trunk as well as the palms, soles, and buttocks (Fig. 81.4B–G). Oral lesions develop in approximately half of patients, and delayed acral desquamation and onychomadesis are common[7]. The eruption may be accentuated in areas of pre-existing skin injury or eczematous dermatitis, with the latter referred to as *"eczema coxsackium"* (see Fig. 81.4F). The differential diagnosis may include eczema herpeticum, varicella, disseminated zoster, Gianotti–Crosti syndrome, erythema multiforme, and autoimmune bullous diseases. In addition, patients with HFMD due to CVA6 are often febrile but do not usually have neurologic or other complications.

Herpangina is a febrile illness, primarily in children 3–10 years of age, characterized by painful vesicles and erosions on the soft palate, uvula, tonsils, pharynx, and buccal mucosa. An exanthem is usually absent. Coxsackievirus groups A and B, as well as echoviruses, are the usual pathogens. Coxsackievirus B5 infection has also been associated with conjunctival hyperemia.

In addition to HFMD and herpangina, enteroviruses cause a diverse spectrum of exanthems that may be morbilliform, rubelliform, roseola-like, urticarial, scarlatiniform, vesicular, pustular, and/or petechial. The majority of enteroviral exanthems feature erythematous macules and papules in a widespread distribution. Petechiae are fairly common, especially with echovirus 9 infection, and may lead to consideration of a more serious infection such as meningococcemia. Non-polio enteroviruses often infect newborns, producing a nonspecific erythematous exanthem and additional features such as fever, gastroenteritis, hepatitis, pneumonia, and meningoencephalitis[8,9].

In 1969, Cherry et al.[10] described four children with echovirus 25 or 32 infection who had fever and transient vascular papules; histologically, dilated blood vessels were seen. The term *eruptive pseudoangiomatosis* was subsequently proposed, and additional cases have been described in adults as well as children, with spontaneous resolution within a few weeks. Associated infections have included other enteroviruses, cytomegalovirus (CMV), Epstein–Barr virus (EBV), adenovirus, parvovirus B19, and SARS-CoV-2 (vaccination as well as infection) [11,12].

While classic HFMD and herpangina are fairly straightforward clinical diagnoses, other less specific exanthematous illnesses due to enteroviruses may have a broad differential diagnosis. Important factors that may point to the etiology include the season, exposure history, geographic location, and clinical signs and symptoms.

Confirmation of an *enteroviral* infection may be accomplished via viral culture, which has low sensitivity (especially for CVA6)[6], or polymerase chain reaction (PCR)-based assays; determination of the specific type of enterovirus via gene sequencing following RT-PCR is currently done only at research and public health laboratories (e.g. the US Centers for Disease Control [CDC]). Viral testing can be performed from vesicular fluid (preferred for HFMD), throat swabs, stool samples, and cerebrospinal fluid (CSF). Serologic diagnosis is difficult due to the large number of different serotypes and the time delay, which make it clinically less useful. Table 81.1 lists types of serologic assays.

Pathology

Skin biopsy is generally not a useful diagnostic procedure in enteroviral infections. Histopathologic features of the vesicular lesions of HFMD include epidermal necrosis with intraepidermal vesicles, a lack of inclusion bodies or multinucleation, and a nonspecific dermal inflammatory infiltrate.

Treatment

For most enteroviral exanthems, the course is self-limited, the prognosis is excellent, and supportive care suffices. However, in certain patient populations, e.g. immunosuppressed individuals or neonates, an enteroviral infection may be associated with potentially life-threatening complications. Pleconaril, a drug that interferes with enterovirus attachment and uncoating by binding to the protein capsid, has been demonstrated to be effective both *in vitro* and in clinical studies, including a randomized, placebo-controlled trial in neonates with enteroviral sepsis[13]; it therefore has potential as a specific antiviral therapy for serious enteroviral infections[14]. Three inactivated enterovirus-71 vaccines are licensed for clinical use in China, and other enteroviral vaccines are under development.

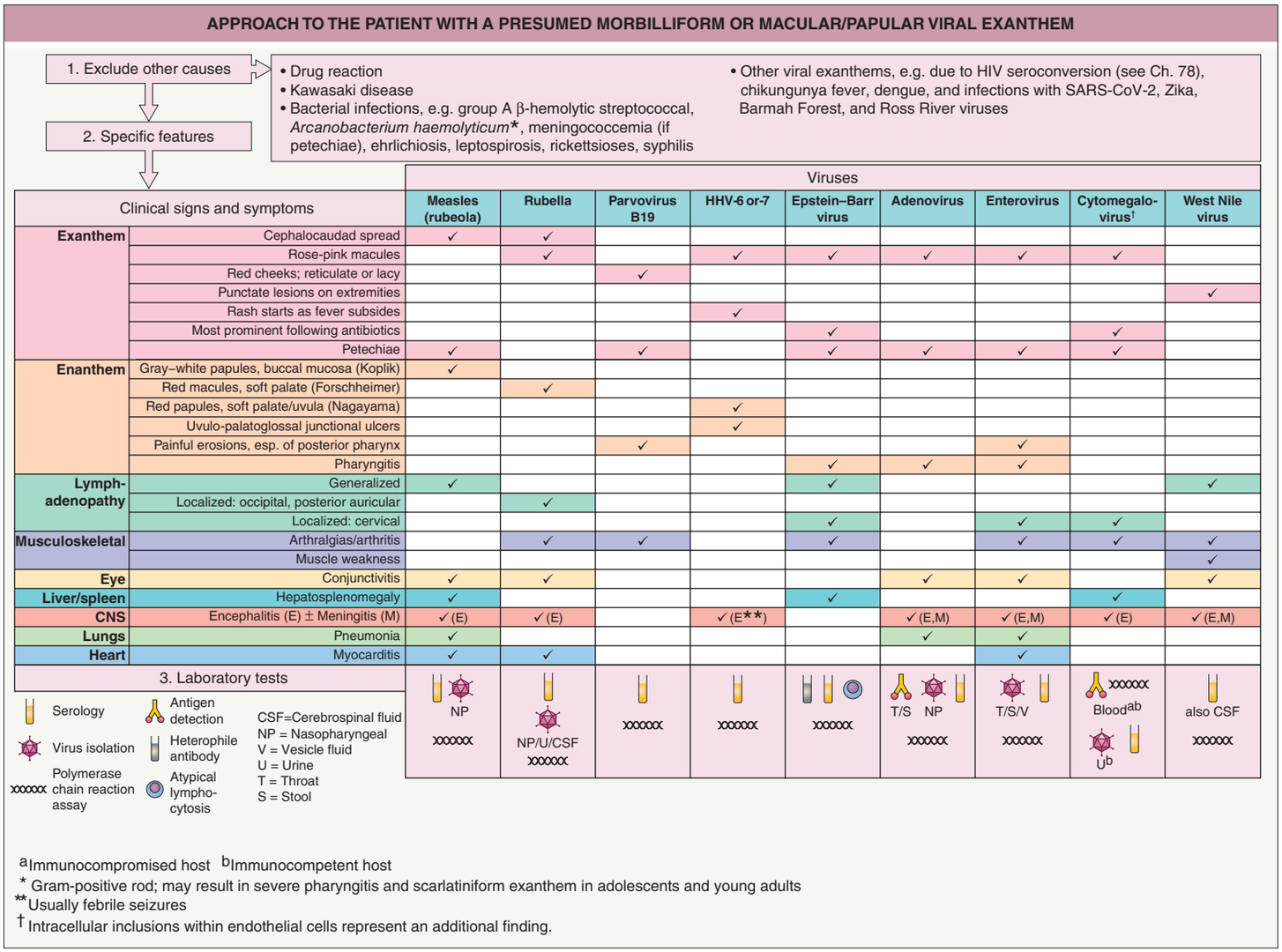


Fig. 81.2 Approach to the patient with a presumed morbilliform or macular/papular viral exanthem.

MEASLES

Synonym: ■ Rubeola

Key features

- Incidence greatly decreased with vaccination
- Prodrome of cough, coryza, conjunctivitis, and Koplik spots
- Cephalocaudad spread of exanthema

Introduction and History

The incidence of measles has markedly decreased since the introduction of the live vaccine in 1963. Despite high vaccination coverage, measles outbreaks continue to occur in both high-income and low-income countries, and the disease is still regarded as a major health burden. Use of the vaccine is estimated to have reduced global measles morbidity and mortality by 75% and 85%, respectively, compared with the prevaccine era[15].

Epidemiology

The incubation period of measles, which is highly contagious and spread via respiratory droplets, is 10–14 days. In the prevaccine era, measles was endemic throughout the year in heavily populated areas, without regard to age or sex. During the 1989–1990 epidemic, reported measles cases in the US increased six- to ninefold over the mean of 3000 cases diagnosed annually between 1985 and 1988. Target populations during that epidemic were unvaccinated children younger than 5 years of age and vaccinated school-aged children who failed to develop immunity against the virus. The latter highlighted the need for more than one dose of vaccine; as a result, a two-dose measles vaccine schedule was recommended in 1989, which greatly decreased the incidence of measles in the US[16]. Although the median number of cases of measles diagnosed annually in the US is now ~100, outbreaks still occur. For example, >1250 measles cases were confirmed in the US in 2019, ~75% of which occurred in Orthodox Jewish communities in New York with low vaccination rates[17]. Such observations underscore the importance of sustained efforts at universal vaccination against measles.

Pathogenesis

Measles is caused by an RNA virus in the Paramyxoviridae family, and humans are the natural host and reservoir of infection. The disease starts with replication of the virus within the epithelial cells of the respiratory tract, with subsequent spread to the lymphoid tissue and blood, resulting in viremia. The virus can then disseminate to internal organs, including the lungs, liver, and gastrointestinal tract.

Clinical Features and Differential Diagnosis

Measles classically presents with a prodrome of fever, cough, nasal congestion, and rhinoconjunctivitis. A pathognomonic enanthem, Koplik spots, appears during the prodrome and is composed of gray–white papules on the buccal mucosa. The exanthem develops over 2–4 days

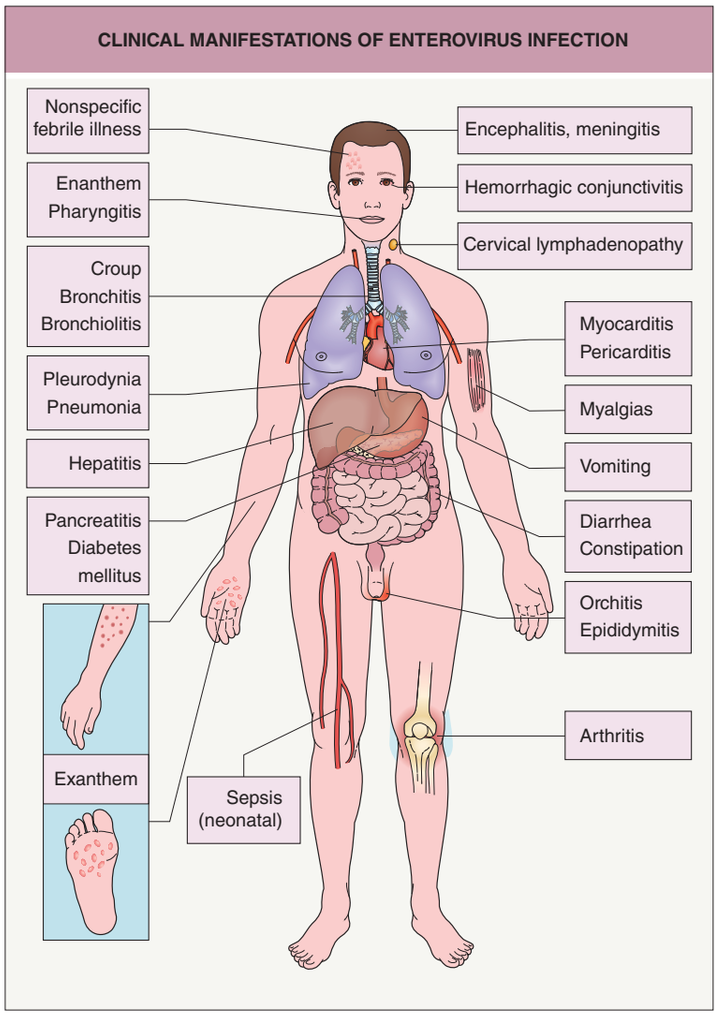


Fig. 81.3 Clinical manifestations of enterovirus infection.

and consists of erythematous macules and papules that begin on the forehead, hairline, and behind the ears and then spread in a cephalocaudad direction (Fig. 81.5). On the fifth day, the exanthem starts to fade in the same order as it appeared.

Morbilliform ("measles-like") eruptions can result from other viral infections, e.g. with enteroviruses, EBV, parvovirus B19, and human herpesvirus-6 (HHV-6)[18]. The differential diagnosis may also include a drug eruption and Kawasaki disease (see Fig. 81.2).

Atypical measles due to infection with wild-type virus in the setting of partial immunity has been reported in several groups, including recipients of killed measles vaccine (used from 1963 to 1968), those who failed vaccination, and immunocompromised individuals. It is characterized by high fevers, cough, and pulmonary infiltrates that reflect immune complex deposition related to non-protective, complement-fixing antibodies. Coryza and conjunctivitis are generally absent, and the exanthem is variable, potentially including vesicles, petechiae, purpura, and acral edema.

Complications of measles include otitis, pneumonia, encephalitis, and myocarditis. Subacute sclerosing panencephalitis is a delayed neurodegenerative disorder that can occur as a complication of measles many years after the acute disease. It is characterized by seizures, personality changes, coma, and death. Laboratory diagnosis of measles can be accomplished by virus isolation or detection via RT-PCR in nasopharyngeal secretions or urine, as well as serologic assays for measles-specific antibodies (IgM or IgG).

Pathology

The histopathologic findings are nonspecific, including a superficial perivascular lymphocytic infiltrate together with variable spongiosis and dyskeratosis.

Treatment

There is no specific antiviral therapy for measles. Because low serum vitamin A levels are associated with increased measles-related morbidity and mortality, the World Health Organization (WHO) recommends that all children with acute measles receive vitamin A once daily for 2 days at the following doses: 200 000 IU if age ≥12 months; 100 000 IU if age 6–11 months; or 50 000 IU if age <6 months.

Prevention of measles by vaccination is the most effective way to reduce measles morbidity and mortality. The current recommendation for measles immunization is an initial vaccine dose at 12–15 months of age and a second dose at 4–6 years of age[19]. For unvaccinated individuals exposed to measles, administration of the vaccine within 3 days or intramuscular or intravenous immunoglobulin (IM/IVIg) within 6 days of the exposure may provide some protection.

RUBELLA

Synonym: ■ German measles

Key features

- Exanthem of rose-pink macules with cephalocaudad spread
- Tender lymphadenopathy, especially occipital and posterior auricular
- Joint involvement common
- Fetal infection is associated with congenital anomalies

Introduction and History

Rubella is caused by an RNA virus in the Togaviridae family. Although usually a mild, self-limited disease in children and adults, it can cause major complications when transmitted to a fetus *in utero*, including miscarriage, stillbirth, and severe congenital malformations.

Epidemiology

The disease is spread via respiratory droplets, with an incubation period of 16–18 days. The incidence of rubella has markedly declined since the licensure of the MMR (measles, mumps, and rubella) vaccine in 1969. Rubella was declared as eliminated from the US in 2005 and from the Americas in 2014; currently all US cases reported since 2012 (<10 per year) were acquired in another country. Rubella has a worldwide distribution and occurs most often in the spring.

Pathogenesis

The primary site of infection is the nasopharynx, followed by spread to regional lymph nodes and a subsequent viremia.

Clinical Features and Differential Diagnosis

Rubella typically presents with a mild prodrome that includes fever, headache, and upper respiratory symptoms. In children, many cases are subclinical. One to 5 days following the prodrome, an eruption of erythematous macules and papules appears on the face, spreading in a cephalocaudad direction. Erythematous petechial macules may also be present on the soft palate (Forchheimer spots). The eruption is often accompanied by tender lymphadenopathy, especially of the occipital, posterior auricular, and cervical regions. The cutaneous eruption tends to fade in 2–3 days in the same order as it appeared.

Rubella may result in arthralgias and arthritis, especially in postpubertal girls and women; less frequent complications include hepatitis, myocarditis, pericarditis, hemolytic anemia, and thrombocytopenia. Encephalitis occurs in ~1 in 6000 infected individuals[20].

Rubella can be diagnosed by detection of anti-rubella IgM antibodies or a fourfold increase in specific IgG antibodies; virus isolation or detection via RT-PCR from a nasal wash, throat swab, or urine sample is also possible. The exanthem of rubella is nonspecific and the differential diagnosis includes other viral exanthems (e.g. adenovirus, enterovirus,



Fig. 81.4 Hand-foot-and-mouth disease. A Vesicle and erythematous macules on the sole in classic hand-foot-and-mouth disease. **B–G** Coxsackievirus A6 infection presenting as: multiple erythematous macules and papules with some targetoid lesions resembling early erythema multiforme on the palm (**B**); vesicles and papulovesicles on the dorsal hand (**C**) and thigh (**D**); perioral monomorphic crusted lesions resembling eczema herpeticum (**E**); more extensive "eczema coxsackium" in toddlers (**F** & **G**) and an infant (**H**) with atopic dermatitis. *A–G, Courtesy Julie V. Schaffer, MD. H, Courtesy Henry Heaton, MD.*

SEROLOGIC ASSAYS OF ANTIBODY RESPONSES	
Assay	**Principle**
Neutralization	Visual read of infected cell monolayers incubated with test sera, looking for CPE inhibition
Radioimmunoassay (RIA)	Ab and Ag bind, then radiolabeled antiglobulin added, *or* radiolabeled Ag added and it binds Ab; radioactivity measured
Enzyme-linked immunosorbent assay (ELISA)	Microplates coated with Ag, serum and enzyme-labeled antiglobulin added, then enzyme substrate added and color change measured
Western blot	Ag mixture separated by electrophoresis, transferred to membrane, serum added and then labeled antiglobulin; seen as colored bands
Latex agglutination	Ag-coated latex particles incubated with serum, Ab agglutinates particles
Hemagglutination inhibition (HI)	Serially diluted test sera mixed with viral Ag, then animal erythrocytes added; inhibition of agglutination measured
Complement fixation	Ag added to serially diluted test sera; Ag–Ab complex binds complement, so the latter is unavailable for lysis of sheep erythrocytes in the presence of Ab to erythrocytes
Immunodiffusion	Ab and soluble Ags combine to produce visible lines of precipitate in a gel
Immunofluorescence	Test sera added to infected cell monolayer, then fluorescein-labeled anti-IgG Ab added; examined with fluorescence microscope

Table 81.1 Serologic assays of antibody responses. Ab, antibody; Ag, antigen; CPE, cytopathic effect.

measles, EBV) and toxin-mediated eruptions such as scarlet fever. The occipital lymphadenopathy and the typical progression of the eruption can be helpful in diagnosing the disease.

Congenital rubella occurs when a nonimmune pregnant woman transfers the virus to the fetus. Birth defects are most commonly observed when infection is during the first 16 weeks of pregnancy. Congenital rubella syndrome is characterized by cataracts, deafness, congenital heart defects (patent ductus arteriosus, ventricular septal defects), and CNS abnormalities (microcephaly, developmental delay). A "blueberry muffin baby" presentation due to dermal hematopoiesis is occasionally observed (see Ch. 121).

Both wild type and vaccine-derived rubella virus have been identified and found to persist for years in macrophages within cutaneous granulomas in individuals with immunodeficiencies characterized by



Fig. 81.5 Measles. Pink macules and minimally elevated papules. *Courtesy Louis A. Fragola, Jr, MD.*

T cell lymphopenia and/or defective lymphocyte cytotoxicity. The latter include ataxia telangiectasia, Griscelli syndrome type 2, and a variety of combined immunodeficiency syndromes (see Ch. 60)[21]. Clinically, these patients present with pink–violet to red–brown papules, nodules, and plaques, often with crusting or ulceration, that favor the extremities and face but may be widespread[21]. Rubella virus has also been identified within cutaneous granulomas (palisaded and necrotizing type) involving the left upper arm (a typical vaccination site) in clinically immunocompetent adults; localized lesions associated with vaccine-derived rubella developed 2 to >10 years after the last MMR vaccine administration[22].

Pathology

Reported histopathologic findings of rubella include a superficial perivascular infiltrate with mild spongiosis. Atypical lymphocytes may be evident in the cutaneous infiltrate as well as in peripheral blood.

Treatment

Treatment of rubella is supportive. The current recommended immunization schedule for rubella vaccine, which is given in conjunction with the measles and mumps vaccines (MMR vaccine), is an initial dose at 12–15 months and a second dose at 4–6 years[19]. In a pregnant woman who has been exposed to rubella, serologic testing (IgG and IgM) should be performed. Prophylaxis via administration of IM/IVIg to rubella-susceptible women exposed to confirmed rubella early in pregnancy may be considered, but it does not reliably prevent fetal infection. If rubella-specific IgM antibodies or a diagnostic rise in IgG anti-rubella antibodies (the latter not useful following IM/IVIg administration) are detected, the patient should be offered prenatal counseling.

ERYTHEMA INFECTIOSUM

Synonyms: ■ Fifth disease ■ "Slapped cheek" disease ■ Parvovirus B19 infection

Key features

- "Slapped cheeks" followed by lacy extremity-predominant eruption, especially in children
- Eruptions in adolescents and adults may be petechial and/or have an acral or periflexural distribution
- Marked affinity of parvovirus B19 for erythrocyte precursors
- Fetal infection may result in anemia, fetal hydrops, or death

Introduction and History

Human parvovirus B19 (B19), the only parvovirus known to infect humans, was accidentally discovered in 1975 by Cossart and colleagues, who were screening blood samples for hepatitis B virus. The small, single-stranded DNA virus, which was named after the panel of sera in which it was found (number 19, row B), was identified as the etiology of erythema infectiosum in 1983. Subsequent elucidation of the pathogenesis of human B19 infections has led to its association with a wide variety of clinical findings (Table 81.2).

PARVOVIRUS B19 CLINICAL ASSOCIATIONS
Established associations
Mucocutaneous
• Erythema infectiosum • Papular-purpuric gloves and socks syndrome • Petechial/purpuric eruptions in a generalized, bathing trunk, periflexural, acral, and/or perioral distribution • Enanthem with erosions and petechiae • Degos-like lesions
Extracutaneous
• Arthropathy • Hydrops fetalis • Transient aplastic crises in at-risk individuals* • Chronic anemia • Thrombocytopenia, neutropenia, pancytopenia • Hepatitis
Possible associations
Vasculitides
• Small vessel vasculitis • Henoch–Schönlein purpura • Cryoglobulinemic vasculitis • Polyarteritis nodosa • Granulomatosis with polyangiitis
Additional exanthems
• Microvesicular eruption • Unilateral laterothoracic exanthem • Gianotti–Crosti syndrome
Other
• Neurologic disease • Chronic fatigue syndrome • Systemic lupus erythematosus-like illness • Hemophagocytic lymphohistiocytosis • Myositis
*Patients suffering from decreased red cell production (e.g. iron deficiency, thalassemias) or increased red cell destruction (e.g. sickle cell anemia, hereditary spherocytosis, pyruvate kinase deficiency, glucose-6-phosphate dehydrogenase deficiency), as well as patients with HIV infection and recipients of allogeneic hematopoietic stem cell or solid organ transplants.

Table 81.2 Parvovirus B19 clinical associations. Asymptomatic infection may also occur.

Epidemiology

Infection with B19 occurs in a seasonal pattern, with a peak incidence of erythema infectiosum during the winter and spring. Transmission is via respiratory secretions, blood products, and vertically from mother to fetus; the incubation period is between 4 and 14 days. B19 infection occurs worldwide and is most common in school-aged children. A cyclical pattern of epidemics seems to have peaks about every 6 years[23], and individual community epidemics last 3–6 months. The seroprevalence of B19 antibodies increases in direct proportion with age, with immunity in 2%–15% of children 1–5 years of age, 15%–60% of those 5–19 years of age, and 30%–80% of adults.

Pathogenesis

B19 has a strong tropism for erythroid progenitor cells, and the erythrocyte "P antigen" (globoside) is the cellular receptor to which the virus binds. In fact, individuals who lack the P antigen (blood group P_1^k or p phenotypes) seem to be naturally resistant to B19 infection[24].

After initial infection of the respiratory tract, a B19 viremia occurs, ending when the anti-B19 IgM antibody appears ~8–10 days post

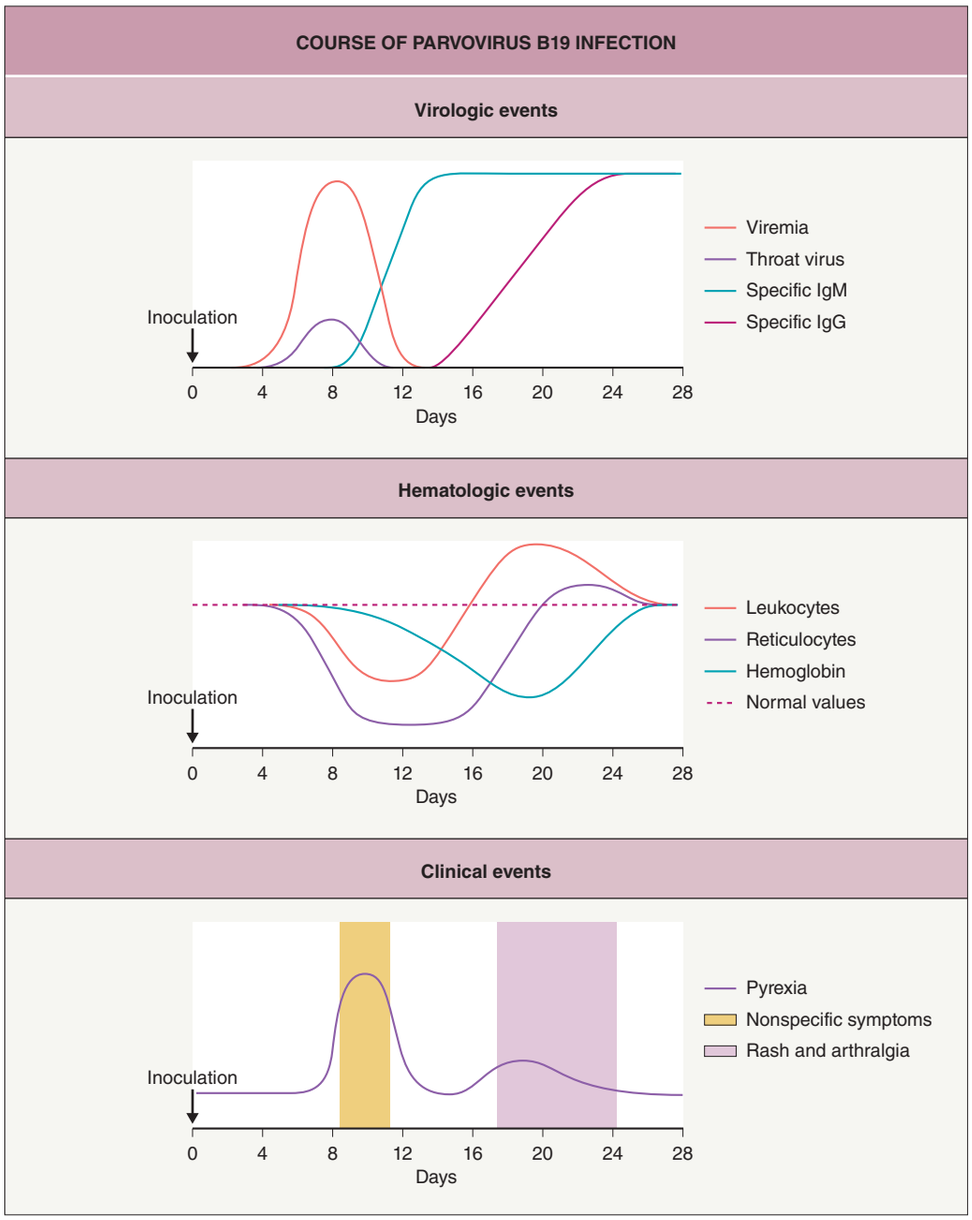


Fig. 81.6 Course of parvovirus B19 infection. Volunteers were infected with parvovirus B19 and the virologic, hematologic, and clinical events that followed were recorded. *Reprinted from Cohen J, Powderly WG. Infectious Diseases, 2nd edn. St Louis: Mosby, 2004.*

inoculation (Fig. 81.6). During the viremic period, reticulocytopenia occurs for 7–10 days[23]. One week after the appearance of IgM antibody, anti-B19 IgG appears and coincides with the appearance of the rash and arthralgia. An immune-mediated process is suggested by the temporal disconnect between the viremia and the clinical symptoms.

The anemia and reticulocytopenia tend to be inconsequential in the normal host but may result in transient aplastic crises in at-risk individuals, such as those with disorders resulting in enhanced red blood cell destruction or decreased production; thrombocytopenia, neutropenia, and pancytopenia may also occur (see Table 81.2). Fetal infection from intrauterine virus transmission causes fetal anemia of varying severity (see below).

Clinical Features and Differential Diagnosis

The most common illness caused by B19 infection is erythema infectiosum, which most often occurs in children 4–10 years of age. Mild prodromal symptoms such as a low-grade fever, myalgias, and headache may develop 7–10 days before the characteristic exanthem appears. The initial stage of the exanthem consists of bright red macular erythema of the cheeks, with sparing of the nasal bridge and circumoral regions (Fig. 81.7A). One to 4 days later, the second stage appears as erythematous macules and papules on the extremities and to a lesser extent the trunk, progressing to form a lacy, reticulated pattern (Fig. 81.7B,C). This exanthem typically lasts 1–3 weeks or occasionally longer; it fluctuates in intensity during this period, often with exacerbations upon exposure to sunlight or overheating. The differential diagnosis of erythema infectiosum may include scarlet fever, enteroviral infection, and rubella, but the diagnosis is usually straightforward when the characteristic eruption is present. Although the evanescent exanthem of systemic juvenile idiopathic arthritis (Still disease) is also accentuated by heat, it is accompanied by episodic high fevers, has a more chronic course, and often exhibits the Koebner phenomenon.

In adolescents and adults with B19 infection, the exanthems tend to be petechial and often have an acral or periflexural distribution (see Table 81.2)[25]. A distinctive *papular-purpuric gloves and socks syndrome* (PPGSS) was first described in 1990[26] and subsequently found to be associated with acute B19 infection, although other infectious etiologies have also been reported, e.g. coxsackievirus B6, HHV-6, and EBV. PPGSS most often develops in the spring, and although it has a predilection for young adults, PPGSS may occur at any age, including in children. The hallmark findings are edema and erythema of the hands and feet, especially the palms and soles, in association with petechiae and purpura (Fig. 81.8). Occasionally, there is extension onto the dorsal surfaces of the hands and feet, and patients may complain of burning and pruritus. Additional manifestations can include an enanthem of erosions and petechiae involving the palate, pharynx, and tongue, as well as fever and mild prodromal symptoms.



Fig. 81.7 Erythema infectiosum. A Bright red macular erythema on the cheeks. **B–D** Lacy, reticulated erythematous eruptions on the extremities during the second stage of the exanthem. *A, D, Courtesy Louis A. Fragola, Jr, MD; B, Courtesy Julie V. Schaffer, MD; C, Courtesy Kalman Watsky, MD.*



Fig. 81.8 Papular-purpuric gloves and socks syndrome. Erythema and edema with associated petechiae and small purpuric papules on the dorsal aspect of the fingers and hands. *Courtesy Luis Requena, MD.*

Therapy of PPGSS is symptomatic, and spontaneous resolution usually occurs over 1–2 weeks. Although few studies have addressed the immune response in PPGSS, based on limited data it appears that patients develop the mucocutaneous lesions while still viremic, which implies contagiousness and therefore has different epidemiologic implications than the classic eruption of erythema infectiosum.

Arthralgia or arthritis occurs in up to 10% of patients with erythema infectiosum and is usually self-limited, typically resolving in 1–3 weeks but sometimes lasting for months. It tends to affect the small joints of the hands as well as the wrists, knees, and ankles. Joint involvement related to B19 infection is more common in adults, especially women, occurring in up to 30%–60% of those with acute infection[27]. Arthropathy may be seen without an accompanying exanthem.

The manifestations of *fetal B19 infection* range from self-limited anemia to hydrops, spontaneous miscarriage, or stillbirth. The greatest susceptibility is associated with infections acquired before 20 weeks' gestation, and most fetal losses occur between 20 and 28 weeks' gestation. Third-trimester fetal demise may also occur, but it is less often associated with fetal hydrops[28]. The overall risk of fetal loss in the setting of acute B19 infection during pregnancy is only 2%–6%[29–31], and the majority of infants born to B19-infected mothers are delivered asymptomatic at term. There is no evidence for long-term neurodevelopmental sequelae for surviving infected infants, and congenital malformations have not been conclusively demonstrated.

When diagnostic confirmation of B19 infection is needed, detection of serum anti-B19 IgM antibody is the preferred method, and its presence indicates infection within the previous 2–4 months. PCR-based assays may be helpful in diagnosing infection in immunocompromised patients.

Pathology

Skin biopsy is generally not useful in the diagnosis of B19 infection. In patients with PPGSS, histologic evaluation demonstrates a lymphocytic dermal infiltrate with frequent extravasation of erythrocytes. Anti-B19 antibodies can highlight infected endothelial cells in superficial dermal blood vessels.

Treatment

No specific antiviral therapy is available for B19 infections. Children with erythema infectiosum usually feel well and often require no treatment. NSAIDs are useful if symptomatic arthropathy is present. Patients who develop an aplastic crisis may require red blood cell transfusions. Pregnant women with confirmed primary B19 infection during the first two trimesters should undergo serial fetal ultrasonography, and management of severely affected fetuses is possible with *in utero* transfusions and other interventions.

ROSEOLA INFANTUM

Synonyms: ■ Exanthem subitum ■ Sixth disease

Key features

- High fever followed by an exanthem at defervescence
- Affects primarily infants and toddlers
- Febrile seizures possible

Roseola infantum is a common febrile illness of infancy that is primarily caused by human herpesvirus-6 (HHV-6) infection and is occasionally associated with human herpesvirus-7 (HHV-7) infection (see Ch. 80). Most cases occur between age 6 months, when levels of protective maternal antibodies wane, and 3 years, with peak incidence at age 6–12 months. Between 40% and 80% of children are seropositive for HHV-6 by age 13 months[26,32], and most of the remainder by 3 years; however, less than a third of infections result in the classic clinical manifestations of roseola infantum. Roseola infantum occurs year-round but is most common in the spring; the incubation period is usually 9–10 days.

The characteristic presentation is a high fever (to 40–40.5°C; 104–105°F) for 3–5 days in an infant who otherwise appears well. Seizures occur during the febrile period in up to 10% of patients. Defervescence is accompanied by the appearance of rose-pink macules and papules on the trunk, neck, proximal extremities, and occasionally the face. Mild upper respiratory symptoms, injection of the tympanic membranes, cervical or occipital lymphadenopathy, edematous eyelids, and a bulging anterior fontanelle may also be present. An enanthem of red papules on the soft palate and uvula (Nagayama spots) can develop, and uvular and palatoglossal junctional ulcers represent a characteristic finding[33]. The skin eruption typically fades over a few days. Nonspecific fevers with or without otitis media in infants may also be due to HHV-6 infection.

Additional pathogenic features and clinical manifestations of HHV-6 infection, including reactivation in the settings of immunosuppression and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, are discussed in Chapter 80.

UNILATERAL LATEROTHORACIC EXANTHEM

Synonym: ■ Asymmetric periflexural exanthem of childhood

Key features

- Initial unilateral distribution, most often affecting the axilla and lateral trunk
- Subsequent generalization, but maintains unilateral predominance
- Spontaneous resolution over 3–6 weeks
- Presumed to be viral in etiology, although exact cause unknown

Introduction and History

This disorder was first described in 1962[34], and the term "unilateral laterothoracic exanthem" (ULTE) was introduced in 1992[35]. ULTE is initially characterized by a unilateral periflexural (often axillary) location, with spread in a centrifugal pattern to the contralateral side over time.

Epidemiology

ULTE occurs most commonly in toddlers and preschool-aged children, with an age range of 6 months to 10 years and a male : female ratio of 1 : 2. It has most often been reported in Europe and North America, and the majority of cases occur in the spring.



Fig. 81.9 Unilateral laterothoracic exanthem. Erythematous macules and papules involving the left axilla and upper flank (**A**) and a slightly more extensive distribution on the left lateral trunk (**B**).

Pathogenesis

The etiology of ULTE remains unknown despite multiple attempts to identify a causative infectious agent. The seasonal pattern, associated prodrome, reports of familial cases, and lack of response to systemic antibiotics suggest a viral etiology. In studies in which screening for multiple viruses (e.g. EBV, CMV, HHV-6, HHV-7) was performed, no etiologic agent has been consistently demonstrated. A relationship to infection with *Spiroplasma*, parvovirus B19, EBV, and SARS-CoV-2 has been noted in individual cases[36,37].

Clinical Features and Differential Diagnosis

The eruption typically begins with a unilateral distribution (Fig. 81.9), most commonly in the axillary region, followed in frequency by the trunk, arm, and thigh. It is usually morbilliform or eczematous in nature and tends to spread to contralateral areas while maintaining a unilateral predominance.

The exanthem may be preceded by a low-grade fever, diarrhea, and/or rhinitis in up to 60% of patients, and pruritus is common. Lymphadenopathy may also be present. The eruption typically lasts 3–6 weeks and then resolves spontaneously, usually without recurrence.

Contact dermatitis is often initially suspected, and the differential diagnosis also includes a nonspecific viral exanthem, a drug eruption, atypical pityriasis rosea, scabies, miliaria, and tinea corporis. If there is prominent involvement of the extremities, Gianotti–Crosti syndrome may also be considered. An eczematous eruption with a distribution pattern similar to ULTE can occur in association with mollusca contagiosa located in the same areas. Laboratory evaluation is generally unnecessary.

Pathology

Histologic features are nonspecific and include mild spongiosis, exocytosis of lymphocytes into the epidermis, and a superficial perivascular infiltrate that is predominantly lymphocytic. The dermal infiltrate may be accentuated around eccrine ducts.

Treatment

Supportive treatment is indicated in symptomatic patients, although topical corticosteroids tend to be of little help. Parents should be reassured that the exanthem will resolve spontaneously in about 3–6 weeks.

GIANOTTI–CROSTI SYNDROME

Synonyms: ■ Papular acrodermatitis of childhood ■ Papulovesicular acrolocated syndrome

Key features

- Symmetric papular eruption on the extremities, face, and buttocks
- EBV and globally hepatitis B virus represent the most common triggers

Introduction and History

Gianotti–Crosti syndrome (GCS) was first described by Gianotti and Crosti in the 1950s. This childhood condition is characterized by the acute onset of a symmetric papular eruption on the face, extremities, and buttocks. In 1964, Gianotti and Crosti reported coexistent anicteric hepatitis, and in the 1970s an association with hepatitis B virus was described. Subsequent reports demonstrated that GCS can result from a variety of viral triggers (Table 81.3).

The term "papulovesicular acrolocated syndrome" was used by Gianotti in 1985 to distinguish a more vesicular variant that is characterized by a lack of hepatitis, more pruritus, and a prolonged course[38]. However, differences in clinical manifestations are not generally related to the etiologic agent[39], and this variant is now included within the spectrum of GCS.

Epidemiology

GCS has a worldwide distribution and occurs most often in young children during the spring and early summer. In one large series, the age range was 6 months to 14 years, with a mean of 2 years[39].

Pathogenesis

GCS is regarded as a self-limited cutaneous response to various infections. Hepatitis B virus and EBV are the most frequently reported agents, with EBV representing the most commonly documented cause in the US. Other potential etiologic associations are summarized in Table 81.3. Although the pathogenic mechanisms in GCS are not clear, there is some suggestion that immunizations or immune imbalance may enhance the risk of developing the exanthem following certain infections.

Clinical Features and Differential Diagnosis

GCS is often preceded by an upper respiratory syndrome with mild constitutional symptoms. The exanthem begins abruptly, with monomorphic, skin-colored to pink–red, edematous papules that are

POTENTIAL ETIOLOGIES REPORTED IN ASSOCIATION WITH GIANOTTI–CROSTI SYNDROME	
Viral	
• **Hepatitis B virus***	• Rotavirus
• **Epstein–Barr virus†**	• Parvovirus B19
• Hepatitis A and C viruses	• Mumps virus
• Cytomegalovirus	• Human herpesvirus-6
• Coxsackievirus	• Herpes simplex virus 1
• Respiratory syncytial virus	• Influenza virus
• Adenovirus	• SARS-CoV-2
• Parainfluenza virus	• Human immunodeficiency virus
Non-viral	
• Group A β-hemolytic streptococci	• *Bartonella henselae*
• *Mycoplasma pneumoniae*	• *Neisseria meningitidis*
Vaccines	
• Polio	• Hepatitis B > A
• Diphtheria–pertussis–tetanus (DPT)	• Influenza
• Measles–mumps–rubella (MMR)	• SARS-CoV-2
*Reported most commonly in Europe. †Most common cause in US.	

Table 81.3 Potential etiologies reported in association with Gianotti–Crosti syndrome. A pruritic Gianotti–Crosti syndrome-like eruption can also occur in patients with molluscum contagiosum (see text). Most common viral etiologies are in bold.

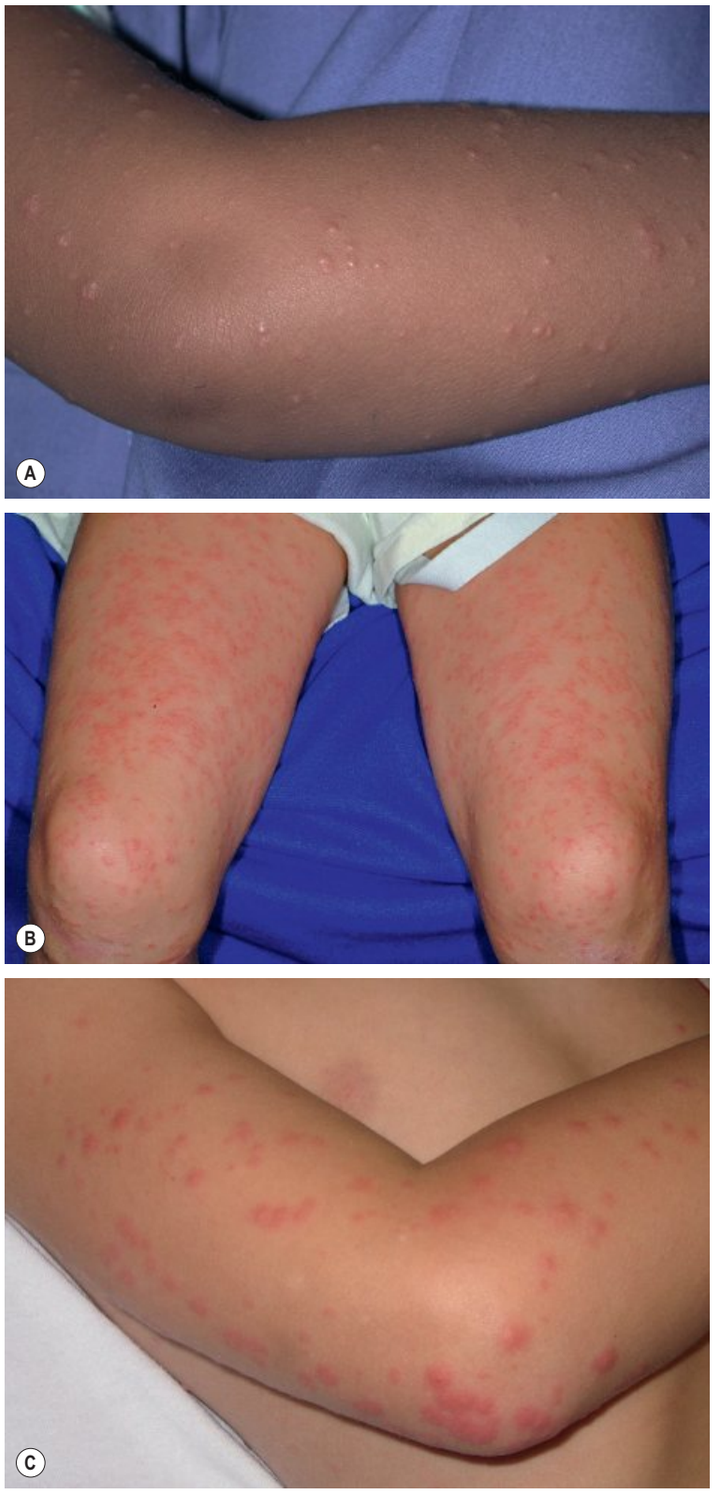


Fig. 81.10 Gianotti–Crosti syndrome. A Monomorphic, small erythematous papules on the elbow. **B** A more exuberant eruption of coalescing edematous, erythematous papules on the thighs and knees. **C** Larger edematous, erythematous papules on the elbow.

symmetrically distributed on the face, buttocks, and extensor surfaces of the extremities (Fig. 81.10). In some patients, lesions may be limited to the face[40]. The trunk is usually spared, although some extension onto the trunk does not exclude the diagnosis[41]. Lesions tend to be asymptomatic and may occasionally be vesicular or purpuric. Systemic manifestations include a low-grade fever and lymphadenopathy (mainly inguinal and axillary) that can persist for a few months; hepatomegaly and splenomegaly occur less often.

The differential diagnosis of GCS may include a drug eruption, papular urticaria, other viral exanthems, erythema multiforme, and molluscum contagiosum. An inflammatory response to molluscum contagiosum, which often heralds clearance of the lesions, can present with an eruption of monomorphic erythematous papules that favor the elbows and knees; this "id" reaction-like phenomenon can resemble GCS but tends to be extremely pruritic and to respond to treatment with topical corticosteroids[42].

Pathology

The histopathologic findings are nonspecific and can include spongiotic and lichenoid changes as well as a lymphocytic vasculitis. Exocytosis of lymphocytes within the lower epidermis and increased numbers of cytotoxic T lymphocytes in the infiltrate may be observed[43,44].

Treatment

The treatment for GCS is supportive, and topical corticosteroids are often of little benefit. A thorough history and physical examination should be performed, and laboratory tests for hepatitis or specific viral agents (e.g. hepatitis B virus, EBV) should only be obtained if clinically indicated. Spontaneous resolution usually occurs within 3–6 weeks, although the eruption may occasionally persist for 8 weeks or longer.

POXVIRUS INFECTIONS

Key features

- Although the last reported case of smallpox was in 1978, it is still considered a bioterrorism threat
- Molluscum contagiosum represents the most common poxvirus infection in humans

The family Poxviridae are large, brick- or ovoid-shaped, double-stranded DNA viruses that are characterized by cytoplasmic replication. Diseases caused by poxviruses include smallpox, vaccinia, cowpox, mpox (previously referred to as monkeypox), tanapox, orf, milker's nodules, and molluscum contagiosum (Table 81.4)[45–50]. The most historically significant of these was smallpox, which at one time was endemic throughout the world and responsible for millions of human deaths. The last epidemic of smallpox in the US was in 1949, and in 1980, the World Health Assembly declared the world free from smallpox. However, two reference collections remain in the US and Russia. The infection that has clinical features most similar to smallpox is varicella; a comparison of these two conditions is provided in Table 81.5.

Because of concerns regarding smallpox being used as a bioterrorism agent[51–53], extensive recommendations have been adopted for handling of a suspected outbreak (emergency.cdc.gov/agent/smallpox/). The current strategy of ring vaccination involves isolation of patients with suspected infection and immunization of all identified contacts as well as their contacts. If given within 3–4 days following exposure, smallpox vaccination may prevent or reduce the severity of disease. If possible, first responders and healthcare workers who come into contact with a suspected patient should have previously been vaccinated[54]. Tecovirimat and brincidofovir are both FDA-approved for the treatment of smallpox in adults and children (weighing ≥13 kg and including neonates, respectively). Recently, tecovirimat access was expanded to include patients with other orthopoxvirus infections, including mpox[55]. Both of these agents as well as the JYNNEOS™ (Modified Vaccinia Ankara) vaccine were utilized in the 2022 international mpox outbreak[45–47] (see Table 81.4).

With the eradication of smallpox, *molluscum contagiosum* (MC) became the only remaining poxvirus infection to specifically afflict humans. The MC virus (MCV) is a member of the *Molluscipox* genus of Poxviridae, and the MCV I and MCV II subtypes result in indistinguishable skin lesions[56]. MC is a common, self-limited condition in children. It also occurs in adults, usually as a sexually transmitted disease, and in immunocompromised hosts, most notably HIV-infected individuals. Transmission is via skin-to-skin contact and, less commonly, fomites.

MC lesions are firm, umbilicated, pearly papules with a waxy surface. They can occur anywhere on the skin surface but are most common in skin folds (e.g. axillae, neck); on the lateral trunk, thighs, and buttocks; and in the genital region (Fig. 81.13A). Facial lesions can also occur and are often especially distressing to the patient (Fig. 81.13B). Widespread, large, and occasionally deforming lesions may be seen in the setting of immunosuppression, particularly AIDS (see Ch. 78).

SELECTED POXVIRUS INFECTIONS

Disease	Virus/genus	Host	Clinical findings	Treatment	Comment
Smallpox	Variola/ Orthopoxvirus	Humans	*Major criteria** • Febrile prodrome (>101°F [38.3°C], 1–4 days prior to rash onset with headache, backache or abdominal pain) • Firm, deep-seated, well-circumscribed vesicles/pustules • Lesions in the same stage of development in any one area of the body *Minor criteria* • Centrifugal distribution† • First lesions in the pharynx, oral mucosa • Patient appears "toxic" • Slow evolution of rash (i.e. 1–2 days for each stage: macule, papule, vesicle) • Lesions on the palms and soles See Table 81.5 for additional findings	Tecovirimat (adults and children weighing ≥13 kg), brincidofovir (any age, including neonates); supportive; prophylaxis with vaccination – ACAM2000® (vaccinia; see below) or JYNNEOS™ (Modified Vaccinia Ankara; approved to prevent smallpox and mpox in adults at high risk of infection)	• Enters via respiratory tract • Incubation period – 7 to 17 days • Variola major = severe form with high mortality rate; variola minor (alastrim) = mild form • Complications: panophthalmitis, blindness, arthritis, encephalitis • Usual causes of death: toxemia, immune complex deposition, hypotension • High risk of smallpox – 3 major criteria; moderate risk – febrile prodrome + *either* 1 other major criterion *or* ≥4 minor criteria; low risk – no febrile prodrome or febrile prodrome + <4 minor criteria • Laboratory diagnosis: variola real-time PCR (+), orthopox real-time PCR (+), non-variola orthopoxvirus real-time PCR (–), EM (if available), viral culture; acceptable specimens: vesicular "touch prep", vesicle roof, vesicular swab, biopsy tissue • Theoretically eradicated; potential use as bioterrorism agent

Table 81.4 Selected poxvirus infections.

Continued

SELECTED POXVIRUS INFECTIONS					
Disease	**Virus/genus**	**Host**	**Clinical findings**	**Treatment**	**Comment**

Vaccinia	Vaccinia/ Orthopoxvirus	Humans	• Papule at the vaccination site (usually deltoid or thigh) develops into vesiculopustules, then crust (Fig. 81.11A)
			• Occasionally, satellite lesions
			• Lymphadenopathy, fever, malaise common
				Supportive; heals with pitted scar	• Used for smallpox vaccination; historically in the general population, currently in military and first responders, including healthcare workers
					• Live vaccine (ACAM2000®) from a single purified isolate of the previous vaccine (Dryvax®; last manufactured in 1978) that is aseptically propagated in cell culture began to be utilized in 2008, with >200 million doses in the US Strategic National Stockpile
					• Possible adverse events‡:
					  • superinfection of the vaccination site or regional lymph nodes
					  • inadvertent autoinoculation (non-ocular)
					  • contact transmission (non-ocular)
					  • ocular vaccinia
					  • generalized vaccinia (more severe in immunocompromised hosts)
					  • eczema vaccinatum (atopic dermatitis, Darier disease) (Fig. 81.11B)
					  • postvaccination non-viral pustulosis
					  • progressive vaccinia (immunocompromised hosts)
					  • erythema multiforme (Fig. 81.11C), Stevens–Johnson syndrome
					  • fetal vaccinia
					  • postvaccinial CNS disease
					  • myo/pericarditis
					  • dilated cardiomyopathy (controversial)
					• Additional cutaneous findings that can develop 1–3 weeks post vaccination include urticarial and exanthematous eruptions lasting 4–15 and 7–20 days, respectively
					• Laboratory diagnosis: variola real-time PCR (–), orthopox real-time PCR (+), non-variola orthopoxvirus real-time PCR (+), viral culture; acceptable specimens as for smallpox

Mpox (previously referred to as monkeypox)	Mpox/ Orthopoxvirus – clade I (Central African; more severe disease), clade IIa (West African), clade IIb (2022 outbreak)	Monkeys (especially captive), rodents, humans	• Malaise, fever, flu-like symptoms, and oral enanthem may precede eruption (more severe with clade I) • Number of lesions varies from a few to >100 (often <10 with clade IIb) • Papules progress to vesiculopustules then crust (Fig. 81.18); various stages may be present simultaneously • Clade I: centrifugal distribution†, often involving the palms and soles; clade IIb: favors genital, perianal, and oropharyngeal inoculation sites • Lymphadenopathy common • May be accentuated in areas of eczematous dermatitis ("eczema mpoxicum"); verrucous lesions or necrotic ulcers may develop in immunocompromised patients	Supportive; tecovirimat (first-line; expanded-access protocol¶), brincidofovir, or cidofovir for severe disease/risk of severe disease or strictures; usually self-limited course; deeper lesions heal with scarring and potentially anogenital strictures; prophylaxis with vaccination (JYNNEOS™) for adults at high risk; smallpox vaccination with ACAM2000® also protective	• Endemic in West and Central Africa • Global outbreak in 2022 (>100 countries, >85 000 cases) declared by WHO as a public health emergency of international concern[45–47]; person-to-person transmission primarily in MSM • US outbreak in 2003 due to contact with infected prairie dogs exposed to an infected imported Gambian giant rat[48] • Acquired from animal or human source via skin/mucosal contact, less often via fomites or inhalation • Incubation period – ~3–17 days • Laboratory diagnosis: variola real-time PCR (–), orthopox real-time PCR (+); acceptable specimens as for smallpox • Histologic findings include enlarged keratinocytes with pale cytoplasm and epidermal necrosis (Fig. 81.19)
Cowpox	Cowpox/ Orthopoxvirus	Cattle (now a rare host), cats, rodents, humans	• Painful papule at site of contact with lesions on infected animals (usually cats) • Hands and face most common sites of involvement • Erythematous, edematous papule rapidly becomes vesicular, pustular, then hemorrhagic • Progresses to ulcer with crust and eschar • Lymphadenopathy, fever and flu-like symptoms	Supportive; heals over 4 weeks with scarring; scars often large and depressed	• Primarily in Europe and Central Asia • Less common than orf or milker's nodule • May be transmitted by cats with subclinical infections • Incubation period – 7 days • Occasionally severe disease, including generalized eruptions in patients with atopic dermatitis

Table 81.4 Selected poxvirus infections.

SELECTED POXVIRUS INFECTIONS					
Disease	**Virus/genus**	**Host**	**Clinical findings**	**Treatment**	**Comment**

Orf (ecthyma contagiosum, sore mouth disease, scabby mouth disease, contagious pustular dermatosis, infectious pustular dermatitis)	Orf/Parapoxvirus	Sheep, goats, reindeer, humans	• Papules (1 to few) on hands (Fig. 81.12A) at sites of contact with infected animals (lesions favor perioral area and udders of ewes), carcasses, or fomites (e.g. fences, barn doors)
			• Progression through several stages:
			  • maculopapular
			  • targetoid
			  • weeping nodule
			  • regenerative dry stage with black dots
			  • papillomatosis
			  • regression with a dry crust
			• May be accompanied by lymphangitis, lymphadenopathy, malaise, fever
				Supportive; topical imiquimod may stimulate early regression; usually heals without scarring	• Endemic in sheep and goats
					• At-risk occupations: shepherds, butchers, veterinary surgeons, sheepshearers
					• Histologic findings depend on stage of the lesion and include epidermal necrosis, vacuolated keratinocytes, a dense mixed dermal infiltrate, and delicate finger-like projections of the epidermis into the dermis; eosinophilic inclusion bodies (intracytoplasmic > intranuclear) (Fig. 81.12B)
					• Laboratory diagnosis: histologic examination of skin lesion ± EM; parapox real-time PCR (+), orf real-time PCR (+)
					• Erythema multiforme occasionally occurs 10 to 14 days later

Milker's nodules (bovine papular stomatitis, pseudocowpox)	Paravaccinia/ Parapoxvirus	Cattle, humans	• Papule develops at site of contact with lesions on infected animals (e.g. muzzles of calves, teats of cows) • Often single lesions; favor hands and forearms • Cutaneous lesions virtually identical to orf	Supportive	• Endemic in cattle • At-risk occupations: dairy farmers, ranchers, butchers, veterinary surgeons • Laboratory diagnosis: histologic findings ± EM (see orf); parapox real-time PCR (+), paravaccinia real-time PCR (+)
Deer-associated parapoxvirus infection	Parapoxvirus	Deer, humans	• Friable violaceous nodule at site of non-healing cut obtained while field dressing a deer carcass • Single lesion on a finger • Fever following biopsy in one patient	Supportive	• Reported in deer hunters in the Eastern US[49] • Histologic findings include epidermal hyperplasia ± necrosis, intracytoplasmic eosinophilic inclusion bodies in keratinocytes, dilated vascular spaces with swollen endothelial cells, and variable lymphohistiocytic and neutrophilic infiltrates • Parapox real-time PCR (+)
Tanapox	Tanapox/ Yatapoxvirus	Non-human primates, humans	• Isolated skin lesion, usually on the leg • Macular, papular, pustular, ulcerative, and crusted stages • Local swelling and lymphadenopathy common • Associated fever and flu-like symptoms	Supportive; heals over 6–8 weeks with scarring	• Endemic in equatorial Africa • Transmission to humans probably occurs via an arthropod vector, although direct transmission also possible[50]

*Per the CDC (emergency.cdc.gov/agent/smallpox/).
†Concentrated on the face and extremities.
‡Case definitions are in ref. 51.
¶cdc.gov/poxvirus/monkeypox/clinicians/Tecovirimat.html

Table 81.4 Selected poxvirus infections. Human infection with a novel orthopoxvirus acquired from cows in the country of Georgia has also been reported to present with painful papules on the hands. CNS, central nervous system; EM, electron microscopy; MSM, men who have sex with men.

An associated molluscum dermatitis is common (Fig. 81.13C), especially in children with atopic dermatitis. Inflammation of MC lesions can occur, often with a pustular or furuncle-like component (Fig. 81.13D); this signals the development of a host immune response. As noted above, an id reaction-like eruption of pruritic erythematous papules that favor the elbows and knees occasionally develops in conjunction with an inflammatory response to MC.

The differential diagnosis of MC may include adnexal tumors, verrucae, condylomata acuminata, basal cell carcinoma, juvenile xanthogranuloma, melanocytic nevi (especially Spitz nevi), papular granuloma annulare, and pyogenic granuloma. In immunocompromised hosts, infectious processes such as cryptococcosis or histoplasmosis can mimic MC. Inflammatory reactions to mollusca may resemble nummular dermatitis, staphylococcal furunculosis, Gianotti–Crosti syndrome, or unilateral laterothoracic exanthem (ULTE). Histologic evaluation of an MC lesion reveals large, intracytoplasmic inclusion bodies (molluscum bodies, Henderson–Patterson bodies) within epidermal keratinocytes, which increase in size as they move toward the skin surface (Fig. 81.13E). A variably dense dermal infiltrate may occasionally have pseudolymphomatous features.

MC resolves spontaneously in immunocompetent children, with the time interval between onset and clearance of the lesions ranging from several months to several years. However, treatment may be requested when there are numerous or cosmetically significant lesions. Therapeutic options include curettage, manual expression, cryotherapy, topical chemovesicants, keratolytics, and cidofovir (Table 81.6). Although imiquimod has been used anecdotally for MC, efficacy was not demonstrated in large controlled studies[57]. In-office use of cantharidin was recently FDA-approved for the treatment of MC in individuals ≥2 years of age, with complete MC clearance in ~50% of patients after 4 applications at 3-week intervals[58] (see Ch. 129). Although cantharidin has the benefit of non-traumatic application, it may require more visits than curettage. Berdazimer 10.3% gel is a nitric oxide-releasing agent shown in randomized controlled studies to result in complete MC clearance in ~30% of patients treated daily for 12 weeks[59]. Treatment of molluscum dermatitis with a topical corticosteroid may help to reduce associated pruritus and prevent autoinoculation from scratching.

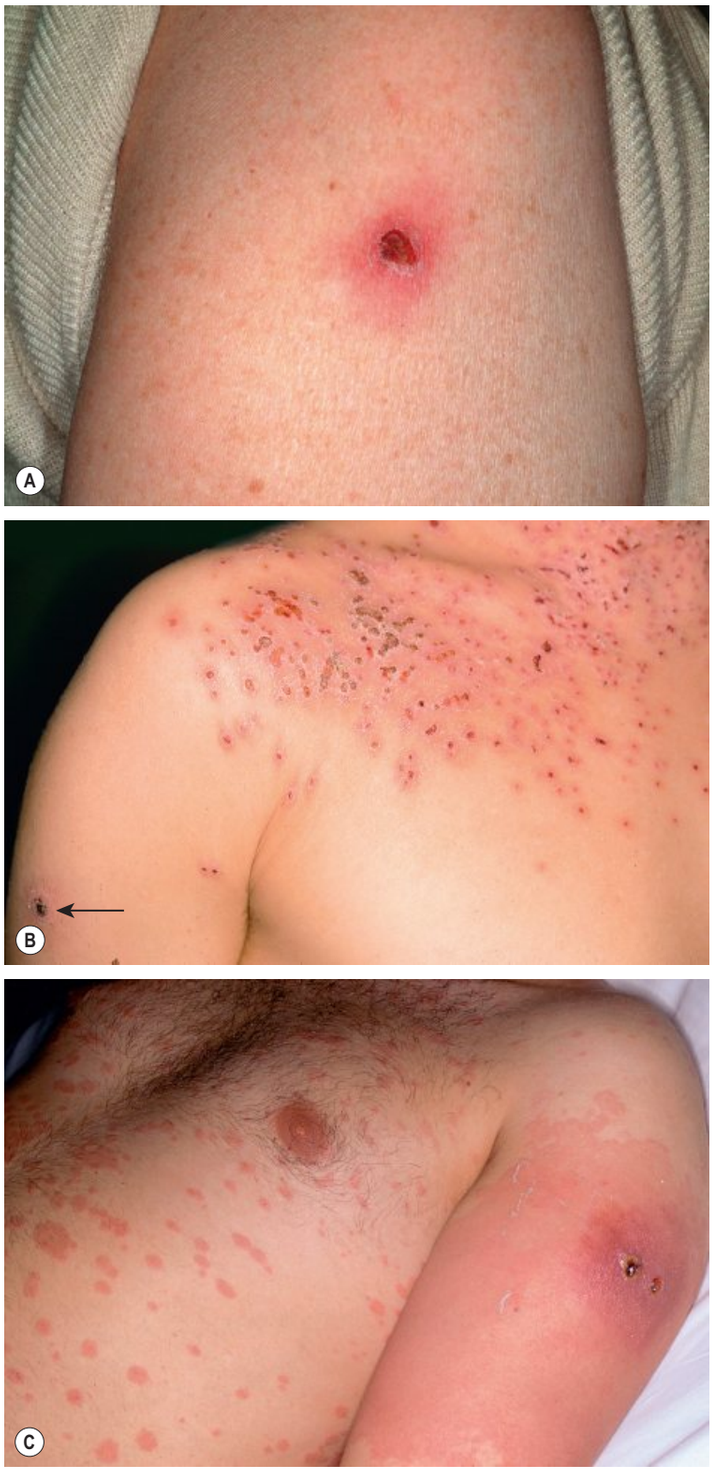


Fig. 81.11 Smallpox vaccine. A Crusted papule at the site of vaccination, 14 days following administration. **B** Eczema vaccinatum in a patient with atopic dermatitis. Spread from the vaccination site (arrow) to areas of eczema occurred due to the impaired skin barrier. **C** Erythema multiforme-like reaction associated with marked erythema and edema at the vaccination site. *B, C, Courtesy Louis A. Fragola, Jr, MD.*



Fig. 81.12 Orf. A Erythematous nodule with oozing and central ulceration on the dorsal aspect of the hand. **B** Histology showing epidermal necrosis, vacuolated keratinocytes, and intracytoplasmic inclusion bodies (inset). *A, Courtesy Luis Requena, MD; B, Courtesy Lorenzo Cerroni, MD.*

VIRAL HEMORRHAGIC FEVERS, INCLUDING DENGUE

The hemorrhagic fevers are a group of zoonotic viral infections that range in severity from a mild, self-limited febrile illness to a severe, life-threatening disease. Cutaneous manifestations of hemorrhagic fevers are nonspecific and include petechiae, purpura, and mucosal hemorrhage. Patients with serious infections suffer from shock, bleeding, and multi-organ failure, with a high mortality rate. Viral hemorrhagic fevers are most common in South America and Africa, although some agents have a worldwide distribution. Table 81.7 lists the epidemiologic characteristics of several viral hemorrhagic fevers.

Dengue, including severe disease classically referred to as *dengue hemorrhagic fever* (DHF) and *dengue shock syndrome* (DSS), is a febrile illness caused by the dengue virus, which has four serotypes, DENV1–4. These viruses are members of the Flaviviridae family, and infection is transmitted to humans by mosquitoes. In endemic areas (Fig. 81.14), the virus can be transmitted vertically from mother to fetus[60]. Epidemics may occur when the virus is introduced into a new geographic area by travelers.

Manifestations of dengue range from asymptomatic infection to potentially lethal disease[61]. After an incubation period of 3–8 days, affected individuals develop a biphasic fever, headaches, myalgias, nausea, vomiting, and retro-orbital pain. A cutaneous eruption develops in up to 50% of patients; it may be morbilliform or scarlatiniform, with areas of sparing referred to as "white islands in a sea of red". Minor hemorrhagic manifestations can occur, including petechiae, epistaxis, and gingival bleeding[62]. Severe dengue (including DHF/DSS), which is more common in children and following reinfection with a second virus serotype, is characterized by plasma leakage resulting in shock and respiratory distress as well as severe hemorrhage and organ impairment. Non-neutralizing, fucosylated IgG1 antibodies that bind the activating Fc receptor FcγRIIIA and appear to cross-react with platelet antigens were recently found to contribute to thrombocytopenia and severe disease[63].

The diagnosis of dengue can be confirmed by serologic assays, RT-PCR analysis, or detection of the viral nonstructural protein 1 (NS1) antigen. No specific therapy exists for dengue, but intensive supportive care can decrease the mortality rate to 1%[62]. CYD-TDV (Dengvaxia®) is a live attenuated vaccine that was FDA-approved in 2019 for individuals 9–16 years of age with a laboratory-confirmed previous dengue virus infection who are living in an endemic area; it should be avoided in seronegative individuals, as it can lead to more severe infection if they later contract natural dengue infection. TAK-003 (Qdenga®), a recombinant chimeric vaccine that has greater efficacy against DENV2 than other dengue virus subtypes, appears to be equally safe and effective in seropositive and seronegative individuals; it is currently approved in several countries, including the Euopean Union, Brazil, and Thailand.

COMPARISON OF VARICELLA/DISSEMINATED ZOSTER TO SMALLPOX		
	Varicella/disseminated zoster	**Smallpox**
Prodrome	None or mild fever and malaise	Fever ≥101°F (38.3°C) for 1 to 4 days prior to onset of eruption, plus prostration, headache, chills, backache, and/or gastrointestinal symptoms
Distribution of lesions	Face/scalp initially; trunk affected more than distal extremities May have an enanthem	Lesions concentrated on face and limbs; can progress to involve entire body surface Enanthem often precedes cutaneous eruption
Stage of lesions	Different stages (papules, vesicles, pustules) are seen simultaneously in any one area of the skin	Adjacent lesions are all at same stage of development (synchronous)
Type of lesions	Relatively superficial, with evolution from macules/papules to vesicles to pustules	Begin as papulovesicles and then become firm, deep-seated pustules with a tendency to confluence
Course	Lesions tend to appear in crops over a 3-day period	Lesions spread over 1–2 weeks, and crusting develops over 1 week
Scarring	Rare in uncomplicated cases	Common and marked

Table 81.5 Comparison of varicella/disseminated zoster to smallpox.

WEST NILE VIRUS INFECTION

West Nile virus (WNV), a single-stranded RNA virus in the Flaviviridae family, is an enzootic agent most commonly found in Africa, Europe, and Asia. It is transmitted among wild birds (e.g. crows, ravens, jays) by *Culex* mosquitos. Since 1999 there has been geographic expansion of the virus within the US, with human cases in all of the contiguous states and ~2700 deaths to date[64–66]. Although transmitted primarily by mosquito bites, transmission can also occur via blood transfusions, solid organ transplantation, and possibly breastfeeding[67–69].

WNV infection most commonly occurs between late spring and early fall, during periods of active mosquito feeding. Approximately 80% of infections are clinically asymptomatic. In symptomatic patients, manifestations include fever, headache, malaise, anorexia, nausea, vomiting, eye pain, lymphadenopathy, encephalitis, myalgias, and muscle weakness. Older patients have a higher risk of more severe neurologic disease.

An exanthem occurs in 25%–50% of symptomatic patients with WNV infection. It has been described as a macular, papular, psoriasiform, or erythematous eruption[67]. Both predominance on the extremities and small punctate lesions have been reported. Development of a rash may be associated with decreased risk of encephalitis and death from WNV[70]. The diagnosis is confirmed by serum or cerebrospinal fluid IgM ELISA or RT-PCR. Treatment is supportive; preventive measures include reducing the number of vector mosquitoes and avoidance of mosquito bites.

ZIKA VIRUS INFECTION

Zika virus is a member of the Flaviviridae family that was initially identified in 1947 in Uganda. It can be transmitted by *Aedes aegypti* and *A. albopictus* mosquitoes, through sexual contact, via blood transfusions, and from mother to fetus. Large Zika virus outbreaks began in 2007 in Micronesia, with subsequent transmissions in other Pacific Islands, Central and South America, Caribbean islands, Mexico, Florida, and Texas; however, since 2018 there have been no reports of Zika virus infections acquired in the US.

In 2016, Zika infection during pregnancy was linked to risk of fetal microcephaly. Approximately 20% of Zika viral infections are symptomatic, with manifestations including fever, arthralgias/arthritis, headache, and conjunctivitis. A morbilliform or scarlatiniform exanthem typically begins on the face and spreads to the trunk and extremities[71]; follicular accentuation and palmar involvement have been described. Zika-related Guillain–Barré syndrome has also been reported. Diagnosis can be confirmed by RT-PCR-based testing of serum or urine as well as serology. Vaccine development is ongoing.

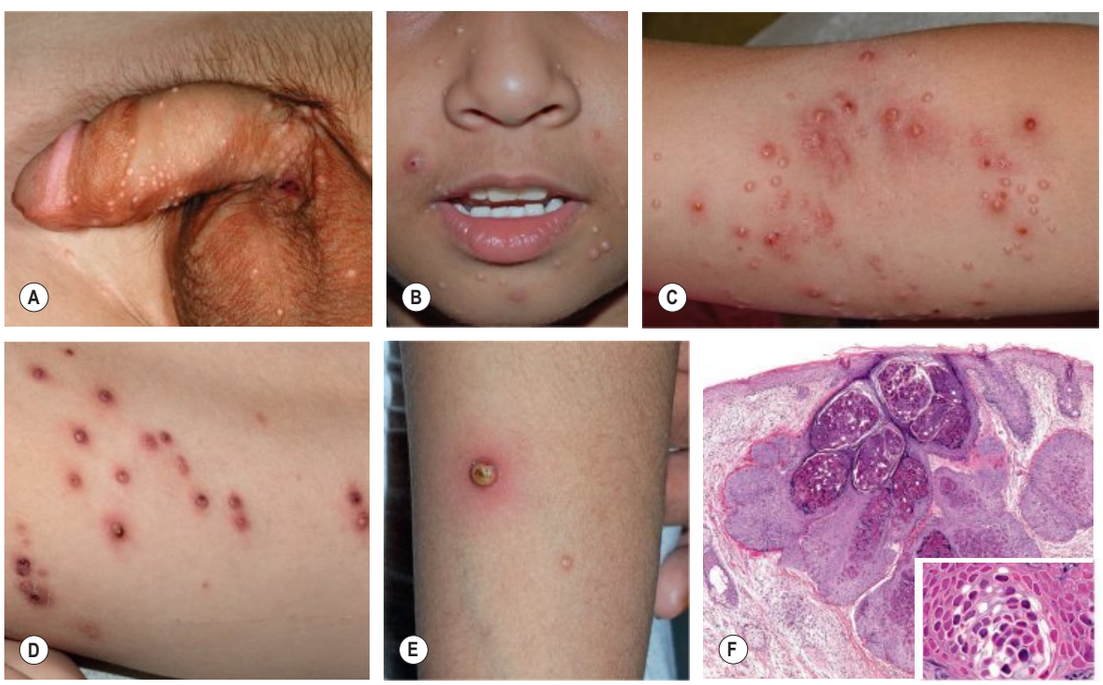


Fig. 81.13 Molluscum contagiosum. Multiple pearly, umbilicated papules in the genital area (**A**) and on the face (**B**); note the inflamed lesion on the right cheek. Inflammatory reactions are a sign of the host immune response to the virus. **C** Inflamed lesions surrounded by "molluscum dermatitis". **D, E** Pustular presentations of inflamed molluscum. Culture revealed only normal skin flora. **F** Histologic evaluation shows numerous molluscum bodies (inset). Demonstrating these bodies in a saline preparation of expressed lesional contents serves as a technique for bedside diagnosis. *B–E, Courtesy Julie V. Schaffer, MD; F, Courtesy Lorenzo Cerroni, MD.*

TREATMENT OF MOLLUSCUM CONTAGIOSUM Rx
No therapy
Eventual spontaneous involution in immunocompetent patients
Risks of spread (especially in atopic patients), associated dermatitis, and pruritus
Physical modalities
Cryotherapy (2)
Curettage (1)
Electrodesiccation (3)
Autoinoculation (1*)
Manual extraction (3)
Topical and intralesional therapy
Berdazimer (1)
Cantharidin (1)
Cidofovir (2)
Podophyllotoxin (1)
Potassium hydroxide 5%–10% solution (1)
Salicylic and lactic acids (2)
Retinoids (3)
Silver nitrate paste (2)
Trichloroacetic acid (1)
Candida antigen, intralesional (2)
Interferon-α, intralesional (3)
Laser therapy
CO_2 (3)
Pulsed dye (2)
Systemic therapy
Cidofovir (in HIV-infected patients) (3)
Cimetidine (2)
Griseofulvin (3)
Antiretroviral therapy (in HIV-infected patients) (3)
Interferon-α, subcutaneous (3)
*A well-developed lesion is pierced with an insulin syringe via a lateral entry point, followed by repeated puncturing (5–7 times).

Table 81.6 Treatment of molluscum contagiosum. Large randomized, placebo-controlled trials showed no benefit of imiquimod. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

CHIKUNGUNYA FEVER

Chikungunya fever is due to the chikungunya virus, a member of the Togaviridae family, that is transmitted primarily by *A. aegypti* and *A. albopictus* mosquitoes. Initially, infections occurred primarily in India, Indian Ocean islands, Southeast Asia, and Africa, with subsequent outbreaks in Italy, France, Central and South America, Caribbean islands, Mexico, and Florida[72]. After a typical incubation period of 2–7 days, patients present with fever, headache, and myalgias.

Acute cutaneous manifestations include morbilliform eruptions; acral or facial erythema and edema (sometimes localized to the nose or ears); and genital, intertriginous, and oral ulcers[73]. Widespread vesiculobullous eruptions are common in infants and occasionally occur in older children and adults. Subsequently, prominent hyperpigmentation often develops on the face (especially the tip of the nose ["chik sign"]) and extremities. Freckle-like macules and flagellate streaks can be seen as well as diffuse or reticulated pigmentation[73]. Severe low back pain and debilitating arthralgias are characteristic and may last for weeks to months. Complications can include meningoencephalitis, Guillain–Barré syndrome, and myocarditis. No specific treatment is available, and several candidate vaccines are under investigation. VLA1553, a single-shot live-attenuated chikungunya vaccine, was found to be safe and immunogenic in a phase 3 clinical trial[73a].

BARMAH FOREST AND ROSS RIVER VIRUS INFECTIONS

Barmah Forest and Ross River viruses are Togaviridae family members that are endemic in Australia and transmitted to humans by *Aedes* mosquitoes[68,69]. Patients present with fever, lethargy, myalgias, and arthralgias/arthritis. An exanthem affects ~90% of patients with Barmah Forest virus infection, often with initial facial erythema and edema (especially of the nose and ears), followed by a widespread macular, maculopapular, vesicular, or purpuric eruption. Either infection can be diagnosed via serology or PCR.

CUTANEOUS MANIFESTATIONS OF HEPATITIS A, B, AND C INFECTION

Infections with hepatitis A, B, and C viruses (especially the latter two) are associated with a variety of cutaneous manifestations. Infections with hepatitis A, an RNA enterovirus, occasionally lead to cutaneous findings such as panniculitis, urticaria, and a scarlet fever-like exanthem[74], whereas infections with hepatitis B and C viruses have been linked to the entities listed in Table 81.8. Viral nucleic acid testing (NAT) for hepatitis B and C represents a sensitive means of screening donated blood for infection[75], monitoring response to antiviral treatment, and detecting viral reactivation in patients receiving immunosuppressive.

POLYOMAVIRUS INFECTIONS

Synonyms: Trichodysplasia spinulosa: ■ Viral-associated trichodysplasia (of immunosuppression) ■ "Cyclosporine-induced" folliculodystrophy ■ Follicular dystrophy of immunosuppression ■ Pilomatrix dysplasia ■ Trichodysplasia of immunosuppression

Human polyomaviruses (HPyVs) were initially described in 1971, when JC and BK viruses were identified in immunosuppressed patients with progressive neurodegenerative disease. HPyVs were subsequently linked to several skin disorders, beginning in 2008 with the discovery that most *Merkel cell carcinomas* are driven by the Merkel cell polyomavirus (see Ch. 115). *Trichodysplasia spinulosa* is an increasingly recognized entity that was first reported in 1999 and found in 2010 to be caused by the trichodysplasia spinulosa-associated polyomavirus (TSPyV)[75–77]. This condition occurs primarily in solid organ transplant recipients receiving immunosuppressive medications and patients undergoing chemotherapy for a leukemia or lymphoma. *Pruritic and dyskeratotic dermatoses* have also been linked to infections with HPyV6 and 7 in immunocompromised individuals (e.g. with solid organ transplantation or HIV infection)[78]. Most recently, *HPyV9 infection* was found to underlie widespread keratotic skin lesions and fatal pulmonary disease in solid organ transplant recipients[79].

Trichodysplasia spinulosa presents with numerous erythematous to skin-colored papules with a central spiny projection on the face (especially the mid portion), ears, and less often extremities and trunk (Fig. 81.15A). Associated alopecia of the eyebrows and eyelashes, or less often other facial and body hair, as well as thickening of the skin resulting in a leonine appearance may develop. Histologic evaluation is characterized by dilated anagen follicles with abnormal maturation and eosinophilic keratinocytes containing large trichohyaline granules[80]. Large eosinophilic inclusions within affected keratinocytes show positive immunohistochemical staining for the polyomavirus middle T antigen, and electron microscopy demonstrates intranuclear icosahedral viral particles. The diagnosis can be confirmed by PCR-based viral detection in skin scrapings or a biopsy specimen. Trichodysplasia spinulosa may improve following reduction or discontinuation of immunosuppressive medications, and successful treatment with topical cidofovir, oral valganciclovir, and leflunomide has been described[81]. Trichodysplasia spinulosa-like hyperkeratosis has also been described in a patient with basal cell nevus syndrome treated with vismodegib[82].

Pruritic and dyskeratotic dermatoses (PDDs) are characterized by scaly pink to gray–brown papules, patches, and/or plaques coalescing on the trunk and extremities, with associated pruritus and/or burning. Additional reported findings have included diffuse involvement with islands of sparing, alopecia, spiny perifollicular papules, and palmar pits or spicules (Fig. 81.15C)[83]. *HPyV9 infection-associated eruptions* presented with keratotic, pink–violet to brown papules and plaques that began acrally and spread to the proximal extremities and trunk;

EPIDEMIOLOGIC CHARACTERISTICS OF SELECTED VIRAL HEMORRHAGIC FEVERS								
	Arenaviruses*		**Filoviruses**		**Bunyaviruses**			**Flaviviruses**
	Lassa virus	**Junin, Machupo, Guanarito, Sabia viruses**	**Ebola virus†**	**Marburg virus†**	**Hantavirus‡**	**Crimean-Congo fever virus†**	**Rift Valley fever virus**	**Yellow fever virus**
Geography	West Africa	South America, North America	Central and West Africa	East and Central Africa	Worldwide	Europe, Asia, Africa	Africa and Arabian peninsula	South America and Africa
Primary source of infection	Rodent (*Mastomys natalensis*)	Rodent (*Calomys* and *Zygodontomys* spp.)	Migratory fruit bats	Fruit bats	Rodents; species depends upon location	Tick-borne (Ixodid ticks, especially *Hyalomma* genus)	Mosquito	Mosquito-borne (*Aedes* and *Haemagogus* spp.)
Transmission	Nosocomial; rodent to human; person-to-person	Rodent to human	Exposure to infected bats, primates, and antelopes (bushmeat); person-to-person, including nosocomial and from corpses	Exposure to infected bats, primates; person-to-person, including nosocomial and from corpses	Rodent to human	Infected ticks or contact with blood from amplifying animal hosts (e.g. cattle, goats); person-to-person, including nosocomial	Mosquito bites; exposure to infected animals	Mosquito to human (human reservoir in outbreaks)
Risk factors	Close contact with *Mastomys* in rural West Africa; close contact with infected persons	Contact with rodents in certain agricultural areas of South America, possibly North America	Close contact with blood or secretions from infected persons or animals (see above) (Ebola & Marburg); possibly caves (Marburg)		Contact with rodent or rodent urine in dust; laboratory work with rodents	Tick bites; contact with infected livestock; contact with blood or secretions from infected people	Mosquito bites in rural Africa	Mosquito bites in rural Africa and South American rainforests
Treatment	Responds to ribavirin when treated early	Junin responds to immune plasma given early; all may respond to ribavirin	Monoclonal antibodies – Inmazeb™, Ebanga™ (Ebola)		Ribavirin for hemorrhagic fever with renal syndrome due to Old World hantaviruses, but not effective for hantavirus pulmonary syndrome	Sensitive to ribavirin *in vitro*; reports of some benefit in patients	No specific treatment; most cases mild and self-limiting	No therapy; does not respond to ribavirin
Vaccine	Vaccinia vectored glycoprotein vaccine protects primates; human vaccine under development	Attenuated vaccine to Junin virus has greatly reduced cases in Argentina; no vaccine available for others	Human vaccines are in final stages of development, shown to be safe and effective	Vaccine protective in primate studies	Vaccines have been shown to elicit neutralizing antibodies in monkeys; human killed-virus vaccines have been used locally in Asia	Killed vaccine available in Eastern Europe; no safe and effective human vaccine currently available	Live-attenuated vaccine for animals; no human vaccine currently available	Live attenuated vaccine since 1940s; one of the most effective human vaccines
Prevention	Avoid rodents	Avoid rodents	Avoid contact with infected animals or bodily fluids of infected humans		Avoid rodents	Avoid ticks and infected animals	Prevent mosquito bites	Prevent mosquito bites

*Arenaviruses have been isolated from wood rats in the southwestern USA – their capacity to cause human disease is uncertain.
†Ecchymoses most prominent in these infections.
‡In the US, hantavirus can cause an illness marked by respiratory failure and cardiovascular collapse, but thrombocytopenia is not as prominent a feature as in Old World hantavirus infections.

Table 81.7 Epidemiologic characteristics of selected viral hemorrhagic fevers. See text for discussion of dengue. *Adapted with permission from Cohen J, Powderly WG. Infectious Diseases, 2nd edn. St Louis: Mosby, 2004.*

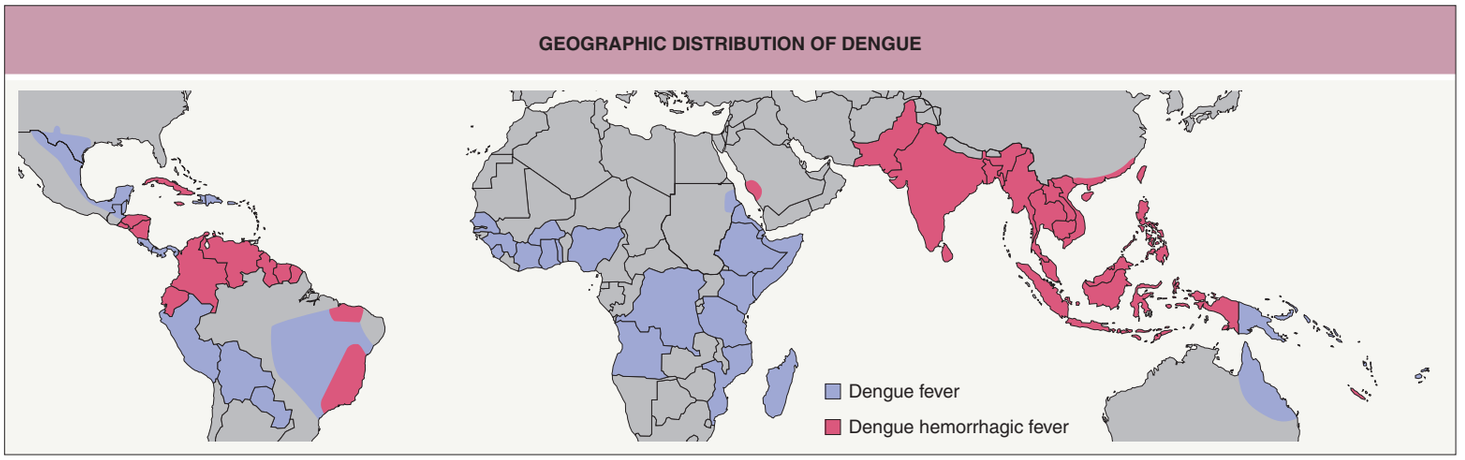


Fig. 81.14 Geographic distribution of dengue. Climate change has been postulated as a factor in expansion of the geographic distribution of dengue in the Americas. *Reprinted from Cohen J, Powderly WG. Infectious Diseases, 2nd edn. St Louis: Mosby, 2004.*

CUTANEOUS MANIFESTATIONS OF HEPATITIS B AND/OR C INFECTION	
Small vessel vasculitis (B, C)	Necrolytic acral erythema (C)
Cryoglobulinemic vasculitis (C>B)	Porphyria cutanea tarda (B, C)
Urticarial vasculitis (B, C)	Pruritus (B, C)
Polyarteritis nodosa (B [classic]>C)	Lichen planus – particularly erosive oral disease (C)
Livedo reticularis (C)	Sarcoidosis (with interferon and/or ribavirin therapy*; C>B)
Serum sickness-like reaction (B, C)	Erythema multiforme (B, C)
Urticaria (B, C)	Erythema nodosum (B>C)
Gianotti–Crosti syndrome (B>C)	

*Employed less nowadays.

Table 81.8 Cutaneous manifestations of hepatitis B and/or C infection.

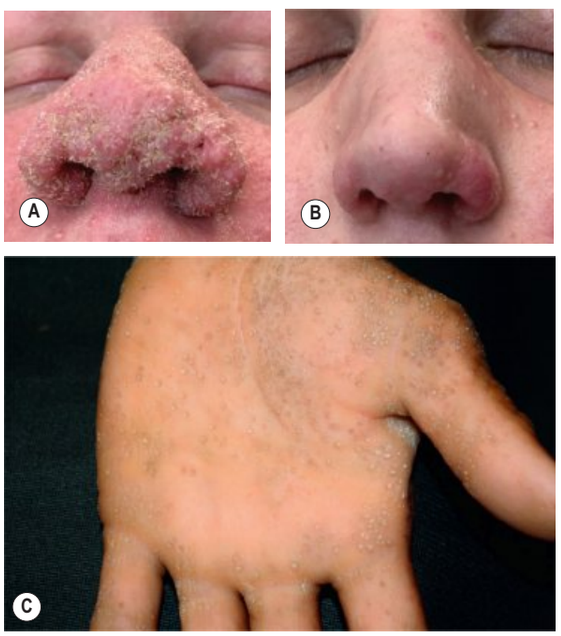


Fig. 81.15 Cutaneous polyomavirus infections. A Trichodysplasia spinulosa presenting as coalescing pink folliculocentric papules with central spiny projections on the nose. **B** Same patient, post-treatment with topical cidofovir. **C** Human polyomavirus 6 (HPyV6) associated spicules on the palm of a renal transplant recipient. *A, B, Courtesy Stephen K. Tyring, MD, PhD; C, Courtesy Jeffrey Callen, MD.*

keratotic spines and lesions resembling keratoacanthomas were noted in one patient[79]. Histopathologically, both of these disorders are characterized by a "peacock plumage" pattern of dyskeratotic cells and irregular columns of parakeratosis[78,79]. Successful treatment of PDDs with acitretin ± topical cidofovir has been described[81,83].

RABIES

While rabies is not accompanied by a cutaneous eruption, dermatologists may be asked to perform a biopsy of nuchal skin that can be assayed for rabies virus antigen or (via PCR) rabies virus RNA.

CUTANEOUS MANIFESTATIONS OF SARS-CoV-2 INFECTION

Since initially being reported in Wuhan, China in December 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic has caused >6.5 million deaths worldwide. While respiratory failure and hypercoagulability are associated with the highest morbidity and mortality, cutaneous findings occur in up to 20% of individuals with SARS-CoV-2 infection, ranging from morbilliform eruptions to retiform purpura[84–86] (Table 81.9). Although SARS-CoV-2 infection in pediatric patients usually has a milder course compared to adults, an exaggerated immune response can result in multisystem inflammatory syndrome in children (MIS-C), which presents with systemic and mucocutaneous manifestations similar to those of Kawasaki disease[87–89] (Table 81.10). In addition, a wide variety of local and widespread cutaneous reactions to SARS-CoV-2 vaccines have been described[85] (see Table 81.9).

KAWASAKI DISEASE

Synonym: ▪ Mucocutaneous lymph node syndrome

Key features

- Fever, conjunctival injection, oral mucosal changes, acral swelling, and cervical lymphadenopathy
- Polymorphous exanthem, often with early perineal involvement
- Represents the most common cause of acquired heart disease in children in the US

Introduction and History

Kawasaki disease (KD) is an acute febrile multisystem disease that primarily affects children ≤5 years of age. Initially described by Kawasaki in Japanese children[90], KD has subsequently been reported worldwide, and in the US it represents the leading cause of acquired heart disease in the pediatric population. Coronary artery aneurysms or ectasias develop in 15%–25% of untreated KD patients, resulting in substantial morbidity and mortality. The clinical manifestations of KD can mimic a variety of other diseases, in particular viral exanthems, and the need to promptly treat KD in order to prevent potentially life-threatening complications makes differentiation among these entities essential.

CUTANEOUS MANIFESTATIONS OF SARS-CoV-2 INFECTION AND VACCINATION	
Cutaneous finding	**Comments**
Manifestations associated with infection	
Morbilliform eruption (Papulo)vesicular eruption Urticaria/urticarial eruption	• Favor the trunk, often pruritic • Typically concurrent with or following other symptoms, often in adults with moderate or (for morbilliform and urticarial) severe disease
Livedo reticularis/racemosa, retiform purpura	• Favor buttocks and extremities • Usually following other symptoms in older adults with severe disease requiring intensive care, often with associated ARDS and other thromboembolic manifestations
Multisystem inflammatory syndrome in children (MIS-C)	• See Table 81.10
Pernio	• Following asymptomatic or mild disease in children and adolescents; likely associated with lifestyle changes during the early pandemic
Additional reported findings include: dengue-like petechiae, erythema multiforme-like and papulosquamous eruptions (e.g. pityriasis rosea-like, psoriasiform), Gianotti–Crosti syndrome, ULTE, Sweet syndrome, erythema nodosum	
Manifestations associated with vaccination	
Injection site reactions	• Swelling, erythema, and pain develop within 3 days of vaccine administration
Delayed large local reactions ("COVID arm")	• Induration and erythema develop >7 days after administration of an mRNA vaccine
Vaccine-related eruption of papules and plaques (V-REPP)	• Range from papulovesicular to pityriasis rosea-like clinically, with variable degrees of spongiosis and interface dermatitis histopathologically
Urticaria Morbilliform eruption Autoimmune bullous disease (bullous pemphigoid > pemphigus vulgaris > others) Erythema multiforme SJS/TEN, AGEP, DRESS (rare) Gianotti–Crosti syndrome, ULTE Small-vessel vasculitis Pernio, erythromelalgia Sweet syndrome, pyoderma gangrenosum	• Immediate hypersensitivity, which may include urticaria, is rare and develops within 4 hours of vaccine administration • Urticaria and morbilliform eruptions typically develop several days after vaccine administration
Flares of inflammatory skin disease, e.g. psoriasis, atopic dermatitis, dermatomyositis, SCLE, rosacea, vitiligo, alopecia areata	• Pre-existing > new onset
Reactions to hyaluronic acid dermal fillers Radiation recall dermatitis Herpes zoster and herpes simplex virus reactivation	• Filler reactions may be related to interaction of SARS-CoV-2 spike proteins with the ACE2 receptor, and treatment with ACE inhibitors has been reported

Table 81.9 Cutaneous manifestations of SARS-CoV-2 infection and vaccination. Telogen effluvium also commonly occurs following SARS-CoV-2 infection and less often vaccination. ACE, angiotensin-converting enzyme; AGEP, acute generalized exanthematous pustulosis; ARDS, acute respiratory distress syndrome; DRESS, drug reaction with eosinophil and systemic symptoms; SCLE, subacute cutaneous lupus erythematosus; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; ULTE, unilateral laterothoracic exanthem.

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C): 2023 CASE DEFINITION AND COMPARISON WITH KAWASAKI DISEASE		
2023 CDC case definition of MIS-C		

An individual <21 years of age, in the absence of a more likely alternative diagnosis, meeting each of the following criteria:
• Subjective or documented fever (T ≥38.0°C)
• Clinical severity requiring hospitalization or resulting in death
• C-reactive protein (CRP) ≥3.0 mg/dl
• New onset manifestations in ≥2 of the following categories:
  • *Cardiac involvement:* coronary artery dilatation/aneurysm, left ventricular ejection fraction <55%, or troponin elevation above normal
  • *Shock*
  • *Mucocutaneous involvement:* exanthem, oral mucosal inflammation*, conjunctivitis/conjunctival injection, or extremity findings (erythema, edema)
  • *Gastrointestinal involvement:* abdominal pain, vomiting or diarrhea
  • *Hematologic involvement:* platelet count <150 000/mcl, absolute lymphocyte count <1000/mcl
• Detection of SARS-CoV-2 nucleic acid/antigen during or up to 60 days prior to hospitalization, or in a postmortem specimen (*for confirmed case*); **OR** detection of SARS-CoV-2 antibodies associated with current illness (*for confirmed case*); **OR** close contact with a confirmed/probable COVID-19 case in the 60 days prior to hospitalization (*for probable case*)		

Comparison between MIS-C and Kawasaki disease		
Typical demographics		
Age	6 months to 5 years	6 to 11 years
Sex	Male:female ~1.5:1	Male:female ~1:1
Racial/ethnic predilection	East Asian	Black, Hispanic
Pathogenesis		
Trigger	Unknown; possible preceding viral or bacterial infection	Onset ~3–6 weeks after SARS-CoV-2 infection
Immunologic similarities	Enhanced IL-1β+ neutrophils and immature neutrophils	
Immunologic differences	T cell activation by conventional antigen High levels of IL-17 Infrequent MAS-like cytokine profile Lymphopenia rare	SARS-CoV-2 spike protein acts as superantigen High levels of IL-15, IFN-γ ~50% with MAS-like cytokine profile Lymphopenia common
Clinical features		
Similarities	Fever, exanthem (see Kawasaki disease text), cervical lymphadenopathy, extremity changes, neurological symptoms	
Differences	More frequent conjunctival injection and oral mucosal changes*	More frequent GI symptoms, myocarditis, coagulopathy, and shock
Management		
Usual	IVIg, systemic corticosteroids, aspirin	
Less common	Infliximab, cyclosporine, anakinra	Anakinra, tocilizumab, cyclosporine
*Mucosal erythema/swelling, drying/fissuring of the lips, or strawberry tongue.		

Table 81.10 Multisystem inflammatory syndrome in children (MIS-C): 2023 case definition and comparison with Kawasaki disease. CDC, Centers for Disease Control and Prevention; IL, interleukin; IFN, interferon; MAS, macrophage activation syndrome. *Adapted from references 88 & 89.*

Epidemiology

The peak incidence of KD is in children ≤2 years of age, and 85% of patients with KD are ≤5 years of age; however, adults with KD have also been reported. The condition is 1.5 times more common in boys than in girls[90]. A peak incidence in late winter to early spring has been observed in North America. Epidemics have occurred in both Japan and the US and are characterized by a wave-like spread over a 2- to 4-year

period[91]. KD is more common in children of Asian descent. Male sex and an age of <1 year or >6 years appear to be risk factors for the development of cardiovascular sequelae, which may be related to delayed diagnosis in the latter group[92].

Pathogenesis

The etiology of KD remains unknown, but several observations suggest an infectious cause, including the clinical features, seasonal variation in incidence, community outbreaks, rarity in infants under 6 months of age with potentially protective maternal antibodies, and infrequent recurrences[90]. However, conventional microbial cultures and serologic studies have failed to identify a causative agent. A pathogenic role for a bacterial toxin that acts as a superantigen has been hypothesized; although this remains unproven, it is supported by the increased prevalence of superantigen-encoded genes in the stool of KD patients compared to other febrile or healthy children[93].

In fatal cases of KD, IgA-producing plasma cells have been found in the coronary arteries, pancreas, kidney, and upper respiratory tract; the latter finding is similar to that seen in children with fatal respiratory viral infections[94]. Oligoclonal KD antibodies synthesized *in vitro* have been shown to bind to cytoplasmic antigen in the proximal bronchial epithelium, coronary arteries, and macrophages of KD patients. Furthermore, electron microscopic studies have provided evidence of virus-like particles within intracellular inclusion bodies in the ciliated bronchial epithelium of patients with KD[95]. These findings are suggestive of a respiratory infectious agent with tropism for vascular tissue.

KD is characterized by marked activation of the immune system, with increased numbers of activated lymphocytes (both T and B) and mononuclear cells as well as increased levels of proinflammatory cytokines. A functional polymorphism in the inositol 1,4,5-trisphosphate 3-kinase C gene (*ITPKC*) has been shown to be significantly associated with KD susceptibility and an increased risk of coronary artery lesions in children from the US and Japan. ITPKC acts as a negative regulator of T cell activation through the nuclear factor of activated T cells (NFAT) signaling pathway; the polymorphism, which reduces the efficiency of ITPKC splicing, may contribute to immune hyperreactivity in Kawasaki disease[96].

Clinical Features and Differential Diagnosis

The diagnostic criteria for KD include fever lasting at least 5 days plus the presence of four of the five following criteria:

- bilateral non-purulent conjunctival injection
- oropharyngeal changes including diffuse hyperemia, strawberry tongue, and lip fissures
- cervical lymphadenopathy (usually unilateral)
- peripheral extremity changes including erythema, edema, and eventual desquamation of the hands and feet
- a polymorphous exanthem.

The diagnosis of KD should be strongly considered in any child presenting with prolonged, unexplained fever in association with skin findings. The fever in KD is usually high-spiking (>39°C; 102°F), and it may not respond to antipyretics[90].

A cutaneous eruption is seen in >80% of patients with KD. It is usually composed of macular and papular erythematous lesions, often in a morbilliform pattern, but may also be erythema multiforme-like, urticarial, scarlatiniform, or even pustular (Fig. 81.16A,E). Petechiae and crusting are unusual findings and vesiculobullous lesions are rarely if ever seen. In some patients, ulceration at the site of a bacillus Calmette–Guérin (BCG) vaccination has been observed during the disease course. A characteristic early cutaneous finding is erythema of the perineum, which often desquamates within 48 hours (Fig. 81.16A–C). Edema and brawny induration of the hands and feet are also common early in the disease course (Fig. 81.16D), with eventual desquamation that is prominent in the periungual regions. Gangrene of the peripheral extremities occasionally occurs. Subacute cutaneous manifestations of KD can include a psoriasiform eruption and transverse orange–brown (pseudo)chromonychia thought to result from nail bed splinter hemorrhages[97,98].

The conjunctival injection of KD is typically bulbar with sparing of the limbus (an avascular zone around the iris); it is not associated with increased tearing or an exudate. Keratitis and photophobia are uncommon and should suggest an alternative diagnosis. Oropharyngeal changes consist of dry, fissured lips, a "strawberry tongue" (Fig. 81.17), and in some patients diffuse hyperemia of the oral mucous membranes.

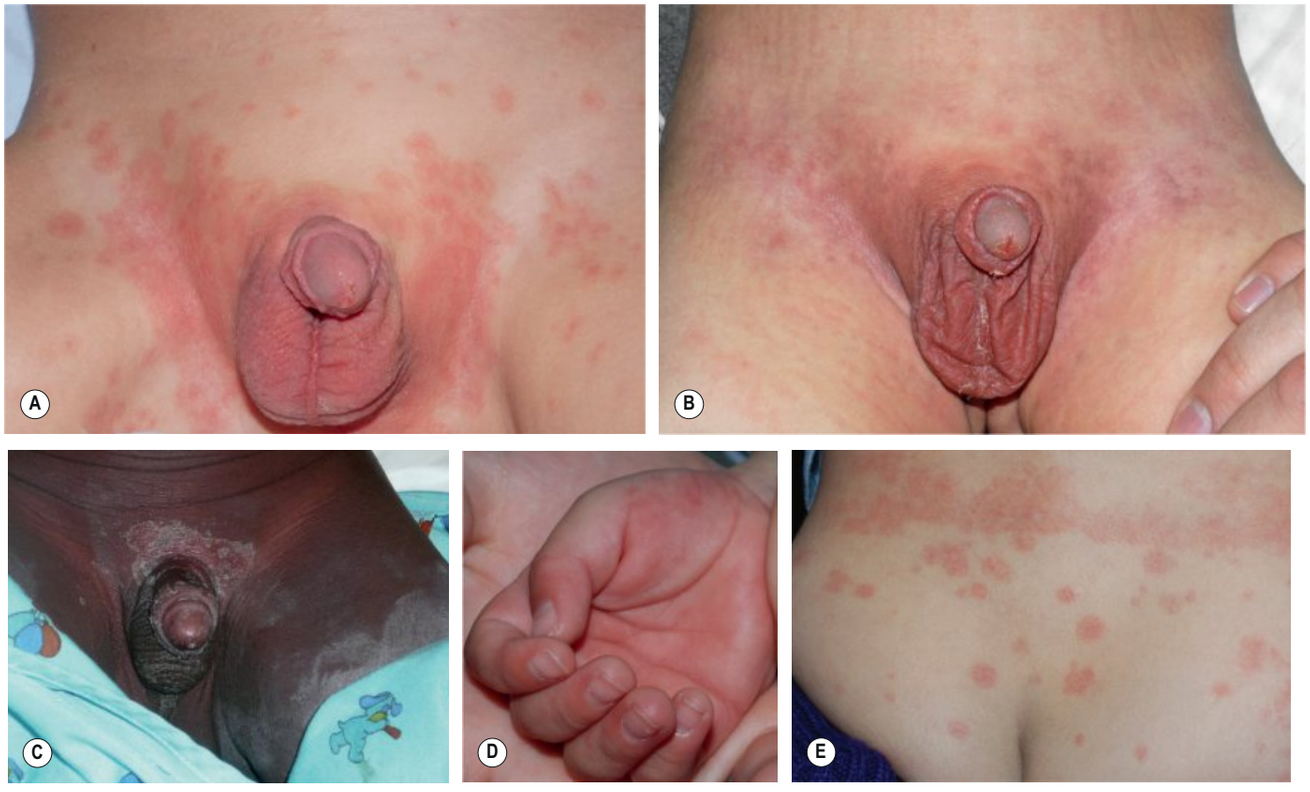


Fig. 81.16 Kawasaki disease. Erythema multiforme-like lesions becoming confluent in the perineal region on the second day of fever (**A**), followed by desquamation 2 days later (**B**). **C** Erythema (less evident due to the patient's darkly pigmented skin) and desquamation in the genital area. Involvement of the skin in this location is a characteristic early finding in Kawasaki disease. **D** Erythema and edema of the palm early in the disease course. **E** Pink papules coalescing along the waistline. *A, B, D, E, Courtesy Julie V. Schaffer, MD.*

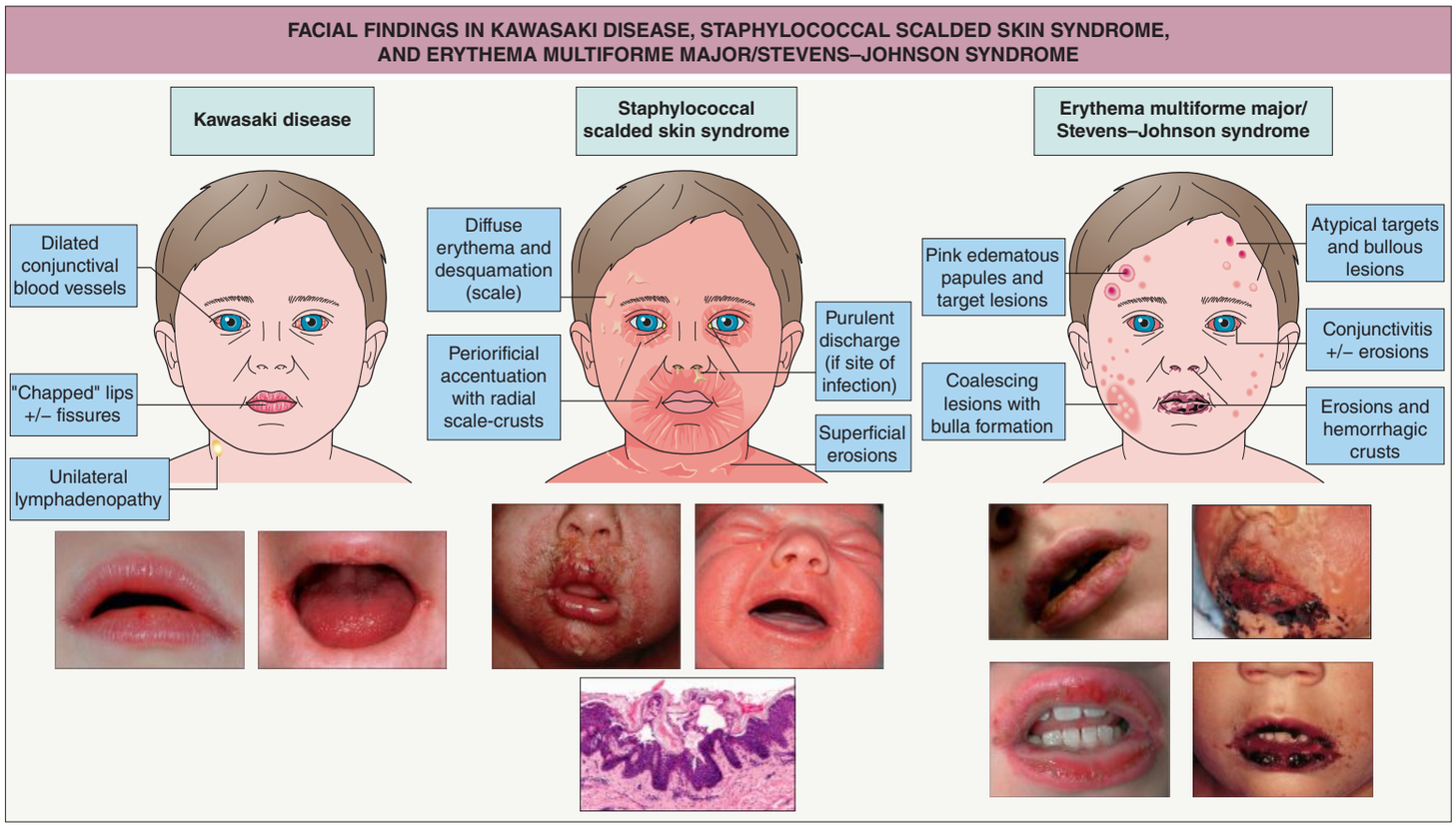


Fig. 81.17 Facial findings in Kawasaki disease, staphylococcal scalded skin syndrome, and erythema multiforme major/Stevens–Johnson syndrome. Hemorrhagic crusting and erosions of the vermilion portion of the lips can also be seen in primary gingivostomatitis due to herpes simplex virus, pemphigus vulgaris, and paraneoplastic pemphigus. Histologic examination of the flaccid sterile bullae of staphylococcal scalded skin syndrome shows cleavage at or below the stratum granulosum (see inset).

Cardiac involvement can include myocarditis, pericardial effusions, congestive heart failure, and coronary aneurysms; the latter represent the source of greatest morbidity in KD. Valvular disease, usually mitral or aortic, may also occur. Tachycardia, murmurs, gallops or distant heart sounds may be noted on cardiac examination. Other possible sites of involvement include the CNS (extreme irritability, aseptic meningitis, cranial nerve palsies, sensorineural hearing loss), gastrointestinal tract (abdominal pain, diarrhea, hepatic dysfunction, obstructive jaundice, gallbladder hydrops), musculoskeletal system (arthralgias, arthritis) and the genitourinary tract (urethritis, meatitis, sterile pyuria).

"Incomplete" ("atypical") KD may be diagnosed in patients with prolonged fever plus coronary artery disease detected by echocardiography or coronary angiography, but fewer than four additional criteria (see above)[91,99]. This presentation tends to be more common in infants, and the diagnosis may be difficult to establish. An algorithm for evaluation of suspected incomplete KD has been proposed and was updated in 2017[99,100]. For children with fever of unknown etiology for ≥5 days who meet 2–3 KD clinical criteria and have an elevated ESR (≥40 mm/hour) and/or CRP level (≥3.0 mg/dl), echocardiography should be performed and treatment initiated if there are signs of cardiac involvement. Both echocardiography and (regardless of the findings) treatment are recommended for those individuals with persistent fever, 2–3 KD clinical criteria, and elevated acute phase reactants who meet ≥3 supplemental laboratory criteria. The latter include hypoalbuminemia, anemia, elevated alanine aminotransferase, white blood cell count ≥15 000/mm^3 (often with neutrophilia), thrombocytosis after 7 days of illness, and sterile pyuria; thrombocytopenia is occasionally observed, although not included as a criterion. Because infants <6 months of age meet KD diagnostic criteria less often and have a greater risk of coronary artery disease, echocardiography is recommended for all patients in this age group with fever of unknown etiology for ≥7 days and an elevated ESR and/or CRP level[101].

Electrocardiographic findings associated with cardiac involvement in KD include decreased R-wave voltage, ST-segment depression, and T-wave flattening or inversion. Higher serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are associated with increased risk of coronary artery disease and IVIg resistance[102], and NT-proBNP may also have utility as a diagnostic marker in young infants[103]. Macrophage activation syndrome is a rare complication of recalcitrant KD that presents with hepatosplenomegaly, cytopenias, hypofibrinogenemia, and marked hyperferritinemia[104] (see Table 91.1).

Although ~25%–50% of patients diagnosed with multisystem inflammatory syndrome in children (MIS-C) also meet criteria for KD, the two entities have distinct epidemiological, immunological, and clinical features[87–89] (see Table 81.10). The differential diagnosis of KD also includes viral exanthems (e.g. adenoviral, enteroviral, EBV, measles), scarlet fever, toxic shock syndrome, staphylococcal scalded skin syndrome, erythema multiforme, drug eruptions, serum sickness-like reaction, recurrent toxin-mediated perineal erythema, systemic juvenile idiopathic arthritis, annular erythema of infancy, infantile polyarteritis nodosa (cutaneous arteritis), and periodic fever syndromes. Fig. 81.17 shows the facial findings that differentiate KD from staphylococcal scalded skin syndrome and erythema multiforme major.

Pathology

Histologic findings are nonspecific and include dermal edema and a perivascular mononuclear infiltrate[91].

Treatment

During its acute phase, the treatment for KD is aimed at decreasing inflammation, and the current first-line therapy is IVIg administered in a single infusion of 2 g/kg over 8–12 hours. This regimen was demonstrated to be more efficacious in preventing coronary aneurysms than the prior recommendation of multiple daily infusions[105]. However, the mechanism of action of IVIg in the treatment of KD is unknown. With the utilization of IVIg, the incidence of coronary aneurysms decreases from 25% to ≤5%–10%, and mortality from 2% to 0.3%. Aspirin is also recommended during the acute phase, with initial administration of 30–100 mg/kg daily (maximum 4 g/day) divided into four doses for 14

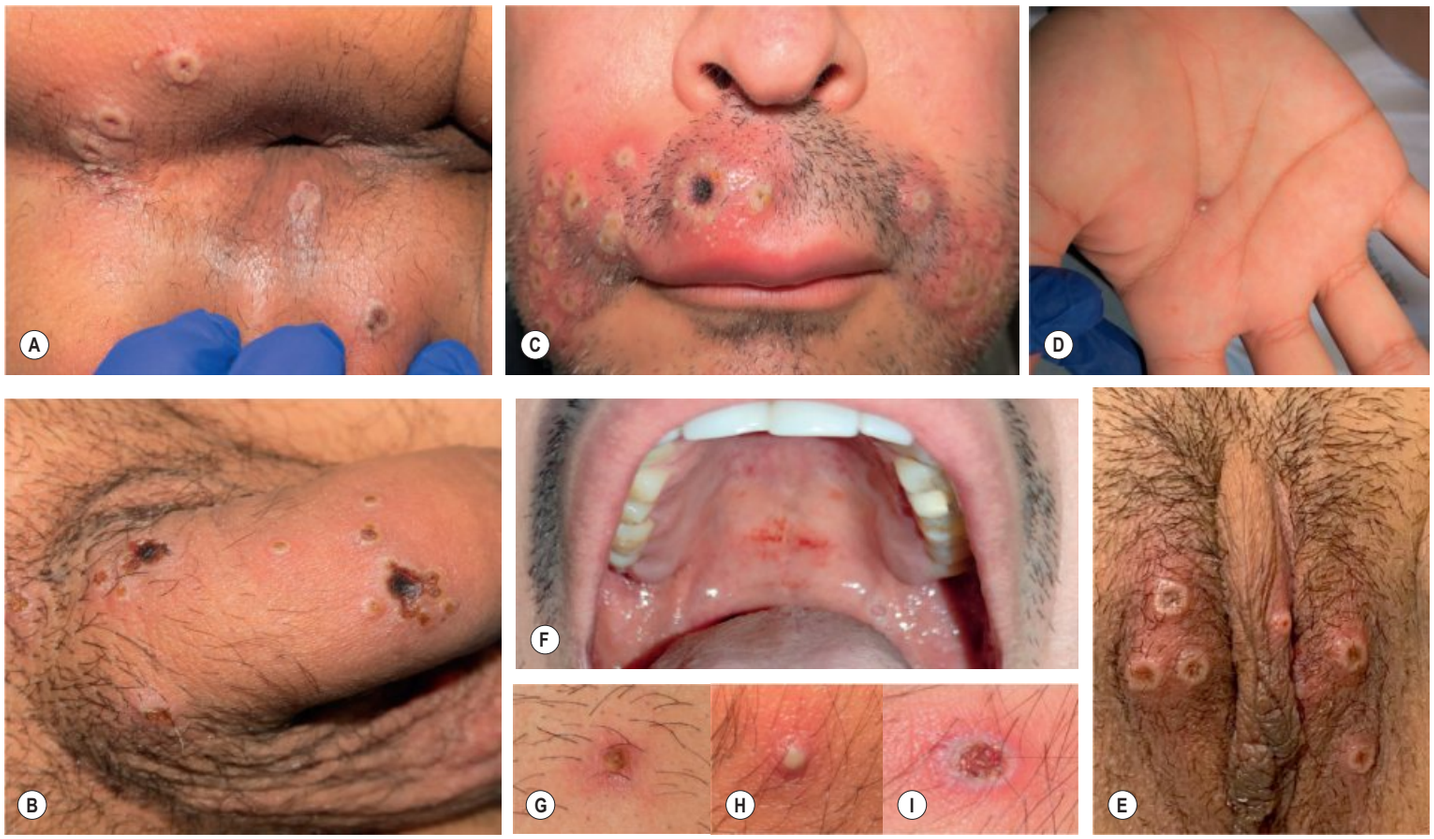


Fig. 81.18 Clinical spectrum of mpox. A-E Umbilicated vesicles, some of which have become necrotic with central hemorrhagic crusts, clustered in the oral and anogenital regions; lesions can also be randomly scattered. A scalloped border is occasionally seen as in herpes simplex viral infection (**B**). **F** Intraoral erosions. **G-I** Primary lesions vary from edematous erythematous papules to pustules to vesicles with a central hemorrhagic crust. *Courtesy, Luis Requena, MD.*

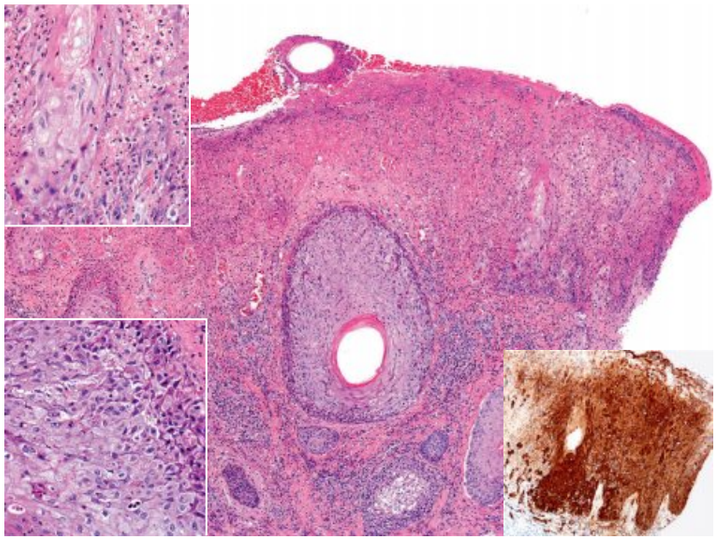


Fig. 81.19 Histopathologic findings in mpox. In addition to epidermal necrosis, hemorrhage, and erosion, there is a brisk lymphohistiocytic infiltrate in the dermis admixed with neutrophils. Note the viral changes (enlarged cells with pale cytoplasm and scattered apoptosis) in the keratinocytes of the epidermis (left upper inset) and hair follicle (left lower inset). Immunohistochemical staining for orthopox antigens can assist in diagnosis (right lower inset). *Courtesy, Luis Requena, MD.*

days or until afebrile for 48–72 hours, followed by a maintenance dosage of 3–5 mg/kg daily, usually for 6 to 8 weeks[99].

Approximately 10%–20% of children with KD have persistent or recrudescent fevers after receiving a single dose of IVIg, and these individuals have a greater risk of coronary artery disease. A second dose of IVIg may be given to patients who fail to become afebrile within 24–48 hours after completion of the first dose. Management options for high-risk or refractory KD include corticosteroids and infliximab administered along with or following failure of IVIg therapy, respectively. One large randomized, double-blind trial found that initial treatment with pulsed corticosteroids plus conventional therapy (IVIg and aspirin) showed no benefit over conventional therapy alone in terms of hospital days, days of fever, rates of retreatment with IVIg, or adverse events[106]. However, another randomized controlled study found that the addition of pulsed corticosteroids to initial IVIg therapy in patients at high risk of having refractory KD was associated with fewer days of fever and a lower likelihood of coronary artery dilation[107]. Randomized controlled studies have shown that infliximab is well tolerated and equally or more effective than a second dose of IVIg in pediatric patients with IVIg-resistant KD[108–110], although it did not decrease the likelihood of resistant disease when given as initial therapy together with IVIg and aspirin[111].

Long-term cardiac follow-up of KD patients is recommended, as adults with a history of KD may have vascular endothelial dysfunction and an increased risk for early-onset atherosclerosis.

Additional figures available in our eBook (see inside front cover for access code).

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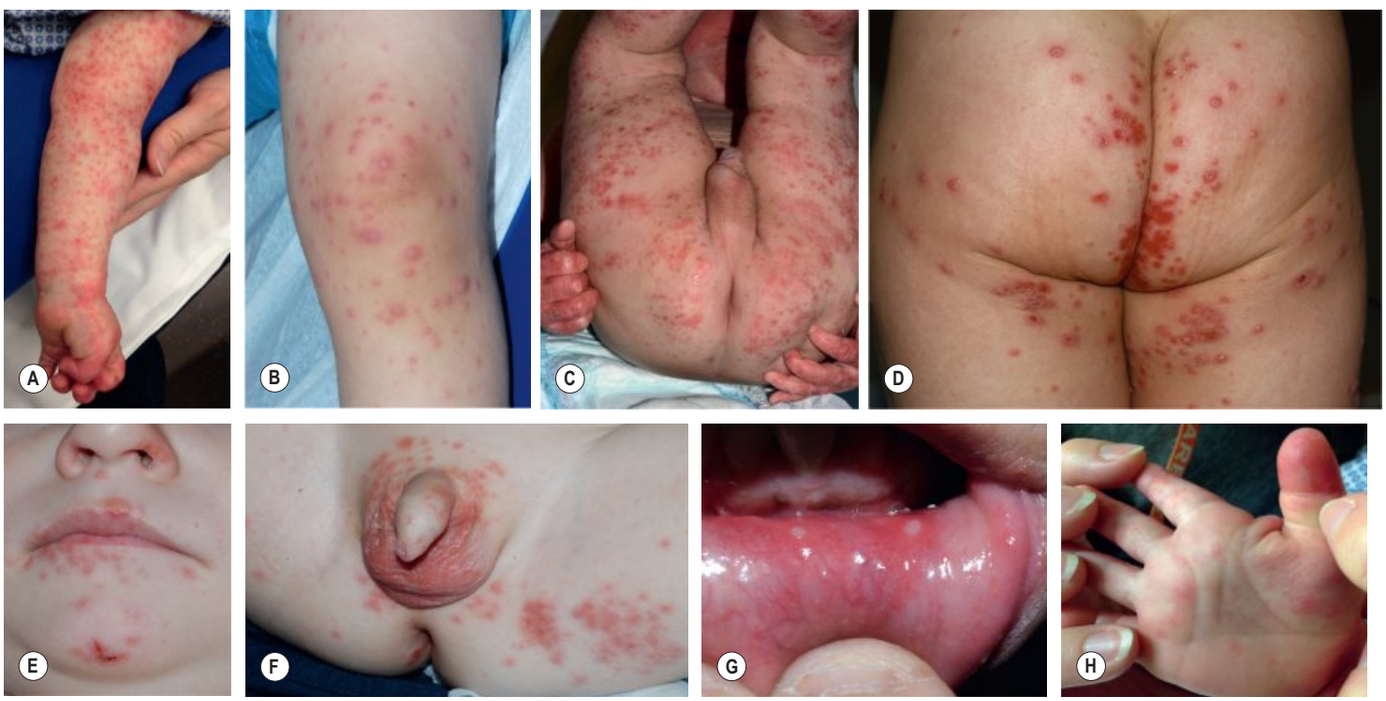
eFig. 81.1 Hand-foot-and-mouth disease. Vesicles with an erythematous base on the finger. *Courtesy Julie V. Schaffer, MD.*



eFig. 81.2 Palmar involvement in hand-foot-and-mouth disease. Multiple tiny vesicles on an erythematous base on the fingertips. *Courtesy Jeffrey P. Callen, MD.*



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eFig. 81.5 Widespread non-blanching enteroviral exanthem. *Courtesy Julie V. Schaffer, MD.*



eFig. 81.6 Erythema infectiosum. Lacy, reticulated erythematous eruptions on the upper arm during the second stage of the exanthem. *Courtesy Julie V. Schaffer, MD.*



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eFig. 81.13 Widespread mpox infection in a patient with atopic dermatitis. The eruption spread rapidly into areas of pre-existing dermatitis ("eczema mpoxicum"). *Courtesy Catherine Baker, MD.*



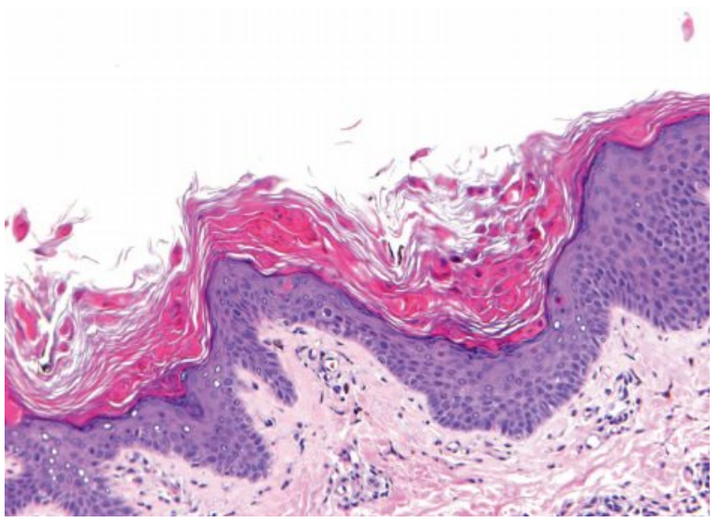
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eFig. 81.15 Delayed local reaction ("COVID arm") due to Moderna® SARS-Cov-2 mRNA vaccine. *Courtesy Jean L. Bolognia, MD.*



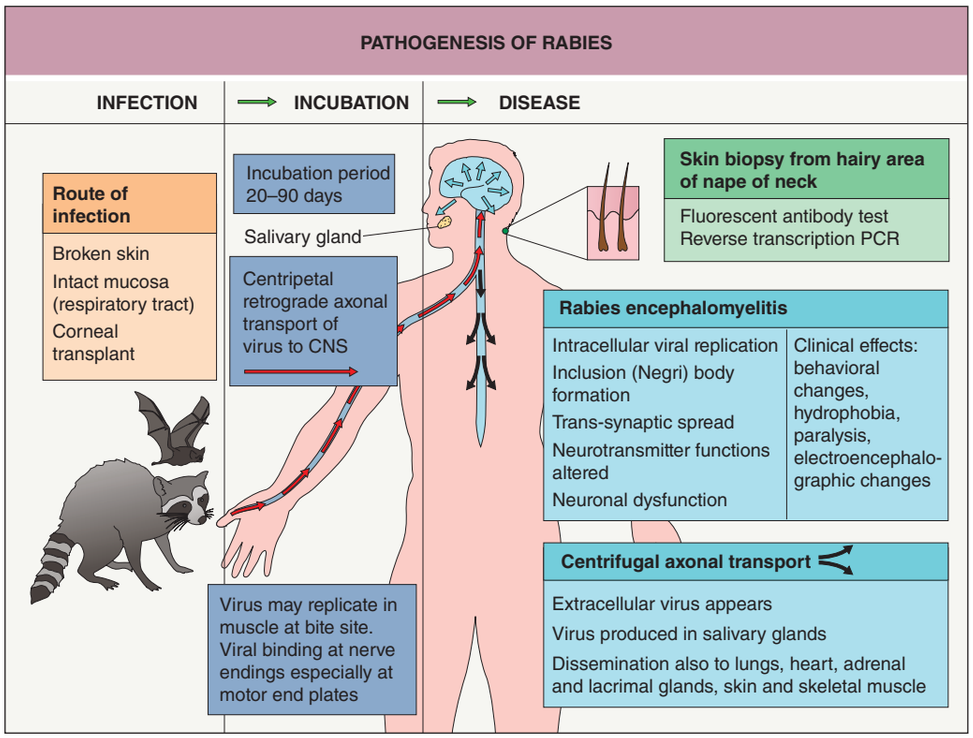
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eFig. 81.17 Human polyomavirus 7 (HPyV7)-associated pruritic dermatosis in a heart transplant recipient – histopathologic features. Multiple inclusions are seen within the thickened stratum corneum. *Courtesy Boni Elewski, MD.*



eFig. 81.18 Human polyomavirus 7 (HPyV7)-associated pruritic dermatosis in a renal transplant recipient. Widespread pink-tan patches were associated with slight textural change. *Courtesy, Edward Cowen, MD.*



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Sexually Transmitted Infections 82

Georg Stary and Angelika Stary

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INTRODUCTION

The term "venereal diseases" was historically used to refer to infections that are sexually transmitted, i.e. syphilis, gonorrhea, chancroid, lymphogranuloma venereum, and granuloma inguinale. These disorders are now referred to as "sexually transmitted diseases" (STDs) or "sexually transmitted infections" (STIs), terms that directly reflect recognition that they are caused predominantly by sexual contact with an infected person. For infections caused by pathogens for which non-sexual routes of transmission predominate, e.g. yeasts or cytomegalovirus, the term "sexually transmissible infections" is used. Table 82.1 lists the names of commonly encountered sexually transmitted or transmissible pathogens.

SEXUALLY TRANSMITTED AND TRANSMISSIBLE PATHOGENS	
Bacteria	*Neisseria gonorrhoeae* *Treponema pallidum* *Haemophilus ducreyi* *Chlamydia trachomatis* *Mycoplasma hominis, M. genitalium* *Ureaplasma urealyticum* *Gardnerella vaginalis* *Atopobium vaginae* *Mobiluncus curtisii, M. mulieris* *Klebsiella (Calymmatobacterium) granulomatis* *Shigella* spp. *Campylobacter* spp. *Helicobacter cinaedi, H. fennelliae*
Viruses	Human immunodeficiency virus, types 1 and 2 Herpes simplex virus, types 2 > 1 Human papillomavirus (several types) Hepatitis viruses, B > C and (via fecal–oral contact) A Cytomegalovirus Molluscum contagiosum virus Human T cell leukemia/lymphotrophic virus, types I and II Human herpesvirus, type 8 Mpox
Protozoa	*Trichomonas vaginalis* *Entamoeba histolytica* *Giardia lamblia*
Fungi	*Candida albicans*
Ectoparasites	*Phthirus pubis* *Sarcoptes scabiei*

Table 82.1 Sexually transmitted and transmissible pathogens.

SYPHILIS

Synonym: ■ Lues

Key features

- Sexually acquired, chronic infection caused by *Treponema pallidum* that is characterized by a variety of clinical manifestations and involvement of multiple organ systems
- Can also be transmitted before birth (congenital)
- Intermittently active disease with primary, secondary, and tertiary stages as well as a latent period of variable length that occurs before the onset of tertiary syphilis
- Mucocutaneous manifestations vary from genital ulcers to widespread papulosquamous eruptions to granulomatous nodules
- Syphilis facilitates the transmission of HIV, especially in countries with a high rate of both infections
- Overall, the incidence of syphilis and other STIs has increased substantially in high-income countries after the introduction of antiretroviral therapy and pre-exposure prophylaxis for HIV

History

Syphilis has been of great historical importance and has played a major role in medicine for centuries. The disease was named after an afflicted shepherd named Syphilus in 1530. Theories on the origin of the disease in the late fifteenth century are controversial. One theory proposes that Christopher Columbus and his crew acquired the disease from Native Americans living in the Caribbean islands and brought it back to a nonimmune population in Europe in 1493, as signs of syphilis have been found in skeletons of pre-Columbian Native Americans[1,2]. Another theory is that venereal syphilis may have already been endemic but became more widespread and severe as a consequence of the wars at that time in Europe. Lastly, the environmental theory claims that venereal syphilis is a variant of other diseases caused by *Treponema* spp. and became modified by environmental factors, especially temperature[3,4].

Information on the natural course of untreated syphilis has come primarily from two large studies (Fig. 82.1). The Oslo Study[5] was a prospective investigation of infected, but untreated, individuals conducted between 1890 and 1910, with a follow-up period of 50 years. Approximately one-quarter of infected persons had at least one additional relapse of secondary syphilis, often occurring during the first year (90%). Approximately 15% of infected persons developed benign tertiary syphilis with gummas of the skin (70%), bones (10%), and mucous membranes (10%). Cardiovascular syphilis was reported in ~14% of men and 8% of women, while neurosyphilis was observed in 10% of men and 5% of women. Altogether, the study concluded that 17% of men and 8% of women died as a result of untreated syphilis.

The Tuskegee Study was undertaken in 1932 in infected Black men, with regular examinations for short- and long-term consequences of untreated infection. This represented a highly unethical investigation, as penicillin treatment was withheld without written consent. The principal finding was an increased mortality rate in the syphilitic group compared to the controls, with an ~20% loss-of-life expectancy at an interval of 12 years. Specific lesions of late syphilis were found in about 14% of infected men at the 20-year evaluation, and 12% after 30 years, with cardiovascular syphilis and neurosyphilis representing the primary causes of death[6–8]. The unethical aspects of this study had serious social implications, contributing to mistrust in the healthcare system amongst African-Americans[9].

Epidemiology

Syphilis is distributed worldwide and is particularly problematic in low-income countries, where it is a leading cause of genital ulcer disease. Worldwide, the rates of primary and secondary syphilis decreased dramatically with the introduction of penicillin treatment after the Second World War. In contrast to Western European countries, an increase in the infection rate was observed during the late 1980s in rural southern and urban regions of the US. Although the number of syphilis cases per year in the US subsequently declined and in 2000 fell to its lowest point since reporting began in 1941, the number of primary and secondary syphilis cases diagnosed per year in men has subsequently increased more than sevenfold (Fig. 82.2). According to the Centers for Disease Control and Prevention (CDC), the incidence rate of primary and secondary syphilis in 2019 in the US was 20.1 cases per 100 000 population in men and 3.9 cases per 100 000 population in women. In the US, the incidence in Hispanic and Black individuals is 2- to 5-fold higher than in other population groups, but the highest risk group is men who have sex with men (MSM) as they accounted for nearly 60% of cases of primary and secondary syphilis in 2019[10].

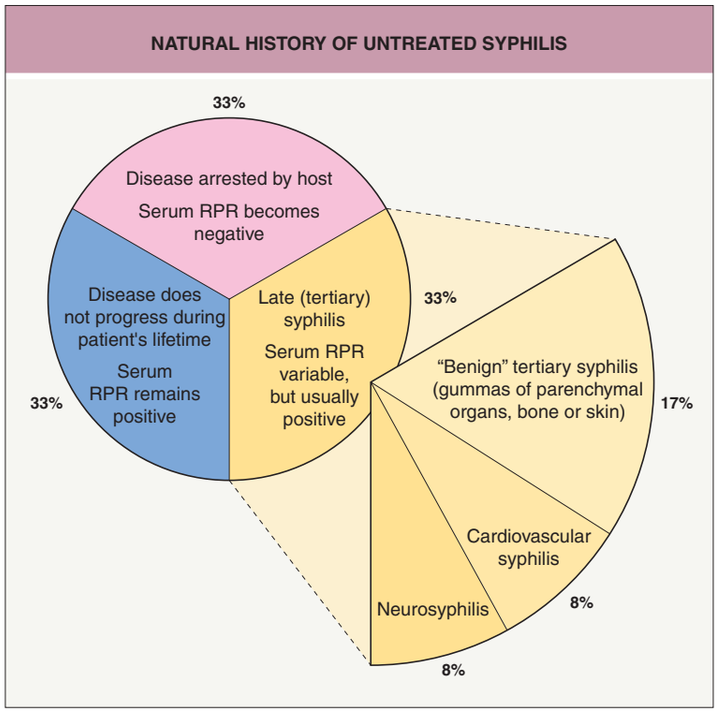


Fig. 82.1 Natural history of untreated syphilis. The data represent a composite of several studies. The specific antibody assays (e.g. MHA-TP, FTA-ABS) remain positive in at least 95% of all patients. RPR, rapid plasma reagin.

With the resurgence of syphilis in Eastern Europe in the 1990s and migration of sex workers from this region to Western Europe, syphilis has also been observed more frequently in Western European countries over the past few decades.

Biology of *T. pallidum*

T. pallidum is a member of the genus *Treponema* of the order Spirochaetales, and it was identified in 1905 by Schaudinn and Hoffmann (Table 82.2)[11]. The characteristics of this microorganism are outlined in Table 82.3. Fig. 82.3 represents a darkfield photomicrograph of *T. pallidum*.

Pathogenesis of Untreated Syphilis

Syphilis is a chronic systemic infection that progresses through active and latent stages (Fig. 82.4). Inoculation and penetration occur via mucosal surfaces and abraded skin, followed by attachment to host cells and multiplication of the microorganism. Within a few hours, treponemes disseminate to the regional lymph nodes and internal organs[12].

Primary stage

The primary lesion develops 10–90 days after infection (median of 3 weeks) as an indolent papule, followed by surface necrosis and the

CLASSIFICATION OF *TREPONEMA* SPECIES

Order Spirochaetales
Genus *Leptospira*
Genus *Borrelia*
Genus *Treponema*

	Disease	Distribution	Transmission
T. pallidum subsp. *pallidum*	Venereal syphilis	Worldwide	Sexual; maternal–fetal
T. pallidum subsp. *pertenue*	Yaws	Tropics	Non-venereal (all ages)
T. pallidum subsp. *endemicum*	Endemic syphilis (Bejel)	Desert	Non-venereal (all ages)
T. carateum	Pinta	Tropics	Non-venereal (all ages)
T. denticola, *T. socranskii*	Periodontal disease	Worldwide	Non-venereal

Common features shared by all spirochetes within the genus *Treponema*: morphology, antigenic properties, many DNA sequences, serologic detection, biochemical properties.
Variable features for spirochetes within the genus *Treponema*: transmission mode, geography, age of patients, appearance of clinical lesions.

Table 82.2 Classification of *Treponema* species.

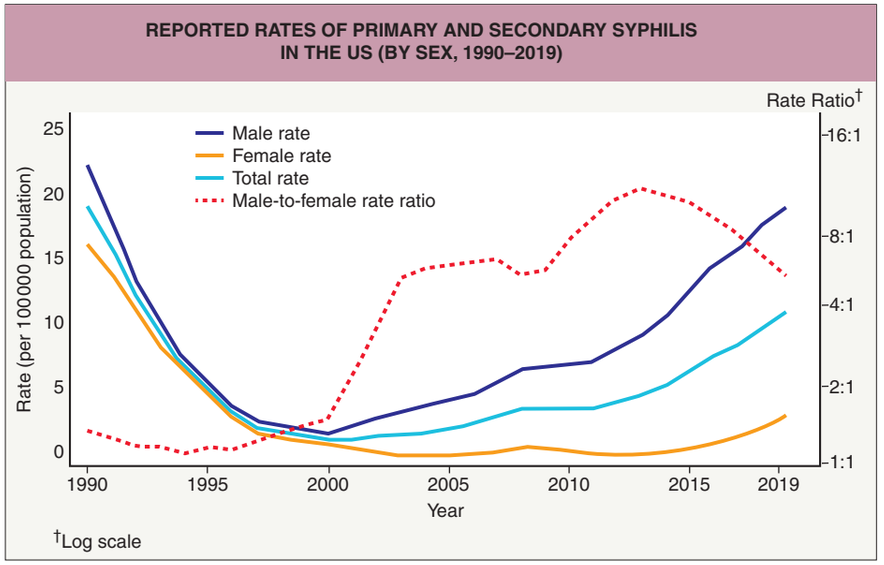


Fig. 82.2 Reported rates of primary and secondary syphilis in the US (by sex, 1990–2019). Note the elevated male : female ratio since 2000. Unfortunately, the use of pre-emptive antiretroviral therapy has been associated with a reduction in the use of condoms, including in men who have sex with men. *From the Centers for Disease Control and Prevention: Sexually Transmitted Disease Surveillance 2019. https://www.cdc.gov/std/statistics/2019/std-surveillance-2019.pdf.*

CHARACTERISTICS OF *TREPONEMA PALLIDUM*

• 6–20 microns in length, 0.1–0.18 microns in diameter
• Regular tight spirals
• Inability to survive outside an animal host
• Cannot be cultured *in vitro* for an extended time period
• Limited capacity for DNA repair
• Outer membrane:
  • lipid-rich
  • contains uniform-sized *t*ransmembrane *r*are *o*uter *m*embrane *p*roteins (TROMP)
  • lacks lipopolysaccharide
• Periplasmic flagella

Table 82.3 Characteristic features of *Treponema pallidum*.



Fig. 82.3 Positive darkfield examination. Treponemes are recognized by their characteristic corkscrew shape, and deliberate forward and backward movement with rotation about the longitudinal axis. *From Morse SA, et al. Atlas of Sexually Transmitted Diseases and AIDS, 3rd edn. London: Mosby, 2003.*

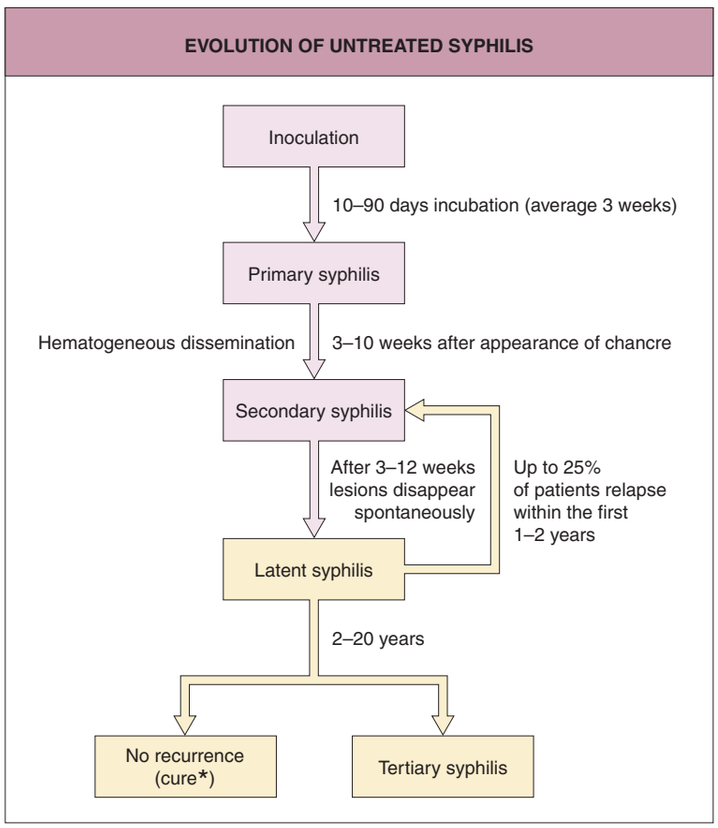


Fig. 82.4 Evolution of untreated syphilis. *Or clinically asymptomatic. *Adapted from Rein MF, Musher DM. Late syphilis. In: Rein MF (ed). Atlas of Infectious Diseases, Vol V: Sexually Transmitted Diseases. New York: Current Medicine, 1995:10.1–10.13.*

typical well-circumscribed ulceration that is firm to palpation (chancre). It is accompanied by enlarged regional lymph nodes. Histopathologically, the microorganism is observed among T cells that produce interferon-γ and interleukin-17[13], which lead to macrophage activation and destruction of a large number of treponemes. Several pathogenic mechanisms have been proposed, including an antigenically inert treponemal cell surface, resistance to phagocytosis, and premature down-regulation of the local host immune response[14].

Secondary stage

The secondary stage is characterized by dissemination and multiplication of the microorganism in different tissues, either simultaneously with the primary local lesion or up to 6 months after the primary lesion has healed. This stage follows primary syphilis in almost every patient who does not receive appropriate treatment. Circulating immune complexes (which contain treponemal outer membrane proteins), human anti-fibronectin antibodies, and complement are present during this stage of the disease and play a role in the pathogenesis of the different types of lesions[15].

Secondary syphilis is characterized by a broad spectrum of cutaneous manifestations as well as systemic signs such as malaise, fever, and generalized lymphadenopathy. It lasts several weeks or months, with relapses in ~25% of patients. Pregnant women can infect a fetus via transplacental passage of the microorganism.

Latency

Latency is the period between healing of the clinical lesions and appearance of late manifestations, and it can last for many years. About 70% of untreated individuals will remain in this stage for the rest of their lives and are immune to new primary infection (see Fig. 82.1). Latent syphilis is divided into early (1 year or less) and late (more than 1 year) subsets, and it is characterized by positive serologic tests for specific antibodies (see below) without clinical signs or symptoms. Infectivity may occur intermittently due to the presence of treponemes in the bloodstream, and pregnant women with latent syphilis may infect the fetus *in utero*.

Tertiary stage

The tertiary stage is also called late syphilis and is characterized by the presence of a small number of organisms and a high cellular immune reactivity against the organism. Signs of late syphilis can be recognized in approximately one-third of untreated individuals several months to years after being infected with treponemes (see Fig. 82.1). The microorganisms may invade the central nervous and cardiovascular systems as well as the skin and other organs (e.g. bones), leading to damage related to host delayed-type hypersensitivity responses, which produce local inflammation and gummas in affected tissues.

Syphilis and HIV

Syphilis and other STIs that produce genital ulcers further increase the risk of acquiring HIV. Reasons for the increased risk of HIV transmission include:

- lack of an epithelial barrier due to ulceration of the skin or mucous membranes
- large numbers of macrophages and T cells with receptors for HIV
- production of cytokines by macrophages stimulated by treponemal lipoproteins.

In addition, syphilitic manifestations are altered in HIV-positive patients[16,17], with a higher likelihood of neurologic findings and (in those with secondary syphilis) ulcerative lesions.

Clinical Features

Syphilis is usually sexually acquired, but maternal–fetal transmission also occurs and can result in congenital syphilis. Syphilis is an intermittent disease with primary, secondary, and tertiary stages as well as a latent period of variable length (divided into early and late subsets) that precedes the onset of tertiary syphilis (see Fig. 82.4)[18]. The definitions of early and late syphilis by the CDC and World Health Organization (WHO) differ slightly. *Early syphilis* includes the primary and secondary stages as well as early latency (CDC: acquired <1 year previously; WHO: acquired <2 years previously). *Late syphilis* extends from late latency (CDC: acquired >1 year previously; WHO: acquired >2 years previously) through the tertiary stage.

Primary syphilis

The chancre usually presents as a single, indolent, round or oval, indurated ulcer (Fig. 82.5) that is associated with regional adenopathy. Some patients report a preceding painless papule that enlarged and ulcerated a few days later. The time of onset ranges from 10 to 90 days (average 3 weeks) after *T. pallidum* exposure. Untreated, chancres heal within a few weeks (Fig. 82.6).

Asymptomatic infections are commonly due to unrecognized chancres, especially when located in the cervical region in women; in these cases, syphilis is more frequently diagnosed during the secondary stage. The same applies to chancres located in the anal, perianal, or rectal areas (see Fig. 82.5D), seen more commonly in MSM. The mechanism of spontaneous healing without treatment is not well understood and seems to depend on local immunity.

Laboratory diagnosis of *primary* syphilis includes the following:

- Detection of *T. pallidum* DNA via PCR from a swab of a chancre is the most sensitive and specific method.
- Darkfield microscopic examination of fluid from the surface of the chancre is also a sensitive, and for the genital region a specific, method for confirming the presence of *T. pallidum* (see Fig. 82.3).
- Immunohistochemical staining of biopsy specimens (or Warthin-Starry staining if immunohistology not available).

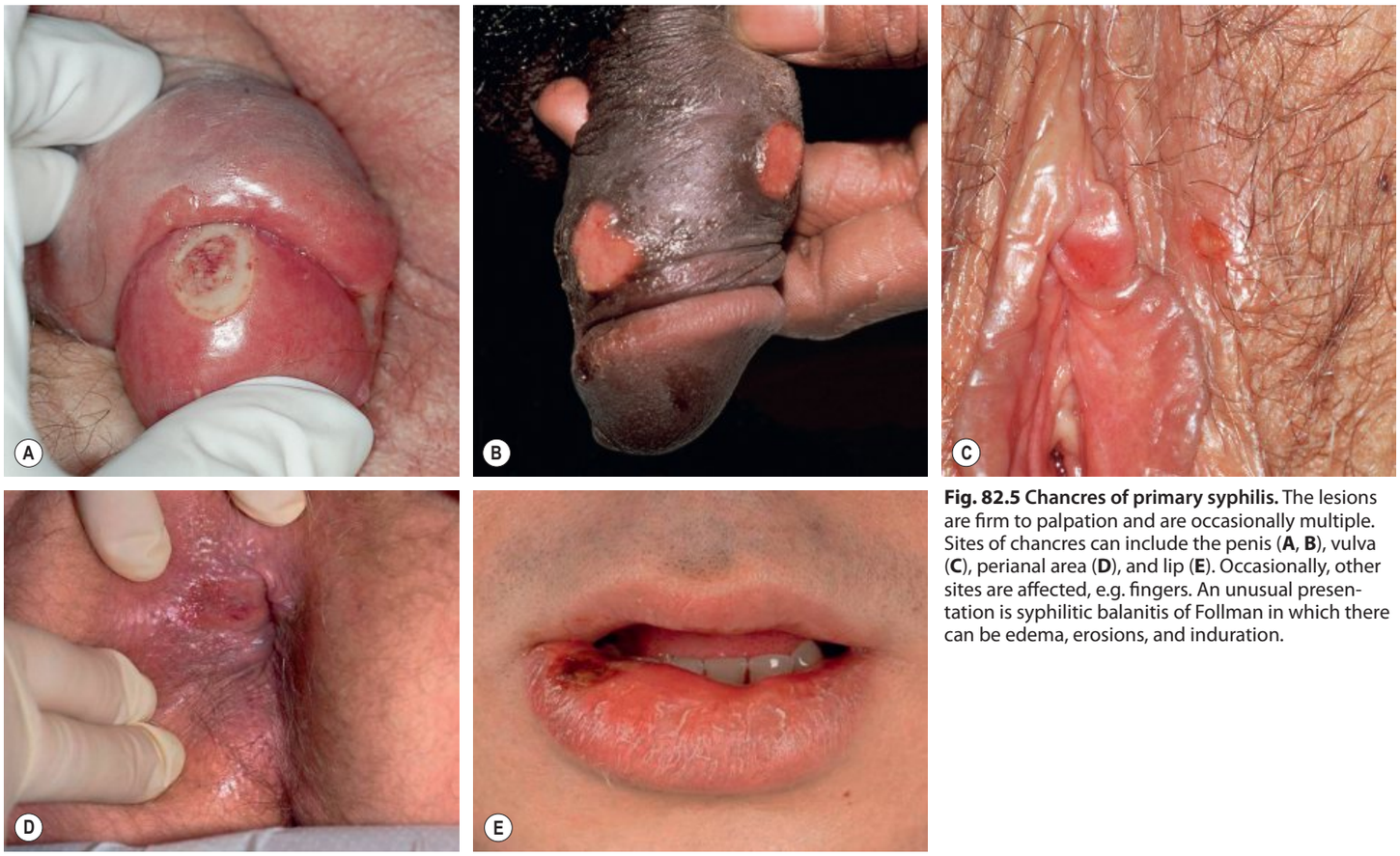


Fig. 82.5 Chancres of primary syphilis. The lesions are firm to palpation and are occasionally multiple. Sites of chancres can include the penis (**A**, **B**), vulva (**C**), perianal area (**D**), and lip (**E**). Occasionally, other sites are affected, e.g. fingers. An unusual presentation is syphilitic balanitis of Follman in which there can be edema, erosions, and induration.

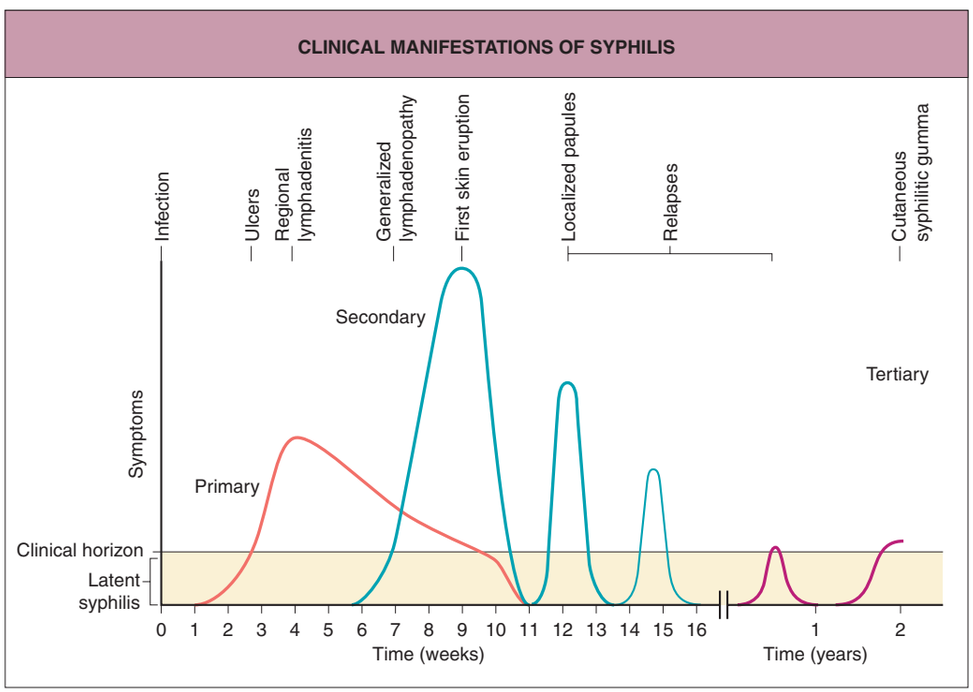


Fig. 82.6 Clinical manifestations of syphilis. *Adapted from Fritsch P, Zangerle R, Stary A. Venerologie. In: Fritsch P (ed). Dermatologie und Venerologie. Berlin: Springer, 2004:865–86.*

- Antibodies to cardiolipin are present in ~80% of individuals at the onset of clinical symptoms. Cardiolipin, a component of mammalian cells, seems to be modified by treponemes such that antibodies are produced by the infected person and can be measured by the rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) assay.
- Antibodies to surface proteins of *T. pallidum* as detected by hemagglutination assays (*T. pallidum h*em*a*gglutination test [TPHA], *m*icro-*h*em*a*gglutination assay for antibodies to *T. pallidum* [MHA-TP]), or *f*luorescent *t*reponemal *a*ntibody *abs*orption (FTA-ABS) assay are present in 90% of patients with clinical symptoms of primary syphilis. Since antibodies usually remain positive for life, a differentiation between primary syphilis and a prior infection may not be possible and PCR or darkfield examination should be undertaken.

Secondary syphilis

The secondary stage of the disease results from the hematogenous and lymphatic dissemination of treponemes after a few weeks or months (3–10 weeks; Fig. 82.7). It is characterized by recurrent disease activity, with mucocutaneous as well as systemic manifestations. Prodromal symptoms include low-grade fever, malaise, sore throat, adenopathy, myalgias, weight loss, and sometimes a headache from meningeal irritation (Table 82.4).

During the second stage of syphilis, the most commonly observed clinical presentation (80%) is a generalized, non-pruritic papulosquamous eruption (Fig. 82.8). Lesions can range from 1–2 mm to 15–20 mm in diameter, and they vary in color from pink to violaceous to red–brown. Mucosal lesions range from small, superficial ulcers that resemble painless aphthae to large gray plaques (Fig. 82.9A,B). Condylomata lata are often observed in the moist regions of the anogenital area due to local spreading of the microorganisms (Fig. 82.9C,D). Lymph node enlargement is present in the majority of patients. Focal neurologic findings occasionally occur as does bone pain.

Additional cutaneous presentations of secondary syphilis include annular or figurate plaques with central hyperpigmentation on the face (Fig. 82.10A), non-scarring "moth-eaten" alopecia, split papules at the oral commissures (Fig. 82.10B), granulomatous nodules and plaques (Fig. 82.10C,D), and crusted necrotic lesions (Fig. 82.10E). Malignant syphilis (lues maligna) is extremely rare; the disseminated lesions resemble primary chancres (Fig. 82.10F).

Without treatment, the lesions resolve over several weeks to months. Relapse occurs in ~20% of patients within 1 year, often with mucosal or mucocutaneous manifestations in the anogenital area.

Laboratory diagnosis of *secondary* syphilis includes the following:

- Presence of treponemes by darkfield examination of serous exudates from localized lesions of the skin and mucous membranes (the exception being the oral cavity; see below).
- Serologic tests are more useful in secondary, as compared to primary, syphilis. Cardiolipin antibodies (e.g. RPR or VDRL tests) as well as specific antibodies are always positive in patients with secondary syphilis; a mistakenly or temporarily negative non-treponemal test rarely occurs due to the prozone phenomenon or HIV infection, respectively (see Table 82.8).
- Immunohistochemical staining of biopsy specimens (or Warthin-Starry staining if immunohistology not available).

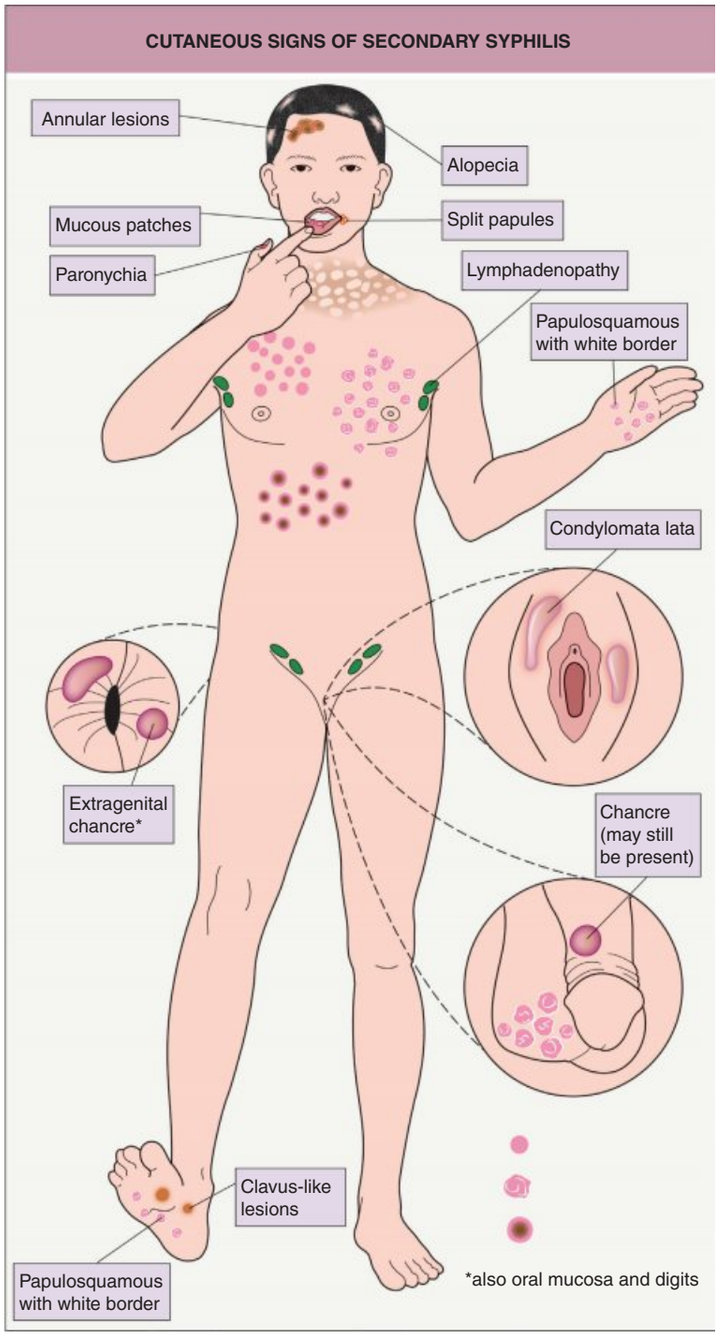


Fig. 82.7 Cutaneous features of secondary syphilis. Additional symptoms include low-grade fever, malaise, sore throat, myalgias, bone pain, and headaches.

CLINICAL FEATURES OF SECONDARY SYPHILIS

- **Prodromal symptoms and signs:**
  Weight loss
  Low-grade fever
  Malaise
  Headache (meningeal irritation)
  Sore throat
  Conjunctivitis (iridocyclitis)
  Arthralgia (periostitis)
  Myalgias
  Hepatosplenomegaly (mild hepatitis)
- **Generalized lymphadenopathy with indolent enlargement of lymph nodes** (50%–85%)
- **Skin manifestations:**
  Early (10%): generalized eruption; non-pruritic, roseola-like, discrete macules, initially distributed on the flanks and shoulders
  Late (70%): generalized maculopapular and papulosquamous eruptions; more infiltrated lesions, often copper-colored; annular plaques on the face; corymbose arrangement (satellite papules around a larger central lesion); occurs in successive waves and is polymorphic
  Localized syphilids (specific infiltrations of treponemes; positive darkfield examination):
  - palms and soles: symmetric papules and plaques with a collarette of scale (collarette of Biett)
  - anogenital area: condylomata lata
  - seborrheic area: "corona veneris" along the hairline

  Hypopigmented macules, mainly on the neck (postinflammatory; "necklace of Venus")
- **Manifestations involving mucous membranes (30%):**
  Syphilitic perlèche, split papules
  Mucous patches: "plaques muqueuses" in the oropharynx (equivalent to condylomata lata in the genital area)
  Syphilitic sore throat: inflammation of the whole pharynx
- **Patchy alopecia** (7%): "moth-eaten" localized areas of hair loss; toxic telogen effluvium

Table 82.4 Clinical features of secondary syphilis.



Fig. 82.8 Secondary syphilis. Widespread exanthem of pink papules (**A**), subtle minimally inflamed lesions localized to the arms in an HIV-positive man (**B**), and generalized papulosquamous lesions (**C**). Genital lesions can resemble psoriasis (**D**) while lesions on the palms and soles (**E, F**) often have a collarette of scale. *B,D, Courtesy Kalman Watsky, MD.*

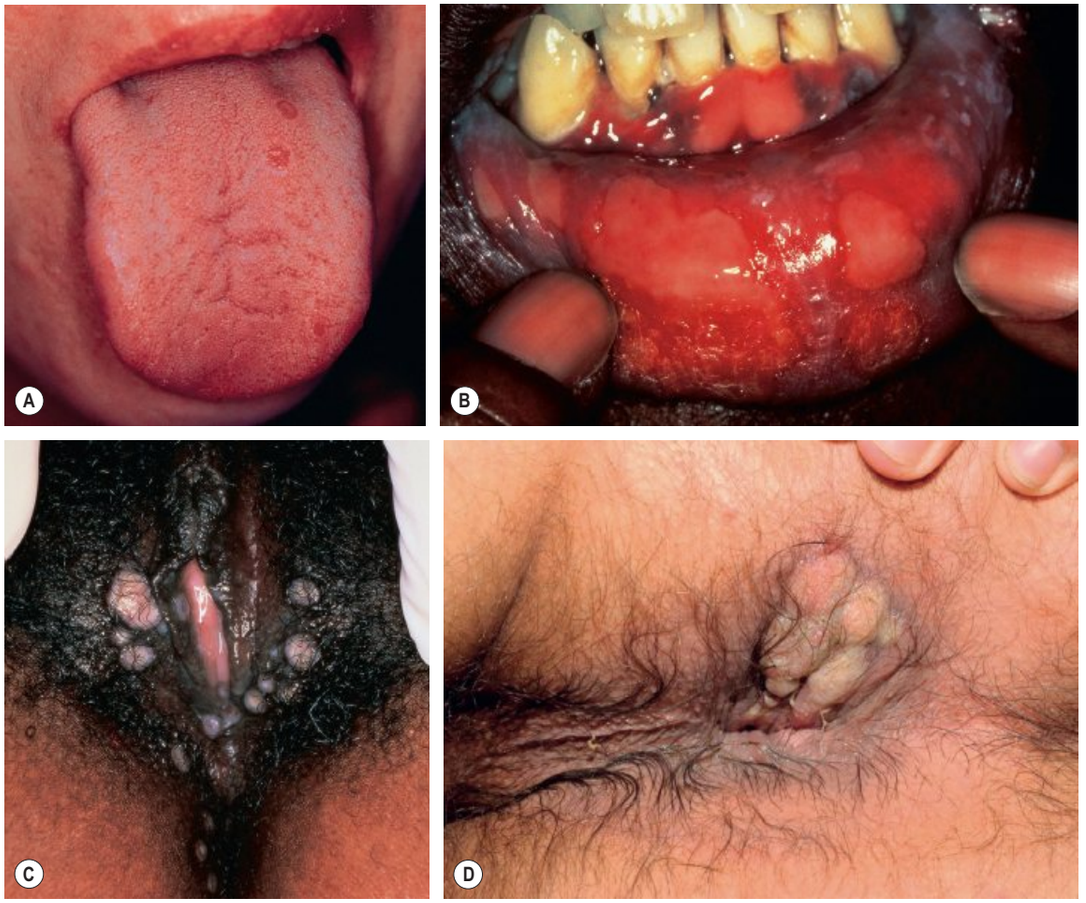


Fig. 82.9 Orogenital lesions of secondary syphilis. Oral lesions can vary from small superficial ulcers (**A**) to mucous patches (**B**). Occasionally, leukokeratosis or nodules are seen. Condylomata lata in the vulvar (**C**) and anal (**D**) areas may be misdiagnosed as HPV infection (i.e. condylomata acuminata).



Fig. 82.10 Less common manifestations of secondary syphilis. A Annular and polycyclic plaques with central hyperpigmentation on the forehead. **B** Split papule at the oral commissure. **C, D** Two elderly patients with granulomatous lesions, varying from numerous, monomorphic, dull pink papules to papulonodules and plaques of varying sizes. **E** Necrotic lesion with scale-crust in a patient with AIDS. **F** "Malignant" syphilis with multiple necrotic, ulcerated and crusted lesions associated with severe constitutional symptoms. *C, Courtesy Department of Dermatology, Medical University of Graz; E, Courtesy Judit Stenn, MD.*

- Spirochetes can be detected by immunohistochemistry in the majority of biopsy specimens (see Fig. 0.33).

Management considerations for patients diagnosed with secondary syphilis include the following:

- All patients should be tested for HIV infection, and testing should be repeated in those who fail to respond to treatment.
- Patients with ocular symptoms (e.g. photophobia, visual changes) should undergo ophthalmologic evaluation, including slit-lamp examination, to assess for uveitis/iritis, neuroretinitis, and optic neuritis.
- A lumbar puncture and cerebrospinal fluid (CSF) analysis should be performed in patients with ocular or neurologic (e.g. headache, hearing loss, cranial neuropathies) signs/symptoms and when treatment failure is suspected (e.g. persistent/recurrent signs/symptoms or failure of non-treponemal test titers to decline fourfold within 6–12 months).
- In patients with symptoms of otosyphilis (e.g. hearing loss, vertigo), an otologic examination is needed. However, CSF evaluation in patients with otosyphilis does not assist in clinical management, so lumbar puncture is not recommended.
- Patients with HIV disease are at increased risk for neurosyphilis, especially if they have a CD4 count <350 cells/ml and/or an RPR titer of ≥1 : 32; however, unless neurologic symptoms are present, CSF examination in HIV-positive patients has not been associated with improved clinical outcomes.

Latent syphilis

After a period of 3–12 weeks, untreated secondary syphilis typically resolves spontaneously, leaving the patient in an asymptomatic state. Diagnosis is based on a positive syphilis serology test result

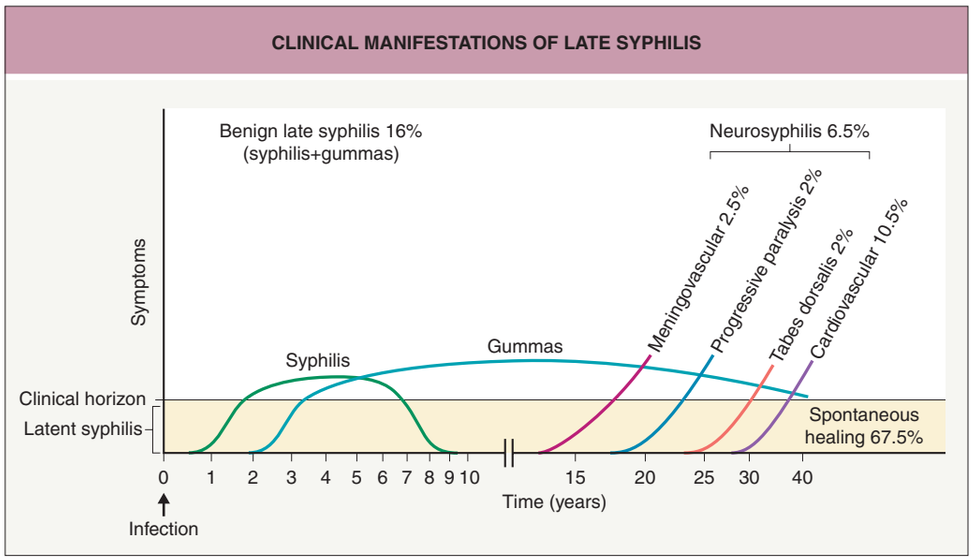


Fig. 82.11 Clinical manifestations of late syphilis.
Adapted from Fritsch P, Zangerle R, Stary A. Venerologie. In: Fritsch P (ed.). Dermatologie und Venerologie. Berlin: Springer, 2004:865–86.

in the setting of no clinical evidence of treponemal infection. The two stages are:

- Early latent stage: within 1 year of the onset of latency (CDC definition), with the possibility of recurrence of the disease. About 90% of secondary relapses occur within the first year.
- Late latent stage: after 1 year from the onset of the disease (CDC definition); relapses after 1 year are very infrequent. This disease state may last for many months or years.

Experience regarding the outcome of late latent syphilis in the absence of treatment is based upon several studies. About one-third of infected individuals have a non-reactive RPR test, no sign of reactivation during the remainder of their lives, and only the specific antibody assays (e.g. MHA-TP, FTA-ABS) remain positive (see Fig. 82.1). Another one-third of patients remain clinically asymptomatic for the rest of their lives, but antibodies against cardiolipin (e.g. RPR, VDRL) persist together with a positive MHA-TP or FTA-ABS assay. In the remaining one-third, clinical symptoms of tertiary syphilis occur.

Diagnosis of latent syphilis is established by reactivity in an RPR or VDRL assay, a positive MHA-TP or FTA-ABS test, and the absence of any clinical signs of the disease. The diagnosis is easy to establish, if there is a history of a chancre or skin manifestations that fit the clinical picture of syphilis. In many cases, however, the medical history provides no useful information regarding the presence of clinical symptoms in the previous weeks to months or whether the patient was previously treated. In such instances, differentiation between early and late latency is not possible and patients are regarded as having late latent syphilis from a management standpoint (see below). Response of latent syphilis to treatment is indicated by a decline in the RPR or VDRL titer. Persistently high (e.g. lack of a fourfold decline within 12–24 months) or rising titers are a sign of treatment failure, and examination of the CSF should be performed.

Tertiary (late) syphilis

Classic tertiary syphilis, as a consequence of untreated syphilis, is nowadays rare. It has a variable range of manifestations that appear months to years after initial infection (Fig. 82.11). In particular, these include involvement of the skin, bones, CNS, heart, and great vessels. Approximately one-half of patients with tertiary syphilis have "benign" late syphilis with the development of gummas, about one-quarter develop cardiovascular manifestations, and one-quarter develop neurologic symptoms (see Fig. 82.1).

In tertiary syphilis, non-treponemal serologic tests are usually positive with high titers. Patients with tertiary syphilis (or any symptoms related to late syphilis) should undergo lumbar puncture and CSF examination to determine if neurosyphilis is present before therapy is initiated.

"Benign" late syphilis

The most common feature of late syphilis is gummas, which are locally destructive lesions in the skin, bones, liver, and other organs. The gummas in the skin are nodular or noduloulcerative lesions, often with an arciform pattern (Fig. 82.12). They remain for weeks to months and then involute with scarring, but eventually new nodules reappear. With treatment, resolution of the lesions is prompt and complete. A solitary gumma that is located subcutaneously may become necrotic, similar to a "cold" abscess, resulting in ulceration of the skin or mucous membranes as well as destruction of underlying bones.



Fig. 82.12 Cutaneous gummas of tertiary syphilis. Arciform, erythematous eroded plaques with central scarring.

Bones are affected as frequently as the skin. Within the bone, a gumma is destructive and is typically accompanied by periostitis and osteitis. Clinical manifestations include pain, swelling, and limited range of motion. Other sites that can be affected by gummas include the tongue and oral cavity, upper respiratory tract, myocardium, and digestive as well as nervous systems.

Cardiovascular syphilis

Cardiovascular syphilis has a late onset, with a latent period of 15–30 years, and it occurs in about 8%–10% of individuals with untreated

infection. During the early stage of the disease, *T. pallidum* demonstrates a predilection for the vasa vasorum of the proximal aorta and produces transmural inflammatory lesions, which lead to endarteritis of the vessels. The organisms then remain there in a latent state for many years.

Neurosyphilis

Although classically a manifestation of tertiary syphilis, neurosyphilis can occur at any stage of the disease. Neurosyphilis is the reflection of a chronic (or sometimes acute) form of meningitis, with vascular and parenchymatous sequelae in the cerebrum and spinal cord (Table 82.5)[19]. Asymptomatic neurosyphilis is defined by the presence of abnormalities in the CSF (see below), but in the absence of any neurologic symptoms or clinical findings. While in some individuals the CSF abnormalities may resolve spontaneously or persist into advanced age, asymptomatic neurosyphilis can progress to late symptomatic neurosyphilis.

The basic pathomechanism for cerebrovascular syphilis is an infarction secondary to syphilitic endarteritis; this can result in hemiparesis or hemiplegia. Parenchymatous neurosyphilis, including general paresis, dementia paralytica, and paretic neurosyphilis, is due to direct invasion of the cerebrum by treponemes. It is a rare and late form of neurosyphilis, with dementia and neurologic symptoms such as paralysis progressing, if untreated, until death occurs.

Tabes dorsalis, which affects up to a third of patients with neurosyphilis after a long latent period, has a number of typical clinical signs and symptoms, including diplopia, lightning pains (painful paresthesias, especially of the extremities), loss of vibratory and position sense, reduced reflexes in the legs, ataxia, sphincter dysfunction, visceral crisis (abdominal, rectal, and laryngeal pain), and Argyll Robertson pupils (abnormal pupillary light reflexes: loss of direct and consensual; retention of accommodation). Tabes dorsalis may burn out even without treatment.

