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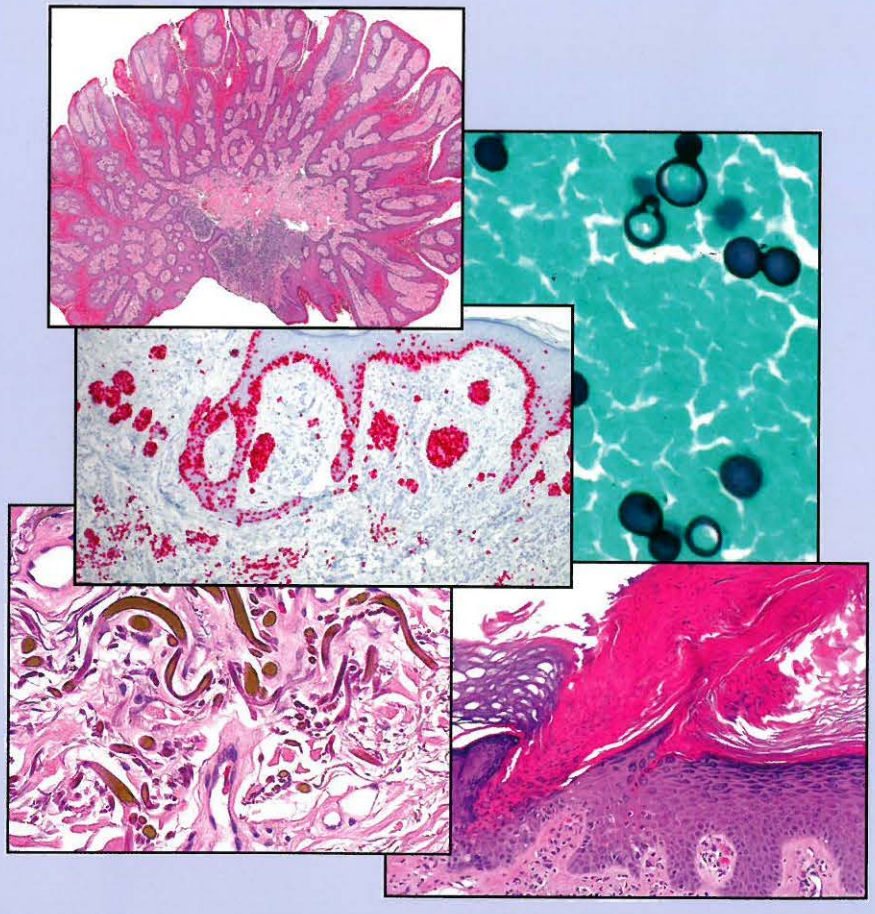
PATHOLOGY SURVIVAL GUIDES
Series 1

Survival Guide to Dermatopathology

Jerad M. Gardner, MD



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Survival Guide to Dermatopathology

Pathology Survival Guides

PATHOLOGY SURVIVAL GUIDES

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Preface

Dermatopathology requires knowledge of the microscopic and clinical aspects of numerous neoplastic and inflammatory skin diseases. Approaching this vast and complicated field is daunting, but this Survival Guide to Dermatopathology will give you a solid start. Most of the common entities in dermatopathology as well as some esoteric ones, particularly if they have very distinct features or are of major clinical significance, are covered. My goal is to reduce anxiety and increase diagnostic confidence by teaching the reader how to recognize treacherous waters and avoid them.

The text focuses on the key features that I personally use to make these diagnoses in my own practice. I meticulously collected numerous vivid high-quality photomicrographs and then annotated the key findings in each with great detail. The book is loaded with practical tips, how to sort out difficult dilemmas, and even how I word the final diagnosis line and comment in my report when I need to "hedge." I discuss how to build rapport with your dermatologist colleagues and how to recognize those times that a clinical photograph or a phone call can be the crucial key to making the right diagnosis. Everything is explained clearly with a conversational tone.

This book will give you an open window into how I currently practice dermatopathology. It will give you an honest look at how I still struggle with some diagnostic problems daily and how my own views on controversial issues are still evolving over time. Learning dermatopathology is a never-ending career-long journey. It may be difficult and trying some days, but it is fascinating and rewarding always. This book will get you started on that journey and well along the road to confidently providing the highest quality of diagnostic care to patients with skin disease.

Jerad M. Gardner, MD

Acknowledgments and dedication

To my amazing wife, Jenny. Thank you for your constant love and encouragement, for making me a better man and better physician than I ever would have been on my own, and for supporting me and guiding me in my career. To my three princesses: Bella, Becca, and Gaby. You bring joy, light, laughter, and happiness to my life every day.

To my teachers and mentors. Thank you for taking a chance on me, for opening doors in my career, for having mercy on my many mistakes, for giving me a love of teaching, for training me in diagnostic pathology, for modeling what it means to provide excellent patient care. Thank you for the precious gift of your time. "You can never repay your mentors; you can only pay them forward." May this book be one payment towards my endless debt to all of you.

To my students, residents, fellows, and colleagues, both near and far, in "real life" and online. Your feedback, support, encouragement, and kind words bring joy to my heart and inspire me to keep teaching. Being a pathologist and educator has been so rewarding and fun because of you.

To Liz Montgomery, thank you so much for creating this brilliant Pathology Survival Guide series and for inviting me to be a part of it!

Jerad M. Gardner, MD

CONTENTS

1 BASICS OF DERMATOPATHOLOGY

Dermatopathology is fun, but it is also difficult, especially for beginners. First, there are numerous cutaneous diseases, both neoplastic and non-neoplastic; I suspect that a greater number of unique disease entities have been described in the skin than in any other organ system in the human body. Skin is the first major barrier that separates the inside of our bodies from the harsh environment of the outside world. It is the first point of contact for numerous pathogens, antigens, irritants, and electromagnetic waves, and myriad skin diseases develop from these injurious agents accordingly. This is in addition to the innumerable genetic and autoimmune diseases that also involve the skin.

The plethora of skin diseases is also because skin is so accessible to clinical and pathologic study. Physicians have been able to examine and describe skin diseases since ancient times, millennia before the inner workings of the human body were ever witnessed or understood. Once the modern specialty of dermatology came into existence in the 18th and 19th centuries, extensive scientific study of skin disease was undertaken and our knowledge of dermatologic diseases expanded exponentially. Microscopic examination expanded that knowledge further, as any papule, nodule, patch, or plaque could easily be biopsied and examined, even in the days before advanced modern surgical techniques, computerized tomography (CT)-guided biopsies, or endoscopy.

This long history has led to many skin diseases with multiple names, some of which are in Latin, and some of which have nothing to do with what the disease actually is by modern standards. Lupus pernio (which is actually sarcoidosis), lupus vulgaris (which is actually cutaneous tuberculosis), and lupus erythematosus (which is what we usually mean when we say "lupus" in modern medicine) are excellent examples. The numerous complicated and overlapping disease names, along with the corresponding eponyms that the dermatology forefathers loved to apply to everything, have greatly increased the challenge of learning dermatopathology in modern times, especially when first starting out.

This book is designed to show how and where to begin the journey of dermatopathology education. Once you acquire the basic skills discussed in this book, you will be able to handle most of the common and classic dermatopathology cases with confidence, you will recognize many of the important pitfalls before falling into them, and you will know when to seek consultative help on difficult or high stakes cases. From there, you can spend the rest of your career continuing to build upon this foundational basic knowledge of dermatopathology.

DISCLAIMERS

Controversy and debate can be found in all corners of pathology, but dermatopathologists in particular seem to love heated debate at least historically. Accordingly, there are divergent opinions and different schools of thought in the field of dermatopathology, and probably every dermatopathologist has at least a few views that are held dearly (and perhaps even rigidly). This book is based on how I personally practice dermatopathology at the time of writing (2019). I have done my best to state accurate information in the text, but I have also included many personal opinions and pragmatic ways that I handle difficult scenarios in my own practice. Some books just stick to the published data for each entity. While that is fine for certain purposes, it often leaves the reader without much practical guidance about handling difficult cases in real practice. How many stains do I need to diagnose this disease? Can I diagnose it with a hematoxylin and eosin (H&E) stain only? How do I word my differential diagnosis and my degree

of uncertainty in the pathology report? Should I get an expert consult before making this diagnosis? These are the kinds of real life questions that I have sought to provide some answers to in this book. My approaches are based on what I actually use for my own patients.

This book is based on a combination of what I have been taught by my mentors, what I have read in the literature, and what I have learned from my own experiences. My approach or terminology may differ from what other dermatopathologists have taught you, and that is okay. I know that some of my views and opinions have changed since I entered practice, and I suspect (and hope) that my understanding will continue to evolve over the coming years.

This book is intended to be an educational guide, not a consensus statement, definitive rule book, or comprehensive text. I hope readers will find my personal opinions and insights useful (or at least interesting), but please do not regard them as dogma. I recommend that you learn dermatopathology from many sources to build a well-rounded understanding of the different viewpoints that exist. Your own views and style of practicing dermatopathology will eventually grow from that foundation over time.

HOW TO APPROACH A SKIN BIOPSY

In my view, there are two major diagnostic approaches to dermatopathology. One is to use the low magnification silhouette or shape of the biopsy findings to recognize the disease entity, or at least to create a focused differential diagnosis list. Dermatology-trained students of dermatopathology often use this approach. They already have a fairly complete list of the various dermatologic entities based on their clinical training, and when they view the biopsy, they are trying to fit the pattern into one of the entities on that list. If clinical information about the case is available, they are able to greatly narrow down the list of possible entities that the biopsy might represent.

The other approach is to examine each layer of the skin systematically (often from top to bottom, starting with the epidermis), creating a mental checklist of each abnormality present, and then from that list of microscopic features arrive at a diagnosis or differential. Pathology-trained students of dermatopathology often use this approach, at least at the start, since they are accustomed to identifying microscopic abnormalities and they often do not have a complete knowledge of all the different entities that might be possible based on the clinical scenario.

Both approaches have their merits, and I use both approaches in my practice. In my experience, the low magnification pattern-based approach is the faster way to learn and practice dermatopathology. However, it is also crucial to know how to systematically examine all of the layers of the skin present in a biopsy to recognize all the subtle features present. For inflammatory diseases and other complicated cases, this systematic approach can be the key to making the diagnosis, or at least excluding important differential diagnostic entities.

In my own practice, I use instant pattern recognition from low magnification (2X objective) when first looking at a slide to make the diagnosis or create a differential. Depending on the case, I may then go to higher magnification to double check that the key diagnostic features are present to confirm the diagnosis. When there is no obvious diagnosis from low magnification, I also use the systematic approach and look at higher power to see if there are any subtle abnormalities present that might provide useful insight about the case.

A thorough knowledge of normal skin histology is essential before learning dermatopathology. Histology is the foundation for all of diagnostic pathology. If you do not know what normal looks like, how can you possibly recognize abnormal? Rather than review all of the normal skin structures in this book, I strongly recommend that the reader watch my free YouTube video on normal skin histology: http://bit.ly/2MwK0n9. It covers all of the normal skin structures that you need to know, along with many practical pearls that will help you learn and practice dermatopathology.

LEARN THE BASICS OF CLINICAL DERMATOLOGY

Dermatology is a different world from the rest of medicine, and the specialty of dermatopathology lives more in that realm than in the realm of pathology. To succeed in learning dermatopathology, one must begin to understand the language, terminology, and customs of the dermatologist. You must learn why the dermatologist is doing the biopsy, what information

she wants to obtain from it. You must read the dermatologist's clinical differential diagnosis or clinical description and recognize whether or not the pathologic diagnosis you want to render will make sense clinically. These things are particularly challenging for learners of dermatopathology who are pathologists (rather than dermatologists) by training. This book only has room for very brief mentions of the clinical dermatology aspects of each disease. I recommend readers obtain a clinical dermatology book so as to develop a better understanding of this important aspect of dermatopathology. I personally am a big fan of *Dermatology: Visual Recognition and Case Reviews* by Christine J. Ko, an introductory level book that teaches clinical dermatology patterns and terms, and correlates them to the underlying microscopic findings. For a more comprehensive textbook, *McKee's Pathology of the Skin* is my daily go-to dermatopathology reference text. Both of these books have numerous high-quality clinical photographs and focus on the aspects of clinical dermatology that are most relevant to the practice of dermatopathology.

Whenever possible, obtain a detailed clinical description of the dermatologic condition, especially when dealing with a rash or other non-neoplastic process. Even if the dermatologist does not include details on the requisition sheet, a phone call will usually allow you to obtain the information you need. Unfortunately, when a non-dermatologist is caring for the patient, you may receive little information (e.g., "erythematous rash" or "lesion"). While it is tempting to become infuriated by this, take a few deep breaths and instead work on convincing the treating physicians to obtain clinical photographs in the future, particularly for rashes or other unusual situations. It may take multiple attempts over time to talk them into this, but it is worth the trouble if you convince them in the end. A picture truly is worth 1000 words when it comes to derm-dermpath correlation. It could potentially save you, the patient, and even the treating physician from medical error and its legal consequences.

INTERPRETING THE REQUISITION SHEET

Some dermatologists provide a detailed clinical description on the dermatopathology requisition sheet that accompanies the specimen (e.g., multiple annular erythematous lesions with slight scale on right arm x 1 month). Others merely provide a clinical impression or differential diagnosis (e.g., tinea versus granuloma annulare versus erythema annulare centrifugum). From the clinical impression or differential, I can usually figure out what the process probably looks like clinically, even if the requisition sheet does not provide an actual description. If the dermatologist notes tinea versus granuloma annulare versus erythema annulare centrifugum, then the patient probably has an annular (ring-shaped) rash. If the differential is lentigo versus lentigo maligna, then I know the dermatologist is seeing a pigmented lesion; I must find something pigmented on the slide to account for the pigment seen clinically. If their differential is BCC (basal cell carcinoma) versus SCC (squamous cell carcinoma), then they are probably seeing a papule or nodule (i.e., a bump) clinically; I must find something on the slide to account for that appearance. If I cannot find anything on the slide to account for what the dermatologist is seeing, then I need to do deeper levels. If the differential is cyst versus lipoma (or some other larger nodule) and the biopsy shows normal skin even after deeper sections, I do not just call it "normal skin." I add a comment that the biopsy may not be representative and a deeper unsampled lesion cannot be excluded. These are just a few examples of how to think beyond what is stated on the requisition sheet to figure out more about what is going on clinically. If the requisition sheet info does not make sense, or if you are seeing something microscopically that does not seem to fit at all with the clinical impression, then a phone call to the dermatologist may be a good idea.

When the biopsy comes from a non-dermatologist, I do not put nearly as much trust in the clinical differential diagnosis, unless I have experience with the practitioner and know that they have good dermatology skills. In the United States at least, board certified dermatologists all receive a full 3 years of residency training in dermatology, ensuring excellence at clinical dermatology. Non-dermatologists (including both physicians and non-physicians) may have very good training in clinical dermatology or little experience in dermatology. It is highly variable. Until I get to know each individual

non-dermatologist by interacting with them over time, I will have no idea what their skill level is at clinical dermatology, and therefore I must use caution in how much trust I place in their clinical differential diagnoses when using that information to help me interpret the biopsy findings. In many cases, I will need to make a phone call or request clinical photographs to further interpret the case.

BUILDING RAPPORT WITH YOUR DERMATOLOGISTS

Regular verbal communication with your dermatologist colleagues is a great way to build rapport with them. It shows them that you care about what you are doing and that you want to help them and the patient. It also may make them feel more comfortable to communicate their preferences about report style, diagnostic terminology, how they wish to be notified about melanoma or other urgent diagnoses, etc. Catering to the needs of your dermatologist is a good way to help forge a long lasting and happy professional relationship between their clinic and your lab. Additionally, when a real problem arises (which will happen, no matter how good you and your lab are!), it is a lot easier to have the difficult conversation about it if you already have a comfortable working relationship. You definitely do not want to wait until a specimen gets lost or an incorrect diagnosis is made to make your first phone call to the dermatologist!

GROSSING AND HISTOLOGY TIPS

Proper grossing, processing, embedding, histologic sectioning, and H&E staining of skin biopsy specimens are all crucial steps in the practice of good dermatopathology. If one of these is suboptimal, do what it takes to fix it. These steps matter so much more than immunostains, molecular analysis, or other fancy ancillary tests. The basics have to be mastered first. The importance of a high quality H&E stain cannot be overemphasized (my favorite H&E protocol: http://bit.ly/2COXLZS). H&E is King.

Work closely with your pathologists' assistants, grossing technicians, and histotechnologists. Tell them "thank you" every time you can. Help them understand the important role their work plays in your ability to provide excellent patient care. Make them feel comfortable to come and ask you any time they have a question. Encourage them to ask you first about how to gross or embed complicated or unusual specimens; it is easier to do it right on the front end than to fix it after it has already been done the wrong way. Work with them in trouble-shooting issues. Encourage them to identify opportunities for improving the systems and work flows in the laboratory; they have a different viewpoint and will identify things that you may have overlooked, sometimes creating easy fixes that make huge improvements in quality or efficiency. Recognize the unique skill sets that histotechnologists possess that you probably lack (have you ever tried to cut perfect sections on hundreds of paraffin blocks early in the morning?). You and your lab staff are on the same team, and that is Team Patient Care. Let them know that they are an essential part of that team. And maybe buy cookies or donuts or lunch for them from time to time for good measure.

Punch biopsies and shave biopsies are usually inked and then bisected, unless they are too small to safely bisect for fear of crushing or distorting the tissue. Punch biopsies smaller than 4 mm are usually left intact and not bisected. Use your best judgment on shave biopsies. Measurement of skin biopsies may not seem that important, but when two specimens are accidentally swapped at some point during processing, 0.9 x 0.8 x 0.2 cm versus 0.4 x 0.3 x 0.1 cm might be the key to correcting the swap and avoiding catastrophe. Measure accurately. We also employ six alternating ink colors in our laboratory to help add a further layer of protection against swapped specimens. Specimen 1 will be inked blue, specimen 2 will be yellow, specimen 3 will be black, specimen 4 will be red, etc. The ink color is noted in the gross description and the same color ink is streaked across the paper requisition sheet to aid in rapid visualization of the correct color for each case. The ink color is checked before finalizing the diagnosis when reporting the biopsy results. If the ink on the tissue section is yellow but it was stated to be black at grossing, then we stop everything, pull the block and check it against the slide to figure out at what point the tissue swap may have occurred. This is an extra step, but it has helped us solve cases for which an accidental swap arose. No matter how good your laboratory is, a mix up between two different specimens is always a very

real and very serious possibility. We must work hard to prevent specimen swaps, and we must also be vigilant to detect any that accidentally happen so that we can correct them before final diagnoses are rendered on the wrong patients.

MICROSCOPIC DESCRIPTIONS

I almost always provide microscopic descriptions for inflammatory dermatoses or for anything unusual or complicated. In my experience, dermatologists generally expect this and will be unhappy if they do not receive it. For routine tumors or other straightforward diagnoses, I usually just give the diagnosis with no microscopic description. I have never received any complaints about this from my dermatology clients. However, I know some dermatopathologists who provide a microscopic description with every case.

"MARGIN" STATUS ON BIOPSIES

When tumor extends to the margin of a biopsy, you can say "margins positive" in the report if you wish. But the reverse is not true. Just because the margins look negative on a shave biopsy, recall that you are only visualizing two points on the entire circumference of that shave biopsy. You can say that the "examined margins are negative" or that the tumor is "not extending to section edges" (the latter phrase is what I prefer to use personally), but you cannot reliably state that the tumor is "completely excised" or has "negative margins". We previously studied this and found that a subset (23 percent) of shave biopsies of BCC or SCC that appeared to have negative margins on initial sections ended up having positive margins when the block was subsequently exhausted (1). From this, we concluded that the best approach was to not comment on margin status for biopsies of non-melanoma skin cancers. Most of the dermatologist colleagues in our community agreed with this approach and informed us that the margin status usually did not impact their management of the patient anyway. They were usually doing a biopsy of a suspected SCC or BCC merely to confirm the diagnosis, and they would then proceed to definitive treatment regardless of what the biopsy margin status was. Worrying about margin status is a lot of wasted time for the dermatopathologist and does not impact patient care. Some dermatologists still want to be informed of the margin status, at least in certain scenarios or in specific cases, and for these I am willing to make an exception upon request.

I still routinely report margin status on biopsies of melanocytic lesions (except for those rare dermatologists who do not want margin status on nevi). Most dermatologists in my community perform shave biopsies of pigmented lesions with the intent to completely remove the lesion. Thus, they usually want to know if the melanocytic lesion extends to the section edges or not, and they may manage the lesion differently based on that information. Our study did not examine melanocytic lesions, but I believe the same caveat likely applies here as well. Just because the examined section edges look negative for melanocytic lesion, we cannot be certain that all of the margins are truly negative. On melanoma biopsy specimens, I report the status of both peripheral and deep margins, either as "positive for (*in situ*/invasive) melanoma" or "negative on examined sections."

DERMPATH EMERGENCIES

I directly notify the dermatologist of any significant or unexpected findings per our laboratory policy. This can be done via phone call, email, or other agreed upon method. This ensures that serious or urgent diagnoses are communicated quickly and allows me to confirm that the diagnosis has been received (electronic medical records and fax machines sometimes fail). Our policy has a list of diagnoses that should be communicated in this way, including an initial diagnosis of melanoma or of aggressive cancers that may require urgent treatment (e.g., angiosarcoma, acute leukemias). It is important to remember that a variety of other non-neoplastic entities in dermatopathology can be just as serious as cancer, or even worse, including calciphylaxis, necrotizing fasciitis, toxic epidermal necrolysis, angioinvasive fungal infection, and fungal infections in an immunocompromised patient (2). I usually discuss biopsies on acutely ill in-patients or other rush biopsies directly with my dermatologists as well.

TO HEDGE OR NOT TO HEDGE?

"To hedge" means to give a diagnosis that is equivocal, less than fully certain, not definitive. It means to give a descriptive diagnosis with a

differential list of possible options, to say "it could be entity X, but entity Y cannot be excluded." Sometimes we must hedge in dermatopathology (at least I must), but we should try to be definitive whenever possible and save our hedging for when we really need it. If you hedge too often, your dermatologists will lose confidence in your diagnostic ability. They will not know when your hedging actually indicates a serious diagnostic difficulty or a complicated case that needs to be managed differently. When the difference in diagnoses does not matter for patient care, then I try to be definitive and avoid hedging. If I cannot decide if a lesion is a seborrheic keratosis or a verruca vulgaris, I do not say "benign keratosis with overlapping features of seborrheic keratosis and verruca vulgaris." If the dermatologist favored verruca, then I will use that clinical impression as an extra point to tip the scale, and I will call it verruca. If they listed both or neither in their differential, then I will just pick one diagnosis and move on to the next case. Both are benign conditions that are usually managed the same way. If I am wrong, and it is actually a seborrheic keratosis rather than a verruca, it is unlikely that anything bad will happen to the patient or to me because of it. On the other hand, when I am uncertain of the diagnosis, and the treatment or prognosis is significantly different for the entities I am debating between, then I will hedge. I like to ask myself: "If I am wrong about the diagnosis, how wrong will I be?" What is at stake for the patient medically and for myself legally? Will being wrong result in potentially morbid therapy (e.g., chemotherapy, irradiation, a huge excision, amputation), inadequate treatment of a serious disease, genetic or family planning implications, excess patient anxiety, poor prognosis, a bad patient outcome, and/or a lawsuit? If yes, and I am uncertain of the diagnosis, then I will hedge. When I do hedge, I try my best to tell the dermatologist which entity I am favoring, why I am having difficulty, and what if anything I want them to do about it (e.g., re-excise the lesion, follow the patient closely, repeat biopsy if the process persists or progresses after treatment, etc). Some dermatopathologists are wary of telling the dermatologist what to do in a report for fear that it will force their hand clinically. I usually say "____ is recommended if clinically feasible" to soften the language so that it is an optional request rather than a demand. I almost never receive complaints from my dermatologists or other clinical colleagues about making these types of recommendations in my report.

If the dermatologist asks me to send the case out in consultation for a second opinion, I happily agree without getting defensive about it. Patient care must always come before ego. If the expert consultant gives a definitive answer when I could not, this helps the patient and the dermatologist and also gives me a chance to learn from the case. If the expert consultant agrees with me that the case is hard and the diagnosis is uncertain, this is validation of my diagnostic skills, both to me personally and to the dermatologist. For beginners in dermatopathology, it is probably better to send out difficult cases for expert consultation rather than hedging, especially if there is a lot at stake for the patient. I still obtain consultation from my dermatopathologist partner on a daily basis. And I still voluntarily send out difficult cases for consultation with world experts from time to time. Sending cases out for expert consultation is a form of quality assurance that helps me continue to hone my diagnostic skills and learn how to better deal with challenging diagnostic scenarios. It also helps me to sleep better at night!

REFERENCES

1. Schnebelen AM, Gardner JM, Shalin SC. Margin status in shave biopsies of nonmelanoma skin cancers: Is it worth reporting? Arch Pathol Lab Med 2016;140:678-81.
2. Abate MS, Battle LR, Emerson AN, Gardner JM, Shalin SC. Dermatologic urgencies and emergencies: What every pathologist should know. Arch Pathol Lab Med 2019 [Epub ahead of print]

2 MISCELLANEOUS CURIOSITIES THAT CONFUSE BEGINNERS

After mastering normal skin histology, one is ready to embark on learning all the abnormalities that the skin has to offer. For the beginner, the difficulty is not always in identifying that something is abnormal, but rather in deciding whether the abnormality is real versus artifactual, or clinically significant versus incidental. This chapter will cover some of the miscellaneous findings that may confuse and concern beginners as well as a few diseases that do not fit well elsewhere in the book. These boil down into five major groups: 1) artifacts and procedure-related changes; 2) reactive changes; 3) unusual ("funny-looking") keratinocytes; 4) pigments; and 5) alien/foreign/exogenous substances from outside the human body.

ARTIFACTS AND PROCEDURE-RELATED CHANGES

Histologic processing and slide preparation produce a variety of artifacts in tissue. Pathologists learn to recognize these quickly during training, but there are a few artifacts in the skin that may be less familiar to beginners.

Tangential sectioning of the epidermis can produce a bizarre appearance that can greatly complicate interpretation of the specimen, especially in melanocytic lesions (see chapter 4, fig. 4-5). When islands of papillary dermis are completely surrounded by epidermis, the specimen has probably been tangentially sectioned. The papillary dermis may have the illusion of increased numbers of vessels, eccrine ducts, and hair follicles, because the section is cutting across the papillary dermis horizontally, showing a much broader area than is usually visualized on normal sections that are vertically oriented. The eccrine ducts and hair follicles may be cross sectioned (they appear to be "coming out of the slide" toward the viewer) rather than longitudinally sectioned (fig. 2-1).

Blood (erythrocytes) can end up outside vessels in the skin due to bleeding during the biopsy procedure, but a variety of pathological processes can also produce extravasation of erythrocytes into the dermis. There are a few tricks that help to separate true hemorrhage (which is pathologic) from artifactual procedure-related bleeding. If there are abundant erythrocytes in an otherwise normal dermis and there is no clinical suspicion of hemorrhage, ecchymosis, vasculitis, hemangioma, or any other description of an erythematous/violaceous/pigmented appearance, then the extravasated erythrocytes are probably related to the biopsy procedure rather than true in vivo hemorrhage. If the dermatologist has listed one of those entities or descriptors on the biopsy requisition sheet, then the blood is probably due to true hemorrhage and an explanation for it should be sought. The presence of hemosiderin suggests true hemorrhage rather than procedural bleeding. The presence of scattered erythrocytes in the papillary dermis is suggestive of hemorrhage (fig. 2-2), whereas large sheets of erythrocytes sitting in the middle of a normal reticular dermis suggests artifactual procedure-related bleeding (fig. 2-3).

Various inflammatory processes can be accompanied by hemorrhage, including leukocytoclastic vasculitis, pigmented purpuric dermatosis, some arthropod bite reactions, and others (see chapter 8). Coagulopathies can display luminal fibrin thrombi or hemorrhage, depending on the scenario. Ecchymosis (bruise), while rarely biopsied, shows hemorrhage in the dermis or subcutis due to previous trauma. Trauma to acral sites can produce collections of blood within the stratum corneum (*talon noir*; fig. 2-4) or beneath the nail plate; these lesions may mimic melanoma clinically. Patients with thrombocytopenia or on aspirin or other antiplatelet therapy may show foci of hemorrhage in the

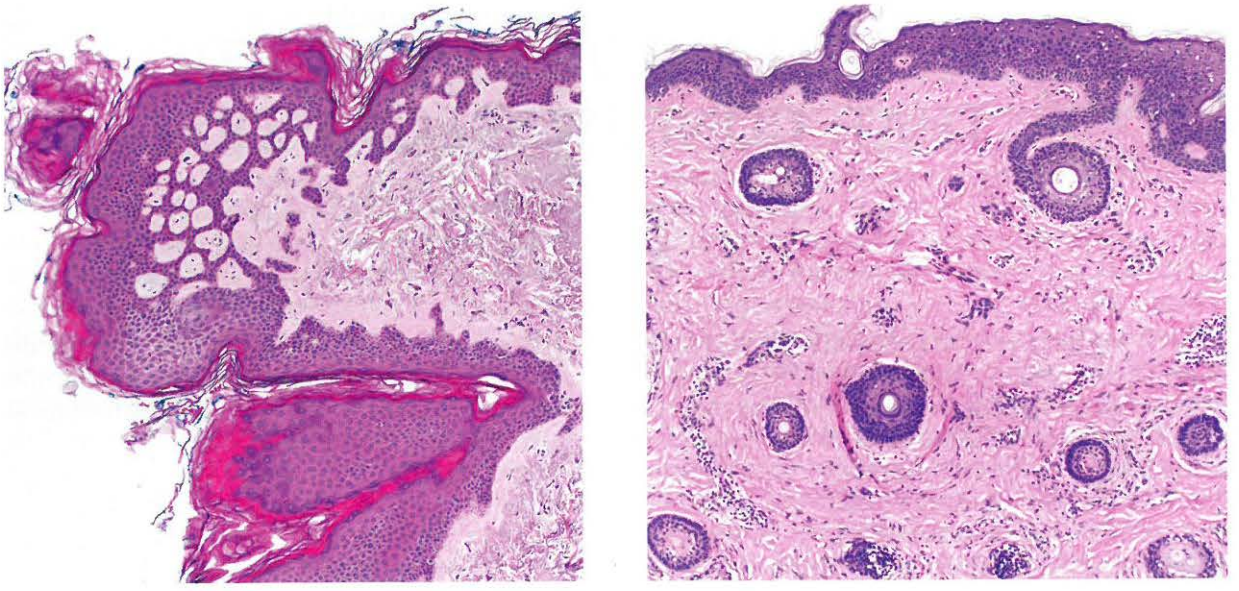


Figure 2-1

TANGENTIAL SECTIONING ARTIFACT

Left: Islands of papillary dermis completely surrounded by epidermis (upper left) and bizarre convolution of the epidermal surface (bottom left) are evidence of tangential embedding/sectioning. The upper right shows normally sectioned skin.

Right: There are more hair follicles than normal, and they are cut in cross section rather than longitudinally (they are round structures). These are subtle clues to tangential sectioning horizontally across the papillary dermis rather than vertically down through it. Most of the dermis seen here is actually papillary rather than reticular dermis.