Neurosyphilis in HIV-infected individuals

In the mid 1970s, the first cases of so-called "atypical neurosyphilis" were described. With the subsequent recognition of co-infections with syphilis and HIV, it became apparent that neurosyphilis is common in HIV-infected individuals, and patients present with manifestations of early-onset neurosyphilis.

Laboratory diagnosis of neurosyphilis

In addition to the clinical findings, the diagnosis of neurosyphilis (including acute syphilitic meningitis, meningovascular syphilis, and parenchymatous neurosyphilis) is based upon reactive blood and CSF antibody testing, which are almost always positive. CSF abnormalities include elevation of pressure, protein concentration, and immunoglobulin level as well as a mononuclear pleocytosis. The presence of specific antitreponemal antibodies in the CSF is mandatory, but it is not proof of the diagnosis of neurosyphilis, since IgG antibodies can diffuse into the CSF or result from contamination of the CSF by blood. Establishment of local antibody synthesis is possible by using the CSF-IgG index, obtained by dividing the CSF to serum IgG ratio by the CSF to serum albumin ratio. A result >0.7 is indicative of IgG synthesis in the brain due to local inflammation. The intrathecal *T. pallidum* antibody index is calculated by dividing the TPHA titer in the CSF by the CSF to serum albumin ratio multiplied by a factor of 10^3, and an index >100 is indicative of the synthesis of treponemal-specific antibodies within the CNS. The presence of nonspecific antibodies, e.g. a positive VDRL test or RPR assay in CSF, is observed in most, but not all, cases, and a negative test does not exclude the presence of neurosyphilis.

Congenital syphilis

Congenital syphilis was initially described in 1497 and is therefore the oldest recognized congenital infection. In 1906, it was demonstrated via the Wassermann test that transmission of syphilis to the fetus required an infection in the pregnant woman.

There was an upsurge in congenital syphilis in Eastern Europe in the late 1990s, which paralleled the increased incidence of syphilis in adults and adolescents in this region. In the early 1990s, an increased frequency of congenital syphilis was also observed in some inner-city minority populations in the US[20]. From 2015–2019, the number of reported cases of congenital syphilis in the US nearly quadrupled[10]. The risk of mother-to-child transmission of untreated syphilis and its potential consequences are outlined in Table 82.6. Therefore, all women should be screened serologically for syphilis at the first prenatal care visit[21].

Early congenital syphilis

Infants generally present with symptoms during the neonatal period or within the first 3 months of life (Fig. 82.13). At the latest, they develop symptoms within the first 2 years of life. Typical manifestations are marasmic syphilis (i.e. cachexia) and skin lesions similar to those of acquired secondary syphilis (Fig. 82.14), except that they may be bullous (pemphigus syphiliticus) and tend to be more erosive. Additional clinical findings are "snuffles" (bloody or purulent mucinous nasal discharge), perioral and perianal fissures, lymphadenopathy, and hepatosplenomegaly. Skeletal involvement (i.e. osteochondritis) may result in pseudoparalysis of Parrot because of reduced movement of the extremities due to pain; other manifestations include anemia, thrombocytopenia, syphilitic pneumonitis (pneumonia alba), hepatitis, nephropathy, and congenital neurosyphilis.

Late congenital syphilis and stigmata

Late congenital syphilis in a child or adolescent corresponds to tertiary syphilis in an adult and is not infectious. The stigmata represent the delayed consequences of localized inflammation at the sites of treponemal infection (Table 82.7). In about one-third of children, an interstitial keratitis is seen; this finding together with typical dental abnormalities (Hutchinson teeth) and neural deafness forms the Hutchinson triad.

Laboratory diagnosis of congenital syphilis

A confirmed diagnosis of congenital syphilis requires laboratory demonstration of treponemes or child-specific antibodies. Serodiagnosis of congenital syphilis poses a difficult problem because IgG antibodies that are present may have been acquired transplacentally from the mother. A serum titer for a non-treponemal test that is fourfold higher than the mother's titer is suggestive of infection, but infected neonates

CLASSIFICATION OF NEUROSYPHILIS
• **Asymptomatic**
• Early
• Late
• **Meningeal**
• Acute syphilitic meningitis
• Meningovascular
• Cerebrovascular
• Spinal form
• **Parenchymatous**
• General paresis (dementia paralytica)
• Tabes dorsalis
• Taboparesis (mixed)
• Optic atrophy
• **Gummatous**
• Cerebral form
• Spinal form
• Both spinal and cerebral

Table 82.5 Classification of neurosyphilis.

MOTHER-TO-CHILD TRANSMISSION OF UNTREATED SYPHILIS AND ITS CONSEQUENCES
Risk
• Infection of the mother from conception to 7th month of pregnancy: risk of transmission is nearly 100% (often fetal demise or severe congenital syphilis)
• Infection at least 2 years before pregnancy: reduced risk of transmission to 50%
• Infection during 7th, 8th, or early 9th month: reduced risk of transmission
• Infection 3–6 weeks before labor: no placental transmission; risk of perinatal transmission
Consequences of infection
• Spontaneous abortion (second or third trimester) (10%)
• Stillbirth (10%)
• Infant death (20%)
• Congenital syphilis (20%)
• Healthy child (40%)

Table 82.6 Mother-to-child transmission of untreated syphilis and its consequences.

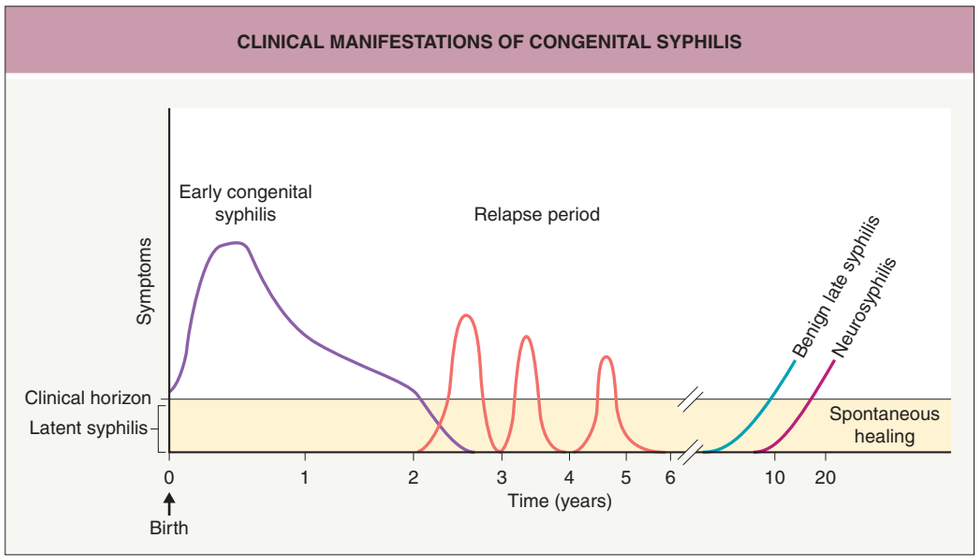


Fig. 82.13 Time course for clinical manifestations of congenital syphilis. *Adapted from Fritsch P, Zangerle R, Stary A. Venerologie. In: Fritsch P (ed). Dermatologie und Venerologie. Berlin: Springer, 2004:865–86.*



Fig. 82.14 Congenital syphilis. Red–brown plaques on the plantar surface.

STIGMATA OF CONGENITAL SYPHILIS
Cutaneous
• Rhagades – radial periorificial (mouth, nose, eyes, anus) scars at sites of previous fissures
Dental
• Hutchinson teeth – peg-shaped, notched permanent incisors*
• Mulberry molars – multiple rounded rudimentary cusps on the permanent first molars
• Caries due to defective enamel
Skeletal
• Saddle nose – depression of the nasal root due to destruction of cartilage/bone
• Frontal bossing of Parrot ("Olympian brow")
• Hypoplastic maxilla, relatively prominent mandible
• High palatal arch ± perforation
• Higouménakis' sign – thickening of the medial clavicle
• Scaphoid scapulae
• Saber shins – anterior tibial bowing
• Clutton's joints – painless synovitis and effusions of the knees
Other
• Eighth nerve deafness*
• Interstitial keratitis leading to corneal ulcers and opacities*
*Components of Hutchinson triad.

Table 82.7 Stigmata of congenital syphilis.

may have lower titers. The detection of chromatographically separated 19S-antibodies in the FTA-ABS-19S-IgM test has a sensitivity of about 90%, similar to the IgM-capture ELISA. More recently, it has been shown that the detection of spirochetemia by PCR can improve the sensitivity of the diagnosis of congenital syphilis in neonates.

In late congenital syphilis, diagnosis is based on clinical findings in association with reactive serologic tests.

Laboratory Diagnosis of Syphilis

The diagnosis of syphilis is based on the direct detection of treponemes or treponemal DNA by microscopy or molecular biologic techniques as well as various serologic tests that assess antibody responses to either cardiolipin (non-treponemal tests) or treponemal antigens (treponemal tests). Diagnosis of the different stages of syphilis depends on the interpretation of laboratory test results, the presence of clinical signs and symptoms, and their history. All patients who have syphilis should also be tested for HIV infection.

Identification of T. pallidum

The detection of the microorganism depends on microscopic examination and molecular assays, since *T. pallidum* cannot be routinely cultured *in vitro*. For propagation and experimental studies, growth in rabbit testicles is possible.

Microscopic examination

Darkfield microscopy permits the definite diagnosis of syphilis by visual detection of motile spirochetes from lesions of the skin (see Fig. 82.3). It requires careful specimen collection, ideally consisting of serous fluid free of red blood cells. Identification is easy for an experienced microbiologist because of the typical episodic movements of the microorganism. Due to the presence of saprophytic spirochetes in the oral cavity, there is limited utility for darkfield examination of serous exudate from lesions in this site. Immunologic detection of the microorganism by the indirect fluorescent antibody test, which utilizes fluorescein-labeled anti-*T. pallidum* antibodies, is especially useful for oral lesions.

In the case of a negative result from microscopic examination, repeat testing is recommended. Serologic tests are also indicated.

Polymerase chain reaction-based assays

PCR-based assays for detection of *T. pallidum* DNA can be useful in special circumstances, e.g. neurosyphilis, congenital syphilis, extragenital primary syphilis, and are increasingly being employed for more classic presentations.

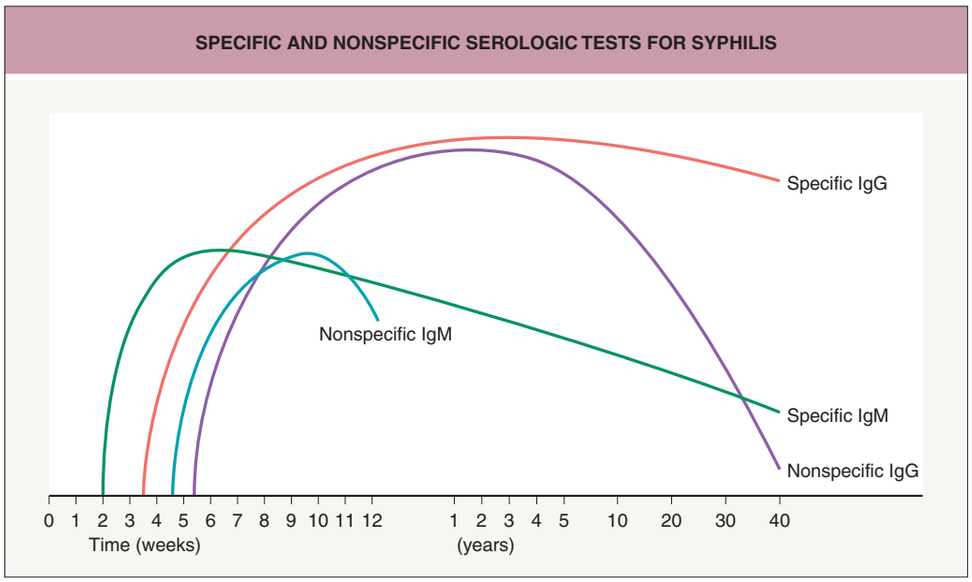


Fig. 82.15 Specific and nonspecific serologic tests for syphilis. These curves represent untreated patients. Non-treponemal tests are nonspecific and treponemal tests are specific. *Adapted from Fritsch P, Zangerle R, Stary A. Venerologie. In: Fritsch P (ed). Dermatologie und Venerologie. Berlin: Springer, 2004:865–86.*

Serologic tests for syphilis

Non-treponemal tests

The VDRL and RPR tests and related assays such as the unheated serum reagin (USR), reagin screen test (RST), and toluidine red unheated serum test (TRUST) detect antibodies to cardiolipin. The latter is a component of mammalian cells that is incorporated and modified by treponemes, which results in the development of host antibodies against it (comparable with autoantibodies directed against phospholipids; see Ch. 23). All these tests measure IgG and IgM antibodies against this lipoprotein-like material released from damaged host cells and from treponemes.

Titers of these antibodies correlate with disease activity and are useful in screening and monitoring treatment (Fig. 82.15). *Qualitative* non-treponemal tests are suitable for screening purposes, and reactive results have to be confirmed by antibody titer. The performance of a *quantitative* non-treponemal test is generally requested even with a positive darkfield examination or PCR assay, in order to provide a baseline for longitudinal evaluation after antibiotic therapy. A fourfold decrease in the antibody titer indicates successful treatment, while a fourfold increase indicates relapse or reinfection. In the case of early and efficacious treatment, non-treponemal assays usually become negative. Limitations of the tests are listed in Table 82.8.

Treponemal tests

The major indication for treponemal tests for syphilis is confirmation of reactive non-treponemal tests. IgM and IgG antibodies are usually detected in these assays by the end of the fourth week after infection. Accurate quantitative evaluation is not useful. The specific treponemal tests generally remain positive indefinitely, except in the case of treatment of very early syphilis where they do revert to negative. The specificity is very high and biologic false-positive reactions seldom occur. The sensitivity varies with the stage of syphilis: between 70% and 100% in primary syphilis, 100% in secondary and latent syphilis, and about 95% in late syphilis[22]. There is no differentiation between antibodies to *T. pallidum* and other treponemes and spirochetes.

Specific assays include the following:

- TPHA, MHA-TP, *T. pallidum p*article *a*gglutination test (TPPA): these assays measure antibodies directed against surface proteins of *T. pallidum* (sonicated fragments of treponemes) attached to rabbit erythrocytes as antigen carriers. Automatization is useful for large-scale testing and screening purposes. A positive result means that the patient had or still has active syphilis, but no assessment about the activity of the disease can be concluded from the qualitative result. Ninety percent of patients are positive at the time they seek medical care for a chancre.
- FTA-ABS assay: the serum reacts with the whole treponeme and forms antigen–antibody complexes visualized by fluorescein-isothiocyanate. To avoid nonspecific reactions with antibodies directed against saprophytic treponemes, a further step with Reiter treponemes is included to absorb nonspecific antibodies. The differentiation into IgM and IgG is possible by including selective anti-Ig antibodies.
- FTA-ABS-19S-IgM test: the isolated IgM antibody fraction is separately tested and provides a higher specificity than other tests. It is restricted to special situations, e.g. congenital syphilis or the differentiation of relapsing syphilis from reinfection.
- Solid *p*hase *hem*adsorption test (SPHA) or IgM ELISA: the SPHA test is used for the detection of specific IgM antibodies that attach to the solid phase of microtiter plates by reacting with the treponemal antigen on rabbit erythrocytes as antigen carriers. IgM antibodies can also be measured by ELISA technology. These tests are useful for the diagnosis of congenital syphilis, neurosyphilis (positive, but low-titer), and reinfection.

LIMITATIONS OF NON-TREPONEMAL AND TREPONEMAL TESTS

Non-treponemal tests

- Lack of reactivity in early darkfield- or PCR-positive primary syphilis
- Usually become negative with effective therapy (~15% of patients with early syphilis do not achieve a fourfold decline in titers 1 year after appropriate treatment, which is considered to represent a therapeutic failure)
- False-negative results
  - Prozone phenomenon: inhibition of flocculation in the setting of high titers of antibodies; requires serum dilution
  - Temporary negative result: secondary syphilis in the setting of HIV infection; reactive on subsequent testing
- Biologic false-positive results due to tissue damage
  - Pregnancy
  - Autoimmune diseases (e.g. lupus erythematosus)
  - Illicit drug abuse
  - Lymphomas
  - Infectious diseases (e.g. malaria)
  - Vaccinations
  - Hepatic cirrhosis
  - Antiphospholipid syndrome
  - Idiopathic, familial
- False-positive: endemic treponematoses and borreliosis

Treponemal tests

- Lack of reactivity in early darkfield- or PCR-positive primary syphilis
- Remain positive indefinitely, so not useful for monitoring response to treatment
- Biologic false-positive: autoimmune diseases, HIV infection, hypergammaglobulinemia
- False-positive: endemic treponematoses and borreliosis

Table 82.8 Limitations of non-treponemal and treponemal tests.

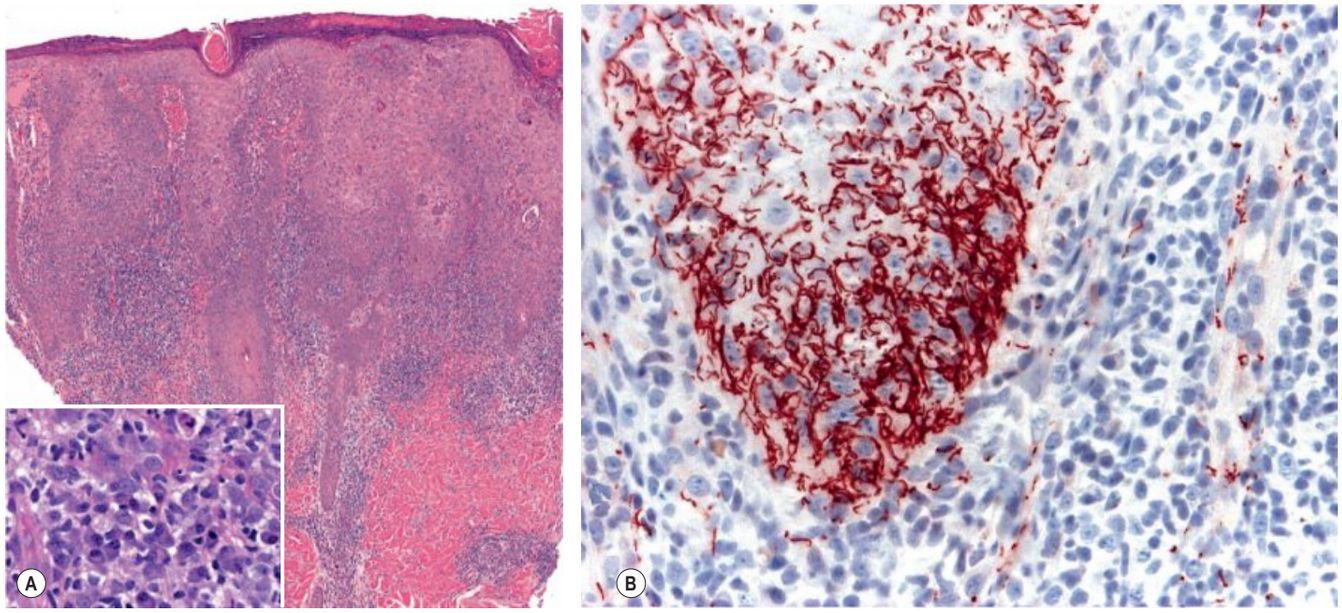


Fig. 82.16 Histology of secondary syphilis. A Psoriasiform epidermal hyperplasia and a dense dermal infiltrate of plasma cells (see inset), lymphocytes, and histiocytes are observed. **B** Positive immunohistochemical staining with an anti-*Treponema pallidum* antibody; note the characteristic elongated, twisted shape of the spirochetes. *Courtesy Lorenzo Cerroni, MD.*

DIFFERENTIAL DIAGNOSES FOR SYPHILIS
Primary syphilis
Other causes of genital ulcers should be considered: • Genital herpes • Genital trauma • Fixed drug eruption • Ulcerative genital carcinoma (e.g. squamous cell carcinoma) • Chancroid: jagged border, yellow exudate, painful • Lymphogranuloma venereum: transient, indurated, painless • Reactive non-sexually related acute genital ulcers (Lipschutz ulcers) • Behçet disease
Secondary syphilis
• Cutaneous: pityriasis rosea, guttate psoriasis, viral exanthems, lichen planus, pityriasis lichenoides, primary HIV infection, drug eruption, nummular eczema, folliculitis • Mucous membranes: lichen planus; chronic aphthae; hand, foot and mouth disease; herpangina; perlèche; pemphigus • Condylomata lata: warts due to HPV, bowenoid papulosis, squamous cell carcinoma
Tertiary syphilis
• Cutaneous: lupus vulgaris, chromoblastomycosis, dimorphic fungal infections, leishmaniasis, lupus erythematosus, mycosis fungoides, sarcoidosis, tumors, venous ulcer

Table 82.9 Differential diagnoses for syphilis.

Pathology

In *primary syphilis*, there is ulceration and a diffuse dermal infiltrate of plasma cells, lymphocytes, and histiocytes. Endothelial swelling is also present. Spirochetes may be detected with Warthin–Starry or immunohistochemical staining.

In *secondary syphilis*, there is great variability in the histopathological pattern, reflecting the variable clinical appearance of the disease. The epidermis may be normal, psoriasiform, necrotic, or ulcerated. Dermal infiltrates of plasma cells, lymphocytes, and histiocytes can be perivascular, lichenoid, nodular, or diffuse (Fig. 82.16A). Older lesions of secondary syphilis may be granulomatous and can resemble sarcoidosis or other granulomatous dermatoses, except for the presence of plasma cells. Endothelial swelling and vascular proliferation can also be seen in secondary syphilis. By immunohistochemistry, spirochetes are identified in the majority of cases (Fig. 82.16B). Lues maligna is characterized by vasculitis.

In *tertiary syphilis*, tuberculoid granulomas (with or without caseation) are present together with plasma cells. Endothelial swelling is evident, but organisms may be difficult to identify.

Differential Diagnosis

The differential diagnoses for the different stages of syphilis are listed in Table 82.9.

Treatment

Penicillin G is still the treatment of choice for all stages of syphilis, and recommended regimens are listed in Table 82.10. A treponemicidal level of the antimicrobial should be achieved in the serum and (for patients with neurosyphilis) in the CSF. A penicillin level of >0.018 mg/L is considered treponemicidal, but the maximally effective *in vitro* concentration is considerably higher (0.36 mg/L)[23,24]. No tendency toward penicillin resistance has been detected in *T. pallidum*. Tetracyclines are used as second-line therapy if penicillin cannot be given; although a single 2 g dose of azithromycin can be effective[25], treatment failures due to macrolide-resistant *T. pallidum* have been reported.

Recommended treatment regimens in the settings of pregnancy and congenital syphilis are summarized in Table 82.11. Although HIV-infected patients are at increased risk for neurologic complications and may have higher rates of treatment failure, prevention of these outcomes by altered therapeutic regimens has not been demonstrated. The CDC and International Union Against Sexually Transmitted Infections (IUSTI) currently recommend that HIV-infected individuals receive the same syphilis regimens as HIV-negative patients. Treatment guidelines and additional information are provided by the CDC (www.cdc.gov/std/treatment-guidelines/STI-guidelines-2021.pdf) and IUSTI (www.iusti.org)[26]. Of note, a Jarisch–Herxheimer reaction characterized by the acute onset of fever, headache, and myalgias can occur upon treatment of early syphilis.

The IUSTI recommends that non-treponemal tests (e.g. VDRL, RPR) be performed 1, 2, 3, and 6 months following antibiotic treatment of early syphilis, then every 6 months for up to 2 years post treatment[26]; the CDC suggests clinical and serologic evaluation at 6 and 12 months for uncomplicated cases, with more frequent and extended evaluation (e.g. at 3, 6, 9, 12, 24 months) for HIV-infected patients. Evaluation of late syphilis at 6-month intervals for up to 3 years is recommended. In the setting of abnormal CSF findings, a CSF examination is recommended at 6-month intervals until cell counts are normal and the CSF-VDRL is negative. Evaluation of sexual partners and reporting are mandatory in many countries.

TREATMENT RECOMMENDATIONS FOR SYPHILIS
Early syphilis (primary, secondary, and early latent [acquired <1 year previously])
Recommended:
• Benzathine penicillin, 2.4 million units* im as a single dose – *or* – • Procaine penicillin, 1.2 million units im daily for 10 days†
Alternative regimens for penicillin-allergic patients‡:
• Doxycycline, 200 mg daily (100 mg po BID preferred over a single 200 mg dose) for 14 days – *or* – • Tetracycline, 500 mg po four times daily for 14 days – *or* – • Ceftriaxone, 1–2 g im or iv daily for 10–14 days – *or* – • Azithromycin, 2 g po as a single dose¶
Late latent (acquired >1 year previously or of unknown duration), cardiovascular and gummatous syphilis; retreatment of primary, secondary or latent syphilis after failed initial treatment§
Recommended:
• Benzathine penicillin, 2.4 million units* im weekly for three doses – *or* – • Procaine penicillin, 1.2 million units im daily for 20 days†
Alternative regimens for penicillin-allergic patients‡:
• Doxycycline, 200 mg daily (100 mg po BID preferred over a single 200 mg dose) for 28 days – *or* – • Tetracycline, 500 mg po four times daily for 28 days
Neurosyphilis and ocular syphilis
Recommended:
• Aqueous penicillin G, 3–4 million units iv q4h (18–24 million units daily) for 10–14 days – *or* – • Procaine penicillin, 2.4 million units im daily plus probenecid, 500 mg po four times daily, both for 10–14 days
Alternative regimens for penicillin-allergic patients:
• Ceftriaxone, 2 g im or iv daily for 10–14 days – *or* – • Consider desensitization
*In children, 50 000 U/kg up to the adult dose. †Alternative treatment regimens in the World Health Organization (WHO) guidelines (http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf) and the guidelines of the International Union Against Sexually Transmitted Infections (http://www.iusti.org/sti-information/guidelines/). ‡Limited data. ¶Resistance reported. §E.g. If RPR/VDRL titers fail to decrease fourfold or symptoms persist/progress; must first examine the CSF to exclude neurosyphilis.

Table 82.10 Treatment recommendations for syphilis. BID, twice daily; h, hours; im, intramuscularly; iv, intravenously; po, orally; q, every. Also see CDC guidelines (https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf).

TREATMENT RECOMMENDATIONS FOR SYPHILIS IN SPECIAL SITUATIONS
Pregnancy
Recommended:
• Benzathine penicillin, 2.4 million units im weekly for two (early syphilis) or three (late syphilis) doses – *or* – • Procaine penicillin, regimen appropriate for the stage of syphilis (see Table 82.10)
In the case of penicillin allergy:

• Desensitization to penicillin – *or* –
• Alternative regimens*:
  • Ceftriaxone, 1 g im daily for 10–14 days – *or* –
  • Azithromycin, 2 gm po as single dose† – *or* –
  • Erythromycin, 500 mg po four times daily for 14 days†

Congenital
Neonate with proven or highly probable disease or born to mother with untreated early syphilis‡:
• Aqueous penicillin G, 50 000 U/kg iv q12h for the first 7 days of life, then q8h for 3 days (100 000–150 000 U/kg/day for a total of 10 days) – *or* – • Procaine penicillin, 50 000 U/kg im daily for 10–14 days
Neonate with no signs of disease born to mother with treated syphilis¶:
• Benzathine penicillin, 50 000 U/kg im in a single dose
*Limited data; not recommended by the Centers for Disease Control (CDC) or European guidelines but included in the World Health Organization (WHO) guidelines. †Do not completely cross placental barrier so infected fetus is not adequately treated; newborns need to be treated soon after delivery. ‡CSF analysis should be performed prior to therapy. ¶Neonate with a normal physical examination and serum non-treponemal antibody titer less than fourfold the maternal titer; treatment is optional if the mother was fully treated before pregnancy.

Table 82.11 Treatment recommendations for syphilis in special situations. h, hours; im, intramuscularly; iv, intravenously; po, orally; q, every.

GONORRHEA

Synonyms: ■ Gonorrhea: "clap" ■ Disseminated gonococcal infection: arthritis–dermatosis syndrome

Key features

- Gonorrhea is the most common reportable STI in high-income countries
- It is caused by *Neisseria gonorrhoeae*, which infects the mucosal surfaces of the human genital tract (as well as the anus, rectum, and oropharynx) after direct – usually sexual – contact with an infected person
- Cutaneous pustules as well as systemic symptoms such as arthritis and fever can result from hematogenous dissemination, which occurs in only a small percentage of infected individuals
- Overall, the incidence of gonorrhea declined during the latter portion of the 20th century as a result of safer sexual practices to avoid transmission of HIV, but afterwards the incidence has increased substantially in high-income countries following the introduction of antiretroviral therapy and pre-exposure prophylaxis for HIV
- Over the past several decades, resistance of *N. gonorrhoeae* to various antimicrobials has increased in frequency

History

Gonorrhea was mentioned in ancient literature from China, Egypt, the Roman Empire and Greece, as well as in the Old Testament[27]. Over the centuries, several names have been used to denote infection with *N. gonorrhoeae*, including: "strangury", as used by Hippocrates; "clap", derived from the district of prostitution called "Les Clapiers" in Paris; "gonorrhea", chosen by Galen (130 CE) to describe the urethral exudate as a "flow of seed"; and "M. Neisser", recognizing Albert Neisser, who discovered the microorganism in 1879 in stained smears from vaginal, urethral, and conjunctival exudates.

Culture of *N. gonorrhoeae* was first described by Leistikow and Lüffler in 1882, and it was improved in 1964 by Thayer and Martin, who devised selective growth conditions on special agar plates[28]. Understanding the differences in the virulence of gonococci and studies of its molecular biology have led to greater insight into the pathology of the organism[29]. Treatment of gonococcal infections was problematic until sulfonamides were introduced in 1936 and penicillin in 1943. For decades, gonorrhea was easily treated with just a single dose of one antibiotic. However, over the past several decades, an increase in antimicrobial resistance to penicillin and other antibiotics, such as tetracyclines and quinolones, has been observed and has become problematic. Declining *in vitro* susceptibility to cefixime led to a change in treatment guidelines, such that dual therapy with ceftriaxone and azithromycin became the recommended therapeutic regimen for uncomplicated gonorrhea. However, a more recent and worrisome development is elevated MICs (minimum inhibitory concentrations) to azithromycin[10,30] and scattered reports of ceftriaxone-resistant, multi-drug-resistant *N. gonorrhoeae*[30a].

Epidemiology

During the past century, the incidence of gonorrhea was influenced by politics, with peaks at the ends of the First and Second World Wars. A sudden decrease in reported cases occurred after the introduction of penicillin and other effective antimicrobials. Subsequently, the

sexual freedom of the 1970s led again to an increase in the incidence of gonorrhea. However, with the advent of the AIDS epidemic, sexual practices again changed due to concerns regarding transmission of HIV, and this had a remarkable impact on the incidence of gonorrhea. Total gonorrhea rates in the US peaked in the mid 1970s and remained relatively low and stable from the 1990s to the mid 2010s.

Political changes in Eastern Europe led to an increased rate of gonorrhea (as well as syphilis) in the 1990s, especially in sex workers and those with sexual exposure to them. Migration of sex workers with a high infection rate also increased the number of reported cases of gonorrhea in other regions of Europe, especially in urban areas and high-risk groups. This probably reflects an increase in unsafe sexual behavior, particularly among young people and in high-risk populations. At the same time, the incidence of gonorrhea decreased in many countries (see above) due to safer sexual practices to avoid transmission of HIV. However, following the introduction of antiretroviral therapy and especially pre-exposure prophylaxis (PrEP) for HIV, there has been a reemergence of infections with *N. gonorrhoeae* as well as other STIs, especially amongst MSM. Of note, the national lockdowns imposed to prevent spread of SARS-CoV2 were associated with a sudden reduction in reported cases. Nonetheless, the trend of an increasing number of reported cases of gonorrhea, driven primarily by MSM, is expected to continue; for example, in many European countries the number of cases among women has also been increasing continuously since 2009 (ECDC Surveillance report: Annual epidemiological report for 2018).

Similar to other venereal diseases, the incidence of gonorrhea varies with age and is highest in the 15- to 24-year-old age group, in which there is a higher rate in women than in men. In the US, African-Americans have a 10-fold higher rate of gonococcal infections than White individuals. This may reflect different sexual behavior patterns and exposures as well as a better reporting system in public health institutions, which are more often utilized by African-Americans.

Transmission

N. gonorrhoeae is a pathogen restricted to humans as its only host and transmitted primarily by sexual contact. The most efficient transmission occurs by vaginal or anal intercourse where there is physical contact with the mucosal surface of a sexual partner with an asymptomatic or mildly symptomatic infection. An exception is indirect contact among prepubescent girls sharing contaminated objects. There is no evidence that gonococci can be spread by air droplet transmission as occurs with meningococci. Vertical transmission can occur from an infected mother to the newborn during parturition, and this may lead to gonococcal conjunctivitis, pneumonia, or even vulvovaginal infection.

Biology of *N. gonorrhoeae*

Gonococci are Gram-negative diplococci that typically grow in pairs. They exhibit multiple colony types when grown on hemoglobin-containing media in a 3% CO_2 atmosphere. The outer membrane structure of *N. gonorrhoeae* is typical for Gram-negative bacteria but, in contrast to *N. meningitidis*, it lacks the polysaccharide capsule that is responsible for the virulence of meningococci. Surface molecules on the outer membrane are involved in attachment, invasion and host injury, and they also represent important antigenic structures, especially the fibrillar pili (composed of 18 kDa pilin subunits)[31].

Gonococci require iron to grow, with sources including transferrin, lactoferrin, and hemoglobin; acquisition of iron is mediated by binding to host proteins via specific receptors. The microorganism cannot tolerate drying or low temperatures, and its growth is optimal at 35–37°C in a 5% CO_2 atmosphere on a complex growth medium containing inorganic iron, glucose, vitamins, and cofactors as well as antibiotics.

Pathogenesis

Although there is increasing knowledge about the pathogenicity of this microorganism, the exact molecular mechanisms of invasion of gonococci into the host cell are still unknown. Several virulence factors are involved in the processes of adherence, inflammation, and mucosal invasion[32]. Because pili increase adhesion to the host cell and allow movement, they also play an important role in pathogenesis; this may explain why non-piliated gonococci have a reduced ability to cause infections in humans. The adherence of gonococci to the human epithelial host cell and to neutrophils is dependent not just on the pili but also on Opa ligands. Anti-pilus antibodies have been shown to block epithelial adherence and increase phagocytic killing. Expression of the transferrin receptor and full-length lipo-oligosaccharide (LOS) appear to increase infectivity. Gonococci are able to multiply and divide intracellularly, where they are immune to host defense mechanisms. Cellular invasion is favored by expression of certain Opa proteins and non-sialylated LOS.

Gonococci have the ability to cause tissue destruction by production of a variety of enzymes and lipids such as phospholipase, peptidases, and lipid A. This plays a role in their damage of fallopian tubes and the development of postinflammatory arthritis.

Clinical Features

Gonorrhea has a broad spectrum of clinical manifestations in both men and women, including asymptomatic infections, local symptomatic mucosal infections (with or without local complications), and systemic dissemination (Table 82.12). Symptoms vary according to the site of infection and strain of organism.

The incubation period for gonorrhea is relatively short; it only takes 2–5 days until signs and symptoms of an infection with *N. gonorrhoeae* appear. Up to 10% of infected men and 50% of infected women lack clinical symptoms, which is especially common in rectal and pharyngeal infections[33].

Gonococcal infection in men

The most common clinical presentation of gonococcal infection in men is an acute anterior urethritis with dysuria and a urethral discharge that is typically purulent and profuse (Fig. 82.17). In about one-quarter of infected men, the urethral symptoms are less pronounced, similar to those of non-gonococcal urethritis, and appear only after urethral manipulation ("stripping"). Without treatment, clinical symptoms disappear in most patients after about 6 months. Local complications can include inflammation of the Cowper and Tyson glands and gonococcal pyoderma; ascension of the infection may lead to epididymitis, prostatitis, and vesiculitis. Patients with gonococcal epididymitis present with unilateral testicular pain and swelling accompanied by urethritis.

Gonococcal infection in women

In about 50% of infected women, gonococcal infection is asymptomatic and therefore remains unnoticed. The primary site of gonococcal infection in women is the endocervical canal, with associated clinical

CLINICAL MANIFESTATIONS OF GONORRHEA
Disseminated infection
• Arthritis • Fever • Tenosynovitis • Acral cutaneous pustules • Scalp abscesses (in neonates at sites of fetal scalp monitor electrodes) • Endocarditis • Meningitis
Direct mucosal infection
• Urethritis • Cervicitis • Proctitis • Pharyngitis • Vulvovaginitis (children) • Ophthalmia neonatorum
Local extension
• Prostatitis • Vesiculitis • Epididymitis • Salpingitis • Oophoritis • Pelvic inflammatory disease

Table 82.12 Clinical manifestations of gonorrhea.



Fig. 82.17 Gonococcal urethritis with a purulent urethral discharge.



Fig. 82.18 Gonococcemia (arthritis–dermatosis syndrome). Pustule with surrounding erythema on the toe.

symptoms consisting of increased vaginal discharge, dysuria, intermenstrual bleeding, and menorrhagia. Clinical inspection shows purulent cervical discharge with erythema and edema; swabbing of the endocervical canal results in a highly characteristic yellow color. Urethral colonization is present in 70%–90% of infected women and is the usual site of infection in women who have had a hysterectomy. Occasionally, inflammation of the Bartholin glands is observed, with acute swelling of the labial folds and appearance of purulent discharge when pressure is applied to the gland.

The most common local complication in women is acute salpingitis or pelvic inflammatory disease (PID) due to ascension of the microorganisms. It occurs in ~10%–20% of infected women (often developing immediately after a menstrual period) and may result in the long-term consequences of infertility, chronic pelvic pain, and ectopic pregnancy. The clinical manifestations of PID vary and include lower abdominal pain, adnexal tenderness, elevation of the ESR, leukocytosis, and fever. Gonorrheic perihepatitis (Fitz-Hugh–Curtis syndrome), with inflammation of the adjacent peritoneal area, is an infrequent complication in which symptoms of PID are accompanied by pain in the right upper quadrant that mimics acute cholecystitis.

Extragenital gonorrhea

Pharyngeal gonorrhea

This can occur in both men and women after oral sexual exposure. Because it is usually asymptomatic, the infection typically goes undetected and spontaneously resolves within a few weeks[34]. Pharyngeal gonorrhea disproportionately affects MSM and may be an important source of urethral gonorrhea in MSM[35]. It is important to address this site of infection, especially in this high-risk group.

Rectal gonorrhea

Rectal gonorrhea is mainly seen in MSM and in heterosexual women who practice receptive anal intercourse. Rectal gonorrhea is asymptomatic in at least 50% of patients, but it may result in gonococcal proctitis that is accompanied by inflammation, rectal discharge, anal pruritus, bleeding, tenesmus, and constipation.

Gonococcal ophthalmia (including ophthalmia neonatorum)

Gonococcal ophthalmia is uncommon in adults but still represents a major cause of blindness in some low-income countries. Primarily due to self-inoculation and unusual sexual practices, it initially presents as purulent conjunctivitis and, if left untreated, can rapidly progress to severe keratitis followed by corneal opacification.

Gonococcal infection in newborns is caused by inoculation with *N. gonorrhoeae* during delivery through an infected birth canal, and most often it presents with purulent conjunctivitis (ophthalmia neonatorum). Due to preventive application of antimicrobial ointment (usually erythromycin) immediately after birth, the rate of this gonococcal infection is currently low.

Disseminated gonococcal infection

Arthritis–dermatosis syndrome (gonococcemia)

The most common clinical manifestation of gonococcal bacteremia is an acute arthritis–dermatosis syndrome, which occurs in ~0.5%–1% of patients with mucosal gonorrhea[36]. Risk factors for disseminated gonococcal infection include: (1) menstruation, with the majority of cases in women developing during or immediately following menses; (2) deficiencies in the late complement components C5–C9 (see Ch. 60); and (3) inhibitors of the cleavage of C5 to C5a and C5b, e.g. ravulizumab, eculizumab. The classic syndrome consists of fever, joint pain, and a paucilesional eruption of hemorrhagic pustules. Gonococcal tenosynovitis affects primarily larger joints (e.g. knees, elbows, wrists, ankles) and is sometimes visible as erythema overlying the tendons.

The cutaneous lesions consist of scattered pustules, often necrotic, due to an embolic septic vasculitis. They occur primarily on the distal portions of the extremities (Fig. 82.18). With a longer duration of symptoms, positive blood cultures become less common.

Laboratory Diagnosis

Laboratory diagnosis is based on the identification of *N. gonorrhoeae* in secretions from infected mucous membranes by using stained smears, molecular biologic techniques, and/or bacterial culture (Fig. 82.19). Samples are typically obtained from the endocervical canal in women (after wiping off exudate), the urethra in men and occasionally in women who have had a hysterectomy, and (when indicated) the posterior pharynx. For diagnosis by nucleic acid amplification methods (see below), a vaginal swab or urine sample can also be used. Anorectal specimens should be obtained via direct visualization using anoscopy if possible.

Staining methods

Direct detection of Gram-negative diplococci within neutrophils in Gram- or methylene blue-stained smears provides an immediate diagnosis (Fig. 82.20), which is especially helpful in symptomatic individuals. It also represents a recommended point-of-care test. Gram-stained urethral exudate detects between 95% and 98% of symptomatic infections in men, whereas Gram-stained cervical smears have a sensitivity of about 50%. The specificity of Gram-stained exudates depends on several factors including the experience of the microscopist, proper collection, the presence of acute symptoms, and bacterial load; specificity may approach 100% in an optimal setting. However, because of its lower sensitivity in asymptomatic individuals, a negative Gram stain should not be considered sufficient for excluding infection in such patients. Smears are not helpful for detection of rectal and pharyngeal gonorrhea due to the presence of a large number of other bacteria.

Culture techniques

Isolation of *N. gonorrhoeae* via culture is still recommended for cases with medicolegal implications. In addition, pustular skin lesions due to gonococcemia should be cultured. Although it does depend on the symptomatic status of the infected person, antibiotic-containing selective media (Thayer–Martin) or selective New York media can have a sensitivity of 80%–95% when *genital* swabs are directly plated at the time of collection. The specificity of bacterial culture is reported to be ~95% for genital samples. However, sensitivity is much lower for *extragenital* swabs such as those from the rectal area (<50%). Confirmation of a positive culture by *N. gonorrhoeae*-specific tests is recommended and is mandatory in cases of extragenital infection.

The advantage of isolating *N. gonorrhoeae* via culture is the ability to perform antimicrobial resistance (AMR) testing. This is particularly

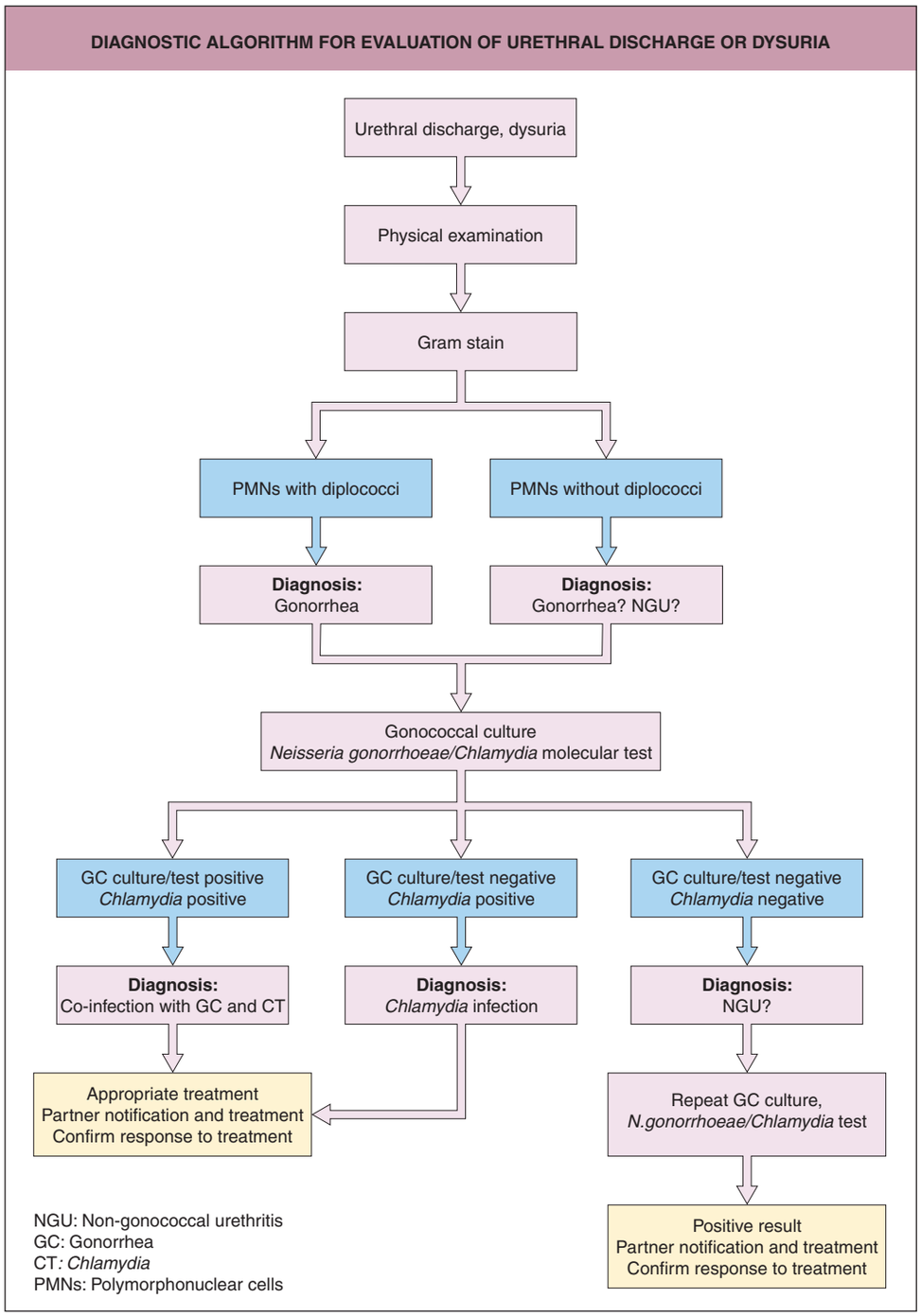


Fig. 82.19 Diagnostic algorithm for evaluation of urethral discharge or dysuria. If cultures are negative, but polymorphonuclear cells are seen on smear, some clinicians will still prescribe doxycycline.

important given the rising number of antibiotic-resistant isolates, and it also allows for regional AMR surveillance. Monitoring antibiotic susceptibility is crucial, especially with the increasingly routine use of non-culture techniques.

Non-culture techniques for gonococcal diagnosis

Molecular techniques for diagnosing gonococcal infections are widely employed and are advantageous over bacterial culture when specimen transport and storage are potential problems. The former are also more sensitive than culture for extragenital sites and when the infection is asymptomatic[37]. In addition, molecular tests can detect gonococci in easy-to-obtain specimens such as urine and are therefore the best test when screening asymptomatic individuals. Another advantage is that multiplex amplification assays can detect *Chlamydia trachomatis* (CT) and other sexually transmitted microbes such as *Mycoplasma genitalium*, in addition to *N. gonorrhoeae* (NG), without the need for an additional specimen (see Fig. 82.19). Their major disadvantage is the lack of antibiotic sensitivity testing (see above).

Nucleic acid amplification techniques (NAATs)

With respect to overall sensitivity, specificity, and ease of specimen transport, NAATs outperform other tests that are currently available for the diagnosis of gonococcal infections.

NAATs are used to detect gonococcal DNA or RNA, often in addition to chlamydial DNA or RNA. Methods include transcription-mediated amplification to detect rRNA (e.g. Aptima Combo 2® assay for CT/NG) and strand displacement amplification (e.g. BD ProbeTec™ ET System). The Xpert® CT/NG test kit can detect *N. gonorrhoeae* within 90 minutes and also co-amplifies CT and NG.

NAATs are continuously being enhanced, leading to faster turnaround times, more user-friendly features, and detection of an increasing number of pathogens from a single sample (e.g. *Trichomonas vaginalis* as well as *C. trachomatis* and *N. gonorrhoeae* via the BD MAX™ CT/GC/TV assay). As previously noted, in addition to physician-collected specimens, samples for NAATs can be obtained "non-invasively", using self-collected vaginal or introital swabs[38] or just urine.

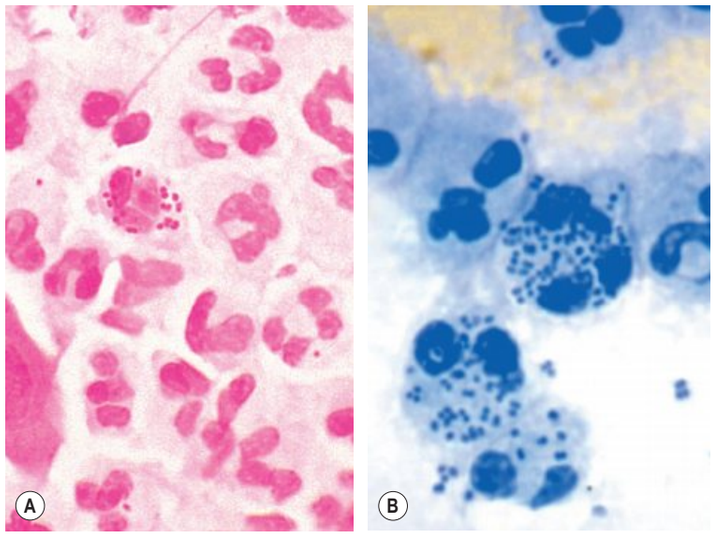


Fig. 82.20 Gonococci in Gram-stained (A) and methylene blue-stained (B) smears of urethral discharge. Neutrophils containing Gram-negative or methylene blue-positive diplococci, consistent with *Neisseria gonorrhoeae*, are evident. *B, Courtesy Harald Moi, MD.*

Pathology

Biopsies of skin lesions due to gonococcemia show a septic vasculitis with extravasated erythrocytes and thrombi. Organisms are usually not demonstrated.

Differential Diagnosis

Other causes of urethral and cervical discharge in men and women must be considered, including infections with *C. trachomatis*, *M. genitalium*, *T. vaginalis*, yeasts, and anaerobic bacteria. The skin lesions of disseminated gonococcemia may need to be distinguished from folliculitis (e.g. bacterial), another disseminated infection, a neutrophilic dermatosis, cutaneous vasculitis, or a pustular drug eruption.

Treatment

Although many antibiotics can be used for the treatment of gonorrhea, selection of therapy depends on the susceptibility of the organism that is isolated (or regional patterns), the anatomic site(s) of the infection, clinical symptoms, and the cost (especially in resource-poor settings) as well as potential side effects of the drug. Over the past several decades, strains of gonorrhea resistant to a number of antibiotics, including sulfonamides, penicillin, tetracyclines, erythromycin, spectinomycin, and more recently quinolones, azithromycin, and some cephalosporins, have emerged. Antibiotic resistance of *N. gonorrhoeae* clearly represents an urgent public health threat.

Over the years, the development of different types of resistance has led to regular revisions of gonococcal treatment recommendations. For example, in 2007, the CDC recommended that fluoroquinolones no longer be prescribed for the treatment of gonococcal infections in the US. Third-generation cephalosporins then became the antibiotics of choice for gonococcal infections (Table 82.13)[39]; however, treatment failures (especially with oral cephalosporins in Asian countries) and decreased *in vitro* sensitivity, e.g. to cefixime, began to appear[40]. In addition to the emergence of a small number of strains with decreased susceptibility to ceftriaxone[41], the first gonococcal strain with ceftriaxone resistance combined with high-level resistance to azithromycin was reported from England and Australia in 2018[42,43]. As a result, the WHO declared antimicrobial-resistant *N. gonorrhoeae* a priority global health issue[44].

The current CDC treatment guidelines recommend a single dose of 500 mg of intramuscular ceftriaxone for uncomplicated gonococcal infections. Alternative regimens are available when ceftriaxone cannot be used to treat urogenital or rectal gonorrhea[45]. Of note, there is a portable, rapid, on-cartridge magnetofluidic purification and testing (PROMPT) PCR test for determining susceptibility of *N. gonorrhoeae* to ciprofloxacin that allows for targeted therapy and leads to a reduction in the use of ceftriaxone[46]. Persons infected with *N. gonorrhoeae* are frequently co-infected with *C. trachomatis* and this co-infection is readily diagnosed by combined NAATs (see above). When confirmed or if *C. trachomatis* infection cannot be excluded, doxycycline is the recommended treatment (see Table 82.13).

For disseminated gonococcal infection, first-line therapy consists of intravenous ceftriaxone (1 g every 24 hours for at least 7 days). Lastly, confirmation of cure, compliance with therapy, and partner notification are legal recommendations for gonococcal treatment and prevention in some countries.

TREATMENT RECOMMENDATIONS FOR GONOCOCCAL INFECTIONS
Uncomplicated gonococcal infections of the urethra, cervix, rectum, or pharynx
Recommended regimens*:
• Ceftriaxone, 500 mg im as single dose† If not excluded, also treat for *Chlamydia trachomatis* with doxycycline 100 mg po BID for 7 days or during pregnancy, azithromycin 1 g po as single dose
Alternative regimen (except for pharynx)*:
• Gentamicin 240 mg im as a single dose PLUS azithromycin 2 g po as single dose – *or* – • Cefixime 800 mg po as single dose
Gonococcal conjunctivitis
• Ceftriaxone, 1 g im as single dose
Disseminated gonococcal infection
***Recommended regimen*:**
• Ceftriaxone, 1 g im or iv q24h • Ceftriaxone administered until 24–48 hours after improvement begins
Alternative regimens*:
• Cefotaxime 1 g iv every 8 hours – *or* – • Ceftizoxime 1 g iv every 8 hours
Neonatal infections
Disseminated gonococcal infection and gonococcal scalp abscesses in newborns
• Ceftriaxone, 25–50 mg/kg iv or im daily for 7 days (10–14 if meningitis) – *or* – • Cefotaxime, 25 mg/kg iv or im q12h for 7 days (10–14 if meningitis)
Ophthalmia neonatorum or asymptomatic neonate born to mother with untreated gonorrhea
• Ceftriaxone, 25–50 mg/kg iv or im as single dose, not to exceed 250 mg
*Alternative treatment regimens in the International Union Against Sexually Transmitted Infections (IUSTI) guidelines 2020 (https://iusti.org/wp-content/uploads/2020/10/IUSTI-Gonorrhoea-2020.pdf). †If patient weighs <150 kg; if ≥150 kg, 1 g is administered.

Table 82.13 Treatment recommendations for gonococcal infections. Based on CDC 2021 Guidelines (www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf). BID, twice daily; h, hours; im, intramuscularly; iv, intravenously; po, orally; q, every.

CHANCROID

Synonyms: ■ Soft chancre ■ Ulcus molle

Key features

- Chancroid is characterized by acute genital ulcers and inguinal adenitis
- It is caused by the sexually transmitted, Gram-negative, and facultatively anaerobic bacterium *Haemophilus ducreyi*
- It is a rare disease in high-income countries, and its occurrence is closely linked with commercial sex workers

History

In 1850, chancroid was first differentiated from syphilis. In 1889, Ducrey described the responsible organism as a streptobacillary rod, which he was able to subcultivate by serial autoinoculations into the forearm of a patient[47,48].

Epidemiology

The disease is common in parts of Africa, the Caribbean, and Southeast Asia and is endemic in many low-income countries (Fig. 82.21), with a worldwide annual incidence of about 7 million[49]. Outbreaks are occasionally reported in cities in high-income countries, predominantly within the US. In the US, the number of chancroid cases peaked in the early 1990s and has been very low for the past 25 years. In most of the disease settings, sex workers are the reservoir for the microorganism, and men are much more frequently affected than women (ratio 10:1). In some low-income countries, chancroid is the most common cause of infectious genital ulcer disease (Table 82.14), with frequencies even higher than those of genital herpes.

Transmission

The source of infection is almost always sexual contact with an infected person who has genital ulcers. The probability of transmitting chancroid after a single sexual contact is 35%, and untreated infected women are estimated to be infectious for up to 45 days (while the clinical lesions are present)[50]. Asymptomatic carriers seem to be rare and there is no evidence that infected individuals harbor the organism for a significantly long period of time without clinical findings.

Chancroid and HIV

Chancroid and other diseases that produce genital ulcers are important risk factors for transmission of HIV. Men infected with HIV more often have had a history of genital ulcers compared with HIV-negative men[51]. The risk of acquiring HIV after having sexual contact with HIV-positive women was highest for uncircumcised men with genital ulcer disease compared with circumcised men with and without genital ulcer disease (29% versus 6% versus 2%). In women, the risk of becoming infected with HIV also increases with the number of episodes of genital ulcer disease.

The presence of increased numbers of $CD4^+$ lymphocytes and macrophages in ulcers due to infection with *H. ducreyi* provides an ideal opportunity for a latent HIV infection to become productive, with excretion of the virus into ulcer secretions. Genital lesions therefore become both a portal of viral entry for non-infected individuals and viral exit for HIV-infected persons[52].

Biology of the Organism

H. ducreyi is a Gram-negative, facultatively anaerobic bacillus of small size that shows a typical chaining pattern on Gram stain (Fig. 82.22). It does not share many similarities with other members of the genus *Haemophilus*.

Pathogenesis

The penetration of the microorganism occurs via microscopic barrier defects in the epidermis. Signs of inflammation develop due to infiltration of lymphocytes, macrophages, and granulocytes in a primarily

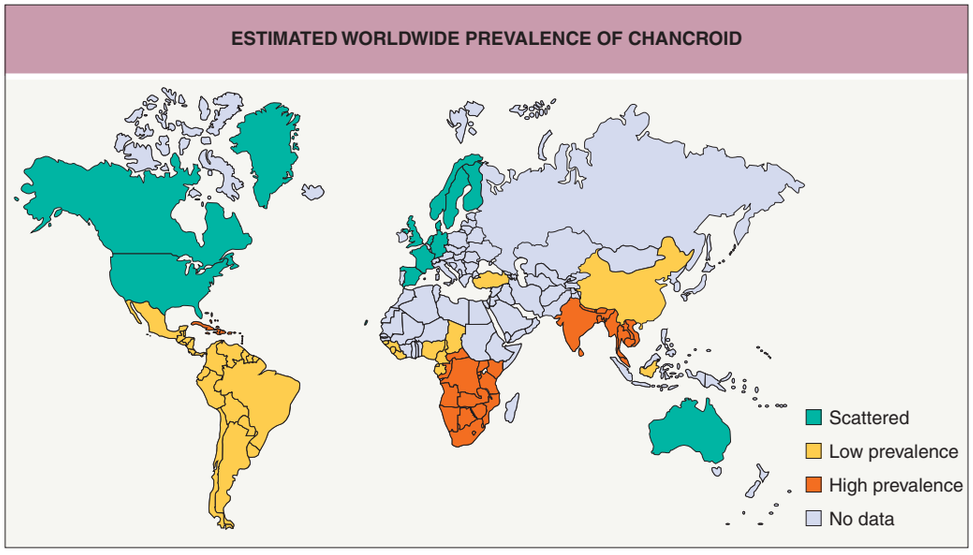


Fig. 82.21 Estimated worldwide prevalence of chancroid[48].

INFECTIOUS CAUSES OF GENITAL ULCER DISEASE				
Disease	**Incubation time**	**Clinical lesion**	**Diagnosis**	**Organism**
Genital herpes	3–7 days	Vesicles, erosions, ulcers; history of herpes viral infection; painful	PCR, culture, DFA, Tzanck (if vesicles)	HSV 2 > 1
Primary syphilis	10–90 days, average 3 weeks	Non-purulent; usually single ulcer; indurated; relatively painless	Darkfield microscopy, serology, PCR	*Treponema pallidum*
Chancroid	3–10 days	Purulent; often multiple ulcers; soft, undermined edges; painful	Culture, PCR	*Haemophilus ducreyi*
LGV	3–12 days	Transient ulcer; indurated; painless	PCR, culture, serology	*Chlamydia trachomatis* serovars L1–3
Donovanosis	2–12 weeks	Chronic ulcer; indurated, beefy red, friable	Smears, histology	*Klebsiella (Calymmatobacterium) granulomatis*

Table 82.14 Infectious causes of genital ulcer disease. DFA, direct fluorescent antibody assay; LGV, lymphogranuloma venereum.

Th1 cell-mediated immune response combined with pyogenic inflammation. Chancroid is associated with regional lymphadenitis due to the spread of the infection and resultant pyogenic inflammation.

Clinical Features

The incubation period is 3–10 days; usually, the onset of clinical symptoms occurs between days 4 and 7. In men, the lesion starts with a papule surrounded by erythema and soon progresses to a pustule and then a painful ulcer. The latter typically has a purulent base and soft, undermined edges and is sharply demarcated (Fig. 82.23A,B). In about one-half of infected men, several ulcers develop due to apposition with the initial lesion, and they can coalesce to form giant ulcers. Most lesions are located on the internal or external surface of the prepuce, in the coronal sulcus (particularly in uncircumcised men), or around the frenulum. They are often accompanied by edema of the prepuce.

Occasionally, a so-called "septic sore" can be observed on the shaft of the penis or prepuce, with pus trapped within the skin in the absence of an obvious ulcer. In this case, the pus that can be expressed is full of microorganisms[47]. In contrast to chlamydial infections, chancroid is symptomatic in almost all infected individuals.



Fig. 82.22 Gram-stained smear in chancroid. This smear of exudate from a genital ulcer shows the characteristic chaining pattern of *Haemophilus ducreyi*.

Co-infections with syphilis or herpes simplex virus (HSV) are possible. In Kenya, ~4% of men with genital ulcer disease have a co-infection with both *T. pallidum* and *H. ducreyi* (ulcus mixtum) and about the same percentage have HSV plus *H. ducreyi*, which makes etiologic diagnosis based on clinical findings impossible.

In women, the majority of lesions are within the introital area; they may also occur on the cervix or vaginal wall, or in the perianal area, but rarely occur in an extragenital location. Lesions in women are sometimes only mildly symptomatic and are more often multiple.

In both men and women, painful inguinal lymphadenitis may accompany the genital lesions. It is more often observed in men (about 40% of patients) and is usually unilateral (Fig. 82.23C). Inguinal buboes may rupture and lead to inguinal ulceration.

Pathology

Biopsies of chancroid classically have three zones of inflammation beneath the ulcers. The first zone has necrotic debris, fibrin, and neutrophils. The middle zone is an area of granulation tissue, and the deepest zone contains lymphocytes and plasma cells. Gram-negative coccobacilli are only rarely found with tissue Gram or Giemsa stains and are best seen with smears.

Diagnosis

Material is usually obtained with a cotton swab, on which the organism can only survive for a few hours without being refrigerated at 4°C. Gram stain of *H. ducreyi* in a smear of the exudate shows a "school-of-fish" or "railroad track" pattern of small Gram-negative bacilli (see Fig. 82.22). The finding is not specific because other bacteria may have a similar arrangement, and it is insensitive because the responsible bacteria are only seen in about a third to a half of infected persons.

Accurate diagnosis of chancroid requires isolation of *H. ducreyi* on special culture media; small, non-mucoid, semiopaque or translucent colonies appear after 24–72 hours if grown at 33–35°C in a 5%–10% CO_2 atmosphere. Further identification methods are needed, such as the porphyrin test, to prove the requirement of hemin (factor X) for growth. There are variations in media (which are not widely available from commercial sources) and the sensitivity of culture is between 60% and 80%, depending on the quality and handling of the specimen, culture conditions, and laboratory experience.

If culture is not possible or is inconclusive, diagnosis can be based on the clinical picture and the exclusion of other microorganisms



Fig. 82.23 Chancroid. A Well-demarcated painful ulcers on the penis. **B** Multiple purulent ulcers with undermined borders. **C** Unilateral lymphadenitis with overlying erythema. *B, Courtesy Joyce Rico, MD.*

TREATMENT REGIMENS FOR CHANCROID
• Azithromycin, 1 g po, single dose – *or* –
• Ceftriaxone, 250 mg im, single dose – *or* –
• Ciprofloxacin, 500 mg po twice daily for 3 days*,† – *or* –
• Erythromycin base, 500 mg po three times daily for 7 days†
*Contraindicated for pregnant or lactating women. †Worldwide, isolates with intermediate resistance.

Table 82.15 Treatment regimens for chancroid. Based on CDC 2021 Guidelines (www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf). im, intramuscularly; po, orally.

that cause genital ulcer disease, such as syphilis or genital herpes, as well as on the epidemiologic data and response to therapy. A genital ulcer disease panel that can detect HSV-1, HSV-2, *T. pallidum*, and *H. ducreyi* via real-time PCR is commercially available in some countries[53].

Other diagnostic procedures, such as antigen detection methods or serologic tests, are still under development and cannot yet be recommended for routine diagnosis.

Differential Diagnosis

Other infections that cause genital ulcers have to be considered (see Table 82.14), as well as trauma, a fixed drug eruption, and, occasionally, carcinoma.

Treatment

Successful treatment can be achieved using several antimicrobial drugs (Table 82.15); ulcers improve within 3 days and typically heal in 14 days or less, depending on the initial lesions. The different treatment regimens cure about 95% of infected individuals, with azithromycin and ceftriaxone requiring only a single dose. Ciprofloxacin is contraindicated in pregnant and lactating women. In patients with HIV infection, the treatment recommendations are the same, but with a longer treatment course; close monitoring may be necessary because of delayed healing and possible treatment failures.

Sexual partners from the 10 days preceding the onset of symptoms should be examined and treatment offered regardless of whether the microorganism can be cultured or clinical symptoms are present.

LYMPHOGRANULOMA VENEREUM

Synonyms: ■ Durand–Nicolas–Favre disease ■ Climatic bubo ■ Strumous bubo ■ Poradenitis inguinale ■ Lymphogranuloma inguinale

Key features

- Lymphogranuloma venereum (LGV) is an STI caused by *Chlamydia trachomatis* serovars L1–3 and can be associated with abscesses, fistulas, and involvement of lymphatic tissue
- LGV is endemic in some areas of Africa, Asia, and South America
- Outbreaks of LGV proctocolitis can occur in high-income countries amongst MSM who also have increased rates of HIV infection
- The disease progresses through three stages: (1) initial infection of the genital mucosa; (2) inguinal lymphadenopathy that is usually unilateral; and (3) a firm mass and bubo with spontaneous drainage and involution, often accompanied by proctocolitis and involvement of perirectal or perianal lymphatic tissue

History

Lymphogranuloma venereum (LGV) has been confused with other diseases that cause inguinal lymphadenopathy, especially syphilis, genital herpes, and chancroid. A major diagnostic advantage arose with the introduction of the Frei test, a specific skin test established in 1925[54]. The first isolation of *Chlamydia* was reported in 1930, enabled by intracerebral inoculation of monkeys, followed in 1935 by cultivation in fertilized eggs[55].

CLINICAL MANIFESTATIONS OF LYMPHOGRANULOMA VENEREUM
Initial manifestations: 3–12 days
• Papule • Erosion or ulcer • Herpetiform vesicle • Nonspecific urethritis or cervicitis
Inguinal syndrome: 10–30 days up to 6 months
• Regional lymphadenopathy (mostly inguinal and femoral; also perirectal, deep iliac) • Overlying erythema • Constitutional symptoms • Eruption of buboes • Pelvic inflammatory disease (PID), back pain
Ano-genito-rectal syndrome: months to years
• Proctocolitis • Hyperplasia of intestinal and perirectal lymphatic tissue • Perirectal abscesses • Ischiorectal and rectovaginal fistulas • Anal fistulas • Rectal strictures and stenoses
Other manifestations
• Urethro-genito-perineal syndrome • Peno-scrotal elephantiasis • Erythema nodosum • Submaxillary or cervical lymphadenopathy associated with oropharyngeal lesions

Table 82.16 Clinical manifestations of lymphogranuloma venereum.

Epidemiology

LGV is endemic in East and West Africa, Southeast Asia, India, South America, and the Caribbean basin. In some countries, it is a reportable disease. LGV classically affected sailors, soldiers, and travelers who acquire the disease in endemic regions. In the past, data regarding the prevalence of LGV have been based on the results of serologic tests and the Frei skin test, both of which are nonspecific and have cross-reactivity with other genito-ocular chlamydial infections.

LGV is reported more often in men than in women and the peak age correlates with the period of maximum sexual activity. However, the frequency of infection following sexual intercourse has not been well investigated. Since 2003, a series of outbreaks of LGV have been reported in Western Europe and the US[56]. The affected individuals are primarily MSM who live in large cities[57], many of whom have concurrent HIV infection. In these outbreaks, LGV can present as ulcerative proctitis or as an asymptomatic infection[58].

Pathogenesis

Caused by specific *Chlamydia trachomatis* serovars (L1–3), LGV affects mainly the lymphatic tissue in the genitorectal area. The organisms enter the body via microscopic defects in the mucosa or the skin. The microorganisms then enter the lymphatics, leading to lymphangitis, perilymphangitis, and infection of lymph nodes. Over a period of many weeks to months, the inflammatory process expands and results in periadenitis, involvement of a few neighboring lymph nodes, the development of abscesses (which can rupture), and the formation of fistulas and strictures. In the rectum, destruction and ulceration of the mucosa may occur. Local progression and systemic dissemination are both influenced by host immunity. Latent persistence of the microorganism within involved tissues may last for many years.

Clinical Features

The clinical manifestations of LGV can be separated into primary lesions, inguinal and ano-genito-rectal syndromes, and other manifestations (Table 82.16).

The initial clinical presentations vary, appearing after an incubation period of 3–12 days (see Table 82.16). In up to half of infected individuals, a herpetiform lesion develops at the site of exposure and heals rapidly without a scar. This transient lesion is most often located on the coronal sulcus in men and on the posterior vaginal wall in women, and it is usually accompanied by local lymphangitis. Cervicitis and urethritis are mild and often remain unrecognized. Rectal exposure might result in proctocolitis associated with rectal discharge, anal pain, and tenesmus. Co-infection with other pathogens can sometimes be observed.

The secondary stage is characterized by the *inguinal syndrome*, in which unilateral lymphadenopathy (depending on the site of the primary infection) is accompanied by overlying erythema. The bubo is initially firm and then undergoes rapid enlargement, becoming more painful. Eventually the overlying skin develops a bluish discoloration and the bubo finally ruptures through the skin; pus may drain through numerous sinus tracts (Fig. 82.24), followed by healing. If untreated, relapses occur in about 20% of patients. Constitutional symptoms such as meningeal irritation, hepatitis, and arthritis are rare and may occur due to systemic spread of the organism. Inguinal adenopathy is only observed in about one-third of infected women; proctitis and pain in the lower abdomen may be the only symptoms.

The manifestations of the *ano-genito-rectal syndrome* include proctocolitis and hyperplasia of the intestinal and perirectal lymphatic tissue. This leads to late manifestations dominated by local abscesses with anal fistulas as well as rectal strictures and stenoses[59].

Additional manifestations include urinary incontinence because of papillary growth of the mucosa of the urethral meatus in women. Extragenital lesions in the oropharynx, due to infection from oral sexual contact, are difficult to diagnose.

Pathology

Histologically, the skin may be ulcerated. A diffuse mixed infiltrate of neutrophils, histiocytes, plasma cells, and sometimes multinucleated giant cells is seen in the dermis. Although abscesses may occur in the skin, characteristic stellate abscesses are usually only observed in the lymph nodes. Organisms are rarely demonstrated within histiocytes (Gamna–Favre bodies) by Giemsa stain. An anti-*C. trachomatis* antibody has been used successfully to demonstrate microorganisms in skin biopsies.



Fig. 82.24 Lymphogranuloma venereum. Inguinal bubo that has ruptured and drained.

TREATMENT REGIMENS FOR LYMPHOGRANULOMA VENEREUM

• Recommended: doxycycline, 100 mg po twice daily
• Alternative and in case of pregnancy:
  • Erythromycin base, 500 mg po four times daily
  • Azithromycin 1 g po once weekly*

Duration for both regimens: 3 weeks
*Because not validated, a test of cure with *C. trachomatis* nucleic acid amplification technique (NAAT) 4 weeks after completion of treatment can be considered.

Table 82.17 Treatment regimens for lymphogranuloma venereum. po, orally. Based on CDC 2021 Guidelines (www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf).

Diagnosis

The diagnosis of LGV is based primarily on the detection of *Chlamydia*-specific DNA in lesional tissue by PCR or other nucleic acid amplification techniques (NAATs). This method is diagnostically more sensitive than is isolation of the organism via tissue culture. Typically, rectal specimens are tested for the presence of *C. trachomatis* and, if positive, are then genotyped in order to diagnose LGV. Serology testing is only recommended if it is performed in conjunction with DNA detection. In serologic assays, such as the complement fixation test or other assays that detect specific antibodies to the serovars L1–3 of *C. trachomatis*, the titer of antibodies is high. A differentiation of antibodies to L1–3 from those to other serovars is difficult but possible in the microimmunofluorescence test. A disadvantage of this diagnostic procedure is the lack of commercial availability.

Differential Diagnosis

Other causes of lymphadenopathy in the genital region (e.g. chancroid, lymphoma, cat scratch disease) or of genital ulcers or erosions should be excluded by additional diagnostic procedures (see Table 82.14). Pyogenic and mycobacterial infections also need to be considered, as well as Crohn disease, especially in the case of the ano-genito-rectal syndrome. Routine syphilis and HIV serologies are recommended and should be repeated after 3–6 months.

Treatment

Doxycycline is the treatment of choice, followed by macrolides (Table 82.17). Antibiotic treatment can cure the infection, but surgical intervention may be required in the case of large buboes.

Examination and treatment of sexual partners is required if contact occurred during the 30 days preceding the onset of symptoms. HIV-positive individuals may need prolonged treatment due to delayed resolution of symptoms.

DONOVANOSIS (GRANULOMA INGUINALE)

Synonyms: ■ Granuloma venereum ■ Granuloma inguinale tropicum ■ Granuloma venereum genitoinguinale ■ Granuloma genitoinguinale ■ Ulcerating sclerosing granuloma ■ Ulcerating granuloma of the pudendum ■ Serpiginous ulceration of the groin ■ Lupoid form of groin ulceration

Key features

- Donovanosis is a rare, chronic, progressive, ulcerative bacterial infection with *Klebsiella granulomatis* (previously known as *Calymmatobacterium granulomatis*), a Gram-negative bacillus
- Ulcers occur primarily in the genital region
- The responsible microorganisms are found within macrophages in smears or biopsy specimens (Donovan bodies)

History

The disease was initially described in India as ulcerations followed by elephantiasis of the genitalia. The microorganism was first identified in 1905 by Donovan, who noted the characteristic Donovan bodies in macrophages and epithelial cells of the stratum malpighii[60]. In 1950, Marmell and Santora proposed the name "donovanosis"[61]. Limited success in culturing the organism until the 1990s explains the slow progress in donovanosis research[62].

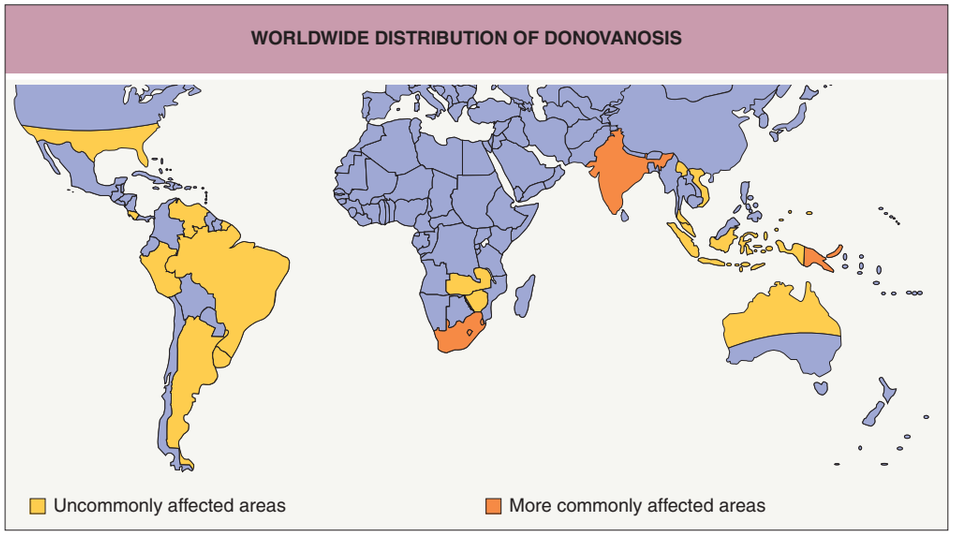


Fig. 82.25 Worldwide distribution of donovanosis.

Epidemiology

In the pre-antibiotic era, donovanosis was distributed in both hemispheres, but now it is restricted primarily to a few low-income countries. A large number of cases, the majority in the 20- to 40-year-old age group, are reported from South Africa, India, Papua New Guinea, and some parts of Australia (Fig. 82.25).

Although donovanosis is listed among the group of STIs, the disease can also occur in individuals who are not sexually active, and a wide variation in the prevalence of the infection (from 0.5% to 50%) is reported in sexual partners[63]. This is probably due to different diagnostic procedures and a long incubation period of up to 1 year. It is also not clear whether fecal contamination represents a route of non-sexual transmission.

Pathogenesis

Donovanosis is caused by *Klebsiella granulomatis* (previously known as *Calymmatobacterium granulomatis*), an intracellular Gram-negative bacillus. The primary lesion is a small cutaneous papule or nodule that contains mononuclear cells with cytoplasmic vacuoles that are filled with microorganisms. The cytoplasmic vacuoles can rupture and release bipolar Donovan bodies[64] of coccoid, coccobacillary, and bacillary morphology.

Clinical Features

The average incubation period is thought to be ~17 days, but a range from 1 day to 1 year has been reported. A small papule or nodule initially appears and eventually ulcerates. The lesions of donovanosis are usually painless or mildly painful and slowly expand over a period of weeks to months. They are often highly vascular, with a beefy red appearance and a tendency to bleed (Fig. 82.26). Extensive tissue destruction may result, and a foul-smelling exudate is characteristic of necrotic donovanosis. Inguinal lesions occur in up to 20% of patients and are often combined with genital involvement. The most frequent sites of lesions in men are the prepuce, glans penis, frenulum, and coronal sulcus. In women, the most common location is the vulvar area, where large ulcers as well as granulomatous or verrucous papules may be observed.

Extragenital lesions due to autoinoculation or secondary to dissemination have been observed in the skin, bones, abdominal cavity, and oral cavity; they can involve any organ, with the bones most commonly affected. In some patients, primary extragenital lesions are seen.

Pathology

Histologically, ulceration with exuberant granulation tissue is evident. Pseudoepitheliomatous hyperplasia may be present at the ulcer edge. A diffuse infiltrate of histiocytes, plasma cells, and a few lymphocytes is present in the dermis, sometimes with small neutrophilic abscesses. The organisms are easier to find in smears than in histologic sections.



Fig. 82.26 Donovanosis (granuloma inguinale). Large ulcers with a characteristic "beefy" appearance. *Courtesy Joyce Rico, MD.*

They are 1–2 microns in diameter and are within histiocytes, as is also characteristic of leishmaniasis, rhinoscleroma, and histoplasmosis (see Table 77.18). Bipolar staining is found at two ends of the organisms (Donovan bodies), giving them a "safety pin" appearance.

Diagnosis

The diagnosis of donovanosis is usually based on the demonstration of Donovan bodies in smears from active lesions by Giemsa, Wright, or Leishman stains. The smears are prepared from tissue scrapings or touch preparations of biopsies taken from the dermis or subcutis of lesions.

There are no serologic tests available for the diagnosis of donovanosis. Nucleic acid amplification assays such as PCR are under investigation, but they are not yet commercially available. Although successful culture of *K. granulomatis* has been reported in human peripheral blood mononuclear cells and Hep2 cells, attempts to grow this organism in fertilized eggs or on routinely available artificial media have been unsuccessful.

Differential Diagnosis

Donovanosis is frequently confused with other diseases of the anogenital region. Other infectious causes of genital ulcer disease have to be considered (see Table 82.14); early lesions of secondary syphilis, especially condylomata lata, often have a clinical appearance similar to donovanosis. Carcinoma, amebiasis, tuberculosis, dimorphic fungal infections, blastomycosis-like pyoderma, Crohn disease, and pyoderma gangrenosum may represent additional diagnostic possibilities.

TREATMENT REGIMENS FOR DONOVANOSIS
Recommended:
• Azithromycin, 1 g po once weekly – *or* – 500 mg po daily
Alternative:
• Doxycycline, 100 mg po BID – *or* – • Trimethoprim–sulfamethoxazole, 1 double-strength (160 mg/800 mg) tablet po BID – *or* – • Erythromycin base, 500 mg po four times daily
Duration for all regimens: until all lesions completely healed (at least 3 weeks)

Table 82.18 Treatment regimens for donovanosis. For any of the regimens, the addition of another antibiotic (e.g. gentamicin 1 mg/kg iv q8h) can be considered if lesions do not respond within the first few days of therapy. Based on CDC 2021 Guidelines (www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf). BID, twice daily; po, orally.

Treatment

The recommended treatment is azithromycin, but treatment regimens in different geographic areas reflect the availability of antibiotics; for example, in Papua New Guinea, chloramphenicol is used. Doxycycline, trimethoprim–sulfamethoxazole, quinolones, and erythromycin (recommended during pregnancy) have also been shown to be effective in the treatment of donovanosis (Table 82.18). For azithromycin, successful treatment with a daily dose of 500 mg for 1 week has been reported[65]. However, the CDC 2021 guidelines recommend 1 g weekly or 500 mg daily for at least 3 weeks and until all lesions have completely healed.

Examination of sexual partners is recommended if there has been sexual contact during the previous 60 days or if the partner is symptomatic. Relapses can occur 6–18 months later, despite effective initial treatment.

Additional figures available in our eBook (see inside front cover for access code).

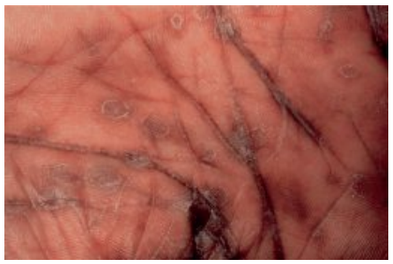
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eFig. 82.1 Secondary syphilis. Lesions on the palms often have a collarette of scale, referred to as Biett's collarette.



eFig. 82.2 Secondary syphilis. The patient had a widespread exanthem of pink papules.



eFig. 82.3 Secondary syphilis. Subtle hyperpigmented macules on the face. *Courtesy Eugene Mirrer, MD.*



eFig. 82.4 Gonococcemia (arthritis–dermatosis syndrome). Hemorrhagic vesicle with surrounding erythema on the toe. *Courtesy James Graham, MD.*

Protozoa and Worms 83

Francisco G. Bravo

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Key features

- Protozoa are responsible for many tropical diseases that not only affect large regions of the world but also can have different clinical presentations in the Old World versus the New World (e.g. leishmaniasis)
- Protozoal infections can lead to significant morbidity in both immunocompromised hosts (e.g. toxoplasmosis) and immunocompetent individuals (e.g. *Balamuthia* spp.)
- Worms (helminths) are common parasites with a worldwide distribution; cutaneous manifestations vary considerably, from pruritus ani to elephantiasis
- Even helminthic diseases with a restricted geographic distribution, such as onchocerciasis and echinococcosis, may be observed in individuals from non-endemic areas due to immigration, tourism, disaster relief efforts, or military service

PROTOZOA

LEISHMANIASIS

Synonyms: ■ Old World cutaneous leishmaniasis: oriental sore, Delhi boil, Baghdad boil ■ New World cutaneous and mucocutaneous leishmaniasis: American tegumentary leishmaniasis, chiclero ulcer (Mexico), uta and espundia (Peru), ulcera de Bauru (Brazil), bush or forest yaws, pian boi (Guyanas) ■ Diffuse cutaneous leishmaniasis: anergic, lepromatous, or pseudolepromatous leishmaniasis ■ Visceral leishmaniasis: kala-azar, Dumdum fever

Key features

- Chronic parasitic (protozoan) disease in which organisms are found within phagolysosomes of mononuclear phagocytes
- The clinical manifestations of leishmaniasis depend on the host's cell-mediated immune response and the species of *Leishmania* involved; clinical subtypes include cutaneous, disseminated cutaneous, diffuse cutaneous, mucocutaneous/mucosal, and visceral leishmaniasis
- The most common cutaneous finding is a papule at the site of inoculation that classically evolves into an ulcer
- The vector is a sandfly infected with promastigotes
- The disease has a worldwide distribution but is endemic in Latin America, the Mediterranean basin, and parts of Asia and Africa

Introduction

Leishmaniasis encompasses a spectrum of chronic infections in humans and several animal species. It is caused by over 20 species of *Leishmania* (Table 83.1), flagellated protozoans belonging to the order Kinetoplastidae. Transmission is via the bite of infected female sandflies from the genera *Phlebotomus* and *Lutzomyia*.

The disease has a worldwide distribution, affecting millions of people in South America, the Mediterranean basin, and parts of Asia and Africa[1] (Figs. 83.1 & 83.2). There are four major clinical patterns: (1) cutaneous, which is restricted to the skin and is seen more often in the Old World; (2) mucocutaneous, which affects both the skin and mucosal surfaces and occurs almost exclusively in the New World; (3) diffuse cutaneous, which occurs mainly in the New World; and (4) visceral, which affects the organs of the mononuclear phagocyte system, e.g. liver, spleen[2,3].

Epidemiology

According to the World Health Organization, more than a million new cases of cutaneous leishmaniasis and ~30 000 new cases of visceral leishmaniasis occur annually[4]. Over 90% of cutaneous infections with *Leishmania* occur in the Middle East (Afghanistan, Algeria, Iran, Iraq, Saudi Arabia, Syria) and South America (Brazil, Peru, Colombia) (Table 83.2), but the disease is also found in the Mediterranean basin, sub-Saharan Africa, Central Asia, and India (see Fig. 83.1). In the US, climate change has led to the expansion of sandfly vectors to northern Texas. One study found that 59% (41/69) of novel cases of cutaneous leishmaniasis reported to laboratories in Texas from 2007–2017 were autochthonous (occurring in patients with no history of travel outside the US), and all 22 of such cases that were confirmed by PCR were due to *L. mexicana*[5].

Mucocutaneous leishmaniasis is endemic in several countries in Central and South America. Although the visceral form of leishmaniasis has a worldwide distribution, it is seen most frequently in Africa and Asia (see Fig. 83.2)[1,2,6].

Old World cutaneous leishmaniasis is usually due to *L. major* or *L. tropica*, and less often *L. infantum* (Mediterranean basin) or *L. aethiopica* (Ethiopia and Kenya) (see Table 83.1 & Fig. 83.1). In the New World, cutaneous leishmaniasis is caused primarily by subspecies of *L. mexicana* and the *L. braziliensis* complex, whereas mucocutaneous/mucosal disease is associated with the latter organisms. Diffuse cutaneous leishmaniasis is most closely associated with *L. amazonensis*[3]. Infections with *L. donovani* (e.g. India, Bangladesh, Sudan) and *L. infantum* (especially in the setting of HIV infection) as well as the subspecies *L. infantum chagasi* (e.g. Central and South America; previously known as *L. chagasi*) are the major causes of visceral leishmaniasis (Table 83.3 & Fig. 83.2).

The species of *Leishmania* can also vary within a particular geographic region. For example, in the Middle East, *L. major* is found in rural areas where the primary animal reservoirs are desert rodents, whereas *L. tropica* is endemic in urban areas[6].

EPIDEMIOLOGIC AND CLINICAL PATTERNS OF INFECTIONS WITH *LEISHMANIA* SPECIES					
Complex	**Major species**	**Major reservoirs**	**Major geographic distribution**	**Clinical patterns (in addition to cutaneous)**	**Clinical forms of the cutaneous pattern**
Leishmania donovani	*L. donovani*	Humans	Sudan, South Sudan, Ethiopia, Kenya, Somalia; India, Nepal, Bangladesh; China	**Visceral, PKD**, mucosal (rare)	(Uncommon)
	L. infantum	Dogs, foxes	Mediterranean region	**Visceral (favors children)**, PKD*, mucosal† (rare)	Favors children (uncommon)
	L. infantum chagasi‡	Dogs, foxes, opossums	Central and South America (mainly Brazil)		
Leishmania tropica	*L. major*	Rodents	Arid areas of Africa (north and south of the Sahara), Middle East and Central Asia	Mucosal (rare)	**Old World zoonotic/rural** (moist, early ulcerative with rapid course), recidivans (rare), lupoid (rare)
	L. tropica	Humans, dogs	Eastern Mediterranean region, Middle East, Central Asia	Visceral (rare), mucosal (rare)	**Old World anthroponotic/ urban** (dry, late ulcerative with chronic course), recidivans, lupoid
	L. aethiopica	Hyraxes	Ethiopia, Kenya, Yemen	Diffuse cutaneous, mucocutaneous	Dry/late ulcerative or moist/early ulcerative
Leishmania mexicana	*L. mexicana*	Forest rodents	Mexico, Central America	Diffuse cutaneous (rare)	**New World** Variants include ulcerative, plaque-like, pustular, impetigo-like, erysipeloid, sarcoidosis-like, papulotuberous, verrucous, sporotrichoid, eczematous
	L. amazonensis	Forest rodents	South America	**Diffuse cutaneous**, mucocutaneous, visceral (rare), PKD (rare)	
	L. venezuelensis, pifanoi, garnhami	Unknown	Venezuela	Diffuse cutaneous (rare)	
Leishmania (Viannia) braziliensis	*L. braziliensis*	Forest rodents	Central and South America	**Mucocutaneous**, visceral†	
	L. guyanensis	Sloths, anteaters	Guyana, Brazil	Mucocutaneous	
	L. panamensis	Sloths	Panama, Costa Rica, Colombia	Mucocutaneous	
	L. peruviana	Dogs	Peru, Argentina		

*Rare/controversial; reported in children and in HIV-infected adults following antiretroviral therapy.
†Especially in immunocompromised hosts.
‡*L. infantum* subspecies in the New World; previously known as *L. chagasi*.

Table 83.1 Epidemiologic and clinical patterns of infections with *Leishmania* species. Common clinical patterns for particular species are in **bold**. Additional minor species include *L. garnhami*, *naiffi*, *lainsoni*, *colombiensis*, *shawi*, *archibaldi*, and *martiniquensis*. *Viannia* is a subgenus of *Leishmania*. Mucosal leishmaniasis refers to oronasal lesions not preceded or accompanied by cutaneous involvement. PKD, post-kala-azar dermal leishmaniasis. *Modified from Lupi O, Barlett BL, Haugen RN, et al. Tropical dermatology: tropical diseases caused by protozoa. J Am Acad Dermatol 2009;60:897–925 and Peters W, Pasvol G. Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

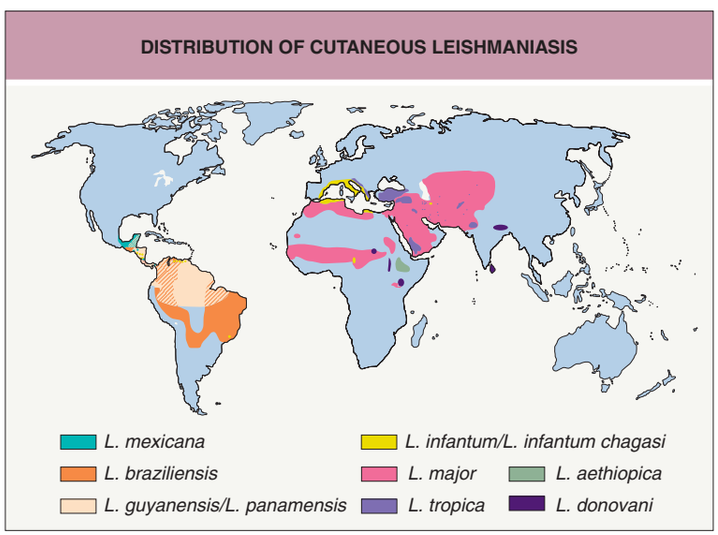


Fig. 83.1 Distribution of cutaneous leishmaniasis. Climate change is expected to lead to expansion of these distributions. For example, autochthonous cases of cutaneous leishmaniasis due to *L. mexicana* have reported as far north as Texas. *Modified from Aronson N, Herwaldt BL, Libman M, et al. Diagnosis and Treatment of Leishmaniasis: Clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Clin Infect Dis 2016;63:1539–57 and Cohen J, Powderly WG, Opal SM (eds). Infectious Diseases, 4th edition. Edinburgh: Elsevier, 2016.*

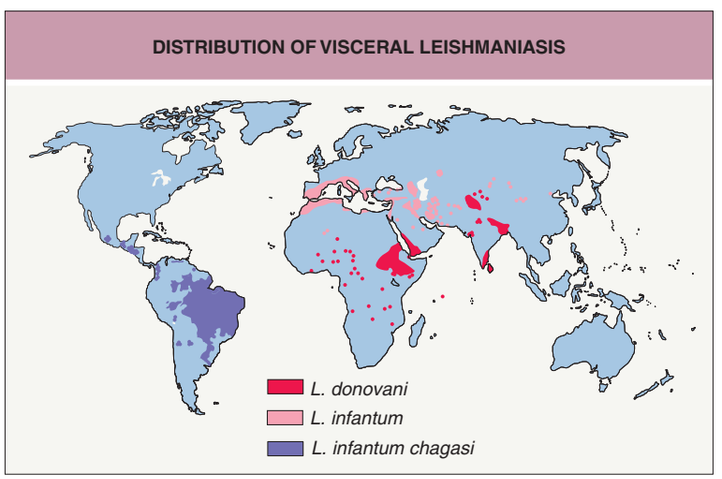


Fig. 83.2 Distribution of visceral leishmaniasis. These organisms, in particular *L. infantum* and *L. donovani*, can also cause cutaneous disease. *Modified from Aronson N, Herwaldt BL, Libman M, et al. Diagnosis and Treatment of Leishmaniasis: Clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Clin Infect Dis 2016;63:1539–57 and Cohen J, Powderly WG, Opal SM (eds). Infectious Diseases, 4th edition. Edinburgh: Elsevier, 2016.*

Canine and rodent species act as the main reservoirs for *Leishmania* (see Table 83.1). Transmission between these species (as well as to humans) is via sandflies, primarily of the genera *Phlebotomus* (Old World) and *Lutzomyia* (New World). Human-to-human spread of *L. tropica* can also occur. In general, humans contract leishmaniasis as accidental hosts when they intrude into the sandfly's habitat. Overall, the disease is most common in men between 20 and 40 years of age, but Old World cutaneous leishmaniasis occurs more often in children[2].

Epidemics of cutaneous leishmaniasis have occurred in populations affected by natural disasters, forced migration, and civil unrest as well as in foreign military personnel serving in endemic areas of the Middle East (e.g. Iran, Afghanistan, Syria, Iraq). Whereas the incidence of visceral leishmaniasis seems to be decreasing in endemic countries such as India, Bangladesh, and Nepal, new areas of epidemic visceral leishmaniasis are appearing in Sudan and South Sudan. Migration from rural areas to peri-urban centers has also contributed to an increasing incidence of visceral leishmaniasis in Brazil. Solid organ and hematopoietic stem cell transplant recipients and other individuals receiving immunosuppressive medications (e.g. tumor necrosis factor [TNF] inhibitors) represent additional groups at increased risk for visceral leishmaniasis[7].

Pathogenesis

Leishmania spp. are obligate intracellular parasites that exist in two forms: promastigote and amastigote. In the gut of the sandfly, the organisms multiply as extracellular flagellated promastigotes. Following migration to the proboscis, the parasites are inoculated (in the promastigote form) via the sandfly bite. Once inoculated into the skin, the parasites are rapidly engulfed by the host's mononuclear phagocytes, where they transform into amastigotes and multiply via binary fission (Fig. 83.3). The incubation time from infection until the first clinical manifestation can vary from ≤2 weeks for cutaneous lesions (typically several weeks to 2 months) to >2 years for mucocutaneous lesions or visceral involvement (typically 3 to 9 months)[8].

COUNTRIES WITH THE HIGHEST INCIDENCE OF LEISHMANIASIS	
Old World cutaneous leishmaniasis	Afghanistan, Algeria, Iran, Iraq, Saudi Arabia, Syria
New World cutaneous leishmaniasis	Brazil, Peru, Colombia
Mucocutaneous/mucosal leishmaniasis	Bolivia, Brazil, Peru
Visceral leishmaniasis	Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, Sudan, Nepal, China

Table 83.2 Countries with the highest incidence of leishmaniasis. The incidence of visceral leishmaniasis has been decreasing in Bangladesh, Nepal, and India. Further information is provided at http://www.who.int/mediacentre/factsheets/fs375/en/ and https://paho.org/en/topics/leishmaniasis.

The clinical manifestations of leishmaniasis depend on the species of *Leishmania* (see Table 83.1), the host's cell-mediated response, and the ability of the parasite to evade host defense mechanisms[9]. A robust Th1 response with production of interleukin-2 (IL-2) and interferon-γ (IFN-γ) is associated with quicker resolution, whereas a lack of a Th1 response and/or the development of a Th2-type response with production of IL-4 and IL-10 is associated with disease progression[10–12]. Depending on the type of immune response, L-arginine metabolism within infected macrophages occurs via two alternative pathways: (1) Th2 cytokines promote its catabolism by arginase to produce L-ornithine, which favors *parasitic* growth; or (2) Th1 cytokines promote nitric oxide synthase-induced generation of L-citrulline plus nitric oxide, and the latter increases host resistance via NLRP3 (NLR family pyrin domain-containing-3) inflammasome-derived IL-1β[13]. Resistance of *L. amazonensis* and *L. braziliensis* promastigotes to nitric oxide *in vitro* correlates with poorer clinical outcomes.

Mucocutaneous disease is associated with the infection of *Leishmania* organisms with *Leishmania* RNA virus-1 (LRV1); this virus is recognized by human Toll-like receptor 3, leading to a proinflammatory cascade that subverts the immune response to *Leishmania*, and allows disease progression[14]. *L. donovani* has been shown to induce epigenetic changes via macrophage DNA methylation that downregulate host defense mechanisms, allowing parasitic replication and survival[15]. Human genetic factors include HLA variants that contribute to leishmaniasis risk and *IL2RA* variants that reduce IL-2-dependent responses and thereby increase susceptibility to cutaneous and visceral leishmaniasis[16].

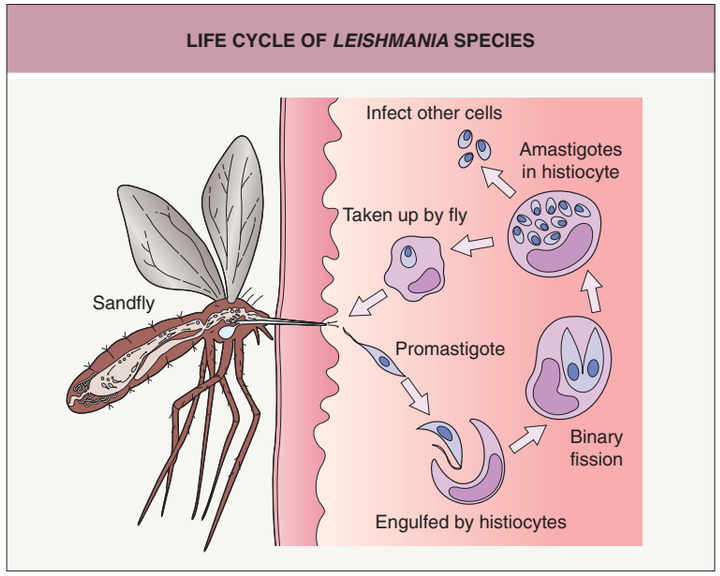


Fig. 83.3 Life cycle of *Leishmania* species. Promastigotes develop within the gut of the sandfly and then migrate to the proboscis.

EPIDEMIOLOGY AND CLINICAL PATTERNS OF VISCERAL LEISHMANIASIS		
Type of disease	**Major species**	**Major geographic distribution**
Kala-azar (60% 10–20 years of age)	*Leishmania donovani*	India, China (north of Yangtze River), Kenya, Sudan
Infantile kala-azar (90% <10 years of age)	*L. infantum*	Central Asia, China, Iraq, France, Italy, Egypt, elsewhere in the Mediterranean basin, Saudi Arabia
	L. infantum chagasi	Brazil, Colombia, Venezuela, Central America, Mexico
Oronasal kala-azar	*L. infantum**	France
Post-kala-azar dermal leishmaniasis	*L. donovani* *L. infantum*† *L. amazonensis*	India, China, Kenya Mediterranean basin, South America
Atypical kala-azar complex (typically in adults)	*L. tropica* *L. amazonensis* *L. braziliensis**	Northeast Saudi Arabia South America South and Central America

*Especially in immunocompromised hosts.
†Controversial (see Table 83.1).

Table 83.3 Epidemiology and clinical patterns of visceral leishmaniasis.

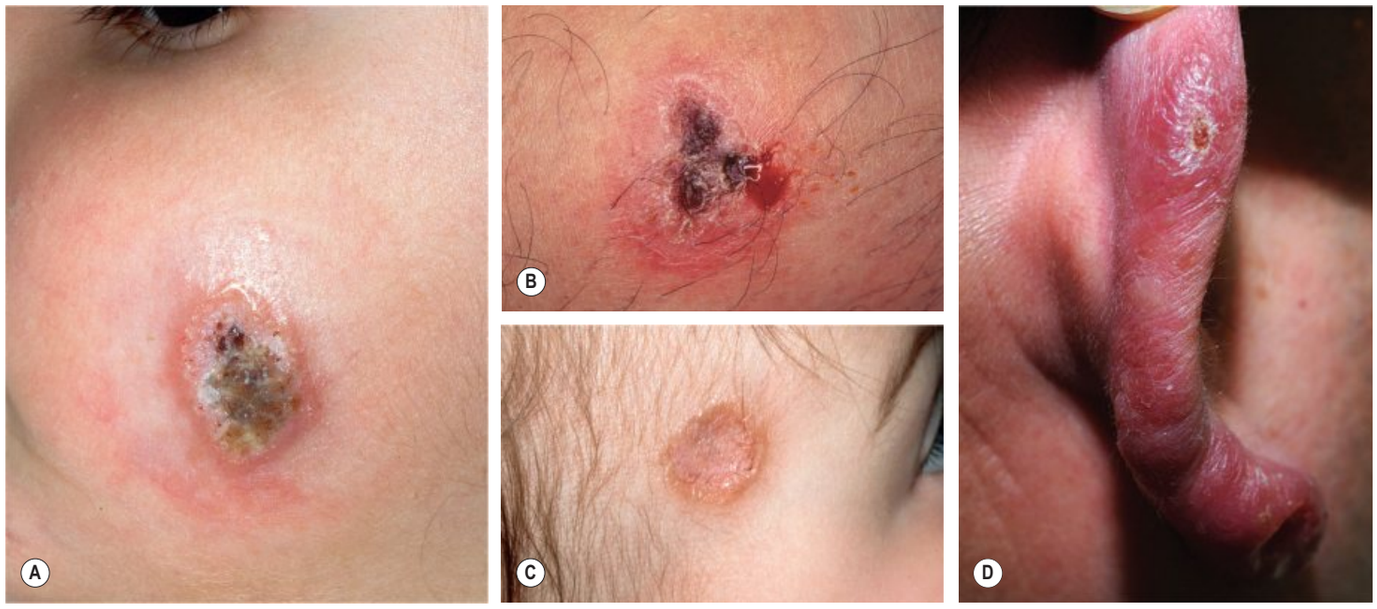


Fig. 83.4 Variable presentations of cutaneous leishmaniasis. A, B Ulcerated plaques with rolled border (**A**) and central crusting (**A, B**). **C** Plaque with translucent borders containing telangiectasias and central scarring. **D** New World cutaneous leishmaniasis of the ear (chiclero ulcer). Cutaneous leishmaniasis is sometimes mistaken for a basal cell carcinoma. *A, C, Courtesy Julie V. Schaffer, MD; D, Courtesy Kalman Watsky, MD.*

IFN-γ is the most potent cytokine involved in the induction of activity against organisms residing within macrophage phagolysosomes. It is produced by Th1 cells and leads to the production of oxygen species. The differentiation of naive $CD4^+$ cells into Th1 cells is aided by IL-12 (see Fig. 4.9), which also stimulates natural killer (NK) cells to produce IFN-γ[10,12,17]. TNF produced by macrophages and NK cells amplifies the IFN-γ-driven macrophage activation[11,18]. Consequently, use of TNF inhibitors increases the risk of developing leishmaniasis, especially the visceral form. More recent studies have also highlighted the role of TNF-dependent IL-32γ in stimulating the production of proinflammatory cytokines and microbicidal molecules in human macrophages infected with New World *Leishmania* spp.[19]. In addition, Th17 cells can potentially contribute to both host resistance and tissue damage in patients with leishmaniasis.

Animals that have recovered from *L. tropica* or *L. donovani* infections acquire immunity against reinfection from the same species of *Leishmania*, but not against other species. Similarly, humans with New World cutaneous leishmaniasis have been inoculated successfully with *L. tropica*. However, it has been reported that surviving an episode of visceral leishmaniasis confers lifelong immunity against all types of leishmaniasis.

Clinical Features

Cutaneous leishmaniasis

Cutaneous leishmaniasis is divided into two subsets based on the geographic region where the infection is acquired: Old World and New World. These two groups differ with regard to the causative organisms, vectors, reservoirs, clinical presentation, and prognosis[3]. Both Old World and New World cutaneous leishmaniasis usually begin as a small, well-circumscribed papule at the inoculation site. This lesion may slowly enlarge over several weeks into a nodule or plaque and then become ulcerated or verrucous (Figs. 83.4–83.6). Exposed sites such as the face, neck, arms, and legs are most commonly involved. For example, the chiclero ulcer results from infection on the ear in forest workers who collect gum from the chicle tree in Mexico and Central America (see Fig. 83.4D). The lesions of leishmaniasis are often solitary but may be multiple, with the formation of satellites or lymphatic spread (sporotrichoid pattern; Fig. 83.7). Unusual clinical presentations include erysipeloid, zosteriform, psoriasiform, and eczematous. Most acute cutaneous infections resolve spontaneously within several months, often with scarring (cicatricial stage)[20]. A minority of patients develop chronic or disseminated disease.

Several clinical forms of ***Old World*** cutaneous leishmaniasis have been described, including zoonotic, anthroponotic, recidivans, and lupoid leishmaniasis. Zoonotic cutaneous leishmaniasis (rural, moist, or early ulcerative form) usually has a mild, rapid course and is caused by *L. major*. Anthroponotic cutaneous leishmaniasis (urban, dry, or late ulcerative form), has a more chronic course and is caused by *L. tropica*[3]. Leishmaniasis recidivans is a chronic, destructive form that is characterized by recurrence at the site of an original ulcer, generally within 2 years and often at the edge of the scar[20]. Anthroponotic or, less frequently, zoonotic cutaneous leishmaniasis occasionally develops into chronic lupoid leishmaniasis, which clinically and histologically (epithelioid granulomas surrounded by lymphocytes) resembles the lupus vulgaris form of cutaneous tuberculosis. Amastigotes are scarce and difficult to find in lupoid leishmaniasis, making the diagnosis more challenging.



Fig. 83.5 Cutaneous leishmaniasis of the nose due to *Leishmania aethiopica*. This patient presented with an infiltrated hyperpigmented plaque with papules at its periphery. Cutaneous leishmaniasis due to *L. aethiopica* often affects the face and can evolve to mucocutaneous disease. *Courtesy Edward Cowen, MD.*

New World cutaneous leishmaniasis has a wide clinical spectrum, including plaque-type, sporotrichoid, pustular, impetigo-like,



Fig. 83.6 Ulcerative cutaneous leishmaniasis on the leg and a positive Montenegro test. This expanding ulcer could be misdiagnosed as pyoderma gangrenosum. *Courtesy Omar P. Sangüeza, MD.*



Fig. 83.7 Sporotrichoid form of cutaneous leishmaniasis.



Fig. 83.8 Diffuse and disseminated cutaneous leishmaniasis. A Small papules in disseminated cutaneous leishmaniasis. **B** Diffuse cutaneous leishmaniasis presenting with large nodules that resemble the lepromatous form of Hansen disease.



Fig. 83.9 Mucocutaneous leishmaniasis. Infiltration of the nose and upper lip is evident. Note the destruction of the nasal alae and crusting of the upper lip. *Courtesy Jaqueline Luque, MD.*

eczematoid, sarcoid-like, lupoid, erysipeloid, papulotuberous, verrucous, disseminated, and diffuse presentations. There is also the potential for developing leishmaniasis recidivans[20].

Disseminated cutaneous leishmaniasis, which most often results from *L. braziliensis* or *L. amazonensis* infection, is characterized by multiple (10 to >300) secondary lesions, either in proximity to or distant from the primary site. The lesions resemble those of classic cutaneous leishmaniasis, including papules and small nodules that may have an acneiform appearance, and ulceration is common (Fig. 83.8A). Up to 25% of affected individuals have concomitant mucosal disease, and patients may have systemic symptoms such as fever and malaise. Disseminated skin disease most likely results from early hematologic spread, and it is associated with decreased production of IFN-γ and TNF[21].

Diffuse cutaneous leishmaniasis is a rare presentation that develops in the setting of reduced cell-mediated immunity, analogous to the lepromatous form of Hansen disease. *L. aethiopica* (in Africa) and *L. amazonensis* (in the Americas) are the most common pathogens (see Table 83.1). Multiple nodular and keloid-like lesions on the face and limbs are usually observed[3] (Fig. 83.8B); ulceration is uncommon but occasionally occurs secondary to trauma. Nasal infiltration and mucosal ulceration may develop due to spread from nearby skin lesions, but destruction of the nasal septum is rare. There may also be laryngeal and pharyngeal involvement[20].

Mucocutaneous/mucosal leishmaniasis

After a variable time period ranging from a few months to more than 20 years, mucocutaneous/mucosal disease develops in some patients infected with *Leishmania* spp. in the *Viannia* subgenus (known as the *L. braziliensis* complex), most commonly *L. braziliensis* and occasionally *L. panamensis*, *L. guyanensis*, or hybrid genotypes[22]. Mucosal lesions range from edema of the lips and nose to perforation of the nasal septum or (less often) the laryngeal cartilage or palate. Infiltration and/or ulceration of the mucosal surfaces of the nose, lips, and oropharynx are typical features (Figs. 83.9 & 83.10); ocular or genital involvement is rare. In some patients, there is extensive loss of tissue in both the mouth and nose, causing a characteristic "tapir face" known as espundia. Hoarseness may result from vocal cord involvement[20–22].



Fig. 83.10 Mucocutaneous leishmaniasis due to *Leishmania braziliensis*. Ulceration and induration of the nasal vestibule extends onto the cutaneous lip. *Courtesy Kalman Watsky, MD.*



Fig. 83.11 Post-kala-azar dermal leishmaniasis. Nodules of various sizes, some pedunculated, are seen in this patient who had been treated for kala-azar over a period of 6 months, 20 years previously. *With permission from Peters W, Pasvol G. Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

SYSTEMIC FEATURES OF VISCERAL LEISHMANIASIS (*L. DONOVANI*)			
Clinical features	**Proportion affected (%)**	**Clinical features**	**Proportion affected (%)**
Age <9 years	20 (*L. infantum* and *L. infantum chagasi* more commonly affect children and infants)	Age <15 years	45
Fever	85–100	Wasting	70–100
Loss of appetite	60–75	Cough	70–85
Epistaxis	45–55	Diarrhea	25–55
Vomiting	2–35	Jaundice	2–7
Splenomegaly	90 (adults); >95 (children)	Hepatomegaly	55–65
Lymphadenopathy	55–85 (uncommon outside of Africa)	Edema	2–7
Laboratory findings			
Globulin >30 g/l	95	Albumin <30 g/l	90
Anemia	60–90	Leukopenia	85
Thrombocytopenia	75	Elevated bilirubin	15
Elevated liver transaminases	20	Elevated alkaline phosphatase	40
Positive *Leishmania* serology	95	Parasitologically proven	95

Table 83.4 Systemic features of visceral leishmaniasis *(L. donovani)*. The duration of symptoms is usually 2 to 4 months, but it is typically shorter in children. *With permission from Davidson RN. Leishmaniasis. In: Cohen J, Powderly WG (eds). Infectious Diseases. Edinburgh: Mosby, 2004.*

Visceral leishmaniasis (kala-azar)

Visceral leishmaniasis, or kala-azar, occurs when the parasite spreads to the bone marrow, spleen, and liver[3]. It is primarily caused by *L. donovani* in adults and *L. infantum* or *L. infantum chagasi* in children (see Fig. 83.2). The incubation period ranges from 1 to 36 months. Fever, wasting, cough, lymphadenopathy, and hepatosplenomegaly are the most common systemic findings (Table 83.4). There may be an abrupt onset or slow progression, and fever may be continuous or intermittent. Additional complications include enteritis, oronasal or gastrointestinal hemorrhage, pneumonia, and nephritis, which may lead to death[20]. Cutaneous manifestations may be disease-specific papules, nodules, or ulcers at infected sites as well as nonspecific findings such as purpura, hyperpigmentation, xerosis, and kwashiorkor-like hair discoloration.

Post-kala-azar dermal leishmaniasis develops as a sequela of untreated or treated visceral leishmaniasis (Fig. 83.11)[3]. This form of cutaneous leishmaniasis is most commonly seen in Sudan and India, where it occurs in 50% and 10% of patients cured of visceral leishmaniasis, respectively[23]. Onset may be up to 20 years after treatment[23]. Skin findings include hypopigmented macules, malar erythema, skin-colored nodules, and verrucous papules[24].

Leishmaniasis and HIV

Co-infection of HIV and leishmaniasis can alter the progression and presentation of leishmaniasis, especially the visceral form (see Ch. 78)[25]. HIV infection increases the risk of developing visceral leishmaniasis 100- to over 2000-fold, with the prevalence of visceral leishmaniasis ranging from 4% to >15% among HIV-infected patients who live in *Leishmania*-endemic areas[25]. Co-infection often results in an atypical clinical presentation, reduced therapeutic response, and increased mortality. Chronic immune activation from the *Leishmania* infection may lead to increased HIV load and accelerated progression of AIDS, while the immunosuppressed state from the HIV infection creates an ideal environment for parasitic growth[24].

Pathology

Histologically, cutaneous lesions typically show ulceration, pseudoepitheliomatous hyperplasia, and a mixed inflammatory infiltrate composed of histiocytes, lymphocytes, plasma cells, and neutrophils. Amastigotes present within dermal macrophages, especially those in the papillary dermis (Fig. 83.12), are evident in ~50% of skin biopsies. Over time, lesions develop an increasing number of giant cells and fewer parasites; in longstanding cutaneous leishmaniasis, tuberculoid granulomas with caseation necrosis may be observed. In the cicatricial stage, the epidermis becomes flattened and hyperpigmented in areas with dermal fibrosis. Identical changes are seen in mucosal lesions. In diffuse cutaneous leishmaniasis, numerous amastigotes are present within foamy histiocytes; in contrast, the disseminated form features a primarily lymphoplasmacytic infiltrate with few amastigotes. The parasite can be detected in the lymph nodes, bone marrow, and spleen in patients with visceral leishmaniasis.

Diagnosis

The diagnosis of cutaneous leishmaniasis can be confirmed by demonstrating the presence of amastigotes in dermal macrophages within skin biopsy specimens, tissue impression smears (touch preparations), and smears obtained by dermal scraping or needle aspiration of skin lesions[2,20,26]. Although routine hematoxylin and eosin staining allows the visualization of the amastigotes, Giemsa, Wright, or Feulgen stains can help to identify the organisms in smears and tissue: the cytoplasm appears blue, the nucleus pink, and the kinetoplast a deep red[20]. CD1a immunostaining can also highlight the amastigotes, but its positivity may vary depending on the species (Fig. 83.12, inset)[27]. The edge of a relatively new ulcer is the location of choice for obtaining dermal scrapings, a biopsy specimen, or a needle aspirate; the latter two types of samples may be used for culture and all three types for polymerase chain reaction (PCR)-based assays (see below)[3,26].

In longer-standing lesions of leishmaniasis, parasites may be scarce. In this context, the delayed skin reaction test (Montenegro skin test or

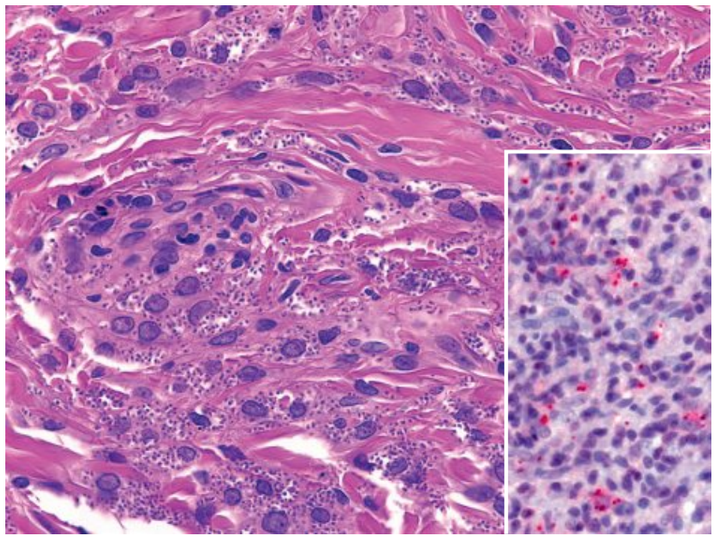


Fig. 83.12 Histopathology of leishmaniasis. Parasitized macrophages that contain amastigotes are seen in the dermis and highlighted by CD1a immunostaining (inset). Each amastigote has a nucleus and kinetoplast (not always visible) at opposite poles. *Courtesy Luis Requena, MD; inset, courtesy Lorenzo Cerroni, MD.*

Leishman reaction), which uses leishmanial antigens to induce a cell-mediated response, has traditionally been an important diagnostic tool. A phenolated suspension of killed promastigotes is injected intradermally, usually on the volar aspect of the forearm. The test is considered positive if a papule >5 mm in diameter forms at the site of inoculation after 48–72 hours (see Fig. 83.6)[20]. It is positive in up to 90% of patients with cutaneous and mucocutaneous leishmaniasis of over 3 months duration[3] and is invariably negative in patients with diffuse cutaneous (anergic) leishmaniasis[20]. However, this test (which is not approved by the US Food and Drug Administration [FDA]) cannot distinguish between past and present infection, so it is most useful in patients who do not reside in areas where leishmaniasis is endemic; positivity develops while the skin lesions are still active, and the test remains positive long after spontaneous cure. The test is usually negative during the febrile phase of visceral leishmaniasis, but it often becomes positive after cure.

For culturing *Leishmania*, specialized media are required, e.g. Nicolle–Novy–MacNeal (NNM) media or chick embryo media. Cultures are positive in ~40% of cases. Serologic and immunologic tests are also available, e.g. indirect immunofluorescence, ELISA, immunoprecipitation, and isoenzyme electrophoresis. Serologic testing is most useful for visceral and occasionally mucocutaneous disease, although it is not specific due to cross-reactivity (e.g. with Chagas disease antibodies)[28]. PCR-based methods represent the most sensitive and specific diagnostic tests, and their availability is increasing[2,20]. The combination of PCR (heat shock protein 70, mini-exon) with histopathology increases sensitivity to >90%. Of note, an FDA-approved real-time PCR assay for the diagnosis of leishmaniasis is available through the Centers for Disease Control and Prevention (CDC)[26].

Differential Diagnosis

The differential diagnosis of *cutaneous* leishmaniasis includes persistent arthropod bite reaction, basal cell carcinoma, tuberculosis, non-tuberculous mycobacterial infections, and subcutaneous mycoses; other infectious causes of lesions in a lymphocutaneous pattern are listed in Table 77.17. *Mucocutaneous* leishmaniasis can resemble paracoccidioidomycosis and tertiary syphilis. In addition, granulomatosis with polyangiitis and angiocentric NK/T cell lymphoma should be considered when ulcerative mucocutaneous lesions affect the central part of the face. Cocaine-induced nasal ulcerations can also mimic the mucosal involvement of leishmaniasis. Histologic examination allows distinction among these diseases[22]. The histologic differential diagnosis includes other infections characterized by parasitized macrophages (see Table 77.18) and neoplasms such as squamous cell carcinoma when pseudoepitheliomatous hyperplasia is present. The morphology and distribution of *diffuse cutaneous* leishmaniasis can mimic the lepromatous form of Hansen disease; however, in leishmaniasis the eyebrows are spared and the lesions are usually less infiltrative[20].

CLINICAL CHARACTERISTICS DIFFERENTIATING SIMPLE AND COMPLEX FORMS OF CUTANEOUS LEISHMANIASIS (CL)

Simple CL	Complex CL or mucocutaneous leishmaniasis
Caused by *Leishmania* species not associated with mucosal leishmaniasis (ML)	Caused by *Leishmania* species with increased risk for ML* or acquired in an increased ML-risk region, especially the "mucosal belt" of Bolivia, Brazil, and Peru†
No mucosal involvement	Mucosal involvement
Lack of subcutaneous nodules or lymphadenopathy	Subcutaneous nodules‡ or regional lymphadenopathy
One or a few small (<1 cm diameter) lesions	≥5 lesions >1 cm in diameter, or an individual lesion ≥5 cm in diameter
Location feasible for local treatment	Location where local treatment is not feasible
Lesions in areas that are not cosmetically or functionally important	Lesions on face (especially eyelids or lips), ears, genitalia, fingers, toes, and skin overlying joints
Immunocompetent host	Immunocompromised host, especially if affecting cell-mediated immunity
Lesion(s) resolving without therapy	Clinical failure of local therapy

*High-risk species for ML in the *Viannia* subgenus (*L. braziliensis* complex): *L. braziliensis, L. guyanensis and L. panamensis.* In general, systemic treatment is offered for infections with these species.
†The highest risk region for ML is south of the Amazon basin in Bolivia, Brazil, and Peru; moderate risk regions extend south of Nicaragua to the Amazon basin, and low risk regions are endemic areas north of Costa Rica. Areas of the Amazonian basin up to an altitude of 2000 meters are considered as increased ML-risk regions.
‡There is ongoing controversy regarding whether systemic therapy is necessary for Old World CL presenting with a few small subcutaneous nodules.

Table 83.5 Clinical characteristics differentiating simple and complex forms of cutaneous leishmaniasis (CL). Patients at risk for mucosal leishmaniasis (ML) based on the geographic region where the infection was acquired or the organism identified should be questioned about mucosal symptoms and undergo examination of the nasal and oropharyngeal mucosa; referral for otorhinolaryngologic evaluation is indicated for those with signs or symptoms of mucosal disease. Systemic treatment is generally required for complex CL, whereas local therapy or, if the lesions are healing spontaneously within 6 months, observation are options for patients with simple CL. Systemic therapy is also necessary for disseminated or diffuse cutaneous leishmaniasis as well as leishmaniasis recidivans. *Modified from Aronson N, Herwaldt BL, Libman M, et al. Diagnosis and Treatment of Leishmaniasis: Clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Clin Infect Dis 2016;63:1539–57.*

Treatment

Factors to consider in the treatment of leishmaniasis include the region of the world in which the infection was acquired, the species of *Leishmania*, the site(s) and severity of the infection, and host factors such as immune status and age (Table 83.5). The benefits of therapy need to be balanced with the goal of minimizing drug toxicity. Without treatment, Old World cutaneous leishmaniasis typically resolves within 2–4 months (*L. major*) or 6–15 months (*L. tropica*). Indications for systemic treatment of Old World cutaneous leishmaniasis include: (1) an immunocompromised host; (2) ≥5 lesions of substantial size (e.g. >1 cm) or individual lesion(s) measuring ≥5 cm; (3) enlarged regional lymph nodes; and (4) involvement of the mucosa, face, ears, genitalia, fingers, toes, or skin overlying a joint[29–31]. For patients who do not meet these criteria, either observation, if the lesions are healing spontaneously within 6 months, or local therapy are options.

New World cutaneous leishmaniasis caused by *L. mexicana* resolves within 3 months in >75% of cases. In contrast, cutaneous disease caused by *L. braziliensis* and *L. panamensis* spontaneously heals in less

than 10% and 35% of cases, respectively. Therefore, systemic treatment is indicated when *L. braziliensis* complex infection is suspected in order to accelerate healing, decrease scarring (especially in cosmetically sensitive sites), and prevent dissemination, relapse, or the development of mucosal or diffuse disease (see Table 83.5)[31].

Both parenteral pentavalent antimonials and miltefosine are first-line systemic treatments for cutaneous and mucocutaneous/mucosal leishmaniasis. While miltefosine is a less toxic therapy, its use can be limited by cost. Liposomal amphotericin B is the treatment of choice for visceral leishmaniasis[29,31]. Table 83.6 summarizes treatment regimens for cutaneous and mucocutaneous/mucosal leishmaniasis[31–37]. Table 83.7 lists frequent adverse reactions to drugs used for the treatment of leishmaniasis. The addition of oral pentoxifylline to antimonial therapy has been utilized for refractory mucocutaneous leishmaniasis and is included as an alternative treatment by the Pan American Health Organization, although RCTs have not consistently shown a benefit[38,39]. Additional interventions that have demonstrated some efficacy for cutaneous or mucocutaneous/mucosal leishmaniasis (in combination with other agents) include thermotherapy, cryotherapy, photodynamic therapy, and allopurinol[40].

Drugs or vaccines that completely prevent leishmanial infection have not yet been developed. The best form of protection is to avoid the bite of the sandfly and eliminate animal reservoirs. Personal protection includes applying DEET-based repellants, bed netting, permethrin-treated clothing, and sleeping in minimal-risk areas. People are at increased risk of bites in the early morning and late evening[32].

CUTANEOUS DISEASES CAUSED BY AMEBAS

Amebas (ameboid protozoa) are single-celled eukaryotes characterized by movement via pseudopodia (temporary cytoplasmic extensions). Organisms in this group that can produce cutaneous disease include enteric pathogens (e.g. *Entamoeba histolytica*) and free-living amebas such as *Acanthamoeba* spp. and *Balamuthia mandrillaris*. *E. histolytica* has a worldwide distribution and may infect the skin via inoculation or extension from the gastrointestinal tract. *B. mandrillaris* and *Acanthamoeba* spp. can cause skin infections and granulomatous encephalitis in immunocompromised and (for *B. mandrillaris*) immunocompetent patients. Acanthamebiasis may present with papules, nodules, and ulcers in the setting of profound immunosuppression, including those with advanced HIV infection (see Ch. 78).

Amebiasis Due to *Entamoeba histolytica*

Key features

- Amebiasis due to *Entamoeba histolytica* usually affects the gastrointestinal tract and rarely spreads to the skin
- The skin can become involved by extension of rectal amebiasis to the anus, perianal skin or vulva, as well as by a fistula from a liver abscess to the skin of the abdominal wall
- Cutaneous lesions are usually painful ulcers or verrucous plaques

Introduction

Amebiasis in humans is primarily a gastrointestinal infection caused by *Entamoeba histolytica*. However, there can be extraintestinal manifestations, including cutaneous involvement[41].

Epidemiology

E. histolytica infection results in ~50 million cases of invasive disease worldwide each year, causing 100 000 deaths annually[3]. Infection is associated with poor sanitation, crowded living conditions, and lower socio-economic status. In high-income countries, risk factors include a history of travel to or residence in high-prevalence areas, institutionalization, immunosuppression, and sexual behavior (especially men having sex with men). Humans are the reservoir for the disease, and an asymptomatic carrier may excrete up to 45 million cysts a day in the stool. Transmission of amebiasis is fecal–oral via contaminated hands, water, or food, and oral–anal sex.

TREATMENT RECOMMENDATIONS FOR LEISHMANIASIS		
Cutaneous leishmaniasis		
First-line systemic drugs	Miltefosine*	50 mg BID if weight is 30–44 kg and TID if weight is ≥45 kg × 28 days
	Sodium stibogluconate†	20 mg/kg/day IV or IM × 20 days Various intralesional regimens, e.g. 0.2–5 ml (5 sites/lesion intradermally for 0.1 ml/cm^2 until blanched) every 3–21 days for 5–8 sessions or until healing
	Meglumine antimonate†	
Alternatives	Paromomycin 15% plus MBCL 12% ointment	Topically BID × 10 days, wait 10 days, then repeat
	Paromomycin 15% plus gentamicin 0.5% cream	Topically daily for 20 days
	Pentamidine	3–4 mg/kg IV or IM every other day × 3–4 doses
	Fluconazole‡	200 mg/day or 6–8 mg/kg/day PO × 6 weeks
	Liposomal amphotericin B‡	3 mg/kg/day IV for a total dose of 20–40 mg/kg
	Amphotericin B deoxycholate	0.5–1 mg/kg IV daily or every other day for a total dose of 15–30 mg/kg
Mucocutaneous leishmaniasis		
First-line systemic drugs¶	Sodium stibogluconate†	20 mg/kg/day IV or IM × 28–30 days
	Meglumine antimonate†	
	Liposomal amphotericin B	<3 mg/kg/day IV for a total dose of 20–40 mg/kg
	Amphotericin B deoxycholate	0.5–1 mg/kg IV daily or every other day for a total dose of <20–45 mg/kg
	Miltefosine*	50 mg BID if weight is 30–44 kg and TID if weight is ≥45 kg × 28 days
Alternative	Pentamidine	2–4 mg/kg IV or IM every other day or 3 times per week for ≥15 doses; 4–7 mg/kg IV or IM every 72 hours x 3 doses

*FDA-approved for the treatment of cutaneous and mucosal leishmaniasis due to *L. braziliensis*, *L. guyanensis*, and *L. panamensis* in patients ≥12 years of age.
†Doses refer to mg of pentavalent antimony – 100 mg/ml for sodium stibogluconate (Pentostam®), 85 mg/ml for meglumine antimonate (Glucantime®).
‡Limited evidence of efficacy; other azole antifungals that have been utilized (with variable results) include itraconazole (7 mg/kg/day PO × 3 weeks).
¶In patients with severe mucosal disease or HIV co-infection, liposomal amphotericin B or amphotericin B deoxycholate are considered first-line therapy.

Table 83.6 Treatment recommendations for leishmaniasis. The treatment regimen (drug, dose, duration) that is chosen depends upon the geographic region, species of *Leishmania*, location and severity (e.g. number and size of lesions) of disease, and host factors. The Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and Pan-American Health Organization (PAHO) represent resources for up-to-date information. Sodium stibogluconate is not approved by the US Food and Drug Administration (FDA), but it is available from the CDC; meglumine antimonate and paromomycin are not readily available in the US. The use of pentoxifylline in addition to stibogluconate is included as an alternative treatment regimen for mucocutaneous disease by the PAHO. Inpatient monitoring and prophylactic corticosteroid administration are typically required for patients with laryngeal/pharyngeal disease. BID, twice daily; IM, intramuscular; IV, intravenous; MBCL, methylbenzethonium chloride; PO, orally; TID, three times daily.

Pathogenesis

Once the cyst is ingested, it travels to the colon, where it becomes a trophozoite. Although trophozoites can be excreted, cysts represent the primary excreted form[41,42]. Infection of intestinal mucosa depends upon interaction of lectins on the surface of the ameba with mucin glycoproteins on the intestinal epithelium[43]. The main mechanism

ADVERSE EFFECTS OF THE MOST COMMONLY USED DRUGS FOR LEISHMANIASIS		
Drug	**Side effect**	**Incidence**
Intralesional pentavalent antimony	Localized pain, erythema, edema	25%–50%
Parenteral pentavalent antimony	Elevated amylase/lipase and/or LFTs (interrupt therapy if clinical pancreatitis)	>50%
	Myalgia, arthralgia, headaches, fatigue	25%–50%
	Abdominal pain/nausea	25%–50%
	Thrombocytopenia/leukopenia	<25%
	ECG changes (e.g. QT prolongation, ST-T wave changes) or cardiotoxicity	<25%
Miltefosine	Motion sickness	>50%
	Nausea (administer with high fat food to reduce), vomiting, and diarrhea	25%–50%
	Elevated serum creatinine	25%–50%
	Mildly elevated LFTs	<25%
	Teratogenicity*	>50%
Pentamidine	Nausea, vomiting, abdominal pain, and dysgeusia	>50%
	Hyperglycemia, hepatotoxicity, nephrotoxicity, cytopenias	<25%
	Cardiotoxicity (QT prolongation); infuse slowly to avoid hypotension	<25%

*Contraindicated during pregnancy. Contraception is required during administration and for 2 months after the drug is discontinued.

Table 83.7 Adverse effects of the most commonly used drugs for leishmaniasis. Side effects of amphotericin B can include fevers/chills, nausea/vomiting, nephrotoxicity, electrolyte abnormalities, and cytopenias (see Ch. 127). ECG, electrocardiogram; LFTs, liver function tests.

by which *E. histolytica* produces disease is through tissue lysis[42]. The trophozoites kill target cells upon direct contact, due in part to the release of proteolytic enzymes, e.g. cathepsin B and collagenase. The trophozoites also have the capacity to destroy neutrophils, resulting in release of their intracellular contents, which further contribute to the destruction of host tissues. The mechanisms of defense against *E. histolytica* include mucosal immune responses (e.g. antiamebic IgA antibodies), cell-mediated immune defense (e.g. cytotoxic T lymphocytes and production of lymphokines such as IFN-γ, which activate macrophages to kill the trophozoites), and non-immune defenses (e.g. production of mucus by colonic mucosa, inhibiting amebic adherence to and lysis of the mucosa).

Clinical features

Patients with symptomatic amebiasis due to *E. histolytica* typically develop colitis and present with abdominal pain, tenesmus, bloody diarrhea, and mucosal ulcerations[41]. Extraintestinal complications, which can occur from hematogenous spread via invasion through the gastrointestinal epithelium, include hepatic abscesses, empyema, and pericardial effusions[41,43]. The skin is affected in <1% of patients with amebiasis. Skin involvement occurs as a result of extension of rectal amebiasis to the anus, perianal skin, or vulva; spread to the abdominal wall from a colostomy or after surgical drainage of a liver abscess; or inoculation of the penis during anal intercourse. Primary cutaneous amebiasis via external inoculation is exceedingly rare but has been reported on the face[44,45].

Cutaneous lesions can present as verrucous plaques or ulcers with a gray–white necrotic base (Fig. 83.13). Ulcerative lesions are usually painful and somewhat oval in shape, with irregular borders and intervening areas of unaffected skin. Extensive tissue destruction is characteristic.

Pathology and diagnosis

Histologically, ulcerated lesions have central necrosis with adjacent pseudoepitheliomatous hyperplasia. Mixed inflammatory infiltrates are present in the dermis and can extend into the subcutaneous tissue.



Fig. 83.13 Cutaneous amebiasis. Multiple large ulcers on the leg of a patient with amebiasis. Note the extensive tissue destruction and resemblance to pyoderma gangrenosum. *Courtesy Omar P. Sangüeza, MD.*

Within the ulcerated and necrotic areas, it is possible to identify the trophozoites of *E. histolytica*. They have ample, finely granular eosinophilic cytoplasm, eccentric nuclei, and prominent nucleoli, and some may contain phagocytized red cells. Chronic lesions show prominent irregular epidermal hyperplasia and inflammatory infiltrates, with few organisms present. Touch and wet drop preparations from the pus may also be utilized to identify the trophozoite[3]. Examination of fresh stool has a low yield for demonstrating the trophozoite, and multiple stool samples must be obtained[41]. Where available, PCR may be used for detection. Once the diagnosis is established, evaluation of other body sites for involvement is recommended.

Differential diagnosis

A diagnosis of amebiasis should be considered in patients with painful anogenital ulcers. In high-income countries, a patient with colitis and necrotic cutaneous ulcers is more likely to have inflammatory bowel disease-associated pyoderma gangrenosum. Other infectious causes of skin ulcers, e.g. streptococci, dimorphic or opportunistic fungi, tuberculosis and mixed bacterial flora (phagedenic or tropical ulcer), should be excluded. Verrucous lesions in the anogenital region may be confused with condylomata acuminata and squamous cell carcinoma.

Treatment

Oral metronidazole is the drug of choice for amebiasis due to *E. histolytica*: for adults, 500–750 mg three times daily for 7–10 days and for children, 35–50 mg/kg/day divided into three doses for 10 days. Other medications that have been used include diloxanide, tinidazole, pentamidine, and iodoquinol[30,43].

Balamuthia mandrillaris Infection

Key features

- *B. mandrillaris* is a free-living ameba that causes a rare, usually fatal encephalitis in immunocompetent individuals
- Skin infection presents weeks to months prior to hematogenous spread to the central nervous system (CNS)
- Slowly growing, indurated plaques favor the central face and occur less often on the extremities

Introduction

B. mandrillaris is a free-living ameba that can infect the skin and subsequently lead to fatal encephalitis.

Epidemiology

At least three genera of free-living amebas cause disease in humans, including *Naegleria*, *Acanthamoeba*, and *Balamuthia*[46]. These amebas

are found worldwide in the soil and (especially for the former two organisms) fresh water. Cutaneous infection with *B. mandrillaris* or *Acanthamoeba* spp. may precede development of granulomatous encephalitis. Such infections may be acquired from exposure of microabrasions or open wounds in the skin to soil and water sources; encephalitis can also result from infection of the nasal/respiratory mucosa via inhalation. *Naegleria fowleri* infection can cause acute, fatal encephalitis but is not known to have skin manifestations.

Although uncommon, *B. mandrillaris* has increasingly been recognized as a cause of encephalitis, with >100 cases reported in the US[47]. Most affected individuals reside in warmer regions, including Latin America and the southern US[48]. Unlike *Acanthamoeba* infections, which only affect immunocompromised patients, most *B. mandrillaris* infections occur in immunocompetent individuals, favoring children as well as the elderly; the male : female ratio is <2–3 : 1[48,49]. In addition, nearly 50% of the *B. mandrillaris* infections identified in the US have been in individuals of Hispanic ethnicity[50,51]. Transmission of *B. mandrillaris* via solid organ transplantation has also been described[52].

Pathogenesis

B. mandrillaris is a free-living ameba that can exist both as a dormant cyst and as an infectious trophozoite. Because *B. mandrillaris* can cause disease in immunocompetent hosts, it is thought to be more virulent than *Acanthamoeba*. However, clinically unaffected individuals have been shown to have antibodies against *B. mandrillaris*[53]. The presence of predisposing factors such as local disruption of the skin or mucosal barrier is likely required for infection. The trophozoites feed on human cells and can spread to the CNS hematogenously[54].

Clinical features

B. mandrillaris causes a subacute to chronic granulomatous encephalitis that has a mortality rate of >80%[49,55]. In a subset of patients, CNS involvement is preceded by the development of a slowly expanding, indurated, asymptomatic plaque on the central face or less often other sites such as an extremity (especially around the knee), the gluteal area, or the oral mucosa (Fig. 83.14)[46]. A skin lesion may be present for 5–8 months before the organism disseminates to the CNS[3]. As the plaque enlarges, it may become infiltrative (Fig. 83.14B) and occasionally ulcerates. Although there is usually a single skin lesion, local "satellite" lesions or involvement of multiple sites can occur. Neurologic manifestations are similar to those in other forms of meningoencephalitis and include headache, altered mental status, cranial nerve dysfunction, and seizures; however, the symptoms may have an insidious onset and chronic course.

Pathology and diagnosis

The diagnosis of *B. mandrillaris* infection is often made at autopsy or by skin biopsy[3]. In the dermis of affected skin, there is a mixed granulomatous infiltrate with many giant cells, but usually few identifiable trophozoites[56]. Immunohistochemical staining or PCR-based analysis of skin specimens can provide definitive diagnosis[57]. Culture and isolation of *B. mandrillaris* requires a complex medium containing fetal bovine serum or a specialized cell type (e.g. monkey kidney cells, human lung fibroblasts)[57]. Examination of the cerebrospinal fluid (CSF) may show motile amebic trophozoites with pseudopodia formation. Brain imaging in patients with advanced disease reveals calcified, mass-like lesions[58].

Treatment

Considering the poor prognosis of *B. mandrillaris* encephalitis, early diagnosis when the disease is limited to the skin is critical. Multiagent therapy for a prolonged period (e.g. 12 months) is recommended, with reported regimens including miltefosine with various combinations (2–5 drugs) of pentamidine, sulfadiazine, flucytosine, an azole antifungal, liposomal amphotericin B, a macrolide antibiotic (clarithromycin or azithromycin), and albendazole[55,58,59]. However, controlled trials are lacking. Surgical excision of cutaneous lesions should also be considered when possible[59].

TRYPANOSOMIASIS

Synonyms: ■ Chagas disease: American trypanosomiasis, Chagas–Mazza disease ■ African trypanosomiasis: African sleeping sickness

Although the genus *Trypanosoma* consists of at least 20 species of protozoa, only two are known to cause human disease. Chagas disease (American trypanosomiasis) is caused by *T. cruzi* infection and transmitted by reduviid bugs, while African trypanosomiasis is caused by *T. brucei* infection and transmitted by tsetse flies.

Chagas Disease

Key features

- An endemic disease in many areas of Central and South America
- Transmission of *T. cruzi* is via infected reduviid bugs and occasionally by contaminated blood
- A serious systemic disease with three phases (acute, indeterminate, and chronic). The chronic phase primarily affects the heart and gastrointestinal tract
- Following inoculation of the parasite into the skin, localized erythema and edema (chagoma) can develop in conjunction with regional lymphadenopathy
- When the conjunctiva is the portal of entry, edema of the palpebral and periocular tissue is seen (Romaña sign)

Epidemiology

T. cruzi and its arthropod vectors (reduviid or kissing bugs) are found in the Americas, from the southern US to southern Argentina (Fig. 83.15)[60]. Reduviid bugs feed mainly on human, animal, or avian blood, but they sometimes engage in cannibalism or coprophagia, which may result in vector-to-vector transmission of *T. cruzi*. A favorite habitat for these bugs is cracks in the walls of mud huts in poor rural areas, and they are known as kissing bugs because of their habit of biting the face of humans. Direct transmission of *T. cruzi* via transfusion of contaminated blood can occur; since 2007, blood donated in the US has been screened for this organism[61]. In addition, transplacental transmission can result in congenital infection.



Fig. 83.14 ***Balamuthia mandrillaris* infection. A** Indurated plaque on the nose. **B** Infiltration that has progressed to involve a large portion of the face. **C** Indurated plaque on the knee, which represents another common site. *A, B, with permission from Tyring S, Lupi O, Hengge U (eds). Tropical Dermatology. Churchill Livingstone, 2005.*

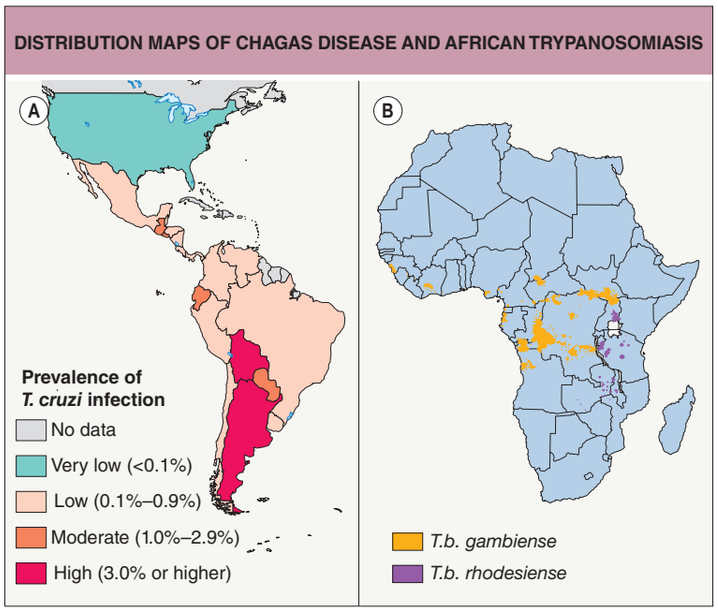


Fig. 83.15 Distribution map of Chagas disease and African trypanosomiasis.
Adapted with permission from Nabarro L, Morris-Jones S, Moore DAJ: Peters' Atlas of Tropical Medicine and Parasitology, 7th edition. London: Elsevier, 2019; and with data from Bern C. Chagas' Disease. N Engl J Med 2015;373:456–66.

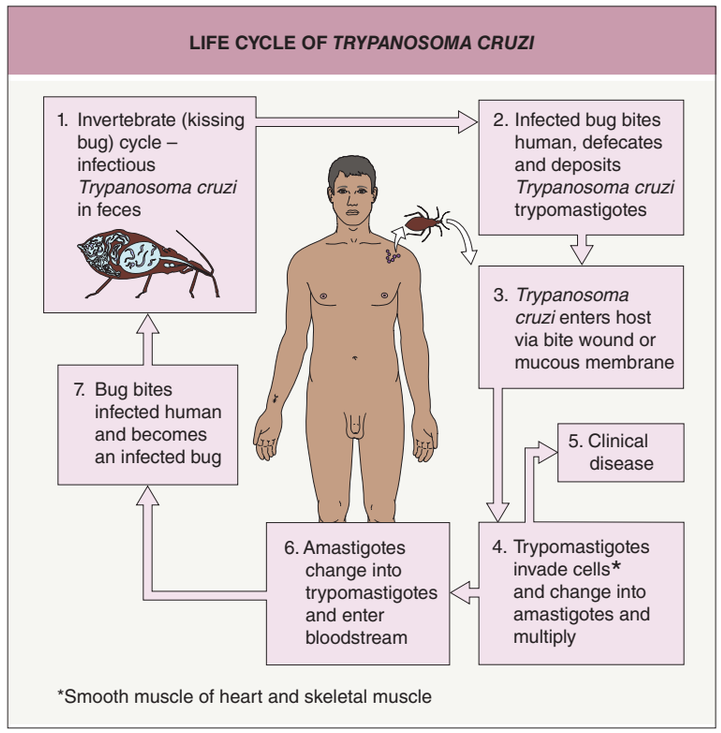


Fig. 83.16 Life cycle of *Trypanosoma cruzi*. *Adapted with permission from Keusch GT. Host response to infection. In: Cohen J, Powderly W (eds). Infectious Diseases, 2nd edition. London: Mosby, 2004.*

It is estimated that ~6 million people in the Americas are infected with *T. cruzi*, including <300 000 individuals in the US, especially immigrants from Latin America living in Texas and California[62,63]. Chagas disease kills ~10 000 people per year[64], mostly in rural areas of Latin America; it represents the leading cause of parasitic death in Latin America and the third leading cause in the world. The acute form of the disease (see below) is seen more commonly in children, and, in some areas, 85% of children under the age of 10 years are infected.

Pathogenesis

Blood-sucking reduviid bugs ingest trypomastigotes from the peripheral blood of vertebrate hosts (Fig. 83.16). Once the bug has become infected, it remains so for the rest of its life. The parasites transform into epimastigotes and multiply in the bug's midgut, later becoming metacyclic trypomastigotes in its hindgut. When the infected bug takes a subsequent blood meal, it usually defecates during or after feeding, depositing infective metacyclic trypomastigotes on the skin. The parasites penetrate the skin (generally via the bite wound) or mucosa (usually the conjunctiva). Following invasion of the host's cells, amastigotes multiply within the cytoplasm and then develop into trypomastigotes. The latter are released when the cells rupture and then can either infect other cells or enter the bloodstream, where they become the source of infection for new vectors. *T. cruzi* can also be transmitted transplacentally as well as through blood transfusions, organ transplantation, laboratory accidents, and occasionally contaminated food.

The autonomic nervous system that innervates the heart and gastrointestinal tract appears to be a primary target of *T. cruzi* infection. The visceral involvement seen in the chronic stage (see below) is thought to reflect neuronal damage during the acute phase. A role for autoimmunity in the chronic phase of the disease has also been hypothesized. In addition, trypomastigotes have the ability to penetrate the smooth muscle of the heart and the wall of the gastrointestinal tract[65].

Clinical features

Chagas disease has acute and chronic phases with distinct clinical manifestations. Although the acute phase can affect individuals of any age, it is usually observed in children and tends to be more severe in those ≤2 years of age[66]. At the cutaneous site of parasitic entry (see Fig. 83.16), some patients develop a chagoma, which is a localized area of erythema and swelling that is often accompanied by regional lymphadenopathy. When the conjunctiva is the portal of entry, the painless edema of the palpebral and periocular tissues that appears is referred to as the Romaña sign or ophthalmoganglionar complex (Fig. 83.17)[3]. The Romaña sign occurs in ~80% of individuals infected by this route. In some patients, the swelling is accompanied by preauricular lymphadenopathy (Parinaud sign)[60].



Fig. 83.17 Chagas disease. Young child with unilateral periorbital edema characteristic of this disease (Romaña sign) when the conjunctiva is the portal of entry. *Courtesy Omar P. Sangüeza, MD.*

These initial clinical findings can be accompanied by fever, malaise, anorexia, and edema of the face and lower extremities. Some patients develop erythematous macules, hepatosplenomegaly, thrombocytosis, leukocytosis, and/or eosinophilia. The acute phase may last for up to 2 months but usually resolves spontaneously. In addition, inflammation at the sites of parasite entry can persist for several weeks[60]. Occasionally, patients develop life-threatening myocarditis or meningoencephalitis[65].

After resolution of the acute phase, patients enter the indeterminate phase of Chagas disease. This stage is characterized by asymptomatic parasitemia and positive serology. Then, many years or even decades after the initial infection, 30% of patients develop symptoms of chronic Chagas disease[66]. The heart is the organ most commonly affected and the clinical manifestations include congestive heart failure, arrhythmias,

and heart block[65]. The gastrointestinal tract is also frequently involved, leading to megacolon and megaesophagus.

If patients who chronically harbor *T. cruzi* become immunosuppressed, reactivation of the disease can occur. When this happens, the disease is often more severe than in typical cases of Chagas disease, and patients may develop nodules and plaques that favor the lower extremities[60,66].

Pathology

Histologically, at the site of parasite entry (chagoma), there is interstitial edema and a mononuclear cell infiltrate. Within cells in the subcutaneous tissue and muscle, aggregates of amastigotes may be seen. Enlarged lymph nodes are hyperplastic and intracellular amastigotes can be observed. In the chronic stage, trypanosomes are rare in affected organs.

Diagnosis and differential diagnosis

The diagnosis of *acute* Chagas disease is typically based upon the microscopic identification of either trypomastigotes in the blood (or CSF) or amastigotes within tissue. Because the concentration of parasites is low even in the acute stage, hemoconcentration techniques are used to enhance the yield. PCR currently represents the most sensitive diagnostic method for acute disease, with positive results days to weeks earlier than microscopy; PCR is especially useful for the diagnosis of infections acquired vertically, via organ transplantation, or after laboratory exposure[67,68]. Cultures of blood, CSF, or tissue are less sensitive for detection of acute *T. cruzi* infection.

Serologic tests such as ELISAs and immunofluorescent antibody assays (IFAs) are used to establish the diagnosis of *chronic* Chagas disease. PCR-based detection has variable sensitivity and limited utility for chronic Chagas disease, although it may serve as an indicator of treatment failure or disease reactivation[63]. Xenodiagnosis represents a specific and fairly sensitive (≤50%) method, and it can be used to confirm a serologic diagnosis[60]; however, this technique is expensive and is only available in large laboratories in endemic areas. For xenodiagnosis, trypanosome-free reduviid bugs are allowed to feed on patients and the feces or hindgut contents of the bugs are examined for epimastigotes 10 to 30 days later.

The nonspecific symptoms that may occur during the acute phase of Chagas disease, such as a macular eruption and influenza-like symptoms, make the differential diagnosis broad. When the site of inoculation is the eye, other entities to consider include a reaction to a bite from another type of insect, angioedema, and bacterial cellulitis.

Treatment

Treatment is most effective early in the course of Chagas disease[67]. Benznidazole and nifurtimox (both available through the CDC) can reduce the severity and duration of symptoms associated with the *acute* phase, with a parasitologic cure in 60%–90% of patients[63,69]. Because benznidazole is better tolerated, it is favored by most experts[63]. The side effects of these two medications are reviewed in Table 83.8.

Benznidazole, allopurinol, itraconazole, and posaconazole have also been evaluated for the treatment of *chronic* Chagas disease[70–72].

ANTIHELMINTHIC DRUGS: THERAPEUTIC USES, SIDE EFFECTS, AND CONTRAINDICATIONS

Drug	Therapeutic use	Toxicity and side effects		Precautions and contraindications
		Direct drug effects	"Allergic" reactions	
Thiabendazole	Strongyloidiasis, cutaneous larva migrans (second-line therapy), dracunculiasis	• GI: nausea, vomiting, anorexia > diarrhea, abdominal pain > elevated transaminases, cholestasis • Neurologic: dizziness, drowsiness > headache, paresthesias, weakness > tinnitus, seizures, hallucinations • Ocular: irritation, blurred vision, xerophthalmia • Other: crystalluria without hematuria, transient leukopenia, xerostomia	• Cutaneous: urticaria (3%), exanthem (<5%) > fixed drug eruption, pruritus, perianal rash, flushing, angioedema, contact dermatitis, Jarisch–Herxheimer reaction, Stevens–Johnson syndrome • Fever, anaphylaxis	• Use in pregnancy if benefits outweigh risks • Discontinue during lactation • Use with caution if hepatic disease
Mebendazole	GI nematode infections (e.g. enterobiasis, ascariasis, ancylostomiasis), toxocariasis, trichinosis, sparganosis	• GI: nausea, vomiting, diarrhea, abdominal pain > elevated transaminases • Neurologic: dizziness, drowsiness > tinnitus, seizures • Hematologic: anemia, thrombocytopenia, leukopenia > agranulocytosis • Other: alopecia, oligospermia	• Cutaneous: exanthem, urticaria, angioedema, pruritus, flushing	• Use in pregnancy if benefits outweigh risks • Use with caution in children <2 years of age
Albendazole	Cutaneous larva migrans, GI nematode infections (as above), gnathostomiasis, echinococcosis, neurocysticercosis, toxocariasis	• GI: nausea, vomiting, diarrhea, abdominal pain, elevated transaminases > cholestasis • Neurologic: headache, dizziness > increased intracranial pressure (with treatment of neurocysticercosis), seizures • Hematologic: leukopenia > thrombocytopenia, agranulocytosis, pancytopenia • Other: alopecia	• Cutaneous: exanthem, urticaria > angioedema, Stevens–Johnson syndrome • Fever, anaphylaxis	• Use in pregnancy if benefits outweigh risks; avoid during first trimester • Avoid during lactation • Use with caution if hepatic disease
Diethylcarbamazine	Filariasis, dirofilariasis, loiasis, toxocariasis (second-line therapy)	• GI: nausea, vomiting, anorexia • Neurologic: headache	• Mazzotti reaction: pruritus, lymphadenopathy > papular exanthem, fever, tachycardia, arthralgias, headache • Nodular swellings along the lymphatics • Leukocytosis, eosinophilia • Ocular: limbitis, punctate keratitis > uveitis, atrophy of the retinal pigment epithelium > retinal hemorrhage (*L. loa*) • Encephalitis (*L. loa*) • Proteinuria	• Appears to be safe for use during pregnancy (controlled studies show no fetal risk) • Avoid population-based administration in regions where onchocerciasis or loiasis is endemic

Table 83.8 Antihelminthic drugs: therapeutic uses, side effects, and contraindications.

ANTIHELMINTHIC DRUGS: THERAPEUTIC USES, SIDE EFFECTS, AND CONTRAINDICATIONS				
Drug	**Therapeutic use**	**Toxicity and side effects**		**Precautions and contraindications**
		Direct drug effects	**"Allergic" reactions**	
Ivermectin	Onchocerciasis, filariasis (second-line therapy), cutaneous larva migrans, gnathostomiasis, ascariasis, strongyloidiasis	• GI: nausea, vomiting, diarrhea, elevated transaminases > cholestasis • Neurologic: dizziness > drowsiness, headache, tremor • Other: leukopenia	• Mazzotti-like reaction and ocular side effects (*O. volvulus*; see above) • Pruritus, urticaria, peripheral edema • Orthostatic hypotension	• Use in pregnancy if benefits outweigh risks • Considered safe during lactation
Moxidectin	Onchocerciasis	• GI: nausea, vomiting, diarrhea • Neurologic: dizziness, headache • Other: musculoskeletal pain, leukopenia	• Mazzotti-like reaction and ocular side effects (see above) • Pruritus, urticaria, peripheral edema • Orthostatic hypotension • Encephalitis (*L. loa*)	• Limited data on use in pregnancy and lactation
Praziquantel	Schistosomiasis; liver fluke and tapeworm infections (e.g. cysticercosis, sparganosis)	• GI: nausea, vomiting, abdominal discomfort > bloody diarrhea, elevated transaminases • Neurologic: headache, dizziness > drowsiness • Other: arrhythmias	• Cutaneous: pruritus > urticaria, exanthem • Arthralgias, myalgias • Fever • Meningismus, CSF pleocytosis, seizures (in neurocysticercosis)	• Controlled studies in pregnant women have not shown adverse outcomes • Considered safe during lactation • Contraindicated for ocular cysticercosis
Levamisole	GI nematode infections (e.g. ascariasis, ancylostomiasis; second-line therapy)	• GI: nausea, vomiting, diarrhea, abdominal discomfort • Neurologic: headache > dizziness, insomnia, paresthesias > multifocal leukoencephalopathy • Hematologic: leukopenia, anemia, thrombocytopenia > agranulocytosis • Other: dysgeusia, xerosis, alopecia, arthralgias	• Cutaneous: exanthem (5%–10%) > pruritus, urticaria, angioedema, fixed drug eruption, lichenoid eruption, vasculitis/vasculopathy (favors the ears), Stevens–Johnson syndrome • Stomatitis (5%) • Fever, anaphylaxis	• Use in pregnancy if benefits outweigh risks • Considered safe during lactation
Nifurtimox	Chagas disease	• GI: nausea, vomiting, anorexia > abdominal pain, diarrhea • Neurologic: paresthesias, weakness, headache, insomnia > psychiatric disturbances, seizures • Other: myalgias > leukopenia, oligospermia	• Cutaneous: exanthem, urticaria, angioedema • Fever, anaphylaxis	• Use in pregnancy if benefits outweigh risks
Benznidazole	Chagas disease	• GI: nausea, vomiting, anorexia • Neurologic: paresthesias, weakness • Hematologic: leukopenia > thrombocytopenia, agranulocytosis • Other: myalgias	• Cutaneous (more common than with nifurtimox): exanthem, urticaria, angioedema, generalized peripheral edema • Fever, lymphadenopathy, anaphylaxis	• Use in pregnancy if benefits outweigh risks
Suramin	African trypanosomiasis	• GI: nausea, vomiting > diarrhea, abdominal pain, elevated transaminases, cholestasis • Neurologic: palmoplantar hyperesthesia/paresthesias, weakness, headache > seizures • Ocular: blepharitis, conjunctivitis, photophobia, excessive lacrimation • Hematologic: leukopenia > agranulocytosis, hemolytic anemia, thrombocytopenia • Other: malaise, dysgeusia, proteinuria > renal or adrenal insufficiency	• Cutaneous: exanthem, urticaria > exfoliative dermatitis, generalized peripheral edema • Stomatitis • Fever, anaphylaxis (1 : 2000)	• Use in pregnancy if benefits outweigh risks • Use with caution if renal disease
Eflornithine	African trypanosomiasis (*T. brucei gambiense*)	• GI: diarrhea (40%) > nausea, vomiting, abdominal pain • Neurologic: dizziness, headache, seizures (~5%) • Hematologic: anemia (50%) > leukopenia (25%) > thrombocytopenia • Other: alopecia > hearing loss	• Cutaneous: exanthem • Fever	• Use in pregnancy if benefits outweigh risks

Table 83.8 Antihelminthic drugs: therapeutic uses, side effects, and contraindications. Emodepside is currently in veterinary use and represents a candidate for onchocerciasis and infections with *Trichuris trichiura* and hookworms in humans. CSF, cerebrospinal fluid; GI, gastrointestinal.

Although these agents can decrease serum parasite load, to date, there is no evidence that pathologic changes or progression of the chronic phase of this disease can be reversed or stopped by any therapy. Thus, chronic disease is managed primarily by supportive care (e.g. antiarrhythmics)[65].

Prevention of the infection involves education about sanitation and the use of residual insecticides in domestic areas. Vaccines are being investigated but are not currently available. Cyanotriazoles, a new class of antiparasitic drugs that inhibit topoisomerase II, may be of utility for the treatment of trypanosomiasis and leishmaniasis.

African Trypanosomiasis

Key features

- In West Africa, the disorder is due to *Trypanosoma brucei gambiense* infection, and in East Africa it is caused by *Trypanosoma brucei rhodesiense* infection
- The vectors are several species of tsetse flies
- Cutaneous manifestations include a localized bite reaction ("trypanosomal chancre") and an annular erythematous eruption that coincides with fever spikes

Epidemiology

The incidence of African trypanosomiasis decreased from <10 000 cases in 2009 to ~750 in 2021[73]. This disease is almost invariably fatal if left untreated and occurs in two forms that are named based on their separate geographic distributions in Africa (see Fig. 83.15). The West African form, which is due to *Trypanosoma brucei gambiense* and accounts for >95% of cases, is a chronic anthroponotic disease with primarily neurologic features. Since 2020, elimination of West African trypanosomiasis has been achieved in several countries, including Togo, Côte d'Ivoire, Benin, Uganda, and Equatorial Guinea[73]. The East African form, caused by *Trypanosoma brucei rhodesiense*, is an acute zoonotic disease (with antelopes as a reservoir) that is often fatal even with treatment. Fortunately, *T. b. rhodesiense* only occasionally infects humans, mainly farmers, hunters, and tourists[74,75].

Both types of *T. brucei* are transmitted to humans by blood-sucking tsetse flies (genus *Glossina*), which are found in Africa. The flies become infected by ingesting blood from infected mammalian hosts (Fig. 83.18). Transmission transplacentally or via blood products may also potentially occur.

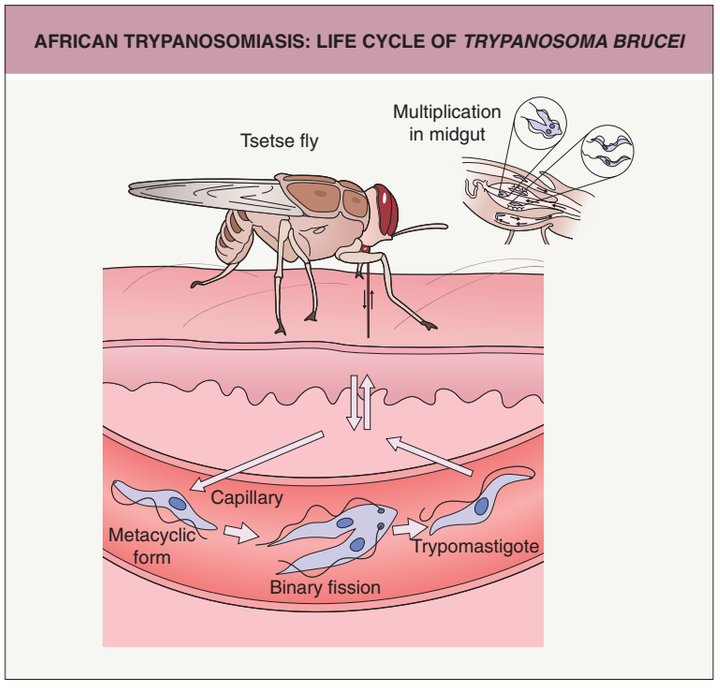


Fig. 83.18 African trypanosomiasis: life cycle of *Trypanosoma brucei*.

Pathogenesis

After inoculation, trypanosomes may produce a local chancre before spreading via the lymphatics to regional (and then distant) lymph nodes. The organisms disseminate to the bloodstream and eventually to the CNS, and they multiply by binary fission[76]. They escape significant immunologic response by continuously changing their surface glycoproteins[74,75].

Clinical features

An indurated, painful reaction develops at the portal of entry of the organisms, referred to as a "trypanosomal chancre" (Fig. 83.19). This is seen more commonly (70%–80% of cases) in the East African form due to *T. b. rhodesiense*[60]. The lesion appears 1–2 weeks after the tsetse fly bite and heals spontaneously over several weeks.

The *first (hemolymphatic) stage* occurs when the trypanosomes enter the lymphatic system and bloodstream 1–3 weeks after infection. Patients develop spiking fevers, malaise, and symmetrical lymphadenopathy. Enlargement of the lymph nodes of the posterior cervical triangle, referred to as the Winterbottom sign, is a classic finding in the West African form due to *T. b. gambiense*. Patients may have peripheral or facial edema, hepatosplenomegaly, and ascites[3]. A transient eruption (referred to as "trypanids") of annular and targetoid erythematous patches or urticarial plaques may occur in concert with fever spikes 6–8 weeks after onset of the illness. The eruption favors the trunk and while reported to occur in ~50% of patients is more easily noted in those with lighter skin phototypes[3,77].

The *second (meningoencephalitic) stage* of the disease is characterized by neurologic manifestations, including irritability, changes in personality, inability to concentrate, and daytime somnolence alternating with nighttime restlessness and insomnia, hence the term sleeping sickness[78]. Deep delayed hyperesthesia after a brisk tap or pinch (Kerandel sign) reflects CNS involvement[77]. CSF examination demonstrates lymphocytic pleocytosis and increased protein content; in some patients, trypanosomes are evident when the fluid is centrifuged.

East African trypanosomiasis tends to follow a more acute course with earlier onset of CNS symptoms, which are often delayed months to years in the West African variant, and the stages are not as well defined. In addition, East African trypanosomiasis may result in heart failure due to myocardial damage, even preceding CNS symptoms[79].

Pathology and diagnosis

Definitive diagnosis requires identification of the parasites in the skin, blood (especially the buffy coat), lymph node, or CSF. Routine histologic sections from skin lesions demonstrate a superficial perivascular lymphocytic infiltrate and mild spongiosis; trypanosomes are usually



Fig. 83.19 Trypanosomal chancre. The bite reaction, the earliest clinical lesion, is known as a "trypanosomal chancre". It resembles a boil but is usually painless. Fluid aspirated from the nodule contains actively dividing trypanosomes. This reaction is seen more commonly in *T. b. rhodesiense* than in *T. b. gambiense* infection. *With permission from Peters W, Pasvol G. Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

not seen. Serologic tests become positive about 2 weeks after the onset of infection[3]. PCR represents the most sensitive test[60], and a CRISPR-based assay suitable for point-of-care diagnosis has been developed.

Differential diagnosis

The differential diagnosis of the chancre includes infectious disorders such as extragenital primary syphilis and primary inoculation tuberculosis; entities that lead to an annular erythema are discussed in Chapter 19.

Treatment

According to current WHO guidelines, oral fexinidazole represents the treatment of choice for first and non-severe second (<100 leukocytes/mcl in CSF) stages of *T.b. gambiense* infection in patients ≥6 years of age weighing ≥20 kg[80]. In children <6 years of age or weighing <20 kg, pentamidine is recommended for the first stage and nifurtimox-eflornithine combination therapy (NECT) for the second stage. NECT is also indicated for severe second-stage disease (≥100 leukocytes/mcl in CSF) in older children and adults. For *T.b. rhodesiense* infections, suramin is utilized for the first stage and melarsoprol for the second stage[80].

TOXOPLASMOSIS

Key features

- A common, worldwide disease caused by the protozoan *Toxoplasma gondii*
- Cutaneous involvement is unusual but occasionally occurs in immunocompromised individuals, pregnant women, and neonates
- In congenital infections, the skin lesions are usually necrotic or hemorrhagic papules

Toxoplasma gondii is an intestinal coccidian parasite of domestic cats and other mammals (Fig. 83.20). *Toxoplasma* infections in humans can be acquired or congenital. In immunocompetent hosts, most infections are asymptomatic or produce only flu-like symptoms, with occasional development of lymphadenopathy or chorioretinitis. In immunosuppressed patients, more severe disease can occur[81]. Cutaneous manifestations are rare and may be seen in both congenital

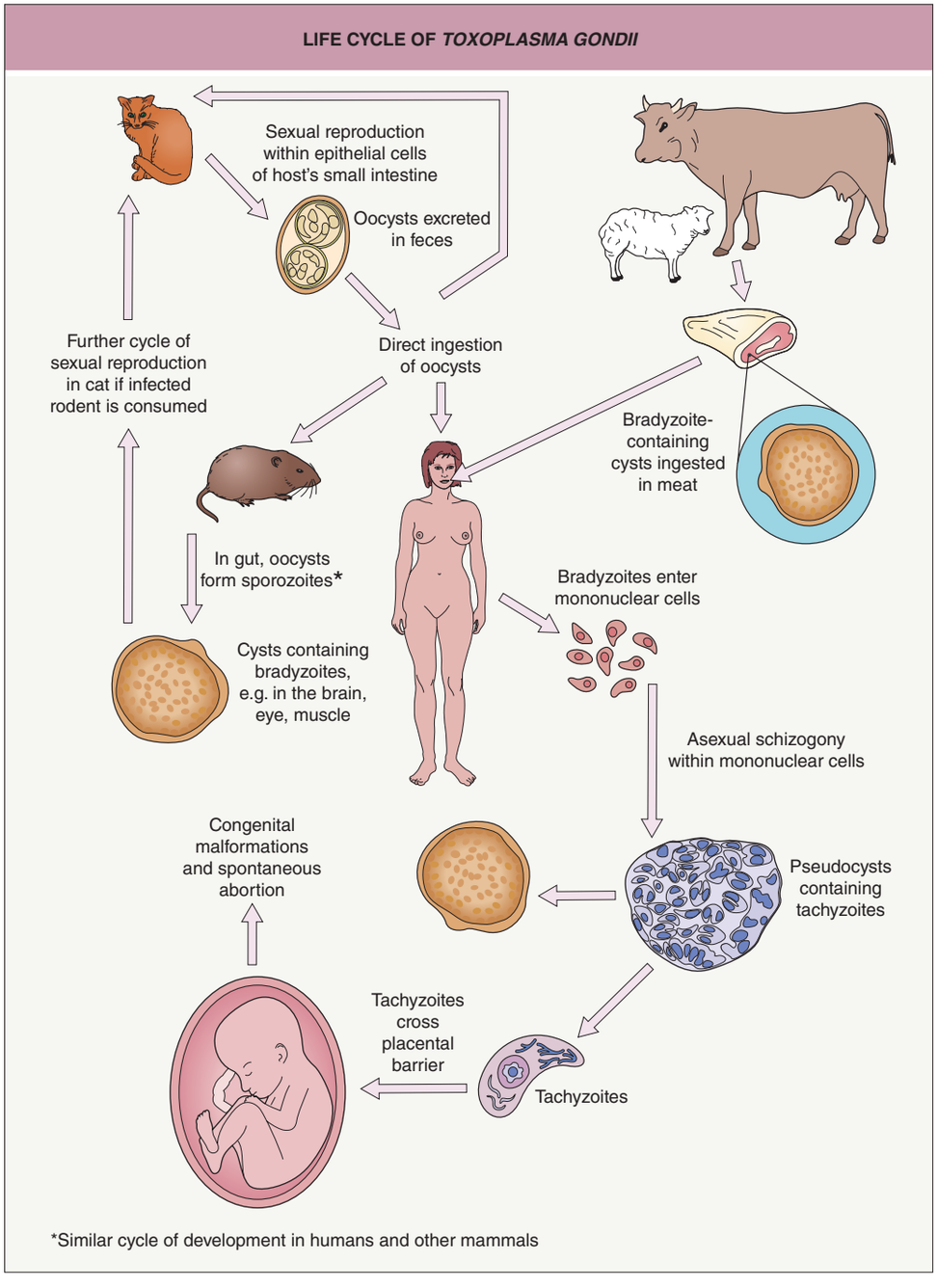


Fig. 83.20 Life cycle of *Toxoplasma gondii*. There is a wide range of mammalian hosts, the most important being the domestic cat. *Adapted from Peters W, Pasvol G. Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

TOXOPLASMOSIS	
Epidemiology	• *Toxoplasma gondii* is found worldwide • In the US, ~10%–15% of the population has antibodies against *T. gondii* • Congenital toxoplasmosis: 1 in 1000 (in Latin America) to <1 in 10 000 (in US) live births
Main definitive host	• Cats and wild felines
Route of infection	• Ingestion of bradyzoite-containing cysts within raw/undercooked meat (especially pork, lamb, and venison) • Ingestion of oocysts from cat feces (e.g. via contaminated soil or water) • Transplacental: more likely in the third trimester, more severe disease if in the first trimester • Organ transplantation or blood transfusion from an infected donor
Extracutaneous clinical features	• Acute acquired infection: asymptomatic (~90% of immunocompetent individuals) or lymphadenopathy and flu-like symptoms (e.g. fever, malaise, myalgias) • In immunocompromised individuals: encephalitis, pneumonitis, pericarditis, myositis, hepatitis • Chronic acquired infection: occasionally chorioretinitis • Congenital infection: asymptomatic (70%–90%) or variable chorioretinitis, deafness, microcephaly, hydrocephalus, seizures, developmental delay, hepatosplenomegaly, pneumonitis, fever, thrombocytopenia
Cutaneous manifestations	• Acquired infection: roseola-like exanthem, erythema multiforme-like eruption, papular urticaria; rarely erythroderma, sclerodermatous, dermatomyositis-like • Congenital: hemorrhagic or necrotic papules favoring the trunk
Skin histopathology	• Superficial and deep perivascular dermal infiltrates of lymphocytes, macrophages, plasma cells, and eosinophils; also dilated capillaries, foci of dermal hemorrhage, and occasionally small vessel vasculitis • Tissue forms of *T. gondii* – trophozoites within macrophage cytoplasm (singly or inside pseudocysts) – evident in <50% of biopsy specimens from lesional skin • Immunoperoxidase staining is very specific
Diagnosis	• *T. gondii* IgM and Ig in acute and convalescent sera • PCR-based assays can detect parasite DNA in blood, CSF, aqueous humor, and bronchoalveolar lavage fluid
Differential diagnosis	• Acquired infection: mononucleosis, other viral exanthems, meningococcemia, syphilis, erythema multiforme, autoimmune connective tissue diseases, urticarial vasculitis • Congenital infection: other TORCH infections (see Chs. 80 & 121)
Treatment for severe acute, active chronic, or congenital disease and in immunocompromised patients	• Pyrimethamine: in adults, a loading dose of 200 mg followed by 50–75 mg daily; in children, a loading dose of 2 mg/kg followed by 1 mg/kg/day Plus • Folinic acid Plus • Sulfadiazine (1–1.5 g q6h daily in adults and 100 mg/kg in two divided doses daily in children) • If sulfonamide allergic, can substitute clindamycin for sulfadiazine

Table 83.9 Toxoplasmosis.

and acquired forms of the disease[82]. The epidemiology, clinical features, diagnosis, and treatment of toxoplasmosis are presented in Table 83.9.

WORMS (HELMINTHS)

Medically important worms, or helminths, belong to two different phyla: Nematoda (roundworms) and Platyhelminthes (flatworms). The roundworms include free-living species as well as parasitic ones; they are unsegmented, and each species has two different sexes, a body cavity, and a digestive tract. The flatworms are primarily parasitic worms that do not have a body cavity; they can be segmented or unsegmented, and most species are hermaphroditic. Flatworms can be further subdivided into two different classes: trematodes or flukes (the cause of schistosomiasis) and cestodes or tapeworms (the cause of cysticercosis and echinococcosis). Several helminthic infections have been chosen for more detailed discussion in the remainder of the chapter, and additional disorders are outlined in Table 83.10.

Of note, an alternative way of classifying worms is by their life cycle[83]. This schema divides associated infections into four classes: (1) soil-transmitted infections, including those due to hookworms (e.g. ancylostomiasis, cutaneous larva migrans) and other nematodes (e.g. strongyloidiasis; Figs. 83.21 & 83.22); (2) infections transmitted mainly by insects, including onchocerciasis, filariasis, and loiasis (Fig. 83.23); (3) infections due to trematodes (flukes) whose life cycle involves snails, such as fascioliasis and schistosomiasis (Fig. 83.24); and (4) infections acquired via ingestion, such as gnathostomiasis, cysticercosis, and echinococcosis, enterobiasis, trichinosis, and toxocariasis (Figs. 83.25 & 83.26).

CUTANEOUS LARVA MIGRANS

Synonym: ▪ Creeping eruption

Key features

- Due to larvae of animal hookworms (intestinal nematodes)
- Skin lesions are serpiginous and pruritic, representing the paths of migration of organisms within the epidermis
- The rate of migration is 1–2 cm per day
- Self-limited disease

Cutaneous larva migrans is a serpiginous cutaneous eruption caused by the accidental penetration and migration of animal hookworm larvae through the epidermis. The infection has a worldwide distribution and occurs most frequently in warmer climates. The skin lesions are usually self-limited[83].

Epidemiology and Pathogenesis

Cutaneous larva migrans is caused by the larvae of hookworms that infect domestic dogs and cats, most often *Ancylostoma braziliense* or *A. caninum* and occasionally *Uncinaria stenocephala* or *Bunostomum phlebotomum*. Although cutaneous larva migrans has a worldwide distribution[84], it is most commonly seen in warm climates, such as the southeastern US, Central and South America, Africa, and other tropical areas[83]. The infection is usually acquired by walking barefoot on ground contaminated with animal feces, but the buttock or other body sites can become infected via contact with contaminated soil or sand. The larvae enter the skin and begin a prolonged process of migration within the epidermis. With rare exceptions, the parasite remains confined to the epidermis, producing visible tracts and intense pruritus. The parasite lacks collagenase, which is necessary to disrupt the basement membrane and enter the dermis.

Clinical Features

Patients have intense localized pruritus that begins shortly after the hookworm penetrates the skin. Several days later, the pruritus is associated with small vesicles and/or one or more edematous, serpiginous

MAJOR PARASITIC WORMS THAT CAUSE DISEASES AND CUTANEOUS MANIFESTATIONS IN HUMANS								
Disease	**Organism**	**Distribution**	**Mode of spread**	**Skin findings**	**Systemic findings**	**Diagnosis**	**Therapy***	**Figure**
Ascariasis (roundworms), intestinal nematode	*Ascaris lumbricoides*	Widespread and high prevalence, esp. in tropical countries	Ingestion of eggs	None	Abdominal pain, diarrhea, intestinal obstruction, nutritional deficiencies, Loeffler syndrome	Detection of eggs in the stools	Mebendazole Albendazole Pyrantel pamoate Ivermectin	83.22
Enterobiasis (pinworms), intestinal nematode	*Enterobius vermicularis*	Widespread and high prevalence, esp. in countries within temperate zones	Ingestion of eggs	Perianal and perineal pruritus	Restlessness Asymptomatic in most patients	Detection of eggs via adhesive cellophane tape pressed against perianal skin	Mebendazole Albendazole Pyrantel pamoate	83.22
Ancylostomiasis (hookworms), intestinal nematode	*Ancylostoma duodenale, Necator americanus*	Tropical and subtropical distribution	Percutaneous via contact with infective larvae in soil	Dermatitis (via contact with infective larvae in soil)	Iron deficiency anemia, GI symptoms, Loeffler syndrome, eosinophilia	Direct fecal smear examination for eggs	Mebendazole Albendazole Pyrantel pamoate	83.22
Strongyloidiasis, intestinal nematode	*Strongyloides stercoralis*	Occurs worldwide, esp. in tropical areas; in cooler climates found in warm humid mines	Percutaneous via contact with infective larvae; occasionally ingestion of larvae Autoinfection via penetration of perianal skin Hyperinfection in immunocompromised patients, due to penetration of intestinal mucosa	Generalized or localized urticarial eruption beginning perianally and extending to the buttocks, thighs, and abdomen (larva currens) "Thumbprint" purpura in hyperinfection (see Fig. 83.21)	Diarrhea, duodenitis, eosinophilia, pulmonary symptoms Symptoms more severe in immunocompromised patients	Examination of stool for larvae; rarely, diagnosis is made by lung biopsy or pulmonary cytology	Ivermectin Albendazole Thiabendazole	83.22
Loiasis, tissue nematode	*Loa*	West and Central Africa	Transmitted by bite of tabanid flies of the genus *Chrysops* (mango flies) carrying infective larvae Mature in connective tissue	Transient localized subcutaneous edema (Calabar swellings), often of the hands, wrists and forearms; represent tracts of migrating adult worms; associated with pruritus and pain	Conjunctivitis (due to movement of adult worms under conjunctiva), eosinophilia, renal disease	Detection of microfilariae in blood during the daytime Occasionally, adult worms can be extracted from the eye	Diethylcarbamazine Albendazole	83.23
Dirofilariasis, tissue nematodes of animals	*Dirofilaria immitis* (dog heartworms); *D. tunuis* (filaria of raccoons); *D. repens* (filaria of dogs and cats); *D. ursi* (filaria of bears)	*D. immitis* occurs worldwide; *D. tunuis* in Southeast US; *D. repens* in Europe and Asia; *D. ursi* in North America and Japan	Transmitted by mosquitoes carrying infective larvae Do not mature in humans	*D. tunuis, D. repens* and *D. ursi* cause small painful subcutaneous nodules with or without inflammation	*D. immitis* causes nodules in the lung	Detection of larvae by biopsy	Surgical excision Ivermectin	

Table 83.10 Major parasitic worms that cause diseases and cutaneous manifestations in humans.

Continued

MAJOR PARASITIC WORMS THAT CAUSE DISEASES AND CUTANEOUS MANIFESTATIONS IN HUMANS								
Disease	**Organism**	**Distribution**	**Mode of spread**	**Skin findings**	**Systemic findings**	**Diagnosis**	**Therapy***	**Figure**
Dracunculiasis (guinea worm), tissue nematode	*Dracunculus medinensis*	Africa, particularly Ghana and Sudan	Ingestion of infected water fleas of the genus *Cyclops* in drinking water migrate from intestine to subcutaneous tissue, usually of the legs	Papulonodule then blister and/or ulceration, usually of the lower extremity; calcified nodules	Anaphylactic shock, rheumatic symptoms	Confirmation of worms in the subcutaneous tissue Immunodiagnosis, e.g. ELISA Sequence analysis of 18 S RNA	Gradual extraction of the worm (e.g. on a stick)	83.23
Trichinosis (Trichinellosis), tissue nematode	*Trichinella spiralis*	Widespread in temperate zones	Ingestion of encysted larvae from raw/undercooked animal meat, usually pork	Periorbital edema in severe infection, splinter hemorrhages	Most infections are subclinical Heavy infection also leads to fever, enteritis, myositis, and eosinophilia; occasionally myocarditis and encephalitis	Confirmation of encysted larvae in the skeletal muscle; fluorescent antibody testing; ELISA	No satisfactory treatment Corticosteroids for severe symptoms plus mebendazole or albendazole	
Toxocariasis (visceral larva migrans), larval stage of dog roundworm, larval nematode	*Toxocara canis*	Worldwide distribution	Ingestion of eggs excreted by dogs Larvae migrate through the viscera as they are unable to mature into adults	Urticaria, cutaneous nodules	Cough, fever, hepatomegaly, eosinophilia; ocular and hepatic granulomas	Diagnosis is usually suggested clinically Confirmation by histologic examination is uncommon Serologic assay (Western blot)	Mebendazole Albendazole Diethylcarbamazine (second-line) Corticosteroids for severe ocular larva migrans	
Sparganosis, larval stage of tapeworms of dogs and cats, cestode	*Spirometra*	Sporadic in most countries, seen most frequently in the Far East	Ingestion of larvae in intermediate hosts (e.g. snakes, frogs, fish) Occasionally application of frogs to eyes as poultice	Painless small subcutaneous nodules at sites of larval proliferation Edema if periorbital involvement	Rarely pulmonary or CNS involvement	Biopsy to identify larvae	Surgical excision Praziquantel	83.26
Fascioliasis (liver fluke), trematode	*Fasciola hepatica*	South America, Europe, Africa, China, Australia	Ingestion of metacercariae on aquatic plants, e.g. wild watercress	Ectopic fascioliasis is occasionally reported; cutaneous cysts	Fever, hepatomegaly, obstruction of bile duct (rare), eosinophilia	Detection of ova in feces or bile Abdominal CT	Triclabendazole Nitazoxanide Bithionol	83.24
Paragonimiasis (lung flukes), trematode	*Paragonimus westermani*	*Paragonimus westermani* in Far East; other species in West Africa, Central and South America	Consumption of flesh of freshwater crustaceans containing living metacercariae	Cutaneous paragonimiasis rare, but has been reported	Productive cough, hemoptysis, bronchitis, lung abscess, pleural effusion Symptoms related to ectopic worms in abdomen, brain, etc.	Examination of sputum or feces for eggs ELISA	Praziquantel Triclabendazole	83.24

*Details regarding the majority of these medications are provided in Table 83.9.

Table 83.10 Major parasitic worms that cause diseases and cutaneous manifestations in humans. Cutaneous larva migrans, gnathostomiasis, onchocerciasis, filariasis, schistosomiasis, cysticercosis and echinococcosis are covered in the text.

tracts (Fig. 83.27). Each larva produces one tract and migrates at a rate of 1 to 2 cm per day ("creeping eruption"). The most frequent location is the distal lower extremities or buttocks. Additional sites of involvement include the hands, thighs, and rarely perianal area[83–85]. In severe infections, hundreds of such lesions may develop. If untreated, a single larval tract may progress, disappear for a few days, reappear, advance further, and so on, for weeks or months; spontaneous resolution occurs after a mean of 2 to 4 weeks.

Unlike human hookworm disease and strongyloidiasis, the larvae rarely progress beyond the skin, and systemic manifestations such as migratory pulmonary infiltrates and peripheral eosinophilia (Loeffler syndrome) are rarely seen. The only common systemic finding is a



Fig. 83.21 Strongyloidiasis hyperinfection. Multiple purpuric lesions (sometimes referred to as "thumbprint" purpura) on the abdomen of an immunocompromised patient. *Courtesy Jean L. Bolognia, MD.*

moderate peripheral blood eosinophilia. Due to intense pruritus and scratching, superimposed bacterial infections may complicate the clinical picture. Vesicles and bullae may develop in previously sensitized patients (see Fig. 83.27)[83,86].

Pathology

Although the diagnosis is usually made clinically, based on the characteristic lesions and history of recent exposure (e.g. walking barefoot), biopsies are sometimes performed. It is unusual to see the parasite in biopsy specimens, but occasionally the larva can be identified within the epidermis. More commonly, cavities left by the parasite are located within the upper epidermis and are associated with spongiosis. In the dermis, there is a mixed inflammatory infiltrate composed of lymphocytes, histiocytes, and numerous eosinophils. Occasionally, collections of eosinophils may be present in the epidermis and within hair follicles[83].

Differential Diagnosis

The cutaneous eruption is characteristic, and the diagnosis is usually straightforward. The human species of intestinal hookworms (*A. duodenale* and *Necator americanus*) penetrate the skin prior to possible migration into venules (see Fig. 83.22), causing a nonspecific pruritic localized rash lasting 1–2 weeks that is referred to as "ground itch"[83,87]. Unlike cutaneous larva migrans, *A. duodenale* and *N. americanus* infections can progress to systemic hookworm disease, which manifests with anemia, malnutrition, and pulmonary and gastrointestinal symptoms (see Table 83.10). With these human species, autoinfection from larvae in the feces can occur, sometimes years after the initial infection.

The differential diagnosis may also include allergic contact dermatitis, impetigo, inflammatory tinea, scabies, myiasis, and other nematode infections such as the superficial form of gnathostomiasis and strongyloidiasis. Larva currens is a localized or occasionally more widespread urticarial eruption that is caused by autoinfection with *Strongyloides stercoralis* in immunocompetent individuals (see Table 83.10); it typically begins in the perianal area and then rapidly extends, as quickly as 5–10 cm per day, onto the buttocks, thighs, and abdomen[88]. The lesions are relatively short-lived, lasting hours to days, but often recur[89].

Treatment

Although cutaneous larva migrans is self-limited, the intense pruritus and prolonged course often necessitate treatment. A single ivermectin dose of 12 mg in adults or 150–200 mcg/kg in children has 80%–100% efficacy. Administration of a single 400 mg oral dose of albendazole to adults and children >2 years of age produces cure rates of 45%–100%, but a dose of 400–800 mg/day in adults or 10–15 mg/kg/day (maximum of 800 mg/day) in children for 3–5 days results in more consistent cure rates of 80%–100%[86]. In the largest series to date, application of ivermectin 1% cream daily for two weeks led to improvement in only 1 of 12 patients with larva migrans involving primarily the feet/ankles[90]; however, a few case reports have described benefit when lesions involved the genitals or thighs, where cutaneous penetration may be higher. Topical 10%–15% thiabendazole solution or ointment (not available in the US) may have benefit for localized disease, but it requires application three times daily for at least 15 days. Oral thiabendazole is also effective but is less well tolerated than either ivermectin or albendazole[86].

GNATHOSTOMIASIS

Synonyms: ■ Nodular migratory eosinophilic panniculitis ■ Shanghai rheumatism ■ Tuao chid ■ Yangtze edema

Key features

- Typically acquired via consumption of raw freshwater fish
- Clinical presentations include nodular migratory panniculitis, a superficial type that mimics cutaneous larva migrans, and furuncular lesions; peripheral eosinophilia is often present

Introduction

Gnathostomiasis is caused by the larvae of nematodes of the genus *Gnathostoma* and the usual definitive hosts are cats, dogs, and pigs. However, humans can become infected by eating raw freshwater fish, which represent an intermediate host during the parasite's life cycle (see Fig. 83.25). The most common clinical presentation is a migratory panniculitis, associated with tissue and peripheral eosinophilia.

Epidemiology

Gnathostomiasis is endemic in Southeast Asia and Japan; it also occurs elsewhere in Asia as well as in Mexico, Central and South America, and South Africa[91]. At least two cases of autochthonous gnathostomiasis have been reported in the US[92]. Local and imported dishes containing raw freshwater fish, eels (e.g. Asian swamp), frogs, birds, and reptiles are the source of infection, and travelers may develop the disease after returning home[93].

Pathogenesis

G. spinigerum is the most common cause of human gnathostomiasis. Other pathogenic species include *G. hispidum*, *G. doloresi*, *G. nipponicum*, *G. malaysiae*, and *G. binucleatum*[94].

The adult worms are enteric parasites of cats, dogs, pigs, wild felines, weasels, and rats (see Fig. 83.25). *Gnathostoma* eggs are passed in the feces of these infected hosts and hatch when they reach the water, e.g. in a nearby river. The first-stage larva is ingested by a copepod (*Cyclops*) and develops into a second-stage larva. The copepod is then ingested by a fish or other aquatic intermediate host, and the larva reaches a third stage in its flesh, which is eaten either by a definitive host or human. The larva penetrates the human gastrointestinal mucosa and starts to migrate, first to the peritoneal cavity and subsequently to the subcutaneous tissues and internal organs.

Clinical Features

Abdominal pain, other gastrointestinal symptoms, and fever may occur during early infection. Cutaneous manifestations typically develop 2–4 weeks after ingestion of the larva. The classic presentation is migratory panniculitis characterized by a single, deep-seated, pruritic or tender inflammatory nodule that disappears spontaneously after a few days to weeks and then reappears a few centimeters away or in a different body region. Sites of involvement may develop a *peau d'orange* appearance. Occasionally, the parasite's migratory pattern becomes more superficial

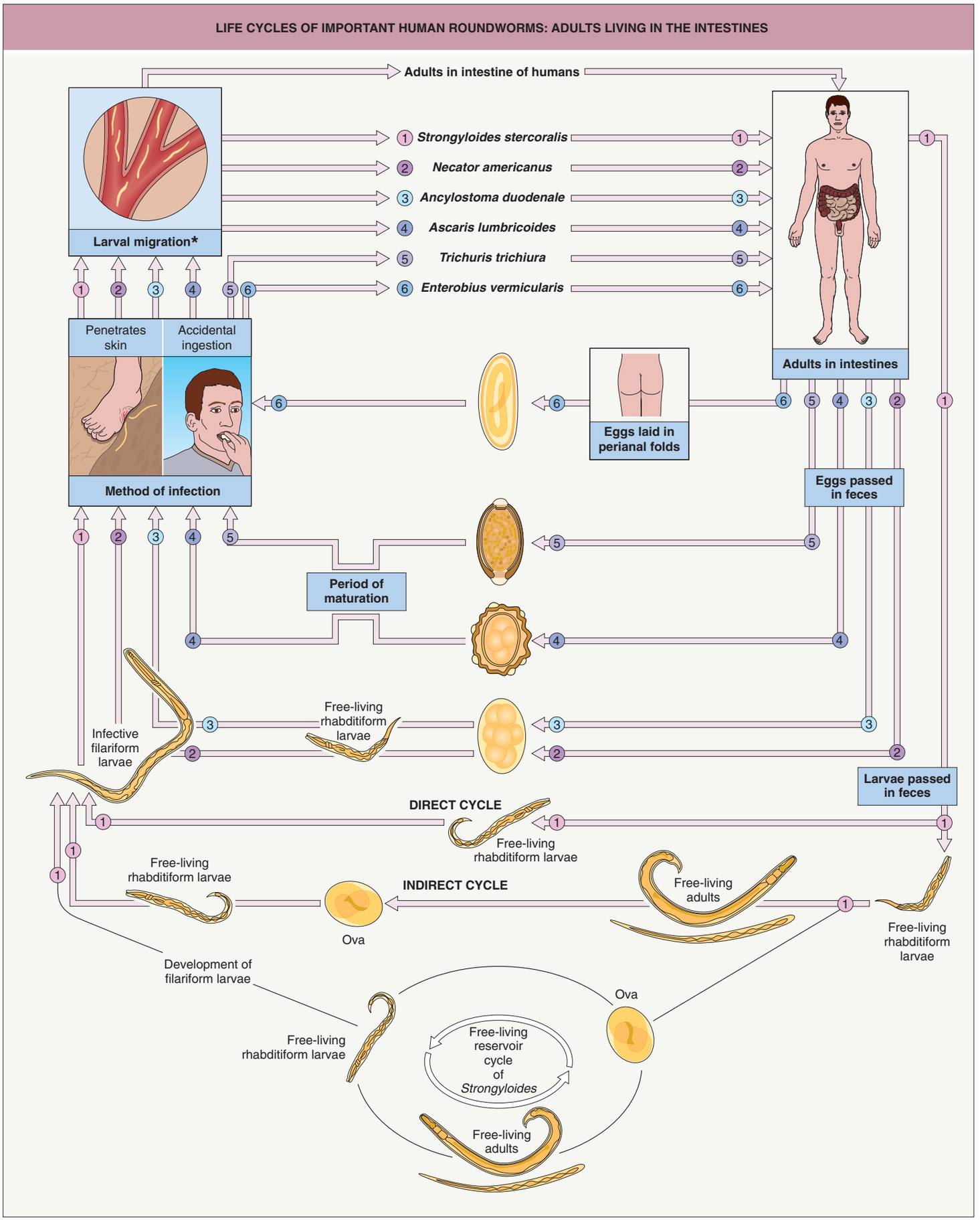


Fig. 83.22 Life cycles of important human roundworms: adults living in the intestines. *Larvae can migrate from venules into the right heart and lungs, then via alveoli into the trachea; eventually they are swallowed. *With permission from Cross JH. Helminths. In Cohen J, Powderly W (eds). Infectious Diseases, 2nd edition. London: Mosby, 2004.*

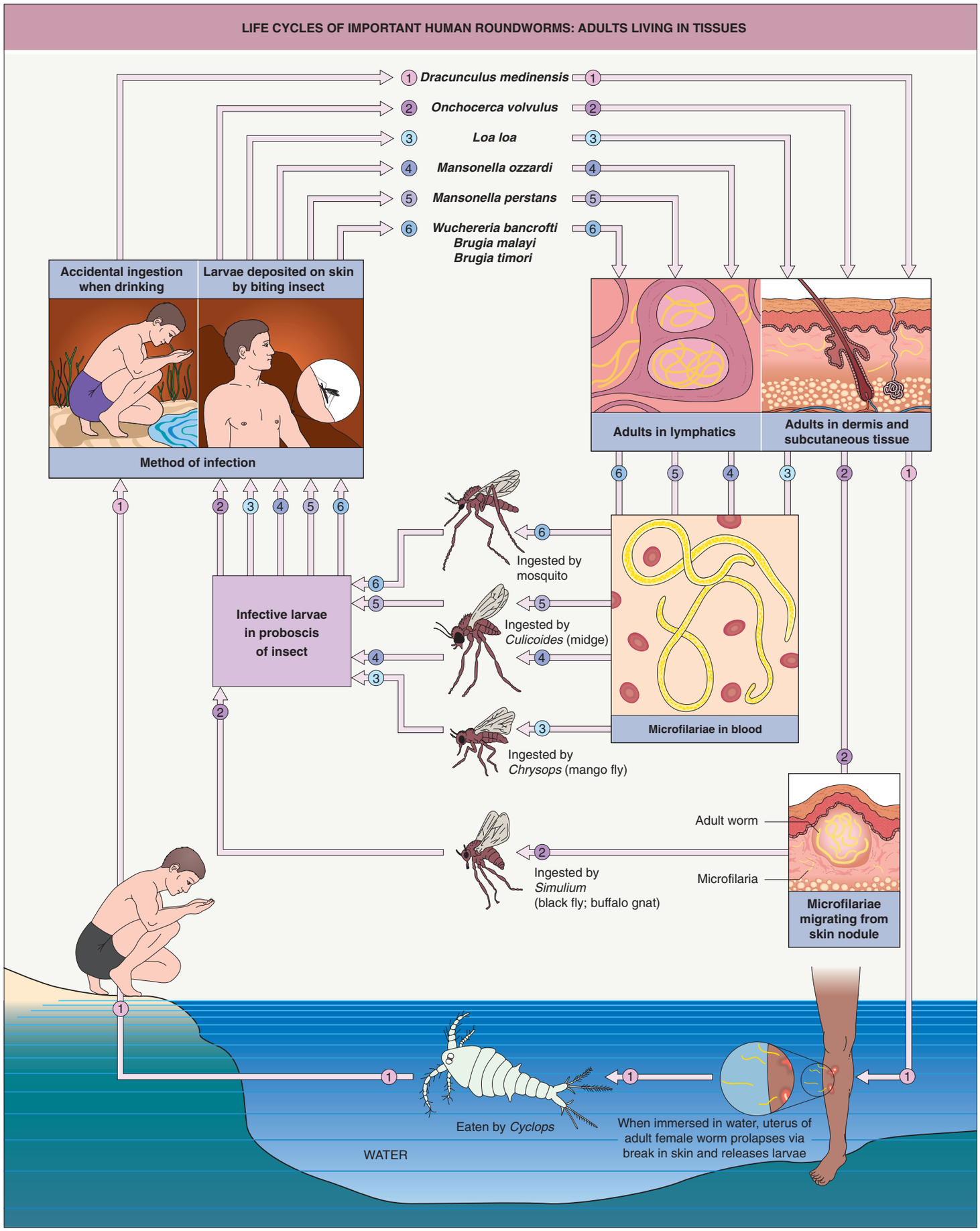


Fig. 83.23 Life cycles of important human roundworms: adults living in tissues. *With permission from Cross JH. Helminths. In Cohen J, Powderly W (eds). Infectious Diseases, 2nd edition. London: Mosby, 2004.*

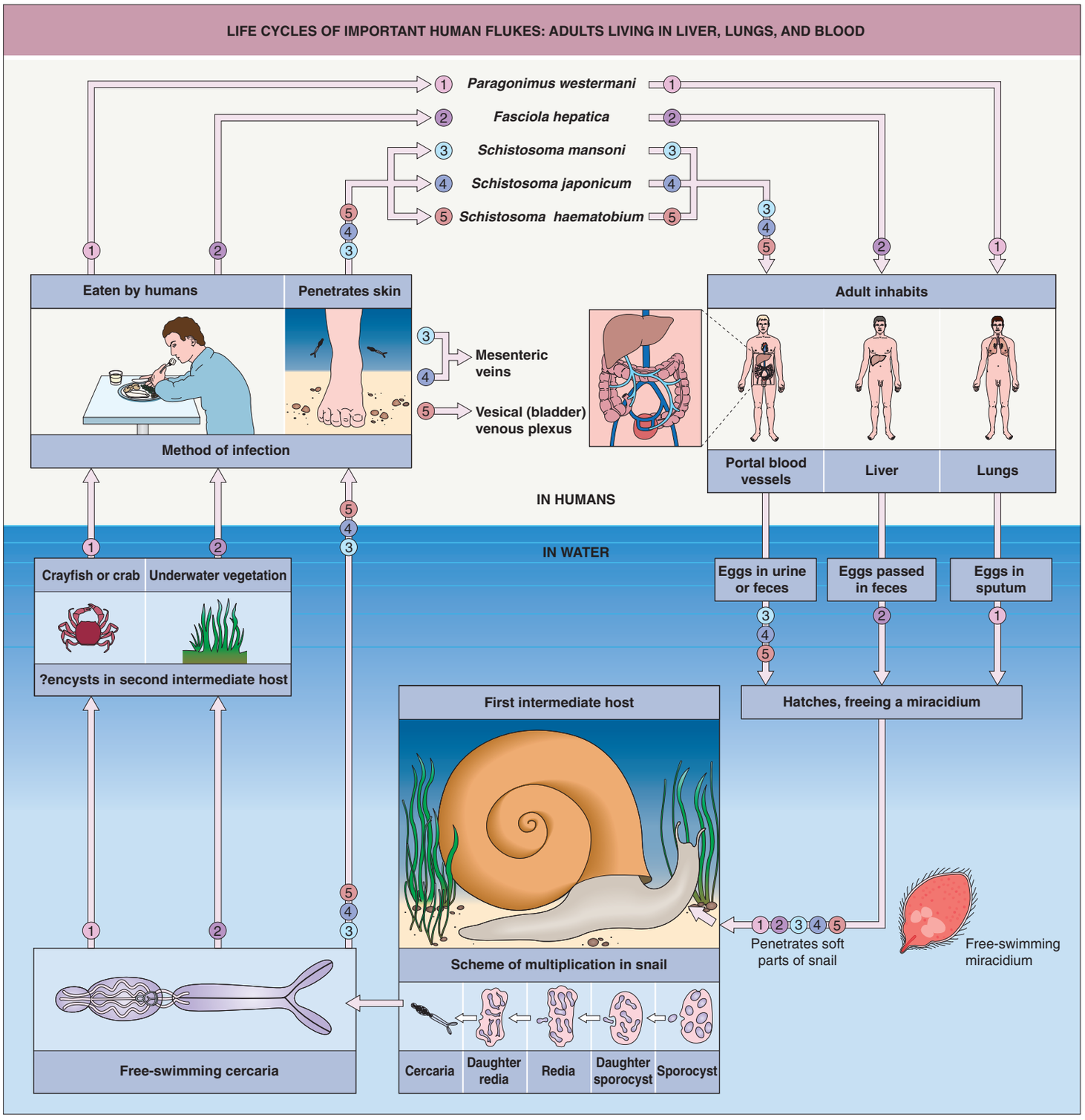


Fig. 83.24 Life cycles of important human flukes: adults living in the liver, lungs, and blood. *Adapted with permission from Cross JH. Helminths. In Cohen J, Powderly W (eds). Infectious Diseases, 2nd edition. London: Mosby, 2004.*

and mimics that of cutaneous larva migrans. Both patterns may be seen simultaneously in the mixed form (Fig. 83.28A). Following treatment, the parasite tends to be located near the skin surface, inducing the formation of a vesicle or pustule overlying a papulonodule; this has been called furuncular gnathostomiasis. Rarely, the parasite reaches the surface and becomes visible[95].

Migration of the larva into deeper tissues can result in pulmonary, gastrointestinal, renal, or ocular involvement. Invasion of the CNS is associated with a mortality rate of up to 25% and may lead to radiculomyelitis, eosinophilic meningitis, and subarachnoid hemorrhage. Neurologic symptoms often wax and wane, reflecting the migratory pattern of infection, and an altered state of consciousness or coma can occur with cerebral involvement.

Pathology

Nodular lesions demonstrate an eosinophilic lobular panniculitis with linear hemorrhage. In superficial lesions, an eosinophilic infiltrate is present in the mid and deep dermis. The parasite itself may be seen, especially in the furuncular type. The worm has a cylindrical shape, measuring 0.2–0.4 mm in diameter, with an external cuticle and central intestine (Fig. 83.28B).

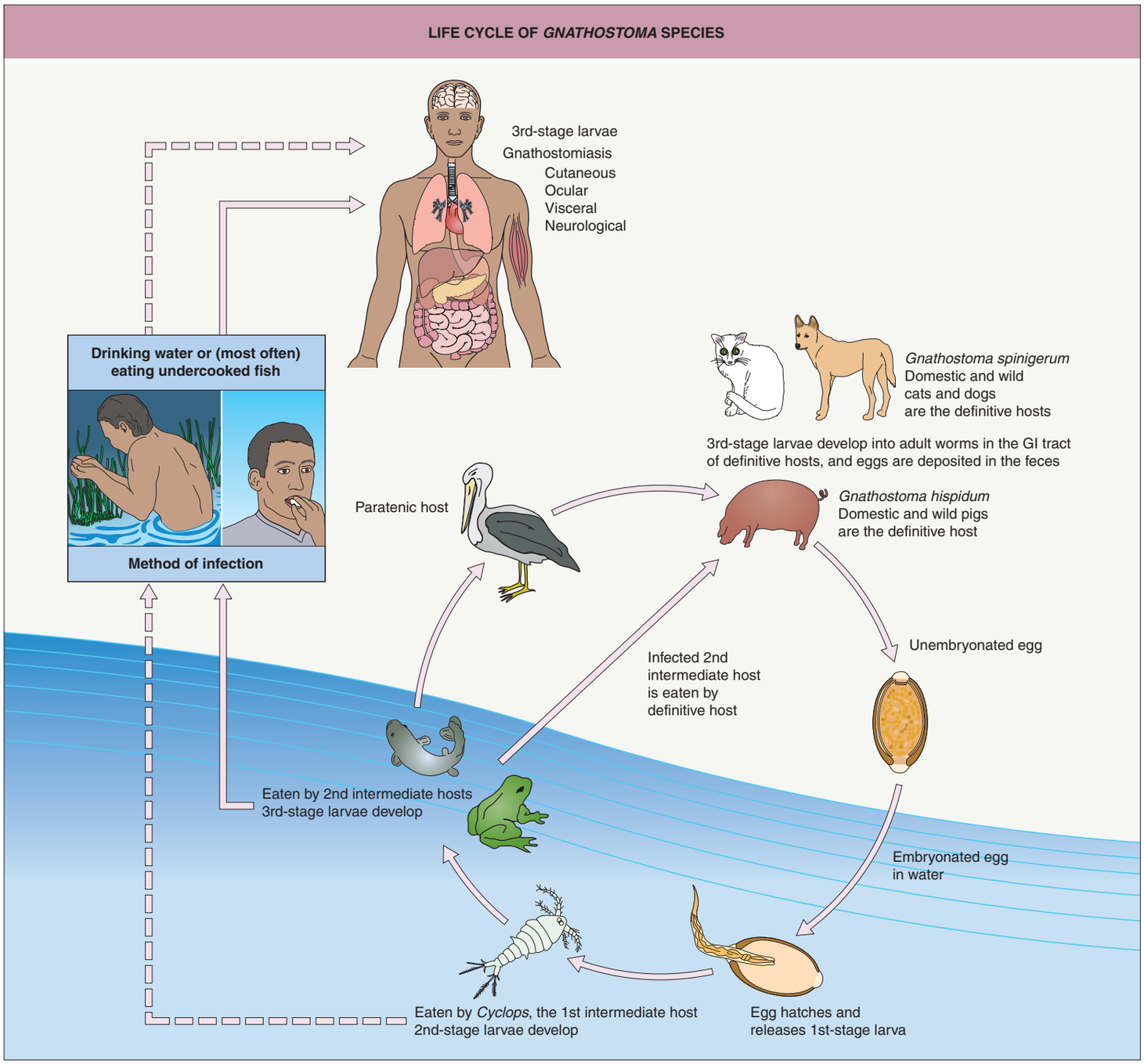


Fig. 83.25 Life cycle of *Gnathostoma* species. Transmission to humans via copepods in drinking water has been postulated but not confirmed. *Modified from www.cdc.gov/parasites/gnathostoma/biology.html.*

Diagnosis and Differential Diagnosis

Gnathostomiasis should be suspected in patients with a migratory panniculitis or dermatitis plus recent consumption of raw fish or another potentially contaminated raw food. The diagnosis is supported by the presence of peripheral eosinophilia (≤50% of cases) as well as tissue eosinophilia. Worldwide serologic testing via immunoblot based on a specific L3 antigen is available in specialized research centers. Development of a rapid filtration-based immunoassay is currently under investigation.

The differential diagnosis includes other nematode infections with migratory skin lesions, including cutaneous larva migrans, strongyloidiasis, and toxocariasis. Similar inflammatory nodules may also be seen in sparganosis, fascioliasis, and myiasis.

Treatment

Recommended therapy is either albendazole 400–800 mg/day for 21 days or ivermectin 200 mcg/kg/day for 1–2 days. Relapses often occur[96].

ONCHOCERCIASIS

Synonyms: ■ River blindness ■ Enfermedad de Robles ■ Erysipelas (erisipela) de la costa ■ Craw-craw

Key features

- *Onchocerca volvulus* is a tissue-dwelling nematode that is mainly found in Africa and transmitted by black flies
- Most clinical manifestations are caused by microfilariae in the skin and eyes
- Cutaneous manifestations include subcutaneous nodules that contain adult worms, a pruritic papular dermatitis, lichenification, and leukoderma
- The diagnosis can be established by identification of microfilariae via microscopic examination of a skin sample (skin snip) or slit-lamp examination of the eyes

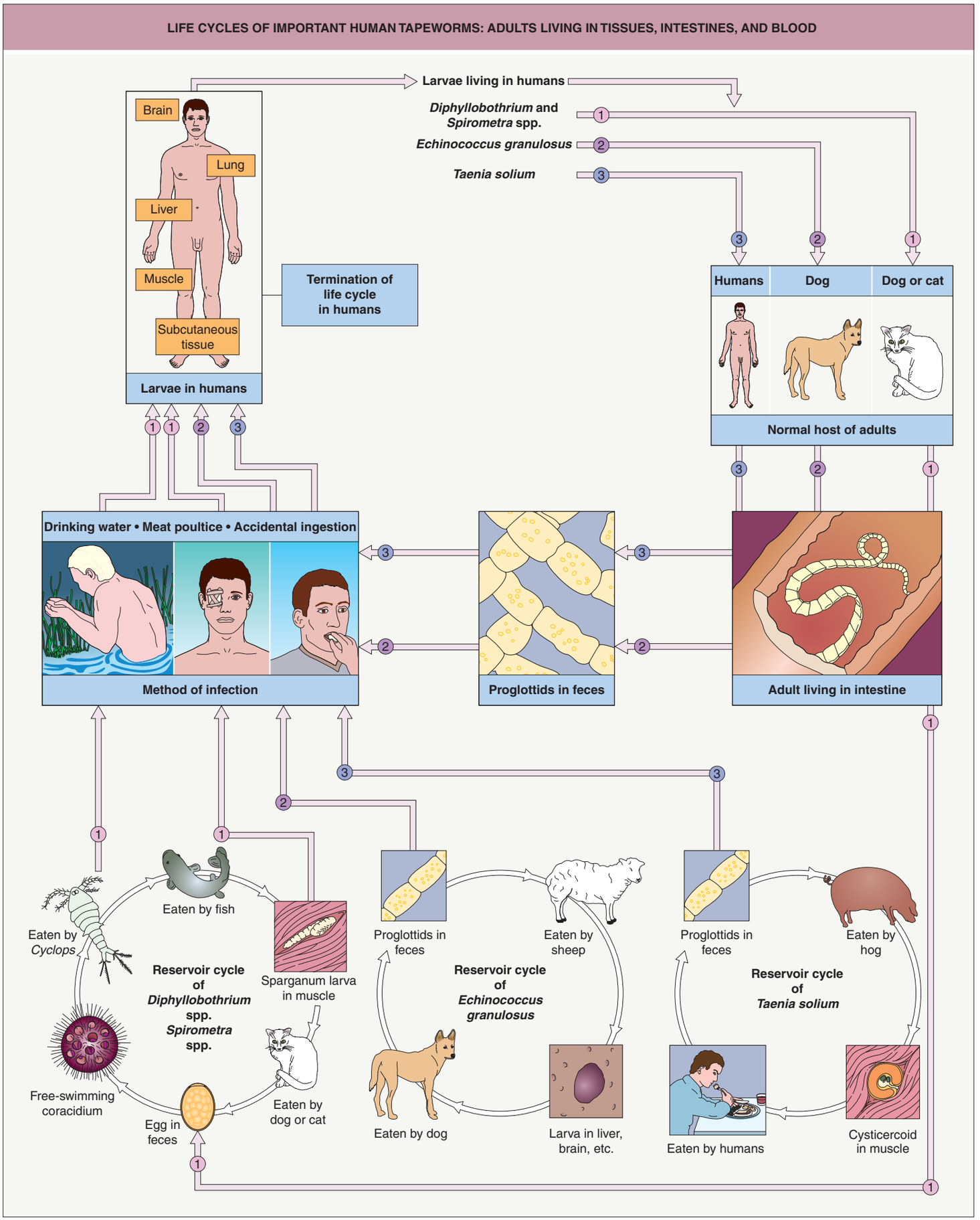


Fig. 83.26 Life cycles of important human tapeworms: adults living in tissues, intestines, and blood. *Adapted with permission from Cross JH. Helminths. In Cohen J, Powderly W (eds). Infectious Diseases, 2nd edition. London: Mosby, 2004.*



Fig. 83.27 Cutaneous larva migrans. Note the characteristic serpiginous erythematous tracts on the lateral foot (**A**), both feet (**B**), the shoulder (**C**), and the ankle (**D**). Vesiculation and crusting (**A,B**) or even bullae (**D**) are sometimes seen. *B, Courtesy Peter Klein, MD; C, D Courtesy Julie V. Schaffer, MD.*

Introduction

Onchocerciasis, or river blindness, predominantly affects cutaneous and ocular tissue and is caused by *Onchocerca volvulus*, a filarial nematode[97]. Onchocerciasis most commonly occurs in inhabitants of tropical Africa and occasionally develops in residents of tropical areas in South America and the Middle East. In the early stage of the disease, cutaneous manifestations include subcutaneous nodules and pruritic papular dermatitis, while skin thickening and leukoderma are later findings. Progressive sclerosing keratitis can lead to blindness.

Epidemiology

Onchocerciasis is a debilitating disease that worldwide affects ~16 million people, in particular those living for prolonged periods of time near fast-flowing rivers in endemic areas[98]. The larvae of *O. volvulus* have an obligatory aquatic stage during which they require high oxygen tension, thus explaining the significant role well-oxygenated water plays in this disease[97,99]. Severe disease requires repeated exposures over many years. Approximately 99% of all cases are acquired in equatorial Africa, but some endemic foci remain in the Middle East, Venezuela, and Brazil (Fig. 83.29). As of 2016, onchocerciasis was considered eradicated in Colombia, Ecuador, Mexico, and Guatemala[100]; in addition, Niger is currently undergoing verification to become the first African nation to eliminate onchocerciasis.

Pathogenesis

Onchocerciasis is transmitted by the bite of an infected black fly (*Simulium* spp.). Because these flies often assume a "hump-backed" stance, they are sometimes referred to as "buffalo gnats". Black flies feed by "rasping" (abrading) the surface of the skin until a pool of blood forms, which they lap up. Microfilariae previously residing in the dermis are present in this blood, and they penetrate the gut wall of the insect and migrate to its thoracic muscles, where they develop into larvae. The larvae then migrate to the proboscis, from which they will be transmitted to another human host during a blood meal (see Fig. 83.23)[99]. *Wolbachia* bacterial endosymbionts are required for normal development of *O. volvulus* larvae and embryos, are thought to support the survival of adult worms, and drive immune responses that contribute to disease pathogenesis[101].

Once in their human host, larvae take almost a year to reach maturity. The adult worms are large, measuring up to 50 cm in length. They are encapsulated within fibrous tissue and reside in nodules close to the surface of the skin or near joints. These nodules are known as onchocercomas (Fig. 83.30). Each female worm produces hundreds of microfilariae, which live for 1–2 years and migrate into the skin, connective tissue, eyes, and lymph nodes. It is the microfilariae that cause most of the serious clinical features of onchocerciasis[102]. There is little inflammation until the microfilariae degenerate, which triggers a hypersensitivity reaction. In the skin, this results in intense pruritus and dermatitis.

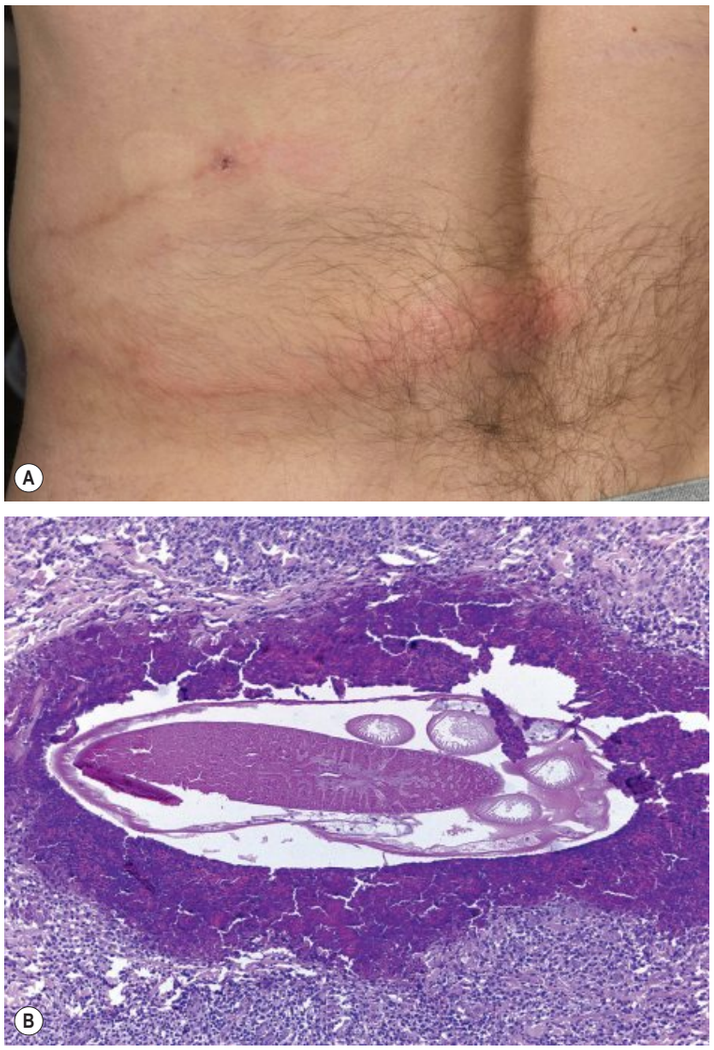


Fig. 83.28 Gnathostomiasis. A In addition to a serpiginous pattern on the lower back that is similar to larva migrans, there is an indurated pink plaque with a peau d'orange appearance. **B** A skin biopsy specimen occasionally reveals the *Gnathostoma* third-stage larva. *A, Courtesy Edward Cowen, MD.*

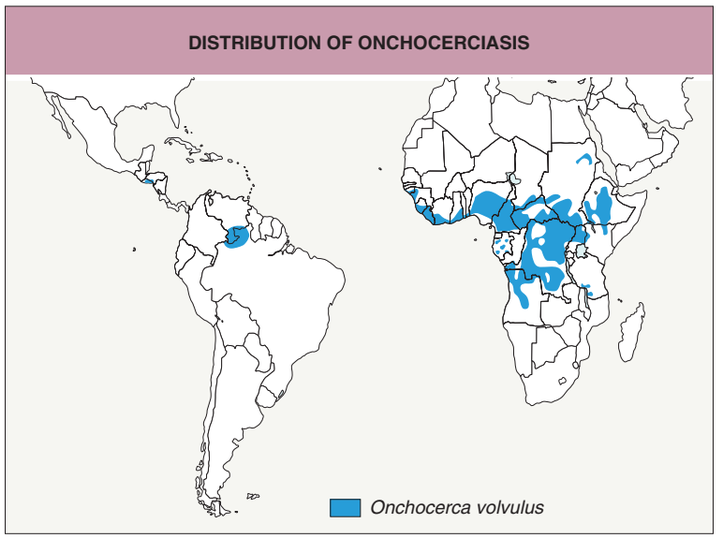


Fig. 83.29 Distribution of onchocerciasis. The disease is found primarily in Africa and focal areas of the Amazon region in South America.

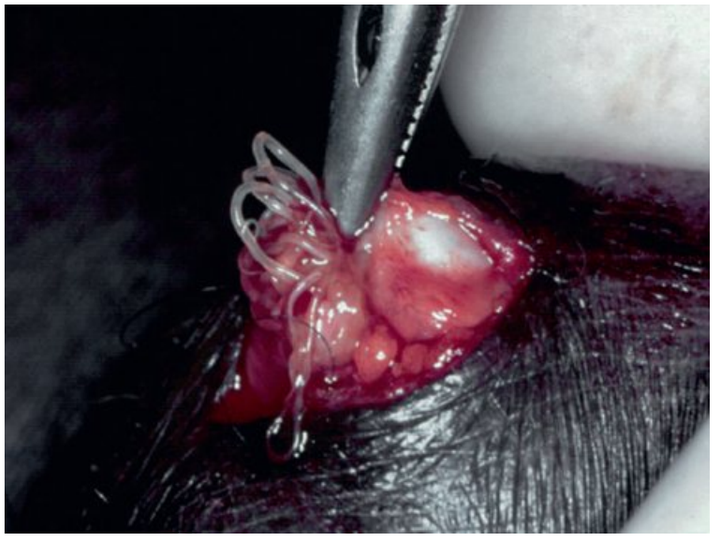


Fig. 83.30 Onchocerciasis. Extraction of adult worms from an onchocercal nodule on the buttocks.

Clinical Features

The primary manifestations of onchocerciasis involve the eye and the skin. Cutaneous findings are classified into the following groups: acute papular onchodermatitis, chronic papular onchodermatitis, lichenified onchodermatitis, onchocercal atrophy, and depigmentation (Fig. 83.31)[103]. Patients first present with subcutaneous nodules that are usually located over bony prominences; they favor the upper part of the body in patients living in South America and the lower part of the body in those from Africa. The subcutaneous nodules represent fibrous tissue surrounding adult worms. An intermittent, intensely pruritic acute papular onchodermatitis follows, in which small papules form around the microfilariae (called "craw-craw" in Africa).

In chronic onchocerciasis, the skin becomes thickened and wrinkled; this is accompanied by lichenification and hyperpigmentation and is sometimes referred to as "lizard" or "elephant" skin or "sowda". The back, thighs, and lower trunk are frequently affected, and hyperpigmentation may develop on one lower extremity in association with inguinal lymphadenopathy (see Fig. 83.31). Atrophy and a loss of pigment with sparing of perifollicular skin are also seen in late stage onchocerciasis. The latter changes, sometimes referred to as "leopard" skin, are most often evident on the shins (see Fig. 83.31 and Ch. 66)[104]. Chronic lymphatic obstruction and involvement of the inguinal lymph nodes can lead to hanging groin or elephantiasis of the genitalia (see Fig. 83.31).

In Central America, young patients who are heavily infested may develop erythema on the face or upper trunk (erisipela de la costa). Older patients may have violaceous papules or plaques (mal morado), which can lead to leonine facies.

In addition to skin lesions, microfilariae can also be found in the conjunctivae; from there they can move through the cornea into the anterior and posterior chambers of the eye, leading to conjunctivitis, sclerosing keratitis, uveitis, chorioretinal lesions, optic atrophy, and glaucoma[97]. Blindness occurs in the most severe cases. Dead microfilariae in the cornea can induce a tissue reaction that produces characteristic "snowflake" opacities.

Pathology

In onchodermatitis, microfilariae are present in all levels of the skin but are most concentrated in the dermal papillae, where they can infect black flies during feeding. Microfilariae are ~250 microns long with two or three pairs of anterior nuclei. Initially, they are surrounded by an infiltrate with numerous eosinophils. Lymphocytes, macrophages, plasma cells, and mast cells may become more prominent at later stages, and epidermal hyperplasia (secondary to rubbing) may develop. The final outcome is fibrosis surrounding the microfilariae with minimal inflammation[105].

The adult female worms are found in a subcutaneous nodule. They are initially surrounded by an infiltrate containing many eosinophils, with progressive development of fibrosis.

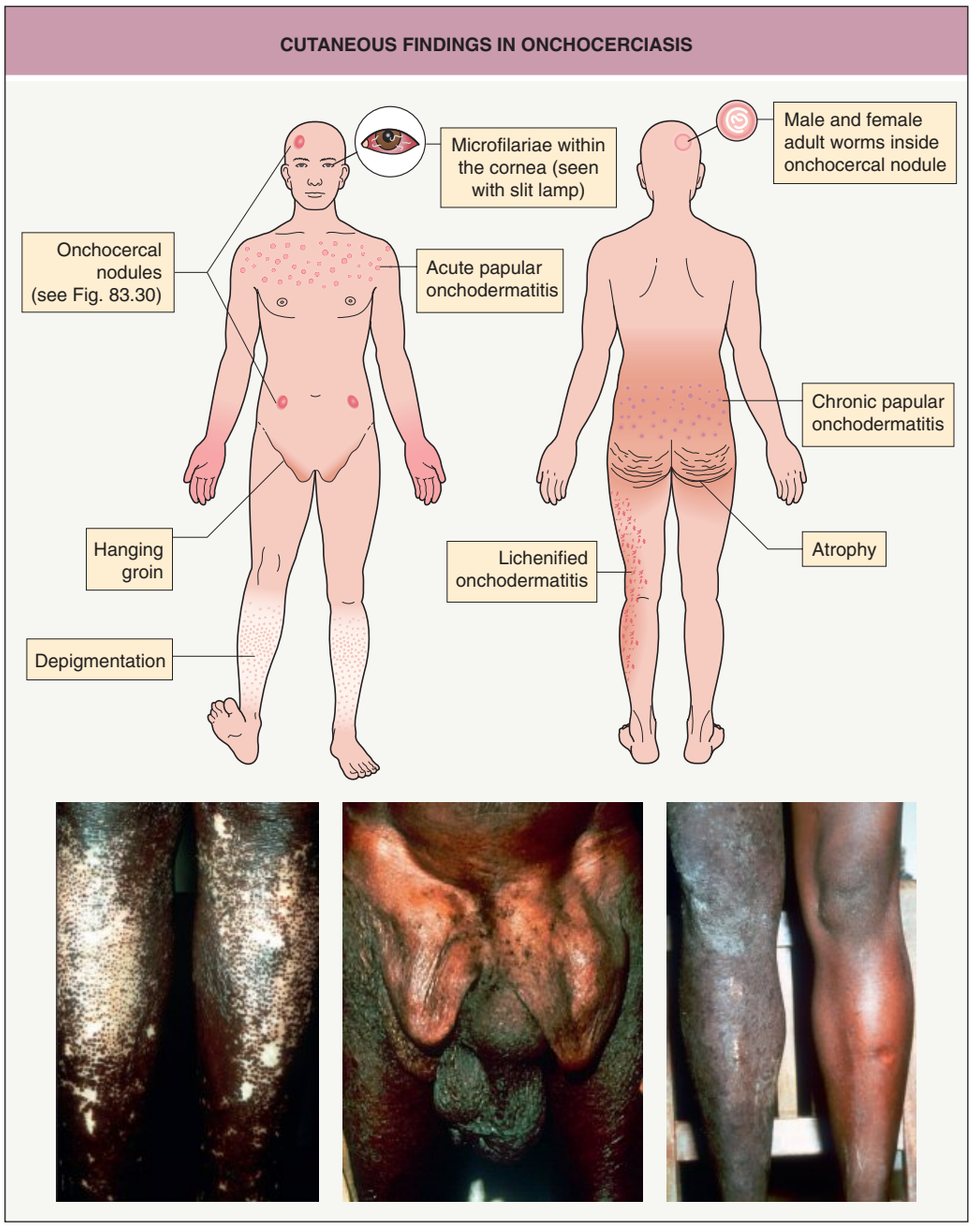


Fig. 83.31 Cutaneous findings in onchocerciasis. Photos: left, depigmentation with perifollicular sparing ("leopard" skin); middle, hanging groin due to chronic lymphatic obstruction and lymph node involvement; right, lichenified onchodermatitis ("sowda"). *Insets, courtesy David O. Freeman, MD.*

Diagnosis

The clinical diagnosis of onchocerciasis is usually not difficult in endemic areas. It is confirmed by microscopic visualization of microfilariae as they emerge from multiple skin snips placed in saline; these small, thin discs (including superficial dermis) are taken from skin near a nodule and over the shins, iliac crests, and/or scapulae[106]. Onchocerciasis can also be diagnosed by the identification of the adult worm in an excised nodule. In heavily infected individuals, microfilariae can be found in the blood, sputum, and urine. By slit-lamp examination, microfilariae (when present) are easily visualized within the anterior chamber of the eye.

When skin snips are negative, the "Mazzotti test" may be helpful in diagnosing onchocerciasis: 50 mg of diethylcarbamazine (DEC) is administered orally, and a pruritic eruption develops within 15 minutes (as the microfilariae die) if the patient is infected. In the "Mazzotti patch test", DEC is applied topically (e.g. in a 10% lotion under occlusion) to a small area of skin, which is examined 24 hours later for the development of papules and edema; this diagnostic method is not as sensitive as oral administration of DEC but less likely to produce a systemic reaction. A dipstick test to detect *Onchocerca volvulus* antigen in the urine or tears has a sensitivity of >90% and a specificity of 100%[107]. Highly sensitive and specific PCR-based tests have also been developed. Tests based on antibody detection cannot distinguish between active and past infections.

Differential Diagnosis

Early lesions of onchocercal dermatitis must be distinguished from insect bites, scabies, and atopic or allergic contact dermatitis. The chronic skin lesions may be mistaken for chronic eczema with postinflammatory pigmentary changes, Hansen disease (leprosy), or the leukoderma of scleroderma. The differential diagnosis of elephantiasis includes other types of filarial infestation (see Fig. 83.23), and a false-positive skin snip can occur if the tissue is contaminated with blood filariae, especially *Mansonella perstans* or *Loa loa*.

Treatment

Therapy for onchocerciasis has drastically improved as a result of the widespread use of oral ivermectin since 1987[108]. This drug is effective in rapidly killing microfilariae and preventing their escape from gravid females. Ivermectin causes few or no adverse reactions and no Mazzotti reaction, whereas older drugs, e.g. diethylcarbamazine and suramin, are associated with severe hypersensitivity or dangerous toxic reactions. Ivermectin is administered as a single dose of 150 mcg/kg every 3 to 12 months. After treatment, microfilariae usually disappear from the skin within 1 week and from the eye within 3 months. Although multiple doses of oral ivermectin can kill adult worms, treatment is typically continued for the worm's lifetime (10–15 years).

Moxidectin is a macrocyclic lactone in the milbemycin family that was recently FDA-approved for the treatment of onchocerciasis. Compared to ivermectin (a macrocyclic lactone in the avermectin family), moxidectin has a longer half-life and greater potency against microfilariae of *O. volvulus* as well as other nematodes such as *Dirofilaria immitis*[109,110]. In addition, moxidectin has potential as an alternative treatment for scabies[109,110]. Administration of doxycycline (100–200 mg/day for 6 weeks) to target *Wolbachia* endosymbionts represents another potential therapeutic approach that can markedly reduce or eliminate *O. volvulus* microfilariae for >18 months[111,112]. Nodulectomy is also a popular treatment in countries where nodules on the head are common (see Fig. 83.31); their removal reduces the chance of ocular disease.

Preventive measures such as spraying black fly breeding sites with larvicides have not significantly changed the epidemiology of the disease. In contrast, mass treatment of endemic populations with ivermectin once or twice yearly has resulted in significant progress toward elimination of the disease in both the Americas and Africa[113]. In addition to onchocerciasis and scabies, mass drug administration of ivermectin or moxidectin targets strongyloidiasis, pediculosis, and cutaneous larva migrans.

FILARIASIS

Synonyms: ■ Lymphatic filariasis, elephantiasis ■ Elephantiasis

Key features

- Filariasis is an infection of the lymphatic system by tissue nematodes (roundworms) acquired via mosquito vectors
- There are acute, chronic, and asymptomatic forms of filariasis
- Manifestations of the acute phase include lymphangitis and orchitis
- Chronic disease is characterized by the sequelae of lymphatic obstruction, e.g. lymphedema, elephantiasis, hydroceles, and chyluria; associated skin findings include hyperkeratosis, verrucous changes, soft tissue hypertrophy, and fibrosis

Introduction

Lymphatic filariasis is an infection of the lymphatic system by two genera of filarial nematodes (roundworms). Several species of mosquitoes act as vectors (see below). Cutaneous findings during the acute and chronic stages include lymphangitis and lymphedema accompanied by changes of elephantiasis.

Epidemiology

There are two major forms of filariasis, Bancroftian (due to *Wuchereria bancrofti*), causing 90% of infections, and Malayan (due to *Brugia malayi* and *B. timori*). The disease affects ~120 million people living in ~50 countries located primarily within the tropical and subtropical regions of South America, Africa, Asia, and the Pacific Islands. *W. bancrofti* is found worldwide, whereas *B. malayi* is restricted to South and East Asia. The distribution of *B. timori* is limited to islands in the Indonesian archipelago[114].

A number of mosquito species act as vectors for filarial nematodes. The most important ones for *W. bancrofti* are *Culex quinquefasciatus*, *Anopheles gambiae*, *Anopheles funestus*, *Aedes polynesiensis*, *Aedes scapularis*, and *Aedes pseudoscutellaris*. Both *B. malayi* and *B. timori* are transmitted by *Anopheles barbirostris*. *B. malayi* can also be transmitted by several species of *Aedes* and *Mansonia* mosquitoes[114,115].

Pathogenesis

Multiple bites from infected mosquitoes seem to be required to produce symptomatic infections, and the incubation period varies from 2 to 18 months. Larvae enter lymphatic vessels and then, once mature, the adult worms mate within the lymphatics or lymph nodes and release sheathed microfilariae into the bloodstream[114]. The mosquito then acquires microfilariae during a blood meal. Over several days, the microfilariae develop into larvae within the mosquito, which can then transmit infection to other humans during subsequent blood meals (see Fig. 83.23).

The clinical manifestations of lymphatic filariasis reflect a complex interplay of the pathogenic potential of the parasite, the immune response of the host, and secondary bacterial and fungal infections. Maturing adult worms provoke an eosinophilic and chronic inflammatory cell infiltrate around lymphatic vessels, leading to dilation and valvular damage with eventual scarring and obstruction of lymphatic flow. The death of worms within lymphatic vessels and lymph nodes results in an intense inflammatory reaction with granulomatous changes and necrosis[114]. *Wolbachia* bacterial endosymbionts are required for the worms' development, embryogenesis, and survival; *Wolbachia* also stimulates an innate and adaptive immune response that leads to expression of vascular endothelial growth factors (VEGFs) that promote lymphangiogenesis, lymphatic endothelial proliferation, and dilation of lymphatic vessels[111].

Clinical Features

There are acute, chronic, and asymptomatic forms of filariasis. Acute episodes of *retrograde adenolymphangitis* typically last up to one week and usually recur 1 to 10 times per year; the inguinal lymph nodes are most often involved. Early on, the affected body part appears clinically normal in between these episodes. Men with *W. bancrofti* infection often present with orchitis and epididymitis. Another disease manifestation is *acute dermatolymphangioadenitis* characterized by cutaneous or subcutaneous inflammatory plaques associated with ascending lymphangitis, regional lymphadenitis, and fever; this may result from a bacterial or fungal superinfection, often with an interdigital entry point[116]. Acute symptoms, which are thought to reflect a lack of tolerance to filarial antigens, are most common in recently infected young adults and older patients. Children residing in endemic areas are often asymptomatic until they reach puberty, when they typically develop chronic manifestations[117].

After 10 to 15 years of infection, the clinical features of chronic disease, i.e. the sequelae of lymphatic obstruction due to both adult worms and granulomatous inflammation, are noted[116]. These include lymphedema, elephantiasis, hydroceles, and chyluria. In some communities in endemic regions, 40%–60% of adult men have hydroceles. In sites of lymphedema and elephantiasis, the skin can be hyperkeratotic, verrucous, and fibrotic with soft tissue hypertrophy and redundant folds. Fissures, ulceration, and gangrene may also develop. Secondary bacterial and fungal infections are common.

There are two major reasons for the predilection of filariasis for the lower extremities and genitalia: (1) the female mosquito flies near the ground, thus it is more likely to bite the lower limbs, which is followed by retrograde involvement of the inguinal region; and (2) due to gravitational forces, the legs are at greater risk for venous hypertension and valvular incompetency and therefore more susceptible to the development of chronic lymphedema[114].

Tropical pulmonary eosinophilia occurs in some patients with filarial infections. Clinical findings include cough, wheezing, dyspnea, chest pain, and fever accompanied by marked eosinophilia and pulmonary infiltrates. This may progress to restrictive pulmonary disease[118].

Travelers to endemic areas who become infected do not manifest the classic findings of filariasis. Instead, they have a hyperresponsive clinical presentation, known as "expatriate syndrome", with more intense inflammatory reactions to the filarial parasites. Clinical findings include lymphangitis, lymphadenitis, and genital pain from the associated lymphatic inflammation, as well as urticaria, nonspecific cutaneous eruptions, and peripheral eosinophilia[97].

Diagnosis

Detection of circulating filarial antigen is now the preferred method for diagnosis of Bancroftian filariasis; immunochromatographic card tests or test strips are typically utilized[111]. Similar tests are not currently available for Malayan filariasis, which can be diagnosed using a dipstick test for IgG4 antibody specific for the *Brugia* antigen BmR1. Alternatively, the diagnosis can be established by the demonstration of microfilariae in the blood, urine, or other body fluids and tissues, or by the identification of adult worms (Fig. 83.32)[119,120]. Visualization

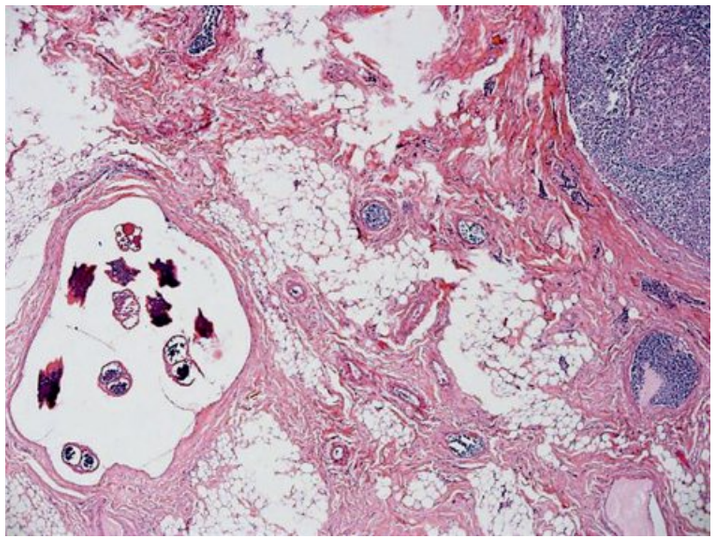


Fig. 83.32 Histopathology of filariasis. Dilated lymphatic with a mature adult worm and surrounding enlarged inguinal lymph nodes.

of motile adult worms may be possible using ultrasound to evaluate the infected lymphatics. As the parasite exhibits a nocturnal periodicity in humans, 10 p.m. to 2 a.m. is the optimal time period for collection and direct smear of blood or other fluids. The use of filters with a pore size of 3 microns has improved the rate of detection of microfilariae in the blood and urine. However, parasite detection is not a particularly reliable method because many symptomatic patients are amicrofilaremic. Species-specific PCR-based assays have been developed and are utilized in research studies on filariasis[121].

Peripheral eosinophilia and elevated serum IgE are very common laboratory findings. In addition, more than 50% of microfilaremic patients with *W. bancrofti* infections have hematuria and/or proteinuria[117].

Differential Diagnosis

The differential diagnosis depends upon the stage of the infection. Acute infection may be misdiagnosed as a bacterial lymphangitis. Lymphedema and elephantiasis have multiple possible etiologies, including recurrent bacterial lymphangitis, severe venous hypertension, lymph node dissections, podoconiosis, Milroy disease, and Klippel–Trenaunay syndrome (see Ch. 105)[122].

Treatment

The drug of choice is diethylcarbamazine, which is active against microfilariae but has a limited effect on adult worms. Filariasis is usually treated with a single 6 mg/kg dose of diethylcarbamazine; a 14–21-day course is recommended for patients with tropical pulmonary eosinophilia[111].

Mass drug administration programs with the goal of eradicating filariasis from endemic countries initially provided at-risk individuals yearly single doses of diethylcarbamazine. Current programs utilize annual administration of a triple-drug regimen including albendazole, ivermectin, and diethylcarbamazine, which has resulted in increased microfilarial clearance[123]. In areas co-endemic for loiasis or onchocerciasis, diethylcarbamzine is held (see below), with albendazole administered alone or together with ivermectin, respectively.

Doxycycline (200 mg/day for 4–8 weeks) targeting the *Wolbachia* endosymbiont can also eliminate microfilariae, kill adult worms, and improve lymphatic drainage. During the treatment period, antihistamines and corticosteroids may be useful in decreasing the allergic reaction that may result from massive disintegration of microfilariae. Because severe reactions may follow the administration of diethylcarbamazine in patients who have loiasis or onchocerciasis, it is important to exclude other helminthic diseases before instituting therapy[122]. Other management strategies include elevation of the affected body part, compression stockings, other anti-inflammatory drugs, treatment of secondary infections, and protection of the affected area from trauma[122].

SCHISTOSOMIASIS AND SWIMMER'S ITCH

Synonyms: ■ Schistosomiasis: bilharziasis ■ Swimmer's itch: clam digger's itch

Key features

- Schistosomiasis is a trematode (fluke) infection caused by five species of anthropophilic schistosomes, each with a specific geographic distribution and distinct intermediate host (snails)
- The disease is most commonly seen in Africa, the Far and Middle East, and South America
- Clinical manifestations include cercarial dermatitis, Katayama fever, and chronic fibro-occlusive disease involving the liver, intestine, and urinary tract
- The cercariae of more than 20 species of animal schistosomes may penetrate human skin and cause a transient dermatitis called swimmer's itch

Introduction

Schistosomiasis is a trematode (fluke) infection endemic to the tropics and subtropics caused by members of the superfamily Schistosomatidea[124]. The disease has a worldwide distribution, affecting more than 200 million people in over 75 countries. Human disease can be caused by five schistosome species, most often *Schistosoma haematobium*, which infects the urinary system, and *S. japonicum* and *S. mansoni*, which infect the gastrointestinal tract[124]. In addition, when the cercariae of other species that usually infect birds and mammals penetrate human skin, they can evoke "swimmer's itch", a local inflammatory response associated with marked pruritus.

Epidemiology

Schistosomes have a two-host life cycle (see Fig. 83.24). Snails serve as the intermediate host, while the definitive host is species-dependent. Humans are the major definitive host for five schistosome species[124], each of which has a specific geographic distribution (Fig. 83.33): *S. mansoni* occurs in Africa, South America, and the Caribbean; *S. japonicum* in Japan, China, and the Philippines; *S. haematobium* in Africa and the Middle East; *S. mekongi* in Southeast Asia; and *S. intercalatum* in West and Central Africa.

The geographic distribution of schistosomiasis has changed significantly in recent decades. It has been nearly eradicated from Japan and the Caribbean islands, and the transmission cycle has been interrupted in North Africa, the Philippines, Saudi Arabia, and Venezuela. However, environmental changes related to water resource development and population movement have led to spread of the disease to previously non-endemic areas such as sub-Saharan Africa. Schistosomiasis is now present in and around several major cities in northeastern Brazil and is a major public health problem in certain regions of China.

Swimmer's itch (a form of cercarial dermatitis) is due to over 20 species of schistosomes that usually infect birds and mammals (e.g. *Trichobilharzia*, *Gigantobilharzia*, *Ornithobilharzia* spp.). It is a cutaneous disease with distribution on every continent except Antarctica. In the US, it occurs most often in the north central states. Outbreaks of swimmer's itch are episodic.

Pathogenesis

Adult worms live in the venous system of the liver, rectum, or urinary bladder of their definitive host. The eggs penetrate the rectum or bladder and are passed into the feces or urine (see Fig. 83.24). In freshwater environments, the eggs hatch and release miracidia that penetrate the body of a snail, which acts as an intermediate host. For each schistosome species, a specific snail species acts as an intermediate host. In the snail, the miracidia develop into cercariae, the infective forms that can penetrate human skin on contact[125].

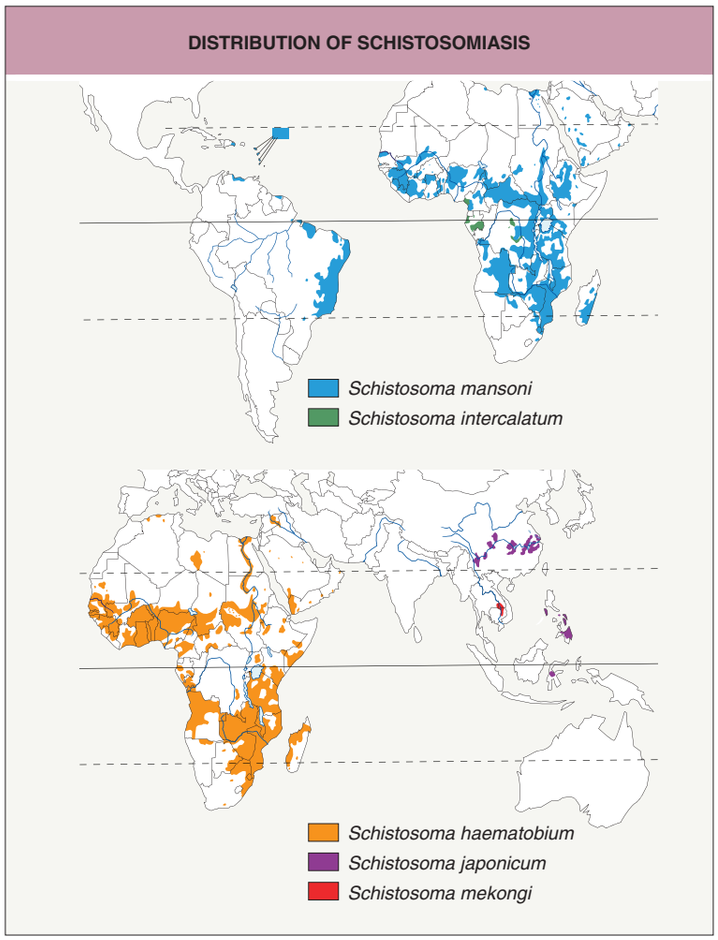


Fig. 83.33 Distribution of schistosomiasis. *Adapted from Gryseels B, Polman K, Clerinx J, Kestens L: Human schistosomiasis. Lancet 2006;368:1106–18.*

The species responsible for swimmer's itch complete their life cycle in birds and animals, including ducks, cows, sheep, and rodents. In contrast to human schistosomes, which cause systemic disease, the cercariae of animal schistosomes die after penetration into human skin, inducing only a local inflammatory reaction. Because humans cannot support the development of these schistosomes, they represent incidental, "dead-end" hosts[124–126].

Clinical Features

The cutaneous manifestations produced by the anthropophilic species of schistosomes can be classified into five categories: cercarial dermatitis, Katayama fever, late nonspecific allergic dermatitis, perigenital papulonodules (bilharziasis cutanea tarda), and extragenital ("ectopic") papules and plaques[127–129]. Lesions in the latter two categories can have an infiltrative granulomatous appearance. *Cercarial dermatitis* is associated with cutaneous penetration by the cercariae. Though fairly common, patients rarely present with this transient, erythematous, pruritic papular or urticarial eruption at the site of inoculation. The reaction is relatively nonspecific and is more severe with *S. japonicum* and *S. mansoni* infections. Within hours of contact, macules develop and then either disappear or, more commonly, are replaced by small pruritic papules that may persist for a few days[125].

In some patients, a systemic allergic reaction (*Katayama fever*) occurs during the acute phase of a moderate or heavy infection. Affected individuals have an acute onset of fever, chills, sweats and headaches, in association with peripheral blood eosinophilia and urticaria. Katayama fever is seen most commonly with *S. japonicum* infections and is due to circulating immune complexes. Approximately 4 to 6 weeks later, some patients experience another *transient cutaneous reaction with nonspecific findings* ranging from urticarial or purpuric lesions to periorbital edema[126,127,129].



Fig. 83.34 Swimmer's itch. Numerous edematous dark red papules on the feet and ankles. *Courtesy Kalman Watsky, MD.*

Bilharziasis cutanea tarda is characterized by papular, granulomatous, or verrucous lesions on genital and perineal skin secondary to the deposition of ova within dermal vessels in this area[126,129]. Occasionally, *"ectopic" cutaneous lesions* have been observed due to inflammatory reactions to deposited ova. They have been described as red–brown to brown papules and plaques and may have a zosteriform distribution on the trunk[127].

Systemically, chronic infections with *S. mansoni* and *S. japonicum* are associated with hepatic fibrosis and cirrhosis as a reaction to the ova; portal hypertension, including ascites and esophageal varices; and splenomegaly. Additional findings include colonic polyps (which contain ova) and granulomas around ova in the liver, lung, and colon (Hoeppli reaction). Urogenital infections with *S. haematobium* can lead to polypoid lesions composed of numerous ova, fibrosis, and calcification. Calcified ova may be seen through the atrophic epithelium, leading to "sandy patches" that are pathognomonic of schistosomiasis on cystoscopy[130]. Additionally, the presence of numerous ova can lead to obstruction of the urinary tract and hydronephrosis. Carcinoma of the bladder is a life-threatening complication.

Lesions of swimmer's itch have an appearance similar to that of cercarial dermatitis, i.e. pruritic papules at sites of inoculation (Fig. 83.34). As a result, areas of skin covered by clothing are spared[131]. The eruption may last for days but is self-limited.

Pathology

Histologically, cercarial dermatitis is characterized by spongiosis and a mixed inflammatory infiltrate composed of histiocytes, lymphocytes, neutrophils, and eosinophils. Edema is present in the dermis. Genital and perineal lesions of bilharziasis cutanea tarda show hyperkeratosis and acanthosis and occasionally prominent pseudoepitheliomatous hyperplasia. The dermis may contain numerous ova, which can be associated with a granulomatous reaction. "Ectopic" extragenital lesions contain ova in the superficial dermis and can also be associated with granuloma formation.

Diagnosis

The diagnosis is usually established by microscopic detection of eggs in the urine or feces. In the case of *S. japonicum* and *S. mansoni* infections, microscopic evaluation of mucosal biopsy specimens may point to the diagnosis. Serologic tests (e.g. ELISA) can detect IgG, IgM, and IgE against worm and egg antigens. Monoclonal antibody-based assays that detect circulating antigens, such as the urine circulating cathodic

antigen (CCA) dipstick, also represent sensitive and specific methods for establishing the diagnosis as well as assessing response to therapy and cure[132]. In addition, sensitive and specific PCR-based tests have been developed for the detection of schistosome DNA in feces, urine, and serum[133].

Differential Diagnosis

The diagnosis of cercarial dermatitis, including swimmer's itch, requires a history of exposure to contaminated water. The lesions may be confused with arthropod bites, but the distribution is clearly distinct from that of seabather's eruption, which affects areas under the swimsuit (see Fig. 85.20). The differential diagnosis of anogenital and ectopic cutaneous ova deposition includes secondary syphilis (in particular the granulomatous form), condylomata acuminata, cutaneous Crohn disease, granuloma inguinale, and sarcoidosis.

Treatment

Praziquantel is an antihelminthic agent that is safe and effective against all five human schistosomal species[134]. The recommended regimen is 40 mg/kg (for *S. mansoni*, *S. haematobium*, and *S. intercalatum*) or 60 mg/kg (for *S. japonicum* and *S. mekongi*) divided into 2–3 oral doses administered over one day[133]. A single 40 mg/kg dose is used in massive population control programs, with an efficacy of 65%–95%. Retreatment in 4 to 6 weeks can improve the cure rate[133]. Side effects are mild and include abdominal discomfort, fever, and headache.

Although topical remedies (e.g. phenolized calamine) and antihistamines have been recommended for swimmer's itch, no controlled studies have defined the most effective therapy[131,135]. If left untreated, the acute episode resolves spontaneously within 7–10 days.

The most effective way to prevent swimmer's itch is to avoid lakes and bodies of fresh water known to be infested, especially those periods of the year when cercariae are most plentiful, i.e. the early and mid summer in temperate regions.

CYSTICERCOSIS AND ECHINOCOCCOSIS

Synonyms: ■ Echinococcosis: hydatidosis, hydatid disease

Key features

- Cestodes (tapeworms) that commonly affect animals (e.g. *Taenia solium*, *Echinococcus granulosus*) can also infect humans
- Cutaneous cysticercosis is characterized by papules and nodules that are usually multiple and asymptomatic; the brain (neurocysticercosis), eye, heart, other muscles, and peritoneal cavity may also be affected
- In echinococcosis, the liver and lungs are the major sites of involvement, with development of one or more hydatid cysts. Allergic symptoms, such as urticaria, asthma and anaphylaxis, are uncommon

Introduction

In the two stages of their life cycle (adult and larval), cestodes (tapeworms) can cause disease in humans. The adult worms reside in the *definitive* host's intestines (including humans) and are often associated with minimal clinical manifestations (see Fig. 83.26). In *intermediate* hosts, the larval stage can lead to clinical disease, e.g. cysticercosis or echinococcosis in humans[136].

Epidemiology

The four most common human cestodes (tapeworms) are *Taenia solium* (pork tapeworm), *Taenia saginata* (beef tapeworm), *Diphyllobothrium latum* (fish tapeworm), and *Hymenolepis nana*. In humans, they cause primarily gastrointestinal symptoms, but the larval stage of *T. solium* also causes cysticercosis. Larvae of *T. solium* and *T. saginata*, respectively, can cause cysticercosis in pigs and cattle. Cysticercosis has a worldwide distribution, affecting more than 50 million people, and it is more common in rural areas. Endemic regions include Central and South America, sub-Saharan Africa, India, and East Asia[137,138].

Echinococcosis is a zoonosis caused by *Echinococcus* species, the definitive hosts of which are dogs and other members of the family Canidae. Humans are only infected by the larval stage, i.e. they are intermediate hosts, and develop cysts within viscera. Most human disease is due to larval stages of *E. granulosus* and *E. multilocularis*. Echinococcosis occurs in tropical and subtropical countries worldwide, primarily in sheep- and cattle-raising areas. Endemic regions include the southern province of Brazil, the Middle East, parts of Asia, and Northern and East Africa. It is particularly common in Lebanon and Greece[136,137].

Pathogenesis

The adult tapeworm can reach a length of up to 30 feet in the intestinal tract of its definitive host. Its body has two main parts: a single head (scolex) for attachment to the host and many proglottids, each of which has male and female reproductive organs. Fertilized eggs accumulate in large numbers inside the uterine horns of the proglottids; the eggs can be released directly into the host's intestine or the entire gravid terminal proglottid can be excreted by the host[136]. Both eggs and proglottids are found in the host's stool (see Fig. 83.26).

When eggs or proglottids are ingested by a susceptible intermediate host, they develop into larvae called oncospheres. In humans, oncospheres can develop into encysted forms (cysticerci in cysticercosis) or generate germinal tissue with a cyst (hydatid in echinococcosis). Subsequent ingestion of cyst-containing tissues by a susceptible definitive host allows the development of the larvae into adults and completion of the life cycle[139].

Humans are the only definitive host for *T. saginata* (beef tapeworm) and *T. solium* (pork tapeworm), becoming infected with the adult form after eating poorly cooked muscle of a diseased animal (see Fig. 83.26). Humans are also intermediate hosts of *T. solium*, developing cysticercosis as a result of ingestion of food or water contaminated with infected human feces or via autoinfection from anus to mouth. In contrast, humans are only intermediate hosts of *E. granulosus* (as are sheep and cattle) as a result of ingesting contaminated dog feces. Dogs are the definitive host of *E. granulosus*, becoming infected with adult tapeworms after eating infected beef or lamb.

When humans are infected by the adult stage of *T. solium* (i.e. are the definitive host), the tapeworms within the intestine usually cause no morphologically identifiable change in the mucosa or submucosa. Some patients may develop moderate peripheral eosinophilia. Immunity plays only a limited role during infections with the adult stage and has little effect on the duration of infection or on the susceptibility to reinfection. However, immunity plays an important role when humans are the intermediate host, i.e. develop cysticercosis. After penetrating the host's intestinal wall and disseminating, the oncosphere matures rapidly and by 10 weeks is fully developed. The cyst that forms is usually 0.5–1.0 cm in diameter and remains viable for 3 to 5 years before degenerating. At this time, the inflammatory response is markedly intensified, and calcification also often takes place[137,140,141]. The signs and symptoms triggered by these reactions depend on the location of the cysts. For example, if there are cysts at the base of the brain, a cysticercic meningitis may ensue. In brain tissue itself, cysts that calcify may cause seizures.

When humans ingest the eggs of *E. granulosus*, oncospheres penetrate the mesenteric vessels. While the majority are trapped by the liver sinusoids, some bypass the liver and are carried in the bloodstream to other organs and tissues. Within hours, an inflammatory response may be seen. If the larvae survive, they develop into hydatid cysts within 5 days. Cell-mediated immunity controls dissemination during the early phase of infection.

Clinical Features

In *cysticercosis*, cysts can develop in almost any organ or tissue in the body. Skin involvement presents as subcutaneous papulonodules that are more often palpable than visible[140,142,143]. They are usually multiple and asymptomatic. The brain, eye, heart, other muscles, and peritoneal cavity may also be affected. Subcutaneous involvement is recognized in <1%–20% of patients[142,143], and it is said to be more common in Asia and Africa than in Latin America[144]. However, in a Brazilian study of 30 patients with

cysticercosis, 90% had cysts in the subcutaneous tissue, skeletal muscle, or mucous membranes, while the CNS was affected in <10%[137].

In *echinococcosis*, the cysts may be single or multiple and they affect primarily the liver (50%–75%) and lungs (20%). The skin is involved in fewer than 2% of the patients. Cysts increase in size at the rate of ~1 cm/year. The clinical features are highly variable and reflect the location and size of the cysts. Most symptoms are due to mechanical pressure by the cyst mass or an allergic reaction (urticaria, wheezing, anaphylaxis) to foreign antigens in leaking cyst fluid[137].

Soft tissue cysts may present as firm subcutaneous nodules or as masses that are fluctuant and nontender. *E. multilocularis* has been noted to cause multiple supraumbilical dermal and subcutaneous nodules with associated ulceration, local inflammation, and painless cutaneous fistulas[137].

Diagnosis

The diagnosis of *cysticercosis* is often made by X-ray examination of the head or extremities, which reveals the calcified cysts. CT or MRI can also demonstrate lesions. ELISA and hemagglutination tests utilizing cyst vesicular fluid as antigen are 80%–95% sensitive and specific. An enzyme-linked immunoblot assay is the serologic test of choice, as its specificity and sensitivity approach 100% and 94%, respectively[137]. Tests that detect circulating cysticercal antigens and PCR-based assays have also been developed.

The diagnosis of *echinococcosis* is based on detection of cysts via ultrasound, CT, or MRI. Examination of the contents of the cyst and identification of the parasite provides confirmation. Peripheral eosinophilia is present in one-third of patients. Western blot and enzyme immunoassays are also available, which have a high degree of cross-reactivity with assays for cysticercosis. The assays have decreased sensitivity when the lesions are calcified, only one cyst is present, or the echinococcal cysts are not located in the liver[106].

Treatment

"Old", inactive lesions of cutaneous cysticercosis are treated surgically. Patients with active disease may be treated with albendazole (15 mg/kg/day with a maximum of 800 mg, for ≥8 days) or praziquantel (50–100 mg/kg/day in three divided doses for 2 weeks). Albendazole is cheaper and has 20% more cysticidal activity than praziquantel[145]. Evaluation for neurocysticercosis is mandatory in patients with cutaneous cysticercosis. Antiparasitic treatment in individuals with multiple CNS cysts may induce cerebral inflammation and edema that can exacerbate neurologic symptoms; concurrent administration of a systemic corticosteroid and close inpatient monitoring are recommended[144].

Surgical removal of the intact cyst is the preferred form of therapy for echinococcosis. Albendazole has been used in doses of 10 mg/kg/day for 8 weeks for the treatment of inoperable disease and as preoperative therapy for 4 days[145].

Control of the deposition of human feces is important for the prevention of cysticercosis. In addition, meat inspection for *T. solium* decreases its transmission[137]. Proper disposal of the carcasses and entrails of sheep, cattle, and hogs can help to prevent infection of dogs and thereby break the cycle of *Echinococcus* spp. transmission.

Additional figures and tables on Guidelines for cutaneous and mucocutaneous leishmaniasis, and Comparison between West African and East African trypanosomiasis, available in our eBook (see inside front cover for access code).

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eFig. 83.1 Cutaneous leishmaniasis. Infiltrated "dry" inflammatory plaques of leishmaniasis in a woman from the Calabria region of Italy.



eFig. 83.2 New World cutaneous leishmaniasis of the ear (chiclero ulcer). *Courtesy Kalman Watsky, MD.*



eFig. 83.3 Scars secondary to previous cutaneous leishmaniasis. Circular scars at previous sites of cutaneous leishmaniasis are often the only sign of a prior infection. *Courtesy Omar P. Sangüeza, MD.*



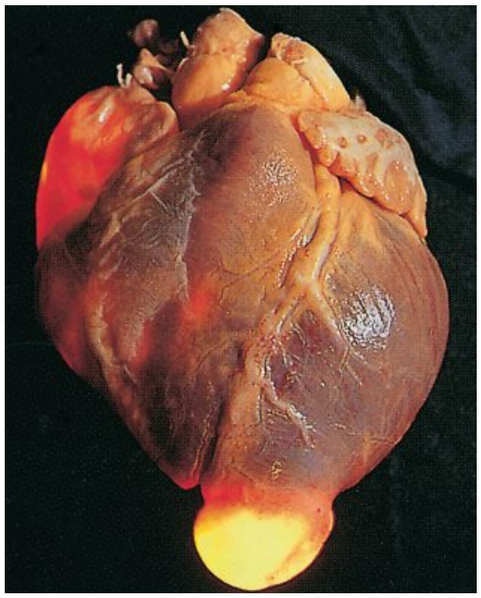
eFig. 83.4 Disseminated cutaneous leishmaniasis of the thigh. Cluster of pink infiltrated papules. *Courtesy Sendy Solórzano Gutiérrez, MD and Maria Sanz Castro, MD.*



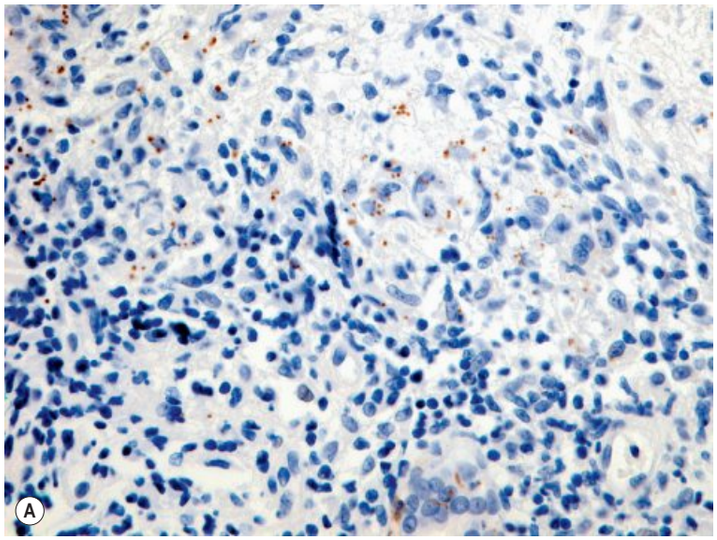
eFig. 83.5 Leishmania recidivans. Reactivation of New World cutaneous leishmaniasis resulted in a more severe disease with ocular involvement. *Courtesy Erika Romero, MD.*

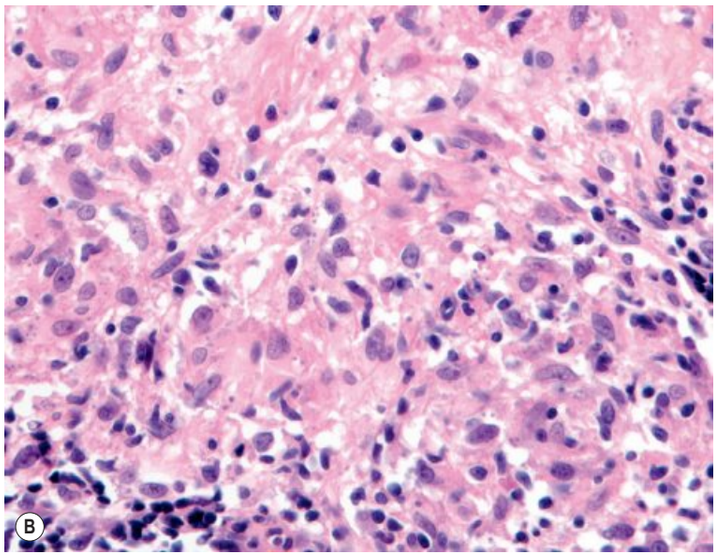


eFig. 83.6 Mucocutaneous leishmaniasis. There is edema and infiltration of the nose as well as focal deep ulceration of the vestibule and upper lip. *Courtesy Omar P. Sangüeza, MD.*



eFig. 83.8 Chagas disease: apical aneurysm of the heart. Mural thrombi may be present at the apex of the left ventricle, with marked thinning of the ventricular wall (illuminated). *With permission from Nabarro L, Morris-Jones S, Moore DAJ: Peters' Atlas of Tropical Medicine and Parasitology, 7th edition. London: Elsevier, 2019. Courtesy Professor F. Köberle.*

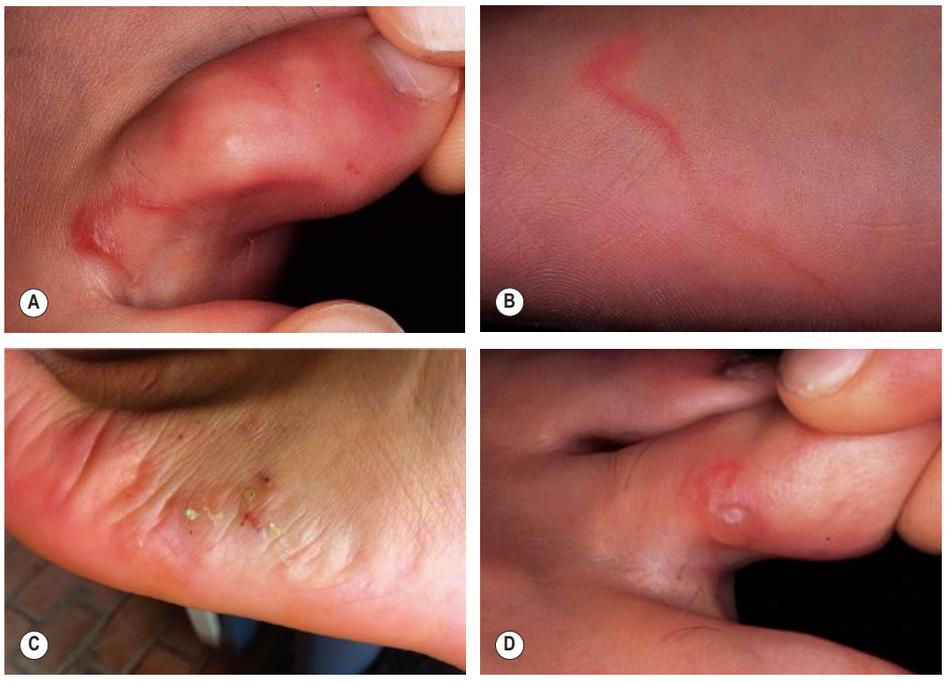




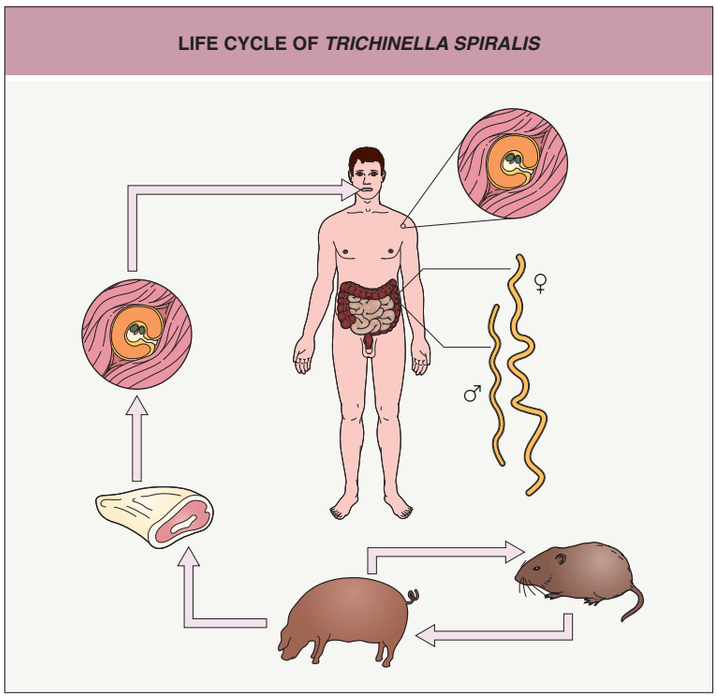
eFig. 83.7 Immunostaining to detect *Leishmania* organisms. Demonstration of improved detection of *Leishmania* organisms via immunostaining with CD1a (**A**) as compared to H&E staining (**B**). *Courtesy Jennifer McNiff, MD.*



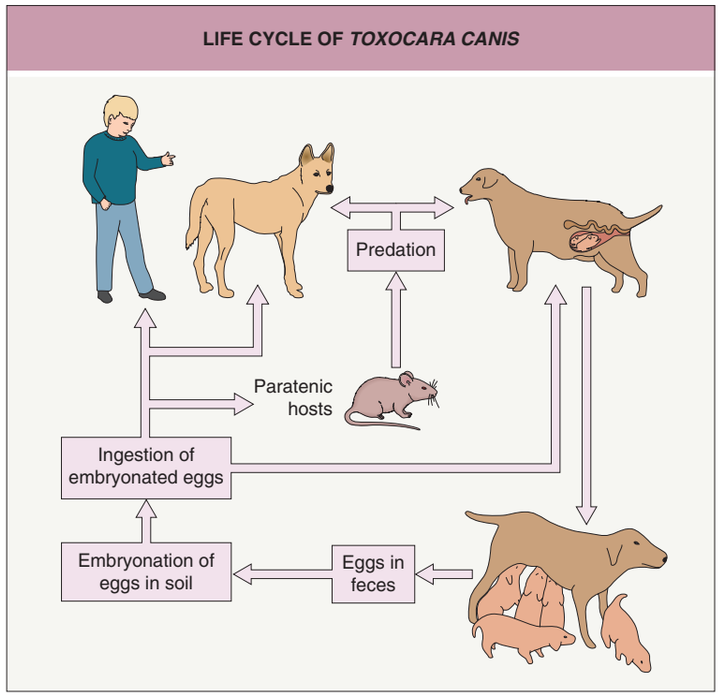
eFig. 83.9 Chagas disease: radiograph of megaesophagus. Muscular degeneration and denervation of segments of the alimentary tract through destruction of the cells of Auerbach's plexus cause megaesophagus, megastomach and megacolon, which can be detected radiologically. *With permission Nabarro L, Morris-Jones S, Moore DAJ: Peters' Atlas of Tropical Medicine and Parasitology, 7th edition. London: Elsevier, 2019.*



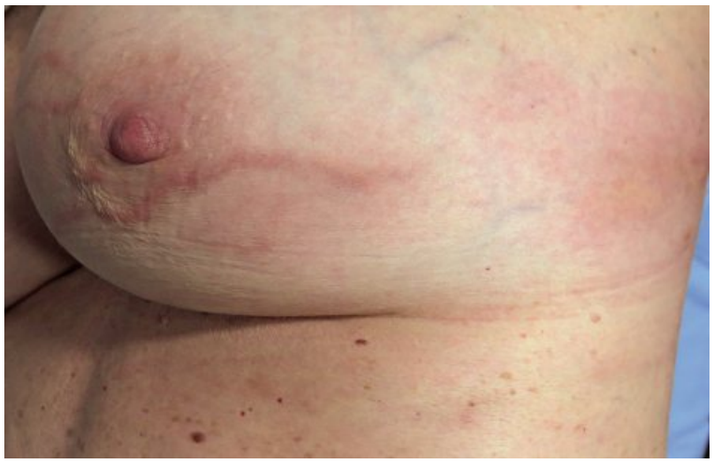
eFig. 83.10 Cutaneous larva migrans. Note the characteristic serpiginous erythematous tracts between the toes (**A**) and on the hand (**B**) and foot (**C**). Vesicobullae can also be seen (**D**). *A, D, Courtesy Kalman Watsky MD. B, Courtesy Julie V. Schaffer MD.*



eFig. 83.11 Life cycle of *Trichinella spiralis*. This nematode is a zoonotic infection that circulates between rats and various carnivores. Trichinosis in humans commonly results from eating raw or inadequately cooked pork products such as sausages. Infection is acquired by eating muscle containing encysted larvae which excyst in the small intestine and develop into adults. Mature females deposit larvae which migrate from the gastrointestinal tract through tissues to reach skeletal muscles in which they then encyst. *With permission from Nabarro L, Morris-Jones S, Moore DAJ: Peters' Atlas of Tropical Medicine and Parasitology, 7th edition. London: Elsevier, 2019.*



eFig. 83.12 Life cycle of *Toxocara canis*. This demonstrates the importance of transplacental transmission in maintaining canine infection, and the role of young dogs in transmitting infection to humans. *With permission from Gillespie S. Migrating worms. In: Cohen J, Powderly W (eds). Infectious Diseases, 2nd edition. London: Mosby, 2004.*



eFig. 83.13 Gnathostomiasis. Note the diffuse erythema and induration resembling a panniculitis and the serpiginous pattern over the breast similar to larva migrans.



eFig. 83.14 Gnathostoma. Punch biopsy of furuncular lesion that developed after institution of therapy, showing the larva attached to the bottom of the specimen.



eFig. 83.15 Onchocerciasis. Diffuse lichenification and hyperpigmentation in a patient with intense pruritus. Focal areas of leukoderma are also present. *Courtesy Omar P. Sangüeza, MD*



eFig. 83.16 Living microfilariae of *Onchocerca volvulus*. After some time, actively moving microfilariae emerge from the skin snip into the surrounding saline, where they can be counted. *With permission from Nabarro L, Morris-Jones S, Moore DAJ: Peters' Atlas of Tropical Medicine and Parasitology, 7th edition. London: Elsevier, 2019.*



eFig. 83.17 Cysticercosis. Subconjunctival nodule. *Courtesy Luis Requena, MD.*

GUIDELINES FOR CUTANEOUS AND MUCOCUTANEOUS LEISHMANIASIS
Epidemiology
Areas endemic for leishmaniasis include: • Asia – Middle East, Central Asia, India • Europe – Mediterranean countries, from Spain through the Balkans • Africa – Mediterranean countries, sub-Saharan countries, Sudan, Ethiopia • Americas – From Texas through Mexico, Central and South America, except Chile and Uruguay *In each country, the endemicity of areas a patient has visited should be assessed*.
Risk factors
Disease can be acquired by residents and visitors to endemic areas, which include rural as well as urban settings. For transmission, close contact is required between vector sandflies (*Phlebotomus* [Old World] and *Lutzomyia* [New World]) and natural reservoirs such as dogs, rodents, and humans.
Clinical
• Incubation period: weeks to months • Classical cutaneous leishmaniasis (CL) presents as an ulcerated or verrucous papule, nodule, or plaque in an exposed area of the body. Multiple lesions may develop, sometimes with satellites or sporotrichoid spread; additional presentations include erysipeloid and zosteriform patterns. • Disseminated and diffuse forms can also occur. • Patients should be assessed for scars suggestive of previous disease. • Mucosal leishmaniasis (ML) often starts as an ulceration of the nasal septum (with eventual perforation) but may involve the mouth, pharynx, and larynx. The nasal and oral mucosa should be examined in those at risk for ML, and otorhinolaryngology evaluation is recommended for those with signs/symptoms of mucosal involvement.
Diagnosis
Diagnosis is definitive with visualization of the amastigote. No test is 100% sensitive, so it is helpful to use multiple forms of assessment, depending on availability. • Clinically compatible morphology • Direct examination smear of fluid from the lesion stained with Giemsa, Wright, or Feulgen • Full-thickness skin biopsy for histopathological assessment and culture (in Nicolle–Novy–MacNeal–Nicolle [NNN] medium). Amastigotes can be seen in 50% of cases on H&E, but less often in long-standing lesions or if well-formed granulomas are present. Immunostaining has been developed but is not available commercially, and the utility of CD1a staining utility remains to be defined. • Delayed skin reaction test via intradermal injection of leishmania antigens; most useful in patients who do not reside in an area where leishmaniasis is endemic. • PCR-based assays on fluids, fresh tissue, or formalin-fixed paraffin-embedded tissue
Therapy
Cutaneous disease
• In *simple* CL(see Table 83.6) – e.g. an immunocompetent patient with ≤4 skin lesions <1 cm in diameter, thought to be infected with a *Leishmania* species not associated with ML – waiting for the lesion(s) to resolve spontaneously or local therapy may be appropriate. • Local therapies include heat, cryotherapy, topical paromomycin, intralesional pentavalent antimonials, and photodynamic or laser therapy. • In patients with CL at risk for ML based on the species or area acquired, even if lesions are healing/recently healed, systemic treatment should be considered; however, watchful waiting with monitoring for signs of ML may be a reasonable approach in some patients. • Systemic treatment with a parenteral pentavalent antimonial or miltefosine is recommended for patients with *complex* CL (see Table 83.6), defined as: disease caused by the *Viannia* subgenus or acquired in Brazil, Bolivia, or Peru; lesions with subcutaneous component, ≥4 in number, ≥5 cm in diameter, or located on the face, ears, fingers, toes, joints, or genitalia; CL occurring in an immunocompromised patient; or clinical failure of local therapy. • Leishmaniasis recidivans, disseminated cutaneous leishmaniasis, and diffuse cutaneous leishmaniasis should receive systemic therapy. • Patients with CL should be monitored for 6 to 12 months to rule out treatment failure.
Mucocutaneous disease
• All patients with mucocutaneous leishmaniasis should undergo otolaryngologic assessment and receive systemic therapy. • Impatient monitoring and prophylactic corticosteroids are recommended for patients with laryngeal/pharyngeal disease. • Systemic treatment options include a pentavalent antimonial, amphotericin B deoxycholate, liposomal amphotericin B, and oral miltefosine. • In patients with severe mucosal disease or HIV co-infection, the first line therapy is liposomal amphotericin B or amphotericin B deoxycolate.

eTable 83.1 Guidelines for cutaneous and mucocutaneous leishmaniasis.

COMPARISON BETWEEN WEST AFRICAN AND EAST AFRICAN TRYPANOSOMIASIS		
	West African trypanosomiasis	**East African trypanosomiasis**
Causative agent	*T. brucei gambiense*	*T. brucei rhodesiense*
Vector	Tsetse fly	Tsetse fly
Main host	Humans	Wild game > humans
Reservoir	Humans	Antelope, cattle
Location	West/central regions of sub-Saharan Africa	Ethiopia, Uganda, Zambia, Botswana, Tanzania, Mozambique
Clinical presentation	• Slow progression (3 years) • Chancre uncommon • Chronic neurologic symptoms • Posterior cervical (Winterbottom sign) and supraclavicular lymphadenopathy • Trypanids (10%–50% of patients, easier to detect in lighter skin phototypes)	• Quick progression (weeks to months) • Chancre common (75% of patients) • Acute neurologic symptoms • Axillary and epitrochlear lymphadenopathy • Trypanids common (easier to detect in lighter skin phototypes) • Myocarditis/heart failure
Treatment		
Hemolymphatic (first stage)	• Oral fexinidazole • IM pentamidine (children <6 years of age or <20 kg)	• Suramin
CNS involvement (second stage)	• Oral fexindazole (non-severe disease) • Nifurtimox + eflornithine (severe disease; children <6 years of age or <20 kg)	• IV melarsoprol

eTable 83.2 Comparison between West African and East African trypanosomiasis. Non-severe second stage: <100 leukocytes/mcl in CSF; severe second-stage: ≥100 leukocytes/mcl in CSF. IM, intramuscular; IV, intravascular.

Infestations 84

Craig N. Burkhart, Craig G. Burkhart and Dean S. Morrell

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SCABIES

Synonyms: ■ Itch mite infestation ■ "Seven-year itch"

Key features

- Human scabies is a pruritic condition caused by infestation with the host-specific mite *Sarcoptes scabiei* var. *hominis*, which lives its entire life within the epidermis
- Although the scabies mite is not a known vector for any systemic disease, secondary bacterial infections with *Streptococcus pyogenes* or *Staphylococcus aureus* may develop
- Transmission typically occurs via direct close contact with an infested person; fomite transmission is also possible, especially with the crusted variant
- Permethrin 5% cream is generally the first-line treatment for classic scabies

Introduction

The scabies mite continues to plague all countries of the world[1]. An estimated 150–200 million individuals are affected globally, with an overall worldwide prevalence of ~2.5%[2,3]. In 2017, the World Health Organization (WHO) designated scabies as a neglected tropical disease to highlight the need for global control strategies. Pruritus associated with this infestation is usually severe, especially at night, and treatment typically requires prescription scabicidal therapy.

History

Scabies has been a common companion of the human species for over 2500 years[1].

Epidemiology

Scabies is a worldwide problem and all ages, races, and socioeconomic groups are susceptible. Environmental factors that promote its spread include overcrowding, institutional settings, delayed treatment, and lack of public awareness of the condition. There is considerable variation in the prevalence of scabies, with rates in low-income countries ranging from 4% to 70%[1–3]. Higher incidences occur in tropical regions, and outbreaks may occur in the setting of natural disasters, wars, economic depression, and refugee displacement[1,4]. Scabies can be transmitted directly by close personal contact, sexual or otherwise, or indirectly via fomites. Prevalence is higher in children and people who are sexually active, and spread of the infestation among family members and other close contacts is common[4]. The scabies mite is not a known vector for systemic disease.

Crusted scabies (formerly called Norwegian scabies) is found in individuals with compromised immune systems, such as the elderly, people infected with HIV or human T cell lymphotropic virus type 1 (HTLV-1), and solid organ transplant recipients; it can also occur in those with decreased sensory functions and/or ability to scratch (e.g. patients with leprosy or paraplegia). These patients may experience minimal pruritus despite their infestation with a large number of mites and are highly contagious[4].

Pathogenesis

The species-specific, eight-legged mite *Sarcoptes scabiei* var. *hominis* causes human scabies (Fig. 84.1). The *Sarcoptes* mites that cause infestations in animals (e.g. *S. scabiei* var. *canis* in dogs) are not a source of human infestation, but they can produce bite reactions (see Ch. 85). The scabies mite is 0.35 × 0.3 mm in size and too small to be seen by the naked eye. The entire 30-day life cycle of these mites is completed within the epidermis (Fig. 84.2). Each day a female mite lays 2–3 eggs, which require approximately 10 days to mature. The number of mites living on an infested host can vary greatly, although there are usually fewer than a hundred and often no more than 10–15. However, patients with crusted scabies may have thousands of mites on their skin surface, and live mites can be recovered in debris from sheets, the floor, curtains, and chairs in the environment of affected individuals[5]. Scabies mites usually live 3 days or fewer off a human host, but those from patients with crusted scabies may live up to 7 days by feeding on sloughed skin.

The incubation period before symptoms develop can range from days to months. In first-time infestations, it usually takes 2–6 weeks before the host's immune system becomes sensitized to the mite or its by-products, resulting in pruritus and cutaneous lesions. In contrast, a subsequent infestation often becomes symptomatic within 24–48 hours. Asymptomatic scabies-infested individuals are not uncommon, and they can be considered "carriers"[5].

Clinical Features

The epidemiologic history (e.g. pruritus in household members or other close personal contacts), the distribution and types of lesions, and pruritus form the basis of the clinical diagnosis. The intense pruritus is classically accentuated at night and by a hot bath or shower. Pruritus may be present before any overt physical signs appear and is thought to be mediated by nonhistaminergic mechanisms[6]. Cutaneous lesions are symmetrical, typically involving the interdigital web spaces of the hands, flexural aspect of the wrists, axillae, posterior auricular area, waist (including the umbilicus), ankles, feet, and buttocks. In men, penile and scrotal lesions are common, while in women, the areolae, nipples, and vulvar area are often affected. In infants, the elderly and immunocompromised hosts, all skin surfaces are susceptible, including the scalp and face[1,5].

Typically, small erythematous papules are present in association with a variable degree of excoriation (Fig. 84.3A–C). Vesicles, indurated nodules, and eczematous dermatitis are also common (Fig. 84.3B–F). The pathognomonic sign is the burrow, representing the tunnel that a female mite excavates while laying eggs. Clinically, the burrow is wavy, thread-like, grayish-white, and 1–10 mm in length (Fig. 84.3G). Many patients, however, do not have obvious burrows on inspection, especially in warm climates.

Acral vesiculopustules can represent a clue to the diagnosis of scabies in infants (see Fig. 84.3D). Crusted scabies often manifests with marked hyperkeratosis that favors acral sites including subungual areas,

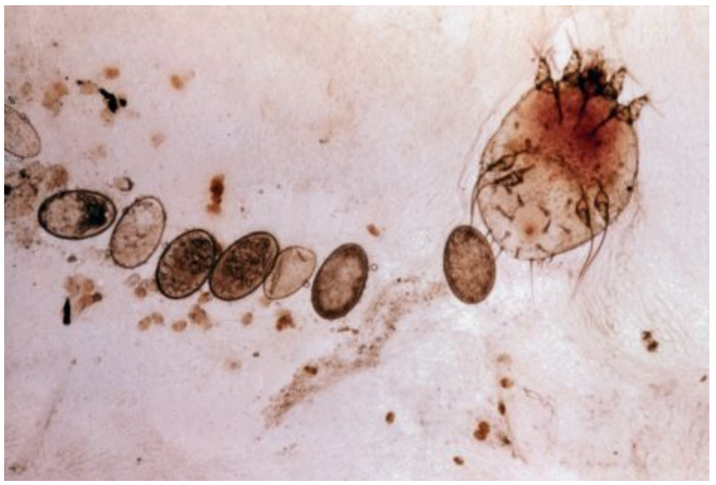


Fig. 84.1 Female scabies mite with eggs and scybala in skin scrapings. Note the mite's flattened, oval body and eight legs.

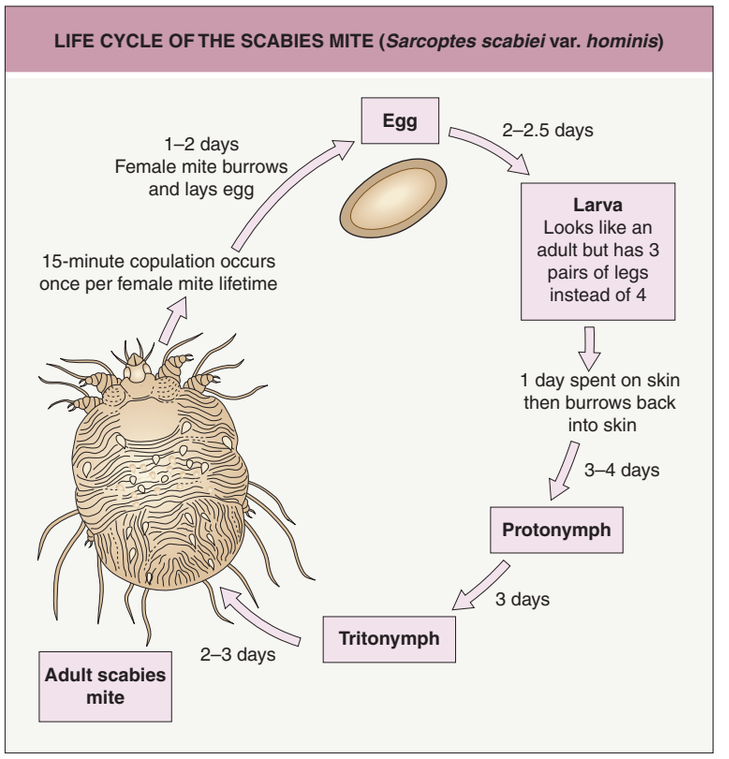


Fig. 84.2 Life cycle of the scabies mite (*Sarcoptes scabiei* var. *hominis*).



Fig. 84.3 Scabies. A–C Erythematous papules and oozing dermatitic plaques in infants with scabies. **D** Vesiculopustules on an infant's foot. Similar findings are seen in acropustulosis of infancy, which can occur following successful scabies treatment. **E** Penile involvement with erythematous papules and nodules. **F** Nodular scabies in an infant. **G** Classic scabetic burrows. Burrows are of high yield for visualizing mites via dermoscopy and isolating mites via skin scraping. *A–D, Courtesy Julie V. Schaffer, MD; F, Courtesy Kalman Watsky, MD.*



Fig. 84.4 Crusted scabies. Scabies incognito presenting as an asymptomatic hyperkeratotic "rash" on the hand in a patient with impaired sensory function (**A**) and on the abdomen of a hospitalized man (**B**). *A, Courtesy Joyce Rico, MD; B, Courtesy Kalman Watsky, MD.*

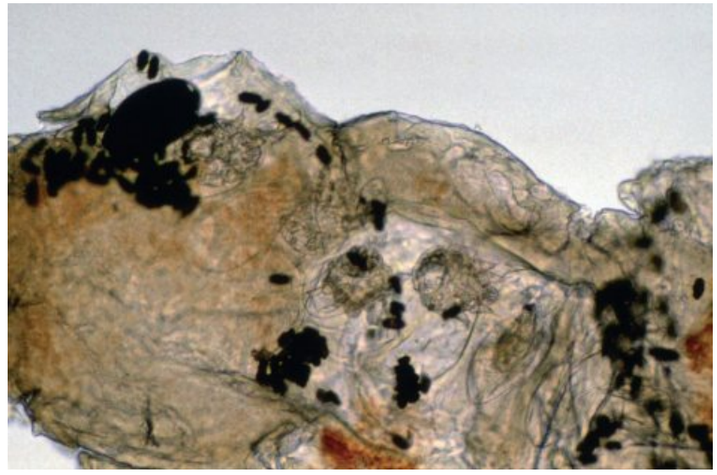


Fig. 84.5 Microscopy of a skin scraping from a patient with scabies. Four mites, eggs, and scybala are present. The mites blend in with the background scale, making them difficult to see.

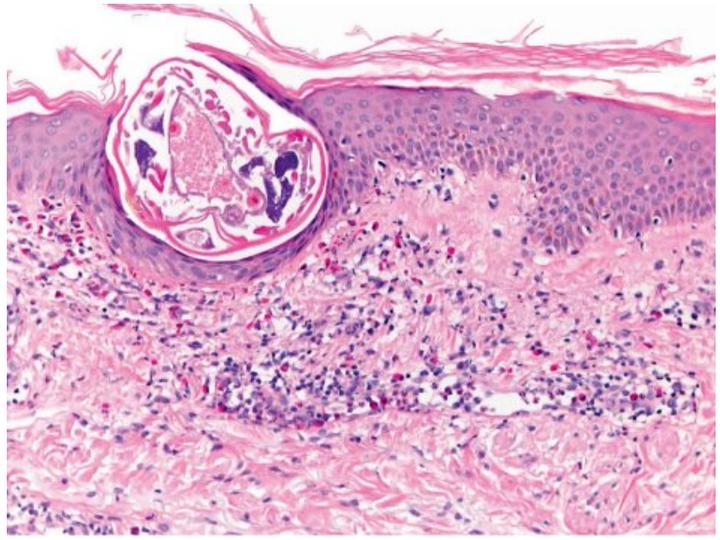


Fig. 84.6 Scabies – histologic features. A mite is evident in the stratum corneum and an eosinophil-rich dermal infiltrate is present. *Courtesy Lorenzo Cerroni, MD.*

but involvement may be widespread (Fig. 84.4). Areas of affected skin have been referred to as pachyderma.

Secondary bacterial infections with *Staphylococcus aureus* or *Streptococcus pyogenes* sometimes complicate scabies. In resource-poor countries with endemic scabies, post-streptococcal glomerulonephritis is a significant issue. Peripheral eosinophilia can be the primary sign of scabies in patients with disorders of keratinization.

Confirmation of the diagnosis can be achieved by light microscopic examination of mineral oil preparations of skin scrapings (from infested areas) for adult mites, eggs, and/or fecal pellets (scybala; Fig. 84.5). A scalpel or curette may be used to obtain the skin sample[7]. Microscopic examination of transparent adhesive tape following its application to infested areas of skin represents another diagnostic technique. Dermoscopy and confocal microscopy can prove useful for direct *in vivo* visualization of mites and eggs (see Fig. 84.5). Recent consensus criteria for a *confirmed* scabies diagnosis require visualization of mites, eggs, or feces either by light microscopy of skin samples or on an individual by a high-powered imaging device or dermoscopy[8]. A skin biopsy may confirm the clinical diagnosis, but only if the specimen obtained happens to contain the mite or its eggs. Often, however, the diagnosis is a clinical one, resting on history and physical findings (e.g. burrows, genital lesions)[8] as well as response to treatment. The diagnostic potential of PCR-based analysis of skin scrapings or swabs and serologic testing to detect IgE specific for a recombinant *S. scabiei* antigen are under investigation[9,10].

Pathology

A patchy to diffuse infiltrate with prominent eosinophils as well as lymphocytes and histiocytes is noted in the reticular dermis. A transected scabies mite may occasionally be seen within the epidermis (Fig. 84.6). Pink "pigtail"-like structures attached to the stratum corneum, which represent fragments of the adult mite exoskeleton, can serve as a clue to the diagnosis of scabies when entire mites, scybala, and eggs are not identified[11].

Differential Diagnosis

Unless burrows or (via dermoscopy) mites and eggs are noted clinically, a wide variety of pruritic skin diseases should be considered in the differential diagnosis. These include atopic, allergic contact, autosensitization ("id" reaction), and nummular dermatitis as well as arthropod bites, pyoderma, dermatitis herpetiformis, and bullous pemphigoid. Occasionally, scabies can mimic Langerhans cell histiocytosis clinically and histologically, as a dense infiltrate of Langerhans cells may be present. The clinical and histologic features of infantile scabies may also resemble findings in the inflammatory stage of incontinentia pigmenti. Acropustulosis of infancy can both mimic scabies and follow scabies as a hypersensitivity phenomenon.

TOPICAL AND ORAL TREATMENTS FOR SCABIES					
Therapy	**Administration**	**Concerns**	**Efficacy & resistance**	**Use in infants**	**Use in pregnancy**
Permethrin cream (5%)	Topically overnight (8–12 hours) on days 1 and 8*	Allergic contact dermatitis in individuals with sensitivity to formaldehyde	Excellent, but some signs of tolerance developing	FDA approved for infants ≥2 months of age	Considered safe
Spinosad suspension (0.9%)	Topically for ≥6 hours on day 1	Skin irritation, dry skin	Good	FDA approved for children ≥4 years of age	Considered safe
Lindane lotion or cream (1%)	Topically overnight on days 1 and 8	Potential CNS toxicity, especially in individuals weighing <110 pounds (50 kg), the elderly and those with crusted scabies, other skin conditions or a history of seizures	Poor, resistance very common	Not recommended for infants, children or breastfeeding mothers; contraindicated in premature infants	Not recommended
Crotamiton lotion or cream (10%)	Topically overnight for 2–5 consecutive days	Irritant contact dermatitis, especially in areas of denuded skin	Very poor; has antipruritic properties and may be used for postscabetic pruritus	Considered safe	Not established
Sulfur ointment (5%–10%)	Topically overnight for 3 successive days	Toxicity studies not performed	Good	Considered safe	Considered safe
Benzyl benzoate lotion or emulsion (10%–25%)	Topically (left on for 24 hours) on days 1 and 8	Irritant contact dermatitis	Good	Not well established	Not established
Ivermectin	Oral dose of 200 mcg/kg on day 1 and repeated on day 8 or 14*,† (available as 3 mg tablets)	Potential risk of CNS toxicity in infants and young children	Excellent	Not well-established, although recent studies suggest safety in children (age ≥1–2 months) weighing <33 pounds (15 kg)	Generally not recommended for scabies in pregnant women
	0.5%–1% lotion/cream topically overnight on days 1 ± 8	Potential skin and eye irritation	Not established	Not established	

*For crusted scabies, the CDC recommends: (1) topical permethrin 5% every 2–3 days for 1 to 2 weeks; (2) oral ivermectin (200 mcg/kg/dose) administered as three doses (days 1, 2 and 8), five doses (days 1, 2, 8, 9, and 15), or seven doses (days 1, 2, 8, 9, 15, 22, and 29), depending upon the severity of the infection; and (3) application of a topical keratolytic (e.g. salicylic or lactic acid) in areas of hyperkeratosis (www.cdc.gov).
†Administration of second dose at 1 week is recommended by the CDC (www.cdc.gov).

Table 84.1 Topical and oral treatments for scabies. Topical therapies for scabies require careful instructions to ensure correct application by patients.

Treatment

Two treatments 1 week apart with an antiscabetic medication are typically recommended, with permethrin 5% cream a standard first-line therapy (Table 84.1)[4,12]. Topical preparations are applied to the entire body surface, from head to toe, in infants and the elderly. In other age groups, the face and scalp can be excluded from treatment. Special attention should be paid to the interdigital spaces, intergluteal cleft, umbilicus, and subungual areas. To reduce the potential for reinfestation by fomite transmission, at the time of each treatment, clothing, linens, and towels used within the previous week can be either washed in hot water and dried on high heat or stored in a bag for 7–10 days[13]. The relatively common occurrence of asymptomatic mite carriers in households necessitates that all family members and other close contacts be treated simultaneously, even if they have not developed any pruritus or clinical signs. Pets cannot harbor human mites and do not have to be treated. Secondary bacterial infections should be treated with appropriate antibiotics.

Following successful treatment, pruritus and skin lesions can persist for 2–4 weeks or longer, especially for acral vesiculopustules in infants and nodules. This is referred to as "postscabetic" pruritus or dermatitis. Patients should be informed that such reactions do not imply treatment failure, but rather represent the body's response to dead mites that are eventually sloughed off (within 2 weeks) along with normal epidermal exfoliation. Many patients, however, experience relief from pruritus within 3 days. The second treatment is performed in order to reduce the potential for reinfestation from fomites as well as to ensure killing of any nymphs that may have survived within the semi-protective environment of the egg and subsequently hatched (see Fig. 84.2).

Permethrin

Permethrin is a synthetic pyrethroid formulated in a 5% cream that is currently the standard topical scabicide[4,12,14a]. Like other pyrethroids, it inhibits sodium transport in arthropod neurons, thereby causing paralysis. Adverse reactions are rare and are usually related to brief stinging on application. Prolonged *in vitro* survival of *S. scabiei* var. *hominis* following permethrin exposure has been noted, but clinical resistance has not been documented.

Spinosad

In 2021, 0.9% spinosad suspension was FDA-approved for the treatment of scabies in patients ≥4 years of age. In a randomized clinical study (n=206), a single application of 0.9% spinosad suspension to the entire body (neck to toes; left on for ≥6 hours) led to a complete cure on day 28 in 78% of patients with scabies, compared to 40% for placebo ($p<0.001$)[14b].

Lindane

Lindane (gamma-hexachlorocyclohexane), an organochlorine agent, is marketed in a 1% lotion and cream. CNS side effects may occur from increased percutaneous absorption through damaged skin, misuse, overuse, or accidental ingestion. Because of the potential for CNS toxicity, lindane is contraindicated in premature infants, individuals with crusted scabies or pre-existing skin conditions (e.g. extensive atopic dermatitis) that may increase its systemic absorption, as well as patients with an uncontrolled seizure disorder. Potential toxicity, relatively poor efficacy, widespread resistance, and issues related to environmental contamination make lindane an inferior treatment choice compared to permethrin or oral ivermectin. In 2003, the US Food and Drug Administration (FDA) issued a "black box" warning for lindane products, stating that they should be used with caution in infants, children, other individuals who weigh <110 pounds (50 kg), and the elderly due to an increased risk of neurotoxicity[4].

Crotamiton

An alternative scabicide is crotamiton, which is formulated in a 10% lotion and cream. Although it has an antipruritic effect, crotamiton

can cause irritation of denuded skin and is less effective than the other prescription options[15].

Sulfur ointment

Another alternative therapy for scabies is three consecutive overnight applications of 5%–10% sulfur in a petrolatum base. A pharmacist must compound the medication, and toxicity studies have not been performed. Sulfur is messy, malodorous, and irritating to the skin and can stain clothing. However, its efficacy has been reported to be as high as 60%–96% with three consecutive 24-hour applications[16a].

Benzyl benzoate

Benzyl benzoate is an ester of benzoic acid and benzyl alcohol that is neurotoxic to mites. It is available over-the-counter (OTC) in a 10%–25% lotion or emulsion (not directly sold in US pharmacies; lower concentrations used in children) that is left on for 24 hours. Regimens include: 2-3 applications over a 24-hour period; applications on 3 consecutive days; and applications on day 1 and day 8. Cure rates of ~90% have been reported, and the main side effect is skin irritation[16b].

Ivermectin

Ivermectin is a macrocyclic lactone produced by *Streptomyces avermitilis*. Although not FDA-approved for scabies, ivermectin represents an effective treatment for this and other ectoparasitic infestations[1,17]. By blocking transmission across nerve synapses that utilize glutamate or γ-aminobutyric acid (GABA), ivermectin causes paralysis of peripheral motor function in insects and acarines[1,17]. Although GABA and glutamate are neurotransmitters within the human cerebral cortex, after early infancy, the blood–brain barrier prevents CNS penetration of the drug. However, neurotoxicity can occur in rare individuals with biallelic nonsense mutations in the *ABCB1* (ATP-binding cassette subfamily B member 1) gene encoding the P-glycoprotein that functions in the blood–brain barrier[18]. Ivermectin is not recommended for pregnant women or breastfeeding mothers because of the lack of safety data in these groups[1]. Oral ivermectin treatment for scabies in infants and children weighing <33 pounds (15 kg) was well-tolerated in a recent large series,[19] although traditionally not recommended in this group.

In clinical studies, oral ivermectin has proven to be extremely safe. Over 18 million people >5 years of age have been treated annually with ivermectin in the WHO Onchocerciasis Eradication Program. An increased death rate in elderly patients who received ivermectin in a single retrospective study[20] was determined to be causally unrelated to the medication by the WHO, medical examiners, and the scientific community. A related medication with a longer half-life, moxidectin, was recently FDA-approved for onchocerciasis and is under investigation as a potential scabies treatment[4].

For treatment of scabies, an oral ivermectin dose of 200 mcg/kg is usually administered twice, 1–2 weeks apart[1,17]. Although there is only one report to date of clinical resistance to this agent by the scabies mite, increased *in vitro* survival times of mites exposed to ivermectin have been described in communities with a high prevalence of scabies[21]. In areas with endemic disease, mass administration of oral ivermectin or topical permethrin (± coadministration of azithromycin) can help to control scabies and reduce the prevalence of impetigo[22].

Topical ivermectin in a 1% concentration (FDA-approved for the treatment of rosacea) also appears to be effective for scabies, but further study is warranted before recommending its routine use for this indication[23]. In patients with subungual disease, addition of a topical scabicide is recommended because a systemic medication will not penetrate into thickened keratotic debris. A combination of oral ivermectin and topical permethrin is often required to treat patients with crusted scabies (see Table 84.1), and use of a topical keratolytic agent (e.g. salicylic or lactic acid) can help to decrease the associated hyperkeratosis.

HEAD LICE

Synonyms: ■ Pediculosis capitis ■ "Cooties"

Key features

- This worldwide infestation is caused by bloodsucking, wingless, six-legged insects that live only on the hairs of the scalp
- Diagnosis is usually confirmed by the presence of 0.8 mm eggs ("nits") firmly attached to scalp hairs
- Head lice are spread by head-to-head contact as well as by fomite transmission
- Resistance to traditional over-the-counter preparations (pyrethrins, permethrin) is growing
- Newer treatments, including topical ivermectin, are now available

Introduction

Lice are bloodsucking, wingless insects belonging to the suborder Anoplura. Twelve million cases per year occur in the US alone, and resistance to traditional treatments is increasing. Prescription products (e.g. topical malathion, topical or oral ivermectin) are often needed to treat resistant cases, requiring greater physician involvement.

History

Head lice have infested mankind for thousands of years. Nits have been found on the hair of Egyptian and Peruvian mummies[1].

Epidemiology

Head lice are found worldwide with no strict limitations based upon age, sex, race, or socioeconomic class. Children 3–11 years of age have the highest incidence. The worldwide prevalence in school-aged children was estimated to be 19% in a recent meta-analysis, with prevalences as high as 60% in some countries[1,24]. Infestation with head lice is more frequent in girls, probably due to their tendency to have longer hair as well as to exchange brushes, barrettes, and other hair accessories. Head lice are distinctly uncommon in African-Americans, as head lice in the US are unable to properly position themselves to lay eggs on coarse curly hair[20].

Pathogenesis

The head louse, *Pediculus capitis*, is a highly host-specific insect approximately the size of a sesame seed (2–3 mm; Fig. 84.7). These obligate human parasites feed on the blood of the host approximately every 4–6 hours. The female louse lives for 30 days, during which time she lays between 5 and 10 eggs a day on hair shafts (Fig. 84.8). The



Fig. 84.7 Head louse family. From left to right: female, male, and nymph. *With permission from Taplin D, Meinking TL. Infestations. In: Schachner LA, Hansen RC (eds). Pediatric Dermatology, 4th edn. Edinburgh: Mosby, 2011:1141–80.*

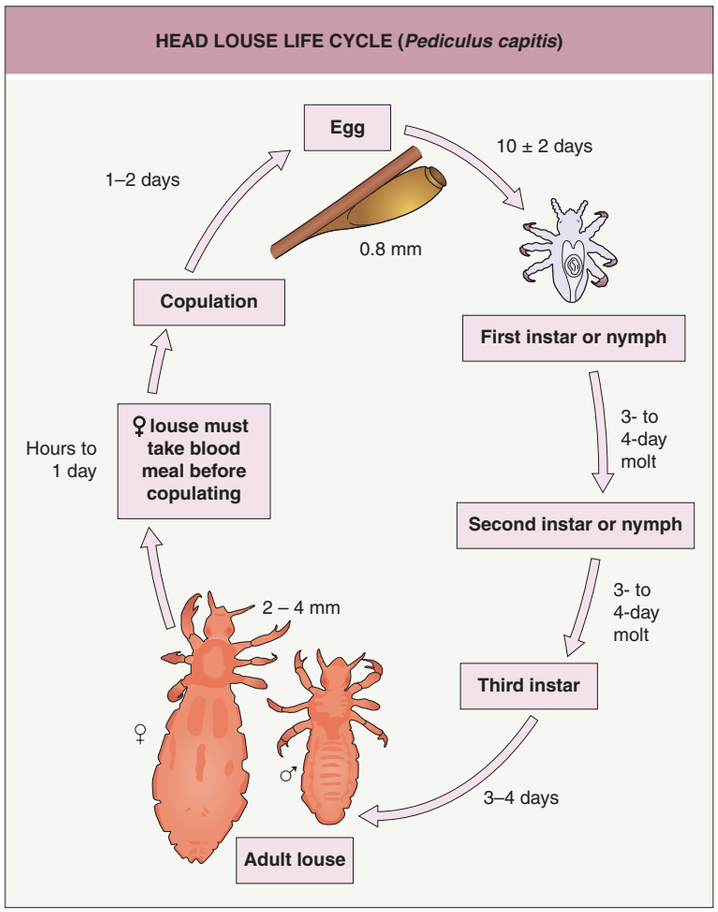


Fig. 84.8 Head louse life cycle (*Pediculus capitis*).

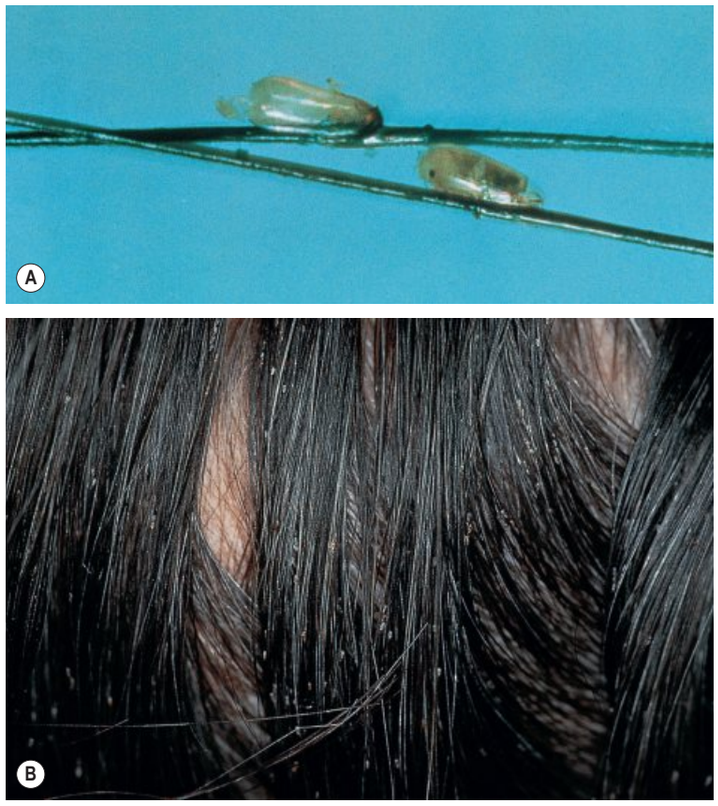


Fig. 84.9 Head lice. A The head louse egg or nit is 0.8 mm in length. **B** Head lice nits on hair. *With permission from Taplin D, Meinking TL. Infestations. In: Schachner LA, Hansen RC (eds). Pediatric Dermatology, 4th edn. Edinburgh: Mosby, 2011:1141–80.*

oval egg capsules (nits) measure 0.8 mm in length and are usually laid close to the scalp for warmth; in general, eggs located within 1 cm of the scalp are unhatched. In warm climates, however, viable nits may be found 15 cm or more from the scalp, especially in the area above the nape of the neck. The nits are cemented to individual hairs by a proteinaceous matrix that closely resembles the amino acid constituents of the human hair shaft itself[25,26]. Head lice rarely live for more than 36 hours away from the host without a blood meal; however, given an appropriate temperature (82–90°F/28–32°C) and level of humidity (70%–90%), nits can survive and hatch after 10 days away from the host. Transmission occurs via direct head-to-head contact or by fomites such as combs, brushes, blow-dryers, hair accessories, bedding, helmets, and other headgear[27].

Clinical Features

Skin findings of head lice infestation are limited to the scalp, behind the ears, and the nape of the neck. The classic symptom of intense pruritus varies among patients. It may take 2–6 weeks following an initial infestation before pruritus is evident, reflecting a delayed immunologic response to components of the lice saliva or excreta. In repeat infestations, pruritus develops within the first 24–48 hours. However, some individuals are asymptomatic "carriers". Although excoriations, erythema, pyoderma, and scaliness of the scalp and posterior neck are common findings, definitive diagnosis is made by the identification of nits and/or adult lice on the scalp hair. Viable eggs are usually tan to brown in color, whereas hatched eggs are clear to white (Fig. 84.9).

Patients occasionally present with a low-grade fever and lymphadenopathy due to a secondary bacterial infection. Head lice can carry *S. aureus* and *Str. pyogenes* on their surfaces and are a common cause of pyoderma of the scalp[1]. There is increasing evidence that head lice may harbor other pathogens such as *Bartonella recurrentis*, *B. quintana*, *Coxiella burnetii*, and *Acinetobacter* spp.; however, it is unclear whether this is associated with disease transmission[28,29].

Pathology

The epidermis and dermis may display nonspecific inflammation.

Differential Diagnosis

Although several dermatoses, such as seborrheic dermatitis and psoriasis, can cause pruritus of the scalp, the finding of nits or adult lice is diagnostic. Nits are more firmly adherent to the hair shaft than dandruff, dried hair products (e.g. sprays, gels) or hair casts, and they must be differentiated from other causes of hair shaft nodules such as piedra (white or black) and trichorrhexis nodosa (see Fig. 77.1).

Treatment

The choice of treatment is based on the efficacy and potential toxicity of different agents, insecticide resistance patterns in the geographic area, and ease of access to prescription remedies[30]. Pediculicides remain the mainstay of therapy (Table 84.2). With all topical preparations (regardless of package instructions), two applications, 1 week apart, are advisable in order to: (1) kill any nits that survived treatment; (2) better defend against the growing resistance to many pediculicides; and (3) reduce the risk of reinfestation by means of fomites. Conditioner should not be applied prior to topical medications, and the hair should not be rewashed for 1–2 days[30].

Unsubstantiated claims of successful treatment with alternative, non-pesticidal products, including petroleum jelly, hair pomade, olive oil, mayonnaise, vegetable oil and mineral oil, persist. Such products may slow the movements of adult lice and allow them to be more easily combed out of the scalp, but these substances are not lethal to lice. Several essential oils (e.g. combinations of tea tree, lavender, and eucalyptus oils) have been reported to be effective as lice therapy,[30,31] and they have been incorporated into various products that are typically found in health food stores. However, additional clinical studies are needed to confirm their safety and efficacy. Oral trimethoprim–sulfamethoxazole may potentially improve the efficacy of topical agents, but its routine use is not recommended[32].

Many school authorities enforce a "no-nit" policy and do not allow children to return to school if they have nits, regardless of whether they

TREATMENTS FOR HEAD LICE				
Treatment	**Group**	**Administration on days 1 and 8**	**Concerns**	**Efficacy & resistance**
Over-the-counter products				
Ivermectin lotion (0.5%)‡	Avermectin	Topical application for 10 minutes to dry hair	Potential skin and eye irritation	Good; single report of resistance to date
Dimethicone liquid gel, lotion, or spray (4%–100%)	Silicone oil	Topical application for 10–15 minutes or overnight	None	Good (varies with different formulations)
Pyrethrins (0.33%) synergized with piperonyl butoxide (4%), various formulations	Natural botanicals	Topical application for 10 minutes to dry hair	Allergic reactions in individuals with sensitivity to chrysanthemums, ragweed and related plants	Poor–fair; resistance common
Permethrin cream rinse or lotion (1%)	Synthetic pyrethroid	Topical application for 10 minutes to clean, dry hair	None	Poor–fair; resistance common
Prescription products (order based upon efficacy, but those ranked as Good are often used as first-line therapies)				
Malathion lotion or gel (0.5%)†	Organophosphate cholinesterase inhibitor	Topical application for 8–12 hours to dry hair (Ovide® and gel products with isopropyl alcohol base are effective at 20 minutes)	Flammable isopropyl alcohol base; burning or stinging at sites of eroded skin	Excellent (in US); resistance noted in Europe and Australia, but to date not in US
Oral ivermectin (available as 3 mg tablets)	Avermectin	Oral dose of 200–400 mcg/kg	Potential risk of CNS toxicity; not recommended for breastfeeding mothers or pregnant women (category C); recent studies suggest safety in children ≥1–2 months of age weighing <33 pounds (15 kg), but use is not well-established in this group	Excellent; single report of resistance to date
Spinosad suspension (0.9%)‡	Bacterial fermentation product	Topical application for 10 minutes to dry hair	Potential skin and eye irritation	Good; no resistance noted to date
Abametapir lotion (0.74%)‡	Metalloproteinase inhibitor	Topical application for 10 minutes to dry hair	Potential skin irritation	Good; no resistance noted to date
Benzyl alcohol lotion (5%)‡	Alcohol	Topical application for 10 minutes to dry hair	Potential skin irritation	Good; no resistance noted to date
Permethrin cream (5%)*	Synthetic pyrethroid	Topical overnight application to clean, dry hair	Allergic contact dermatitis in individuals with sensitivity to formaldehyde	Poor–fair; resistance common
Lindane shampoo (1%)	Organochlorine	Topical application for 4 minutes to clean, dry hair, then add water to lather and rinse	Potential CNS toxicity; not recommended for infants, children, breastfeeding mothers or pregnant women (category C)	Poor; resistance common
Carbaryl shampoo (0.5%)	Carbamate cholinesterase inhibitor	Topical application for 8–12 hours	Possible carcinogen	Poor–fair; resistance common (not approved in the US)

*Approved for individuals ≥2 months of age; considered safe during pregnancy.
†Approved for individuals ≥6 years of age; considered safe during pregnancy.
‡Approved for individuals ≥6 months of age; spinosad cream rinse, abametapir lotion, and benzyl alcohol lotion are considered safe during pregnancy.

Table 84.2 Treatments for head lice. In general, treatments should be given on two separate occasions, 1 week apart. However, the FDA-approved regimen for treatment of head lice with 0.5% ivermectin solution and abametapir 0.74% lotion is a single application. Airallé® is an FDA-cleared medical device that uses hot air to treat head lice via dehydration of their eggs and, to a lesser degree, hatched lice. Isopropyl myristate 50% in cyclomethicone solution (Resultz®) was FDA-approved as an over-the-counter treatment for head lice in 2017; it is available in Canada and Europe but has not yet been marketed in the US. Benzyl benzoate 10%–25% lotion or emulsion (over-the counter; not directly sold in US pharmacies) may be used for head lice, although there are few investigational studies; it is applied to the hair for 12–24 hours on days 1 and 8.

are viable or not. As a result, the tedious task of physically removing all nits via combs with closely spaced metal teeth is required. Currently there are no products that easily aid in nit removal[33]. Flexibility and understanding by school boards would be more welcomed than a straight adherence to a "no-nit" policy.

Pyrethrins

In the US, pyrethrins, 1% permethrin, and 0.5% ivermectin are FDA-approved, OTC topical pediculicides. Pyrethrin insecticides are derived from a natural extract of flower heads of *Chrysanthemum cinerariaefolium*. Patients allergic to chrysanthemums, ragweed, or related plants have experienced wheezing and dyspnea with use of the crude extract. Pyrethrins are presently formulated into lotions, shampoos, foam mousse, and cream rinses. The addition of piperonyl butoxide slows the biotransformation of pyrethrins by partially inhibiting the insects' cytochrome P450 enzymes, thereby initially improving effectiveness. Pyrethrin products are applied to the head for 10 minutes and then rinsed off. Due to growing resistance to this insecticide, treatment failures are now commonplace[1].

Permethrin

Permethrin is the only synthetic pyrethroid that is used worldwide for head lice. The OTC 1% permethrin cream rinses and lotions are applied for 10 minutes; however, an 8–12-hour application of the 5% cream used for scabies is an alternative therapy. Unfortunately, resistance to even the higher-concentration products has developed in head lice and other insects. Point mutations in the gene encoding the α-subunit of the insects' voltage-sensitive sodium channels commonly lead to a reduction

in the binding affinity of permethrin and other pyrethroids. However, some studies have found >85%–90% success rates for treatment with permethrin in children whose lice had these mutations, suggesting that other factors play a role in pyrethroid resistance[34].

Malathion

The prescription organophosphate malathion is a cholinesterase inhibitor. Although the recommended application time for topical malathion is 8 to 12 hours, with repeated treatment in 7 days if live lice are present, high efficacy has also been reported when the duration of application is reduced to 20 minutes[35]. The existing US product (Ovide® lotion) contains 78% isopropyl alcohol, which enhances its effectiveness but raises the issue of flammability. Some resistance to malathion products has been reported, especially in Europe and Australia[36].

Ivermectin

A 0.5% *topical* ivermectin preparation (Sklice® lotion) was FDA-approved in 2012 for the treatment of head lice in patients ≥6 months of age and is now available OTC. Topical ivermectin has been shown to kill permethrin-resistant head lice,[37] and the viability of lice hatched from treated eggs is severely compromised[38]. In two randomized controlled studies (total n = 765), 74% of patients treated with a single 10-minute application of 0.5% ivermectin lotion to dry hair were lice-free after 15 days, compared to 18% of those who received a vehicle control ($p<0.001$)[39].

Oral ivermectin represents another therapeutic option for resistant head lice infestations. In a large multicenter clinical trial, 95% of patients with head lice that previously failed topical therapy (pyrethrin or malathion) who received 400 mcg/kg of ivermectin on days 1 and 8 were lice-free on day 15, compared to 85% of those treated with two applications of topical malathion[40]. In several other controlled studies, >90% of children treated with 200 mcg/kg of ivermectin on days 1 and 8 were lice-free at 2-week follow-up[41]. Because lice are only exposed to the drug while feeding, oral ivermectin has no ovicidal activity and (unlike topical ivermectin) two treatments are required. Of note, clinical ivermectin resistance associated with a mutation in the ivermectin target site was documented in head lice from two children from rural Senegal following a second oral ivermectin treatment[42].

Dimethicone

Dimethicone is a silicone oil that is used as an emollient in skin care products. Dimethicone-containing products may suffocate lice or block their ability to excrete water and result in death due to osmotic stress[43]. In several randomized controlled studies, 10-minute to overnight application of 4%–100% dimethicone liquid gel, lotion, or spray (e.g. LiceMD®, Hedrin®, NYDA®) on day 1 ± day 8 resulted in 70%–97% of patients being lice-free on day 14, representing significantly higher efficacy than treatment with 1% permethrin cream rinse or 0.5% malathion liquid in some reports[44,45].

Spinosad

In 2011, 0.9% spinosad topical suspension (Natroba™) was approved by the FDA as a therapy for head lice, and it is currently indicated for children ≥6 months of age. Spinosad is a fermentation product of the bacterium *Saccharopolyspora spinosa* that induces muscle spasms and paralysis in lice when applied topically. A clinical trial (n = 1038) showed that 0.9% spinosad suspension left on for 10 minutes without nit combing on day 1 ± day 7 had superior efficacy to 1% permethrin cream with nit combing (~86% vs ~44%; $p<0.001$), and spinosad therapy led to no significant adverse effects[46].

Abametapir

In 2020, 0.74% abametapir lotion (Xeglyze™) was FDA-approved for the treatment of head lice in children ≥6 months of age. This metalloproteinase inhibitor targets metalloproteinases critical to the development of lice and their eggs. In two clinical trials (n = 704), 86% of patients treated with a single 10-minute application of 0.74% abametapir lotion to dry hair were lice-free through day 14, compared to 63% of those treated with the vehicle ($p<0.001$)[47].

Benzyl alcohol

In 2009, the FDA approved 5% benzyl alcohol lotion (Ulesfia®) as a prescription treatment for head lice in children ≥6 months of age; benzyl alcohol is thought to act via asphyxiation by preventing lice from closing their respiratory spiracles, which become blocked by the lotion; it is not ovicidal. In two randomized, double-blind, controlled clinical studies (total n = 250), 75% of patients were lice-free 14 days after the last of two 10-minute applications of benzyl alcohol (administered 1 week apart), compared to 5%–25% of those treated with a vehicle control[48]. Ulesfia has been discontinued; however generic benzyl alcohol may be commercially available.

Lindane

Lindane, a chlorinated hydrocarbon, is available as a 1% prescription shampoo that is applied for 4 minutes. Because of possible CNS side effects, especially after prolonged applications beyond the recommended time interval, the FDA has issued a "black box" warning that lindane is reserved for patients who fail to respond to other approved lice therapies. However, resistance to lindane is commonly observed.

Carbaryl

Like malathion, carbaryl is a cholinesterase inhibitor. It is available in a 0.5% lotion and shampoo in the UK and other countries. This product is not presently available in the US. In comparison to malathion, carbaryl is potentially more toxic to patients, while being less lethal to lice.

CRAB LICE

Synonyms: ■ *Pthirus pubis* or *Phthirus pubis* ■ Pubic lice ■ Pediculosis pubis ■ "Crabs"

Key features

- More properly designated "crab lice" (rather than "pubic lice") because infestations may involve other hair-bearing sites such as the beard, eyelashes, axillae, and perianal region
- Transmitted by sexual or close contact and to a lesser extent via contaminated clothing, towels, and bedding

Introduction

Infestation with *Pthirus pubis*, the crab louse, causes discomfort, pruritus, and embarrassment and may coexist with other sexually transmitted infections.

History

The parasitic relationship between humans and crab lice dates back to prehistoric times.

Epidemiology

The incidence rate may be slightly higher in men, probably because they have a greater amount of coarse body hair. Infestations with crab lice can be found in all socioeconomic and ethnic groups, although those of Asian descent or with minimal pubic hair are rarely affected. The incidence of crab lice has decreased with current cultural practices of hair removal from the pubic region[49]. Infestation is most frequently observed in those 15 to 40 years of age, correlating with increased promiscuous sexual activity. The highest prevalence is in men who have sex with men. Although infestation is often considered a sexually transmitted disease, individuals who have had no sexual exposures are occasionally infested via fomite transmission from contaminated clothing, towels, or bedding[1].

Pathogenesis

Crab lice, *Pthirus pubis*, are approximately 1 mm in length and resemble tiny crabs, with a wider, shorter body than head lice (Fig. 84.10). Crab lice eggs, which are found attached to human hairs, are viable for up to 10 days; the adult crab louse can live for at least 36 hours away from the host. Crab lice have serrated edges on their first claw that enable them to ambulate on the entire body surface. Thus, infestation occurs not only in pubic hair, but also in hair of the scalp, eyebrows, eyelashes,



Fig. 84.10 Adult crab louse. Respiratory spiracles and circulatory system are easily seen (45×). *Courtesy Tony Burns, MD.*

moustache, beard, axillae, and perianal area. Indeed, 60% of patients with pubic lice are infested in at least two hair-bearing sites. When the pubic area is shaved or treated, surviving crab lice can travel to other hairy areas of the body, including the scalp.

Clinical Features

Crab lice infestations typically present with pruritus in the pubic region. Crab lice cling to the base of hairs (Fig. 84.11A) and can be brown to skin-colored or mimic hemorrhagic crusts. Other findings may include nits at the base of hair shafts, erythema around hair follicles, excoriations, evidence of a secondary bacterial infection, and lymphadenopathy. When the eyelashes are affected (Fig. 84.11B), feces that accumulate can resemble flecks of mascara. Macula caerulea are asymptomatic, slate-gray to bluish, irregularly shaped macules that measure 0.5–1 cm in diameter and favor the trunk and thighs. These lesions, which typically develop in chronic crab lice infestations, are thought to result from the breakdown of bilirubin to biliverdin by enzymes in louse saliva.

In individuals with crab lice, the possibility of additional sexually transmitted infections should be considered and the original source of the infestation sought in order to reduce the risk of recurrence.

Pathology

Crab lice cause nonspecific inflammatory changes in the epidermis and dermis. Because lice live on the surface of the skin, they are not evident histologically.

Differential Diagnosis

The identification of crab lice and/or their nits is diagnostic (see Fig. 84.10). Skin diseases associated with pruritus that may be considered in the differential diagnosis include other infestations (e.g. scabies) and arthropod bites. Nits on pubic or axillary hairs must be distinguished from white piedra and trichomycosis pubis or axillaris.

Treatment

Topical insecticides are the standard therapy for crab lice. Sexual partners should be treated simultaneously. Most commonly, permethrin (1% or 5%) and synergized pyrethrin products are utilized (Table 84.3). As with head lice, the topical insecticide should be applied on two occasions, 1 week apart, to ensure complete eradication of hatched eggs. Moreover, all hairy areas of the body must be inspected for the existence of lice and treated if there is a possibility of infestation. A single application of topical products to only pubic hair may limit success rates to as low as 55%[50].



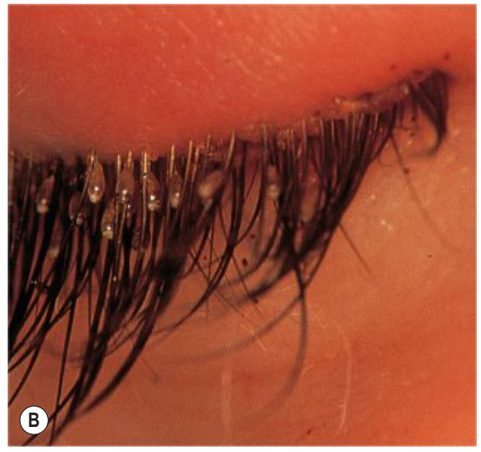


Fig. 84.11 Crab lice. **A** Both adult crab lice and nits are evident on pubic hairs. **B** Crab lice nits and feces on the eyelashes. *A, Courtesy Louis A. Fragola, Jr, MD; B, With permission from Taplin D, Meinking TL. Infestations. In: Schachner LA, Hansen RC (eds). Pediatric Dermatology, 4th edn. Edinburgh: Mosby, 2011:1141–80.*

Currently, the safest and most effective topical treatment is 5% permethrin cream applied generously overnight to all potentially infested hairy areas, and then repeated 1 week later[40]. Lindane has poor efficacy and higher toxicity, and the shampoo is not approved for extensive body application. Oral ivermectin on days 1 and 8 can be used for patients with perianal or eyelash involvement or when topical therapy is unsuccessful (see Table 84.3)[30,51].

BODY LICE

Synonyms: ■ Pediculosis corporis ■ Clothing lice

Key features

- An infestation of humans and their clothing, body lice most commonly affect the homeless, refugees, and victims of war and natural disasters
- Body lice do not live or lay eggs on people but in their clothing
- Infections transmitted by body lice include epidemic typhus, trench fever, and relapsing fever

Introduction

Body lice infestations are associated with overcrowding, poor hygiene, poverty, war, and natural disasters. These insects are the primary vectors for diseases caused by *Rickettsia*, *Borrelia* and *Bartonella* spp. (see Chs. 74 & 76). Body lice resemble head lice but are larger in size.

TREATMENTS FOR CRAB LICE			
Treatment	**Administration on days 1 and 8**	**Concerns**	**Efficacy**
Permethrin (1%) cream rinse or synergized pyrethrin shampoo*	Topical application for 10 minutes to clean, dry hair	None	Fair
Permethrin cream (5%)	Topical application for 8–12 hours	Allergic contact dermatitis in individuals with sensitivity to formaldehyde	Good
Lindane shampoo (1%)	Topical application for 4 minutes to dry hair, then add water to lather and rinse	Potential CNS toxicity; not recommended for infants, children, breastfeeding mothers or pregnant women (category C)	Poor
Ivermectin	0.5%–1% lotion/cream topically overnight	Potential skin and eye irritation	Not established
	Oral dose of 250 mcg/kg (available as 3 mg tablets)	Potential CNS toxicity; not recommended for breastfeeding mothers or pregnant women (category C)†	Excellent

*Over-the-counter products.
†Recent studies suggest safety for children ≥1–2 months of age weighing <33 pounds (15 kg), but use is not well-established in this group.

Table 84.3 Treatments for crab lice. All crab lice treatments should be given on two separate occasions, 1 week apart, i.e. days 1 and 8. Benzyl benzoate 10%–25% lotion or emulsion (over-the counter; not directly sold in US pharmacies) may be used for crab lice, although there are few investigational studies; it is applied three times over a 24-hour period without an intervening bath.

Epidemiology

Body lice are found worldwide. Increased prevalence rates of body lice are tied to poor hygiene, poverty, and homelessness. There are no racial, age, or sex restrictions.

Pathogenesis

Pediculosis corporis is caused by an infestation of humans and their clothing by *Pediculus humanus* var. *corporis*. In addition to exposure to conditions conducive to obtaining body lice, infestation requires an inability to wash and change clothes.

Several important human diseases are transmitted by the body louse. These include epidemic typhus (*Rickettsia prowazekii*) and relapsing fever (*Borrelia recurrentis*) as well as several diseases caused by *Bartonella quintana* – trench fever, bacillary angiomatosis, and endocarditis[30,52]. Whether this louse has a role in transmission of *Acinetobacter baumannii* or *Yersinia pestis* to humans remains to be determined[52]. Transmission of microorganisms from body lice to humans occurs not from louse bites, but rather from inoculation of louse feces into the skin via scratching or by inhalation of dry, powdery louse feces from infested bedding or clothing.

Clinical Features

P. humanus var. *corporis* measures between 2.5 and 4.0 mm in length. Unlike head and crab lice, the nits and lice are rarely found on the patients' skin, save for feeding, as they reside primarily on the clothing of their hosts. This infestation leads to severe pruritus. The back, neck, shoulders, and waist areas are commonly involved. Clinical findings include pinpoint red macules, small erythematous papules, crusts and excoriations, occasionally complicated by impetigo and lymphadenopathy. Blood and fecal pellets often stain clothing and bedding. On inspection, nits and adult lice are found along clothing seams that are in contact with the neck, axillae, and waistline (Fig. 84.12).

Pathology

The epidermis has minimal spongiosis with nonspecific infiltrates of eosinophils and neutrophils in the dermis.

Differential Diagnosis

Other causes of widespread pruritus and excoriations that may be considered in the differential diagnosis of body lice include systemic diseases (e.g. hepatic or renal impairment), drug reactions, atopic dermatitis, contact dermatitis (irritant or allergic), and other infestations (e.g. scabies).

Treatment

Preferably, the clothing and bedding of infested individuals should be discarded in tightly sealed, plastic biohazard bags and incinerated.



Fig. 84.12 Body lice eggs in the seams of clothing.

Only if the latter is not possible should disinfection be attempted. This involves fumigating the clothing or laundering it using hot water (temperature of ≥130°F/55°C), followed by machine drying with high heat. Hot ironing of the seams of upholstered furniture can also be performed, and exposure to untreated infested items should be strictly avoided for 2 weeks. Topical insecticide regimens similar to those used for scabies can eradicate concurrent scabies or crab lice infestations as well as kill any body lice adherent to hairs.

Mass delousing in crowded, large populations due to natural disaster, war, or famine is accomplished by dusting powders. These powders may contain DDT, malathion, dieldrin, lindane, or permethrin.

TUNGIASIS

Synonyms: ■ *Tunga penetrans*: chigoe flea, jigger flea, burrowing flea, sand flea ■ Pique ■ Nigua ■ Pio and bicho de pie

Key features

- This infestation is caused by the burrowing flea, *Tunga penetrans*
- It is endemic in the Caribbean islands and parts of Central and South America, Africa, Pakistan, and India
- The female flea burrows into the skin and then enlarges to create a nodule with a central punctum through which eggs are ejected

Introduction

The burrowing flea, *Tunga penetrans*, is the causative agent of tungiasis. A female flea burrows into the upper dermis and enlarges to approximately 1 cm in diameter, creating a nodule with a central punctum through which eggs (fertilized or unfertilized) are eventually discharged.



Fig. 84.13 Tungiasis in a child.

History

Tungiasis was first reported in crew members on Christopher Columbus' original trip to the New World in 1492.

Epidemiology

Tungiasis can occur in anyone exposed to the flea, regardless of sex, race, or age. Areas of high incidence include the Caribbean islands, parts of Central and South America, and sub-Saharan Africa. In endemic areas, risk factors include walking barefoot, wearing open-toed shoes, and living in homes with dirt or unclean floors[30].

Pathogenesis

Tunga penetrans is a wingless flea that is 1 mm in size and usually lives in warm, dry soil. Both sexes of this flea require an occasional blood meal from a warm-blooded animal for maturation[53]. Due to the fleas' limited jumping ability, the most common location for bites is the foot. Female fleas, rather than simply obtaining a blood meal, burrow headfirst into mammalian skin. They subsequently undergo marked abdominal hypertrophy, growing to 1 cm in diameter. The flea protrudes its rear cone through a central punctum that is always maintained; whether or not fertilization occurs via mating of the embedded female flea with a free-roaming male flea, over a hundred eggs are discharged within 3 weeks[53]. After expelling the eggs, the female dies and its remains are eventually sloughed from the skin.

Clinical Features

Bites of immature fleas cause no symptoms; however, burrowing of the female flea into the skin can cause significant clinical morbidity. The burrowing is initially asymptomatic, but varying degrees of pain or pruritus usually develop. The first sign of disease is a small black dot, which evolves into a pearl-like whitish papule and then a larger nodule that is said to resemble a watch glass, with a clearly demarcated white halo surrounding the black central punctum. A peripheral zone of erythema is frequently evident. When the flea dies, a black crust covers the involuting lesion. The Fortaleza classification scheme divides tungiasis into stages based upon symptoms, lesion size and the clinical appearance[53].

The most common site of disease is the periungual area of the toes, followed by the soles and toe webs (Fig. 84.13). Ulceration, secondary infection, and lymphangitis can occur; less frequent complications include tetanus, gangrene, and amputation of a digit[53]. Over half of periungual infections lead to deformation or loss of the nail, and heavy infestations produce substantial morbidity in resource-poor communities within endemic areas[54,55].

Pathology

A nonspecific inflammatory infiltrate surrounds the flea within the dermis.

Differential Diagnosis

The differential diagnosis may include myiasis, tick bite reactions, cercarial dermatitis, pyoderma, plantar warts, verruga peruana, and squamous cell carcinoma.

Treatment

Spontaneous recovery does occur; however, most clinicians and patients prefer to treat the infestation by removal of the female flea. In an early infestation, a sterile needle can be used to pry the insect from the skin. Covering the punctum with dimethicone, liquid paraffin, or a mixture of neem and coconut oils may prevent flea growth and expedite removal[54–56]. If treatment is delayed, curettage, electrodesiccation, or surgical excision may be required. Careful cleaning of the cystic cavity speeds clinical resolution, and antibiotic therapy may be needed for secondary infections. Tetanus prophylaxis should be strongly considered. Topical application of ivermectin, metrifonate, or thiabendazole may lead to more rapid demise of embedded fleas, but this has limited clinical benefit[54,55]. In a randomized controlled study, oral ivermectin was not found to have significant efficacy compared to placebo.

Preventative measures include wearing closed shoes or boots and avoiding ground contact in endemic areas. A plant-based insect repellent containing coconut and jojoba oils has also been shown to prevent sand flea infestation[55].

CUTANEOUS MYIASIS

Synonym: ■ Names for the various flies associated with this entity include human botflies, screwworms, blowflies, fleshflies, and tumbu flies

Key features

- Infestation of the skin by fly larvae (maggots)
- The larvae inhabit cutaneous wounds (wound myiasis) or burrow into the dermis causing boil-like lesions (furuncular myiasis)
- Although they usually cause minimal morbidity, larvae can cause problems when they involve the nasal cavity and sinuses

Introduction

Cutaneous myiasis is an infestation of the skin by developing larvae (maggots) of a variety of fly species within the arthropod order Diptera. The two main clinical types are wound and furuncular myiasis.

History

Maggots were central to Francesco Redi's experiment rejecting the theory of spontaneous generation. Wound debridement by maggots has been used for centuries, including during the American Civil War and by Napoleon's troops.

Epidemiology

Myiasis is a worldwide infestation with seasonal variation whose prevalence is related to latitude and the life cycle of the various species of flies. Its incidence is higher in the tropics and subtropics of Africa and the Americas. The flies responsible prefer a warm and humid environment, thus they are restricted to the summer months in temperate zones, while living year-round in the tropics.

Pathogenesis

Myiasis is the infestation of living humans (or other vertebrates) with dipterous larvae that feed on the host's tissues, liquid body substances, or ingested food. Myiasis can be caused by several species of arthropods

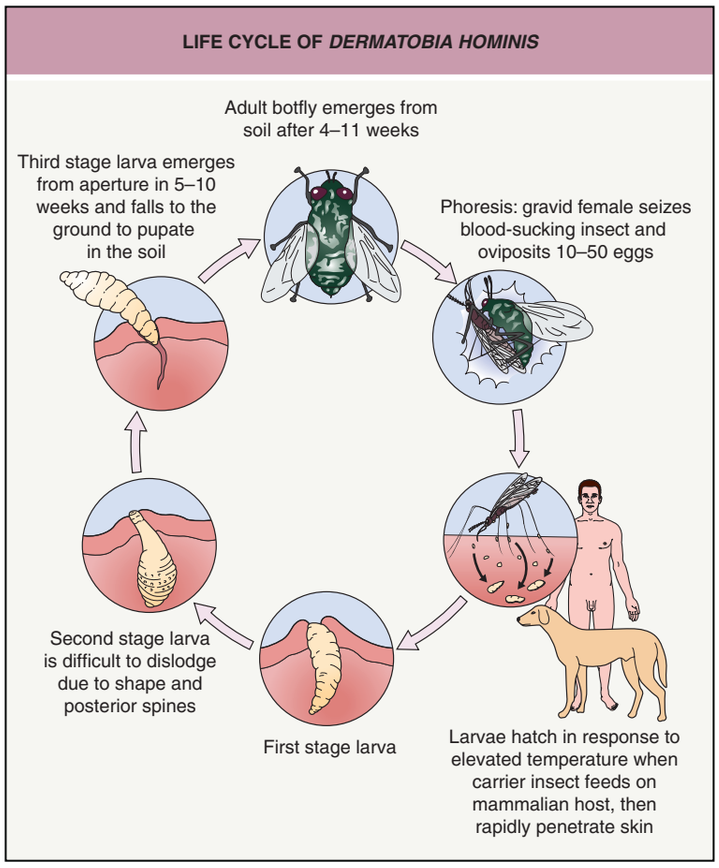


Fig. 84.14 Life cycle of *Dermatobia hominis* in cutaneous myiasis.

within the order Diptera, the two-winged true fly. The causative flies can be classified by: (1) taxonomic family; and (2) differences in pathogenic behavior of the fly species.

Worldwide, the most common flies that cause human infestation are *Dermatobia hominis* (human botfly) and *Cordylobia anthropophaga* (tumbu fly). The routes of transmission of fly larvae to human hosts differ among the fly species. For example, *D. hominis* lays its eggs on mosquitoes, which in turn deposit them on a warm-blooded mammal (Fig. 84.14). *C. anthropophaga* deposits its eggs on moist clothing and soiled blankets and in sand. The larva can live 15 days without feeding, but once it makes contact with a host, it penetrates the skin, which initiates further maturation. In endemic areas, people often iron their clothes after hanging them out to dry to kill the fly eggs. In wound myiasis, an open wound or orifice attracts flies to deposit their eggs. Any body area can be infested, and the most serious sequelae occur when the nasal cavity, sinuses, or scalp are involved. The incubation period for larvae to mature into adulthood depends on the fly and can range from 1 to 12 weeks.

Clinical Features

Furuncular cutaneous myiasis, which is caused by the human botfly and tumbu fly, causes boil-like lesions. Whereas myiasis from the tumbu fly typically occurs on the trunk, thighs and buttocks, botfly lesions are usually on exposed areas of the body, including the scalp, face, forearms and legs. A pruritic papule develops within 24 hours of penetration, enlarging to a 1–3 cm nodule with a 2–3 mm central punctum (Fig. 84.15A–C). These lesions can be painful or tender and may become crusted and purulent; there may be a sensation of movement.

In *wound* myiasis, the larvae are deposited in a suppurating wound or on decomposing flesh. *Cochliomyia hominivorax*, a screwworm, is the most common cause of this form of myiasis in the Americas, while *Chrysomya bezziana* is typically seen in Africa, Australia, and Asia. The diagnosis is obvious when larvae are visible on the surface of the wound (Fig. 84.15D) and more difficult when they have burrowed beneath the surface.

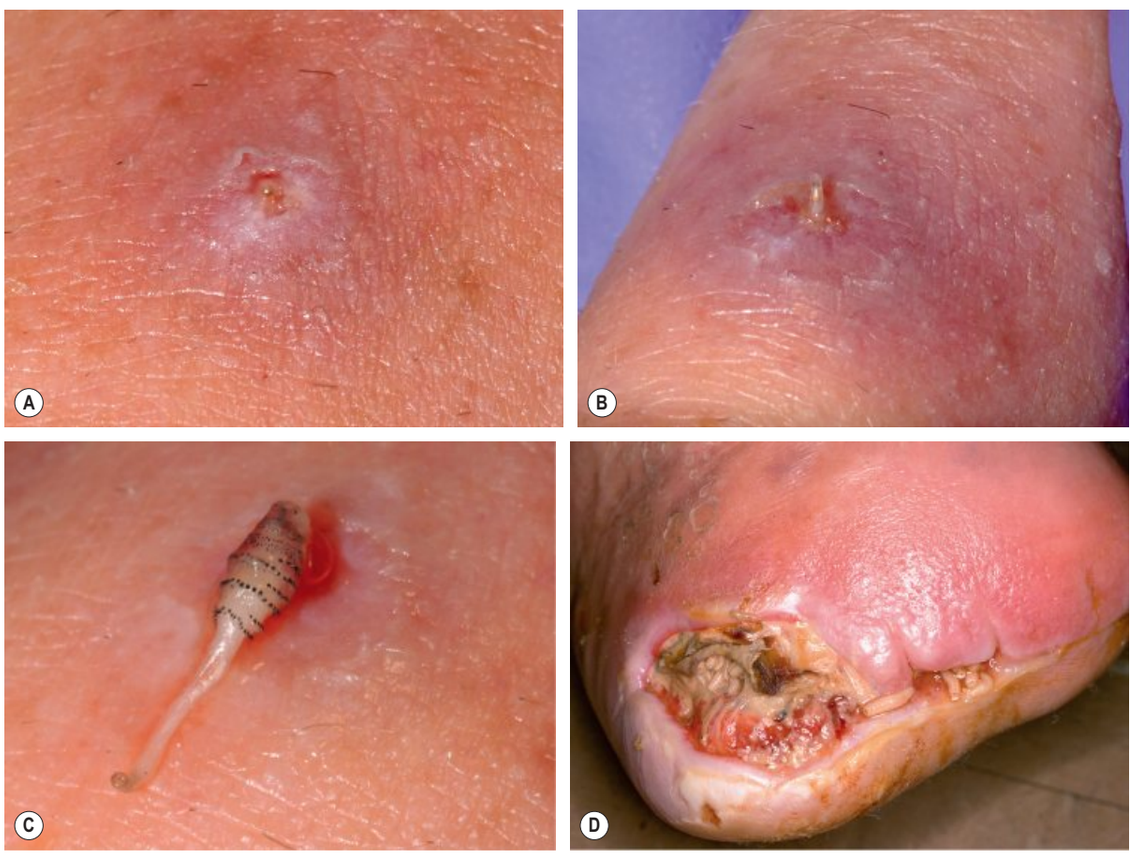


Fig. 84.15 Cutaneous myiasis. **A–C** Furuncular myiasis on the forearm presenting as a papulonodule with a central punctum (**A**) through which the larva's posterior end, which contains respiratory spiracles, may protrude (**B**). Note the characteristic appearance of the extracted botfly larva, with parallel rows of dark spines and hooks (**C**). **D** Wound myiasis in an amputation stump. *A–C, Courtesy Edward W. Cowen, MD; D, Courtesy Louis A. Fragola, Jr, MD.*

Creeping (or migratory) cutaneous myiasis may be caused by *Hypoderma bovis* if there is exposure to infested cattle, or by *Gasterophilus intestinalis* in those who work with horses. This form of myiasis resembles cutaneous larva migrans, but the fly larvae migrate more slowly, persist for longer (often months), and are larger than helminth larvae.

Myiasis is a self-limiting infestation with minimal morbidity in the vast majority of cases. The major reasons for treatment are reduction of pain, cosmesis, and psychological relief. However, larvae such as *C. hominivorax* can infest around orifices of the head and may burrow into brain tissue.

Pathology

Histologically, an inflammatory response occurs in stages in which lymphocytes, giant cells, neutrophils, eosinophils, mast cells, and plasma cells participate. The larvae can be seen in cross-section.

Differential Diagnosis

Furuncular cutaneous myiasis should be differentiated from a ruptured epidermoid cyst, an abscess, furunculosis, a foreign body reaction, onchocerciasis, tungiasis, an exaggerated arthropod bite reaction, and lymphadenopathy.

Treatment

The larva in furuncular cutaneous myiasis should not be forcibly removed through the central punctum because its tapered shape with rows of spines and hooks prevents simple extrusion (see Fig. 84.15C). Surgical debridement under local anesthesia is curative, although a foreign body reaction can occur if parts of the larva remain[56]. Occlusion/suffocation approaches involve placement of petroleum jelly, liquid paraffin, beeswax, nail polish, heavy oil, lard, or strips of bacon over the central punctum[56,57]. Such blockage forces the aerobic larva to surface for air over the course of several hours – at which time, forceps aid in their capture. Alternatively, ethyl chloride sprays, liquid nitrogen, chloroform in vegetable oil, or insecticides have been used alone or in combination. In addition, the larva can be forced to the surface by injecting lidocaine into the base of the tissue cavity or by using a suction-based venom extractor[57,58]. After removal of larvae, antiseptic dressings are indicated, as are antibiotics if secondary infection is present.

Wound myiasis requires debridement with irrigation to eliminate the larvae from the wound, or surgical removal. If burrowing has occurred, the method of extraction is identical to that for furuncular cutaneous myiasis.