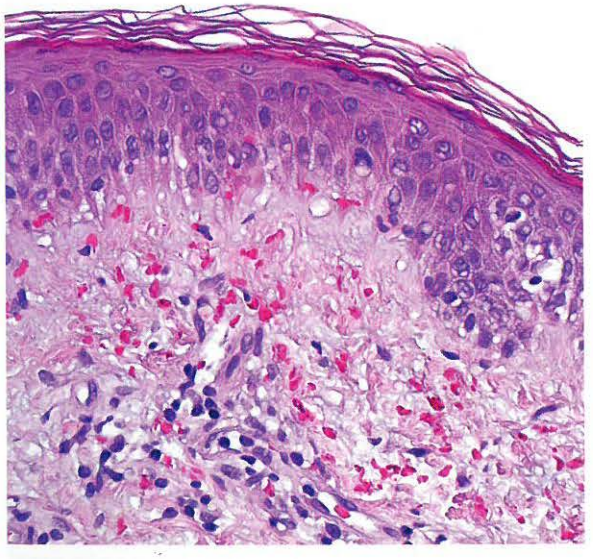


Figure 2-2

TRUE HEMORRHAGE

Scattered erythrocytes in the papillary dermis are suggestive of true hemorrhage. This biopsy is from petechiae.

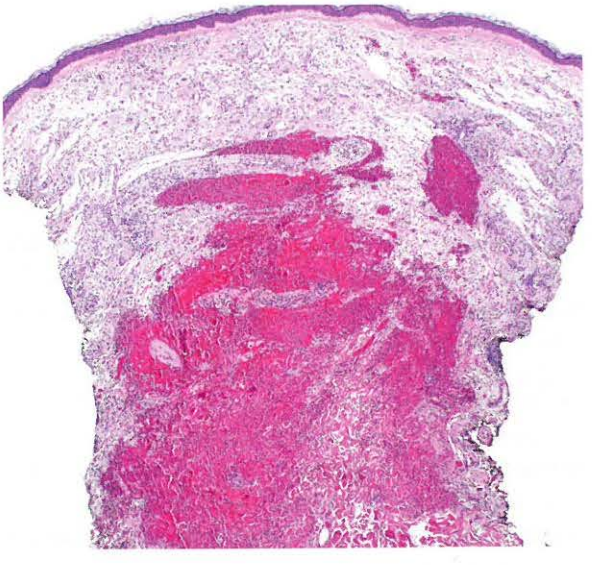


Figure 2-3

PROCEDURE-RELATED BLEEDING (ARTIFACTUAL)

Large sheets of erythrocytes fill the mid and deep dermis. This pattern usually represents artifactual procedure-related bleeding rather than true hemorrhage. This punch biopsy is from a xanthoma. The lesion was yellow clinically, and no hemosiderin was present microscopically.

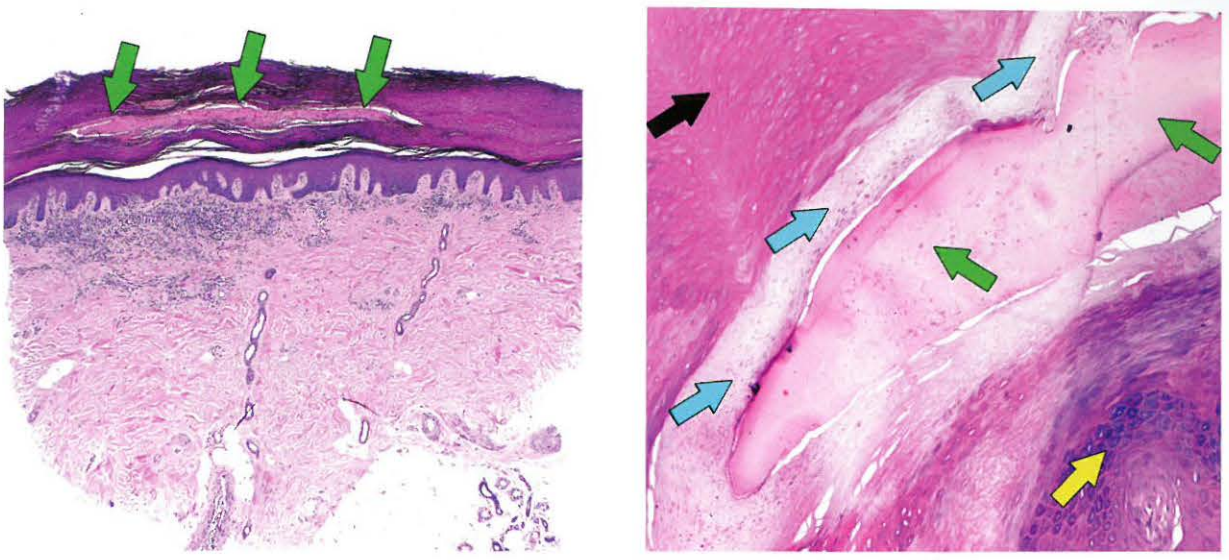


Figure 2-4

TALON NOIR

Left: A pocket of hemorrhage (arrows) became entrapped within the acral stratum corneum due to previous trauma. Right: Erythrocytes may be present, but in many cases, only serum and debris remain within the intracorneal hemorrhage at the time of biopsy (arrows: green = serum, black = stratum corneum, blue = parakeratosis, yellow = granular layer of epidermis).

papillary dermis. Elderly patients with severe solar damage (thick solar elastosis and thin atrophic epidermis) may develop spontaneous dermal hemorrhage (solar purpura).

Another procedure-induced change is *electrical/cautery artifact* (fig. 2-5). In my practice, I usually see this only in specimens submitted by surgeons, since dermatologists usually use blades to perform biopsies rather than cutting skin via electrosurgery. Electrical current (whether from electrosurgery/cautery or unintended electrical shock) produces distortion of both epidermal keratinocytes and dermal collagen when it passes through the skin.

REACTIVE CHANGES

Solar elastosis is caused by chronic exposure to sun or other ultraviolet light (fig. 2-6). This results in increased amounts of disorganized elastic fibers in the reticular dermis. In elderly extremely sun-damaged white patients, *solar elastosis* can form a thick blue-gray layer that completely replaces the pink dermal collagen.

Elastosis first forms in the superficial reticular dermis (a thin band of collagen in the papillary dermis is often spared), and as it accumulates over time, it replaces and pushes the reticular dermal collagen further and further down into the deeper dermis. In patients with this degree of solar elastosis, the presence of pink collagen replacing a zone of the blue-gray elastosis in the reticular dermis is a useful clue to new collagen deposition (fig. 2-7). This collagen was not part of the original dermis but was deposited after the patient got old and sun damaged (i.e., after the solar elastosis was formed) (see chapter 4, fig. 4-37). This trick only works for markedly sun-damaged patients with abundant solar elastosis.

Longstanding nevi on sun-damaged facial skin often accumulate unusual purple tangled solar elastosis fibers within the midst of the intradermal nevus cells, but they have little or no solar elastosis in the dermis deep to the nevus since the nevus has protected the underlying dermis from years of sun exposure (*umbrella sign*) (figs. 2-8, 2-9). In contrast, melanomas in sun-damaged skin tend to have solar elastosis under them since they arise after the solar elastosis was formed, pushing the solar elastosis downward (1,2).

Recognizing the range of features of granulation tissue is a crucial skill (fig. 2-10). The plump spindle to stellate myofibroblasts in *granulation tissue* can look atypical to the untrained eye since they are large and often have mitotic activity.

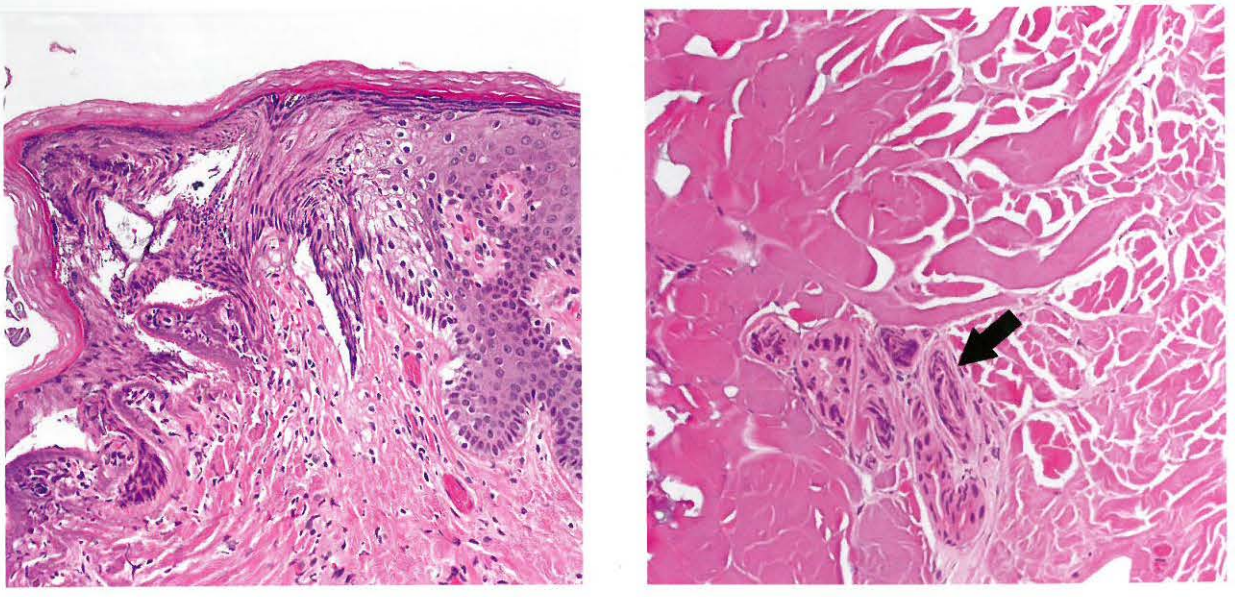


Figure 2-5

ELECTRICAL CURRENT/CAUTERY ARTIFACT

Left: The epidermis at the margin of this excision specimen is distorted by streaming, stretched out keratinocyte nuclei due to electrosurgery/cautery effect (left). Contrast with normal epidermis (right).

Right: Dermal collagen at the excision margin is swollen, smudgy, and darker in color due to electrosurgery/cautery effect (left). Contrast with normal dermis (right). Note the streaming, stretched out nuclei in a distorted eccrine coil (arrow).

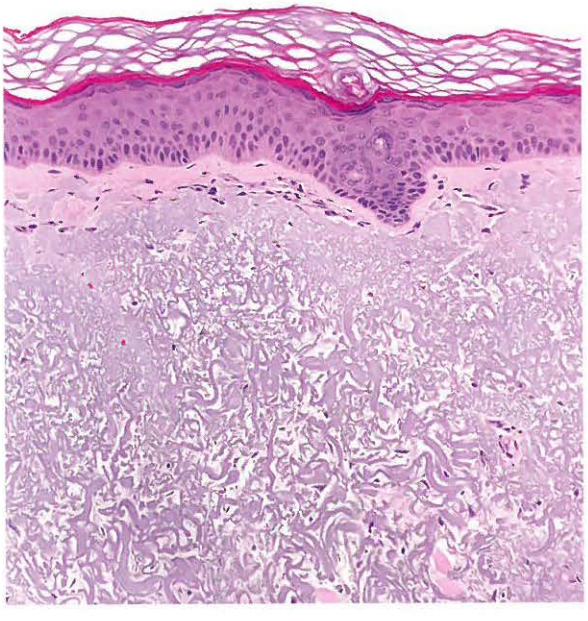


Figure 2-6

SOLAR ELASTOSIS

A tangled matt of thick blue-grey elastic fibers has accumulated over many years of chronic sun exposure, completely replacing the normal pink reticular dermal collagen.

As emphasized in our Soft Tissue book, studying granulation tissue at biopsy sites or in other situations that are obviously benign and reactive can aid the pathologist in interpreting reactive processes, nodular fasciitis, and related lesions in more difficult clinical situations. Granulation tissue consists of myofibroblasts/fibroblasts loosely arranged in a myxoid or edematous background, with inflammation and proliferating small blood vessels. As granulation tissue ages and matures into scar, the myofibroblasts/fibroblasts become more spindled and elongated, and develop a fascicular arrangement that runs parallel to the overlying epidermis (see fig. 4-38). Increased amounts of pink collagen fibers are present between the parallel spindled myofibroblasts/fibroblasts. The purple/amphophilic cytoplasm and the presence of intervening collagen are useful clues to distinguish myofibroblasts/fibroblasts from smooth muscle (fig. 2-11). My video demonstrates this in more detail: http://bit.ly/2SqI6FY.

Recognition of biopsy site changes is also important (fig. 2-12). In wide local excisions performed after a biopsy diagnosis of malignancy, the area directly adjacent to the biopsy site is

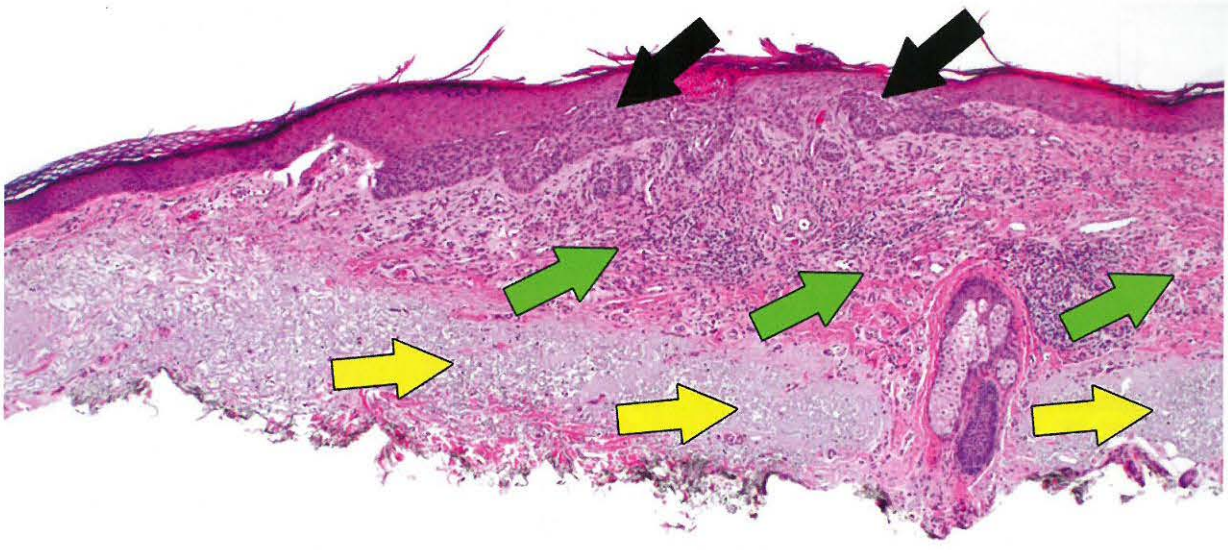


Figure 2-7

NEW COLLAGEN REPLACING SOLAR ELASTOSIS

This patient's background dermis (left) is filled with blue-gray solar elastosis (similar to the dermis seen in fig. 2-6). A zone of new pink collagen (green arrows) has replaced and pushed down that solar elastosis (yellow arrows). The new collagen in this particular case is a surgical scar adjacent to a recurrent basal cell carcinoma (black arrows).

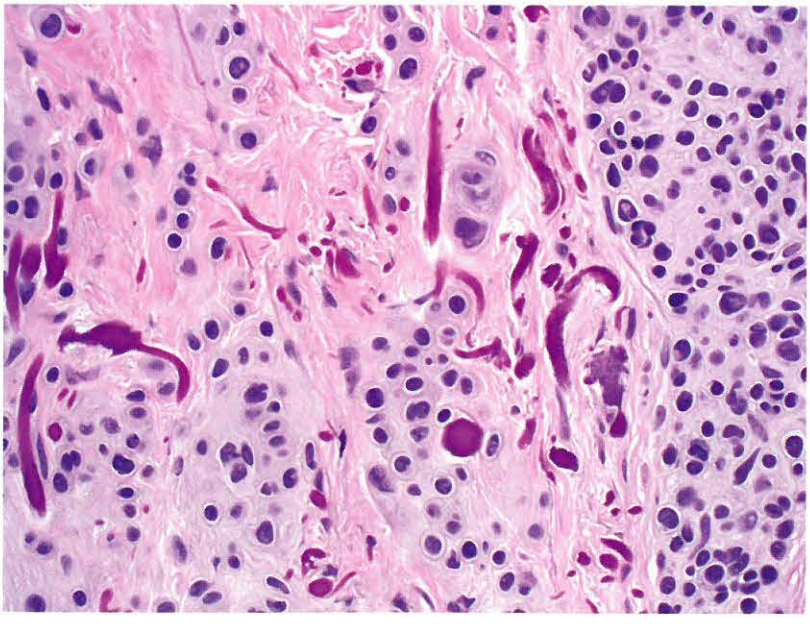


Figure 2-8

TANGLED PURPLE SOLAR ELASTOSIS IN A NEVUS

Congenital pattern nevi on sun-damaged facial skin often accumulate these unusual purple tangled solar elastosis fibers, which intermingle with the nevus cells in the dermis. This is a reassuring finding against melanoma, as it is evidence that the melanocytic lesion has been present for many years.

the most likely to show residual tumor. Lack of an obvious biopsy site on an excision specimen may indicate that the excision was performed at the wrong site or that there is an unusual clinical situation that needs clarification. Sometimes the history of a previous biopsy is not provided, and in those situations the recognition of microscopic changes to suggest a previous biopsy may be crucial in avoiding misdiagnosis (e.g., recurrent nevus versus melanoma; see chapter 4).

Biopsy sites in skin display granulation tissue or scar depending on how long ago the initial biopsy was performed. There will also be alteration of the epidermis at the site of the biopsy. This

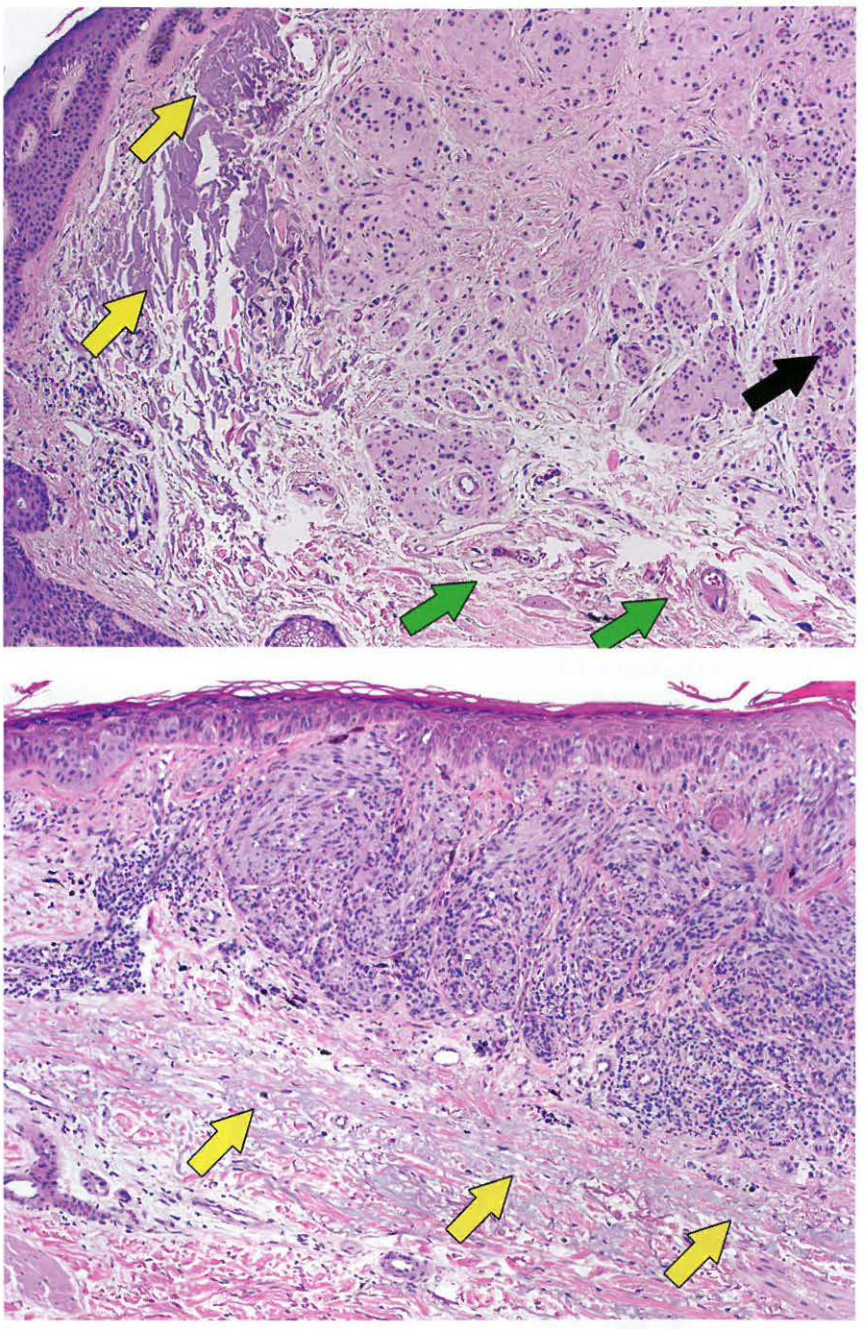


Figure 2-9

UMBRELLA SIGN

Top: Congenital pattern nevus with an "umbrella sign." There is solar elastosis in the dermis adjacent to the nevus (yellow arrows), but the dermis deep to the nevus lacks solar elastosis (green arrows). The longstanding nevus has provided an "umbrella" that sheltered the deep dermis from the sun over the years. Those unique purple tangled solar elastosis fibers (see fig. 2-8) are present focally within the nevus (black arrow).

Bottom: Melanoma lacking an "umbrella sign." There is a band of solar elastosis (yellow arrows) beneath the melanoma, indicating that this melanocytic proliferation is new rather than longstanding. It arose after the patient became old and sun damaged.

initially shows ulceration with underlying granulation tissue or cauterized collagen. Later, granulation tissue fills in the defect and epidermis grows to completely cover the surface.

The new epidermis has a variety of reactive changes that can look worrisome to those who are not familiar with them: enlarged reactive keratinocytes, increased basal layer mitotic activity, and a jagged interface between the basal layer and the underlying dermal collagen. Eccrine ducts within the dermal granulation tissue can display squamous metaplasia, cystic dilation, and reactive atypia, all of which can make them mimic nests of invasive squamous cell carcinoma.

The subcutis underlying a biopsy site often shows pockets of fat necrosis, even if the original biopsy was only a superficial shave that did not approach the subcutis; I suspect this may

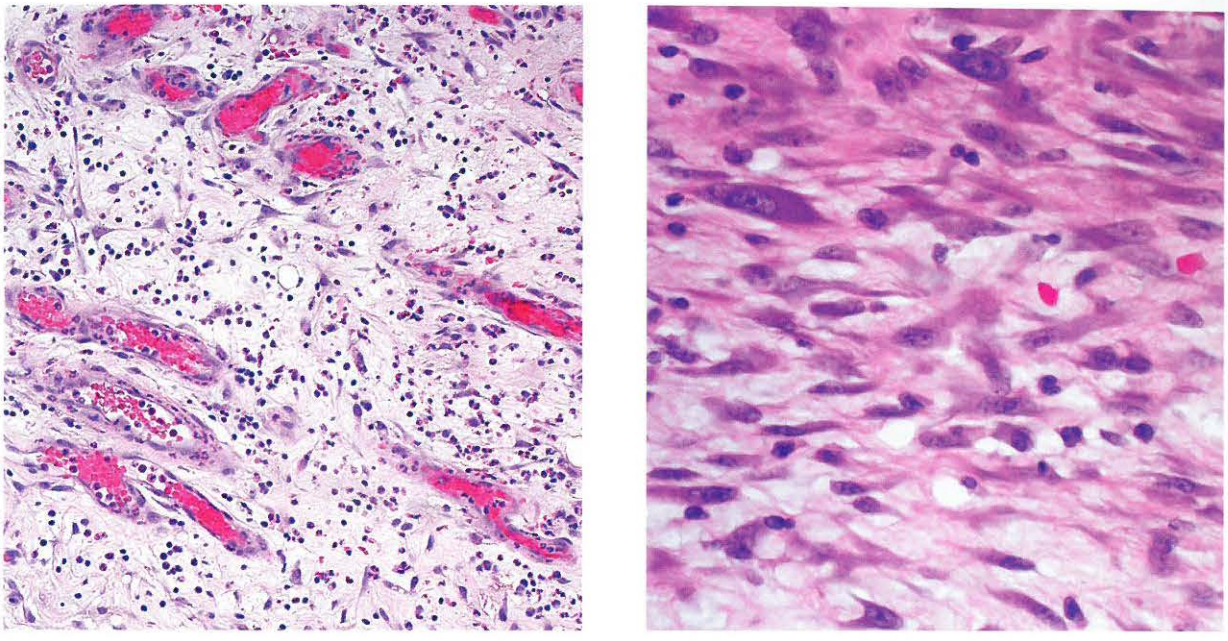


Figure 2-10

GRANULATION TISSUE

Left: Granulation tissue consists of spindle to stellate myofibroblasts loosely arranged in a myxoid or edematous background with inflammation and proliferating small blood vessels.

Right: Plump spindle to stellate myofibroblasts in the granulation tissue/scar may look atypical, especially when viewed on high magnification. Do not confuse these with residual tumor cells. The purple amphophilic cytoplasm and spaced out hypocellular arrangement in a loose myxoid/edematous background are clues to recognizing myofibroblasts.

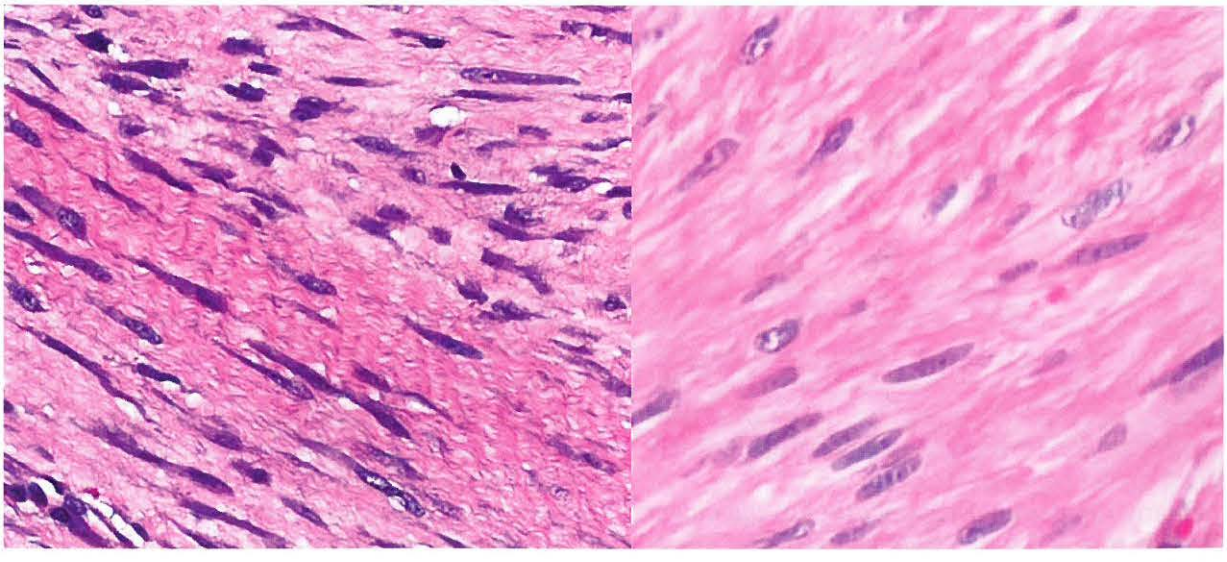
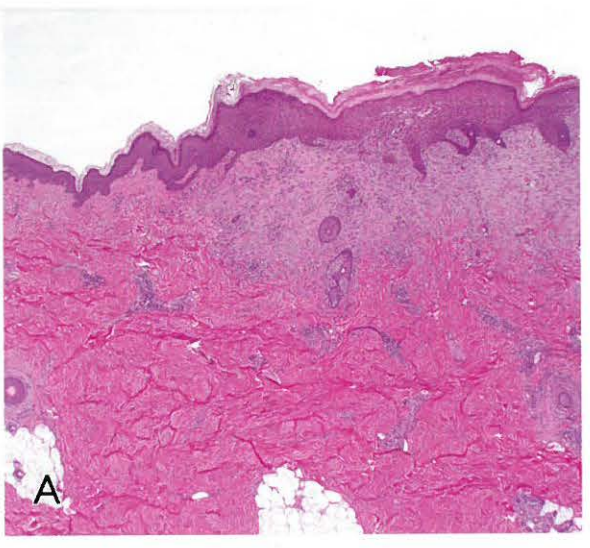
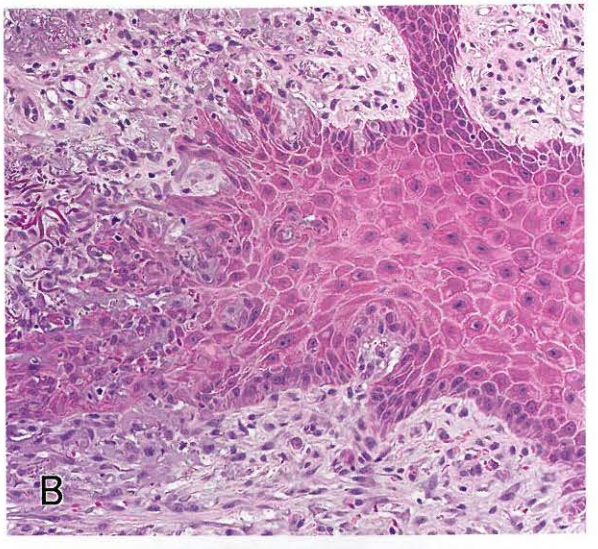


Figure 2-11

MYOFIBROBLASTS VERSUS SMOOTH MUSCLE

Myofibroblasts (left) and smooth muscle (right) both form pink fascicles of parallel spindle cells, but myofibroblasts have purple/amphophilic cytoplasm and are divided from each other by intervening collagen fibers whereas smooth muscle cells have abundant pink cytoplasm (due to intracytoplasmic contractile filaments) and are packed closely together with minimal intervening collagen.





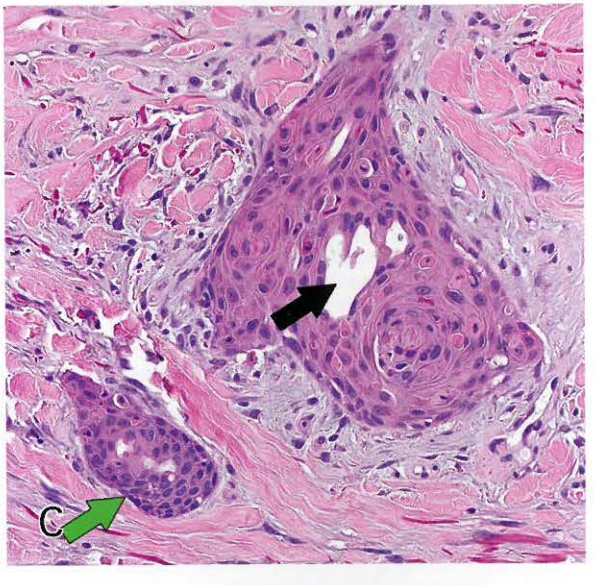


Figure 2-12

BIOPSY SITE CHANGES

A: The biopsy site (upper right) in this wide local excision specimen is easily recognized at low magnification. The pale zone of granulation tissue and evolving scar looks distinctly different from the normal bright pink collagen that makes up the rest of the dermis. The overlying epidermis shows reactive proliferative changes.