An alternative treatment for all types of myiasis is oral ivermectin, which has proven especially helpful with oral and orbital involvement[56]. Surgical removal is not required unless requested by the patient, as the larvae are naturally sloughed within 2 weeks. Myiasis can be a portal of entry for *Clostridium tetani*, and vaccination of affected individuals should be considered.

Preventative Measures

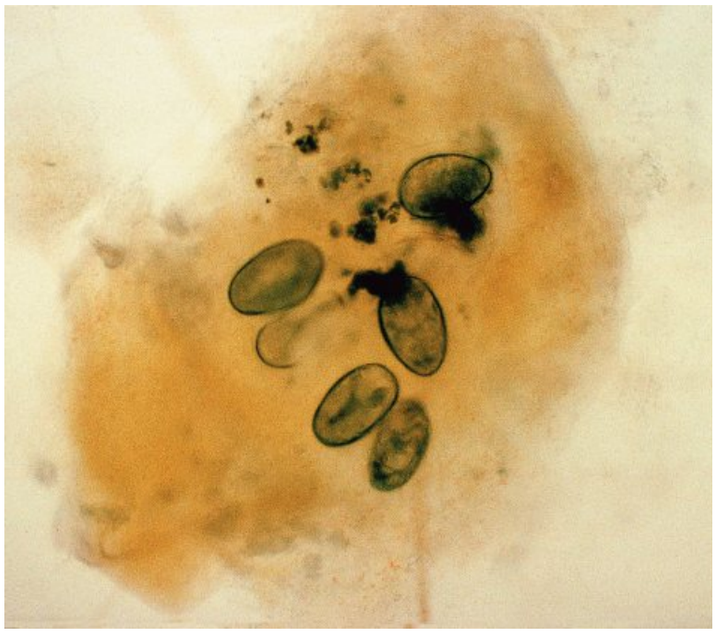
In endemic areas, it is important to avoid activities that increase the risk of myiasis, such as wearing damp clothing or resting in sandy areas. The use of insect repellents (including on the scalp) can be useful in preventing mosquitoes that are harboring the larvae of the human botfly from depositing their living cargo.

Additional figures and tables on Diagnostic criteria for scabies, and Inpatient management of classic scabies and crusted scabies, available in our eBook (see inside front cover for access code).

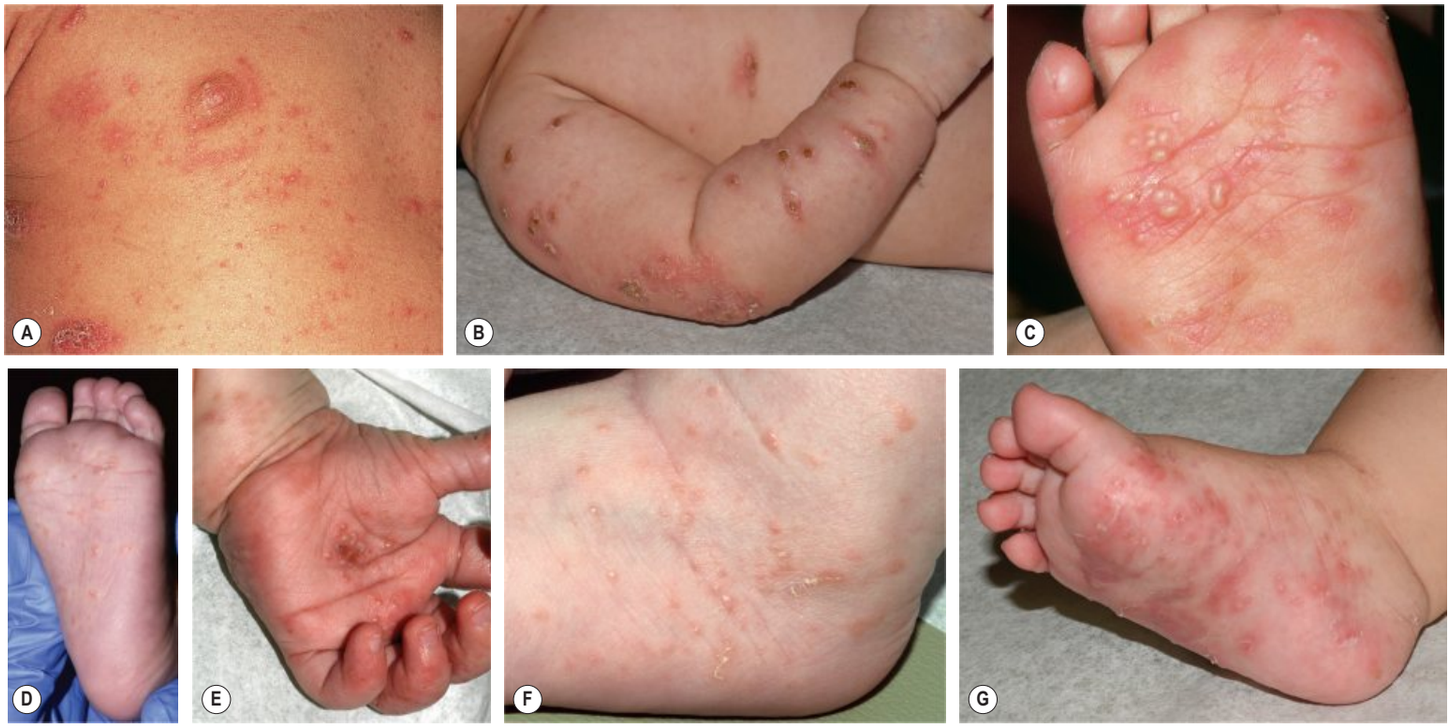
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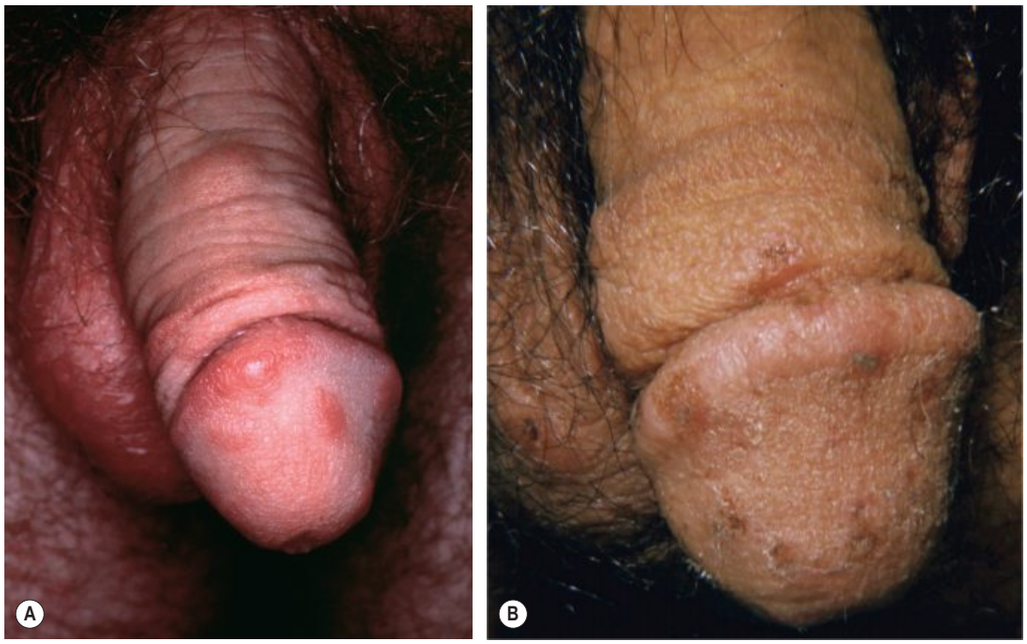
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eFig. 84.1 Direct microscopy of a scraping from a patient with scabies. Note the eggs and scybala.



eFig. 84.2 Scabies in infants. A, B Erythematous papules, plaques, burrows, and areas of crusting. **C–G** Acral vesiculopustules and burrows. *B, D–F, Courtesy Julie V. Schaffer, MD.*



eFig. 84.3 Scabies. A, B Penile involvement with erythematous papules and nodules. *A, Courtesy Robert Hartman, MD; B, Courtesy Eugene Mirrer, MD.*





eFig. 84.4 Crusted scabies. Thick scale of the ear and scalp (**A**) and hands (**B**). Note the subungual hyperkeratosis. *A, Courtesy M. Joyce Rico, MD.*

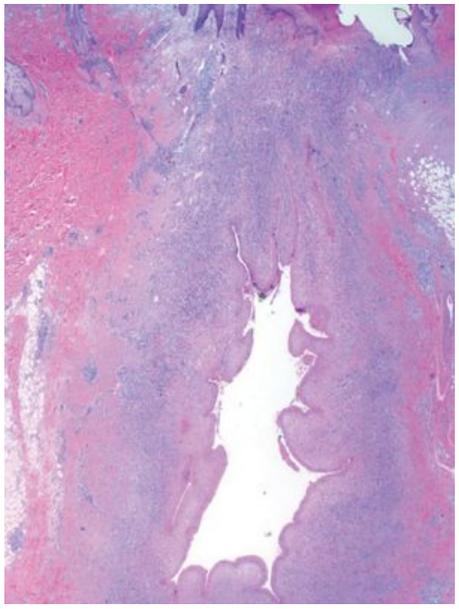




eFig. 84.5 Crusted scabies. Keratotic plaques in the periumbilical area (**A**) and on the scalp and forehead (**B**). *A, Courtesy Regional Dermatology Training Centre, Moshi, Tanzania; B, Courtesy, Jeffrey Callen, MD.*



eFig. 84.6 Crab lice. Note the erythema around hair follicles and lice mimicking hemorrhagic crusts. *Courtesy Kalman Watsky, MD.*



eFig. 84.7 Myiasis – histopathologic features. Large cavity within the deep dermis and subcutis that contains the cross-section of the larva and is surrounded by a heavy, mixed inflammatory infiltrate. In addition, there is a superficial and deep lymphocytic infiltrate within the dermis. *Courtesy Helmut Kerl, MD.*

SUMMARY OF THE 2020 INTERNATIONAL ALLIANCE FOR THE CONTROL OF SCABIES CONSENSUS CRITERIA FOR THE DIAGNOSIS OF SCABIES
A. Confirmed scabies
At least one of: A1: Mites, eggs or feces on light microscopy of skin samples A2: Mites, eggs or feces visualized on an individual using a high-powered imaging device A3: Mite visualized on an individual using dermoscopy
B. Clinical scabies
At least one of: B1: Scabies burrows B2: Typical lesions affecting male genitalia B3: Typical lesions in a typical distribution and two history features
C. Suspected scabies
One of: C1: Typical lesions in a typical distribution and one history feature C2: Atypical lesions or atypical distribution and two history features
History features
H1: Itch H2: Positive contact history
Diagnosis can be made at one of the three levels (A, B, or C). A diagnosis of clinical or suspected scabies should only be made if other differential diagnoses are considered less likely than scabies.

eTable 84.1 Summary of the 2020 International Alliance for the Control of Scabies Consensus Criteria for the Diagnosis of Scabies. *From Engelman D, Yoshizumi J, Hay RJ, et al. The 2020 International Alliance for the Control of Scabies Consensus Criteria for the Diagnosis of Scabies. Br J Dermatol 2020;183:808-20.*

INPATIENT MANAGEMENT OF CLASSIC SCABIES & CRUSTED SCABIES

Background

- Both classic and crusted scabies present challenges in management and infection control in the institutional setting
- In individuals with crusted scabies, live mites can be recovered from the debris in the environment (e.g. bedding, clothes)
- Mites typically live no more than 3 days off of human hosts; however, in crusted scabies they can live up to 7 days on sloughed skin
- Crusted scabies is most commonly found in the elderly and HIV+ or other immunosuppressed populations

Management of classic scabies

- Debrief the medical team immediately – all teams following the patient should be notified
- Initiate contact precautions, which can be discontinued 24 hours after beginning treatment
- Initiate medical treatment:
  - Head to toe permethrin cream once then repeated again at 7 or 14 days **OR**
  - Ivermectin 0.2 mg/kg/dose (14 mg for 70 kg individual) once then repeated again at 7 or 14 days
- Machine wash and dry all bedding/clothes items using hot water and high heat cycles (temperatures in excess of 50 degrees C for 10 minutes will kill mites and eggs)
  - Includes bedding/clothing 3 days before treatment
- Contact the institutional Department of Infection Prevention to determine their role in management
- Thoroughly clean and vacuum the room when the patient leaves the facility or moves to a new room

Management of crusted scabies

- Debrief the medical team immediately – all teams following the patient should be notified
- Initiate contact precautions and isolate the affected individual from other patients
- Initiate medical treatment (note that this is far more intensive than a standard scabies regimen described above):
  - Head to toe permethrin cream daily × 7 days **AND**
  - Ivermectin 0.2 mg/kg/dose (14 mg for 70 kg individual) on days 1, 2, 8, 9, and 15
- Trim nails and use a nail brush to remove mites
- Contact the institutional Department of Infection Prevention
- Machine wash and dry all bedding/clothes items using hot water and high heat cycles (temperatures in excess of 50 degrees C for 10 minutes will kill mites and eggs)
  - Includes bedding/clothing 3 days before treatment
- Clean the room regularly to remove contaminating skin crusts and scales
- Thoroughly clean and vacuum the room when the patient leaves the facility or moves to a new room
- Tasks completed in coordination with the Infection Prevention team:
  - Maintain records of all staff who provided hands-on care to the patient before implementation of infection control measures
  - Identify and treat all patients, staff, and visitors who may have been exposed to a patient with crusted scabies or to clothing, bedding, furniture or other items used by such a patient
  - Contact family and/or skilled nursing facility to determine additional contacts prior to admission
- Maintain contact precautions until skin scrapings from a patient with crusted scabies are negative
  - Reasonable target would be repeat scraping after two weeks after initiation of treatment
- Staff generally can return to work the day after receiving a dose of treatment with permethrin or ivermectin (if felt indicated by the Infection Prevention team)

eTable 84.2 Inpatient management of classic scabies and crusted scabies.
Courtesy Jeff Gehlhausen, MD.

Bites and Stings 85

Dirk M. Elston

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INSECTS

Insect Bites and Stings (Class Insecta)

Key features

- Pruritic papules sometimes progress to vesiculobullae or persistent prurigo nodularis-like lesions
- Papular urticaria may be localized to sites of bites or generalized
- Pseudolymphomatous reactions occasionally occur
- Anaphylaxis is mainly related to hymenopterid stings
- Secondary infection is most often staphylococcal

Introduction

Insect bites and stings are prevalent throughout the world. In temperate climates they are primarily a seasonal phenomenon, although indoor infestations can persist year-round. Insects are important disease vectors worldwide, and many emerging infectious diseases are linked to arthropod vectors. Personal protection against bites plays a major role in disease prevention.

Arthropods produce a wide spectrum of clinical lesions. Bullous arthropod reactions may suggest a diagnosis of immunobullous disease, and positive direct immunofluorescence has been reported, especially in the setting of scabies infestation. Pseudolymphomatous reactions can also occur (see Ch. 121).

Epidemiology

While some diseases have a single arthropod vector, others have multiple vectors and/or additional means of transmission. For example, bites from ticks and handling of infected animals are the most common modes of tularemia transmission in the US, but the disease can also be acquired through bites by deerflies and other horseflies. The vector has an important influence on the patient population affected by a particular disease. For example, cat ownership is a risk factor for cat scratch disease, which is associated with *Bartonella henselae* transmission by fleas, while homelessness is a risk factor for trench fever, which is caused by *Bartonella quintana* transmission by lice; however, either organism–vector pair can cause *Bartonella* endocarditis and bacillary angiomatosis, explaining why these diseases affect both patient populations. Vector-borne diseases often become epidemic during war or following natural disasters, and poverty and homelessness contribute to the spread of vector-borne disease.

Pathogenesis

Insect venoms and saliva are complex. Immediate reactions are commonly related to histamine, serotonin, formic acid, or kinins. Delayed reactions are typically manifestations of the host's immune response to proteinaceous allergens. Patients with large local reactions to insect stings, defined as a swelling measuring >10 cm and lasting >24 hours, often have elevated serum levels of venom-specific IgE[1].

Roughly one-quarter of reported cases of anaphylaxis are due to stings from insects in the order Hymenoptera (meaning membranous wings), which includes bees, wasps, hornets, and ants. These insects can possess specialized stingers and produce complex venoms that contain substances such as formic acid, kinins, and proteinaceous allergens. Insect sting hypersensitivity is more common in individuals with an atopic diathesis, and patients with mastocytosis may develop more severe reactions.

Clinical features

Characteristic insect bite reactions are grouped or disseminated, 2 to 8 mm, erythematous urticarial papules that are markedly pruritic and often excoriated (Fig. 85.1); they typically resolve over 5–10 days. Occasionally, bite reactions present as evanescent wheals or longer-lasting disseminated "papular urticaria" that persists for weeks or even months, sometimes reactivating when new bites occur in different locations. Edematous plaques, targetoid lesions, purpuric papules, nodules, and vesiculobullous reactions can also occur (Fig. 85.2; see Ch. 33). Chronic or resolving lesions are often hyperpigmented (see Figs. 67.2B & 85.6B), and prurigo nodularis-like lesions may develop, especially on the extremities. Secondary infection is common; although staphylococcal infections are seen most frequently, streptococcal infections also occur.

Insect bite reactions are most frequent in children 2–10 years of age and tend to involve exposed areas of the head, neck, and extremities. Commonly, only one member of a family is affected, as most clinical manifestations relate to the individual's immune response rather than the bite itself.



Fig. 85.1 Mosquito bite reactions. This patient has excoriated edematous papules and papulovesicles. *Courtesy Julie V. Schaffer, MD.*







Fig. 85.2 Spectrum of insect bite reactions. Sometimes patients develop large, erythematous, edematous plaques (**A**), frank bullae (**B**), or purpuric lesions that may be mistaken for leukocytoclastic vasculitis (**C**). *A, B, Courtesy Julie V. Schaffer, MD; C, Courtesy Jean L. Bolognia, MD.*

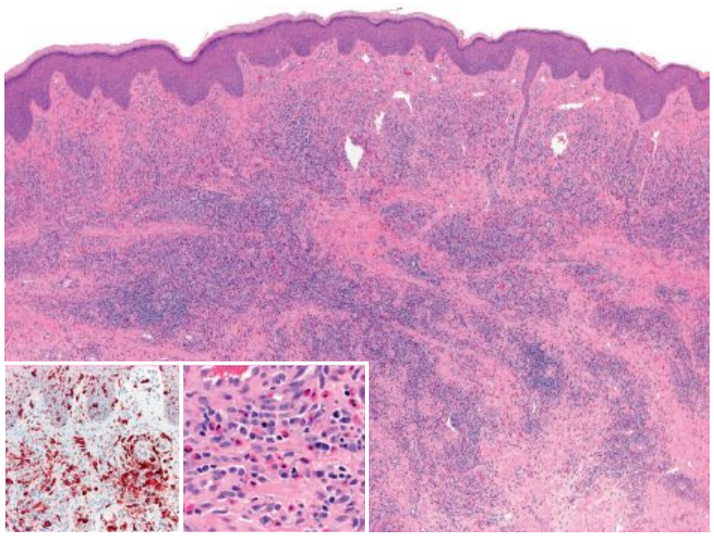


Fig. 85.3 Insect bite reaction with Langerhans cell hyperplasia. Note the dense superficial and deep lymphohistiocytic infiltrate with prominent eosinophils (right inset) and CD1a-positive, dendritic Langerhans cells (left inset). *Courtesy Lorenzo Cerroni, MD.*

Exaggerated insect bite reactions (e.g. papulovesicular, nodular) can represent a manifestation of chronic lymphocytic leukemia and less often other hematologic malignancies (see Ch. 33). In addition, hypersensitivity to mosquito bites with bullous and necrotic skin lesions may occur in individuals (typically Asian or Hispanic children and adolescents) with chronic EBV infection and proliferation of EBV-carrying natural killer (NK) cells; this may overlap with severe hydroa vacciniforme (HV)-like eruptions or HV-like lymphoproliferative disorder (see Ch. 87)[2]. Screening for hematologic malignancies and latent EBV infection, including *in situ* hybridization to detect EBV RNA in biopsy specimens of lesional skin if positive serology, should be considered in patients with unusual arthropod bite reactions.

Bee and wasp stings typically produce immediate burning pain, which is followed by the development of local erythema and swelling that usually subsides within a few hours to days but can be more severe and persistent in sensitized individuals. Atrial arrhythmias have been reported after bee stings in the absence of anaphylaxis. Killer bee and wasp attacks may be associated with myoglobinuria or hemoglobinuria and acute tubular necrosis. Although bee stings have been utilized as an alternative therapy for inflammatory arthritis, beekeepers may develop a chronic arthropathy related to stings.

Pathology

Histologic features suggestive of a bite or sting include the presence of a wedge-shaped perivascular lymphocytic infiltrate with eosinophils, endothelial prominence, and overlying spongiosis or focal epidermal necrosis. Marked spongiosis can result in blister formation, and Langerhans cell hyperplasia may be evident (Fig. 85.3).

Differential diagnosis

Arthropod reactions account for many "cryptic" chronic skin eruptions. Features that should suggest an arthropod reaction include grouping of papules, patterns of eruption that correlate with exposure, and the histologic features noted above. When an arthropod reaction is suspected, a detailed history of outdoor exposures, pets, work environment, and hobbies may prove helpful.

Treatment

Camphor and menthol lotion and gel formulations may be useful in the control of pruritus. Topical anesthetic preparations can also be helpful, and those containing pramoxine are readily available and present a low risk of contact dermatitis. For more persistent bite reactions, topical corticosteroids are often required. In young children, mid-strength corticosteroid preparations may suffice, while in older children and adults, class 1 or 2 corticosteroids are preferable. These agents can be applied under occlusion to enhance efficacy, but for a predetermined time period to avoid potential side effects of cutaneous atrophy and striae.

When topical agents fail, intralesional corticosteroid injection (e.g. triamcinolone 5–10 mg/ml) or excision of the pruritic nodule may be necessary. Occasionally, pseudolymphomatous nodules may require higher triamcinolone concentrations (e.g. 20–40 mg/ml). Cutaneous atrophy can occur, especially if a higher concentration of corticosteroid is injected superficially or into uninvolved surrounding skin. Atrophy may also be noted in a distribution corresponding to lymphatic drainage.

COMMONLY USED INSECT REPELLENTS	
Conventional skin-applied repellents in EPA classification	
DEET (N,N-diethyl-3-methylbenzamide)*	Effective against a wide range of arthropods Long history of use
Picaridin (KBR 3023)	Good evidence for mosquitoes Fewer studies support repellent effect against ticks
Biopesticide skin-applied repellents in EPA classification	
IR 3535 (3-[N-butyl-N-acetyl]-aminopropionic acid, ethyl ester)	Good evidence for mosquitoes in some, but not all, studies Fewer studies support repellent effect against ticks
Oil of lemon eucalyptus/p-menthane-3,8-diol†	Good evidence for mosquitoes Fewer studies support repellent effect against ticks
2-undecanone	Limited data available; may have strong odor
Botanicals (e.g. soybean oil, oil of citronella, neem oil, fennel oil, geraniol, catnip oil)	Have consumer appeal as "natural" repellents Best published evidence is for neem oil Lack of evidence does not necessarily equate to lack of efficacy, but available evidence to date suggests they are inferior to the synthetic repellents listed above
Repellent-treated clothing	
Permethrin	Can be sprayed on or impregnated in clothing, nets, tents, and sleeping bags Repels and kills mosquitoes, ticks, and chiggers

*There is a plateau of efficacy at 30% with long-acting products, and higher concentrations should generally be avoided. Because sunscreens require frequent reapplication and DEET does not, combination products with these ingredients are not recommended.
†The active ingredient of oil of lemon eucalyptus; use on children less than 3 years of age is not recommended.

Table 85.1 Commonly used insect repellents. Agents are listed in order of decreasing evidence of efficacy. EPA, Environmental Protection Agency.

Prevention of bites is best accomplished through the use of protective clothing and repellents. The most commonly used repellents are listed in Table 85.1. Factors that can influence the choice of a repellent include its efficacy, cost, convenience, odor and potential for irritation, as well as common arthropod pests in the area and the time of day, duration and environment of the exposure. DEET (N,N-diethyl-3-methylbenzamide, previously called N,N-diethyl-m-toluamide) remains the most widely used repellent for the prevention of bites from mosquitoes and most other insects. DEET can be applied to exposed skin or clothing. While mosquitoes that carry dengue virus tend to bite during the day, the anopheline mosquitoes that carry malaria tend to bite at night, and pyrethroid-impregnated mosquito netting represents an additional preventative measure. Treatment of clothing and other fabrics with permethrin can also be helpful.

The duration of efficacy of DEET depends primarily upon the dose applied. It provides less protection in women than in men, an observation that appears to be independent of serum estradiol levels. Efficacy may be reduced by the presence of skin abrasions. Rare toxic reactions include anaphylaxis and encephalopathy, and high concentrations of DEET can occasionally produce bullous eruptions.

Because of the potential for toxicity, the lowest effective DEET dose should be selected, especially in children. Many products with 10% or lower concentrations are available, although the American Academy of Pediatrics has stated that concentrations as high as 30% can be used safely in children 2 months of age or older (see Table 85.1). Sunscreen application over DEET may enhance DEET absorption, so sunscreen should be applied first when they are used concurrently[3].

Picaridin, IR3535, and p-menthane-3,8-diol perform reasonably well against a variety of mosquitoes and generally outperform soybean oil, citronella, neem oil, fennel oil, and geraniol (see Table 85.1)[4]. For protection against the common mosquitoes *Aedes aegypti* and *Culex quinquefasciatus*, IR3535 may be comparable to DEET. The Mediterranean monk's pepper plant (*Vitex agnus-castus*) has demonstrated efficacy in repelling *Ixodes ricinus* and *Rhipicephalus sanguineus* ticks as well as some mosquitoes, biting flies and fleas, and pyrethroid acids show promise as mosquito repellents[5]. Transfluthrin-treated sandals were shown to confer protection against mosquito bites in areas endemic for malaria[6].

Because insect stings are often unexpected, individuals with known hypersensitivity to stinging insects should always have an epinephrine (adrenaline) autoinjector (e.g. EpiPen®, AUVI-Q®) readily available in a dose appropriate for their body weight: 0.3 mg if >66 pounds (30 kg), 0.15 mg if 33–66 pounds (15–30 kg), and 0.1 mg if 16.5–33 pounds (7.5–15 kg). Patients must receive instructions regarding the use of the autoinjector, which needs to be protected from heat and light as well as inspected periodically for brown discoloration of the contents. Bee stingers should be removed as rapidly as possible.

Venom immunotherapy has been shown to improve quality of life for patients allergic to stings[7], reducing anxiety as well as the incidence and severity of local and systemic reactions. Desensitization protocols vary and should be discussed with an allergist. Rush (accelerated) immunotherapy can be performed for those with severe reactions, and it has a reasonable safety profile[8]. In the setting of mastocytosis, immunotherapy may need to be continued indefinitely, frequently induces immediate hypersensitivity reactions, and is only partially effective. Omalizumab has been used in conjunction with immunotherapy for patients refractory to standard regimens, and this may help prevent immunotherapy-related anaphylaxis[9].

Fire Ants

Key features

- Imported fire ants are red–brown in color and 1–2 mm in length
- When their mounds are disturbed, the ants swarm and sting in great numbers
- Immediate burning pain is followed by intensely pruritic, grouped vesicles and pustules
- Fire ant allergy is an important cause of anaphylaxis in endemic areas

Introduction

The range of *Solenopsis invicta*, the red imported fire ant (originally from South America), has spread to encompass much of the southern and southwestern US, and its territory continues to expand. The size of fire ant mounds varies in proportion to the amount of rainfall. The mounds may be inconspicuous during periods of drought, but they can reach more than a foot (30 cm) in height after heavy rains. When the mound is disturbed, the ants swarm. Because of their small size, they are not felt until they all begin to sting simultaneously in response to a chemical signal. Fire ants are attracted to electrical boxes and therefore present a hazard to electricians. Indoor attacks by swarms of fire ants can be particularly dangerous to infants and elderly individuals with impaired mobility[10].



Fig. 85.4 Fire ant bites presenting as clusters of sterile pustules on the foot.



Fig. 85.5 Bedbugs. Red–brown in color with a segmented abdomen and vestigial wings.

Pathogenesis

Fire ant venom is complex and acts by increasing membrane permeability and allowing release of histamine from mast cells. Allergic responses are directed at proteins within the venom. The venom is less concentrated in winter months, so winter sting reactions may be milder.

Clinical features

Fire ant stings begin as extremely painful wheals and evolve into intensely pruritic vesicles and sterile pustules (Fig. 85.4). The fire ant first grasps the skin with its mandibles; it then pivots and delivers a series of stings in a circular fashion, which may produce a rosette pattern. Scattered individual lesions are also common, especially when the victim is able to remove the ants before they have a chance to sting again. Secondary staphylococcal infections sometimes occur after fire ant stings. The absence of persistent tenderness can help differentiate sterile pustular reactions from secondary infections. Life-threatening anaphylactic reactions to fire ant stings have become a significant problem in the southern US[11].

Treatment

Patients with a life-threatening fire ant allergy should carry an epinephrine autoinjector with them at all times. Immunotherapy improves quality of life for individuals with severe fire ant allergies, and rush immunization protocols can be successful for those at high risk of stings[12,13]. Unfortunately, it is often impossible to avoid stings in endemic areas. Local reactions may be treated with potent topical or intralesional corticosteroids. A variety of methods of fire ant control are available, including bait insecticides that have a low environmental impact and are reasonably effective, as well as insecticide treatments for individual mounds.

Bedbugs

Key features

- Flattened oval body that is red–brown in color and 5–7 mm long in adults
- Segmented abdomen and vestigial wings
- Blood-sucking insects that feed at night and produce rows of pruritic, edematous papules

Introduction

In the past two decades, there has been a worldwide resurgence of bedbugs, which are now frequently found in homes, hotels, and dormitories[14–16]. Increased international travel, expanded immigration, changes in pest control practices, and the development of insecticide resistance have likely contributed to this trend.

Bedbugs belong to the family Cimicidae (order Hemiptera) and are blood-sucking mammalian and avian ectoparasites. They have a flattened oval body, a segmented abdomen, a retroverted labium (sucking mouthpiece), a semicircular to triangular scutellum (dorsal sclerotic plate), and antennae with four segments (Fig. 85.5). *Cimex lectularius* (the common bedbug) and *C. hemipterus* (found in warmer climates) affect humans most frequently; *C. lectularius* also parasitizes bats, chickens, and other domestic animals. *C. lectularius* ranges in size from 5 to 7 mm, with females slightly longer than males. *C. hemipterus* is roughly 25% longer than *C. lectularius*. Interspecies mating occurs in nature.

Bedbugs are nocturnal. They hide in mattress seams and crevices (e.g. within the bed frame and other furniture, behind baseboards, under peeling paint) during the day and feed at night, especially just before dawn. Red–brown fecal staining and nit-like ova are commonly visible in mattress seams.

Pathogenesis

Bedbug bite reactions result from an immune response to salivary proteins (e.g. nitrophorin) injected by the insect while feeding. Bedbugs digest their blood meal very slowly. The blood in the bug's gut remains relatively unclotted and is not membrane-bound.

Clinical features

Bedbug bites typically present as pruritic, erythematous, edematous papules, sometimes with a visible central hemorrhagic punctum (Fig. 85.6). As with other insect bites, the clinical appearance and duration of lesions vary depending on the individual's degree of sensitization. Some individuals have little or no reaction to bedbug bites, and it is common for only one or a few family members (even among those sleeping in the same bed) to report lesions. Most bites occur in exposed areas. Three lesions in a row (referred to as "breakfast, lunch, and dinner"; see Fig. 85.6B) are characteristic of, but not specific to, bedbug bites. Although affected individuals classically awake with new lesions, bite reactions can take several days to appear, and the latency tends to decrease with exposure to additional bites[14,16].

To date, transmission of infectious diseases to humans by bedbugs has not been documented[17]. Although hepatitis B virus has been detected within wild bedbugs, laboratory studies have failed to demonstrate viral multiplication or transmission to chimpanzees[17]. However, the possibility of bedbugs serving as vectors of American trypanosomiasis has been raised, and a recent laboratory study found that *Trypanosoma cruzi* could be transmitted among mice by bedbugs[18]. Bedbug dung may play a role in asthma. In a recent study in patients presenting to the emergency department, having bedbug bites was associated with an increased risk of anemia, with chronic blood loss and inflammation hypothesized as possible mechanisms[19].

Treatment

Bedbug bites can be treated as described above for other insect bites (e.g. with topical corticosteroids). Eradication of bedbugs from infested homes is difficult and usually requires the assistance of professional exterminators. Integrated pest management strategies utilizing both

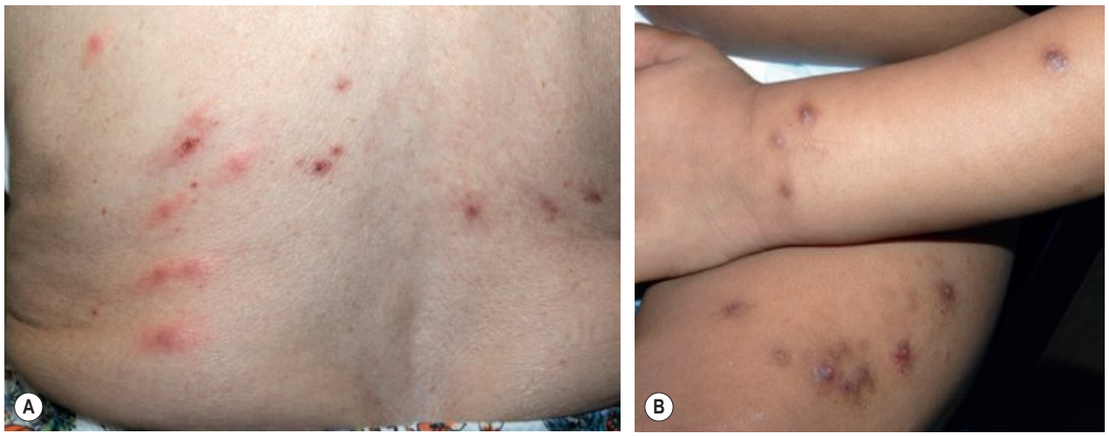


Fig. 85.6 Bedbug bite reactions. A Multiple pink edematous papules with either a central punctum or excoriation. **B** Excoriated hyperpigmented papules in an arcuate array ("breakfast, lunch, and dinner") in a young child with Fitzpatrick phototype IV. Residual hyperpigmentation following bug bite reactions is common in individuals with darker skin types and can persist for months. *A, Courtesy Kalman Watsky, MD; B, Courtesy Julie V. Schaffer, MD.*

insecticides and non-chemical methods (e.g. heating/steaming, freezing, elimination of cracks and crevices) are most effective.

Triatomine (Reduviid) Bug

Synonym: ■ Kissing bug

Key features

- Half-membranous wings (hard proximally and membranous distally) whose tips overlap
- Tan and dark "tiger stripes" on the abdomen
- Vector for American trypanosomiasis (Chagas disease)
- Bites can produce large, persistent edematous plaques

Introduction

Triatomine bugs are a type of reduviid bug that feeds on the blood of mammals and other vertebrates. Like bedbugs, they are true bugs of the order Hemiptera. Triatomine bugs are typically 1.5–3 cm in size as adults and have half-membranous wings that overlap. Characteristically, the wings fail to cover the lateral portions of their "tiger-striped" abdomen (Fig. 85.7). The antennae are long, thin and composed of four segments; the position of the antennae is used to classify the bugs. The labium (sucking mouthpiece) is straight and composed of three segments. Behind the head is a triangular pronotum (first segment of the thorax) with a broad posterior base.

Triatomine bugs are vectors for American trypanosomiasis (Chagas disease; see Ch. 83). The bugs have a pronounced gastrocolic reflex, resulting in defecation as they eat. Infectious feces are then inoculated into the bite site or conjunctiva by scratching or rubbing.

Triatomine bugs are primarily nocturnal and live in peri-domestic sites in Central and South America and the southern US, especially cracked stone walls and piles of tiles or bricks. They commonly feed on domestic animals, and trypanosome transmission may cross over between domestic and sylvatic (wild animal) life cycles. Control of this vector has been difficult, and insecticide spraying in affected communities is often followed by reinfestation originating from nearby livestock enclosures or wild populations of triatomine bugs.

Clinical features

Triatomine bug bites are typically painless, and the first sign is delayed erythema, swelling, and pruritus at the site. Exaggerated responses in the form of large urticarial plaques or vesiculobullous lesions occasionally develop. These insects are known as "kissing bugs" because of their tendency to bite the face, especially around the lips. Unilateral eyelid and periorbital swelling 1–2 weeks after conjunctival exposure to infected triatomine feces is referred to as Romaña sign and represents a chagoma. Trypanosomes subsequently infect the autonomic nervous system, resulting in chronic complications that include cardiomegaly and megacolon (see Ch. 83). Triatomine bugs and cockroaches share antigens that are strongly immunogenic in atopic patients.



Fig. 85.7 Triatomine bug. Note that the wings fail to cover the lateral portions of the abdomen and the tan and dark "tiger stripes" on the abdomen.

Blister Beetles

Synonym: ■ Spanish fly

Key features

- Oblong bodies (1–2 cm long) and antennae composed of multiple short segments
- Wide variety of colors and patterns
- Contact with beetles results in vesicles and bullae due to their production of cantharidin

Introduction

Blister beetles (order Coleoptera) belong to the family Meloidae. These insects produce the blistering agent cantharidin, which serves to protect them from predators. Members of the family Oedemeridae are classified as "false" blister beetles but also produce cantharidin, whereas rove beetles of the family Staphylinidae make another vesicant, pederin (see below).

Much of what is known about blister beetles is extrapolated from studies of a few species. In *Epicauta funebris*, cantharidin has been identified in all ten life stages of the beetle, and it accumulates during the first five larval stages. When threatened, larvae protect themselves by exuding cantharidin in a milky oral fluid, rather than in the hemolymph that adult beetles discharge from leg joints. Adult male beetles contain up to 10% cantharidin by weight. If kept in isolation, females lose their larval reserves and must mate to preserve their stores of cantharidin. During mating, the female acquires cantharidin from her mate as a copulatory gift. She then transfers the cantharidin to her eggs, rendering them resistant to predation.

Clinical features

Contact with blister beetles typically results in the development of vesicles and bullae within 12–24 hours. Topical application of cantharidin has been used for the treatment of molluscum contagiosum and warts since the 1950s (see Chs. 79 & 81).

Pathology

Histologic sections of the blisters demonstrate acantholysis in suprabasal keratinocytes. Disruption of cell outlines and cellular necrosis may be noted. The profile of adhesion molecule loss in cantharidin blisters is similar to that seen in Darier disease.

Treatment

Avoidance is the best measure, but immediate washing with soap and water may be of some benefit.

Rove Beetles

Synonym: ■ Nairobi fly

Key features

- Narrow bodies (0.5–1.5 cm long), a red–orange abdomen, and short forewings
- A vesiculopustular eruption can result from contact with pederin-containing beetle hemolymph

Introduction

Rove beetles belong to the Staphylinidae family. The hemolymph of some rove beetles in the *Paederus* genus contains the vesicant pederin, which is thought to be produced by endosymbiotic bacteria. *Paederus* dermatitis (dermatitis linearis) is a streaky vesiculopustular eruption that results from release of pederin when a rove beetle is crushed or injured on the skin. Outbreaks of *Paederus* dermatitis have been reported in warm climates worldwide, typically occurring when beetle populations increase during the rainy season. *Paederus* dermatitis has also been described in returning travelers[20]. Epidemics of vesiculobullous skin lesions in military units and hospital wards with open windows have been attributed to the rove beetle's attraction to ultraviolet light (e.g. from fluorescent bulbs).

Clinical features

Contact with pederin leads to inflamed skin with erythema and often pustules as well as vesicles (Fig. 85.8), in contrast to the relatively non-inflammatory vesicles produced by cantharidin. These changes usually begin to develop 24–36 hours after exposure, and "kissing lesions" may be seen on adjacent flexural surfaces. "Nairobi eye" represents periocular dermatitis and keratoconjunctivitis caused by *Paederus eximius*, a rove beetle found in Northern Kenya.

Pathology

Histologic features include suprabasal acantholysis, reticular degeneration, and necrosis of the epidermis together with an inflammatory infiltrate containing neutrophils.

Treatment

Immediate washing with soap and water is recommended. Preventative measures include use of insect-proof netting at night, changing to light sources without ultraviolet emission, and removing beetles from the skin without crushing them.

Carpet Beetles

Synonyms: ■ Khapra beetle ■ Hide beetle

Key features

- Adults have rounded bodies (1.5–3.5 mm long) with three bright bands; larvae measure 4–5 mm with stripes and dense hairs
- A pruritic papulovesicular eruption can result from contact with hastae (specialized hairs) on carpet beetle larvae



Fig. 85.8 *Paederus* dermatitis. Erythematous plaque with multiple small vesicles and vesiculopustules. *Courtesy Vidal Haddad, Jr, MD.*

Introduction

Carpet beetle dermatitis represents a hypersensitivity reaction to the hastae (larval hairs) or hemolymph of beetles in the Dermestidae family, including *Attagenus*, *Dermestes*, *Anthrenus*, and *Trogaderma* spp. The larvae feed on household organic materials such as wool and hide, e.g. in rugs and furniture.

Clinical features

Contact with hastae typically results in a pruritic papulovesicular eruption[21]. Other reactions that have been described include superficial bullae, erosions, urticarial papules, and vasculitis[22]. Lymphadenopathy and inflammation of the eyes and upper respiratory tract can also occur.

Treatment

Skin lesions respond to topical corticosteroids. The infestation should be eliminated via cleaning, removal of contaminated items, and extermination as needed.

Fleas

Key features

- Laterally compressed bodies and large hind legs
- The most common flea on dogs is *Ctenocephalides felis*, the cat flea
- Produce intensely pruritic papules, vesicles and bullae, often grouped on the lower extremities
- Serve as vectors for endemic (murine) typhus, flea-borne spotted fever, and plague

Introduction

Fleas (order Siphonaptera) are ubiquitous pests and show little host specificity. The most common flea on dogs is *Ctenocephalides felis*, the cat flea. *Pulex irritans*, the human flea (Fig. 85.9), is a common dog flea in some locations. It is also found on wild animals with no human contact. *Ctenocephalides* fleas have two ctenidia (combs) that resemble a mane of hair (pronotal comb) and mustache (genal comb) (Table 85.2).

Clinical features

Flea bites present as intensely pruritic papulovesicles, usually located on the lower legs. Other parts of the body may also be affected, especially when an infested pet has been groomed or held. Flea allergy is common, and allergic patients tend to react to a wide range of fleas. Flea pupae can lie dormant for many months then hatch rapidly in response to



Fig. 85.9 *Pulex irritans*, the human flea. The body is laterally compressed and no combs are present.

CHARACTERISTIC ANATOMIC FEATURES OF SEVERAL COMMON TYPES OF FLEAS	
Flea	**Characteristics**
Pulex	Round frons (forehead); single pair of hairs behind antennae
Xenopsylla	Round frons; several pairs of hairs behind the antennae; pleural rod (vertical thickening in mesothorax)
Ctenocephalides felis	Two ctenidia (combs) on the head*; sloped frons; six hair-bearing notches on dorsal hind tibia
Ctenocephalides canis	Two ctenidia (combs) on the head*; round frons; eight hair-bearing notches on dorsal hind tibia
Sticktight flea	Flat frons; broad lacinia (serrated piercing lance-like mouthpart)
*Resemble a mane of hair and a mustache.	

Table 85.2 Characteristic anatomic features of several common types of fleas.

vibration. Individuals who enter a vacant house can find that fleas rapidly besiege them.

Fleas serve as vectors for endemic (murine) typhus, flea-borne spotted fever, plague, and (primarily among cats) *Bartonella henselae* infection (see Chs. 74 & 76). Endemic typhus is common in southern Texas and California, where the cat flea and *Xenopsylla cheopis* (the oriental rat flea) are the primary vectors, respectively. The disease has also emerged with a worldwide distribution. Feeding alone can transmit endemic typhus, although fleas also defecate infectious bloody feces when feeding.

Tungiasis (caused by the jigger or sand flea, *Tunga penetrans*) usually presents with papular necrotic lesions on the feet, often located adjacent to the great toenail (see Ch. 84). The incidence peaks during dry weather. A gravid female flea is typically found within the upper dermis of the lesions. Infestation most often occurs in beach areas and urban slums, and the flea is common on dogs, cats, and rats.

Treatment

Options for treatment and prevention of flea infestation in animals include *topical* fipronil, neonicotinoids (e.g. imidacloprid), selamectin, flumethrin, and indoxacarb as well as *oral* spinosad, isoxazolines (e.g. afoxilaner), nitenpyram, and lufenuron. Boric acid, growth regulators such as pyriproxyfen, and insecticides may be helpful adjunctive treatments for the infested environment. The best source of information is a knowledgeable veterinarian.

Tungiasis is usually treated surgically. A double-blinded randomized controlled trial of oral ivermectin (300 mcg/kg on two consecutive days) showed it to be ineffective in treating patients with multiple lesions. Wearing protective footwear is preventative.



Fig. 85.10 Characteristic train-track hemorrhage from exposure to *Megalopyge opercularis* (puss caterpillar) .

Lepidopterism

Key features

- Caterpillar dermatitis is caused by the larval form of a butterfly or moth
- Dermatitis may also result from the hairs or scales of adult lepidopterids
- Severe systemic reactions may occur with some species
- Important cause of ophthalmia nodosa

Introduction

Lepidopterism refers to the broad spectrum of adverse reactions to caterpillars, cocoons, butterflies, and moths. Some authors use the term erucism for solely cutaneous reactions to these organisms or specifically for reactions to caterpillars[23,24]. A wide variety of species has been implicated[23].

Pathogenesis

Much of the irritation due to contact with the hairs of lepidopterids is purely mechanical in nature. Toxin-mediated reactions may be related to histamine, kinins, plasminogen activators and other proteinaceous toxins associated with hairs (setae), spines, or hemolymph. Allergy usually does not play a significant role in the reactions.

Clinical features

Cutaneous manifestations include pain, pruritus, erythema, swelling, hemorrhage (Fig. 85.10), papules, and urticaria. Cutaneous reactions may be accompanied by systemic reactions, e.g. respiratory distress or a bleeding diathesis with intracranial hemorrhage (Table 85.3). Contact with Australia's white-stemmed gum moth (*Chelepteryx collesi*) produces yellow discoloration of the skin.

Dermatitis due to gypsy moth caterpillars may result from direct contact with the caterpillar or from hairs on clothesline-dried clothing. Erythematous urticarial papules and macular erythema with pruritus are commonly localized to the flanks, feet, inner aspects of the arms and legs, and collar region.

Ocular lesions caused by caterpillar hairs (ophthalmia nodosa) are similar to those caused by tarantula hairs. Ocular reactions to hairs include acute "toxic" conjunctivitis, chronic mechanical keratoconjunctivitis, subconjunctival granulomatous nodules, iritis, and vitreoretinal involvement. The hairs tend to migrate inward in the direction of the sharp tip.

Children who ingest caterpillars may develop focal or diffuse erythema and edema of the lips, tongue, and buccal mucosa. Esophageal and tracheobronchial involvement can also occur. Removal of hairs and spines may require endoscopy.

CUTANEOUS AND SYSTEMIC REACTIONS ASSOCIATED WITH LEPIDOPTERISM			
Moth/caterpillar common name	**Scientific name**	**Region**	**Clinical findings**
Gypsy moth caterpillar	*Lymantria dispar*	Northeastern US	"Dermatitis" from direct contact or from hairs on clothesline-dried clothing
Io moth caterpillar	*Automeris io*	US	Immediate stinging sensation, "dermatitis" (often transient urticarial papules)
Saddleback caterpillar	*Acharia stimulea* (formerly *Sibine stimulea*)	US	Immediate stinging sensation, "dermatitis" (often transient urticarial papules)
Buck moth caterpillar	*Hemileuca maia*	Eastern US	Immediate stinging sensation, "dermatitis"
Puss caterpillar	*Lagoa crispata* (also known as *Megalopyge crispata*)	Oklahoma and eastern US	Immediate burning sensation, "dermatitis"; in Oklahoma, spines contain high concentrations of tannins (ingested from oak trees)
Southern flannel caterpillar, puss caterpillar, wooly asp	*Megalopyge opercularis*	Southern US, Mexico, Central America	Immediate intense radiating pain; characteristic "railroad track" pattern of hemorrhage (Fig. 85.10); edema, hives, and systemic symptoms
Saturniid moth caterpillar, giant silkworm moth	*Lonomia achelous, L. oblique*	Latin America	Local reactions, bleeding diathesis, renal failure
Processionary caterpillars: pine, Cyprus, and oak (characteristically travel single-file)	*Thaumetopoea pityocampa*, *T. wilkinsoni*, *T. processionea*	Mediterranean region, central Europe, Britain	Urticaria (often immunologic), angioedema, conjunctivitis, respiratory distress, abdominal pain, phalangeal osteolysis; widespread reactions from airborne urticating hairs
Pine moth caterpillar and cocoon	*Dendrolimus punctatus*	China, imported elsewhere	"Dermatitis", arthritis (usually monoarticular), chondritis, ophthalmia nodosa
Tussock moth caterpillar	*Orgyia pseudotsugata*	Western US, especially Pacific Northwest	"Dermatitis", pruritus of the skin and eyes, respiratory symptoms (irritant and allergic mechanisms); forestry workers
Yellowtail moth (adult female)	*Hylesia metabus*, *H. alinda*	Mexico and South America (including Venezuelan port of Caripito)	Papular urticaria (Caripito itch in ship crew)

Table 85.3 Cutaneous and systemic reactions associated with lepidopterism. "Dermatitis" can include pruritic urticarial papules as well as eczematous reactions. Tape stripping of skin has been used to identify caterpillar hairs (setae). Caterpillars can have short spines projecting from a long slender shaft or short tapered shafts with ball-in-socket structures resembling trichorrhexis invaginata.

ARACHNIDS

Tick Bites (Class Arachnida: Subclass Acarina)

Key features

- Hard ticks are common disease vectors
- *Ornithodoros* soft ticks transmit borrelial relapsing fever
- *Dermacentor* ticks hidden in the scalp can cause fatal tick paralysis
- Tick bites may lead to galactose-α-1,3-galactose sensitization and red meat allergy
- Tick control measures are important in preventing disease

Introduction

Patients with tick bites often present with the tick still attached[25]. Scalp attachment is particularly common for *Dermacentor* ticks, and the patient may be unaware of a tick that is hidden by hair. This is of concern considering that *Dermacentor* ticks produce a neurotoxin that can cause paralysis when the tick is attached for ≥4 days[26,27]. Symptoms resolve rapidly upon tick removal, and any child presenting with rapidly progressive ascending flaccid paralysis should be examined for ticks. In Australia, *Ixodes* ticks can cause paralysis, but this occurs primarily in dogs. Tick bites (especially *Amblyomma* spp.; see below) can result in sensitization to the carbohydrate antigen galactose-α-1,3-galactose associated with red meat allergy[8].

Correct identification of an attached tick (see Fig. 76.1) provides the physician with an opportunity to discuss tick control measures and symptoms of tick-borne disease[28,29]. Most hard ticks have a three-host life cycle. Larval (seed) ticks have six legs and feed on small animals in nature. The nymphs and adults feed on larger animals. Nymphs resemble small adult ticks, with eight legs, but are sexually immature. Because they attach for one long blood meal during each phase of their life cycle and search for a new host for each blood meal, ticks are efficient disease vectors. Hard ticks have a hard dorsal plate (scutum) and account for most medically important ticks, transmitting human diseases including Lyme borreliosis, ehrlichiosis, human granulocytic anaplasmosis, babesiosis, and a variety of rickettsial infections (including Rocky Mountain spotted fever [RMSF]) (see Table 76.1). Soft ticks such as *Ornithodoros* (the vector of borrelial relapsing fever) lack a scutum and have retroverted mouthparts. These ticks tend to live in close association with a single host.

Clinical features

Once the tick has been removed, hypersensitivity reactions at the site are common. Papular, nodular, and vesiculobullous lesions can occur and are typically pruritic. Hypersensitivity reactions presenting as erythematous plaques are commonly misinterpreted as erythema migrans. Nodules with pseudolymphomatous histology can also develop.

Treatment

Milder tick bite reactions may respond to application of a potent (class 1 or 2) topical corticosteroid; occlusion of these agents can increase efficacy. More intense reactions may require intralesional corticosteroid injection or surgical excision.

Most tick-borne diseases respond readily to tetracyclines. Suspected RMSF requires empiric therapy, which should not be delayed until confirmatory tests are available (see Ch. 76). Delayed treatment of RMSF has led to deaths in children[30]. Doxycycline is the drug of choice for children as well as adults with RMSF. Staining of teeth is unlikely with a short course of doxycycline, and chloramphenicol is less effective for RMSF.

TICK CONTROL MEASURES	
Personal	**Environmental**
Protective clothing tightly laced, snapped or tied	Removal of leaf debris
Clothing treated with permethrin	Area acaricide application
Clothing treated with repellents such as DEET	Exclusion of animal hosts
Regular tick inspections	Acaricide-treated feed corn

Table 85.4 Tick control measures. DEET, N,N-diethyl-3-methylbenzamide.

Environmental measures

Exclusion of animal hosts from communities and recreational areas can be helpful in control of tick-borne illness (Table 85.4), although this may be difficult to achieve for small animal hosts (e.g. mice, rabbits). There is evidence that communities located close to wildlife reserves have higher rates of tick-borne illnesses. Oral agents, such as the avermectins, can be placed in corn eaten by deer to kill ticks that feed on the deer. Injectable ivermectin is helpful in reducing tick infestation of livestock. Removal of leaf debris is a critical part of tick control efforts because it: (1) enables acaricides to reach the ticks; and (2) leads to a reduction in tick numbers via dehydration of adults (which require leaf debris to maintain hydration) and eggs (which require sufficient humidity to hatch).

Repellents

Permethrin has been marketed as a tick repellent. The spray formulation is most widely available. Once applied to clothing, permethrin is stable through several wash cycles. It is also suitable for treating sleeping bags, tents, and fabric used for insect screening. A liquid concentrate can be used to impregnate fabric for the life of the garment. Permethrin is particularly helpful in the prevention of tick and chigger bites, since these crawling arthropods must travel across the treated fabric, whereas flying insects tend to be attracted directly to exposed skin. The combination of a DEET-containing repellent and permethrin-treated clothing is generally highly effective against a wide range of biting arthropods.

Some North African camel ticks have demonstrated high-level resistance to permethrin. Instead of killing the tick, permethrin may produce a pheromone-like attachment response. This attachment phenomenon has not yet been described in North American ticks, but permethrin resistance does occur. High-level permethrin resistance in cattle ticks has been linked to outbreaks of bovine babesiosis and anaplasmosis in Mexico[31].

Methods to eliminate and prevent tick infestations in dogs include: *topical* application of products containing fipronil, permethrin, or fluralaner every month; *oral* administration of an isoxazoline (e.g. afoxolaner) every 1–3 months; and collars impregnated with imidacloprid/flumethrin, deltamethrin, or amitraz[32].

Tick removal

Ticks should be removed as completely as possible, and care should be taken not to squeeze the abdomen. Gentle traction is generally preferred, but a twisting motion can also be used; the latter technique may leave a small mouthpart. Inexpensive plastic tick removal devices (e.g. Tick Nipper™, Tick Twister®) can be utilized to grasp the tick just behind the mouthparts without severing them. A tick removal device can also be made by cutting a V-shaped notch in a plastic spoon or credit card with a sharp pair of scissors or hot blade. Petroleum jelly, fingernail polish, isopropyl alcohol, and hot matches are generally ineffective. Hands should be washed if they were in contact with the tick.

Antibiotic prophylaxis after tick bites

Antibiotic prophylaxis after tick bites remains controversial, and most authorities do not recommend its routine use, including for prevention of Lyme disease (see Ch. 19). In endemic areas (>20% of ticks infected), if a nymphal or adult *I. scapularis* has been attached for >36 hours and prophylaxis can be started within 72 hours of tick removal, a single 200 mg dose of doxycycline may decrease the risk of developing Lyme disease (from 3.2% in the placebo group to 0.4% in the treatment group in one study)[33,34]. A meta-analysis of antibiotic prophylaxis concluded that in order to prevent one case of Lyme disease, 50 people bitten by an *Ixodes* tick would need to be treated – the risk in the placebo group was 2.2% compared with 0.2% in the antibiotic-treated group[35]. Routine serologic testing for Lyme disease in individuals bitten by *Ixodes* ticks is not useful, and there is no evidence that molecular testing for *Borrelia burgdorferi* in a tick is helpful in predicting the risk of Lyme disease in a human bitten by that tick[36]. Treatment regimens for erythema migrans are outlined in Table 19.4.

The utility of antibiotic prophylaxis in preventing other tick-borne illnesses has not been established. For example, in a guinea pig model of RMSF, a single dose of oxytetracycline was found to prevent disease if given shortly before the expected onset of illness. However, administration any earlier merely delayed the development of clinical symptoms, making correct timing of administration of a single dose difficult. Single-dose doxycycline for Lyme disease prophylaxis should be avoided in RMSF-endemic areas, since changing the course of RMSF could potentially delay definitive treatment.

Amblyomma Ticks

Synonym: ■ Lone star tick

Key features

- Ornate scutum (hard dorsal plate)
- Single white dorsal spot on female *Amblyomma americanum*
- Papular, nodular, and bullous lesions at attachment sites
- *Amblyomma* ticks are vectors of ehrlichiosis, several rickettsial infections, southern tick-associated rash illness (STARI), and tularemia
- *Amblyomma* tick bites have been associated with the development of red meat allergy

Introduction

Amblyomma ticks are particularly common in the southern US. This, plus the characteristic white dorsal spot of the female *A. americanum* (Fig. 85.11; see Fig. 76.1), has given rise to the common name "lone star tick". Males have ornate markings that often form pale "inverted horseshoes" on the posterior portion of their dark scutum. *Amblyomma* ticks have prominent eyes, festoons (grooves in the posterior edge of the scutum), and long anterior mouthparts.

A. americanum has a wide distribution, now ranging from Texas to Iowa and Maine (see Fig. 76.12), that is continuing to expand due to the explosion in the white-tailed deer population[37]. Other species of *Amblyomma* ticks are common in Africa, the Caribbean, and Central and South America. Some *Amblyomma* ticks attach to birds, and migration of avian hosts has been implicated in dissemination of tick-borne diseases.



Fig. 85.11 *Amblyomma americanum* (lone star tick). Note the characteristic white dorsal spot on the female ticks. The female's scutum often covers only a portion of the body to allow room for engorgement.

Clinical features

Amblyomma tick attachments favor the legs, buttocks, and groin and often affect people who work outdoors or take part in outdoor recreation (e.g. construction workers, fishermen, hunters, hikers), especially when new development displaces the tick's usual hosts. Patients usually become aware of *Amblyomma* tick bites while the tick is still attached. This is partly because the ticks often attach in large numbers. Once the tick has been removed, delayed-type hypersensitivity to tick antigens can lead to a reaction at the attachment site. Papular, nodular, and bullous lesions are common.

A. americanum is the major vector of *Ehrlichia chaffeensis*, the agent of human monocytic ehrlichiosis[38]. This disease has been documented in more than 30 states, with systemic symptoms similar to those of RMSF (e.g. fever and headache) and variable cutaneous manifestations (see Ch. 76). *A. americanum* is also the primary vector for *Ehrlichia ewingii* infection.

Southern tick-associated rash illness (STARI; "Missouri Lyme disease") was originally described in Missouri but can also occur in other southern and southeastern states. It presents with an expanding erythematous annular plaque 3–14 days after *A. americanum* attachment, often in association with fever, headache, myalgias, and arthralgias. *Borrelia lonestari* has been implicated as a potential cause.

Amblyomma ticks have been implicated in the transmission of RMSF (*Rickettsia rickettsii*; primarily in Central and South America, where it may be referred to as Brazilian spotted fever), American tick bite fever (*Rickettsia parkeri*), African tick bite fever (*Rickettsia africae*), and tularemia (see Chs. 74 & 76). In the midwestern and southern US, *A. americanum* is also the vector of Heartland virus disease and likely Bourbon virus infection, which are due to a phlebovirus and thogotovirus, respectively. A related phlebovirus causes severe fever with thrombocytopenia syndrome, an emerging infection in Asia transmitted by *Haemaphysalis* ticks, which have recently been identified in the eastern US.

Bites from *Amblyomma* ticks have been most strongly associated with allergy to beef, pork, and lamb via development of IgE antibodies specific to galactose-α-1,3-galactose, a blood group substance of non-primate mammals[39]. Urticaria, angioedema, or anaphylaxis typically develops 3–5 hours after eating red meat[40]. Of note, IgE against galactose-α-1,3-galactose has also been implicated in cetuximab-induced anaphylaxis.

Dermacentor Ticks

Synonyms: ■ *D. andersoni:* Rocky Mountain wood tick ■ *D. variabilis*: American dog tick

Key features

- Large ticks
- Ornate scutum (hard dorsal plate) with deep punctuations
- The adult tick prefers to attach to the head, neck, and shoulder
- *D. variabilis* is the major vector for RMSF in the United States, while *D. andersoni* can transmit Colorado tick fever as well as RMSF

Introduction

Dermacentor ticks are commonly found in open areas with low bushy vegetation, but they are scarce in heavily wooded areas. Peak abundance of the tick is in April and May, declining by July. *Dermacentor* ticks have an ornate scutum, prominent eyes and festoons (grooves in the posterior scutum), small anterior mouthparts, and a rectangular basis capituli. Both *D. variabilis* (Fig. 85.12; see Fig. 76.1) and *D. andersoni* have brown legs, and coxa 1 (the attachment base for the first pair of legs) is bifid. Coxa 4 is greatly enlarged in the male, and males have no ventral plates. As in most hard ticks, the scutum in the female is smaller, leaving a portion of the abdomen exposed.

D. variabilis is found throughout the US, except for the Rocky Mountain states. In parts of Canada, its range overlaps with that of *D. andersoni*, which is generally confined to the Rocky Mountains. In Georgia and South Carolina, *D. variabilis* is the second most common tick found on humans (*A. americanum* being the most common).



Fig. 85.12 ***Dermacentor variabilis*** **tick (engorged female) with an ornate scutum.** This species is the major vector for Rocky Mountain spotted fever in the US.

Pathogenesis

During the course of engorgement, *D. andersoni* saliva downregulates local cell-mediated immunity. This phenomenon may explain the delayed onset of many nodular tick bite reactions. It might represent an adaptive mechanism, allowing the tick to feed unnoticed.

Clinical features

Dermacentor ticks preferentially attach to the head and neck region; in contrast, *Amblyomma americanum* prefers the lower legs, buttocks, and groin, and *Ixodes scapularis* shows less site preference but most often attaches to the trunk. Prolonged attachment of a *Dermacentor* tick is the most frequent cause of tick paralysis in the US (see above).

D. variabilis is the major vector for RMSF in the US[41]. The highest incidence of RMSF is in the eastern states, especially in North Carolina (see Fig. 76.2). RMSF typically presents with fever and headache. An acral eruption of erythematous macules and/or petechiae may be evident but is commonly absent early in the disease process. As many as 40% of patients with RMSF are not aware of a recent tick bite. As the mortality rate in RMSF is heavily dependent on the interval between onset of symptoms and initiation of antibiotic therapy, the disease should be considered in every patient with fever and a headache in endemic areas.

D. andersoni is the major vector for RMSF in the Rocky Mountain states, and it is also the vector for the viral illness Colorado tick fever. Because the symptoms of Colorado tick fever overlap with those of RMSF, specific diagnostic tests such as paired serologic studies (acute and convalescent) and immunohistochemical staining, direct immunofluorescence, or PCR-based analysis of lesional skin biopsy specimens can help to confirm the diagnosis of RMSF; however, empiric treatment should not be delayed until the results are available. Additional diseases that can be transmitted by *Dermacentor* ticks include tularemia, rickettsial infections in Europe and Asia, Pacific Coast tick fever in California (*Dermacentor occidentalis*), and occasionally, human monocytic ehrlichiosis and Q fever.

Rhipicephalus Ticks

Synonym: ■ Brown dog tick

Key features

- Common dog ticks
- Most are brown with brown legs, a teardrop shape and inornate scutum (hard dorsal plate)
- Vectors for boutonneuse fever and (occasionally) RMSF in the southwestern US



Fig. 85.13 *Rhipicephalus* ticks. Common brown dog ticks; the lower tick is engorged with blood.



Fig. 85.14 *Ixodes scapularis* tick. The inornate brown scutum is overshadowed by the large, cream-colored, engorged abdomen.

Introduction

Rhipicephalus ticks (Fig. 85.13) are common dog ticks that are typically brown in color with an inornate scutum. They have prominent eyes and festoons (grooves in the posterior scutum), but small mouthparts attached at a hexagonal basis capituli.

Clinical features

Rhipicephalus ticks carry RMSF (primarily in the southwestern US and Mexico) and boutonneuse fever (see Ch. 76). They may also be vectors for Congo–Crimean hemorrhagic fever virus, although *Hyalomma* ticks usually transmit this condition.

Ixodes Ticks

Synonyms: ■ Blacklegged tick ■ Deer tick

Key features

- Teardrop shape, often with dark legs
- Inornate brown scutum (dorsal hard plate) that is small relative to the large abdomen in females
- Vectors for Lyme disease, human granulocytic anaplasmosis, babesiosis, viral encephalitis (e.g. due to Powassan virus), and other borrelial and rickettsial infections

Introduction

Ixodes scapularis (formerly also known as *I. dammini*), the eastern blacklegged tick, is the best known of the *Ixodes* ticks. Adult females are typically found attached to the host in late fall and spring. Their small, inornate brown scutum is often overshadowed by a large, soft, cream-colored engorged abdomen (Fig. 85.14; see Fycks have short anterior mouthparts, prominent broad "antennae", and an upside-down U-shaped ventral groove with its apex anterior to the anus.

Clinical features

Ixodes ticks are vectors for Lyme disease, babesiosis, and human granulocytic anaplasmosis (HGA)[42,43]. Babesiosis is a malaria-like illness, whereas HGA is an acute febrile illness characterized by leukopenia, thrombocytopenia, and increased serum hepatic transaminases. In the western US, *I. pacificus* (the western blacklegged tick) is the major vector for Lyme disease (see Fig. 76.12). In the Great Lakes region and eastern US, *I. scapularis* is the major vector. *I. ricinus* and *I. persulcatus* are important vectors for Lyme disease in Europe and Eurasia, respectively. Because the larval and nymph stages of the tick often attach to birds in the spring and summer, avian migration (particularly of robins) may be responsible for the broad geographic distribution of the tick and of Lyme disease.

A single *Ixodes* tick may transmit more than one disease. In one study of a rural New Jersey county, 55% of adult *I. scapularis* ticks carried at least one disease (Lyme disease, 43%; babesiosis, 5%; HGA, 17%) and 10% carried more than one of the three diseases. Co-infection with more than one of these three diseases is also common in Wisconsin and Minnesota, and *I. scapularis* has been reported to carry both Lyme disease and HGA in New York City parks.

Ixodes ticks carry viral encephalitis in Europe and transmit rickettsial infections in Europe and Australia (see Table 76.1). Emerging infectious diseases that are transmitted by *Ixodes* ticks include a viral-like illness or relapsing fever due to the spirochete *Borrelia miyamotoi* (Asia, Europe, North America), Powassan encephalitis due to a flavivirus (northeastern US, Great Lakes region), ehrlichiosis due to *E. muris eauclairensis* (Minnesota and Wisconsin), and neoehrlichiosis due to *Candidatus* Neoehrlichia mikurensis (Europe and Asia).

Mites (Class Arachnida: Subclass Acarina)

Key features

- Mites are identified by their mouthparts and legs; the shape of their body, dorsal plates, and shields (sternal, anal, and genitoventral); and the setae (bristles or hairs) on the latter structures
- Trombiculid mites are typically larval (chiggers; six-legged) when attached to a host; they are vectors for scrub typhus
- *Cheyletiella* mites are commonly found on pets and may produce papular or vesiculobullous lesions in the owner
- Species that parasitize birds, mammals, and grains can produce dermatoses; the house mouse mite is a vector for rickettsialpox

Introduction

Mites are small arachnids that range from 0.1 to 2 mm in length. Tens of thousands of species exist worldwide (Table 85.5). The majority of mites

MITE FAMILIES	
Acaridae	Food mites
Demodicidae	Follicle mites
Dermanyssidae	Bird, rodent mites
Glycyphagidae	Food mites
Haemoganasidae	Straw mites
Psoroptidae	Mange, scab mites
Pyemotidae	Grain mites, straw mites
Sarcoptidae	Scabies mites
Trombiculidae	Chigger, harvest mites

Table 85.5 Mite families.

MITES OF MEDICAL IMPORTANCE	
Acarus siro	Grain mite: hay, grain, house dust; **baker's itch**
Cheyletiella spp.	**Walking dandruff on pets**
Cheyletus malaccensis	Wheat mite; **wheat warehouse itch** (Japan)
Demodex spp.	**Folliculitis;** possibly **rosacea, blepharitis; demodectic mange** in dogs and cats
Dermanyssus gallinae, D. avium	Fowl mite: chickens, wild birds, rodents, rabbits
Dermatophagoides farinae, D. pteronyssinus	Dust mite (**allergy**): dust, blankets, mattresses, pillows, pets, stored foods and grains
Euroglyphus maynei	Dust mite; **allergy, cross-reactions with other dust mites**
Glycyphagus domesticus	Cheese mite, barn mite, grocer's mite: cheese, grains, hay, mattresses; **grocer's itch**
Laelaps spp., *Androlaelaps* spp., *Eulaelaps* spp.	Rodent mites
Lepidoglyphus destructor	Dust mite, hay mite
Liponyssoides (Allodermanyssus) sanguineus	House mouse mite; **rickettsialpox**
Neotrombicula autumnalis	Harvest mite (Northern Europe)
Ophionyssus natricus	Snake mite
Ornithonyssus sylviarum, O. bacoti, O. bursa	Tropical rat mite, fowl mite, tropical fowl mite, northern fowl mite: rodents, chickens, wild birds, carnivores
Pyemotes ventricosus, P. tritici	Straw itch mite, grain mite: parasites of insects in grains and straw; **Pyemotes dermatitis**
Trombicula (Eutrombicula) alfreddugesi	Chigger mite, red bug, harvest mite (US)
Trombicula (Leptotrombidium) akamushi, L. deliense, L. fletcheri, L. arenicola, L. pallidum, L. pavlovskyi, L. scutellare	Scrub mite; **scrub typhus**
Tyrophagus putrescentiae	Mold mite, grain storage mite; **copra itch**

Table 85.6 Mites of medical importance. Scientific names, common names and associated diseases (in bold) are listed. With the exception of *Demodex* and dust mites, mite bites typically lead to pruritic papular eruptions in humans.



Fig. 85.15 Avian mite bites. Multiple erythematous pruritic papules, several of which have hemorrhagic crusts. The exposure was birds nesting on the patient's house. *Courtesy Jean L. Bolognia, MD.*

are free-living, but thousands of species parasitize animals or plants. Like fleas, most mites lack host specificity. Mites of medical importance may cause skin lesions, incite allergic reactions (especially in atopic individuals), or spread disease (Table 85.6). Like ticks, mites mature through larval, nymph, and adult stages. Typically, there is a single larval stage (referred to as chiggers in trombiculid mites) and several nymphal stages. Most mites lay eggs, but some, such as the spiny rat mite (*Laelaps echidninus*), are viviparous, producing non-motile larvae. The straw itch mite (*Pyemotes tritici*) retains its young until they emerge as sexually mature mites. Sarcoptic mites are relatively species-specific and complete their entire life cycle on the host (see Ch. 84).

Clinical features

Cutaneous reactions to mites are common and include papular, papulovesicular, bullous, urticarial, and morbilliform eruptions (Fig. 85.15). Chigger bites most often affect the lower legs, skin at the edges of underwear, and the genital region. Larvae of trombiculid mites in Asia are vectors for scrub typhus, while house mouse mites transmit rickettsialpox (see Ch. 76). Eschars at the site of the bite are a clue to rickettsial disease, and serologic testing can be helpful. As with tick-borne rickettsial diseases, biopsy of the eschar can be sent for immunohistochemical staining or PCR to distinguish typhus group organisms from the spotted fever group.

Differential diagnosis

Mite-induced dermatoses are often misdiagnosed. Bullous lesions are especially common, and false-positive direct immunofluorescence has been described. Histologic features resembling those of an insect bite may suggest the correct diagnosis, as may a clinical pattern of skin lesions corresponding to areas of exposure. However, eosinophil-rich subepidermal bullae occur in both mite infestation and bullous pemphigoid, so a careful history is essential.

Mite-induced dermatitis can be associated with pets, rodents, straw bedding, bird nests, grains, and even onion bulbs (see Table 85.6). Avian mite dermatitis may also be associated with pet rodents, such as gerbils. Pets should be examined by a knowledgeable veterinarian; skin scraping, adhesive tape stripping, or biopsy may reveal the mite(s) on the animal. Vacuum cleaners can also be fitted with filters to collect mites (Table 85.7). Another helpful technique is to spray areas of dandruff or crust on a pet with an acaricidal agent recommended by a veterinarian. A fine-toothed comb or toothbrush is then used to remove the scale-crust, which is placed in a sealed bag. When alcohol is added to the bag, scale-crust and hair will sink, whereas mites will float.

Treatment

Some types of mites inflict a "bite and run" injury, while others remain attached for a prolonged meal. Scraping, tape stripping, or vigorous washing with soap and water are all effective in removing or killing attached mites. Scrapings, tape strippings, and biopsy specimens may be helpful diagnostically as well as therapeutically.

PREPARATION OF COLLECTED MITES FOR MICROSCOPIC EXAMINATION
Preferred method
• Clear with either lactic acid or lactophenol (may take hours to days) • Wash with water • Mount in Hoyer's medium*
Rapid method
• Mount live or alcohol-fixed mites directly in Hoyer's medium* • Mount live mites in Permount™ (details of mites less obvious)
*Prepared by adding 30 g of gum arabic to 50 ml distilled water, then adding 200 g chloral hydrate followed by 20 g glycerin; filter through cheesecloth.

Table 85.7 Preparation of collected mites for microscopic examination. If mites are collected onto filters inside a vacuum cleaner, the filter samples are treated with potassium hydroxide (KOH) and then floated in concentrated sugar solution to collect the mites.

Definitive treatment requires avoidance or treatment of the infested source. Mite identification can be helpful in establishing the likely source. Management strategies differ for free-living, zoonotic, and grocery mites. An acarologist can be of immeasurable value in this setting, and the *Medical and Veterinary Entomology* text by Gary Mullen and Lance Durden is an excellent resource. As noted above, animals should be examined and treated by a veterinarian. In public parks and training areas, animal exclusion and acaricides may be helpful measures. Personal protection with permethrin-treated clothing is also of value.

Skin lesions in humans may be treated with topical antipruritics such as camphor and menthol, or with topical anesthetics such as pramoxine. Potent topical corticosteroid preparations can be helpful, especially when occluded. Intralesional corticosteroid injections and excision of pruritic nodules may be necessary. Bullous and excoriated lesions can develop secondary infections, and appropriate wound care is important. Home remedies typically attempt to remove or kill attached mites and reduce itch with counterirritants (e.g. propylene glycol-containing deodorant sticks). Patients may present with irritant and allergic contact dermatitis to antiseptics, nail polish, or even battery acid.

Chiggers

Introduction

Trombiculid mites are oviparous, depositing their eggs on the ground, leaves, or blades of grass. After several days, the egg cracks, but the mite remains in a quiescent prelarval stage. Following the prelarval stage, the six-legged larvae (chiggers) actively search for a suitable host. It is the larval mite that is found attached to the host. After a prolonged meal, the larvae drop off and mature through the eight-legged free-living nymph and adult stages.

Clinical features

Chigger bites are intensely pruritic, especially in highly sensitized individuals. Grouped papules, vesicles, or bullae are typically found on the lower extremities, or where elastic meets the skin. Seasonal penile swelling associated with pruritus and dysuria in children, referred to as "summer penile syndrome", appears to represent a hypersensitivity response to chigger bites.

Treatment

The topical antipruritics and anesthetics discussed above may be helpful. Most patients presenting to a dermatologist require potent topical or intralesional corticosteroid therapy. Vigorous washing with soap and water immediately after the exposure is helpful. Treatment of clothing with permethrin is a useful strategy for prevention.

Cheyletiella

Introduction

Cheyletiella are non-burrowing mites that are commonly found on cats (*C. blakei*), rabbits (*C. parasitovorax*), and dogs (*C. yasguri*). In humans, they are a frequent cause of cryptic mite-induced dermatitis. Infestations in animals are variably pruritic and produce a subtle dermatitis that presents with dry white scales, which is sometimes termed "walking dandruff". The animal should be evaluated by a veterinarian, and it is important to note that a single negative scraping does not exclude cheyletiellosis. In a study of dogs with *Cheyletiella*, samples collected by using a vacuum cleaner on the dog were shown to be significantly more sensitive than tape stripping, hair plucking, or skin scraping.



Fig. 85.16 *Cheyletiella* bites. These mites are non-burrowing and are found on cats, rabbits, and dogs.

Clinical features

The typical patient with *Cheyletiella* dermatitis is a young or middle-aged woman who presents with grouped pruritic papules (Fig. 85.16). Bullous eruptions have also been described. It is uncommon to find the mite on the patient.

Treatment

Skin reactions in humans should be treated as described above. Treatment of the animal should be directed by a veterinarian.

Spider Bites (Class Arachnida: Order Araneae)

Spiders are arachnids related to scorpions, ticks, and mites. Many species of toxic spiders are found worldwide. The bite of *Phoneutria* wandering spiders in Brazil can be fatal in children, but most spider bites result only in a local cutaneous reaction. Toxic spiders are often regional in distribution, and many are poorly characterized. The most clinically significant spiders are discussed below. It is noteworthy that many important species in the US were not native to North America, but were imported in recent years as a result of worldwide travel and commerce. Examples are the hobo spider and *Loxosceles laeta* spider.

Widow Spiders (*Latrodectus*)

Key features

- Black widows are large, shiny black spiders with a round abdomen
- A variety of black, brown and red widow spiders exist worldwide
- In *Latrodectus mactans*, a red hourglass shape is seen on the ventral abdomen
- Acute pain and edema occur at the bite site
- Systemic symptoms mimic acute abdomen and may include rhabdomyolysis

Introduction

Widow spiders (*Latrodectus* spp.) are found worldwide, with five species including black, brown, and red variants in North America alone. *Latrodectus mactans* is the most common black widow spider in

North America, with a range that extends to the Caribbean islands. *L. tredecimguttatus*, *L. curacaviensis*, and *L. indistinctus* are black widow spiders found in Europe, South America, and Africa (referred to as a button spider), respectively. Female black widow spiders from North American species have a red hourglass-shaped mark on the ventral abdomen, while species from other areas of the world have different red patterns. Brown (*L. geometricus*) widow spiders characterized by an orange ventral hourglass shape have a widespread distribution that includes the US, South America, and Africa. Australia has the red-back spider (*L. hasselti*) and New Zealand the red katipo spider (*L. katipo*).

Widow spiders are typically found in woodpiles, in shoes, and under outhouse seats. Human envenomation usually occurs when the spider's environment is disturbed, and the spider is inadvertently trapped or pressed against the skin. Widow spiders are more aggressive when protecting an egg sack.

Pathogenesis

Black widow venom contains latrotoxins that act by depolarizing neurons, increasing intracellular calcium, and stimulating uncontrolled exocytosis of neurotransmitters. Divalent cation-dependent tetramers related to α-latrotoxin can insert into lipid bilayers, forming membrane pores. Calcium-independent receptors for latrotoxin have also been identified.

Clinical features

The degree of morbidity caused by widow spider bites varies depending upon the amount of venom injected and the site of the bite as well as the species, age, and sex of the spider, with only adult females capable of envenomation. Local skin reactions are usually limited to transient erythema, edema, sweating, and piloerection. Extracutaneous manifestations are often prominent and can include painful muscle spasms (initially around the bite site, then more widespread), symptoms suggestive of an acute surgical abdomen, headache, and nausea; generalized diaphoresis may also occur. The symptoms of brown widow bites tend to be milder and restricted to the tissues near the bite.

Treatment

Benzodiazepines and intravenous calcium gluconate can be helpful for associated tetany. In one study, calcium gluconate was shown to be superior to methocarbamol (Robaxin®). Antivenin can produce rapid relief of tetany and complications such as priapism that are unresponsive to other agents. Purified equine Fab fragment-based antivenin is associated with a lower risk of hypersensitivity reactions than classic antivenin.

Loxosceles Spiders

Key features

- Brown recluse spider (*Loxosceles reclusa*) has a small body and long legs
- Dark brown fiddle pattern present on cephalothorax
- Dermonecrotic bite reactions
- Systemic reactions include shock, hemolysis, renal insufficiency, and disseminated intravascular coagulation
- Other *Loxosceles* spiders can produce similar reactions

Introduction

Loxosceles spiders are found throughout the world and classically have a dark brown, violin-shaped marking on the dorsal cephalothorax (Fig. 85.17). In the US, bites from *L. reclusa* (the brown recluse spider), *L. laeta*, *L. rufescens*, *L. deserta*, and *L. arizonica* can cause skin necrosis, although reactions to the latter three species are generally mild. Many other spiders are capable of producing dermonecrotic or systemic reactions, and bites of these spiders are often erroneously attributed to the brown recluse spider. Brown recluse spiders are most common in the south central US, from Tennessee and Missouri to Oklahoma and Texas (Fig. 85.18). They are often found in woodpiles, in attics, and under radiators.

Most bites occur when the spider has been disturbed. *Loxosceles* spiders are non-aggressive, and there are reports of families living in houses infested by thousands of brown recluse spiders without a single bite. This suggests that brown recluse bites are overdiagnosed, especially in regions where the spider is rare. The diagnosis can be confirmed by an enzyme immunoassay to detect *Loxosceles* venom in a skin biopsy specimen or plucked hairs (obtained up to 4 days after the bite) or by a passive hemagglutination inhibition test (up to 3 days after the bite); in addition, reduced glycophorin A on the erythrocyte surface may represent a marker of venom exposure.



Fig. 85.17 Brown recluse spider (*Loxosceles reclusa*). This spider has a small body, long legs, three pairs of eyes, and a dorsal violin pattern on the cephalothorax.

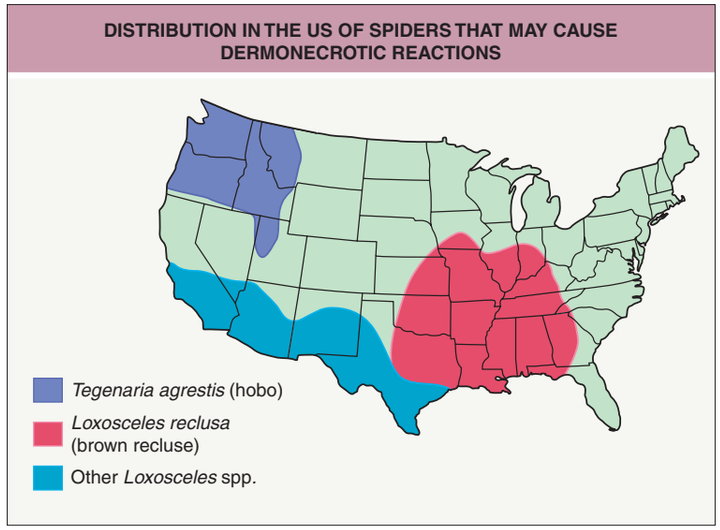


Fig. 85.18 Distribution in the US of spiders that may cause dermonecrotic reactions. The potential for hobo spider bites to result in dermonecrosis is debated in the literature. *Adapted from: Sams HH, Dunnick CA, Smith ML, et al. Necrotic arachnidism. J Am Acad Dermatol. 2001;44:561–73.*

Pathogenesis

Sphingomyelinase D is the major toxin in brown recluse venom, and it interacts with serum amyloid protein. Hyaluronidase allows eschars to spread in a gravity-dependent fashion. Neutrophils are not directly activated by the venom, and neutrophil activation may be dependent upon the interaction between the venom and endothelial cells. The venoms of geographically diverse spiders such as *L. reclusa*, *L. laeta*, *L. deserta*, *L. gaucho*, and *L. intermedia* have similar sphingomyelinase activity and electrophoretic profiles, with a major protein band at 32–35 kDa. All contain hyaluronidase as well as metalloproteinases



Fig. 85.19 Dermonecrotic spider bite. Note the central dusky necrosis. The patient was initially misdiagnosed with cellulitis and hospitalized after failure to respond to oral antibiotic therapy.

with fibrinogenolytic activity. The similarity of these venom components and documented cross-reactivity suggests the potential for a single global *Loxosceles* antivenin[44].

Clinical features

The majority of bites by *Loxosceles* spiders, including the brown recluse, do not cause serious reactions. Local pain is frequently delayed until several hours after the bite, which most often occurs on an extremity (Fig. 85.19). Cutaneous reactions typically begin with erythema and then develop central vesiculation or duskiness with a blanched halo, which may evolve into hemorrhagic bullae and necrosis[45]. Dermonecrotic reactions can eventuate in dry, necrotic eschars or ulceration. Upper airway obstruction caused by envenomation of the neck by brown recluse spiders has been reported. Systemic reactions include thrombocytopenia and Coombs-positive hemolytic anemia[46,47]. *L. arizonica*, a spider found in the southwestern US, causes less severe necrosis but has been implicated as a cause of shock.

Pathology

Histologic findings have been best described in laboratory models of brown recluse spider envenomation in rabbits[48]. The findings are time-dependent, with early biopsy specimens demonstrating a neutrophilic infiltrate. Later changes include "mummified" coagulative necrosis of the epidermis, adnexal epithelium, and superficial dermis. A neutrophilic band-like infiltrate may still mark the border between viable skin and eschar. Small vessel vasculitis and thrombosis are often evident adjacent to the neutrophilic band, and larger vessel vasculitis resembling polyarteritis nodosa may account for the extent of tissue necrosis seen after some bites. Arterial thrombosis leading to gangrene of the foot has been reported[49].

Treatment

Optimal treatment to prevent dermonecrotic reactions remains elusive. Most bites can be treated with rest, ice, and elevation. Intradermal injection of polyclonal anti-*Loxosceles* Fab fragments can attenuate necrosis in an animal model up to 4 hours after envenomation, and antivenin may reduce the ultimate size of the necrotic area even when administered up to 48 hours after envenomation[50]. Hyperbaric oxygen therapy may decrease the final size of ulceration, although results have varied. Studies with more widely available agents such as dapsone, colchicine, and prednisone have been inconsistent and often disappointing[51]. Dapsone therapy is complicated by the risk for hemolysis, especially in individuals who have a glucose-6-phosphatase dehydrogenase (G6PD) deficiency. Current recommendations for systemic therapy are limited to antivenin (if available) and prednisone (for systemic reactions). Anecdotal reports and some animal data also suggest that intralesional triamcinolone may have some efficacy for dermonecrotic reactions[51]. The complement inhibitor eculizumab was shown to prevent brown recluse venom-induced hemolysis *in vitro*, and clinical studies are needed to determine the drug's therapeutic potential for brown recluse bite reactions.

Funnel Web Spiders

Key features

- Large, hairy, aggressive spiders found in dark, moist areas such as basements
- Funnel-shaped webs
- *Tegenaria agrestis* (hobo spider, aggressive house spider), found in the northwestern US, Canada and Europe, is 4–5 cm in diameter and may occasionally cause dermonecrotic reactions
- Other funnel web spiders can produce local and systemic reactions

Introduction

When *Tegenaria agrestis* (hobo spider) was imported to North America from Europe, this spider found few major competitors and became common in human dwellings in the northwestern US (see Fig. 85.18), usually in basement webs at soil level in contact with concrete or stone. In Europe, the hobo spider has a largely rural habitat while the less aggressive *T. gigantea* (also known as *T. duellica*; giant house spider) and *T. domestica* (domestic house spider) are more likely to be found in human dwellings. The sternum of the hobo spider has a lightly colored center and dark vertical bands on the sides.

The most medically important funnel web spiders, *Hadronyche* and *Atrax*, are endemic to eastern Australia. These spiders produce potent neurotoxins, and their bites can result in severe systemic symptoms (see below). Similar reactions may occur following bites from *Phoneutria*, spiders in South America (especially Brazil) and Costa Rica.

Pathogenesis

Australian funnel web spider robustoxin contains small peptide neurotoxins (δ-atracotoxins) that slow tetrodotoxin-sensitive, voltage-gated sodium channel inactivation, resulting in catecholaminergic and cholinergic excess when severe envenomation occurs in humans. In contrast, agatoxins from the native American funnel web spider (*Agelenopsis aperta*) target ion channels and paralyze insect prey but are not medically significant to humans.

Clinical features

Whether *T. agrestis* bites can potentially produce dermonecrosis or systemic symptoms represents a subject of controversy[52]. There are very few documented reactions to bites from this spider in the literature, and studies have failed to demonstrate induction of cutaneous necrosis or hemolysis by *T. agrestis* venom in animal and laboratory models[53]. Bites of Australian funnel web spiders of the genera *Hadronyche* and *Atrax* are often associated with extreme pain, puncture marks, local redness, and bleeding. For these spiders, severe envenomation is characterized by autonomic excitation (e.g. diaphoresis, hypersalivation, brady- or tachycardia, hypertension) and neuromuscular symptoms (e.g. paresthesias, fasciculations, muscle spasms), which may culminate in myocardial injury and shock without antivenin therapy.

Tarantulas (Family Theraphosidae)

Key features

- Typically large hairy spiders, up to 15 cm in diameter
- Normally non-aggressive
- Urticating hairs are thrown at skin and eyes
- Important cause of ophthalmia nodosa

Introduction

Tarantulas are large hairy spiders common in the southwestern US, and related species are found throughout the world. They are often sold in pet stores. Most tarantula bites do not produce severe systemic toxicity.

Many species of tarantulas possess urticating hairs in a characteristic patch on the dorsal abdomen. These hairs are used in a defensive

fashion to drive predators from the spider's burrow. Vibrations of the hind legs are used to flick hairs at the perceived attacker. Urticating hairs are absent on most African and Asian species.

Clinical features

Itching at the site of urticating hair penetration may persist for several weeks after exposure. Hairs that penetrate the cornea can result in ophthalmia nodosa, a chronic granulomatous reaction that can lead to loss of vision.

Pathology

Urticating tarantula hairs penetrate the stratum corneum and epidermis and may extend as deep as the reticular dermis.

Scorpions (Class Arachnida: Order Scorpiones)

Key features

- Large anterior claws
- When threatened, the long tail is curved upward to sting
- Blunt thorn on the tail of *Centruroides* spp.

Introduction

Many toxic scorpions exist worldwide[54]. Scorpions are typically found under tabletops, in woodpiles, and in shoes. They sting when disturbed and accidentally trapped by a hand or foot. Several clinically relevant species are listed in Table 85.8.

Clinical features

Local and systemic symptoms (e.g. pain, paresthesia) are typically out of proportion to cutaneous signs such as erythema and edema, which are not usually prominent at the site of the sting. Most fatalities are related to cardiorespiratory manifestations, including cardiogenic shock and pulmonary edema, in children younger than 10 years of age. Pancreatitis is also an important cause of morbidity after scorpion envenomation.

Treatment

Antivenin is available in endemic areas and, along with supportive care, has been shown to reduce morbidity and mortality from severe scorpion envenomation[55,56]. However, application of ice is sufficient for most minor scorpion envenomations. Prazosin reverses the autonomic storm characteristic of Indian red scorpion (*Hottentotta tamulus*) envenomation, resulting in accelerated recovery and preserved myocardial function. Tacrolimus was also found to have protective effects against systemic toxicity from scorpion envenomation in an animal model[57].

SELECTED CLINICALLY IMPORTANT SCORPION SPECIES

Region	Species	Comments
Africa, Asia	*Parabuthus granulatus, P. transvaalicus, Androctonus australis, A. crassicauda, Leiurus* spp., *Hemiscorpius lepturus*	*Parabuthus* (Africa) and *Androctonus* (North Africa, Middle East) spp. have fat tails; highly toxic
North Africa, Europe	*Buthus* spp.	Less toxic
South Asia	*Hottentotta (Mesobuthus) tamulus*	Red color; toxic
Brazil	*Tityus serrulatus*	Yellow color; implicated as a cause of death in children
Southwestern US, especially Arizona	*Centruroides exilicauda*	Very rarely associated with deaths; public health risk has been overestimated
Central US, especially Texas	*Centruroides vittatus*	Painful sting
US, Mexico, Central America	*Centruroides sculpturontus, C. noxius*	More toxic; some deaths attributed to *C. exilicauda* may be due to these species

Table 85.8 Selected clinically important scorpion species.

CENTIPEDES (CLASS CHILOPODA) AND MILLIPEDES (CLASS DIPLOPODA)

Key features

Centipedes

- Long, worm-like bodies that are flattened dorsoventrally
- 17 or more segments; up to 20 cm in length
- Each segment, except the last one, has one pair of legs
- Pain, edema and erythema at bite sites

Millipedes

- Long, cylindrical, worm-like bodies with many segments
- Each segment has two pairs of legs and two pairs of respiratory spiracles
- Do not bite (biting jaws are absent), but can cause chemical irritant contact dermatitis

Introduction

Centipedes are fierce hunters. They inject a neurotoxic venom through ducts in their jaws. Millipedes do not bite but can cause burn-like reactions.

Clinical features

Centipede bites may produce pain, erythema, and edema. The bites can bleed profusely and are frequently associated with paresthesia. Centipede ingestion by children can result in systemic toxicity. Rarely, bites lead to severe systemic manifestations such as myocardial ischemia, rhabdomyolysis, proteinuria, and renal failure. The Vietnamese centipede, *Scolopendra subspinipes*, is a large, aggressive tropical centipede that has recently become popular as a pet, and local bite reactions can be severe.

Millipedes do not bite, but they can secrete noxious substances that result in chemical irritant contact dermatitis. Millipede burns frequently involve the eyes, and millipedes in line-dried clothing can produce widespread dermatitis. Of note, millipede burns and associated brownish skin discoloration (which can persist for months) may be misdiagnosed as child abuse.

Treatment

Centipede bites seldom require more than symptomatic treatment, although systemic symptoms may be very frightening to the patient. Children bitten by a centipede often report they have been bitten by a snake. The minor degree of edema compared to that associated with snake bites as well as the characteristic chevron shape of the centipede bite can be helpful distinguishing features. Ice packs, analgesics, and hot water immersion provide similar improvements in pain after centipede envenomation[58].

SNAKE BITES

Key features

- Rapid onset of pain and swelling
- Symptoms depend on the species and amount of venom injected
- Antivenin may be life-saving, but it does not prevent all complications and may cause anaphylaxis

Introduction

Snake bites occur primarily in individuals who engage in outdoor activities, especially camping and hiking. Occupational bite injuries may

also affect those who raise snakes and are particularly common in those who extract venom. Death from a snake bite is rare in the US but more common in Africa and Asia[59].

Clinical features

Snake bites are typically associated with marked edema within an hour of the envenomation. Hemorrhage and necrosis are common. The presence of paired bite marks is often noted.

Treatment

Antivenin therapy is an important part of management and may be of benefit even when administration is delayed. Adverse reactions to antivenin include serum sickness and anaphylaxis. Preparations to treat anaphylaxis should be made before initiating antivenin therapy. Hypersensitivity to antivenin is a particular problem for those who have been previously treated. The evaluation of antivenin reactions is complicated because serum sickness and snake bites share some signs and symptoms, and repeated snake bites can be independently associated with IgE-mediated anaphylaxis. Even in individuals who have never received previous treatment, snake antivenin can result in anaphylactoid reactions.

Thrombocytopenia induced by rattlesnake venom is only partially reversed by antivenin (Crotalidae) administration, and disseminated intravascular coagulation caused by North American crotalid snakebites can occur even after antivenin treatment. The risk of severe bleeding is higher in patients who take antiplatelet drugs[60].

Tourniquets to limit systemic toxicity from the venom may lead to tissue ischemia if improperly applied. Studies have not been performed for all snakes, but tourniquet application appears to be of little benefit.

DOG AND CAT BITES

Key features

- Bites may be unprovoked, especially with dogs
- Infection is common and pathogens include *Pasteurella* spp. and *Capnocytophaga canimorsus*
- Antibiotic treatment is generally considered mandatory

Introduction

Cat bites are commonly provoked, whereas dog bites are often unprovoked. Dog bites are particularly common in children, and the dog is usually a family pet or a neighbor's dog.

Rabies still occurs almost everywhere in the world, with exceptions including New Zealand, parts of Europe, parts of South America, and isolated Pacific islands. Rabies associated with dog bites remains a problem in low-income countries. Fortunately, because of vaccination programs, rabies related to dog bites is rare in high-income countries, where most human rabies is associated with bat exposure. In the US, rabies is carried primarily by bats, raccoons, and skunks. Although unvaccinated dogs occasionally acquire rabies from wild animals, the canine rabies virus variant that is responsible for dog-to-dog transmission has not been detected in the US since 2004. Oral rabies vaccination programs using bait to target gray foxes and coyotes in Texas and raccoons in the eastern US have helped to decrease the spread of rabies.

Local health authorities should be contacted to report a dog or cat bite and (if necessary) to arrange for quarantine. Latex agglutination testing of dog saliva for rabies antigen is 95% sensitive compared to fluorescent antibody testing on brain smears. A scalp biopsy from the hairy area on the nape of the neck can be sent for PCR or fluorescent antibody testing.

Clinical features

Common pathogens associated with bite wounds include streptococci, staphylococci, *Pasteurella* spp., *Capnocytophaga canimorsus*, and anaerobes. Breast implant infection and lung abscesses due to *Pasteurella multocida* have been linked to cat exposure, and staphylococcal endocarditis has been reported after a cat bite (without a preceding local infection); brain abscess formation has been observed following a dog bite. In immunocompromised patients, there is a significant risk of *Pasteurella* or *Capnocytophaga* sepsis. *Capnocytophaga canimorsus* sepsis has a high mortality rate and has been associated with purpura fulminans. Human bites have a higher likelihood of infections with *Staphylococcus aureus* and *Eikenella corrodens*. The most common pathogens associated with bite wound infections are listed in Table 85.9.

Treatment

A combination of a β-lactam antibiotic and a β-lactamase inhibitor (e.g. amoxicillin/clavulanic acid) provides good coverage for most organisms associated with dog and cat bites[61,62]. Alternatives include: (1) second-generation cephalosporins with anaerobic activity (e.g. cefoxitin, cefotetan); (2) penicillin plus a first-generation cephalosporin; or (3) clindamycin plus a fluoroquinolone. The need for hospitalization of patients with *Pasteurella*-infected animal bite wounds is strongly associated with initial use of suboptimal antibiotic therapy. A 3- to 5-day course of preemptive antimicrobial therapy is recommended for patients with immunocompromise, asplenia, advanced liver disease, or edema of the affected area (preexisting or resultant) as well as for injuries that are moderate to severe (especially of the hand or face) or penetrate the periosteum or joint capsule[63]. In addition to appropriate antibiotic therapy, early primary repair is typically indicated for dog bites to the face but is generally not recommended for other body sites[64].

LEECHES

Key features

- Found in fresh water
- Purpura and bleeding

Introduction

Leech attachments occur after contact with bodies of fresh water such as ponds or rivers.

PATHOGENS ASSOCIATED WITH HUMAN AND ANIMAL BITE WOUND INFECTIONS

Bite	Pathogens
Human bites	• *Staphylococcus aureus* • *Streptococcus pyogenes* • *Eikenella corrodens* • Various anaerobes†
Cat bites	• *Pasteurella multocida* (~75%)* • *Moraxella* spp. • *Neisseria weaveri* • *Bergeyella zoohelcum* • Various anaerobes†
Dog bites	• *Pasteurella* spp. (*canis* > *multocida*) (~50%)* • *S. aureus* (~20%) • *Str. pyogenes* • *N. weaveri* • *Capnocytophaga canimorsus* • *B. zoohelcum* • Various anaerobes†
Horse and sheep bites	• *Actinobacillus* spp. • *Pasteurella* spp. • Various anaerobes†
Marine animal bites	• *Vibrio* spp. • *Aeromonas hydrophila* • *Pseudomonas* spp. • *Plesiomonas shigelloides*

*Relatively short incubation period of 12–24 hours.
†May include *Fusobacterium*, *Bacteroides*, *Porphyromonas*, and *Prevotella* spp.

Table 85.9 Pathogens associated with human and animal bite wound infections. Most infections are polymicrobial and include aerobic and anaerobic bacteria (median of 4–5 isolates), which can originate from the skin of the patient as well as the oral flora of the biting animal or human.

Pathogenesis

Leeches prevent blood coagulation, partly through interference with platelet aggregation. Medical leeches have been associated with *Aeromonas hydrophila* wound infection[65].

Clinical features

Leech attachment sites often become purpuric and may bleed freely when the leech is removed. Leeches can attach to the tonsils (resulting in hemoptysis) or inside the nose (causing epistaxis). Disordered coagulation associated with massive bleeding and anemia has been reported after a leech bite.

Treatment

Leech removal is often complicated by bleeding or infection. Saturated salt solutions have been used to facilitate leech removal.

Leech therapy

Medical leeches and hyperbaric oxygen have been used together to enhance the survival of skin flaps subjected to venous occlusion. Sated leeches can be induced to continue feeding from the flap by posterior crop (stomach) incision and immersion in a serotonin solution.

MARINE INJURIES

Key features

- Marine organisms contain some of the most potent toxins known
- Drowning can occur after loss of consciousness following envenomation
- Penetrating injuries are prone to secondary infection
- Marine *Vibrio* infections are more common in patients with liver disease
- First aid for most marine venoms includes immersion in hot, but not scalding, water

Introduction

Penetrating marine injuries may be complicated by secondary bacterial infection. *S. aureus* is the most common organism, but *Vibrio* infections also occur. *Vibrio vulnificus* sepsis is strongly associated with liver disease, especially cirrhosis (see Ch. 74). Although most infections are related to ingestion of oysters or injuries in brackish water, the organism can survive on the skin for more than 24 hours, and infection has been reported after a penetrating injury on dry land. With warming of the oceans, there has been a northward extension of the geographic range of *Vibrio*. Seal finger, resulting from seal bites to the hand, is caused by *Mycoplasma* infection. Cutaneous infections with *Erysipelothrix rhusiopathiae* (see Ch. 74), *Aeromonas hydrophila*, and *Mycobacterium marinum* (see Ch. 75) can also be acquired from trauma in an aquatic environment.

Pathogenesis

Cnidarians (including jellyfish, corals, and sea anemones) are aquatic animals that produce specialized epidermal cells called cnidocytes with organelles referred to as nematocysts or stinging capsules. A physical (e.g. contact with a foreign body) or osmotic trigger causes a coiled, inverted, hollow filament within the nematocyst to be ejected externally and discharge its toxic contents.

Clinical features

Sea urchins are echinoderms with fragile spines that break easily in the skin. Pigment from the spine often diffuses into the wound, making it difficult to find and remove the spine. Only about 80 of the roughly 600 species of sea urchin described are known to be hazardous to humans. Long-spined urchins such as the black sea urchin (*Diadema setosum*) are often a problem, and spines embedded near joints have been associated with synovitis and arthritis. Sea cucumbers, another type of echinoderm, can eject an irritating visceral liquid.

Seabather's eruption (sea lice) is characterized by pruritic papules located under the bathing suit (Fig. 85.20) and in intertriginous areas. It may be caused by a variety of stinging larvae, including those of the thimble jellyfish (*Linuche unguiculata, L. aquila*), common in southern waters (e.g. the Florida coast and Caribbean). Seabather's eruption acquired off the coast of Long Island, New York, is typically caused by larvae of a sea anemone (*Edwardsiella lineata*). Swimmer's itch, in contrast, affects exposed skin after wading or swimming in bodies of fresh water; this condition is related to cercariae (free-swimming larvae) of avian schistosomes (see Ch. 83).

Jellyfish stings result in immediate pain as well as delayed and occasionally recurrent cutaneous reactions. Erythematous, urticarial, or hemorrhagic streaks may be observed (Fig. 85.21), and they tend to be longer and fewer in number following contact with larger jellyfish. A lichen planus-like eruption and inflammation distant from the site of envenomation have also been reported. *Chironex fleckeri*, the Pacific box jellyfish or sea wasp, is generally considered the most dangerous of the jellies, and stings often result in shock. Confirmation of envenomation can be obtained by tape stripping of nematocysts from skin. *Physalia physalis*, the Portuguese man of war, is found in southern waters of the Atlantic while *Physalia utriculus*, the blue bottle jellyfish, is seen in the Pacific. These *Physalia* spp. contain nematocysts but are actually siphonophores, not true jellyfish. *Cyanea* and *Chrysaora* sea nettles are common causes of jellyfish dermatitis. Storms frequently drive jellies into shallow water in great numbers.

Haloclava producta, the "ghost anemone", is a burrowing sea anemone found off the east coast of the US and in the Gulf of Mexico.



Fig. 85.20 Seabather's eruption. Edematous pink papules in the same distribution as the bathing trunks. *Courtesy Kalman Watsky, MD.*



Fig. 85.21 Jellyfish sting. Painful red papules and papulovesicles in multiple linear streaks. *Courtesy Joyce Rico, MD.*

It is responsible for summer outbreaks of dermatitis off the coast of Long Island, New York. Corals are another group of stinging cnidarians in the same class (Anthozoa) as sea anemones. Coral cuts can be slow to heal and should be washed vigorously. Fire corals are false corals that produce intense stinging and a papular eruption that can last for several days. Cnidarian nematocysts found in seaweed and in the dorsal papillae of nudibranch sea slugs can also cause dermatitis. Exposure to algae alone can lead to dermatitis as well, referred to as seaweed dermatitis (see Ch. 17).

Red sponges and fire sponges (members of the phylum Porifera) both cause dermatitis. Sponge dermatitis is related to spicules embedded in the skin, but sponge diver's disease is caused by the stings of sea anemones attached to the base of sponges. Local itching and burning progress to erythema and vesiculation. Systemic symptoms such as nausea, vomiting, and headache are common.

Two classes of the phylum Mollusca, cephalopods and gastropods, have been linked to human envenomation. The blue-ringed octopus contains a potent venom. This small cephalopod is often only 10 cm long and is found in waters off the coast of Australia. Envenomation from cone shells (marine gastropods) may be associated with a 20% mortality rate. The shells are about 10 cm in length and tend to be found in shallow water, mainly in tropical and subtropical climates.

Encounters with stingrays can result in soft tissue injury and embedded spines. Death has been reported after a penetrating chest injury from a stingray barb resulting in venom-induced myocardial necrosis. Injuries inflicted by stingrays occur in both fresh and salt water, and pain is the major manifestation.

Lionfish are common in subtropical and tropical waters. Since August 2000, lionfish have been reported along the eastern coast of the US, from Florida to New York. Lionfish belong to the family of scorpionfish (Scorpaenidae). The family includes the genera *Pterois* (lionfish), *Scorpaena* ("true scorpionfish", bullrout and sculpin), and *Synanceia* (stonefish). Stonefish are the most toxic members of the family, although all produce local pain as well as systemic symptoms. Catfish spine injuries occur in both salt and fresh water. They may be associated with local pain, bleeding, and systemic symptoms.

Pathology

Marine *Vibrio* infections cause intense cellulitis affecting the subcutis and dermis. The superficial dermis is devitalized and lacks an inflammatory infiltrate. Bullae are subepidermal in location and non-inflammatory. Many organisms are present, especially around vessels.

Sea urchin spines examined by polarized light microscopy exhibit an ornate symmetric structure produced by calcite crystals. Cutaneous granulomatous reactions may occur.

Histologic sections from sites of jellyfish stings may demonstrate nematocysts penetrating the epidermis and papillary dermis.

Treatment

Avoidance is the best means of preventing injury, which can result from specimens in salt water fish tanks as well as in the ocean. When envenomation occurs in a swimmer, the individual should immediately be removed from the water to prevent drowning. Initial treatment for all marine envenomations includes soaking the site in hot, but not scalding, water to denature some of the venom proteins[66].

Antivenin is available for some of the more toxic species such as *C. fleckeri*, and it was shown to neutralize cardiovascular effects of *C. fleckeri* envenomation in an animal model. In contrast, verapamil did not improve cardiovascular status and increased mortality in the same animal model. In an animal model of envenomation by the *Chiropsalmus* species of box jellyfish, pretreatment with *C. fleckeri* antivenin or $MgSO_4$ did not have any effect on the venom-induced hypertensive response or subsequent cardiovascular collapse. This highlights the importance of species identification following box jellyfish envenomation.

In a study of acute *Carybdea alata* box jellyfish stings, hot water immersion (40–41°C) was more effective than papain meat tenderizer or vinegar. Topical jellyfish sting inhibitors, including lotions in which they are combined with sunscreens, are available. Sea water can be used to remove jellyfish tentacles. Inactivation with acidic or alkaline solutions can be risky, as it may also lead to unexpected discharge of nematocysts. Treatment with topical corticosteroids and calcineurin inhibitors may be helpful for delayed reactions.

Most fish envenomations should be treated with hot water immersion. In a study of fresh water ray envenomation, hot water immersion controlled acute pain, but it did not prevent skin necrosis.

Additional figures and a table on Approach to the Evaluation and Management of Bedbug Infestations, available in our eBook (see inside front cover for access code).

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eFig. 85.1 Insect bite reactions. This patient has excoriated edematous papules, papulovesicles, and hyperpigmented macules. *Courtesy Julie V. Schaffer, MD.*



eFig. 85.2 Sterile pustules at the sites of fire ant stings. *Courtesy Jean L. Bolognia, MD.*





eFig. 85.3 *Paederus* dermatitis. A Erythematous plaque with multiple small vesicles and vesiculopustules. **B** Rove beetle of the genus *Paederus* whose hemolymph contains pederin. *Courtesy Vidal Haddad, Jr, MD.*



eFig. 85.4 *Ixodes scapularis* ticks attached with local inflammatory response (A, B). *Courtesy Kalman Watsky, MD.*



eFig. 85.5 Mite bites in a child after playing on hay bales. *Courtesy Julie V. Schaffer, MD.*



eFig. 85.6 Saturniidae caterpillar. The hairy spines can produce urticaria. *Courtesy Vidal Haddad, Jr, MD.*





eFig. 85.7 Sea urchin injury. A Embedded spines in the plantar surface of the foot. **B** Black sea urchin. *Courtesy Vidal Haddad, Jr, MD.*



eFig. 85.8 Jellyfish sting. Linear vesicles and bullae on the wrist in a woman stung by a Portuguese man o' war (*Physalia physalis*). The linear distribution corresponds to areas of contact with the jellyfish tentacles. *Courtesy José M. Mascaro, Jr, MD.*



eFig. 85.9 Stingray injuries. A, B Reticulated erythema, purpura, and necrosis. **C** *Potamotrygon motoro* freshwater stingray. *Courtesy Vidal Haddad, Jr, MD.*

APPROACH TO THE EVALUATION AND MANAGEMENT OF BEDBUG INFESTATIONS
Diagnosis
• Evaluation begins with assessment for clinical symptoms and environmental findings suggestive of insect bites, which can result in a wide range of skin manifestations depending on the degree of sensitization. Some individuals have little or no reaction, and it is common for only one or a few family members (even those sleeping in the same bed) to report lesions. • Bites usually occur at night on exposed areas of skin, most often the face, neck, arms, and legs. Although patients classically awake with new lesions, the reaction can take several days to appear. • Patients typically present with pruritic, erythematous, edematous papules, sometimes with a visible central hemorrhagic punctum. • The size, degree of itching, and propensity toward vesiculation all increase with repeated exposure. • Patient may observe a linear series often consisting of three bites (“breakfast, lunch, and dinner”). • The psychological consequences of bedbug bites should be considered, including sleep deprivation and phobias.
Management of Infestations
• Patients should carefully scrutinize the bedroom for signs of bedbug infestation. One may encounter fecal smears or flecks of blood on bed linens, inside furniture cracks and crevices, and behind peeling wallpaper. Bedbugs may travel as far as 20 feet for a meal. Densely infested rooms may also have a distinctive, pungent, soda syrup–like odor. • Vacuuming is effective in removing bedbugs but does not remove the eggs. Wash bedsheets and clothing in hot water with detergent with at least 20 minutes in a dryer. Bedbugs have a high thermal death point of 45° C (113° F) and also may survive at temperatures as low as 7° C (44.6° F). Some companies perform a treatment in which the room is heated above 50° C (122° F), which is a lethal temperature for all stages of a bedbug’s life cycle. Coating bedposts with antifriction or adhesive substances such as petrolatum or duct tape may hinder bedbugs from gaining access to the bed. • A combination of chemical and physical intervention is often necessary for complete eradication. All hiding areas must be carefully inspected and cleaned. Treatment may include pesticides, laundering, heat, freezing, vacuuming, and hiring a professional service to eradicate bedbugs. • A pest control professional should be consulted for safe eradication.

eTable 85.1 Approach to the evaluation and management of bedbug infestations. *Adapted from Ferri FF: Bedbug bite. In Ferri FF: Ferri’s Clinical Advisor 2023. Philadelphia: Elsevier, 2023.*

86 Ultraviolet Radiation

Peter Wolf and Thomas M. Rünger

Key features

- Exposure of the skin to UV light has acute, short-term effects and chronic, long-term effects, both of which are wavelength-dependent and occur even at non-erythemogenic doses
- UV light is sensed via absorption by chromophores; these include urocanic acid, nucleotide bases, membrane lipids, tryptophan, and 7-dehydrocholesterol (provitamin D_3)
- UV light induces several types of DNA damage in a wavelength-dependent manner, including 6-4 photoproducts, pyrimidine dimers, and oxidative guanine base modifications; pyrimidine dimers are the most important pre-mutagenic DNA lesions
- UV light-induced mutations play a pivotal role in photocarcinogenesis; some base substitution mutations (e.g. C→T, CC→TT) are so typical for UV light that they have been termed signature or fingerprint mutations
- UV light triggers both pro- and anti-inflammatory responses, primarily via innate immunity and adaptive immunity, respectively
- UV-induced immunosuppression contributes to skin carcinogenesis by induction of regulatory T cells and immunosuppressive cytokines such as IL-10
- The proapoptotic, immunomodulatory, antipruritic, antifibrotic, and propigmentary properties of UV light are employed to treat various inflammatory and neoplastic skin disorders

INTRODUCTION

Dermatologists are confronted daily with the effects of UV light on the skin and often deal with them in a seemingly contradictory way. On the one hand, they have the responsibility of warning their patients against the deleterious effects of sunlight, such as sunburn, photoaging, and sun-induced skin cancers, and on the other hand, they use UV irradiation to treat skin disease[1]. As with all medical interventions, dermatologists are weighing the risks versus the benefits when they use UV light for therapeutic purposes.

SPECTRUM OF UV LIGHT AND ABSORPTION SPECTRA

The sun emits UV radiation as part of an electromagnetic spectrum (see Fig. 134.1). It is usually subdivided, rather arbitrarily, into UVC (200–290 nm), UVB (290–315 nm), and UVA (315–400 nm). UVA has been further subdivided into UVA1 (340–400 nm) and UVA2 (315–340 nm). Of note, some authors use 320 nm as the demarcation between UVA and UVB. More than 95% of the sun's UV radiation that reaches the Earth's surface is UVA. Practically all UVC, and much of the UVB, are absorbed by the oxygen and ozone in the Earth's atmosphere so that UV radiation below 290 nm is virtually undetectable at ground level. However, the remaining UV radiation can still be absorbed by biologic molecules (DNA, protein, lipids) and can damage cells.

In order to survive in our environment, all living organisms have had to develop protective mechanisms to prevent UV-induced lethality and to maintain the stability of their genome. These protective mechanisms include the development of UV-absorbing and -reflecting surface layers, enzymatic and non-enzymatic anti-oxidative defenses, repair processes, and removal of damaged cells. Via evolution, humans have lost most of their UV-protective fur, which remains an effective UV-protector only on the scalp. Nonetheless, the human skin is quite effective in protecting the rest of the organism from the harmful effects of solar UV irradiation, since UV radiation does not penetrate any deeper than the skin.

Within the skin, the penetration depth of UV light is wavelength-dependent[2,3] – i.e. the longer the wavelength, the deeper the penetration (Fig. 86.1). While UVA readily reaches the dermis, including its deeper portions, most of the UVB is absorbed in the epidermis such that only a small proportion reaches the upper dermis. UVC is absorbed or reflected predominantly by the stratum corneum and the upper layers of the epidermis. However, when considering the biologic effects of different wavelengths in the different layers of the skin, it is necessary to keep in mind that a particular wavelength can even have a biologic effect in a layer that it does not reach. One mechanism is secretion of proinflammatory mediators in the epidermis that can produce subsequent effects in the dermis[4] and subcutaneous fat[5]. For example, keratinocyte-produced soluble IL-6 appears to gain access to the circulation and may function, via its pyrogenic as well as acute phase-inducing effects, as an important mediator of a systemic sunburn reaction with symptoms including malaise, somnolence, fever, and chills[5a].

Some of the UV light reaching the skin is absorbed by biomolecules, with light-absorbing molecules referred to as chromophores. Upon absorption of the radiation's energy, the chromophore is elevated to an excited state. The resulting photochemical reactions can either directly alter the chromophore or indirectly alter a molecule other than the chromophore by energy transfer in a so-called photosensitized reaction. Absorption is wavelength-dependent and if a photon is not absorbed due to its wavelength, a photochemical reaction cannot occur. For UVB, the most important chromophore is DNA, while a typical UVA- and visible light-absorbing chromophore is porphyrin. Other important chromophores/their mediators include *trans*-urocanic acid/*cis*-UCA, membrane lipids/platelet-activating factor, tryptophan/aryl hydrocarbon receptor ligands, and

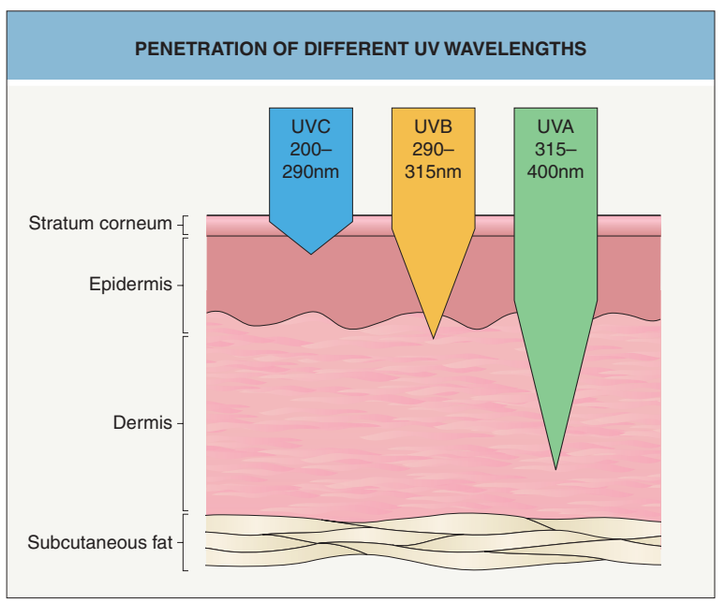


Fig. 86.1 Depth of penetration of different wavelengths of UV light into human skin. Depth of penetration varies greatly with the thickness of the different skin layers and their composition (e.g. melanin content). The beginning of the wedge-shaped portion of the penetration symbol represents a decrease to approximately one-third of the incident energy density, and the tip of the symbol represents a decrease to approximately 1%. Of note, some authors use 320 nm as the demarcation between UVA and UVB. Figure not drawn to scale.

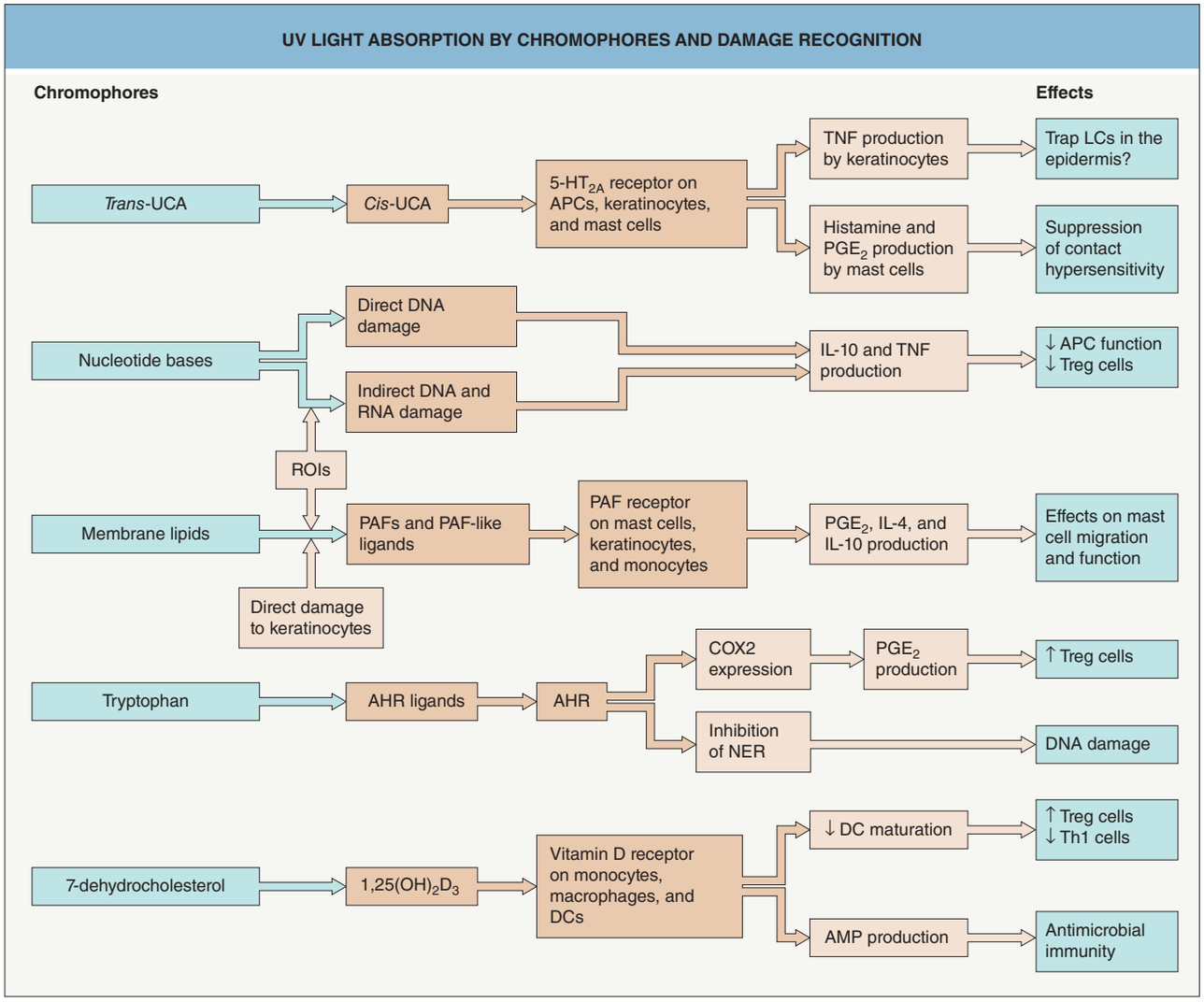


Fig. 86.2 UV light absorption by chromophores and damage recognition. *Cis*-urocanic acid (*cis*-UCA), an imidazole derivative produced by the isomerization of *trans*-UCA following absorption of UV light, initiates many of the immunomodulatory effects of UV by binding to the serotonin receptor (5-HT_{2A}) on antigen-presenting cells (APCs), keratinocytes, and mast cells. *Cis*-UCA stimulates the release of tumor necrosis factor (TNF) from keratinocytes, which might trap Langerhans cells (LCs) in the epidermis and prevent the presentation of antigen to T cells in the draining lymph node. *Cis*-UCA also stimulates histamine and prostaglandin E_2 (PGE_2) production by mast cells. UV causes direct damage to DNA, which induces the release of IL-10 and TNF and also impairs the function of APCs, resulting in impaired induction of regulatory T (Treg) cells. In addition to direct UV-induced DNA damage, the generation of reactive oxygen intermediates (ROIs) by UV causes indirect damage to both DNA and RNA. The oxidation of phosphatidylcholine by ROIs results in the production of platelet-activating factor (PAF)-like molecules at the cell membrane. PAF (produced by direct damage to keratinocytes) and PAF-like ligands induce immunosuppression by binding to the PAF receptor on mast cells, keratinocytes, and monocytes and stimulating the release of PGE_2, IL-4, and IL-10. The absorption of UVB by cytosolic tryptophan results in the formation of high-affinity aryl hydrocarbon receptor (AHR) ligands. AHR signaling results in increased expression of cyclooxygenase 2 (COX2), which can contribute to UV-induced immunosuppression through PGE_2 production and the induction of Treg cells. Also, AHR signaling inhibits nucleotide excision repair (NER) by inducing the proteasomal degradation of the $p27^{KIP1}$ tumor suppressor protein. 7-Dehydrocholesterol absorbs UV and converts to pre-vitamin D_3, which then isomerases to the active metabolite 1,25-dihydroxyvitamin D_3 (1,25$(OH)_2D_3$). 1,25$(OH)_2D_3$ modulates immunity by directly stimulating antimicrobial peptide (AMP) production and by inhibiting dendritic cell (DC) maturation. 1,25$(OH)_2D_3$-modulated DCs have suboptimal APC function, thereby inducing the expansion of Treg cell populations and suppressing T helper 1 (Th1) cell responses.
Reproduced with permission from Bernard JJ, Gallo RL, Krutmann J. Photoimmunology: how ultraviolet radiation affects the immune system. Nat Rev Immunol 2019;19:688–701.

7-dehydrocholesterol/1,25$(OH)_2D_3$. Activation of various receptors and pathways following absorption of UV light by chromophores results in numerous downstream effects (Fig. 86.2).

Knowledge of absorption spectra of molecules is critical for understanding the photobiologic consequences of UV absorption, including photomutagenesis of DNA by UVB, the efficacy of UV filters in sunscreens, and the elicitation of photodermatoses by specific wavelengths of UV light. An absorption spectrum defines the probability that a molecule will be excited by a particular wavelength. While the absorption maximum indicates the wavelength at which absorption is most likely, other wavelengths can still be absorbed. For example, the absorption maximum of DNA is 260 nm, which is within the UVC range. However, UVB still effectively excites DNA, and even UVA and visible light can do so. This explains why DNA photoproducts, a type of DNA damage induced by a photochemical reaction following direct excitation of the DNA molecule, are not only induced by UVB, but also by UVA or visible light, albeit at a much lower efficacy.

Both short- and long-term effects of exposure to UV light are wavelength-dependent. However, when comparing the photobiologic properties of UVB with those of UVA, it should be noted that the division between UVA and UVB is somewhat arbitrary and there is a continuum of wavelengths whose properties change gradually.

SHORT-TERM EFFECTS OF ULTRAVIOLET LIGHT: SUNBURN AND TANNING

Visible, short-term, cutaneous effects of UV irradiation include sunburn (solar erythema and possibly blister formation, followed by desquamation) and tanning. Microscopically, short-term effects include epidermal edema with spongiosis, acanthosis, hyperkeratosis, formation of sunburn cells (apoptotic keratinocytes), depletion of Langerhans cells, an increase in epidermal melanin, vasodilation, and an inflammatory infiltrate of lymphocytes and neutrophils. On a cellular and molecular

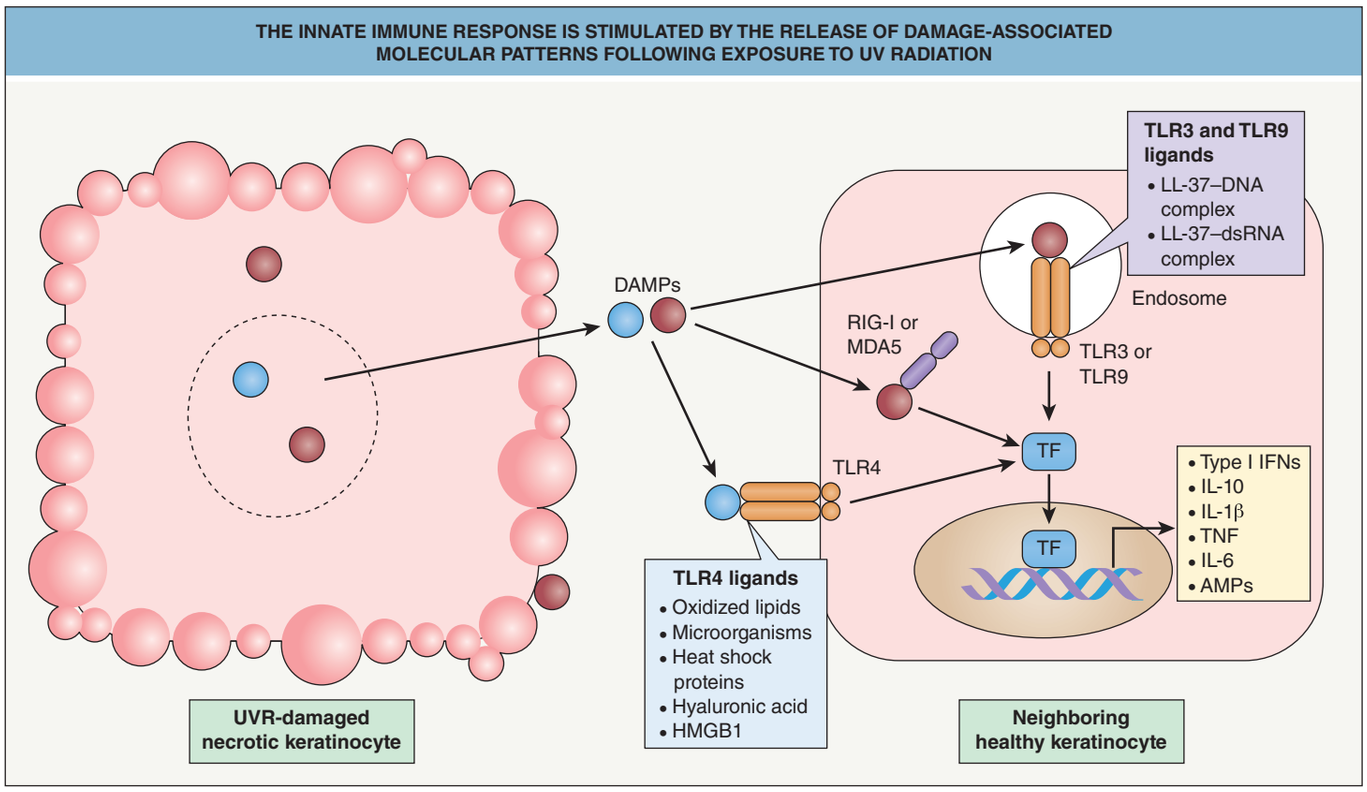


Fig. 86.3 The innate immune response is stimulated by the release of damage-associated molecular patterns following exposure to UV radiation (UVR). UVR induces the formation and release of damage-associated molecular patterns (DAMPs) from necrotic keratinocytes that activate Toll-like receptor (TLR) signaling. UVR can induce the formation and/or release of DAMPs that are recognized by the innate immune system as non-self, such as LL-37–DNA complex, LL-37–double-stranded RNA (dsRNA) complex, oxidized lipids, microorganisms, heat shock proteins, hyaluronic acid, and high-mobility group box 1 protein (HMGB1). TLR signaling in neighboring healthy keratinocytes leads to a type I interferon (IFN) response and the release of tumor necrosis factor (TNF), IL-10, IL-1β, IL-6, and antimicrobial peptides (AMPs). Cell responses to DNA and dsRNA are also mediated by the cytosolic receptors retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5), which trigger the release of the above-mentioned cytokines and AMPs. TF, transcription factor. *Reproduced with permission from Bernard JJ, Gallo RL, Krutmann J. Photoimmunology: how ultraviolet radiation affects the immune system. Nat Rev Immunol 2019;19:688–701.*

level, UV exposure induces a multitude of damage responses, including the induction of stress proteins and repair processes as well as production of cytokines (e.g. IL-1, -6, -10, TNF) and antimicrobial peptides (AMPs; Fig. 86.3). In a dose-dependent manner, exposed cells can either undergo apoptosis (visible histologically as sunburn cells) or cease proliferating (cell cycle arrest) to allow time for repair. However, this initial growth arrest may be followed by hyperproliferation, visible histologically as epidermal thickening. The inflammatory response in the sunburn reaction is likely due to activation of innate immunity. Lastly, UVB-induced activation of transient receptor potential ion channels in keratinocytes with subsequent calcium influx has been shown to mediate sunburn pain[6].

The ability to induce sunburn rapidly declines with increasing wavelength. For example, UV light with a wavelength of 360 nm is ~1000-fold less erythemogenic than UV light with a wavelength of 300 nm. UVB-induced sunburn reaches its peak between 6 and 24 hours after exposure; an immediate erythema reaction is rarely observed. In contrast, after exposure to a high dose of UVA, an immediate erythema reaction can occur, followed by a distinct delayed erythema after 6 to 24 hours. However, the doses of UVA present in natural sunlight are not sufficient to cause sunburn unless patients have increased UV sensitivity (see Ch. 134).

The tanning response of human skin to sun exposure is biphasic and wavelength-dependent. *Immediate* pigment darkening occurs primarily with UVA and develops during and immediately after exposure. It is due to alteration (e.g. oxidation) and redistribution of existing melanin. *Delayed* tanning is primarily due to UVB and peaks ~3 days after sun exposure. Fair skin (phototype II) usually tans only with UVB doses greater than the erythema threshold, i.e. only after a sunburn. Darker skin (phototypes III and higher) tans following suberythemogenic doses, i.e. without a sunburn. A UVB-induced tan is characterized by an increased number of melanocytes, increased melanin synthesis, increased arborization of melanocytes, and increased transfer of melanosomes to keratinocytes (see Ch. 65). A UVA-induced tan, such as from the use of a tanning bed (Fig. 86.4), provides 5–10 times



Fig. 86.4 Sequelae of exposure to UV light. A UVA-induced tan with reduced pigmentation within an area of relative ischemia (due to pressure while lying on a tanning bed); this leads to reduced UVA-induced, oxygen-dependent melanin oxidation within this area. Excessive sun exposure plus long-term use of tanning beds has led to a leather-like appearance to the skin. **B** Sharp demarcation on the thigh of solar lentigines and the dyspigmentation of photodamaged skin. The patient consistently wore Spandex shorts. *Courtesy Jean L. Bolognia, MD.*

less protection against sunburn from subsequent UV exposure than a UVB-induced tan, probably because a UVA-induced tan is characterized by less pronounced epidermal thickening and hyperkeratosis.

An individual's tendency to develop sunburn and tanning after sun exposure has been used to categorize skin phototypes (see Table 134.4).

These categories of an individual's susceptibility to short-term effects also correlate with the individual's susceptibility to long-term effects following sunlight exposure. In general, individuals with higher acute sun sensitivity also have a higher risk of developing skin cancer after chronic UV exposure.

EFFECTS ON THE CUTANEOUS IMMUNE SYSTEM

While sunburn represents a proinflammatory state, UV light also has anti-inflammatory properties as demonstrated by the efficacy of UV phototherapy in the treatment of inflammatory skin disorders. Currently, the *immunostimulatory* effects of UV light are thought to be primarily due to activation of innate immunity (see Fig. 86.3), whereas its *immunosuppressive* effects are mainly due to inhibition of adaptive, antigen-specific immunity (Fig. 86.5)[7]. However, a simple dichotomy is unlikely, as there are multiple factors that influence these immune effects, including dose- and wavelength-dependent differences that go beyond variations in skin phototype. An example of individual factors is the observation that the majority of patients with psoriasis improve with UV phototherapy, but a small minority flares. Another example is polymorphic light eruption in which inhibition of contact hypersensitivity by UV light is *reduced*, presumably predisposing patients to reactions to photo-induced allergens or toxins[8]. In individuals with both psoriasis and polymorphic light eruption, exposure to UV light often leads to psoriatic Koebner phenomena that involve induction of AMPs such as LL-37[9]. The ability of UVB to promote both double-stranded RNA and LL-37 may also be responsible for increased photosensitivity in patients with rosacea[10].

UV light-induced effects on the immune system involve not only the cutaneous sites directly exposed to UV light, but also non-irradiated areas. An example of systemic immunosuppression is the development in non-exposed skin of antigen-specific immune tolerance to antigens that were initially applied to UV-exposed skin. This effect is known to be mediated by the release of immunosuppressive cytokines such as interleukin (IL)-10 and then ultimately by UV-induced regulatory T cells.

The downside of photo-induced immunosuppression and immune tolerance is that they inhibit the recognition of tumor antigens and thereby contribute to photocarcinogenesis. The upside is the prevention of autoimmune reactions, e.g. diseases such as lupus erythematosus (LE) would likely be more prevalent without effective suppression of immune reactions against self-antigens unmasked by UV-induced cell damage. Another example of this equilibrium is polymorphic light eruption, in which less efficient UV-induced immunosuppression is balanced by a lower risk of UV-induced skin cancer[11].

Cellular photoreceptors that mediate signaling which leads to UV-induced immune responses include: DNA (via formation of DNA damage), urocanic acid in the stratum corneum (via UV-induced isomerization from the *trans*- to the *cis*-isoform)[12], membrane lipids (via UV-induced alteration of the membrane redox potential), and activation of the NLRP1 inflammasome (see Fig. 4.2). The latter acts as a sensor within keratinocytes whose activation was found to be a consequence of a UVB-induced ribotoxic stress response[12a]. While the immunosuppressive effects of UVB are well established, the relative contribution of UVA is still controversial[13].

While both acute and chronic UV exposure can lead to a selective loss of fibroblasts within the papillary dermis, repair consisting of local fibroblast proliferation can follow acute UV irradiation (UVR) whereas a permanent reduction in fibroblast number follows chronic UVR. Recruited T cells and neutrophils were found to promote fibroblast survival[13a].

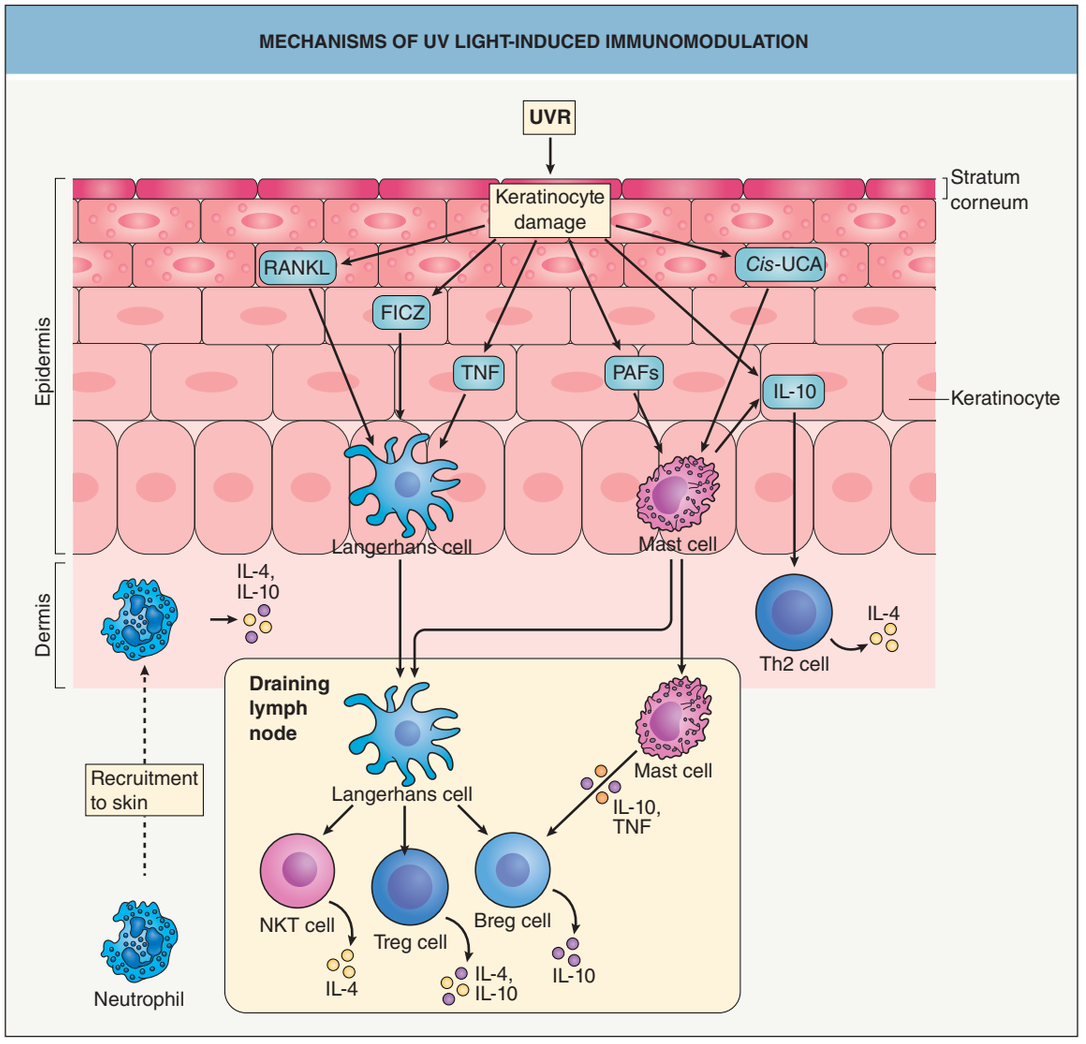


Fig. 86.5 Mechanisms of UV light-induced immunomodulation. As a direct result of ultraviolet light (UV)-induced epidermal damage, keratinocytes produce and release immunomodulators, including, but not limited to, *cis*-urocanic acid (*cis*-UCA), platelet-activating factors (PAFs) and PAF-like ligands, IL-10, 6-formylindolo[3,2-*b*] carbazole (FICZ), epidermal-derived receptor activator of nuclear factor-κB ligand (RANKL), and tumor necrosis factor (TNF). TNF, FICZ, and RANKL stimulate Langerhans cells; PAFs and *cis*-UCA stimulate mast cells. From these reactions, multiple signaling pathways and cells are activated and more soluble mediators are produced. For example, IL-10 released from UV-exposed keratinocytes and mast cells promotes a T helper 2 (Th2) cell response. PAFs stimulate the migration of mast cells to the draining lymph node, where they produce IL-10 and TNF and promote the formation of IL-10-producing regulatory B (Breg) cells. Collectively, the signaling pathways induced by UV exposure lead to an immunosuppressive environment, with high levels of TNF, IL-4, and IL-10 being associated with Langerhans cell migration to the lymph node and neutrophil recruitment to the skin. This leads to the induction of IL-4-producing natural killer T (NKT) cells, as well as regulatory T (Treg) cells and Breg cells, which promote cell-mediated and humoral immunosuppression. *Reproduced with permission from Bernard JJ, Gallo RL, Krutmann J. Photoimmunology: how ultraviolet radiation affects the immune system. Nat Rev Immunol 2019;19:688–701.*

LONG-TERM EFFECTS OF ULTRAVIOLET LIGHT: PHOTOAGING AND PHOTOCARCINOGENESIS

The long-term effects of chronic sun exposure include photoaging and photocarcinogenesis. In photocarcinogenesis, UV exposure provides a one-two punch: (1) it generates DNA damage, leading to mutations and malignant transformation; and (2) it has immunosuppressive properties. The latter include the induction of specific tolerance to antigens from UV-induced skin tumors which reduces the ability of the host immune-defense system to recognize and remove malignant cells. UV irradiation also impairs immune surveillance against cells infected with viruses (e.g. certain HPV types) and thereby promotes skin cancer formation.

The advantage of reduced immune reactivity following exposure to UV light is the prevention of illicit (auto)-immune reactions to transiently UV-altered cells (see above). Any shift in the balance between pro- and anti-inflammatory responses toward a more immunosuppressed state increases the risk of UV-induced tumor formation, as occurs in chronically immunosuppressed patients. Shifting this balance toward proinflammatory responses and autoimmunity increases the risk of developing photodermatoses or photoaggravated skin diseases such as LE. The critical nature of this equilibrium is also illustrated by the observation that effective photoprotection often leads to spontaneous resolution of actinic keratoses, even though these precursor lesions have identifiable genetic changes that provide growth advantage over non-mutated cells (see Ch. 107).

Photoaging

Photoaging encompasses the clinical, histologic, and physiologic changes present in chronically sun-exposed skin. This extrinsic skin aging is classically distinguished from intrinsic aging, which refers to age-dependent changes in sun-protected skin. Photoaging affects all components of the skin, including the epithelium, the pigmentary system, the vasculature, the dermal connective tissue, and possibly even the subcutaneous fat[14].

Due to its ability to penetrate deeper into the dermis, UVA is thought to play an important role in inducing the dermal changes of photoaging. Since UVA, but not UVB, penetrates through window glass, the patient in Fig. 86.6 illustrates the ability of UVA to induce photoaging[15]. However, wavelengths of UV light that do not reach the dermis, particularly UVB, could still contribute to photoaging of the dermis via signals originating from the epidermis[4]. In addition to differences in their depths of penetration, UVA and UVB also produce different cellular effects that likely influence their effects on photoaging.

In contrast to photocarcinogenesis, in which the immunosuppressive effects of UV light play a pivotal role, photoaging is thought to be the result of chronic and repetitive inflammatory responses to UV light. This results in upregulation of extracellular matrix-degrading proteases and downregulation of collagen synthesis, resulting over time in loss of collagen and deposition of abnormal degenerative elastotic material within the dermis (actinic elastosis). However, if photoaging were merely due to UV-induced inflammation, wrinkling and other features should be reversible with complete photoprotection, but of course this is not the case[16].

UV-Induced Tumor Formation

Exposure to UV light is a major risk factor for developing skin cancer[17]. UV-induced cutaneous carcinomas may evolve via the photocarcinogenesis cascade outlined in Fig. 86.7. Carcinogenesis often entails the stepwise accumulation of genomic aberrations in a single cell, with subsequent clonal expansion. Usually, it takes decades until a tumor arises and in one study, over 25% of epidermal cells in aged chronically sun-exposed skin were found to contain cancer-causing mutations[18]. However, cancer can also arise from a single catastrophic cellular event, termed chromothripsis, in which there are hundreds of clustered mutations and chromosomal rearrangements (see Ch. 107). Chromothripsis provides a mechanism for the rapid accumulation of numerous genomic aberrations within a few cell divisions, thus challenging the conventional tumor progression model consisting of the gradual acquisition of somatic mutations over time[19,20].

While the carcinogenic properties of short-wavelength UV light, in particular UVB, are well established, UVA was originally thought to be harmless due to its relative inability to induce sunburn. More recently, however, it was shown that UVA can induce cutaneous SCC in mice and is now recognized as an independent class I carcinogen[17]. Natural sunlight contains much more UVA than UVB (depending on the time of day and weather: 20- to 100-fold more), which offsets the weaker effects of UVA. Because UVA is less filtered by window glass and clothing and it penetrates more effectively to the basal layer of the epidermis, these properties may further increase the relative contribution of UVA to the carcinogenic properties of sunlight.

Although less is known about the action spectrum for the induction of melanoma, it is known that the burden of UV-signature mutations varies from low in acral and mucosal melanomas to high in lentigo maligna melanoma[21]. There are several lines of evidence for a role for

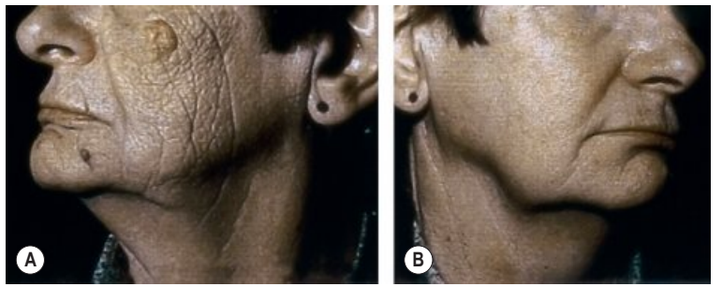


Fig. 86.6 Unilateral photoaging following 15 years of unilateral sun exposure through window glass. A Exposed side of face. **B** Nonexposed side of face. This individual had been working in the same office for 15 years, close to a window, with the left cheek always facing the window. Biopsy confirmed the diagnosis of nodular cutaneous elastosis with cysts and comedones (Favre–Racouchot disease). Since UVB does not penetrate window glass, this observation identifies UVA as an effective promoter of photoaging. *Reproduced with permission from Moulin G, Thomas L, Vigneau M, Fiere A. Un cas unilateral d'élastose avec kystes et comédons de Favre et Racouchot. Ann Dermatol Venereol 1994;121:721–3.*

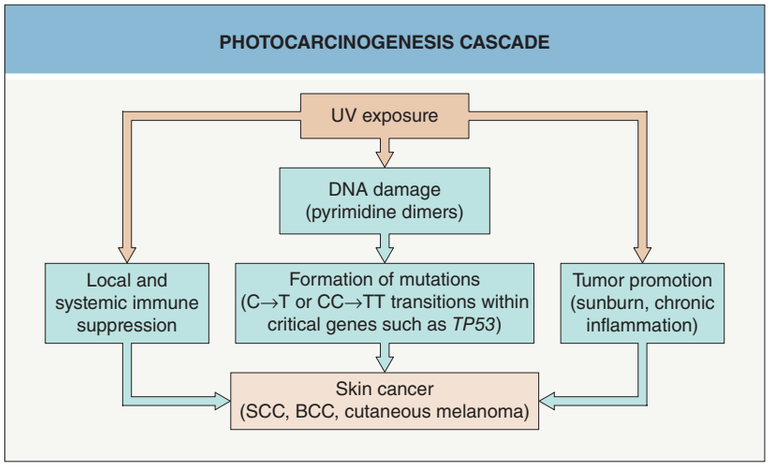


Fig. 86.7 Photocarcinogenesis cascade. UV-induced DNA damage generates mutations and after accumulation of a sufficient number of mutations in critical genes, this may finally result in malignant transformation of single keratinocytes or melanocytes and subsequent formation of skin cancer.

UVA, including increased melanoma risk with tanning bed use[22]. For example, a case–control study found adjusted overall melanoma risks of 2.86 and 4.44 for users of UVB-enhanced and primarily UVA-emitting indoor tanning units, respectively[23]. In a mouse melanoma model, both UVB and UVA were shown to induce melanoma[24].

One hypothesis to explain why melanomas commonly arise in intermittently sun-exposed skin rather than in chronically sun-exposed areas is that because of their relative inability to undergo apoptosis, melanocytes might be more prone to UV-induced mutagenesis following a single high dose of UV light[25]. Melanocytes contain high levels of anti-apoptotic proteins such as Bcl-2, providing a possible explanation for why sunburn-induced apoptosis has not been described in melanocytes. As a result, melanocytes with a high amount of DNA damage are more likely to survive than are keratinocytes, which readily undergo apoptosis.

In chronically sun-exposed skin, adaptive responses that follow repeated exposures to low-dose UV radiation (e.g. increased pigmentation, upregulation of DNA repair) may help to protect cells from mutagenic assaults. However, keratinocytes are more prone to UV-induced mutagenesis because they proliferate more rapidly and are more likely to replicate unrepaired DNA. This may explain why keratinocytes are more vulnerable than melanocytes to the mutagenic effects of low-dose UV irradiation observed in chronically sun-exposed skin.

UV INDUCTION OF DNA DAMAGE

Different wavelengths of UV light induce different types of DNA damage. UVC and UVB, but much less so UVA, are capable of exciting the DNA molecule directly and subsequently generating DNA photoproducts[26]. Indeed, DNA is regarded as the chromophore for most of the biologic effects of UVB and UVC, including erythema, tanning, immunosuppression, and mutagenesis. DNA photoproducts are dimers, formed by covalently binding two adjacent pyrimidines in the same polynucleotide chain. The two major types of pyrimidine dimers are cyclobutane–pyrimidine dimers and 6,4-photoproducts.

Cyclobutane–pyrimidine dimers (CPDs) are the most common DNA photoproducts formed by UV irradiation. They are generated upon saturation of the 5,6 double bonds and formation of a four-membered cyclobutyl ring (Fig. 86.8). CPDs are observed at all possible dipyrimidine sites, with the thymine–thymine dimer (T–T) being the most common, followed by C–T and T–C dimers. C–C dimers are the least common. The formation of CPDs is not a random phenomenon: it is influenced by the sequence and conformational context of the affected DNA sequence. More recently, an additional molecular mechanism for the formation of CPDs was described, consisting of photoexcitation of melanin and formation of peroxynitrite. Due to the long half-life of these reactive molecules, this mechanism adds to CPD formation for hours after UV irradiation, but only in melanin-containing cells. These CPDs have been termed "dark CPDs"[27].

The *6,4-photoproduct* is a non-cyclobutane dipyrimidine photoproduct, which is formed upon covalent linkage between the C-6 position of one pyrimidine and the C-4 position of the 3′ adjacent pyrimidine (Fig. 86.9). The T–C (6–4) dimer is the most common dimer of this type, but C–C and T–T dimers are also observed after UV irradiation. Upon further irradiation with UV wavelengths between 280 and 360 nm, the normal isomers of 6,4-photoproducts can be converted to their Dewar valence isomers, which are less mutagenic than the normal isomers but may still contribute to solar mutagenesis[28]. Although eightfold fewer in number than CPDs, 6,4-photoproducts can activate the ATR-CHK1 DNA damage response pathway and may be the major trigger for UV-induced DNA damage responses[29]. A few other rare DNA photoproducts have been described, such as complex purine lesions and pyrimidine hydrates, but their physiologic significance in cutaneous photobiology is unknown.

The absorption maximum of DNA is at 260 nm. This makes UVC the most effective wavelength for the induction of DNA photoproducts in naked DNA. However, *in vivo*, due to the absorption of shorter wavelengths in upper layers of the epidermis, 300 nm (UVB) is the most effective wavelength for inducing DNA photoproducts in the basal layer of the epidermis (Fig. 86.10)[30]. It is now well recognized that when solar-available doses are compared, UVA can also generate pyrimidine dimers, albeit at a lower frequency than UVB[31].

While formation of UVB-induced pyrimidine dimers results from the direct absorption of photons by bases of DNA, UV irradiation can also damage DNA indirectly. After absorption of photons by chromophores other than DNA, energy can be transferred either to DNA (type I photosensitized reaction) or to molecular oxygen, with reactive oxygen species in turn being able to damage DNA (type II photosensitized reaction). Many of the biologic properties of UVA, including its toxicity to cells, are dependent upon the presence of molecular oxygen, which points to a prominent role for reactive oxygen species. Although these reactive

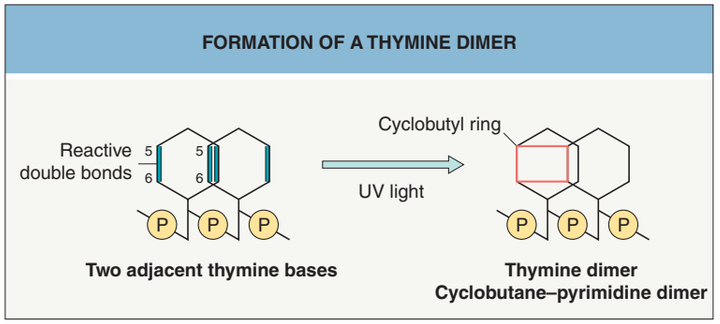


Fig. 86.8 Formation of a thymine dimer. Following excitation of the bases by UV light, a cyclobutane–pyrimidine dimer is formed by covalent linkage between two adjacent pyrimidines (here two thymine bases) and formation of a cyclobutyl ring.

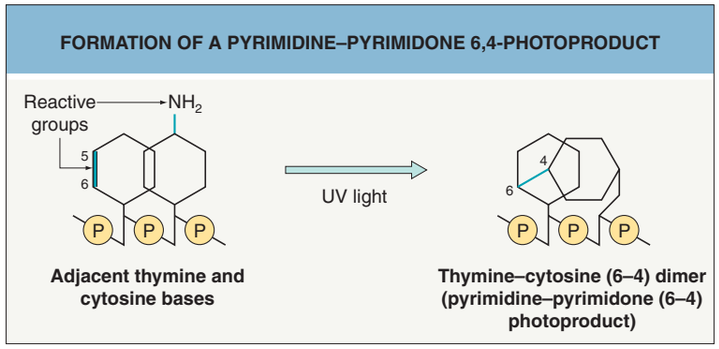


Fig. 86.9 Formation of a pyrimidine–pyrimidone 6,4-photoproduct. A pyrimidine–pyrimidone (6–4) photoproduct is formed by covalent linkage between C-6 and C-4 of two adjacent pyrimidines (here a thymine and a cytosine base), following excitation of the bases by UV light.

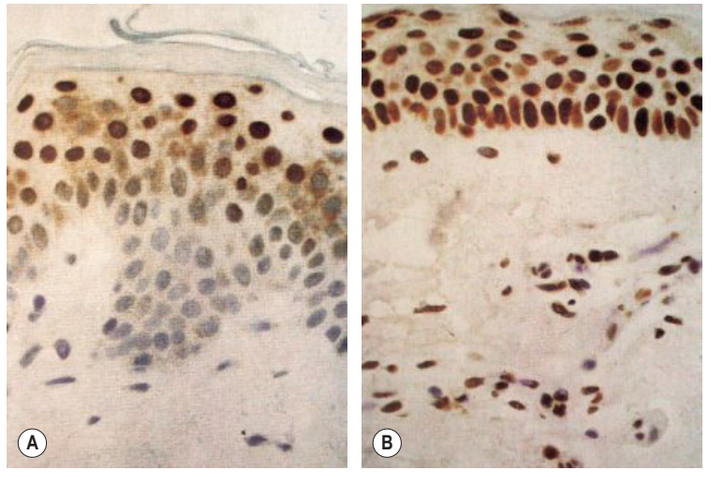


Fig. 86.10 A wavelength of 300 nm is more effective than one of 290 nm in inducing thymine dimers in the basal layer of the human epidermis. A After irradiation of human skin with monochromatic 290 nm UVB (2 MED) and staining with anti-thymine dimer antibodies, most cells in the basal layer show only blue counterstaining, while suprabasal layers demonstrate pronounced reactivity. **B** In contrast, with 2 MED of monochromatic 300 nm UVB, a pronounced immunostaining is also evident in the basal layer of the epidermis (as well as in cells within the dermis). *Reproduced with permission from Young AR, Chadwick CA, Harrison GI, et al. The similarity of action spectra for thymine dimers in human epidermis and erythema suggests that DNA is the chromophore for erythema. J Invest Dermatol 1998;111:982–8.*

oxygen species are also formed by UVB, UVA is responsible for almost all oxidative DNA damage after exposure of cells to natural sunlight[32].

UV-induced reactive oxygen species include singlet oxygen and probably others such as hydrogen peroxide and the superoxide radical[33]. Even the highly reactive hydroxyl radical may be formed by a reaction of hydrogen peroxide with nuclear metals through a Fenton reaction. This oxidative stress affects not only DNA, but also membranes and proteins. Singlet oxygen and other reactive oxygen species react predominantly with guanine and generate several DNA changes, including the mutagenic and well-studied 7,8-dihydro-8-oxoguanosine (8-oxoG; Fig. 86.11).

Kielbassa et al.[34] published a UV action spectrum for the formation of dimers and oxidative guanine base modifications in mammalian cells (Fig. 86.12). Differences between the DNA-damaging properties of UVA, UVB, and UVC are gradual, and, as noted previously, only a few pyrimidine dimers are generated by UVA. There is mounting evidence that pyrimidine dimers are the most important pre-mutagenic DNA lesions, not only in UVB-induced, but also in UVA-induced, mutation formation, with oxidative DNA damage playing only a minor role in mutagenesis[35]. Lastly, DNA double-strand breaks are probably not formed by either UVB or UVA[36].

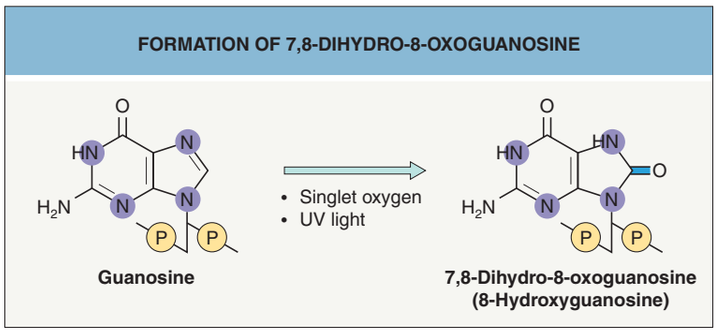


Fig. 86.11 Formation of 7,8-dihydro-8-oxoguanosine. 7,8-Dihydro-8-oxoguanosine (tautomer: 8-hydroxyguanosine) is an oxidation product of guanosine. It is formed by singlet oxygen, which is generated through a photosensitized reaction after excitation of a cellular chromophore by UV light.

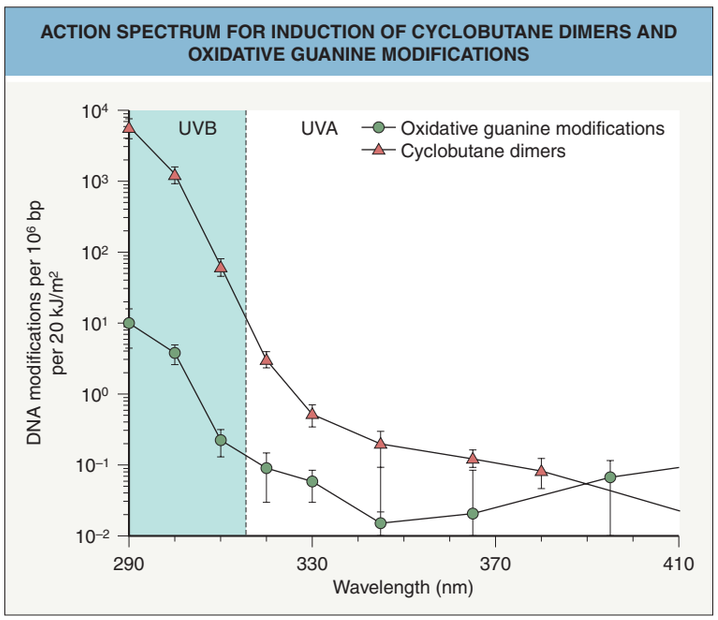


Fig. 86.12 Action spectrum for the induction of cyclobutane dimers and oxidative guanine modifications in Chinese hamster ovary cells. The number of DNA lesions was assessed by the ability of repair enzymes to incise DNA from cells irradiated with different wavelengths from a monochromator. The ability of UV light to induce cyclobutane dimers and oxidative DNA damage rapidly declines with increasing wavelengths, e.g. 320 nm UV light is approximately 1000-fold less capable of inducing cyclobutane dimers than is 290 nm UV light. This decline parallels well with the decline of skin cancer formation in mice from 300 to 340 nm (Utrecht–Philadelphia skin cancer action spectrum[75]). This decline does not mean that longer wavelengths do not contribute to photocarcinogenesis, because longer-wavelength UVA is much more abundant in natural sunlight than is UVB, which offsets at least some of the weaker effects of UVA. The second peak of oxidative base damage formation in the UVA range parallels with a second peak of skin cancer formation at 380 nm. Since there is no second peak of cyclobutane dimer formation with UVA, this has been interpreted as evidence that oxidative base damage contributes to mutagenesis and skin cancer formation. However, more recent data indicate that pyrimidine dimers are the most important pre-mutagenic DNA lesion not only for UVB, but also for UVA.

REPAIR OF UV-INDUCED DNA DAMAGE

The bulky DNA photoproducts (pyrimidine dimers) are usually repaired via the nucleotide excision repair (NER) pathway. In patients with xeroderma pigmentosum (XP), defects in the NER pathway increase UV mutagenesis and this leads to a higher incidence of melanoma and keratinocyte carcinomas (Fig. 86.13). XP includes seven genetic complementation groups (XPA through XPG), which represent different proteins in the NER pathway (Fig. 86.14), in addition to a separate form, XP variant. The latter is due to dysfunction of DNA polymerase-η which normally bypasses T–T dimers with correct insertion of two A residues (see below).

NER involves recognition of DNA damage, incision of the DNA strand containing a lesion, and DNA synthesis and ligation to replace an excised oligonucleotide (see Fig. 86.14). In active genes, the transcribed strand is corrected up to 10 times faster than the non-transcribed strand. Here, recognition of DNA damage is mediated via the RNA polymerase stalled at the site of a pyrimidine dimer plus recruitment of CSA and CSB (protein products of *C*ockayne *s*yndrome complementation group *A* and group *B* genes); this initiates *transcription-coupled repair*. In non-transcribed genes and non-coding regions, the XPC and XPE proteins bind to UV-damaged DNA, marking it for further processing; this initiates *global genome repair*. After either form of DNA damage recognition, all subsequent steps of NER are identical. A key intermediate is an open, unwound structure formed around a DNA lesion in a reaction that uses the helicase activities of XPB and XPD. This creates sites for cutting by the endonucleases XPG on the 3′ side of the lesion and the XPF–ERCC1 complex on the 5′ side. A 24- to 32-residue oligonucleotide is released, and the gap is filled by DNA polymerase δ or ε and then sealed by DNA ligase 1.

Defects in NER are found not only in XP, but also in two other photosensitive disorders, Cockayne syndrome and the photosensitive form of the brittle hair syndrome trichothiodystrophy (see Table 87.4). These disorders are not cancer-prone, but sometimes have features that overlap with those of XP. It is remarkable how different mutations in *XPB/ERCC3*, *XPD/ERCC2*, and *XPG/ERCC5* are associated with dissimilar clinical phenotypes. The transcription/repair syndrome hypothesis has been put forward to explain these various discrepancies. According to this hypothesis, mutations in XPD or XPB could affect



Fig. 86.13 Xeroderma pigmentosum. A 17-year-old with skin phototype V who has hyper- and hypopigmentation admixed with scarring, lentigines, and seborrheic keratoses. Note the squamous cell carcinoma *in situ* of the lower lip in association with severe actinic cheilitis. *Courtesy Julie V. Schaffer, MD.*

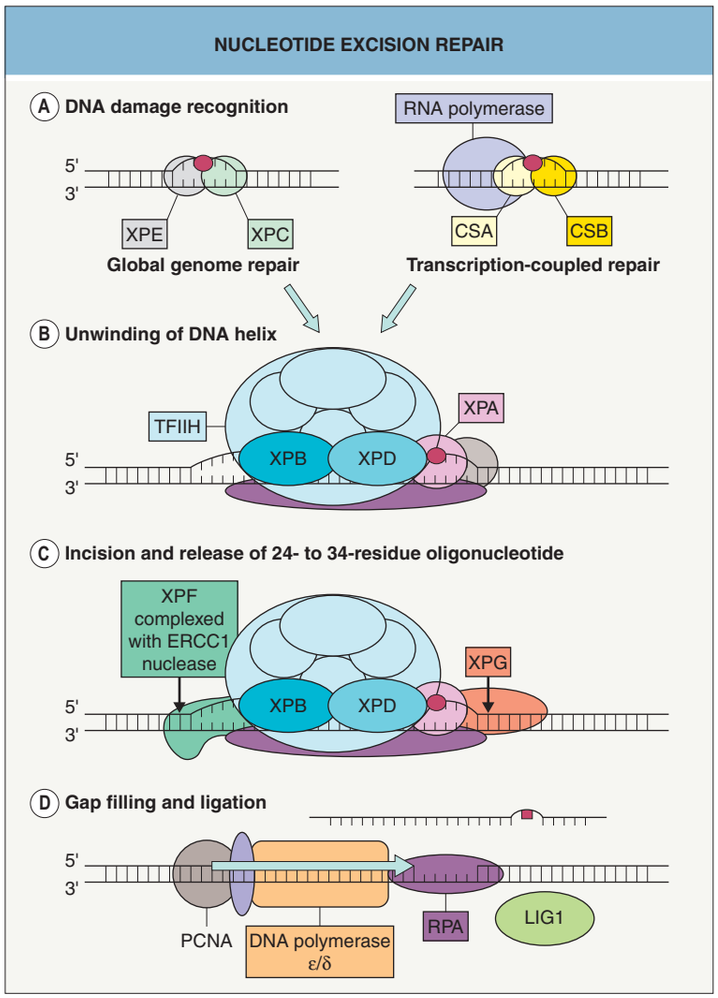


Fig. 86.14 Nucleotide excision repair. This pathway repairs "bulky" DNA lesions, including pyrimidine dimers (red dot). **A** DNA damage recognition in global genome repair is mediated by XPC and XPE. In transcription-coupled repair, DNA damage recognition is mediated by a stalled RNA polymerase plus recruitment of CSA and CSB. These two types of DNA damage recognition are then followed by identical steps in DNA repair. **B** Unwinding of the DNA double strand around the lesion by the helicase activity of XPB and XPD. **C** Incision 5′ and 3′ of the lesion by the endonucleases XPF and XPG. **D** Repair synthesis and gap closing after release of a 24- to 34-residue oligonucleotide. CSA/CSB, proteins that are dysfunctional in Cockayne syndrome; ERCC1, excision repair cross-complementation group 1; LIG1, DNA ligase 1; PCNA, proliferating cell nuclear antigen; RPA, replication protein A; TFIIH, transcription factor IIH; XP, xeroderma pigmentosum. *Adapted with permission from Lindahl T, Wood RD. Quality control by DNA repair. Science 1999;286:1897–905.*

the *repair function* of transcription factor IIH (TFIIH; see Fig. 86.14), resulting in photosensitivity and cancer development, and/or affect the *transcription function* of TFIIH, accounting for the typical phenotypes of trichothiodystrophy and Cockayne syndrome.

Cells from patients with XP variant have an intact NER, yet a phenotype that is indistinguishable from the other XP complementation groups. These patients have a deficiency in what they do with unrepaired DNA photoproducts during replication within the S phase of the cell cycle[37]. Replicative DNA polymerases usually stall at unrepaired DNA lesions and detach from the DNA strand. For this situation, cells have several specialized DNA polymerases that are able to bypass different kinds of DNA damage and extend replication forks through damaged sites. Due to a mutation in *POLH*, patients with XP variant lack the ability of DNA polymerase-η to bypass T–T dimers and correctly insert two A residues[38]. This indicates that NER does not always repair all DNA lesions and that the function of a high-fidelity translesional DNA polymerase is crucial for maintaining genomic stability. In XP variant patients, NER can remove most of the T–T dimers, but because polymerase-η is deficient, any remaining dimers are more likely to be bypassed by translesional DNA polymerases (other than DNA polymerase-η) that insert incorrect residues. This causes a UV-mutator phenotype. If DNA polymerase-η, or any other specialized translesional DNA polymerase, fails to bypass DNA damage during S phase, the cell is faced with a stalled replication fork. In these instances, DNA recombination repair, which utilizes strand invasion from the sister chromatid, can resolve the stalled replication fork[39].

In contrast to the bulky pyrimidine dimers, which can only be repaired by NER, the non-bulky oxidative DNA base modifications can be processed via base excision repair[40]. As the name implies, the initial step in base excision repair is the removal of a base rather than a nucleotide. This step is carried out by a DNA glycosylase, which removes the damaged DNA base by hydrolytically cleaving the base–deoxyribose glycosyl bond, leaving an apyrimidinic/apurinic site for further processing. This DNA glycosylase has substrate specificity for a particular kind of DNA base damage. The human DNA glycosylase, 8-oxoG DNA glycosylase 1, has specificity for oxidized guanine bases such as 8-oxoG (see Fig. 86.11), and it initiates processing of these lesions via base excision repair.

Lastly, the cytokines IL-12 or -23 can interfere with DNA repair. They are capable of effectively rescuing UV-irradiated cells from apoptosis by triggering DNA repair mechanisms that inhibit immune suppression, most likely due in part to abrogation of induction of regulatory T cells (Tregs). In particular, IL-23 may counteract photocarcinogenesis[41–43].

UV-INDUCED MUTATIONS

Many of the previously discussed forms of UV-induced DNA damage can result in mutations. The principal mechanism by which DNA damage results in a base substitution mutation is via mispairing during DNA replication in the S phase of the cell cycle. Because mutations in several specific genes are usually required for a normal cell to undergo malignant transformation and these mutations are quite unlikely to occur in a single cell, genetic instability (a mutator phenotype) is thought to be required for the development of cancer, including skin cancer[44]. XP serves as an example of an inherited genetic instability. While the amount of DNA damage formed in the skin following UV exposure is the same as in normal individuals, deficient repair of this damage results in many more mutations at sites of DNA damage as compared to repair-intact individuals.

Most of the *TP53* mutations in cutaneous SCCs and their precursors are C→T single base transition mutations at dipyrimidine sites[45]. Tandem CC→TT transition mutations are found in 10% of cutaneous SCCs. This spectrum of *TP53* mutations is very different from *TP53* mutations found in malignancies of internal organs; the latter do not have the preponderance of C→T mutations nor do they have any CC→TT mutations. This, together with the fact that pyrimidine dimers most commonly cause C→T and some CC→TT mutations, provides convincing evidence for a crucial role of pyrimidine dimers in photocarcinogenesis. Therefore, C→T, and especially CC→TT mutations, have been termed "signature mutations" for UV-induced mutagenesis (Fig. 86.15). However, to date, studies have not found an increased risk of skin cancer in patients with skin disorders treated with standard regimens of UVA1, UVB, or NB-UVB[46,47].

MECHANISMS OF UV-BASED PHOTOTHERAPY

UV irradiation is an effective treatment for a variety of skin diseases, from psoriasis, atopic dermatitis, prurigo, and vitiligo to lichenoid dermatoses (e.g. lichen planus, pityriasis lichenoides, graft-versus-host disease), morphea, and cutaneous T cell lymphoma (CTCL; see Ch. 134)[1,48]. The therapeutic mechanisms are complex and depend upon the particular disease and the administered wavelengths, e.g. NB-UVB versus UVA1. UV radiation has proapoptotic, immunomodulatory, antipruritic, antifibrotic, propigmentary, and proprebiotic properties, which alone or in combination lead to clinical improvement. Despite having diverse etiologies, most photoresponsive disorders have disturbances in the cutaneous immune microenvironment.