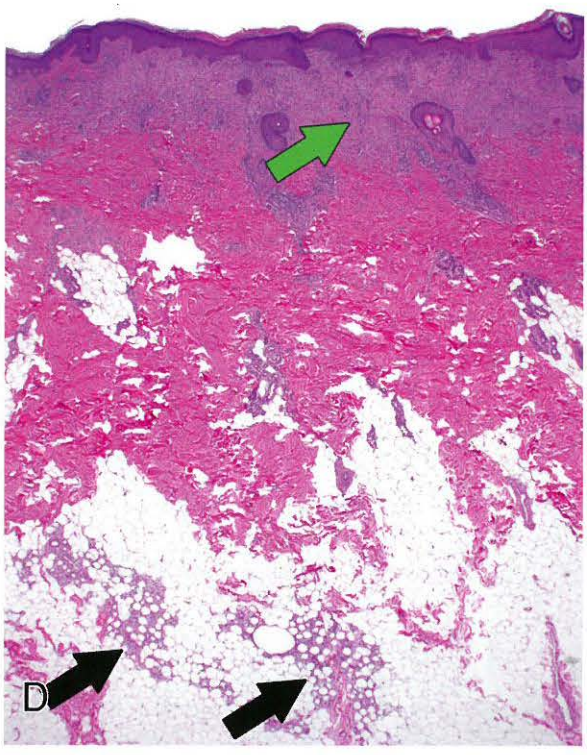
B: The new epidermis over the biopsy site shows enlarged keratinocytes with mitoses and reactive atypia. There is often a jagged interface with the underlying dermis. Proliferation of the epidermis can be so robust that it mimics squamous cell carcinoma (pseudoepitheliomatous/pseudocarcinomatous hyperplasia).

C: Regenerating eccrine ducts adjacent to the biopsy site are often distorted in shape and greatly expanded in size, with prominent squamous metaplasia. Do not confuse the large glassy keratinocytes in these ducts with squamous cell carcinoma. The presence of duct lumen (black arrow) and association/connection with a more obvious eccrine duct (green arrow) are useful clues.

be due to damage of the subcutis from injection of anesthetic agents prior to the initial biopsy. As the biopsy site ages, the epidermis loses the unusual reactive features and becomes a thin atrophic epidermis without rete ridges, overlying a mature dermal scar (fig. 2-13).

Many dermatologists apply topical *aluminum chloride* to the wound immediately after shave biopsy to achieve hemostasis. Aluminum chloride produces two distinct microscopic findings: 1) histiocytes with grayish granular cytoplasm, and 2) distorted, purple, sometimes calcified bundles of reticular dermal collagen (fig. 2-14). Finding either of these in the dermis near granulation tissue or scar suggests that a biopsy was previously performed at that site (likely by a dermatologist). These histiocytes may be a potential mimic of intracytoplasmic infectious diseases such as histoplasmosis or leishmaniasis, although I believe it is hard to truly confuse these aluminum chloride-laden histiocytes with infection or anything else once one has become familiar with them.

Monsel solution (ferric subsulfate) was used in the past for chemical hemostasis after biopsy, although many dermatologists now use aluminum chloride instead, because Monsel solution can cause discoloration of the skin at the biopsy site ("Monsel tattoo"). This is due to deposition



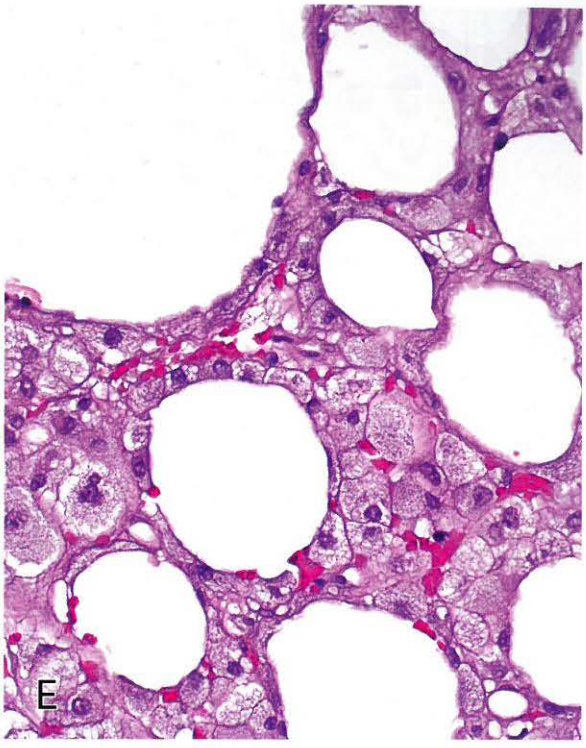


Figure 2-12, continued

D: The subcutis underlying a biopsy site often shows pockets of fat necrosis (black arrows), even though the original shave biopsy site (green arrow) is very superficial and does not approach the subcutis.

E: Fat necrosis under a biopsy site. Foamy histiocytes intervene between mature adipocytes.

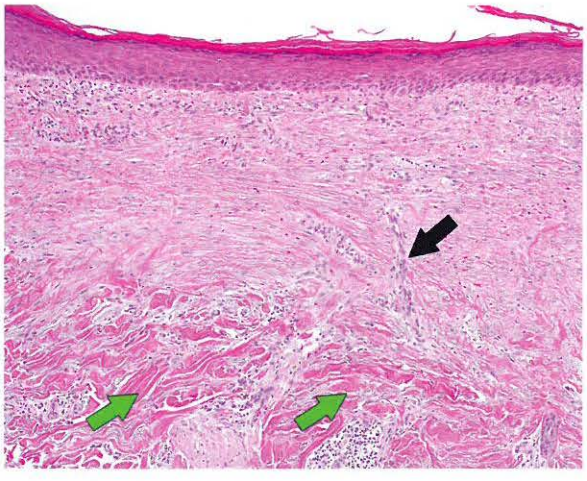


Figure 2-13

SCAR AT HEALED BIOPSY SITE

In scar, spindled fibroblasts/myofibroblasts are often parallel to the epidermis, while blood vessels tend to be perpendicular/vertical (black arrow). The new collagen of the scar is distinctly different from the bundles of preexisting collagen in the underlying reticular dermis (green arrows). The overlying epidermis is atrophic, lacking rete ridges.

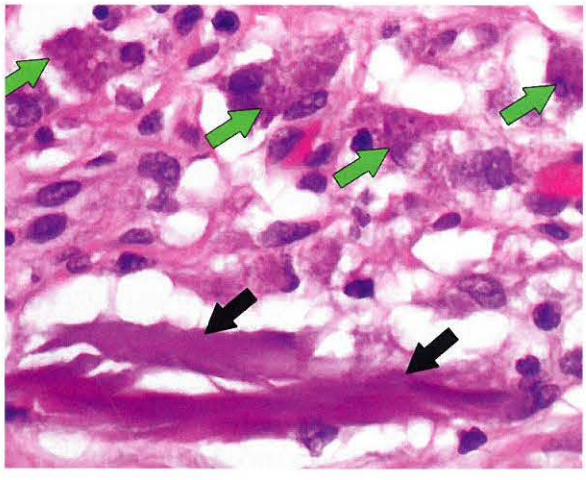


Figure 2-14

ALUMINUM CHLORIDE

Histiocytes with gray to purple granular cytoplasm (green arrows) and distorted purple bundles of collagen (black arrows) within the dermis are evidence of a previous biopsy site. These changes are the result of topical aluminum chloride used as a hemostatic agent following the biopsy procedure.

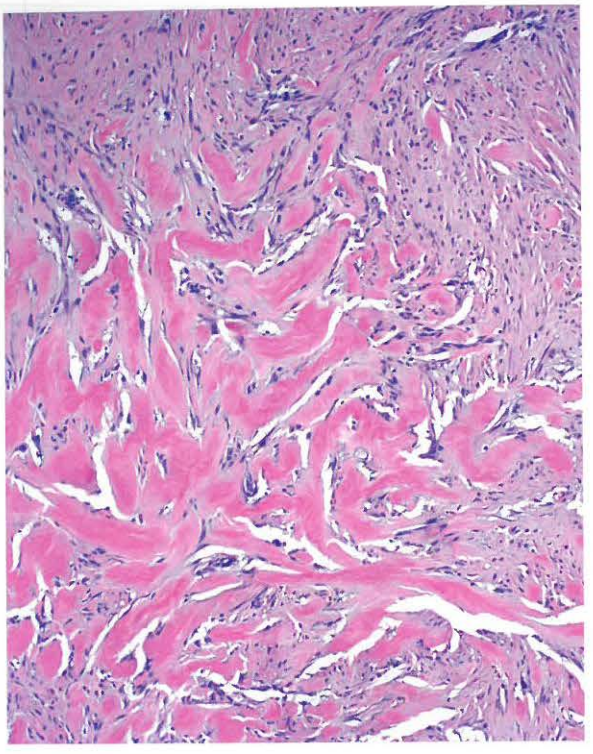


Figure 2-15

KELOIDAL SCAR

Thick bright pink "keloidal" collagen bundles are a characteristic finding in keloids and hypertrophic scars.

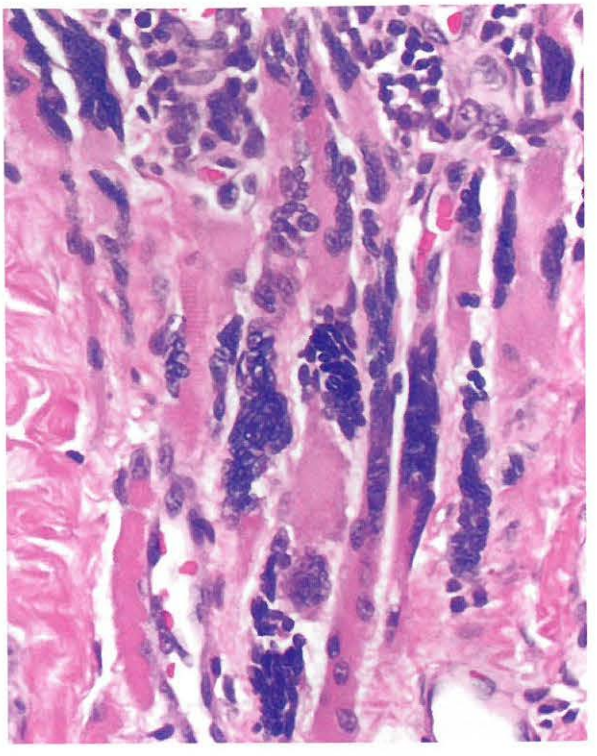


Figure 2-16

SKELETAL MUSCLE ATROPHY

Atrophy of skeletal muscle cells leads to decreased cytoplasm, which causes the multiple peripheral nuclei to overlap. These overlapping nuclei can mimic multinucleated histiocytes or even pleomorphic tumor cells.

of golden-brown hemosiderin-like pigment at the biopsy site, sometimes with a corresponding reactive proliferation of histiocytes and giant cells. The cellularity and pigment together can cause confusion with residual melanoma if one is not familiar with the effect.

Some scars enlarge over time into a *hypertrophic scar* or a *keloid*. The distinction is mostly clinical: keloids extend beyond the margin of the original surgical defect and hypertrophic scars do not. Both look similar microscopically and are composed of variable numbers of thick bright pink "keloidal" collagen bundles embedded within background scar (fig. 2-15). I use "keloidal scar" as my diagnosis for this finding, unless clinical information is provided to determine whether it is a hypertrophic scar or a keloid.

Skeletal muscle atrophy is another important reactive change to recognize, not only in deep soft tissue but also in skin. Skeletal muscle is normally found in the dermis in the face. Inflammatory/reactive processes or infiltrative tumors can cause atrophy of skeletal muscle cells, which leads to decreased contractile proteins and corresponding decreased cytoplasmic volume. This in turn causes the multiple peripheral skeletal muscle nuclei to overlap, which can cause these atrophic cells to resemble multinucleated histiocytes or even large pleomorphic tumor cells (fig. 2-16). Recognition of other similar cells nearby is a helpful clue, as skeletal muscle fibers normally are arranged in bundles. If the tissue sample is large enough, these multinucleated cells can be traced back to areas of normal tissue and a transition to more obvious skeletal muscle cells seen.

Thermal (burn) or cryogenic (freeze) injury in skin usually show zones of partial to full thickness epidermal necrosis (fig. 2-17). This can be seen when a skin lesion is frozen with liquid nitrogen and then a biopsy is performed not long after. The clinical history is helpful here. The dermis is usually uninvolved unless the injury is extensive.

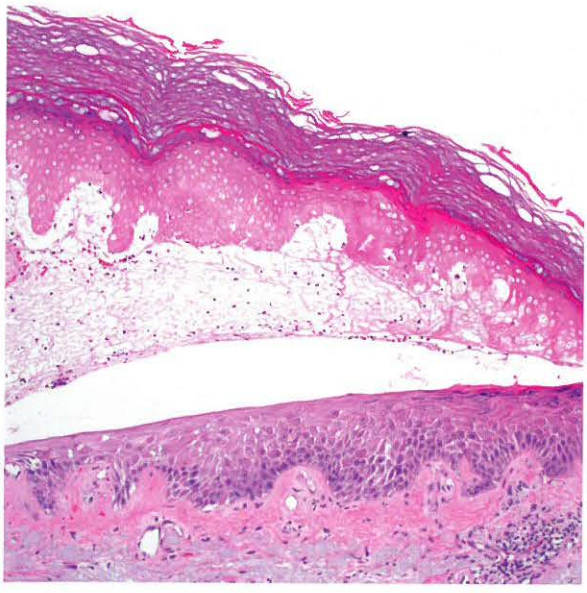


Figure 2-17

CRYOGENIC (FREEZE) INJURY

This skin was treated with liquid nitrogen cryotherapy and the resulting blister was later biopsied. The epidermis became completely necrotic from the freeze injury, and then detached to form the blister roof. The blister roof is a "shadow" of the original epidermis, complete with a corneal layer and rete ridges, but it is completely pink and devoid of viable nuclei. Contrast this with the partial layer of new epidermis that has "re-epithelialized" the blister floor.

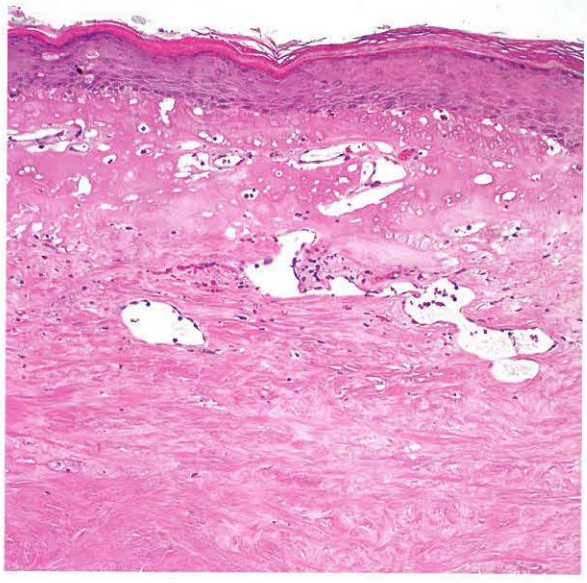


Figure 2-18

RADIATION EFFECT

This severe case shows epidermal atrophy, marked dermal sclerosis, and dilated blood vessels. The superficial dermis shows a homogenized pink zone of fibrin. Radiation changes can resemble morphea or lichen sclerosus (see chapter 8). The fibrin and dilated vessels here are useful clues for radiation therapy.

Radiation therapy produces a variety of reactive changes in skin (fig. 2-18). The epidermis becomes atrophic and sometimes shows spongiosis. The dermis becomes sclerotic with ectatic blood vessels. Hemorrhage, fibrin, and hemosiderin may be seen. There are scattered enlarged "radiation fibroblasts" in the dermis, which may show prominent hyperchromasia and pleomorphism. These benign degenerative changes should not to be confused with malignancy; the scattered hypocellularity of these cells is an important reassuring clue. The subcutis may show thickened sclerotic fibrous septa between the fat lobules. Perineural fibrosis may also be present. Angiosarcoma and other forms of postradiation sarcoma can develop in this setting. If there is any concern that a partial biopsy may not be representative, especially for unusual vascular changes in an irradiated site, I add a comment recommending follow up and repeat biopsy if there are violaceous/purpuric skin changes, growing mass, or other causes of clinical concern. Patients should be routinely asked at admission to the dermatology clinic if they have a history of radiation therapy. Irradiated sites should be routinely examined by the dermatologist and self-examined by the patient. This is a free and easy improvement to current dermatology practice that could potentially lead to early detection of postradiation angiosarcomas.

Venous stasis produces reactive vascular changes in the lower legs. Almost all adults have some degree of this, which means that recognizing subtle stasis change can be a useful clue to the anatomic site of a biopsy in the absence of clinical information. Stasis changes tend to be more prominent in older adults and in patients with other causes of venous insufficiency. The key microscopic feature is the presence of clustered lobular proliferations of thick-walled capillaries in the papillary dermis (fig. 2-19). There may also be dermal fibrosis, hemorrhage, and hemosiderin, depending upon the chronicity and severity.

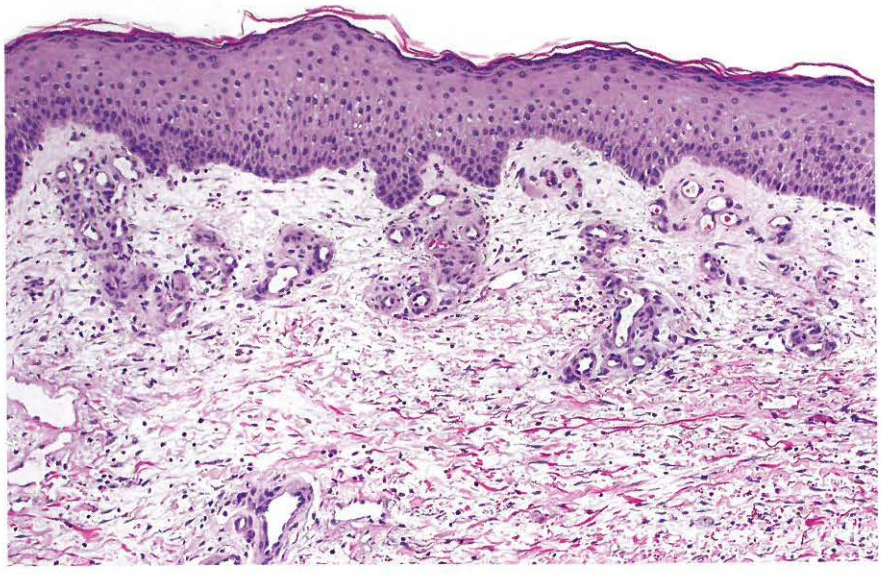


Figure 2-19

VENOUS STASIS

Multiple clustered lobular proliferations of thick-walled capillaries are present in the papillary dermis. This biopsy was from the ankle.

In very severe cases, stasis changes are so robust as to resemble Kaposi sarcoma, both clinically and histologically; this is called "acroangiodermatitis" ("pseudo-Kaposi sarcoma"). A human herpesvirus (HHV-8) immunostain is essentially always positive in Kaposi sarcoma. If HHV-8 is unavailable, endothelial markers like CD34 or ERG can be used (CD31 is sometimes weak or negative in Kaposi sarcoma) (3). Both entities have true vascular channels, which stain with endothelial markers, but the intervening spindle cells in acroangiodermatitis are fibroblasts whereas they are spindled endothelial cells in Kaposi sarcoma. CD34 and ERG are positive in the spindle cells of Kaposi sarcoma but negative in the spindle cells of acroangiodermatitis.

Chronic lymphedema results from long-term lymphatic stasis. This can occur in the legs of elderly or obese patients, in the overhanging abdominal pannus of morbidly obese patients, and in extremities from which the draining lymph nodes have been surgically removed. In early lymphedema, there is increased space between reticular dermal collagen bundles due to build up of interstitial fluid. This may be hard to recognize, but the presence of irregular ectatic lymphatic channels in the dermis is a useful clue (fig. 2-20). Over time, the dermis becomes fibrotic and shows increased collagen fibers within edematous areas as well as scattered spindle to stellate reactive fibroblasts. The epidermis may show prominent reactive acanthosis and papillomatosis, resulting in a verrucous appearance both clinically and microscopically (when severe, this is called "elephantiasis nostras verrucosa"). In morbidly obese patients, there may be mass formation (massive localized lymphedema), in which lobules of mature adipocytes are separated by widened fibrotic, edematous septa with scattered spindle to stellate reactive fibroblasts; do not confuse this with atypical lipomatous tumor/well-differentiated liposarcoma.

When patients chronically scratch, rub, itch, or pick at their skin, the epidermis becomes acanthotic and hyperkeratotic as a reactive protective mechanism. This is referred to as *lichen simplex chronicus* (when there is a diffuse plaque clinically) or *prurigo nodularis* (when there is a solitary papule or nodule clinically) (figs. 2-21, 2-22). This phenomenon often occurs as a "secondary change" on top of an underlying primary process (e.g., secondary lichen simplex chronicus due to chronic itching of primary eczematous/atopic dermatitis, secondary prurigo nodularis developing adjacent to a primary actinic keratosis that the patient has been picking at). Recognizing these secondary "lichenification" changes is crucial. If the skin is lichenified, then the process is likely chronic, as these changes take some time to develop. Aggressive picking or scratching of the skin can partially erode or fully ulcerate the epidermis, leading to an excoriation, another type of secondary change (fig. 2-23). Secondary changes

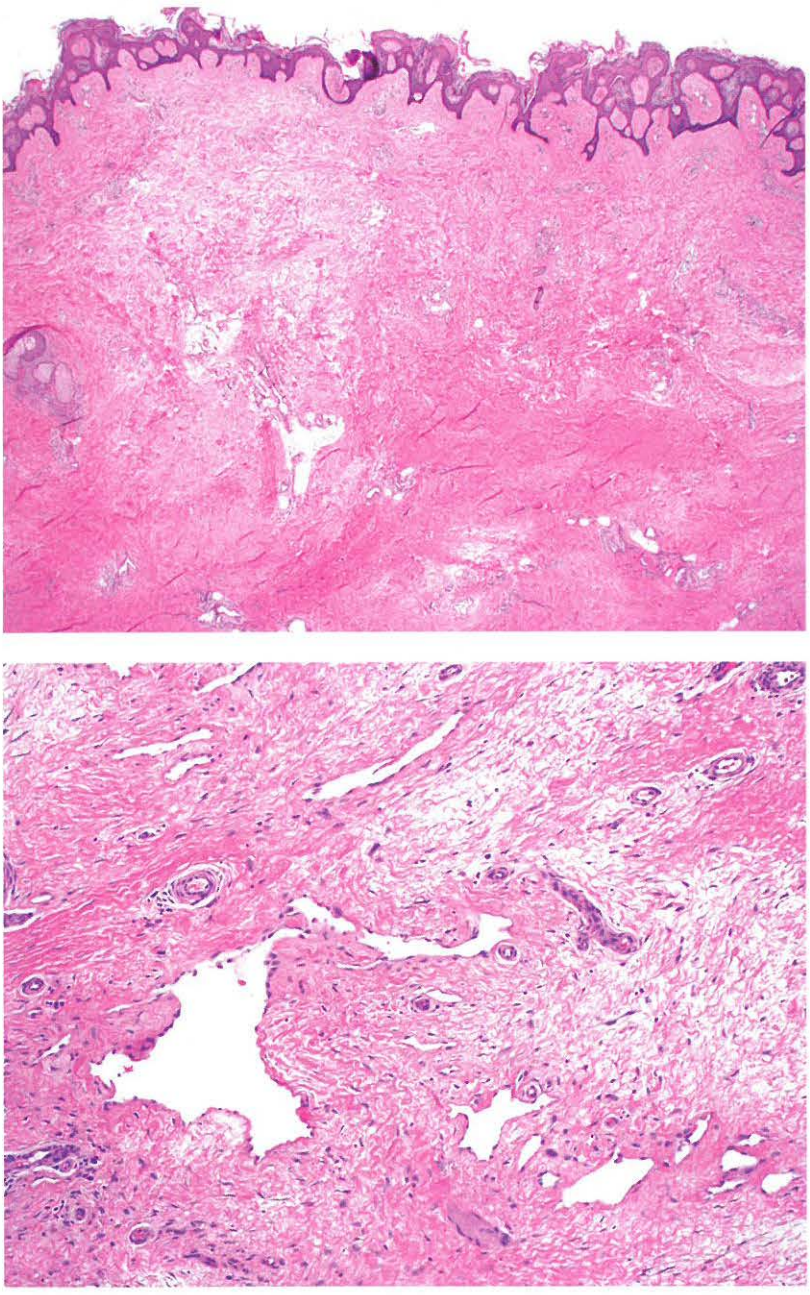


Figure 2-20

CHRONIC LYMPHEDEMA

Top: The dermis is markedly expanded by pink fibrosis intermingled with pale edematous zones. In some cases, the epidermis shows prominent reactive papillomatosis and acanthosis, imparting a verrucous appearance.

Bottom: The dermis is fibrotic, but with intervening pale spaces between collagen fibers representing background edema fluid. Dilated branching lymphatic channels are present, a useful clue for lymphedema.

may be so abundant as to obscure the underlying primary process; this should be mentioned in a comment so the dermatologist recognizes that the biopsy may not be representative of the underlying dermatosis.

Lichen simplex chronicus and lichenification have nothing to do with true lichenoid interface dermatoses (such as lichen planus), which are defined by a band of lymphocytes beneath the epidermis and vacuolar interface alteration (see chapter 8). "Lichen" is one of the many frustrating terms in dermatology that has different meanings depending on the disease. When I diagnose lichen simplex chronicus on a biopsy performed by a non-dermatologist (especially if it is a vulvar biopsy from a gynecologist), I add this comment to help avoid confusion over the terminology: "These findings are due to chronic rubbing, scratching, or other irritation. Features of lichen sclerosus or lichen planus are not identified."

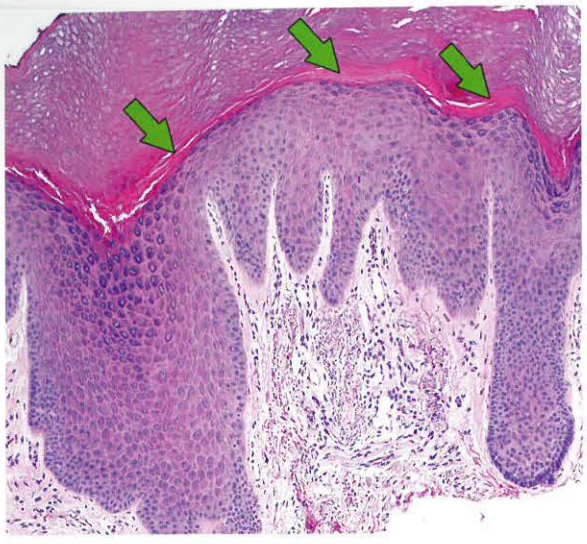


Figure 2-21

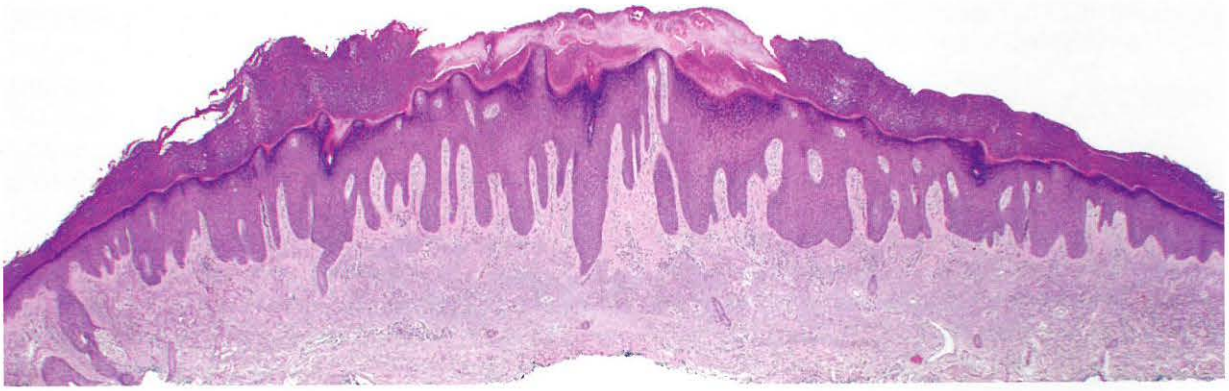
LICHEN SIMPLEX CHRONICUS (LSC)

The epidermis is acanthotic, with irregularly elongated rete. There is hypergranulosis with thickening of the stratum corneum, usually with compact orthokeratosis. A pale band of pink keratin just above the granular layer represents the stratum lucidum (arrows); this layer is only seen in acral skin or in skin that has been chronically rubbed, scratched, or otherwise "lichenified."

FUNNY-LOOKING KERATINOCYTES

A variety of unusual changes can be seen in keratinocytes. Some of these are artifacts, others are real but incidental or clinically insignificant findings, and others are important diagnostic clues.

Keratinocytes sometimes develop artifactual perinuclear cytoplasmic vacuoles due to shrinking of the cells during tissue processing. Keratinocyte cytoplasm is filled with cytokeratin intermediate filaments, which are attached to desmosomes in the cell membranes, which are attached to desmosomes of adjacent keratinocytes, which are attached to cytoplasmic cytokeratin filaments, and on and on. All of the keratinocytes in the epidermis thus form an incredibly strong interconnected network that holds together against outside forces. When tissue shrinks during processing, the keratinocyte nucleus is left naked and alone in the middle of the cell since it has shrunk away from the surrounding cytoplasm (fig. 2-24). The keratinocyte cytoplasm is held tightly against the cell membrane at the periphery of the cell (because the keratin filaments are attached to the desmosomes).



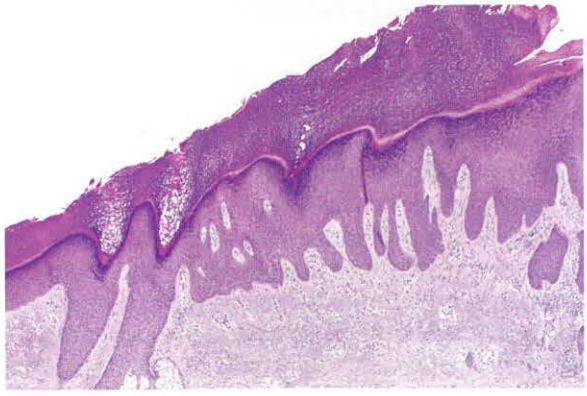


Figure 2-22

PRURIGO NODULARIS

Above: When the entire lesion is present on the biopsy, a "crescendo-decrescendo" pattern of acanthosis can often be seen, starting with normal skin at one edge of the lesion, getting thicker and thicker moving toward the center of the lesion, and then getting smaller and smaller back to normal epidermis at the other edge of the lesion.

Right: A closer look at prurigo nodularis shows the same features as LSC. There are elongated rete, hypergranulosis, hyperkeratosis, and a pale pink stratum lucidum dividing the granular layer from the corneal layer. Both LSC and prurigo can show some papillomatosis of the surface, imparting a slightly verrucous appearance.

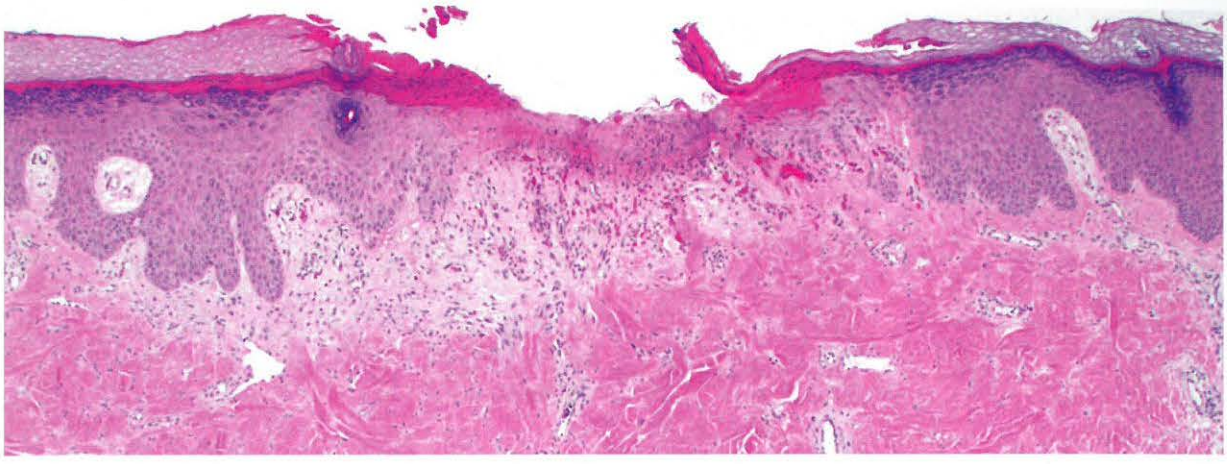


Figure 2-23

EXCORIATION

There is a small ulcer through the epidermis. Fibrin is present in the ulcer bed, and there is granulation tissue in the underlying dermis. Note the obvious LSC changes in the epidermis adjacent to the ulcer, evidence that the patient has caused or contributed to this ulcer by scratching or picking.

The artifactual vacuoles in keratinocytes may have a signet ring appearance (fig. 2-25). Melanocytes may also develop artifactual vacuoles, but they tend to be around the outside of the cell, leaving the cytoplasm and nucleus of the vacuole hugging one another (fig. 2-26). Melanocytes lack cytokeratin filaments and desmosomes, so they are not bound tightly to their neighbors like the keratinocytes are. When they shrink, the cytoplasm stays connected to the nucleus. This is an easy way to tell vacuolated keratinocytes from vacuolated melanocytes on H&E-stained slides (my short video discusses this topic further: http://bit.ly/2tt9pFi).

Epidermolytic hyperkeratosis (EHK) is a rare congenital ichthyosis caused by germline mutations in the genes for keratin 1 or 10, which are the main keratins present in spinous layer keratinocytes. The mutations result in misfolded keratin filaments, which clump together instead of evenly filling the cytoplasm of the spinous layer keratinocytes. The microscopic appearance is a focal area of epidermis where the keratinocytes have clear cytoplasm and disorganized pink cytoplasmic globules of misfolded keratin proteins, creating the false appearance of an epidermis that is dissolving (thus the term "epidermolytic") (fig. 2-27). The affected portion of epidermis also usually has hypergranulosis and overlying hyperkeratosis. Although the diffuse congenital ichthyotic form of EHK is rare,

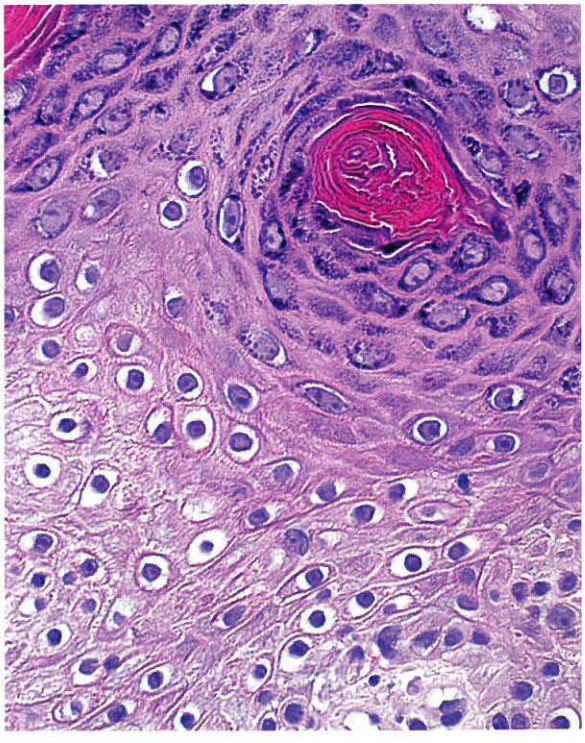


Figure 2-24

VACUOLATION ARTIFACT OF KERATINOCYTES

Vacuolation artifact in keratinocytes results in naked nuclei surrounded by empty white halos. The pink cytoplasm of each keratinocyte is seen at the periphery of the vacuole/halo, where it is connected to adjacent keratinocytes by desmosome "spines."

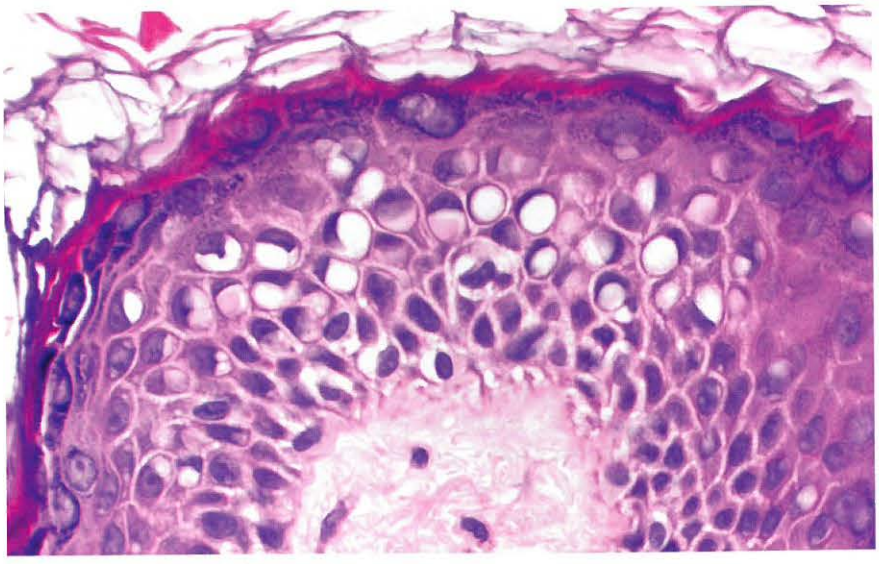


Figure 2-25

SIGNET RING VACUOLATION ARTIFACT OF KERATINOCYTES

Artifactual vacuoles in keratinocytes may sometimes have a signet ring appearance rather than a full halo around a naked nucleus.

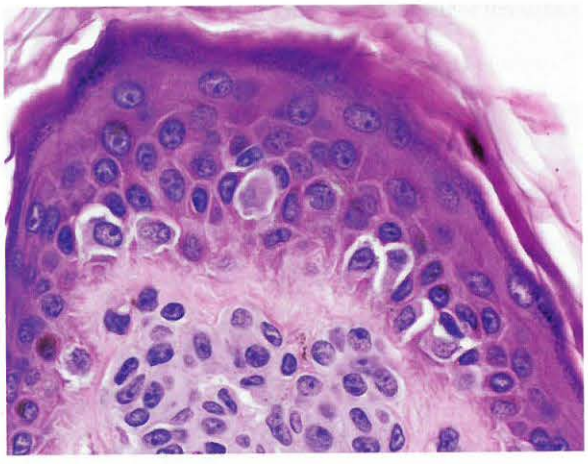


Figure 2-26

VACUOLATION ARTIFACT OF MELANOCYTES

Artifactual vacuoles in melanocytes tend to be around the outside of the cell, leaving the cytoplasm in the center of the vacuole clinging to the nucleus. These large junctional melanocytes are from the epidermis overlying a congenital nevus (similar to fig. 4-1B).

tiny microscopic foci of EHK are commonly seen in the skin of otherwise normal individuals. Incidental foci of EHK are of no clinical significance and do not need to be mentioned in the pathology report. It is only discussed here because it can confuse beginners in dermatopathology.

Epidermodysplasia verruciformis (EDV) is a form of verruca plana (flat wart) caused by a variety of different HPV serotypes. There is a rare inherited form of EDV in which patients have a genetic susceptibility to these HPV serotypes and develop numerous verruca plana. Sporadic foci of EDV, however, are common in the skin of normal patients (4). These foci show enlarged keratinocytes in the spinous layer, with characteristic blue-gray voluminous cytoplasm (fig. 2-28). Small incidental foci of EDV are of no clinical significance and need not be reported.

Porokeratosis is a common skin disease with a characteristic microscopic feature: the "cornoid lamella" (fig. 2-29). This is a tall vertical tower of parakeratosis with vacuolation and apoptosis of the underlying keratinocytes. Clinically, the cornoid lamella results in a peripheral grooved ridge or ring of thickened keratin, which borders a central zone of epidermal atrophy, erythema, and/or hyperpigmentation (5). A shave biopsy through a small ring-like lesion of porokeratosis shows two peripheral cornoid lamellae, corresponding to both sides of the ring of scale seen clinically. The skin between the cornoid lamellae may show a variety of unusual changes, including epidermal atrophy or acanthosis, dermal fibrosis, or mixed dermal inflammation.

Acantholytic dyskeratosis is a distinct microscopic pattern that is important to recognize, as it is the key finding in several dermatologic entities (fig. 2-30). The epidermal keratinocytes detach from one another and the epidermis falls apart (acantholysis), forming a suprabasilar intraepidermal blister, which can mimic the tombstone pattern seen in pemphigus (see chapter 9). Detached acantholytic keratinocytes have rounded cell

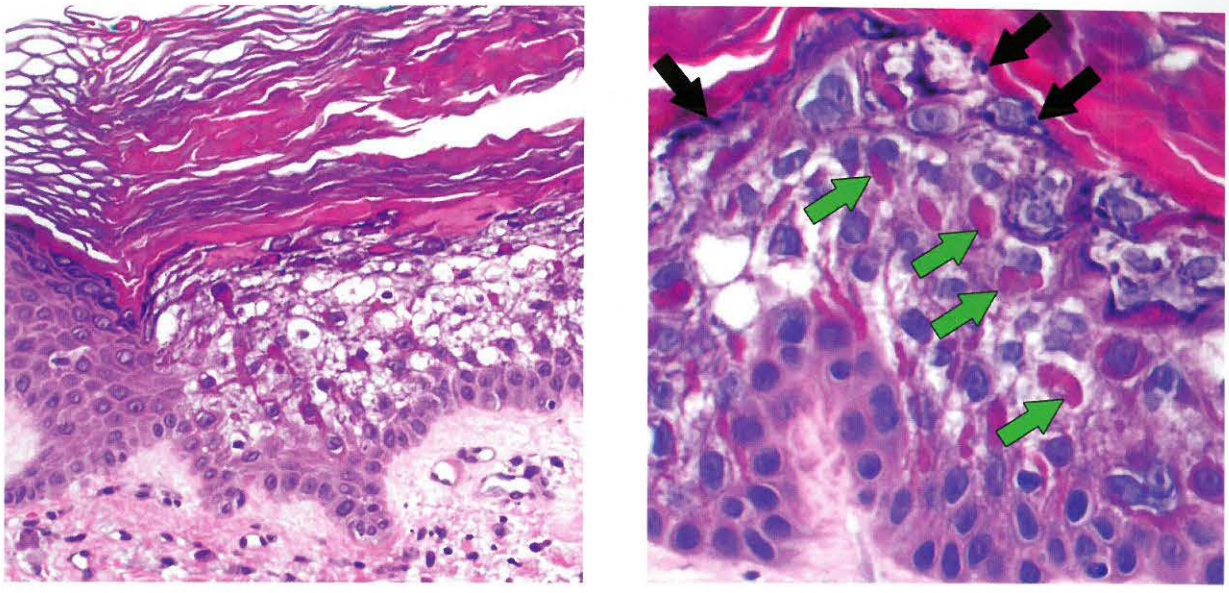


Figure 2-27

EPIDERMOLYTIC HYPERKERATOSIS (EHK)

Left: The spinous layer keratinocytes have clear cytoplasm, creating the false appearance of an epidermis that is disintegrating. There is thick overlying hyperkeratosis. Contrast with normal epidermis on the left.

Right: The pink globules (green arrows) within the clear keratinocytes represent misfolded keratin filaments (keratin 1 or 10). The basal layer (which has keratins 5 and 14 rather than 1 and 10) is uninvolved. Large irregular purple keratohyaline granules are another common finding in EHK (black arrows).

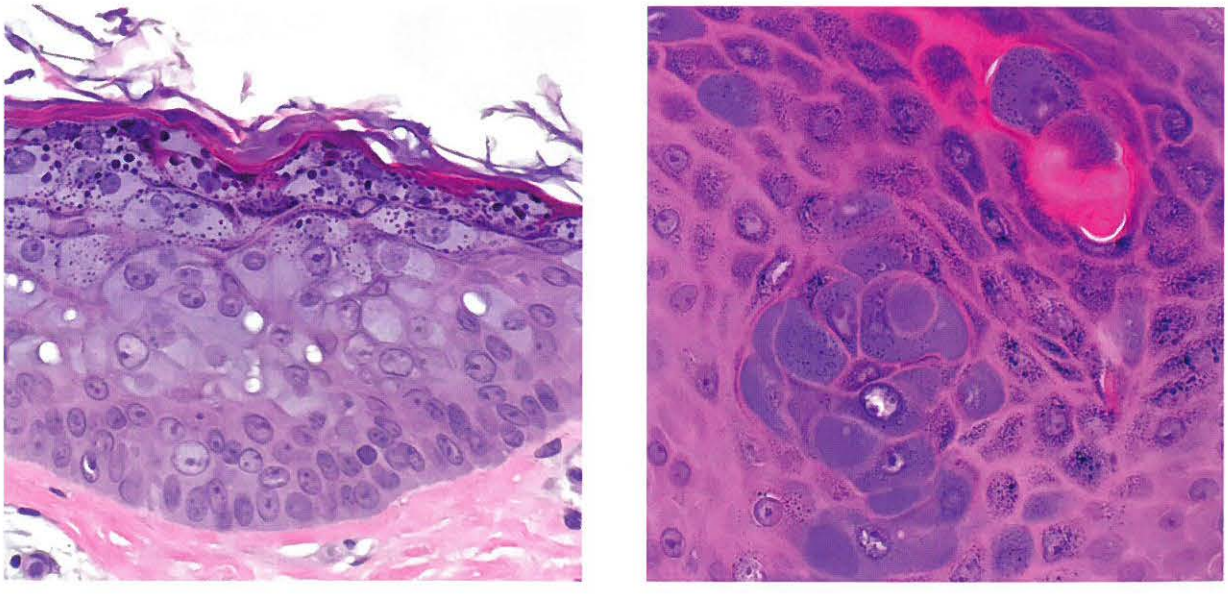


Figure 2-28

EPIDERMODYSPLASIA VERRUCIFORMIS (EDV)

Left: Like other forms of verruca plana (flat wart), EDV shows an acanthotic epidermis and large purple keratohyaline granules in the granular layer. The spinous layer keratinocytes have enlarged nuclei with abundant blue-grey cytoplasm; this unique form of human papillomavirus (HPV) effect is characteristic of EDV.

Right: Voluminous homogeneous keratinocyte cytoplasm in this particular hue of blue-gray is pathognomonic for EDV.

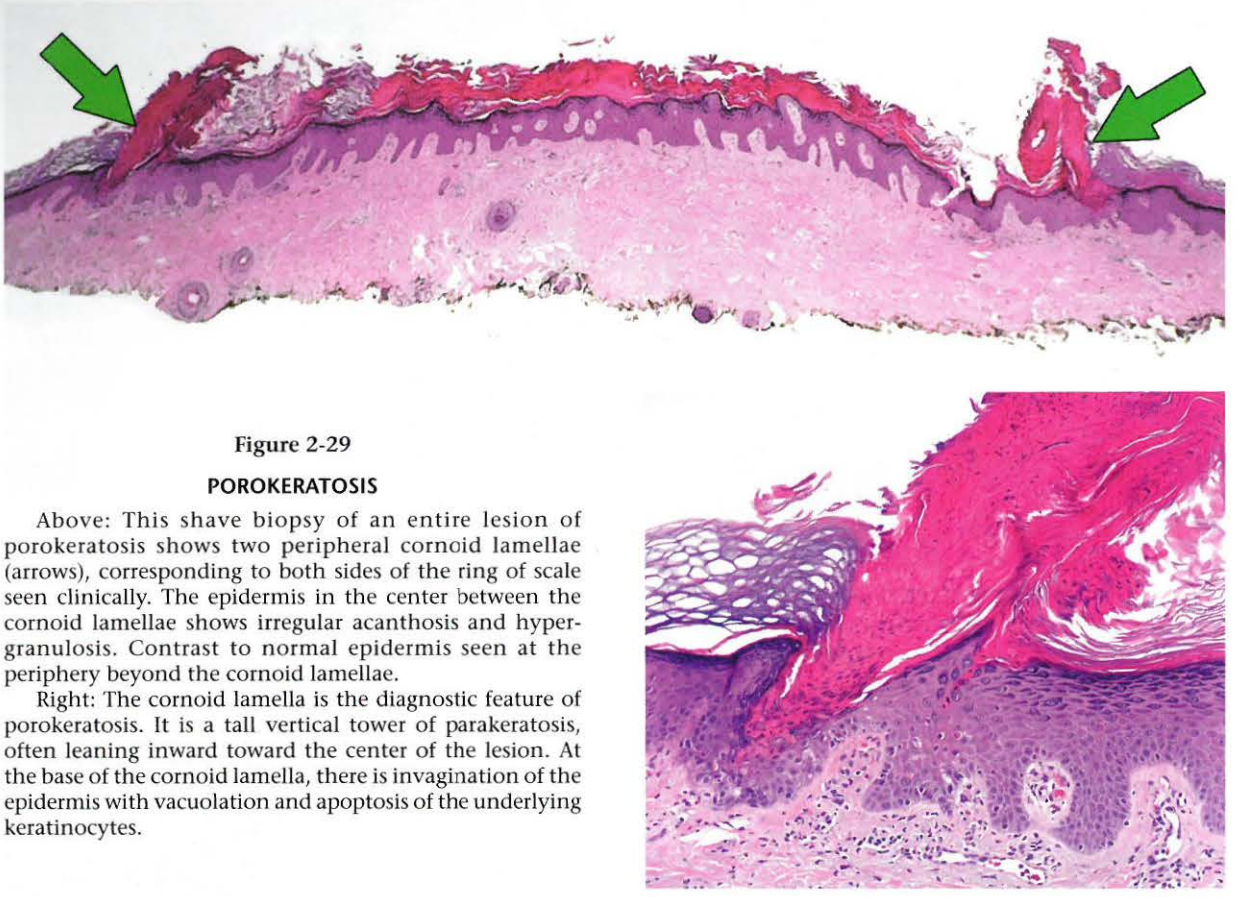


Figure 2-29

POROKERATOSIS

Above: This shave biopsy of an entire lesion of porokeratosis shows two peripheral cornoid lamellae (arrows), corresponding to both sides of the ring of scale seen clinically. The epidermis in the center between the cornoid lamellae shows irregular acanthosis and hypergranulosis. Contrast to normal epidermis seen at the periphery beyond the cornoid lamellae.

Right: The cornoid lamella is the diagnostic feature of porokeratosis. It is a tall vertical tower of parakeratosis, often leaning inward toward the center of the lesion. At the base of the cornoid lamella, there is invagination of the epidermis with vacuolation and apoptosis of the underlying keratinocytes.

borders and dense, more deeply eosinophilic cytoplasm due to the dense bunching up of keratin filaments around the nucleus instead of stretching out between neighboring keratinocytes like normal. As the acantholytic keratinocytes die, their nuclei become pyknotic and hyperchromatic, and eventually disappear, and their cytoplasm becomes even more deeply eosinophilic (dyskeratosis).

Dyskeratotic keratinocytes take two forms: enlarged rounded "corps ronds" or flattened "grains" with cigar-shaped nuclei. Corps ronds sometimes have abundant irregular keratohyaline granules (fig. 2-31) (5). Darier disease, Grover disease, warty dyskeratoma, and acantholytic dyskeratotic acanthoma all show acantholytic dyskeratosis microscopically; they are mostly distinguished by their differing clinical presentations.

Darier disease is a hereditary genetic syndrome due to germline mutation of *ATP2A2*. This results in greasy crusted plaques on the upper chest, back, scalp, ears, face, and neck (5). Biopsy shows multiple zones of acantholytic dyskeratosis with variable hyperkeratosis. On a small biopsy, however, it can look just like Grover disease or other diseases that show the acantholytic dyskeratosis pattern.

Grover disease (transient acantholytic dermatosis) presents as multiple small itchy papules, often on the trunk. Small foci of acantholytic dyskeratosis are seen in the epidermis, often with underlying mixed inflammation, including lymphocytes and eosinophils (fig. 2-32). Sometimes the changes are subtle at first. Deeper levels are a good idea when there is no obvious lesion and the biopsy was performed to rule out Grover disease, folliculitis, or multiple small papules. Focal subepidermal inflammation or focal hypergranulosis (see the superficial epidermis in fig. 2-31) are both clues that Grover disease might show up on deeper sections.

The term focal acantholytic dyskeratosis refers to a small focus of acantholytic dyskeratosis when it is unclear whether the clinical scenario fits well for Grover disease. I add a comment that

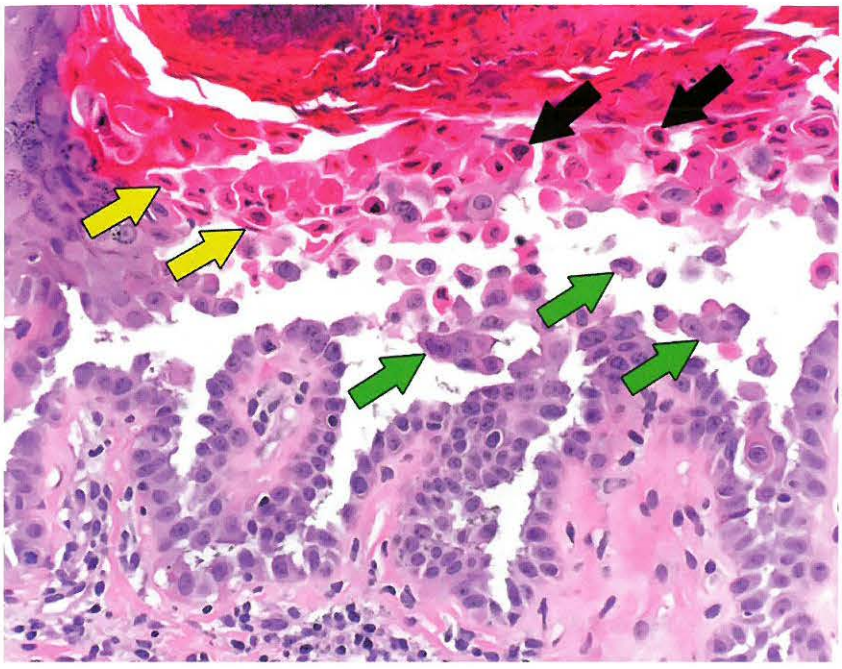


Figure 2-30

ACANTHOLYTIC DYSKERATOSIS PATTERN

The epidermal keratinocytes detach from one another and the epidermis falls apart (acantholysis), forming a suprabasilar intraepidermal blister. Detached acantholytic keratinocytes (green arrows) transition into dyskeratotic cells with pyknotic hyperchromatic nuclei and deeply eosinophilic cytoplasm, which take the form of rounded "corps ronds" (black arrows) or flattened "grains" (yellow arrows).

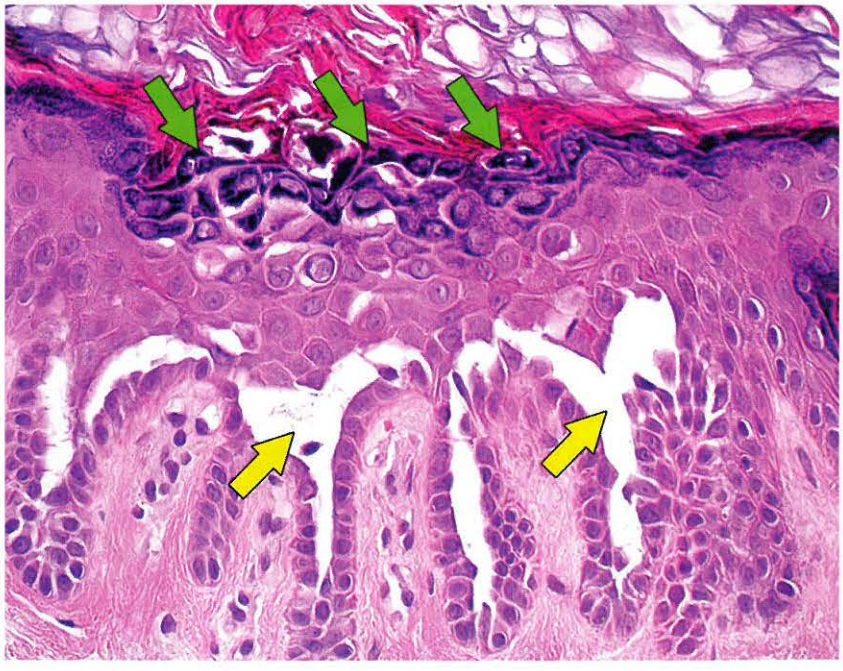


Figure 2-31

"PURPLE DYSKERATOSIS"

Corps ronds may sometimes have abundant irregular keratohyaline granules, creating a unique pattern of "purple dyskeratosis" that resembles a focal area of marked hypergranulosis (green arrows). Sometimes this finding is the only clue for a small papule of Grover disease that will be revealed on deeper sections. The focal acantholysis (yellow arrows) involves just a few rete.

if there are multiple papules, the findings likely represent Grover disease. Focal acantholytic dyskeratosis can also be seen as an incidental finding in background skin adjacent to other lesions (similar to EDV and EHK as discussed above). Grover disease and Darier disease can look essentially identical on a small biopsy; clinical information is the key to distinguishing them.

Warty dyskeratoma (fig. 2-33) and *acantholytic dyskeratotic acanthoma* are both solitary lesions with prominent acantholytic dyskeratosis. The former has a cup shape and often extends down hair follicles while the latter lacks these features and is instead a flat acanthotic intraepidermal lesion (6).

Hailey-Hailey disease is a hereditary genetic syndrome due to germline mutation of the

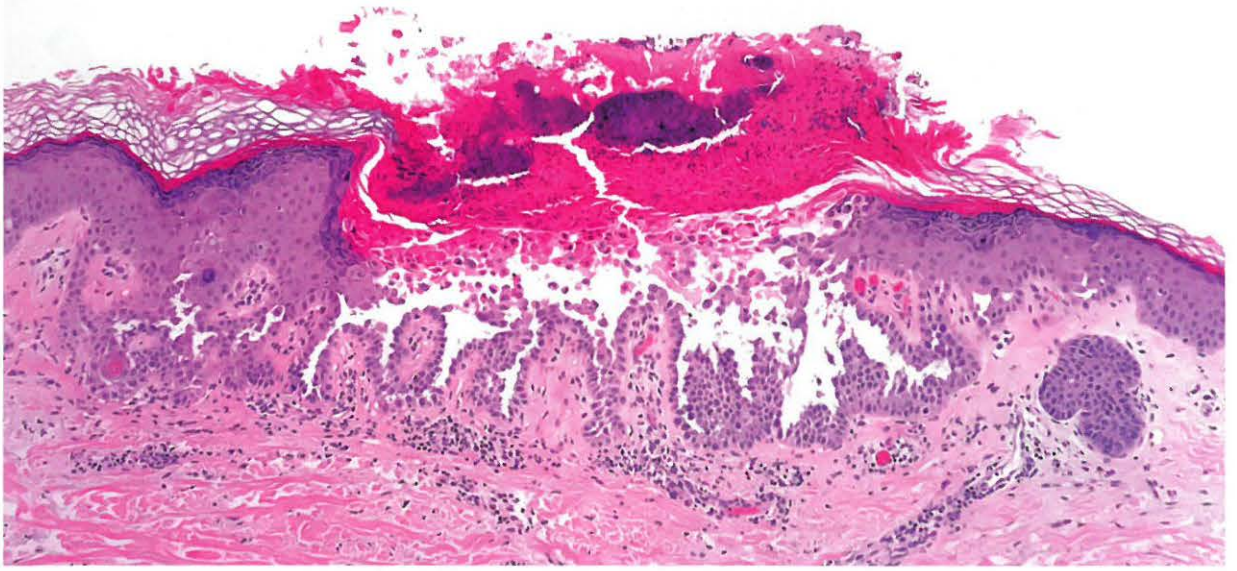


Figure 2-32

GROVER DISEASE

These are small discrete lesions of acantholytic dyskeratosis corresponding to the small papules seen clinically. Inflammation is often present in the dermis just beneath the lesion.

ATP2C1 gene. It enters the microscopic differential diagnosis with the above entities due to the prominent epidermal acantholysis (fig. 2-34). Unlike those diseases, however, Hailey-Hailey usually lacks significant dyskeratosis. Clinically, it presents as weeping macerated plaques in the fold regions, particularly the groin, axilla, and neck.

PIGMENTS

Hemosiderin is a golden brown refractile pigment resulting from the breakdown of iron-based heme molecules from extravasated erythrocytes (fig. 2-35). The presence of hemosiderin indicates previous hemorrhage. Hemosiderin stains with the Prussian blue iron stain.

Melanin is a brown (not black!) pigment and is not usually as refractile as hemosiderin, although sometimes they are difficult to tell apart with certainty on H&E stain. It is positive with the Fontana-Masson stain, which makes the brown melanin turn black, but it is negative with the Prussian blue iron stain. Melanin is normally produced by intraepidermal melanocytes and stored in basal layer keratinocytes (fig. 2-36). Interface dermatitis or other inflammatory damage to the epidermis can cause melanin to "drop out" of the epidermis into the superficial dermis (pigment incontinence), where it is ingested by histiocytes (melanophages). These scattered papillary dermal melanophages create abnormal pigmentation of the skin clinically (*postinflammatory pigmentary alteration*, since it may cause either hyper or hypopigmentation) (fig. 2-37). Melanocytic neoplasms also make variable amounts of melanin pigment. When a brisk host inflammatory response causes a melanoma (or nevus) to completely regress, a dense zone of melanin pigment and fibrosis may be all that is left behind (*tumoral melanosis*) (fig. 2-38). Since there are no remaining melanocytes, it is not possible to know for sure whether the original lesion was melanoma or nevus.

Drug pigmentation can be seen secondary to a variety of oral medications, including minocycline, amiodarone, chlorpromazine, imipramine, quinacrine, and others. Drug pigments are usually present within macrophages in the dermis, often with accentuation around vessels. They are often yellow to golden brown and may be highlighted by the Fontana-Masson stain, Prussian blue iron stain, or both depending on the exact drug (5). *Drug pigmentation* can mimic hemosiderin or melanin, but further discussion is beyond the scope of this book.

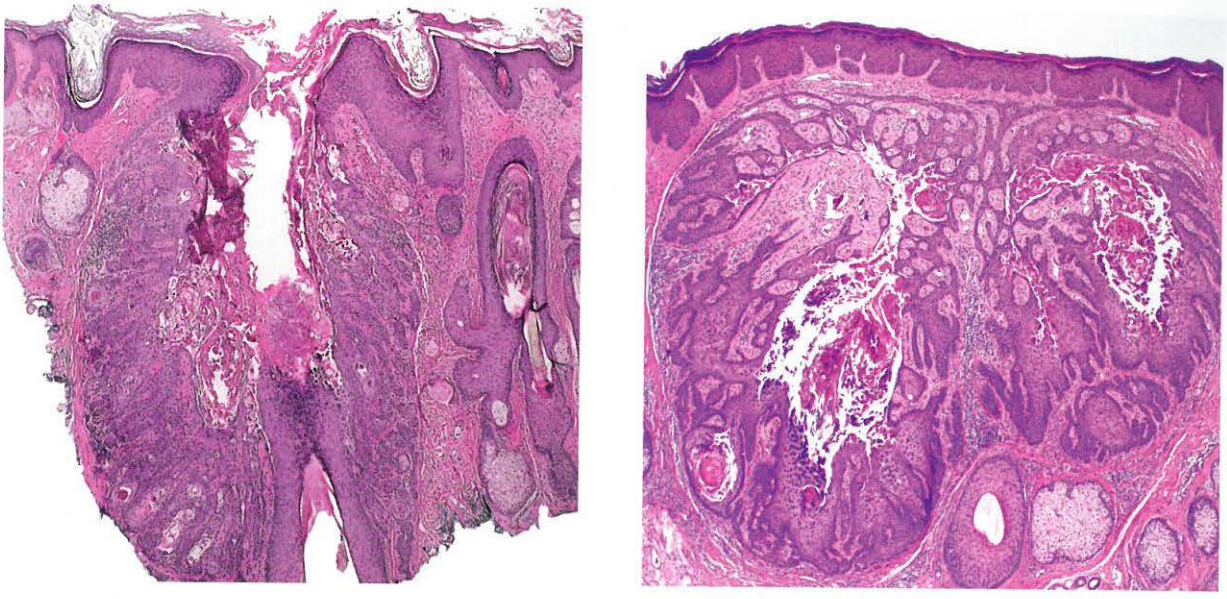


Figure 2-33

WARTY DYSKERATOMA

Left: These are solitary lesions with prominent acantholytic dyskeratosis, forming a cup shape due to their extension down a hair follicle (bottom center).