As depicted in Figs. 86.3 and 86.5, UV irradiation induces various mediators including cytokines, chemokines, AMPs, *cis*-urocanic acid, platelet activating factor (PAF), and PAF-like molecules that simultaneously influence the cutaneous micromilieu and its interplay with the microbiota of the skin. In particular, the induction of regulatory

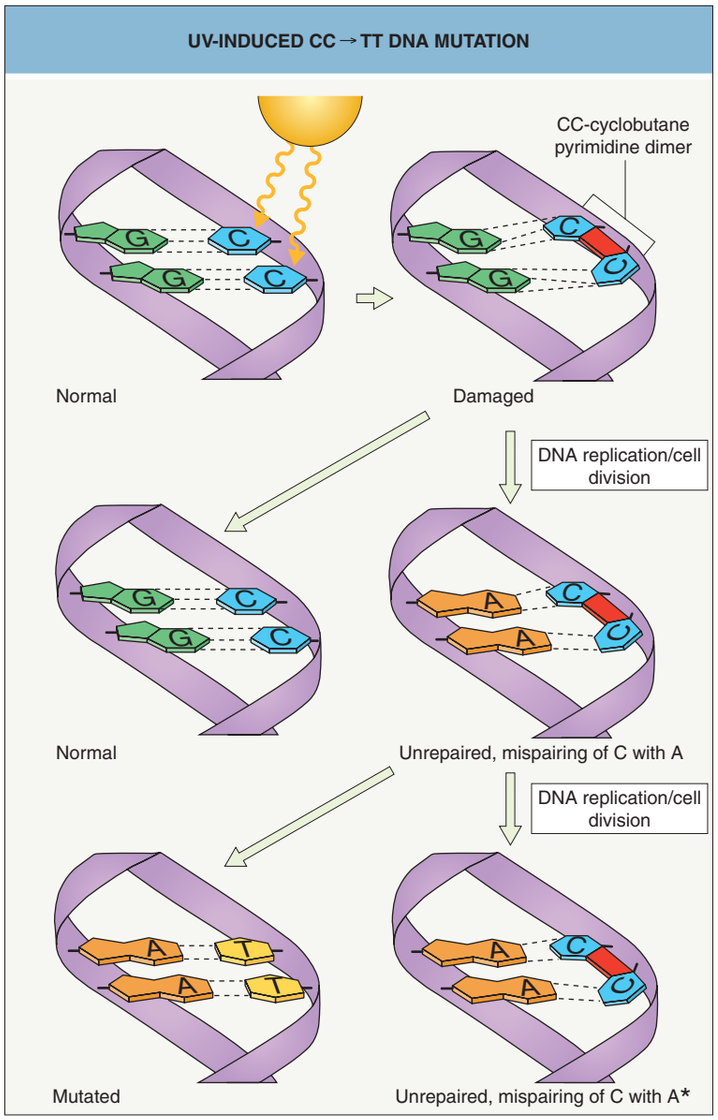


Fig. 86.15 UV-induced CC→TT DNA mutation. Following formation of a pyrimidine dimer between two adjacent cytosines and subsequent cell division, a CC→TT mutation results. This represents a UV-signature mutation. *May give rise to more C→T mutations.

T cells, along with downregulation of the Th17/IL-23 axis, may be crucial for months-long disease remission in disorders such as psoriasis even after treatment is discontinued[1,48,49]. In mycosis fungoides, phototherapy can disrupt the cutaneous proinflammatory microenvironment, along with diminishing the growth of T cells via suppression of the production and secretion of IL-9[50,51]. In both atopic dermatitis and CTCL, UV irradiation affects the cutaneous microbiota (e.g. inhibits the growth of *Staphylococcus aureus*) which suppresses the proinflammatory microenvironment of the skin[1,52]. In fibrotic skin diseases such as morphea, phototherapy (UVA1) induces matrix metalloproteinase and Smad7 expression as well as downregulation of IL-6, leading to increased collagenase activity and effectively reducing tissue fibrosis[1].

UV irradiation can also lead to vitamin-dependent and -independent systemic effects that may affect gut microbiota[53,54], thereby playing a potential role in a variety of skin disorders[1]. In patients with psoriasis, phototherapy decreases systemic inflammation as measured by serum levels of C-reactive protein (CRP) and IL-6; it can also increase levels of high-density lipoprotein (HDL)-P and restore HDL composition and function which may reduce aortic inflammation[55] and cardiovascular risk[56,57], respectively. Lastly, exposure to UV light may benefit multiple sclerosis[58,59] as well as alter mood, behavior and cognition, possibly due to increased synaptic release of glutamate and enhanced motor learning and memory[60].

PHOTOPROTECTION BY UV FILTERS AND OTHER MODALITIES

To ensure that most of the damage inflicted by sun exposure will not lead to the formation of skin cancer, UV-exposed cells have several lines of defense against the photocarcinogenesis cascade (Fig. 86.16). For example, the epidermis can increase its thickness, which reduces UV exposure in the basal layer. Anti-oxidative enzymes quench reactive oxygen species and reduce the formation of oxidative DNA damage. Cellular melanin is a mixture of different polymerized pigments that absorb UV radiation (see Ch. 65). Illumination of the brown to black eumelanin generates the superoxide radical within the molecule, but it is very rapidly scavenged. However, red or yellow pheomelanin is a less effective radical scavenger, and upon UV exposure, pheomelanin is degraded, with a net formation of superoxide. Therefore, pheomelanin is regarded as a photosensitizer, rather than a photoprotector like eumelanin.

To prevent mutation formation after UV-induced DNA damage, cells have several different DNA repair systems (see above) as well as the ability to bypass DNA damage without inducing mutations. Cells can also halt proliferation (cell cycle arrest via increased expression of p53) to allow more time for repair and to reduce the chance of replicating a damaged template. Some of these protective mechanisms can be upregulated, facilitating an adaptive response to repeated UV "attacks". They include pigmentation, skin thickening, antioxidant enzymes, and DNA excision repair. In contrast, immune surveillance is downregulated following UV exposures (see above), likely contributing significantly to photocarcinogenesis.

Exposure to UVA cannot be regarded as harmless, and dermatologists must warn not only against UVB but also UVA exposure. Because broad-spectrum sunscreens do not filter UVA as efficiently as UVB, the use of sunscreens may actually increase UVA exposure[61]. The use of high-dose UVA emitters for cosmetic purposes in tanning parlors also continues to be popular, and an increase in melanoma incidence has already been linked to tanning parlors in Iceland[22].

In order to prevent or reduce UV irradiation of the skin, one can limit outdoor activities, especially around midday, stay in the shade, wear protective clothing, and/or wear sunscreens. Sunscreens are topical preparations that attenuate UV radiation before it enters the skin, by reflection, absorption, or both (see Ch. 132). They not only protect against the acute skin injury of sunburn, but also against UV-induced immune suppression, photoaging, and skin cancer[62,63]. The sun protection factor (SPF) of sunscreens, which indicates by what factor *sunburn* is prevented by sunscreen use (see Table 132.2), does not correlate well with protection factors for other non-erythema endpoints[64]. Therefore, the SPF cannot be regarded as a reliable guide to non-erythema and chronic endpoints.

A good sunscreen should provide broad-spectrum protection against UVB and UVA, ideally in a balanced way with equal protection against both UVA and UVB. Additionally, it should be photostable and have a comfortable vehicle to ensure its regular use. Filters that degrade with UV exposure lose their effectiveness and need reapplication. In addition, degradation products may induce further reactions, providing an explanation for why unstable sunscreen filters are more likely to cause photoallergic reactions[65]. Lastly, sunscreens should not be used to prolong sun exposure, because this would offset any protective effect and might even increase exposure to unfiltered or less-well-filtered wavelengths, such as UVA.

In order to prevent oxidative damage – in particular, oxidative DNA damage – the addition of antioxidants to sunscreens has been advocated. However, their protective effects against any of the above-mentioned endpoints have not been well established, or are marginal at best[66]. In addition, the finding that oxidative DNA damage might not contribute significantly to UVA-induced mutagenesis (as was previously thought) brings into question whether antioxidants provide any protection against skin cancer. Reactive oxygen species are not only damaging to cells, but also induce cellular responses that can protect against photocarcinogenesis, including induction of senescence via generation of the aging-associated protein progerin[67]. Thus, in theory, antioxidants could actually promote photocarcinogenesis.

Topical application of immunoprotective DNA repair enzymes has been shown to increase DNA repair in skin cells and to accelerate removal of DNA photoproducts[68]. In patients with XP, such applications

MECHANISMS THAT PROTECT AGAINST OR PREVENT THE PHOTOCARCINOGENESIS CASCADE AND DISORDERS THAT PREDISPOSE TO SKIN CANCER BECAUSE OF IMPAIRED INTRINSIC PROTECTIVE MECHANISMS

Intrinsic protective mechanisms	Hereditary or acquired disorders with an increased risk for UV-induced skin cancer	Extrinsic methods to prevent skin cancer
UV exposure		
Hair/fur	Alopecia, in particular androgenetic	Sun avoidance Protective clothing, hats
Pigmentation Epidermal thickening and hyperkeratosis Anti-oxidative enzymes	Oculocutaneous albinism	Broad-spectrum sunscreens Antioxidants
DNA damage		
DNA repair High-fidelity translesional DNA synthesis Cell cycle arrest/apoptosis	Xeroderma pigmentosum Xeroderma pigmentosum variant Familial melanoma Basal cell nevus syndrome	Antioxidants DNA repair liposomes Nicotinamide
Mutations		
Removal of mutated cells (immune surveillance)	Immunosuppression, e.g. solid organ transplant patients	Improve immune surveillance (e.g. PD-1 inhibitors)
Skin cancer		

Fig. 86.16 Mechanisms that protect against or prevent the photocarcinogenesis cascade and disorders that predispose to skin cancer because of impaired intrinsic protective mechanisms. Several intrinsic mechanisms protect against the formation of skin cancer following UV exposure at different points of the photocarcinogenesis cascade of events. These mechanisms are impaired in disorders with increased risk for UV-induced skin cancer. Each step of the photocarcinogenesis cascade can be targeted for therapeutic modification and reduction of skin cancer risk.

have been reported to reduce the occurrence of actinic keratoses[69]. Similarly, oral nicotinamide may have the capacity to reduce the rates of keratinocyte carcinomas and actinic keratoses[70]. Its mechanism of action has yet to be determined, but it is a substrate and inhibitor of the nuclear enzyme poly-ADP-ribose polymerase, which plays a central role in DNA repair. This indicates that it may be possible to prevent the formation of mutations after the introduction of DNA photoproducts with the use of enzymatic sunscreens or other modalities. Interestingly, the cutaneous microbiome has recently been found to have immunoprotective properties[71], with UV exposure not only capable of inducing AMPs but also shifting the microbiota of the skin[72,73]. It remains to be determined how application of sunscreens interferes with the cutaneous microbiome in humans[74].

Additional figures and tables on Deficient DNA repair genes in xeroderma pigmentosum (XP) complementation groups XPA to XPG, trichothiodystrophy (TTD), Cockayne syndrome (CS), and XP variant, and Types of impaired function in inherited disorders with abnormal DNA repair, available in our eBook (see inside front cover for access code).

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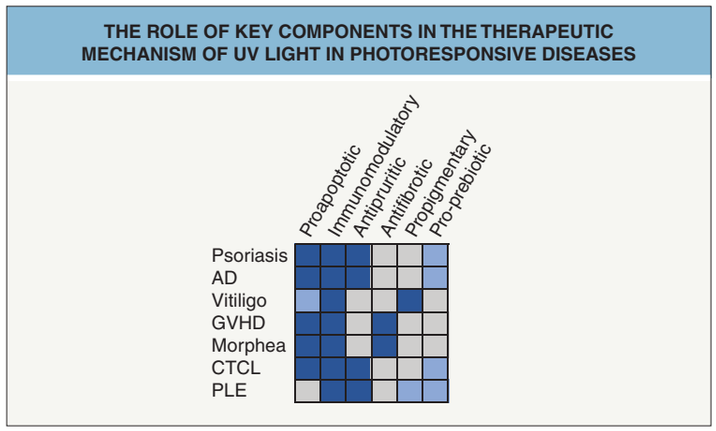
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eFig. 86.1 Second-degree sunburn with blister formation. *Courtesy Kalman Watsky, MD.*



eFig. 86.2 Schematic diagram of the role of key components in the therapeutic mechanism of UV light in photoresponsive diseases. Dark blue indicates strong evidence, light blue moderate evidence, and grey no evidence for a differential key component. AD, atopic dermatitis; CTCL, cutaneous T cell lymphoma; GVHD, graft-versus-host disease; PLE, polymorphous light eruption. *Reproduced with permission from Vieyra-Garcia PA, Wolf P. A deep dive into UV-based phototherapy: mechanisms of action and emerging molecular targets in inflammation and cancer. Review Pharmacol Ther 2021;222:107784.*

DEFICIENT DNA REPAIR GENES IN XERODERMA PIGMENTOSUM (XP) COMPLEMENTATION GROUPS XPA TO XPG, TRICHOTHIODYSTROPHY (TTD), COCKAYNE SYNDROME (CS), AND XP VARIANT

Complementation group or inherited disorder	Function of affected gene product in DNA repair	Also associated with
Nucleotide excision repair		
XPA	High affinity for injured DNA (single strands)	
	Has many interactions with other NER proteins	
	Might have a role in assembling the DNA repair machinery around the DNA lesion	
XPB	Subunit of the transcription factor TFIIH	
	Unwinds the DNA helix around the DNA lesion with its 3′→5′ helicase function	XP/CS*, TTD
XPC	DNA damage recognition	
	Only required for global genome repair, not for transcription-coupled repair	
XPD	Subunit of the transcription factor TFIIH like XPB	
	Unwinds the DNA helix around the DNA lesion with its 5′→3′ helicase function	TTD
XPE	Affinity for UV-damaged DNA	
	Might have an auxiliary role in DNA damage recognition	
XPF	5′-repair endonuclease	
	The ERCC1/XPF complex cuts at the single-strand to double-strand transition 5′ of the DNA lesion	XP/CS*
XPG	3′-repair endonuclease	
	Cuts at the single-strand to double-strand transition 3′ of the DNA lesion	
	Stabilizes TFIIH	XP/CS*
TTDA	Subunit of TFIIH (TFB5)	
	See XPB and XPD	
CSA	Only required for transcription-coupled repair	
	Regulates recruitment of repair factors and chromatin remodelers upon stalling of RNA polymerase at the DNA lesion	
CSB	Only required for transcription-coupled repair	
	Regulates recruitment of repair factors and chromatin remodelers upon stalling of RNA polymerase at the DNA lesion	
Translesional DNA synthesis		
XP variant	DNA polymerase-η	
	Bypasses T–T dimers with correct insertion of two A residues	

*Xeroderma pigmentosum/Cockayne syndrome overlap syndrome.

eTable 86.1 Deficient DNA repair genes in xeroderma pigmentosum (XP) complementation groups XPA to XPG, trichothiodystrophy (TTD), Cockayne syndrome (CS), and XP variant. In addition, mutations in the gene that encodes TTDN1, a protein that may have a role in maintaining cell cycle integrity, can lead to a non-photosensitive form of TTD. ERCC1, excision repair cross complementing gene 1; NER, nucleotide excision repair; TFIIH, transcription factor IIH.

TYPES OF IMPAIRED FUNCTION IN INHERITED DISORDERS WITH ABNORMAL DNA REPAIR				
	Global genome NER	**Transcription-coupled NER**	**Translesional DNA synthesis**	**Mismatch DNA repair**
Xeroderma pigmentosum (XP)	+	+	+ (XP variant)	
Cockayne syndrome (CS)		+		
XP–CS overlap	+	+		
Trichothiodystrophy		+		
Muir–Torre syndrome				+

eTable 86.2 Types of impaired function in inherited disorders with abnormal DNA repair. Patients with Cockayne syndrome and trichothiodystrophy are not at increased risk of developing skin cancer. NER, nucleotide excision repair.

87 Photodermatologic Disorders

Henry W. Lim and Cheryl F. Rosen

INTRODUCTION

All skin phototypes react to sunlight because the skin contains molecules (chromophores) capable of absorbing ultraviolet radiation (UVR) or visible light. This absorbed energy is then either re-emitted harmlessly as biologically inactive radiation or diverted to driving thermochemical reactions, leading to molecular, cellular, tissue, and clinical changes. These alterations are either subsequently repaired or result in permanent changes. Nucleic acids are the most ubiquitous chromophores and can initiate UVR-induced changes. In melanocytes, opsin-3 may play a role as a sensor for visible light[1] although opsin-3 appears to be a negative regulator of melanin production[2].

Photodermatoses result from either *abnormal* tissue responses following absorption of photons by endogenous molecules or *expected* responses to absorption by porphyrins or photosensitizing drugs or chemicals (Table 87.1). Clues to the diagnosis of specific photodermatoses are provided in Fig. 87.1.

ABNORMAL CUTANEOUS RESPONSES TO LIGHT

Worldwide, polymorphous light eruption is the most common photodermatosis. Photoaggravated dermatoses, drug-induced photosensitivity, and chronic actinic dermatitis are also commonly observed photodermatoses, depending upon the population, while solar urticaria is relatively uncommon[3]. All have a significant negative effect on patients' quality of life[4].

Immunologically-Mediated Photodermatoses

This group of disorders is outlined in Table 87.2.

Polymorphous light eruption

Synonyms: ■ Polymorphic light eruption ■ Benign summer light eruption (clinical variant) ■ Juvenile spring eruption (clinical variant)

Key features

- The most common photodermatosis
- Papules, vesicles, or plaques appear within hours following sun exposure; lasts for a few days
- In patients with darker skin phototypes, the most common primary lesion is a pinhead-sized papule
- Action spectra: UVB, UVA, and rarely visible light
- Management: photoprotection and narrowband (NB)-UVB hardening

Introduction and history

Polymorphous light eruption (PMLE) is a common, sunlight-induced eruption affecting individuals of all races and skin colors[3,5]. Within minutes to hours of sun exposure, pruritic, erythematous papules, papulovesicles, or rarely vesicles develop. In patients with darker skin phototypes, pinhead-sized papules represent the most common morphology. Lesions resolve within a few days without scarring. The eruption is generally most severe in the spring and early summer, especially in temperate climates. As summer progresses, PMLE becomes milder, a phenomenon known as "hardening".

PMLE was first described by Carl Rasch in 1900 and mentioned again by Haxthausen in 1918.

Epidemiology

The prevalence of PMLE in the general population is inversely related to latitude, being highest in Scandinavia (22%), high in the UK and northern US (10%–15%), and low in Australia (5%) and equatorial Singapore (~1%)[5]. This is probably due to the development of UVR-induced immunologic tolerance ("hardening") due to constant year-round solar exposure in sunny climates. Women are affected slightly more often than men, with the second and third decades being the most common times of onset.

Pathogenesis

Attacks of PMLE are triggered by exposure to UVR (and occasionally visible light) from sunlight or other sources such as tanning beds and phototherapy units. Spring and summer sunlight in temperate regions is most likely to induce outbreaks. The action spectrum ranges from UVB to UVA and rarely to visible light. Patients typically have normal minimal erythema doses (MEDs) to UVB, UVA, and visible light,[5] although severely abnormal phototesting results have been reported in some patients[6].

PMLE is considered to be a delayed-type hypersensitivity (DTH) response to as-yet-undefined, *photoinduced* endogenous cutaneous antigens[5]. Timed biopsy specimens, following solar-simulated irradiation (~0.6 MED), have shown perivascular infiltrates of lymphocytes, primarily $CD4^+$ (within hours) and $CD8^+$ (within days), in association with an increased number of dermal and epidermal antigen-presenting cells[7]. Following UV exposure, reductions in IL-4 and IL-10 production as well as in infiltrates of neutrophils and mast cells have been observed[5].

Susceptibility to PMLE appears to be genetic, with up to 70% of the population having a propensity for developing this condition, but not all expressing it because of variations in disease penetrance[8]. There appears to be a *resistance* to the normal UVR-induced suppression of the induction,[9] but not the elicitation,[10] of cutaneous DTH responses. As a result, in PMLE, a lesser degree of cutaneous immunosuppression following UVR exposure (compared to normal individuals) likely results in a persistent ability to mount a DTH response against UVR-altered endogenous cutaneous molecules, leading to the development of clinical lesions. Possible underlying mechanisms include: (1) an under-expression of apoptotic-cell clearance genes in keratinocytes, thus prolonging antigen presence; and/or (2) inefficient free radical removal, thereby increasing photoantigen production. UVR-induced cutaneous immunosuppression may protect against developing disruptive PMLE, but it can also increase the risk of skin cancer. Indeed, PMLE patients have been reported to have a reduced tendency to develop such cancers[11].

Clinical features

In temperate climates, PMLE usually occurs during the spring and early summer, following minutes to hours of sun exposure[5]. Outbreaks may also occur after exposure to snow-reflected sunlight, tanning beds, or UV phototherapy. The eruption fades over one to several days, but may recur. PMLE tends to improve over the summer or a lengthy sunny vacation, presumably due to the development of immunologic tolerance, also known as "hardening"[5].

Typically, some, but virtually never all, of the exposed skin is affected. Lesions are usually symmetrically distributed in a patchy fashion. Areas that are normally continuously exposed to sunlight (e.g. face) are often spared (Fig. 87.2). The distribution pattern and morphology of lesions in a given patient are usually consistent over time. Areas commonly affected are the neck, outer aspects of the arms, and dorsal hands (Fig. 87.3), but there may be more widespread involvement of sun-exposed sites (Fig. 87.4).

Clinically, mildly to markedly pruritic, grouped, erythematous or skin-colored papules of varying sizes, sometimes coalescing into large, smooth or unevenly surfaced plaques, are seen. In darkly pigmented individuals, the most common morphology is grouped, pinhead-sized papules in sun-exposed areas (see Fig. 87.3D); upon resolution, shiny pinhead-sized macules may be observed. Vesicles, bullae, papulovesicles, and confluent edematous swelling are additional manifestations; rarely, only pruritus occurs. Occasionally, particularly in boys, the helices of the ears may be principally affected in a form of PMLE referred to as juvenile spring eruption. Vesicles are commonly observed in this variant. In a 32-year follow-up of 94 patients, the disease improved or resolved in 58% over a period of 16 years, and in 75% over a period of 32 years.

CLASSIFICATION OF PHOTODERMATOSES

• Immunologically mediated (see Table 87.2)
• Defective DNA repair and chromosomal instability disorders
• Photoaggravated dermatoses
• Chemical- and drug-induced photosensitivity
  • Exogenous: ingested or externally applied drugs or chemicals
  • Endogenous: cutaneous porphyrias, pellagra, Smith–Lemli–Opitz syndrome

Table 87.1 Classification of photodermatoses.

IMMUNOLOGICALLY MEDIATED PHOTODERMATOSES
• Polymorphous light eruption • Actinic prurigo • Hydroa vacciniforme • Chronic actinic dermatitis • Solar urticaria

Table 87.2 Immunologically mediated photodermatoses.

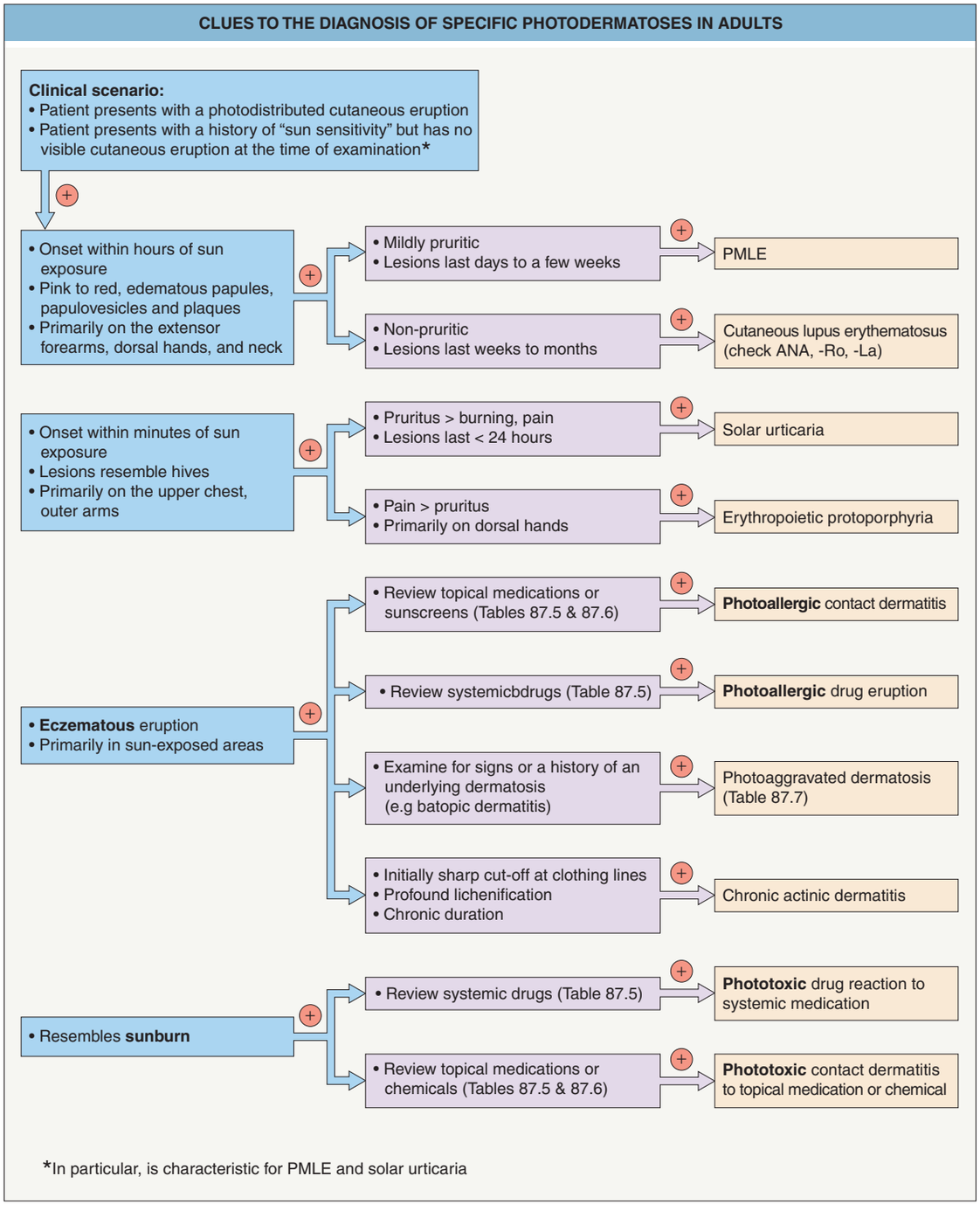


Fig. 87.1 Clues to the diagnosis of specific photodermatoses in adults. PMLE, polymorphous light eruption.





Fig. 87.2 Polymorphous light eruption of the face. A Larger erythematous patch on the nose as well as erythematous plaques on the malar eminence and chin. **B** Edematous erythematous plaques on the cheek in a young child.

Pathology

There is variable epidermal spongiosis and a superficial and deep, perivascular and periappendageal, lymphohistiocytic dermal infiltrate, often with scattered eosinophils and neutrophils. Significant papillary dermal edema occurs commonly (Fig. 87.5). Occasionally, difficulty in distinction from cutaneous lupus may occur if interface changes are significant. $CD123^+$ cells are usually present in lupus erythematosus (LE) but absent in PMLE.

Differential diagnosis

PMLE can often be distinguished from LE, photoaggravated dermatoses (e.g. atopic dermatitis, seborrheic dermatitis), solar urticaria, and rarely, erythropoietic protoporphyria (EPP) by the natural history and clinical appearance of the cutaneous lesions. Occasionally, clinicopathologic correlation and laboratory evaluation are required (Table 87.3; see Fig. 87.1). For photoaggravated dermatoses, the characteristic clinical features of the primary disorder usually allow for distinction.

Treatment

PMLE in its milder forms can be managed by photoprotection, including the use of broad-spectrum, high SPF sunscreens and physical barriers. In patients with more severe disease, two-to-three times per week sessions of NB-UVB, usually for 15 sessions in the spring, can produce hardening and be effective for several months[12]. An initial starting dose of 30%–50% of the MED for NB-UVB is recommended, with the dose then increased by 10%–15% per treatment. Oral prednisone (0.5–1 mg/kg) may be used during the initial seven to ten days of phototherapy to minimize photoexacerbation. Once hardening is achieved, it may be possible to maintain the effect by having patients expose themselves weekly to sunlight between 10 AM and 2 PM for 15–20 minutes (without sunscreen) for the remainder of the sunny season.

Other therapeutic options for prevention of PMLE include oral prednisone (<0.5 mg/kg, usually given for 5–7 days during vacations to a sunny climate)[13] and less commonly, hydroxychloroquine[14,15].

Actinic prurigo

Synonyms: ■ Hutchinson's summer prurigo ■ Familial (or hereditary) polymorphous light eruption of American Indians ■ Hydroa aestivale

Key features

- Severe form common in Native Americans, often with cheilitis and conjunctivitis
- Can occur in all races
- Childhood onset; often resolution by adolescence, but can persist indefinitely
- Intensely pruritic, crusted papules or nodules in sun-exposed sites
- Strong association with HLA-DR4 (DRB1*0401) and subtype DRB1*0407
- Primary management: photoprotection, NB-UVB, topical calcineurin inhibitors, and thalidomide

Introduction and history

Actinic prurigo is a fairly uncommon, sunlight-induced, pruritic and crusted, papular or nodular eruption involving uncovered and, to a lesser extent, covered skin[16]. It was first described in the 1960s and 1970s, and was noted to affect North, Central, and South Americans of indigenous or mixed race.

Hutchinson first described this disorder in 1879, followed in 1918 by Haxthausen, who described it as a PMLE variant. In 1968, Londoño coined the term "actinic prurigo".

Epidemiology

Actinic prurigo is particularly common in Native Americans, especially Mestizos (mixed American Indian and European ancestry) living at high altitudes. It also occurs, but much less commonly, in Europe and Asia. A familial form is relatively common.

Pathogenesis

Actinic prurigo is triggered by UVR exposure and therefore typically flares during the spring and summer, especially in temperate climates. Phototesting results are abnormal in approximately two-thirds of patients and cutaneous lesions can be provoked by UVB or UVA.

The immunologic nature of actinic prurigo is supported by a study of Mexican Mestizo patients, where the remarkable therapeutic efficacy of thalidomide has been shown to be associated with an inhibition of TNF synthesis and the modulation of interferon-γ-producing $CD3^+$ cells. The presence of a dense lymphocytic infiltrate and lymphoid follicles in lesional biopsy specimens from the lips provides further support for this concept[16].

Actinic prurigo may represent a persistent variant of PMLE, as clinical conversion between actinic prurigo and PMLE has been observed, and in family studies, the two disorders are closely linked[17]. There is also a strong association of actinic prurigo with HLA-DR4 (DRB1*0401) and subtype DRB1*0407[17], and this may be the genetic factor that transforms PMLE into actinic prurigo. Indeed, the presence of this HLA subtype is strongly suggestive of the diagnosis.

Clinical features

Actinic prurigo usually appears during childhood and is more frequently seen in girls. It often resolves by adolescence, but may persist indefinitely[16]. The eruption is usually worse during the summer in temperate

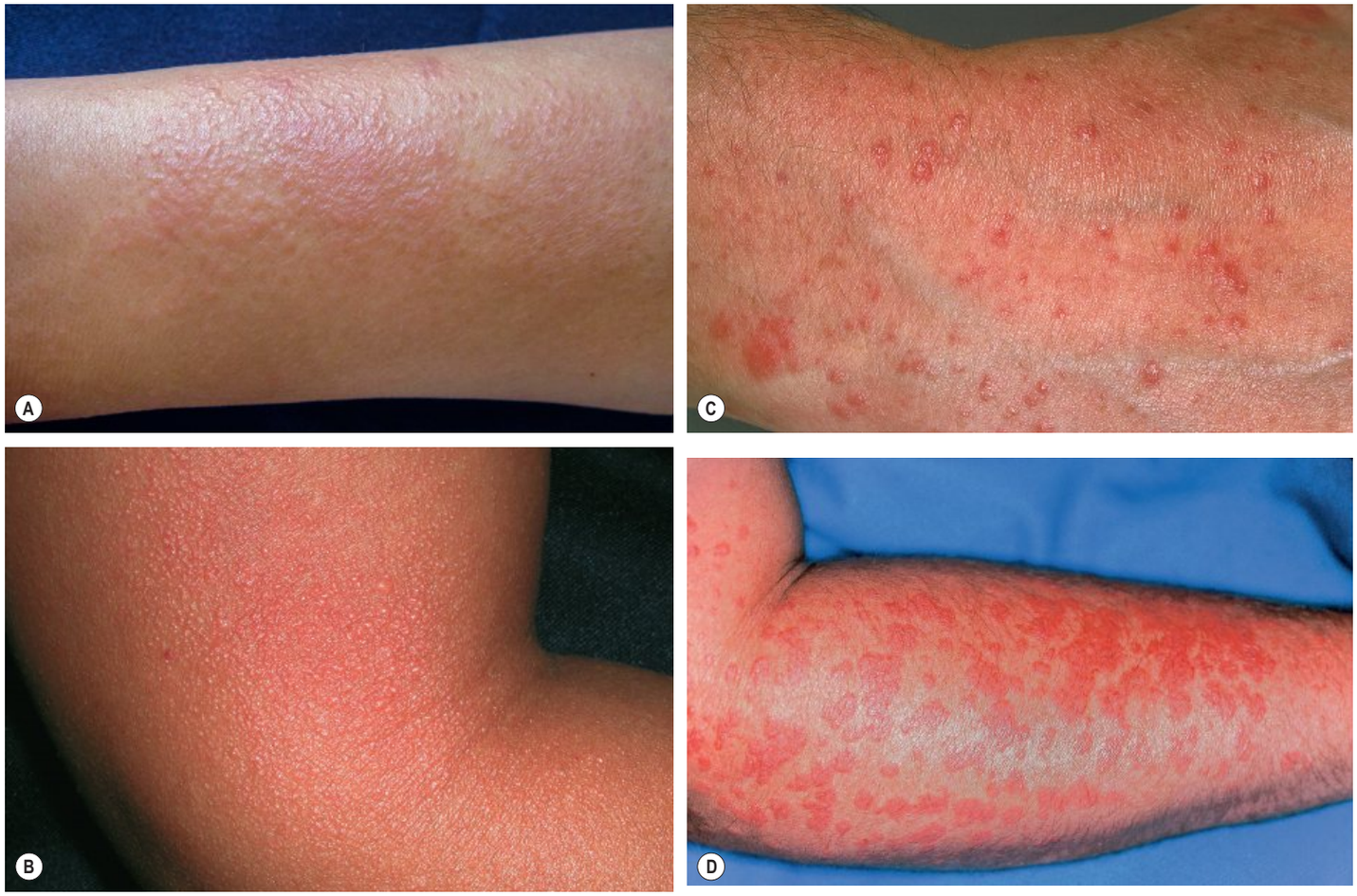


Fig. 87.3 Polymorphous light eruption of the upper extremity. A Small pink edematous papules that are coalescing into plaques on the forearm of an Asian patient. **B** Pinhead-sized papules in a patient with skin phototype IV. **C** Scattered discrete papulovesicles. **D** Larger and more pronounced edematous erythematous papules and plaques.

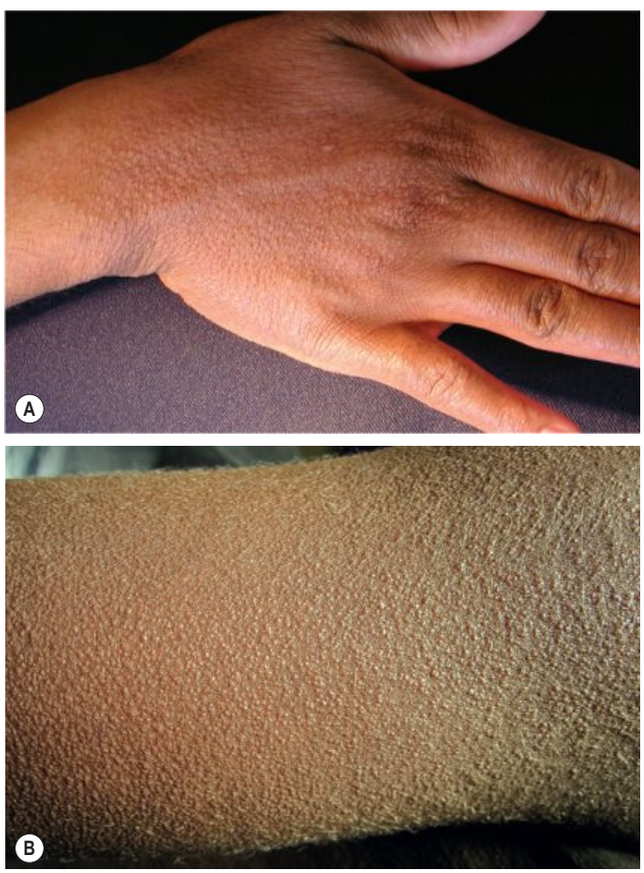


Fig. 87.4 Papular variant of polymorphous light eruption. A,B Pinhead-sized papules on the hand and extensor forearm in two African-American adults.

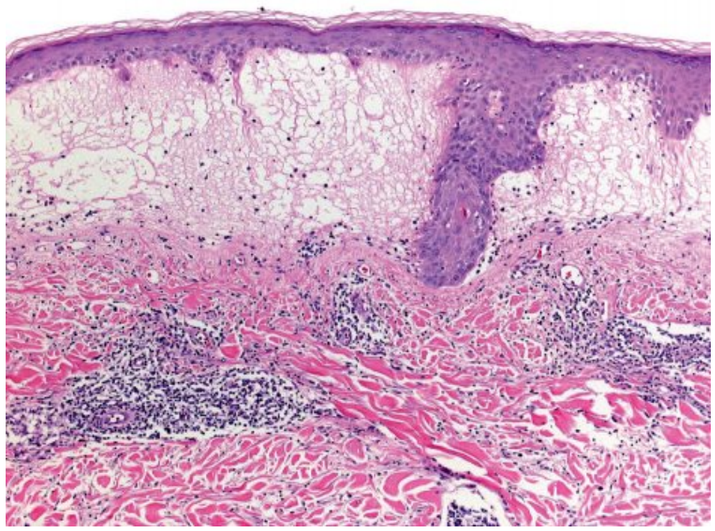


Fig. 87.5 Polymorphous light eruption – histopathologic features. Within the dermis, there is a perivascular mononuclear cell infiltrate as well as marked papillary edema. *Courtesy Lorenzo Cerroni, MD.*

climates, but may not always be clearly related to sun exposure. In tropical regions of Latin America, it can persist year-round.

Erythematous papules or nodules, sometimes with hemorrhagic crusts due to excoriation, are present in sun-exposed sites, especially the face (including the nose) and the distal limbs (Fig. 87.6). Lesions may be scattered or densely distributed, and there are sometimes eczematous features or lichenification. Fine linear or pitted scars may appear as facial papules heal. In patients from the UK, involvement of covered sites, particularly the buttocks, has been well described (Fig. 87.7).

EVALUATION OF PHOTOSENSITIVITY WITH SUGGESTED LABORATORY INVESTIGATIONS
• Routine histology • Antinuclear antibodies • Anti-SSA/Ro, -SSB/La antibodies • Plasma porphyrins, followed by complete porphyrin profile if positive (see Ch. 49) • Phototesting to UVA, UVB, and visible light • Photopatch testing (see Fig. 87.19)

Table 87.3 Evaluation of photosensitivity with suggested laboratory investigations.



Fig. 87.6 Actinic prurigo. Multiple papules on the upper cheek, several of which have central crusts. A linear excoriation is seen on the lower portion of the upper eyelid.



Fig. 87.7 Actinic prurigo. More severe actinic prurigo with involvement of the buttocks as well as sun-exposed sites. *Courtesy John L. M. Hawk, MD.*

Cheilitis and conjunctivitis are common, with cheilitis often being the only clinical manifestation (Fig. 87.8)[16].

Pathology

In early lesions, there is epidermal spongiosis, acanthosis, and a dermal perivascular mononuclear cell infiltrate with occasional eosinophils, but, unlike in PMLE, papillary edema is usually absent[16]. Later, crusts, more pronounced acanthosis, variable lichenification, excoriations, focal dermal papillary fibrosis, and a heavier mononuclear cell infiltrate can be seen. These latter features are nonspecific and may resemble those of chronic dermatitis, prurigo nodularis, or, very rarely, cutaneous B cell lymphoma. Dermal lymphoid follicles have been observed in biopsy specimens taken from the lips[16]. Direct immunofluorescence microscopy is negative.



Fig. 87.8 Actinic prurigo. The cheilitis is more severe on the lower vermilion lip. On the upper lip, chronic inflammation has led to blurring of the border between vermilion lip and the cutaneous lip. *Courtesy Jean L. Bolognia, MD.*

Differential diagnosis

The history and clinical features often suggest the diagnosis. Clinicopathologic correlation and laboratory evaluation aid in excluding LE and childhood porphyrias (see Table 87.3). Lesions of prurigo nodularis are not accentuated in sun-exposed skin. Patients with CARMIL2-related immunodeficiency can develop an actinic prurigo-like photosensitivity in addition to Epstein–Barr virus (EBV)-associated smooth muscle tumors and impaired T cell function[18].

Treatment

Rigorous photoprotection is helpful. For milder disease, topical corticosteroids and topical calcineurin inhibitors may be used. NB-UVB should be considered next, with protocols similar to those for PMLE (see above). Resistant disease is best treated with oral thalidomide (50–100 mg nightly)[16], administered for several weeks until remission is achieved and then tapered to as low a maintenance dose as possible (e.g. 50 mg every second or third night). However, the risks of teratogenicity and peripheral neuropathy require very careful patient selection and supervision (see Ch. 130). Other possible systemic therapies include corticosteroids, azathioprine, cyclosporine, dupilumab, and lenalidomide or pomalidomide. In comparison to thalidomide, the latter have significantly less neuropathy, fatigue, and constipation.

Hydroa vacciniforme

Synonym: ■ Bazin's hydroa vacciniforme

Key features

- Very rare, childhood-onset photodermatosis
- Two types: classic hydroa vacciniforme (HV) and HV-like lymphoproliferative disorder (LPD)
  - Classic HV: photodistributed papules and plaques develop umbilicated vesiculation, followed by hemorrhagic crusting (often severe) and varioliform scarring
  - HV-like LPD: papulovesicles in sun-exposed and sun-protected sites, facial edema, lymphadenopathy, and systemic symptoms; may progress to systemic EBV^+ T cell or natural killer (NK) cell lymphoma
- Inclusion of classic HV as a subtype of HV-like LPD has been proposed
- Management requires rigorous photoprotection

Introduction and history

Classic hydroa vacciniforme (HV) is a rare, sunlight-induced, childhood-onset, intermittent but permanently scarring disorder. The condition was first reported by Bazin in 1862.

Epidemiology

HV is well recognized globally, including in the US, UK, Europe, Korea and Japan, and in these countries has been reported to have a predilection for lightly pigmented individuals. The condition typically has its onset during childhood, affecting boys slightly more often than girls and with more severe disease in boys. The disorder can resolve during adolescence or early adulthood[19]; rare familial cases have been noted.

The 2018 update of the WHO-EORTC classification of primary cutaneous lymphomas contains a new category in which patients have chronic active EBV infection. Of particular interest to dermatologists, this category includes HV-like LPD (usually $CD8^+$ T cell phenotype) and severe mosquito bite allergy (usually NK cell phenotype)[20]. Per this classification scheme, the term HV-like LPD encompasses patients previously referred to as having HV as well as HV-like T cell or NK cell lymphoma. However, inclusion of classic HV remains controversial. In patients with HV-like lesions, the development of facial edema, lymphadenopathy, and hepatosplenomegaly points to the diagnosis of HV-like LPD or even lymphoma. The latter disorders have been observed primarily in Asians and indigenous populations of Latin America[21,22].

Pathogenesis

Although tropical sunlight or summer sunlight in temperate regions is generally required to provoke the eruption, abnormal erythematous, or rarely vesicular, phototest responses to repeated monochromatic or broad-spectrum UVR exposure can be induced. The exact pathophysiology of the cutaneous reaction in HV is unknown.

In a study from Japan, T cells positive for EBV RNA were detected in lesional skin infiltrates from 94% of children with clinically typical HV (17/18) and 11/11 patients with severe HV-like eruptions associated with systemic symptoms, but 0/32 skin biopsy samples from patients with various other dermatoses, including photodermatoses[21]. While the relationship between EBV infection and classic HV remains a matter of debate, it is likely that classic HV and HV-like LPD reside along a clinical spectrum[22].

Clinical features

Within hours of summer sun exposure, symmetric, clustered, pruritic or stinging, erythematous macules develop in a photodistribution, especially on the face and dorsal aspects of the hands. Over the next several hours, the macules become tender papules or plaques surmounted by vesicles or bullae (often hemorrhagic), before umbilicating and condensing into hemorrhagic crusts over a span of several days (Fig. 87.9A,B). Healing then occurs over a period of weeks, leaving individual or confluent, sometimes telangiectatic, varioliform scars (Fig. 87.9C). Generalized malaise with fever or headache rarely accompanies the attacks. However, quality of life in affected children is negatively impacted by their inability to play outdoors[19].

In addition to fevers, lymphadenopathy, hepatosplenomegaly, and facial edema, the development of more severe HV-like papulonodules (including in sun-protected sites), oral and labial ulcerations, and panniculitis point to HV-like LPD (Fig. 87.10). These patients may also have exaggerated reactions to mosquito bites, increased NK lymphocytes, hemophagocytic lymphohistiocytosis with leukopenia and thrombocytopenia, and elevated hepatic transaminases. A high circulating EBV DNA load is generally detected by PCR.

Pathology

Progressive epidermal spongiosis precedes findings that are almost pathognomonic: prominent, reticular keratinocyte degeneration; the formation of intraepidermal vesicles containing fibrin and acute inflammatory cells; and confluent epidermal and occasionally focal upper dermal necrosis (Fig. 87.11). Early on, a variably dense perivascular lymphohistiocytic infiltrate admixed with neutrophils and occasionally a few eosinophils is seen; this is followed by epidermal necrosis. Direct immunofluorescence microscopy findings are nonspecific. *In situ* hybridization for EBV RNA shows positivity within the lymphoid infiltrate.

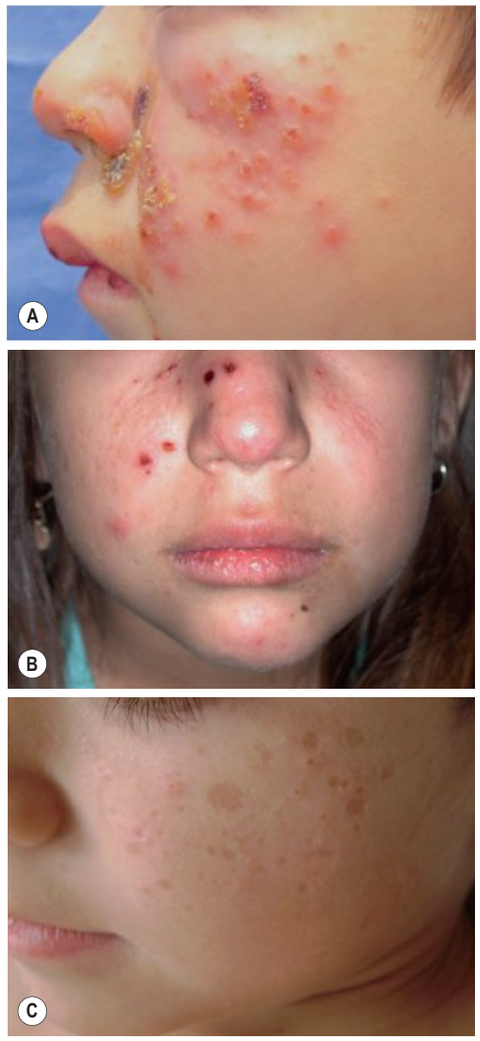


Fig. 87.9 Hydroa vacciniforme – classic form. A Papulovesicles with crusting of the nose, cheeks, and lips appeared a few days after sun exposure. **B** Hemorrhagic crusts are admixed with varioliform scars; the latter are the sequelae of repeated acute attacks. Note the scaling and erosions of the lower vermilion lip. **C** Varioliform scars and postinflammatory hyperpigmentation on the cheek. *A,C, Courtesy Tor Shwayder, MD; B, Courtesy Jean L. Bolognia, MD.*



Fig. 87.10 Hydroa vacciniforme-like lymphoproliferative disorder. Extensive involvement of the face by erythematous edematous and infiltrated plaques with hemorrhagic crusts at sites of vesiculation.

Differential diagnosis

LE and childhood porphyrias can be excluded by clinicopathologic correlation and laboratory evaluation (see Table 87.3), while herpes simplex is excluded by a negative PCR, DFA assay, or viral culture. Occasionally, other photodermatoses such as the vesicular form of PMLE and actinic prurigo may be considered.

Treatment

HV is almost always refractory to treatment. Rigorous photoprotection can be useful in mild to moderate disease. Anecdotally, the following have been reported to be helpful: broadband (BB)-UVB, NB-UVB, PUVA, β-carotene, antimalarials, azathioprine, thalidomide, cyclosporine, and dietary fish oil. Systemic therapies such as thalidomide and interferon are also used for HV-like LPD while treatment of EBV^+ T cell lymphoma includes systemic chemotherapy and allogeneic hematopoietic stem cell transplant.

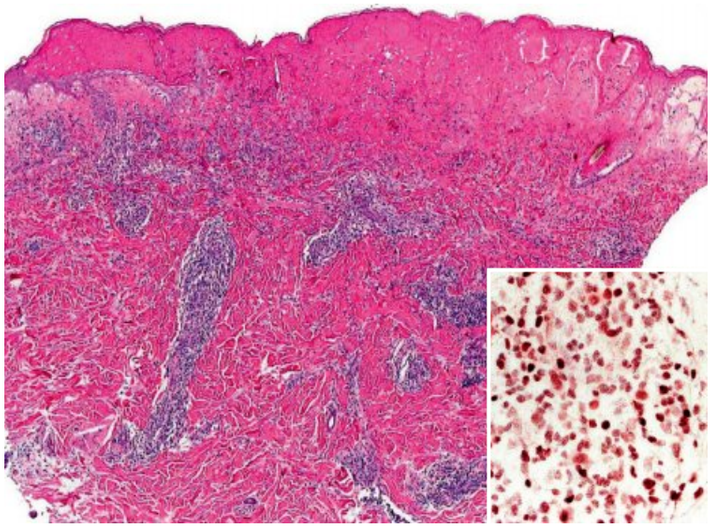


Fig. 87.11 Hydroa vacciniforme – histopathologic features. Necrosis of the epidermis with dense, mainly perivascular, infiltrates of lymphocytes within the entire dermis. Note positivity of lymphocytes for Epstein–Barr virus as detected by *in situ* hybridization for EBER-1 (inset). *Courtesy Lorenzo Cerroni, MD.*

Chronic actinic dermatitis

Key features

- In sun-exposed areas, chronic eczematous eruption (acute, subacute or chronic lichenified) or pseudolymphomatous lesions
- Most common in men over 50 years of age
- Positive phototests to varying combinations of UVB, UVA, and visible light
- Positive patch or photopatch tests common
- Management includes photoprotection, avoidance of (photo) contact sensitizers, intermittent oral and topical corticosteroids, topical calcineurin inhibitors, low-dose PUVA, cyclosporine, azathioprine, mycophenolate mofetil, and/or dupilumab
- Probability of spontaneous resolution is 10% over 5 years, 20% over 10 years

Introduction and history

Chronic actinic dermatitis (CAD) is a persistent, often disabling dermatosis of uncovered (and to a lesser extent, covered) skin, generally affecting older men, particularly in the summer[3,23]. It is evoked by UVR and occasionally also visible light exposure. CAD probably represents a contact allergy-like DTH response against endogenous photoinduced antigen(s).

Reference to a condition suggestive of CAD was first made in 1933 by Haxthausen, then in the 1960s by Wilkinson in the UK and Jillson and Baughman in the US, with the latter authors terming it "*persistent light reaction*". In 1969, its severe form, *actinic reticuloid*, was described, followed shortly thereafter by reports of two milder variants, *photosensitive eczema* and *photosensitivity dermatitis*. In 1979, the current encompassing term, CAD, was introduced by Hawk and Magnus[24].

Epidemiology

CAD has been regularly observed throughout the world. It occurs primarily in temperate zones and more commonly affects older men[2,23]. However, CAD has been increasingly recognized in younger women as well as in patients with darker skin phototypes.[3,25] Familial incidence has not been noted.

Pathogenesis

The action spectra for CAD include UVB, UVA and/or visible light, with UVB plus UVA being the most common. The eczematous clinical and histologic appearances of CAD, its dermal infiltrate of primarily $CD8^+$ T lymphocytes, and its pattern of adhesion molecule activation all closely mimic the DTH response of allergic contact dermatitis. This strongly suggests that CAD is presumably a reaction against endogenous, photoinduced, cutaneous antigen(s).



Fig. 87.12 Chronic actinic dermatitis. Chronic eczematous changes of the posterior neck with lichenification and a sharp cut-off at the collar in a patient with phototype V skin.

CAD was initially described as most common among individuals who spent a lot of time outdoors. However, a significant number of patients, especially those with darker skin phototypes, do not have a history of frequent outdoor activities[23,25]. It is possible that in CAD chronic photodamage leads to a partial abrogation of normal cutaneous immunosuppression, thereby permitting enhanced cutaneous immune responsiveness against an otherwise weak endogenous photoantigen. It should be noted that positive patch testing to *Compositae*, commonly observed in the UK, has not been confirmed in the US and Japan.

It is likely that nucleic acids may be involved as chromophores in the pathogenesis of CAD, in that the shape of the CAD induction spectrum resembles that of sunburn inflammation, for which UVR absorption by nucleic acids is known to be responsible[23].

Clinical features

CAD may develop in previously normal skin, in patients with a prior history of dermatitis (in particular, photoallergic contact dermatitis, allergic contact dermatitis, and atopic dermatitis), or rarely following longstanding oral drug photosensitivity or PMLE. Coexistent allergic contact sensitivity to plant antigens, fragrances, or topical medications is common. The eruption consists of pruritic papules and lichenified plaques in sun-exposed areas (Fig. 87.12); during disease flares, involvement of sun-protected sites, albeit less severe, can be seen. Scattered or widespread, erythematous, shiny, infiltrated, pseudolymphomatous papules or plaques may be present in severely affected individuals.

Lesions develop primarily within sun-exposed sites, frequently with a sharp cut-off at the lines of clothing, and often with sparing in the depths of skin furrows, upper eyelids, finger webs, nasolabial folds, or postauricular areas (Figs. 87.13–87.15). Occasionally, palmoplantar eczematous changes may also be present, while eyebrow or scalp hairs may be stubbly or sparse from rubbing or scratching. Rarely, erythroderma develops in severely affected patients. The probability of resolution has been estimated to be 10% over 5 years, 20% over 10 years, and 50% over 15 years[26].

A rather uncommon photodermatosis, *broad-spectrum abnormal localized photosensitivity syndrome*, also known as *fixed sunlight sensitivity*, is probably a variant of CAD. It is characterized by localized erythema, edema, and blistering that is induced by broad-spectrum UV radiation and occurs most commonly on the extremities[26a].

Pathology

There is epidermal spongiosis and acanthosis, lymphocytic exocytosis, and a superficial and deep, frequently dense, perivascular lymphohistiocytic dermal cellular infiltrate, often containing eosinophils and plasma cells[23]. In more severely affected skin, erosions, focal epidermal necrosis, Pautrier microabscess-like epidermal cellular collections, dermal–epidermal junction fibrin deposition, dermal neutrophils with nuclear dust, vertically streaked papillary dermal collagen, and/or small, multinucleated dermal giant cells are often seen. In addition, the dense infiltrate, epidermal lymphocyte exocytosis, and frequent nuclear polymorphism may on occasion suggest a histologic diagnosis of cutaneous T cell lymphoma (CTCL).



Fig. 87.13 Chronic actinic dermatitis. Lichenification and hyperpigmentation in sun-exposed sites with areas of depigmentation. Note the sparing of sun-protected areas (e.g. nasolabial fold).



Fig. 87.14 Chronic actinic dermatitis. Chronic eczematous changes of the dorsal hand and wrist with associated hyperpigmentation and scaling. Note the sharp cut-off on the distal forearm.

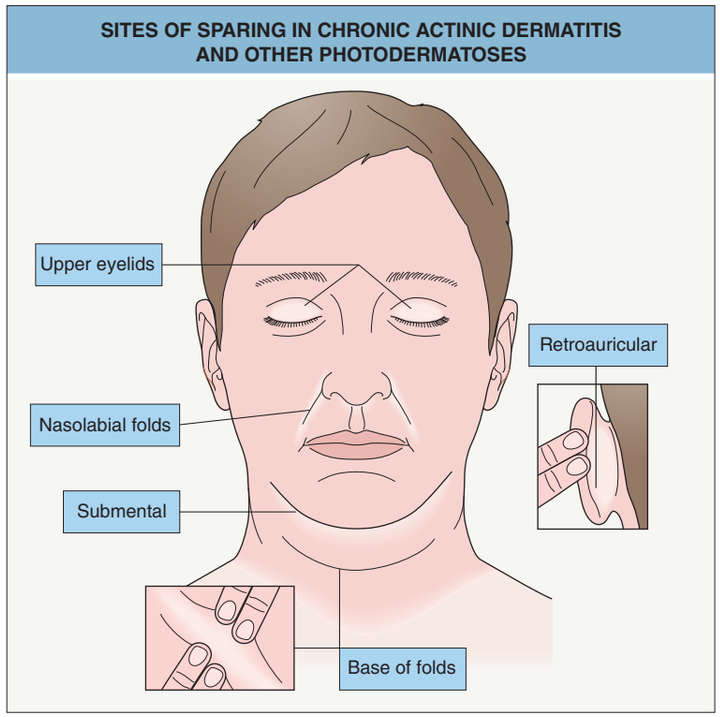


Fig. 87.15 Sites of sparing in chronic actinic dermatitis and other photodermatoses. Relatively sun-protected sites include the upper eyelids, the nasolabial folds, the retroauricular areas, the submental region and the deepest portion of skin furrows. In airborne contact dermatitis these areas are usually involved.

Differential diagnosis

Photoaggravated dermatoses are differentiated by the characteristic clinical features of the underlying primary disorder and normal cutaneous irradiation responses. In drug- and chemical-induced photosensitivity, there is usually a history of exposure to a relevant drug or allergen or clinical evidence (e.g. positive photopatch testing results; see below).

In contrast to CTCL, CAD infiltrates are predominantly $CD8^+$ cells[23] and T cell receptor gene rearrangement studies are negative. Very rarely, primary CTCL may present with severe CAD features and should therefore be considered if apparent CAD is totally refractory to treatment[27]. Erythrodermic CAD must be differentiated from other causes of erythroderma (see Ch. 10), but histologic features may not allow discrimination so phototesting after the erythroderma has been controlled can assist in establishing the diagnosis.

Treatment

Strict photoprotection and the avoidance of relevant contact allergens are of primary importance. Of note, computer and video screens are safe. Commercially available films that block UVR can be placed on home and car windows. Topical or intermittent oral corticosteroids, along with emollients, are generally needed, and topical calcineurin inhibitors may also be helpful[23]. Therapy for refractory disease includes mycophenolate mofetil (1–2 g/day) cyclosporine (3.5–5 mg/kg/day), or azathioprine (1–2.5 mg/kg/day). Dupilumab has recently been reported to improve recalcitrant CAD[27].

Solar urticaria

Key features

- A physical urticaria induced by sun exposure; lesions appear within 5 to 10 minutes and resolve over 1 to 2 hours
- The action spectrum generally includes both UVA and visible light, but rarely UVB
- There is a slight female predominance, often with an onset during the third decade of life
- Estimated probability of resolution is 15% at 5 years, 25% at 10 years
- Management: photoprotection; high-dose, non-sedating antihistamines; omalizumab; cyclosporine; low-dose UVA; PUVA; plasmapheresis; and IVIg

Introduction and history

In solar urticaria, transient wheals appear within 5 to 10 minutes of exposure to UV or visible radiation. Lesions then resolve over 1 to 2 hours. Solar urticaria was first reported in 1905.

Epidemiology

Solar urticaria is a form of inducible urticaria; one study from Scotland reported a prevalence of ~3.1 per 100 000[28]. There is a slight female predominance, and the onset is most frequently during the third decade of life. Solar urticaria may occasionally coexist with PMLE, CAD, and very rarely, EPP[28].

Pathogenesis

As in other forms of urticaria (see Ch. 18), mast cells play a major role. Although factors triggering their degranulation have not been fully elucidated, an IgE-mediated response against photoinduced, endogenous cutaneous antigen(s) is a likely mechanism. This is supported by observations that omalizumab, which blocks the binding of IgE to its receptor, is effective in many patients.

Clinical features

Patients present with whealing limited to sun-exposed areas, particularly the upper chest and extensor arms, within 5 to 10 minutes of sun exposure. Occasionally, erythema without urtication may occur. The lesions then resolve over 1 to 2 hours. Patients almost invariably note an accompanying pruritus, burning sensation, or rarely pain, while severe attacks are rarely associated with malaise, light-headedness, nausea, bronchospasm and/or syncope.

Although solar urticaria is oftentimes classified by its action spectrum, in an individual patient, the spectrum may gradually change over time[29]. Most commonly, visible light is responsible, but usually with extension into the UVA waveband. In some patients, the action spectrum may include UVB[30].

Occasionally, continued regular skin exposure to UVR may decrease the likelihood of attacks of solar urticaria, a phenomenon referred to as "hardening". The probability of spontaneous resolution has been estimated as being 15% at 5 years and 25% at 10 years after onset[28].

There are several uncommon manifestations of this disorder. Fixed solar urticaria is limited to specific areas, presumably due to mast cell alterations just at those sites[30]. "Drug-induced" solar urticaria has been reported following exposure to chlorpromazine, tetracycline, or tar. Solar angioedema occurs 2-10 hours after exposure and takes days to resolve.

Pathology

The histologic findings are similar to those of other urticarias. There is mild dermal edema with a sparse perivascular mixed neutrophilic and eosinophilic infiltrate; mononuclear cells may also be seen. In addition, eosinophil major basic protein has been demonstrated within the dermis by immunofluorescence.

Differential diagnosis

The differential diagnosis includes other forms of urticaria, particularly heat urticaria, PMLE, and very rarely, EPP. A detailed history should differentiate solar urticaria from idiopathic urticaria and other physical urticarias. Phototesting of affected patients generally results in typical whealing within minutes (Fig. 87.16), while the use of a water filter in front of the light source eliminates heat to exclude heat urticaria. Patients with EPP complain of a more deep-seated pain following sun exposure, and they have elevated free RBC protoporphyrin levels (see Ch. 49). The time course of PMLE is distinct from that of solar urticaria, and LE can be excluded via laboratory evaluation (see Fig 87.1 and Ch. 41).

Treatment

Oral non-sedating antihistamines, often in high doses and taken regularly or about an hour or so before expected sun exposure, are effective in ~50% of patients. Those with very mild disease may occasionally require only photoprotective measures; however, sunscreens do not generally provide sufficient protection against long-wavelength UVA and visible light to be effective[31]. Omalizumab is often effective[32]. Graduated exposures to UVA, UVA1 or PUVA are occasionally helpful[33]. Other treatment options, including methotrexate, cyclosporine, plasmapheresis, or IVIg,[34] have been reported to be successful.

Photosensitivity Due to Hereditary Defects in DNA Repair

The major disorders characterized by both defective DNA repair and photosensitivity are discussed below and outlined in Table 87.4.



Fig. 87.16 Solar urticaria. Wheal and flare responses within minutes of exposure to UVB radiation in a patient undergoing phototesting.

The underlying pathogenesis is reviewed in greater detail in Chapter 86. Five of the disorders are associated with defects in one of the nucleotide excision repair (NER) proteins: xeroderma pigmentosum, Cockayne syndrome, cerebro-oculo-facio-skeletal (COFS) syndrome, UV-sensitive syndrome, and the photosensitive form of trichothiodystrophy[35,36].

Xeroderma pigmentosum

Introduction and history

Xeroderma pigmentosum (XP) is an autosomal recessive condition associated with a marked increase in the development of malignancies, especially cutaneous. Eight complementation groups, corresponding to eight genotypes, have been identified. XP was first described by Hebra and Kaposi in 1874.

Epidemiology

XP has an estimated incidence of 2.3 per million live births in Western Europe, 1 in 20 000 in Japan, and 1 in 250 000 in the US[37].

Pathogenesis

XP can result from defects in one of eight genes. The seven complementation groups A through G are each associated with a different site of impairment in global genomic nucleotide excision repair (GG-NER), i.e. impairment in the removal of DNA damage from any part of the genome[37]; the damaged DNA then accumulates, leading to mutations and cancer. XP-A through XP-G represent different proteins in the NER pathway (see Fig. 86.14). It should be noted that different mutations in *ERCC3* (*XPB*), *ERCC4* (*XPF*), and *ERCC5* (*XPG*) can be associated with different phenotypes – either XP or XP/Cockayne syndrome – and mutations in *ERCC3* (*XPB*) and *ERCC2* (*XPD*) can also be associated with photosensitive forms of trichothiodystrophy (see below). Mutations in an eighth gene, which encodes DNA polymerase-η, lead to the XP variant phenotype. This enzyme is responsible for bypassing unrepaired DNA photoproducts during DNA replication; mutations thus result in the insertion of erroneous residues during replication.

Phototesting in XP patients has shown the action spectrum for inflammatory erythema of the skin to be in the 290 to 340 nm range. The MEDs corresponding to those wavelengths are generally quite reduced, with the peak responses often vesicular and delayed by a day or two.

Clinical features

Fifty percent of patients have marked photosensitivity in addition to an early onset for all major types of skin cancer (see Table 87.4)[37]. From an early age, many patients easily develop sunburns with erythema, edema and vesicles following minimal sun exposure. By the age of 2 years, practically all patients have developed solar lentigines (Fig. 87.17). With continued sun exposure, the skin gradually becomes xerotic, accounting for the term "xeroderma pigmentosum".

Actinic keratoses, basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs), and less frequently, melanomas then develop in sun-exposed sites, also prematurely. In addition to the lips, SCCs of the distal tongue can also develop. Individuals with severe photosensitivity are less likely to develop skin cancers than those who are less photosensitive, presumably due to more rigorous photoprotective behaviors in the former group[38].

Ocular abnormalities are observed in ~40% of patients. Severe photophobia, keratitis, corneal opacification, and vascularization are common manifestations, while loss of eyelashes, ectropion, and SCC and melanoma of the UVR-exposed parts of the eyes are also frequently reported[38].

Approximately 20%–30% of XP patients develop neurologic degeneration, especially those in the XP-D group. The most severe presentation is the DeSanctis–Cacchione syndrome, in which microcephaly, a progressive decline in intellectual capacity, delayed growth and sexual development, deafness, choreoathetosis, ataxia, and quadriparesis may all occur. However, some XP patients develop a limited number of clinical manifestations, such as isolated hyporeflexia and progressive deafness. XP variant patients usually have no neurologic problems. Deep tendon reflex testing and audiometry are good screening tests for the presence of neurologic involvement. It has been postulated that these neurologic abnormalities are due to defective DNA repair in nerve cells, resulting in neuronal death. Patients with XP have an ~10- to 20-fold increase in the incidence of internal malignancies, including tumors of the brain, lung, oral cavity, gastrointestinal tract, kidney, and hematopoietic system.

INHERITED PHOTOSENSITIVITY DISORDERS ASSOCIATED WITH DEFECTIVE DNA NUCLEOTIDE EXCISION REPAIR OR CHROMOSOME INSTABILITY					
Disorder	**Clinical features**	**Inheritance**	**Photosensitivity**	**Action spectrum**	**Laboratory findings**
Xeroderma pigmentosum (XP)	• 1 in 20 000 in Japan; 1 in 250 000 in US; 2.3 per million in Western Europe • Photosensitivity (50%), early-onset lentigines (typically by 2 years of age) • Basal cell carcinomas, squamous cell carcinomas, and melanomas in sun-exposed areas • Median age for development of first non-melanoma skin cancers: 9 years & for melanoma, 22 years • Photophobia, keratitis, corneal opacification, and vascularization • Neurologic abnormalities: hyporeflexia, deafness, seizures (most common in groups A and D) • Median lifespan: 37 years (29 years in those with neurodegenerative disease) • Death most commonly due to: skin cancer, neurologic degeneration, internal malignancies • Support group: www.xps.org	AR	Yes	290–340 nm	• Complementation groups A to G: defective global genomic nucleotide excision repair (GG-NER) of UVR-induced DNA damage (e.g. pyrimidine dimers) from any part of the genome • XP variant: defective DNA polymerase-η, resulting in insertion of incorrect nucleotides during replication of DNA with UVR-induced damage • Defective genes for all the XP groups have been identified* • Cells are hypersensitive to killing by UVR
Cockayne syndrome (CS)	• Prevalence: 2.5 per million • Photosensitivity, pigmented macules, thinned skin, alopecia, clubbing of nails, acral edema, sunken eyes due to loss of adipose tissue, prominent ears, dental caries • Hypogonadism, stooped posture, joint contractures, short stature with extremely thin body habitus ("cachectic dwarfism"), microcephaly, intellectual impairment, deafness • Calcification of basal ganglia, demyelination, pigmentary retinal degeneration, osteoporosis • No increase in malignancies in "pure" CS • CS type I: 80% of patients; onset at birth to 2 years of age, progressive; life expectancy: second to third decades • CS type II: symptoms at birth, life span = 6–7 years • CS type III: late onset, normal growth and development • Combined XP/CS: solar lentigines, skin cancers, pigmentary retinal degeneration, basal ganglion calcification • Support group: http://cockaynesyndrome.org/	AR	Yes	UVB, UVA	• Defective transcription-coupled nucleotide excision repair (TC-NER), which targets transcriptionally active regions of the genome • CS cells are defective in the repair of pyrimidine dimer photoproducts and oxidative DNA base modifications typically induced by UVB and UVA, respectively • To date, ~30 mutations in *ERCC8* (*CSA*) and ~80 mutations in *ERCC6* (*CSB*) identified
Cerebro-oculo-facio-skeletal (COFS) syndrome	• Microcephaly, congenital cataracts and/or microphthalmia, arthrogryposis, severe developmental delay, postnatal growth retardation • Facial dysmorphism with prominent nasal root and/or overhanging upper lip	AR	Yes	UVB, UVA	• Mutations in *ERCC6 (CSB), ERCC2 (XPD), ERCC5 (XPG), ERCC1*

UV-sensitive syndrome (UV^sS)	• Fewer than 20 patients reported to date
	• Milder phenotype than CS
	• Clinical overlap with CS (types I and II) UV^sS due to mutations in same genes as CS
	• Photosensitivity, solar lentigines; otherwise normal
		AR	Yes	Unclear	• Similar to CS: defective TC-NER, normal GG-NER; however, unlike CS, patients with UV^sS only have a defect in repair of UVB-induced photoproducts (not in the repair of oxidative damage)
					• Mutations:
					  • Type 1 – *ERCC6* (*CSB*)
					  • Type 2 – *ERCC8* (*CSA*)
					  • Type 3 – *UVSSA*

Trichothiodystrophy (TTD)	• Over 110 patients reported to date
	• PIBIDS: *p*hotosensitivity, *i*chthyosis, *b*rittle hair, *i*ntellectual impairment, *d*ecreased fertility, *s*hort stature
	• Other features: microcephaly, receding chin, protruding ears
	• No increase in malignancies
	• 9 types: types 1–3 are photosensitive while types 4–9 are non-photosensitive†
		AR	Yes (in ~50% of patients) TTD1, 2, 3	Unclear	• Hair shaft: alternating light and dark bands ("tiger tail banding"), trichoschisis, trichorrhexis nodosa-like changes, "ribboning"
					• Reduction of cysteine-rich matrix proteins and low sulfur content in hair shafts
					• Mutations in photosensitive forms:
					  • TTD1 – *ERCC2* (*XPD*)
					  • TTD2 – *ERCC3* (*XPB*)
					  • TTD3 – *GTF2H5*

Table 87.4 Inherited photosensitivity disorders associated with defective DNA nucleotide excision repair or chromosome instability.

INHERITED PHOTOSENSITIVITY DISORDERS ASSOCIATED WITH DEFECTIVE DNA NUCLEOTIDE EXCISION REPAIR OR CHROMOSOME INSTABILITY					
Disorder	**Clinical features**	**Inheritance**	**Photosensitivity**	**Action spectrum**	**Laboratory findings**
Bloom syndrome	• 265 patients currently listed in Registry; one-quarter are of Jewish ancestry • Carrier rate in Ashkenazi Jewish population: 1 in 100 • Malar erythema and telangiectasias, café-au-lait macules and areas of hypopigmentation, elongated facies with malar hypoplasia and prominent nose, short stature • Normal intelligence • Recurrent infections, especially otic and pulmonary • Additional internal manifestations: lymphoma, leukemia, carcinomas (e.g. GI) in up to half of patients; diabetes and chronic lung disease less common • Men: sterile due to defective sperm; women: reduced fertility • Average lifespan: 26 years • Patient registry: https://pediatrics.weill.cornell.edu/research/bloom-syndrome-registry	AR	Yes	Unclear	• Decreased IgA, IgM, sometimes IgG • Mutations in *BLM*, resulting in increased sister chromatid exchanges, chromosomal breakage and rearrangement • Quadriradial configurations in lymphocytes and fibroblasts are diagnostic
Rothmund–Thomson syndrome	• Over 300 patients reported to date • Erythema, edema and vesicles on the cheeks and face during the first few months of life, followed by poikiloderma that typically affects the dorsal aspect of the hands/forearms and the buttocks • Sparse hair (scalp, eyebrows, eyelashes), hypoplastic nails, acral keratoses (in adolescents and adults), short stature, skeletal (e.g. radial ray defects, osteoporosis) and dental abnormalities, juvenile cataracts, chronic diarrhea/vomiting during infancy, pituitary hypogonadism (may be associated with midface hypoplasia/ "saddle nose") • Osteosarcoma (10%–30% in type 2), squamous cell carcinoma (<5%; often acral) • Normal immune function, intelligence and lifespan (in the absence of malignancy)	AR	Transient (early childhood)	UVA	• Mutations in *ANAPC1* (type 1) or *RECQL4* (type 2), resulting in dysfunctional DNA helicase • Genomic instability accounts for propensity for malignancies

* *XPA, ERCC3 (XPB), XPC, ERCC2 (XPD), DDB2 (XPE), ERCC4 (XPF), ERCC5 (XPG).*
† Non-photosensitive forms due to mutations in *MPLKIP* (TTD4; AR), *RNF113A* (TTD5; XLD), *GTF2E2* (TTD6; AR), and *TARS1* (TTD7; AR).

Table 87.4 Inherited photosensitivity disorders associated with defective DNA nucleotide excision repair or chromosome instability. Kindler syndrome also has photosensitivity (UVA, UVB), along with early-onset blistering, mucosal involvement, skin atrophy, and progressive poikiloderma and it is due to mutations in *FERMT1* (*KIND1*) with dysfunction of kindlin-1 resulting in abnormal cell adhesion and proliferation. ERCC, excision repair cross-complementation; UVR, ultraviolet radiation.



Fig. 87.17 Xeroderma pigmentosum. Multiple solar lentigines of the face and a history of photosensitivity in this four-year-old child. *Courtesy Antonio Torrelo, MD.*

Treatment

Management consists of extremely rigorous photoprotection. Oral calcium and vitamin D supplementation should also be recommended for these patients. Cryotherapy, topical 5-fluorouracil and imiquimod, electrodesiccation and curettage, surgical excision, and Mohs micrographic surgery are used to manage the premalignant and malignant skin tumors. Oral retinoids can be used as chemopreventive agents. Topical application of the DNA repair enzymes – T4 endonuclease V/T4N5 or photolyase (incorporated into sunscreen) – have been successful in decreasing the development of actinic keratoses and keratinocyte carcinomas[39].

Cockayne syndrome

Introduction and history

Cockayne syndrome is a rare, progressive, multisystem disease with photosensitivity that is transmitted in an autosomal recessive fashion (see Table 87.4).[40,41] This entity was first described by Cockayne in 1936.

Epidemiology

Cockayne syndrome has been reported from the US, Europe and Japan, with over 120 genetically confirmed patients from Western Europe[39].

Pathogenesis

The fundamental defect in NER in Cockayne syndrome is different from that of XP (see Fig. 86.14). In the former, there is defective transcription-coupled NER (TC-NER), a repair that specifically removes transcription-blocking lesions from the genome. This defect results in the inability to recover mRNA synthesis after exposure to UVR. In contrast, XP cells have defective global genomic NER (GG-NER; see above).

In contrast to XP, skin cancers on sun-exposed areas are not observed in patients with Cockayne syndrome, whose average lifespan is only 12 years (although there is considerable variation)[40]. One explanation is that cells with low-level damage due to defective TC-NER are eliminated, protecting the body from carcinogenesis, but at the expense of accelerated aging. Rigorous photoprotection may also play a role in reducing the formation of skin cancers[41].

Two-thirds of the patients have mutations in *ERCC6* (also known as *CSB*) while one-third have mutations in *ERCC8* (also known as *CSA*) (see Table 87.4)[41].

Clinical features

Patients with Cockayne syndrome have been classified into three types based upon severity of symptoms and age of onset[41]. In the most severely affected individuals, there is a congenital onset and the clinical manifestations overlap with those of cerebro-oculo-facial-skeletal (COFS) syndrome (see Table 87.4). In a more recent series of 16 patients with Cockayne syndrome and COFS, patients were noted to have sensitivity to UVB and UVA, pigmented macules, stellate scars, clubbing of the nails, and acral edema[40].

Treatment

This consists of photoprotection and symptomatic treatment only.

UV-sensitive syndrome

UV-sensitive syndrome (UV^{s}S) is a rare, photosensitive, autosomal recessive disease. To date, fewer than 20 patients have been reported (Japan, France, Israel, Iran and Pakistan)[42,43]. Although it shares defective TC-NER with Cockayne syndrome (see above), clinically patients only have UV photosensitivity (see Table 87.4). However, the action spectrum is unknown. In addition to mutations in *ERCC8* (*CSA*) and *ERCC6* (*CSB*), mutations in a gene that encodes a UV-stimulated scaffold protein A (*UVSSA*) have been identified in these patients.

Trichothiodystrophy

Introduction and history

Trichothiodystrophy (TTD) is an autosomal recessive disorder with over 110 patients reported to date (see Table 87.4)[44]. The term "trichothiodystrophy" was coined by Price in the late 1970s.

Epidemiology

The disorder appears to occur worldwide and affects men and women.

Pathogenesis

To date, mutations in three genes have been identified in patients with photosensitive TTD – *ERCC3* (*XPB*), *ERCC2* (*XPD*), and *GTF2H5* (*TTDA*) – with mutations in an additional six genes detected in those with non-photosensitive TTD (see Table 87.4). While mutations in *ERCC3* (*XPB*) and *ERCC2* (*XPD*) are also found in patients with XP, dysfunction of *g*eneral *t*ranscription *f*actor *IIH* subunit *5* has only been observed in TTD (see Fig. 86.14).

Clinical features

TTD has a broad range of phenotypes, from individuals with just brittle hair and scaly skin to those with severe neurodevelopmental defects and death at an early age[44,45]. Unlike XP, TTD is not associated with skin cancers, and pigmentary alterations are uncommon.

The clinical features of TTD are frequently described by the acronym PIBIDS[44,45]:

Photosensitivity: Photosensitivity has been reported in up to 50% of affected patients, but the action spectrum is not known.

Ichthyosis: A non-bullous congenital ichthyosiform erythro (*TTDA*) derma phenotype is commonly observed during infancy, and patients occasionally present with a collodion membrane. The erythema tends to fade over time, eventuating in ichthyosis of variable severity (see Ch. 57).

Brittle hair: This is the hallmark of TTD and is present in most, but not all, patients[45,46]. By polarizing microscopy, hair shafts demonstrate alternating bright and dark bands ("tiger tail banding") (see Fig. 69.24). Light microscopic findings include an irregular contour, trichoschisis (transverse fractures through the shafts) and, sometimes, trichorrhexis nodosa-like features. Hair shafts are flattened and may fold like a ribbon. There is also a reduction in cysteine-rich matrix proteins, resulting in defective cross-linking of the intermediate keratin filaments and a low sulfur content within the hair shaft. This defect may also account for the brittle nails and the ichthyosis seen in TTD.

Intellectual impairment: This ranges from mild to severe.

Decreased fertility: This has been reported in patients of both sexes, but is not a prominent feature.

Short stature: Growth retardation is present to a varying degree.

Other manifestations include a characteristic facies with a receding chin and protruding ears, sideroblastic anemia, eosinophilia, and hepatic angioendotheliomas.

Treatment

No specific treatment is available.

Photosensitivity Due to Chromosomal Instability

Bloom syndrome

Synonym: ■ Congenital telangiectatic erythema

Introduction and history

Bloom syndrome is a rare autosomal recessive genetic disorder (see Table 87.4). The Bloom Syndrome Registry maintains a database and provides clinical information for patients with this syndrome[47]. The condition was first reported by David Bloom, an American dermatologist, in 1954.

Epidemiology

Bloom syndrome was initially described as occurring most frequently amongst Ashkenazi Jews. However, when 265 patients in the Bloom Syndrome Registry were reviewed, three-quarters were not Jewish[47].

Pathogenesis

Bloom syndrome is due to mutations in *BLM*, a gene that encodes for the DNA helicase RECQL3[47,48]. The RECQ family consists of five DNA helicases. They are highly conserved throughout evolution and are critical for maintenance of genomic stability. Mutations in *BLM* result in an increased susceptibility to cancer development[49].

Clinical features

Beginning within the first few weeks of life, patients typically develop erythema and telangiectasias of the malar areas and occasionally the dorsal aspects of the hands and forearms. Blisters on the lower lip may also occur. In addition, café-au-lait macules with adjacent areas of hypopigmentation are commonly seen. The action spectrum for the photoexacerbated erythema remains unclear. Growth delay and short stature with a disproportionately small head are usually the most common reasons parents seek medical care (see Table 87.4)[47].

Treatment

Symptomatic management and photoprotection are the only treatment strategies.

Rothmund–Thomson syndrome

Synonym: ■ Poikiloderma congenitale

Introduction and history

Rothmund–Thomson syndrome is a rare entity with autosomal recessive inheritance. To date, over 300 cases have been reported in the English literature[50] (see Table 87.4). In 1868, the disorder was first recognized by Auguste Rothmund, a German ophthalmologist. Sydney Thomson, a British dermatologist, then described a similar entity in 1923. In 1957, William Taylor proposed the eponym Rothmund–Thomson syndrome.

Epidemiology

Patients have been reported worldwide.

Pathogenesis
Rothmund–Thomson syndrome is due to mutations in *ANAPC1* (type 1), whose protein product mediates ubiquitination and controls progression through mitosis and G1 of the cell cycle, or *RECQL4* (type 2), which encodes a DNA helicase. As in Bloom syndrome, helicase dysfunction in type 2 Rothmund–Thomson syndrome results in an increased susceptibility to cancer[51].

Clinical features
Patients typically present during the first few months of life with photodistributed erythema, edema, and vesicles of the cheeks and face, which may extend to involve the buttocks and extremities. Over months to years, poikiloderma develops (see Fig. 63.12)[50,51]. Other features are summarized in Table 87.4 and Table 63.9.

Differential diagnosis
In addition to the entities listed in Table 87.4, the differential diagnosis includes hereditary benign telangiectasia and poikiloderma with neutropenia. The latter is a rare autosomal recessive disorder (~30 patients reported to date) due to mutations in *USB1*. Its protein product, U6 SnRNA biogenesis phosphodiesterase 1, is thought to interact with RECQL4 via SMAD4 proteins, thereby accounting for the clinical overlap with Rothmund–Thomson syndrome[52].

Treatment
Management includes regular surveillance for cancer and symptomatic treatment.

Chemical- and Drug-Induced Photosensitivity

Key features
- *Phototoxicity* is characterized by an exaggerated sunburn-like reaction, usually caused by medications
- *Photoallergy* presents with eczematous lesions, most commonly related to topical photoallergens
- The cutaneous porphyrias are an example of phototoxicity induced by endogenous agents
- Management includes identification and avoidance of the offending agent, in addition to photoprotection.

Exogenous photosensitivity
Introduction and history
Photosensitivity induced by exogenous agents can be divided into phototoxicity and photoallergy (Table 87.5). *Phototoxicity* is the result of direct tissue and cellular injury following UVR-induced activation of a phototoxic agent; theoretically, phototoxicity can be induced in any individual. In contrast, *photoallergy* is a delayed-type hypersensitivity response consisting of a sensitization phase, an incubation period of 7 to 10 days (following the first exposure), and a clinical elicitation reaction with any subsequent challenge; only immunologically sensitized individuals can develop photoallergy.

Phototoxic agents have been used as medications from as early as 4000 BCE, with the inhabitants of Mesopotamia (and later the Indians and Egyptians) employing plant-derived psoralens for the treatment of leukoderma. In 1913, Meyer-Betz demonstrated hematoporphyrin-induced phototoxicity on himself, while the current method of PUVA therapy was introduced in the 1970s. Photoallergy was first recognized in 1939 based on a classic study of sulfanilamide by Epstein.

Epidemiology
While the exact prevalences of phototoxicity and photoallergy in the general population are unknown, their frequency in photodermatology referral centers has ranged from 3% to 16% for phototoxicity and 1% to 8% for photoallergy. Both are more common in White as compared to Black individuals[3,53,54].

Pathogenesis
The pathogenesis of phototoxicity involves the generation of free oxygen radicals, superoxide anions, hydroxyl radicals and singlet oxygen, which leads to a host of cytotoxic tissue effects. Other mechanisms of damage include the generation of stable photoproducts (e.g. chlorpromazine, tetracyclines), the formation of photoadducts (e.g. psoralens), and the recruitment of inflammatory mediators (e.g. porphyrins, demeclocycline)[55].

The pathogenesis of photoallergy is identical to that of allergic contact dermatitis, with the exception of the requirement for the presence of UVR to induce photoallergen formation.

COMMON PHOTOTOXIC AND PHOTOALLERGIC AGENTS

Common phototoxic agents	Common photoallergic agents

• Antiarrhythmics
  • Amiodarone
  • Quinidine
• Anti-fibrotic agents
  • Pirfenidone
• Calcium channel blockers
  • Diltiazem
• Diuretics
  • Furosemide
  • Thiazides
• Nonsteroidal anti-inflammatory drugs
  • Nabumetone
  • Naproxen
  • Piroxicam
• Phenothiazines
  • Chlorpromazine
  • Prochlorperazine
• Photodynamic therapy agents
  • Aminolevulinic acid
  • Methyl aminolevulinate
• Psoralens (oral or topical)
  • 5-Methoxypsoralen
  • 8-Methoxypsoralen
  • 4,5′,8-Trimethylpsoralen
• Quinolones
  • Ciprofloxacin
  • Lomefloxacin
  • Nalidixic acid
  • Sparfloxacin
• St. John's wort
  • Hypericin
• Sulfonamides
• Sulfonylureas
• Tar (topical)
• Targeted therapies
  • BRAF inhibitors (e.g. vemurafenib)
  • Anti-CCR4 antibody (mogamulizumab)
  • EGFR inhibitors
  • Avapritinib
  • Enzalutamide
• Tetracyclines
  • Doxycycline
  • Demeclocycline
• Triazole antifungals
  • Voriconazole
	Topical agents:
	• Sunscreens: active UV absorbers (e.g. oxybenzone [benzophenone-3], octocrylene)
	• Fragrances
	  • 6-Methylcoumarin
	  • Musk ambrette
	  • Sandalwood oil
	• Antimicrobial agents
	  • Bithionol
	  • Chlorhexidine
	  • Fenticlor
	  • Hexachlorophene
	• Nonsteroidal anti-inflammatory drugs
	  • Diclofenac
	  • Etofenamate (outside US)
	  • Ketoprofen
	• Phenothiazines
	  • Chlorpromazine
	  • Promethazine
	• **Systemic agents:**
	• Antiarrhythmics
	  • Quinidine
	• Antimalarials
	  • Quinine
	• Antifungals
	  • Griseofulvin
	• Antimicrobials
	  • Quinolones (e.g. enoxacin, lomefloxacin)
	  • Sulfonamides
	• Nonsteroidal anti-inflammatory drugs
	  • Ketoprofen
	  • Piroxicam*

*Often have positive patch test to thimerosal.	

Table 87.5 Common phototoxic and photoallergic agents. EGFR, epidermal growth factor receptor; UV, ultraviolet.

Clinical features
Phototoxicity
Following cutaneous or systemic exposure to a phototoxic agent *and* appropriate UVR, phototoxicity develops within hours. For the vast majority of such agents, the action spectrum falls within UVA[56]. Erythema and edema as well as burning and stinging sensations characterize the initial presentation, with vesicles and bullae seen in severely affected patients. Phototoxic reactions due to oral medications resemble an exaggerated sunburn. These reactions then resolve spontaneously with desquamation and hyperpigmentation once the photosensitizer or UVR is avoided[56].

Other less common manifestations of phototoxicity include pseudoporphyria (frequently caused by nonsteroidal anti-inflammatory drugs [NSAIDs], especially naproxen), photo-onycholysis (reported with



Fig. 87.18 Exogenous drug-induced photosensitivity and hyperpigmentation. Gray–brown patches involving the sun-exposed skin of a patient receiving diltiazem.

tetracyclines and psoralens), slate-gray hyperpigmentation (reported with amiodarone, tricyclic antidepressants, and diltiazem) (Fig. 87.18), lichenoid eruptions (seen with quinine and quinidine), and sensations of burning or pain (amiodarone). In a systematic review of phototoxicity due to oral agents, evidence was strongest for vemurafenib, NSAIDs, and antibiotics (fluoroquinolones and tetracylines)[57]. The medications most commonly associated with phototoxicity are listed in Table 87.5.

5-Fluorouracil (5-FU), methotrexate, and retinoids, three commonly used medications in dermatology, have also been associated with photosensitivity reactions; however, none is typically associated with classic phototoxicity or photoallergy. Exacerbation of 5-FU-induced inflammation by UVR usually occurs in sites with actinic keratoses. The administration of methotrexate can cause a recurrence ("recall") of previous UVR-induced erythema. However, phototesting in patients taking methotrexate has been normal, and the mechanism for this "recall" reaction remains unclear. Phototesting in patients taking isotretinoin or acitretin, or who apply topical tretinoin, is also usually normal. The propensity for these patients to develop UVR-induced erythema is most likely due to retinoid-induced thinning of the stratum corneum.

Phytophotodermatitis is another phototoxic reaction, with linear streaks of erythema occurring a day or so after skin contact with plants containing furocoumarins plus subsequent exposure to UVA in sunlight. Linear postinflammatory hyperpigmentation is a classic finding. Plants capable of inducing phytophotodermatitis include yarrow, parsley, celery, lime, and fig (see Ch. 17). Therefore, this condition most commonly occurs in individuals whose outdoor activities expose them to such plants, such as vegetable harvesters and bartenders who mix drinks outdoors. Roofers and road workers occasionally develop phototoxicity secondary to exposure to tar and concomitant UVA from sunlight.

St John's wort (*Hypericum perforatum*), used in non-traditional medicine to treat a variety of ailments including depression, contains hypericin, another known phototoxic agent. Voriconazole is often prescribed for months or even years in immunocompromised hosts as a prophylactic systemic antifungal agent. This can cause phototoxic reactions, actinic cheilitis, and lentigines, as well as an increased risk for developing large hypertrophic actinic keratoses, aggressive cutaneous squamous cell carcinomas, and cutaneous melanoma. There are alternatives for voriconazole, e.g. posaconazole, that are not associated with phototoxicity. Vemurafenib, a selective BRAF inhibitor, has been shown to be phototoxic with an action spectrum in the UVA range[58].

Photoallergy

In previously sensitized individuals, exposure to photoallergens and sunlight results in the development of a pruritic eczematous eruption. In more severely affected patients, vesicles and bullae may develop, though less commonly than in phototoxic reactions. While phototoxic reactions usually resemble sunburns and photoallergic reactions often resemble allergic contact dermatitis, these two reaction patterns may not always be easily distinguishable by morphology alone[56].

In the UK and the US, sunscreen agents (especially benzophenone-3 [oxybenzone]) were the most common causes of photoallergy[59]. However, the overall prevalence of photoallergy amongst sunscreen users is very low. In Europe, topical NSAIDs, especially ketoprofen and etofenamate, were the most common cause (see Table 87.5)[60]. Photoallergy can generally be confirmed by photopatch testing, where duplicate sets of photoallergens are placed on the patient's back and only one set is irradiated with UVA (Table 87.6). The interpretation of results from such testing is shown in Fig. 87.19.

Pathology

Phototoxicity is characterized by scattered necrotic keratinocytes ("sunburn cells") and a superficial dermal infiltrate of primarily lymphocytes and neutrophils. In contrast, photoallergy is characterized by epidermal spongiosis plus a superficial dermal lymphohistiocytic infiltrate, indistinguishable from other causes of spongiotic dermatitis.

Differential diagnosis

Inflammatory phototoxic reactions should be distinguished from ordinary sunburn, which requires more UVR exposure, and LE (see Table 87.3). The differential diagnosis of photoallergic reactions includes all other forms of dermatitis that can involve sun-exposed areas, particularly airborne contact dermatitis and atopic dermatitis. In airborne contact dermatitis, all exposed sites can be involved, including the upper eyelids, submental region, and postauricular areas; these sites are frequently spared in photoallergic contact dermatitis (see Fig. 87.15).

Treatment

The identification and avoidance of the offending agent are of prime importance. Sometimes it is not possible to discontinue the culprit medication and strict photoprotection (UVB and UVA) is required. For phototoxic and photoallergic reactions, analgesia may be helpful. Topical corticosteroids, and, for severe flares, short courses of systemic corticosteroids, can be used for photoallergic dermatitis. Occasionally, evening dosing of a phototoxic drug can be implemented so that peak systemic levels occur during the night.

Endogenous photosensitivity

The cutaneous porphyrias, discussed in Chapter 49, represent the most obvious examples of photosensitivity induced by endogenous agents. The mechanism of porphyrin-induced phototoxicity involves reactive oxygen species, the complement system, mast cells, and neutrophils (Fig. 87.20).

Smith–Lemli–Opitz syndrome is an autosomal recessive disorder with an early onset of photosensitivity to UVA in 55% to 75% of patients[61]. Its frequency is 1 in 40 000 conceptions. Mutations in *DHCR7*, which encodes 7-dehydrocholesterol reductase, result in an accumulation of 7-dehydrocholesterol. The mechanism of the photosensitivity is unknown. Pellagra, which is due to niacin deficiency, is also associated with photosensitivity but its pathogenesis remains unclear as well[62].

Photoaggravated Dermatoses

Key features

- The primary underlying disease is not caused, but rather exacerbated, by sun exposure, sometimes severely
- Phototesting is usually normal, with lupus erythematosus being the exception
- Therapy focuses on treatment of the underlying disease

Introduction and history

A number of skin diseases that are not directly caused by UVR exposure may, in some patients, be worsened by it (Table 87.7). The reasons for

COMMONLY EMPLOYED PHOTOPATCH TEST SERIES			
Class of photoallergen	**Photoallergen**	**North American photopatch series**	**European photopatch baseline series**
		Conc/vehicle	
Sunscreen ingredients	Ethylhexyl methoxycinnamate (octinoxate, Parsol MCX)	7.5% pet	10% pet
	Benzophenone-4 (sulisobenzone)	2% pet	2% pet
	PABA (para-aminobenzoic acid)	10% pet	10% pet
	Ethylhexyl dimethyl PABA (padimate O)	10% pet	
	Benzophenone-3 (oxybenzone)	10% pet	10% pet
	Ethylhexyl salicylate (octisalate)	5% pet	
	Butyl methoxydibenzoyl methane (avobenzone, Parsol 1789)	5% pet	10% pet
	Homosalate (homomethyl salicylate)	5% pet	
	Methyl anthranilate	5% pet	
	Benzophenone-8	10% pet	
	Ensulizole	10% pet	
	4-methyl-benzylidene camphor (Eusolex 6300, enzacamene)		10% pet
	Octocrylene		10% pet
	Isoamyl p-methoxycinnamate		10% pet
	Bis-ethylhexylphenol methoxyphenol triazine (bemotrizinol, Tinosorb® S)		10% pet
	Drometrizole trisiloxane (Mexoryl™ XL)		10% pet
	2-(4-Diethylamino-2-hydroxybenzoyl)-benzoic acid hexylester (Uvinul® A Plus)		10% pet
	Ethylhexyl triazone		10% pet
	Methylene bis-benzotriazolyl tetramethylbutylphenol (bisoctrizole, Tinosorb® M)		10% pet
	Diethylhexyl butamido triazone (iscotrizinol, Uvasorb® HEB)		10% pet
	Terephthalylidene dicamphor sulfonic acid		10% aq
Microbicides	Dichlorophene	1% pet	
	Triclosan	2% pet	
	Hexachlorophene	1% pet	
	Chlorhexidine diacetate	0.5% aq	
	3,4,5-Tribromosalicylanilide	1% pet	
	Bithionol	1% pet	
	2,2'-thiobis(4-chlorophenol) (Fentichlor)	1% pet	
Anti-psychotics	Promethazine hydrochloride		0.1% pet
NSAIDs	Ketoprofen	5% pet	1% pet
	Etofenamate		2% pet
	Piroxicam		1% pet
	Benzydamine hydrochloride		2% pet
Fragrances	Musk ambrette	1% pet	
	Lichen acid mix	0.3% pet	
Plants	Sesquiterpene lactone mix	0.1% pet	
Miscellaneous	Sandalwood oil	2% pet	
	Thiourea	0.1% pet	

Table 87.6 Commonly employed photopatch test series. A petrolatum (100%) patch test is also applied as a control. When comparing to sunscreen agents in Chapter 132, octyl = ethylhexyl. aq, aqueous solution; Conc, concentration; pet, petrolatum.

such aggravation, however, have been poorly studied, with the exception of lupus erythematosus (LE) (see Ch. 41)[63].

Epidemiology

Photoaggravated dermatoses occur worldwide[63]. In photodermatology referral centers, as a group, the prevalence ranges from 15% to 25%[3,54].

Clinical features

The primary dermatosis may be mildly or severely exacerbated by UVR exposure (Fig. 87.21), usually within minutes to hours, but sometimes a day or more later. The UVR-exacerbated eruption is usually limited to sites characteristically involved by the underlying condition. Less often the flare involves all sun-exposed skin.

Pathology

The histology is that of the underlying dermatosis.

Differential diagnosis

In general, photoaggravated dermatoses are recognized by the features of the underlying skin disease (see Table 87.7). The differential diagnosis often includes PMLE, although PMLE is typically papular and mildly pruritic, has negative lupus serology, and can be induced by

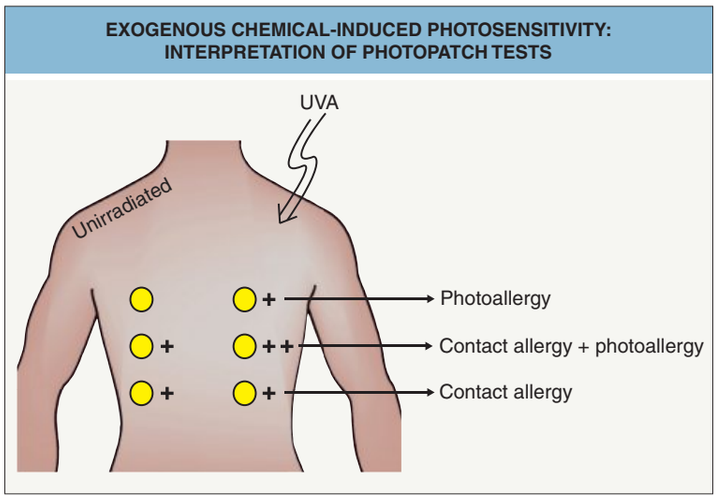


Fig. 87.19 Exogenous chemical-induced photosensitivity: interpretation of photopatch tests. This schematic demonstrates the interpretation of photopatch tests. The UVA dose is usually the lower of: 5 J/cm^2 or 50% of the MED to UVA.

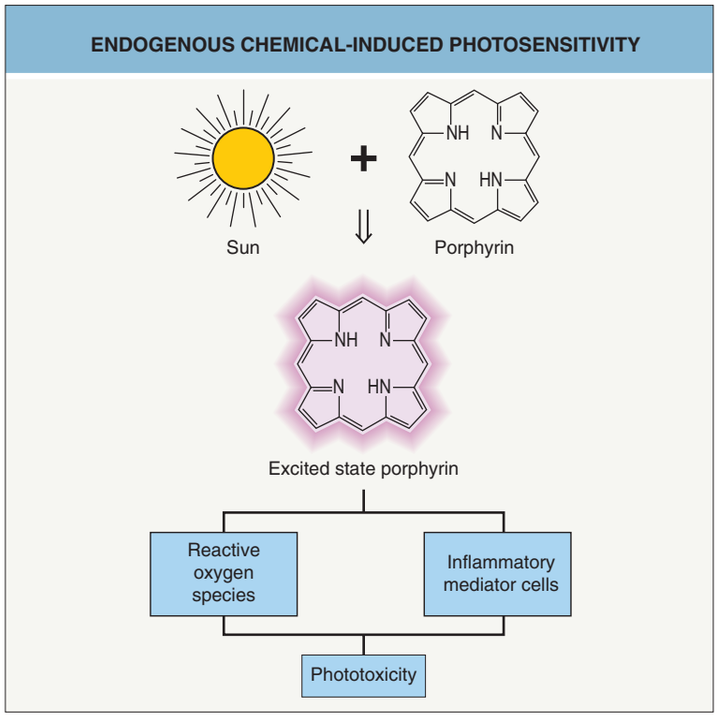


Fig. 87.20 Endogenous chemical-induced photosensitivity. The pathophysiology of phototoxicity as seen in the cutaneous porphyrias is shown.

PHOTOAGGRAVATED DERMATOSES
• Acne vulgaris
• Atopic dermatitis
• Bullous pemphigoid
• Carcinoid syndrome
• Cutaneous T cell lymphoma (Sézary syndrome)
• Darier disease (keratosis follicularis)
• Dermatomyositis
• Disseminated superficial actinic porokeratosis
• Erythema multiforme
• Hailey–Hailey disease (familial benign chronic pemphigus)
• Hartnup syndrome
• Lichen planus and lichenoid drug eruptions
• Lupus erythematosus
• Pellagra
• Pemphigus, including pemphigus foliaceus (erythematosus)
• Pityriasis rubra pilaris
• Psoriasis (in some patients)
• Reticular erythematous mucinosis (REM)
• Rosacea
• Seborrheic dermatitis
• Grover disease (transient acantholytic dermatosis)
• Viral infections, including herpes simplex, exanthems

Table 87.7 Photoaggravated dermatoses. This often applies to a subset of patients.



Fig. 87.21 Photoaggravated atopic dermatitis induced by the solar simulator. This was the appearance 24 hours after irradiation. *Courtesy John L.M. Hawk, MD.*

photoprovocation tests (~80% of patients). However, the latter requires repeated daily UVR exposures and is therefore not commonly done. It is important to note that PMLE may sometimes coexist with photoaggravated dermatoses, in particular LE. Photoaggravated atopic dermatitis is characterized by a confirmed history of atopic dermatitis plus photosensivity and positive phototest results.

Treatment

Treatment should focus on the underlying disorder and photoprotection. Topical corticosteroids and low-dose NB-UVB may sometimes lead to improvement. Rarely, short courses of oral corticosteroids are required.

Grover Disease

Grover disease, also known as transient (and later persistent) acantholytic dermatosis, most commonly occurs in White men over 40 years of age who have significant photodamage. Some patients flare in the summer while others flare during the winter. Pruritic, often crusted, skin-colored to pink papules and papulovesicles appear on the trunk, primarily in sun-exposed sites (Fig. 87.22). In addition to UV exposure, exacerbating factors include sweating, heat, and occasionally, friction and ionizing radiation. While lesions may resolve over weeks to months, they commonly recur.

Histologically, four major patterns are seen (sometimes in combination): Darier disease-like, Hailey–Hailey disease-like, pemphigus vulgaris- or foliaceus-like, and spongiosis with acantholysis (Fig. 87.23). Rarely, there may be acantholytic cells that appear multinucleated and this pattern has been referred to as pseudoherpetic. The differential diagnosis of Grover disease includes folliculitis, miliaria rubra, arthropod bites, multiple lichenoid keratoses, early pemphigus foliaceus, and when chronic, Darier disease (see Fig. 59.4). Except for the latter two entities, histologic examination allows distinction; the focal nature of the histologic findings, negative immunofluorescent microscopy, and lack of additional clinical features (e.g. palmar keratoses, longitudinal erythronychia with notching) point to the diagnosis of Grover disease. Therapy includes topical agents (e.g. corticosteroids, pramoxine, calcineurin inhibitors, vitamin D analogues) and oral antihistamines, in addition to avoidance of exacerbating factors. Oral retinoids, PUVA, and UVA1 have also been tried with some success, and most recently, dupilumab.



Fig. 87.22 Grover disease. A Crusted erythematous papules on the mid anterior trunk, a common location. **B** Obvious sparing of the sun-protected skin of the buttocks in this man with significant photodamage. **C** Papules may be eroded or have central hemorrhagic crusts. *A, B, Courtesy Jean L. Bolognia, MD; C, Courtesy Kalman Watsky, MD.*

NORMAL CUTANEOUS EFFECTS OF UVR AND VISIBLE LIGHT EXPOSURE

Key features

- Acute and subacute effects of UVR exposure include acute inflammatory erythema (sunburn), pigment darkening, delayed pigmentation, epidermal hyperplasia, immunologic changes, and vitamin D_3 synthesis
- Visible light can induce pigmentation in individuals with darker skin phototypes and immediate erythema in fair-skinned individuals
- Chronic effects include photoaging and photocarcinogenesis (keratinocyte carcinomas and melanoma)

This discussion is limited to the clinical aspects of UVR and visible light as the underlying mechanisms are reviewed in Chapter 86.

Acute and Subacute Effects

These effects are primarily the result of UVR absorption by DNA and RNA and the possible interaction of visible light with opsin-3 on melanocytes in darkly pigmented individuals.

Acute inflammatory erythema (sunburn)

Excessive UVR exposure leads to the acute inflammatory reaction of sunburn. In terrestrial sunlight, wavelengths around 300 nm are the most erythemogenic. The lowest dose capable of inducing erythema (MED) in individuals with skin phototype I is about 30 mJ/cm^2 (300 J/m^2) for broadband UVB (280–320 nm), and 30 J/cm^2 (300 kJ/m^2) for broadband UVA (320–400 nm). UVB-induced sunburn pain is thought to result from activation of epidermal TRPV4 ion channels.

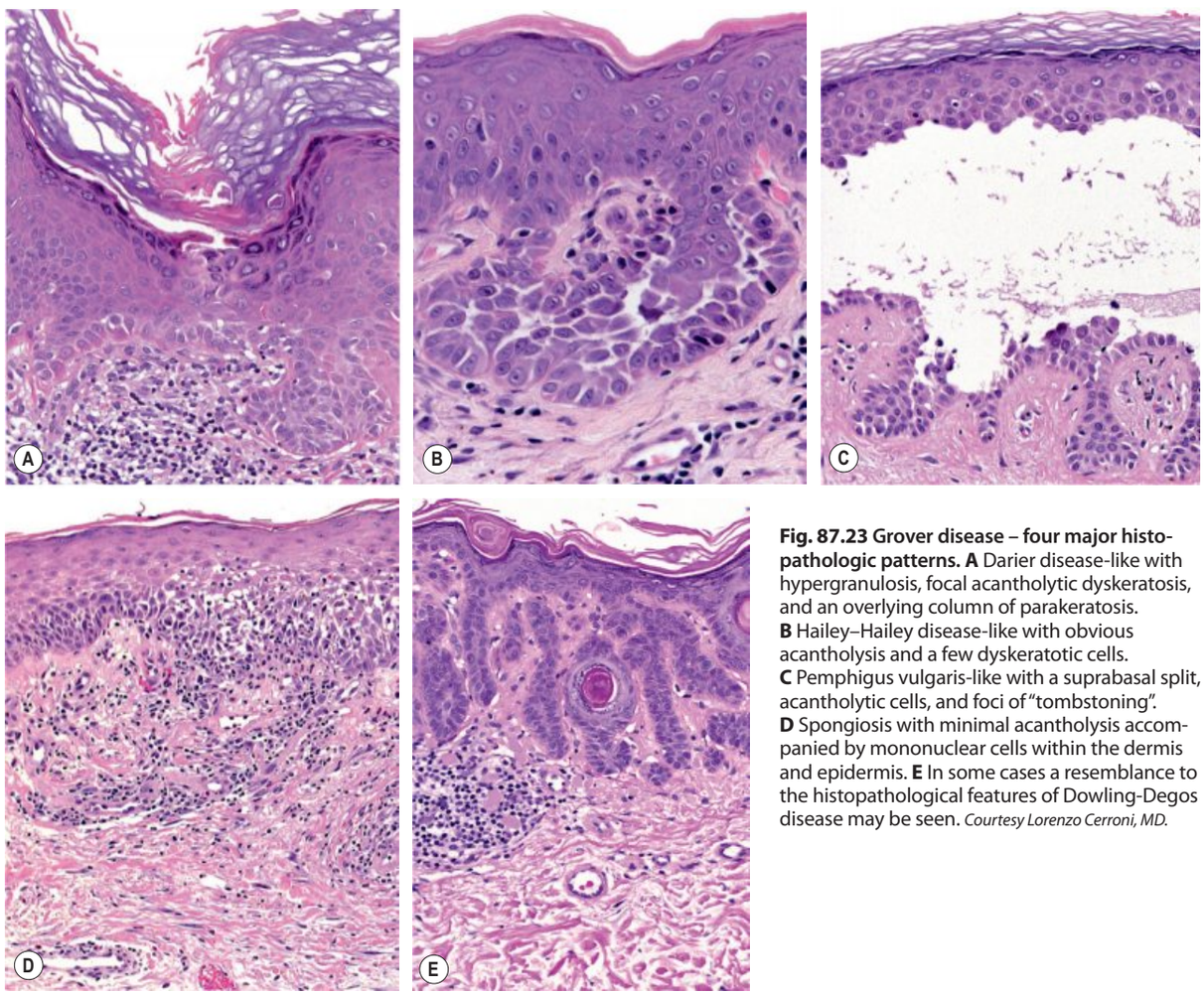


Fig. 87.23 Grover disease – four major histopathologic patterns. A Darier disease-like with hypergranulosis, focal acantholytic dyskeratosis, and an overlying column of parakeratosis. **B** Hailey–Hailey disease-like with obvious acantholysis and a few dyskeratotic cells. **C** Pemphigus vulgaris-like with a suprabasal split, acantholytic cells, and foci of "tombstoning". **D** Spongiosis with minimal acantholysis accompanied by mononuclear cells within the dermis and epidermis. **E** In some cases a resemblance to the histopathological features of Dowling-Degos disease may be seen. *Courtesy Lorenzo Cerroni, MD.*

In a few individuals, brief immediate erythema occurs within seconds of UVR exposure and lasts for minutes. Otherwise, the typical delayed bright red appearance of a sunburn develops confluently on all sufficiently exposed skin, beginning within 30 minutes to 8 hours, peaking at 12 to 24 hours and diminishing over hours to days in the case of UVB exposure. With exposure to UVA alone, however, the reaction is deeper red in color and is usually more persistent. After excessive exposure, edema and blistering may occur, which if widespread, may lead to systemic symptoms such as chills and malaise. Such reactions are generally followed by pruritus and desquamation over a period of days to weeks. In individuals with lighter skin phototypes, visible light has been shown to produce immediate erythema[64].

Photoprotection is the best preventive measure. In the case of excessive UVR exposure, symptomatic treatment is instituted as soon as possible after exposure. This includes increased fluid intake, emollient creams or lotions, topical corticosteroids, and oral nonsteroidal or steroidal anti-inflammatory agents. Of note, in a placebo-controlled trial involving 20 healthy adults, 200 000 IU of vitamin D_3 administered one hour after an experimental sunburn led to a reduced expression of pro-inflammatory mediators (e.g. TNF), reduced skin redness, and increased expression of the anti-inflammatory mediator arginase-1 in those with higher serum vitamin D_3 levels[65].

Pigment darkening and delayed tanning

Immediate, often grayish, darkening of irradiated skin that lasts for 10–20 minutes may occur within seconds of ~2–12 J/cm^2 of UVA irradiation; however, this response can last for up to 3 months[1]. In darkly pigmented individuals, the blue spectrum of visible light induces similar changes, possibly due to absorption of the blue light by opsin-3, a receptor on the surface of their melanocytes (see above)[66]. Transient pigmentary changes, known as *immediate pigment darkening*, result from photo-oxidative darkening and the cellular redistribution of melanin within epidermal melanocytes. Pigmentation that persists for more than 2 hours after irradiation is referred to as *persistent pigment darkening*; it is brownish in color, lasts for up to 24 hours, and is also due to oxidation of pre-existing melanin. Persistent pigment darkening then blends with *delayed pigmentation*, or *tanning*, which develops in genetically competent individuals over hours to days and persists for weeks to months following ~40 mJ/cm^2 of broadband UVB (slightly higher than the MED, particularly in fair-skinned persons), and 15–20 J/cm^2 of broadband UVA (a little less than the MED). As a result of delayed tanning, further sunburning sensitivity is mildly decreased by a factor of two to four.

Epidermal hyperplasia

Hyperplasia lasting a month or so occurs over a period of hours to days following UVB, but generally not UVA, exposure. This results from a markedly increased cellular mitotic rate and DNA, RNA and protein synthesis, following several initial hours of inactivity. Hyperplasia of the viable epidermis and thickening of the stratum corneum result in several-fold protection against later sunburning; this adds to, and may exceed, that simultaneously provided by delayed tanning, particularly in fair-skinned individuals. UV-induced epidermal hyperplasia is generally neither visible nor apparent by palpation.

Immunologic changes

Exposure to UVB and UVA radiation alters epidermal Langerhans cell function, generates suppressor T lymphocytes, and changes the cutaneous cytokine profile. This topic is discussed in greater detail in Chapter 86.

Vitamin D_3 synthesis

UVB (maximum: 300 ± 5 nm) irradiation quickly converts epidermal 7-dehydrocholesterol into previtamin D_3 (see Fig. 51.11)[67]; the latter then isomerizes to vitamin D_3 (cholecalciferol), which is then converted in the liver to 25-hydroxyvitamin D and subsequently in the kidneys to 1,25-dihydroxyvitamin D, its active form. UVR-induced vitamin D_3 synthesis is maximal at suberythemogenic doses. The action spectrum for vitamin D synthesis is similar to that for DNA damage. Ideally, vitamin D homeostasis is achieved by a combination of incidental outdoor daylight exposure and dietary sources rather than through intentional exposure to sunlight or tanning beds.

Other changes

Occasionally, otherwise healthy individuals who are not on any medications may develop *photo-onycholysis* and increased skin fragility with blistering (*pseudoporphyria*) following intense exposure to sunlight or tanning beds. *Mid-dermal elastolysis* is characterized by patches of finely wrinkled skin and loss of elastic fibers in the mid-reticular dermis (see Ch. 99); its onset is frequently associated with intense UVR exposure. *Brachioradial pruritus*, characterized by primary pruritus of the outer arm, is associated with cervical radiculopathy; however, in many patients, UVR may act as a trigger of the symptoms (see Ch. 6).

Chronic Effects

Photoaging in fair-skinned patients

Photoaging refers to cutaneous changes secondary to long-term exposure to sunlight (Table 87.8). Characteristic clinical manifestations are outlined below.

Solar (actinic) elastosis develops in chronically sun-exposed areas and presents as thickened skin with a yellow hue. It is most commonly seen on the face, neck, and extensor aspect of the mid arms (Fig. 87.24A). More widespread involvement can be seen in those from tropical climates, especially when there is minimal constitutive pigmentation (Fig. 87.24B). Histologically, a marked increase in abnormal, altered dermal elastic fibers is seen. *Cutis rhomboidalis nuchae* refers to similar changes occurring on the posterior neck (Fig. 87.24C); it is characterized by deep furrowing associated with a leathery texture.

A *solar lentigo* is a light brown to dark brown, even-colored or reticulated macule or patch that occurs in sun-exposed areas, most often as multiple lentigines. The dorsal aspects of the hands, extensor forearms, upper trunk, and face are the most commonly affected sites (see Ch. 109). An *ephelide*, also known as a freckle, presents as a light red–brown to medium brown macule, usually <6 mm in diameter. Such lesions occur primarily in sun-exposed areas, are usually clustered, and are more apparent after sun exposure (see Ch. 112). Histologically, a solar lentigo is associated with elongation and hyperpigmentation of the rete ridges and a mild increase in the number of melanocytes, while

CUTANEOUS SIGNS OF SIGNIFICANT PHOTODAMAGE
Common
• Solar elastosis (Fig. 87.24A,B) • Cutis rhomboidalis nuchae (Fig. 87.24C) • Wrinkling (coarse > fine) • Favre–Racouchot syndrome (nodular elastosis with cysts and comedones) (Fig. 87.24E) • Poikiloderma of Civatte ("red neck"; Fig. 87.24D) • Solar purpura and hemosiderin deposition (Fig. 87.24F,G) • Fragility and skin tears* (Fig. 87.24H) • Pseudoscars (Fig. 87.24H) • Erosive pustular dermatosis (Fig. 87.24I; see Ch. 25) • Dyschromia, including idiopathic guttate hypomelanosis • Solar lentigines, ephelides • Weathering nodules
Uncommon
• Acquired elastotic hemangioma • Adult colloid milium • Elastoma of Dubreuilh • Elastotic nodules of the ear • Keratoelastoidosis marginalis (Fig. 87.24J) • Solar elastotic bands
Neoplasms
• Actinic keratoses • Squamous cell carcinoma • Basal cell carcinoma • Cutaneous melanoma, including lentigo maligna • Merkel cell carcinoma
*Classification scheme – tear can (1a) or cannot (2a) be realigned to the normal anatomic location and flap color is *not* pale, dusky, or darkened; tear can (1b) or cannot (2b) be realigned to the normal anatomic location and flap color is pale, dusky or darkened; skin flap is absent (3).

Table 87.8 Cutaneous signs of significant photodamage.



Fig. 87.24 Cutaneous signs of significant photoaging. A Solar elastosis of the neck and V of the chest; note the thickening and furrowing of the skin. **B** Solar elastosis of the neck extending onto the back in a patient with oculocutaneous albinism from sub-Saharan Africa. **C** Cutis rhomboidalis nuchae with deep furrowing of the posterior neck. **D** Poikiloderma of Civatte with sparing of the submental region and follicular skin. **E** Multiple open comedones of the periorbital region in Favre–Racouchot syndrome. **F, G** Solar (actinic) purpura and residual discoloration due to hemosiderin. There is also evidence of skin fragility. **H** Skin tear due to fragility of atrophic photodamaged skin (dermatoporosis) and pseudoscars from previous tears. **I** Erosive pustular dermatosis of the bald scalp. **J** Keratoelastoidosis marginalis with keratotic papules in a marginal distribution on the medial aspects of the forefingers. **K** Given her age, this 93-year-old woman has relatively fine wrinkling of her face, in addition to scattered seborrheic keratoses. *A, Courtesy Kalman Watsky, MD; B, Courtesy Rosemarie Moser, MD; D, G, H, Courtesy Jean L. Bolognia, MD; I, Courtesy Harvey Lui, MD; J, Courtesy Karynne O. Duncan, MD.*

hyperpigmentation of the basal layer without elongation of the rete ridges is observed in an ephelide.

Idiopathic guttate hypomelanosis favors chronically sun-exposed sites of the extremities, especially the forearms and shins, but typically spares the face. Well-demarcated hypopigmented macules are typically 3–10 mm in diameter (see Ch. 66).

Poikiloderma of Civatte refers to reticulated red to red–brown patches composed of telangiectasias that spare perifollicular skin. It is most commonly observed on the lateral aspects of the neck in fair-skinned individuals with significant cumulative sun exposure (Fig. 87.24D). Characteristically, there is sparing of the central submental region. Mild atrophy and hyperpigmentation are sometimes present.

Histologically, telangiectasias, mild epidermal atrophy, melanophages, and dermal solar elastosis are observed.

In *Favre–Racouchot syndrome*, multiple large open comedones develop on the lateral and inferior aspects of the periorbital area (Fig. 87.24E), in association with marked solar elastosis of the surrounding skin. In some patients, cigarette smoking may be a cofactor. Histologically, there are dilated pilosebaceous openings and cyst-like spaces filled with horny material in addition to marked solar elastosis.

Solar purpura occurs in areas of cumulative photodamage that are subject to trauma, e.g. dorsal hands, extensor forearms, shins (Fig. 87.24F,G). As lesions resolve over weeks, a brown discoloration due to hemosiderin may appear. It is often accompanied by skin fragility (Fig. 87.24H).

Adult colloid milium is characterized by translucent yellow papules that measure 1–3 mm in diameter. There are usually numerous, closely spaced lesions in chronically sun-exposed sites, especially the neck, face and dorsal hands. Histologically, homogeneous masses of PAS-positive, diastase-resistant colloid are present in the papillary dermis; positive staining with thioflavin T and Congo red has been reported in some cases. The exact nature of the colloid deposits is still debated, but it has been suggested that, at least in some forms, they may represent elastin degeneration.

Erosive pustular dermatosis of the scalp classically presents as sterile pustules, keratotic crusts, erosions, and mild inflammation arising within the atrophic, photodamaged skin of a bald scalp[68] (Fig. 87.24I). However, similar clinical findings can occur in other sites with atrophic or fragile skin, e.g. the lower extremities of older patients with venous hypertension, sites of injury in neonates (see Ch. 25).

Acquired elastotic hemangiomas present as erythematous plaques within actinically damaged skin, usually on the neck or upper extremities. Histologically, there is a horizontal proliferation of capillaries in the upper reticular dermis and prominent solar elastosis.

Photoaging in patients with dark skin phototypes

Photoaging is much less pronounced and has a delayed onset in individuals with more darkly pigmented skin[69] (Fig. 87.24K). Small seborrheic keratoses, melasma, and mottled hyperpigmentation are common signs of photoaging in East Asians, such as Chinese, Japanese, Koreans, and Filipinas; in addition, any wrinkles are fine and do not usually appear before 50 years of age. South Asians, such as Indians, Pakistanis, Sri Lankans and Bangladeshis, often have darker skin than East Asians and dyspigmentation and fine wrinkles are the primary signs of photoaging. Lightly pigmented Latinos have changes similar to those seen in White individuals, while those with brown skin photoage in a manner similar to that seen in South Asians. Black-skinned individuals, including African-Americans, Afro-Caribbeans and people from Africa, have a wide range of skin phototypes, from III to VI. Dyspigmentation is common and fine wrinkles appear late in life.

Photocarcinogenesis

Chronic sun exposure has been associated with the development of actinic keratoses (AKs), SCC, BCC and melanoma, in particular lentigo maligna. Epidemiologic studies have shown that SCCs tend to develop within chronically sun-exposed areas in fair-skinned individuals; e.g. people who migrate to Australia early in life have a higher risk of developing SCC than immigrants who arrive when older. Furthermore, the incidence of BCC is higher in native-born Australians than immigrants, and a statistically significant association between *intermittent* sun exposure and the risk of BCC has also been reported. These findings are supported by the observation that the use of sunscreens led to a decrease in the development of AKs, SCC, melanoma, and to a lesser extent, BCC[70]. Exposure to tanning beds is associated with an increased risk for developing cutaneous melanoma as well as SCC and BCC.

In studies of populations in which there was a greater proportion of individuals with darkly pigmented skin, a higher melanoma incidence associated with an increased UV index and lower latitude was only seen in non-Latino White populations, but not in Black or Latino populations[69,71].

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 87.1 Polymorphous light eruption of the thigh. Edematous papules becoming confluent and forming plaques. *Courtesy Jean L. Bolognia, MD.*



eFig. 87.2 Polymorphous light eruption. Papulovesicles on the upper back. Some have a central crust.



eFig. 87.3 Actinic prurigo. Papules, plaques with scale, and excoriations on dorsal hand and extensor forearm. *Courtesy John L.M. Hawk, MD.*





eFig. 87.4 Actinic prurigo. A The clinical features, including a photodistribution and worsening in the summer, are somewhat suggestive of polymorphous light eruption, but the lesions were persistent and the HLA type was that seen in association with actinic prurigo. Note the involvement of the ears. **B** The crusted papules are more dense on the distal arms. *Courtesy John L.M. Hawk, MD.*



eFig. 87.5 Hydroa vacciniforme – early phase of the classic form. There is a polymorphous light eruption-like appearance, but with vesicles around the mouth and umbilicated lesions on the nose. *Courtesy John L.M. Hawk, MD.*



eFig. 87.6 Hydroa vacciniforme-like lymphoproliferative disorder. This Hispanic child had >50 000 copies of EBV DNA/100 000 WBCs as well as EBV RNA within skin lesions by *in situ* hybridization; he subsequently died of lymphoma. Note the facial edema, erythema, papulovesicles, hemorrhagic crusts and varioliform scars. *Courtesy Richard Antaya, MD.*



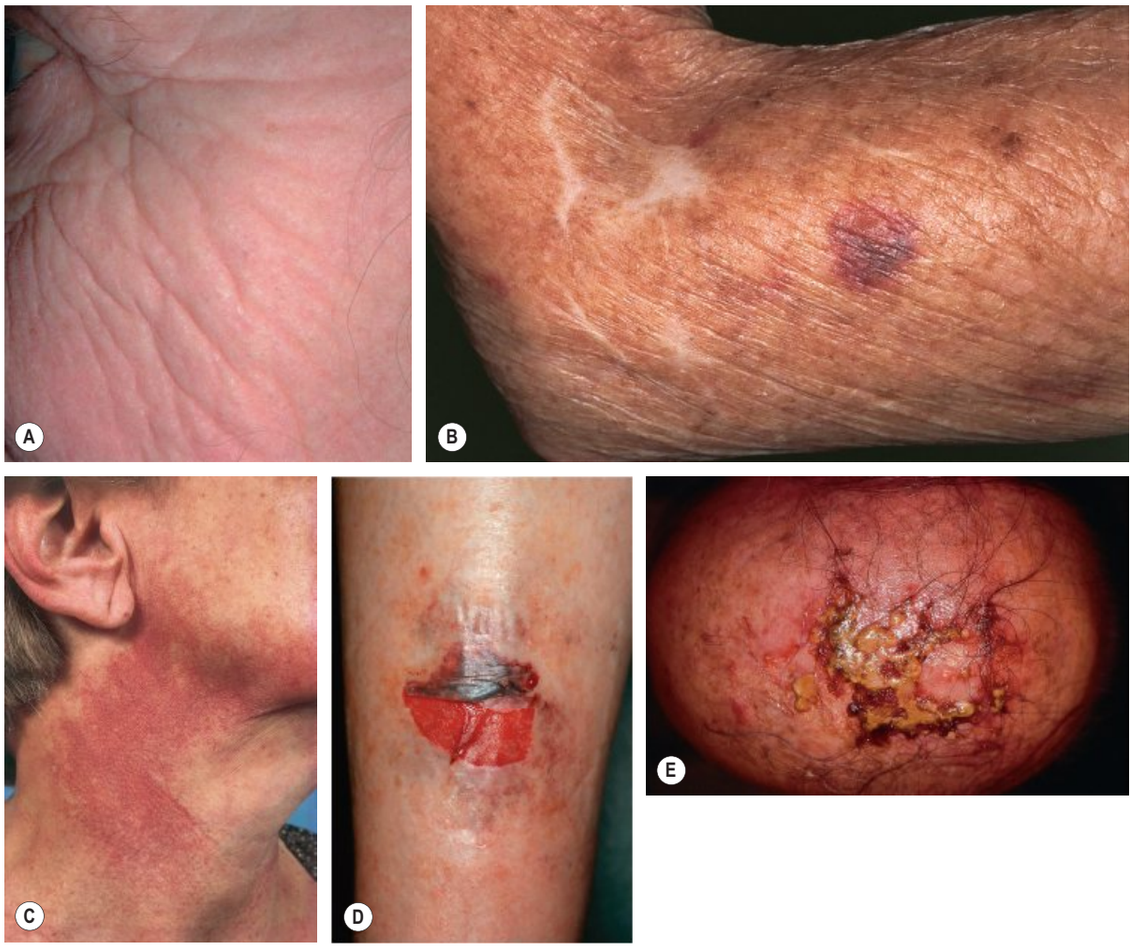
eFig. 87.7 Postinflammatory hyperpigmentation due to a photoeruption secondary to hydrochlorothiazide. *Courtesy Kalman Watsky, MD.*



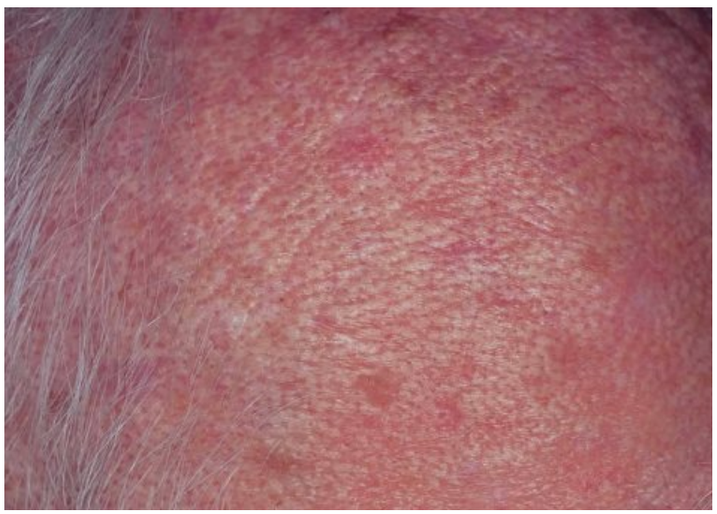
eFig. 87.8 Phototoxic drug eruption due to doxycycline. The most prominent sites of involvement overlie the metacarpophalangeal joints. *Courtesy Kalman Watsky, MD.*



eFig. 87.9 Grover disease. Crusted erythematous papules on the mid to lower back. The trunk is the most common site of involvement. *Courtesy Jean L. Bolognia, MD.*



eFig. 87.10 Cutaneous signs of significant photoaging. A Solar elastosis of the cheek with yellow discoloration and thickening of the skin. **B** Solar (actinic) purpura and pseudoscars that follow skin tears due to fragility. Both occur in sites of actinic damage plus trauma. **C** Poikiloderma of Civatte with sparing of the anterior neck and follicular skin. **D** Skin tear due to fragility of atrophic photodamaged skin (dermatoporosis). **E** Erosive pustular dermatosis of the bald scalp. *B, D, Courtesy Jean L. Bolognia, MD.*



eFig. 87.11 Yellow discoloration of the lateral forehead due to solar elastosis. *Courtesy Jean L. Bolognia, MD.*



eFig. 87.12 Favre–Racouchot syndrome – a sign of photodamage. Multiple open comedones of the temple and malar eminence. *Courtesy Kalman Watsky, MD.*



eFig. 87.13 Favre–Racouchot syndrome – a sign of photodamage. Cluster of open comedones on the malar eminence.



eFig. 87.15 Keratoelastoidosis marginalis – a sign of photodamage. Papules and scale in a marginal distribution on the medial aspect of the forefinger and lateral aspect of the thumb as well as the intervening web space. *Courtesy Richard Haber, MD.*



eFig. 87.14 Skin tear in severely photodamaged skin. Healing of such tears leads to pseudoscars. *Courtesy Jean L. Bolognia, MD.*

Environmental and Sports-Related Skin Diseases

88

Sarah Hannam and Michael L. Smith

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The skin is our primary interface with the environment. Amongst Earth's creatures, humans are unique in their ability to manipulate the environment by manufacturing clothing, shelter, and heating or cooling devices to allow them to live in a variety of environmental extremes. Despite technologic advances that have allowed humans to live, work and play in most of the environments on this planet, deliberate or inadvertent exposure to those environments may subject individuals to injury. The following discussion will focus upon chemical, frictional, traumatic, and water immersion skin injuries, temperature-related skin diseases, electrical burns, cutaneous diseases due to heavy metals, sports-related dermatoses, and skin issues in amputees and instrumental musicians.

INJURY DUE TO HEAT EXPOSURE

Heat-Related Illnesses and Thermal Burns

Synonyms/variants: ■ Heat-related illnesses: heat cramps, heat syncope, heat edema, heat exhaustion, heat stroke ■ Thermal burns: burns

Key features

- Heat-related illnesses occur when the body's thermoregulatory mechanisms fail; correction of fluid and electrolyte balance is critical in their treatment
- Management of thermal burns requires assessment of burn depth (i.e. first, second, or third degree) and body surface area involved
- Burn treatment includes prevention of infection, serial excisions, and skin substitutes

Introduction

Humans, like all other mammals and all birds, are homeothermic organisms that maintain their core body temperature within a narrow range by varying cutaneous and visceral blood flow. Normal core body temperatures vary between 36°C and 37.5°C (96.8°F and 99.5°F). At normal core temperature, cutaneous blood flow is about 4% of cardiac output or 250 ml/min. Modulation of cutaneous blood flow is performed by the hypothalamus via a delicate balancing act between heat retention and loss. Cutaneous, muscle, and spinal cord temperature sensors send signals to the preoptic area of the anterior hypothalamus. Communication with the posterior hypothalamus sets up the subconscious thermoregulatory mechanisms of vasomotor control, sweating, and shivering.

When prolonged exposure to a hot environment leads to an increase in core temperature, the subsequent decrease in sympathetic output results in peripheral vasodilation, allowing an increase in cutaneous blood flow of up to 6–8 L/min. Cholinergic output stimulates sweating. These changes allow radiant, conductive, convective, and evaporative heat loss. In contrast, cold temperature exposure leads to increased sympathetic output with peripheral vasoconstriction. Countercurrent heat exchange between parallel arteries and veins further reduces heat loss to the skin, thereby conserving core heat. The behavioral response of shivering generates heat through muscular activity[1].

Pathologic conditions arise when the normal hypothalamic regulatory set point is overcome by extremes of temperature (Table 88.1). The following discussion will explore heat-related illnesses and thermal burns. Heat-induced urticaria is covered in Chapter 18.

History

It has been speculated that King Edward and his armored crusaders lost the final battle of the Holy Land because the Arab horsemen were adapted and dressed appropriately for the severe heat.

Epidemiology

The frequency of heat-related illnesses is unknown, since milder forms resolve with simple measures. Heat-related illness accounted for more than 8000 deaths in the US between 1979 and 1999, and is responsible for ~7% of wilderness deaths. The European heat wave of 2003 contributed to the deaths of about 14 800 individuals in France[1]. In US high school athletes, the incidence of heat-related illness is ~9000 cases annually, with the highest rates during football season and representing the third leading cause of death in this cohort. From 2006 to 2010, five in 10 000 visits to the emergency department were for heat-related illnesses: 75% with heat exhaustion and 5% with heat stroke[2]. Risk factors are listed in Table 88.2.

Burn injuries are far more commonly reported, with more than half a million Americans presenting for medical treatment each year, resulting in 40 000 hospitalizations and >3000 deaths, half of which occur in children[3–5]. The male to female ratio is ~2:1, and the major sources of burns in children are scald, flame, and electrical. Abuse or neglect may account for up to 20% of pediatric burns. Mortality rates have steadily declined due to improved resuscitative and surgical management. In the 1940s, burns in children involving 50% body surface area (BSA) had a 50% survival rate, whereas today, 50% of children with 90% BSA burns survive[4,5].

A unique form of burn injury is that due to fireworks. In the US alone, there were at least 25 000 emergency department visits for injuries due to fireworks between 2006 and 2010. Half of the visits were by individuals <20 years of age, with a predominance of male patients (~75%). The most common injuries were distal extremity burns, followed by ocular injury, open wounds of distal extremities, and ocular burns[6].

Pathogenesis

Athletic activity can generate 800 to 1000 kcal/h of heat for prolonged periods. This results in a 1°C rise in core body temperature every 5 to 8 minutes. The normal thermoregulatory mechanisms dissipate this heat as it is generated. When these regulatory mechanisms fail, heat injury occurs. Heat illnesses are not defined by a specific temperature, but by the abnormal response to heat. Table 88.1 outlines the pathogenesis of heat-related disorders.

HEAT-RELATED ILLNESSES				
Condition	**Core temperature**	**Clinical features**	**Treatment**	**Pathogenesis**
Heat cramps	Normal	Painful spasm in large muscle groups, weakness, fatigue, N/V, **marked sweating**, tachycardia, ↑BP	Fluid and salt replacement	Dilutional hyponatremia due to free water (but not electrolytes) being replaced
Heat syncope	Normal	Nausea, sighing, yawning, restlessness, fainting (brief)	Avoid standing still in heat, flex legs, lie down if prodrome, cool off, replace fluid	Decreased cerebral blood flow due to volume depletion, peripheral vasodilation, and decreased vasomotor tone in poorly acclimatized or elderly individuals
Heat edema	Normal	**Dependent edema** from vasodilatory pooling	None needed (self-limited)	Vasodilatory pooling
Heat exhaustion	Normal to 39°C (102.2°F)	Weakness, dizziness, headache, N/V, irritability, dyspnea/hyperventilation, malaise, myalgias/muscle cramps, tachycardia, orthostatic hypotension, **profuse sweating, piloerection**, impaired judgment, syncope *Hypernatremic* form: thirst, rare cramps *Hyponatremic* form: fatigue, cramps, history of excessive free water intake, altered mental status	Intravenous fluids and electrolytes, sprinkle water and fan or use ice packs, rest, cool environment	Volume and/or salt depletion
Heat stroke	>40°C (104°F)	**Anhidrosis to profuse sweating**, ↓BP, N/V, diarrhea, altered mental status (profound), seizures, coma, cardiac arrhythmias, ↑transaminases, rhabdomyolysis, acute kidney injury, DIC, respiratory alkalosis Poor prognostic indicators: T >42.2°C (108°F); coma >2 h; AST >1000 (day 1)	Rapid lowering of core temperature to 38°C (100.4°F), intravenous hydration, intensive care unit	End result of thermoregulatory failure; volume depletion leads to peripheral vasoconstriction and reduced transfer of heat peripherally; resultant core heating leads to organ failure

Table 88.1 Heat-related illnesses[1,2]. Cutaneous features are indicated in **bold**. AST, aspartate transaminase; BP, blood pressure; DIC, disseminated intravascular coagulation; N/V, nausea and vomiting; T, temperature.

RISK FACTORS FOR HEAT-RELATED ILLNESS	
• Occupational exposure	• Age (elderly, young child)
• Poverty	• Insufficient acclimatization
• Drug and alcohol use, mental illness, dementia	• Obesity, deconditioning, or sedentary lifestyle
• Medications (anticholinergics, phenothiazines, diuretics; see Table 39.9)	
Environmental factors (absence of shelter or shade, high temperatures and/or humidity, lack of access to water)	
Medical conditions	
• Excessive fluid loss (e.g. diarrhea, uncontrolled diabetes mellitus) • Suboptimal sweating (e.g. ectodermal dysplasias; see Tables 39.8 & 39.10) • Excessive sweating (see Tables 39.2, 39.3 and 39.4) • Inadequate fluid intake (see above) • Decreased thirst (e.g. cystic fibrosis) • Abnormal thermoregulation (prior heat illness, malnutrition)	

Table 88.2 Risk factors for heat-related illness[1,2].

Thermal burns occur when skin is exposed to infrared radiation (800 to 170 000 nm) from an external heat source with a temperature exceeding 44°C (111°F). Time and temperature curves have been developed to determine maximum threshold thermal exposure times. Necrosis of the epidermis occurs in about 45 minutes at 47°C (117°F) but in only 1 second at 70°C (158°F). Denaturation and coagulation of cellular proteins occur in thermal injury. Interstitial edema develops from altered osmotic pressure and capillary permeability. Several chemical mediators with vasoactive and tissue-destructive properties are released, including prostaglandins, bradykinin, serotonin, histamine, lipid peroxides, and oxygen radicals[5].

Clinical features

Although heat-related illnesses are not primary skin diseases, they can present with cutaneous findings. Their clinical features are summarized in Table 88.1.

Thermal burns of the skin differ in their clinical presentation, depending upon the depth of injury (Table 88.3)[5,7,8]. Conventional nomenclature categorizes cutaneous burn wounds as *first degree* (superficial; limited to epidermis), *second degree* (partial-thickness), and *third degree* (full-thickness). Second-degree burns are further subdivided into superficial (Fig. 88.1) and deep variants. Burns involving deeper structures such as muscle are sometimes referred to as fourth-degree burns. However, a definitive determination of wound depth may not be possible for the first 24 to 72 hours because of vascular occlusive changes.

At sites where the dermis is thinner (ears, volar forearms, medial thighs, perineum), burns may be deeper than the initial presentation might suggest; this is also the case in the comparatively thinner skin of children and the elderly. Wounds that appear dull red from entrapment of clot (denatured hemoglobin) imply full-thickness injury[7].

The severity of burn injuries is based upon depth and BSA involvement. BSA is estimated in adults by the "rule of nines" (Fig. 88.2). This formula cannot be applied to children, since the head accounts for ~19% BSA in a 2-year-old, 15% in a 7-year-old, and 13% in a 12-year-old. Lund & Browder charts are useful for more accurate assessment of BSA involvement[5,7]. Initial evaluation should address airway and circulatory status; associated inhalation injury is seen in up to 25% of burn patients. Cardiovascular evaluation must address the issue of hypovolemic shock, regardless of burn severity. Urine output must be monitored because of the significant fluid loss and rhabdomyolysis that may compromise renal function[4,5,7].

Pathology

Pathologic features of thermal burns are summarized in Table 88.3.

Differential diagnosis

The differential diagnosis of heat injury is listed in Table 88.1. Although there is considerable overlap in clinical features, an important distinction is the degree of neurologic compromise. The most important diagnostic issue with thermal burns is the depth of the injury (see Table 88.3).

Treatment

Management of heat-related injuries involves removal from the hot environment, rest, rehydration, restoration of electrolyte balance, and evaluation of involved systems (Table 88.1; see Atha[1] for more details).

Initial management of burn victims includes assessment of cardiopulmonary status as well as the extent and depth of the burn. Information regarding resuscitation of burn victims is beyond the scope of this text, but can be found in references 4, 5, and 7. For first- and second-degree burns, the burn wound itself should initially be rinsed with room temperature/cool running water for 20 minutes in order to ease pain, reduce heat, and reduce burn depth[5]. Then the wound should be gently cleansed to remove any foreign material. The next step is prevention of infection, followed by creation of a proper healing environment. Topical

CLINICAL AND PATHOLOGIC FEATURES OF THERMAL BURNS			
Type	**Depth**	**Clinical features**	**Pathology**
First degree	Epidermis only	Pain, tenderness, erythema No blistering Heals without scar	Upper epidermal necrosis
Second degree – superficial	Epidermis and superficial dermis	Severe pain, tenderness, serous or hemorrhagic bullae, deep rubor, erosion, and exudation Heals in 10–21 days with mild but variable scarring	More extensive epidermal necrosis with vertical elongation of keratinocytes Necrotic areas may have serous crust with neutrophils, fibrin, and cellular debris Subepidermal bullae possible
Second degree – deep	Epidermis and most of dermis destroyed, including deep follicular structures	Intense pain but reduced sensation, deep red to pale and speckled in color Serosanguineous bullae and erosions May appear devitalized initially Prolonged healing time Hypertrophic scars and marked wound contracture	Destruction of entire epidermis, dermal collagen, and most of adnexal structures Collagen bundles may be fused, with eosinophilic appearance Thrombosis of deep vessels common Granulation tissue present at junction of normal and injured tissue
Third degree	Full-thickness epidermal and dermal destruction	Dry, hard, charred, non-blanching, hypo- or anesthetic areas of coagulation necrosis Small lesions heal with significant scarring Most require surgical correction	Necrosis of entire epidermis and dermis, with extension into subcutis Inflammatory infiltrate at interface between burned and normal skin When scar forms, it exhibits hyalinized collagen, decreased elastic tissue, and loss of arrector pili muscles

Table 88.3 Clinical and pathologic features of thermal burns[5,7,8].



Fig. 88.1 Thermal burn. This superficial second-degree burn is characterized by bullae that contain serous fluid. *Courtesy Kalman Watsky, MD.*

antimicrobial agents shown to be effective in burn wound care include silver sulfadiazine, mafenide acetate, and silver nitrate. Silver sulfadiazine has gained wide acceptance for both pediatric and adult burn treatment, but it is known to be cytotoxic and percutaneous absorption can lead to leukopenia. Silver sulfadiazine also produces a pseudoeschar that may interfere with burn depth assessment and prolonged application may lead to localized argyria. Some experts therefore prefer mafenide acetate.

While superficial wounds may require minimal additional therapy[4,5,7], deeper burn wounds need more aggressive therapy, with the standard approach being serial excision and autografting (if there are sufficient donor sites). Third-degree burns are excised early, with indeterminate and deep second-degree wounds delayed until maximum depth and extent are known. Biologic dressings (e.g. pig skin, human allograft) were popular for several years, but have been largely displaced due to higher infection risk and poorer healing. Skin substitutes such as acellular human dermal matrix (Alloderm®), bilaminar bovine collagen–shark chondroitin sulfate (Integra® Dermal Regeneration Template), and cultured epithelial autografts are increasingly being utilized[7] (see Ch. 145).

Erythema Ab Igne

Synonyms: ■ Toasted skin syndrome ■ Fire stains

ASSESSING THE EXTENT OF BODY SURFACE AREA (BSA) INVOLVEMENT IN BURN INJURUES: RULE OF NINES

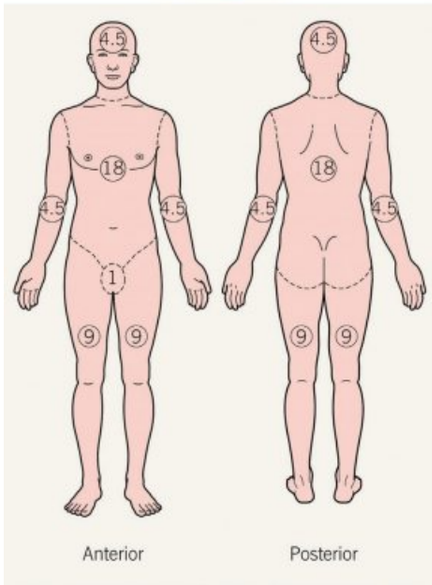


Fig. 88.2 Assessing the extent of body surface area (BSA) involvement in burn injuries: rule of nines. In adults, an estimate of burn extent is often based on this surface area distribution chart. Infants and children have a relatively increased head:trunk surface area ratio and this chart is ineffective for them. Note that the palm is ~1% of BSA and can be used for estimating patchy areas. These estimates are also used for primary cutaneous disorders. Only partial- and full-thickness burns are considered in BSA measurements. The most accurate method of estimating the BSA involvement of burn injury in adults and children is with the Lund–Browder chart (www.ncbi.nlm.nih.gov/pmc/articles/PMC449823/).

Key features

- Localized areas of reticulated erythema and hyperpigmentation
- Chronic exposure to heat below the threshold for a thermal burn
- Commonly in lumbosacral region (heat applied to relieve pain) and shins (in regions without central heating in homes)
- Squamous atypia histologically (in later lesions)
- Risk of cutaneous malignancy, particularly squamous cell carcinoma

Introduction

Chronic exposure to low levels of infrared heat can lead to the characteristic reticulated cutaneous pattern of erythema ab igne (EAI), with subsequent risk of malignant degeneration.

History

EAI, once a very common entity, was first described in the UK as a result of standing near stoves fired with peat. In the southern US, the custom

HEAT SOURCES REPORTED TO CAUSE ERYTHEMA AB IGNE	
• Heating pads	• Steam radiators
• Hot water bottles	• Heated car seats
• Electric stove/heater	• Heated reclining chairs
• Open fires	• Heating blanket
• Peat fires	• Hot bricks
• Coal stoves	• Infrared lamps
• Wood stoves	• Microwave popcorn
• Sauna belt	• Laptop computer*
• Prolonged hot bathing	• Motorcycle muffler/silencer
*Anterior thighs >> abdomen; heat originates from the battery, optical drive, or ventilation fan.	

Table 88.4 Heat sources reported to cause erythema ab igne[9–12].

of sitting around pot-bellied stoves to keep warm while socializing also led to its development. Although the advent of central heating in much of the industrialized world has led to a dramatic decline in incidence, creative cultural and therapeutic applications of various heating devices continue to induce EAI[9–11].

Epidemiology

In the past, EAI was seen up to 10 times more frequently in women than in men. The vast majority of those affected were middle-aged or older. Risk factors include lack of central heating, occupations with close heat exposure, and medical conditions with symptoms relieved by heating or associated with decreased sensation. More recently, EAI has been associated with technologic advances such as heated car seats and recliners as well as laptop computers. The latter lead to EAI in a wide range of age groups and characteristically lead to an asymmetric distribution pattern[10,11].

Pathogenesis

Long-term exposure to heat below the threshold for thermal burn is the primary etiologic factor in EAI. The precise pathophysiology is unknown, but the clinical pattern corresponds with the dermal venous plexus. Repeated exposure to heat below 47°C (116.6°F) produces reticulated erythema followed by hyperpigmentation in the same pattern[9]. Heat sources reported to cause EAI are found in Table 88.4[9–12].

Clinical features

The initial presentation is transient macular erythema in a broad reticulated pattern that easily blanches. The overall size and shape often approximates that of the heat source. With recurrent heat exposure, the erythema evolves into a dusky hyperpigmentation; lesions become fixed and are no longer blanchable (Fig. 88.3). Epidermal atrophy may overlie the reticulated pigmentation. Later-stage lesions can become somewhat keratotic and bullae may appear. Lesions are characteristically asymptomatic, although a slight burning sensation is sometimes noted[9].

Once the heat source is identified, it is important to determine if it is being used to relieve pain and, if so, the cause of the pain. A lumbosacral location usually points to musculoskeletal disease or, less often, bone metastases. EAI of the abdomen, flank, or mid back may reflect an attempt to relieve pain from inflammation (e.g. pancreatitis, peptic ulcer disease) or malignancy (e.g. pancreatic, gastric). Symptoms of pain should prompt a thorough review of systems and consideration of a search for occult disease. An inquiry into occupation and hobbies is also important, as EAI can develop in exposed areas, e.g. the forearms of bakers, the face or arms of glass blowers and foundry workers, and the anterior thighs or abdomen in those with prolonged use of laptop computers[10,11,13].

The possible development of cutaneous squamous cell carcinoma (SCC) or Merkel cell carcinoma represents the major long-term risk. The latent period may be 30 years or more. The risk of developing SCC is reportedly highest with hydrocarbon-fueled heat exposure, e.g. "peat fire cancers" on the shins of women, Japanese "Kairo cancers" and "Kangri ulcers" in Kashmir due to coal-fired clothing warmers, and Chinese and Tibetan "Kang cancers" from sleeping on coal fire-heated bricks ("Kang beds")[9,10]. Basal cell carcinoma and cutaneous marginal zone B cell lymphoproliferative disorder have also been reported in association with EAI[10,13].

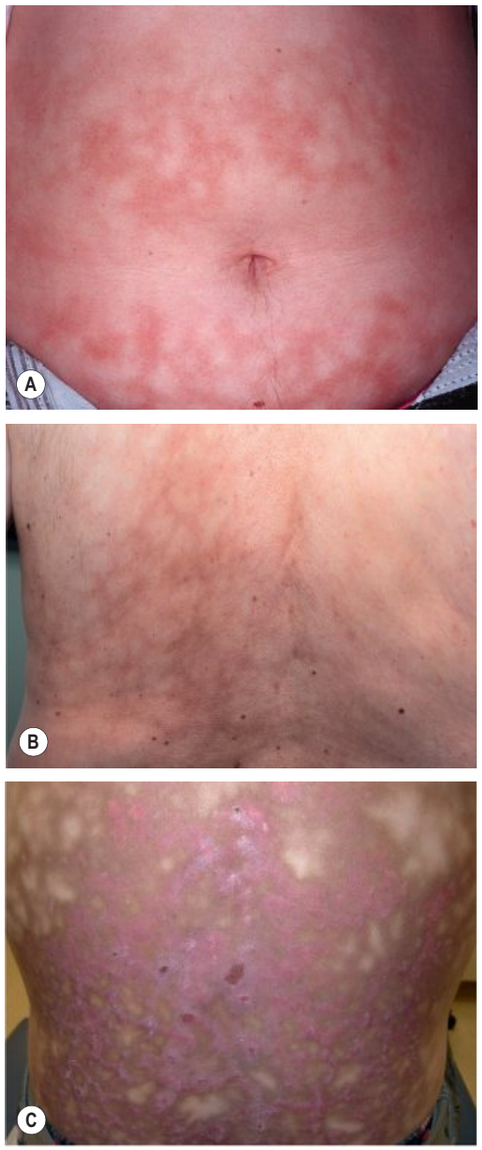


Fig. 88.3 Erythema ab igne – clinical features. A Early phase with pink reticulated patches predominating over reticulated hyperpigmentation. **B** Later phase with unilateral hyperpigmented reticulated patches. **C** Late phase with large area of reticulated hyperpigmentation and superimposed pink keratotic plaques. *A, Courtesy Jeffrey P. Callen, MD; B, Courtesy Kalman Watsky, MD; C, Courtesy Peter Klein, MD.*

Pathology

The earliest histopathologic changes include epidermal atrophy, vasodilation, and dermal pigmentation (both melanin and hemosiderin) (Fig. 88.4). As lesions progress, the epidermal atrophy becomes more pronounced, with flattening of the rete ridges. Basal cell vacuolization has been reported and the dermal–epidermal junction may exhibit interface dermatitis. The dermis appears thinned and sometimes edematous, with accumulation of abnormal elastic tissue and pigment as well as ectatic capillaries. Dermal capillaries may exhibit enlarged endothelial cells with hyperchromatic nuclei. Later lesions may also show basophilic degeneration of connective tissue. Hemosiderin deposition and prominent telangiectasias are seen most often in leg lesions. Focal hyperkeratosis and dyskeratosis may be noted, along with squamous atypia, in long-standing lesions. Ultrastructural evaluation also shows increased melanocyte dendritic processes, suggesting melanocyte activation[9].

Differential diagnosis

EAI needs to be distinguished from livedo reticularis, which is a temperature-sensitive vasculopathy that favors the extremities and only occasionally develops associated hyperpigmentation (see Ch. 106). Cutis marmorata and cutis marmorata telangiectatica congenita are less commonly considered in the differential diagnosis of EAI. The presence of telangiectasias along with atrophy and hyperpigmentation raises the possibility of poikiloderma and its various causes, e.g. cutaneous T cell lymphoma (see Ch. 120), dermatomyositis (see Ch. 42), several genodermatoses (see Ch. 63).

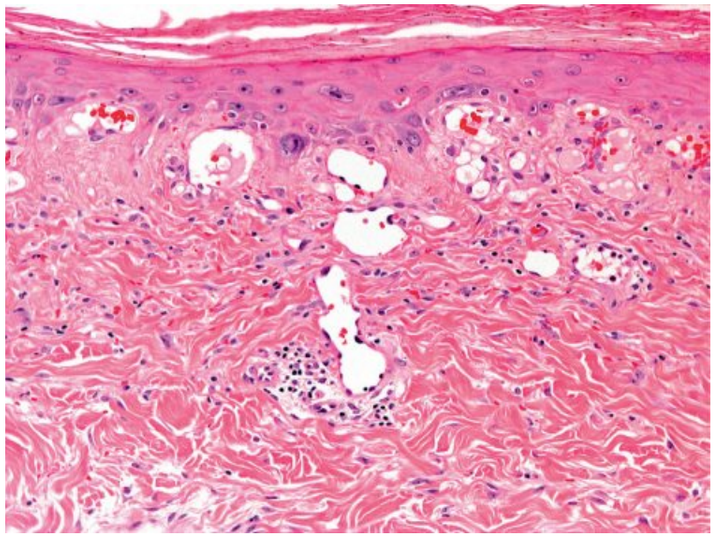


Fig. 88.4 Erythema ab igne – histologic features. The blood vessels within the superficial dermis are markedly dilated. There is hyperkeratosis and a sparse inflammatory infiltrate. Note also thinning of the epidermis with some apoptotic keratinocytes and atypical cells. *Courtesy Lorenzo Cerroni, MD.*

Treatment

Management consists primarily of removal of the offending heat source. The epidermal atypia is comparable to that of actinic keratoses, and anecdotally it has been treated successfully with topical 5-fluorouracil. As mentioned above, the use of heat to treat symptoms of pain should prompt an evaluation to determine its etiology[9–14].

Burns and Cutaneous Radiation Injury Associated With Magnetic Resonance Imaging (MRI) and Fluoroscopy

Key features

- MRI may produce first-, second-, or third-degree burns due to metal or wire contact with skin, creating a closed-loop conduction system
- Fluoroscopy, particularly when repeatedly performed in patients with cardiovascular disease, may result in radiation-induced injury

Introduction

The radiologic literature is replete with reports of superficial to full-thickness thermal or electrical burns occurring during MRI. Risk factors for MRI burns are listed in Table 88.5[15]. In addition, there are reports in the radiologic and dermatologic literature of ulcerations, most commonly on the back, following repeated fluoroscopy[16–18].

Pathogenesis

Although the precise cause of MRI burns is unknown, the presence of both pulsed radiofrequency and pulsed magnetic gradient fields is thought to play a role. If an electrically conductive loop is formed between the patient and an electrode, patient and wiring, or even small areas of skin–skin contact, current can be produced by the changing magnetic flux, causing a thermal or electrical burn. Resistance at the skin surface may create a thermal injury, while contact with wiring may create electrical injury via current induction. Alternatively, the burn may result from formation of a resonant conducting loop with an extended wire creating a resonant antenna, heating maximally at the antenna tip[15,19].

In addition to thermal burns, cutaneous complications of fluoroscopy include allergic drug reactions, irritant and allergic contact dermatitis, non-target embolization to the skin, intravascular catheter-related infections, and radiation dermatitis[17]. The mechanism behind fluoroscopy-induced radiodermatitis is related to the dose of radiation that is delivered, the interval between radiation exposures (dose fractionation), and the size of the irradiated area[16]. Repeated procedures are notorious for increasing the risk[18]. Additional potential risk factors include smoking, diabetes mellitus, obesity with overlapping skin folds, autoimmune connective tissue diseases (e.g. systemic sclerosis), genetic DNA repair defects, and various drugs including chemotherapeutic agents[16,17]. Radiation recall, which can occur days to years after fluoroscopy, has been observed following the administration of drugs such as methotrexate[16].

RISK FACTORS FOR BURNS DURING MAGNETIC RESONANCE IMAGING	
• ECG leads	• Metallic body piercing jewelry
• Monitoring cables	• Tattoos
• Pulse oximeter	• Extremity skin-to-skin contact
• Pins in halo fixation device	• Clothing with metal threads
• Transdermal patches	

Table 88.5 Risk factors for burns during magnetic resonance imaging[15–17]. ECG, electrocardiogram.



Fig. 88.5 Fluoroscopy-induced radiation dermatitis. The left upper back is a characteristic location for patients who have undergone attempts at coronary artery revascularization (e.g. angioplasty, stent placement). *Courtesy Jeffrey P. Callen, MD.*

Clinical features

Thermal burns appear soon after MRI, and may be partial- to full-thickness (see Table 88.3). The shape and size of the burns are determined by the conductor causing the injury (e.g. circular burns under ECG electrodes; figurate burns conforming to the shape of metallic wires or tattoo pigment deposition)[15,19].

Fluoroscopy-induced radiation dermatitis may be acute, but, as time passes and the acute injury resolves, the patient may continue to develop further changes, including epilation of hair, desquamation, telangiectasias, permanent erythema, and eventual ulceration due to dermal necrosis (Fig. 88.5). The left upper back is a characteristic location for patients with cardiovascular disease who have had cardiac catheterizations with attempts at revascularization (e.g. angioplasty, stent placement)[18]. Although often referred to as cutaneous complications, severe radiation injuries can extend into the subcutaneous fat and muscle[16]. Rarely, skin burns develop at the site of an indifferent electrode in those undergoing radiofrequency catheter ablation of cardiac arrhythmias[18a].

Differential diagnosis

Because of the proximity of the MRI event to the detection of a burn injury, the diagnosis is generally straightforward. However, in the case of a tattoo burn, allergic contact dermatitis or foreign body granuloma formation within the tattoo may be considered. Timing of the event plus the sensation of a burn rather than pruritus should allow a distinction.

The differential diagnosis of fluoroscopy-induced disease includes fixed drug eruptions, contact dermatitis, herpes virus infection, impetigo, and spider bites.

Treatment

Prevention of this injury by avoiding risk factors is ideal (see Table 88.5). However, when burns occur, they should be managed as any other thermal burn, or, in the case of fluoroscopy-induced injury, by limiting the dose delivered.

Airbag Burns

Key features

- Deployment of airbags causes numerous cutaneous injuries, including frictional and blunt trauma, thermal burns, and possibly chemical burns
- Friction due to contact with the bag, thermal burning from the bag and its released gases, and exposure to corrosive aerosol produce the injuries

Introduction

Automobile airbags provide additional crash protection, reducing driver and passenger fatalities by up to 30%. Although patented in 1953, US manufacturers only began installation of airbags in the mid-1970s. European airbag installation began in 1981. The US Federal Motor Vehicle Safety Standard 208 was amended in 1984, requiring that all vehicles made after 1989 have passive restraints. Further revisions in 1998 made dual front seat airbags mandatory. Despite the beneficial effect, numerous injuries have resulted from airbag deployment, including burns, abrasions, and lacerations[20,21].

Pathogenesis

Airbag activation consists of detection, inflation, and deflation phases. The sudden deceleration caused by impact triggers sensors in the front bumper to fire a sodium azide canister inside the nylon rubber bag. The sodium azide ignites with an explosive release of hot nitrogen gas which inflates the bag in about 10 milliseconds at speeds exceeding 160 km/h. The hot nitrogen gas and other by-products are then vented out the upper sides of the bag away from the occupant, thus deflating the bag. Vented aerosol contains nitrogen, carbon mono- and dioxides, sodium hydroxide, ammonia, nitric oxide, metallic oxides and other trace gases, creating a corrosive environment. Friction and pressure from the bag, heat from the bag and gases, and contact with the corrosive aerosol may produce injury[20–22].

Clinical features

The cutaneous injuries produced by airbag deployment are summarized in Table 88.6. Chemical burns occur rarely, but appear to be a result of skin exposure to small amounts of the corrosive alkaline aerosol. The aerosolized particles need to dissolve in a water layer such as tears or sweat before creating a corrosive injury. Of note, alkali burns of the skin may continue to deepen and extend over time, unless all the corrosive chemical is washed away[20–22].

Differential diagnosis

The pattern of injury and history of airbag deployment makes the diagnosis obvious. However, it is important to determine whether a burn injury is purely thermal or if it has a chemical component. Assessment of tissue pH and monitoring for continued extension of the burn help determine whether an alkali injury exists.

Treatment

Prevention is, of course, the most effective approach. Newer airbag designs include repositioning the exhaust vents in order to direct the escape of hot gases away from areas of potential skin contact. Seats should be positioned as far back from the airbag module as possible. Children too small to benefit from the adult three-point restraint should not be in the front passenger area. Children in any type of car seat or booster should never be put in the front seat. When a thermal or frictional injury occurs, local wound care and protection from secondary infection usually suffice.

Alkali burns require copious irrigation to dilute the corrosive substance. Acidic neutralization is contraindicated because of possible extension of injury by the resulting exothermic reaction. When the tissue pH is normal, local wound care is adequate.

AIRBAG INJURIES TO SKIN		
Type	**Frequency**	**Clinical features**
Abrasions/ friction burns	65%	Patches of erythema or ecchymosis, typically with superficial erosion
Contusion	40%	Ecchymosis
Lacerations	20%	Variable severity
Thermal burns	8%	First- and second-degree most common (see Table 88.3)
		Localized full-thickness burn may result from metallic accessories or melted clothing
		Face and forearms, followed by hands and chest
Chemical burns	?	Painful, superficial, violaceous erythema and edema
		Partial- to full-thickness, often in splash pattern
Irritant dermatitis	?	Erythema and edema of upper chest, arms, and face
		Burning or stinging sensation
		Desquamation and postinflammatory hyperpigmentation common

Table 88.6 Airbag injuries to skin[20–22].

INJURY DUE TO COLD EXPOSURE

Frostbite

Synonym: ■ First-degree frostbite – frost-nip

Key features

- Frostbite can occur when the skin temperature drops below about −2°C (28°F)
- Erythema, edema, and numbness are followed by marked hyperemia and pain
- Tissue freezing, vasoconstriction, and inflammatory mediator release are central to the pathophysiology of frostbite
- Rapid rewarming in a warm water bath is the cornerstone of therapy

Introduction

Exposure to cold environments, whether during occupational or recreational activities, poses a risk of cold-related injury. Prolonged exposure may lead to hypothermia, frost-nip, or frostbite. Hypothermia, i.e. a decline in core temperature below 35°C (95°F), is a systemic process with minor cutaneous features and therefore will not be discussed in detail.

History

Cold injury predates recorded history – the quest for clothing, shelter, and fire as protection from the elements must have preoccupied prehistoric humans. Mass casualties from cold injury have historically been seen most often in military conflicts. However, as interest in outdoor activities and the number of homeless individuals have risen, there has been increased exposure to cold among the general population[23–25].

Epidemiology

Environmental risk factors for the development of frostbite include prolonged duration of exposure, higher wind chill, and immersion. A history of psychiatric illness, alcohol and illicit drug use, or smoking are additional risk factors as are previous cold injury, peripheral arterial disease, and dehydration[23,25].

Pathogenesis

The underlying pathophysiology of frostbite is a combination of freezing, vascular insufficiency (constriction and occlusion), and damage due to

FOUR STAGES OF FROSTBITE		
Phase	**Physiologic events**	**Clinical findings**
I (cooling)	• Cyclic vasoconstriction and vasodilation • Extracellular ice formation (–2°C, 28°F) • Intracellular ice crystal formation (if rapid freeze of >10°C or 18°F/min) • Intravascular ice formation leads to erythrocyte sludging and vessel occlusion	Cool extremity Blanched appearance Numbness Hard, woody texture
II (thawing and rewarming)	• Ice melts • Dehydrated cells start to swell • Loss of integrity of vessel walls, creating edema • Vascular tone is compromised, leading to vasodilation • Inflammatory mediator release leads to aggregation of platelets and leukocytes, causing thrombosis	Erythematous to violaceous color Intense pain Blisters form
III (extension of injury)	• Thromboxane A2 levels increase • Platelet and leukocyte aggregation extends into bordering tissue, creating vascular compromise	Blisters rupture
IV (resolution)	• Tissue either re-epithelializes or desiccates and mummifies • Vasomotor instability may persist indefinitely	Healing or amputation

Table 88.7 Four stages of frostbite[23,24].



Fig. 88.6 Frostbite. **A** Erythema, edema, and hemorrhage are seen on the fingertips in first-degree frostbite. **B** Bullae filled with clear fluid on the distal plantar surfaces in second-degree frostbite. *B, Courtesy Timothy Givens, MD.*

inflammatory mediators. As extremities cool, the "hunting response of Lewis" (alternating vasoconstriction and vasodilation) occurs, ending with vasoconstriction. This tends to conserve the core temperature at the expense of the extremity, which shifts toward ambient temperature. The head does not exhibit a vasoconstrictor response, except for the nose and ears. The trunk surface may cool slightly, but the core temperature is maintained. Frostbite is therefore unusual on the trunk or head (except the nose and ears), unless there is direct contact with ice or a refrigerant. The pathophysiologic stages of frostbite are summarized in Table 88.7, along with key clinical features[23,24].

Clinical features

Frostbite has been divided into four categories of severity, analogous to burn injuries. These are only recognizable upon rewarming. *Frostnip* (first-degree frostbite) presents with erythema, edema, cutaneous anesthesia, and transient pain (Fig. 88.6A). Full recovery is expected, with only mild desquamation. *Second-degree frostbite* is characterized by marked hyperemia, edema and blistering, with clear fluid in the bullae (Fig. 88.6B). Healing occurs, but many patients have long-term sensory neuropathy, often with significant cold sensitivity.

Third-degree frostbite consists of full-thickness dermal loss, with hemorrhagic bulla formation or development of waxy, dry, mummified skin. The latter features are poor prognostic indicators for tissue loss. In *fourth-degree frostbite*, there is full-thickness necrosis leading to skin, muscle, tendon, and bone damage and tissue loss. Injuries of this severity lead to amputation[23,24]. Some authors advocate a simpler classification consisting of superficial or deep injury, citing better prognostic accuracy.

Pathology

Superficial dermal edema and subepidermal bulla formation are typical findings in early frostbite. Vascular permeability leads to hemorrhage that is most pronounced in deep injury. The epidermis and involved dermis become necrotic, with an inflammatory infiltrate and granulation tissue at the junction with normal tissue[8].

Differential diagnosis

Frostbite injuries should be readily recognizable, given an exposure history and typical presentation. A greater diagnostic challenge is determining the depth of the injury (see above). One possible diagnosis in the differential is cold water immersion foot (see Table 88.9).

Treatment

Fundamental therapeutic goals in frostbite are rapid rewarming, prevention of further cold exposure, and restoration of circulation. Once the patient is in a setting in which re-freezing cannot occur, rapid water bath rewarming is indicated. The water bath temperature should be about 37–39°C (99–102°F), ideally a whirlpool is utilized so a steady temperature can be maintained. This process of rewarming may be painful, so appropriate analgesia should be provided. Rubbing the frozen extremity with ice, using dry heat, and slow rewarming are all contraindicated. In the hypothermic patient with frostbite injury, it is important to complete fluid resuscitation and core rewarming before limb rewarming, to prevent sudden hypotension and shock. Accurate clinical assessment of the degree of injury, routine wound care, protective dressings, monitoring for infection, and consideration of tetanus prophylaxis should then follow. Radiologic evaluation (e.g. MRI, bone scan, plain films) may help determine extent of injury and prognosis. Nowadays, angiography and triple-phase bone scans are considered the standard of care for assessing tissue viability and guiding care during the initial days following injury[23].

Additional therapeutic suggestions have been based on animal studies, case reports, or small series. Because of increased blood viscosity and sludging, thrombolytic therapy (e.g. heparin, tissue plasminogen activator, streptokinase) ± a vasodilator (e.g. iloprost, limaprost) has been suggested. Superficial non-hemorrhagic bullae may be aspirated or debrided to avoid prolonged exposure to prostaglandins and thromboxanes within blister fluid. Aloe vera, a thromboxane inhibitor, has been shown to be useful as a topical agent in superficial frostbite. The problem of vasoconstriction has been addressed by sympathectomy, with the most impressive effect being prevention of re-injury with repeat exposure to cold conditions. Pentoxifylline has been found to be useful, as have anti-inflammatory agents such as methylprednisolone, methimazole, and aspirin. Hyperbaric oxygen therapy reduces edema in post-ischemic tissues, but its delivery requires adequate blood flow. Increased viscosity and thrombosis in sites of frostbite injury may explain the variable results with this therapy[23,24,26].

Pernio

Synonyms: ■ Chilblains ■ Perniosis

Key features

- Cold-sensitive inflammatory disorder in which erythrocyanotic discoloration of acral skin is accompanied by a sensation of itching, burning, or pain
- Common trigger is exposure to cold, wet, non-freezing conditions
- Must be distinguished from chilblain lupus and cold-sensitive blood dyscrasias
- Nifedipine can be used to treat moderate to severe pernio

Introduction

Pernio is an abnormal inflammatory response to cold, damp, non-freezing conditions[27]. It is most common in areas without central heating.

History

Over a hundred years ago, pernio/chilblains was apparently common enough in Europe and the UK that the condition was well recognized. In 1881, Piffard[28] described it quite well:

"This affection, so common in cold climates, affects, by preference, the face, hands, nose, and ears. It is characterized by redness, usually with a purplish tinge, together with more or less pain of a burning character giving little or no trouble during the summer, but causing inconvenience and suffering as cold weather sets in."

Epidemiology

Exposure to cold, wet conditions is the major risk factor for pernio. This disorder has been reported most frequently in the UK and northwestern Europe, particularly in those whose homes lack central heating. It also occurs more often in individuals whose work and leisure activities are outdoors. Young women, children, and the elderly are most commonly affected, as well as those with a lower body mass index. Elderly patients may have a prolonged course, while younger patients improve spontaneously[29–31].

Pathogenesis

Pernio can be either primary (idiopathic) or secondary, i.e. due to an underlying condition. The precise pathogenesis of idiopathic pernio is unknown, but it is thought to represent an abnormal inflammatory response to vascular ischemia caused by prolonged vasoconstriction in the setting of extended exposure to cold, damp environments[27]. In children and adults, it may be associated with cryoglobulins or cold agglutinins[31,32].

Clinical features

Pernio presents with single or multiple, erythematous to blue–violet macules, papules or nodules (Fig. 88.7A–C). In severe cases, blistering and ulceration may be seen (Fig. 88.7D). Lesions are often symmetrically distributed on the distal toes and fingers, and less often on the heels, nose, and ears. Overlying scale can also develop (see Fig. 88.7B). Deep pernio may be seen on the thighs, calves, and buttocks as blue–erythrocyanotic plaques. Patients describe itching, burning or pain. Onset is often within 24 hours of exposure to cold, and lesions typically resolve within 1 to 3 weeks. Elderly patients with venous insufficiency are the exception, as lesions can become chronic[30,31].



Fig. 88.7 Pernio (chilblains) – clinical and histologic features. A Distal erythema of multiple toes with some edema in a symmetric pattern. **B** Violaceous patches and thin plaques, primarily on the toes; note the associated scaling on the hallux. **C** Erythematous papules and plaques of the distal fingers with scaling and an erosion. **D** Recurrent, more severe disease with thin violaceous papules and plaques, hemorrhage, desquamation, scarring, and postinflammatory dyspigmentation. **E** A dense perivascular and peri-eccrine lymphocytic infiltrate. Detail of predominantly lymphocytic perivascular infiltrate without atypical features (inset). Note the thickened stratum corneum characteristic of an acral site. *A,C,D, Courtesy Kalman Watsky, MD; B, Courtesy Jean L. Bolognia, MD; E, Courtesy Lorenzo Cerroni, MD.*

Pathology

There are variable degrees of dermal edema plus a superficial and deep lymphohistiocytic infiltrate with peri-eccrine accentuation (Fig. 88.7E). The infiltrate is composed predominantly of T lymphocytes. Necrotic keratinocytes and lymphocytic vasculitis have been noted[30].

Differential diagnosis

Idiopathic pernio needs to be distinguished from several other cold-induced syndromes (Table 88.8)[29–32]. In addition to clinical features, e.g. retiform purpura, these entities can be further assessed by laboratory evaluation including: (1) complete blood count to exclude hemolytic anemia, myelogenous leukemia, or myelodysplastic syndrome; (2) cryoglobulin, cold agglutinin, and cryofibrinogen levels to eliminate cold-sensitive dysproteinemia; and (3) serum protein electrophoresis and immunofixation electrophoresis to exclude a monoclonal gammopathy.

Chilblain lupus (Hutchinson), whose clinical features are similar to pernio, may also be indistinguishable from pernio histologically.

DIFFERENTIAL DIAGNOSIS OF SKIN LESIONS INDUCED BY NON-FREEZING COLD EXPOSURE

Disorder	Features	Possible associated conditions	Chapter reference
Acrocyanosis	Red to purple discoloration Hands and feet Painless	Erythromelalgia	106
		Cryoproteins	23
		Anorexia nervosa	51
Pernio	Erythrocyanotic Symmetric distribution Painful	Secondary pernio: AI-CTD Interferonopathies (Table 45.7). Cold agglutinins* Cryoglobulins Hematologic disorders (e.g. acute myelogenous leukemia, myelodysplastic syndrome, paraproteinemia) Possibly SARS-CoV-2 infection	88, 45
Raynaud phenomenon	Clearly demarcated pallor, followed by blue then red discoloration Idiopathic form usually does not ulcerate	AI-CTD Blood dyscrasias Drugs Trauma	43 (Tables 43.4 & 43.5)
Livedo reticularis	Bluish, broad reticulated patches May be idiopathic	Peripheral arterial disease AI-CTD Hematologic disorders Vasculopathies & thrombophilia (e.g. antiphospholipid syndrome) Infections Medications	105, 106 (Tables 105.9 & 106.1)
Cold panniculitis	Erythematous indurated plaques, most often on cheeks Children more commonly affected Upper lateral thighs in equestrians† Can resolve in 2 weeks		100
Cold urticaria	Cold-induced wheals May be idiopathic	Cryoproteins (see below) Infections Familial cold autoinflammatory syndrome	18
Chilblain lupus	Cold-induced acral lesions Histologic features may be indistinguishable from pernio, but features of interface dermatitis are usually more marked Coexistent lupus erythematosus		41
"Pulling boat hands"	Rowing in cold, wet conditions Papules to vesicles Itching, burning, tenderness		
Retiform purpura due to cryoproteins‡	Favors acral sites		23
Cryoglobulins	Cold *serum* protein precipitate	Plasma cell dyscrasias Lymphoproliferative disorders	
Cryofibrinogen¶	Cold *plasma* protein precipitate	AI-CTD Infections Malignancies	
Cold agglutinins¶	RBCs agglutinate in cold Occasional RBC lysis in cold	Infections (e.g. with *Mycoplasma*, EBV, CMV) Lymphoproliferative disorders	
Cold hemolysins¶	RBC lysis in cold Paroxysmal hemoglobinuria	Infections (e.g. viral, syphilis)	

*Clinical significance oftentimes unclear.
†Because inflammation is primarily in the dermis, use of the term panniculitis has been challenged.
‡Acrocyanosis, Raynaud phenomenon, livedo reticularis, and cold urticaria can also be observed in association with cryoproteins.
¶Rarely cause cold-related occlusion syndromes.

Table 88.8 Differential diagnosis of skin lesions induced by non-freezing cold exposure[29,30,33]. AI-CTD, autoimmune connective tissue disease; CMV, cytomegalovirus; EBV, Epstein–Barr virus; RBC, red blood cell.

However, features of interface dermatitis are usually more marked in chilblain lupus and patients have serologic evidence of autoimmunity (e.g. positive antinuclear antibody screen). Patients with type I interferonopathies, such as Aicardi–Goutières syndrome/familial chilblain lupus and proteosome-associated autoinflammatory syndrome/CANDLE syndrome, also develop pernio-like lesions (see Table 45.7). Symmetric lividity of the palms and soles (pressure points) can involve the distal fingers and toes but is due to occlusive footwear, usually in association with hyperhidrosis. Diagnosis of the lupus pernio form of sarcoidosis, which favors the nose, is confirmed by the presence of the histologic features of sarcoidosis[29,33].

During the SARS-CoV-2 pandemic, an increased incidence of pernio has been reported ("COVID toes"), most often in children and teenagers. The vast majority of patients have been SARS-CoV-2 PCR-negative and did not develop anti-SARS-CoV-2 antibodies. As a result, there is an ongoing debate as to the relationship of pernio to SARS-CoV-2 infection. Nonetheless, patients with pernio should be questioned regarding symptoms of SARS-CoV-2 infection and possible contacts[34,35]. In general, those individuals who were infected had a mild clinical course.

Treatment

Adequate clothing and avoidance of cold, damp conditions are important preventive measures, as are keeping feet dry and avoidance of smoking. In a double-blind, placebo-controlled trial, nifedipine (20 to 60 mg daily) was found to be efficacious for the treatment of pernio. None of the nifedipine-treated patients relapsed, while all of the placebo-treated patients developed new lesions[36]. It is effective in about 70% of patients with pernio. Medium- to high-potency topical corticosteroids are often prescribed, but supportive evidence is lacking. Other anecdotal remedies include topical 0.2% nitroglycerin, topical minoxidil, oral nicotinamide, pentoxifylline, phenoxybenzamine, sympathectomy, and erythemogenic UVB phototherapy[29].

INJURY DUE TO WATER EXPOSURE

Immersion Foot

Synonyms: ■ Trench foot ■ Tropical jungle foot ■ Shelter foot ■ Paddy-field foot ■ Swamp foot ■ Jungle rot ■ Foxhole foot ■ Peripheral vasoneuropathy ■ Nonfreezing cold injury

Key features

- Injury occurs after continuous exposure of feet to moist, occluded conditions
- Cold water, warm water, and tropical variants exist
- The underlying pathologic process is overhydration of the stratum corneum
- Nonfreezing cold injury can lead to peripheral vasoneuropathy
- Neuropathy may persist indefinitely
- Feet exposed to immersion injury are more sensitive to re-injury

Introduction

Immersion injury occurs in either cold or warm environments when the feet are exposed to continuous moisture with no opportunity for intermittent drying. Severe injury may produce permanent peripheral neuropathy and long-term morbidity.

History

Soldiers on the Western Front in World War I spent extended periods of time in the cold, wet, muddy conditions of trench warfare, leading to the death of ~75 000 British soldiers and the term *trench foot*. *Immersion foot* emerged during World War II, with shipwrecked troops spending days in partially submerged lifeboats. The Korean conflict and the Vietnam War led to more variations and tremendous numbers of casualties. Immersion foot also occurs outside armed conflicts, including in persons experiencing homelessness, fishermen, skiers, and revelers at music festivals[37–39].

Epidemiology

Susceptibility to immersion foot is widely variable. Use of sandals or open shoes, constant activity, thinner plantar stratum corneum, and intermittent air drying seem somewhat protective. Risk factors for immersion foot include: prolonged occupational or recreational exposure to wet conditions, constrictive clothing, immobility or prolonged dependency of feet, dehydration, poor nutritional status, altered mental status, smoking, peripheral vascular disease, uncontrolled diabetes, tinea pedis, trauma, and experiencing homelessness[37,39].

Pathogenesis

The underlying pathophysiology of all forms of immersion foot is overhydration of the stratum corneum. The permeability coefficient of plantar skin is ~10 times that of the dorsal foot skin, leading to increased water absorption. The plantar stratum corneum can absorb ~200% of its dry weight in water, with a proportionately higher absorption of fresh water than saline.

Warm water immersion foot (WWIF) results from severe hyperhydration of the stratum corneum, with subsequent maceration. Plantar skin temperature reaches body core temperature after about an hour in an impervious boot with 19°C (66°F) water. As the injury continues, inflammatory changes develop and may progress to a lymphocytic vasculitis with vascular compromise and erythrocyte extravasation (*tropical immersion foot* [TIF]). Eventual involvement of the dorsal foot skin develops with striking inflammation. Secondary infection may develop in the compromised tissue after 3–4 days, further complicating management and worsening morbidity[24,40].

Cold water immersion foot (CWIF), also referred to as nonfreezing cold injury, is more severe due to the addition of cold-induced vasospasm. Because water conducts heat 23 times faster than air, the cold water immersion invokes "thermo-protective" peripheral vasoconstriction. This creates hypoxic injury to nerves (initially large myelinated axons, but eventually all types) and muscle, with later injury to subcutaneous fat and blood vessels. With reperfusion, there can be additional injury superimposed on ischemic tissue damage[38,41].

Clinical features

The clinical syndromes of immersion foot are divided into the three variants previously discussed: WWIF, TIF, and CWIF (Table 88.9)[24,37]. Although TIF is sometimes viewed simply as a prolonged and more severe variant of WWIF, it is discussed separately because prolonged warm water exposure leads to different clinical features.

Pathology

All forms of immersion foot demonstrate edema, thickening, and fragmentation of the stratum corneum. Variable superficial dermal edema is noted. In more severe forms (TIF, CWIF), superficial dermal capillaries are narrowed due to edema or even frank lymphocytic vasculitis. Immunohistochemical staining for nerve fibers was shown to be reduced, perhaps playing a role in the vasoneuropathy[41]. CWIF leads to damage of much deeper blood vessels (narrowing and fibrosis), muscle, nerves, and bone.

Differential diagnosis

The differential diagnosis of immersion foot includes dermatophyte infection, cellulitis, contact dermatitis, pitted keratolysis, Gram-negative or complex toe web infections, erythrasma, and (occasionally in diabetics) candidiasis. The latter three conditions are usually predominantly within the toe web spaces, and dermatophytosis is usually more patchy, with fine scale and no significant maceration outside the web spaces. Pitted keratolysis can be distinguished by history and by the presence of punched-out tiny pits in the plantar surface of the forefoot and heel. Cellulitis is not limited at the immersion water mark, and it can progress proximally. Maceration due to occlusive footwear, usually in association with hyperhidrosis, is seen in symmetric lividity of the palms and soles.

Treatment

Prevention is the best treatment. Once the condition develops, thorough and rapid drying is essential to restore function. CWIF patients must remain some distance from a heat source because the neuropathic insensitivity poses further risk of inadvertent thermal injury. WWIF can be prevented by frequent drying breaks and the use of silicone grease.

IMMERSION FOOT: WARM WATER, TROPICAL, AND COLD WATER VARIANTS					
Variant	**Exposure temperature**	**Exposure time**	**Clinical features**	**Complications**	**Duration**
Warm water	15.5–32°C (60–90°F)	1–3 days	Thickening, softening, and exaggerated wrinkling of soles (thicker soles worse) Ambulation painful ("walking on rope")		3 days
Tropical	21–32°C (70–90°F)	3–7 days	Prolonged warm water exposure In addition to plantar hyperhydration, dorsal foot becomes inflamed and edematous Pruritus, erythema, and scattered vesicles Later purpura, brawny edema, maceration, and scaling Fever, lymphadenopathy		>5 days
Cold water	15.5–21°C (60–70°F)	>7 days	Feet cold, heavy, stiff, and numb May appear swollen Waxy white to mildly cyanotic	Infection Muscle atrophy Chronic venous stasis Joint contractures Trophic ulcers Myonecrosis Permanent axonal damage Bony changes such as hammer toe	
			Three phases after rewarming: 1. Pre-hyperemic – feet cold, edematous and numb, with stocking anesthesia; purpura, blisters, and necrosis possible; pulses not palpable 2. Hyperemic – return of vascular and nerve function; tingling, pain, and throbbing; increasing erythema and edema; skin anhidrotic, hot, and painful to touch; ambulation difficult; vasomotor instability; dependent rubor, pallor upon elevation; bullae, intermittent cyanosis; infection risk high 3. Post-hyperemic – cold sensitivity with digital blanching, intermittent edema, hyperhidrosis, persistent peripheral neuropathy		Hours to days
					Up to 10 weeks
					Years

Table 88.9 Immersion foot: warm water, tropical, and cold water variants[24,37,38].

The silicone has minimal value in TIF and is of no use in CWIF[38,40]. Although evidence is lacking, possible treatment options include vasodilators (e.g. iloprost, papaverine), nicotine tartrate, sympathectomy, and medications that address neuropathic pain (e.g. gabapentin, amitriptyline, pregabalin). Co-existing tinea pedis and cellulitis should be treated[38].

INJURY DUE TO ELECTRICITY

Electrical Burns

Key features

- The extent of an electrical burn injury may be much worse than the cutaneous contact burns suggest
- Contact point burns may be partial- to full-thickness
- Neurovascular, muscular, and skeletal tissue may be damaged
- Lightning strikes can result in an erythematous, transient fern-like pattern on the skin

Introduction

Although electricity and lightning claim hundreds of lives each year, many more non-fatal injuries occur. The majority of electrical burns are work-related, particularly among electricians, linesmen, and construction workers. Children are also a major risk group, with low-voltage (<1000 V) injury more common under 6 years of age and high-voltage injury in older children and adolescents. A survey of 700 electrical injury admissions to Parkland Memorial Hospital over a 20-year period showed electric arc (flash burn, no current) injury to be the most common (40%), followed by high voltage (38%), low voltage (20%), and lightning strikes (2%). Mortality was highest with lightning strikes[42].

Lightning is the second leading cause of weather-induced death in most of the world, with the incidence peaking during the summer months. Most lightning strike victims are men (usually between 15 and 45 years of age) involved in outdoor activities[42,43]. Worldwide, lightning strikes lead to an estimated 0.2–1.7 deaths/1 million people/year. Death occurs in 10%–30% of lightning strike victims and about three-quarters of survivors will have permanent sequelae[43].

Pathogenesis

The severity of an electrical injury depends upon the strength and frequency of the electrical field, the duration of exposure, path of current, and relative resistance of the tissue. Acute tissue damage by strong (high-voltage) low-frequency fields is due to holes punched in cell membranes (electroporation), Joule heating of the extracellular fluid, and cell membrane protein denaturation through electroconformational coupling. The thermal effects (i.e. Joule and dielectric) depend upon tissue resistance to the flow of current. For example, bone has the most resistance of any body tissue and therefore generates the most heat. The order of resistance then decreases through fat, tendon, skin, muscle, blood vessels, and, finally, nerves (least resistance). An additional indirect effect is field-generated formation of free radicals with subsequent lipid peroxidation and membrane disruption[44,45].

Lightning injury follows similar electrothermal principles, but with three important differences: (1) current and voltage are massive, e.g. 30 000 to 50 000 amperes (A), and a difference between clouds and object of 2 million V/m; (2) the superheating of air through which the current passes to 30 000°K, creating a high-pressure thermoacoustic shock wave (thunder) that may generate 100 atm of air pressure locally; and (3) the creation of internal conduction loops as the large magnetic field passes through the body. Injury can occur from a radial spread of current after lightning strikes the ground, from a direct hit, from flashover (current around body), or from blast effect[43].

Clinical features

Electrical burns usually range from partial- to full-thickness, and high-tension burns often involve deep tissue, with the current damaging muscle, nerves, and vessels. Erythema, edema, and blisters (partial-thickness damage) may result from a current of 20 to 35 mA/mm^2 with an exposure time of 20 seconds (heats skin to 50°C). At a higher current of 75 mA/mm^2 with the same exposure time, the temperature could rise to 90°C, causing skin perforation and charring.

Identification of so-called "entrance" and "exit" wounds is of no value, since 60 Hz alternating current (AC) has current changing directions 120 times per second. More important is determination of the extent of skin and internal injury. In some cases, current may arc between body parts, creating "kissing" wounds. High-voltage injuries may result in electroplating of skin with black metallic debris that leaves charred craters when removed. Additional thermal injury may occur when clothing or nearby items are ignited by an electrical arc[43,45].

Deep tissue injury can be considerably more severe than the cutaneous wounds might suggest. Muscle injury may be deceptively deep, since bone (with higher electrical resistance) retains heat more readily than other tissues. Edema in deep burns may result in compartment syndromes. Additional complications include cardiac

arrhythmias, which may become chronic and recurrent; myoglobinuria due to muscle injury; and solid organ injuries such as bowel perforation. Patients can also develop cataracts as well as cognitive and neuropsychologic impairment[43–46].

Lightning burns generally are more superficial due to the very brief contact. A unique pattern of skin lesions after a lightning strike is the "lightning print", "feathering", or Lichtenberg figures. These markings are transient, erythematous, linear fern-like patterns that resolve in hours to days. While not a true burn, they are pathognomonic of lightning strike injury. Other cutaneous changes may include patchy mottling, erythema, blistering, full-thickness punctate skin loss, flash burns, thermal burns from ignited clothing, and contact burns from grounding. Although internal burn injuries are uncommon in lightning strikes because of the very brief duration, the internal electrical currents that are created are strong enough to cause cardiac arrest or seizures. Additional sequelae include profound neuromuscular shutdown (keraunoparalysis), confusion, temporary amnesia, deafness and blindness, and prolonged or permanent neurologic disturbances such as peripheral sensory neuropathy[43,45].

Pathology

Electrical burns are characterized by epidermal necrosis, with cytoplasmic strands extending into the cavity between damaged and normal skin. Keratinocytes may be elongated vertically, and collagen appears homogenized. Severe electrical burns destroy the entire skin, including the subcutis, often with accompanying necrosis of deeper blood vessel walls. The Lichtenberg figures after lightning injury usually display no pathological changes or variable degrees of hemorrhage[8].

Treatment

Electrical injuries are very complex, often involving multiple organ systems, since any organ in the path of current can be damaged, and initial assessment may underestimate the extent of injury. Although full management of electrical burns should be carried out in level one trauma centers, initial management includes isolation of the patient from the power source, assessment of vital signs, cervical spine immobilization, determination of contact points on the skin, and, if possible, venous access. For more details, see the section above on thermal burns.

One special circumstance should be noted. Toddlers who sustain oral commissure burns from biting into electrical cords are at risk for delayed bleeding. About 10–14 days after the burn, the eschar comes off, often exposing a damaged labial artery. Direct pressure will control the bleeding, pending definitive care[43–45].

Chemical Burns and Exposures

These entities are discussed in several chapters, including those on irritant contact dermatitis (Ch. 15), occupational dermatoses (Ch. 16), plant dermatoses (Ch. 17), and child abuse (Ch. 90).

INJURY DUE TO CHEMICAL EXPOSURE

Chemical Hair Discoloration

Synonym: ■ Green hair – chlorotrichosis

Key features

- Hair discoloration may be an intentional cosmetic change or the result of a chemical or metal exposure
- Green hair may result from exposure to copper or selenium
- Most hair discoloration normalizes spontaneously over time

Introduction

Decorative hair coloring has risen to new heights with the flamboyant artistry of the past several decades. Brilliant pink, green, purple, blue and orange and myriad styles, from a buzz cut to dramatic multicolored spikes, adorn many of today's youths. Much of this is deliberate decoration, but hair discoloration at any age may be inadvertent and sometimes unwanted.

History

Green hair among copper workers was noted as early as 1654. More recently, such discoloration has been attributed to swimming pools[47].

Epidemiology

Most patients with unwanted hair discoloration have blond or white hair, although brunette and black hair may become discolored as well. Risk factors include exposure to the substances in Table 88.10[47–50], in addition to frequent contact with chlorinated water (especially swimmers), use of an alkaline shampoo, coloring or peroxide bleaching of hair, and mechanical or sun-induced hair damage[47–50].

Pathogenesis

When due to exposure to copper-containing water in swimming pools or domestic supplies, green hair discoloration results from binding of the copper to proteins within the hair shaft[49]. Damage to the hair cuticle from bleaching, permanent wave treatments, frequent water exposure, and sunlight allows the copper to penetrate the hair more readily. The copper content of discolored green hair (or golden hair in Asian patients) is considerably higher than in non-discolored hair in the same individual. Of note, increased systemic copper (e.g. Wilson disease) is not associated with green hair color[47–50].

Nanko et al.[48] speculated that the golden color of Japanese swimmers' hair was due to water friction injury of the cuticle, allowing hypochlorous acid from the chlorination process to invade the cortex and degrade melanosomes. Copper appeared to play a role as well, but the mechanism was unclear.

Clinical features

The presenting concern is a progressive yellow to green discoloration of the hair. Scalp hair is the only hair involved, and the surface hair is more noticeably discolored than underlying hair.

Pathology

By electron microscopy, loss of the hair cuticle and wearing of the cortex layers were seen in discolored, golden hairs in Japanese swimmers (see above)[48]. In addition, there was a reduced number and density of melanosomes in the discolored hair relative to controls. X-ray spectrography demonstrated an increased chlorine content in both the discolored and normal hair of swimmers relative to controls, and a reduced sulfur content in only the discolored hairs. Atomic absorption spectroscopy can be used to detect copper within hair shafts as can staining with rhodanine[49].

Differential diagnosis

Hair discoloration is readily visible. The specific etiology and subsequent therapy needed may be determined by ascertaining the type of exposure that led to the color change (see Table 88.10). For example, copper from cosmetic plant extracts and metallic eyeglass frames can produce green hair.

Treatment

Discontinuation of the offending exposure and avoidance of risk factors is recommended. Penicillamine- and EDTA-containing shampoos can

CAUSES OF UNINTENTIONAL HAIR DISCOLORATION		
Green	**Yellow to orange to golden**	**Purple**
• Copper* • Selenium sulfide • Tar shampoo • Cobalt • Chromium • Nickel • Yellow mercuric oxide • Phenylketonuria†	• Tar shampoo • Anthralin • Minoxidil • Copper*	• Alkalinized anthralin
*Includes exposure to copper sulfate used as an algaecide in swimming pools as well as water from copper pipes, in particular if the plumbing has not been used for prolonged periods. †Speculative.		

Table 88.10 Causes of unintentional hair discoloration[47–50].

be used to chelate copper molecules, followed by rinsing to remove complexes. Numerous anecdotal remedies have been described, including hot vegetable oil, hydrogen peroxide, alkaline shampoos, lemon juice, commercial hair decolorizers, and hydroxyethyl diphosphonic acid[47,50].

Arsenical, Elemental and Heavy Metal Dermatoses

Key features

- Chronic arsenic exposure may occur via contaminated drinking water or occupational exposure
- Chronic arsenicism is characterized by mottled hyperpigmentation with areas of hypopigmentation, keratoses on the palms and soles (and other sites), and multiple non-melanoma skin cancers, particularly Bowen disease
- Histologically, arsenical neoplasia is almost identical to actinic neoplasia

Introduction

Arsenic is a ubiquitous metalloid, ranking 20th in abundance among all the elements. Exposure occurs via drinking water, agricultural uses, ore mining, and medicinal applications. Chronic exposure poses significant health risks, including development of benign and malignant tumors (Table 88.11)[51,52,55,56]. Additional toxic elements and heavy metals, along with their cutaneous impact, are outlined in Table 88.12[51,52,55–69]. Allergic contact dermatitis due to metals is covered in Chapter 14.

History

Medicinal effects of arsenic have been known since the days of Hippocrates and Galen. Early applications of arsenic included the treatment of inflammatory dermatoses (e.g. psoriasis, eczema, lupus, urticaria), infections (e.g. furuncles, syphilis, leprosy, warts, molluscum contagiosum), epitheliomas, and lichen rubor[28]. Even in the late 1800s, cutaneous side effects of arsenic exposure were noted, including pruritus, papulosquamous eruptions, and palmoplantar keratoses.

Chemical forms of therapeutic arsenic include Fowler's solution (liquor potassii arsenitis), arsenici bromidum, arsenici iodidum, Salvarsan (arsphenamine), Pearson's solution (liquor sodii arseniatis), arsenicum hydrogenisatum, Donovan's solution (liquor arseni et hydrargyri iodidi), and Asiatic pills (arsenic with opium or pepper)[28]. Apparently, Fowler's solution and Asiatic pills were the most widely used, with the latter still available in India and the Far East. Traditional Chinese medicine may continue to use inorganic arsenic. Most of the Western world has abandoned arsenicals, although treatment of asthma with Fowler's solution continued until the 1960s in parts of the US. Arsenic trioxide is now used therapeutically for acute promyelocytic leukemia[51,55].

Metallic arsenic has been consumed in large quantities by the arsenic eaters of the Swiss and Austrian Alps, believing that such consumption improved physical strength. Inorganic arsenic (the toxic form) is believed to have caused Napoleon's death during his second exile at St Helena[51].

Treatment of acute arsenic poisoning was developed during World War I to decrease the toxicity of the vesicant lewisite (2-chlorovinyldichloroarsine). British anti-Lewisite (BAL; dimercaprol) binds to the arsenic in lewisite[55].

Epidemiology

Accidental exposure to arsenic still occurs via contaminated drinking water in more than 30 countries, including India, Bangladesh, China, Taiwan, the Philippines, Thailand, Chile, Argentina, and western states in the US. Careless contamination of drinking water has resulted from mining of ores containing silver, gold, tin, copper, lead, tungsten, zinc, and cobalt. Arsenic is also present in foods and supplements such as seaweed, shellfish, tuna, and cod liver oil. Occupational exposure to arsenic occurs with pesticides, herbicides, and chromated copper arsenate-treated wood, as well as during electroplating, mining or smelting, wine making, and the manufacture of glass and gallium arsenide computer microchips[51,57].

The current World Health Organization provisional guideline value and the US Environmental Protection Agency limit of arsenic concentration in drinking water is 0.01 mg/L. In 2006, it was decreased from the previous limit of 0.05 mg/L, since cutaneous and internal cancers may develop with the latter level of exposure. However, no chronic skin changes have been noted with arsenic concentrations <0.017 mg/L in drinking water. It is estimated that globally more than 200 million people are exposed to arsenic levels in drinking water that are >0.01 mg/L[51,52,55–57].

An estimated cumulative dose of arsenic capable of producing arsenical keratoses or skin cancer is about 0.5 to 1 g. As noted previously, adverse effects have been noted when arsenic is in drinking water at a concentration as low as 0.05 mg/L. Despite this, a number

CLINICAL FEATURES OF ACUTE AND CHRONIC ARSENIC POISONING
Acute
Skin
• Flushing, erythema, facial edema, acrodynia, urticaria • Loss of hair and nails • Remaining nails show Mees' lines after 8 weeks
Gastrointestinal
• Nausea, vomiting, severe abdominal pain, profuse watery diarrhea, malabsorption
Neurologic
• Acute peripheral neuropathy • May progress to Guillain–Barré-like ascending paralysis
Other
• Pancytopenia, metallic breath odor, cardiac arrhythmias, renal failure, respiratory failure
Chronic
Skin

• Hyperpigmentation of axillae, groin, nipples, palms, soles and pressure points, with superimposed guttate hypopigmentation ("raindrops on a dusty road")
• Alopecia
• Arsenical keratoses – precancerous papules on palms and soles (Fig. 88.8)
  • Symmetric, yellow, punctate, corn-like papules measuring 2–10 mm
  • Favor thenar and hypothenar eminences, distal palms, lateral fingers, dorsal aspect of IP joints, weight-bearing plantar surfaces
  • Rarely on trunk, proximal extremities, eyelids, genitalia
  • May coalesce to plaques
• Blackfoot disease (vascular occlusive disease with blackening of skin)

Other
• Nasal septum perforation • Peripheral neuropathy • Bone marrow hypoplasia • Diarrhea • Hepatomegaly, hepatic fibrosis • Obstructive or restrictive lung disease • Diabetes mellitus
Malignancies

• Bowen disease
• Any skin surface
  • If no HPV, occurrence on sun-protected skin might suggest arsenic exposure
  • Skin-colored to erythematous papules and plaques that become keratotic
  • Scale-crust removal leaves red, moist, papillomatous base
  • Multiple lesions common
  • Invasive squamous cell carcinoma develops in 5%–20%
• Squamous cell carcinoma
  • Arising in arsenical keratosis or Bowen disease, has more aggressive behavior
  • Metastasis in one-third
• Basal cell carcinoma
  • Multiple, superficial, may resemble Bowen disease
• Extracutaneous malignancies
  • Genitourinary, especially bladder, prostate
  • Lung
  • Liver

Table 88.11 Clinical features of acute and chronic arsenic poisoning[51–54].
HPV, human papillomavirus; IP, interphalangeal.

MUCOCUTANEOUS FINDINGS ASSOCIATED WITH EXPOSURE TO TOXIC ELEMENTS AND HEAVY METALS					
Metal/ element	**Form**	**Cutaneous health hazards**	**Treatment and protection**	**IDLH***	**Cancer risk**
Aluminum	Alum, sulfates	Irritant contact dermatitis, vaccine hypersensitivity	Wash off	–	–
Antimony	Metal	Irritant contact dermatitis	Soap wash immediately	50 mg/m^3	–
Arsenic	Inorganic	See Table 88.11	Avoidance, chelation Soap and water wash immediately	Cancer: 5 mg/m^3	Lung, bladder, and skin cancer
	Arsine	Cold injury with arsine gas, including frostbite	See text	Cancer: 3 ppm	Lung cancer, lymphoma
Barium	Chloride, nitrate	Irritant contact dermatitis, burns	Water flush immediately	50 mg/m^3	–
Beryllium	Metal	Dermatitis, granulomas in skin, lung and liver	–	Cancer: 4 mg/m^3	Lung cancer
Bismuth	Telluride	Irritant contact dermatitis, black tongue	Soap wash immediately	–	–
Boron	Borates, oxide, tribromide, trifluoride	Erythema, irritant contact dermatitis, burns, anagen effluvium, loss of eyelashes	Soap wash, water flush promptly	25 ppm as trifluoride; 2000 mg/m^3 as oxide	–
Cesium	Hydrate, hydroxide	Irritant contact dermatitis, burns	Water flush immediately	–	–
Chromium	Hexavalent	Allergic and irritant contact dermatitis, skin ulceration, burns; systemic absorption can lead to renal failure, hepatic failure, anemia, coagulopathy	Water flush promptly	Cancer: 15 mg/m^3 as Cr VI	Lung, nasopharyngeal, liver, GU, and GI cancers Possibly skin cancer
Cobalt	Metal dust	Dermatitis, diffuse nodular fibrosis, cobalt-related asthma due to inhalation	Soap wash	20 mg/m^3	–
Copper	Metal dust	Dermatitis	Soap wash promptly	100 mg/m^3	–
Gold	Elemental salts	Most common: lichen planus, lichenoid drug eruption, allergic contact dermatitis, eczematous dermatitis, PR-like eruption, pruritus, flushing, erosive stomatitis Less common: chrysiasis, erythema nodosum, erythema multiforme, TEN, exfoliative dermatitis	Avoid gold-laden liquor	–	–
Indium	Metal	Irritant and allergic contact dermatitis	Soap wash	–	–
Iron	Salts	Irritant contact dermatitis, mucosal irritation	Soap wash	2500 mg/m^3 (iron oxide dust, fume)	–
Lead	Metal	Irritant contact dermatitis, gingival lead line	Soap wash promptly	100 mg/m^3	–
Lithium	Hydride	Irritant contact dermatitis, burns	Brush off gently, DO NOT WASH	0.5 mg/m^3	–
Magnesium	Carbonate	Irritant contact dermatitis	–	500 mg/m^3	–
Manganese	Cyclopentadienyl tricarbonyl	Irritant contact dermatitis	Soap wash	–	–
Mercury	Elemental, inorganic, organic	Acrodynia, tattoo reaction (cinnabar), granulomas, exanthem, slate-gray discoloration, allergic and irritant contact dermatitis, baboon syndrome, alopecia, stomatitis	Soap wash promptly Avoid mercury-laden cosmetics	10 mg/m^3 (elemental) 2 mg/m^3 (organic)	–
Nickel	Metal	Allergic contact dermatitis, systemic contact dermatitis	Water wash immediately	10 mg/m^3	Lung and nasal cancer
Osmium	Tetroxide	Irritant contact dermatitis	Soap wash immediately	1 mg/m^3	–
Platinum	Metal	Irritant contact dermatitis	Soap wash	4 mg/m^3	–
Polonium	^{210}Po radionuclide	Erythema, alopecia; ulceration in higher doses Triad of early emesis, hair loss, and bone marrow failure is characteristic of acute radiation sickness	Avoid ingestion; wash off	0.1–0.3 GBq (fatal in 3–4 weeks)	
Selenium	Elemental, alloy	Irritant contact dermatitis, conjunctivitis, skin burns, alopecia, Mees' lines	Soap wash immediately	1 mg/m^3	–
Silver	Metal, nanocrystalline	Argyria, irritant contact dermatitis, skin ulceration	Water flush	10 mg/m^3	–
Tantalum	Metal	Irritant contact dermatitis		2500 mg/m^3	
Tellurium		Dermatitis, garlic smell of sweat	Soap wash promptly	25 mg/m^3	–

Table 88.12 Mucocutaneous findings associated with exposure to toxic elements and heavy metals[51–69].

MUCOCUTANEOUS FINDINGS ASSOCIATED WITH EXPOSURE TO TOXIC ELEMENTS AND HEAVY METALS					
Metal/ element	**Form**	**Cutaneous health hazards**	**Treatment and protection**	**IDLH***	**Cancer risk**
Thallium	Soluble	Alopecia, acneiform papules, keratotic plaques on hands and feet, Mees' lines, hyperpigmentation Systemic absorption may lead to GI symptoms, followed by polyneuropathy	Water wash promptly Prussian blue, dialysis	15 mg/m^3	–
Tin	Metal, organic	Irritant contact dermatitis, skin burns, pruritus	Water flush immediately	100 mg/m^3 (metal) 25 mg/m^3 (organic)	–
Tungsten		Irritant contact dermatitis	Soap/water wash immediately	–	–
Uranium		Irritant contact dermatitis, skin burns	Soap/water wash immediately	10 mg/m^3	Lung cancer
Vanadium	Dust, fume	Irritant contact dermatitis, green tongue	Soap wash promptly	35 mg/m^3	–
Zinc	Chloride	Irritant contact dermatitis, skin burns (fixes tissue *in situ*), mucocutaneous hyperpigmentation, oral lichen planus (dental fillings)	–	50 mg/m^3	–
Zirconium		Irritant contact dermatitis, granulomas, blue–gray skin discoloration	Soap wash	25 mg/m^3	

*Concentration posing immediate danger to life and health (IDLH). Since 1979, the National Institute for Occupational Safety and Health (NIOSH) has not allowed detectable levels of known carcinogens.

Table 88.12 Mucocutaneous findings associated with exposure to toxic elements and heavy metals[51–69]. Additional information is included in Table 15.4. GBq, gigabecquerel; GI, gastrointestinal; GU, genitourinary; PR, pityriasis rosea; TEN, toxic epidermal necrolysis.

of authors have suggested that higher concentrations of 0.4 to 0.6 mg/L are actually required[53].

Chronic exposure to inorganic arsenic poses an increased risk for developing several types of cancer (see Table 88.11). Trivalent inorganic arsenic is the most toxic form, with a latent period for chronic manifestations of 30 to 50 years[51].

Pathogenesis

Many of the toxic effects of arsenic are through interference with cellular respiration and uncoupling of oxidative phosphorylation. Arsenic can cause chromosomal alterations and gene amplification, induce sister chromatid exchanges, inhibit DNA repair, and transform mammalian cells *in vitro*. The precise mechanism of tumor promotion is unknown, but arsenic has been shown to modulate expression of several key transcription factors, including p53, NF-κB, and activating protein-1 (AP-1)[51,52,55–57]. In addition, epigenetic modifications of *CDK2NA* and *DAPK* via hypermethylation of their promoter regions was found to be associated with a higher risk of developing arsenic-induced skin lesions[52].

Clinical features

Arsenic exposure can be divided into acute and chronic forms. Acute exposure (medicinal, homicidal, suicidal) produces myriad cutaneous and systemic features (see Table 88.11). Chronic arsenic exposure (drinking water, occupational) produces altered pigmentation, keratoses, and substantial malignancy risk (Fig. 88.8). The presence of arsenic-induced keratoses and skin cancers may serve as biomarkers of internal malignancy. Hazard ratios for the development of lung and urinary tract carcinomas are significantly higher (4.64 and 2.02, respectively) for patients with cutaneous features of arsenicism, as compared to those having similar arsenic exposure but no cutaneous manifestations[53].

Arsenic may be detected in blood, urine, hair and nails, with quantitative measurements via inductively coupled plasma–mass spectroscopy usually performed on blood or urine samples[57]. Patient preparation prior to sampling of blood or urine should include avoidance of vitamins, minerals, nutritional supplements, seafood, and shellfish for 48–72 hours. In addition, for urine arsenic quantitation, the patient should not have had iodinated contrast media for one month prior to testing (see chapter appendix). The normal reference interval for blood arsenic is 0–13 mcg/L and a potentially toxic level is >600 mcg/L; the normal range for urine is 0–35 mcg/L.

Pathology

Arsenical keratoses exhibit marked hyperkeratosis with scattered parakeratosis and mild to moderate keratinocyte atypia. There are no features that clearly distinguish arsenical keratoses from actinic keratoses. Lesions with only minimal atypia may resemble hyperkeratotic seborrheic keratoses.

Arsenical Bowen disease exhibits the same epidermal histologic features as common Bowen disease (see Ch. 108). Although the superficial type is most commonly observed, the basal cell carcinomas (BCCs) associated with arsenic can be any of the clinicopathologic subtypes (see Ch. 108)[51,54].

Differential diagnosis

Arsenical keratoses may resemble punctate palmoplantar keratoderma (including the porokeratotic variant) and verruca vulgaris. Small pits are often noted when central keratotic plugs are removed from the papules in the inherited keratodermas, but not with arsenical keratoses. Family history and early onset are helpful in distinguishing palmoplantar keratodermas. In the basal cell nevus syndrome, there are persistent pits due to the localized absence of stratum corneum; additional clues are the characteristic facial features, odontogenic jaw cysts, and typical basaloid proliferative histology in the palmar pits (see Ch. 108).

Treatment

Chelation therapy is the mainstay of treatment for *acute* arsenicism. Dimercaprol is the most widely used agent. Other chelating agents reported as being efficacious include dimercaptosuccinic acid (DMSA) and dimercaptopropane sulfonate (DMPS). DMPS is the treatment of choice and can improve the neuropathy and respiratory symptoms. For *chronic* arsenicism, chelation is controversial, but may reduce arsenic stores. Oral retinoids have been reported to reduce arsenical keratoses and decrease formation of arsenical BCCs. Surgical extirpation, curettage, cryosurgery, topical imiquimod or 5-fluorouracil, and photodynamic therapy have been reported with some success. These treatments are all anecdotal or based upon small series[51,54].

Illness due to Aquatic Toxin Ingestion

Introduction

Ingesting pufferfish (fugu) can result in neurotoxicity due to tetrodotoxin, while eating predatory fish that contain toxins produced by dinoflagellates leads to the gastrointestinal and neurologic symptoms of ciguatera. However, neither is associated with cutaneous manifestations. In contrast, scombroid poisoning presents with generalized flushing and sweating, facial swelling, and urticaria following consumption of scombroid fish that has not been properly refrigerated.







Fig. 88.8 Cutaneous manifestations of exposure to arsenic. A Guttate hypopigmentation superimposed on hyperpigmentation resembles "raindrops on a dusty road". **B, C** Arsenical keratoses on the plantar and palmar surface. *A, Courtesy John Steinbaugh, MD; C, Courtesy Jeffrey P. Callen, MD.*

Epidemiology

In the 1990s, scombroid poisoning accounted for 38% of all seafood-related outbreaks in the US and 32% in England and Wales[70]. Based upon analyses of data from the Foodborne Disease Outbreak Surveillance System (2000–2007) and the National Poison Data System (2005–2009), plus taking into account underreporting, it was estimated that ~15 900 cases of ciguatera and 35 000 cases of scombroid poisoning occur annually in the US[71].

Pathogenesis

Fish of the family Scombridae (including tuna and mackerel) have high levels of free histidine in their muscle tissue. While these fish were among the first reported causes of scombroid poisoning, many other fish species have subsequently been implicated, including mahi mahi, bluefish, marlin, bonito, amberjack, sardines, anchovies, herring, swordfish and salmon, with all but the last two also having high levels of muscle histidine[70].

When any of these fish are kept improperly refrigerated, bacterial histidine decarboxylase converts the histidine to histamine. Upon ingestion, the victim receives a very large dose of histamine, with prompt deleterious effects due to its binding to histamine receptors. However, some of the myriad effects cannot be explained by histamine content alone. Proposed contributing factors include potentiation of histamine absorption and inhibition of its catabolism, an as-yet-unidentified "scombrotoxin" that degranulates mast cells, and the possibility of histamine intolerance, particularly by those individuals more severely affected[70–72].

Clinical features

Symptoms of scombroid poisoning typically appear 10 minutes to 1 hour after consumption of the fish. They may include a metallic taste, headache, dizziness, tachycardia, and dysphagia. The most obvious cutaneous findings are generalized flushing, urticaria, and facial swelling. Some patients also develop nausea, vomiting, and diarrhea. Recovery can take several days. Rare cases of serious illness, including anaphylaxis, have been reported[70]. The various causes of generalized flushing are found in Tables 106.2 & 106.3.

Treatment

Antihistamines are the mainstay of treatment[70].

FRICTIONAL AND TRAUMATIC INJURY TO THE SKIN

Mechanical injuries due to plant parts (e.g. spines, glochids) are discussed in Chapter 17 and marine injuries (e.g. from sea urchins, corals) are reviewed in Chapter 85.

Corns and Calluses

Synonyms: ■ Corn – clavus, heloma ■ Hard corn – heloma durum ■ Soft corn – heloma molle ■ Callus – callosity, tyloma, intractable plantar keratosis

Key features

- Corns and calluses are keratotic lesions resulting from repeated trauma
- Ill-fitting footwear, bony protuberances, and specific activities are contributing factors
- Hard corns are found on the dorsal aspects of the toes, while soft corns are in the interdigital web spaces
- Proper footwear and medical management usually suffice

Introduction

Repeated mechanical trauma to the feet, whether from poorly fitting footwear, anatomic deformities, or work or leisure activities, produces hyperkeratosis. This otherwise natural protective response to injury may result in the formation of uncomfortable thickened areas of skin known as corns or calluses. Corns are more narrowly based and sharply defined, whereas calluses are broad-based. Calluses also form on the hands from repeated trauma, but are usually asymptomatic[73].

Epidemiology

Risk factors for the development of corns and calluses on the feet include bony protuberances, abnormal biomechanical foot function, poorly fitted shoes, and repetitive trauma due to athletic activity[73].

Pathogenesis

Bony protuberances such as the condyles of metatarsal and phalangeal bones create outward pressure on the skin. Footwear and activities (walking, running) create counterpressure at these sites.

The repeated friction and pressure leads to hyperkeratosis. The latter further compromises the site by increasing pressure. The cycle of friction, pressure, and thickening continues until a corn or callus develops[73].

Clinical features

Hard corns (heloma durum) are firm, small, dome-shaped papules with translucent central cores, most commonly found on the dorsolateral fifth toes and dorsal aspects of other toes as well as within plantar calluses overlying the second and third metatarsal heads (Fig. 88.9). Soft corns (heloma molle) are painful keratoses in the interdigital web spaces; they often become macerated. Opposing toes may exhibit "kissing lesions". Broad keratotic plaques, often under the metatarsal heads, are calluses.

A unique callus is seen on the tip of the second (and sometimes third) toe, with associated transverse ridging, thickening, and splinter hemorrhages in the nail. This is known as tennis toe (see Fig. 88.17) or center's callus. Also seen in gymnasts, soccer players, runners, football players and dancers, it results from sudden stops with repeated collision between toe tip and shoe. In many cases, the second toe is found to project further forward than the hallux[73,74]. Distal tips of hammer toes can also develop calluses (Fig. 88.10).

Differential diagnosis

These common lesions seldomly elude diagnosis, but must be distinguished from verruca vulgaris. Warts and corns interrupt dermatoglyphics, while calluses often demonstrate accentuated lines. Paring of a corn reveals a central translucent whitish yellow core, as opposed to the intracorneal hemorrhages and multiple bleeding points seen in a wart. Paring of a callus reveals layers of yellowish keratin, without the multiple punctate intracorneal hemorrhages of a mosaic plantar wart.



Fig. 88.9 Callus plus hard corns. Calluses are broad-based and have accentuated skin markings while corns are round, more sharply defined papules with a central translucency and an interruption in dermatoglyphics. The skin overlying the second and third metatarsal heads is a common location for such lesions. *Courtesy Jean L. Bolognia, MD.*



Fig. 88.10 Toe tip callus due to a hammer toe deformity. There is also a small central hemorrhagic crust and subungual hyperkeratosis of the third toe. *Courtesy Kalman Watsky, MD.*

Treatment

Treatment should be directed toward both symptomatic relief and correction of the biomechanical conflict. Paring of the callosity, with removal of the corn's central core, provides prompt relief. Filing after warm water soaking can be performed periodically by the patient. Topical agents such as salicylic acid or urea can also be used to soften the callosity. Some clinicians employ curettage or cryotherapy.

Soft cushions (silicone sheet, sheepskin) reduce friction and improve comfort. Properly fitted footwear and the use of appropriate orthotics are also recommended. If all of these maneuvers fail, a radiograph to look for exostoses and referral to orthopedic surgery may be indicated[73,74].

Black Heel and Palm

Synonyms: ■ Talon noir ■ Tache noir ■ Intracorneal hemorrhage (of the skin) ■ Post-traumatic cutaneous intracorneal blood ■ Calcaneal petechiae ■ Post-traumatic punctate intraepidermal hemorrhage

Key features

- Black macules on the palms or soles due to hemoglobin within the thickened stratum corneum
- Lesions are secondary to impact trauma and resolve with paring or time

Introduction

Black heel (or palm) is a post-traumatic intraepidermal hemorrhage seen most often in athletes. This harmless and self-healing process is a potential source of concern because of its dark black color.

History

Black heel was first described in 1961 by Crissey and Peachey[75] as calcaneal petechiae. A variety of subsequent reports under different monikers (see above) has led to confusion and debate over the proper nomenclature. The association with sports has been recognized since the beginning, with basketball being the prototypical sport.

Epidemiology

Adolescents and young adults comprise the majority of patients with this entity. Sports participation is of paramount importance, particularly basketball, lacrosse, tennis, football, gymnastics, and marching. Elderly patients with unusual palm and sole trauma may also be predisposed. Self-inflicted hammer injury can produce a similar clinical finding[75–77].

Pathogenesis

Black heel is a traumatic phenomenon thought to be due to shearing forces, often produced by sudden stopping or landing on the floor or ground. These shearing forces rupture papillary dermal blood vessels, with subsequent leakage of blood into the epidermis[77]. Hemoglobin resides in the stratum corneum for a longer transit time, and because the blood is out of reach of phagocytic cells in this location, the molecular structure of hemoglobin remains intact[76,77].

Clinical features

The black or violet–black macules are asymptomatic and may be isolated or clustered. They can form linear or horizontal arrays on the posterior or posterolateral aspect of the heel (Fig. 88.11A). Lesions are usually unilateral and favor the edge of the thick plantar keratin. Forefoot, toe, and palmar lesions have also been observed (Fig. 88.11B,C); in patients with thickened stratum corneum due to disorders of cornification, extra-palmoplantar lesions can be seen. Paring of the stratum corneum reveals red–brown to red–violet specks of dried blood, and dermoscopy can also prove useful.

Pathology

Hyperkeratosis with "lakes of hemorrhage" within the stratum corneum form the characteristic histopathology[77]. Iron stains may be negative (especially Prussian blue). Both the benzidine and Patent Blue V stains for hemoglobin are positive, perhaps because the intracorneal location has no phagocytic or proteolytic activity to allow formation of hemosiderin[76,77].

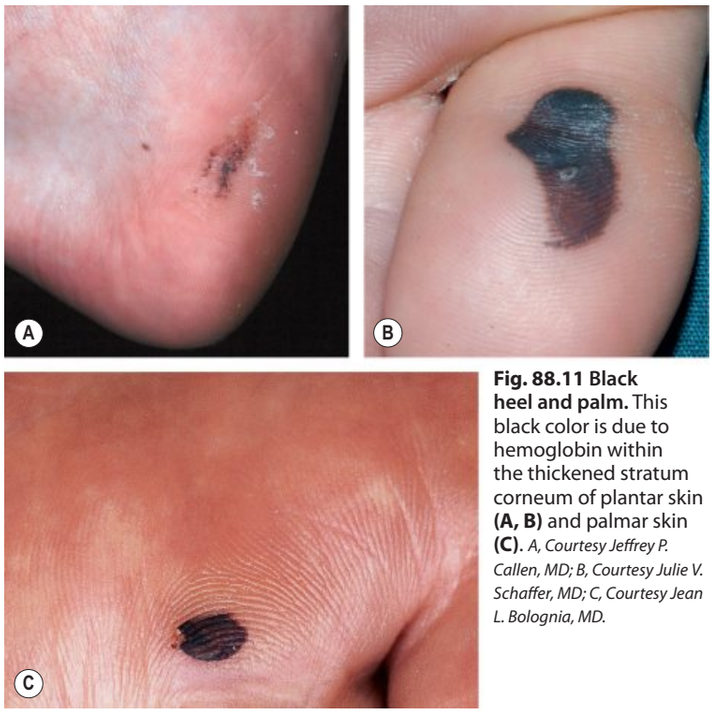


Fig. 88.11 Black heel and palm. This black color is due to hemoglobin within the thickened stratum corneum of plantar skin **(A, B)** and palmar skin **(C).** *A, Courtesy Jeffrey P. Callen, MD; B, Courtesy Julie V. Schaffer, MD; C, Courtesy Jean L. Bolognia, MD.*



Fig. 88.12 Senile gluteal dermatosis (sitter's sign). Symmetric plaques with horizontal ridging in a triangular pattern on the mid to upper buttocks. There are also areas of hyperkeratosis and irritant contact dermatitis. *Courtesy Jean L. Bolognia, MD.*

SENILE GLUTEAL DERMATOSIS
• Synonyms: sitter's sign, hyperkeratotic lichenified skin lesion of the gluteal region, grandfather's disease • Risk factors: elderly, low body mass, prolonged sitting, men > women • Etiology: pressure and friction • Clinical features: gradual appearance of poorly defined, ridged brown plaques; ridges are horizontal and can be keratotic (Fig. 88.12) • Locations: medial aspects of the mid to upper buttocks, upper gluteal cleft, over ischial tuberosities • Distribution pattern: usually bilateral and there may be a triangular distribution pattern • Symptoms: asymptomatic (~60%), pruritic (~35%), painful (<10%) • DDx: anosacral amyloidosis, lichen simplex chronicus due to scratching or rubbing by patient • Treatment: relieve pressure via cushions

Table 88.13 Senile gluteal dermatosis. See reference 78 regarding symptoms.

Differential diagnosis

The major entities in the differential diagnosis are cutaneous melanoma and verruca vulgaris. The ability to remove the lesion with gentle paring allows one to exclude a melanocytic lesion; positive staining for hemoglobin provides additional evidence. One author found the standard stool guaiac test (e.g. Hemoccult®) to be useful for confirming the presence of hemoglobin in parings[77].

Treatment

Once the diagnosis is ascertained, treatment is unnecessary.

Senile Gluteal Dermatosis

The details of this disorder are outlined in Table 88.13.

ENVIRONMENTAL DERMATOSES OF THE EXTERNAL EAR

The external ear is uniquely vulnerable to environmental stresses and trauma, given its protuberance and the thin skin overlying cartilage (Table 88.14). It is particularly susceptible to cold injuries (see above) and chronic photodamage, especially in men. Unique environmental exposure-induced conditions of the ear due to trauma, pressure, friction, or UVR include chondrodermatitis nodularis helicis (Fig. 88.13), acanthoma fissuratum (Fig. 88.14), weathering nodules (Fig. 88.15), and auricular hematoma (Fig. 88.16)[73–77,79,80].

SPORTS-RELATED DERMATOSES

Variants: ■ Tennis toe ■ Jogger's toe ■ Turf toe ■ Surfer's nodules ■ Surfer's knots ■ Jogger's nipple

Key features

- Cutaneous trauma produces abrasions, blistering, ecchymoses, callosities, and unique sport-specific stigmata
- Allergic contact dermatitis in athletes is often due to rubber antioxidants and adhesives
- Cutaneous bacterial, viral, and fungal infections occur more often in those engaged in sports with close physical contact
- Existing dermatoses may be exacerbated by sports participation

Introduction

Participation in sports may be associated with many types of cutaneous injuries or infections. Most of these problems are minor inconveniences. The following discussion will be organized into: mechanical trauma (acute, chronic); exposure-related dermatoses; infections; and exacerbation of existing conditions.

History

Cutaneous injury has been an accepted consequence of athletic activity at least since ancient Greece. Stigmata such as the wrestler's "ear-mark" have been viewed as marks of athletic prowess.

Epidemiology

Sports participation has shown a steady increase over the past several decades. Along with the gain in popularity of athletic activity has come an increase in sports-related dermatoses and infections. For example, herpes simplex viral infections among wrestlers are becoming increasingly common, with prevalence rates of herpes gladiatorum ranging from 2% to 40%. Similarly, the prevalence of tinea gladiatorum among wrestlers has been reported in up to 60%, along with multiple

ENVIRONMENT-RELATED CUTANEOUS DISORDERS OF THE EXTERNAL EAR				
Disorder	**Chondrodermatitis nodularis helicis (and antihelicis)**	**Acanthoma fissuratum**	**Weathering nodules**	**Auricular hematoma**
Synonyms	Chondrodermatitis nodularis chronica helicis, ear corn, chondrodermatitis nodularis chronica helicis et antihelicis	Granuloma fissuratum, spectacle frame acanthoma, eyeglass frame acanthoma		Wrestler's ear, cauliflower ear
Pathogenesis	Precise etiology unknown, but contributing factors include local ischemia due to pressure (often affects most protruding portion of the ear), actinic damage, cold exposure, and trauma, leading to inflammation	Ill-fitting eyeglass frames create a frictional injury	Precise pathogenesis unknown, but presence of chronic photodamage suggests a role for UV light	A glancing blow or twisting movement against the anterolateral pinna avulses the anterior perichondrium from the underlying cartilage Shearing forces rupture vessels that then bleed into the subperichondrial or intracartilaginous space
Clinical features	Usually seen in older adults Men tend to develop lesions on the helix at an earlier age, while women often develop antihelix lesions Skin-colored to erythematous, dome-shaped papules with central crusts or occasionally keratin-filled craters (Fig. 88.13A) Can be painful and tender	Firm, skin-colored to erythematous plaque or nodule on the upper portion of the postauricular sulcus or upper lateral nose, with a central vertical groove or fissure (Fig. 88.14) Tenderness, a serous discharge, slight hyperkeratosis, or an inflammatory halo may be present	Occur primarily in men with skin phototypes I and II and evidence of chronic photodamage Asymptomatic, 1–3 mm, white to skin-colored papules along the free margin of the helix (Fig. 88.15) Usually bilateral and create a scalloped appearance to the helical rim	Most commonly occurs in wrestlers, boxers, rugby players, and piano movers Painless to slightly tender swelling appears on the upper anterior aspect of the pinna in the scaphoid or triangular fossa; swelling can persist, especially if left untreated, becoming either firmer due to fibroneocartilage production or soft and cystic Color varies from skin-colored to slightly bluish Repeated injury produces the multinodular deformity known as cauliflower ear (Fig. 88.16)
Pathology	Well-circumscribed area of acanthosis, parakeratosis, and hypergranulosis; a central crater with epidermal disruption may be filled with a keratotic plug or dermal debris (Fig. 88.13B) The underlying dermis shows degenerative changes with fibrosis and variable lymphohistiocytic inflammation; the infiltrate extends into a thickened perichondrium	Irregular acanthosis, most marked at the lesion's periphery, with occasional pseudoepitheliomatous hyperplasia The central depression may show epidermal thinning with compact orthohyperkeratosis and patchy areas of parakeratosis near the central groove Dermal papillae exhibit dilated vessels and a moderately dense perivascular inflammatory infiltrate comprised of lymphocytes, histiocytes and plasma cells, with occasional neutrophils; slight fibrosis may be noted in the superficial and mid dermis	Fibrous tissue spur with cartilage metaplasia extending upward from disrupted perichondrium No inflammation or epidermal disruption are noted	Hematoma plus fibrosis and foci of new cartilage formation Older lesions may exhibit calcification and even ossification within the hematoma
Differential diagnosis	AK, SCC, BCC, cutaneous horn, verruca > KA, weathering nodule, calcinosis cutis, gouty tophi, reactive perforating collagenosis	BCC, SCC *in situ*, lichen simplex chronicus superimposed on seborrheic or allergic contact dermatitis > keloid	Gouty tophi, calcinosis cutis, CNH, elastotic nodules, amyloidosis, granuloma annulare	Auricular pseudocyst, relapsing polychondritis, epidermoid cyst
Treatment	Padding to relieve pressure, surgical excision, cryotherapy, corticosteroid injections, topical corticosteroids, laser ablation, soft tissue fillers, nitroglycerin gel and patches	Lesions usually clear within a few months of discontinuation, replacement, or proper adjustment of the offending spectacles Excision can be considered for persistent lesions Intralesional corticosteroids (case reports)	Treatment rarely required Cryosurgery (case reports)	Evacuation of the hematoma and prevention of fluid reaccumulation via aspiration or incision and drainage (with or without cartilage removal) then splinting

Table 88.14 Environment-related cutaneous disorders of the external ear[79–85]. Elastotic nodules of the ears are due to chronic photodamage and favor the antihelix. AK, actinic keratosis; BCC, basal cell carcinoma; CNH, chondrodermatitis nodularis helicis; KA, keratoacanthoma; SCC, squamous cell carcinoma.

epidemics[86,87]. Cutaneous infections with community-acquired MRSA have also been observed among athletes, with nasal colonization rates in team athletes higher than in the general population (4%–23% vs 1.3%, respectively)[88,89]. Risk factors include frictional injuries, weight, poor hygiene, and sharing clothing and towels with team members.

Pathogenesis

The types of frictional and mechanical trauma that can lead to dermatoses in athletes are summarized in Table 88.15. For example, acne mechanica is thought to occur when the local microenvironment of the skin is altered by a combination of pressure, heat, moisture (perspiration), friction, and occlusion[90].

Exposure to heat and cold are discussed in other sections of this chapter.

Clinical features

Acute or chronic mechanical trauma during sports activity creates unique cutaneous lesions summarized in Table 88.15.

In some patients, chronic friction on extensor extremities during the summer is thought to produce frictional lichenoid dermatitis

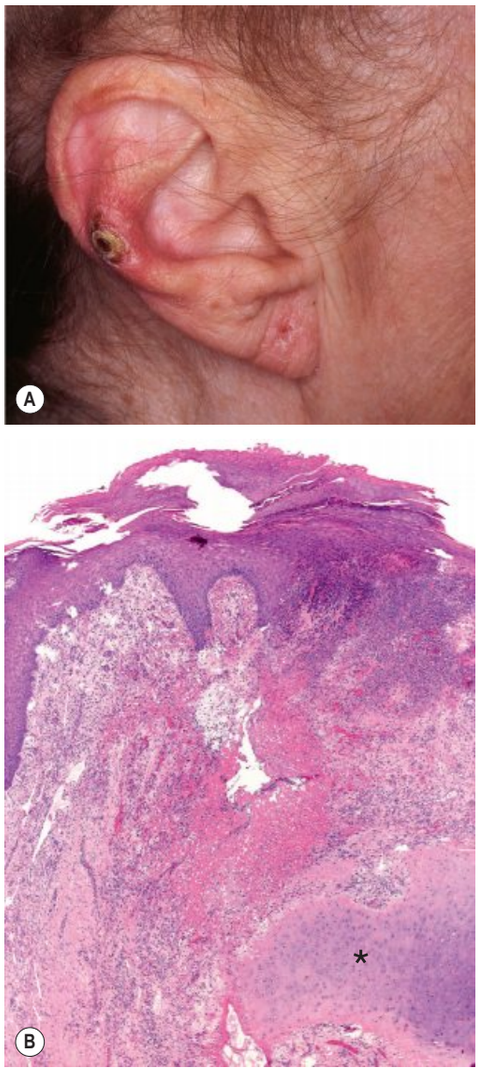


Fig. 88.13 Chondrodermatitis nodularis (anti)helicis. **A** Tender, erythematous papulonodule with central scale-crust on the mid antihelix of an older woman. This represented the site most susceptible to pressure-induced ischemia. **B** Central hyperkeratosis with scale-crust, epithelial hyperplasia, chronic inflammation, hemorrhage, fibrosis, granulation tissue, and degenerated cartilage (*) are seen on histologic examination. *A, Courtesy Kalman Watsky, MD; B, Courtesy Lorenzo Cerroni, MD.*



Fig. 88.14 Acanthoma fissuratum. Keratotic plaque of the postauricular sulcus; note the linear fissure. *Courtesy Luis Requena, MD.*



Fig. 88.15 Weathering nodules. Multiple asymptomatic, small, whitish papules along the helix of an older man with photodamage. *Courtesy Jean L. Bolognia, MD.*



Fig. 88.16 Multinodular deformity of the external ear, often referred to as cauliflower ear, in a jiu-jitsu fighter. It is the result of repeated auricular hematomas. *Courtesy Kalman Watsky, MD.*

(summertime pityriasis). This malady affects prepubertal children (mostly boys) and is characterized by irregular clusters of pale to skin-colored, flat-topped, lichenoid papules on the elbows, knees, and dorsal metacarpophalangeal and interphalangeal joints, as well as extensor shins and forearms. Mild pruritus may develop, although most children are asymptomatic[91].

Another common finding in athletes is the presence of striae distensae, or stretch marks (see Fig. 99.6). Although striae appear in non-athletic settings (e.g. Cushing syndrome, obesity, pregnancy, overuse of corticosteroids) and they are thought to occur in 70% of adolescent girls and 40% of adolescent boys[90], weightlifting has been identified as a risk factor. Striae are therefore commonly observed in football players, wrestlers, gymnasts, and body builders[86,87] and favor the anterior shoulders, lower back, and thighs.

Environmental exposure creates additional challenges for sports enthusiasts, especially with activity during temperature extremes. Summer heat poses risks such as heat exhaustion and heat stroke (see above). Mountain climbers, skiers (downhill and Nordic), biathletes, winter hikers, and others are at risk for cold injury (see above). Water exposure in swimming, diving, snorkeling, and scuba diving has intrinsic risks as well. Overhydration of the stratum corneum increases susceptibility to blisters, skin breakdown, and cutaneous infection.

As in the general population, irritant contact dermatitis is more prevalent than allergic contact dermatitis (ACD), and while the latter is likely to be as common among athletes as the general population, specific presentations reflect the use of specialized equipment. Erythema in the distribution of a swimmer's goggles or scuba mask ("mask burn") may be seen, and individuals with more severe reactions can also develop vesiculation, weeping, crusting, pruritus, and pain. Rubber antioxidant allergy is known to occur in this setting, with mercaptobenzothiazole, tetramethylthiuram, and paraphenylenediamine derivatives being the major allergens. Rubber compounds in athletic shoes pose risks to individuals with contact sensitivity, particularly with thiourea, mercaptobenzothiazole, and thiuram antioxidants. The resulting erythema, desquamation, vesiculation, fissuring, pain, and pruritus of the feet can prove quite disabling for the athlete, particularly when alternative footwear

FRICTIONAL AND MECHANICAL DERMATOSES IN ATHLETES				
Condition	**Clinical features**	**Sports**	**Etiology/pathogenesis**	**Prevention/treatment**
Friction blisters (see Ch. 33)	Bullae and superficial erosions	Any	Friction or tangential impact to foot while in warm moist shoes	Frequent drying of feet, lubrication, proper shoe fit, drain blisters/ leave roof
Contusion	Ecchymosis	Any	Perpendicular mechanical trauma producing vascular damage	Padding
Subungual hematoma		Running, tennis, basketball	Sudden impact of toe tip with end of shoe	Enlarged shoe toe box with proper arch and metatarsal support, drainage of hematoma may be needed
Black heel/talon noir	See text			
Turf toe	Painful, erythematous, edematous hallux	Football, soccer	Acute dorsal and plantar tendonitis	Rest
Jogger's nipple	Pain, erythema, fissuring, occasional bleeding	Running	Repeated friction of rough shirt fabric	Woman: jogging bra Man: taping, lubrication, semisynthetic or silk shirt
Callosities	See text	Many		
Tennis toe	Toe tip callus, nail thickening, subungual hyperkeratosis (Fig. 88.17)	Tennis, running, ice hockey, skating	Repeated trauma of longest toe against inside of toe box	Proper shoe fit, enlarged toe box, improved arch support
Nail dystrophy	Onycholysis, hematoma, subungual hyperkeratosis, paronychia, onychocryptosis (ingrown nail)	Many	Repeated trauma to nails	Keeping nails trimmed with a straight edge, proper shoe fit
Fibrotic nodules (e.g. surfer's knots)	Thick fibrotic nodules on knees, knuckles, dorsal feet	Surfing, boxing, football, marbles, cricket, baseball, ice hockey, skating	Chronic pressure over bony prominences	Padding, position change, prone rather than kneeling on surfboard
Skate bite	Painful inflammatory plaques or pseudonodules under the tongue of the skate	Ice hockey, figure skating	Pressure from a rigid skate tongue over the anterior ankle or dorsal foot	Padding under the skate tongue or improve pliability of the tongue
Piezogenic papules	Multiple asymptomatic to tender yellowish outpouchings on the medial and lateral aspects of the heels when standing (Fig. 88.18)	Distance running, high-impact sports, figure skating	Herniation of subcutaneous fat through small tears in plantar fascia	None known
Runner's rump	Small ecchymoses in upper gluteal cleft	Running	Constant friction with each stride	Lubrication
Rower's rump	Well-demarcated, lichenified plaques of the buttocks	Rowing	Repeated friction and trauma between buttocks and unpadded seat of a rower	Padded seat or shorts Potent topical or intralesional steroids
Swimmer's shoulder	Erythematous plaque on shoulder	Swimming	Friction of unshaven beard against the shoulder during the swim stroke	More frequent shaving
Alopecia and hypertrichosis	Transient alopecia on forearms followed by hypertrichosis	Gymnastics	Frictional alopecia, compensatory regrowth	

Table 88.15 Frictional and mechanical dermatoses in athletes[86–98]. Acne mechanica and auricular hematoma are discussed in the text and Table 88.14, respectively. Auricular pseudocyst, which is seen most commonly in rugby players, is reviewed in Ch. 110.



Fig. 88.17 Chronic "tennis toe". Chronic and repeated trauma of the longer second toe against the end of the tennis shoe toe box during sudden stops creates the distal callus formation and nail plate thickening known as tennis toe.



Fig. 88.18 Piezogenic papules. Yellowish outpouchings on the heel represent herniation of subcutaneous fat through the plantar fascia in this sometimes painful condition.

without rubber (e.g. soccer cleats, baseball cleats) is not readily available. However, the development of polyurethane shoes by a few manufacturers offers an alternative for runners allergic to rubber components.

Acetophenone azine is an emerging allergen that has been identified in ethyl vinyl acetate-containing foam that is used in shin guards, shoe soles, and flip-flops. The resultant ACD has been referred to as shin guard dermatitis[99]. Adhesives in tape, benzoin, topical antiseptics and antibiotics, dyes, and leather tanning agents also may be problematic in athletes[89,90,96]. For excellent reviews of contact allergens in sports equipment, see references 89 and 92.

Acne mechanica occurs commonly in athletes in whom occlusive uniforms or protective gear create the right microenvironment. Football players flare during the August pre-season practice with follicular papules, pustules and nodules on the forehead, preauricular areas, chin and shoulders, corresponding to forehead and ear pads of the helmet, chin strap, and shoulder pads, respectively. Acne keloidalis of the lower occiput may be aggravated by the helmet as well. Other sports in which protective headgear may create acne mechanica include hockey, lacrosse, and wrestling. Occlusive synthetic clothing of dancers and gymnasts, plastic benches of weight lifters, golf bag shoulder straps, and the cradling of the shot against the neck in shot putters may also produce acne mechanica[87,90,96].

Heat, moisture, friction, and contact with other athletes or various surfaces increase the risk of several cutaneous infections (Table 88.16). Common monikers attest to these associations, such as "jock itch", "herpes gladiatorum", "athlete's foot", and "swimmer's ear". A report that evaluated the risk of staphylococcal infections in football players within a professional team noted that weight and turf injuries were risk factors and, therefore, linemen were more prone to developing this infection. However, habits of the trainers and the use of whirlpool equipment also pointed to risks associated with poor hygienic practices[88].

The final issue of sports-related skin disease is aggravation of pre-existing conditions. Psoriasis, vitiligo, and lichen planus may exhibit a Koebner phenomenon, flaring in areas of skin injury such as abrasions. Epidermolysis bullosa simplex, localized (formerly Weber–Cockayne) is worsened by friction on the feet and hands, particularly in warm summer months (see Ch. 32). Photosensitive dermatoses may be exacerbated by outdoor sun exposure (see Ch. 87). Both cholinergic and exercise-induced urticaria may worsen with heavy physical exertion[89] (see Ch. 18). Vibratory angioedema has also been reported with bicycling, walking, and jogging[93]. The reader is referred to the American Academy of Pediatrics guide for further information on medical conditions affecting sports participation[94].

CUTANEOUS INFECTIONS IN ATHLETES

Condition	Common name	Clinical features	Organisms	Typical sport
Impetigo		Small vesicles to large bullae on glistening erythematous bases; honey-colored crusts	*Staphylococcus aureus*, β-hemolytic streptococci	Most sports, especially close contact
Folliculitis		Erythematous follicular papules and pustules	*S. aureus*	Most sports
Hot tub folliculitis		Markedly erythematous, edematous follicular papulopustules, few in number, often involving axillae, breasts, pubic area, and buttocks	*Pseudomonas aeruginosa*	Swimming; use of whirlpool, hot tub, or Jacuzzi
Pseudomonas hot-foot syndrome		Tender nodules on soles	*P. aeruginosa*	Use of wading pool
Furuncles	Boils	Tender, warm, red nodules or abscesses on trunk or extremities	*S. aureus*, including MRSA	Football, wrestling, basketball, swimming
Erythrasma		Reddish-brown dry patches in axillae, groin, or toe webs	*Corynebacterium minutissimum*	Most sports, especially with occlusive clothing
Pitted keratolysis	Toxic sock syndrome	Malodorous feet with 1–3 mm, punched-out, plantar erosions extending only through the stratum corneum of overhydrated skin	*Corynebacterium* spp., *Kytococcus* (*Micrococcus*) *sedentarius*, *Dermatophilus congolensis*	Running, tennis, basketball, ice hockey, skating
Otitis externa	Swimmer's ear	Pruritus may be followed by pain, discharge, tenderness of the pinna, sensation of fullness, and reduced hearing	*P. aeruginosa* most common; also streptococci, diphtheroids, and staphylococci	Swimming, diving (those with an atopic diathesis at risk)
Swimming pool granuloma		Firm, acral, red papules	*Mycobacterium marinum*	Swimming
Verruca vulgaris	Warts	Verrucous, keratotic papules and plaques	Human papillomavirus	Any that use locker-room showers or public pools
Herpes simplex viral infection	Herpes gladiatorum	Clustered vesicles on erythematous bases at point of skin-to-skin contact	Herpes simplex virus	Wrestling
Molluscum contagiosum		Shiny, umbilicated 2–3 mm papules at the skin contact site	Parapoxvirus	Wrestling, swimming
Tinea pedis	Athlete's foot	Maceration, scaling, pruritus in toe webs; diffuse plantar erythema and scale	*Trichophyton rubrum, T. interdigitale, Epidermophyton floccosum*	Any sport
Tinea cruris	Jock itch	Annular to polycyclic erythema with scaly, active borders; perifollicular papules or pustules; favors upper inner thighs	Same as tinea pedis	Any sport
Tinea corporis	Tinea gladiatorum	Except for location, the same as tinea cruris	*Trichophyton* spp.	Wrestling
Seabather's eruption	Sea lice	Pruritic papules on areas covered by bathing suit	*Edwardsiella lineata, Linuche unguiculata*	Salt water swimming
Swimmer's itch	Cercarial dermatitis	Pruritic erythematous papules on exposed skin	Avian schistosome cercaria	Fresh water pond and lake swimming and wading

Table 88.16 Cutaneous infections in athletes[86–91,97,100].

DERMATOLOGIC CONDITIONS IN LIMB AMPUTEES AND TREATMENT STRATEGIES				
Physical/mechanical effects	**Allergic contact dermatitis (most common allergens)**	**Infections**	**Exacerbation of pre-existing condition**	**Other**

• Irritant contact dermatitis
• Pruritus
• Sensitive and/or painful skin
• Altered temperature sensation
• Hyperhidrosis
• Erythema
• Callus and verrucous hyperplasia
• Hypertrichosis
• Edema
• Blisters
• Abrasions
• Ulceration
• Folliculitis (normal flora), pseudofolliculitis, follicular hyperkeratosis
• Epidermoid inclusion cyst, milia
	• Para-phenylenediamine (PPD)
	• Formaldehyde
	• Epoxy resin
	• Mercapto mix
	• Fragrance mix
		• Group A β-hemolytic *Streptococcus*
		  • impetigo, cellulitis
		• *Staphylococcus aureus*
		  • impetigo, cellulitis, folliculitis
		• *S. epidermidis*
		• Dermatophytes
		• *Candida* spp.
			• Psoriasis
			• Eczema/atopic dermatitis
			• Pyoderma gangrenosum
				• Stasis dermatitis
				• Acroangiodermatitis
				• Localized bullous pemphigoid
				• Marjolin ulcer (SCC)
				• Verrucous carcinoma
				• Angiosarcoma

Treatment strategies				
Folliculitis	• Clipping of hairs rather than shaving • Laser hair removal of pigmented hairs, avoiding hairs within tattoos as this can lead to ulceration			
Hyperhidrosis	• Topical aluminum chloride (see Table 39.7) • Topical and oral anticholinergics • Botulinum toxin injections • Microwave thermoablation			

Table 88.17 Dermatologic conditions in limb amputees and treatment strategies[102–104]. SCC, squamous cell carcinoma. *Courtesy Tim Durso, MD.*

Pathology

Many of the friction-induced conditions discussed here have histologic features similar to callosities (see above). Surfer's nodules show hyperkeratosis and mild acanthosis of the epidermis with increased numbers of normal-appearing collagen bundles. The overall histologic appearance is similar to that of a collagenoma[95]. The infectious processes are covered in detail in their respective chapters, as are the existing dermatoses aggravated by sports participation.

Treatment

Therapy for the non-infectious conditions discussed in this section is based primarily upon anecdotal reports and small series, and it is summarized in Table 88.15. Frictional lichenoid dermatitis responds to friction avoidance, the use of clothing to protect extensor surfaces, and moderate-potency topical corticosteroids[89–91,96]. Education and changes in practice behavior may aid in the prevention of infections in athletes. Therapeutic regimens for cutaneous infections are discussed elsewhere in the text.

AMPUTEE-RELATED DERMATOSES

Whether amputation is due to traumatic injuries (vehicular accidents, war-related, sports-related), environmental exposure, or a chronic medical condition (e.g. diabetes mellitus, peripheral artery disease, congenital abnormality, tumor), skin disorders are a frequent complication, with reported incidences ranging from 35% to 75%. For example, a survey of lower limb amputees found that 63% reported at least one skin problem during the preceding month, with the most common being severe sweating (50%), persistent redness after prosthesis removal (46%), and skin sensitivity (36%)[101]. In a clinical study of 124 lower limb amputees attending an orthopedic clinic, the prevalence of skin problems was 36%, and the latter led to reduced prosthetic use and decreased walking time without taking a break[102].

Table 88.17 lists dermatologic conditions observed in amputees. Implicated risk factors include higher level of amputation, higher activity level, and soft socket (as opposed to silicone) prostheses[103]. A meta-analysis of 27 studies (3105 patients) also found that traumatic below-knee and through-knee amputations were associated with a better quality of life in almost all their measures, when compared to above-knee amputations[103,104].

Treatment

While a detailed discussion of the management of these multisystem injuries is beyond the scope of this text, there are noteworthy studies. In a randomized controlled study involving 20 transtibial amputees with residual cutaneous ulcers or delayed wound healing, a vacuum-assisted active suction socket system led to a faster recovery and significant improvement in early ambulation (median 62 hours/week vs 5 hours/week); by 6 months there was no difference between the groups[105].

Battlefield injuries due to improvised explosive devices (IEDs) can lead to large BSA damage, contaminated wounds, and multiple amputations. As a result, there may be minimal healthy skin to serve as donor tissue, and the associated severe physiologic compromise makes grafting difficult. Therefore, alternative wound coverings are being utilized, e.g. a dermal bovine collagen regenerative matrix[106].

MUSICAL INSTRUMENT-RELATED DERMATOSES

Variants: ■ Cellist's chest or knee ■ Clarinetist's cheilitis ■ Drummer's digit ■ Fiddler's neck ■ Flautist's chin ■ Garrod's pads ■ Guitar nipple ■ Harpist's fingers

Key features

- Cutaneous disorders in musicians include frictional injury, irritant and allergic contact dermatitis, hyperhidrosis, acne mechanica, and vascular compromise
- Dermatoses tend to be recurrent unless the posture, use, or contact can be avoided
- Identification of the mechanism of injury is critical for successful therapy

Introduction

Musicians have unique cutaneous reactions related to countless hours of practice and performance required to master their art. Skin and associated soft tissue and musculoskeletal changes are therefore not uncommon. The major categories of injury in musicians are contact dermatitis, repetitive motion injury, and dysautonomia.

History

One of the first reports of an occupational dermatosis is reputed to be the recognition of fiddler's neck in 1713. About the same time, Italian physician Bernadino Ramazzini noted the peculiar distension and soft tissue laxity of the cheeks in horn players, and summarized the occupational problems of musicians[107].

DERMATOSES CAUSED BY MUSICAL INSTRUMENTS			
Condition (synonym)	**Clinical features**	**Pathogenesis**	**Associated instruments**
Acne mechanica and/or LSC (fiddler's neck, clarinetist's cheilitis, flautist's chin)	Follicular papules and pustules, lichenification, hyperpigmentation	Repetitive friction and pressure, coupled with occlusion and moisture (sweat, saliva)	Violin, viola, clarinet, saxophone, flute
Cellist's chest	Sternal skin tenderness, erythema, edema, hyperpigmentation	Pressure and friction	Cello
Cellist's knee	Erythema, scale, callus, and hyperpigmentation of left medial knee	Friction callus	Cello
Finger calluses	Hyperkeratotic callosities on fingertip pads	Repetitive friction	All strings
Drummer's digit	Vesicle or erosion on the radial aspect of the left ring finger distal and middle phalanx, followed by callus formation	Friction from holding left drumstick in classical position	Drums
Garrod's pads (violinist's pads)	Calluses on dorsal aspect of proximal interphalangeal joints of left index and middle fingers	Repeated extension and flexion of extensor tendon over tightly flexed joint	Violin, viola
Guitar nipple	Unilateral mastitis with erythema, edema, pain	Pressure and friction of guitar sound box pressed against chest	Guitar
Paronychia, onycholysis, subungual hemorrhage		Repeated trauma to nail apparatus	Piano, strings (especially playing pizzicato), harp, guitar

Table 88.18 Dermatoses caused by musical instruments[107–109]. LSC, lichen simplex chronicus.

Epidemiology

The injuries discussed below all require considerable devotion of time to practice and performance of the chosen instruments. Some of these conditions are considered marks of virtuosity, such as cellist's thumb. The impact of these conditions is greatest on professional musicians, although amateurs, and even beginners, may be afflicted[108].

Pathogenesis and clinical features

The clinical features and pathogenesis of dermatoses caused by musical instruments are summarized in Table 88.18.

Another common dermatosis that may occur in musicians is "lip licker's" dermatitis, characterized by erythema, fissuring, and scaling in wind instrument players. Intraoral hyperkeratosis of the lip or shallow erosions may develop in patients with dental irregularities or orthodontic appliances. Salivary abnormalities may interfere with performance with wind instruments. Xerostomia is devastating to the wind player (especially brass), while increased salivation is problematic for the recorder player. Sialolithiasis has been seen in association with fiddler's neck.

Sharing of mouthpieces may increase the risk of transmission of infections such as herpes simplex virus, EBV, cytomegalovirus, and hepatitis A and B viruses. Latent herpes simplex may be reactivated by the frictional trauma of wind instruments, with brass players tending to have upper lip lesions and woodwind players having lower lip lesions[109].

Hyperhidrosis of the palms may lead to corrosion of metal instruments or the inability to maintain proper contact with instrument keys or strings[110].

Allergic contact dermatitis associated with musical instruments is summarized in Table 88.19.

Pathology

Diagnosis of most of these conditions does not require histologic evaluation. However, fiddler's neck has been shown to exhibit epidermal hyperplasia with elongation of the rete ridges, follicular plugging, folliculitis and perifolliculitis, and epidermoid cyst formation[109].

Differential diagnosis

Fiddler's neck needs to be distinguished from localized cervical lymphadenitis, an inflamed epidermoid cyst, draining dental abscess, and acne mechanica from other causes (e.g. telephone, headset). Clinical history should suffice, along with the characteristic location and clinical features. For example, a dental abscess, scrofuloderma, or cervical actinomycosis with fistula formation often leaves the area indented and bound to underlying structures.

ALLERGIC CONTACT DERMATITIS ASSOCIATED WITH MUSICAL INSTRUMENTS		
Sensitizer/contactant	**Skin distribution**	**Instrument**
Rosin/colophony (abietic acid)	Hands, face, neck	Violin, viola, cello, double bass
Rosewood	Lips, chin, cheek	Strings, reeds
Makassar ebony	Chin	Violin
Cocobolo wood	Lips	Recorder
African blackwood	Lips	Recorder, oboe
Nickel	Chin	Violin
	Fingers, hands	Cello, sitar
	Lips, chin	Flute, brass
Reed (perhaps only irritant)	Lips	Saxophone, clarinet
Propolis (bee glue)	Hands	Violin
Chromium	Hands	Harp, violin
Paraphenylenediamine	Chin	Violin, viola

Table 88.19 Allergic contact dermatitis associated with musical instruments[107–111].

Treatment

Discontinuation of the instrument is curative in almost all cases, but usually quite impractical. Professional musicians, in particular, need other options. Frictional injuries may be addressed with padding, or change in position of the instrument. Fiddler's neck, for example, seems less common if the dropping neck position is avoided. Anecdotal remedies for the treatment of fiddler's neck include astringents, benzoyl peroxide, keratolytics, tretinoin, topical antibiotics, and application of French brandy.

Treatment of excess salivation with a transdermal scopolamine patch has been reported. Remedies for hyperhidrosis include topical aluminum-based drying agents, iontophoresis, β-adrenergic blocking agents (especially if the hyperhidrosis is due to "stage fright"), calcium channel blockers, botulinum toxin A, and ganglionectomy (see Ch. 39). Anticholinergic therapy is not useful for many musicians because of the frequent side effects of dry mouth and blurred vision[107–109]. If allergic contact dermatitis is suspected, patch testing can be performed (see Ch. 14).

APPENDIX

ARUP Laboratories at the University of Utah – measurements of blood (http://ltd.aruplab.com/tests/pub/0099045) and urine (http://ltd.aruplab.com/tests/pub/0025000) arsenic levels

Mayo Clinic Laboratories – measurements of blood (Test ID: ASB) and urine (Test ID: ASU) arsenic levels

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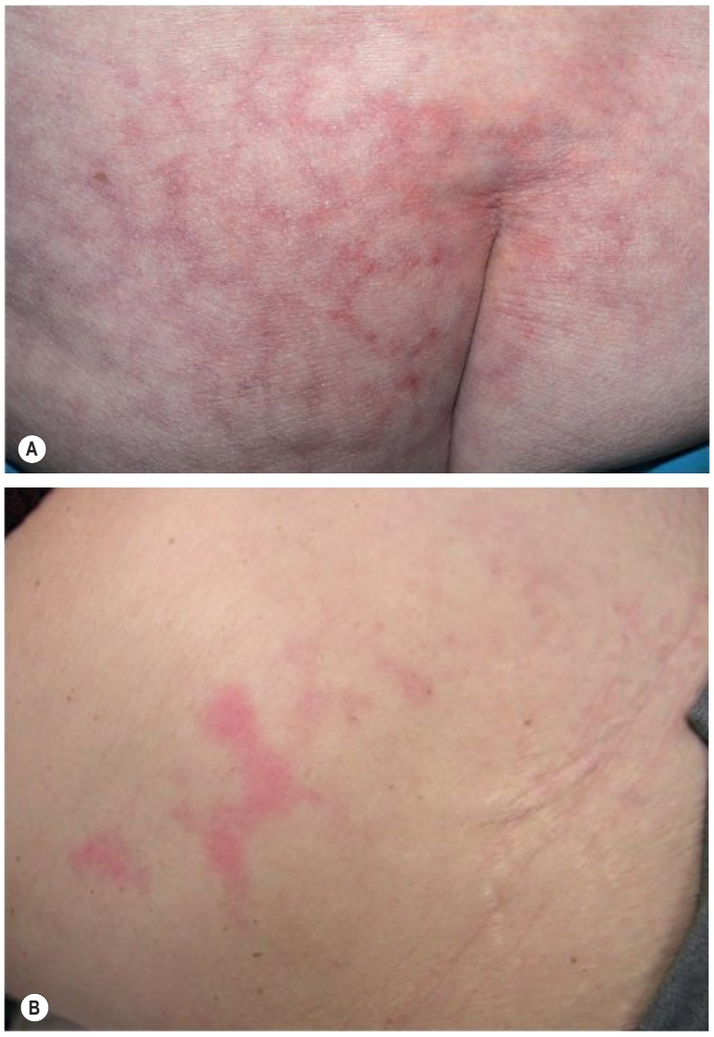
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eFig. 88.1 Erythema ab igne. A Reticulated erythema of the buttocks that corresponds to the dermal venous plexus and is due to chronic exposure to heat. **B** Initial lesions vary from pink to violet in color. *Courtesy Kalman Watsky, MD.*



eFig. 88.2 Erythema ab igne. Violet-colored reticulated patch at the site of heat application. *Courtesy Karynne O. Duncan, MD.*



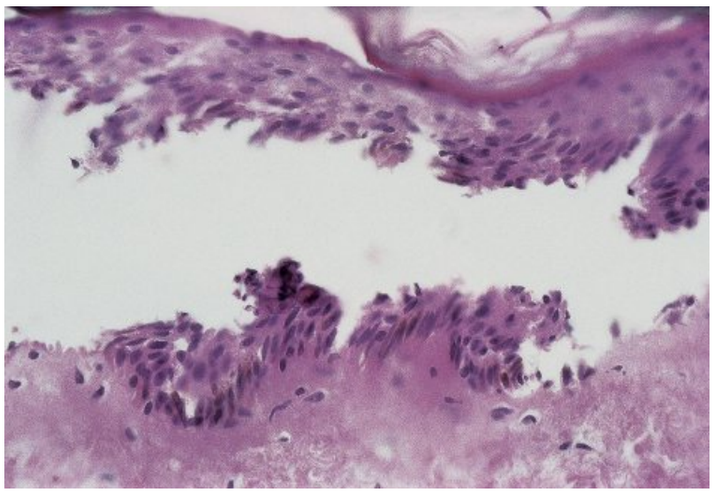
eFig. 88.3 Pernio (chilblains). Violaceous macules and patches, primarily on the toes, but also on the plantar surface of the foot.



eFig. 88.4 Severe pernio (chilblains). Red–brown thin plaques on the heel with desquamation and postinflammatory dyspigmentation. *Courtesy Kalman Watsky, MD.*



eFig. 88.5 Electrical burn. It is characterized by erythema, edema, bulla formation, and sloughing of the necrotic epidermis. *Courtesy Timothy Givens, MD.*



eFig. 88.6 Pathology of an electrical burn. Blistering seen in a biopsy from a patient who died of an electrical burn. Notice the elongated keratinocyte nuclei. *Courtesy Ronald P. Rapini, MD.*



eFig. 88.7 Hammer toes with callus and early corn formation overlying the interphalangeal joints. The changes are most pronounced on the second toes bilaterally. *Courtesy Kalman Watsky, MD.*



eFig. 88.8 Soft corn. Keratotic plaque in the interdigital web space that often becomes macerated and can be painful. *Courtesy Jean L. Bolognia, MD.*



eFig. 88.9 Chondrodermatitis nodularis helicis. Tender, erythematous papulonodule with central scale on the superior helix of an older woman. *Courtesy Harvey Lui, MD.*



eFig. 88.10 Acanthoma fissuratum. Thin pink plaque with scale of the postauricular sulcus (arrow). Note the linear fissure.



eFig. 88.11 Subungual hematoma. The violaceous color as well as the proximal clearing that become visible with retraction of the cuticle. *Courtesy Jean L. Bolognia, MD.*



eFig. 88.12 Sock line bands. Symmetric linear pink–brown streaks on the ankles of an infant who wore tight socks. *Courtesy Julie V. Schaffer, MD.*

Signs of Substance Use Disorder 89

Yul W. Yang and Mark R. Pittelkow

INTRODUCTION

The 2013 Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) defines substance use disorder as "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems" (Table 89.1). The disorder encompasses ten classes of drugs: alcohol; caffeine; cannabis; hallucinogens; inhalants; opioids; sedatives, hypnotics or anxiolytics; stimulants; tobacco, and other (or unknown) substances[1,2]. Any one of these drugs can result in changes in brain physiology and pathologic behavior. Prior to DSM-5, substance use disorder was subdivided into substance abuse and substance dependence. While this distinction may still be used clinically, *substance use disorder* represents the overarching and currently preferred term[2].

A wide range of cutaneous findings are associated with substance use disorders and they can serve as a clue to the diagnosis. The skin is reportedly the tissue most evidently affected by intravenous drug addiction[3]. Complications may be local or systemic and can be due to the drug itself, adulterants, or contaminants including infectious agents.

SUBSTANCE USE DISORDER AS DEFINED BY DSM-5
A problematic pattern of use leading to clinically significant impairment or distress is manifested by two or more of the following within a 12-month period:
1. Often taken in larger amounts or over a longer period than was intended
2. There is a persistent desire or unsuccessful efforts to cut down or control use
3. A great deal of time is spent in activities necessary to obtain, use, or recover from the substance's effects
4. Craving or a strong desire or urge to use the substance
5. Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home
6. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance
7. Important social, occupational, or recreational activities are given up or reduced because of use
8. Recurrent use in situations in which it is physically hazardous
9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
10. Tolerance, as defined by either of the following: a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect b. A markedly diminished effect with continued use of the same amount of the substance
11. Withdrawal, as manifested by either of the following: a. The characteristic withdrawal symptoms for the substance (refer to DSM-5) b. The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms

Table 89.1 Substance use disorder as defined by DSM-5. Grading: mild (2–3), moderate (4–5), and severe (6 or more). *Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (Copyright ©2013). American Psychiatric Association. All Rights Reserved.*

Alcohol

Drinking alcohol can lead to euphoria and a lowering of inhibitions as well as impaired functioning. In the US, alcohol use disorder has a 12-month prevalence of 8.5% amongst adults[1]. Acutely, ingestion of alcohol may lead to transient flushing, especially in individuals (e.g. East Asians) with variants in alcohol metabolizing enzymes[4]. Trauma-induced ecchymoses secondary to falls due to ataxia or vehicular accidents may point to alcohol-induced impairment. Cutaneous findings such as spider telangiectasias, palmar erythema, and jaundice can develop in patients with alcoholic hepatitis and cirrhosis (see Ch. 53)[5–7]. Porphyria cutanea tarda and rosacea are examples of disorders that may be exacerbated by alcohol.

Stimulants

Stimulants include amphetamines (e.g. dextroamphetamine), cocaine ("coke", "blow" [powder form]; "crack" [freebase crystallized form]), methamphetamine ("meth"), methylphenidate, and cathinones (e.g. khat, mephedrone, "bath salts"). Routes of administration include oral ingestion, snorting, inhalation via smoking, and intravenous injection. While many of these stimulants represent illicit drugs, dextroamphetamine and methylphenidate are prescribed for narcolepsy and attention deficit hyperactivity disorder. Stimulants lead to a feeling of euphoria and confidence, with reduced appetite, restlessness, insomnia, and increased or distorted sensations. Patients can also develop tachycardia and hypertension, as well as flushing, sweating, uncontrollable movements, and seizures.

Stimulants, in particular crystallized methamphetamine ("crystal meth"), are highly addictive and high-intensity or chronic abusers can develop xerostomia, xerosis, pruritus, acne excoriée and formication, along with dental caries and loss of teeth ("meth mouth"). Cocaine use has also been associated with Raynaud phenomenon, cutaneous small vessel vasculitis, necrotizing granulomatous vasculitis, acute generalized exanthematous pustulosis, and Stevens–Johnson syndrome[8]. Ventricular arrhythmias and myocardial or cerebrovascular infarctions are additional side effects. When cocaine is adulterated with levamisole, neutropenia, pyoderma gangrenosum, and ischemic vasculopathy with necrotizing purpura and ulcerations may develop (see below).

Hallucinogens

Hallucinogens include phencyclidine (PCP; "angel dust"), ergolines (e.g. lysergic acid diethylamide [LSD; "acid"], lysergic acid amide from morning glory seeds), and phenylalkylamines (e.g. mescaline). Ketamine is a dissociative anesthetic that also has some hallucinogenic effects while 3,4-methylenedioxy-methamphetamine (MDMA; "ecstasy", "molly", "E", "X") is both a stimulant and hallucinogen. Psilocybin-containing mushrooms ("magic mushrooms"), dimethyltryptamine-containing Amazonian plants, *Salvia divinorum*, and *Datura stramonium* (jimsonweed) are additional natural sources of hallucinogens.

Hallucinogens may be ingested orally, smoked, snorted, or injected. They can produce alterations in mood, cognition, and perception, including visual pseudohallucinations. Side effects of PCP include sweating, sialorrhea, combative behavior, tachycardia, and hypertension; higher doses can lead to seizures, hypotension, and coma. Hyperthermia with rhabdomyolysis and renal failure can result from high doses of MDMA.

Opioids (Includes Opiates)

Opioids may be synthesized or extracted from opium poppies (*Papaver somniferum L.*). They are prescribed primarily for pain control, including morphine, hydrocodone, oxycodone, oxymorphone, and fentanyl. Methadone is also used to treat chronic pain in addition to opioid use disorder related to heroin (diacetylmorphine) and prescription opioids. In opioid use disorder, there is compulsive, prolonged, self-administration of opioids either without a legitimate medical purpose or in doses that exceed those required for a particular medical condition[1].

Opioids may be taken orally, snorted, smoked, or injected intravenously or subcutaneously. With lipid-soluble opioids such as heroin that quickly cross the blood–brain barrier, there can be a "rush" of euphoria immediately. Associated side effects include dry mouth/nose, flushing, decreased gastrointestinal motility, pupillary constriction, pruritus, and altered mental function. Overdose-related respiratory depression can be fatal and the exponential increase in the use of fentanyl as well as fentanyl- and carfentanil-laced drugs has led to an epidemic of overdose deaths.

Opioids may also contain additives that result in significant cutaneous disease. For example, desomorphine ("krokodil") is a fast-acting morphine derivative that is ten times more potent than morphine[9]. The drug can be synthesized by combining red phosphorus from match strikers with codeine and iodine derived from over-the-counter medications; unfortunately, it is frequently contaminated with these and other agents[10]. Injection of this "flesh-eating drug" can cause serious damage to the skin, blood vessels, bone, and muscles, leading to limb amputation in long-term users[10,11]. Of note, the tissue injury is due to iodine, phosphorus, and other toxic substances that remain after synthesis, not the opioid itself[10].

Gamma-Hydroxybutyrate

Gamma-hydroxybutyrate (GHB; "liquid X", "liquid ecstasy", "liquid G") and its precursors, gamma-butyrolactone (GBL) and 1.4-butanediol (BDO), are rapid-acting CNS depressants popular among revelers for its relaxant, euphoric, and purported aphrodisiac properties. GHB can lead to a loss of consciousness as well as induce amnesia, and like flunitrazepam (Rohypnol® ["roofie"]), it is used as a "rape drug". Because it reportedly promotes muscle mass and has been shown to elevate human growth hormone *in vivo*, GHB is also misused by bodybuilders.

Benzodiazepines

Benzodiazepines are among the most frequently prescribed medications in the US and the UK, where surveys indicate that ~10% of the population uses benzodiazepine sedatives/anxiolytics regularly. Although they are only mild euphoriants, benzodiazepines, in particular flunitrazepam (Rohypnol®; "roofies"), are commonly misused by polydrug addicts, alcoholics, and recreational drug users. Benzodiazepines are ingested (often with alcohol), snorted, or occasionally injected. They can lead to a decrease in alertness and a lack of coordination. Other side effects of benzodiazepines include disinhibition, anterograde amnesia, depression, and confusion, and with an overdose or intravenous use, hypotension and hypoventilation.

Cannabis

Cannabis ("marijuana", "pot", "grass", "herb", "weed") is a mixture of dried shredded leaves and flowers of the *Cannabis sativa* plant, which contains the chemical delta-9-tetrahydrocannabinol (THC). Medical marijuana is currently legal in over 39 states in the US and recreational use is legal in 21 states. It is usually smoked as a cigarette or through a pipe or bong. Marijuana cigarettes may be laced with other drugs, such as crack or heroin. The minimal amount of THC required to produce a perceptible psychoactive effect is ~10 mcg/kg body weight. Altered perception may be accompanied by an impairment of concentration, psychomotor coordination, and/or short-term memory. Arteritis has also been reported, and it may represent a particular form of Buerger disease, with cannabis acting as a cofactor in young smokers.

In many countries, including the US, there has been an increase in the use of synthetic cannabinoids ("K2", "Spice", "Black Mamba"), which also bind the THC receptor, but may have increased vasoactive and psychoactive effects, including psychosis. Cannabinoids can be sprayed onto dried plants or inhaled via vaporizer electronic cigarettes.

Anabolic Steroids

Anabolic steroids promote the growth of skeletal muscle and the development of male sexual characteristics. They are ingested (e.g. oxandrolone, oxymetholone, stanozolol) or injected intramuscularly (e.g. nandrolone, testosterone, boldenone) to increase muscle mass and boost physical performance. Their use can lead to androgenetic alopecia and acne (Table 89.2). Complications of anabolic steroid misuse include cardiovascular disease, hepatic disorders (e.g. peliosis hepatis, hepatic adenomas), acute and potentially chronic kidney injury, and mood disorders.

PATHOPHYSIOLOGY OF SUBSTANCE USE DISORDERS

Administration of addictive drugs, directly or indirectly, leads to direct activation of the brain reward system, resulting in feelings of pleasure and what is commonly referred to as a "high". Dopamine, opioid peptides, gamma-aminobutyric acid, and endocannabinoids play an important role in stimulation of the mesolimbic reward circuit[12].

EPIDEMIOLOGY

In 2020, the United Nations Office on Drugs and Crime estimated that globally 36 million people suffered from drug use disorders[13], but only a minority had received necessary treatment. According to the 2019 National Survey on Drug Use and Health (NSDUH), 20.4 million Americans age 12 years or older experienced a substance use disorder during that year (Fig. 89.1)[14]. The statistics were as follows: 71% had an alcohol use disorder, 41% had an illicit drug use disorder, and 12% had both. Drug abuse and addiction has cost American society more than $740 billion annually in lost workplace productivity, healthcare expenses, and crime-related costs.

CLINICAL FEATURES

Scars, Ulcerations, and Skin Necrosis

Intravenous drug users have a number of recognizable stigmata, identifying their habit to anyone with experience in illicit drug use. The most prominent of these are "skin tracks", which represent scarred veins with overlying hyperpigmentation (Fig. 89.2); inflammation from repeated non-sterile injections as well as injections of irritating drugs and adulterants lead to scarring. Intravenous drug users also have trails of punctures, hemorrhagic crusts, and ecchymoses along the veins of their extremities. The veins of the arms are often used initially for injections, and when these become scarred, drug is injected into the vessels of the hands, feet, legs, and neck. After years or decades of injecting drugs, more unusual locations such as the groin and digits become sites for injections[15]. Multiple injections into the distal extremities can lead to chronic, non-pitting edema, also known as puffy hand syndrome[16].

When attempting to inject veins, accidental extravasation can occur, leading to local tissue injury. In addition, as patent vessels become scarce, drugs are injected intradermally or subcutaneously. The resulting "skin popping" scars are depressed, irregular or circular, and often dyschromic (Fig. 89.3)[17]. Another method employed by individuals with no intact veins is to rub powdered drugs into self-inflicted lacerations or to inject drugs into the granulation tissue of self-perpetuated ulcerations (Fig. 89.4). These chronic non-healing ulcers have been referred to as "shooter's patches"[18,19].

Powdered drugs, such as cocaine and heroin, may be mixed or "cut" with other powdered substances[20]. *Diluents* (e.g. glucose, sucrose, lactose, mannitol) are pharmacologically inactive and serve to increase quantity and profits whereas *adulterants* are pharmacologically active. The latter include phenacetin, levamisole, caffeine, diltiazem, hydroxyzine, and lidocaine. Several adulterants, in particular quinine and dextrose, are highly sclerosing. Quinine was a popular adulterant

CUTANEOUS SIGNS OF DRUG ABUSE		
Lesion type	**Route(s)/associated drug(s)**	**Other associated signs**
Skin tracks	IV	Lymphedema
Skin popping scars	sc or dermal	Lymphedema
Ulcerations	IV/cocaine IV/propoxyphene sc/barbiturates sc, IM/pentazocine (± tripelennamine) IV, IM/xylazine	Circumferential pigmented bands (IV administration)
Retiform purpura with ulceration	Snorting, IV/cocaine adulterated with levamisole Smoking/crack cocaine adulterated with levamisole	Neutropenia, leukopenia Arthralgias, pulmonary hemorrhage, seizures, glomerulonephritis Autoantibodies: ANA, ANCAs (including anti-PR3, elastase), anti-dsDNA, lupus anticoagulant
Sclerosis	sc, IM/pentazocine sc/barbiturates sc/cocaine	
Palmar and digital hyperkeratosis	Smoking/crack cocaine	Madarosis Linear and circular black plaques on the fingers and palms Cuts and blisters on the lips
Nasal verrucae	Snorting/cocaine or heroin	Nasal irritation Septal perforation
Pseudoaneurysm	Arterial injection	Petechiae/purpura Local suppuration Reduced peripheral pulses
Thrombophlebitis (aseptic or septic)	IV, sc	Tender cord (if superficial) or deep vein thrombosis Extremity edema
Cellulitis	IV, sc, intradermal	Osteomyelitis and septic arthritis Infective endocarditis
Cutaneous *Pseudomonas* infection	IV, sc, intradermal/heroin sc/pentazocine ± tripelennamine	Folliculitis
Wound botulism (*Clostridium botulinum*, especially type A)	IM, sc/black tar heroin or quinine-adulterated heroin	Lymphedema Skin popping scars
Excoriations & self-induced ulcers	Methamphetamine	Dry leathery skin Red dry nose Dental caries/loss of teeth Weight loss Paranoia
Formication or delusions of parasitosis	Cocaine (chronic) Methamphetamine	
Pruritus	Opioids, including heroin Cocaine (chronic) Methamphetamine	With heroin: Flushing Pseudoacanthosis nigricans
Papulopustular acneiform eruption	MDMA (ecstasy)	
Acne vulgaris	Anabolic steroids	Coarse skin Hirsutism Male and female pattern alopecia Gynecomastia (in men) Testicular atrophy Clitoral enlargement Striae
	Methamphetamine Marijuana	Excoriations
Perinasal and perioral irritant dermatitis	Sniffing of volatile solvents and inhalants	

Table 89.2 Cutaneous signs of drug abuse. Additional signs include foreign body granulomas, hyperhidrosis (amphetamines, LSD), and parrot-beaked clawing of the nails (cocaine). ANA, anti-nuclear antibody, ANCA, anti-neutrophil cytoplasmic antibody; ds, double-stranded; IM, intramuscular; IV, intravenous; MDMA, methylenedioxymethamphetamine; PR3, proteinase 3; sc, subcutaneous.

because it has a bitter taste similar to heroin and it may accentuate the narcotic euphoria[21]. Levamisole-adulterated cocaine is associated with the development of retiform purpura, cutaneous necrosis, and pyoderma gangrenosum (see below).

Cocaine is highly vasoconstrictive and even inhaled freebase cocaine has induced skin and muscle infarction[22]. Injection of pentazocine, which may be combined with tripelennamine, can cause brawny, sclerodermatous skin thickening and large, irregularly shaped, deeply penetrating ulcers that may extend to muscle and then heal with significant atrophy[23] (Fig. 89.5). Fibrous myopathy, joint restriction, muscle contractures, brachial plexus neuropathy, inflexible ankylosis, and suppurative tenosynovitis are musculoskeletal and neurologic complications from intracutaneous and intravenous injections[3].

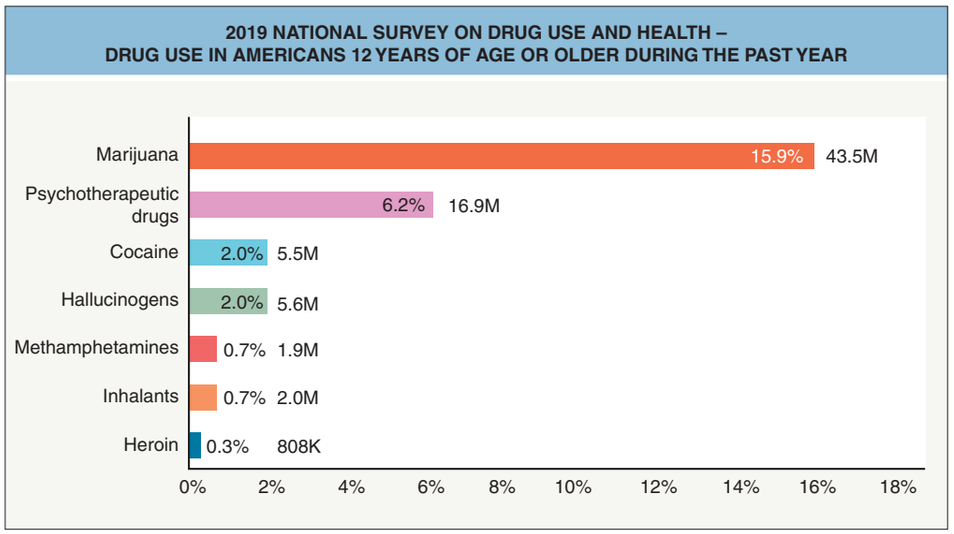


Fig. 89.1 2019 National Survey on Drug Use and Health – drug use in Americans 12 years of age or older during the past year. An estimated 10.8 million individuals experienced illicit drug use disorder +/- alcohol use disorder. Hallucinogens include MDMA (ecstasy), lysergic acid (LSD), and phencyclidine (PCP). *From Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health (HHS Publication No. PEP20-07-01-001, NSDUH Series H-55). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration 2020. Available at: https://www.samhsa.gov/data/.*



Fig. 89.2 Injection sites ("skin tracks") in an intravenous drug user. There is overlying hyperpigmentation and scarring of veins due to inflammation from repeated non-sterile injections as well as injections of irritating drugs and adulterants.

Bacterial Infections

Unless they participate in needle exchange programs, parenteral drug users rarely use sterile technique and may share needles, predisposing them to infections (Table 89.3). Skin and soft tissue infections are the most common disorders for which drug addicts seek healthcare or are hospitalized[24]. In one study, 32% of injection drug users had active abscesses, cellulitis, or both[25]. The most common presentation of cellulitis is an erythematous, tender, warm, edematous, indurated plaque (Fig. 89.6); however, only tenderness and edema may be apparent initially, and in darkly pigmented skin, erythema may be difficult to appreciate. In contrast to the general population, cellulitis more frequently involves the upper extremity.

Lymphangitis is commonly associated with these skin infections. In addition, underlying osteomyelitis or septic arthritis should be considered in cutaneous infections associated with injections. Although cellulitis is most frequently caused by *Staphylococcus aureus* followed by streptococci[24], bacterial cultures and sensitivity testing are required to identify organisms such as Gram-negative bacilli and anaerobes, which occur more commonly in this setting, as well as polymicrobial infections.

Black tar heroin, whose name reflects its dark and sticky consistency, is notably associated with *Clostridium* infections[26], perhaps due to its high water content which supports bacterial growth. Wound botulism due to *Clostridium botulinum* type A occurs almost exclusively in drug addicts, especially those who skin pop black tar heroin[27,28]. The spores of *C. botulinum* are not destroyed by heating the contaminated heroin and are inoculated into the subcutaneous tissue, where they germinate and produce toxin[26]. In the early stages, there is usually pain, tenderness and swelling, but a cellulitis or abscess may not be apparent. Botulism causes acute, usually descending and symmetric, flaccid paralysis with ophthalmoplegia, ptosis, or other cranial nerve dysfunction. Culture of the wound and detection of the toxin are confirmatory tests. Treatment consists of high-dose penicillin, antitoxin, and respiratory support.

There are other clostridial species that may lead to disease in those who inject drugs. *C. sordelli* infection can present as toxic shock syndrome, and an outbreak of *C. novyi* type A with a high mortality rate was linked to drug users who injected heroin extravascularly[29,30]. Tetanus has also been linked to injection drug use[26].

In addition to frequent injections and non-sterile technique (e.g. dirty needles), additional risk factors for the development of cutaneous abscesses include "skin popping", injecting speedballs (a mixture of cocaine and heroin that can induce ischemia within soft tissues), HIV infection, and "booting" (refilling the syringe with blood then reinjecting to ensure no drug left in the syringe)[25,31,32]. Abscesses from subcutaneous drug injection are often deep and multilobulated with extensive necrosis, requiring exploration and debridement. Those that are superficial may rupture spontaneously, leaving punched-out ulcers.

Abscesses may be contiguous with underlying bone in the setting of associated osteomyelitis. In intravenous drug users, acute or chronic osteomyelitis develops from an infection in surrounding soft tissue, hematogenous seeding of bacteria, or direct penetrating trauma from needles. The presence of osteomyelitis should be considered in anyone with continued pain after treatment of a soft tissue infection or when the infection recurs or responds slowly to appropriate treatment with antibiotics. Occasionally, septic arthritis can develop via these same mechanisms and may involve more unusual sites, e.g. the sternoclavicular joint in those who "shoot the pocket" (jugular vein)[24].

Cervical abscesses usually occur in the anterior cervical triangle and may cause life-threatening complications such as mediastinitis, pneumomediastinum, airway obstruction, internal jugular vein thrombosis, and extension into the carotid sheath. Abscesses in the groin may present with only tenderness and edema. These abscesses can be deep and extensive, especially if they originate in the femoral triangle. In general, the degree of pain usually exceeds that anticipated from the clinical findings.

MRI is superior to CT imaging in detecting the presence of fluid and purulent collections in skin, joints, or tendon sheaths, but both are valuable in confirming the presence of deep and groin abscesses[33]. Sinography can be employed to delineate the extent of an abscess cavity or fistula. In those who inject illicit drugs, it is crucial to recognize that necrotizing fasciitis with or without myositis can present as erythema (77%), fluctuance (20%), edema (20%), or induration (43%), clinically resembling a non-fluctuant abscess yet requiring extensive subfascial debridement[34].



Fig. 89.3 "Skin popping" scars. A–C Multiple circular depressed scars, some with rims of postinflammatory hyperpigmentation, admixed with circular hemorrhagic crusts overlying ulcerations. Cocaine was injected into the thighs.

Fever and leukocytosis are often present. In some cases, only swelling or subtle cellulitis is apparent. However, severe pain, disproportionate to the physical findings, is typically present (85% of patients with necrotizing fasciitis in one series)[35]. If this complaint is disregarded or misinterpreted as a request for narcotics, the outcome can be devastating.

Notably, the classic cutaneous findings of necrotizing fasciitis, such as bullae (noted in 3% of patients), tissue crepitus (3%), and skin necrosis (10%), are only present in a small minority of those who inject illicit drugs[34]. For this reason, surgical exploration is mandatory in any parenteral drug user with cellulitis and unexplained severe pain. Any necrotic tissue should be debrided surgically and cultured (Fig. 89.7).

Fungal Infections

Dermatophytosis is very common in addicts. Disseminated candidiasis associated with injections of brown heroin was reported in the 1980s and found to be caused by an overgrowth of yeast in the lemon juice used to dissolve the heroin[36]. These patients developed high fevers, rigors, headaches, myalgias, and occasionally jaundice, but, at this stage, blood and urine cultures rarely demonstrated organisms. Most patients eventually developed pustular folliculitis and painful nodules in hair-bearing areas (scalp, moustache, and beard)[36]. The lesions resembled bacterial folliculitis but potassium hydroxide examination and lesional biopsy specimens demonstrated the presence of yeast[36].

In 2017, 10% of patients with candidemia were found to have a history of recent intravenous drug use, increasing to ~35% in individuals ages 19–44 years[37]. Of note, injection drug use is also a predisposing factor for zygomycosis. The characteristic cutaneous lesion is a cellulitic plaque or abscess with extensive necrotic tissue.

Granulomas

Injection of hydrous magnesium silicate (talc) or starch can produce granulomatous responses in the walls of veins as well as in the deep dermis and subcutaneous tissue, resulting in the formation of firm, movable cutaneous nodules[38] (Fig. 89.8; see Ch. 94). Talc can be found in tablets that have been crushed, diluted in liquid, and then injected. Talc granulomas may also develop in the lungs, liver, lymph nodes, spleen, and bone marrow. Granulomas may not appear for up to 50 years after subcutaneous injection and results from the conversion of larger silica particles to smaller particles in colloidal form[38]. When the inflammatory nodules ulcerate, they can heal with epidermal pigmentary changes, woody induration of the dermis and subcutaneous tissue, and retracted cicatrices.

Mucous Membrane Lesions

Snorting cocaine causes erythema of the nasal mucosa, nasal irritation, anosmia, and rhinitis, and it may lead to epistaxis, perforation of the nasal septum, and osteolytic sinusitis. Nasal verrucae (snorters' warts) can also develop. Less often, sniffing heroin causes these findings. A complex consisting of nasal collapse, septal perforation, palatal retraction, and pharyngeal wall ulceration has been described in cocaine snorters. Cuts and blisters on the lips from glass or metal smoking pipes have been noted in addicts who smoke crack cocaine, while ageusia, halitosis, and repeated lip smacking are additional signs of cocaine abuse. The labial mucosa may become dry in heroin or amphetamine users, and amphetamine use may also cause dysgeusia and xerostomia. There are reports of men and women applying cocaine



Fig. 89.4 Chronic, self-perpetuated, non-healing ulceration of the hand ("shooter's patch"). The patient injected heroin into the granulation tissue. *Courtesy Jake Wang, MD, and Jean L. Bolognia, MD.*



Fig. 89.5 Atrophic depressions of the thighs and extensive calcification from multiple pentazocine injections.

powder to their genitalia, including the glans penis[39]. These practices can lead to priapism, irritant dermatitis, and ulceration. Penile ulcers have also developed after injections of heroin into the shaft veins[40].

Chronic drug users frequently have marked dental and gingival disease due to poor hygiene (Fig. 89.9). Areca palm seeds (betel nuts) contain the stimulant arecoline and habitual chewing of these nuts, a practice in some areas of Asia, stains the teeth and is associated with the development of oral leukoplakia and oral submucous fibrosis[41]. The addictive habit of chewing *Catha edulis* tree leaves (also referred to as khat or qat), which contain the alkaloid stimulant cathinone, is popular in several African and Middle Eastern countries and can lead to oral keratotic white plaques[42].

Red or "bloodshot" eyes due to conjunctival vascular injection can occur with marijuana, cocaine, or phencyclidine (PCP) use. Repeated sniffing of volatile solvents and inhalants, such as glues, lighter fluid, butane gas, spray paints, gasoline, cleaning fluids, and aerosol sprays, can cause nasal, labial, perioral, and perinasal irritant dermatitis (sniffer's rash). The skin lesions may be discrete papules or erosions that are often confused with acne.

INFECTIOUS COMPLICATIONS OF DRUG ABUSE	
Type of infection	**Organisms and/or associated features**
Bacterial	
Abscesses and cellulitis	• *Staphylococcus aureus* > *Streptococcus* spp. > Gram-negative bacilli, anaerobes • Often polymicrobial • Lymphangitis is common • *Clostridium* infection (e.g. *C. botulinum* type A) with adulterated heroin (e.g. black tar skin popping), *C. tetani* • *Pseudomonas aeruginosa* with pentazocine ± tripelennamine or heroin injections • *Eikenella corrodens* with methylphenidate injections (esp. into the femoral triangle)
Necrotizing fasciitis	• Polymicrobial in 60%–85% of cases • Includes anaerobes in ~10%
Pyomyositis	• *S. aureus* most common, but can be polymicrobial • AIDS is an additional risk factor
Septic thrombophlebitis	• Associated with endocarditis or pulmonary emboli
Septic arthritis	• Increased likelihood of Gram-negative bacilli (esp. *Pseudomonas* spp.)
Osteomyelitis	• In *Pott's puffy tumor*, frontal sinusitis leads to frontal bone osteomyelitis and a subgaleal abscess; may be complicated by an epidural abscess
Endocarditis	• *S. aureus* > *Streptococcus viridans* > Gram-negative (esp. *Pseudomonas* spp.), polymicrobial • Often right-sided (e.g. tricuspid valve)
Fungal	
Candidiasis	• Disseminated candidiasis with pustular folliculitis; historically associated with injections of brown heroin • Septic arthritis, osteomyelitis, endocarditis (*C. parapsilosis, C. tropicalis*), septicemia ("fungemia syndrome")
Aspergillosis	• Pulmonary infections from contaminated marijuana • Dissemination and endocarditis may occur
Zygomycosis	• Cellulitic plaques or necrotic abscesses
Viral	
Hepatitis	• Hepatitis B viral infection may be associated with immune complex disease (e.g. arthritis, urticarial vasculitis) during the period of antigenemia • Syringe/needle sharing accounts for more than half of new cases of hepatitis C in the US
HIV	• Adults and adolescents who inject drugs account for 10% of new HIV infections in the US

Table 89.3 Infectious complications of drug abuse.

Burns

Burns are common in addicts with an altered state of mind, including burns from lit matches, cigarettes, paraphernalia, and contact with fire during cooking. Cigarette burns typically occur on the digits and sternum as the cigarette was being held or smoked prior to loss of



Fig. 89.6 Cellulitis of the lower extremity in an intravenous drug user.



Fig. 89.7 Necrotizing fasciitis of the upper extremity with extensive tissue necrosis in an intravenous drug user. Surgical debridement has been performed.

consciousness. Singeing of the eyelashes and eyebrows, resulting in madarosis, may be caused by rising hot vapors during the smoking of crack cocaine. Crack addicts may also have linear or circular black plaques on the fingers and palms.

Formication

Prolonged use of cocaine may lead to the development of formication, i.e. tactile hallucinations of insects crawling on or under their skin ("coke bugs"). Repetitive, stereotypical skin picking leading to



Fig. 89.8 Foreign body granuloma formation leading to papules at the sites of injection of adulterated heroin.



Fig. 89.9 Tooth decay is a common physical finding in hardcore drug addicts (arrow). The term "meth mouth" is applied to those who abuse methamphetamines.

excoriations and disfiguring skin ulcers on the face and extremities is a common finding in methamphetamine abusers. Not uncommonly, these individuals also feel that bugs are crawling under their skin, and cocaine or crystal methamphetamine use should be considered in anyone who presents with delusions of parasitosis as well as neurotic excoriations (Fig. 89.10). In addition to "meth mites", other cutaneous signs of methamphetamine abuse are dry skin, pruritus with lichenification, acne excoriée, a red dry nose, sweating, an unpleasant body odor, and premature aging. Patients may also have tooth decay, aggressive behavior, and paranoia.

Additional Cutaneous Findings

Circumferential, pigmented bands due to pressure from tourniquets are common in intravenous drug users with darkly pigmented skin. "Soot tattoos" are produced by injections of residual carbon on the needle after flaming[43]. Hyperkeratosis of the fingers and palms is common in heavy users of crack cocaine. Traumatic bullae at the site of injection are occasionally observed. Pressure erythema, bullae, and ulcers may develop in comatose patients after an overdose with barbiturates or other sedative drugs (Fig. 89.11; see Ch. 33).

As noted previously, use of both cocaine and crystal methamphetamine can lead to pruritus. The feeling of euphoria induced by heroin is frequently accompanied by skin flushing and itching, as well as a dry mouth, watery eyes, and rhinorrhea. Generalized or focal, especially genital, itching during the euphoric stage following heroin administration has been named "high pruritus"[44].

Hyperhidrosis is a common adverse effect of amphetamines and LSD. Within 30 to 90 minutes of LSD ingestion, the user feels a wide range





Fig. 89.10 Multiple excoriations in a cocaine addict. A, B The patient felt "crawling" sensations of his skin.

of emotions, accompanied by sweating, increased body temperature, dry mouth, tremors, and dilated pupils. Piloerection, paresthesias, and flushing are manifestations of the somatic phase of LSD intoxication, while pseudohallucinations and synesthesias occur during the perceptual phase. Hypoesthesia is a common manifestation of low-dose exposure to PCP.

There have been scattered reports in habitual MDMA (ecstasy) users of a papulopustular (acneiform) facial eruption, which may indicate a higher risk of severe adverse effects, such as hepatic damage. In some cases, the eruption responded to topical metronidazole[45]. Acne ranging from mild to cystic, especially on the trunk, is common among users of anabolic steroids. Other cutaneous effects of anabolic steroid abuse include oily hair and skin, male and female pattern alopecia, hirsutism in women, and coarse skin (see Table 89.2). Most are reversible if the abuser stops taking the drugs, but some are permanent.

Drug-Induced Reactions

Drug hypersensitivity reactions (especially morbilliform eruptions), urticaria (opioids, barbiturates, amphetamines), bullous eruptions, fixed drug reactions, small vessel vasculitis, Stevens–Johnson syndrome, and toxic epidermal necrolysis occur more frequently in illicit drug users than in the general population (Table 89.4). Pigmented circular patches on the skin and mucous membranes of addicts may reflect a fixed drug eruption.



Fig. 89.11 Coma bulla. Large bulla with subsequent erosion on the medial ankle due to prolonged coma from barbiturate overdose.

DRUG-INDUCED CUTANEOUS REACTIONS					
	Opioids	**Barbiturates**	**Amphetamines**	**Cocaine**	**Marijuana**
Morbilliform eruption	✓	✓	✓		✓
Bullous eruption	✓	✓		✓*	
Fixed drug eruption	✓	✓	✓	✓*	✓*
Small vessel vasculitis	✓†	✓	✓	✓‡	
Stevens–Johnson syndrome	✓	✓	✓*	✓	
Toxic epidermal necrolysis	✓	✓	✓*		
Urticaria	✓	✓	✓	✓	✓
Angioedema	✓	✓	✓	✓	
Acute generalized exanthematous pustulosis	✓*	✓*		✓*	✓*
Vasculopathy with retiform purpura				✓¶	

*Isolated case reports.
†Also polyarteritis nodosa with heroin.
‡Also eosinophilic granulomatosis with polyangiitis.
¶Levamisole-adulterated; can be accompanied by small vessel vasculitis.

Table 89.4 Drug-induced cutaneous reactions. Pemphigus (vulgaris, vegetans) has been reported with intranasal cocaine use. In patients with a morbilliform eruption, consider the possibility of DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome.

Vascular Lesions

The most common vascular lesions are ecchymoses and even hematomas over injected vessels. Petechiae may form distal to the placement of a tourniquet. Vascular compromise of the hands is characterized by discoloration, edema, and a cold temperature. Intense burning pain is often experienced after intra-arterial injection of drugs[46]. This is followed within hours by edema of the affected limb. Although the peripheral pulses usually remain strong, cyanosis and patches of livedo reticularis can develop followed by distal ischemia and even necrosis and ulceration. Other manifestations reported after accidental or intentional drug injections into an artery include distal purpuric and pustular nodules, presumably as a result of embolization (Fig. 89.12).

Septic thrombophlebitis results in tender, swollen extremities with or without erythema. A tender cord may be present when the affected vein is superficial, but deep vein thrombophlebitis is easily misdiagnosed as cellulitis or an abscess, either of which may be an associated complication. Deep vein thromboses are diagnosed via Doppler ultrasonography.

Infected pseudoaneurysms result from non-sterile injuries to arteries (arterial wall or perivascular tissue) during intra-arterial injection of drugs. They are most commonly seen in the groin, followed by the extremities, with the close proximity of the femoral artery to the femoral vein one possible explanation for inadvertent arterial injections[47,48]. The typical lesion is a tender, diffusely indurated mass in the setting of intravascular drug use. In some patients, the mass may be pulsatile, suppurative, or purpuric; a bruit and decreased peripheral pulses may be present. Imaging assists in distinguishing infected pseudoaneuryms from abscesses[47,48], and treatment options include parenteral antibiotics, ligation, and reconstruction.



Fig. 89.12 Purpuric papules of the palm due to emboli of pill fragments following an intra-arterial injection. *Courtesy Jean L. Bolognia, MD.*

Bacteremia should be excluded in all injection drug users with skin and soft tissue infections and, if present, *infective endocarditis* should then be excluded. The latter is most commonly due to staphylococci and less often streptococci, and the tricuspid valve is involved in up to 80% of patients. In contrast, ~15% of all cases of infective endocarditis have right-sided cardiac involvement. Although symptoms of right-sided endocarditis include fever, cough, dyspnea, and pleuritic chest pain, there may be a delay in diagnosis. In patients with paradoxical emboli or left-sided endocarditis, brain and splenic abscesses from septic emboli can develop as well as several cutaneous signs: conjunctival hemorrhages, splinter hemorrhages, Janeway lesions, Osler nodes, and purpuric, ischemic, or necrotic lesions due to septic emboli. Infective endocarditis associated with injection drug use is also one of the rare settings in which polymicrobial endocarditis is encountered[24,49,50]. Of note, mycotic aneurysms occur in 15%–25% of patients with infective endocarditis, most frequently in the femoral artery.

Levamisole-adulterated cocaine is associated with neutropenia and retiform purpura that can become necrotic (Fig. 89.13)[51–54]. Histologic examination demonstrates microvascular thromboses within the dermis, sometimes accompanied by leukocytoclastic vasculitis (Fig. 89.14). Patients may also have anti-neutrophil cytoplasmic antibodies or anti-phospholipid antibodies and decreased levels of protein C and S. Pyoderma gangrenosum has also been associated with levamisole-contaminated cocaine[55]. While levamisole can be identified in the urine, it may not be detectable at the time of evaluation due to its half-life of 4 hours[56]. However, drug paraphernalia can still be tested for levamisole[57]. Cocaine-induced hypercoagulability (thrombophilia) can lead to superficial and deep venous thromboses, arterial thromboses, and cutaneous infarctions, and cocaine use may unmask subclinical systemic sclerosis. Illicit use of xylazine ("tranq", "zombie drug"), a veterinary sedative, can lead to multiple cutaneous ulcerations, possibly due to vasoconstriction.

Systemic Complications

In addition to infective endocarditis, parenteral drug users are at high risk for contracting bloodborne viruses, with a recent multistage systematic review estimating the worldwide prevalence of HIV to be ~18%, HCV ~50%, and HBV ~9%[58]. Globally, up to 40%–45% of new HCV infections are thought to be due to injection drug use[59].



Fig. 89.13 Retiform purpura due to levamisole-adulterated cocaine – clinical features. A, B Multiple sites of retiform purpura on the legs and arm in two patients. **C** The earlobe is a common site of involvement and purpuric lesions of the earlobe had been described previously as a side effect of levamisole. Up to 70% of the cocaine in the US at the time of writing contained levamisole but <3% of the heroin supply. *A, Courtesy Boni Elewski, MD and India Hill, MD; B,C, Courtesy Jeffrey P. Callen, MD.*

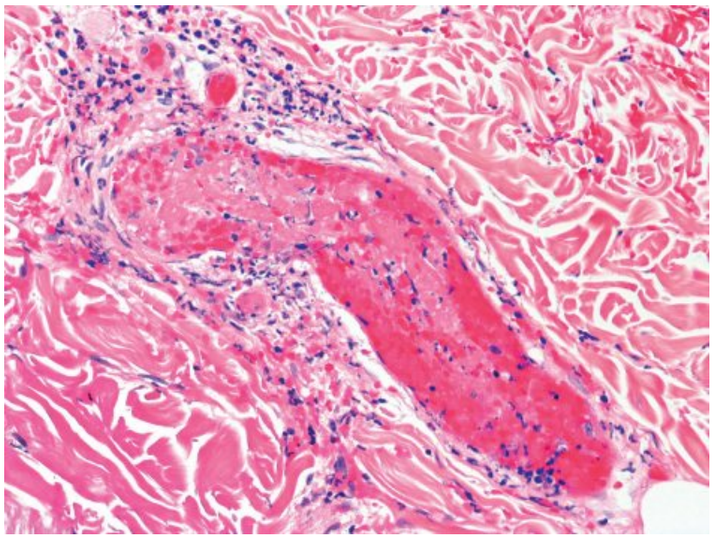


Fig. 89.14 Vasculopathy due to levamisole-adulterated cocaine – histopathologic features. There is often a mixed picture with evidence of microvascular thrombi as well as leukocytoclastic vasculitis. *Courtesy Luis Requena, MD.*

TREATMENT OF DRUG ADDICTION	
Drug	**Treatments**

Opioids	• Drug detoxification
	  • Buprenorphine + naloxone
	  • Clonidine + naltrexone
	• Maintenance therapy
	  • Agonist (methadone, levomethadyl*)
	  • Partial agonist (long-acting buprenorphine)
	  • Antagonist (naltrexone, including long-acting form)
	• Additional measures (counseling, psychotherapy, acupuncture)

Cocaine	• Drug rehabilitation, psychosocial interventions • Desipramine, bupropion, or citalopram may be used
Amphetamines	• Drug rehabilitation, psychosocial interventions • Stimulant agonists (e.g. dextroamphetamine, methylphenidate), naltrexone, or topiramate may be used • Antidepressants (e.g. bupropion, mirtazapine), riluzole, and pexacerfont are less effective
*Withdrawn from the US market due to risk of cardiac arrhythmias.	

Table 89.5 Treatment of drug addiction. Buprenorphine appears to act as a partial agonist of μ and κ opioid receptors; tolerance with chronic use may not develop, presumably due to the lack of δ-agonist activity. Buprenorphine is available as a sublingual tablet, subcutaneous depot, or subdermal implant as well as in combination with naloxone as a sublingual tablet or transmucosal film. Injection of the transmucosal formulations has been associated with soft tissue infections. GABA, gamma-aminobutyric acid.

Cutaneous manifestations of these viral infections may also be present (see Table 81.8 & Ch. 78).

Drug users also have a high prevalence of sexually transmitted diseases, due to multiple partners, the sex trade, and failure to use condoms[60]. However, narcotic abuse is a cause of false-positive non-treponemal syphilis screening tests (e.g. VDRL, RPR). In these cases, treponemal tests (e.g. MHA-TP, FTA-ABS) will be non-reactive. In addicts who have had syphilis, both types of tests will be positive, and the titers of the non-treponemal test may not decrease rapidly after treatment.

Nephrotic syndrome from amyloidosis has been reported in heroin skin poppers and intravenous drug users with chronically draining skin lesions.

TREATMENT

A detailed discussion of the management of drug addiction is beyond the scope of this chapter. When providing care to persons suspected of drug use disorder, it should be remembered that even admission of drug use is difficult, as patients risk disapproval and overt or concealed rejection even from medical professionals.

The selection of antibiotics to treat skin infections should be guided by antibiotic sensitivities of the cultured organisms (Table 89.5). With the emergence of community-acquired MRSA and the increased risk of polymicrobial infections, broad-spectrum coverage is recommended until culture results and antibiotic sensitivities are determined. However, even with aggressive surgical and medical treatment, the mortality rate of necrotizing fasciitis in drug addicts is ~20% and limb amputation is necessary in another 18%[34], necessitating prompt recognition and surgical consultation.

Skin grafting of large ulcers may be necessary when healing does not occur with compression and appropriate dressings. Some substance abusers may deliberately sabotage the skin graft by injecting through it or into the vacuum (VAC) dressing tubing[19]. Recovered parenteral drug users often wear long-sleeved shirts and other garments to hide the stigmata of their past addiction and may seek help in diminishing the appearance of these signs. Hypertrophic scars improve with intralesional injections of corticosteroids and pulsed dye laser treatments (see Ch. 98). Hyperpigmented scars require the use of pigment-specific lasers and bleaching agents, including hydroquinone. Tissue augmentation with hyaluronic acid or fat can improve the appearance of depressed scars. Such scars may also respond to low-fluency treatments with visible light lasers.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 89.1 Linear supravenous hyperpigmentation due to previous injections of speedballs (mixture of heroin and cocaine). *Courtesy Jean L. Bolognia, MD.*



eFig. 89.3 Large purpuric plaque with irregular inflammatory border due to levamisole-adulterated cocaine. *Courtesy Ian W. Tattersall, MD, PhD.*



eFig. 89.2 Large scar due to previous shooter's patch. *Courtesy Jake Wang, MD and Jean L. Bolognia, MD.*

90 Skin Signs of Abuse

Sharon S. Raimer, Lauren Raimer-Goodman and Ben G. Raimer

Chapter Contents

Child Abuse *1622*
Elder Abuse *1626*

CHILD ABUSE

Synonym: ■ Battered child syndrome

Key features

- Signs of physical abuse include: unexplained bruises; injuries of the thorax, abdomen, buttocks, genitals, chin, ears, or neck; curvilinear marks; and cigarette burns or other well-demarcated burns
- Signs of sexual abuse include laceration or bruising of genital or perianal tissue, complete transection of the posterior hymen, and scars of the perianal area or posterior fourchette

Introduction

Child abuse encompasses the broad spectrum of non-accidental maltreatment of children, including physical, emotional, and sexual abuse as well as neglect. Physical abuse is defined as non-accidental injury of a child; the injury may be the result of a single abusive episode or occur over a longer period of time. In the US, ~2.5 in 100 infants <1 year of age and one in 100 children 1–3 years of age are victims of abuse or neglect[1]. Because they are demanding, less verbal, and defenseless, infants and children <3 years of age are at greatest risk, accounting for almost 30% of child abuse victims. In 2016, 8.5% of childhood injuries reported to the National Trauma Data Bank were due to intentional assault, and 6% of assault-related injuries resulted in the child's death[2]. Abused children are more likely to sustain serious intracranial, thoracic, and abdominal injuries than children who are injured accidentally[3].

Parents may describe abused children as "difficult", which in fact may be true; however, the parents' attempts to intervene in an excessive and inappropriate manner constitute abuse. Premature infants, disabled children, and children with behavioral problems are at increased risk of abuse. Parents who abuse their children were often themselves abused as children. They are frequently immature, dependent, socially isolated individuals. Often, they do not handle stress well, and a personal or family crisis may trigger an abusive episode. It is important that all physicians recognize signs of physical abuse in children, as it tends to be repeated, and an intentionally injured child is at high risk for severe physical injury in the future.

Physical neglect is a failure to provide the necessities of life for a child, including nutrition, clothing, housing, medical care, and a safe, supervised environment. Emotional abuse or neglect results when parents fail to provide a nurturing environment that permits the child to grow and reach his or her full potential.

Sexual abuse can be defined as engaging a child in a sexual activity that the child cannot comprehend, for which the child is developmentally unprepared and cannot give informed consent, and/or that violates the social and legal taboos of society[4]. The child's involvement may be coerced with physical threats, rewarded through bribes, or induced via misrepresentation of moral values. Sexual abuse can be assaultive or non-assaultive. Non-assaultive sexual abuse often goes unreported since there is usually little or no physical injury to the child. In contrast, assaultive sexual abuse is characterized by physical injury and violence. Both types of sexual abuse may result in severe emotional trauma to the child.

History

Maltreatment of children has always existed, but in 1946, Dr John Caffey, a pediatric radiologist, initiated medical concern about child abuse by reporting six children who presented with skeletal fractures and subdural hematomas that were clearly related to trauma[5]. The immense importance of this problem was not generally recognized until 1962, when Kempe et al.[6] coined the term *battered child syndrome*, the findings of which include inadequately explained signs of trauma, multiple fractures at different stages of healing, and/or failure to thrive that responds to nutritional therapy or placing the child in an emotionally supportive environment.

Epidemiology

Child abuse is a worldwide problem that occurs among all ethnic and racial groups and in families of all socioeconomic and educational levels. In the US, single-parent families with incomes below 200% of the poverty threshold have much higher probabilities of violence[7]. Child abuse occurs more frequently when other problems such as unemployment, substance abuse, unplanned pregnancies, or discord between parents increase the stress on individuals within the family. Boys are at greater risk for serious injury than are girls, and infant boys have the highest fatality rate[1].

The perpetrator of sexual abuse is often a person well known to the child, most often the natural father, followed in frequency by a stepfather or another close relative. Although reports of abuse are about three times more likely in girls than in boys[8], sexual abuse in boys may be more likely to go undetected and/or unreported. The risk for sexual abuse rises during preadolescence and in family situations with a stepfather in the household, children living without one or both of their natural parents, and children whose mothers are disabled, ill, or extensively out of the home[8]. Overcrowded living conditions may also be associated with an increased risk of child sexual abuse[9].

Sexual abuse occurring during sex trafficking of minors, which involves the engagement of youth in sexual acts in exchange for money or items of value, is an increasingly recognized global health crisis[10]. The United Nations Children's Fund estimates that 1.2 million children are trafficked for sexual exploitation worldwide annually, including 200 000 children in the US. The average age of child sex trafficking victims is 12–14 years[11]. While many domestically trafficked children are homeless, runaways from abusive homes, or vulnerable due to unmet needs, others from stable homes are recruited via social media or lured away from public places such as malls and bus stops[11].

Clinical Features

Physical abuse

Physical abuse is frequently identified by *bruises* (ecchymoses) (Fig. 90.1) that may be located in areas not normally prone to accidental injury, most commonly the head and neck (particularly the face) followed by the buttocks, trunk, and arms[12]. They are often large, multiple, and in clusters. The shape of the bruises may help to identify the object with which the child was struck. Linear bruising is produced when an object such as a rod, stick, or strap is used to strike a child. Hematomas and traumatic fractures of underlying bone may be present.

Loop marks are perhaps the single most characteristic finding in child abuse. Such curvilinear marks are produced by small ropes, electrical cords, or belts and appear randomly over the body as a result of striking a struggling child[13].

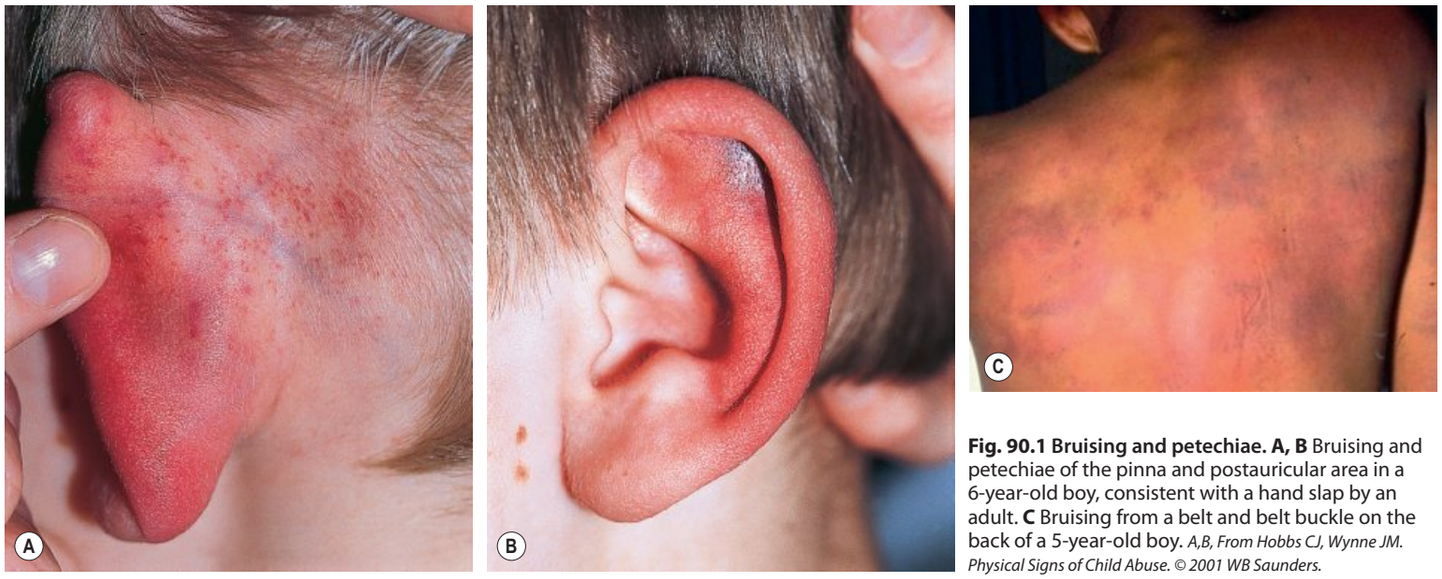


Fig. 90.1 Bruising and petechiae. A, B Bruising and petechiae of the pinna and postauricular area in a 6-year-old boy, consistent with a hand slap by an adult. **C** Bruising from a belt and belt buckle on the back of a 5-year-old boy. *A,B, From Hobbs CJ, Wynne JM. Physical Signs of Child Abuse. © 2001 WB Saunders.*



Fig. 90.2 Healing injury due to binding around the ankles.



Fig. 90.3 Injury produced by a cigarette burn.

Buckle imprints from belts can often be matched to the particular belt buckle used to strike the child. Buckles produce deep ecchymoses (see Fig. 90.1C) and can result in injury to underlying organs and bones.

Pinch marks, particularly on the ears or in the genital region of boys, should alert the examining physician to the possibility of abuse. Male toddlers rarely sustain bruises on the genitalia secondary to a fall.

Blunt trauma can be a very severe form of abuse that may or may not result in cutaneous lesions. Blunt trauma to the abdomen can lead to severe injury or even death of a child. Soft intra-abdominal organs are injured when they are slammed against the vertebral column by a kick or severe blow delivered to the abdomen. Blunt trauma in the form of slapping injury causes capillaries to break between the digits, producing linear bruises that outline the fingers. This often leaves the imprint of a hand on the child's skin, which can frequently be matched to the perpetrator.

Binding injuries are more likely to occur when the perpetrator is emotionally disturbed or psychotic. Acute binding injuries cause edema of the soft tissue around the wrists and ankles that may resemble rope burns with redness and warmth or abrasions (Fig. 90.2). Chronic binding injuries may result in bands of postinflammatory hyperpigmentation.

Traumatic alopecia results from forcefully pulling out the scalp hair. The occipital region is the most common location. When a large tuft of hair is abruptly pulled out, the underlying scalp may hemorrhage with subsequent hematoma formation.

Human bite marks leave the indelible mark of the perpetrator and may serve to identify the abuser. Adult human bite marks, which can be identified by the width of the dental arch (>4 cm), must be distinguished from those of a child, since toddlers may be bitten by their peers. Human bites produce a crushing type of injury, whereas animal bites typically result in puncture wounds.



Fig. 90.4 Branding injury on the thigh from a fork.

Thermal burns constitute an especially traumatic form of injury to the young child, and the abuser in such cases is likely to be suffering from a psychiatric disorder. Cigarette burns represent a frequent form of thermal injury and tend to be randomly distributed (Fig. 90.3). Branding injuries take the shape of the heated object (Fig. 90.4). Dunking scald injuries occur most often in infants and toddlers, and scalds on the



Fig. 90.5 Burn injury due to dunking in hot water. Note the sharp, symmetric lines of demarcation on the lower legs. *Courtesy Leo Litter, MD.*

buttocks may be associated with attempts to toilet train an infant. "Donut-type sparing" on the child's buttocks may be apparent when the buttocks are held against the cooler tub or basin while the surrounding hot water scalds the remaining immersed skin. Dunking scalds of the extremities leave a characteristic "stocking and glove" distribution with a very sharp demarcation of the burn (Fig. 90.5). In non-accidental burns, the adults responsible for the child (and possibly the burn) frequently claim not to have witnessed the burning incident, and other relatives commonly bring the child to the hospital. A delay between the injury and seeking medical care often occurs with inflicted burns.

A child may present with skin signs of multiple types of physical abuse. Such a child is at high risk for severe injury concurrently or in the future. Both acute and healing injuries are frequently present in chronically abused children.

Factitious disorder imposed on another, also known as *Munchausen syndrome by proxy*, is an uncommon form of abuse that typically affects children. In this condition, a parent or caregiver induces or feigns illness in a child for psychological gain. The perpetrator is often the mother, and the father is classically absent or uninvolved in care of the child. Cutaneous manifestations occur in ~9% of cases[14].

Physical neglect

Physical neglect usually results in a constellation of relatively obvious findings, including signs of poor nutrition, hygiene, and general health. Children may have old untreated injuries, dermatitis, and infestations of the skin and hair, and they typically have not received required childhood immunizations.

Emotional deprivation

Emotional neglect or deprivation accounts for at least half of the children in high-income countries diagnosed with *failure to thrive*. These children fail to grow and develop in their home environment despite adequate caloric intake, while they thrive with food and stimulation in a hospital setting or foster home. There are no characteristic physical findings or diagnostic laboratory tests for these children. The diagnosis can be rendered only after other potential causes of failure to thrive have been excluded, and it is usually confirmed when the child demonstrates "catch-up" growth and development outside the disturbed home environment.

Sexual abuse

The diagnosis of child sexual abuse is based on a combination of findings in the patient's history, physical examination and, when indicated, laboratory evaluation. Children rarely fabricate reports of sexual abuse, and any such description by a child should be thoroughly investigated. Unfortunately, false accusations by parents involved in custody disputes do occasionally occur and are a burden to the medical and legal systems.

Physical signs that are suggestive of childhood sexual abuse are described in Table 90.1. However, physical findings are present in a small minority of sexually abused children. Many types of sexual molestation, such as fondling and oral sodomy, usually do not leave physical signs. Even when mild or moderate injuries occur (e.g. petechiae, ecchymoses, abrasions, superficial lacerations), healing in the anogenital area often takes place within days, resulting in very subtle or undetectable physical findings[15,16]. In a large study of sexually abused girls, physical findings were present in 21% (73/340) of those examined acutely (within 72 hours) but only 2% (26/1160) of those examined nonacutely[17]. In the absence of a plausible history of accidental injury, findings that should alert the physician to the possibility of abuse include laceration or bruising of genital or perianal tissues, complete transection of the posterior hymen, and scars of the perianal area or posterior fourchette[18,19] (Fig. 90.6; see Table 90.1).

It is important to be aware of normal physical findings in the genital area of female children. Studies of newborn girls have noted that a hymen is invariably present and anterior hymenal clefts are common, but posterior clefts are not normally seen[15]. A complete hymenal cleft located between 4 and 8 o'clock is suggestive of penetration[16,17]. The presence of semen, detected via testing for prostatic acid phosphatase, or sperm is indicative of abuse; non-perinatally acquired syphilis, gonorrhea, or (if other modes of acquisition are excluded) HIV infection confirms mucosal contact (most likely sexual) with infective bodily

PHYSICAL FINDINGS SUGGESTIVE OF CHILD SEXUAL ABUSE
Findings from trauma to genital/perianal tissue *highly suggestive of abuse**
• Laceration or bruising of the labia, posterior fourchette, hymen, vagina, penis, scrotum, perineum, or perianal area • Petechiae or abrasions of the hymen • Scar of the posterior fourchette or perianal area • *Complete* hymenal transection/cleft *below* the 3–9 o'clock location, extending to or through the base of the hymen • Signs of female genital mutilation, such as loss of part or all of the clitoral hood, clitoris, labia minora or labia majora, or a vertical linear scar adjacent to the clitoris
Genital/perianal findings associated with abuse in some studies
• Complete anal dilation with relaxation of internal and external anal sphincters, in the absence of predisposing factors such as constipation, encopresis, sedation, and neuromuscular conditions • *Incomplete* hymenal notch/cleft *below* the 3–9 o'clock location, extending *nearly* to the base of the hymen† • *Complete* hymenal transection *at* the 3–9 o'clock location, extending to or through the base of the hymen†
Sexually transmitted infections‡
• Genital, rectal, or pharyngeal *Neisseria gonorrhea* or *Chlamydia trachomatis* infection • Syphilis • *Trichomonas vaginalis* infection • HIV, if transmission by blood products or contaminated needles is excluded
*Unless the child and/or caregiver provides a timely and plausible description of accidental anogenital straddle, crush, or impalement injury, or there is a history of past surgical interventions confirmed by review of medical records. †Should be confirmed using additional examination positions and/or techniques, to ensure that not normal variants. ‡Confirmed using appropriate testing, with perinatal transmission excluded.

Table 90.1 Physical findings suggestive of child sexual abuse. Perianal lacerations must be distinguished from anal fissures, which may be seen in children with constipation. *Adapted from Adams JA, Farst KJ, Kellogg ND. Interpretation of medical findings in suspected child sexual abuse: an update for 2018. J Pediatr Adolesc Gynecol 2018;31:225–31.*



Fig. 90.6 Bruising of the buttocks and perianal area of a sexually abused 2-year-old child.

secretions[15]. Perinatally acquired infections with *Chlamydia trachomatis* have been documented to persist as long as 28 months; therefore, infections with this organism in children younger than 3 years of age are not as suggestive of abuse.

Anogenital warts in children (see Ch. 79) may be perinatally acquired, transmitted during the routine care of children, autoinoculated from other sites of infection, or (especially for genital warts) acquired as a result of sexual abuse. In most studies, proven abuse is uncommon in children with anogenital warts who are younger than 3 years of age[20].

Human trafficking

Victims of human trafficking may demonstrate signs of physical, emotional, or sexual abuse as noted above. In addition, tattoos in locations ranging from highly visible (e.g. hands, face) to discrete (e.g. lower back, genitals) have been used by some traffickers to brand their victims[21], with common motifs depicting a male name, hearts, symbols of wealth, and profanity. Recognition of these tattoos, which are often low-quality, may help to identify victims of human trafficking[21].

Differential Diagnosis

Although it may be difficult to differentiate abuse from accidental injury in a child, the distribution of injuries is often helpful. Abused children have significantly more soft tissue injuries on the cheeks, trunk, genitalia, and upper legs than accidentally injured children[12]. Labbe and Caouette[22] performed over 2000 skin examinations in 1467 normal children to determine the type and location of recent skin injuries. The majority of children over 9 months of age had at least one injury, usually a bruise, but 15 or more injuries was rare. The lower limbs were the most commonly involved sites. Less than 2% of the children had injuries to the thorax, abdomen, pelvis, or buttocks, and less than 1% to the chin, ears, or neck. Bruises were rare in infants who were not yet independently mobile. Therefore, injury in infants or in the locations mentioned above should arouse suspicion of the possibility of abuse.

There are several cutaneous disorders that can mimic child abuse (Table 90.2; Fig. 90.7 & 90.8). In addition, normal anatomic variants are sometimes mistaken for signs of childhood sexual abuse. For example, 25% of newborn girls have a white line (linea vestibularis) in the posterior vestibule that could be confused with scar tissue produced by sexual abuse. Other conditions that are occasionally misdiagnosed as sexual abuse are listed in Table 90.3.

CONDITIONS THAT CAN MIMIC CHILD ABUSE

Condition	Comments
Bleeding into the skin (ecchymoses, purpura)	
Multiple bruises due to platelet or clotting disorders	• Areas most commonly traumatized by children (e.g. shins, knees)
Ehlers–Danlos syndrome, especially the vascular type	• Common sites of trauma, especially shins
Bruising due to "cupping" or cao gio (coin rubbing)	• Primarily children from SE Asia (see Ch. 133)
Vasculitis, particularly Henoch–Schönlein purpura (HSP) and acute hemorrhagic edema of infancy	• Favors lower extremities as well as the buttocks in HSP and the face in acute hemorrhagic edema; associated edema and arthritis
Blue discoloration of skin mistaken as bruising	
Dermal melanocytosis	• Lack of progression of color to green or yellow; favors presacrum and back
Infantile hemangioma (deep) or vascular malformation	
Linear hyperpigmentation	
Phytophotodermatitis (see Fig. 90.8A)	
Sock-line or mitten-line hyperpigmentation	
Vesicles, bullae, or erosions mistaken as non-accidental burns or other intentional injuries	
Impetigo, ecthyma, blistering distal dactylitis	
Erythema multiforme, fixed drug eruption	
Bullous mastocytosis	
Irritant contact dermatitis	• e.g. laxative-induced irritant contact dermatitis mimicking an immersion burn, chemical burns from topical application of garlic or apple cider vinegar (see Fig. 90.7)
Arthropod bite reaction	
Moxibustion Maquas	• Primarily children from SE Asia (see Ch. 133) • Small burns produced by hot metal spits or coals in areas of illness or pain; Bedouin, other Arabic, and Russian cultures
Burn from a hot car seat or seat-belt buckle	
Genetic disorders of skin fragility, e.g. forms of epidermolysis bullosa (see Ch. 32) or porphyria (see Ch. 49)	
Other	
Osteogenesis imperfecta	• Multiple fractures, blue sclerae
Hair tourniquet	
Self-inflicted injury	

Table 90.2 Conditions that can mimic child abuse.

Evaluation and Management

When any lesion suspicious for abuse is present, the entire cutaneous surface of the child as well as the oral, anal, and genital mucosae should be examined. Child abuse should be suspected if parents lack an explanation for a child's injuries, relate circumstances not compatible with the physical findings, describe activities for which a child is developmentally incapable, give differing accounts, or change their stories. A summary of recommended steps in the evaluation and management of suspected child abuse is provided in Table 90.4. Most countries (including the US) require physicians to report suspected physical abuse, neglect, and sexual abuse of children. Legal protection is generally given to healthcare providers who make such reports in good faith.

When a child gives a history of sexual abuse or has physical findings highly suggestive of abuse, an immediate referral should be made to a child protective services agency. If the history and physical findings are less certain, it may be most appropriate for experienced medical personnel to make the decision of whether sexual abuse is likely and referral to child protective services is warranted, since the potential negative impact of misdiagnosis on the family structure is substantial. Whenever feasible, any child suspected of being sexually abused should be examined by a pediatrician or gynecologist experienced in evaluating children for signs of abuse. Anogenital examination by multiple physicians should be avoided if possible, given the potential trauma this may impose on the child. Lastly, because physical signs of sexual abuse may resolve within a few days, children should be evaluated by an experienced provider as soon as possible[15].

When the history and/or physical findings suggest the possibility of oral, genital, or rectal contact, cultures and serologic tests to evaluate for sexually transmitted diseases are indicated. If the abuse occurred within 24 hours of the examination, samples should also be collected for forensic evidence[15].

Victims of all types of abuse may suffer long-term psychologic consequences. Some children withdraw and develop feelings of worthlessness, helplessness, hopelessness, and depression. Others exhibit aggressive and impulsive behavior and are at risk for delinquency, substance abuse, absenteeism from school or work, adolescent pregnancy, sexual promiscuity, and prostitution. Abused children are more likely as adults to abuse their own children and spouses. Thus, long-term psychologic support for abused children is desirable.



Fig. 90.7 Chemical burn from topical application of apple cider vinegar mimicking child abuse in an infant. Note the sharply demarcated erythema with angular borders and sparing of the skin folds, as well as the superficial blistering and desquamation.

In summary, the dermatologist may be the first physician to encounter the abused child, so it is important to be alert for signs of abuse, perform the appropriate documentation and testing, and report it to the proper authorities. It is often necessary to enlist the help of a primary care physician or gynecologist experienced in the evaluation of abuse. An atlas by Hobbs and Wynne[23] provides additional information and color illustrations.

ELDER ABUSE

Key features

- An intentional action by a caregiver or trusted person that causes harm or creates a serious risk of harm to an older adult constitutes elder abuse
- Failure by a caretaker to satisfy the basic needs of an elder or to protect the elder from harm also represents elder abuse

Introduction

In 1997, the International Network for the Prevention of Elder Abuse was established to address elder abuse around the world[24]. In most countries, both the healthcare system and legal statutes recognize the types of elder abuse listed in Table 90.5. Approximately one in four elders is at risk of abuse, and ~6% have experienced significant abuse in the past month[24,25].





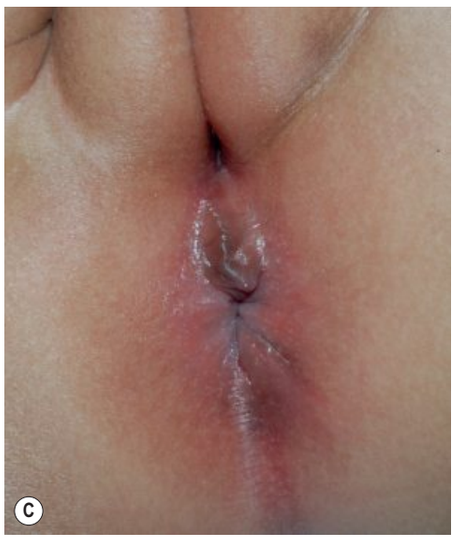




Fig. 90.8 Cutaneous disorders that may be misdiagnosed as physical or sexual abuse. **A** Hyperpigmented streaks on the back of a 2-year-old girl due to phytophotodermatitis; the mother had lime juice on her hand when she touched the child. **B** Genital lichen sclerosus may have associated purpura or hemorrhagic bullae. **C** A perianal pyramidal protrusion in the typical location, just anterior to the anus in the midline. This finding is most common in infant girls. **D** Self-induced suction purpura from a drinking glass on the upper lip of a young girl.
A, Courtesy Anthony J. Mancini, MD; B–D, Courtesy Julie V. Schaffer, MD.

CONDITIONS OCCASIONALLY MISDIAGNOSED AS CHILD SEXUAL ABUSE
• Accidental injury • Anal fissure or dilation due to constipation • Perianal streptococcal infection (see Fig. 74.11D) • Lichen sclerosus (may be associated with purpura or hemorrhagic bullae; see Fig. 90.8B) • Genital vitiligo • Localized vulvar bullous pemphigoid or other bullous diseases • Crohn disease (see Fig. 93.17) • Infantile hemangioma (especially if ulcerated; see Fig. 103.11) or vascular malformation in the genital area • Entities misdiagnosed as genital or perianal warts – Perianal pyramidal protrusion (see Fig. 90.8C) – Molluscum contagiosum – Pseudoverrucous papules and nodules due to fecal or urinary incontinence – Verrucous herpetic infections in immunocompromised hosts – Perianal papillomatous lesions of Goltz syndrome • Anatomic variants, e.g. anterior hymenal cleft, enlarged hymenal opening, linea vestibularis

Table 90.3 Conditions occasionally misdiagnosed as child sexual abuse.

EVALUATION AND MANAGEMENT OF SUSPECTED CHILD ABUSE
• Examine the entire cutaneous surface as well as oral, anal, and genital mucosae; estimate the ages of individual traumatic lesions and identify any associated injuries • Detail all traumatic lesions in the medical record • Photograph injuries whenever possible • Funduscopic examination to assess for retinal hemorrhages* • Otoscopic examination to exclude hemotympanum • Skeletal survey to assess for unsuspected fractures, especially in children under 5 years of age • Treat acute injuries or infections • Report suspected abuse, initially by telephone and subsequently in writing, to the local child protective services agency • Protect the child from further injury while suspected abuse is being investigated • Long-term counseling for proven abuse
*Can occur secondary to head trauma or severe shaking; the presence of extensive, bilateral retinal hemorrhages in a child <3 years of age is strongly suggestive of abuse.

Table 90.4 Evaluation and management of suspected child abuse.

TYPES OF ELDER ABUSE	
Physical abuse	• Use of physical force that results in pain, injury, or impairment • Inappropriate use of drugs, restraints, or confinement
Psychological abuse	• Use of verbal or nonverbal means to cause emotional pain or distress
Sexual abuse	• Nonconsensual sexual contact with an older adult
Material exploitation	• Unauthorized use of funds, assets, or property • Authorization for use of resources gained through intimidation of an elder
Neglect*	• Failure of a caretaker to satisfy the basic needs of an elder or to protect the elder from harm
*Elder self-neglect is more common than elder abuse or neglect by others.	

Table 90.5 Types of elder abuse.

POTENTIAL FINDINGS IN ELDER ABUSE OR NEGLECT	
Behavior observations	• Withdrawal • Absence of eye contact with interviewer • Infantilizing of patient by caregiver • Functionally impaired patient who presents without designated caregiver
General appearance	• Hygiene, cleanliness, and appropriateness of dress
Skin and mucous membranes	• Skin turgor, other signs of dehydration • Multiple abrasions in various stages of evolution • Wrist or ankle lesions suggestive of restraint use • Bruises (shape may suggest implement used) • Decubitus ulcers • Lack of care provided for established skin lesions • Infestations • Immersion (stocking/glove distribution) or cigarette burns
Head and neck	• Traumatic alopecia (distinguishable from androgenetic alopecia on basis of distribution) • Scalp hematomas, lacerations, abrasions
Genitourinary	• Rectal or vaginal bleeding could indicate sexual abuse
Musculoskeletal	• Examination for occult fracture, pain • Observe gait • Fractures that are not explained by mechanisms of reported injury

Table 90.6 Potential findings in elder abuse or neglect. *Adapted from Lachs MS, Pillemen K. Elder abuse. Lancet 2004;364:1263–72.*

Risk Factors for Elder Abuse

Because of increased opportunities for contact and thus for conflict and tension, a shared living arrangement is a major risk factor for elder abuse. Abuse also occurs in residential and nursing care facilities. Elderly individuals living alone are more likely to be victims of financial abuse, but they are at lower risk for other forms of abuse[26]. Physical abuse is reported to occur more frequently in elders with dementia, especially those with a history of aggressive behavior. Social isolation has also been identified as a risk factor, with victims more likely to be isolated from friends and family other than the person with whom they are living than are non-victims[24]. Pathologic characteristics of perpetrators of elder abuse include mental illness, particularly depression, and alcohol abuse. Additionally, people who abuse elders may actually be dependent (e.g. financially) on the person they are abusing. In some cases, abuse stems from attempts by relatives (particularly adult offspring) to obtain the victim's resources[26,27].

Clinical Features and Assessment

Potential findings in abused or neglected elders are listed in Table 90.6. Tools such as the Elder Abuse Suspicion Index have also been developed to improve physician identification of elder abuse[28,29]. Unfortunately, abused elders may not always have findings clearly attributable to abuse. Conversely, older individuals may have findings that mimic abuse but which are actually a result of accidental injuries or chronic disease[24,30,31].

When elder abuse is suspected, the clinical findings should be photographed and documented in the medical record. The patient should not be interviewed in the presence of the suspected abuser. The presence of other healthcare staff should also be minimized, since many patients are ashamed to admit that they are victims of elder abuse[24]. The patient may also hesitate to disclose abuse due to fears of being placed in a long-term care facility, perpetrator retaliation, severing family relationships, and legal implications for the perpetrator[32]. Although direct questions about abuse are appropriate, the interviewer may prefer to begin with general questions about safety issues and the home environment. The physician must use considerable caution in interacting with a suspected abuser. One of the risks of confronting an alleged abuser is that access to the elderly person may be lost. If the physician deems it necessary to interview a suspected abuser, an empathetic non-judgmental approach may be helpful[24].

Elder self-neglect is a related entity that occurs three times more commonly than abuse by others and is associated with a 16-fold increase in risk of death during the first year after diagnosis[33]. The CDC describes it as vulnerable elders who fail or refuse to address their own basic physical, emotional, or social needs in a way that threatens their health and safety. Elder self-neglect typically reflects impaired coping and decision making because of cognitive and/or functional impairments[33].

Management

Because elder abuse is multifactorial, potential interventions are based on the context of abuse. A multidisciplinary team involving physicians, nurses, social workers, elder care attorneys, adult protection agencies and, when appropriate, law enforcement officials is helpful when dealing with elder abuse. If the abused person is competent to make medical decisions and willing to accept intervention, education regarding elder abuse can be provided, a safety plan implemented, and the patient as well as family members referred to appropriate services. Reporting by healthcare providers of suspected cases of elder abuse or self-neglect to adult protective services is mandated by law in most states in the US, even if the elder is unwilling to accept intervention. The National Center on Elder Abuse website (https://ncea.acl.gov) provides additional information.

In summary, dermatologists should remain vigilant in looking for physical signs of abuse in elderly patients, especially those who are dependent on caregivers. Dermatologists who encounter signs of elder abuse are responsible for initiating the evaluation process that protects these fragile members of society.

Additional figures and a table on Interventions for elder abuse available in our eBook (see inside front cover for access code).

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eFig. 90.1 Burn injury due to dunking in hot water. Note the sharp line of demarcation of the burn on the arm (arrow).



eFig. 90.2 Multiple erosions and ulcerations in a child who was sexually abused. *Courtesy Ronald P. Rapini, MD.*



eFig. 90.3 Syphilitic chancre on the penis of a prepubertal boy.

INTERVENTIONS FOR ELDER ABUSE	
Context of elder abuse	**Potential interventions**
Abuse potentially related to stress from caring for impaired family member	Respite services
	Adult daycare
	Caregiver education programs (e.g. on what constitutes abuse)
	Recruitment of other family, informal, or paid caregivers to share burden of care
	Psychotherapy for caregiver
	Treatment for depression
	Social integration of caregiver to reduce isolation
Violence related to substance or alcohol misuse	Referral to alcohol or drug misuse rehabilitation programs as appropriate
Violence related to behavioral problems associated with mental health	Treatment referral
Spousal violence (often longstanding)	Marital counseling
	Support groups
	Shelter
	Orders of protection
	Victim advocacy
Abuse by aggressive dementia patient	Geriatric medical assessment of causes of underlying behavior
Financial exploitation by family members	Guardianship proceeding, power of attorney (transfer of legal authority)
	Protective services
Financial exploitation by paid caregiver	Referral to legal services
	Involvement of law enforcement
	Protective services

eTable 90.1 Interventions for elder abuse. *From Lachs MS, Pilleman K. Elder abuse. Lancet 2004;364:1263–72.*

Histiocytoses 91

Sylvie Fraitag and Stéphane Barete

OVERVIEW

The histiocytoses represent a group of proliferative disorders that share a common CD34$^+$ progenitor cell in the bone marrow. Three "histiocytic cells" of cutaneous importance are: (1) the *Langerhans cell*, which initially migrates from the embryonic yolk sac to the epidermis[1] and functions as a potent antigen-presenting cell (APC); (2) the *mononuclear cell/macrophage*, which migrates to and from the dermis and has both phagocytic and APC properties; and (3) the *dermal dendrocyte/dendritic cell*, of which there are two subtypes. Type 1 dermal dendrocytes are factor XIIIa-positive and generally reside within the papillary dermis, whereas type 2 dermal dendrocytes are CD34-positive and are generally found within the reticular dermis. Type 1 dermal dendrocytes may be involved in phagocytosis, antigen presentation, inflammation, collagen production, and wound healing, while the function of type 2 dermal dendrocytes is less certain. These two types represent myeloid dendritic cells and are distinct from plasmacytoid dendritic cells.

Dysfunction of these various histiocytes has led to a group of well-known, but poorly understood, disorders. For years, many of the histiocytoses were known by numerous names, reflecting the lack of understanding and agreement regarding their origin. Initially electron microscopy, then immunohistochemical stains, and most recently molecular pathology have provided insights into these conditions. Over the past decade, multiple types of histiocytoses were shown to be neoplasms of myeloid origin driven by somatic gain-of-function mutations that lead to activation of the mitogen-activated protein kinase (MAPK) signaling pathway. *BRAF* was found to be the most frequently altered gene. However, genes encoding membrane receptors (e.g. *CSF-1R, NTRK1, RET, ALK*) and components of the RAS-RAF-MEK-ERK (MAPK) pathway, both upstream (e.g. *NRAS, KRAS*) and downstream (e.g. *MAP2K1/MEK1*) of BRAF may also be involved (see Fig. 113.1). Less commonly, there is activation of the PI3K-AKT signaling pathway. In patients with disseminated disease, the mutation found in an affected organ can also be detected in blood cells and/or hematopoietic progenitors.

In the new classification scheme from the Histiocyte Society, histiocytoses are classified into five main groups based upon their clinical, histologic, and molecular characteristics: (1) Langerhans-related histiocytoses (L group); (2) cutaneous and mucocutaneous histiocytoses (C group); (3) malignant histiocytoses (M group); (4) Rosai–Dorfman disease (R group); and (5) hemophagocytic lymphohistiocytosis and macrophage activation syndrome (H group)[2].

This chapter covers the most common histiocytic disorders as well as several rare forms (Table 91.1).

"L" GROUP: LANGERHANS-RELATED HISTIOCYTOSES

Langerhans Cell Histiocytosis

Synonyms:

- Langerhans cell histiocytosis (LCH): class I histiocytosis, histiocytosis X
- Subtypes (historical names):
  - Acute (Letterer–Siwe disease)
  - Chronic (Hand–Schüller–Christian disease)
  - Localized (eosinophilic granuloma)
  - Congenital self-healing Langerhans cell histiocytosis (congenital self-healing reticulohistiocytosis; Hashimoto–Pritzker disease)

Key features

- A clonal proliferation of Langerhans cells, CD1a$^+$/CD207$^+$ dendritic cells derived from the bone marrow
- Somatic gain-of-function mutations, most commonly *BRAF* V600E, lead to activation of the mitogen-activated protein kinase (MAPK) signaling pathway; as a result, ERK phosphorylation is a consistent finding
- Histopathologic diagnosis is aided by immunohistochemistry, e.g. anti-VEI antibody, and DNA sequencing to detect associated mutations
- Systemic manifestations include osteolytic bone lesions and diabetes insipidus
- Targeted therapy consists of selective BRAF inhibitors (e.g. vemurafenib) and/or MEK inhibitors

Introduction

Langerhans cell histiocytosis (LCH) is a clonal proliferative disorder in which Langerhans cells, CD1a$^+$/CD207$^+$ dendritic cells, accumulate within a variety of organs. It is characterized by a broad spectrum of clinical presentations and outcomes, ranging from localized and self-healing to generalized and fatal.

History

Letterer–Siwe disease, Hand–Schüller–Christian disease, and eosinophilic granuloma were described in the early twentieth century. In 1953, Lichtenstein[3] grouped these three disorders into a single entity which he called *histiocytosis X*. Twenty years later, Hashimoto and Pritzker[4] described the entity *congenital self-healing reticulohistiocytosis*. Immunologic and ultrastructural studies confirmed the relationship of the pathologic cells in histiocytosis X and congenital self-healing reticulohistiocytosis to Langerhans cells, providing a basis for the Writing Group of the Histiocyte Society, in 1987, to reclassify them as "Langerhans cell histiocytoses"[5].

Epidemiology

LCH occurs worldwide and most commonly develops in children ages 1–3 years, although disease can occur at any age. The reported incidence of LCH varies widely. However, an annual incidence of at least five per million children is often quoted, with the adult incidence suspected to be less than one-third that of children. LCH is more common in boys, with a male : female ratio of nearly 2 : 1. In adults, there may be a slight female predominance.

Some cases of LCH appear to be familial. One study described simultaneous development of LCH in four of five monozygotic twin pairs and in one of three dizygotic pairs[6]. Additionally, in two families with affected non-twin siblings, parental consanguinity was known in one and possible in the other.

Pathogenesis

Until recently, the pathogenesis of LCH was unknown. In 2010, a significant percentage (55%–60%) of LCH specimens were shown to harbor the *BRAF* V600E mutation[4,7]. This strongly suggested that LCH was a clonal neoplasm, a finding supported by further studies in which clonality of CD1a$^+$ histiocytes was uniformly demonstrated[8–10]. In high-risk patients, *BRAF* V600E mutations were also detected in CD34$^+$ hematopoietic progenitor cells within the bone marrow as well as circulating CD11c$^+$/CD14$^+$ monocytic cells. As a result, LCH is now regarded to be a myeloid neoplasm[11,12].

As in melanoma, somatic gain-of-function mutations in *BRAF* point to activation of the mitogen-activated protein kinase (MAPK) signaling pathway (see Fig. 113.1). Of note, *BRAF* V600E mutations have been more commonly observed in patients with multisystem LCH than in those with isolated disease[13]. Mutations in genes that encode other kinases in the RAS-RAF-MEK-ERK (MAPK) pathway (e.g. *MAP2K1* [also referred to as *MEK1*]) as well as membrane receptors were subsequently detected (see Overview). The end result is phosphorylation of ERK. *BRAF* and *MEK1* mutations are mutually exclusive, and ~50% of LCH patients with wild-type *BRAF* have *MEK1* mutations[14].

Clinical features

Clinical manifestations of LCH vary from unifocal or single-system (S-S) disease to multifocal involvement to *multisystem (M-S) Letterer–Siwe-type disease*. The latter nearly always develops prior to age 2 years, and commonly presents in children less than 1 year of age. Cutaneous involvement occurs in most patients as 1–2 mm pink to skin-colored or purpuric papules, pustules, and/or vesicles in the scalp, flexural areas of the neck, axilla and perineum, and on the trunk (Fig. 91.1A–C). Rarely, the lesions resemble mollusca contagiosa (Fig. 91.1D)[7]. Scale and crust with secondary impetiginization are common findings, as is the development of petechiae and purpura (Fig. 91.1E). The lesions tend to

CLINICAL FEATURES OF THE HISTIOCYTOSES

Histiocytosis	Usual age	Most common mucocutaneous sites	Other findings
Langerhans cell histiocytoses			
Acute form	0–2 years	Scalp, flexural areas, trunk	Visceral and bone lesions
Chronic form	2–6 years	Scalp, flexural areas, trunk, gingival	Diabetes insipidus, bone lesions, exophthalmos
Localized form (eosinophilic granuloma)	7–12 years	Skin lesions rare	Bone lesions primarily
Congenital self-healing Langerhans cell histiocytosis	Congenital	Widespread, localized, or single lesion	Spontaneous resolution, but children should be followed longitudinally
Indeterminate cell histiocytosis	Any	Solitary or generalized Trunk & extremities > head & neck, genitalia	Uncommon visceral and bone lesions; possible association with B cell lymphoma and acute myelogenous leukemia
Erdheim–Chester disease	Any, but primarily adults	Eyelids, trunk, extremities, head and neck	Fever, bone pain (osteosclerosis of long bones); involvement of the lungs, kidneys, adrenals, heart (up to 50%), CNS, retroperitoneum (fibrosis), and testes
Non-Langerhans cell histiocytoses			
Primarily cutaneous, usually self-resolving			
Juvenile xanthogranuloma	0–2 years (adult form exists)	One to a few lesions ≫ numerous & widespread Head and neck > upper trunk > extremities	Rare eye and visceral lesions; spontaneous resolution; association with CALM, NF1, and/or juvenile myelomonocytic leukemia
Benign cephalic histiocytosis	0–3 years	Face and neck > trunk and extremities	Usually none (diabetes insipidus rare); spontaneous resolution
Generalized eruptive histiocytosis	<4 and 20–50 years	Widespread (axial)	Recurrent crops; spontaneous resolution > persistent; may relapse
Primarily cutaneous, often persistent/progressive			
Papular xanthoma*	Any	Generalized (discrete yellow papules and papulonodules with relative sparing of flexural sites)	Mucous membrane involvement can occur occasionally
Progressive nodular histiocytosis	Any	Generalized (discrete yellow papules and nodules, sometimes with prominent facial involvement)	May represent same entity as the progressive form of papular xanthoma[85]; mucous membrane involvement can occur
Hereditary or sporadic progressive mucinous histiocytosis	Childhood/ adolescence	Generalized (skin-colored to erythematous papules and nodules)	Usually occurs in female patients; histologically, abundant dermal mucin in addition to histiocytes
Cutaneous, with frequent systemic involvement			
Necrobiotic xanthogranuloma	17–60 years	Periorbital > other face, trunk, extremities	Paraproteinemia due to plasma cell dyscrasia or lymphoproliferative disorder, hepatosplenomegaly
Multicentric reticulohistiocytosis	30–50 years	Head; hands, elbows (over joints); mucosa (oral, nasopharyngeal)	Arthritis (often destructive); up to 30% with internal malignancy
Rosai–Dorfman disease	10–30 years	Eyelids and malar area	Massive lymphadenopathy in a subset of patients, fever, hypergammaglobulinemia; skin-limited form increasingly recognized
Xanthoma disseminatum	Any	Flexural areas to widespread > mucosa (oral, nasopharyngeal)	Diabetes insipidus
Systemic, with skin involvement rare to unusual			
Sea-blue histiocyte syndrome (sea-blue histiocytosis)* • Inherited • Acquired	Usually adolescence/ young adulthood (inherited form)	Skin involvement rare (inherited form): facial (macular hyperpigmentation and nodules)	Histiocytes contain cytoplasmic granules that stain azure blue with May–Gruenwald stain; multiple organs involved; can be fatal

Table 91.1 Clinical features of the histiocytoses.