Right: Like other cup-shaped invaginated lesions (e.g., molluscum, trichofolliculoma), if the plane of section is not directly through the center of the lesion, it will look more like a cyst than a cup. Superficial cystic-appearing lesions may connect with the epidermis and open up to the skin surface even if that connection is not visualized in the examined tissue section.

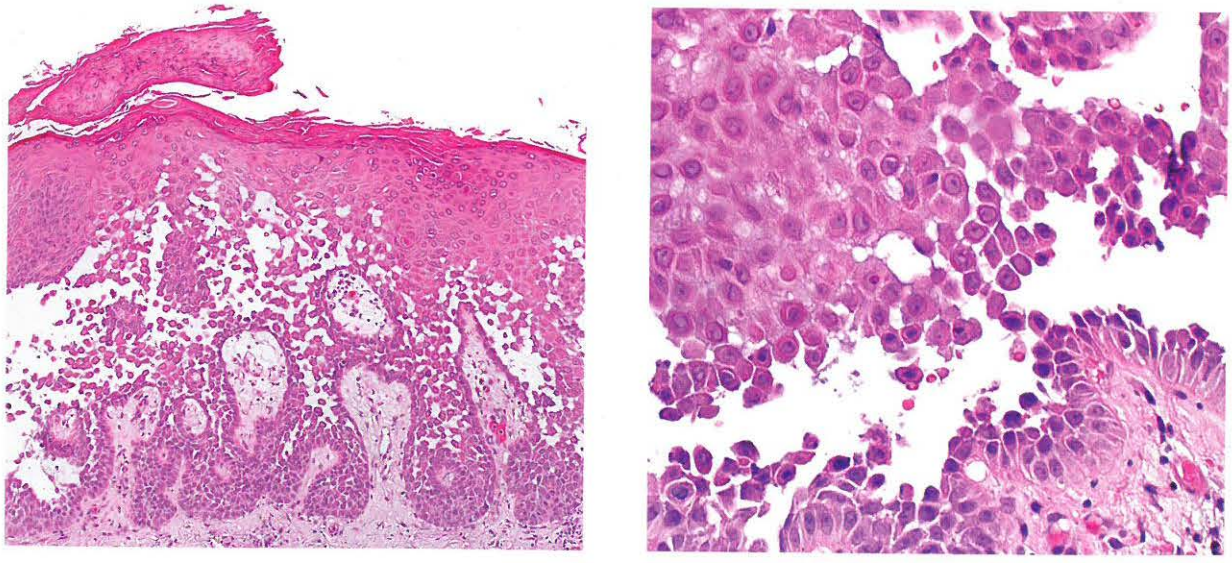


Figure 2-34

HAILEY-HAILEY DISEASE

Left: There is prominent epidermal acantholysis but usually little or no dyskeratosis. The low-power appearance has been likened to a "dilapidated brick wall" (rounded worn-down bricks separated by intervening mortar on a very old brick building).

Right: A classic example of acantholysis. Keratinocytes are separated from one another and have rounded contours and deeply eosinophilic cytoplasm. The acantholytic keratinocytes are detaching from the underlying intact basal layer; pemphigus vulgaris may have a similar pattern.

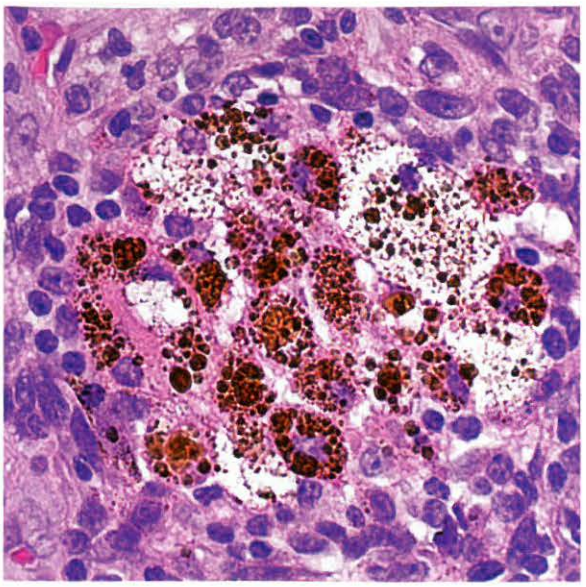


Figure 2-35

HEMOSIDERIN

Hemosiderin is a golden brown refractile pigment that is often present as irregular "chunky" aggregates. Hemosiderin is definitive evidence of previous hemorrhage. This is a pocket of hemosiderin (much of which is present within histiocytes) in an aneurysmal dermatofibroma.

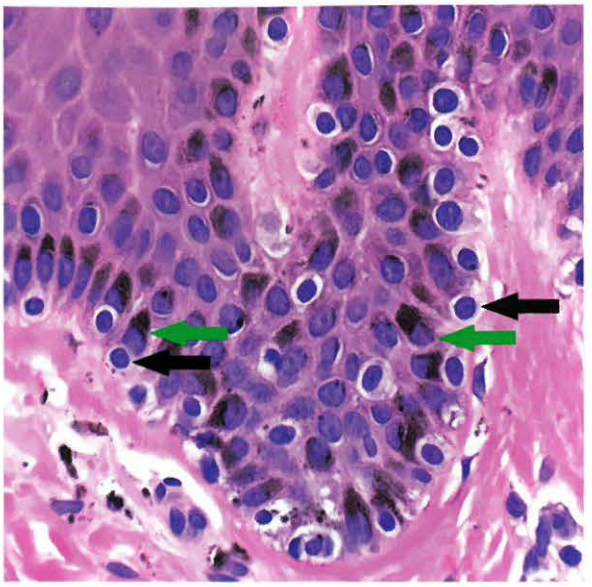


Figure 2-36

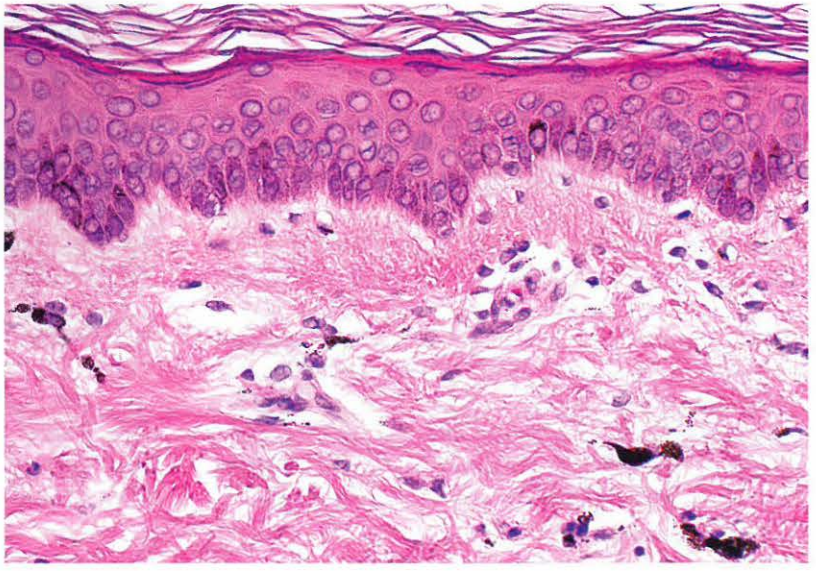
MELANIN IN BASAL KERATINOCYTES

Melanin is produced by intraepidermal melanocytes but stored in basal layer keratinocytes. Thus, paradoxically to beginners in dermpath, brown pigmented cells along the basal layer are usually not melanocytes but are actually keratinocytes (green arrows). In contrast, melanocytes usually have pale grey cytoplasm (black arrows). This is demonstrated in this lentigo simplex (same case as fig. 4-19).

Figure 2-37

PIGMENT INCONTINENCE (MELANIN IN DERMIS)

Scattered melanin pigment in the superficial dermis is called "pigment incontinence." It may arise from previous interface dermatitis or other inflammatory damage to the epidermis, particularly in patients with dark skin (note the abundant melanin pigment in the normal basal layer keratinocytes in this patient). It may also be seen under pigmented lesions (note the scattered dermal melanin in the bottom left of fig. 2-36). Sometimes it is subtle and focal, requiring examination at high magnification for identification.



ALIEN SUBSTANCES

Exogenous (foreign) material can enter the dermis after penetrating trauma to the epidermis, whether intentional or accidental. The immune system responds to foreign material in the dermis by creating foreign body granulomas, in which histiocytes and multinucleated giant cells surround the alien material (fig. 2-39).

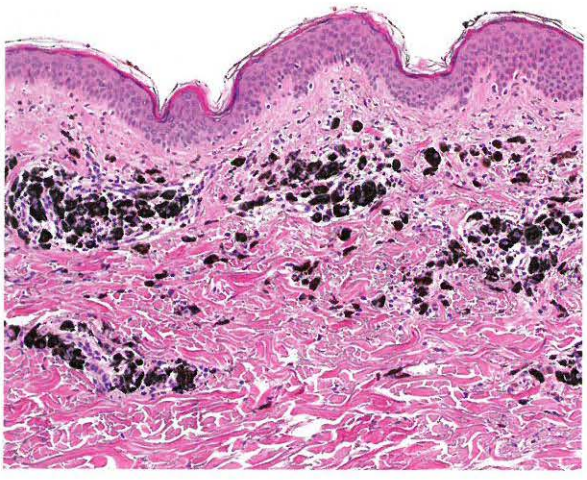


Figure 2-38

TUMORAL MELANOSIS

A focal zone of densely aggregated dermal melanin should raise the possibility of a completely regressed melanocytic lesion. The melanin here is much more abundant than would be seen in postinflammatory pigment incontinence.

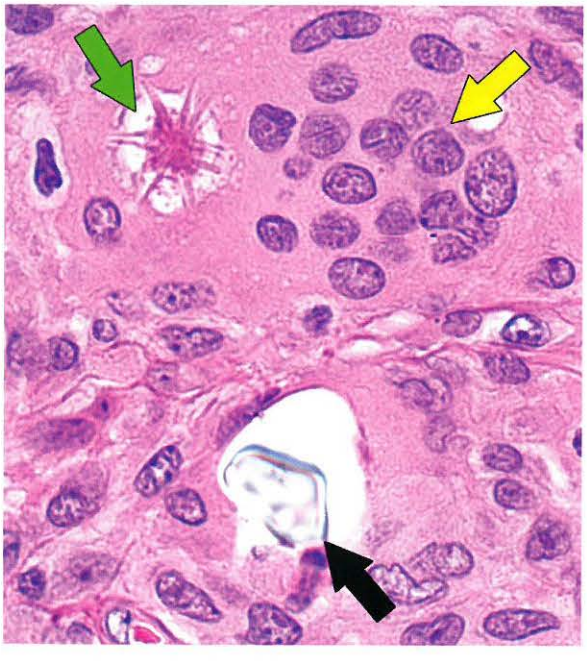


Figure 2-39

FOREIGN BODY GRANULOMA

A fragment of translucent refractile foreign material (black arrow) is surrounded by histiocytes in the middle of this foreign body granuloma. The adjacent multinucleated giant cell (yellow arrow) contains an asteroid body (green arrow). These star-shaped aggregates of degenerated collagen are a classic buzzword for sarcoidosis, but I actually see them much more often in foreign body granulomas.

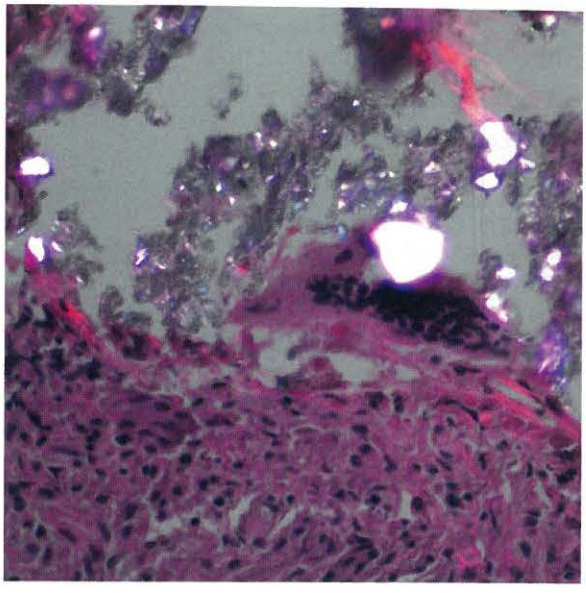


Figure 2-40

POLARIZABLE FOREIGN MATERIAL

The fragmented foreign material in this granuloma glows strongly under polarized light. Sometimes close examination at high magnification is needed to see this. The light source must be very bright to properly examine tissue for polarizable material.

Many types of foreign material are polarizable, so examining granulomatous dermatitis under polarized light is worthwhile (fig. 2-40). Hard fragments of either exogenous foreign material (e.g., sand, rock, glass, metal) or of endogenous material native to the patient (such as calcifications or bone) may drag across the tissue section as it is being prepared on the microtome, creating artifactual tears or rips in the tissue (fig. 2-41). When this tear/rip artifact is seen and no calcification or bone is present, search the slide carefully for foreign material via polarized light. Infectious organisms are often introduced into the skin via penetrating injury as well, so while the presence of foreign material is proof of penetrating injury, it does not exclude the possibility of coexisting infection.

Wood splinter can be used as a generic term for not only wood but any plant material that gets embedded in the dermis or subcutis due to traumatic penetrating injury, including thorns, sticks, and pencil tips. The fragment of wood/plant material is composed of geometrically arranged plant cells, which are recognized by

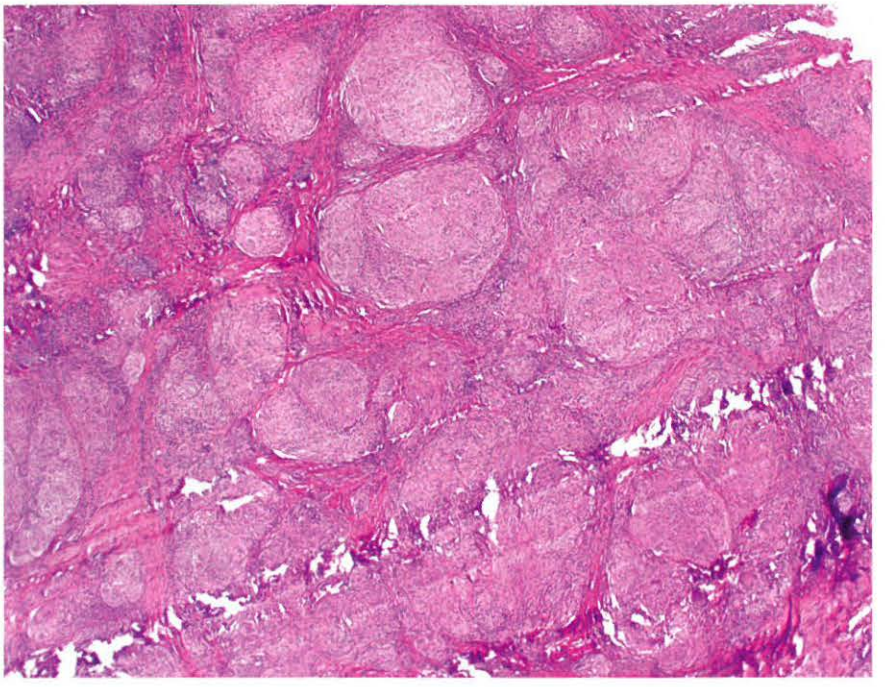


Figure 2-41

STREAK/TEAR ARTIFACT FROM FOREIGN MATERIAL

Hard fragments of foreign material may create artifactual linear tears or rips in the tissue section when it is cut on the microtome. I jokingly refer to this as the "Wolverine sign," as if adamantium claws sliced across the tissue. This artifact should prompt a careful search for foreign material via polarized light (or for bone or calcification, which can also produce this artifact). Note the numerous round pink nodular granulomas, which are easily visible at low magnification in this case.

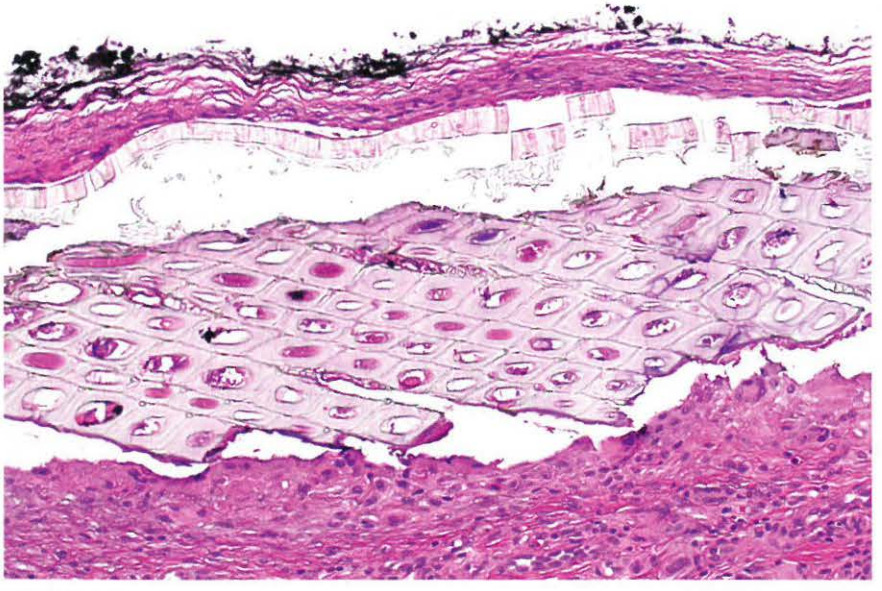


Figure 2-42

WOOD SPLINTER

A fragment of wood is present in the dermis. Wood or other plant material is characterized by the presence of refractile thick-walled plant cells, which are usually square or polygonal and arranged in a repeating pattern.

their square shape and thick carbohydrate cell walls (fig. 2-42). Plant cells are refractile and often polarizable. Granulomatous reaction or abscess may surround the fragment.

Pigmented dematiaceous fungal organisms are often present on wood splinters and represent "passenger" fungi that were growing on the wood in the environment before implantation into the patient's skin. When these fungi are only seen on the wood itself and not in the surrounding dermis away from the wood, their presence is likely incidental rather than evidence of fungal infection. In this scenario (which is common in the warm humid climate where I practice), I mention in the report the presence of the fungus, with a comment that it is likely just an incidental passenger (fig. 2-43). If the lesion resolves after biopsy, then no antifungal treatment is needed. If the lesion persists or recurs following biopsy, this is suspicious for active fungal infection

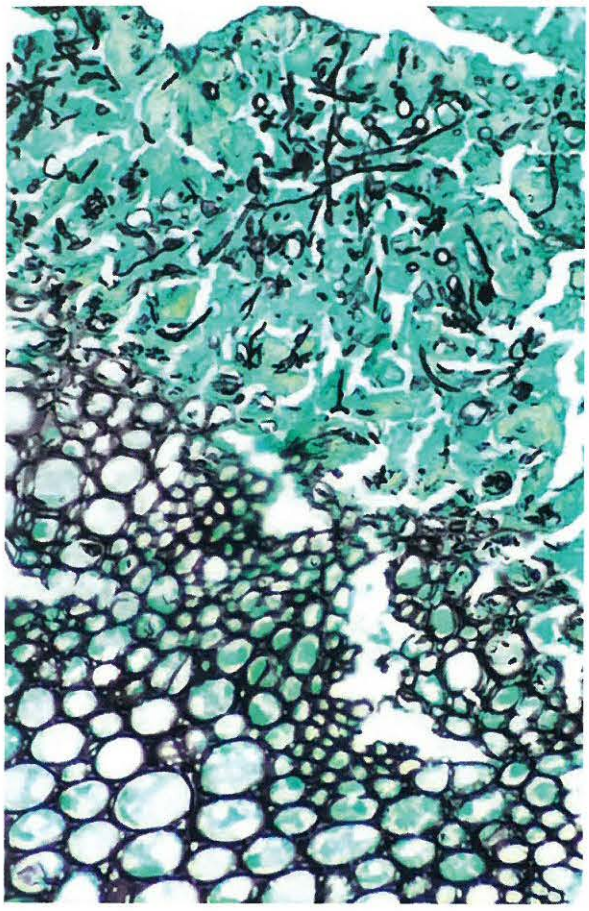


Figure 2-43

WOOD SPLINTER WITH "PASSENGER" FUNGUS

A thick layer of fungal hyphae (top) is adherent to the outer surface of a large wood fragment (bottom). Both the fungi and wood stain black on Gomori methenamine silver (GMS) stain. These fungi were likely incidental passengers rather than evidence of infection, as they were only present on the wood but not in the adjacent tissue.

(phaeohyphomycosis) (see chapter 7) and culture and treatment would then be recommended.

Sometimes foreign material is inserted into the skin intentionally. *Suture material* is a prime example. It may brilliantly polarize (depending on the type of suture) and it often induces a robust granulomatous response (fig. 2-44). Suture or other foreign materials may eventually be expelled out of the skin through the epidermis via a process called "transepidermal elimination" (similar to that seen in perforating disorders; see chapter 8). Suture may perforate out of the skin many years after it was initially placed there.

Cosmetic filler that is injected into the skin to fill in wrinkles or plump lips can induce a granulomatous reaction (fig. 2-45). There are many types of filler with different microscopic appearances (7). Consider this possibility when there is unusual foreign material or granulomas near the lips, eyes, or elsewhere on the face.

Tattoo pigment ("ink") is also intentionally injected into the skin. Granular black (or red, green, yellow, blue, etc.) pigment will be seen in the dermis, usually with no or minimal inflammation (fig. 2-46). However, if the patient has an immune reaction to the tattoo ink, a brisk inflammatory infiltrate may develop, sometimes robust enough to mimic lymphoma (fig. 2-47). Some tattoo pigments are polarizable.

Graphite "tattoo" is a small black/gray macule on the skin at the site of a previous penetrating injury from a pencil tip (fig. 2-48). Graphite particles are refractile black granules, often larger, more irregular, and angulated than professional decorative tattoo pigment. Wood from the pencil tip may occasionally be present adjacent to the graphite.

The human body makes various pigments of brown, green, red, and yellow hues, but it does not make any truly black pigment. Melanoma may look black clinically, but under the microscope, melanin pigment is always brown. Black pigment in the human body is always exogenous and is often from carbon or various metals (e.g., carbon in the lungs from polluted air, dental amalgam, metal fragments from arthroplasty implants, silver deposits from drinking colloidal silver).

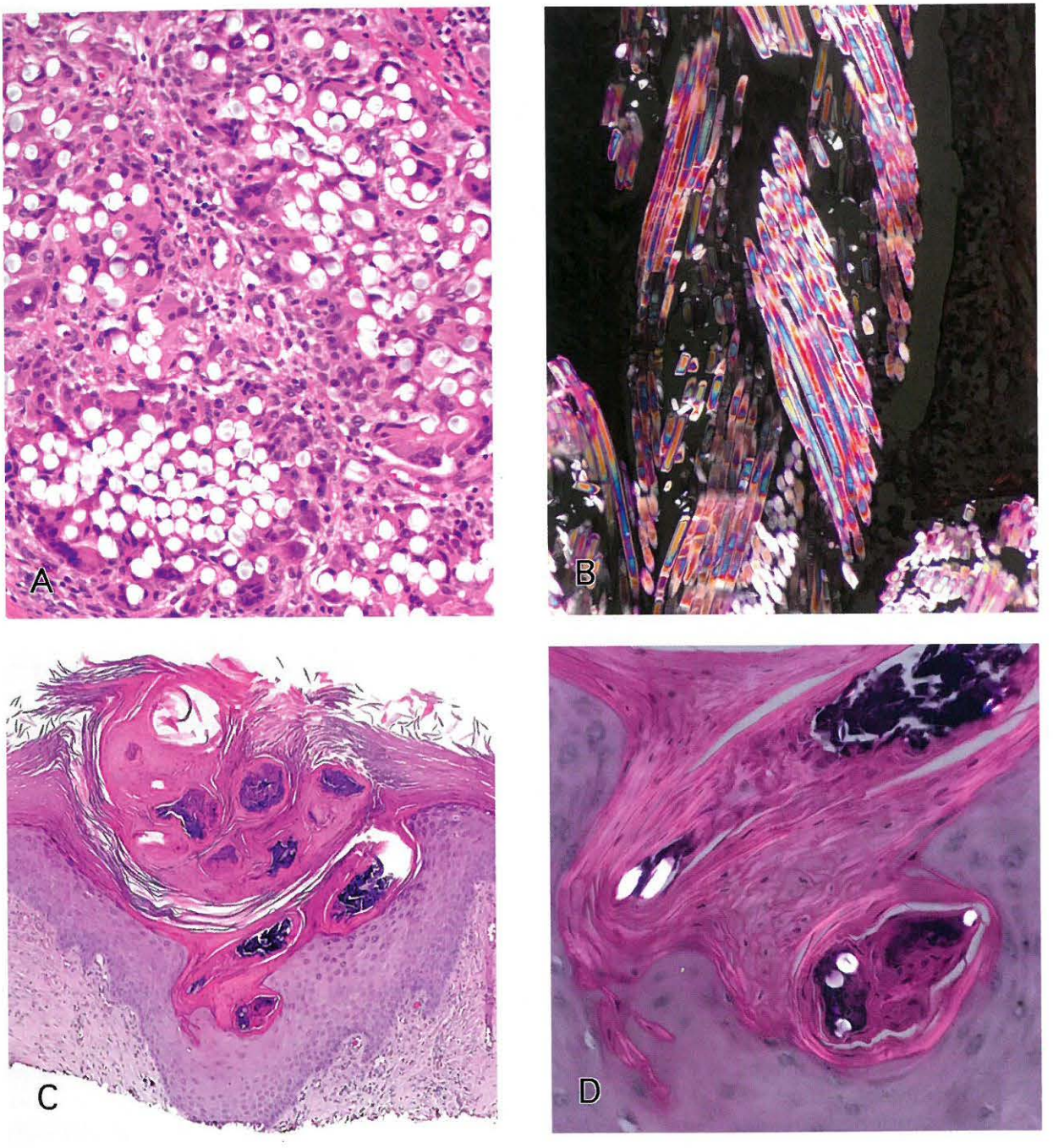


Figure 2-44

SUTURE

A: Suture often incites a granulomatous reaction. Each round hole in the cytoplasm of these multinucleated foreign body giant cells represents a filament of suture material. Some holes are empty because the suture itself fell out during processing, but others still contain the refractile suture filament.

B: Suture often polarizes, sometimes with a brilliant rainbow of colors, like this thick bundle of braided suture.

C: Suture may be ejected from the skin via transepidermal elimination, the same process seen in perforating disorders. There is a cup-shaped invagination of the epidermis containing keratin and purple degenerated debris.

D: Suture fragments glow bright white within the cup-shaped epidermal invagination under polarized light examination (same case as fig. 2-44C).

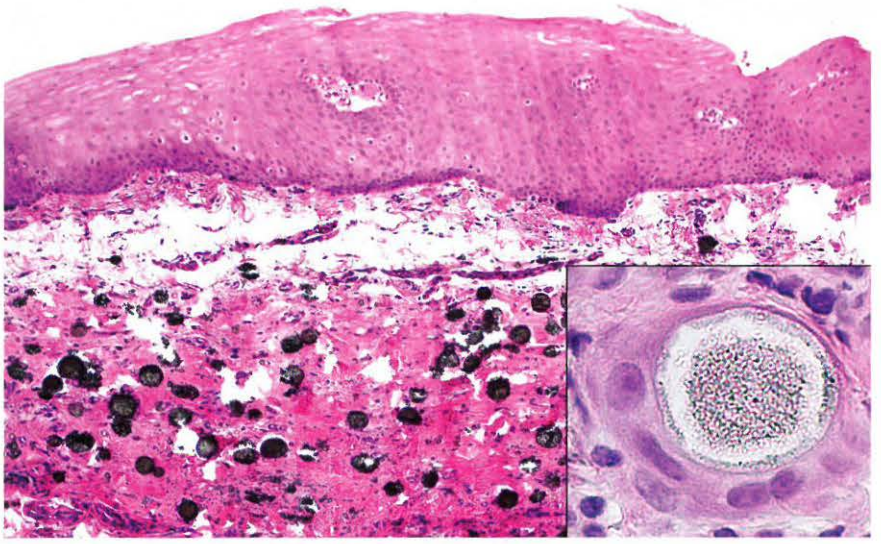
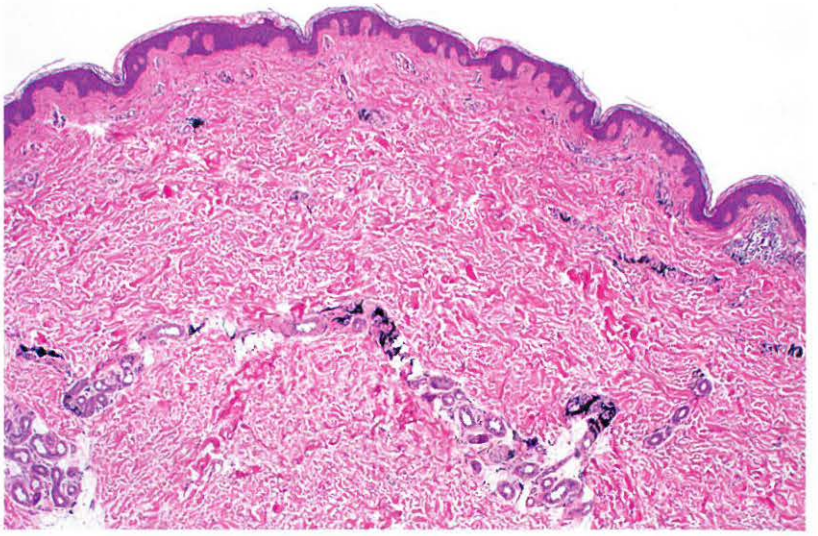


Figure 2-45

COSMETIC FILLER

Calcium hydroxylapatite microsphere filler in the lip (this is mucosa: stratified squamous epithelium without adnexa, granular layer, or corneal layer). Numerous refractile spheres are present in the submucosa/dermis. Artifactual tears in the tissue section (irregular white spaces) are present due to the foreign material. Inset: A round microsphere of granular calcium hydroxylapatite is engulfed by a giant cell. Do not confuse this with fungus or other infectious organisms.