CLINICAL FEATURES OF THE HISTIOCYTOSES			
Histiocytosis	**Usual age**	**Most common mucocutaneous sites**	**Other findings**

Hemophagocytic lymphohistiocytosis (HLH; hemophagocytic syndrome)*
• Primary (genetic; see Table 60.6)
  • Familial HLH†; Chédiak–Higashi syndrome, Griscelli syndrome type 2 > Hermansky–Pudlak type 2; X-linked lymphoproliferative syndrome;
• Secondary (acquired)
  • Infection-associated (e.g. EBV, CMV, dengue)
  • Malignancy-associated (e.g. NK/T cell lymphoma, B cell lymphoma)
  • Macrophage activation syndrome (MAS) associated with autoimmune connective tissue disease (e.g. sJIA, Still disease, systemic lupus erythematosus)
	Primary: 0–2 years
	Secondary: any
		Generalized (purpuric macules and papules, morbilliform eruptions, erythroderma, keratotic nodules) or acral (erythematous macules); malignancy-associated forms may present with lesions of cutaneous/subcutaneous cytotoxic NK/T cell lymphomas; skin biopsy specimens rarely demonstrate hemophagocytosis	• HLH diagnosed if genetic mutation detected or if at least 5 of the following 8 criteria: (1) fever for >7 days; (2) splenomegaly; (3) cytopenias; (4) hypertriglyceridemia or hypofibrinogenemia; (5) histologic evidence of hemophagocytosis (in the bone marrow, lymph nodes or spleen); (6) low or absent natural killer cell activity; (7) hyperferritinemia‡; and (8) elevated soluble CD25, plus evidence of infectious agent, malignancy, autoinflammatory disorder, or autoimmune connective tissue disease in secondary forms
			• Some of the patients with secondary forms may be heterozygous for genetic mutations that cause primary HLH
			• MAS in the setting of sJIA requires fever and ferritin >684 ng/ml *plus* any 2 of the following: thrombocytopenia, transaminitis, hypertriglyceridemia, hypofibrinogenemia
			• CNS dysfunction, hemorrhages, hepatomegaly, arthritis, and elevated levels of S100A12 may be present
			• Treatments include corticosteroids, cyclosporine, JAK inhibitors, emapalumab, etoposide, allogeneic hematopoietic stem cell transplant

*Not covered in the body of the text.
†In the US, most commonly due to mutations in the gene that encodes perforin (*PRF1*), referred to as subtype 2; additional genes include *UNC13D* (subtype 3), *STX11* (subtype 4), and *STXBP2* (subtype 5). Their protein products play a role in the cytotoxic activity of lymphocytes, including the exocytosis of cytotoxic granules by NK cells.
‡The primary differential diagnosis is iron overload, Still disease, HLH or MAS, infection, and malignancy.

Table 91.1 Clinical features of the histiocytoses. CALM, café-au-lait macule; CD25, interleukin-2 receptor alpha; CMV, cytomegalovirus; EBV, Epstein–Barr virus; NF, neurofibromatosis; sJIA, systemic juvenile idiopathic arthritis.

coalesce and become tender, especially when fissures develop in intertriginous zones (Fig. 91.1B,F). Palmoplantar and nail involvement can occur, as can soft tissue nodules (Fig. 91.1G). In patients with darkly pigmented skin, the lesions may appear relatively hypopigmented (Fig. 91.1H). The eruption is most often confused with seborrheic dermatitis, various forms of diaper dermatitis or intertrigo (see Figs. 13.4 and 13.12), and arthropod bites (including scabies) when pruritic.

During the course of the disease, many organs can become infiltrated by clonal LCH cells. However, only if the key functions of the organ are affected is such involvement of prognostic significance. Lung, liver, lymph node, and bone involvement commonly occur at some point during the illness. Osteolytic bone lesions are painful, usually multiple, and most frequently involve the cranium. Occasionally, the hematopoietic system can be affected, with thrombocytopenia and anemia portending a poor prognosis.

Another early-onset form of cutaneous LCH is known as *congenital self-healing Langerhans cell histiocytosis* or *Hashimoto–Pritzker disease*. It is present at birth or develops during the first few days of life. Clinical features include vesicles and/or pustules that can be mistaken for varicella as well as red–brown, crusted papulonodular lesions that often have central necrosis (Fig. 91.2). Some newborns may have a "blueberry muffin baby" presentation (see Table 121.4)[15]. Rarely, there is a single neonatal nodule, referred to as a *Langerhans cell histiocytoma*[16]. While congenital self-healing LCH is usually a benign, self-resolving disorder, its relationship to other LCH variants suggests a cautious approach with respect to prognosis, and longitudinal evaluation is recommended.

The triad of diabetes insipidus, bone lesions, and exophthalmos (*formerly called Hand–Schüller–Christian disease*) typically begins between the ages of 2 and 6 years. These patients tend to have a chronic, progressive course and often do not have the complete triad. Approximately 30% of patients develop skin or mucous membrane lesions (Fig. 91.1I). While early cutaneous lesions are similar to those seen in the M-S form, older lesions can become xanthomatous. Ulcerative nodules may develop in the oral and genital areas, with premature loss of teeth possible secondary to gingival lesions.

At least 80% of patients develop bone lesions, the cranium being preferentially involved. Chronic otitis media occurs commonly in these patients and in patients with all forms of LCH. Diabetes insipidus, secondary to infiltration of the posterior pituitary by LCH cells, develops in ~30% of patients and is more common in those individuals with cranial bone involvement.

A localized variant of LCH, formerly called *eosinophilic granuloma* generally affects older children, boys more than girls. The cranium is most frequently affected, though lesions can also develop within the ribs, vertebrae, pelvis, scapulae, and long bones. A spontaneous fracture or otitis media may be the first sign of disease. Skin and mucous membrane lesions are rare.

Adults rarely develop LCH, but when they do, the most commonly involved sites are the skin, lung, and bone (see Fig. 91.1F). Diabetes insipidus can also develop and, as in children, is more likely when bony involvement of the skull is present. Severe multisystem disease is rare in adults. However, LCH can be a progressive disease in adults, especially when both bone and extra-skeletal sites are involved. Pulmonary involvement can be isolated or be a component of multisystem disease and it favors men who smoke cigarettes[17].

There are two patterns of associations between LCH and malignancy[18]. The first is the development of acute leukemias and solid tumors in patients with a history of LCH who have been treated with chemotherapy, radiotherapy, or both, and the malignancies are likely to be treatment-related. There are reports of a few patients who developed skin or solid tumors (e.g. basal cell carcinoma, osteosarcoma) within the fields of radiotherapy for their LCH.

A second more interesting association is an apparent increased incidence of LCH in patients with hematologic malignancies, including acute myelogenous leukemia, acute lymphocytic leukemia, chronic myelomonocytic leukemia, and lymphomas of both T and B cell origin. These malignancies can occur prior to, concurrently, or following the diagnosis of LCH[19]. In contrast to treatment-related (often referred to as secondary) hematologic malignancies, it has been demonstrated in several patients that the LCH and the hematologic malignancy are clonally related, suggesting origin from a common neoplastic stem cell[20].



Fig. 91.1 Langerhans cell histiocytosis – clinical spectrum. A Scalp involvement may initially be diagnosed as seborrheic dermatitis; however, there are usually more discrete papules and crusting. **B** Pink, thin plaques with fissuring along the inguinal creases can also resemble seborrheic dermatitis. **C** Advanced disease with coalescence of papules into large plaques and prominent inguinal lymphadenopathy. **D** Pale pink to skin-colored papules, several of which have central umbilication and resemble mollusca contagiosa. **E** The presence of petechiae and purpuric papules is a clue to the diagnosis. **F** In an adult, the clinical presentation of inguinal involvement is similar to that of infants. **G** This subcutaneous nodule on the scalp involved the skull and represented the initial manifestation of multisystem Langerhans cell histiocytosis in an infant. **H** In patients with highly pigmented skin, the papules can be hypopigmented. **I** Eroded erythematous plaque of the labial mucosa. *B, Courtesy Richard Antaya, MD; D, Courtesy Kristen Hook, MD; E, G, H, Courtesy Julie V. Schaffer, MD.*

The prognosis of patients with LCH varies dramatically. Involvement of "risk organs" – hematopoietic system, liver, lungs, and/or spleen – substantially increases the risk of disease-related mortality. However, in individuals with single-system disease or multisystem disease that does not involve risk organs, mortality rates are very low (e.g. <5% in the latter group). As with hematologic malignancies, the response to initial systemic treatment is an important prognostic indicator in LCH. Of note, in one study patients with high-risk LCH had *BRAF* V600E mutations in their CD34$^+$ hematopoietic progenitor cells, while the mutation was limited to lesional CD207$^+$ (Langerin$^+$) dendritic cells in low-risk LCH patients[21].

Pathology

In a typical papule of LCH, a proliferation of neoplastic cells is present in the papillary dermis (Fig. 91.3A). They are medium-sized cells, 10–15 microns in diameter, with a reniform (kidney-shaped) nucleus and a pink, non-xanthomatous (non-foamy) cytoplasm. The LCH cells are often admixed with eosinophils, lymphocytes, and red blood cells. Epidermotropism is commonly observed, resulting into a spongiform pattern and focal parakeratosis (Fig. 91.3B). In nodular lesions of congenital self-healing LCH, including LC histiocytoma, epidermotropism is not a feature and the dermal infiltrate can extend into the deep dermis. Some of the histiocytes within the infiltrate have abundant eosinophilic cytoplasm and are intermixed with LCH cells and giant cells[16].

Like Langerhans cells, LCH cells are characterized by a CD1a$^+$, CD207$^+$ (Langerin$^+$) phenotype (Fig. 91.3C,D); CD207 is the major protein of Birbeck granules. Both CD207 and CD1a have important roles in the uptake, processing, and presentation of non-peptide (e.g. lipid) antigens by Langerhans cells (Table 91.2) In addition, LCH cells commonly stain positive for CD68, while they are negative for CD163 (macrophage/monocyte marker) and FXIIIa (Fig. 91.4). Electron microscopy demonstrates Birbeck granules, which are rod- or racquet-shaped cytoplasmic structures pathognomonic for Langerhans cells and LCH cells (Fig. 91.5). However, electron microscopy is no longer routinely performed.



Fig. 91.2 Congenital self-healing Langerhans cell histiocytosis (Hashimoto–Pritzker disease). Cluster of crusted red–brown papules as well as a large hemorrhagic crust on the posterior ankle of a neonate. *Courtesy Kristen Hook, MD.*

Molecular analysis and immunohistochemistry are increasingly being utilized as diagnostic tools in that up to 60% of cases of LCH harbor a clonal *BRAF* V600E mutation. The VE1 mutant-specific antibody is useful in detecting this mutation[22]. In addition, pERK expression as well as cyclin D1 nuclear positivity are always observed in LCH, irrespective of the *BRAF* V600E mutational status[22], since mutations other than *BRAF* V600E can lead to activation of the MAPK pathway (see Fig. 113.1)[23].

Differential diagnosis

The clinical differential diagnosis is vast and includes seborrheic dermatitis, various forms of diaper dermatitis or intertrigo (see Figs. 13.4 and 13.12), and arthropod bites (including scabies), as well as leukemia, B and T cell lymphomas, multiple myeloma (bony lesions), maculopapular cutaneous mastocytosis, and the non-Langerhans cell histiocytoses (see Table 91.1). However, the characteristic histologic features of LCH will lead one to suspect the diagnosis, which is confirmed by the combination of positive immunostaining for CD1a and CD207 (Fig. 91.6). Occasionally, dense dermal infiltrates of $CD1a^+$ dendritic cells can be seen in insect bite reactions, including scabies, and lead to misdiagnosis (see Fig. 85.3)[24]. However, these cells do not express CD207.

Treatment

All patients diagnosed with LCH should undergo evaluation of the hematologic, pulmonary, hepatosplenic, renal, and skeletal systems to determine the extent of disease. Depending on age and extent of involvement, some patients may not require specific treatment, while others will require systemic therapy. The latter include corticosteroids, vinblastine, cladribine, and/or interferon alpha-2a as well as targeted therapies such as selective BRAF and MEK inhibitors[25].

For mild, single-system *skin disease* (if treatment is required), topical agents, including corticosteroids, antimicrobials, mechlorethamine (nitrogen mustard) and imiquimod, as well as phototherapy (narrowband UVB, PUVA) have been reported to be effective in case series. For more extensive cutaneous disease, based upon case reports, thalidomide, azathioprine, or methotrexate may be effective[17,24]. Other chemotherapeutic treatments such as cladribine and cytarabine have been used for refractory disease[26,27] as have autologous hematopoietic stem cell transplants.

Targeted therapy in the form of selective BRAF and MEK inhibitors has revolutionized treatment strategies for patients with aggressive, resistant disease; however, aspects of their use such as duration are still under debate[28,29]. Updated information regarding ongoing clinical trials is available at www.clinicaltrials.gov and www.histiocytesociety.org.

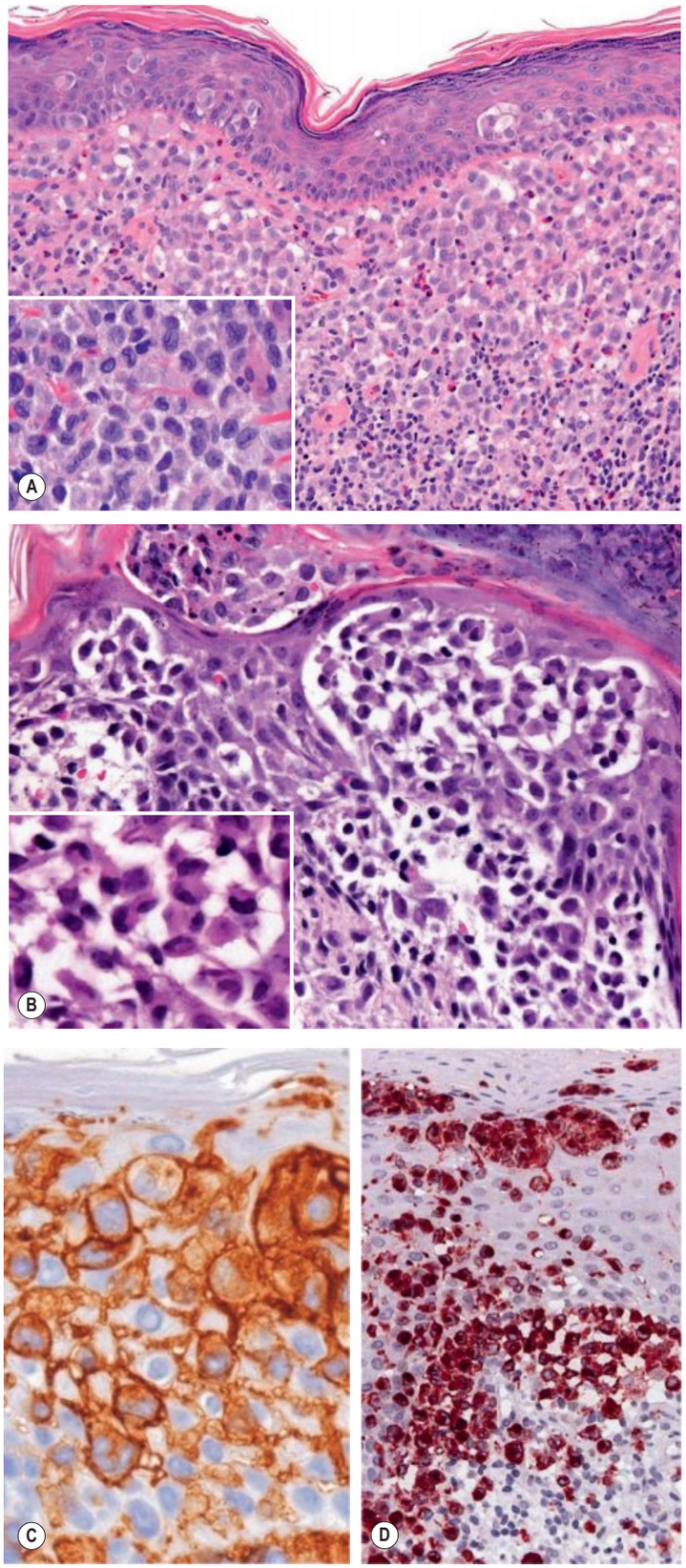


Fig. 91.3 Langerhans cell histiocytosis (LCH) – histopathologic features. **A** A somewhat lichenoid infiltrate of large LCH cells with some involvement of the epidermis; the infiltrate also contains lymphocytes and numerous eosinophils. Inset: note the reniform-shaped nuclei. **B** Another example with larger collections of Langerhans cells within the epidermis. **C** CD1a immunostain highlighting large LCH cells within the epidermis. **D** Positive CD207 (Langerin) immunostaining. *B, D, Courtesy Lorenzo Cerroni, MD*

ANTIGENIC MARKERS OF THE HISTIOCYTOSES					
Histiocytic disorder	**S100protein**	**CD1a**	**CD207 (Langerin)**	**CD68/CD163 (KP1/KiMP or PGM1)**	**Factor XIIIa***
Langerhans cell histiocytoses	+	+	+	CD68 commonly + / CD163 –	–
Indeterminate cell histiocytosis	+	+	–	CD68 commonly + / CD163 –	–
Erdheim Chester disease	–	–	–	+ / +	+
Juvenile xanthogranuloma	– (+)	–	–	+ / +	+
Benign cephalic histiocytosis	–	–	–	+ / +	+
Generalized eruptive histiocytoma	–	–	–	+ / +	+
Papular xanthoma†	–	–	–	+ / +	+
Progressive nodular histiocytosis†	–	–	–	+ / +	+
Hereditary† progressive mucinous histiocytosis	–	–	–	+ / +	+
Necrobiotic xanthogranuloma	–	–	–	+ / +	–
Multicentric reticulohistiocytosis	–	–	–	+ / +	–
Rosai–Dorfman disease	+	–	–	+ / +	–
Xanthoma disseminatum	–	–	–	+ / +	+

*Classic dermal dendrocyte marker.
†Not covered in the body of the text.

Table 91.2 Antigenic markers of the histiocytoses. Classic results are provided and results may vary in specific cases.

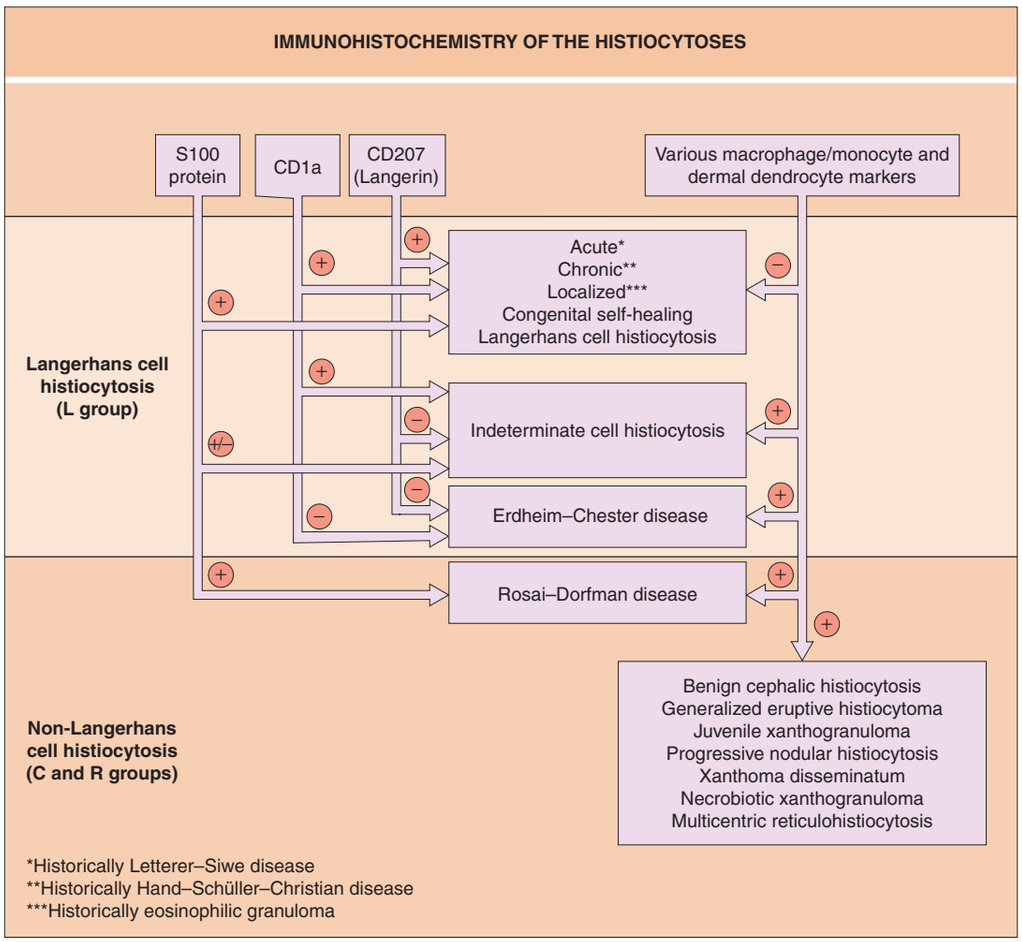


Fig. 91.4 Immunohistochemistry of the histiocytoses. Examples of classic macrophage/monocyte markers are CD68 and CD163; an example of a classic dermal dendrocyte marker is factor XIIIa.

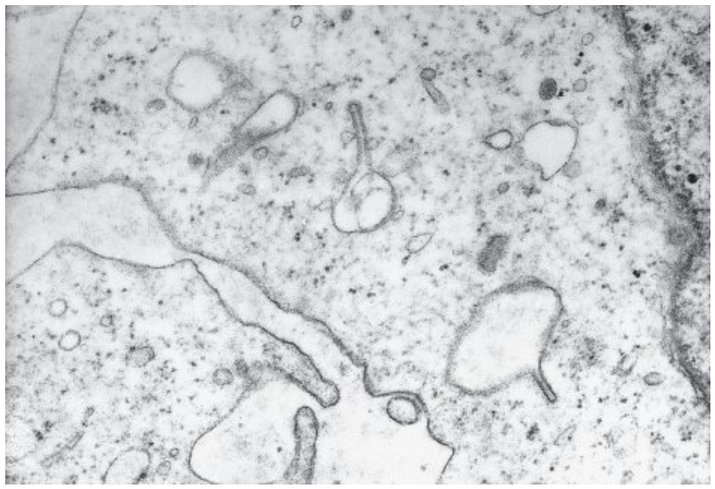


Fig. 91.5 Langerhans cell histiocytosis (Birbeck granules). Electron micrograph demonstrates classic racquet-shaped Birbeck granules in the cytoplasm of an LCH cell.

Indeterminate Cell Histiocytosis

Key features

- Currently classified within the L group (Langerhans-related histiocytoses) due to mutations in *BRAF* V600E in nearly all patients
- Occurs in adults and children with both generalized and solitary variants
- Cells display the phenotype of dendritic cells: CD1a$^+$, S100$^+$, CD207$^-$
- Primarily a cutaneous disorder, but occasionally there is visceral involvement and associated hematologic malignancies

Introduction

Indeterminate cell histiocytosis (ICH) is a very rare proliferative disorder comprised of histiocytes that have both LCH and non-LCH immunophenotypic features. There are two clinical variants – solitary and generalized.

History

Indeterminate cells were described in 1963, and a patient with features first recognized as ICH was reported by Wood et al.[24] in 1985. To date, ~60 cases have been reported in the literature. ICH is thought to be closely related to LCH because the pathologic cells are positive for CD1a, although they do not express CD207.

Epidemiology

ICH is quite rare and has no apparent sex predominance. It can occur at any age, from infancy to adulthood, and a congenital form has been reported.

Pathogenesis

Most cases of ICH harbor a gain-of-function mutation in *BRAF* V600E. Translocations involving *NCOA2* (nuclear receptor co-activator 2) and *ETV3* (Ets variant 3) have also been reported[30].

Clinical features

While the majority of patients with ICH have involvement of the trunk and extremities, lesions have also been observed on the genitalia and in the head and neck region, including the eyelids and ears. Both a generalized form and a solitary form have been described. In the generalized form, cutaneous lesions usually begin as firm red to brown papules or nodules (Fig. 91.7). The solitary form presents as a single, often soft, erythematous nodule that is usually ~1 cm in diameter. Ulceration can occur and as lesions age, they become brown to yellow. The clinical course is variable, with some patients experiencing a partial or complete regression of lesions (which may wax and wane), while others have a progressive course.

Although mucous membrane involvement is rare, both corneal and conjunctival lesions have been reported. Patients are usually in good health, but because visceral involvement and death can occasionally occur, periodic evaluation is warranted. There is a report of an infant who developed an aggressive form of ICH with a fatal outcome; the disease initially presented in the bone and then eventually spread to visceral organs and the skin[31]. Several cases have been associated with hematologic malignancies including mast cell leukemia, acute myelogenous leukemia, and low-grade B cell lymphoma.

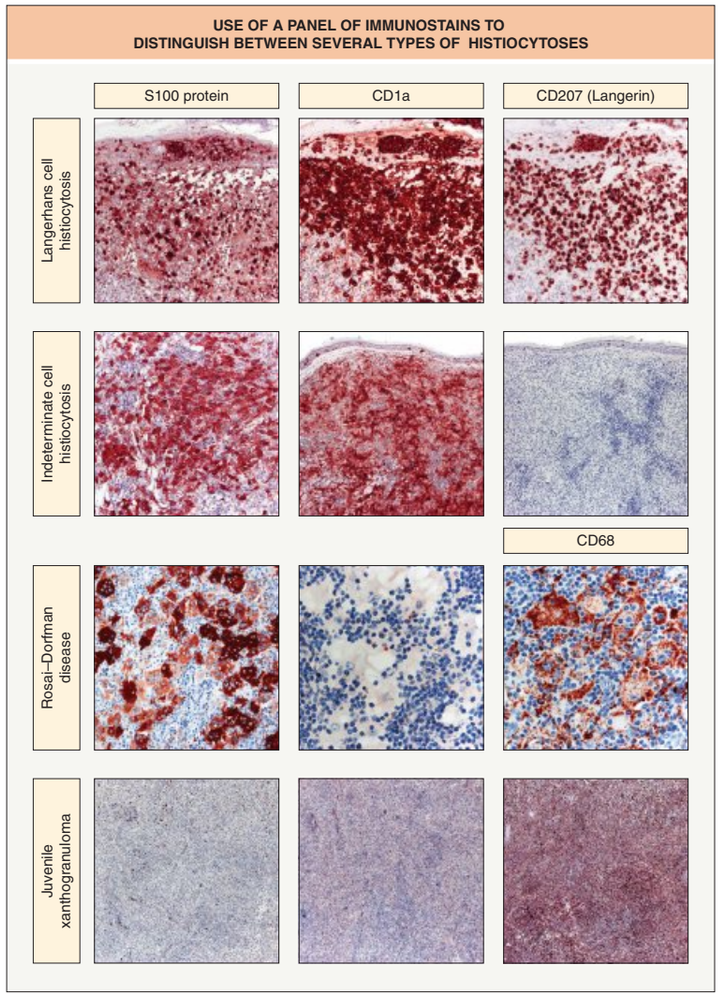


Fig. 91.6 Use of a panel of four immunostains to distinguish between Langerhans cell histiocytosis and several types of non-Langerhans cell histiocytosis. *Courtesy Lorenzo Cerroni, MD.*

Pathology

There is usually a predominantly monomorphous infiltrate of histiocytes, either well-circumscribed or more diffusely distributed within the dermis. Epidermotropism is less common than in LCH. Histiocytes often have an oncocytic appearance, with occasional spindled, scalloped, or vacuolated cell variants. Touton giant cells can be present. Lymphocytes are commonly present and eosinophils are occasionally observed.

The immunophenotype of ICH consists of positivity for CD68 and CD1a, but negativity for CD207. S100 may be either positive or negative, making this marker less helpful in establishing the diagnosis (see Fig. 91.4 & Table 91.2)[32–34].

Differential diagnosis

The clinical appearance of the cutaneous lesions of ICH is not unique. Similar-appearing papules in the same distribution can be found in generalized eruptive histiocytoma, juvenile xanthogranuloma, and congenital self-healing LCH (see Table 91.1). When lesions are limited to the head and neck region, benign cephalic histiocytosis should be considered as well. The clinical differential diagnosis also includes eruptive syringomas, maculopapular cutaneous mastocytosis, and lymphomatoid papulosis. While the diagnosis of ICH can be suspected based upon histopathology, confirmation requires demonstration of the characteristic CD1a$^+$, CD207$^-$ immunophenotype.

Treatment

Treatment of cutaneous lesions is usually not required as the lesions are asymptomatic and ICH is often either self-limited or non-progressive. A

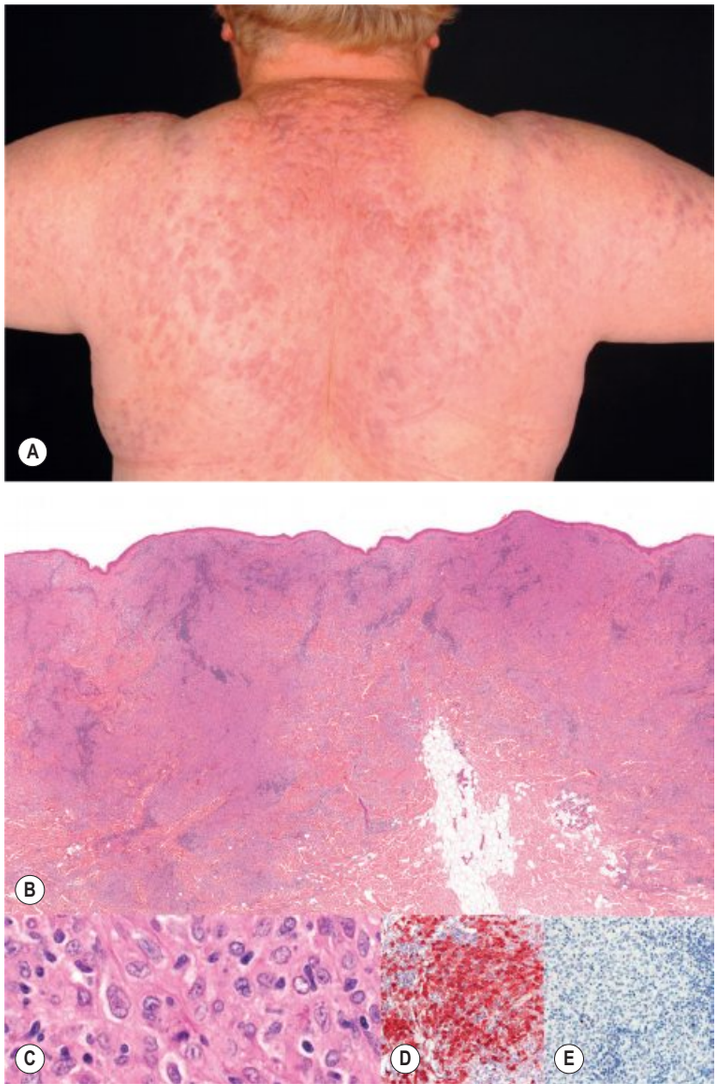


Fig. 91.7 Indeterminate cell histiocytosis. A Multiple pink-violet papules, plaques, and small nodules on the back. **B** Histologically, dense infiltrates were seen throughout the entire dermis and superficial subcutaneous fat. These infiltrates were composed of medium-to-large histiocytic cells (**C**) that were positive for S100 (**D**) and negative for CD1a (**E**). *Courtesy Lorenzo Cerroni, MD.*

single lesion can be removed surgically. Patients with extensive, disfiguring cutaneous disease have been treated with systemic chemotherapy (e.g. vinblastine, 2-chlorodeoxyadenosine, cyclophosphamide, and/or etoposide). There are also reports of the use of thalidomide, isotretinoin, methotrexate, NB-UVB, PUVA, or total skin electron beam therapy. As with LCH, selective BRAF and MEK inhibitors can be considered. Because visceral involvement and leukemia can occur, longitudinal evaluation of all patients with indeterminate cell histiocytosis is recommended[35].

Erdheim–Chester Disease

Key features

- Erdheim–Chester disease (ECD) is a severe form of histiocytosis which usually affects adults
- As in LCH, gain-of-function mutations in *BRAF* V600E are observed in >50% of patients; mutations in other genes that lead to activation of the MAPK pathway (e.g. *MAP2K1/MEK1*) also occur
- Cutaneous lesions occur in ~25% of patients and are accompanied by symmetric diaphyseal and metaphyseal osteosclerosis of the long bones as well as periaortic, retroperitoneal, and perirenal fibrosis
- Histologically, there are dermal infiltrates of histiocytes
- Treatment primarily consists of a selective BRAF inhibitor (e.g. vemurafenib) and/or a MEK inhibitor (e.g. cobimetinib)

Introduction

Erdheim–Chester disease (ECD) is a severe form of histiocytosis with visceral involvement characterized by xanthomatous or xanthogranulomatous infiltrates within tissues. It is a rare histiocytosis classified in the "L" group of histiocytoses[2].

History

ECD was first described in 1930 by the American physician Dr. William Chester while he was doing a postdoctoral fellowship with the Viennese pathologist Dr. Jakob Erdheim[36]. Although originally considered an aggressive histiocytosis of unclear origin, ECD is now regarded as a clonal hematopoietic disorder characterized in nearly all patients by an underlying *BRAF* V600E mutation or mutations in other genes that lead to activation of the RAS-RAF-MEK-ERK (MAPK) signaling pathway (see Fig. 113.1). More rarely, there is activation of the PI3K-AKT signaling pathway.

Epidemiology

The exact incidence of ECD is not known. Although it is considered an extremely rare disease, the incidence appears to be increasing. It occurs during adulthood (mean age = 55 years), with exceptional cases in children.

Pathogenesis

Originally classified as a non-Langerhans cell histiocytosis, it is now included with LCH in the "L" group[2] in light of the detection of *BRAF* V600E mutations in ~55%–60% of patients. Mutations in other genes that lead to activation of the MAPK pathway (e.g. *NRAS*, *KRAS*, *MAP2K1/MEK1*, *ALK*) have also been described[37,38]. Nearly 20% of patients with ECD have concomitant features of LCH, sometimes with cellular infiltrates of both entities within the same biopsy, further supporting placing ECD and LCH within the same group of histiocytoses[2].

Clinical features

Facial sinus osteosclerosis is suggestive of ECD, although it is often asymptomatic and discovered incidentally by CT or MRI. Bilateral hypermetabolic and sclerotic metaphyseal–diaphyseal involvement of long bones is highly suggestive of ECD, and this is usually associated with bone pain[39]. Plain radiography (skeletal survey) may not detect these lesions, but whole body low-dose CT, MRI, skeletal scintigraphy (bone scan), or ^{18}F-FDG PET scan represent more sensitive imaging tests. Diabetes insipidus may be an initial clinical manifestation. Patients can also develop respiratory symptoms, with pleural and pericardial (as well as peritoneal) thickening seen by CT or MRI. Approximately half of patients have periaortic fibrosis, described radiographically as a "coated aorta". Retroperitoneal fibrosis is a hallmark sign of ECD, with ~60% of patients having perirenal fibrosis ("hairy kidney") on CT scans[39].

Cutaneous involvement is present in 25% of patients, typically presenting as bilateral, symmetric, periocular xanthelasma-like lesions. Multiple yellow papules or plaques favor the medial upper eyelids and may precede other symptoms by several years. Yellow to brown plaques and papulonodules can also develop on the trunk, extremities, and head and neck region (Fig. 91.8), but mucosal involvement is rare[40,41]. Recently described cutaneous manifestations include panniculitis-like nodules and granuloma annulare-like lesions.

Pathology

Within the dermis, there is a granulomatous infiltrate with foamy histiocytes, a few multinucleated histiocytes or Touton giant cells, lymphocytes, and occasional plasma cells and eosinophils. Fibrosis may be prominent. The histiocytes express CD68, CD163, and focally FXIIIa, but are CD1a- and CD207-negative. However, pERK is consistently positive due to activation of the MAPK pathway, and VE1 mutant-specific antibody staining is positive in ~55%–60% of cases, reflecting the presence of the *BRAF* V600E mutation.

Differential diagnosis

The primary differential diagnosis includes xanthelasma and the yellow periocular plaques seen in patients with necrobiotic xanthogranuloma. When there is involvement of the trunk and extremities, other histiocytoses or granulomatous disorders need to be considered. An associated



Fig. 91.8 Erdheim–Chester disease. Red–brown papules and large confluent yellow–brown and brown plaques. The patient had concomitant features of LCH (mixed histiocytosis).

myeloid malignancy may develop in 20%–30% of patients and clonal hematopoiesis has been detected in almost half of patients with ECD; the most frequently mutated genes in the bone marrow are *TET2, ASXL1, DNMT3A,* and *NRAS*[42].

Treatment

Selective BRAF inhibitors such as vemurafenib are an effective treatment for patients who harbor the *BRAF* V600E mutation[39]. MEK inhibitors (e.g. cobimetinib) are very effective in patients with other mutations that activate the MAPK pathway[43]. For this reason, it is important to determine the mutational status of patients[44].

"C" GROUP: CUTANEOUS AND MUCOCUTANEOUS HISTIOCYTOSES

Synonym: ■ Histiocytoses of mononuclear phagocytes other than Langerhans cells

Benign Cephalic Histiocytosis

Synonym: ■ Infantile histiocytosis with intracytoplasmic worm-like bodies

Key features

- Infants <1 year of age are most commonly affected
- Red to brown macules and papules on the face and neck
- Self-limiting disease

Introduction

Benign cephalic histiocytosis (BCH) is a rare, self-limited histiocytic proliferative disorder of young children, primarily affecting the face.

History

Gianotti et al.[45] in 1971 described the condition as "infantile histiocytosis with intracytoplasmic worm-like bodies", based upon findings of comma-shaped structures by ultrastructural studies. When it became clear that several histiocytic disorders (e.g. LCH, juvenile xanthogranuloma) had similar ultrastructural findings, the disorder was renamed "benign cephalic histiocytosis", based upon typical clinical findings.

Epidemiology

BCH is a rare disorder but is probably under-reported. It typically begins by the age of 1 year and nearly always within the first 3 years of life. There may be a male predominance[46].

Pathogenesis

The pathogenesis of BCH is not known. However, due to the histopathologic and immunohistochemical features it shares with juvenile xanthogranuloma and generalized eruptive histiocytoma, several investigators have suggested that these three non-Langerhans cell histiocytoses should be viewed as a single disease with a spectrum of clinical presentations[47].

Clinical features

The eruption of BCH is characterized by the evolution of 2–5 mm, pink–red to red–brown macules and papules, initially on the face (Fig. 91.9A,B), with subsequent appearance on the ears and neck. Occasionally, lesions may develop on the trunk and arms, with infrequent involvement of the buttocks and thighs. The papules eventually flatten, often leaving residual hyperpigmentation that fades over time. Spontaneous resolution occurs over a period of months to years. Most children are otherwise healthy without involvement of the mucous membranes or internal organs. However, diabetes insipidus has been reported in a young girl with BCH[48]. The clinical course can be marked by exacerbations or evolution into generalized eruptive histiocytosis.

Pathology

The most typical finding is a well-circumscribed infiltrate of histiocytes that is confined to the upper dermis. Occasionally, a diffuse dermal infiltrate has been described. The histiocytes have regularly shaped nuclei and slightly vacuolated eosinophilic cytoplasm (Fig. 91.9C). Foamy cells and eosinophils are rarer than in juvenile xanthogranuloma. While multinucleated histiocytes and Touton giant cells were previously said to be absent, their presence has been described.

The histiocytes in BCH express typical (non-Langerhans) histiocytic markers including CD11b, CD11c, CD14b, CD68, CD163, HAM56, and factor XIIIa (see Fig. 91.4, Table 91.2)[2,49]. However, usually only immunostains for CD68 or CD163 and occasionally factor XIIIa are routinely performed.

Differential diagnosis

The differential diagnosis includes LCH, urticaria pigmentosa, and other non-LCH disorders (see Table 91.1). BCH overlaps with generalized eruptive histiocytoma and multiple juvenile xanthogranulomas in addition to sharing some features with progressive nodular histiocytosis and papular xanthoma. However, the clinical appearance and number of lesions as well as the distribution pattern usually allows for distinction of BCH from other non-LCH disorders while the immunophenotype of the histiocytic cells assists in excluding LCH (see Fig. 91.4).

Treatment

BCH is a self-limiting disorder and no treatment is usually needed. However, longitudinal evaluation of all patients is recommended, as both exacerbations of the disease and diabetes insipidus can occur.

Generalized Eruptive Histiocytoma

Synonyms: ■ Eruptive histiocytoma ■ Generalized eruptive histiocytosis

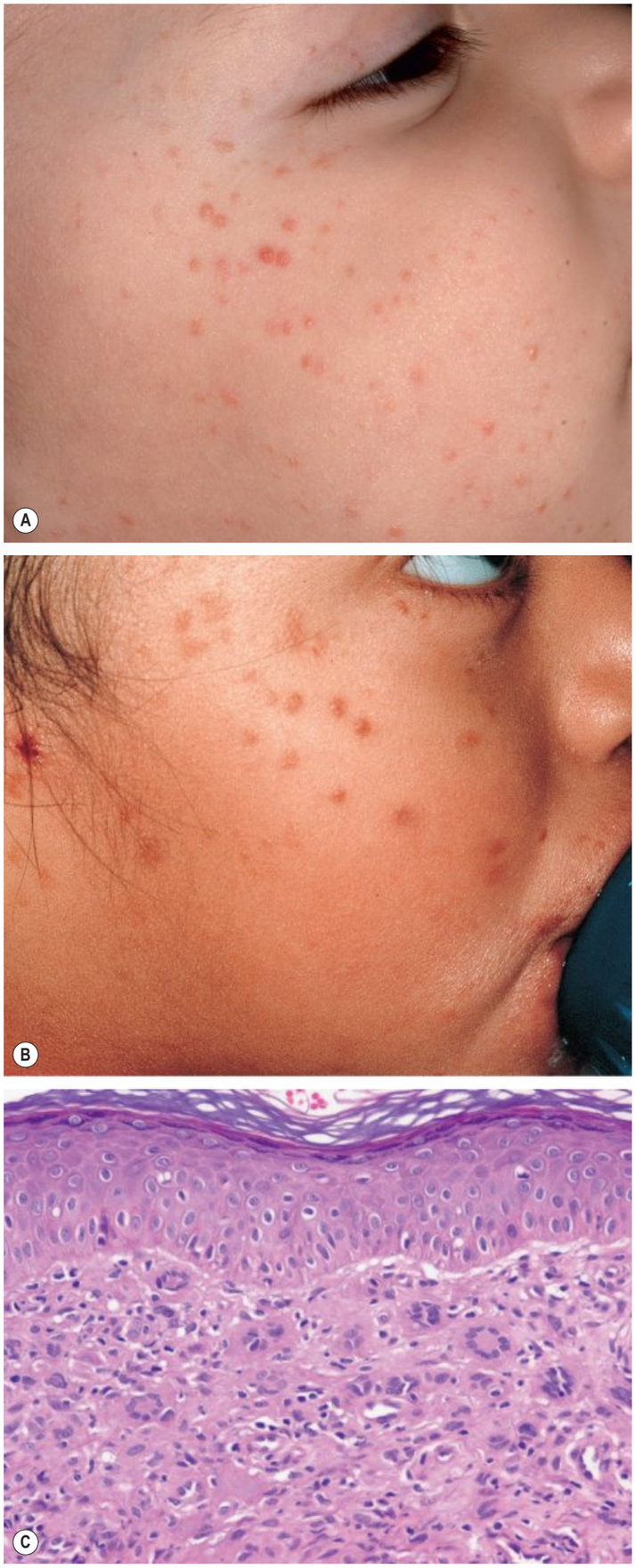


Fig. 91.9 Benign cephalic histiocytosis. Multiple papules that vary in color from light pink–brown (**A**) to brown (**B**) on the face of two young children with different skin phototypes. **C** Photomicrograph of the upper dermal infiltrate of histiocytes admixed with occasional Touton-like giant cells. *A, Courtesy Julie V. Schaffer, MD.*

Key features

- Adults affected more commonly than children
- Recurrent crops of numerous, small, red to brown papules
- Widespread axial distribution
- Self-limiting disease
- Rarely associated with leukemia (primarily acute or chronic myelomonocytic)

Introduction

Generalized eruptive histiocytoma is a rare disorder characterized by recurrent crops of small papules that are axially distributed and heal with hyperpigmented macules.

History

In 1963, Winkelmann and Muller first described three adult patients with generalized eruptive histiocytoma[50]. The disorder has since been reported in children.

Epidemiology

Generalized eruptive histiocytoma is a rare disease that is probably under-reported. Approximately one-quarter of the cases in the literature have been in children. There may be a male predilection. Onset in adults is from the third to sixth decade while in children, it is usually before the age of 4 years.

Pathogenesis

The cause of generalized eruptive histiocytoma is unknown, but there was a case report of a novel *LMNA-NTRK1* fusion. As discussed in the section on BCH, several authors have suggested that generalized eruptive histiocytoma, BCH, and juvenile xanthogranuloma represent different expressions of the same disorder. Generalized eruptive histiocytoma-like presentations have been seen early in the course of other non-LCH disorders, leading some investigators to suggest that generalized eruptive histiocytoma may be an early, indeterminate stage of non-LCHs (e.g. xanthoma disseminatum, progressive nodular histiocytosis)[51,52]. There are a few case reports of generalized eruptive histiocytoma in patients with leukemia, in particular acute or chronic myelomonocytic leukemia. In one patient, interphase FISH analysis showed that the cutaneous lesions of generalized eruptive histiocytoma were clonally linked to the hematologic malignancy[52].

Clinical features

The eruption is characterized by recurrent crops of red to brown papules. At each occurrence, hundreds of papules, less than 1 cm in diameter, are distributed on the trunk, proximal extremities, and occasionally the face (Fig. 91.10). The papules are usually arranged symmetrically, and mucosal surfaces are occasionally involved. Complete resolution may occur within several months or lesions may persist; recurrences have been observed. In some children, there may be a less symmetric distribution pattern and papules can become xanthomatous. Internal involvement has not been described and the affected individuals are otherwise healthy.

Pathology

The superficial and mid dermis typically contain a nearly uniform infiltrate of slightly vacuolated histiocytes with a few lymphocytes. Xanthomatous cells are rare as are multinucleated cells[53]. The histiocytes stain for mature histiocytic markers such as CD68, CD163, and factor XIIIa (see Fig. 91.4, Table 91.2)[54].

Differential diagnosis

The differential diagnosis includes LCH, urticaria pigmentosa, eruptive syringomas, widespread papular granuloma annulare, and other non-LCH disorders. Of the latter, juvenile xanthogranuloma, xanthoma disseminatum, BCH, indeterminate cell histiocytosis, and papular xanthoma (see Table 91.1) can be the most difficult to differentiate from generalized eruptive histiocytoma. However, the clinical features plus the histologic and immunohistochemical findings usually allow for distinction. Occasionally



Fig. 91.10 Generalized eruptive histiocytoma. Multiple firm red to red–brown papules on the trunk.

infections that lead to granulomatous inflammation (e.g. leishmaniasis, leprosy, atypical mycobacterial infections) need to be excluded.

Treatment

No treatment is usually required as the disorder lacks systemic involvement and is often self-limited. There are, however, scattered reports of the use of isotretinoin, cryotherapy, and PUVA. Longitudinal evaluation is recommended, as more serious forms of non-LCH (e.g. xanthoma disseminatum) and rare cases of leukemia have been reported to develop in patients with generalized eruptive histiocytoma[54].

Juvenile Xanthogranuloma

Key features

- Most common histiocytosis
- Usually occurs in infants and young children, with involvement of the head and neck region and upper body
- There are both small and large nodular forms, and lesions acquire a yellow color as they mature
- In patients with multiple lesions, a very small minority also have ocular involvement
- Rare association with both neurofibromatosis type 1 and juvenile myelomonocytic leukemia

Introduction

Juvenile xanthogranuloma (JXG) is a fairly common non-LCH, most often affecting infants and young children. Cutaneous lesions usually resolve and most patients have an otherwise unremarkable course. Although ocular JXG can lead to blindness and there is an association of JXG with neurofibromatosis type 1 (NF1) and juvenile myelomonocytic leukemia, these are unusual occurrences.

History

The term "juvenile xanthogranuloma" was suggested by Helwig and Hackney[55] in 1954 based upon histologic findings of xanthomatous histiocytes and giant cells. However, multiple cases of JXG, under different names, had previously been reported during the first half of the twentieth century. The first case of JXG was actually reported in 1905 by Adamson[56], who named the disorder "congenital xanthoma multiplex".

Epidemiology

JXG is a fairly common disorder and the most common histiocytic disease of childhood[57]. However, the true incidence may be underestimated, as many lesions, especially those which are solitary and small, may go unrecognized. In children, there is a male predominance of approximately 1.5 : 1; no sex predilection is noted in adults. A significant majority of those reported are White individuals. In almost 75% of cases lesions appear during the first year of life, with >15% of patients having them at birth. JXG is rare in adults, with a peak incidence during the late twenties to early thirties, although lesions have also been reported in the elderly. Most adult patients have solitary lesions.

Pathogenesis

The cause of JXG is not known; it is often suggested that the condition is reactive, with histiocytes possibly responding to a traumatic or infectious stimulus. However, in a recent series of 55 patients with both cutaneous and extracutaneous JXG, ~75% had a genetic mutation that would lead to activation of the MAPK pathway[58]. The reason for the progressive lipidation of histiocytes in the absence of hyperlipidemia is not clear. However, it has been shown that in adult patients with xanthogranulomas, the uptake of low-density lipoprotein and the synthesis of cholesterol within macrophages is increased[59]. As discussed in the section on BCH, several authors have suggested that generalized eruptive histiocytoma, BCH, and JXG may represent different expressions of the same disorder.

Clinical features

Gianotti and Caputo[60] described two common clinical variants of JXG: a small nodular form and a large nodular form. Patients with the small nodular form, also known as the micronodular form, present with multiple pink to red–brown, dome-shaped papules, 2–5 mm in diameter. The lesions are widely scattered on the upper part of the body and rapidly become yellow. In contrast, the more common large nodular form is characterized by one or a few nodules 1–2 cm in diameter. The two forms may coexist.

The most common location for JXG is the head and neck (Fig. 91.11), followed by the upper torso, the upper extremities, and then the lower extremities. Oral JXG is rare and usually presents as a solitary yellow nodule on the lateral aspect of the tongue or the midline of the hard palate. Unusual morphologic presentations include keratotic, pedunculated, subcutaneous, clustered, plaque-like, and giant lesions.

Extracutaneous lesions have been reported in many organs, with the eye being most commonly affected. The lung represents the second most frequent extracutaneous site of disease. Other visceral, bone, and CNS involvement is unusual and disease-related deaths are rare[61]. Ocular JXG is almost always unilateral and develops in <0.5% of patients with cutaneous lesions. However, ~40% of patients with ocular JXG have cutaneous lesions, always multiple, at the time of diagnosis[62]. Ocular involvement usually occurs before 2 years of age and often affects the iris. Hyphema (hemorrhage into the anterior chamber) and glaucoma are serious complications which can result in blindness. Early referral to an ophthalmologist for evaluation and possible treatment is important.

A well-recognized association exists between JXG and café-au-lait macules. Some of these patients have a family history of NF1, while others fulfill the clinical criteria for NF1 (see Table 61.3). Another well-known association is that of JXG and juvenile myelomonocytic leukemia; patients with NF1 also have an increased risk of developing juvenile myelomonocytic leukemia. A so-called "triple association" consisting of JXG, NF1, and juvenile myelomonocytic leukemia has been observed in several patients, and patients with JXG and NF1 have at least a 20× increased risk of developing juvenile myelomonocytic leukemia[63]. Other hematologic malignancies have been reported in association with JXG, e.g. chronic lymphocytic leukemia or B cell lymphoma in adults with multiple lesions.

In the majority of patients with disease limited to the skin, the course is self-limited and benign. These patients are otherwise in good health and lesions usually regress within 3–6 years. Hyperpigmentation, mild atrophy, or anetoderma may remain. However, in adults, the xanthogranulomas are usually solitary and persistent[2].

Pathology

In small lesions, there is a well-demarcated, dense infiltrate of histiocytes within the superficial dermis, which extends into the subcutis in larger

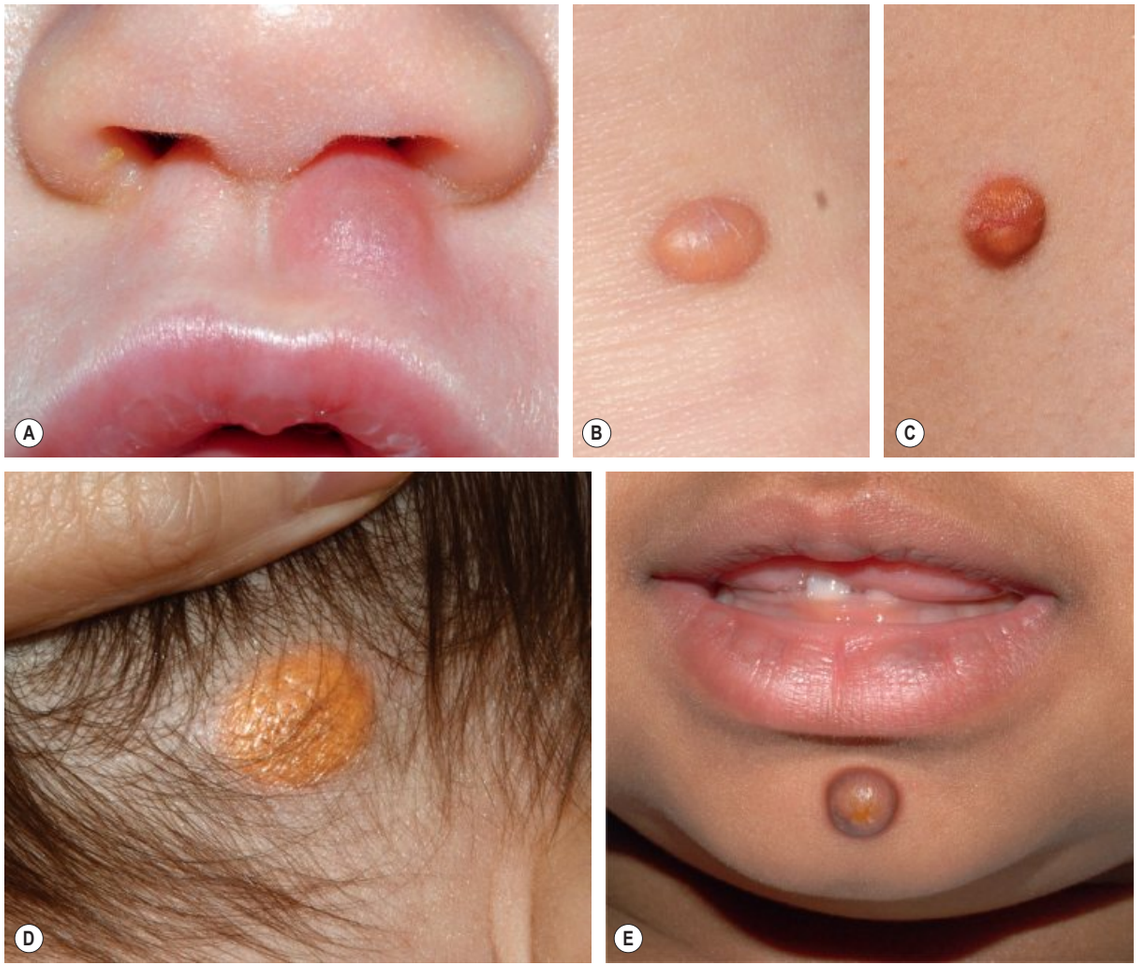


Fig. 91.11 Juvenile xanthogranuloma. A Pink nodule with a few telangiectasias representing an early lesion. Well-developed lesions that vary in color from pale yellow (**B**) to red–yellow (**C**) to yellow–orange (**D**) to yellow–brown (**E**), with the yellow hue reflecting the accumulation of lipid within histiocytes. *Courtesy Julie V. Schaffer, MD.*

lesions. A loss of the rete ridges is often seen, and ulceration occurs in some cases. Early lesions usually have monomorphous histiocytes with abundant eosinophilic cytoplasm (Fig. 91.12A). In mature lesions, the histiocytes develop lipid in their cytoplasm, creating a foamy "xanthomatous" appearance. Touton giant cells are a characteristic finding, but they may be absent in early lesions (Fig. 91.12B). Lymphocytes, eosinophils, plasma cells, and even neutrophils are also scattered throughout the infiltrate. Variants with spindle cells have been reported, which may be misinterpreted as another spindle cell tumor[37]. Other morphologic variants include mononuclear cells with an oncocytic appearance, vacuolated cells, and cells with a polygonal or spiculated cytoplasm[64,65].

The cells in JXG stain positively for mature histiocyte markers such as CD68, CD163, and factor XIIIa (see Table 91.2). In some cases there is expression of S100 protein on the large-sized cells, whereas CD1a and CD207 (Langerin) are always negative.

Differential diagnosis

The major entities to consider when there are multiple lesions are other histiocytic disorders including LCH. In a child with a single JXG, the initial clinical differential diagnosis can be broad (e.g. molluscum contagiosum, Spitz nevus, mastocytoma). A solitary lesion in an adult may be diagnosed clinically as a more common melanocytic nevus or dermatofibroma. The so-called "solitary reticulohistiocytoma" is simply a xanthogranuloma in which oncocytic macrophages and giant cells with ground-glass cytoplasm dominate[2].

In general, the constellation of clinical and histopathologic features allows for distinction between JXG and either BCH or generalized eruptive histiocytoma, although some cases of BCH can have giant cells (see Fig. 91.9C), and these three disorders may indeed exist within a spectrum. LCH can be differentiated from JXG via immunophenotyping (see Fig. 91.6).

Treatment

Due to the self-limiting nature of JXG, no treatment is usually required. Occasionally, lesions are removed for cosmetic concerns, despite the anticipated spontaneous resolution. While ocular lesions often require intervention (e.g. topical corticosteroids for iris lesions, excision for limbal lesions), sites of systemic involvement can be followed without treatment unless their location interferes with normal function. For these patients, various chemotherapeutic regimens, radiotherapy, high-dose systemic corticosteroids, and cyclosporine have been administered. Given the possibility of spontaneous involution, however, it is sometimes difficult to evaluate the response to treatment in a given patient.

Progressive Nodular Histiocytosis

Key features

- Affects primarily the elderly of either sex
- Hundreds of lesions of two types: small superficial papules and nodules or deep nodules and tumors
- Mucosal lesions may be seen
- Chronic without spontaneous regression

Introduction, epidemiology, and pathogenesis

Progressive nodular histiocytosis (PNH) is an extremely rare, clinically distinct disorder affecting primarily the elderly. It has a chronic course and an unknown etiology and pathogenesis. However, an *IRF2BP2-NTRK1* fusion was detected in a patient with PNH/xanthogranulomatosis.

Clinical features

Patients typically develop multiple lesions that progressively become widespread, but usually spare the flexural areas. Two distinct types of lesions have been described: (1) superficial xanthomatous papules and nodules that are 2–10 mm in diameter; and (2) deep fibrous nodules and tumors, 1–3 cm in diameter, that are primarily on the trunk. The face is

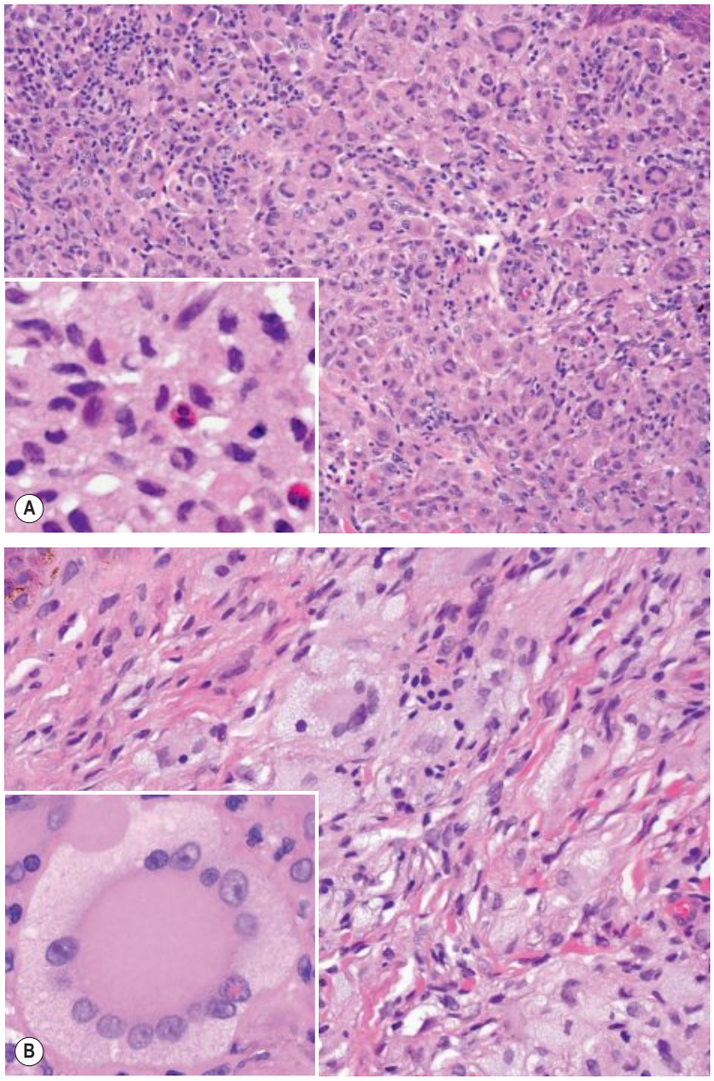


Fig. 91.12 Juvenile xanthogranuloma. A Earlier lesion – the dermal histiocytic infiltrate contains relatively few Touton giant cells. Lymphocytes and eosinophils are also present (inset). **B** Older lesion – multiple foamy (xanthomatous) histiocytes and giant cells as well a classic Touton giant cell with a "wreath-like" arrangement of nuclei (inset).

often involved and confluent nodules can lead to a "leonine facies" (see Table 46.5). A key to the diagnosis is the presence of these two distinct types of lesions. There may be conjunctival, oral, and laryngeal involvement.

In patients followed over a course of many years, the lesions have rarely regressed[66,67]. Visceral involvement has not been observed nor have consistent associations with other diseases. The significance of a report of a patient with PNH and chronic myeloid leukemia, hepatosplenomegaly, hyperuricemia, and hypocholesterolemia is unclear[68].

Pathology

The smaller papules contain foamy xanthomatous cells and occasional Touton giant cells, mimicking papular xanthomas. The larger nodules are distinctive and show features of spindle-cell xanthogranulomas. The cells express markers of mature dendritic histiocytes such as CD68, CD163, and FXIIIa.

Differential diagnosis

Other non-LCHs, especially those that do not regress spontaneously such as progressive mucinous histiocytosis, as well as sarcoidosis and leprosy represent the primary entities in the clinical differential diagnosis.

Treatment

The natural history is chronic and progressive, with an increase in the number of lesions. Treatment consists of removal of nodules via surgical excision or CO_2 laser.



Fig. 91.13 Xanthoma disseminatum. Symmetric involvement of the major flexures is a characteristic finding. Note the yellow discoloration of some of the coalescing papulonodules. *Courtesy David Wetter, MD.*

Xanthoma Disseminatum

Synonym: ■ Xanthoma disseminatum of Montgomery

Key features

- Classic triad of cutaneous xanthomas, mucous membrane xanthomas, and diabetes insipidus
- Symmetric distribution of lesions
- Favors flexural areas and intertriginous zones
- Corneal and conjunctival lesions can threaten vision

Introduction

Xanthoma disseminatum is a rare, normolipemic, histiocytic proliferative disorder that affects the skin, mucous membranes, and frequently, the hypothalamus and pituitary gland, leading to transient diabetes insipidus.

History

Four cases of "xanthomatosis disseminata" were described by Montgomery and Osterberg[69] in 1938. A review and characterization of the disorder was provided by Altman and Winkelmann[70] in 1962.

Epidemiology

Xanthoma disseminatum is a rare condition, with ~100 cases reported to date. Men are more commonly affected than women. Age of onset ranges from 8 months to 85 years, with >60% of patients developing the disease before the age of 25.

Pathogenesis

The etiology is unknown. As most patients have normal lipid levels, it has been suggested that xanthoma disseminatum represents a reactive proliferative disorder of histiocytes with secondary accumulation of lipid.

Clinical features

Patients may have the classic triad of cutaneous xanthomas, xanthomas of mucous membranes, and diabetes insipidus. The primary xanthomatous lesion is a yellow, red, or brown papule. Disease onset is marked by an eruption of hundreds of papules, symmetrically arranged on the face and in the major body folds and flexural areas of the trunk and proximal extremities (Fig. 91.13). The lesions tend to cluster into well-formed, potentially disfiguring plaques (Fig. 91.14). Older lesions may become atrophic.

Mucous membrane lesions are found in 40%–60% of patients, with the upper airway and oral mucosa being commonly involved. Corneal



Fig. 91.14 Xanthoma disseminatum. Sclerotic form of xanthoma disseminatum in a patient who developed multiple myeloma. Note the associated scarring.

and conjunctival lesions can threaten vision. CNS involvement of the hypothalamus and pituitary stalk results in diabetes insipidus in ~40% of patients. The latter is usually mild, transient, and sensitive to vasopressin. Rarer associations include monoclonal gammopathies due to plasma cell dyscrasias and thyroid disorders.

Caputo et al.[71] suggested that patients follow one of three clinical courses: (1) a rare, self-healing form with spontaneous resolution of lesions; (2) the common persistent form in which lesions may never resolve; and (3) the very rare progressive form with organ dysfunction and CNS involvement. A few disease-related deaths have been reported, including one patient with CNS involvement outside the pituitary gland and hypothalamus[72].

Pathology

In the early stages, there is a dense dermal infiltrate of scalloped macrophages in addition to a few foamy cells or other inflammatory cells. Well-developed lesions contain a mixture of scalloped cells, foamy cells and other inflammatory cells, as well as Touton and foreign body giant cells. The histiocytes express typical non-LCH markers such as CD68, CD163, CD11b, CD14, CD11c, and factor XIIIa (see Fig. 91.4, Table 91.2)[71].

Differential diagnosis

The disorders most likely to be confused with xanthoma disseminatum include generalized eruptive histiocytoma, papular xanthomas, eruptive and plane xanthomas (see Ch. 92), ECD, multiple JXGs, progressive nodular histiocytosis, and multicentric reticulohistiocytosis. In general, these can be fairly easily differentiated based on clinical and histopathologic features.

Treatment

As xanthoma disseminatum is a rare disease, there are no controlled trials of systemic therapies. Radiotherapy has been used to control obstructive airway disease. No significant improvement in cutaneous and mucosal lesions has been observed with oral corticosteroids. Physical modalities including surgery, radiotherapy, cryosurgery, and laser therapy have all been tried, as have systemic medications such as cyclophosphamide, cyclosporine, and 2-chlorodeoxyadenosine (2-CdA). In a case series, all five patients who received 2-CdA experienced a remission and long-term control of cutaneous lesions[72].

Progressive Mucinous Histiocytosis

Key features

- Affects primarily women
- Usually an autosomal dominant disorder but can be sporadic
- Involvement, which is limited to the skin, is chronic and unremitting

Introduction and pathogenesis

Progressive mucinous histiocytosis is an extremely rare form of non-LCH. Most cases are inherited in an autosomal dominant pattern, but rare sporadic cases have also been observed[73]. A germline gain-of-function missense mutation in *PDGFRB* (platelet-derived growth factor receptor beta) was recently detected in the original pedigree[73a].

Epidemiology

Most affected patients are women, but an explanation for this skewing is lacking. To date, eight families with the hereditary form have been described[74].

Clinical features

Cutaneous lesions appear during childhood or adolescence and persist indefinitely. They consist of multiple, discrete, skin-colored to red–brown papules or nodules that favor the face, hands, forearms, and legs in a symmetric distribution pattern. There is neither mucosal nor visceral involvement and no associated diseases have been described[67,73,74]. The clinical course is chronic with no spontaneous remissions.

Pathology

Progressive mucinous histiocytosis is characterized by an accumulation of spindled or epithelioid histiocytes in the upper and mid dermis that is accompanied by mucin deposition. The histiocytes express the phenotype of mature macrophages with positivity for CD68 and CD163.

Differential diagnosis

The differential diagnosis includes other non-LCHs, multinucleated cell angiohistiocytoma, and multiple dermatofibromas. These entities can be distinguished by clinical, histopathologic, and immunohistochemical features.

Treatment

There are no specific treatments. Lesions may be removed by surgery, CO_2 laser, or cryotherapy. Use of PDGFR inhibitors (e.g. imatinib) may represent an additional therapy.

Necrobiotic Xanthogranuloma

Synonym: ■ Necrobiotic xanthogranuloma with paraproteinemia

Key features

- Multisystem histiocytic disease that can present with hepatosplenomegaly as well as ocular and skin involvement
- In at least 70% of patients, there is an IgG monoclonal gammopathy due to a plasma cell dyscrasia or lymphoproliferative disorder (e.g. B cell chronic lymphocytic leukemia)
- Average age of onset is the sixth decade
- Firm nodules and plaques with a yellow hue are seen and they may develop ulceration
- Most common site of involvement is the periorbital region

Introduction

Necrobiotic xanthogranuloma (NXG) is a rare, progressive multisystem histiocytic disease in which characteristic cutaneous lesions point to the diagnosis. The majority (~80%) of patients have a monoclonal gammopathy due to either a plasma cell dyscrasia or a B cell lymphoproliferative disorder (see Ch. 119)[75].

History

Necrobiotic xanthogranuloma was codified in 1980 by Kossard and Winkelmann[76]. Their original eight patients demonstrated yellowish plaques, subcutaneous nodules, and an associated dysproteinemia. These authors also noted several reports published prior to 1980 representing unrecognized cases of NXG.

Epidemiology

Necrobiotic xanthogranuloma is a rare disorder with over 200 cases reported to date. In 1992, Mehregan and Winkelmann[77] described 32 patients with NXG and reviewed the 16 reported cases from the world literature. Men and women are generally equally affected. The average age of onset is the sixth decade.

Pathogenesis

While the pathogenesis of NXG is as yet unknown, its strong association with monoclonal gammopathies has led to several hypotheses. The M protein may act either as a primary inciting agent or as a cofactor in eliciting a giant cell granulomatous reaction. In a review of 17 cases, there was no evidence of a monoclonal proliferation of plasma cells within the inflammatory infiltrate of skin lesions[78]. It has been suggested that NXG and normolipemic plane xanthoma exist within a spectrum, given their shared relationship to monoclonal gammopathies[79].

Clinical features

Cutaneous lesions, typically multiple, develop in all patients with NXG. The classic skin lesion is an asymptomatic indurated papule, nodule, or plaque with a yellow, "xanthomatous" hue (Fig. 91.15). Other reported features include telangiectasias, atrophy, ulceration and scarring, with scars being common sites for the development of new lesions.

The periorbital region is the most common site of involvement. The trunk, remainder of the face, and proximal extremities are also frequently involved. From 15% to 50% of patients have ophthalmic manifestations, which include orbital masses, ectropion, ptosis, conjunctival lesions, keratitis and scleritis, episcleritis, anterior uveitis, and proptosis[75,80].

A hallmark feature of NXG is the associated IgG monoclonal gammopathy, which is found in ~80% of patients[75]. The M protein can be detected by serum protein electrophoresis and/or the more sensitive immunofixation electrophoresis. Other common findings include hepatomegaly, splenomegaly, an increased ESR/CRP, leukopenia, hypocomplementemia, and an underlying plasma cell dyscrasia (including multiple myeloma). Less commonly, cryoglobulinemia and/or an underlying B cell lymphoproliferative disorder are observed. Of the 48 patients described by Mehregan and Winkelmann[77], a plasma cell dyscrasia was found in 17 patients (with 8 fulfilling the criteria for multiple myeloma) and a lymphoproliferative disorder in 2 patients. In a more recent retrospective study from the same institution, a higher percentage of patients (12 of 17 [71%]) had a monoclonal gammopathy, with 3 patients fulfilling the criteria for multiple myeloma[78]. Postmortem examination has demonstrated involvement of multiple organ systems, with endocardial NXG found in most cases.

In one series, when patients with NXG developed a plasma cell dyscrasia or a lymphoproliferative disorder (10 of 26 patients), these disorders often arose after the onset of cutaneous manifestations and did not tend to be aggressive[79]. Overall survival was 100% at 10 years and 90% at 15 years.

Pathology

Classic, non-ulcerated lesions have a normal epidermis and superficial dermis. A palisading xanthogranuloma is found in the mid dermis extending into the panniculus (Fig. 91.16). The granulomas consist of histiocytes, foam cells, lymphoid follicles, plasma cells, and giant cells with zones of collagen degeneration ("necrobiosis"). Cholesterol clefts are found in areas of necrobiosis. A prominent feature is the presence of both Touton giant cells and large, bizarre foreign body giant cells. These cells are found scattered within the granuloma and often at the margins of areas of necrobiosis. Lymphoid or lymphoplasmacytic nodules are also common, and clonal infiltrates can be seen in patients with B cell chronic lymphocytic leukemia (CLL)[78]. Histiocytic cells stain positively for non-LCH markers such as CD68 and CD163, but are negative for FXIIIa (see Fig. 91.4, Table 91.2)[77,80,81].

Differential diagnosis

The clinical differential diagnosis includes necrobiosis lipoidica, normolipemic plane xanthomas, xanthelasma, non-LCH disorders (xanthoma disseminatum, ECD, multicentric reticulohistiocytosis, JXG), adult-onset asthma and periocular xanthogranuloma (AAPOX), foreign body granulomas, and sarcoidosis. However, most of these disorders can be excluded on the basis of morphology, distribution pattern, histologic features, and associated systemic manifestations (if any).

Treatment

No controlled clinical studies are available regarding the treatment of NXG. In the past, alkylating agents (e.g. chlorambucil, melphalan) were often tried but due to the availability of other therapeutic options and the risk of myelodysplastic syndrome and acute myelogenous leukemia, their use has declined[78]. In a multicenter cohort of 34 patients, IVIg was found to be the most effective therapy (9/9 patients), followed by antimalarial drugs (4/5) and intralesional triamcinolone (6/8)[75]. When the patient meets the criteria for multiple myeloma, combination therapy that can include an immunomodulatory drug (e.g. lenalidomide), proteosome inhibitor (e.g. bortezomib, carfilzomib), anti-CD38 antibody (e.g. daratumumab), and dexamethasone consistently leads to disappearance of the M protein. These medications can also be considered for patients with severe recalcitrant disease, even if they do meet the criteria for symptomatic



Fig. 91.15 Necrobiotic xanthogranuloma. Yellow–brown papules and plaques in a periorbital distribution in a patient with chronic lymphocytic leukemia. Such lesions may initially be mistaken for xanthelasma. *Courtesy Kalman Watsky, MD.*

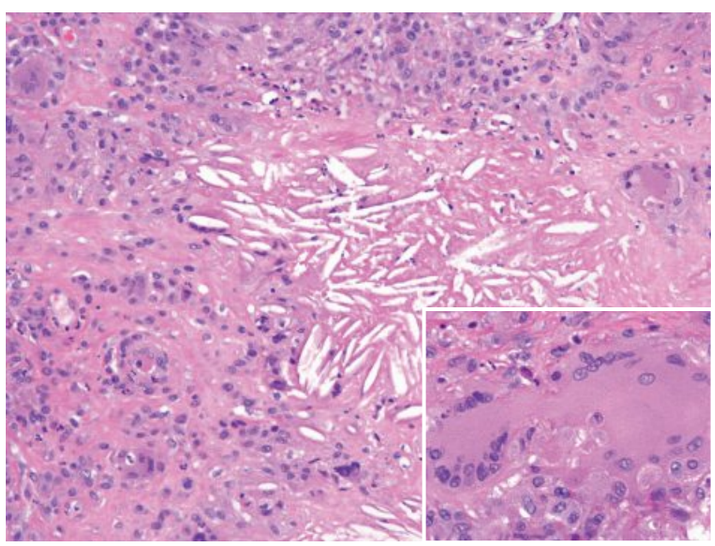


Fig. 91.16 Necrobiotic xanthogranuloma. A necrobiotic area contains cholesterol clefts. The presence of bizarre, large multinucleated giant cells is a typical feature (inset).

myeloma. For B cell CLL, current treatments include BTK inhibitors (e.g. ibrutinib, acalabrutinib, zanabrutinib), bcl-2 inhibitors (e.g. venetoclax), and anti-CD20 antibodies (e.g. obinutuzumab, rituximab).

Topical JAK inhibitors (e.g. tofacitinib 2% cream) may lead to improvement of cutaneous lesions. A recurrence rate of ~40% was observed in one series following surgical excision of lesions[80].

Multicentric Reticulohistiocytosis

Key features

- Occurs primarily in adults
- Papules and nodules favor the head, hands, and elbows; periungual papules have been likened to "coral beads"
- 50% of patients develop mucous membrane lesions (oral and nasopharyngeal)
- Multicentric reticulohistiocytosis is associated with a destructive arthritis and, in some patients, solid organ malignancies
- Histiocytes have a characteristic "ground glass" appearance

Introduction

Multicentric reticulohistiocytosis (MRH) is a rare form of non-LCH which most commonly affects adults. This disorder is characterized by both cutaneous and systemic features. Well-developed lesions demonstrate a classic histopathology consisting of mononucleated and multinucleated giant cells with a "ground glass" appearance.

History

The term *multicentric reticulohistiocytosis* was introduced in 1954 by Goltz and Laymon[81] to define cases with both cutaneous and systemic manifestations. Familial histiocytic dermatoarthritis, described in 1973, is a very rare variant of MRH, characterized by a familial occurrence and associated glaucoma, uveitis, and cataracts[82].

Epidemiology

MRH is uncommon, occurring most frequently in women during their fifth or sixth decade of life.

Pathogenesis

The pathogenesis of MRH is unknown. In one study from the 1960s, 56% of patients had a positive tuberculin skin test[83], leading to the suggestion that mycobacteria could be a possible trigger. In addition, MRH has been reported to respond to antituberculosis treatment. However, confirmation of mycobacteria within skin nodules is lacking. Others have proposed that the histiocytic response in MRH is an immunologic process related to an underlying neoplastic or autoimmune disorder. There is evidence that TNF, which can promote osteoclast formation, may play a role in its pathogenesis[84].

Clinical features

Patients with MRH usually have cutaneous and mucous membrane involvement in addition to a severe arthropathy, although histiocytic infiltrates can be found in multiple organs (see below). There is an association with hyperlipidemia, a positive tuberculin skin test, systemic vasculitis, and autoimmune disease (e.g. systemic lupus erythematosus, Sjögren syndrome). Up to 25%–30% of patients have reportedly had an associated malignancy, with a range of solid and hematologic malignancies[85]. An elevated ESR and anemia have been noted in approximately half of patients, and one-third demonstrate hypercholesterolemia. Rarely, monoclonal gammopathies or cryoglobulinemia have been observed. Fever and weight loss can also occur.

Cutaneous lesions range from a few millimeters to 2 cm and are skin-colored to pink, red–brown, or yellow. Lesions tend to have an acral distribution. Favored sites include the head, hands, fingers, ears, and articular regions of the limbs (Fig. 91.17). Small papules aligned



Fig. 91.17 Multicentric reticulohistiocytosis. A Grouped, firm, red–brown papules on the dorsal surface of the fingers, hand, and wrist in this 73-year-old African-American woman. **B** Grouped pink papulonodules on the elbow in a second patient. **C** A more subtle presentation in a third patient, with small pink papules and thin plaques that favor the skin overlying the small joints of the hands; this is the form that can initially be confused with dermatomyositis. **D** Telescoping of fingers due to arthritis mutilans. *A, Courtesy Susan D. Laman, MD; B, Courtesy Jean L. Bolognia, MD; C,D, Courtesy Kalman Watsky, MD.*

along the proximal and lateral nail folds result in a characteristic "coral bead" appearance. Approximately one-half of patients develop papules and nodules of the oral, pharyngeal, and/or nasal mucosae. Less common findings include a "leonine facies" secondary to severe facial involvement, periarticular rheumatoid-like nodules, an initial photodistribution, and secondary nail changes.

A 6- to 8-year course of symmetric, erosive arthritis of multiple joints is common, and there is progression to arthritis mutilans in ~45% of patients. The joints of the fingers and hands, as well as the knees and wrists, are most commonly involved, although any joint may be affected. Cartilaginous destruction of the nose and ears can lead to facial disfigurement. Rarely, there is histiocytic infiltration of the heart, eye, lungs, thyroid, liver, kidney, muscle, salivary gland, and/or bone marrow. In most patients the disease resolves spontaneously within 5–10 years, although patients are often left with significant disability. Fatal disease has been rarely reported in patients with widespread systemic involvement.

Pathology

In well-developed lesions there are numerous multinucleated giant cells and oncocytic macrophages that have eosinophilic, finely granular cytoplasm, often with a "ground glass" appearance (Fig. 91.18). The abundant eosinophilic granular cytoplasm (oncocytic change) is a reflection of accumulated mitochondria and lysosomes, which is evident by electron microscopy. The multinucleated cells have nuclei arranged haphazardly, aligned at the periphery, or clustered in the center.

Histiocytes in MRH express CD68, CD163, CD11b, CD14, and HAM56 (see Fig. 91.4, Table 91.2)[86]; S100 protein is usually negative as is FXIIIa.

Differential diagnosis

MRH must be differentiated from rheumatoid arthritis, dermatomyositis (especially when lesions are photodistributed), paraneoplastic reactive granulomatous dermatitis, and other non-LCH histiocytoses such as JXG, generalized eruptive histiocytosis, and cutaneous Rosai–Dorfman disease. The entity that may prove the most challenging to exclude is fibroblastic rheumatism; some authors consider fibroblastic rheumatism to be a type of histiocytosis while others view it as a fibromatosis[87].

Treatment

Systemic therapies for MRH often focus on treating the symptoms, and frequently they are not effective in achieving remission or in altering the course of the disease. Based upon case reports or case series, various combinations of NSAIDs, oral corticosteroids, JAK inhibitors, methotrexate, tocilizumab, cyclophosphamide, TNF inhibitors, and anakinra (an interleukin-1 antagonist) have been employed[84,88]. Other immunosuppressive drugs (e.g. azathioprine, leflunomide, cyclosporine) have also been tried, as well as hydroxychloroquine and isoniazid.

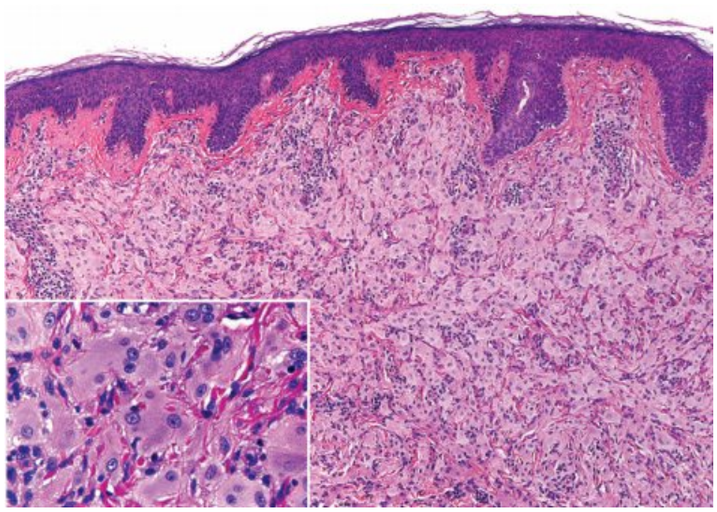


Fig. 91.18 Multicentric reticulohistiocytosis. Numerous mononucleated and multinucleated histiocytes within the dermis. The histiocytes have abundant eosinophilic, finely granular cytoplasm, creating a "ground glass" appearance (inset). *Courtesy Luis Requena, MD.*

"R" GROUP: ROSAI–DORFMAN DISEASE

Synonyms: ■ Sinus histiocytosis with massive lymphadenopathy ■ Destombes–Rosai–Dorfman syndrome

Key features

- Children and young adults are most commonly affected
- Massive, painless, bilateral cervical lymphadenopathy is characteristic
- Involvement of extranodal sites can be the sole manifestation of the disease, with a skin-limited form increasingly being recognized
- In the systemic form, cutaneous lesions occur in a minority of patients (~10%), are usually multiple, and are clinically nonspecific
- Fever and polyclonal hypergammaglobulinemia are often seen
- In the lymph nodes and the skin, emperipolesis is a common histologic feature
- A rare familial form due to mutations in *SLC29A3* falls within the histiocytosis–lymphadenopathy plus syndrome

Introduction

Rosai–Dorfman disease (RDD) is an uncommon, often protracted, histiocytic proliferative disorder. It is characterized by massive, but painless, bilateral cervical lymphadenopathy, fever, anemia, elevated ESR/CRP, neutrophilia, and polyclonal hypergammaglobulinemia. Cutaneous lesions occur in a minority of patients with systemic disease, are usually multiple, and are clinically nonspecific. However, there is a form of RDD with only cutaneous involvement, and this skin-only form is currently classified within histiocytosis group C not group R.

History

Sinus histiocytosis with massive lymphadenopathy was described as a distinct entity by Rosai and Dorfman in 1969[89]. However, the eponymous designation "Rosai–Dorfman disease" is more appropriate as some patients have extranodal lesions as the sole manifestation of the condition[90].

Epidemiology

A repository for cases of RDD, rather than a true registry, was available during 1980s–1990s. In 1990, the repository contained 423 patients, and by 1995, almost 600 cases had been reported[91,92]. RDD has a widespread geographic distribution, although there is a higher incidence in the West Indies. The systemic form occurs most commonly in children and young adults and is more frequently seen in male patients. In 1990, an equal percentage of White and Black patients, 44% of each, were in the repository[91]. On the other hand, the skin-limited form occurs primarily in adults and favors women.

Pathogenesis

Somatic genetic mutations that lead to activation of the MAPK pathway have been detected in patients with RDD (see Fig. 113.1)[93]. These genes include *MAP2K1/MEK1* and *NRAS*, as well as *MET, KRAS*, and *ARAF* but rarely *BRAF*[94,95]. Heterozygous germline mutations in *FAS*, which lead to defects in Fas-mediated apoptosis, lead to type IA autoimmune lymphoproliferative syndrome and may be associated with RDD (see Table 60.6)[96]. There is also a familial form of RDD due to germline mutations in *SLC29A3*, which encodes an equilibrative nucleoside transporter hENT3[97]. These latter patients fall within the histiocytosis–lymphadenopathy plus syndrome which includes the H syndrome (see Table 70.2), pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome, and Faisalabad histiocytosis.

In addition, a viral pathogenesis has been postulated, including an association with HHV-6, cytomegalovirus, and Epstein–Barr virus. While HHV-6 sequences have been detected in involved lymph nodes[98], this finding is nonspecific given the presence of HHV-6 in many reactive

and infectious disorders of lymphoid tissue[99]. To date, no clear link has been proven[93].

Clinical features

While RDD is often an indolent, self-limited disease, a protracted course marked by remissions and exacerbations occurs in a number of patients. The characteristic clinical feature is massive, painless, bilateral cervical lymphadenopathy. However, any nodal site may be involved, unilateral involvement may occur, and an absence of lymph node involvement has also been reported. Fever is a frequent occurrence and most individuals have an elevated ESR/CRP and polyclonal hypergammaglobulinemia. A common finding is mild anemia, although severe anemia has been observed. Neutrophilia is occasionally seen. There are multiple reports of Hodgkin and non-Hodgkin lymphomas occurring in association with, or prior to, development of RDD. Of note, there was a report of a histiocytic sarcoma arising in a patient with autoimmune lymphoproliferative syndrome and associated RDD[100].

Immune disorders occur in ~15% of patients with RDD. Anti-red blood cell autoantibodies and joint disease are the most common findings. Patients with immunologic abnormalities have an unfavorable prognosis. In one analysis, 10 of 14 fatal cases were noted to have some form of immune dysfunction[101]. Other unfavorable prognostic signs include disseminated nodal disease or involvement of the liver, kidney, or lower respiratory tract.

Over 40% of patients with RDD have at least one extranodal site of involvement. The most common extranodal sites are the skin and soft tissue, the eyelid and orbit, the upper respiratory tract, major salivary glands, CNS, and bone. However, virtually any organ can be involved. In patients with hearing loss, there is overlap with H syndrome (see above)[97].

Cutaneous involvement occurs in ~10% of patients with the systemic form. The skin may be the only organ involved, with skin-limited disease increasingly being recognized. Cutaneous lesions are often multiple and appear as nonspecific red to red–brown or xanthomatous macules, papules, nodules, or plaques (Fig. 91.19); in the skin-limited form, there may be a single lesion. Panniculitis has also been reported. The eyelids and malar regions are frequent sites of involvement.

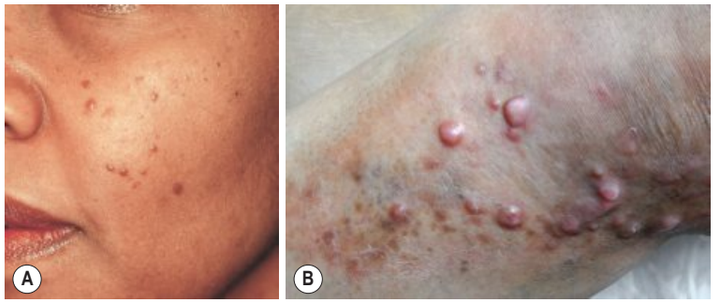


Fig. 91.19 Cutaneous Rosai–Dorfman disease. A Discrete, dome-shaped, brown papules on the cheek. **B** Multiple firm pink papulonodules arising within a yellow–brown plaque. *B, Courtesy Boni Elewski, MD.*

Pathology

The diagnosis requires the presence of histiocytic cells with abundant emperipolesis, i.e. engulfment of erythrocytes, plasma cells, and lymphocytes. The histiocytic cells stain positively for S100, CD68, CD14, and CD163; they are negative for CD1a and CD207 (Fig. 91.20; see Table 91.2). In addition, involved tissues usually contain abundant polyclonal plasma cells. Most cases demonstrate cyclin D1 and pERK expression, indicating activation of the MAPK pathway[102]. Recently, OCT2-positive nuclear staining was observed in all cases of RDD (51/51), but this finding is nonspecific as a variable number of neoplastic cells show positive staining in other histiocytoses[102a]. Although IgG4-positive plasma cells are found within the infiltrate of RDD, the relationship between RDD and IgG4-related disease, if any, is yet unclear.

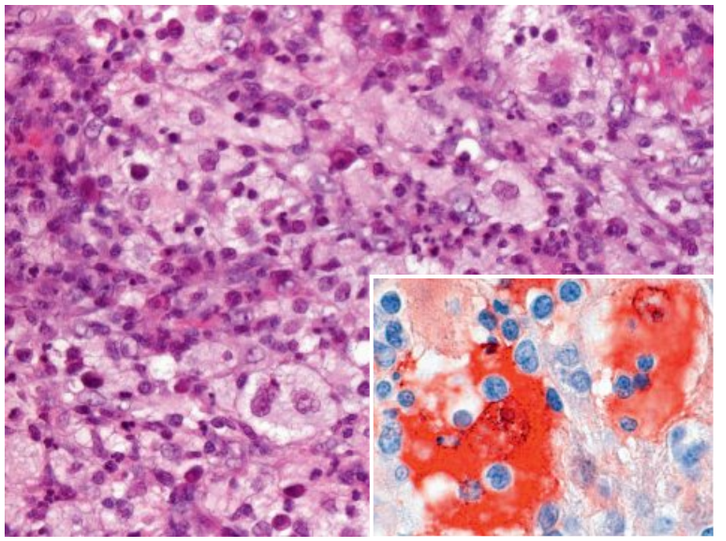


Fig. 91.20 Rosai–Dorfman disease. Large histiocytes with clear cytoplasm admixed with small lymphocytes and plasma cells. The large cells stain positively for S100 (inset), and the immunostain highlights lymphoid cells within the cytoplasm of large histiocytes (emperipolesis). *Courtesy Lorenzo Cerroni, MD.*

Differential diagnosis

Given the clinically nonspecific cutaneous lesions found in RDD, the differential diagnosis includes the other histiocytoses, sarcoidosis, granulomatous infectious diseases, and adnexal tumors. Of the histiocytoses, JXG in particular may resemble RDD as the former can also have large $S100^+$ macrophages and, rarely, emperipolesis. The diagnosis of cutaneous RDD is based upon the combination of characteristic histologic and immunohistochemical findings.

The differential diagnosis of massive lymphadenopathy includes Hodgkin and non-Hodgkin lymphoma, chronic lymphocytic leukemia, metastases, infectious lymphadenopathies, and Kikuchi disease (a histiocytic necrotizing lymphadenitis that often affects young Asian women). RDD is differentiated by a typical combination of clinical and laboratory findings plus confirmatory histology and immunohistochemistry.

Treatment

Many lesions are asymptomatic and heal spontaneously, thus not requiring treatment. When treatment is indicated due to destructive lesions, disseminated disease or lesions causing physical compromise, radiotherapy, surgical excision, and/or systemic corticosteroids are usually employed, but there are no controlled trials to date. Based upon case reports, improvement has been observed with thalidomide, imatinib, 2-chlorodeoxyadenosine, and clofarabine[103].

"M" GROUP: MALIGNANT HISTIOCYTOSES

Synonym: ■ Histiocytic, interdigitating cell, Langerhans cell or indeterminate cell sarcomas

The malignant histiocytoses represent a group of very rare undifferentiated tumors with an anaplastic histology. Diagnosis is mainly one of exclusion and is based on extensive immunohistochemical analysis and expression of at least two of the following histiocyte/dendritic cell markers: CD68, CD163, CD4, and lysozyme[2]. These tumors develop primarily in adults and are often aggressive, with the most common sites being the lymph nodes, skin, soft tissue, and GI tract.

Miscellaneous

ALK^+ histiocytosis

A few cases of histiocytoses, including cutaneous histiocytoses, have been noted to express anaplastic lymphoma kinase (ALK)[104]. ALK^+ histiocytosis affects primarily young children and there is usually systemic involvement including hepatosplenomegaly and dramatic hematologic abnormalities. However, lesions may be restricted to the skin.

In ALK^+ histiocytosis, the histiocytes are very large with irregularly folded nuclei and abundant eosinophilic cytoplasm, sometimes with

emperipolesis. Over time, there may an increase in the number of foamy histiocytes and Touton giant cells, thereby resembling a JXG. By immunohistochemistry, the histiocytes are positive for ALK, histiocytic markers (CD68, CD163) and variably S100; they are negative for CD1a, CD207, and BRAF V600E. Gene fusions can be present, in particular *KIF5B–ALK* and *COL1A2–ALK*[90]. In unresectable or disseminated disease, ALK inhibitors may be tried[105].

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Additional figures available in our eBook (see inside front cover for access code).

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eFig. 91.1 Acute Langerhans cell histiocytosis (Letterer–Siwe variant). Erythematous, eroded plaques in the inguinal creases.



eFig. 91.4 Erdheim–Chester disease. Xanthelasma-like yellow plaques on the eyelids.



eFig. 91.2 Langerhans cell histiocytosis in an adult. Clinically, it may be diagnosed as sebopsoriasis, but the crusting can provide a clue to the diagnosis. *Courtesy Peter W. Heald, MD.*



eFig. 91.5 Generalized eruptive histiocytomas. Multiple brown to pink–brown papules on the lateral aspect of the trunk in a young child. *Courtesy Julie V. Schaffer, MD.*



eFig. 91.3 Congenital self-healing Langerhans cell histiocytosis. Red–purple papule on the forehead. *Courtesy Katie Given, MD, PhD.*



eFig. 91.6 Juvenile xanthogranuloma. Red–brown nodule with central yellow color that had been present for 5 months. *Courtesy Anthony J. Mancini, MD.*



eFig. 91.7 Juvenile xanthogranuloma. Note the yellow–red color. *Courtesy Luis Requena, MD.*







eFig. 91.9 Xanthoma disseminatum. A–C Involvement of the major flexures is a characteristic finding. The majority of the lesions are erythematous but a few of the papulonodules on the anterior upper arm are yellow–red in color. *Courtesy David Wetter, MD.*



eFig. 91.8 Xanthoma disseminatum. Flexural involvement is common. In this patient, multiple red–yellow papules are seen in the axilla, as well as on the shoulder and proximal arm. *Courtesy Grant J. Anhalt, MD.*



eFig. 91.10 Xanthoma disseminatum. Sclerotic form of xanthoma disseminatum in a patient who developed multiple myeloma.



eFig. 91.11 Progressive mucinous histiocytosis. Symmetric distribution of multiple, red–brown, dome-shaped papules on the dorsal hands and wrists of a 30-year-old woman.



eFig. 91.12 Rosai–Dorfman disease. Pink–yellow papules and plaques of the cheek and chin.



eFig. 91.13 Rosai–Dorfman disease. Cluster of pink–brown nodules on the buttock. *Courtesy Jonathan Leventhal, MD.*



eFig. 91.14 Indeterminate cell histiocytosis. Multiple pink -violet to violet-brown papules and papulonodules on the leg. *Courtesy Jean-François Emile, MD, PhD.*

Xanthomas 92

William Trent Massengale

Key features

- Cutaneous xanthomas can signal the presence of an underlying hyperlipidemia or monoclonal gammopathy
- An understanding of basic lipid metabolism provides insight into the underlying hyperlipoproteinemias as well as the formation of xanthomas
- The major forms of xanthomas associated with hyperlipidemia are: eruptive, tuberous, tendinous, and plane (including xanthelasma)
- Normolipemic plane xanthomas occur in association with monoclonal gammopathies
- Histologically, lipid-laden macrophages (foam cells) are seen in the dermis
- Prompt recognition and proper treatment can lead to xanthoma resolution as well as prevention of potentially life-threatening complications

INTRODUCTION

Cutaneous xanthomas develop as a result of deposition of lipid in the dermis, primarily within macrophages (foam cells) but also extracellularly. One of their major distinguishing clinical features is a characteristic yellow to orange hue. Xanthomas may present with a variety of morphologies, from macules and papules to plaques and nodules. As discussed below, the morphology and anatomic location of the lesions often suggest the type of underlying lipid disorder or the presence of a paraproteinemia.

Xanthomas can develop in the setting of primary or secondary disorders of lipid metabolism. Thus, early recognition of these lesions can make a significant impact on the diagnosis, management, and prognosis of patients who suffer from an underlying disease. It is therefore important for dermatologists to become familiar with the basic concepts of lipid metabolism and the associated disease states, as well as to be able to recognize the often pathognomonic cutaneous findings.

EPIDEMIOLOGY

Hyperlipidemia is quite common in the general population. In North America alone, it is estimated that over 100 million people currently have an elevated serum cholesterol level >200 mg/dl. Despite the large number of people who suffer from hyperlipidemia, only a minority will develop cutaneous xanthomas. Also, because the exact mechanism by which xanthomas form is not yet fully understood, it is not always possible to predict who will develop them. Xanthomas are thought to result from the permeation of circulating plasma lipoproteins through dermal capillary blood vessels followed by phagocytosis of the lipoproteins by macrophages, forming lipid-laden cells known as foam cells[1]. However, the precise steps and their regulation are still an area of investigation.

PATHOGENESIS

There is strong evidence to support the theory that the lipids found in the various xanthomas are the same as those in the circulation[2]. The majority of plasma lipids are transported in complex structures known as lipoproteins. The basic structure of the lipoprotein allows the delivery of triglycerides and cholesterol to peripheral cells for their metabolic needs. This structure consists of a hydrophilic outer shell and a hydrophobic core. The outer shell consists of phospholipids, free cholesterol, and non-covalently linked specialized proteins known as apolipoproteins or apoproteins (apo). The inner core contains triglycerides and cholesterol esters.

Lipoproteins differ in their core lipid content. Triglycerides are the major core lipids in chylomicrons and very-low-density lipoproteins (VLDLs), while cholesterol esters dominate the core of low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), and remnants of chylomicrons and VLDLs. The apoproteins found in the outer shell can also differ amongst the various lipoproteins (Table 92.1). These apoproteins serve several important functions, such as mediating the binding of lipoproteins to their respective receptors in target organs and activating enzymes involved in their metabolism.

There are two major pathways of lipoprotein synthesis (Fig. 92.1A). The *exogenous* pathway begins with dietary fat intake. Through the action of pancreatic lipase and bile acids, dietary triglycerides are degraded to fatty acids and monoglycerides. After absorption by the intestinal epithelium, the triglycerides are reformed and packaged with a small amount of cholesterol esters into the central core of a chylomicron. The outer shell of the chylomicron consists of phospholipids, free cholesterol, and several apoproteins, including B-48, E, A-I, A-II, and C-II.

Chylomicrons then enter the lymphatics and eventually the systemic circulation via the thoracic duct. Once in the circulation, hydrolysis of the core triglycerides occurs, releasing free fatty acids to the peripheral tissues. This is mediated through the action of the enzyme lipoprotein lipase that is bound to capillary endothelium. The activation of the lipoprotein lipase system is complex and involves not only hormones such as insulin, but also apoproteins such as C-II, located on the lipoprotein outer surface, and GPIHBP1, a protein expressed on endothelial cells that binds lipoprotein lipase and shuttles it to its site of action in the capillary lumen.

After hydrolysis of ~70% of the original triglyceride content, a chylomicron "remnant" exists. The central core now contains predominantly cholesterol ester that has been acquired from circulating HDL molecules. The chylomicron remnant is taken up by the liver via specialized high-affinity apo B-100/E receptors that recognize the apoproteins E_3 or E_4 on the remnant's outer shell. Once in the liver, the remaining lipids enter hepatic storage and apoproteins such as B-48 are degraded.

IMPORTANT APOPROTEINS		
Apoprotein	**Lipoprotein association**	**Function and comments**
A-I	Chylomicrons, HDLs	Major protein of HDL; activates *l*ecithin:cholesterol *acyl*transferase (LCAT)
B-48	Chylomicrons, chylomicron remnants	Unique marker for chylomicrons
B-100	VLDLs, IDLs, and LDLs	Major protein of LDL; binds to LDL receptor
C-II	Chylomicrons, VLDLs, IDLs, and HDLs	Activates lipoprotein lipase
E (at least 3 alleles [E_2, E_3, E_4])	Chylomicrons, chylomicron remnants, VLDLs, IDLs, and HDLs	Binds to LDL receptor (B-100/E receptor)

Table 92.1 Important apoproteins. See Fig. 92.1. Lipoprotein X appears in the sera of patients with severe cholestatic liver diseases. HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

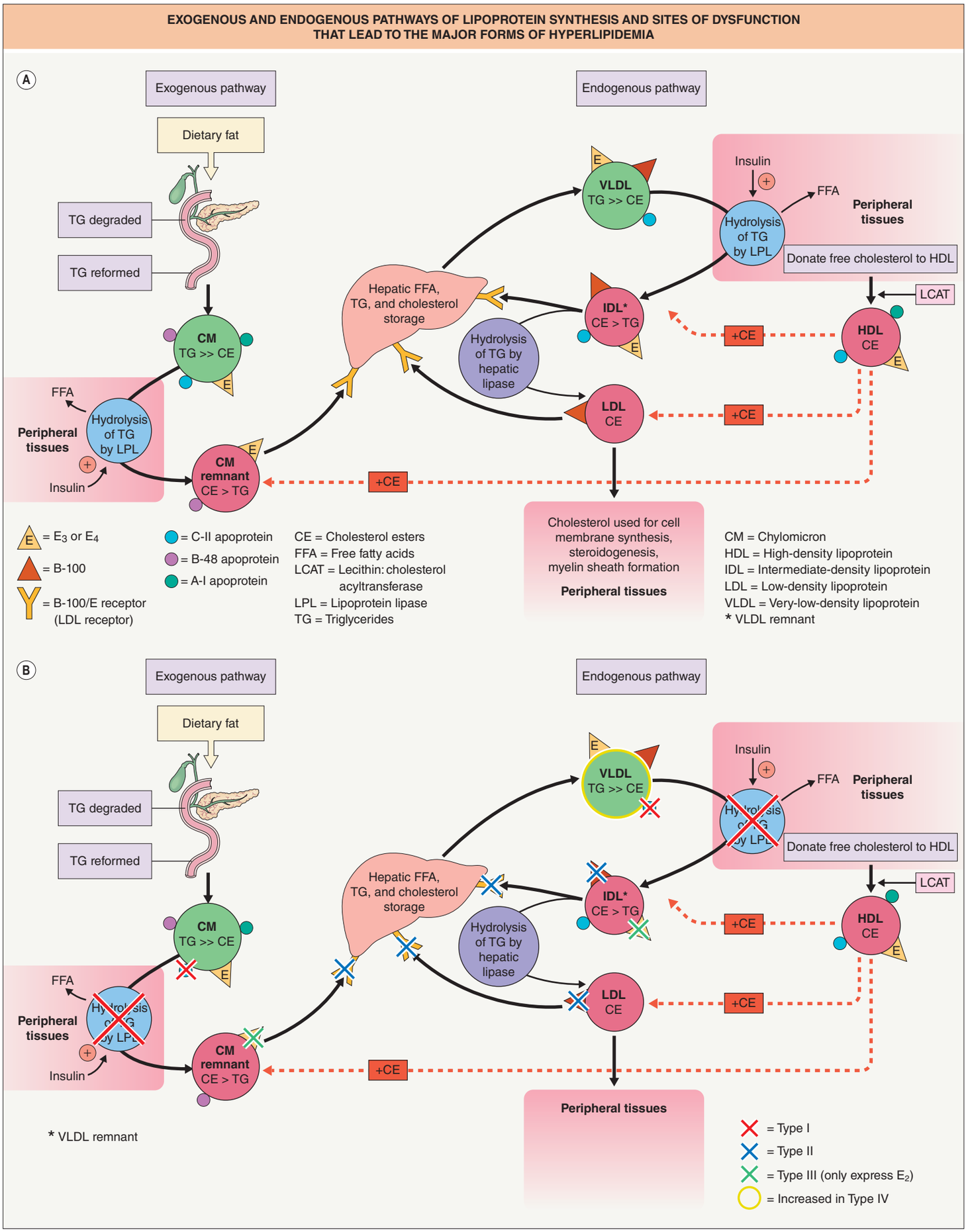


Fig. 92.1 Exogenous and endogenous pathways of lipoprotein synthesis (A) and sites of dysfunction that lead to the major forms of hyperlipidemia (B). Lipoprotein lipase (LPL) is activated by the C-II apoprotein.

The *endogenous* pathway begins with the hepatic formation of VLDL particles. The central core of the VLDL consists primarily of triglycerides, which are derived from circulating free fatty acids and hepatic triglyceride stores. Important apoproteins found on the outer shell include B-100, E, and C-II. In a fashion similar to the chylomicron, lipoprotein lipase mediates hydrolysis of the VLDL molecule, removing the majority of its triglyceride content, and its cholesterol esters are acquired from HDL molecules. Lipoprotein lipase activation requires the presence of apo C-II on the VLDL outer shell. After removal of the majority of the triglyceride content, the VLDL "remnant", also known as an intermediate-density lipoprotein (IDL), can then be taken up by the liver via apo B-100/E receptors and degraded. IDLs that escape uptake by the hepatocyte are stripped of their remaining core triglycerides by extracellular hepatic lipases and enter the circulation as LDLs.

The LDL contains predominantly cholesterol ester in its central core and expresses B-100 on its surface. LDL delivers cholesterol ester to peripheral tissues, where it can be converted to free cholesterol. Cholesterol has several important functions within the body, including being an essential component of cell membrane bilayers. It is also important in the production of the myelin sheath of nerves, adrenal and gonadal steroidogenesis, and the production of bile acids. Hepatocytes play the major role in the catabolism of LDLs. Their uptake is mediated through the high-affinity apo B-100/E receptor found on the cell surface of the hepatocytes. Of note, the LDL receptors on hepatocytes are catabolized by PCSK9 (proprotein convertase subtilisin/kexin type 9). Free cholesterol in excess of metabolic needs is re-esterified for storage.

HDLs serve several important functions in cholesterol metabolism (see Fig. 92.1A). One of the primary functions of HDLs is the removal of cholesterol from the peripheral tissues. During this process, free cholesterol and phospholipids are transferred from the cell membranes of peripheral cells to the HDL molecules. The free cholesterol is then esterified by the enzyme *l*ecithin:*c*holesterol *a*cyl*t*ransferase, or LCAT. This enzyme requires the presence of the HDL apoprotein A-I. HDL molecules then transfer the cholesterol esters to other lipoproteins such as LDLs and remnants of chylomicrons or VLDLs for transportation back to the liver.

The liver plays the central role in the overall cholesterol economy. Hepatic intracellular cholesterol levels have a direct impact on the activity of HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis, and on the expression of the high-affinity apo B-100/E receptor. When intracellular cholesterol levels are low, HMG-CoA reductase becomes activated and high-affinity apo B-100/E receptor expression increases. The increase in high-affinity receptors leads to increased uptake of cholesterol-containing lipoproteins such as chylomicron remnants, IDLs, and LDLs. This is followed by the lowering of plasma cholesterol levels. As discussed later, this mechanism will be the basis for many of the pharmacologic interventions aimed at lowering cholesterol levels.

CLINICAL FEATURES

Due to the complexity of cholesterol homeostasis, there are several possible ways in which hyperlipidemia may occur, from inherited disorders to metabolic diseases such as diabetes mellitus. Genetic mutations can affect important enzymes, receptors, or receptor ligands, with such defects leading to the overproduction of lipoproteins or the inhibition of their clearance (Fig. 92.1B). Each possible defect would lead to a different abnormal lipid profile.

In 1965, Lees and Frederickson[3] published a system for classifying various disorders of lipid metabolism based upon the electrophoretic migration of the serum lipoproteins present. This system for phenotyping hyperlipoproteinemias is used today in a modified form (Table 92.2). In the next section, descriptions of underlying lipid disorders will reference not only the Frederickson classification system, but also the specific molecular defects when possible.

With the exception of the homozygous form of familial hypercholesterolemia (type II) and rare disorders such as sitosterolemia and biliary atresia, most cutaneous xanthomas do not appear until adulthood. Once the diagnosis is established, treatment of associated disorders (e.g. metabolic syndrome [see Table 53.5]) should reduce the incidence of potential systemic sequelae such as myocardial infarctions, cerebrovascular accidents, and hepatic steatosis[4].

Eruptive Xanthomas

Eruptive xanthomas appear as erythematous to yellow papules, approximately 1 to 5 mm in diameter (Fig. 92.2 & 92.3). They are usually distributed on the extensor surfaces of the extremities, buttocks, and hands. Early in their development, lesions may have an inflammatory halo (likely due to their triglyceride component), which may be accompanied by tenderness and pruritus. The Koebner phenomenon has been reported to occur with eruptive xanthomas[5].

Eruptive xanthomas can be seen in the setting of primary or secondary *hypertriglyceridemia*. Triglyceride levels in patients with eruptive xanthomas often exceed 3000 to 4000 mg/dl. In the Frederickson classification of hyperlipidemias, hypertriglyceridemia can be seen in type I (elevated chylomicrons), type IV (elevated VLDLs), and type V (elevated chylomicrons and VLDLs).

One reason for elevated triglyceride levels is failure to remove such lipids from the circulation (Fig. 92.4). Deficient activity of lipoprotein lipase will lead to accumulation of triglyceride-rich chylomicrons and VLDLs (see Fig. 92.1B). This can be related to either abnormalities in the enzyme itself, as in *lipoprotein lipase deficiency* (*chylomicronemia syndrome*), or in other controlling factors such as *dysfunctional apoprotein C-II* or *impaired insulin activity*[6,7]. In addition to *deficiency of GPIHBP1*, autoantibodies against GPIHBP1 can also lead to hypertriglyceridemia[8].

Another reason for increased triglyceride levels is hepatic overproduction of triglyceride-rich lipoproteins via the endogenous pathway. In *endogenous familial hypertriglyceridemia*, a genetic defect exists that causes the liver to respond abnormally to dietary carbohydrates and insulin, with overproduction of hepatic VLDLs. The result is a Frederickson type IV pattern of hypertriglyceridemia. Secondary acquired defects in lipoprotein lipase activity, such as those due to diabetes mellitus, are not uncommon in these patients. With this second insult, the lipoprotein lipase system can become saturated and, as a result, no longer handles dietary lipids, leading to chylomicron elevations as well. This pattern is classified as a Frederickson type V phenotype.

Environmental factors and underlying diseases commonly exacerbate genetic defects of triglyceride metabolism, leading to worsening of the hypertriglyceridemia with eruptive xanthoma formation (see Fig. 92.4). Such factors include obesity, high caloric intake, diabetes mellitus, alcohol abuse, oral estrogen replacement, and systemic medications that can lead to hypertriglyceridemia (e.g. retinoids, protease inhibitors, olanzapine). The resultant pattern usually leads to a Frederickson type IV phenotype. Oral retinoid therapy, especially bexarotene, can elevate triglyceride levels through an elevation in hepatic VLDL secretion. With isotretinoin, this elevation seems to be more prevalent in genetically predisposed individuals and may signal an increased risk for future metabolic syndrome[9]. Two of the five criteria for the clinical diagnosis of metabolic syndrome are lipid abnormalities – elevated triglycerides and reduced HDLs (see Table 53.5).

The treatment of eruptive xanthomas involves the identification and treatment of the underlying causes of the hypertriglyceridemia (see Fig. 92.4). Failure to recognize and treat the patient with hypertriglyceridemia could lead to complications such as acute pancreatitis. Pharmacologic and dietary lowering of the circulating triglycerides to reasonable levels will result in the prompt resolution of the eruptive lesions.

Tuberous/Tuberoeruptive Xanthomas

Tuberoeruptive and tuberous xanthomas are clinically and pathologically related and often described as being on a continuum. Tuberoeruptive xanthomas present as pink–yellow papules or nodules on extensor surfaces, especially the elbows and knees (Fig. 92.5). Tuberous lesions are noted to be larger than tuberoeruptive lesions and may exceed 3 cm in diameter (Fig. 92.6). Together, these lesions can be seen in hypercholesterolemic states such as *dysbetalipoproteinemia* (Frederickson type III) and *familial hypercholesterolemia* (Frederickson type II; see below). In contrast to eruptive xanthomas, tuberous xanthomas are usually slow to regress following institution of appropriate therapy.

Dysbetalipoproteinemia, or broad beta disease, is a genetic disorder of lipid metabolism that is usually inherited in an autosomal recessive fashion. It is caused by the presence of an isoform of apo E, primarily

IMPORTANT HYPERLIPOPROTEINEMIAS				
Type	**Pathogenesis**	**Laboratory findings**	**Clinical findings**	
			Skin (types of xanthoma)	**Systemic**
Type I (familial LPL deficiency, familial hyperchylomicronemia)	(a) Deficient or abnormal LPL (AR) (b) Apo C-II deficiency (AR) (c) Deficient glycosyl-phosphatidylinositol-anchored HDL-binding protein 1 [GPIHBP1] (AR) (d) Apo A-V* deficiency (AR)	Slow chylomicron clearance Reduced LDL and HDL levels **Hypertriglyceridemia**	Eruptive	No increased risk of coronary artery disease Recurrent pancreatitis
Type II (familial hypercholesterolemia)	(a) LDL receptor defect (AD)† (b) Reduced affinity of LDL for LDL receptor due to dysfunction of apo B-100 (ligand) (AD) (c) Accelerated degradation of LDL receptor due to missense *PCSK9* mutations (AD‡) (d) Defective LDL receptor adaptor protein 1 (required for receptor internalization) (AR)	Reduced LDL clearance **Hypercholesterolemia**	Tendinous, tuberoeruptive, tuberous, plane (xanthelasma, intertriginous areas, interdigital web spaces¶)	Atherosclerosis of peripheral and coronary arteries
Type III (familial dysbetalipoproteinemia, remnant removal disease, broad beta disease, apo E deficiency)	Hepatic remnant clearance impaired due to apo E abnormality; vast majority of patients only express the apo E_2 isoform that interacts poorly with the apo E receptor (AR >> AD)	Elevated levels of chylomicron remnants and IDLs **Hypercholesterolemia** **Hypertriglyceridemia**	Tuberoeruptive, tuberous, plane (palmar creases) – most characteristic Tendinous	Atherosclerosis of peripheral and coronary arteries
Type IV (endogenous familial hypertriglyceridemia)	Elevated production of VLDL associated with glucose intolerance and hyperinsulinemia; may be associated with heterozygous variants, e.g. in apo A-V*, LPL, or the glucokinase regulator protein	Increased VLDLs **Hypertriglyceridemia**	Eruptive	Frequently associated with type 2 non-insulin-dependent diabetes mellitus, obesity, alcoholism (see Fig. 92.4)
Type V	Elevated chylomicrons and VLDLs; may be associated with heterozygous variants, e.g. in apo A-V*, LPL, or the glucokinase regulator protein	Decreased LDLs and HDLs **Hypertriglyceridemia**	Eruptive	Diabetes mellitus

*Apolipoprotein A-V (apo A-V) interacts with the LDL receptor and activates lipoprotein lipase, inhibiting VLDL-TG production and modulating HDL maturation and cholesterol metabolism.
†In patients with the *LDLR* IVS14+1G-A mutation, the phenotype can be altered by SNPs in the genes that encode apo A-II, cytoplasmic epoxide hydrolase 2, or growth hormone receptor.
‡Gain-of-function mutations cause autosomal dominant hypercholesterolemia[28], whereas loss-of-function mutations (most prevalent in African-Americans) result in low LDL levels[29].
¶Said to be pathognomonic for homozygous state.

Table 92.2 Important hyperlipoproteinemias. Autoantibodies against GPIHBP1 can also lead to hypertriglyceridemia. In **bold** are the major lipid abnormalities found on routine screening. AD, autosomal dominant; Apo, apolipoprotein; AR, autosomal recessive; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very-low-density lipoprotein.



Fig. 92.2 Eruptive xanthomas due to hypertriglyceridemia. In this patient the lesions favored the extensor surface of the lower extremities, in particular the knees.

apo E_2, that is a poor ligand for the high-affinity apo B-100/E receptor (see Fig. 92.1B). This results in the poor hepatic uptake of chylomicron and VLDL remnants. As a result, the serum levels of both triglycerides and cholesterol are elevated. The cutaneous lesions that are most characteristic of this disease are tuberous or tuberoeruptive xanthomas (present in 80% of patients) and plane xanthomas of the palmar creases (*xanthoma striatum palmare*), which are present in two-thirds of patients (see below)[10].

Tendinous Xanthomas

Tendinous xanthomas are firm, smooth, nodular lipid deposits that can affect the Achilles tendons (Fig. 92.7) or the extensor tendons of the hands (Fig. 92.8), knees, or elbows. The overlying skin is normal in appearance. Ultrasound can aid in the diagnosis of subtle lesions of the Achilles tendon by demonstrating hypoechoic nodules or an increase in the anteroposterior diameter of the tendon[11]. The presence of tendinous xanthomas is almost always a clue to an underlying disorder of lipid metabolism. Lipid disorders that have been associated with this type of xanthoma include familial hypercholesterolemia, dysbetalipoproteinemia, and hyperlipidemia secondary to hypothyroidism (Table 92.3).

Tendinous xanthomas are most frequently seen in the setting of *familial hypercholesterolemia*. This disorder results from a deficiency of normal LDL receptors on cell membranes, which leads to the poor hepatic clearance of circulating LDLs and, therefore, elevated LDL cholesterol levels (Frederickson type II). This condition is inherited in an autosomal dominant fashion with a high degree of penetrance. Homozygotes can have LDL cholesterol levels of 800 to 1000 mg/dl with widespread atherosclerosis and the appearance of xanthomas during the first decade of life. Heterozygosity for the disorder is more common and is estimated to occur in 1 in 500 individuals in the US. The types of xanthomas seen in this disorder include tendinous, tuberous, tuberoeruptive, and plane (including xanthelasma). Because of its relatively

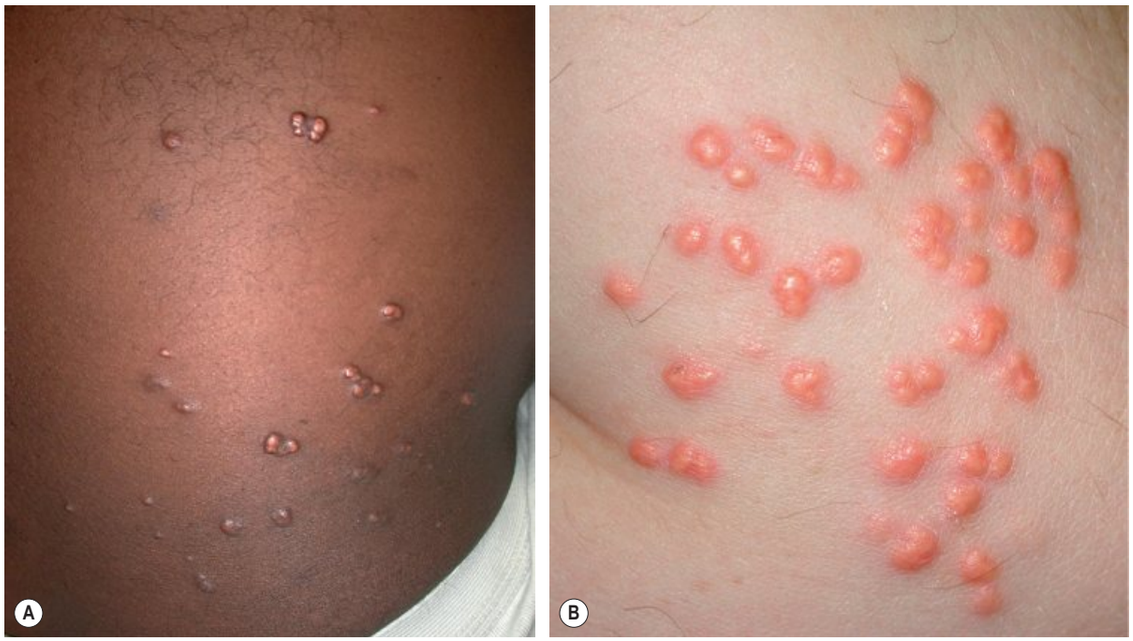


Fig. 92.3 Eruptive xanthomas. A, B The yellowish hue is influenced by the degree of pigmentation of the skin. Note the clustering of some of the lesions.

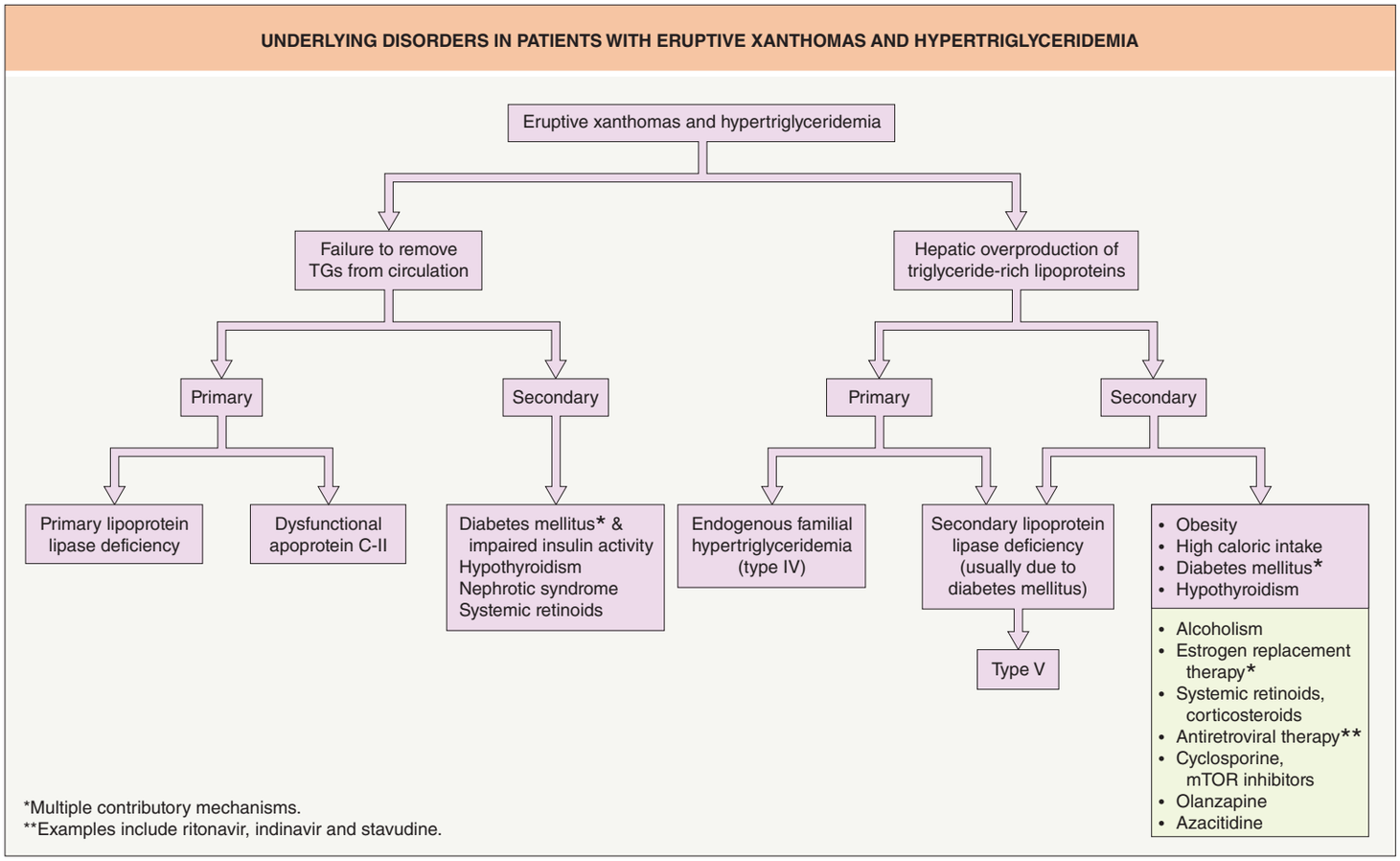


Fig. 92.4 Underlying disorders in patients with eruptive xanthomas and hypertriglyceridemia. mTOR, mammalian target of rapamycin; TGs, triglycerides.

common occurrence, patients with tendinous xanthomas are more likely to have the heterozygous form of the disease than the rare homozygous state. Plane xanthomas of the intertriginous web spaces of the fingers are thought to be pathognomonic for the homozygous condition (see Fig. 92.8)[12].

There is a closely related disorder, known as *familial defective apolipoprotein B-100*. In this dominantly inherited genetic disorder, the LDL receptor is normal. However, there is decreased affinity of LDL for the LDL receptor because the mutation affects its ligand, apo B-100 (see Fig. 92.1B). Patients may present with identical clinical findings as in familial hypercholesterolemia, although usually not as severe[13]. From a therapeutic standpoint, distinguishing this disorder from dysfunction or accelerated degradation of the LDL receptor (see Table 92.2) will become more important in the future as treatments aimed at correcting LDL receptor function become commercially available (e.g. evinacumab)[13a].

Rarely, tendinous xanthomas can develop in the absence of a lipoprotein disorder. Two examples are *cerebrotendinous xanthomatosis* and *sitosterolemia*. In cerebrotendinous xanthomatosis, an enzymatic



Fig. 92.5 Tuberoeruptive xanthomas on the elbow of a child with homozygous familial hypercholesterolemia. Note the yellowish hue. *Courtesy Julie V. Schaffer, MD.*



Fig. 92.6 Nodular tuberous xanthoma of the elbow. *Courtesy Lorenzo Cerroni, MD.*



Fig. 92.7 Tendinous xanthoma. Linear swelling of the Achilles area, representing a tendinous xanthoma in a patient with dysbetalipoproteinemia.



Fig. 92.8 Tendinous xanthomas of the fingers in a patient with homozygous familial hypercholesterolemia. Note intertriginous plane xanthomas of the web spaces.

SECONDARY HYPERLIPIDEMIA – SELECTED UNDERLYING DISORDERS

- Diabetes mellitus*
- Cholestasis
  - Primary biliary cholangitis (often plane xanthomas, including palmar)
  - Alagille syndrome (elbows/knees, flexures, fingers, palms, helices)*,†
- Biliary atresia*
- Hypothyroidism*
- Nephrotic syndrome*
- Type I glycogen storage disease (von Gierke)*
- Lipodystrophy syndromes (see Fig. 101.1)

*Xanthomas can develop during childhood.
†Autosomal dominant disorder due to mutations in *JAG1*, which encodes the Notch signaling pathway ligand Jagged-1, or (in ~5% of patients) *NOTCH2*. Patients have cholestasis due to a paucity of intrahepatic bile ducts, elevated LDL (cholesterol) levels, cardiac defects, peculiar facies, growth retardation, and posterior embryotoxon; xanthomas within body folds may become very firm[30–32].

Table 92.3 Secondary hyperlipidemia – selected underlying disorders. In addition to a fasting lipid panel, screening blood tests include fasting glucose, liver function tests, TSH, and albumin. Other rare causes include pregnancy, multiple myeloma, and autoimmune connective tissue diseases (e.g. systemic lupus erythematosus, juvenile dermatomyositis)

defect exists in the bile acid synthetic pathway, leading to the abnormal accumulation of an intermediate known as cholestanol. This intermediate is deposited in most tissues, including the brain, and can also form tendinous xanthomas[14]. In sitosterolemia-1 and -2, an abnormal accumulation of plant sterols occurs, leading to tendinous and tuberous xanthoma formation.

Plane Xanthomas and Xanthelasma

Plane xanthomas appear as yellow to orange, non-inflammatory macules, papules, patches, and plaques. They can be circumscribed or diffuse. While anatomic locations vary, the site often serves as a clue to the particular underlying disease state. For example, intertriginous plane xanthomas may occur in body folds including the antecubital fossae (Fig. 92.9 & 92.10) or the web spaces of the fingers (see Fig. 92.8), where they are almost pathognomonic for homozygous familial hypercholesterolemia[12]. Plane xanthomas of the palmar creases, or *xanthoma striatum palmare*, are nearly diagnostic for dysbetalipoproteinemia, especially when accompanied by tuberous xanthomas[15].

Xanthelasma, or *xanthelasma palpebrarum*, are commonly observed plane xanthomas of the eyelids (Fig. 92.11). Although the presence of xanthelasma warrants investigation for hyperlipidemia, the latter is present in only about one-half of the patients with these lesions. Younger patients or those with a strong family history of hyperlipidemia are more likely to have an underlying lipid disorder and should be appropriately screened.

Plane xanthomas of cholestasis may occur as a complication of diseases such as biliary atresia or primary biliary cholangitis (previously primary biliary cirrhosis). In these conditions, unesterified cholesterol

begins to accumulate in the blood, leading to plane xanthoma formation. The lesions often begin as localized plaques on the hands and feet, but can become generalized.

Plane xanthomas can also occur in a normolipemic patient, where they may signal the presence of an underlying monoclonal gammopathy (Fig. 92.12), usually due to a plasma cell dyscrasia, but occasionally secondary to a lymphoproliferative disorder such as B cell lymphoma or Castleman disease (see Ch. 119). This type of xanthoma can also be seen in patients with chronic myelomonocytic leukemia. In gammopathy-associated plane xanthomas, monoclonal IgG is thought to bind to circulating LDL, rendering the antibody–LDL complex more susceptible to phagocytosis by macrophages[16]. Favored locations include the neck, upper trunk, flexural folds, and periorbital region. In the setting of a monoclonal gammopathy, the coexistence of plane xanthomas and necrobiotic xanthogranuloma has been observed, suggesting a disease overlap[17]. Of note, there is an entity known as hyperlipidemic myeloma in which xanthomas appear on the elbows and knees as well as within the palmar creases.

Verruciform Xanthomas

Verruciform xanthomas are asymptomatic, planar or verrucous, solitary plaques that are usually 1 to 2 cm in diameter. They occur primarily in the mouth (Fig. 92.13), but sometimes in periorificial, anogenital (including the scrotum), and acral sites. The latter are sometimes referred to as Vegas (verruciform genital-associated) and Vacas (verruciform acral-associated) xanthomas. These lesions may persist for years and there is usually no associated hyperlipidemia.

Single or multiple lesions are also seen in the setting of lymphedema, epidermolysis bullosa, pemphigus, discoid lupus erythematosus, lichen planus, and GVHD as well as within dermatofibromas and cutaneous lesions of the X-linked dominant disorder CHILD (*c*ongenital *h*emidysplasia with *i*chthyosiform erythroderma and *l*imb *d*efects) syndrome. The latter is due to mutations in *NSDHL*, which encodes 3β-hydroxysteroid dehydrogenase, an enzyme involved in cholesterol biosynthesis (see Ch. 57). In a molecular study of sporadic verruciform xanthomas, two of nine lesions were found to have a missense somatic mutation in exon 6 of *NSDHL* (only exons 4 and 6 were examined) which differed from the mutations seen in CHILD syndrome[18].

One proposal is that enzymatic dysfunction leads to an excess formation and accumulation of lipid storage droplets, followed by formation of lipid-laden dermal macrophages. Another hypothesis suggests that the foam cells result from damage to the epithelium



Fig. 92.11 Xanthelasma palpebrarum with typical yellowish hue.



Fig. 92.9 Plane xanthomas of the antecubital fossae. This young patient had dysbetalipoproteinemia.



Fig. 92.12 Normolipemic plane xanthoma. The large thin plaques have a yellow–orange color. The patient was found to have a monoclonal gammopathy. *Courtesy Whitney High, MD, JD.*

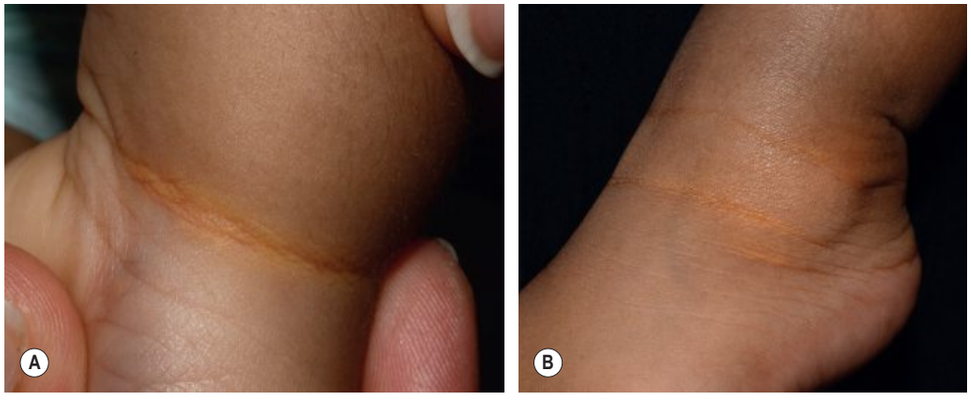


Fig. 92.10 Intertriginous plane xanthomas. Yellow–orange color in the skin folds of the wrist (**A**) and ankle (**B**) in an infant with homozygous familial hypercholesterolemia. *Courtesy Julie V. Schaffer, MD.*



Fig. 92.13 Verruciform xanthoma of the oral mucosa. *Courtesy Kishore Shetty, DDS.*

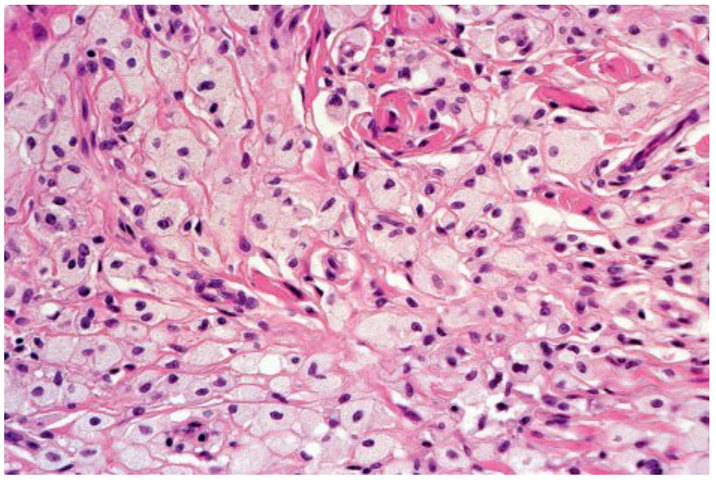


Fig. 92.14 Histology of a tuberous xanthoma. Foamy macrophages fill the dermis. *Courtesy Lorenzo Cerroni, MD.*

(e.g. from lichenoid dermatoses) and subsequent engulfing of lipids by macrophages within the dermal papillae, analogous to the amyloid deposits within the dermal papillae in lichen amyloidosis. The few foam cells beneath the epithelium may be subtle and easy to miss, in which case verruciform xanthomas may be confused histologically with warts and other papillomatous disorders. Surgery is generally curative.

PATHOLOGY

The characteristic histologic finding in xanthomas is the foam cell. Foam cells consist of macrophages that contain imbibed lipid within their cytoplasm (Fig. 92.14). All xanthomas contain dermal infiltrates of lipid, but they may vary in the degree of lipid content, the inflammatory infiltrate, the amount and location of the infiltrate, and the presence of extracellular lipid. The histologic appearance of xanthomas is somewhat altered by routine processing, as formalin fixation can remove deposits of lipid and leave artifactual clefting. Immunohistochemical staining for adipophilin can be performed to detect lipid accumulation[19]. Adipophilin, also known as adipose differentiation-related protein, is a lipid droplet-associated protein.

Eruptive xanthomas contain lipid deposits in the reticular dermis. Of note, early in lesion development, foam cells are relatively small in number and size. The initial inflammatory infiltrate is mixed, containing both neutrophils and lymphocytes. As an increase in lipidization occurs, the appearance of the lesion becomes more typical of a xanthoma, but foam cells remain fewer in number compared with other types of xanthomas. Extracellular lipids are present in the dermis, which are seen as artifactual clefts filled with a wispy faint blue–gray material.

Tuberous xanthomas demonstrate large aggregates of foam cells in the dermis, often accompanied by fibrosis, but without a large number of inflammatory cells. *Tendinous xanthomas* have a similar histology, with foam cells that are even larger in size. Cholesterol esters are present in these lesions and can be seen with polarized microscopy.

DIFFERENTIAL DIAGNOSIS OF XANTHOMAS

- Eruptive xanthomas
  - Non-Langerhans cell histiocytoses
    - Xanthoma disseminatum
    - Papular xanthoma
    - Generalized eruptive histiocytoma
    - Indeterminate cell histiocytosis
    - Rosai–Dorfman disease
    - Juvenile xanthogranuloma (micronodular form)
  - Xanthomatous lesions of Langerhans cell histiocytosis
  - Disseminated granuloma annulare
- Tuberous xanthomas
  - Erythema elevatum diutinum
  - Multicentric reticulohistiocytosis
  - Juxta-articular fibroid nodules of *Borrelia* infection
- Tendinous xanthomas
  - Giant cell tumor of the tendon sheath
  - Rheumatoid nodule
  - Subcutaneous granuloma annulare
  - Erythema elevatum diutinum
- Xanthelasma
  - Syringomas
  - Necrobiotic xanthogranuloma
  - *A*dult-onset *a*sthma and *p*erio*c*ular *x*anthogranuloma (AAPOX)
  - Sebaceous hyperplasia
  - Palpebral sarcoidosis

Table 92.4 Differential diagnosis of xanthomas. Occasionally, xanthomatous cells may be observed histologically in some cutaneous tumors (e.g. dermatofibroma), unrelated to xanthomas.

Plane xanthomas such as xanthelasma can have a unique histologic appearance. The foam cells in this type of xanthoma are more superficial than in other types of xanthomas. Small aggregates of foam cells are often present in the superficial dermis. The lesions are non-inflammatory and have minimal fibrosis. With xanthelasma, there are often clues as to the location of the lesion, such as a thin epidermis, fine vellus hair follicles, and striated muscle fibers that are characteristic of the eyelid. In *verruciform xanthomas*, there is usually hyperkeratosis, acanthosis and papillomatosis, with foamy macrophages limited to the submucosa or dermal papillae.

A distinctive *papular neutrophilic xanthoma*, in which dermal foam cells are intermingled with neutrophils and prominent nuclear dust, has been described in HIV-infected patients with an IgA gammopathy. *Xanthomatized neutrophilic dermatosis* in the setting of myelodysplastic syndrome may represent a similar condition[20]. Lastly, dermal xanthomatous cells observed in biopsies of cutaneous GVHD may be indicative of hepatic GVHD[21].

DIFFERENTIAL DIAGNOSIS

A selection of the diseases included in the differential diagnosis of xanthomas is listed in Table 92.4.

TREATMENT

The treatment of xanthomas associated with hyperlipidemia requires the identification of the underlying lipoprotein disorder and other possible exacerbating factors. In addition to dietary measures, there are several medications available for lowering lipid levels in patients with primary and secondary hyperlipidemia. Table 92.5 outlines their mechanisms of action, clinical effects, and side effects. Correction of the underlying lipid disorder leads to the eventual resolution of the xanthomas in many patients. Xanthomas that have grown slowly over years, such as tendinous and tuberous xanthomas, are often slow to regress, whereas eruptive xanthomas may disappear within weeks of aggressive therapy.

Dietary measures are an important component of lipid-lowering therapy, in addition to oral medications (see Table 92.5). Decreasing total caloric intake and the achievement of ideal body weight alone can make a significant impact on lipid levels in some patients. Dietary fat restriction to <30% of total caloric intake should be attempted. Mono-unsaturated fats such as olive oil should comprise the majority of the fat intake. Alcohol avoidance is essential, especially in patients with hypertriglyceridemia.

LIPID-LOWERING MEDICATIONS				
Class of drug	**Mechanism of action**	**Clinical effects**	**Side effects/ interactions**	**Comments**
HMG-CoA reductase inhibitors ("statins")	• Competitive inhibition of the rate-limiting enzyme of hepatic cholesterol synthesis, with depletion of hepatocellular stores of cholesterol • Upregulation of hepatic LDL receptors (bind LDL & IDL; see Fig. 92.1) • Decreased endogenous VLDL production	• 25%–45% decrease in LDL levels • 25% decrease in VLDL levels • 10% increase in HDL levels	• Elevations in hepatic transaminases • Myopathy (risk may be increased with coadministration of other medications, e.g. cyclosporine, nicotinic acid, fibrates) • Drug-induced dermatomyositis • Interstitial granulomatous drug reaction • May increase warfarin levels	• Useful for many lipid disorders, including *heterozygous* familial hypercholesterolemia, hypercholesterolemia due to diabetes • Not effective in *homozygous* familial hypercholesterolemia (LDL receptor function is lacking)
Bile acid-binding resins (e.g. cholestyramine, colestipol, colesevelam)	• Bind to bile acids in the small intestine, preventing their reabsorption in the terminal ileum • Because of enhanced bile acid secretion, the liver must increase its synthesis of bile acids from cholesterol • Decrease in hepatic cholesterol stores leads to upregulation of hepatic LDL receptors (also increased HMG-CoA reductase activity)	• 10%–35% decrease in LDL levels (even with increase in hepatic cholesterol synthesis)	• Elevation of triglyceride levels, especially if dysbetalipoproteinemia or pre-existing hypertriglyceridemia • GI upset & gritty texture of resin • Affect absorption of medications such as digoxin, thyroxine, warfarin	• Lowering of LDL levels can be further enhanced by the addition of an HMG-CoA reductase inhibitor or nicotinic acid • Effective in *heterozygous* familial hypercholesterolemia • Not effective in *homozygous* familial hypercholesterolemia
Nicotinic acid (niacin)	• Lowers VLDL synthesis (and subsequently lowers LDL levels) • Enhances lipoprotein lipase activity (and subsequently lowers triglyceride levels)	• 20%–80% decrease in triglyceride levels (rapid) • 10%–15% decrease in LDL levels (slower) • 20–30 mg/dl increase in HDL	• Intense flushing and pruritus are common • Hepatitis • Worsening of glucose intolerance • Acanthosis nigricans, hyperpigmentation, xerosis • Increased risk of myopathy & rhabdomyolysis when coadministered with HMG-CoA reductase inhibitors	• Can be used in combination with HMG-CoA reductase inhibitors or bile acid-binding resins • Combination therapy for familial hypercholesterolemia • Treatment of severe hypertriglyceridemia refractory to fibric acid derivatives (to prevent pancreatitis)
Fibric acid derivatives (e.g. gemfibrozil, fenofibrate, clofibrate)	• Activation of lipoprotein lipase in peripheral tissues (e.g. muscle) • Decreases VLDL synthesis by suppression of the endogenous lipid pathway	• Dramatic improvement in lipid levels, with resolution of tuberous & palmar xanthomas (patients with dysbetalipoproteinemia) • Lowers triglyceride levels; prevents pancreatitis & eruptive xanthoma formation (patients with severe hypertriglyceridemia & chylomicronemia syndrome) • Increases levels of HDL	• Because of inhibition of the cytochrome P450 3A4 system, possibility of dermatologic drug–drug interactions (e.g. increased plasma levels of bexarotene or cyclosporine) • Increased risk of myopathy when administered with HMG-CoA reductase inhibitors	• Treatment of hypertriglyceridemia
Ezetimibe	• Inhibits intestinal absorption of dietary and biliary-excreted cholesterol	• ~15% reduction in LDL-C • Increases HDL by 3%	• Diarrhea • Rarely, elevated hepatic transaminases when coadministered with HMG-CoA reductase inhibitors	• Can be used in combination with HMG-CoA reductase inhibitors
PCSK9 inhibitors (e.g. alirocumab, evolocumab)	• Decreases LDL receptor degradation • Increases recirculation of the LDL receptor to the hepatocyte cell surface	• Lowers LDL cholesterol levels by 40%–60%	• Injection site reactions • Pruritus, urticaria, exanthem, cutaneous small vessel vasculitis • Transaminitis • Nasopharyngitis	• Effectively reduces LDL-C in patients with hypercholesterolemia except for those with *homozygous* familial hypercholesterolemia who lack the LDL receptor (receptor negative) • Administered subcutaneously or intravenously • No myopathy
Adenosine triphosphate-citrate lyase (ACL) inhibitors (e.g. bempedoic acid)	• ACL is an enzyme that functions upstream of HMG-CoA reductase • ACL catalyzes the formation of acetyl-CoA, a precursor of fatty acids and cholesterol • Inhibition of ACL yields similar results as HMG-CoA reductase inhibitors • Inhibits cholesterol synthesis	• 15%–25% reduction in LDL-C levels	• Upper respiratory tract infections, bronchitis • Muscle spasms • Hyperuricemia • Back, abdominal, or extremity pain • Anemia • Concomitant use with HMG-CoA reductase inhibitors may increase risk of statin-induced myopathy	• May be associated with reduced risk of cardiovascular events and diabetes • May be alternative for patients intolerant of statins or with statin-induced myopathy

Table 92.5 Lipid-lowering medications.

Continued

LIPID-LOWERING MEDICATIONS				
Class of drug	**Mechanism of action**	**Clinical effects**	**Side effects/ interactions**	**Comments**
Angiopoietin-like 3 (ANGPTL3) inhibitors (e.g. evinacumab)	• Binds to ANGPTL3 which is expressed primarily in the liver • ANGPTL3 inhibits lipoprotein lipase and endothelial lipase; inhibitors rescue enzyme activity • Promotes VLDL processing and clearance upstream of LDL formation	• Lowers levels of LDL-C (independent of the presence of LDL receptors), HDL-C, and triglycerides	• Injection site reaction • Cough, cold-like symptoms • Dizziness	• Treatment of *homozygous* familial hypercholesterolemia • Administered intravenously in combination with other lipid-lowering drugs (e.g. "statin", PCSK9 inhibitor)
Small interfering RNAs (siRNAs)	• Inclisiran inhibits translation of PCSK9	• 50% reduction in LDL-C levels	• Injection site reactions • Arthralgia, bronchitis	• Effective in *heterozygous* familial hypercholesterolemia • Administered subcutaneously in combination with a "statin"
Lipoprotein apheresis	• Physical removal of circulating lipoprotein(a)	• Lowers levels of circulating lipoprotein(a) by >60% per treatment and by ~30% long-term	• Venipuncture and anticoagulation required for procedure • Hypotension during procedure	• Treatment of *homozygous* familial hypercholesterolemia • Could be considered in patients with very high risk hyperlipidemia/cardiovascular disease • Lifelong therapy

Table 92.5 Lipid-lowering medications. Metreleptin is indicated for patients with congenital or acquired generalized lipodystrophy to address their leptin deficiency and hypertriglyceridemia. Additional treatments, e.g. apolipoprotein C-II mimetic peptides, are under investigation. C, cholesterol; GI, gastrointestinal; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein-cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very low-density lipoprotein. Based on references 4,33–44.

Xanthomas, particularly xanthelasma, can be treated surgically by excision or destructive methods. When xanthelasma excision is performed, it may be followed by suture or second intention healing[22]. Reported destructive methods for xanthelasma include laser surgery (e.g. CO_2, pulsed dye, erbium:YAG), chemical agents such as trichloroacetic acid, and cryosurgery[23–26]. Despite the initial success of the chosen method, the lesions often recur. Surgical excision has also been employed in the management of tendinous xanthomas. This can be technically difficult, however, as the lipid deposits may be intertwined with the involved tendon[27]. Application of topical lovastatin/cholesterol ointment has led to improvement of the cutaneous lesions in CHILD syndrome (see Ch. 57).

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Additional figures and table on Laboratory evaluation of suspected hyperlipidemia, available in our eBook (see inside front cover for access code).

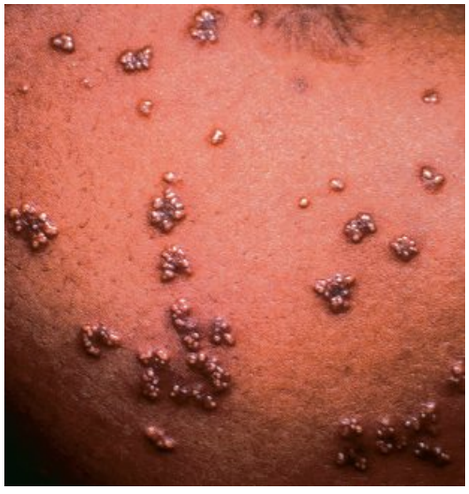
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eFig. 92.1 Eruptive xanthomas. Note the central yellow color.



eFig. 92.2 Eruptive xanthomas. Note the yellowish hue and "mulberry" pattern in a patient with Frederickson type IV disease.



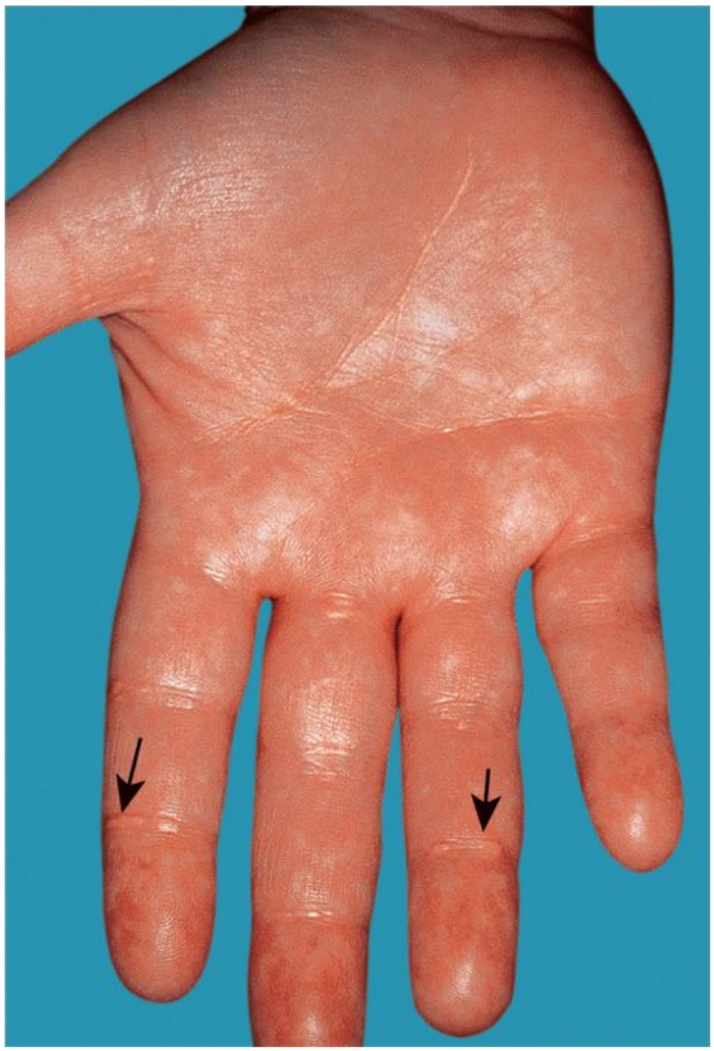
eFig. 92.3 Tuberoeruptive xanthomas of the elbow. Note the yellowish hue.



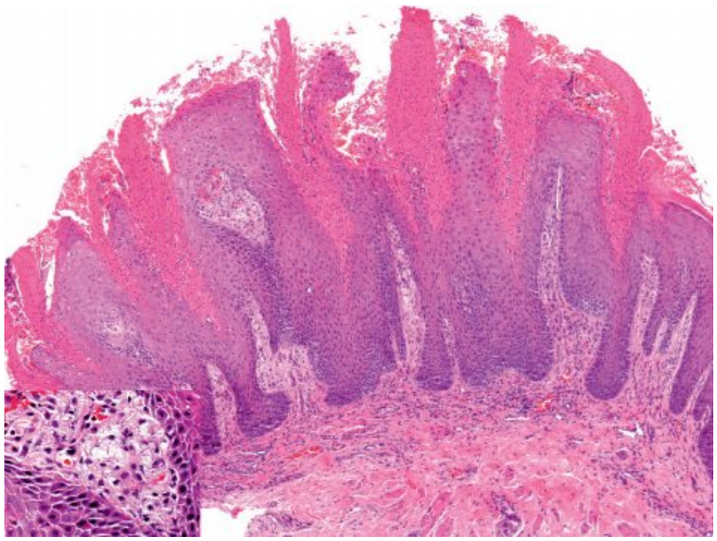
eFig. 92.4 Nodular tuberous xanthomas of the elbows. This form occurred in a young patient with familial hypercholesterolemia.



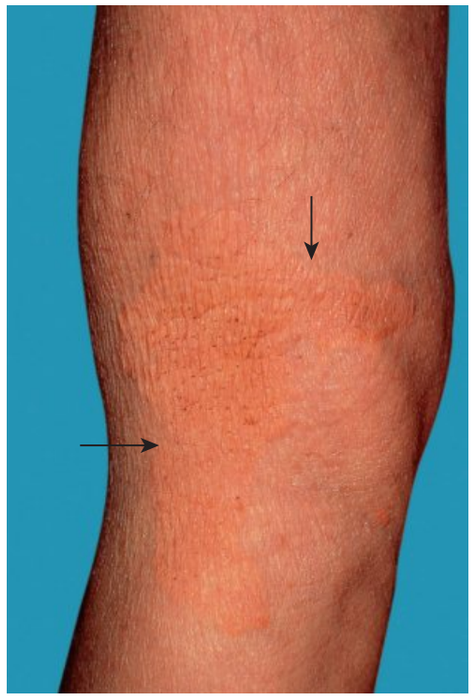
eFig. 92.5 Large, multilobulated, nodular tuberous xanthoma of the elbow. *Courtesy Jeffrey M. Cohen, MD.*



eFig. 92.6 Plane xanthomas of the palmar creases (arrows) in a patient with dysbetalipoproteinemia. They are seen in approximately two-thirds of patients with this disorder. Plane xanthomas are also seen in the setting of cholestasis, e.g. biliary atresia or primary biliary cholangitis (previously primary biliary cirrhosis).



eFig. 92.8 Verruciform xanthoma. Marked parakeratosis, papillomatosis, and acanthosis. The collection of foam cells immediately below the epithelium is subtle (inset). *Courtesy Luis Requena, MD.*



eFig. 92.7 Normolipemic plane xanthoma in a patient with a monoclonal IgG gammopathy. These lesions can be subtle clinically; arrows point to the edge of the xanthoma.



eFig. 92.9 Eruptive xanthomas in the setting of hypertriglyceridemia and uncontrolled diabetes mellitus. *Courtesy Catherine Baker, MD.*

LABORATORY EVALUATION OF SUSPECTED HYPERLIPIDEMIA
• Fasting lipid panel*
• Fasting serum glucose or hemoglobin A1C
• Liver function tests†
• Thyroid-stimulating hormone (TSH) level
• Serum albumin
*If elevated serum lipids, evaluate for systemic disease.
†If elevated serum alkaline phosphatase and bilirubin, evaluate for biliary disease.

eTable 92.1 Laboratory evaluation of suspected hyperlipidemia.

93 Non-infectious Granulomas

Misha A. Rosenbach and Karolyn A. Wanat

Chapter Contents

Sarcoidosis *1660*
Granuloma Annulare *1667*
Necrobiosis Lipoidica *1671*
Cutaneous Crohn Disease *1674*
Foreign Body Granulomas (See Ch. 94) *1675*
Orofacial Granulomatosis (OFG; See Ch. 72) *1676*
Reactive Granulomatous Dermatitis – Includes Interstitial Granulomatous Dermatitis, Palisaded Neutrophilic and Granulomatous Dermatitis, and Interstitial Granulomatous Drug Reaction *1676*

INTRODUCTION

The granulomatous diseases discussed in this chapter may be defined as having an inflammatory cutaneous infiltrate in which histiocytes are the preponderant inflammatory cells. While cutaneous sarcoidosis is the prototype of non-infectious (sterile) granulomatous dermatitides, there are a number of other entities in this group (Fig. 93.1 & Table 93.1). Additional non-infectious granulomatous disorders are covered in other chapters, including rheumatoid nodules in Chapter 45, cheilitis granulomatosa in Chapter 72, foreign body granulomas in Chapter 94, necrobiotic xanthogranuloma in Chapter 91, and primary immunodeficiency-associated granulomatous dermatitis in Chapter 60.

SARCOIDOSIS

Synonyms/subsets: ■ Löfgren syndrome – erythema nodosum, hilar adenopathy, fever, arthritis ■ Heerfordt syndrome – parotid gland enlargement, uveitis, fever, cranial nerve palsy ■ Darier–Roussy disease – subcutaneous sarcoidosis

Key features

- A systemic granulomatous disorder of unknown origin that most commonly involves the lungs
- Cutaneous manifestations of sarcoidosis are seen in up to one-third of patients and may be the first clinical sign of the disease
- Red–brown to violaceous papules and plaques appear most often on the face, in particular the nose, as well as the neck, upper back, extremities, and within scars and tattoos
- Erythema nodosum is a nonspecific inflammatory skin finding that may be associated with an acute form of sarcoidosis which tends to remit
- Histologically, sarcoidosis is characterized by non-caseating epithelioid granulomas, usually with a sparse or absent surrounding lymphocytic inflammation (i.e. "naked" granulomas)

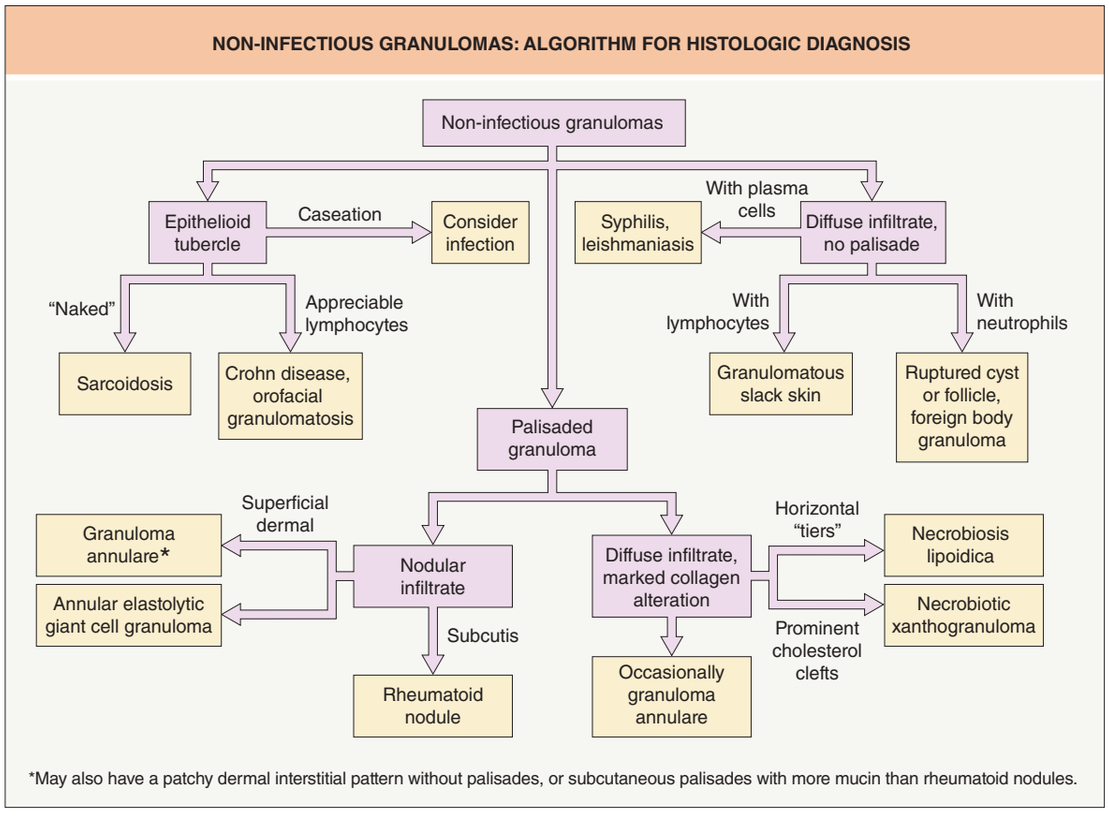


Fig. 93.1 Non-infectious granulomas: algorithm for histologic diagnosis. Reactive granulomatous dermatitis (interstitial granulomatous dermatitis, palisaded neutrophilic and granulomatous dermatitis, and interstitial granulomatous drug eruption) represents an additional diagnostic consideration (see Table 93.4).

CLINICAL FEATURES OF THE MAJOR NON-INFECTIOUS GRANULOMATOUS DERMATITIDES						
	Sarcoidosis*	**Classic granuloma annulare†**	**AEGCG**	**Necrobiosis lipoidica**	**Cutaneous Crohn disease**	**Rheumatoid nodule**
Average age (years)	25–35, 45–65	<30	50–70	30	35	40–50
Sex predilection	Female	Female	Female	Female	Female	Male‡
Racial/ethnic predilection in US	African-American	None	White	None	Ashkenazi Jews	None
Sites	Symmetric on face, neck, upper trunk, extremities	Hands, feet, extensor aspects of extremities	Face, neck, forearms (sites of chronic sun exposure)	Anterior and lateral aspects of shins	Anogenital region, buttocks, lower > upper extremities	Juxta-articular areas, especially elbows and hands
Appearance	Protean; most commonly red–brown or violaceous papules and plaques	Papules coalescing into annular plaques	Annular plaques	Plaques with elevated borders, telangiectasias centrally	Dusky erythema, lymphedema, ulceration, vegetating plaques	Skin-colored, firm, mobile subcutaneous nodules
Size of lesions	0.2 to >5 cm	1–3 mm papules, annular plaques usually <6 cm	2 to >10 cm	3 to >10 cm	Variable	1–3 cm
No. of lesions	Variable	1–10	1–10	1–10	1–5	1–10
Associations	Systemic manifestations of sarcoidosis (see Table 93.3); can be drug-induced (e.g. IFN, TNF inhibitors) or reaction pattern to underlying lymphoma	Possible diabetes mellitus, thyroid disease, or hyperlipidemia; rare reports of HIV infection, drugs, malignancy	Actinic damage	Diabetes mellitus, thyroid disease	Intestinal Crohn disease	Rheumatoid arthritis
Special clinical characteristics	Develop within sites of trauma including scars and tattoos	Central hyperpigmentation	Central atrophy and hypopigmentation	Yellow–brown atrophic centers, ulceration	Draining sinuses and fistulas	Occasional ulceration, especially at sites of trauma

*Clinical variants include lupus pernio and subcutaneous (Darier–Roussy), psoriasiform, ichthyosiform, angiolupoid, and ulcerative sarcoidosis.
†Clinical variants include generalized/disseminated, micropapular, nodular, perforating, subcutaneous, and patch granuloma annulare.
‡Although rheumatoid arthritis has a female : male ratio of 2–3 : 1.

Table 93.1 Clinical features of the major non-infectious granulomatous dermatitides. AEGCG, annular elastolytic giant cell granuloma; HIV, human immunodeficiency virus.

History

Sarcoidosis was described initially by Sir Jonathan Hutchinson in 1875 and cutaneous sarcoidosis (lupus pernio) by Besnier in 1889. Ten years later, Caesar Boeck coined the term "multiple benign sarkoid", noting that the lesions resembled benign sarcomas.

Epidemiology

Sarcoidosis, which occurs in patients of all races and ages as well as both sexes, is characterized by a bimodal age distribution, with peaks between 25 and 35 years and then between 45 and 65 years in women. In the US, there is an increased incidence of sarcoidosis in African-Americans, ranging from 18 to 70 per 100 000. Middle-aged African-American women have the highest incidence (107 per 100 000), with African-American women having a lifetime risk of developing the disease of 2.7%[1]. In comparison, the incidence in White individuals in the US ranges from 10 to 14 per 100 000. Sarcoidosis in African-Americans also tends to be more chronic and severe with a higher mortality rate than in other populations[2]. Worldwide, the incidence of sarcoidosis is highest in Sweden (64 per 100 000) and the UK (20 per 100 000) and lowest in Spain and Japan (both 1.4 per 100 000). A greater number of patients with new-onset sarcoidosis are reported in the winter and spring[3].

Pathogenesis

Immune mechanisms

Sarcoidosis is a multisystem granulomatous disease characterized by hyperactivity of the cell-mediated immune system. Patients with a genetic susceptibility are exposed to a triggering antigen, leading to activation of macrophages and T cells, with subsequent granuloma formation. While classically considered a Th1-predominant immune response, the inflammatory cascade in sarcoidosis likely spans multiple pathways, including the innate immune system (via activation of pattern recognition receptors such as Toll-like receptors or NOD-like receptors) and the Th17 arm of the immune system[4,5]. Specifically, $CD4^+$ T helper cells differentiate into Th1 and Th17 effector cells that produce IFN-γ as well as Th17 cells that produce IL-17[1]. This is triggered by antigen presentation by monocytes bearing MHC class II molecules, which initiates formation of epithelioid granulomas in a variety of tissue types[6]. In the lung, an oligoclonal α/β T cell population has been described, suggesting that antigenic triggers of sarcoidosis favor a progressive accumulation and activation of specific T cell clones[7].

Increased production of Th1 cytokines, including interleukin (IL)-2, IL-12, IL-18, and interferon (IFN)-γ, as well as release of tumor necrosis factor (TNF) by macrophages and some $CD8^+$ T cells, leads to persistent Th1 activity and persistent IFN-γ elevation. There is macrophage accumulation and hyperactivity, along with B cell stimulation and hypergammaglobulinemia. TNF and GM-CSF promote fusion of activated macrophages into the multinucleated cells seen within the granuloma[5].

Monocyte chemotactic factor (MCF), produced by activated T helper cells, attracts monocytes from the circulation into peripheral tissues. Compartmentalization of granuloma-forming T lymphocytes and monocytes within peripheral tissues leads to lymphopenia and decreased delayed-type hypersensitivity to common antigens (anergy), most pronounced during the initial stages of sarcoidosis. In addition, T regulatory cells may play a role in this anergic state. However, in some patients, there actually may be inadequate regulatory T cell function such that production of TNF or IFN-γ is not suppressed[8].

As macrophages differentiate into epithelioid cells and antigen-presenting cells, the phagolysosomal pathway plays an important role in sarcoidosis granuloma formation via promotion of mTORc1 (mechanistic target of rapamycin complex 1)/STAT3 signal transduction. In addition, IFN-γ stimulates the JAK (Janus kinase)/STAT pathway (see Fig. 128.11). With the discovery that this pathway plays a key role in

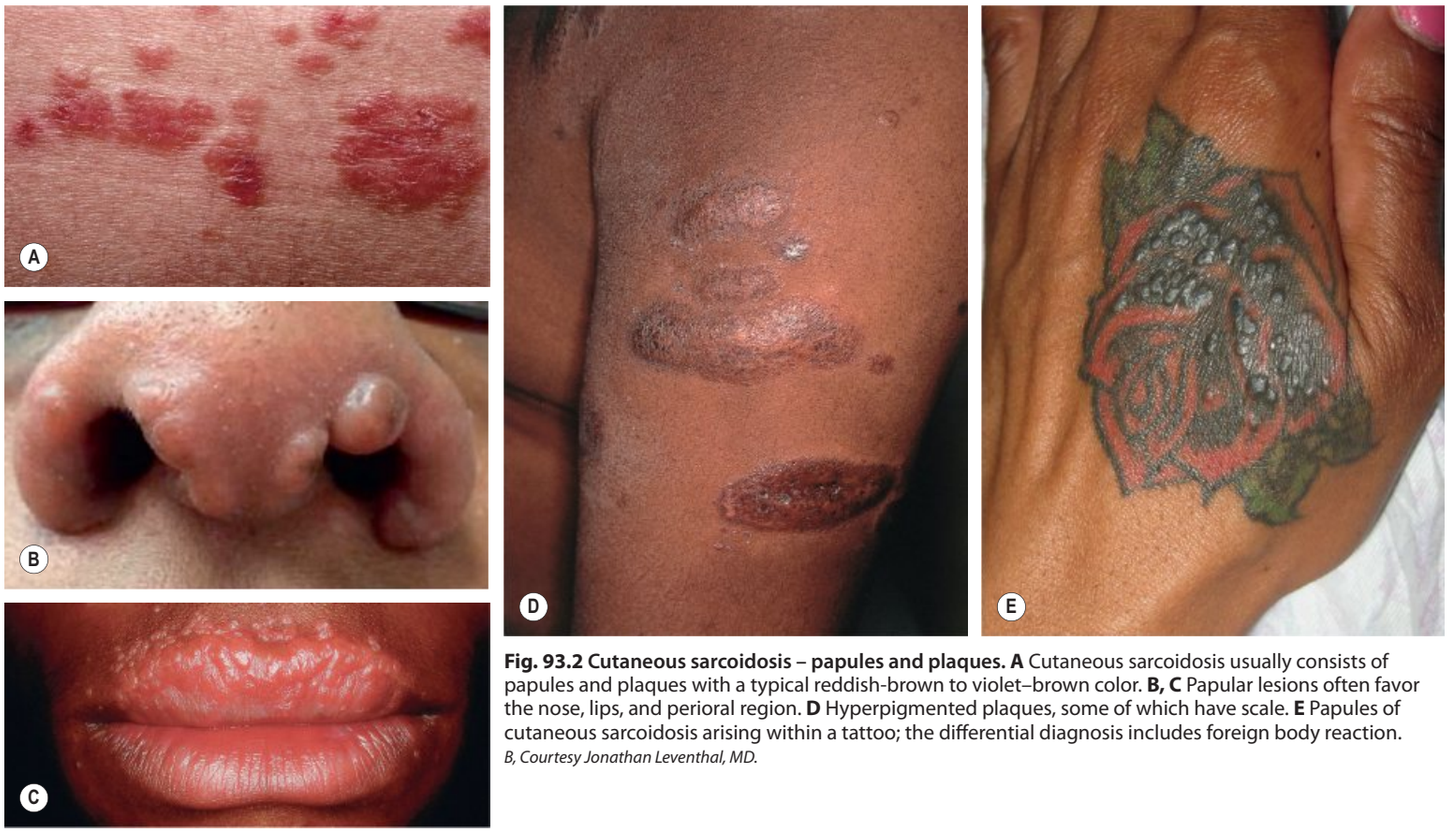


Fig. 93.2 Cutaneous sarcoidosis – papules and plaques. A Cutaneous sarcoidosis usually consists of papules and plaques with a typical reddish-brown to violet–brown color. **B, C** Papular lesions often favor the nose, lips, and perioral region. **D** Hyperpigmented plaques, some of which have scale. **E** Papules of cutaneous sarcoidosis arising within a tattoo; the differential diagnosis includes foreign body reaction. *B, Courtesy Jonathan Leventhal, MD.*

SPECTRUM OF CUTANEOUS MANIFESTATIONS OF SARCOIDOSIS	
Common	
• *Papules* – favor periorificial sites on face	• *Plaques* – favor trunk and extremities
• *Lupus pernio* – favors nose and central face	• Scar-associated – initial insult weeks to decades prior
• *Tattoo-associated* – favors sites of red and yellow pigments	
Uncommon	
• *Annular*	• Atrophic – favors head and neck region
• Lichenoid	• *Psoriasiform*
• Subcutaneous (Darier–Roussy) – favors extremities	
Rare	
• Alopecia – scarring or nonscarring	• *Angiolupoid* – favors face and can mimic rosacea
• Erythrodermic	• *Hypopigmented*
• *Ichthyosiform*	• Micropapular
• Nail dystrophy – subungual hyperkeratosis, onycholysis	• Photodistributed/photo-exacerbated
• Ulcerative	• Verrucous
Nonspecific and common	
• *Erythema nodosum*	

Table 93.2 Spectrum of cutaneous manifestations of sarcoidosis. Photographs of entities in chapter or online in *italics*. *Adapted from Haimovic A, et al. Sarcoidosis: a comprehensive review and update for the dermatologist: part I. Cutaneous disease. J Am Acad Dermatol 2012;66:699.e1–18.*

granuloma formation in a range of disorders including sarcoidosis, JAK inhibitors have become a therapeutic option[9].

Triggers

The identity of the antigen responsible for the cascade of events leading to granuloma formation in patients with sarcoidosis remains uncertain. Some investigators have proposed an autoimmune etiology, while others have searched for exposures to inorganic dusts and particles (e.g. zirconium, talc)[10] or an infectious cause. The latter is suggested by several observations, including the identification of microbial components such as mycobacterial DNA sequences in different sarcoidal tissues[11], the transmissibility of sarcoidal lesions via the Kveim reagent, and the observation that sarcoidal granulomas have developed in patients receiving organ transplants from donors with sarcoidosis. In a meta-analysis, mycobacterial nucleic acids were identified in ~25% of sarcoidal tissues[12]. Also, the catalase-peroxidase (mKatG) protein from *Mycobacterium tuberculosis* has been proposed as a potential triggering antigen for granulomatous inflammation.

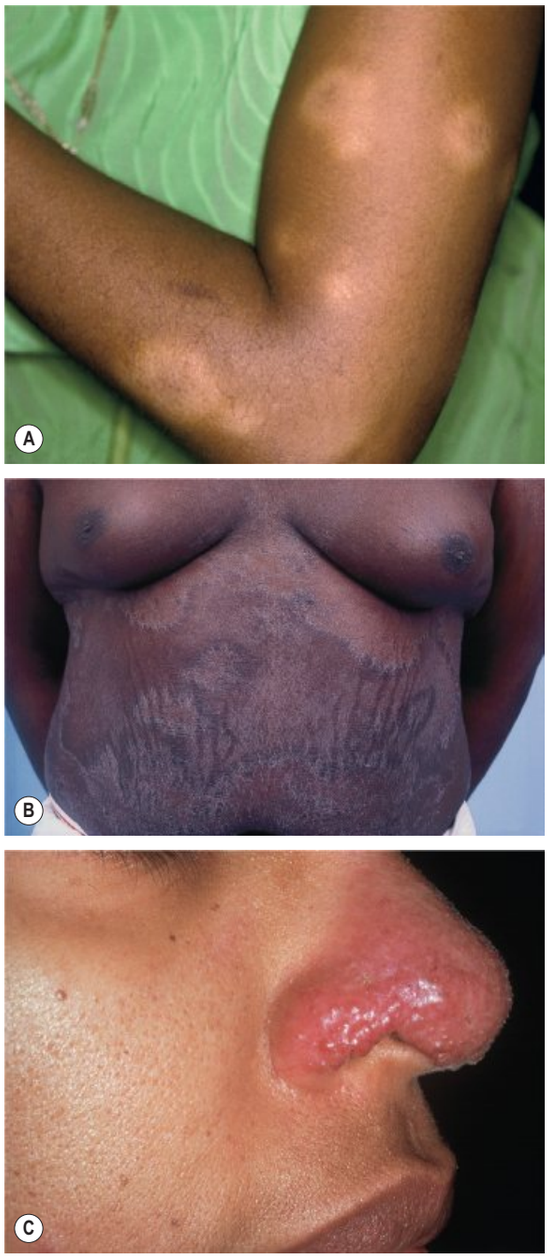


Fig. 93.3 Cutaneous sarcoidosis – clinical variants. A The hypopigmented variant is more noticeable in individuals with darkly pigmented skin. **B** Ichthyosiform presentation with obvious scale. **C** Coalescing violaceous papules on the nose in lupus pernio; note the notching of the nasal rim. *A, Courtesy Louis A. Fragola, Jr, MD; B, Courtesy Jean L. Bolognia, MD.*

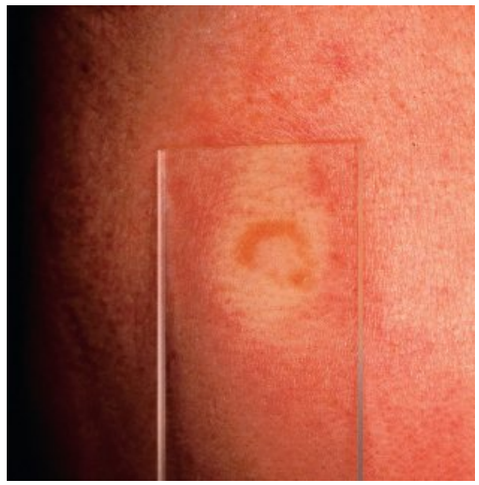


Fig. 93.4 Cutaneous sarcoidosis – diascopy. With diascopy, a yellow–brown, "apple jelly" color is seen.



Fig. 93.5 Erythema nodosum in a patient with sarcoidosis. These patients often have hilar lymphadenopathy. Löfgren syndrome consists of erythema nodosum, hilar lymphadenopathy, fever, and arthritis. *Courtesy Louis A. Fragola, Jr, MD.*

However, arguments against a purely infectious etiology include the observation that sarcoidosis patients do not develop fulminant infectious symptoms when placed on immunosuppressive agents. In addition, mycobacteria have not been cultured from sarcoidal tissues or from the sarcoid-like lesions that develop during antiretroviral-induced immune reconstitution[13]. Occupational associations have been noted in healthcare workers, navy personnel on aircraft carriers, and firemen[11], with a marked increase in sarcoidosis-like illnesses in the first responders to the 9/11 World Trade Center terrorist attacks. In addition, exposure to beryllium can lead to berylliosis, a granulomatous disease that can closely mimic pulmonary sarcoidosis. Additional proposed triggers of sarcoidosis include viruses[14], *Cutibacterium acnes*, and an abnormal accumulation of serum amyloid A (SAA).

Over the past two decades, an increasing number of medications have been reported to induce cutaneous sarcoidosis and sarcoid-like granulomatous eruptions, including IFN, other systemic immunomodulators (e.g. TNF inhibitors > IL-17 inhibitors, IL-1 receptor antagonists), immune checkpoint inhibitors (e.g. ipilimumab, nivolumab, pembrolizumab), and targeted kinase inhibitors (e.g. vemurafenib), as has administration of the SARS-CoV-2 vaccine. Patients with lymphoma may also develop secondary sarcoidal reactions, most commonly in lymph nodes but occasionally in the skin.

Genetics

Sarcoidosis is a polygenic not a monogenic disease. A genetic component is supported by a twin study in which the monozygotic twins of patients with sarcoidosis had an 80-fold increased risk of having sarcoidosis[15]. The largest case–control study to date demonstrated a familial relative risk of 4.7[16]. The heritability of sarcoidosis has been estimated to range from 40% to 70%[1]. The impact of HLA alleles varies significantly, depending upon disease subtype and racial group. Overall, HLA-DRB1*01 and DRB1*04 protect against sarcoidosis in some populations, while DRB1*03, DRB1*11, DRB1*12, DRB1*14, and DRB1*15 appear to confer risk[17]; HLA-B8/DR3 may be associated with the development of Löfgren syndrome (see below). In African-Americans, HLA-DQB1 alleles may play a role[17], and patients with DRB1*03 may have a better prognosis. Specific susceptibility genes include *TNF* (variants associated with Löfgren syndrome) and *IL23R* (variants confer risk for Crohn disease and sarcoidosis)[17]. Whole genome sequencing of 41 members of a family with a high rate of sarcoidosis found variants within 34 candidate genes, one of which was *JAK2* (see above)[18].

While the etiologic agent clearly remains elusive, investigation of the immunopathogenesis of the disease (see above) has been aided by examining the cutaneous reaction produced by injection of a tissue suspension prepared from sarcoidal spleen. The suspension (Kveim–Siltzbach antigen) causes characteristic non-caseating granuloma formation in the skin of patients with sarcoidosis[6]. Nowadays, however, this skin test is rarely performed.

Clinical Features

Up to a third of patients with systemic sarcoidosis develop skin lesions, which may be the first or only clinical manifestation of the disease.

Although cutaneous sarcoidosis most commonly presents as papules and plaques, often red–brown to violaceous in color (Figs. 93.2A–D), the skin manifestations are protean (Table 93.2). Sarcoidal lesions are fairly symmetric in distribution and favor the nose, especially the alae, and the periocular and perioral regions of the face, followed by the neck, upper trunk, and extremities. Involvement at sites of prior injuries, e.g. scars, tattoos, is a characteristic finding (Fig. 93.2E). Unusual variants include hypopigmented, ichthyosiform, micropapular, psoriasiform, and ulcerative (Fig. 93.3A,B; see Table 93.2).

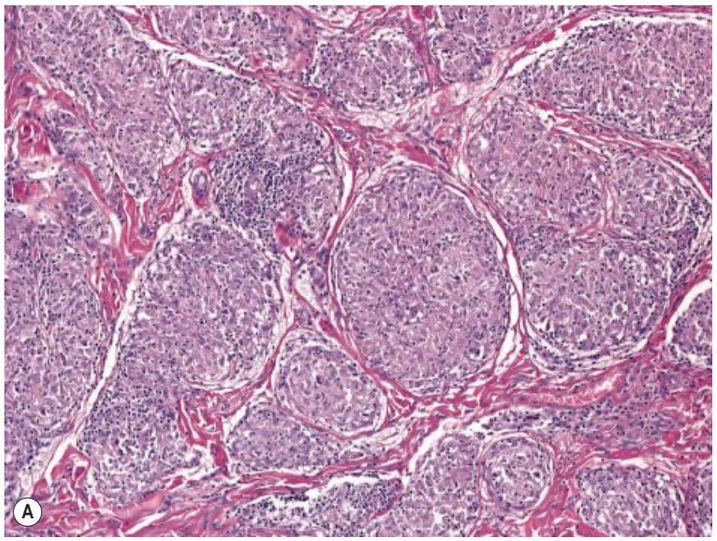
Although many lesions are red–brown to violaceous in color, they can vary from yellow–brown to erythematous, especially in lightly pigmented skin. Upon diascopy, in which pressure induces blanching, the lesions are said to have the color of "apple jelly" (Fig. 93.4); this finding is usually easier to appreciate in lightly pigmented skin. Individual plaques can develop central clearing leading to an annular configuration or they can contain prominent telangiectasias (angiolupoid sarcoidosis). Dermoscopic features include small translucent yellow to orange globules, linear vessels, and central scar-like areas.

Additional variants of sarcoidosis of relevance to dermatologists include Löfgren syndrome, Darier–Roussy disease, and lupus pernio. Patients with *Löfgren syndrome* present acutely with fever, arthritis, hilar adenopathy, and erythema nodosum. They often require supportive measures and occasionally systemic corticosteroids, with spontaneous resolution occurring over 1–2 years. Patients with *Darier–Roussy sarcoidosis* present with painless, firm, subcutaneous nodules or plaques without epidermal changes. This variant represents sarcoidosis limited to the panniculus and, like other forms of cutaneous sarcoidosis, is often associated with systemic sarcoidosis. *Lupus pernio* is characterized by papulonodules and plaques, which are often on the nose and cheeks and have a violaceous color, sometimes along with scale;

SYSTEMIC MANIFESTATIONS OF SARCOIDOSIS			
Organ	**% of patients affected**	**Clinical manifestations/radiographic and laboratory findings**	**Evaluation**
Lungs	90–95	Dyspnea, non-productive cough/pulmonary infiltrates, fibrosis, restrictive lung disease (↓VC, ↓RV, ↓TLC, ↓DLCO)	CXR, high resolution chest CT scan (more sensitive than CXR), PFTs that include DLCO
Lymph nodes (LN)	30–40*	Lymphadenopathy/enlarged hilar and/or paratracheal LN	CXR, high resolution chest CT scan (more sensitive than CXR)
Eyes	25	Uveitis (can be asymptomatic despite being severe), conjunctivitis, sicca symptoms	Yearly ophthalmologic examination; more frequently if ocular disease
Liver/spleen	10–20	Hepatomegaly and/or splenomegaly (rarely clinically relevant), cirrhosis, consequences of splenic enlargement (e.g. thrombocytopenia)/↑LFTs, ↓plts	• LFTs, physical examination • If clinically relevant hypersplenism suspected, abdominal/pelvic CT scan (lymphadenopathy common finding)
Heart	25 (10–15 clinically relevant)	Palpitations, sudden death, CHF/arrhythmias, cardiomegaly	• EKG, baseline and if history of palpitations • If any abnormalities, referral to cardiologist as patients may require echocardiogram, Holter monitor, cardiac MRI, or cardiac PET scan
CNS and peripheral nervous system	10–20	Neuropathies – cranial, spinal cord, peripheral, small fiber	• Dictated by symptoms (e.g. MRI, nerve conduction studies) • Referral to neurologist
Upper respiratory tract, including sinuses	5–10	Sinusitus, nasal congestion, stridor, parotiditis	• Referral to otolaryngologist and/or dedicated imaging • Also prompted by presence of lupus pernio
Bones	5–10	Usually asymptomatic/lytic bone lesions	• Radiography • Bone mineral density, especially in the setting of systemic corticosteroid use
Joints/muscles	5–10	Arthritis, weakness (up to a third of patients have severe fatigue), myopathy	• Referral to rheumatologist • EMG
Bone marrow	50	• Lymphopenia (↓$CD4^+$:$CD8^+$ ratio), leukopenia, eosinophilia, hypergammaglobulinemia, nonhemolytic anemia (5%) • Elevated risk of developing lymphoma is debatable†	CBC, SPEP, quantitative immunoglobulins
Kidneys	10–40	Nephrolithiasis/hypercalciuria, ↓renal function	• BUN, crt, serum calcium, spot urine calcium : crt ratio, 24-hour urine for calcium excretion • Referral to nephrologist
Endocrine	5–10	• Pituitary or thyroid dysfunction • Hypercalcemia (increased calcitriol synthesis by sarcoidal histiocytes)	• Thyroid function tests • Expanded hormonal testing when clinically indicated • Serum calcium levels • Measure both 1,25-dihydroxyvitamin D_3 (calcitriol) and 25-hydroxyvitamin D_3 (the latter is the routinely ordered test)
Other	<1 (rare)	• "Masses" – GI tract (luminal), ovarian, testicular – often asymptomatic • Granulomatous breast infiltration that can lead to ulceration	Site-specific imaging

*Pertains to peripheral lymphadenopathy; up to 90% have hilar lymphadenopathy.
†An association is based primarily on two studies, one of which found two cases of lymphoma in 2544 patients with sarcoidosis and the other had a standardized incidence ratio of 1.52 with a CI of 1.12–2.02. Multiple other studies have failed to find an association.

Table 93.3 Systemic manifestations of sarcoidosis. CHF, congestive heart failure; CT, computed tomography; CXR, chest X-ray; DLCO, diffusion lung capacity for carbon monoxide; EMG, electromyography; LFTs, liver function tests; MRI, magnetic resonance imaging; PET, positive emission tomography; PFTs, pulmonary function tests; plts, platelets; RV, residual volume; SPEP, serum protein electrophoresis; TLC, total lung capacity; VC, vital capacity. *Adapted from Chen ES, Moller DR. Sarcoidosis – scientific progress and clinical challenges. Nat Rev Rheumatol 2011;7:457–67 and Haimovic A, Sanchez M, Judson MA, Prystowsky S. Sarcoidosis: a comprehensive review and update for the dermatologist: part I. Cutaneous disease. J Am Acad Dermatol 2012;66:699.e1–18.*



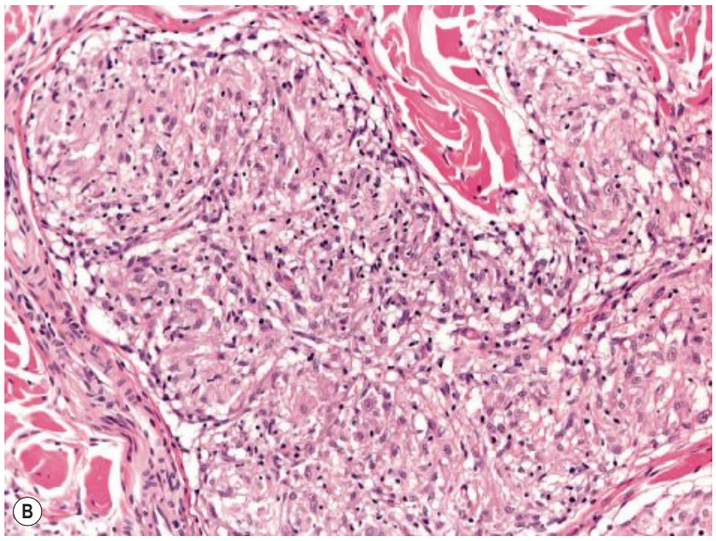


Fig. 93.6 Cutaneous sarcoidosis – histopathologic features. A Nodular aggregates of epithelioid histiocytes forming tubercles filling the dermis. **B** A sarcoidal tubercle with a sparse admixture of lymphocytes ("naked tubercle"). *Courtesy Lorenzo Cerroni, MD.*

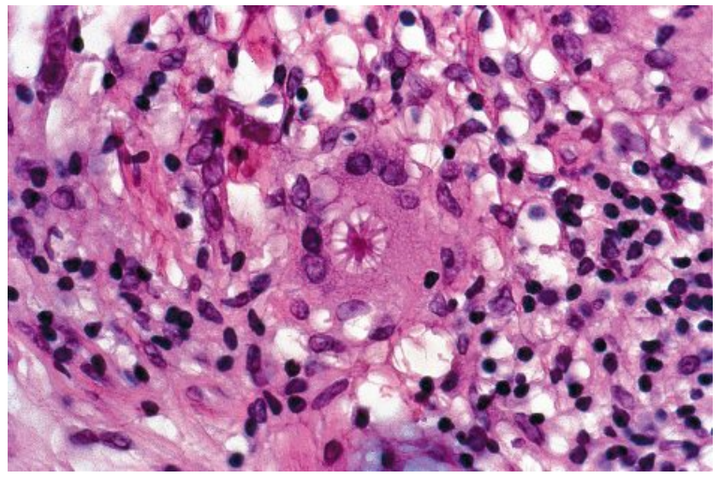


Fig. 93.7 Cutaneous sarcoidosis – histopathologic features. An asteroid body within the cytoplasm of a multinucleated epithelioid histiocyte ("giant cell").



Fig. 93.8 Immune checkpoint inhibitor-induced cutaneous sarcoidosis. The patient had received both ipilimumab and nivolumab. A search for internal involvement, e.g. lung, lymph nodes, is warranted. *Courtesy Department of Dermatology, Medical University of Graz.*

there may be a beaded appearance along the nasal rim (see Fig. 93.3C). Recognition of lupus pernio is important because of its association with chronic sarcoidosis of the lungs (~75% of patients) and of the upper respiratory tract (~50% of patients), as well as its recalcitrant nature that often requires more aggressive therapy[19].

The most common and important nonspecific cutaneous manifestation of sarcoidosis is erythema nodosum (Fig. 93.5). In addition to its association with Löfgren syndrome, the presence of erythema nodosum portends a subacute, transient course of sarcoidosis that usually resolves spontaneously and typically does not require chronic immunosuppressive therapy. In general, there are no additional cutaneous manifestations.

Nail changes can be seen in sarcoidosis, including clubbing, subungual hyperkeratosis, and onycholysis. Oral sarcoidosis may affect the soft mucosa, gingival tissue, tongue, hard palate, and major salivary glands. Heerfordt syndrome (uveoparotid fever) includes parotid gland enlargement, uveitis, fever, and cranial nerve palsies, usually of the facial nerve.

Systemic manifestations of sarcoidosis are also protean. Lung disease occurs in ~90% of patients, ranging from alveolitis to granulomatous infiltration of the alveoli, blood vessels, bronchioles, pleura, and fibrous septa[20]. The end stage of pulmonary sarcoidosis is fibrosis with bronchiolectasis and "honeycombing" of the lung parenchyma. Hilar and/or paratracheal lymphadenopathy, which is usually asymptomatic, occurs in 90% of patients. Additional systemic manifestations are outlined in Table 93.3.

Childhood sarcoidosis is rare, and it usually presents with a triad of arthritis, uveitis, and cutaneous lesions, along with constitutional symptoms. Peripheral lymphadenopathy is frequently present. If sarcoidosis is being considered in a child, it is important to exclude Blau syndrome (see Ch. 45).

Pathology

The histopathologic hallmark of sarcoidosis is the presence of superficial and deep dermal epithelioid cell granulomas devoid of prominent infiltrates of lymphocytes or plasma cells ("naked tubercles") (Fig. 93.6). Central caseation is usually absent, although fibrinoid deposition may be observed in up to 10% of cases. Multinucleated histiocytes ("giant cells") are usually of the Langhans type, with nuclei arranged in a peripheral arc or circular fashion. The giant cells may contain eosinophilic stellate inclusions known as asteroid bodies (Fig. 93.7) or rounded laminated basophilic inclusions known as Schaumann bodies, although neither is specific or required for the diagnosis. Asteroid

bodies represent engulfed collagen, whereas Schaumann bodies likely represent degenerating lysosomes. Notably, up to 25% of biopsies of sarcoidosis contain polarizable material; therefore its presence does not exclude the diagnosis. Rarely, the granulomatous infiltrate is arranged in a superficial ("lichenoid") band. In vulvar sarcoidosis, transepidermal elimination of the granulomas may be seen.

A range exists within the histologic spectrum of sarcoidosis, from the characteristic tubercles with minimal or no surrounding lymphocytic inflammation to unusual cases with dense lymphocytic and plasmacytic infiltrates around and within the nodular histiocytic aggregates. Occasionally, these aggregates may extend into the subcutaneous fat, producing the clinical features of Darier–Roussy sarcoidosis.

Diagnosis and Differential Diagnosis

Sarcoidosis is a diagnosis of exclusion, both clinically and histologically. In order to establish the diagnosis, a supportive clinical history must be accompanied by the histologic presence of non-caseating granulomas in at least one organ system. Details of systemic manifestations are outlined in Table 93.3. An algorithm for initial and longitudinal evaluation has been proposed[21].

Serologically, elevated anti-nuclear antibody titers occur in ~30% of patients. The serum angiotensin-converting enzyme (ACE) level is elevated in ~60% of patients but is nonspecific for sarcoidosis; it has a false-positive incidence of 10%, making it a more useful test for monitoring disease progression in select patients where it is elevated, rather than for establishing the diagnosis. An ACE level >2–3 times the upper limit of normal is more suggestive of sarcoidosis but its clinical utility may still be limited. In sum, most sarcoidosis experts do not routinely order ACE levels.

Like syphilis, sarcoidosis is a great mimicker, and the clinical differential diagnosis depends upon the type of presenting clinical lesions. For example, a list of other disorders, in addition to sarcoidosis, that can present with annular lesions is provided in Table 19.1. Papules, nodules, and plaques may be nonspecific clinically, dictating a biopsy, and then the differential diagnosis rests upon the histopathologic findings. It is important to exclude the possibility of drug-induced cutaneous sarcoidosis (e.g. IFN-α for hepatitis C viral infection [use declining], TNF inhibitors, immune checkpoint inhibitors) (Fig. 93.8).

The histologic differential diagnosis is broad, and includes multiple infections that lead to granulomatous inflammation. Special stains for acid-fast and fungal organisms should be obtained. When clinically appropriate, tissue culture should be performed. Increasingly, PCR is being utilized to exclude infections, including mycobacterial. Both tuberculoid leprosy and lupus vulgaris are in the differential diagnosis and for the latter, a QuantiFERON®-TB Gold test may provide additional information. It is especially important to exclude infectious etiologies before initiating immunosuppressive agents.

Other histologic mimics include foreign body reactions to zirconium, beryllium, silica, tattoo ink, or soft tissue fillers. Special laboratory techniques, including histochemical, microincineration or spectrophotometric examinations, may be required to identify the causative agents (see Table 94.3). Specimens should be polarized to exclude birefringent foreign material as a causative agent, although up to 25% of known sarcoidal granulomas will have foreign material present within them. This finding is particularly common in lesions from the elbows and knees. Therefore, the dermatologic diagnoses of foreign body granuloma and sarcoidosis are not mutually exclusive[22].

In addition, granulomatous mycosis fungoides, Hodgkin disease, granulomatous rosacea, cutaneous Crohn disease, Blau syndrome (see Ch. 45), cheilitis granulomatosa, and the sarcoidal reaction to an underlying lymphoma can have histologic appearances similar to sarcoidosis. The histologic differences between sarcoidosis, granuloma annulare, annular elastolytic giant cell granuloma (AEGCG), necrobiosis lipoidica, rheumatoid nodule, and the reactive granulomatous dermatitides are outlined in Table 93.4.

HISTOLOGIC FEATURES OF THE MAJOR NON-INFECTIOUS GRANULOMATOUS DERMATITIDES

	Sarcoidosis	Granuloma annulare	AEGCG	Necrobiosis lipoidica	Cutaneous Crohn disease	Reactive granulomatous dermatitis		Rheumatoid nodule*
						Interstitial granulomatous dermatitis	Palisading neutrophilic and granulomatous dermatitis	
Typical location	Superficial and deep dermis†	Superficial and mid dermis†	Superficial and mid dermis	Entire dermis, subcutis	Superficial and deep dermis	Mid and deep dermis	Entire dermis	Deep dermis, subcutis
Granuloma pattern	Tubercle with few peripheral lymphocytes ("naked")	Palisading or interstitial; patchy with discrete foci	Palisading, irregular	Diffuse palisading and interstitial‡; horizontal "tiers"	Tubercle with surrounding lymphocytes	Interstitial and small "rosettes" around single collagen fibers	Palisading and interstitial; prominent neutrophils and leukocytoclasia	Palisading
Necrobiosis (altered collagen)	No	Yes ("blue")	No	Yes ("red")	No	Yes ("blue")	Yes ("blue")	Yes ("red")
Giant cells	Yes	Variable	Yes	Yes	Yes	Variable	Variable	Yes
Elastolysis	No	Variable	Yes	Variable	No	Variable	Variable	No
Elastophagocytosis	No	Variable	Yes	No	No	No	No	No
Asteroid bodies	Yes	Variable	Yes	Variable	No	Variable	Variable	No
Mucin	No	Yes¶	No	Minimal	No	Minimal	Variable	Variable
Extracellular lipid	No	No	No	Yes	No	No	No	Variable
Vascular changes	No	Rare	No	Yes	No	No	Yes	Yes

*See Ch. 45.
†Subcutaneous variant can also occur.
‡Rare sarcoidal variants seen.
¶Even amid areas of uninvolved dermis.

Table 93.4 Histologic features of the major non-infectious granulomatous dermatitides. Interstitial granulomatous dermatitis and palisading neutrophilic and granulomatous dermatitis are thought to fall within the spectrum of reactive granulomatous dermatitis. Tan-shaded column is not covered in this chapter. AEGCG, annular elastolytic giant cell granuloma.

TREATMENT OF CUTANEOUS SARCOIDOSIS
Topical or intralesional corticosteroids (2)
Topical calcineurin inhibitors (3)
Oral tetracyclines (e.g. minocycline, doxycycline) (2)
Oral hydroxychloroquine or chloroquine (2)
Methotrexate (2)
TNF inhibitors (adalimumab, infliximab)* (1)
Systemic corticosteroids (2)
Thalidomide (2)
Phosphodiesterase inhibitors (pentoxifylline, apremilast) (2)
Leflunomide (2)
JAK inhibitors (2)
Azathioprine (3)
Intralesional chloroquine (3)
Allopurinol (3)
Isotretinoin (3)
PUVA (psoralen plus UVA) (3)
Mycophenolate mofetil (3)
Antimycobacterial therapy (levofloxacin, ethambutol, azithromycin, and rifampin) (1)
Pulsed dye or CO_2 laser (3)
Photodynamic therapy (3)
Surgical excision (3)
*Can rarely trigger sarcoidosis, particularly etanercept.

Table 93.5 Treatment of cutaneous sarcoidosis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. TNF, tumor necrosis factor.
Adapted from Wanat KA, Rosenbach M. A practical approach to cutaneous sarcoidosis. Am J Clin Dermatol 2014;15:283–97.

Treatment

Corticosteroids, in either topical, intralesional, or systemic form, are the mainstay of therapy for systemic sarcoidosis (Table 93.5). Therapy is guided by organ involvement, disease severity and progression, and impact on patient quality of life. The typical oral prednisone dose for systemic disease is 0.5–1 mg/kg/day for 4–6 weeks, followed by a slow taper over months to years as dictated by the pulmonary disease, sarcoidosis of the upper respiratory tract, ocular disease, or other internal manifestations. The goal is alternate-day prednisone at the lowest possible dose that will maintain a remission. Cutaneous sarcoidosis may respond from the onset to lower doses of prednisone as well as every-other-day regimens. For limited cutaneous disease, topical or intralesional corticosteroids may suffice.

For treatment of more widespread cutaneous disease, alternative nonsteroidal systemic medications include hydroxychloroquine (200–400 mg/day), chloroquine (250–500 mg/day), minocycline or doxycycline (200 mg/day), and methotrexate (10–25 mg weekly). The use of thalidomide has declined, given recent negative studies, associated toxicities, and more effective alternative therapies. Improvement of both systemic and cutaneous sarcoidosis has been observed with TNF inhibitors, including infliximab and adalimumab[23]. These agents may be particularly effective for chronic, recalcitrant sarcoidosis (e.g. lupus pernio), but notably TNF inhibitors occasionally can trigger sarcoidosis (most commonly etanercept)[24,25]. In selected patients, pentoxifylline, retinoids, and apremilast have been reported to be helpful. While additional immunosuppressives (e.g. leflunomide, mycophenolate mofetil, azathioprine) are more often used for extracutaneous sarcoidosis, they may have a role in some patients. A treatment algorithm, based upon evidence-based methodology, has been proposed[21]. More recently, sustained responses have been observed with oral JAK inhibitors such as tofacitinib[9].

GRANULOMA ANNULARE

Synonyms: ■ Pseudorheumatoid nodule – subcutaneous granuloma annulare variant ■ Generalized granuloma annulare – disseminated granuloma annulare

Key features

- Small grouped papules assuming an annular configuration, often in a symmetrical and acral distribution
- Seen primarily in children and young adults
- Clinical variants include localized, generalized, and subcutaneous forms
- Possible associations with systemic diseases, including diabetes mellitus, hyperlipidemia, thyroid disease, and rarely HIV infection, remain controversial
- Histologically, there is an infiltrative or palisading granulomatous dermatitis with focal degeneration of collagen and elastin and deposition of mucin

History

Calcott Fox first described "ringed eruption of the fingers" in 1895. Radcliffe-Crocker called this entity granuloma annulare (GA) in 1902. Some authors consider annular elastolytic giant cell granuloma (AEGCG) to be a variant of GA; in 1975, O'Brien first referred to this entity as actinic granuloma and then it was renamed AEGCG by Hanke et al.[26] in 1979. Previous names included atypical (annular) necrobiosis lipoidica of the face and scalp[27], Miescher's granuloma of the face[28], and possibly granuloma multiforme[29]. Although controversy continues regarding the role of actinic damage in AEGCG and whether it is simply a variant of GA[30], in this chapter it will be considered a variant.

Epidemiology

Granuloma annulare typically presents during the first three to five decades of life. Subcutaneous GA occurs more commonly in children, whereas generalized GA is more often observed in older patients. While uncommon it is not a rare disease, representing 0.1%–0.4% of visits to dermatologists in several single-center studies. The female-to-male ratio is over 2 : 1, and GA is diagnosed more frequently in White patients. Compared to GA, AEGCG tends to occur in an older population.

Pathogenesis

The etiology of GA is unknown. Trauma, insect bite reactions, tuberculin skin testing, vaccination, UV exposure, *Borrelia*, and a number of viral infections have all been proposed as inciting factors[31,32]. Based on the T cell subpopulations identified in GA lesions, a delayed-type hypersensitivity reaction to an unknown antigen has been postulated as the precipitating event[33]. Morphologic similarities to other granulomatous processes suggest that GA is caused by a Th1 inflammatory reaction, with elevations in IL-2R-positive lymphocytes, IFN-γ-producing lymphocytes, and TNF production by macrophages[34,35]. These lymphocytes release cytokines, including macrophage inhibitory factor, that cause monocytes to accumulate within the dermis and release lysosomal enzymes that can degrade connective tissue[36]. In addition to inflammatory gene signatures associated with Th1 and innate immunity, when lesional skin was compared to non-lesional skin, there was upregulation of Th2 cytokines (IL-4, IL-31) and the JAK/STAT pathway (see Fig. 128.11)[37]. As with sarcoidosis (see above), this latter pathway is thought to play an important role in granuloma formation. As with other granulomatous disorders, elastophagocytosis may be observed in GA, but this most likely represents a secondary phenomenon.

Familial cases of GA have been reported, including cases in identical twins, and one small study suggested that an association may exist between generalized GA and HLA-Bw35[38]. Vessel-based mixed inflammatory cell infiltrates with endothelial swelling are sometimes detected in routine histopathologic specimens, and direct immunofluorescence studies of GA may show vessel-based deposits of immunoreactants, but a role for these findings in the pathogenesis of this disease has not been established.

Granuloma annulare has also been described in association with various medications including systemic immunomodulators (e.g. TNF

inhibitors, secukinimab, tocilizumab)[39], antiepileptics (levetiracetam, topiramate), amlodipine, thalidomide, allopurinol, and paroxetine[40]; the latter was in a photodistribution. The granulomatous eruptions seen with increasing frequency following administration of immune checkpoint inhibitors include GA as well as sarcoidosis[41].

With regard to AEGCG, its pathogenesis is not well understood but may be related to inflammation precipitated by actinic damage. Specifically, O'Brien postulated that "a state of auto-aggression develops in relation to the damaged [elastic] fibers", in an attempt to repair or remodel damaged skin. Infiltrating T lymphocytes are predominantly of the helper subset, suggesting that the pathogenesis may involve a cell-mediated immunologic response to a weakly antigenic determinant on altered elastotic fibers[30]. However, destruction of elastic tissue has also been observed in classic GA and necrobiosis lipoidica, leading to the argument that this finding may represent a secondary event caused by the granulomatous inflammation rather than a precipitating one, and occasionally, a patient may have both AEGCG and necrobiosis lipoidica or sarcoidosis[26].

Clinical Features

GA is a benign, usually self-limited, cutaneous disease that presents as arciform to annular plaques on the dorsal hands or feet of young people (Fig. 93.9)[32]. However, there is a wide array of clinical presentations, from a papular form to lesions that are subcutaneous, macular (patch form), or have central perforation (Fig. 93.10). Distribution patterns also vary, from localized to occasionally photodistributed or generalized/disseminated (see Fig. 93.10C)[40,42]. In general, the distribution of GA is: 60% isolated to the hands and arms, 20% on the legs and feet, 7% on both upper and lower extremities, 5% on the trunk, and 5% on the trunk plus other areas[43]. Facial lesions are rare. The plaques may be skin-colored, pink, or violaceous in color, and, upon close inspection, are found to be composed of individual small papules measuring a few millimeters in diameter. The lesions are usually asymptomatic.

In *generalized/disseminated* GA, the widespread, symmetrically distributed lesions can be annular plaques or discrete papules and they favor the trunk and/or extremities. This form is uncommon and has a later age of onset, poorer response to therapy, and an increased prevalence of the HLA-Bw35 allele. In one study of 100 patients with generalized GA, 45% had lipid abnormalities, including hypercholesterolemia, hypertriglyceridemia or both, while ~20% had diabetes mellitus[42]. Thyroid disease has been reported in ~25% of patients with GA.

Deep dermal or *subcutaneous* GA manifests as large, painless, skin-colored nodules which may be mistaken for rheumatoid nodules, leading to the term pseudorheumatoid nodule (see Fig. 93.10E). It has a predilection for children <6 years of age. Typical locations include the palms, hands, anterior tibial surfaces and feet, as well as the buttocks, scalp, and rarely the eyelids[32]. As many as 50% of individuals with deep GA lesions also have associated classic lesions.

In *perforating* GA, the small papules have central umbilication, scale-crust or focal ulceration, and they occur primarily on the dorsal hands and fingers (see Fig. 93.10A). This variant occurs in up to 5% of patients with GA, and histologically transepidermal elimination of degenerating collagen is seen[44]. While umbilicated GA has been described, it probably represents a variant of perforating GA.

Patch GA is a distinct, unusual variant that is characterized by patches of erythema on the extremities and trunk. Symmetrical lesions on the dorsum of the feet often present as macular (i.e. "patch") disease. Although an annular configuration may be absent, presence of the classic histopathologic findings of interstitial GA (see below) allow for the diagnosis to be made microscopically.

Patients with *AEGCG* have medium-sized to large annular plaques with a raised erythematous border (3–5 mm) and a slightly atrophic, hypopigmented center, distributed primarily in chronically sun-exposed areas (Fig. 93.11). The sites of predilection include the neck, face, upper trunk, and arms. Early on, skin-colored or pink papules may appear, either singly or in small groups, which then coalesce into annular plaques. Scale is rarely observed. In contrast to necrobiosis lipoidica, there is an absence of yellow color, telangiectasias, or associated alopecia. Individual lesions measure 1–10 cm in diameter, and the total number of lesions is generally fewer than 10. Patients are usually asymptomatic, although pruritus has been reported. A single plaque lasts for months to years, after which spontaneous remission may occur, leaving mottled dyspigmentation or normal-appearing skin. Conjunctival lesions with similar clinical and histologic features have also been described[45].

Rarely, GA has been reported as a possible paraneoplastic granulomatous reaction to solid organ tumors, Hodgkin disease, non-Hodgkin lymphoma, or granulomatous mycosis fungoides[46–49]. In these patients, the clinical pattern is frequently atypical, with painful lesions in unusual locations, including the palms and soles. In a literature review and in a case–control study, a relationship between GA and malignancy was not identified; however, patients with atypical presentations may warrant a complete physical exam with focused, age-appropriate screening[50,51]. While *photodistributed* GA has been reported, some of these patients may have had AEGCG.

Many reports either supporting or refuting the association of GA with diabetes mellitus have been published, but to date there have been no large-scale epidemiologic studies. In a retrospective study of 84 patients, 12% were found to have diabetes mellitus, and these patients were more likely to suffer from chronic relapsing GA than were non-diabetic patients[52]. In a larger retrospective study of 1383 patients, diabetes mellitus was diagnosed in ~20% of patients with generalized GA, compared with ~10% of patients with localized GA[42]. However, in a case–control study of 126 patients, an association was not identified[53].



Fig. 93.9 Granuloma annulare – clinical features. A–D Annular pink to pink–brown plaques. The dorsal aspects of the hands and feet are a common location. Lesions can be skin-colored as well as pink (**C**). Grouped discrete papules may also be seen, with a more subtle annular or arciform configuration (**A,C**). *C, Courtesy Julie V. Schaffer, MD; D, Courtesy Kalman Watsky, MD.*



Fig. 93.10 Granuloma annulare (GA) – less common variants. A Perforating GA: papules characteristically have a central keratotic plug. **B** Micropapular GA: several of the lesions have a central dell. **C** Generalized/disseminated GA: discrete red–brown papules, many of which are in clusters. **D** Papular and nodular GA: the skin-colored nodules may be confused with rheumatoid nodules. **E** Skin-colored nodules of subcutaneous GA. *A, Courtesy Ronald P. Rapini, MD; B, Courtesy Joyce Rico, MD; C, Courtesy Luis Requena, MD; D, Courtesy Kalman Watsky, MD; E, Courtesy Department of Dermatology, Medical University of Graz.*

An increased incidence of thyroid disease, in up to 25% of patients, has been described.

Classic GA and perforating GA may develop within herpes zoster scars (see Table 80.7)[54] and following BCG vaccinations. Atypical variants of GA, including photodistributed, have been associated with HIV infection[55]. Additional reported associations, based upon small studies, include hepatitis, post-vaccination, and post-SARS-CoV-2 infection[40]. Rarely, based upon case reports, AEGCG has been observed in patients with lymphoma or leukemia[56,57].

Pathology

GA is a granulomatous dermatitis characterized by focal degeneration of collagen and elastic fibers, mucin deposition, and a perivascular and interstitial lymphohistiocytic infiltrate in the upper and mid dermis. The key to the histopathologic diagnosis of GA is the presence of mucin plus the identification of histiocytes in one of two patterns. The most common is the interstitial or infiltrative pattern, in which scattered histiocytes are distributed between collagen fibers (Fig. 93.12). Degeneration of collagen fibers is minimal, but granular, basophilic mucin deposition between collagen bundles can be highlighted with Alcian blue and colloidal iron stains[36]. The second pattern is more obvious and is easier to diagnose. It consists of one to several palisading granulomas characterized by central connective tissue degeneration surrounded by a rim ("palisade") of histiocytes and lymphocytes (Fig. 93.13). Mucin is abundant in the center of the palisaded granuloma, and fibrin, neutrophils, and nuclear dust may also be present. Rarely, a prominent ("pseudolymphomatous") lymphoid infiltrate is seen.

Increased mucin can be detected in ~90% of biopsy specimens from GA lesions. The sensitivity of detection is increased by using at least two different mucin stains, such as colloidal iron and Alcian blue. Elastic tissue is reduced or absent within the histiocytic aggregates in ~20% of generalized GA and 35% of localized GA cases[58]. Collagen degeneration is more common in localized GA than in generalized GA[58], and elastophagocytosis is occasionally noted, but not as often as in AEGCG.

As noted previously, vascular changes in GA are variable, but include fibrin, C3, and IgM deposition in vessel walls (detected by direct immunofluorescence) and occlusion of vascular lumina[59]. One study found that the presence of leukocytoclastic or granulomatous vasculitis or a thrombotic vasculopathy within the lesions of GA was predictive of associated systemic disease[60], and the possibility of palisading neutrophilic and granulomatous dermatitis as a reflection of disorders such as rheumatoid arthritis needs to be considered.

Subcutaneous GA is characteristically a septal panniculitis with palisaded granulomatous inflammation and it can closely mimic a rheumatoid nodule histologically. An interstitial pattern is not observed in this form of GA. In *perforating* GA, there is a superficial histiocytic infiltrate with transfollicular and/or transepidermal elimination of granulomatous inflammation and degenerated collagen.

In *AEGCG*, a non-palisading granulomatous infiltrate composed of histiocytes, foreign body-type multinucleated giant cells (with haphazardly arranged nuclei), and lymphocytes is present within the mid to upper dermis; there is an absence of altered collagen or mucin or lipid deposition[61]. Elastic fibers are identified adjacent to and within the giant cells (elastophagocytosis; Fig. 93.14). Elastophagocytosis and asteroid bodies can be seen less frequently in other granulomatous disorders such as GA and necrobiosis lipoidica and therefore they are not specific for AEGCG. Elastic tissue stains, such as Verhoeff–van Gieson, show a characteristic complete absence of elastic fibers in the areas affected (or previously affected) by granulomatous inflammation. There is a sparse perivascular lymphocytic infiltrate, but no vascular changes.

Differential Diagnosis

GA is diagnosed based on its clinical and histopathologic features – there are no laboratory tests which aid in confirming the diagnosis.

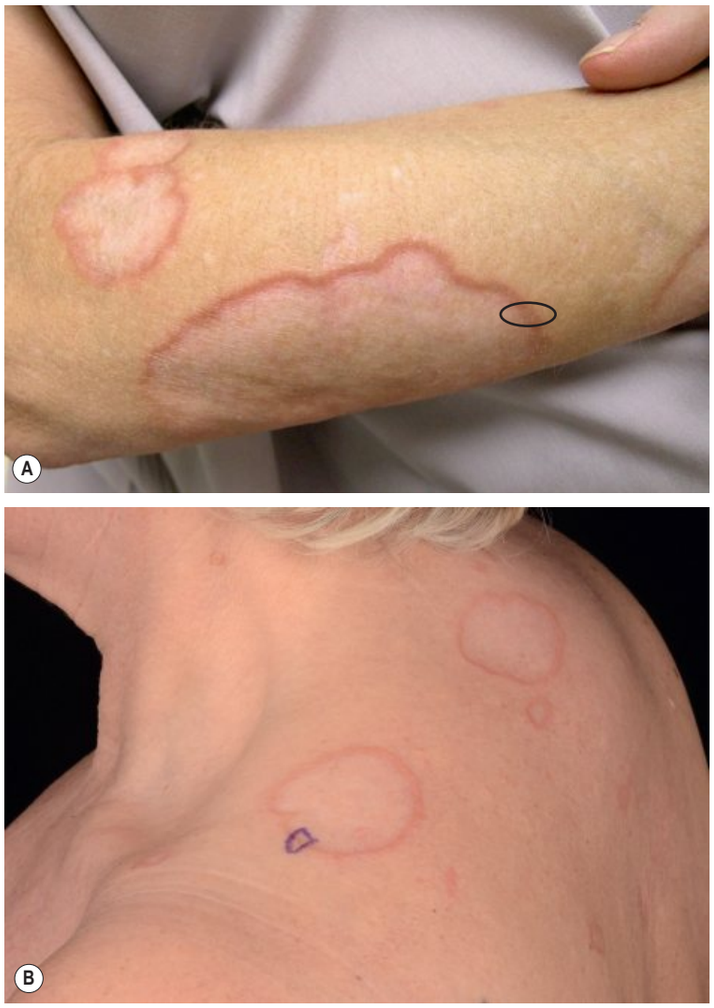


Fig. 93.11 Annular elastolytic giant cell granuloma – clinical features. A, B The inflammatory border resembles granuloma annulare but the central portion is hypopigmented and/or atrophic. A biopsy specimen that includes the areas outlined would contain the three characteristic histologic zones: absence of elastic fibers, granulomatous inflammation, and normal skin. Longitudinal sectioning of the surgical specimen is preferred. *B, Courtesy Department of Dermatology, Medical University of Graz.*

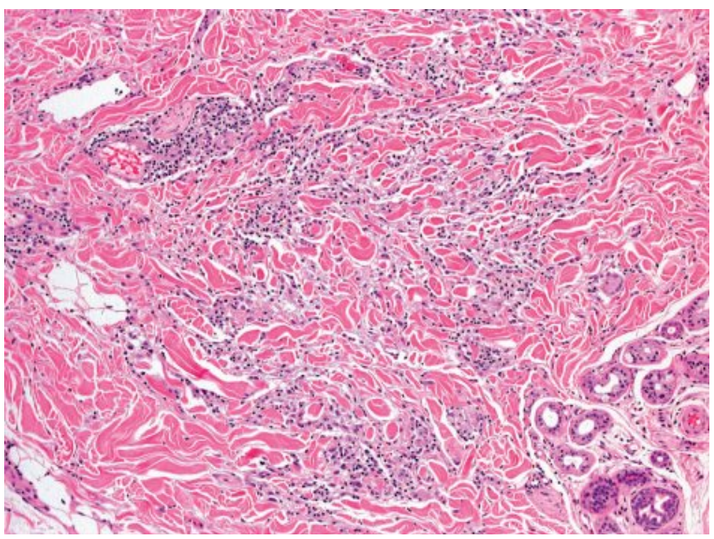


Fig. 93.12 Granuloma annulare – interstitial or infiltrative pattern. Infiltration of histiocytes between the dermal collagen fibers, with scant mucin. *Courtesy Lorenzo Cerroni, MD.*

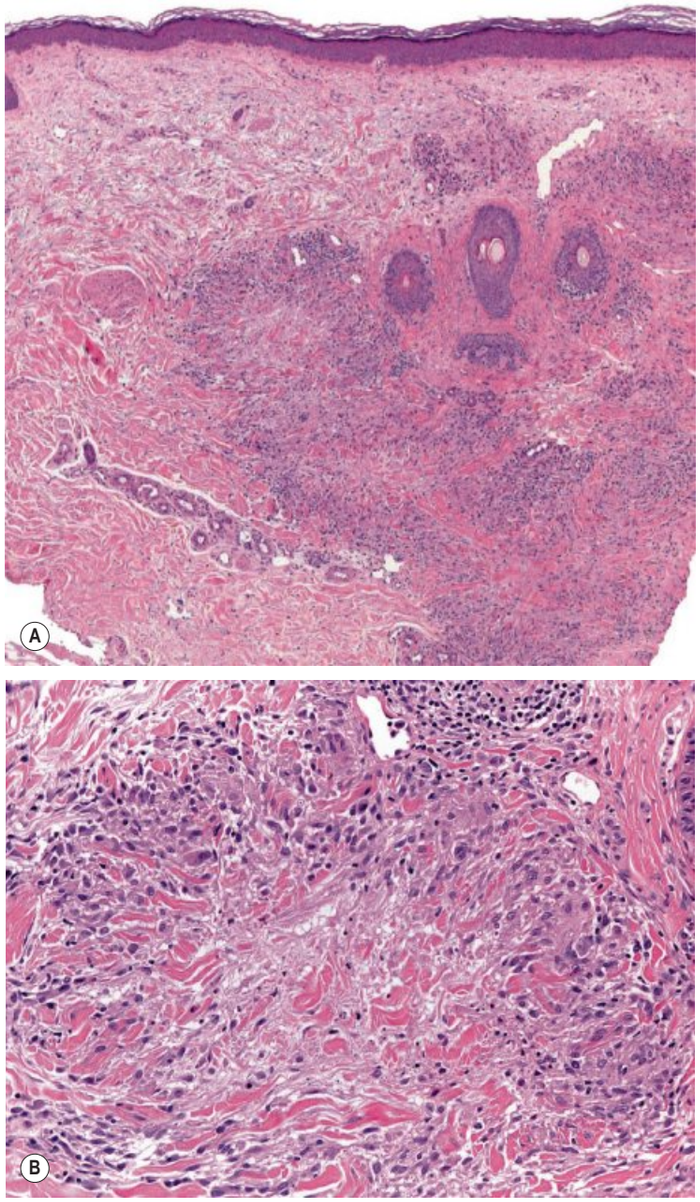


Fig. 93.13 Granuloma annulare – palisading granuloma pattern. A Multiple palisaded granulomas within the dermis. Degenerative collagen and mucin deposition are present in the central portion of the granulomas. **B** A palisaded granuloma with epithelioid histiocytes surrounding an anuclear dermis characterized by altered collagen and pallor due to deposition of acid mucopolysaccharides/glycosaminoglycans (mucin). *Courtesy Lorenzo Cerroni, MD.*

When the diagnosis of deep GA versus rheumatoid nodule is in question, rheumatoid factor and anti-cyclic citrullinated peptide antibody levels can aid in identifying patients at risk for the latter. Rheumatoid nodules also demonstrate fibrin rather than mucin histologically.

The clinical differential diagnosis for conventional GA includes the annular entities listed in Table 19.1, including annular sarcoidosis and AEGCG. A clue to the latter is central hypopigmentation and/or atrophy. Arcuate and annular plaques of mycosis fungoides or borderline leprosy may also simulate GA, requiring biopsy for definitive diagnosis.

Papular GA can simulate flat warts, secondary syphilis, early eruptive xanthomas, and the non-X-histiocytoses (see Ch. 91). *Subcutaneous* GA can be clinically similar to rheumatoid nodules, the nodules of rheumatic fever, tendinous xanthomas, epithelioid sarcoma, subcutaneous sarcoidosis, idiopathic granulomatous mastitis, and deep granulomatous infections. *Perforating* GA must be differentiated from primary perforating disorders (see Ch. 96) and, occasionally, perforating calcinosis cutis, perforating gout, or molluscum contagiosum[32].

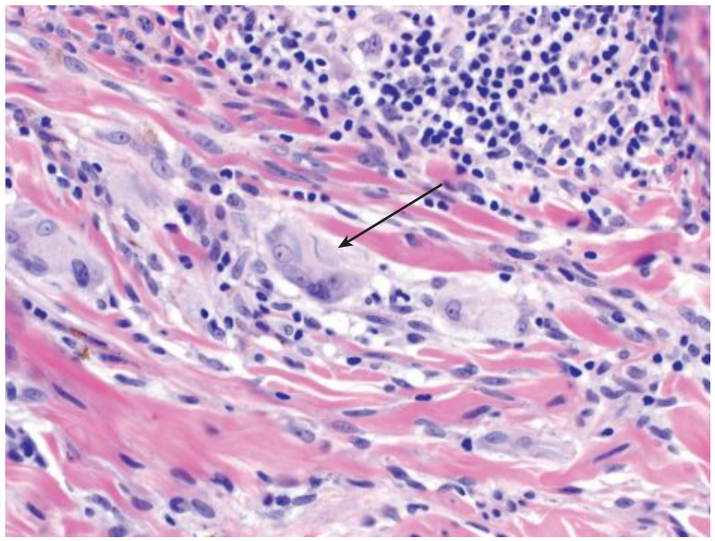


Fig. 93.14 Annular elastolytic giant cell granuloma – histopathological features. A dermal inflammatory infiltrate with several histiocytic giant cells. The presence of a fragmented elastic fiber within a giant cell (elastophagocytosis) is a characteristic finding (arrow).

TREATMENT OF GRANULOMA ANNULARE
Local therapy
Topical corticosteroids (2)
Intralesional corticosteroids (2)
Cryosurgery (2)
Topical calcineurin inhibitors (3)
Topical imiquimod (3)
Topical JAK inhibitors (3)
Phototherapy (NB UVB, PUVA, UVA1) (2)
Photodynamic therapy with topical 5-aminolevulinic acid (2)
Lasers: CO_2, pulsed dye (585 nm), excimer (308 nm) (3)
Electrodesiccation (3)
Surgical excision (3)
Intralesional interferon-γ (3)
Systemic therapy
Hydroxychloroquine or chloroquine (2)
Dapsone (2)
Niacinamide (nicotinamide) (3)
TNF inhibitors (adalimumab, infliximab) (2)
Pentoxifylline (2)
Methotrexate (2)
JAK inhibitors (3)
Retinoids (isotretinoin, acitretin) (3)
Apremilast (3)
Minocycline + ofloxacin + rifampin* (3)
Prednisone (3)
Dupilumab (3)
5-lipoxygenase inhibitor (zileuton) plus vitamin E† (3)
Cyclosporine (3)
Fumaric acid esters (3)
*Administered monthly: minocycline (100 mg), ofloxacin (400 mg) and rifampin (600 mg) × 3 months; improvement not observed in subsequent studies.
†Doses of 2400 mg po daily (zileuton) and 400 IU po daily (vitamin E).

Table 93.6 Treatment of granuloma annulare. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. NB UVB, narrowband ultraviolet B; PUVA, psoralens plus ultraviolet A; UVA, ultraviolet A. From references 40, 42, 63, 64, 66, 69a, 69b, and 69c.

The clinical and histologic differences between GA, sarcoidosis, AEGCG, necrobiosis lipoidica, rheumatoid nodule, and reactive granulomatous dermatitides are outlined in Tables 93.1 and 93.4. The histopathologic differential diagnosis of GA also includes morphea, cutaneous T cell lymphoma, xanthomas, epithelioid sarcoma and, rarely, scleromyxedema. Lastly, the possibility of drug-induced GA needs to be considered.

Treatment

Given the self-limited and benign nature of GA, reassurance and clinical observation may be the treatment of choice for localized, asymptomatic disease. High-potency topical corticosteroids with or without occlusion and intralesional corticosteroid injections are the usual first-line local therapies. Cryosurgery, photodynamic therapy, pulsed dye laser, and topical tacrolimus may also be effective. For more extensive disease, systemic medications can be considered including: (1) anti-inflammatory drugs or immunomodulators (e.g. antimalarials, tetracycline-class antibiotics, pentoxifylline, niacinamide, dapsone, apremilast, retinoids); (2) phototherapy – PUVA, NB-UVB, or UVA1 (especially patch variant[62]); and (3) immunosuppressants (TNF inhibitors, with adalimumab most often reported), while weighing the risk:benefit ratio (Table 93.6)[40,42,63–69]. In patients with photodistributed GA, oral medications such as dapsone are preferred over phototherapy. More recently, topical JAK inhibitors (e.g. compounded tofacitinib 2% ointment) have been used to treat GA as have oral JAK inhibitors.

Spontaneous resolution of GA occurs within 2 years in 50% of patients, but there is a 40% recurrence rate. The recurrent lesions tend to occur at the original sites, but clear more rapidly (80% within 2 years). The duration of untreated lesions has been reported to range from a few weeks to several decades[70].

NECROBIOSIS LIPOIDICA

Synonym: ■ Necrobiosis lipoidica diabeticorum (NLD)

Key features

- Plaques with violaceous to red–brown, palpable peripheral rims and yellow–brown atrophic centers with telangiectasias
- The most common site is the shins
- Ulceration can occur following trauma
- The proportion of patients with diabetes mellitus varies from 15% to 65%, but there is a strong association
- Pathogenesis is unknown
- Pathology shows a palisading granulomatous dermatitis with histiocytes and altered collagen that has a "layered" appearance and is often accompanied by perivascular plasma cells

History

First called "dermatitis atrophicans diabetica" by Oppenheim in 1929, the condition was renamed necrobiosis lipoidica diabeticorum by Urbach in 1932. The first non-diabetic patient with this condition was described in 1935 by Goldsmith, generating the more general term necrobiosis lipoidica (NL), which is currently the preferred term.

Epidemiology

NL typically occurs in young to middle-aged adults, with a female:male ratio that ranges from 3:1 to 8:1, depending on the study[71–73]. Diabetic patients present at a younger age than those without diabetes, e.g. in a multicenter study, the mean ages were 45 years and 52 years, respectively[71]. In a study of 171 patients with NL, diabetes mellitus, usually type 1, was present in ~65%; an additional 12%–15% had abnormal

glucose tolerance tests[72]. Also, over half of the patients with no evidence of diabetes and a normal glucose tolerance test reported a positive family history of glucose intolerance[72,73]. However, a more recent retrospective study of 65 patients with NL seen in a dermatology outpatient clinic found that only 11% had type 1 or type 2 diabetes mellitus at the time of presentation. An additional 11% were later diagnosed with impaired glucose tolerance or diabetes[74].

Only 0.3% of patients with diabetes develop NL. However, there is no proven connection between a patient's level of glycemic control and the likelihood of developing NL lesions. Diabetic patients with NL may or may not have a higher rate of diabetes-related complications such as peripheral neuropathy, retinopathy, and limited joint mobility, again depending upon the study[75]. In retrospective reviews, thyroid dysfunction was noted in 15%–25% of patients with NL[71,76].

Pathogenesis

The cause of NL remains unknown. Immunologically mediated vascular disease has been suggested as the primary cause of the altered collagen seen in NL. This hypothesis is supported by the presence of immunoreactants deposited in vessel walls of lesional and uninvolved skin in patients with NL[77]. Previous immunofluorescence studies had also found evidence for immune complex vasculitis in NL[78]. In addition, it has been postulated that the microangiopathic vessel changes seen in diabetic patients could contribute to the development of collagen degeneration and subsequent dermal inflammation. A shared pathogenesis would provide an explanation for the high rate of complications such as retinopathy observed in some series of patients with NL.

When lesions favor the lower extremities of adults, venous hypertension as a contributing factor needs to be considered. Both venous insufficiency and hyperlipidemia have been proposed as triggers that incite an inflammatory cascade in some patients[79]. Elevated plasma levels of fibronectin, factor VIII-related antigen, and α_2-macroglobulin have been detected in patients with NL, but the significance of these findings has not been determined[80]. Theories regarding abnormally elevated platelet adhesion, increased thromboxane A_2 production, and increased blood viscosity within NL lesions remain speculative.

Some investigators consider NL to be primarily a disease of collagen, with inflammation occurring as a secondary event. Anti-collagen antibodies have been detected in patients with both NL and GA, but no significant increase in antibody levels as compared with control patients has been demonstrated[81]. The concentration of collagen is decreased in NL lesions, and electron microscopy reveals a loss of the cross-striations of collagen fibrils and significant variation in the diameter of individual fibrils. Fibroblasts cultured from NL lesions synthesize less collagen than their counterparts from unaffected skin[82]. Although there are fewer collagen fibers overall, areas of fibrosis are seen. Overhydration of collagen due to hyperglycemia can lead to increased collagen cross-linking and stiffness, but it is unclear if this phenomenon occurs in NL.

From central Europe, there was a report of the detection of *Borrelia* spp. via focal floating microscopy in NL[83], but these findings need to be confirmed.

Clinical Features

Necrobiosis lipoidica is characterized by yellow–brown, atrophic, telangiectatic plaques with an elevated violaceous rim, most often in the pretibial region (Fig. 93.15). The plaques are usually multiple and bilateral. Lesions start as small, firm, red–brown papules that gradually enlarge and then develop central epidermal atrophy. Ulceration has been reported in 15%–35% of patients (see Fig. 105.20D), usually following minor trauma. Development of lesions secondary to Koebner phenomenon has also been reported[84]. Less typical anatomic locations for NL include the upper extremities, face, and scalp, where the lesions may be more annular or serpiginous in configuration and are often less atrophic. As a result, they may resemble AEGCG clinically.

Decreased sensation to pinprick and fine touch, hypohidrosis, and partial alopecia can be observed within NL plaques. Decreased S100 staining within the cutaneous nerves of inflammatory plaques has been described, with degenerative neural changes possibly accounting for the loss of sensation[75]. Of note, the cutaneous nerves in GA demonstrate normal S100 staining patterns. Although the lesions of NL are typically asymptomatic, some patients report pruritus, dysesthesia, or pain. Lesions that ulcerate after trauma or from transepidermal elimination of altered collagen and elastic fibers can be very painful. Rarely, squamous cell carcinoma has been reported to develop within lesions of NL[85]. By dermoscopy, comma-shaped vessels and an irregular pattern of arborizing vessels are observed in early and more advanced lesions, respectively; whitish areas correspond to degenerated collagen and yellow to orange patches to granulomatous inflammation[86,87].

There are reports of patients with NL who also had GA or sarcoidosis[88–90]. Possible versus random associations include systemic sclerosis, rheumatoid arthritis, and previous jejunoileal bypass surgery. The association of NL with diabetes mellitus and thyroid dysfunction are discussed in the Epidemiology section[91–93].

Pathology

In the palpable inflammatory border, a diffuse palisaded and interstitial granulomatous dermatitis that involves the entire dermis and extends into the subcutaneous fat septae is usually seen (Fig. 93.16). "Layered" tiers of granulomatous inflammation are composed of histiocytes surrounding horizontal tiers of degenerated collagen. The histiocytes are often multinucleated and the collagen fibers have irregular sizes and shapes. In areas of sclerosis, focal loss of elastic tissue may be seen. Extracellular lipid deposition can be demonstrated via adipophilin staining of routinely processed tissue sections or via oil red O staining of frozen tissue sections (latter rarely done nowadays). There is an associated superficial and deep perivascular infiltrate that is predominantly lymphocytic but often contains plasma cells and occasionally eosinophils. The epidermis is normal or atrophic.

In contrast to GA, there is no significant mucin deposition within the center of the palisading granulomas. Although early lesions of both NL and GA may have foci of leukocytoclasia, NL shows more prominent endothelial cell swelling, fibrosis, and hyalinization; the latter can lead to blood vessel wall thickening or even endarteritis obliterans. The vessel walls often contain a PAS-positive, diastase-resistant material suggesting neutral glycosaminoglycans[80].

Occasionally, NL lesions have less sclerotic collagen and more typical epithelioid cell granulomas rather than the horizontally tiered pattern of altered collagen and palisaded granulomatous inflammation described above. Vascular changes are rare, and this form of NL is felt to have a weaker association with diabetes mellitus than the classic lesions[80].

Differential Diagnosis

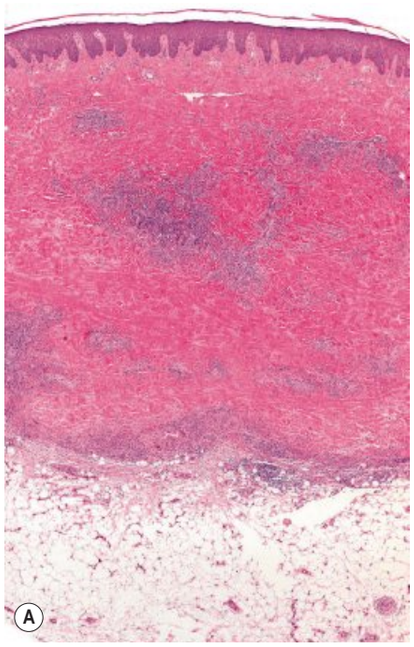
Clinically, the differential diagnosis of NL includes primarily GA, necrobiotic xanthogranuloma (NXG; see Ch. 91), sarcoidosis, diabetic dermopathy (see Ch. 53), and lipodermatosclerosis. Other entities in the differential diagnosis include additional forms of panniculitis (see Ch. 100), granulomatous infections (e.g. leprosy, dimorphic fungal infections, tertiary syphilis), morphea, lichen sclerosus, and sclerosing lipogranuloma.

Lesions of GA and sarcoidosis generally do not exhibit the same degree of atrophy, telangiectasias, or yellow–brown color as NL lesions, although prominent telangiectasias can be present in angiolupoid sarcoidosis and can occur following injections of triamcinolone. Ulcerated NL may be difficult to distinguish from ulcerative sarcoidosis or NXG[94].

Histopathologically, NL most commonly has to be distinguished from GA (see Table 93.4). NXG is also in the differential diagnosis, but there are abundant cholesterol clefts and larger zones of degenerated collagen. However, one case report did describe NL with prominent cholesterol clefts and transepithelial elimination of cholesterol crystals via hair follicles[95].



Fig. 93.15 Necrobiosis lipoidica – range of clinical features. A Annular and arciform pink–brown plaques on the shins with central atrophy. **B** Pink plaques on the shin with telangiectasias and peripheral hyperpigmentation; centrally there is atrophy. **C** Single yellow plaque with prominent telangiectasias and a dull pink rim. **D** Pink–yellow plaques with a brown rim on the shins; centrally there is atrophy, focal scarring, and telangiectasias. *B, Courtesy Jeffrey Cohen, MD; C, Courtesy Aisha Sethi, MD.*



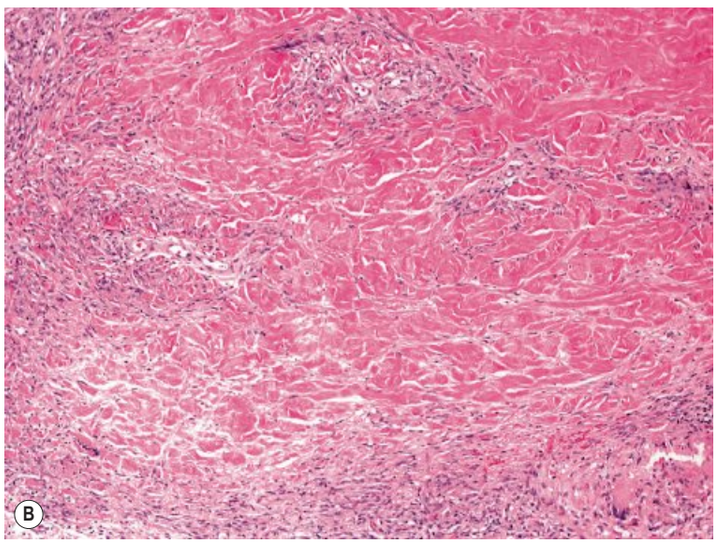


Fig. 93.16 Necrobiosis lipoidica – histopathologic features. A Multiple granulomas within the entire dermis extending into the subcutaneous fat. Note the layered tiers of granulomatous inflammation aligned parallel to the skin surface. **B** Palisaded granuloma composed of epithelioid histiocytes with altered collagen centrally. *Courtesy Lorenzo Cerroni, MD.*

Treatment

No treatment for NL has proven to be effective in large, double-blind, placebo-controlled studies. In patients with diabetes mellitus, control of blood glucose levels may not have a significant effect on the course of NL. Spontaneous remission after an average of 8 to 12 years was observed in only 17% of 171 patients with NLD in one study[72].

First-line therapy consists of potent topical corticosteroids (including under occlusion) for early lesions and intralesional corticosteroids injected into the active borders of established lesions. Because the histologic changes can extend well into normal-appearing skin in clinically active NL lesions[75], some authors advocate the injection of intradermal corticosteroids into a rim of clinically normal skin around expanding plaques in an effort to halt disease progression. Careful monitoring for steroid-induced atrophy is important. Topical tacrolimus 0.1% ointment led to improvement of NL in uncontrolled case series[96–98]. Topical GM-CSF or bovine collagen[99] has been applied to ulcerations and tretinoin gel (0.025% BID) has been used to decrease lesional atrophy[100].

In addition to avoidance of trauma and local care of ulcers (see Ch. 145), therapies directed at increasing fibrinolysis, decreasing platelet aggregation, and/or decreasing thromboxane A_2 synthesis have been employed in order to decrease the microangiopathy and vascular thrombosis. Pentoxifylline, stanozolol, inositol niacinate (inositol nicotinate), nicofuranose, and ticlopidine hydrochloride are all agents that have been tried in anecdotal reports or uncontrolled case series. The use of stanozolol is limited by its potential hepatotoxicity and ticlopidine can cause agranulocytosis. Controlled trials of aspirin versus placebo or aspirin plus dipyridamole versus placebo showed no significant differences compared to placebo[101,102]. Perilesional injections of heparin have been reported in the Russian literature[103].

Based upon case series of patients, several systemic anti-inflammatory medications have been described as beneficial – antimalarials[104], niacinamide[80], mycophenolate mofetil[105], doxycycline, colchicine, methotrexate, thalidomide[106], TNF inhibitors, IL-12/23 inhibitors[107], and cyclosporine (severe ulcerations)[108,109]. As with sarcoidosis and GA, JAK inhibitors have emerged as a promising therapeutic option for selected patients[110]. In addition, 5-week courses of systemic corticosteroids were found to be effective in a series of six patients with an average follow-up period of 7 months, but this can be associated with side effects such as elevation of serum glucose levels[111].

Multiple prospective, uncontrolled studies have demonstrated improvement in ~50% of patients with topical PUVA therapy[112,113]. Lastly, there are case reports of beneficial effects from UVA1 phototherapy[114], pulse-dyed laser, fractional CO_2 laser, or photodynamic therapy.

Surgical therapy may be necessary in patients with severe, refractory ulcerations. Excision to deep fascia or periosteum must be performed to minimize the chance of recurrence. Split-thickness skin grafting is performed following excision.

CUTANEOUS CROHN DISEASE

Variants: ■ Contiguous Crohn disease ■ Distant/non-contiguous ("metastatic") Crohn disease

Key features

- Erythematous plaques, lymphedema, and knife-like ulcerations most commonly occur in the anogenital region
- Cutaneous non-caseating granulomatous lesions that are not contiguous with intestinal Crohn disease have been referred to as "metastatic"
- Approximately 20% of patients with cutaneous lesions have no preceding diagnosis of gastrointestinal Crohn disease

History

Crohn disease, first described in 1932, is characterized by segmental granulomatous inflammation of the intestinal tract and frequently involves cutaneous tissues as well. In 1965, cutaneous involvement was first described.

Epidemiology

Crohn disease usually begins between the second and fourth decades of life. Mucocutaneous findings occur in 20%–45% of patients (see Table 53.8)[115]. They can be subdivided into: (1) specific lesions including distant/non-contiguous cutaneous ("metastatic") Crohn disease, contiguous perianal Crohn disease, and oral Crohn disease; (2) nonspecific or reactive dermatologic disorders, e.g. erythema nodosum, Sweet syndrome, pyoderma gangrenosum; (3) nutritional skin changes secondary to malabsorption; and (4) treatment-related side effects[116–120].

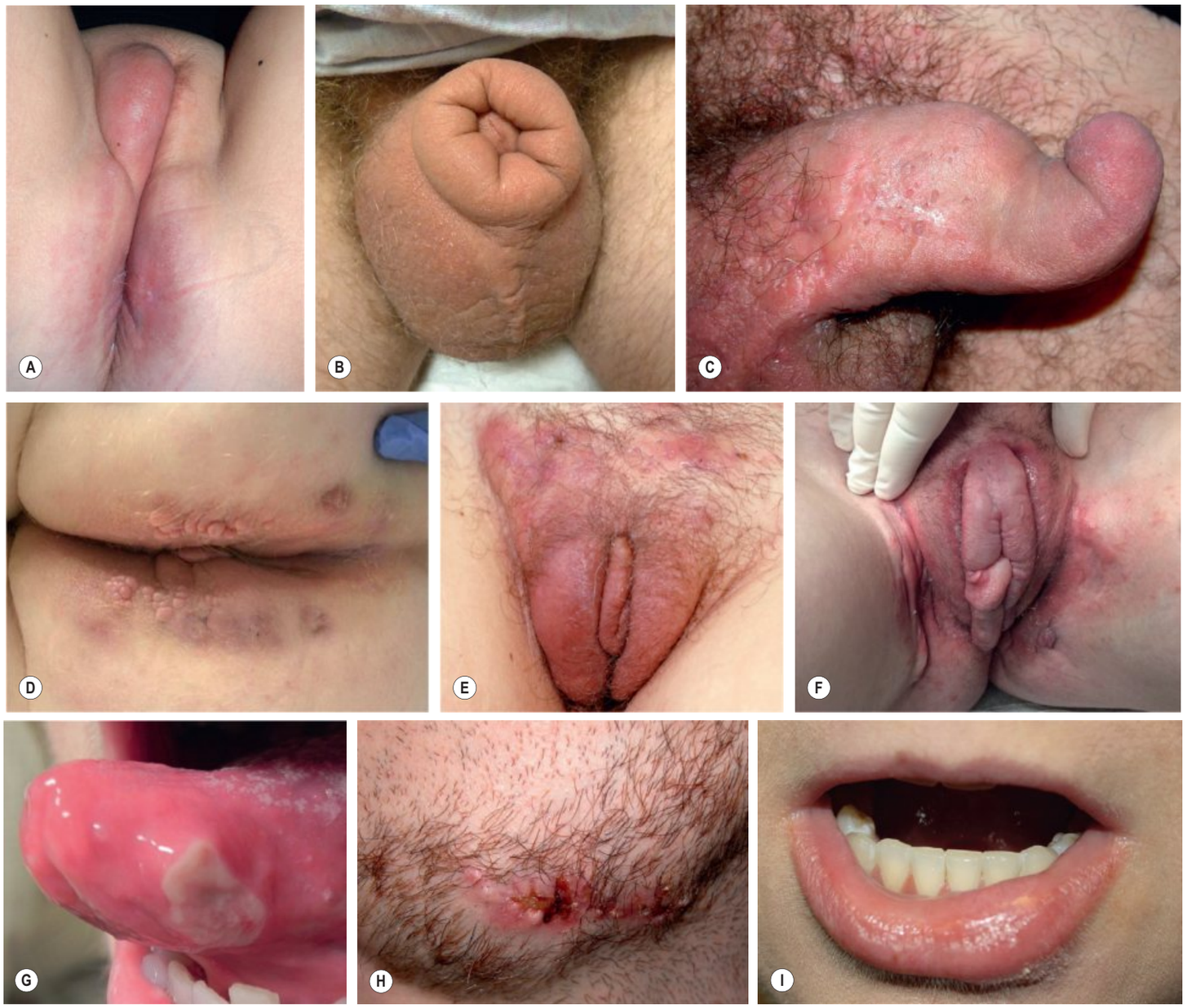


Fig. 93.17 Mucocutaneous Crohn disease. A Vulvar and perianal erythema and induration. Note the marked asymmetric vulvar swelling and perianal erosions. **B** Marked lymphedema of the prepuce with lymphedema and induration of the scrotum. **C** Inflammation and lymphedema leading to twisting of the penis along its long axis, referred to as a "saxophone penis". **D** Perianal tags and indurated plaques. **E** Firm erythematous plaques of the mons pubis and labia majora and minora. There are also draining sinuses. **F** Symmetric erythematous plaques, lymphedema, and a "skin tag"; note the marked swelling of the labia minora. **G** Intraoral ulcer that resembles a major aphthous ulcer. **H** Ulcerated erythematous plaque of the mandible with draining sinuses. **I** Asymmetric enlargement of the lower vermilion lip due to granulomatous inflammation. *A, Courtesy Julie V. Schaffer, MD; C, E, H, Courtesy Luis Requena, MD; D, Courtesy Mary Stone, MD; F, I, Courtesy Jeffrey P. Callen, MD, and Courtney R. Schadt, MD.*

Cutaneous Crohn disease is relatively rare with <300 cases reported in the literature to date and <100 cases in children. Two-thirds of the patients are women, and the mean age of onset is 35 years. Approximately 20% of the reported cases had skin disease that preceded the diagnosis of intestinal Crohn disease by 3 months to 8 years.

Pathogenesis

Cutaneous Crohn disease occurs in association with or precedes intestinal Crohn disease, reflecting a multisystem disease. A number of genetic abnormalities which can lead to an exaggerated T cell response to certain commensal enteric bacteria and defective microbial clearance, including after breaks in the mucosal barrier or an alteration in the balance in gut flora (dysbiosis), have been linked to Crohn disease. The protein products of these genes have several functions, including regulation of NF-κB function (e.g. *NOD2* [*CARD15*]) and autophagy (*ATG16L1*, *IRGM*). Patients with variants in *TRAF3IP2*, a psoriasis susceptibility gene, may have a greater risk of cutaneous involvement[121]. Like psoriasis, Crohn disease is a predominantly Th1- and Th17-mediated disease, with elevated levels of IL-23 and IL-17 within involved tissues[122].

Clinical Features

Cutaneous Crohn disease may be either genital or extragenital, with genital involvement found in approximately two-thirds of children and one-half of adults. Labial, penile, or scrotal erythema and/or lymphedema are common presenting signs and can be dramatic[123] (Fig. 93.17A–C,F). Linear or "knife-like" ulcerations that are within body folds (e.g. inguinal creases, perianal region, axillae) or involve the oral mucosa are relatively specific for mucocutaneous Crohn disease (see Figs. 53.28 and 72.25)[121].

Perianal involvement, which may extend to the adjacent perineum, buttocks or abdomen, consists of sinus tracts, fissures, ulcers, and vegetating plaques (Fig. 93.17D,E)[124]. These findings occur in approximately one-third of patients with intestinal Crohn disease. Perianal skin tags, thought to be secondary to lymphedema, are observed in up to 40% of patients; as with other sites of lymphedema, granulomatous inflammation may be present as well. Sites of abdominal surgery, e.g. laparotomies, colostomies, ileostomies, may also develop granulomatous inflammation. For semantic purposes, the latter is considered to be "contiguous" rather than non-contiguous ("metastatic") Crohn disease.

Oral lesions occur in 5%–20% of patients with Crohn disease, and these may consist of cobblestoning of the buccal mucosa, tiny gingival nodules, gingival hyperplasia, aphthae-like ulcers (Fig. 93.17G), linear, knife-like ulcerations, pyostomatitis vegetans (see Fig. 25.9A), angular cheilitis and ulceration, secondary orofacial granulomatosis (Fig. 93.17I), diffuse oral swelling, or indurated fissuring of the lower lip. Histologically, 90% of oral lesions associated with Crohn disease contain granulomas[124].

Non-genital disease presents with dusky erythematous plaques, often followed by the development of ulceration with undermined edges, draining sinuses and fistulas, and scarring (Fig. 93.17H). These lesions have been observed on the lower extremities and soles (40%), abdomen and trunk (25%), upper extremities and palms (15%), face and lips (10%), flexural areas (8%), and in a generalized distribution (4%)[116,125]. Other reactive cutaneous manifestations of Crohn disease include cutaneous arteritis (cutaneous polyarteritis nodosa), erythema nodosum, erythema multiforme, finger clubbing, cutaneous small vessel vasculitis, epidermolysis bullosa acquisita, vitiligo, palmar erythema, a pustular response to trauma (pathergy), Sweet syndrome, and pyoderma gangrenosum (see Ch. 53). Zinc deficiency may cause an acrodermatitis enteropathica-like syndrome in patients with severe Crohn disease[116].

Based upon a large retrospective series, cutaneous involvement may be indicative of colonic, rather than ileal, involvement[117,118]. No consistent correlation exists between mucocutaneous disease activity and degree of gastrointestinal involvement. However, levels of fecal calprotectin can reflect the degree of intestinal inflammation.

Pathology

In both cutaneous and oral lesions of Crohn disease, small, nodular, non-caseating, epithelioid granulomas with surrounding lymphocytes are found in the superficial and deep dermis, sometimes extending into the subcutaneous fat. There are a few scattered multinucleated Langhans-type giant cells and a sparse perivascular lymphohistiocytic infiltrate; overlying ulceration may be present. Of note, the combination of lichenoid and granulomatous inflammation plus granulomatous perivasculitis can serve as a histopathologic clue[126]. The walls of perianal sinuses and fistulas have similar granulomatous inflammation. However, the granulomatous foci may be subtle, requiring multiple sections to identify the granulomas, and clinicopathologic correlation as well as additional biopsies may be required.

Differential Diagnosis

Clinically, the differential diagnosis of cutaneous Crohn disease includes other granulomatous disorders such as cutaneous sarcoidosis, mycobacterial infections, deep fungal infections, and foreign body reactions. Other infections, such as actinomycosis or cellulitis, may mimic cutaneous Crohn disease. Ulcerated lesions may be misdiagnosed as pyoderma gangrenosum. In the case of genital swelling and ulcerations, one must consider granuloma inguinale, schistosomiasis, hidradenitis suppurativa, and chronic lymphedema due to obstruction[125].

The histopathologic picture of cutaneous Crohn disease can be indistinguishable from other granulomatous diseases with tuberculoid features, including lupus vulgaris. In the latter, central necrosis within tubercles is a helpful distinguishing clue. Differentiating cutaneous Crohn disease from sarcoidosis can also be challenging, although Crohn disease usually has denser collections of lymphocytes and granulomatous perivasculitis as well as the features described above. Foreign body granulomas and infectious granulomas should be considered in the histologic differential diagnosis. Special stains for acid-fast bacilli and fungal organisms should be obtained, and all skin biopsies should be polarized to look for foreign bodies. Pyoderma gangrenosum and cutaneous Crohn disease can sometimes have overlapping clinical and histopathologic features as neutrophilic inflammation may be present in both, but granulomas are absent in pyoderma gangrenosum.

Treatment

Cutaneous Crohn disease tends to be chronic, and its severity does not always correlate with the activity of the patient's intestinal disease. For localized disease, topical or intralesional corticosteroids and/or topical calcineurin inhibitors may be utilized[127]. Oral metronidazole (250 mg TID for at least 4 months) can be an effective treatment. For more extensive disease, use of systemic medications including corticosteroids, sulfasalazine, azathioprine, 6-mercaptopurine, and thalidomide may lead to improvement. By targeting the underlying immunopathogenesis, TNF inhibitors (e.g. infliximab, adalimumab)[128] and ustekinumab have been reported to improve cutaneous disease. IL-17 inhibitors have been reported to exacerbate Crohn disease. Surgical excision of lesions is often complicated by wound dehiscence and disease recurrence, but can be considered for refractory disease.

FOREIGN BODY GRANULOMAS (SEE CH. 94)

Key features

- The most common cause of a foreign body granuloma is rupture of a follicle or cyst
- Inflammation may be suppurative, granulomatous, or more commonly mixed suppurative and granulomatous
- Clues to the inciting foreign body should be sought by polarizing the specimen as well as by searching for cornified cells, tattoo pigment, suture remnants, splinter material, etc.

OROFACIAL GRANULOMATOSIS (OFG; SEE CH. 72)

Key features

- Persistent non-tender swelling of the lip and/or face
- Histologically, non-caseating granulomatous inflammation; biopsy of mucosal (inner) lip preferred
- Both primary (idiopathic) and secondary subtypes
- Primary OFG includes cheilitis granulomatosa and Melkersson–Rosenthal syndrome while secondary OFG includes sarcoidosis, foreign body reactions, and Crohn disease

REACTIVE GRANULOMATOUS DERMATITIS – INCLUDES INTERSTITIAL GRANULOMATOUS DERMATITIS, PALISADED NEUTROPHILIC AND GRANULOMATOUS DERMATITIS, AND INTERSTITIAL GRANULOMATOUS DRUG REACTION

Synonyms: ■ Interstitial granulomatous dermatitis (IGD) with arthritis – IGD with plaques and arthritis, IGD with plaques, IGD with cutaneous cords and arthritis ■ Palisaded neutrophilic and granulomatous dermatitis (PNGD) – rheumatoid papules, Churg–Strauss granuloma, cutaneous extravascular necrotizing granuloma, superficial ulcerating rheumatoid necrobiosis ■ Entire spectrum – reactive granulomatous dermatitis, reactive interstitial granulomatous dermatitis

Key features

- The overlap of interstitial granulomatous dermatitis with both palisaded neutrophilic granulomatous dermatitis and interstitial granulomatous drug reaction has led to the concept of *reactive granulomatous dermatitis* as a unifying term
- Clinical findings vary from erythematous crusted papules on extensor surfaces or linear cords to annular plaques and large thin plaques that resemble granuloma annulare
- Underlying disorders include autoimmune connective tissue diseases (rheumatoid arthritis, seronegative inflammatory arthritis, systemic lupus erythematous [SLE]), granulomatosis with polyangiitis, and occasionally a myelodysplastic syndrome or malignancy
- Histologically, there are palisaded or interstitial histiocytes with tiny foci of degenerated collagen, scant mucin deposits, and variable amounts of neutrophils and eosinophils; small foci of vasculitis also may be present

Introduction

Palisaded neutrophilic and granulomatous dermatitis (PNGD) and interstitial granulomatous dermatitis (IGD) with arthritis represent two patterns of granulomatous dermatitis that occur in patients with RA and other autoimmune disorders. Since these entities exhibit overlapping clinicopathologic features and may represent a disease spectrum, the overarching term *reactive granulomatous dermatitis* has been proposed[129].

History

In 1994, Chu and colleagues[130] proposed the term "palisaded neutrophilic and granulomatous dermatitis" for the histologic reaction pattern that characterizes papular eruptions on the extensor extremities that present in the context of autoimmune connective tissue disease and other conditions characterized by immune complex generation. Such skin lesions were originally described in the setting of eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), and their association with a broad spectrum of autoimmune and inflammatory disorders was first recognized by Winkelmann in 1978 (cutaneous extravascular necrotizing granuloma). Some authors include "interstitial granulomatous dermatitis with arthritis", a term coined by Ackerman in 1993, within the PNGD spectrum. Others argue that the former represents a separate entity with distinct clinical (annular plaques and cords favoring the lateral trunk and skin folds) and histologic (histiocytic rosettes without evidence of vasculitis) features. More recently, the term *reactive granulomatous dermatitis* was introduced as an overarching term[129,131].

Pathogenesis

It is thought that the initiating insult in reactive granulomatous dermatitis is immune complex deposition on or around the walls of small dermal blood vessels as a result of the underlying disease, which leads to a subacute or chronic neutrophil-rich small vessel vasculitis. This then impairs blood flow to the area in a smoldering fashion, as opposed to the abrupt vascular occlusion of classic vasculitis; consequently, there is degeneration of the local collagen rather than acute necrosis. The degenerated collagen incites an immune response resulting in a palisading lymphohistiocytic infiltrate. This cascade of events is likely aggravated or precipitated by exogenous trauma, which explains the predilection of lesions for the extensor surfaces. Variable sizes, amounts, and sites of immune complex deposition (e.g. dermal venules versus the interstitial dermis), chronicity of the process, and different triggers and underlying systemic inflammatory disorders may account for the spectrum of clinical and histologic features.

Clinical Features

In classic descriptions of PNGD, skin-colored to erythematous papules develop symmetrically on extensor surfaces, particularly the elbows and



Fig. 93.18 Reactive granulomatous dermatitis, encompassing IGD and PNDG – clinical features. A Multiple violet–brown plaques, some of which are annular, on the lower extremities of a young woman with mixed connective tissue disease. **B** Firm, linear subcutaneous cord along the axillary line (arrows) in a patient with rheumatoid arthritis. **C** Violaceous plaques on the back in a patient with Hodgkin lymphoma. *A, Courtesy Lorenzo Cerroni, MD; B, Courtesy Kathryn Schwarzenberger, MD; C, Courtesy Department of Dermatology, Medical University of Graz.*

INTERSTITIAL GRANULOMATOUS DRUG REACTION – ASSOCIATED MEDICATIONS AND SUPPLEMENTS	
Common	
• **Calcium channel blockers**: diltiazem, verapamil, nifedipine • **Angiotensin-converting enzyme inhibitors**: enalapril, lisinopril • β-blockers: labetalol, metoprolol, atenolol, propranolol • Furosemide • **HMG-CoA reductase inhibitors**: simvastatin, pravastatin, lovastatin • Antihistamines (H1 or H2 blockers): famotidine, cimetidine, ranitidine, brompheniramine • **TNF inhibitors**: infliximab, etanercept, adalimumab; lenalidomide, thalidomide • Anakinra	
Uncommon	
• Allopurinol • Bosutinib • Bupropion • Carbamazepine • Chinese herbal medications • Darifenacin • Diazepam • Hydrochlorothiazide (HCTZ) • Febuxostat	• Ganciclovir • Gemfibrozil • Methotrexate • Nivolumab • Sennoside • Sorafenib • Soy • Strontium ranelate • Topiramate • Trastuzumab

Table 93.7 Interstitial granulomatous drug reaction – associated medications and supplements. It is also referred to drug-induced interstitial granulomatous dermatitis and can fall within the spectrum of reactive granulomatous dermatitis. Most common classes of drugs are in bold. HMG, β-hydroxy-β-methylglutaryl; TNF, tissue necrosis factor.

fingers. Central umbilication with crusts or perforation (with extrusion of necrobiotic collagen) may be present (see Fig. 53.2), and ulceration occasionally occurs. Such papular lesions have been observed most commonly in patients with SLE, rheumatoid arthritis, or systemic vasculitis, particularly granulomatosis with polyangiitis.

IGD with arthritis has been described as erythematous plaques, often with an annular configuration (Fig. 93.18A), or linear cords (the "rope sign"; Fig. 93.18B) that favor the lateral trunk, axillae, and girdle area (see Fig. 53.1). Extensive areas of involvement can be seen (Fig. 93.18C). This presentation has been described most often in women with rheumatoid arthritis, seronegative arthritis, or polyarthralgias and it may be associated with autoimmune thyroiditis. However, in a large retrospective series, the rope sign was noted in only two patients with autoimmune disease-associated IGD[131].

When viewed as a disease spectrum, the skin findings in reactive granulomatous dermatitis consisted of plaques, often annular, as well as macules, papules, or nodules located primarily on the extremities and trunk[131]. Associated conditions were observed in 75% of patients, irrespective of whether they were classified histologically as having IGD versus PNGD; the majority of these underlying disorders were autoimmune diseases (54%), followed by malignancies (12%). In addition to myelodysplasia, PNGD can develop in patients with chronic myelomonocytic leukemia, including those with *SRSF2* mutations.

Reactive granulomatous dermatitis also encompasses interstitial granulomatous drug reactions. The most likely culprits are calcium channel blockers and HMG-CoA reductase inhibitors ("statins"; Table 93.7), but the list of incriminated medications continues to expand. Cutaneous lesions typically appear after months to years of exposure to the drug. Of note, in patients with rheumatoid arthritis and psoriatic arthritis, TNF inhibitors have led to the development of IGD- and PNGD-like lesions[132].

Pathology

In that PNGD and IGD have overlapping clinical features, it follows that the histopathologic features of PNGD and IGD also constitute a spectrum, with features depending on the stage of evolution of the lesion that is biopsied. One series demonstrated overlapping histopathologic findings in 25% of cases, lending support for use of the overarching term reactive granulomatous dermatitis[131].

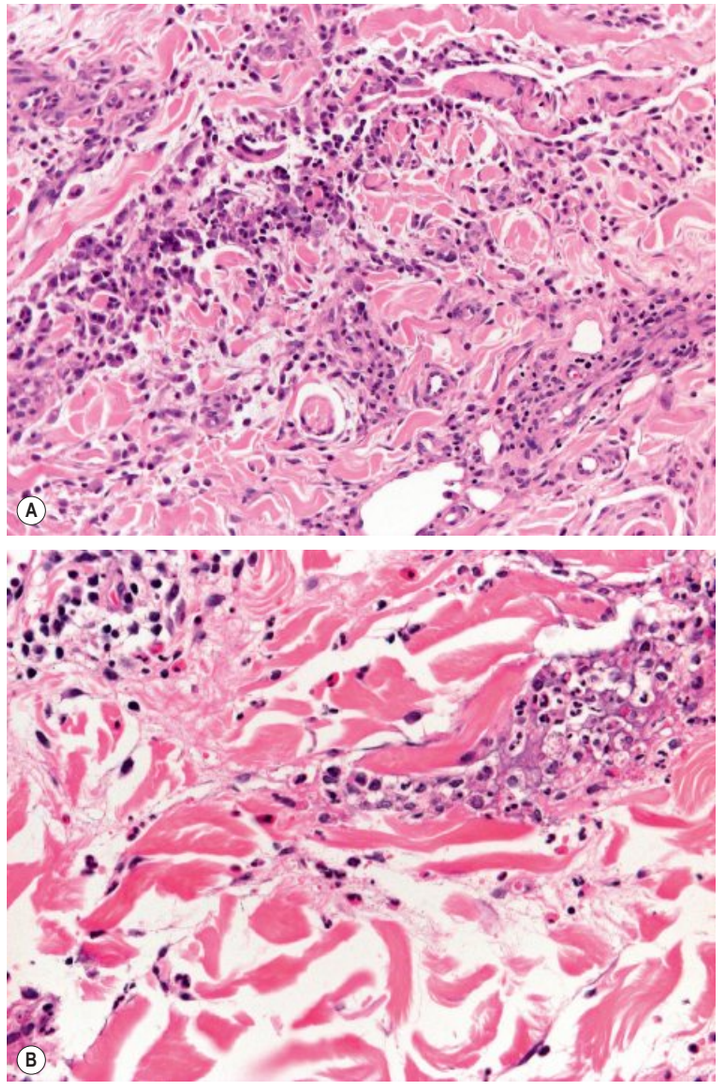


Fig. 93.19 Reactive granulomatous dermatitis, encompassing IGD and PNDG – histopathologic features. A Fully developed lesions usually demonstrate neutrophils and histiocytes in association with basophilic degenerating collagen bundles; some eosinophils may be present as well. **B** Details of histiocytes admixed with lymphocytes, neutrophils and eosinophils. *Courtesy Lorenzo Cerroni, MD.*

Early lesions of PNGD often show a pandermal infiltrate of neutrophils, sometimes with focal leukocytoclastic vasculitis. Classic, fully developed lesions are characterized by zones of basophilic degenerated collagen surrounded by palisades of histiocytes, neutrophils, and nuclear debris (Fig. 93.19). "Incomplete" early lesions may display focal basophilic collagen necrosis and histiocytes without orderly palisading in association with prominent neutrophils. On the other hand, late lesions can exhibit well-developed palisading granulomas with only a sparse complement of neutrophils. Mucin is rare to absent.

The histologic pattern of IGD features smaller "rosettes" of palisading histiocytes surrounding tiny, discrete foci of degenerated collagen (piecemeal fragmentation) within a dense, "bottom-heavy" dermal interstitial infiltrate that contains variable numbers of neutrophils and sometimes eosinophils. There is no evidence of vasculitis, and dermal mucin is usually absent.

In interstitial granulomatous drug eruptions, histopathologic features overlap with both PNGD and IGD, but there may be more tissue eosinophilia, lymphocyte atypia, and interface vacuolar changes.

Differential Diagnosis

The clinical differential diagnosis is broad. For classic PNGD lesions, it includes perforating disorders, early rheumatoid nodules, accelerated

SPECTRUM OF GRANULOMATOUS, NEUTROPHILIC, AND VASCULITIC DERMATOSES IN PATIENTS WITH RHEUMATOLOGIC DISORDERS		
Prevalent vasculitic changes	**Prevalent histiocytic infiltrates**	**Prevalent neutrophilic infiltrates**
Erythema elevatum diutinum	Interstitial granulomatous dermatitis	Palisaded neutrophilic and granulomatous dermatitis
Rheumatoid or other AI-CTD-associated vasculitis	Rheumatoid nodule	Sweet syndrome*
ANCA-associated vasculitis		Rheumatoid neutrophilic dermatitis
*Histiocytoid cells, rather than neutrophils, may be the prevalent population in some cases of Sweet syndrome (histiocytoid Sweet syndrome).		

Table 93.8 Spectrum of granulomatous, neutrophilic, and vasculitic dermatoses in patients with rheumatologic disorders. AI-CTD, autoimmune connective tissue disease; ANCA, anti-neutrophil cytoplasmic antibodies.

rheumatoid nodulosis, and papular granuloma annulare (GA). The clinical presentation of IGD with plaques may resemble patch-type GA, the inflammatory stage of morphea, erythema migrans, or mycosis fungoides.

The histologic differential diagnosis includes other palisaded granulomatous dermatitides such as GA, necrobiosis lipoidica, and rheumatoid nodules. GA is more likely to have a patchy infiltrate concentrated in the upper dermis ("top heavy") and mucin deposition. A paucity of neutrophils and leukocytoclasis distinguishes GA from PNGD, whereas the presence of either larger palisades or a lack of palisades (e.g. in the interstitial pattern seen in patch-type GA) differentiates GA from IGD. Rheumatoid nodules can be recognized by their central eosinophilia (rather than basophilia) and predominantly subcutaneous location (see Fig. 45.10). All of these entities may show transepidermal elimination of degenerated collagen. Additional diagnostic considerations for an interstitial granulomatous infiltrate with variable neutrophils may include dimorphic fungal or atypical mycobacterial infections, borreliosis, and leprosy. Histologic features that favor an interstitial granulomatous drug reaction over IGD include a vacuolar interface dermatitis, atypical lymphocytes, prominent eosinophils, a paucity of neutrophils, and minimal collagen degeneration.

The relationship of PNGD and IGD with other dermatoses that have granulomatous, neutrophilic, or vasculitic components and affect this patient population are shown in Table 93.8. Lastly, neonates with primary immunodeficiencies can develop perforating neutrophilic and granulomatous dermatitis associated with immunodeficiency in which papules develop into vesicles, pustules, crusts, and ulcers; histologically there is evidence of transepidermal elimination via hair follicles.

Treatment

Treatment of the underlying disorder or removal of the inciting medication can lead to resolution of existing lesions and prevent recurrences. For recalcitrant skin disease, improvement has been reported with the use of high-potency topical or intralesional corticosteroids, dapsone, hydroxychloroquine, and nonsteroidal immunosuppressants, guided by any underlying etiology.

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Additional figures available in our eBook (see inside front cover for access code).

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eFig. 93.1 A, B Lesions of sarcoidosis often favor the nose, including the nasal rim. *A, Courtesy Louis A. Fragola, Jr, MD.*



eFig. 93.2 Linear lesions of sarcoidosis on the neck.



eFig. 93.3 Cutaneous sarcoidosis. Large pink plaque of the forehead with a few peripheral papules. *Courtesy Jeffrey P. Callen, MD.*



eFig. 93.4 Papules of cutaneous sarcoidosis arising within a tattoo. The differential diagnosis includes foreign body reaction.



eFig. 93.5 Annular lesions of sarcoidosis, some of which are hypopigmented. *Courtesy Kalman Watsky, MD.*



eFig. 93.6 Lupus pernio. Violaceous plaques and nodules with scaling, most prominent on the distal nose and cheeks.



eFig. 93.8 Immune checkpoint inhibitor-induced cutaneous sarcoidosis. *Courtesy Department of Dermatology, Medical University of Graz.*



eFig. 93.7 Angiolupoid sarcoidosis. Note the prominent telangiectasias on the nose and cheeks and the annular plaque on the lower left cheek. *Courtesy Irwin Braverman, MD.*



eFig. 93.9 Granuloma annulare. Larger lesion on the arm with a figurate border composed of coalescing papules. Note the red–brown color of previously involved skin.

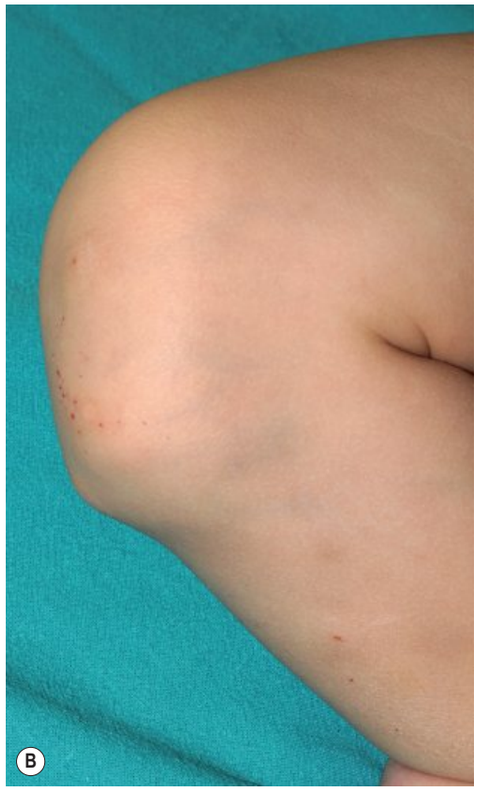


eFig. 93.10 Granuloma annulare. Dull pink plaques with elevated rims composed of coalescing papules. *Courtesy Julie V. Schaffer, MD.*



eFig. 93.11 Granuloma annulare. Several annular and figurate plaques. The patient had type 2 diabetes mellitus and the differential diagnosis would include annular elastolytic giant cell granuloma. *Courtesy Kalman Watsky, MD.*





eFig. 93.12 Variants of granuloma annulare (GA). A Patch type with large subtle annular lesion in a child. **B** Subcutaneous GA presenting as skin-colored nodules; this form favors young children. *Courtesy Dr A. Hernández-Martín.*



eFig. 93.13 Granuloma annulare. Multiple arciform plaques on the back composed of pink papules with confluence inferiorly, leading to the appearance of a skip area of normal skin. *Courtesy Kalman Watsky, MD.*



eFig. 93.14 Granuloma annulare. Multiple arciform and figurate plaques composed of dull pink papules. *Courtesy Kalman Watsky, MD.*



eFig. 93.15 Generalized/disseminated granuloma annulare. Multiple annular pink plaques. *Courtesy Kalman Watsky, MD.*



eFig. 93.16 Generalized/disseminated granuloma annulare. Numerous papules and small annular plaques.



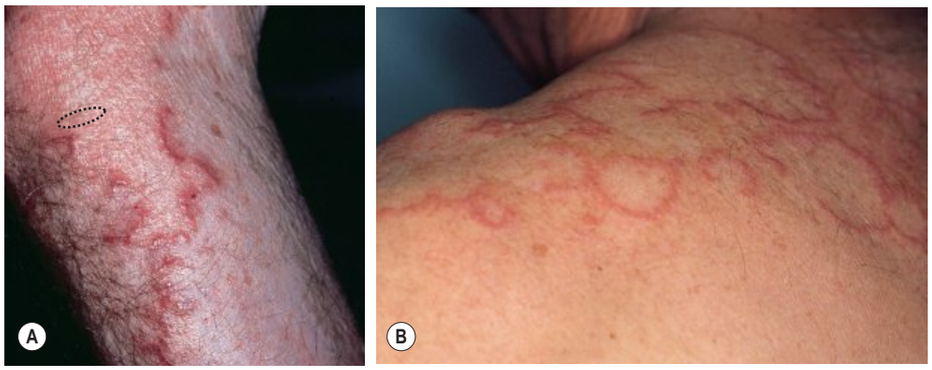
eFig. 93.17 Generalized/disseminated granuloma annulare. Numerous small annular plaques on the trunk of a child. *Courtesy Antonio Torrelo, MD.*



eFig. 93.18 Generalized/disseminated granuloma annulare. Numerous discrete pink papules with midline confluence. *Courtesy Luis Requena, MD.*



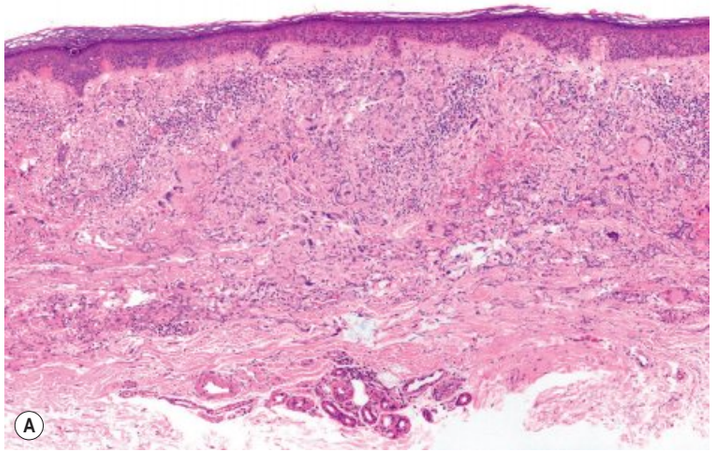
eFig. 93.19 Generalized/disseminated granuloma annulare. A Numerous discrete red–brown papules on the back with a large area of confluence centrally. The papules on the arms are a dull pink color. **B**, **C** Discrete red to red–brown papules on the legs, many of which are in clusters. *Courtesy Luis Requena, MD.*

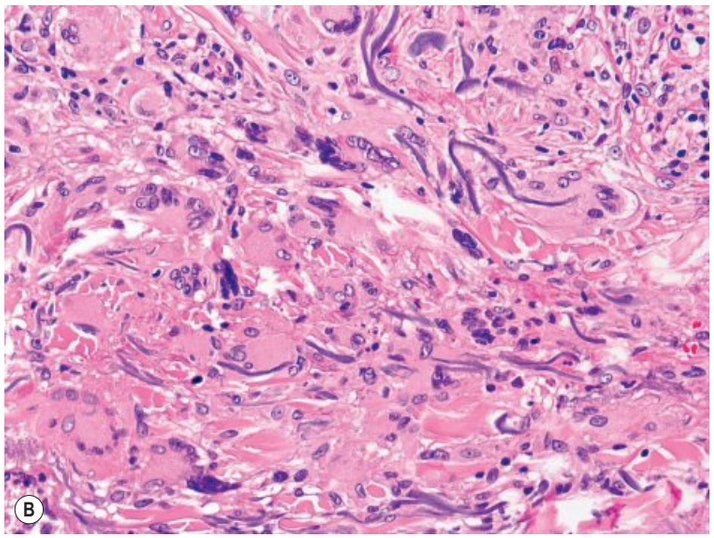


eFig. 93.20 Annular elastolytic giant cell granuloma – clinical appearance. A, **B** The inflammatory border resembles granuloma annulare but the central portion is hypopigmented and/or atrophic. A biopsy specimen that includes the outlined area would contain the three characteristic histologic zones: absence of elastic fibers, granulomatous inflammation, and normal skin. Longitudinal sectioning of the surgical specimen is preferred. *B, Courtesy Kalman Watsky, MD.*

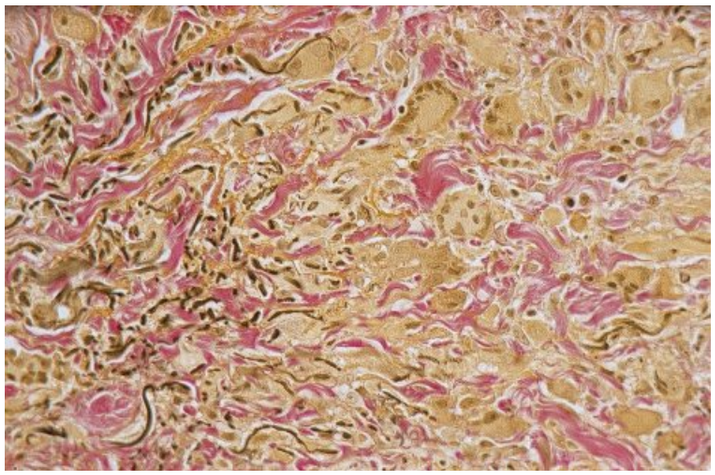


eFig. 93.21 Annular elastolytic giant cell granuloma - clinical appearance. Multiple annular plaques on the trunk. Some authors view this as a variant of granuloma annulare. *Courtesy Luis Requena, MD.*





eFig. 93.22 Annular elastolytic giant cell granuloma – histopathologic features. **A** There is a dermal inflammatory infiltrate with several histiocytic giant cells. **B** Fragmented elastic fibers, some within giant cells (elastophagocytosis), are a characteristic finding. *Courtesy Luis Requena, MD.*



eFig. 93.23 Annular elastolytic giant cell granuloma – histopathologic features. Loss of elastic fibers (black) is seen amid the granulomatous infiltrate (yellow). The remaining collagen is stained red (Verhoeff–van Gieson stain). *Courtesy Ronald P. Rapini, MD.*



eFig. 93.24 Annular elastolytic giant cell granuloma – histopathologic features. Loss of elastic fibers (black) is seen amid the granulomatous infiltrate (yellow). The remaining collagen is stained red (Verhoeff–van Gieson stain). *Courtesy Ronald P. Rapini, MD.*



eFig. 93.25 Necrobiosis lipoidica. Pink–brown plaque on the shin with central atrophy and subtle yellow color.



eFig. 93.26 Necrobiosis lipoidica. Annular pink–brown plaques with central telangiectasias and pale yellow color.



eFig. 93.28 Mucocutaneous Crohn disease. Swelling of the penis. *Courtesy Sonya K. Burton, MD.*



eFig. 93.27 Mucocutaneous Crohn disease. Note the swelling and violaceous discoloration of the labia majora in this prepubescent girl. *Courtesy Joseph L. Jorizzo, MD.*



eFig. 93.29 Large pink patches and thin plaques that can resemble patch-type granuloma annulare. *Courtesy Department of Dermatology, Medical University of Graz.*

Foreign Body Reactions 94

M. Abdel Rahim Abdallah, Mahmoud M.A. Abdallah and Marwa Abdallah

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Foreign Body Reactions to Inorganic and Metallic Compounds. 1683
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Key features

- Foreign body reactions represent inflammatory responses to inorganic and high-molecular-weight organic materials that have been introduced into the skin and are variably resistant to degradation
- Routes of introduction can vary from accidental or self-inflicted to surgical and cosmetic procedures to topical application of various compounds
- The most common clinical presentation is red to red–brown papules, nodules, or plaques (with or without ulceration) that are due to granulomatous inflammation
- Less common clinical presentations include lichenoid and pseudolymphomatous lesions, or the development of a fistula or draining wound
- Histopathologic findings vary from granulomas (foreign body, sarcoidal, palisading) to lichenoid, eczematous, or pseudolymphomatous patterns
- Diagnosis of foreign body reactions requires a high index of suspicion, thorough history, recognition of distinctive distribution patterns, and histologic examination (including polarized microscopy)

GENERAL CONSIDERATIONS

Definition

Literally, any material – living or non-living – introduced into the body is a "foreign body" and is treated by our immune system as "non-self" in order to elicit an appropriate response. Such a broad definition also includes infectious agents, but they are covered elsewhere (see Chs. 74–85). This chapter will focus on non-living materials that have been introduced into the dermis or subcutis[1–3]. They represent inorganic compounds or organic material of high molecular weight (or their products) that resist degradation by the body's inflammatory cells. Although granulomatous reaction patterns are most commonly observed, there is a broad range of clinicopathologic presentations. Foreign bodies reported to elicit skin reactions are listed in Table 94.1.

Routes of Entry

Accidental

Inoculation with foreign bodies may occur unintentionally during various activities such as gardening (wood splinters, cactus spines) or swimming and diving (coelenterate envenomation, sea urchin spines), or it may result accidentally, such as in a blast injury (silica particles) or motor vehicle accident.

Surgical procedures

Contamination of wounds by talc or starch powders used for lubrication of surgical gloves may incite a foreign body reaction. Surgical sutures also cause a foreign body response and this is routinely seen in surgical re-excisions (see Fig. 151.19). In addition, foreign body reactions have been observed in association with 2-octyl cyanoacrylate, a tissue adhesive used for small superficial wounds and lacerations, as well as a copolymer-containing lubricating agent used for liposuction[4].

Iatrogenic

Foreign material implanted into the skin for the purpose of tissue augmentation, e.g. injectable soft tissue fillers, can induce reactions in some individuals (Fig. 94.1). Paraffin is still being used illegally for tissue augmentation (see below), and a paraffin foreign body reaction can also occur after the application of paraffin-containing materials such as nasal packs[5].

Tattooing

Tattooing is the introduction of an exogenous pigment into the dermis, either deliberately or accidentally, resulting in permanent discoloration of the skin.

Topical application

When applied to the skin surface, antiperspirant and antipruritic preparations that contain zirconium oxide or zirconium lactate were noted to cause foreign body reactions. As a result, zirconium lactate was generally banned in 1978 (see below). These zirconium compounds have subsequently been replaced by aluminum–zirconium complexes and while the latter are less sensitizing, they may occasionally lead to foreign body reactions[6].

Self-inflicted

Self-administered intravenous and subcutaneous injections, a common practice among individuals with substance use disorder, may lead to the introduction of foreign material into the skin. An example is the injection of crushed talc-containing tablets.

Pathogenesis

The initial tissue response to most foreign substances involves an accumulation of neutrophils, which usually fail to properly deal with the foreign body. Its persistence attracts monocytes and local tissue macrophages that engulf the foreign material and become activated. Engulfed material may resist degradation and remain sequestered within the macrophages. Activated macrophages secrete a variety of specific biologically active substances, e.g. cytokines and chemokines, that attract additional macrophages and blood monocytes. The formation of a chronic granuloma represents an attempt by the body to sequester a persistent indigestible material. Individual macrophages may become larger (epithelioid histiocytes) or fuse to form multinucleated foreign body giant cells (Fig. 94.2)[7]. The infiltrate also contains T lymphocytes and fibroblasts. The pathogenesis of other patterns of reactions, e.g. lichenoid, pyogenic granuloma-like, pseudolymphomatous, remains speculative.

Clinical Features

The host response and, consequently, the clinical presentations of foreign body implantation are variable (Table 94.2 & 94.3). An acute inflammatory response occurs shortly after the entry of the foreign material. This may resolve, to be followed weeks, months, or even years later by a chronic inflammatory response. Although the latter may have a variety of clinical presentations, red to red–brown papules, nodules, and plaques (with or without ulceration) are most commonly observed. Over time, the lesions may become firmer due to fibrosis. The pattern

CLASSIFICATION OF FOREIGN BODIES ACCORDING TO THEIR ORIGINS AND ROUTES OF ENTRY		
Origin		**Route of entry**
Non-biologic (inorganic/metallic compounds)		
	Tattoo inks	Decoration Cosmetic Accidental Iatrogenic
	Ferrous subsulfate (Monsel's solution)	Hemostasis (iatrogenic)
	Paraffin	Tissue augmentation Iatrogenic
	Silicone (polydimethyl siloxane) liquid or gel	Tissue augmentation
	Silica	Wound contamination Blast injuries
	Talc	Surgical procedures Wound contamination Umbilical stump contamination Intravenous injection of self-prepared drugs
	Zirconium	Topical application: antiperspirants
	Beryllium	*Local cutaneous:* Laceration by broken fluorescent lamps (historical) *Systemic:* Penetration of intact skin by fine particles (<1 micron) Inhalation
	Aluminum	Subcutaneous injection of aluminum-containing vaccines
	Zinc	Subcutaneous injection of insulin–zinc preparations
	Other synthetic fillers, e.g. poly-L-lactic acid, calcium hydroxylapatite, polymethylmethacrylate	Tissue augmentation
Biologic		
Produced in the skin but normally isolated from body's immune surveillance	Hair keratin (see Ch. 38)	Ruptured follicle or cyst* Ingrown hair Pilonidal sinus Interdigital pilonidal sinus (hairdressers, barbers, dog groomers)
	Nail keratin	Ingrown nail
Produced by other living organisms	Starch	Surgical procedures, plasma expander
	Cactus spines	Accidental Occupational
	Jellyfish and corals	Accidental Swimming or diving
	Sea urchin spines (see Ch. 85)	Accidental Swimming or diving
	Silk sutures	Surgical procedures
	Hyaluronic acid	Tissue augmentation
	Bovine collagen†	Tissue augmentation
Miscellaneous	Corticosteroids	Intralesional injection
	Sutures, primarily absorbable (rarely nylon or polypropylene)	Surgical procedures
	Polyamide synthetic "hair" fibers	Scalp "hair" restoration
	2-octyl cyanoacrylate	Tissue adhesive for small, superficial wounds and lacerations
	Hydrophilic polymer and potassium ferrate (WoundSeal® powder)	Hemostasis
	Vitamin C serum	Via microneedling for rejuvenation

*Most common cause of a foreign body reaction in the skin.
†The only commercially available filler in the US that contains collagen also contains polymethylmethacrylate (PMMA) microspheres (Bellafill®).

Table 94.1 Classification of foreign bodies according to their origins and routes of entry.

and arrangement of the cutaneous lesions will correspond to the route of inoculation, and observation of this patterning, in association with a relevant patient history, is crucial.

In addition to nodules and plaques, other forms of foreign body reaction include pyogenic granuloma-like lesions[8], lichenoid lesions[9,10], and a chronic draining fistula or wound[11,12].

Pathology

Apart from the acute reaction to the trauma that accompanies the introduction of the foreign body, a chronic reaction is the usual response. Although different patterns of chronic local tissue reactions have been described, including lichenoid[9], eczematous, and pseudolymphomatous[13], the most common is the granulomatous type of reaction[7,14]



Fig. 94.1 Foreign body reaction at site of bovine collagen injection. Formation of granulomas at bovine collagen injection sites occurs in ~1% of patients who have had two negative skin tests.

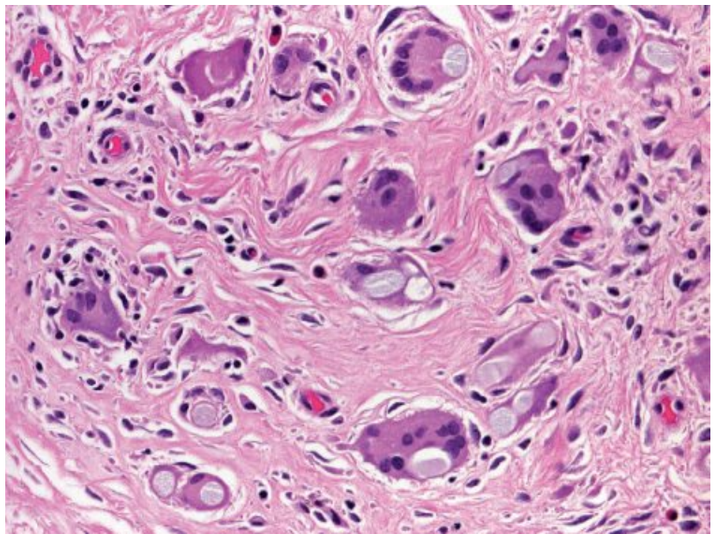


Fig. 94.2 Foreign body reaction to sutures. The foreign bodies have been engulfed primarily by foreign body-type giant cells; one Langhans-type giant cell is present at 12 o'clock. *Courtesy Lorenzo Cerroni, MD.*

(see Table 94.3). Granulomas that develop as a reaction to foreign bodies are of two major types:

- allergic (immunologic)
- non-allergic ("foreign body").

The allergic type is characterized by the presence of collections of individual epithelioid histiocytes associated with variable numbers of lymphocytes and fewer multinucleated Langhans-type giant cells[7]. In the non-immunologic type, the foreign body giant cell is the most conspicuous component of the infiltrate (see Fig. 94.2), which also contains histiocytes, lymphocytes, and other inflammatory cells[14].

A histologic decision as to whether a granuloma is of the foreign body type or of the allergic type is not always possible and different patterns may be seen in the same section. The foreign material inciting a reaction may be detected in conventional H&E-stained sections or may require special procedures for its identification (see Table 94.3).

Diagnosis

Foreign body reactions should be considered in the differential diagnosis of localized inflammatory nodules and plaques, especially when there is a persistent draining wound or sinus. Occasionally, these reactions present as pyogenic granulomas or localized lichenoid papules. Clinical morphology is usually not distinctive, but there may be a suggestive distribution pattern, and a thorough history is indispensable for arriving at the correct diagnosis.

Histopathologic examination can confirm the granulomatous nature of a lesion and occasionally foreign bodies may show distinctive microscopic features in H&E-stained sections (Fig. 94.3)[14]. Because some foreign bodies are better visualized via polarized microscopy, this is routinely performed (Fig. 94.4). In addition to detecting radiolucent foreign bodies, high frequency ultrasound has been employed to assess the severity and depth of inflammatory reactions to tattoos and soft tissue fillers[14]. CT, MRI, and PET-CT have also been used to evaluate foreign body reactions but can have limitations with regard to detection of small cutaneous foreign bodies.

Identification of the chemical nature of the foreign body requires sophisticated physicochemical procedures (e.g. energy-dispersive X-ray analysis, laser-induced breakdown spectroscopy) that are available in only a few research centers[15].

To summarize, accurate identification of a foreign body reaction depends on a high index of suspicion, thorough history-taking, and histologic examination, including polarized microscopy.

CLINICAL PRESENTATIONS OF FOREIGN BODY REACTIONS

Clinical presentation	Foreign substance
Erythema, induration, papules, nodules, plaques (with or without ulceration)	Tattoo inks, paraffin, silicone*, silica*, beryllium (local), starch, soft tissue fillers (e.g. hyaluronic acid)
Sarcoidosis-like granulomatous papules	Tattoo inks, talc, zirconium, beryllium (systemic), soft tissue fillers (e.g. hyaluronic acid, bovine collagen)
Pyogenic granuloma-like lesions	Talc, keratin (ingrown nail)
Pseudofolliculitis barbae, "ingrown" hairs of the pubic region and upper thighs	Keratin
Pruritic lichenoid papules and plaques (often in an irregular linear pattern)	Tattoo inks, jellyfish and coral stings
Abscess	Keratin (e.g. pilonidal sinus), zinc, paraffin, soft tissue fillers
Sinus tract/fistula	Suture, keratin (pilonidal sinus, interdigital pilonidal sinus [barbers, hairdressers])
Persistent subcutaneous nodules at injection site	Aluminum, soft tissue fillers (see Table 94.5)
Pseudolymphomatous reaction	Aluminum, tattoo inks
Photoallergic eczematous reaction	Tattoo ink containing cadmium sulfide (yellow), cadmium selenide (red), or azo dyes (yellow, red)

*Often a delayed onset (years).

Table 94.2 Clinical presentations of foreign body reactions.

FOREIGN BODY REACTIONS TO INORGANIC AND METALLIC COMPOUNDS

Tattoo

A tattoo may occur accidentally or deliberately for cosmetic and decorative purposes. Accidental tattooing results from unintentional deposition of exogenous pigmented substances such as asphalt, carbon, or graphite (pencils) within injured skin (Fig. 94.5). Automobile, bicycle, and skating accidents as well as puncture wounds are the most common causes of traumatic tattoos. In decorative tattooing, the pigment is introduced into the dermis via needles or a tattoo gun to create various designs, group-identity symbols, or writings. Cosmetic tattoos are also done to define the contours of lips and eyebrows, permanently replace eyeliner, make eyebrows appear fuller (via microblading), or camouflage an abnormality in skin color. An iatrogenic tattoo may remain after the use of ferrous subsulfate (Monsel's solution) for hemostasis. Other hemostatic agents, e.g. aluminum chloride, may cause a foreign body reaction histologically (see below), but do not lead to discoloration of the skin.

Decorative tattoos often contain a number of pigments that are combined to create different hues, but the composition of tattoo inks has not been standardized. The pigments may be inorganic salts of metals, such as mercury in cinnabar (red, becoming historical), cobalt

CLINICAL AND HISTOPATHOLOGIC FEATURES OF FOREIGN BODY REACTIONS				
Foreign body	**Clinical presentations**	**Histologic reaction patterns**	**Other distinctive features**	**Birefringent**
Tattoo inks	Erythema, induration, papules, nodules	Foreign body or (with certain dyes) sarcoidal granulomas‡ Pseudolymphoma	Pigment granules scattered throughout the infiltrate, extra- and intracellular (macrophages)	
	Lichenoid papules and plaques	Lichenoid dermatitis		
	Eczematous dermatitis (includes allergic* and photoallergic reactions†)‡	Spongiotic dermatitis		
	Verrucous papules and plaques	Pseudoepitheliomatous hyperplasia		
Silica	Nodules, indurated plaques within scar Disseminated papules (blast injuries) Prolonged incubation period	Granulomas (sarcoidal > foreign body)	Colorless crystals, extra- and intracellular	√
Talc	Sarcoid-like papules Thickening and erythema of an old scar Involvement of intertriginous zones, iv injection sites Umbilical stumps	Sarcoidal or foreign body granulomas	Needle-shaped or round talc crystals: clear, blue–green, or yellow–brown	√
	Pyogenic granuloma-like	Pyogenic granuloma-like		
Zirconium	Persistent, soft, brownish papules Involvement of axillary vault	Sarcoidal granulomas		
Beryllium, local cutaneous reaction	Nodule, ulcer (historical)	Caseating granulomas		
Beryllium, systemic	Widely scattered papules (<1% of cases)	Sarcoidal granulomas		
Aluminum	Persistent subcutaneous nodules at injection site	Granulomas with peripheral lymphocytes and eosinophils Pseudolymphoma	Basophilic granular material within the cytoplasm of histiocytes	
Zinc	Furuncles at injection sites	Early: dense neutrophilic infiltrate Late: granulomas and fibrosis	Rhomboidal crystals	√
Starch	Papules, nodules	Foreign body granulomas	Ovoid basophilic starch granules PAS-positive	√ ("Maltese cross"-like appearance)
Cactus spines	Dome-shaped, skin-colored papules with a central black dot	Early: neutrophils Late: sarcoidal or foreign body granulomas	Spines, extra- and intracellular (giant cells) PAS-positive	√
Jellyfish, corals, sea urchin spines	Pruritic lichenoid papules and plaques (onset 2–3 weeks after exposure) Linear, zig-zag and whip-like (flagellate) patterns of erythema/edema (early), hyperpigmentation or lichenoid papules (late)	Lichenoid dermatitis	Calcite crystals (sea urchin spines)	√ (sea urchin spines)
Keratin	Pseudofolliculitis/acne keloidalis	Foreign body granulomas	Other inflammatory cells	√
	Pyogenic granuloma-like lesions (ingrown nails) Pilonidal sinus	Pyogenic granuloma-like		
Intralesional corticosteroids	Skin-colored to yellow–white papules or nodules develop at the site of a previous intralesional injection of corticosteroid The incubation period varies between weeks to months	Foreign body granulomas	Pale bluish material in H&E-stained sections	
Suture	Wound appears inflamed, red, edematous (or develops papules or nodules) and opens to form a fistula	Foreign body granulomas		√

*May also be due to nickel contained in the tattoo gun or preservatives within the tattoo mixture.
†May be associated with a change in the original tattoo color.
‡Allergic reactions most commonly develop within areas of red color and sarcoidal reactions within areas of black color; Rush phenomenon represents the sudden appearance of sarcoidal reactions in multiple tattoos following a reaction in one of them.

Table 94.3 Clinical and histopathologic features of foreign body reactions. The order of the entities in this table corresponds to that in the text. Injectable soft tissue fillers are reviewed in Table 94.5. Energy-dispersive X-ray analysis (EDXA) or laser-induced breakdown spectroscopy can be used to detect tattoo inks, silica, talc, zirconium, aluminum, and zinc. iv, intravenous; PAS, periodic acid Schiff.

(blue), chromium (green), cadmium (yellow, red), ferric hydrate (sienna) and manganese (purple), or organic preparations.

Clinical features

Foreign body reactions may occur within a few weeks of the tattoo placement, but have been reported decades later[16]. Most commonly, erythematous papules, nodules, or plaques are seen (Fig. 94.6), but lesions may be verrucous, lichenoid, pseudolymphomatous, or eczematous. The reactions are usually confined to the site of the tattoo, with the degree of tenderness and erythema reflecting the intensity of the associated inflammation. "Allergic" reactions most frequently occur within the red-colored areas of the tattoo (Fig. 94.7)[13], while sarcoidal

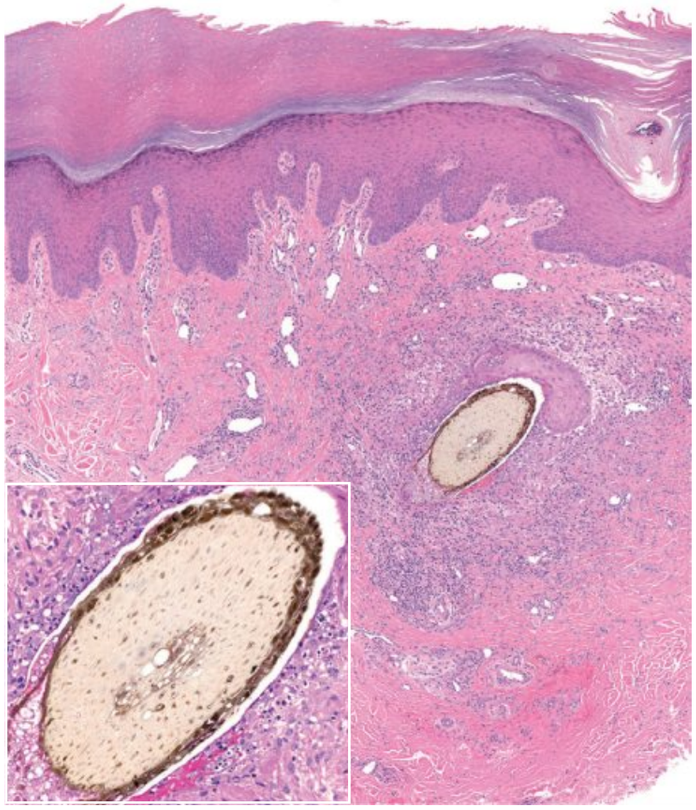


Fig. 94.3 Granulomatous foreign body reaction to implanted organic material in acral volar skin. A plant is the source of the foreign body and the latter is surrounded by a granulomatous reaction as well as neutrophils, lymphocytes, and cellular debris (inset). Superior to the foreign body is a portion of an epidermal cyst due to implantation of epidermal fragments into the dermis. *Courtesy Lorenzo Cerroni, MD.*

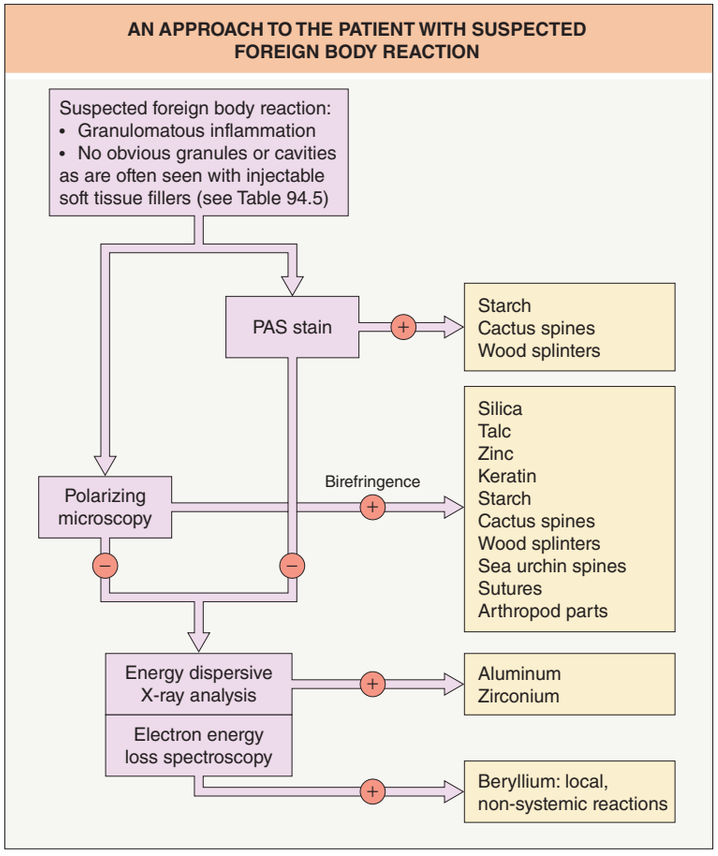


Fig. 94.4 An approach to the patient with suspected foreign body reaction. PAS, periodic acid Schiff.



Fig. 94.5 Traumatic tattoo of the eyelid due to asphalt following a motor vehicle accident. This type of tattoo responds favorably to Q-switched laser therapy.

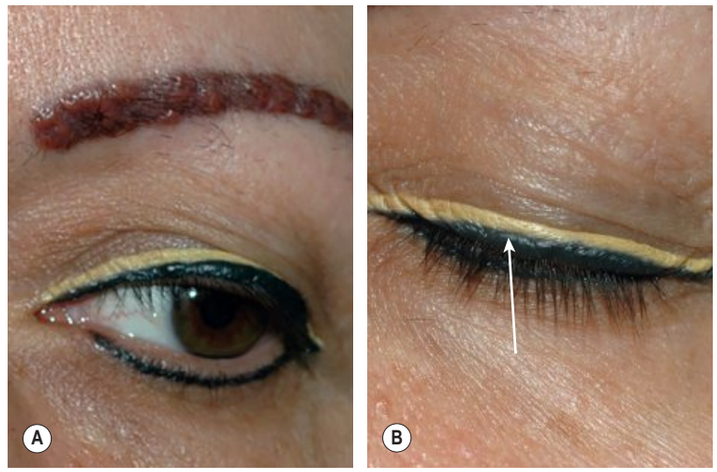


Fig. 94.6 Foreign body reaction to cosmetic tattoos. A Multiple erythematous papules within the eyebrow. **B** Small papules within black eyeliner (arrow). *Courtesy Luis Requena, MD.*



Fig. 94.7 Granulomatous reaction within the red portions of a tattoo. Over the past several years, cinnabar (mercuric sulfide) has been gradually replaced by cadmium selenide (cadmium red), ferric hydrate (sienna), and organic compounds. *Courtesy Lorenzo Cerroni, MD.*

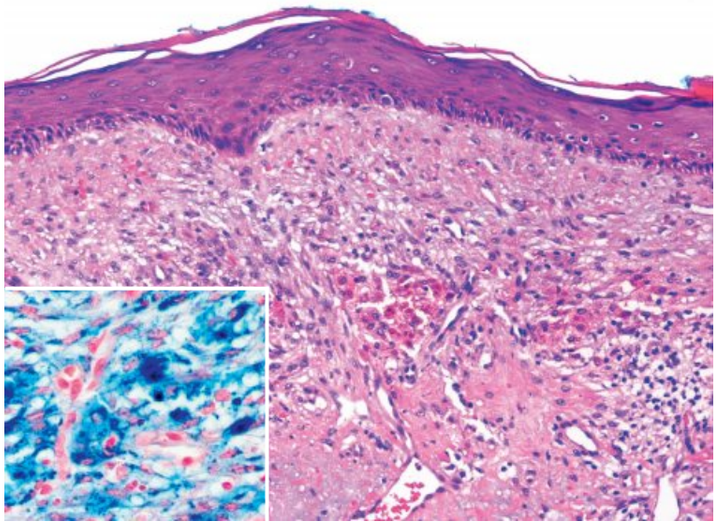


Fig. 94.8 Ferrous subsulfate (Monsel's solution) – iatrogenic tattoo and granulomatous reaction. Coarse granular brown pigment is seen within macrophages and between collagen fibers. The pigment is positive with Perls' stain (inset).
Courtesy Luis Requena, MD.

reactions favor sites of black color. In some patients, granulomatous papulonodules within a tattoo can be a manifestation of cutaneous or systemic sarcoidosis[17]. Rarely, a photoallergic reaction, presenting as pruritic, inflamed nodules, occurs in red or yellow tattoos containing cadmium sulfide following exposure to UV light[16].

Verrucous lesions and pseudoepitheliomatous hyperplasia can also develop within tattoos and may be misdiagnosed as human papillomavirus (HPV) infection or squamous cell carcinoma (SCC). The development of keratoacanthomas or SCCs within tattoos is rare. Tattoo pigments may migrate to the regional lymph nodes and at the time of lymph node sampling may clinically mimic metastatic melanoma[13,18].

Development of inflammation within older tattoos is occasionally triggered by a new tattoo that contains the same pigments. In the Rush phenomenon, granulomatous papulonodules initially develop in the new tattoo then within older tattoos, with sarcoidosis representing a risk factor[17].

Pathology

Different patterns of an inflammatory response can be elicited, including sarcoidal, foreign body granulomatous, lichenoid, eczematous, and pseudolymphomatous[13]. The majority of tattoo pigments appear black in H&E-stained sections, regardless of the color of the pigment (see Fig. 72.23B). Occasionally, colors other than black are seen (see below)[19]. The pigment is deposited in the upper and mid dermis, both extracellularly between collagen bundles and around blood vessels as well as a smaller amount within the cytoplasm of macrophages.

The pigment deposits in professional tattoos are relatively small and homogeneous in size and shape, while in traumatic tattoos they are larger and vary in size and shape[14]. Coarse, granular brown pigment within macrophages and between collagen fibers are seen in iatrogenic tattoos due to ferrous subsulfate (Monsel's solution; Fig. 94.8).

Diagnosis and differential diagnosis

The presence of inflammatory lesions confined to the site of a tattoo suggests the diagnosis. Inoculation of certain infectious agents (e.g. atypical mycobacteria) may mimic pigment-induced inflammation within a tattoo (Table 94.4). In addition to hypertrophic scars and keloids, unrelated benign and malignant tumors can also develop within tattoos.

Identification of the causative pigment is generally unnecessary unless further tattooing is anticipated. Other causes of dermal pigmentation include melanin, hemosiderin, lipofuscin, exogenous ochronosis, silver, gold, minocycline, amiodarone, and chlorpromazine. Special stains to identify melanin and iron (hemosiderin) may be useful (see Ch. 0).

INFECTIONS AND INFLAMMATORY DERMATOSES WITHIN TATTOOS	
Disorder	**Examples**
Infections (reflecting inoculation)	Streptococcal, staphylococcal; atypical mycobacteria (mycobacteria other than tuberculosis); HPV, molluscum contagiosum, HSV
Reactions to pigments	Eczematous, lichenoid, granulomatous foreign body reaction, sarcoidal*, pseudolymphomatous, pseudoepitheliomatous, photoallergic
Koebner phenomenon	Psoriasis, lichen planus, sarcoidosis
Thermal burn induced by MRI	Favors pigments that contain iron oxide
*Evaluate patient for sarcoidosis.	

Table 94.4 Infections and inflammatory dermatoses within tattoos. Systemic infections (e.g. hepatitis C virus, hepatitis B virus, tetanus) have also been reported following tattoo placement. HPV, human papillomavirus; HSV, herpes simplex virus; MRI, magnetic resonance imaging.

Treatment

Topical or intralesional corticosteroids can be used to treat inflamed tattoos. If injections do not lead to significant improvement, surgical excision, if feasible, to remove the inciting pigment is an option. Q-switched and picosecond lasers are commonly employed to remove the various pigments in tattoos (see Fig. 137.16 & Table 137.4)[18], but it is recommended that laser therapy be limited to non-inflamed tattoos[20]. There are reports of systemic reactions, presumably due to the release of pigment from macrophages, following laser therapy[21] and inflamed tattoos may be at greater risk for this side effect. Anecdotally, hydroxychloroquine, tetracyclines, and allopurinol as well as systemic corticosteroids have been used to treat resistant cases.

Paraffin

Paraffin, being a mineral oil, is not hydrolyzed by tissue lipases and is treated by the body as a foreign substance. Augmentation of body contour by local injection of paraffin, although banned in most countries, is still performed in some regions of the world and is mostly done by non-medical personnel. Accidental paraffinoma of the orbit and palpebra has been reported following intraoperative placement of paraffin-impregnated gauze packs within the nasal cavity[5].

Clinical features

In those cases due to injected paraffin, the genitalia, buttocks, and breast are the most common sites of involvement. Penile paraffinomas, also referred to as sclerosing lipogranulomas of the penis, can lead to significant deformity (Fig. 94.9A). Clinically, non-tender firm nodules and indurated plaques are seen, sometimes with ulceration or abscess formation and involvement of subcutaneous tissue (see Ch. 100). The interval between the time of injection and the development of lesions varies from weeks to decades.

Pathology

The dermis shows a characteristic "Swiss cheese" appearance due to the presence of numerous ovoid or round cavities where the paraffin resided prior to processing (Fig. 94.9B). Between the cavities, there is fibrotic connective tissue and a cellular infiltrate composed of macrophages, variable numbers of multinucleated foreign body giant cells, and lymphocytes. Some of the macrophages have foamy cytoplasm. In specially processed tissue, the foreign material stains with fat stains[22], although less intensely than neutral fats, helping to differentiate paraffinoma from reactions to silicone, which also have numerous cavities but negative fat stains.

Treatment

Excision with appropriate tissue reconstruction is the only means of therapy.

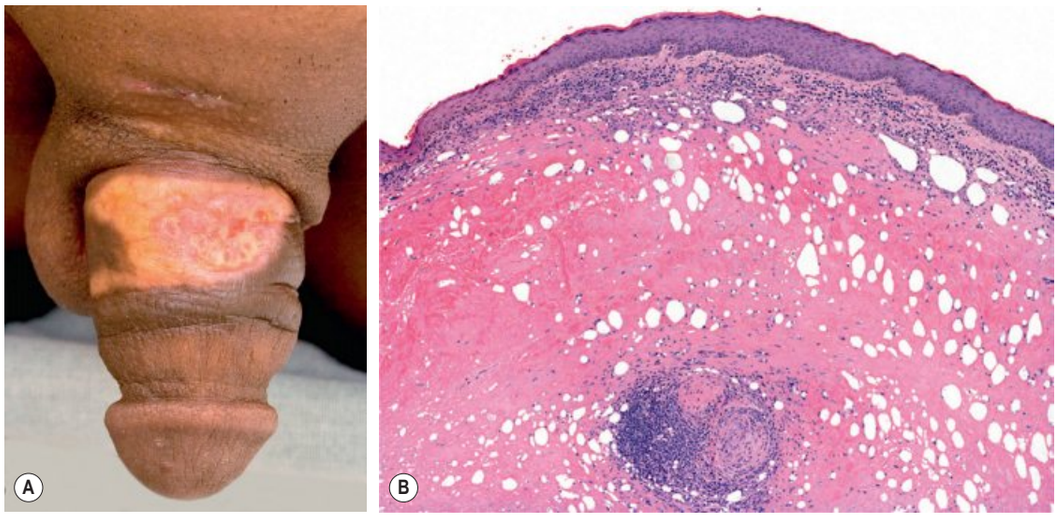


Fig. 94.9 Sclerosing lipogranuloma of the penis. A The penis was injected with paraffin in order to relieve urinary retention following a motorbike accident, and an ulcerated, indurated yellow plaque with telangiectasias developed at the site. **B** Histologic examination showed sclerosis as well as multiple circular and oval empty spaces within the dermis. *Courtesy Glen Foxton, MD and Clare Tait, MD.*

Silicone

Silicone (polydimethyl siloxane), in a liquid, gel, or solid form, is used for tissue augmentation. While silicone is generally regarded as an inert substance, in some patients its use has been followed by foreign body reactions.

Clinical features

Silicone gel-filled implants are widely used for breast augmentation as well as reconstruction after mastectomy and leakage due to permeability loss or rupture can occur. Silicone injections and implants have also been employed for body and facial contour augmentation, including correcting HIV-related lipoatrophy. When a cutaneous foreign body reaction occurs, nodules and plaques develop at the site of injection or placement after a period of months to years. Skin lesions also appear at distant sites, reflecting the tendency for silicone to migrate, including in a dependent, gravity-driven direction. With progression, sclerosis and ulcerations can be seen. Whether the immune system is recognizing the silicone itself versus additives or contaminants including microbes remains speculative[23].

In a recent systematic review, hypercalcemia with renal failure was noted in association with silicone-induced foreign body granulomas and, to lesser extent, polymethylmethacrylate-, paraffin-, and mineral oil-induced foreign body granulomas[24]. An increased risk of autoimmune connective tissue diseases (e.g. Sjögren syndrome, systemic sclerosis, rheumatoid arthritis) in patients with silicone breast implants has been observed in some, but not most, studies[25]. Agreement does exist that textured breast implants, both saline and silicone, are associated with anaplastic large cell lymphoma of the breast.

Pathology

A biopsy specimen is critical to establishing the diagnosis. Histologic sections have a multivacuolated appearance due to the presence of silicone-filled cavities surrounded by histiocytes, lymphocytes, and eosinophils. The histiocytes may be foamy or multinucleated. Fibrous tissue within the areas separating the cavities is also seen. In contrast to paraffinomas, the cavity contents do not stain with lipid stains. Occasionally, silicone granulomas can mimic a low-grade liposarcoma.

Treatment

Excision of persistent symptomatic lesions is recommended.

Silica

Wounds or penetrating injuries accidentally contaminated with silica (silicon dioxide) contained in sand, soil, rocks, and glass may be followed some years later by the formation of a foreign body reaction. The period between inoculation and development of a reaction may be as long as 25 years. This extended "incubation" period is due to the very slow release of colloidal silica (the only form capable of inciting a reaction) from the large particles of silica introduced into the body[26]. Reactions to silica are thought to be due to a delayed-type hypersensitivity response.

Clinical features

At first, the wound heals, but then papules, nodules, or indurated plaques develop within the scar years later. Multiple disseminated lesions may follow trauma produced by the explosion of land mines and bombs[26]. Patients with sarcoidosis may be at increased risk for immunologic responses to silica[27].

Pathology

The dermis contains multiple nodular aggregates of granulomas, usually sarcoidal and less often foreign body, separated by strands of connective tissue. Langhans- and foreign body-type giant cells are usually numerous in both types of granuloma. Colorless crystals may be observed within the cytoplasm of the giant cells or lying free in the interstitium. These bodies are birefringent when examined with polarized microscopy.

Differential diagnosis

Granulomatous lesions occurring at the site of an old scar may mimic cutaneous sarcoidosis clinically and histologically[28]. However, the presence of foreign material within a sarcoidal granuloma does not exclude sarcoidosis, given the attraction of sarcoidosis to existing scars. Examination under polarized light will identify silica crystals.

Treatment

Excision of persistent symptomatic lesions is recommended. Spontaneous resolution of silica granulomas, although reported, is exceptional.

Talc

Talc (hydrous magnesium silicate) is a common cause of foreign body granulomas given its presence in dusting, antifungal, and antibiotic powders. In addition, it is still preferred by some surgeons as a lubricant for surgical gloves. Talc can therefore contaminate wounds, erosions, and umbilical stumps, or it may enter the skin via abrasions and fissures, particularly in intertriginous zones in obese individuals who apply talc powder liberally[29].

Individuals with substance use disorder who inject solutions intravenously or subcutaneously that contain crushed tablets may also develop foreign body reactions to talc as talc is a common filler in tablets. The foreign body reactions may arise at injection sites or at distant sites (e.g. pulmonary intravascular talcosis)[30].

Clinical features

As with reactions to other forms of silica, the lesions usually take a long time to appear. The clinical appearance is varied: it may take the form of erythematous papules and nodules or simply thickening and erythema of an old scar, similar to the range of findings in sarcoidosis. Rarely lesions may resemble a pyogenic granuloma. Despite the long latency period, the diagnosis should be considered, especially when lesions appear in certain sites, e.g. the umbilicus in infants, inguinal area in patients with a history of intertrigo, injection sites in those with a history of intravenous drug use.

Pathology

The histologic features may be similar to those of sarcoidosis or non-caseating tuberculosis. Alternatively, there may be granulomatous inflammation consisting of histiocytes and foreign body giant cells. A few of these cells may contain clear, blue–green, or yellow–brown, needle-shaped or round crystals. Under polarized light, talc crystals are birefringent. A picture simulating a pyogenic granuloma plus giant cells has also been described[5].

Treatment

Excision of persistent symptomatic lesions is recommended.

Zirconium

Some zirconium salts were once components of antiperspirant preparations as well as over-the-counter preparations used in the treatment of allergic contact dermatitis. Sodium zirconium lactate was the first salt incriminated as a cause of foreign body reactions and while banned in the late 1970s, it was replaced by aluminum–zirconium complexes. Subsequently, zirconium oxide and aluminum–zirconium complex were shown to be capable of producing the same reaction. Development of foreign body granulomas represents a delayed-type hypersensitivity reaction to zirconium[6].

In sensitized individuals, persistent, soft, red–brown papules appear in areas to which zirconium-containing preparations were applied. The axillary skin is the most frequently affected site.

Histologically, non-caseating granulomas resembling a sarcoidal reaction are seen[6]. The small size of the zirconium particles does not allow their detection with polarized light microscopy; however, energy-dispersive X-ray analysis can prove their presence.

Beryllium

Chronic beryllium disease is an immunologically mediated occupational disease, primarily affecting workers exposed to beryllium during its manufacture and recycling or in alloy production. Inhalation of beryllium particles was thought to be the source of exposure, but more recent evidence points to both penetration of fine particles (<1 micron) through intact skin, as well as inhalation, as possible routes[31]. In systemic berylliosis, the primary pathology is in the lung and skin involvement is rare (<1%). The cutaneous granulomas of systemic berylliosis consist of widely scattered papules with no secondary changes.

Histologically, cutaneous lesions of systemic berylliosis are indistinguishable from sarcoidosis. In the past, when beryllium was used in the manufacture of fluorescent light bulbs, local cutaneous berylliosis was noted to have a caseating tuberculoid pattern. In systemic berylliosis, bronchioalveolar lavage is recommended for diagnosis.

Aluminum

Rare hypersensitivity reactions to the aluminum adjuvant in vaccines and hyposensitization immunotherapy do occur. Persistent subcutaneous granulomatous nodules can appear at the sites of injection several months after vaccination[32]. Histologically, a central zone of degenerated collagen is surrounded by a rim of both histiocytes, whose cytoplasm contains bluish-grey granules, and lymphoid aggregates, some of which form germinal centers[32,33]. There are also abundant eosinophils. Special stains (e.g. staining for aluminon in which the aluminum appears red) may make aluminum particles more evident. Of note, application of *topical* aluminum chloride for hemostasis can result in the presence of basophilic granules of varying size and shape within the cytoplasm of macrophages[34].

Zinc

A zinc-induced granuloma at the site of an injection is a rare complication of zinc-containing insulin[35]. Sterile furuncles develop at the injection sites and eventually heal with atrophic scars. Histologically, an initial stage characterized by a dense neutrophilic infiltrate is followed by granuloma formation that ends in fibrosis. By polarizing microscopy, birefringent rhomboid crystals are seen.

Treatment

Zirconium, beryllium, aluminum, and zinc granulomas may be surgically excised if they are symptomatic.

REACTIONS TO ORGANIC AND BIOLOGIC PRODUCTS

Starch

Granulomas may result from the contamination of wounds with starch used as a lubricant for surgical gloves.

Pathology

Foreign body granulomas with multinucleated giant cells are seen. Starch granules appear as ovoid basophilic structures. They stain positively with periodic acid Schiff (PAS) and with polarized light are birefringent with a characteristic "Maltese cross"-like appearance[36].

Cactus Spines

Accidental implantation of cactus spines into the skin results from contact with cacti in gardens and fields. Occupational exposure occurs in persons peeling and selling prickly pear fruit, especially in the Middle East and Latin America. Most of the reported cases are due to contact with the genus *Opuntia*[37].

At the time of injury, acute inflammation occurs and then, in some patients, eventually evolves into a typical foreign body reaction. The lesions occur primarily on the hands and fingers as clusters of dome-shaped, skin-colored papules with a central black dot, sometimes called "Sabra dermatitis" (see Ch. 17). This may resemble scabies or fiberglass dermatitis.

Pathology

Foreign body granulomas occupy the entire dermis and surround the spine fragments, which stain intensely red with PAS stain[14,37]. Wood splinters and thorns of other plant origin have a similar suppurative or granulomatous reaction. However, most splinters appear brown with a geometric pattern of cell walls. Fungal hyphae may be present within the plant material, but they seldom invade the surrounding dermis in a healthy host.

Cnidaria (Coelenterata) – Jellyfish, Corals

Members of the phylum Cnidaria (Coelenterata) include jellyfish, corals, and sea anemones (see Ch. 85). Almost all cnidarians possess nematocysts which contain highly coiled, hollow harpoon-like structures that inject a toxin into the skin upon contact.

Clinical features

Jellyfish and coral stings elicit similar cutaneous reactions: an early primary irritant toxic reaction in all exposed persons, and a delayed-type hypersensitivity reaction in a small percentage. A sharp burning pain is felt and, within minutes, the affected area becomes erythematous and edematous and may form blisters (see Fig. 85.20). The acute response may be accompanied by an immediate-type hypersensitivity reaction including urticaria, angioedema, and even anaphylaxis. The lesions resolve, leaving postinflammatory hyperpigmentation in a streaky flagellate fashion corresponding to where the coral or jellyfish brushed the skin. In some individuals, new lesions appear a

few weeks later at previously involved sites (average 3 weeks)[8]. The latter are severely pruritic, shiny, lichenoid papules and plaques and are arranged in a number of patterns, including linear, zig-zag, and whip-like.

Pathology

The lesions that comprise the delayed response have a lichenoid tissue reaction.

Treatment

First aid includes soaking the site in hot, but not scalding, water (denatures proteins). Subsequent use of topical potent corticosteroids, antihistamines, and systemic corticosteroids is controversial. Treatment of acute reactions is reviewed in Chapter 85. Intralesional corticosteroids are the most effective therapy for delayed-type hypersensitivity reactions.

Keratin

Keratin, normally sequestered from the body's immune surveillance by the surrounding epithelium, is treated as foreign if it directly contacts the dermis. This may occur as a result of the rupture of hair follicles, epidermoid cysts, or acne lesions as well as from external keratin sources such as ingrown nails or ingrown hairs; the latter occur in pseudofolliculitis and in pilonidal sinuses. Another source is accidental entry of hairs into interdigital skin, especially in barbers, hairdressers, and dog groomers.

Pseudofolliculitis barbae

In pseudofolliculitis barbae, there is a foreign body inflammatory reaction surrounding a hair that has been previously shaved or plucked (see Ch. 38). This condition affects mainly those with curly hair, with an incidence of more than 50% amongst Black individuals. Certain inherent properties of the hairs in affected individuals, in particular a curled flattened elliptical shape, play an important pathogenic role. Because the shaft is curved, it grows back toward the skin surface. When shaved, the flattened elliptical hair shaft develops a pointed tip, which facilitates re-entry of the hair into the skin (extrafollicular penetration). Transfollicular penetration can also occur (see Fig. 38.10). A foreign body reaction to keratin results in the development of inflammatory papules and pustules that are often followed by hyperpigmentation or small keloidal scars (see Fig. 38.11)[11].

Pseudofolliculitis also affects women or men who regularly remove hair from the pubic region, axillae, and legs by plucking or shaving. Papules containing embedded hairs, pustules, and crusted papules develop in affected areas, often resolving with significant postinflammatory hyperpigmentation.

Treatment

Apart from cessation of shaving or laser epilation of the affected areas, nearly all therapeutic modalities are unrewarding. For further details, see Chapters 38 and 137.

Pilonidal sinus

Most cases of pilonidal sinus occur in the sacrococcygeal region (see Ch. 38). Much less often, it is seen in the umbilical region[38], and, rarely, interdigitally in barbers[39].

Sacrococcygeal pilonidal sinuses may be asymptomatic (debris-filled pit) or present as a draining sinus or an acute abscess. The condition is more common in young men. There is often an underlying cyst with associated granulation tissue, fibrosis, and frequently tufts of hairs. Excisional specimens reveal a sinus tract extending into the dermis and subcutaneous tissue, surrounded by chronic inflammation. Hairs are found in the sinuses in three-quarters of the cases[40].

Small, asymptomatic or slightly tender, openings in the interdigital web spaces of the hands have been observed in barbers, hairdressers, and dog groomers. When these individuals cut hair while wearing sandals, lesions can develop in the web spaces of the feet as well. Penetration of short hairs into the interdigital spaces incites an inflammatory foreign body granuloma. The clinical course is usually self-limited but can be complicated by repeated infections, which may require surgical excision of the involved area[39]. Histologically, a sinus tract lined by epidermis and containing one or several hairs is seen. Hairs extending deeper than the sinus tract incite a foreign body reaction.

INJECTABLE SOFT TISSUE FILLERS

With the exception of autologous fat, all injectable soft tissue fillers, resorbable or non-resorbable, represent foreign bodies and therefore have the potential to cause foreign body reactions (Figs. 94.10 & 94.11; see Ch. 158). Two types of reactions have been reported: non-immunogenic and immunogenic. The former is characterized by localized tissue necrosis, which occurs shortly after implantation, and such reactions are probably the result of local vascular interruption; two-thirds of local necrotic events occur in the glabellar area[41]. Depending upon the particular filler, associated foreign body reactions can range from relatively common (e.g. paraffin) to rare (e.g. hyaluronic acid)[42]. Paraffin and silicone are discussed above and the histopathologic features of inflammatory reactions to various fillers are outlined in Table 94.5[41]. Foreign body reactions usually appear within 1–2 years after injection, and spontaneous resolution occurs in the majority of cases within a year, while the remainder have lesions that wax and wane[43,44].

Hyaluronic Acid

Currently, hyaluronic acid is the most commonly utilized injectable soft tissue filler, in part because the incidence of foreign body reactions is much lower (0.4%) than that reported for bovine collagen (3%–4%)[42]. When a reaction does occur, the injected site becomes firm, tender, edematous, and erythematous, and an abscess may form. This reaction responds to intralesional injections of corticosteroid or hyaluronidase (see Ch. 158)[44], although some patients may be willing to wait for spontaneous resolution which can occur over several months.

Bovine Collagen

In general, bovine collagen alone has been replaced by other less antigenic soft tissue fillers, especially hyaluronic acid. However, there are fillers in which bovine collagen is combined with polymethyl methacrylate microspheres, e.g. Bellafill® (formerly Artefill®). Despite negative skin testing (which is required prior to treatment), a small proportion of patients injected with bovine collagen still develop a local reaction (see Fig. 94.1)[44].



Fig. 94.10 Granulomatous reaction due to silicone injections. The procedure was performed in a beauty salon for cosmetic purposes.

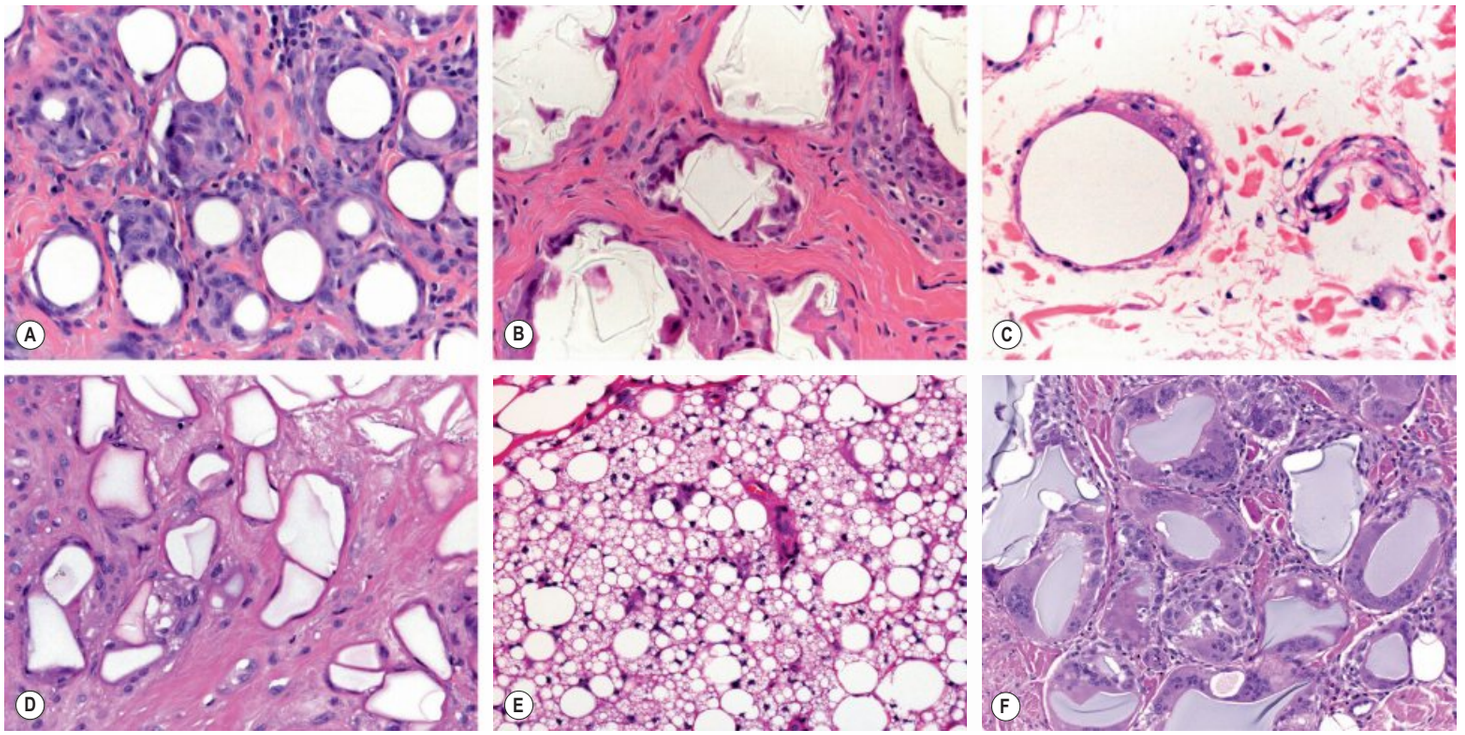


Fig. 94.11 Histopathologic features of granulomatous reactions to different injectable soft tissue fillers. A Multiple uniform vacuoles within an area of granulomatous inflammation due to polymethylmethacrylate microspheres suspended in bovine collagen (Bellafill®, previously known as ArteFill®). **B** Translucent, polygonal and irregularly shaped deposits plus fibrosis and granulomatous inflammation due to silicone elastomer particles and polyvinylpyrrolidone (Bioplastique®). **C** Rounded deposits of silicone surrounded by histiocytic giant cells in a granulomatous reaction to silicone that leaked from a breast implant. **D** Light pink to translucent deposits with a prominent rim in addition to fibrosis due to fragments of hydroxyethylmethacrylate/ethylmethacrylate fragments and hyaluronic acid (Dermalive®). **E** In this granulomatous reaction to silicone injected into the lip, the histiocytes have a foamy appearance due to engulfed silicone. **F** Homogeneous blue-gray deposits of hyaluronic acid within multiple foreign body giant cells. *A–D, F, Courtesy Lorenzo Cerroni, MD; E, Courtesy Luis Requena, MD.*

MISCELLANEOUS

Intralesional Corticosteroids

Foreign body reactions to intralesional corticosteroids are quite rare despite the widespread use of this treatment modality. Reactions result from failure of the injected material to disperse in the usual manner or from incomplete absorption, leaving a small residuum that evokes a foreign body reaction[45].

Histologically, pools of granular, lightly stained material surrounded by a histiocytic and foreign body granulomatous infiltrate are seen in the dermis. Cellular reactions are absent around sites of recent injections[45].

Sutures

Nylon and polypropylene sutures used in contemporary surgery are relatively inert (see Ch. 144), but most other materials regularly produce chronic inflammation and granuloma formation (see Fig. 151.19). The incubation period varies from weeks[46] to years[47].

The incision site may appear inflamed, red, and edematous. A sinus tract may develop, through which the suture material is extruded. Inflammation persists until the suture material is totally removed.

Histologically, granulomatous inflammation of various types is seen surrounding suture material: foreign body, histiocytic, palisading, or a combination thereof (see Fig. 94.2)[46,47]. Transepidermal elimination of the suture material occurs[46].

Polyamide "Hair" Implants

In patients with androgenetic alopecia in whom autologous hair transplantation is not feasible (e.g. inadequate donor sites), polyamide "hair" fibers have been used for synthetic scalp hair restoration. Although some authors have reported complications in only ~1% of patients, foreign body reactions are a real risk (Fig. 94.12)[48]. Polyamide fiber hair restoration is not approved in the US.



Fig. 94.12 Foreign body reactions to polyamide synthetic "hair" implantation. In addition to multiple perifollicular granulomas, there is evidence of chronic folliculitis.

Mesotherapy

Mesotherapy involves placement of a pharmacologic substance into the "mesoderm" (dermis and subcutis). For example, injections of deoxycholic acid (Kybella®) have been approved for the reduction of submental fat and may lead to a temporary chemical panniculitis. However, non-standardized combinations such as phosphatidylcholine plus a detergent solvent (e.g. deoxycholic acid) are also used for lipolysis. With

HISTOPATHOLOGIC FEATURES OF INJECTABLE SOFT TISSUE FILLERS		
Category	**Chemical composition**	**Histopathologic features**
Resorbable within months	Hyaluronic acid	• Irregular clusters of basophilic material surrounded by histiocytes and giant cells • Alcian blue stain positive
	Bovine collagen	• Palisading granulomas with foreign body giant cells and eosinophilic bovine collagen in the center of the granulomas • Appearance with polarization differs from human collagen* • IHC – positive staining with anti-bovine collagen type I antibodies
	Human collagen – bioengineered, cadaveric, autologous	• Granulomatous reaction • Appearance with polarization differs from bovine collagen*
Resorbable within years	Hyaluronic acid plus dextranomer microparticles	• Suppurative granulomas surround bluish-grey filamentous material and round, bluish, spherical particles
	Poly-L-lactic acid microspheres plus sodium carboxymethyl-cellulose	• Foreign body granulomas surround fusiform or oval translucent particles • Birefringent under polarized light
	Calcium hydroxylapatite plus carboxymethylcellulose	• Foreign body granulomas surround bluish, rounded particles
Permanent	Paraffin†	• Foreign body granulomas with "Swiss cheese" appearance (Fig. 94.9B) • Positive fat stains (e.g. oil red O) • Detected by IRS
	Silicone oil or silicone gel	• Foreign body granuloma with a multivacuolated appearance (also referred to as "Swiss cheese"; Fig. 94.11C) and histiocytes may be foamy (Fig. 94.11E) • Negative fat stains • Detected by EDXA and in an X-ray, appears radio-opaque
	Silicone particles (100–600 microns) suspended in polyvinylpyrrolidone	• Foreign body reaction with translucent, irregular, non-birefringent particles dispersed in a sclerotic stroma (Fig. 94.11B)
	Polymethylmethacrylate microspheres plus bovine collagen	• Granulomatous infiltrates around vacuolar structures of homogeneous shape and size (Fig. 94.11A)
	Hydroxyethylmethacrylate/ethylmethacrylate fragments in hyaluronic acid	• Foreign body granulomas surround polygonal, irregular, translucent pink structures (Fig. 94.11D)
	Polyacrylamide hydrogel	• Foreign body granulomas surround basophilic, multi-vacuolated material
	Polyalkylimide gel	• Basophilic, amorphous, granular material surrounded by inflammatory infiltrates
	Polyvinylhydroxide microspheres suspended in polyacrylamide gel	• No reports of cutaneous side effects to date; limited local reactions at test sites in volunteers
	Alginates	• Severe granulomatous reaction • Filler material may not be visible or may appear as large, basophilic, oval particles

*Human collagen is birefringent under polarized light and stains green with Masson trichrome stain, whereas bovine collagen is not birefringent with polarized light and stains pale gray–violet with Masson trichrome stain.
†Banned in most countries; also seen after application of paraffin-impregnated gauze packs.

Table 94.5 Histopathologic features of injectable soft tissue fillers. For trade names of the various fillers, see Ch. 158. EDXA, energy dispersive X-ray analysis; IHC, immunohistochemical; IRS, infrared spectrophotometry (non-processed tissue). *Adapted from references 42 & 44.*

these latter combinations, irritant cutaneous necrosis and atypical mycobacterial infections have been observed as well as granulomatous reactions[49]. Lastly, application of moisturizers prior to microneedling for facial rejuvenation can lead to granulomatous reactions[50].

Gouty tophi

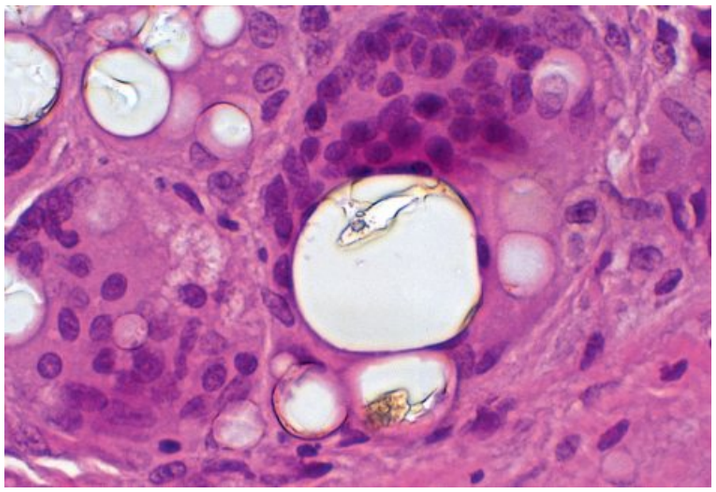
Gouty tophi consisting of urate crystals form multiple lobules separated by fibrous septa surrounded by histiocytes and multinucleated foreign body giant cells, resembling a foreign body reaction (see Fig. 48.3). In long-standing tophi, calcium pyrophosphate dehydrate crystals have been detected and they may be dispersed or condensed and present at the edge or inside the tophus lobules. These calcium crystals appear to be a late event and may contribute to the persistence of gout tophi despite success in lowering serum urate levels[51].

Additional figures available in our eBook (see inside front cover for access code).

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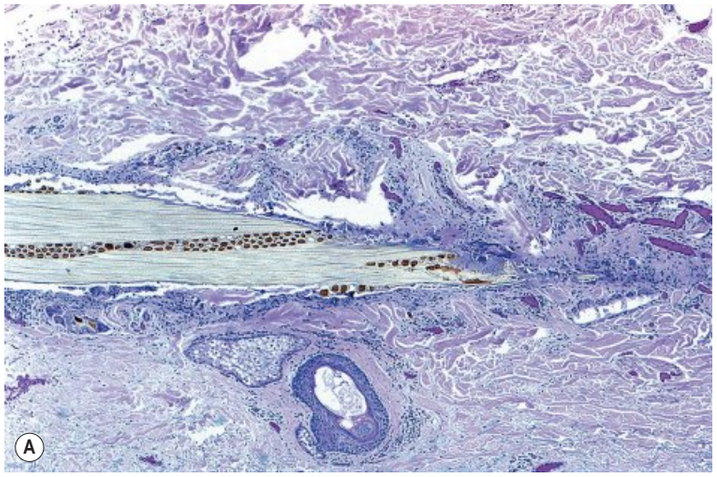
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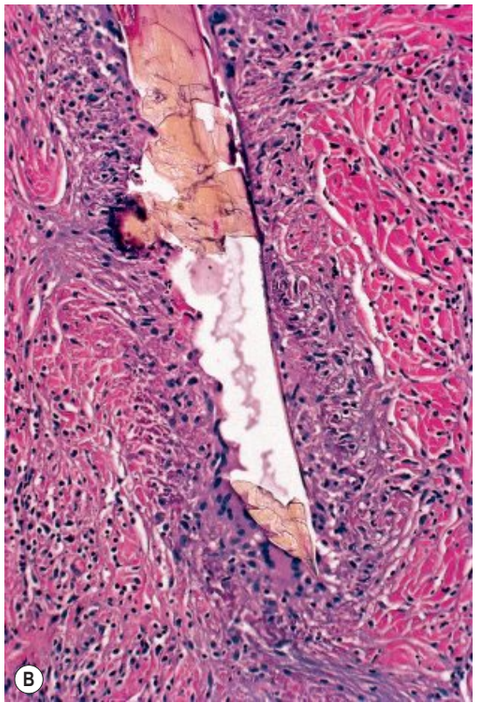


eFig. 94.1 Birefringent foreign body is engulfed by a foreign body-type giant cell with the typical haphazard array of nuclei. *Courtesy Thomas D Horn, MD.*



eFig. 94.3 Granulomatous reaction to the red (cinnabar) portions of a tattoo. Over the past several years, cinnabar (mercuric sulfide) has been gradually replaced by cadmium selenide (cadmium red), ferric hydrate (sienna), and organic compounds. *Courtesy Ronald P. Rapini, MD.*





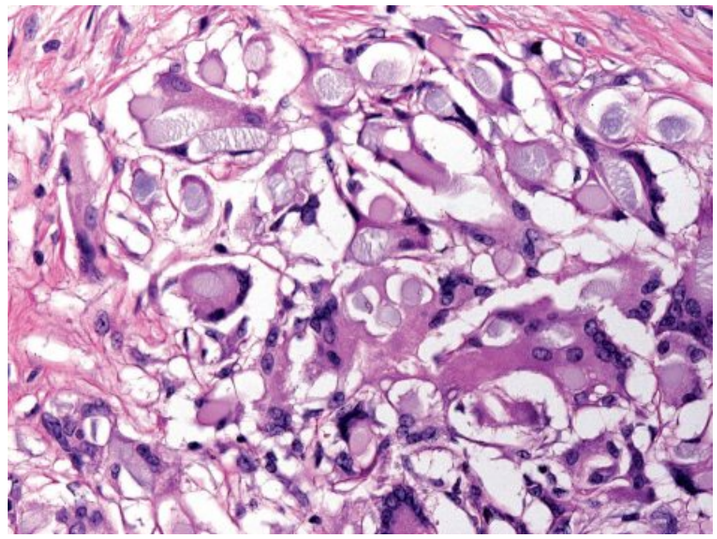
eFig. 94.2 Granulomatous foreign body reactions to implanted organic material. Wood splinter (**A**) versus bee stinger (**B**). Most splinters appear brown with a geometric pattern of cell walls. *A, Courtesy Ronald P. Rapini, MD.*



eFig. 94.4 Coral envenomation. Delayed lichenoid reaction on the calf. The patient accidentally came into contact with a coral reef and developed acute dermatitis that resolved, to be followed 3 weeks later by this severely pruritic eruption that responded favorably to intralesional triamcinolone injection.



eFig. 94.5 Foreign body reaction to silica. *Courtesy Louis A. Fragola Jr, MD.*



eFig. 94.6 Foreign body reaction to sutures. The foreign bodies have been engulfed by foreign body-type giant cells. *Courtesy Lorenzo Cerroni, MD.*