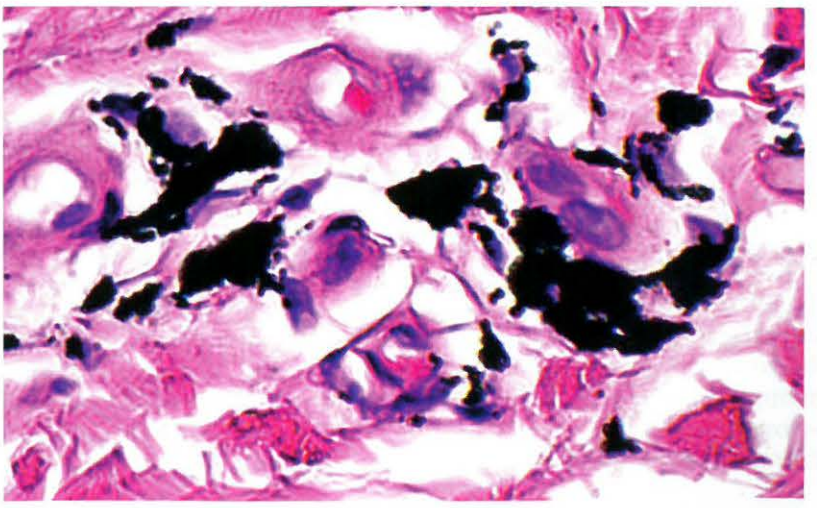


Figure 2-46

TATTOO PIGMENT

Top: Multiple aggregates of black pigment (or other colors) are present in the dermis, often around vessels, and usually with little or no inflammation.

Bottom: Granular refractile black pigment is present around dermal vessels.

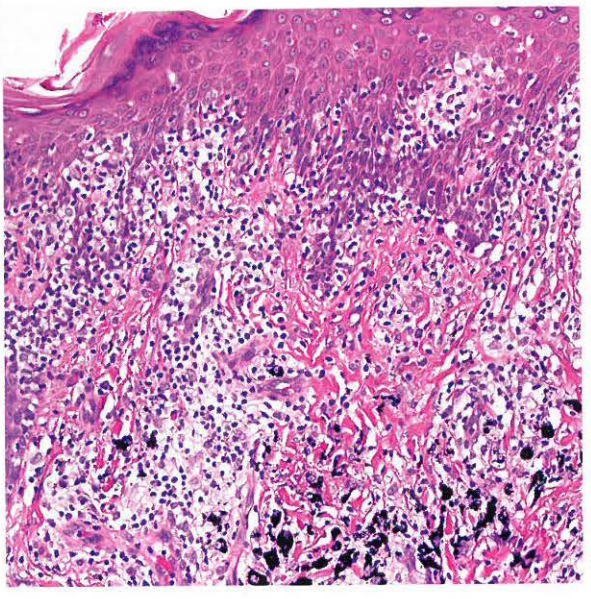


Figure 2-47

PSEUDOLYMPHOMATOUS TATTOO REACTION

There is a brisk lymphocytic infiltrate filling the dermis and infiltrating the acanthotic epidermis; this could easily be mistaken for the epidermotropism of mycosis fungoides (see chapter 11) if one did not recognize the black tattoo pigment (bottom right) or know the clinical scenario. This tattoo had to be removed by staged excision because the reaction was so severe and persistent.

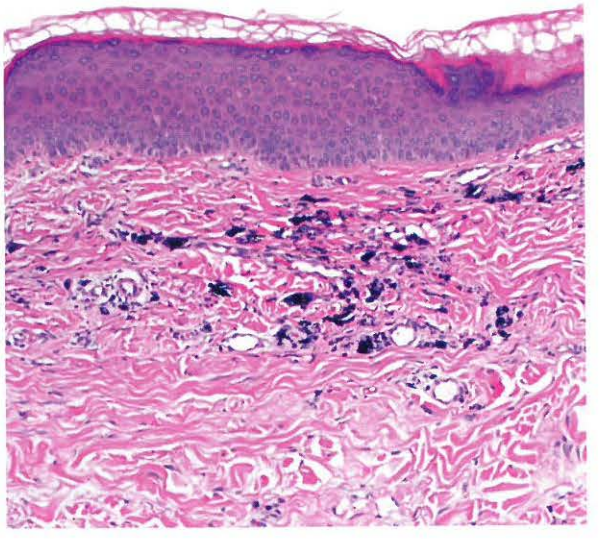


Figure 2-48

GRAPHITE "TATTOO"

A small localized area of black pigment with associated fibrosis is present in the dermis. Graphite particles are often more irregular and angulated in contrast to the fine granules of decorative tattoo pigment, but the clinical appearance and history are the best ways to make the distinction with certainty.

REFERENCES

1. Harvey NT, Wood BA. A practical approach to the diagnosis of melanocytic lesions. Arch Pathol Lab Med 2018. [Epub ahead of print]
2. Wood BA, Harvey NT. The "Umbrella Sign": a useful clue in the diagnosis of melanocytic lesions in sun damaged skin. Am J Dermatopathol 2016;38:504-9.
3. Pantanowitz L, Moses AV, Früh K. CD31 immunohistochemical staining in Kaposi Sarcoma. Arch Pathol Lab Med 2012;136:1329.
4. Ko CJ, Iftner T, Barr RJ, Binder SW. Changes of epidermodysplasia verruciformis in benign skin lesions: the EV acanthoma. J Cutan Pathol 2007;34:44-8.
5. Calonje JE, Brenn T, Lazar A, McKee P. McKee's Pathology of the skin: with clinical correlations, 4th ed. Edinburgh: Elsevier/Saunders; 2012.
6. Ko CJ, Barr RJ, Subtil A, McNiff JM. Acantholytic dyskeratotic acanthoma: a variant of a benign keratosis. J Cutan Pathol 2008;35:298-301.
7. Dadzie OE, Mahalingam M, Parada M, El Helou T, Philips T, Bhawan J. Adverse cutaneous reactions to soft tissue fillers—a review of the histological features. J Cutan Pathol 2008;35:536-48.

3 KERATINOCYTIC/EPIDERMAL PROLIFERATIONS

Seborrheic keratosis, squamous cell carcinoma, actinic keratosis, basal cell carcinoma... these keratinocytic/squamous/epidermal proliferations are the bread and butter of daily dermatopathology service work. This chapter details these common entities and their variants, as well as other entities that may enter the clinical or microscopic differential diagnosis, even if they are not truly of keratinocytic or epidermal derivation.

SEBORRHEIC KERATOSIS

Seborrheic keratosis (SK) is a "stuck-on," usually pigmented papule or plaque that occurs in adults. If a lesion resembles SK but the patient is a child, it is probably a nevus sebaceus or epidermal nevus (two closely related benign hamartomatous epidermal proliferations that are unrelated to melanocytic nevi; see chapter 5).

The microscopic appearance of SK can vary widely (fig. 3-1). Some lesions are thin and show overlapping features with solar lentigo (some SKs probably arise from solar lentigo). Others are acanthotic or papillomatous/verrucous intraepidermal proliferations of bland keratinocytes with scattered horn pseudocysts. These pseudocysts are filled with orthokeratin, and despite looking like small cysts within the epidermis, they are actually invaginations that open to the skin surface (thus, pseudocysts). SK can also show a reticulated pattern with an interconnecting network of cords of keratinocytes extending down from the epidermis.

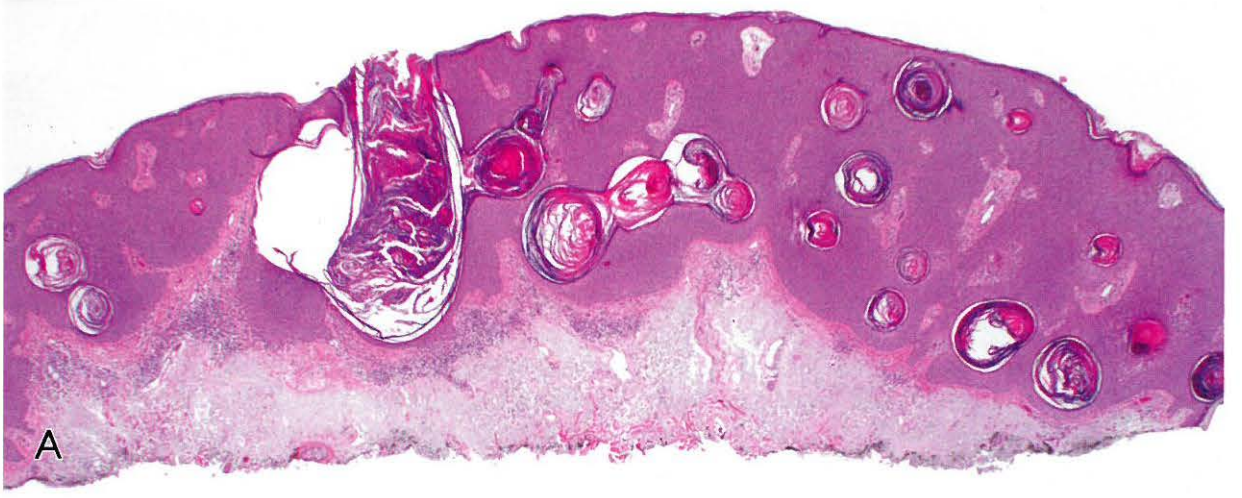
SKs tend to have a flat base and do not usually push down deeply into the dermis (as opposed to invasive squamous cell carcinoma). One can usually draw a straight line under the base of a SK that is approximately on a level with the rete tips of adjacent normal epidermis.

Pedunculated SKs may clinically resemble a fibroepithelial polyp (acrochordon, skin tag). Both entities are polypoid with a fibrovascular core resembling normal dermis, but pedunculated SK has acanthosis and papillomatosis (and sometimes horn pseudocysts) of the epidermis lining the surface of the polyp (fig. 3-2), whereas a fibroepithelial polyp just has a thin epidermis (fig. 3-3). Fibroepithelial polyps usually lack adnexal structures. They sometimes have abundant fat in the dermis. If they become strangulated (either accidentally due to torsion or intentionally because the patient tied thread or hair around the stalk), they develop reactive vascular changes from the ischemia or infarction.

"Clonal" SK refers to populations of uniform round keratinocytes embedded within the lesion that cause it to microscopically mimic pagetoid squamous cell carcinoma (fig. 3-4). SK can become briskly inflamed, sometimes showing lichenoid interface alteration (see chapter 8). The keratinocytes then become large, glassy, and atypical (fig. 3-5). When the base of the lesion is not visualized on a shave biopsy, inflamed SK may mimic squamous cell carcinoma. Recognizing areas of obvious SK adjacent to the atypical inflamed zones is a helpful clue, as is the presence of horn pseudocysts. When I am uncertain, I add this comment: "there is atypia favored to be reactive, but if the lesion persists, recurs, or if there is continued clinical concern, a repeat biopsy would be recommended" (hereafter referred to as the "persist comment"; I use this often in my practice). Whorled areas within an SK are known as "squamous eddies"; these are a sign of irritation.

INVERTED FOLLICULAR KERATOSIS

Inverted follicular keratosis (IFK) is a keratinocytic lesion with many features similar to irritated seborrheic keratosis (it has prominent squamous eddies), except that the lesion grows downward into the dermis with a bulging pushing border (fig. 3-6). IFK may merely be an irritated SK growing within a hair follicle. IFK tends to be inflamed



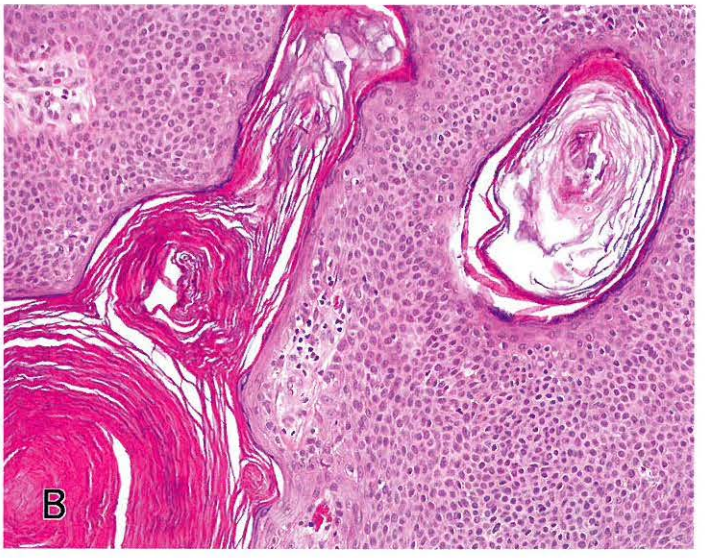


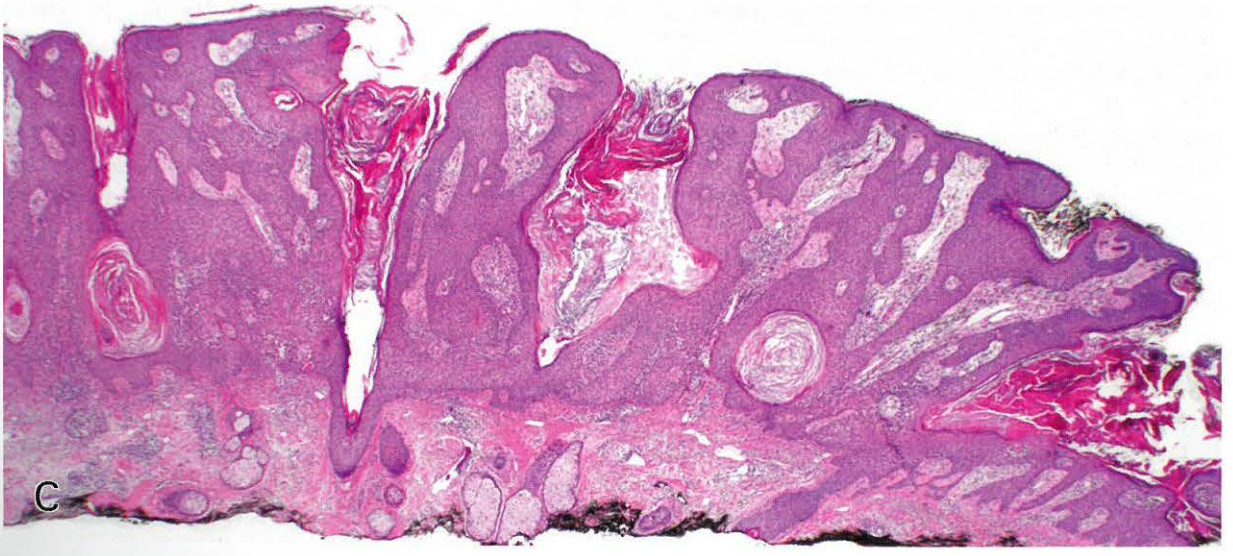
Figure 3-1

SEBORRHEIC KERATOSIS (SK)

A: Multiple keratin-filled horn pseudocysts are present within the markedly acanthotic epidermis.

B: SK is often composed of small keratinocytes with uniform monotonous round nuclei. The horn pseudocysts are usually filled with concentric layers of loose orthokeratin (although there may sometimes be parakeratosis, especially in inflamed/irritated SK).

C: Most SKs grow upward (rather than down into the dermis). The lesion sits high above the surface of the adjacent normal skin (right); this accounts for the classic "stuck on" clinical appearance. The base of the lesion is often flat; a straight line could be drawn along the base of the SK (left) and it would be approximately on level with the adjacent normal skin (right).



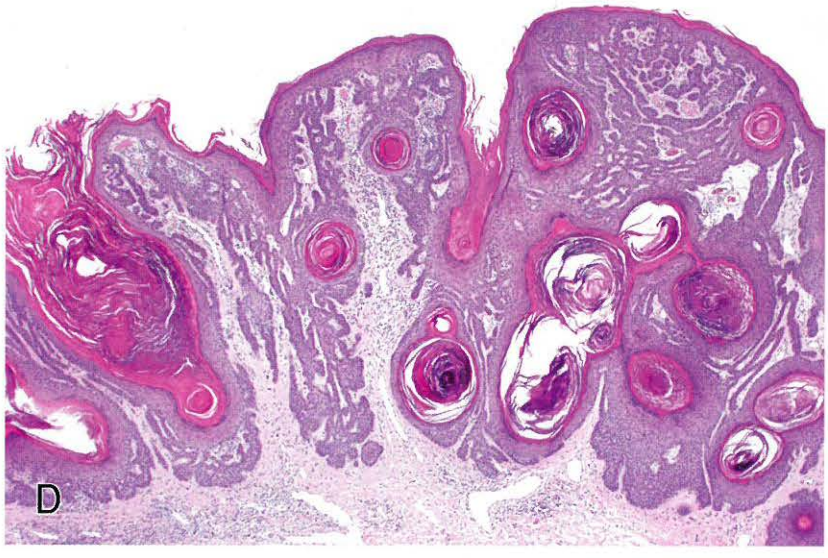
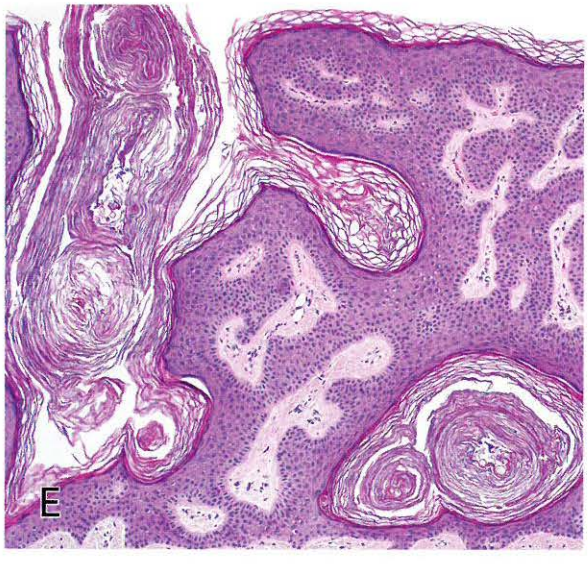


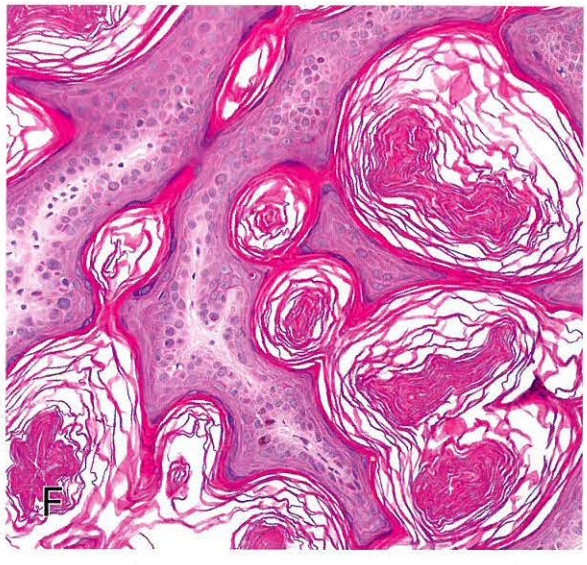
Figure 3-1, continued

D: Some SKs have a papillomatous, undulating, or even verrucous surface pattern. Rather than the solid acanthotic pattern seen in A, this SK has a more reticulated pattern of interconnected elongated rete (upper right). Note the many horn pseudocysts.

E: Horn pseudocysts are "pseudo" because they are not truly cysts but are actually keratin-filled invaginations that connect and open to the surface of the lesion. Depending on the plane of section, that connection may be seen (left) or not (right).

F: Horn pseudocysts have concentric or swirling layers of loose flaky keratin, usually orthokeratin (no retained nuclei).





and show reactive atypia, and as it often arises on the face, biopsies usually are transected at the base. Accordingly, I often add the "persist comment" discussed above to my report.

IFK and trichilemmoma can have overlapping features (see chapter 5). Since both are benign, the distinction is not important for patient care. The important thing is to not overinterpret them as carcinoma.

ACANTHOSIS NIGRICANS

Acanthosis nigricans is a velvety hyperpigmented plaque arising on the neck or other fold regions. It is associated with obesity, diabetes, and other diseases and syndromes. The clinical appearance is usually distinct, but it is sometimes biopsied. It is mentioned here because the elongated rete, papillomatosis, and hyperkeratosis can create an appearance similar to that of SK microscopically (fig. 3-7). *Confluent and reticulated papillomatosis (CARP)* has an essentially identical histologic appearance and sometimes enters the clinical differential with acanthosis nigricans.

CLEAR CELL ACANTHOMA

Clear cell acanthoma is a benign keratinocytic lesion arising as a solitary papule or plaque usually on the lower leg. It displays epidermal acanthosis composed of keratinocytes with pale cytoplasm and intervening spongiosis (fig. 3-8).

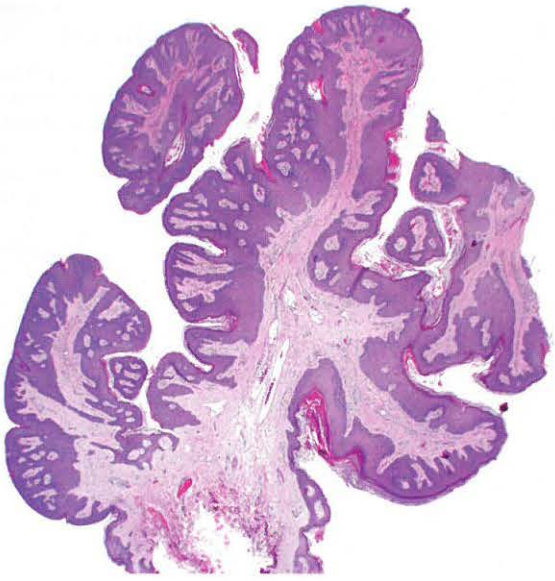


Figure 3-2

PEDUNCULATED SEBORRHEIC KERATOSIS

Pedunculated SK has a polypoid shape and is connected to the underlying skin by a narrow stalk. If a lesion looks like an acrochordon (skin tag) but has acanthosis or papillomatosis of the epidermis and/or horn pseudocysts (not seen in this case), it is a pedunculated SK.

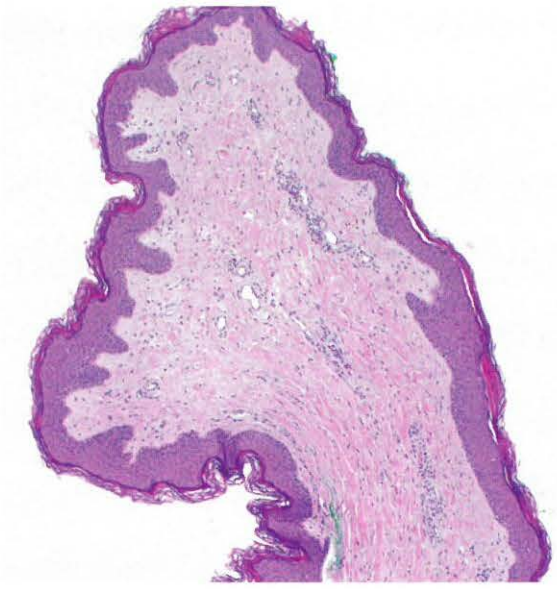


Figure 3-3

FIBROEPITHELIAL POLYP/ACROCHORDON ("SKIN TAG")

Skin tags are pedunculated polypoid lesions lined by a thin epidermis. Adnexal structures are usually absent. The dermal core of the lesion may resemble normal dermis (as seen here), but some cases become partially strangulated and show edema, inflammation, and a reactive proliferation of dilated vessels.

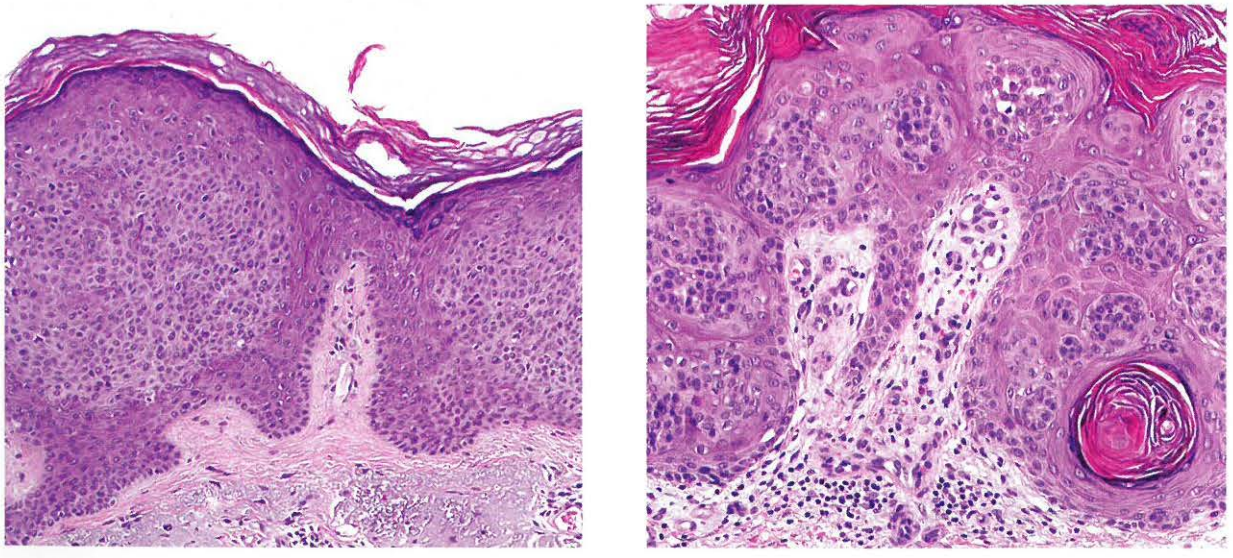


Figure 3-4

CLONAL SEBORRHEIC KERATOSIS

Left: Discrete areas of the lesion have pale uniform keratinocytes that look like one another (thus, "clonal") but clearly look a bit different from the rest of the lesion or the normal epidermis.

Right: In some cases, the clonal change may be striking, forming multiple small round aggregates of uniform keratinocytes that have a nested appearance. These cases can be confused with pagetoid squamous cell carcinoma *in situ* or a melanocytic lesion. The presence of horn pseudocysts (bottom right) or adjacent areas of obvious SK (not shown) are useful clues to a clonal SK.

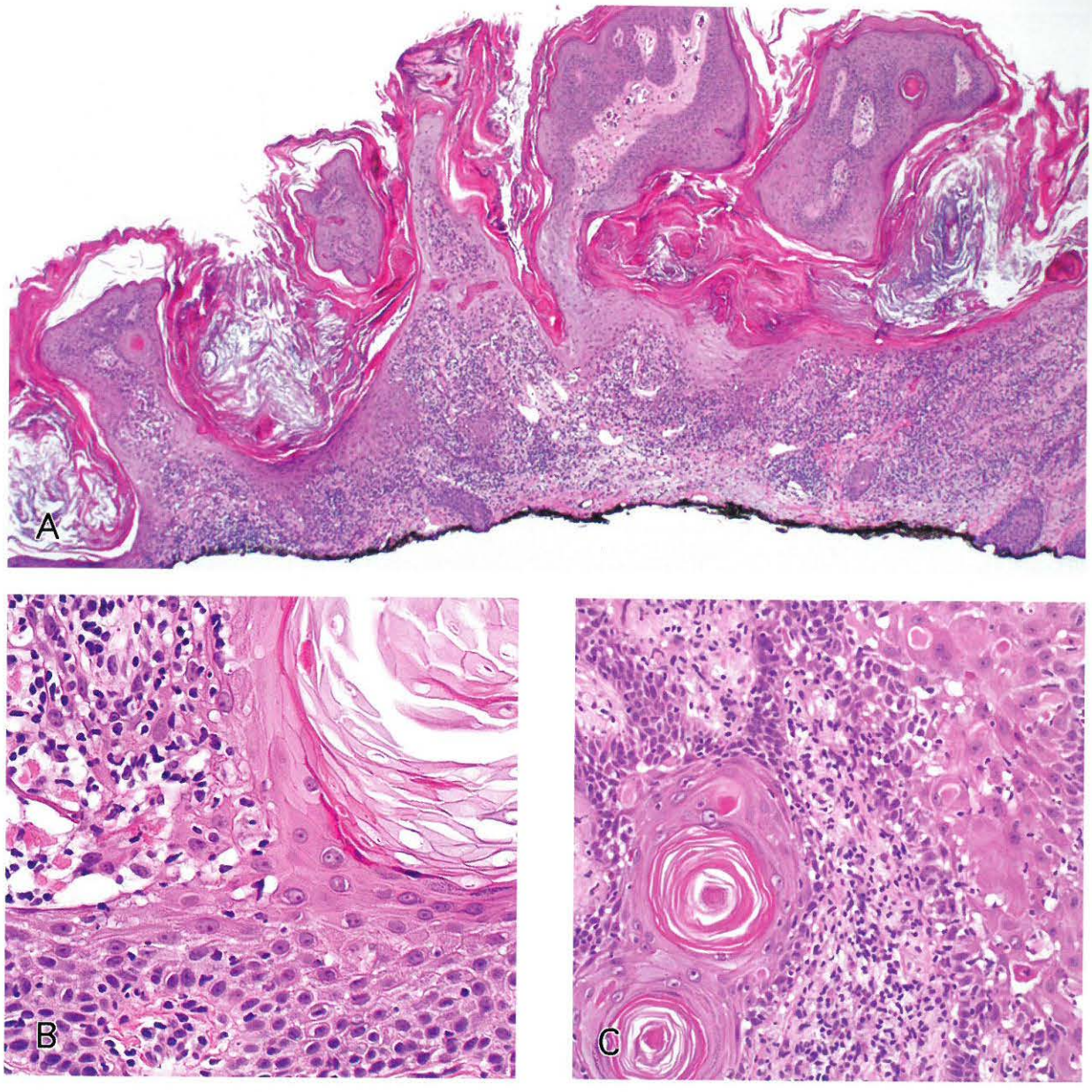


Figure 3-5

INFLAMED SEBORRHEIC KERATOSIS (ISK)

A: There is a brisk lymphocytic infiltrate beneath the lesion. Zones of parakeratosis are commonly seen in ISK.

B: ISK often show lichenoid interface alteration, with numerous dying keratinocytes (left). Note the horn pseudocyst (right).

C: Keratinocytes may become glassy and atypical (right) in the inflamed areas of an ISK. Sometimes this is dramatic enough to closely mimic squamous cell carcinoma. The presence of horn pseudocysts (left) or adjacent areas of obvious SK (not shown) help distinguish ISK from carcinoma.

Some prefer the name "pale cell acanthoma" because the cells are pale rather than truly clear. The granular layer is markedly diminished and there is diffuse overlying parakeratosis. Scattered neutrophils are usually present in the epidermis and the overlying stratum corneum. The changes in the stratum corneum closely resemble those of psoriasis (see chapter 8). A very characteristic feature of this entity is a sharp line of demarcation between the pale

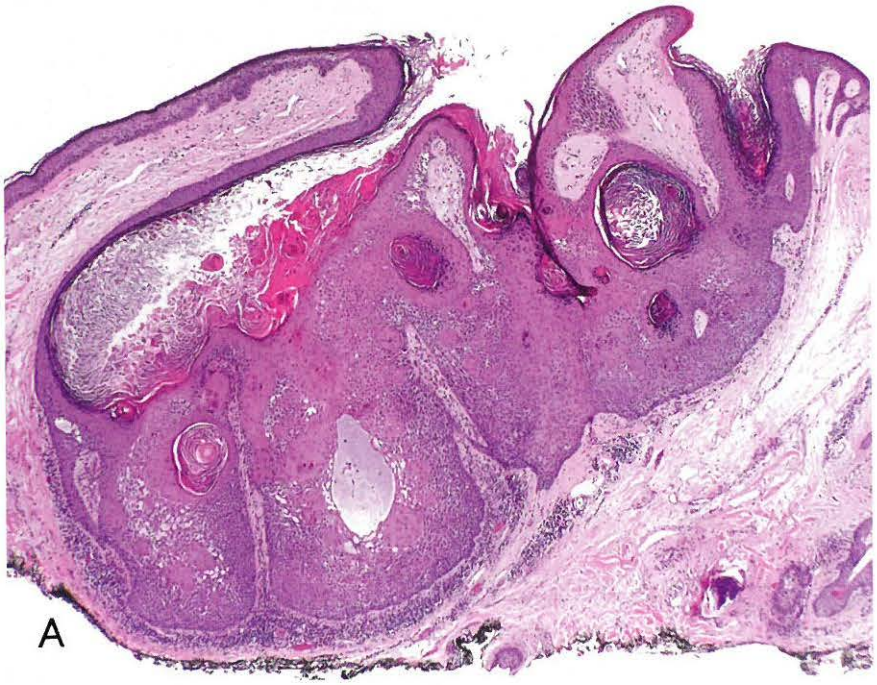
Figure 3-6

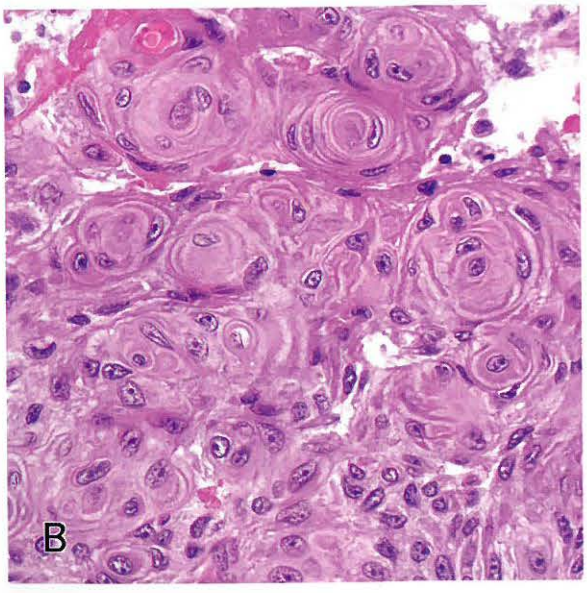
INVERTED FOLLICULAR KERATOSIS (IFK)

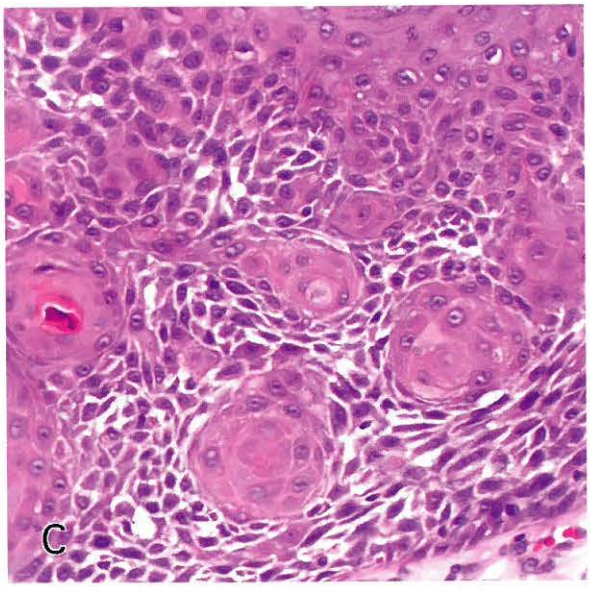
A: The appearance is similar to an SK but it is growing downward into the dermis with a bulging/pushing border (because it is actually growing within an expanded hair follicle). IFK often has glassy keratinocytes with reactive atypia; do not confuse it with squamous cell carcinoma.

B: Whorled clusters of keratinocytes ("squamous eddies") are present within the lesion. This classic finding is seen both in IFK and in irritated SK.

C: Some squamous eddies have a less whorled and more ball/nest-like appearance that overlaps with the pattern seen in clonal SK.







lesional keratinocytes and the adjacent normal epidermis at the periphery of the lesion.

BASAL CELL CARCINOMA

Basal cell carcinoma (BCC) is the most common malignancy in humans. Although it rarely metastasizes or causes mortality, BCC can cause serious morbidity, particularly when long neglected, when arising in anatomically sensitive sites, or when displaying aggressive growth patterns.

Most BCCs are the result of sun/ultraviolet (UV) exposure. They usually present in older adults with chronic sun damage. However, I regularly see BCC in patients in their 30s or even 20s, whereas I rarely see squamous cell carcinoma (SCC) in this age range. This is because even intermittent episodes of high intensity UV

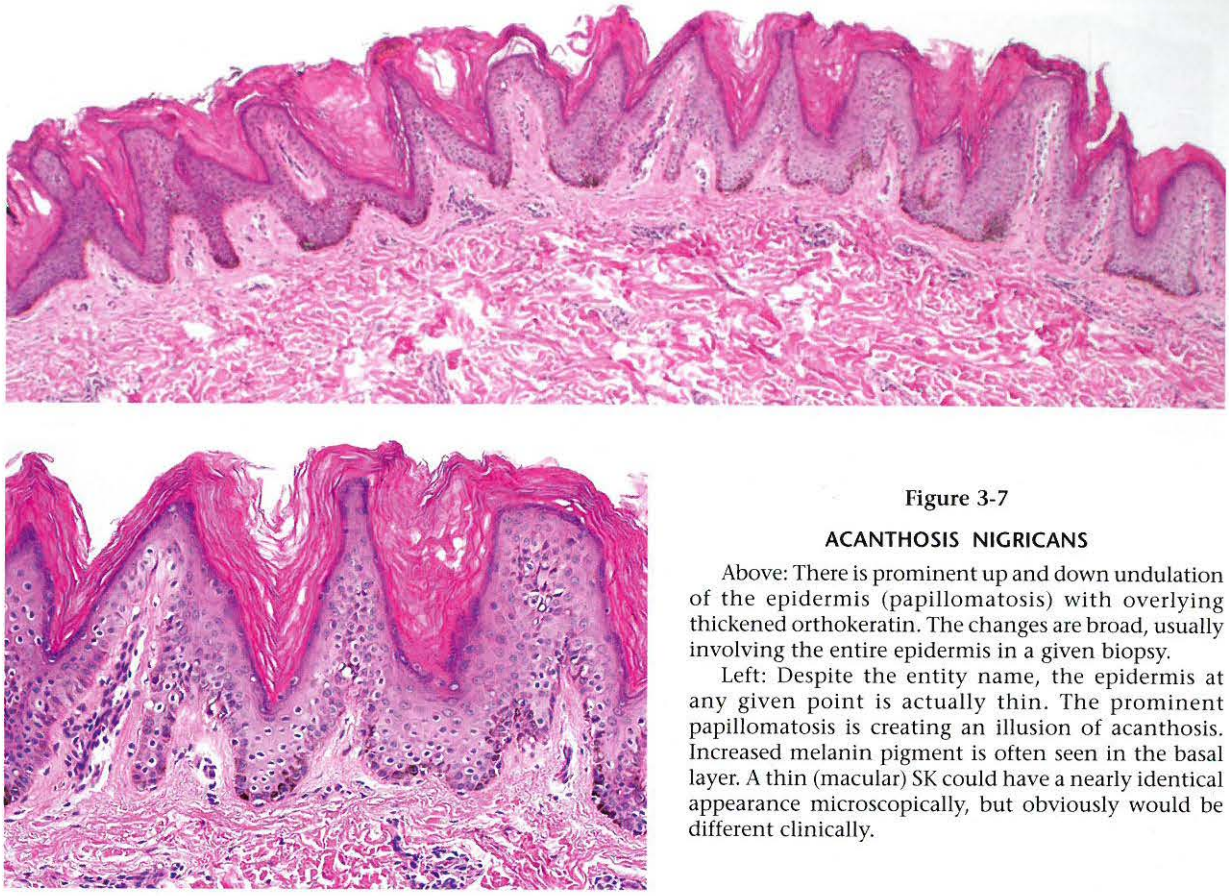


Figure 3-7

ACANTHOSIS NIGRICANS

Above: There is prominent up and down undulation of the epidermis (papillomatosis) with overlying thickened orthokeratin. The changes are broad, usually involving the entire epidermis in a given biopsy.

Left: Despite the entity name, the epidermis at any given point is actually thin. The prominent papillomatosis is creating an illusion of acanthosis. Increased melanin pigment is often seen in the basal layer. A thin (macular) SK could have a nearly identical appearance microscopically, but obviously would be different clinically.

exposure (i.e., weekend sunburns, tanning bed use) can result in BCC whereas SCC usually requires years of chronic sun exposure.

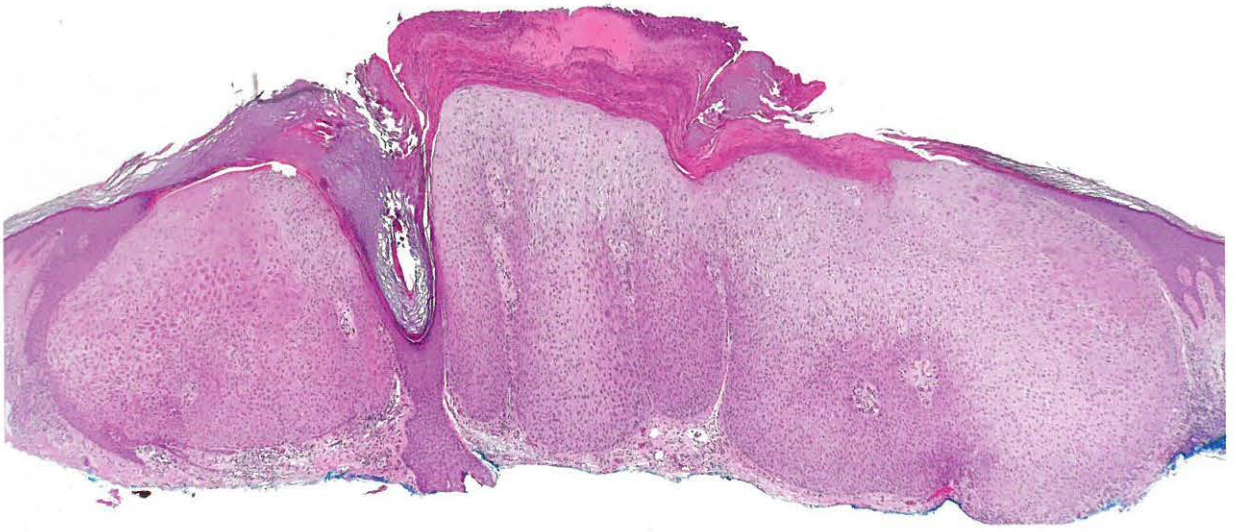
Children can also get BCC, albeit rarely. In a child, a benign follicular tumor such as trichoblastoma should always be considered before making a diagnosis of BCC. When a child has a true BCC, I usually recommend genetic counseling to exclude hereditary syndromes such as Gorlin syndrome (nevoid basal cell carcinoma syndrome).

BCC is typically composed of uniform blue "basaloid" cells with scant cytoplasm. These are arranged in nests set in a loose myxoid/mucinous and fibrous stroma. The basal cells are more columnar and palisaded around the periphery of the nests. There is often clefting artifact separating the periphery of the nests from the adjacent stroma, and myxoid/mucin may be present in the cleft space.

There are many morphologic subtypes of BCC. *Superficial BCC* has multiple nests of basaloid cells that bud down from the epidermis but remain attached (fig. 3-9). Sometimes these nests are small and subtle, which can make distinction from actinic keratosis difficult. The presence of myxoid/mucinous stroma and focal cleft artifact is a helpful clue. Clinically, superficial BCC is often broad and thin, making it resemble squamous cell carcinoma *in situ* or even inflammatory dermatoses such as psoriasis or nummular dermatitis.

Nodular BCC has larger nests of basaloid cells centered in the dermis, with or without an epidermal connection (fig. 3-10). This form clinically presents as a white to pink "pearly" papule or nodule, often with overlying telangiectasias ("spider veins") and sometimes with ulceration with rolled borders.

Infiltrative BCC has angulated nests and cords of basaloid cells that infiltrate the dermis (fig. 3-11); I use this term to encompass morpheaform, sclerosing, and micronodular subtypes of BCC. There is often a brisk desmoplastic stroma, with both myxoid change and increased fibroblasts. The thin infiltrative cords usually



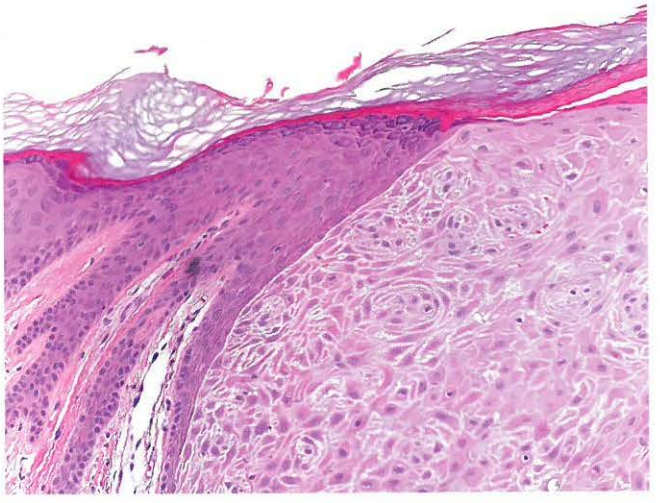


Figure 3-8

CLEAR CELL ACANTHOMA

Above: This is a discrete acanthotic epidermal lesion with a pale appearance. It usually has confluent overlying parakeratosis, although in some cases this may be detached or eroded.

Right: The lesional keratinocytes have pale (rather than truly clear) cytoplasm and often show intervening spongiosis. There is a sharp discrete cutoff between the lesional cells (right) and the adjacent normal epidermis (left) at the periphery of the lesion; this is a characteristic diagnostic feature.

lack peripheral palisading and clefting artifact, but if the biopsy is large enough, at least a few nests of obvious classic BCC may be seen. Infiltrative BCC can be scar-like clinically. It tends to be more aggressive, with a higher risk of local recurrence, and thus it is often treated either with complete excision or Mohs surgery, which is why it is important to recognize this subtype and mention it in the report.

Various subtypes of BCC can coexist in the same lesion. There are many other esoteric morphologic variants of BCC, only a few of which will be discussed here.

Any of the BCC subtypes can be pigmented, and this is sometimes enough to mimic melanoma clinically. Biopsy shows foci of melanin deposition within tumor cells or tumor stroma (fig. 3-12). I usually mention this in the report to reassure the dermatologist that I have identified the cause of the hyperpigmentation that is seen clinically. Sometimes scattered hyperpigmented dendritic melanocytes are present as "passengers" within the tumor. A similar phenomenon can be seen in SK, IFK, or SCC. Do not confuse this with melanoma *in situ*. The presence of pigmented cytoplasmic dendritic processes, lack of nesting, and lack of spread into adjacent epidermis are all reassuring features (1).

Adenoid BCC has multiple cystic pools of mucin/myxoid present within the tumor nests (fig. 3-13). This can be striking enough in some cases to resemble adenoid cystic carcinoma, which

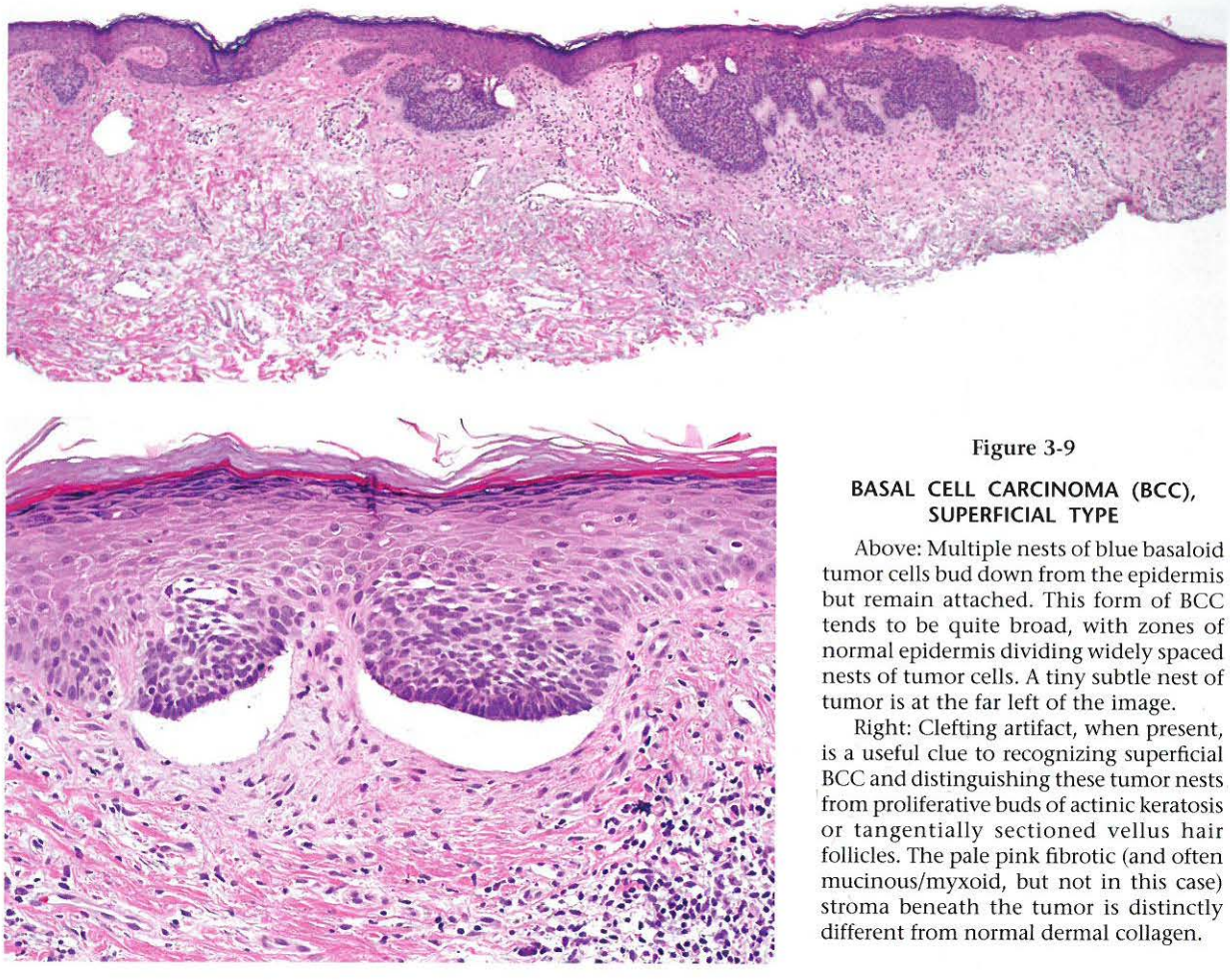


Figure 3-9

BASAL CELL CARCINOMA (BCC), SUPERFICIAL TYPE

Above: Multiple nests of blue basaloid tumor cells bud down from the epidermis but remain attached. This form of BCC tends to be quite broad, with zones of normal epidermis dividing widely spaced nests of tumor cells. A tiny subtle nest of tumor is at the far left of the image.

Right: Clefting artifact, when present, is a useful clue to recognizing superficial BCC and distinguishing these tumor nests from proliferative buds of actinic keratosis or tangentially sectioned vellus hair follicles. The pale pink fibrotic (and often mucinous/myxoid, but not in this case) stroma beneath the tumor is distinctly different from normal dermal collagen.

can rarely arise in the skin. The distinction is usually easy using an (H&E) stain, as adenoid BCC has irregular-shaped mucin pools of varying size whereas adenoid cystic carcinoma has uniform, perfectly round mucin pools with a cookie-cutter punched out appearance. Additionally, adenoid BCC usually has some areas that look more like conventional BCC. I usually just diagnose these as "BCC, nodular type" with no mention of the adenoid change in the report so as to avoid unnecessary clinical concern.

BCC sometimes shows focal areas of adnexal differentiation, including mature sebocytes, sweat duct formation, apocrine cells, or follicular structures. If the overall features fit best with BCC (e.g., peripheral palisading, clefting artifact, myxoid stroma), then I make a diagnosis of BCC with adnexal differentiation rather than trying to fit the tumor into the category of an unusual adnexal neoplasm (see chapter 5) (1).

Fibroepithelioma of Pinkus is regarded by some as a variant of BCC but by others as a benign follicular neoplasm related to trichoblastoma (2,3). I personally use "basal cell carcinoma, fibroepithelioma of Pinkus type" in the diagnosis line of my report. Regardless of the name, it has a very distinct microscopic appearance: cords of keratinocytes intermingled with basaloid nests extend down from the epidermis forming an interconnected net-like proliferation (fig. 3-14).

Shave biopsy of a small pearly papule (especially on the face) to rule out early BCC is a very common specimen in my practice. It is useful to know the list of entities that can present as a small papule mimicking BCC clinically: milia or other cysts (see fig. 6-4), folliculitis (fig. 3-15), ruptured follicle (see fig. 6-5), dilated/plugged hair follicle +/- telangiectasia (dilated blood vessels in the superficial dermis) (fig. 3-16), fibrous papule (angiofibroma), and lichenoid

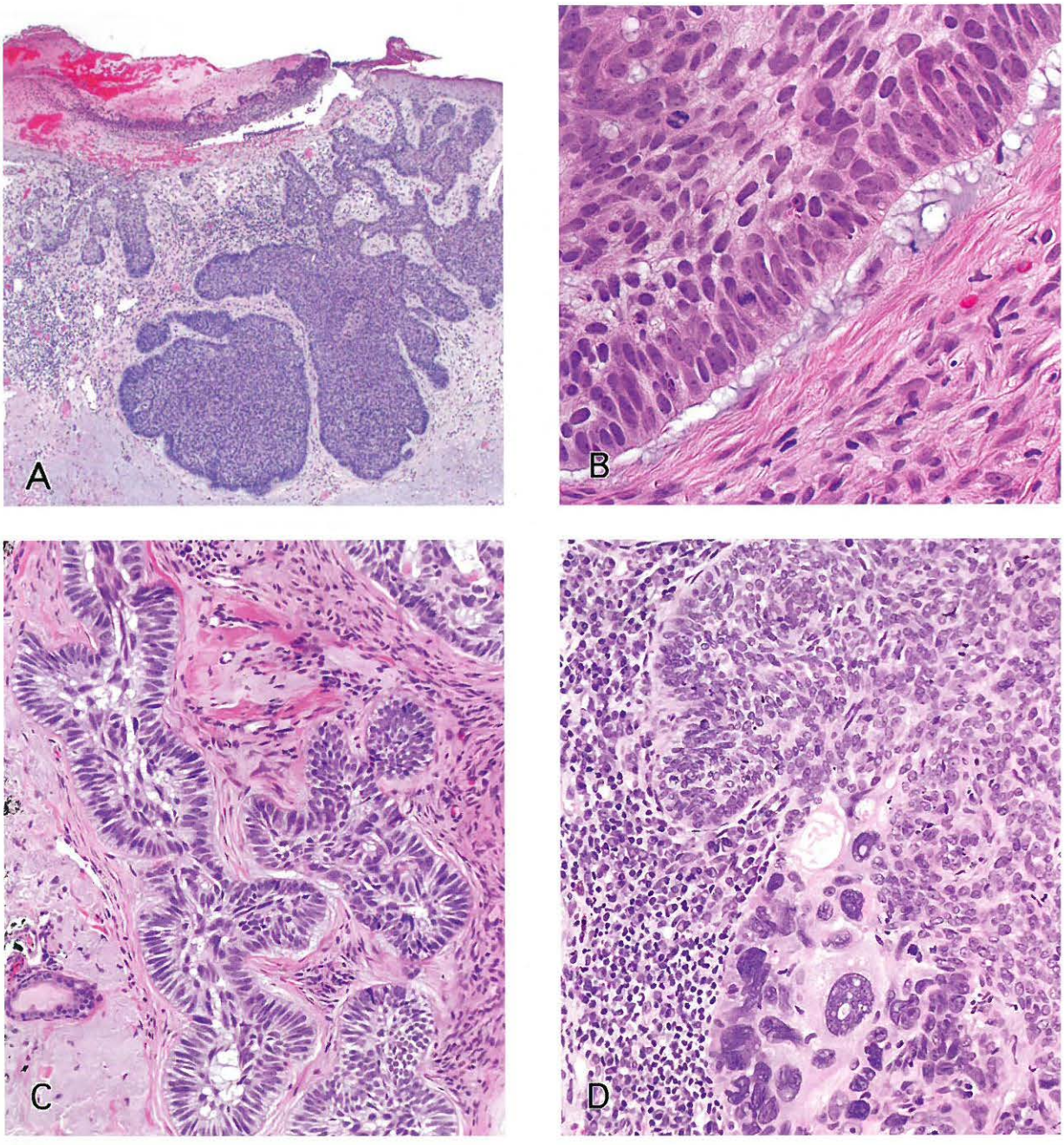


Figure 3-10

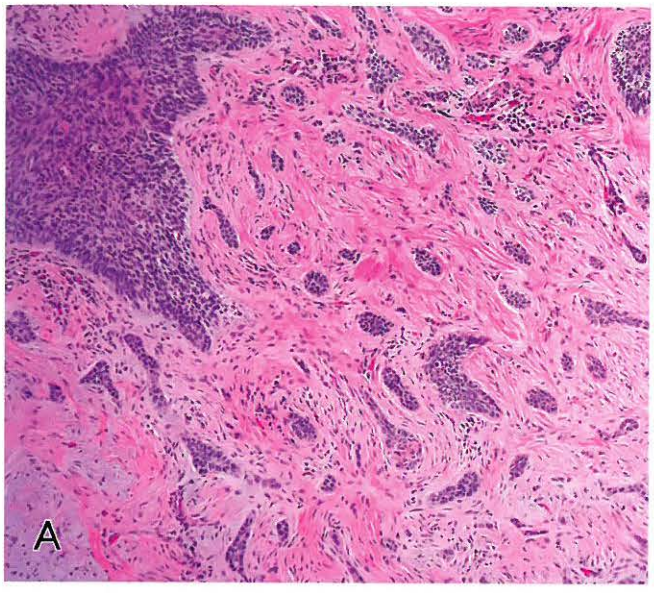
BASAL CELL CARCINOMA, NODULAR TYPE

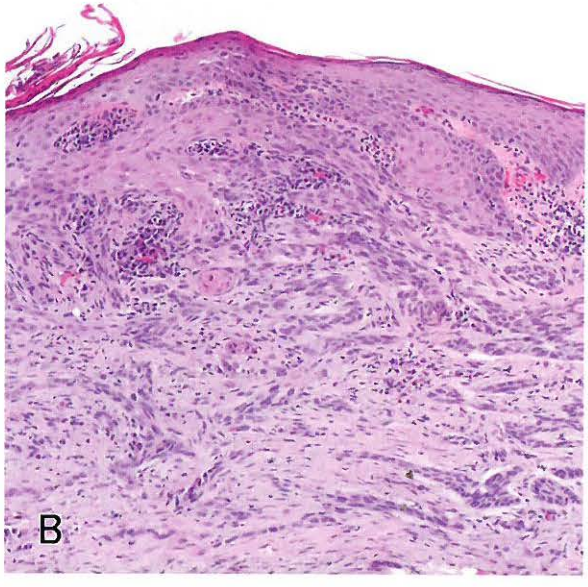
A: Large nodules of blue basaloid tumor cells invade downward into the dermis. Some retain connection to the epidermis. Ulceration (left) is a common finding. The pale fibrous stroma around the tumor differs from the solar elastosis of the background dermis (bottom).

B: At the periphery of the nests, tumor cell nuclei are usually tall/elongated and arranged in a row ("peripheral palisading"). There is often clefting artifact separating the periphery of the nests from the adjacent stroma, and myxoid/mucin may be present in the cleft space.

C: Peripheral palisading is particularly striking in this case.

D: Zones of dramatic pleomorphism (bottom) may be seen in BCC. These are usually focal, and areas of classic BCC (top) are almost invariably present alongside it. There is no prognostic significance to this finding.





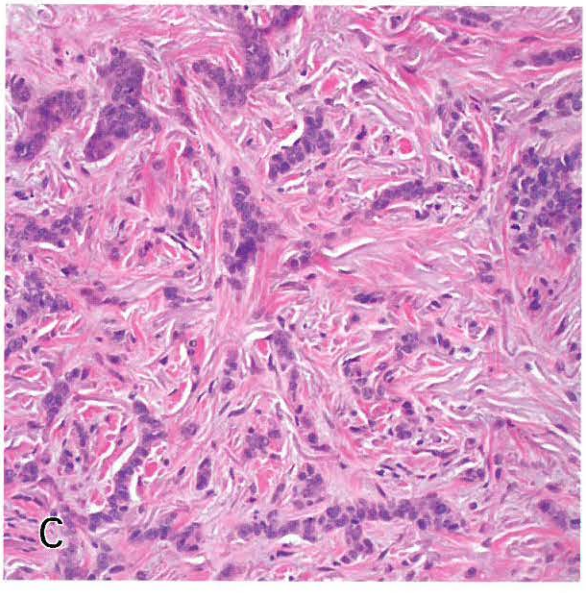


Figure 3-11

BASAL CELL CARCINOMA, INFILTRATIVE TYPE

A: Angulated nests and cords of basaloid cells infiltrate deeply into the dermis producing a brisk desmoplastic stroma with pale collagen and increased spindled fibroblasts. Larger nests of more obvious BCC are often present, at least focally (top left), providing a clue to the diagnosis.

B: Many of the angulated infiltrative nests are easy to see (right), but the thin pale cords of infiltrative tumor (bottom left) may blend in with the desmoplastic stroma and be easily overlooked on a small superficial shave biopsy. Deeper levels (and a pancytokeratin immunostain in difficult cases) can be useful.

C: The thin cords and tiny nests of basaloid cells are more obvious in this example.

keratosis. When BCC is not present on a small shave biopsy, I try to find one of these entities to explain the lesion that the dermatologist was seeing clinically. These entities may be subtle sometimes. If I do not see any obvious abnormality, I typically cut deeper levels x5 exhausting the block (hereafter referred to as "exhaust x5") to ensure that I am not missing a small focus of BCC deeper in the block. To do this, I ask my histotechnologists to cut all the way through the tissue block saving only 5 representative tissue sections along the way. This allows the entire block to be sampled but using only 1 to 2 glass slides rather than numerous ribbons of tissue sections on 5 or more glass slides. I feel that this strikes a good balance of due diligence for patient care without being inefficient or excessive. Using this method, I have found focal BCC that was not present on initial sections on multiple occasions. I believe the small additional delay and cost of this is worth it for avoiding a missed diagnosis of BCC, especially in a sensitive anatomic site such as the nasal tip or inner canthus.

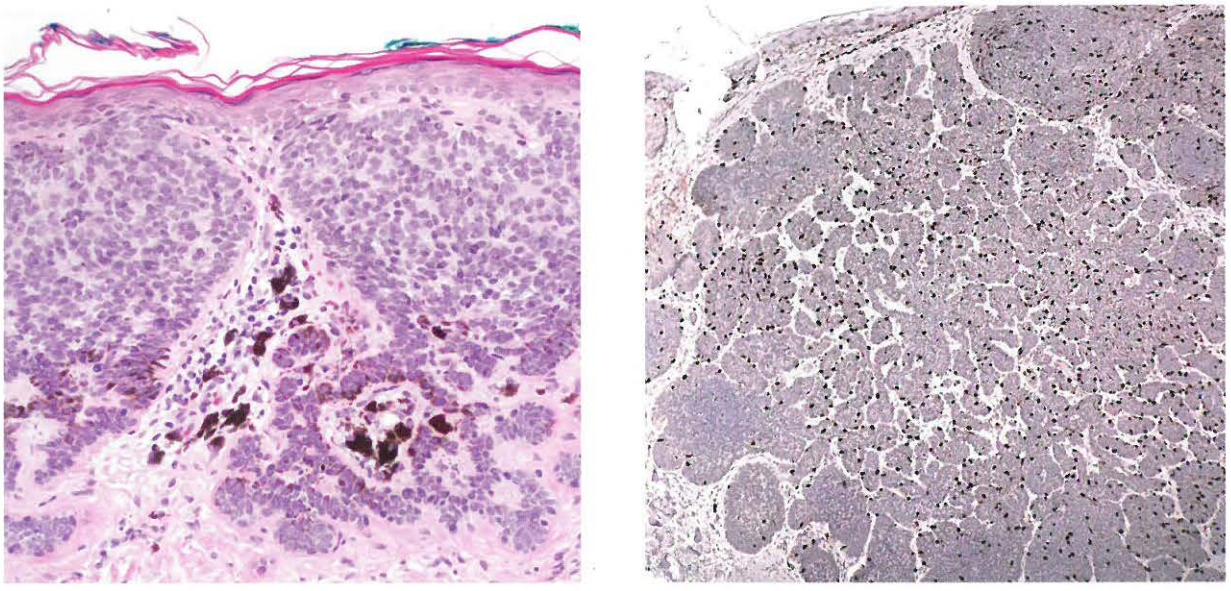


Figure 3-12

PIGMENTED BASAL CELL CARCINOMA

Left: Melanin pigment is present within the basaloid tumor cells, and melanophages are present in the underlying stroma. Pigment may be present in any of the BCC subtypes.

Right: Scattered hyperpigmented dendritic melanocytes may be present within BCC (or SK, IFK, SCC), highlighted here by SOX-10 immunostain. These are merely "passengers" within the tumor; do not confuse this with melanoma *in situ*. The presence of pigmented cytoplasmic dendritic processes, lack of nesting, and lack of spread into adjacent epidermis are all reassuring features.

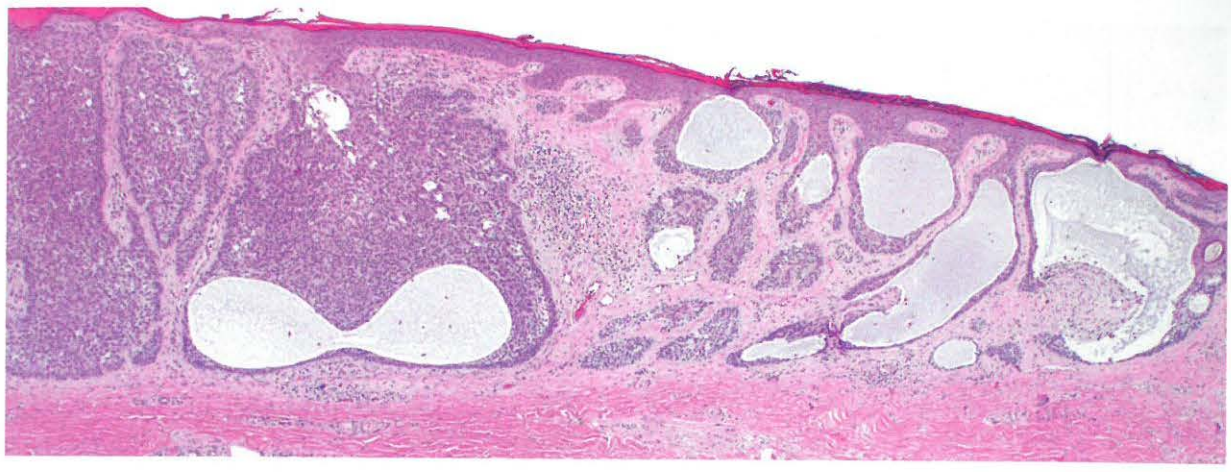
FIBROUS PAPULE

Fibrous papule (angiofibroma) (FP) arises on the face of adults, most often on the nose. It is a small white papule that mimics BCC clinically. It has collagenous stroma, scattered enlarged spindle to stellate (triangle, or boomerang-shaped) fibroblasts, and dilated blood vessels (fig. 3-17). In patients with abundant solar elastosis, a useful clue is that fibrous papule will replace the solar elastosis with pink collagen. Many variants of fibrous papule exist, including cellular, myxoid, and clear cell variants, as well as some with scattered degenerative nuclear pleomorphism. Fibrous papule should be high on the differential diagnosis list for any benign-appearing dermal spindle cell proliferation on the nose. Children with tuberous sclerosis develop numerous angiofibromas on the face (so-called "adenoma sebaceum," which is a misnomer).

LICHENOID KERATOSIS

Lichenoid keratosis is a solitary lesion, usually on the trunk, that mimics BCC clinically. It shows a band-like infiltrate of lymphocytes along the dermal-epidermal junction, with vacuolar interface change and dying keratinocytes (fig. 3-18). The appearance is similar to lichen planus but the lesion is solitary rather than a multifocal eruption (see chapter 8 for a more detailed discussion of the lichenoid inflammatory pattern).

Lichenoid keratosis probably arises from a preexisting lentigo or thin SK that has become briskly inflamed; sometimes a residual portion of the preexisting lesion can still be seen. The diagnoses of "inflamed lentigo," "inflamed SK," or "lichenoid keratosis" are essentially equivalent in my opinion. Melanin pigment incontinence can be prominent in some cases, causing the dermatologist to consider seborrheic keratosis or even melanoma in the clinical differential diagnosis; I diagnose these as "lichenoid keratosis with prominent pigment incontinence" to let the dermatologist know that I see a microscopic cause for the pigmentation they are seeing clinically. Keep in mind that melanoma *in situ*



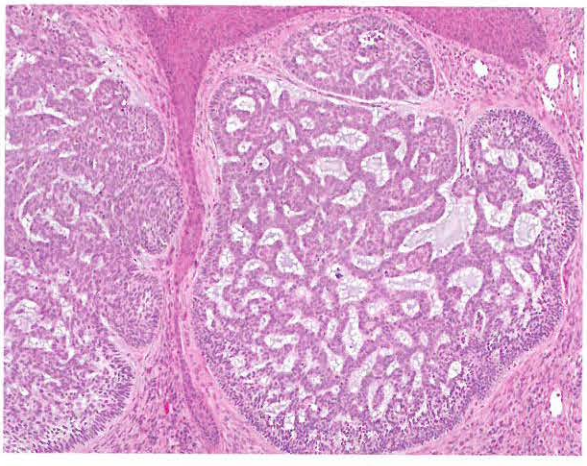


Figure 3-13

BASAL CELL CARCINOMA, "ADENOID" PATTERN

Above: Pools of mucin/myxoid are present within the tumor nests in this nodular BCC. Adjacent nests of BCC with conventional features are also present (far left). There is no prognostic significance to the adenoid pattern, but it may cause diagnostic confusion with adenoid cystic carcinoma or true adenocarcinoma for the unaware pathologist.

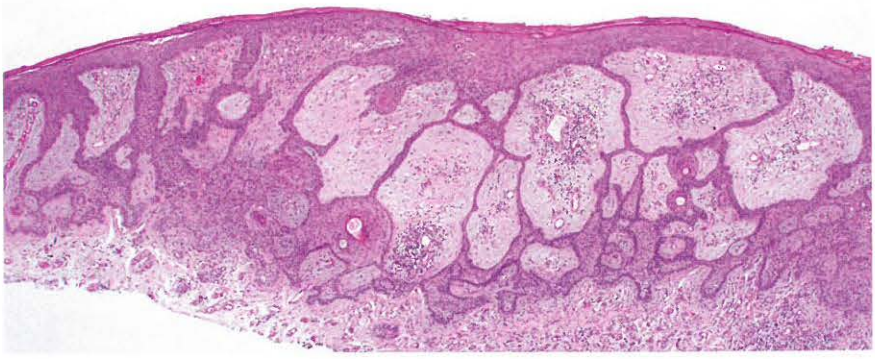
Right: The pools here are irregular in size and shape, and not as uniformly sharp, round, and "cookie cutter" as in adenoid cystic carcinoma. Rather than individual glands within the dermis as metastatic carcinoma would have, these mucin pools are within large basaloid nests that display peripheral palisading (bottom left) and clefting artifact (top left).

can sometimes have a brisk lymphocytic infiltrate ("host response"), which can obscure the melanoma cells within the dense inflammation. To avoid missing this, I usually go to higher power and scan along the dermal-epidermal junction to ensure I am not missing atypical melanocytes. The finding of dying keratinocytes (not just brisk inflammation) is also reassuring, as inflamed melanomas usually do not have these since the lymphocytes are attacking the melanocytes rather than the keratinocytes (although I have seen occasional exceptions). If there is any doubt, one can perform SOX-10 or MART-1 immunostains.

MERKEL CELL CARCINOMA

Merkel cell carcinoma (primary cutaneous neuroendocrine carcinoma) is an uncommon aggressive carcinoma arising in elderly adults, usually in sun-exposed sites. It is often a red to violaceous nodule clinically, but the appearance may be nonspecific.

Microscopically, it resembles small cell carcinoma of the lung. There is a blue basaloid dermal proliferation arranged as nodules, solid sheets, or infiltrative aggregates that intercalate between reticular dermal collagen bundles (fig. 3-19). The low-power appearance can sometimes resemble BCC, which is a dangerous pitfall, as the treatment and prognosis are very different. The absence of peripheral palisading, clefting artifact, or typical myxoid stroma in an apparent BCC at low power should prompt closer examination to exclude Merkel cell carcinoma. At high power, Merkel cell carcinoma is composed of uniform round blue cells with scant cytoplasm. The nuclei have fine powdery or stippled ("salt and pepper") chromatin that is typical of neuroendocrine tumors. Adjacent tumor nuclei mold together with one another. Mitotic activity is usually florid, with some cases showing over 100 mitoses per mm^2. BCC can sometimes have numerous mitoses, as well, so mitotic activity alone is not a



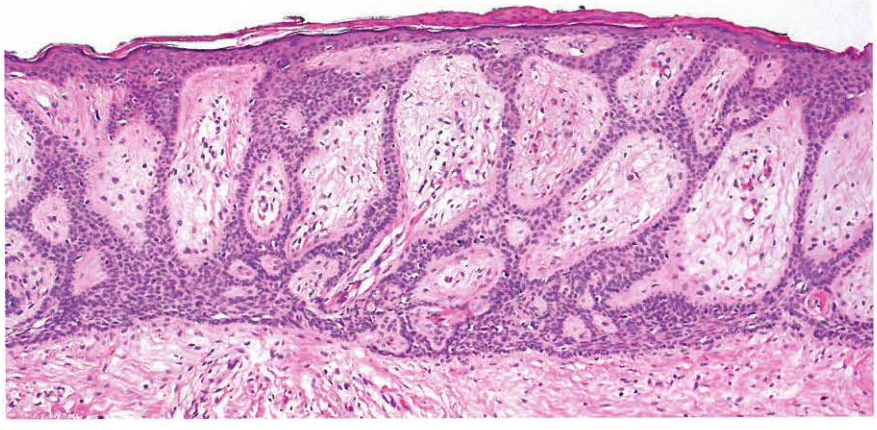


Figure 3-14

FIBROEPITHELIOMA OF PINKUS

Top: Cords of keratinocytes intermingled with basaloid nests extend down from the epidermis, forming a broad interconnected net-like proliferation.

Bottom: The net-like pattern of this entity is very distinct.

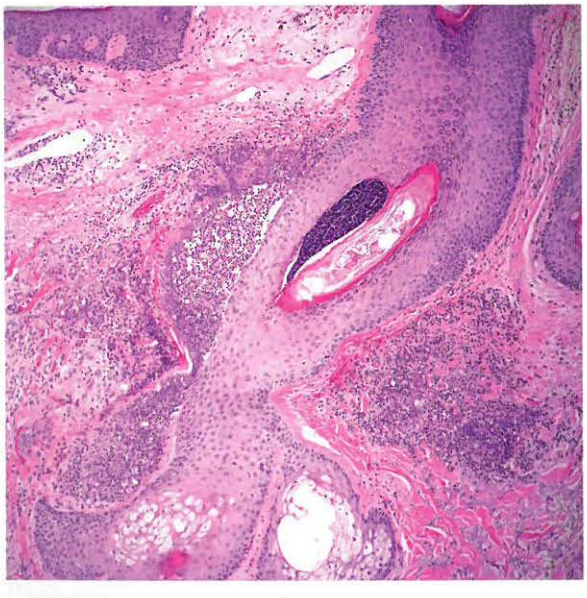


Figure 3-15

FOLLICULITIS

Neutrophils are present within the lumen of a dilated distorted hair follicle and have ruptured through the follicular epithelium, spilling out to form small abscesses in the adjacent dermis. Solitary inflamed/dilated follicles on the face are a common clinical mimic of BCC and are thus often biopsied.

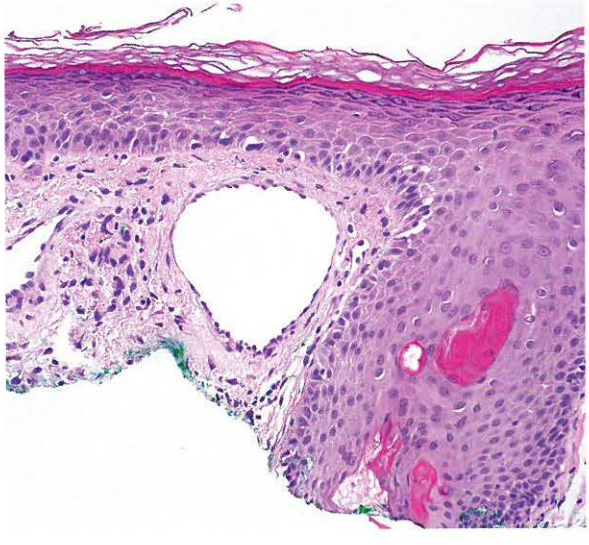
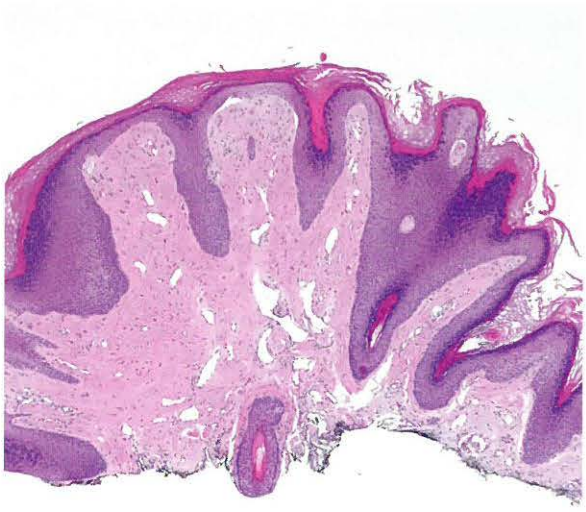


Figure 3-16

TELANGIECTASIA

Telangiectasias are thin-walled ectatic (dilated) vessels in the superficial dermis. Unlike a hemangioma or vascular malformation, there is usually only one or a few lumens seen in a given area. When telangiectasia is present next to a dilated hair follicle (as seen here), they can produce a "pearly papule with telangiectasia" appearance clinically, prompting biopsy to rule out BCC.



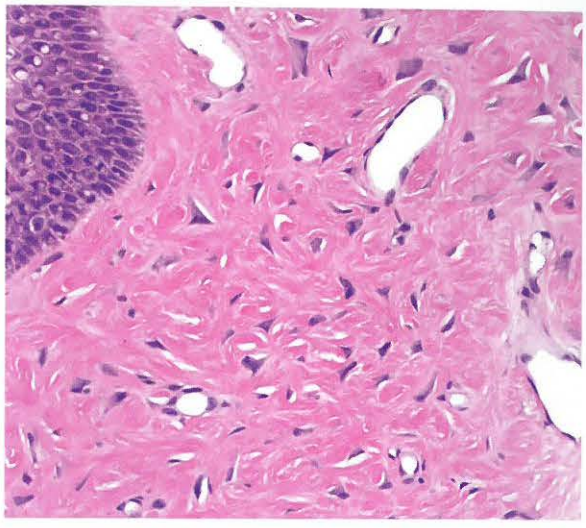
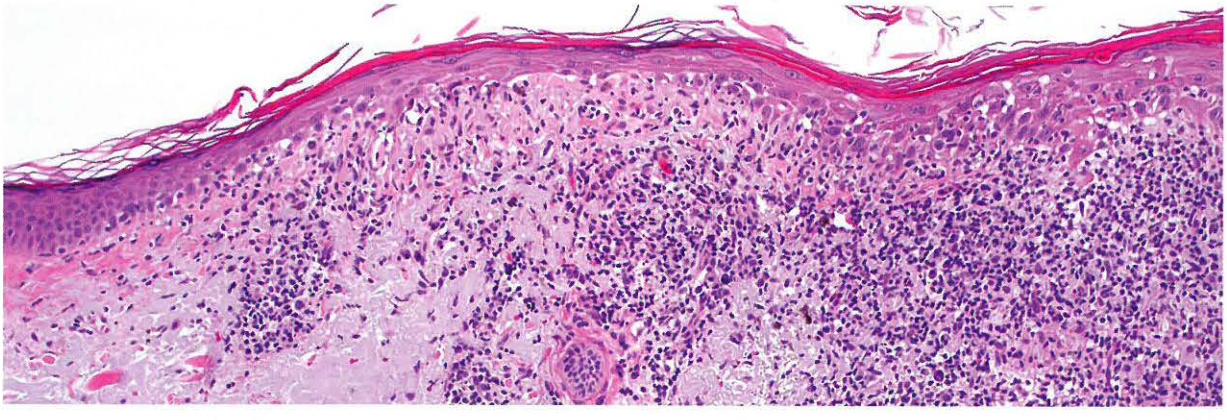


Figure 3-17

FIBROUS PAPULE (ANGIOFIBROMA)

Left: These are dome-shaped papules, usually on the nose. The dermis is replaced by dense sclerotic collagen in which multiple dilated vessels are embedded. This case is particularly large; most fibrous papules are much smaller.

Right: The fibrous papule triad: collagenous stroma, scattered enlarged spindle to stellate (triangle- or boomerang-shaped) fibroblasts, and dilated blood vessels.



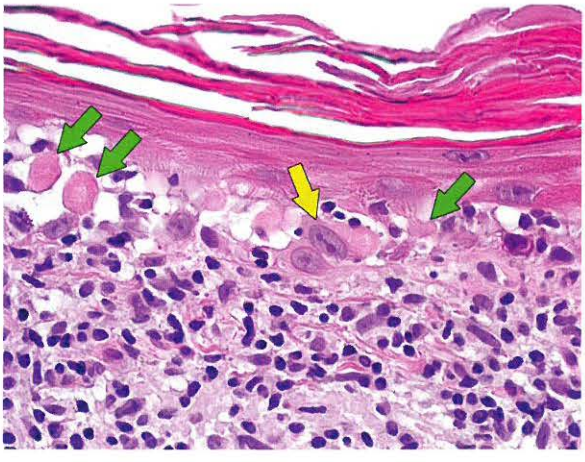


Figure 3-18

LICHENOID KERATOSIS

Above: There is a band-like infiltrate of lymphocytes along the dermal-epidermal junction with vacuolar interface change and dying keratinocytes (see chapter 8). The appearance is similar to lichen planus or other lichenoid dermatoses, but rather than a multifocal eruption, this was a solitary lesion on the chest that clinically resembled BCC.

Left: There is basal vacuolation with large pink dying keratinocytes (green arrows). The inflammatory damage to the basal keratinocytes often produces focal reactive nuclear atypia (yellow arrow). If there are many atypical keratinocytes, the lesion may be a lichenoid actinic keratosis; I usually reserve this diagnosis for when there is obvious actinic keratosis extending beyond the lichenoid area. The distinction is usually not important clinically.

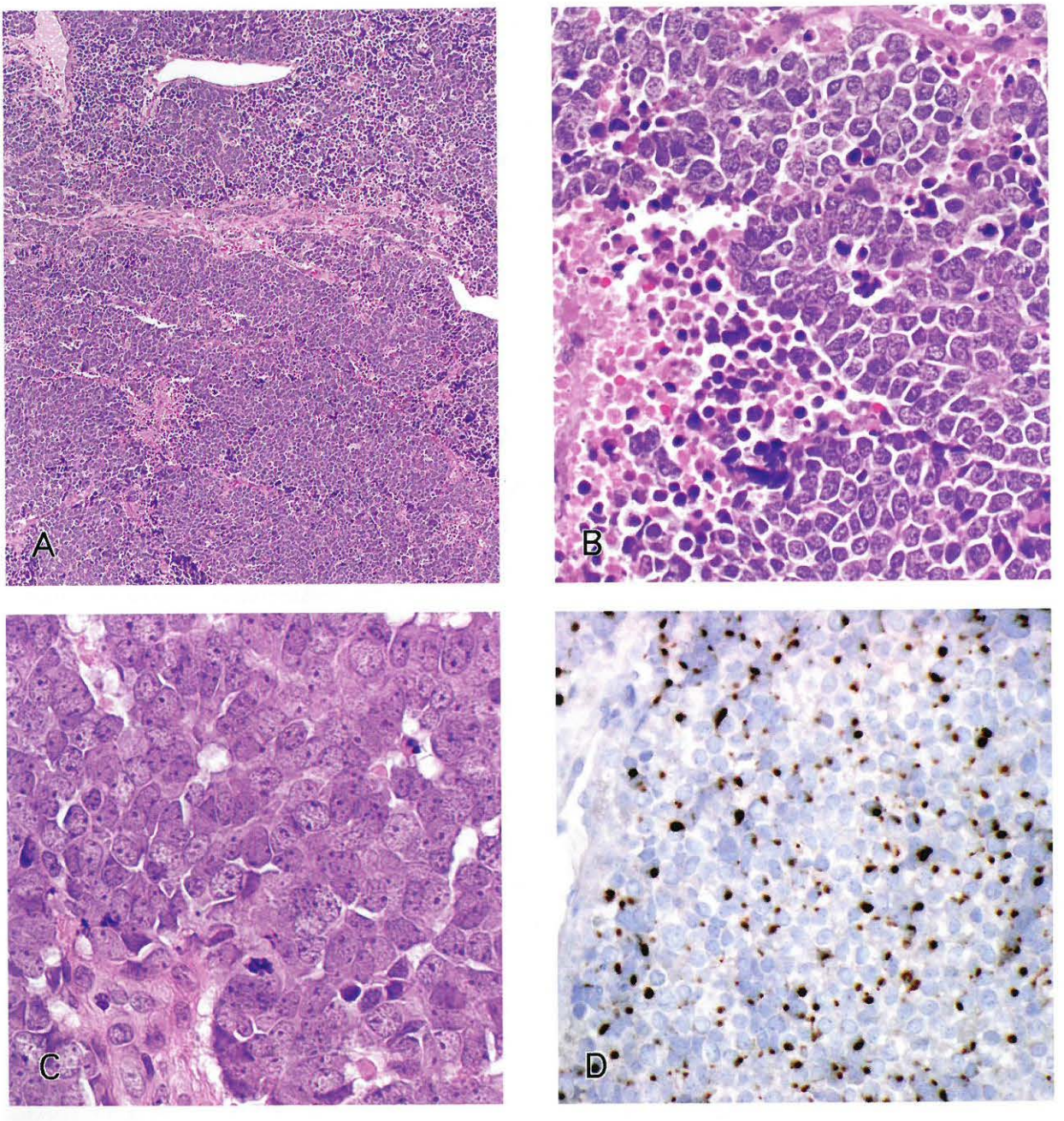


Figure 3-19

MERKEL CELL CARCINOMA

A: The dermis is replaced by cellular sheets of round blue cells. Cases with this pattern could be confused with lymphoma or leukemia cutis; those with a more nodular growth pattern could be mistaken for BCC. These would be disastrous mistakes, as treatment and prognosis differ drastically between all of these entities.

B: At high power, Merkel cell carcinoma is composed of uniform round blue cells with scant cytoplasm. The adjacent nuclei tend to conform in shape to their neighbors (nuclear molding – best seen in bottom right). The nuclei often show the stippled ("salt and pepper") chromatin that is typical of many neuroendocrine tumors. Tumor necrosis is seen (bottom left).

C: Some cases have a delicate, fine, powdery, or smudgy chromatin pattern.

D: Most cases are positive for CK20, classically with this distinct perinuclear dot-like pattern (this pattern is not required; solid cytoplasmic CK20 staining is also completely acceptable). If a skin tumor in an adult looks like Merkel cell carcinoma on H&E and CK20 is positive, the diagnosis usually can be made without performing any other immunostains.

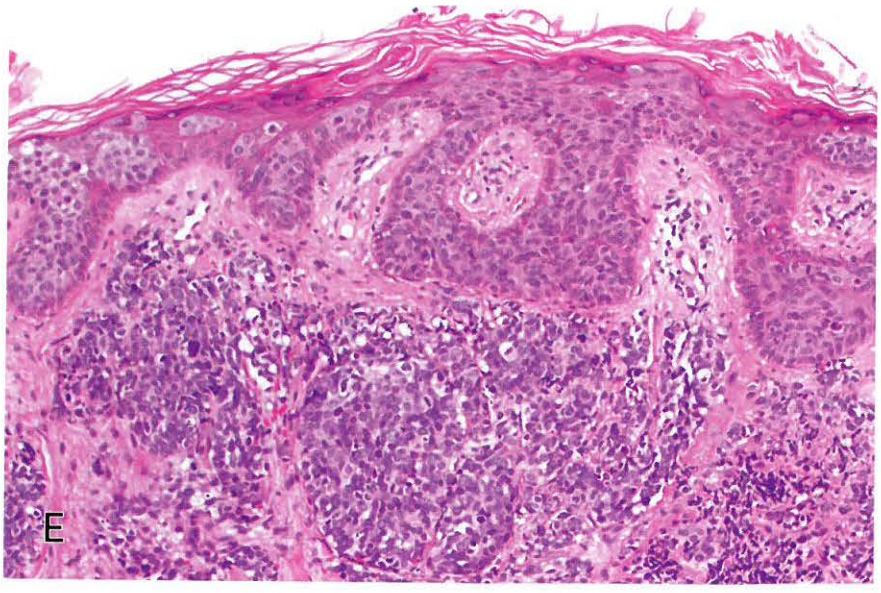


Figure 3-19, continued

E: Squamous cell carcinoma *in situ* is present in the epidermis overlying a Merkel cell carcinoma. Squamous cell carcinoma (*in situ* or invasive) has a tendency to coexist with Merkel cell carcinoma.

specific discriminator between BCC and Merkel cell carcinoma. Lymphovascular invasion (LVI) is almost invariably present. As my colleague, Dr. Sara Shalin, likes to say: "If you don't find LVI in a Merkel cell carcinoma, go back and look again!" Occasionally, though, LVI will be absent, particularly on a small biopsy. SCC, either *in situ* or invasive, often coexists with Merkel cell carcinoma. Rare cases show epidermal involvement by *in situ* Merkel cell carcinoma.

Merkel cell carcinoma is positive for CK20 (with very rare exceptions), often in a perinuclear dot-like pattern, as well as synaptophysin, chromogranin, and neurofilament protein/NFP (may also be dot-like). Merkel cell polyoma virus T antigen immunostain is also usually positive, although I have limited experience with this marker as H&E plus CK20 (and/or NFP) are usually all I need to make the diagnosis. If a tumor looks classic for Merkel cell carcinoma on H&E and CK20 is positive, I diagnose the case as Merkel cell carcinoma without performing any other workup. If CK20 is negative, I expand my panel to include CK7, TTF-1, synaptophysin, and chromogranin to rule out metastatic small cell carcinoma from the lung or other visceral primary sites, which may rarely present as skin metastasis with no known primary. TTF-1 expression may also be seen in small cell carcinomas of extrapulmonary sites, although it is only rarely expressed in Merkel cell carcinoma (4,5). A lung primary should be suggested as a possibility if TTF-1 is positive, but imaging studies are essential to identify the primary site.

Depending on the results of the 2nd expanded stain panel, I may do an even broader 3rd round of stains including S-100 protein, pancytokeratin, CD45, CD43, TdT, CD99, MUM-1, desmin, or others to rule out small cell melanoma, lymphoma, myeloma, Ewing sarcoma, alveolar rhabdomyosarcoma, and other less common entities. I do not use neuron "specific" enolase (NSE) (ever) or CD56 (in this context) as they are not specific for neuroendocrine differentiation (CD56 has utility in the workup of some hematopathology cases, of course).

A different scenario is when I favor a tumor to be BCC on H&E, but some feature makes me wonder if it could be a subtle Merkel cell carcinoma. In this case, I do CK20 so I can sleep at night without worrying that I missed the diagnosis. If CK20 is negative, I diagnose the case as BCC without any additional workup. I do not recommend doing synaptophysin/chromogranin in this scenario, as some BCCs may have neuroendocrine marker expression (6). If synaptophysin/chromogranin is positive but CK20 is negative, what then? You will worry a lot more, do many additional immunostains, possibly get the patient imaging studies and invasive workup, cause anxiety for the dermatologist and patient...and all of that for what is very likely just a BCC with some aberrant neuroendocrine expression. That is a Pandora's Box I try to avoid

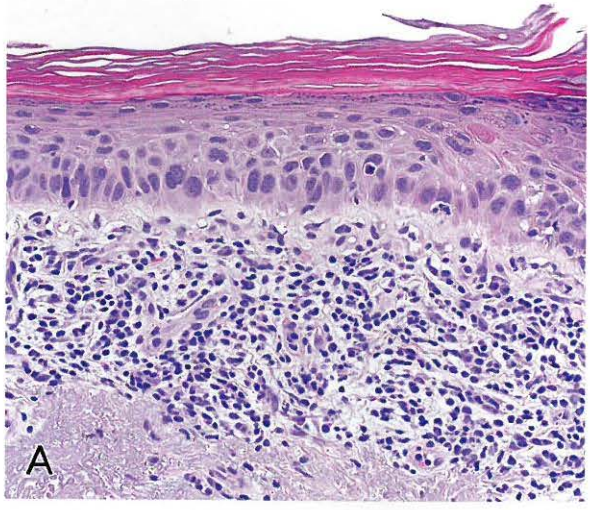
Figure 3-20

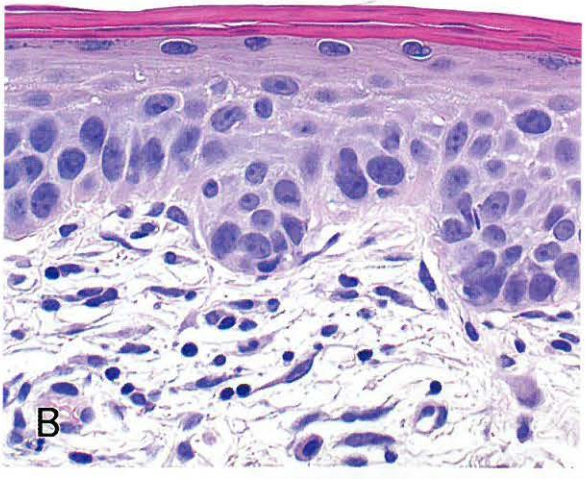
ACTINIC KERATOSIS (AK)

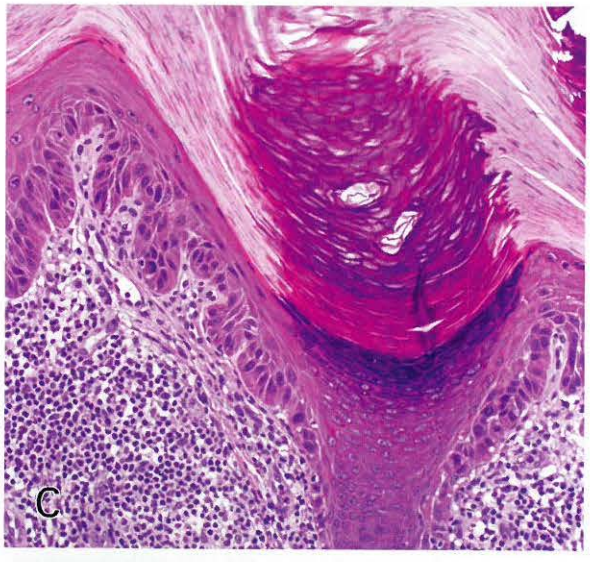
A: Large atypical basal layer keratinocyte nuclei have a disorganized jumbled arrangement, but they are confined to the lower portion of the epidermis. They still mature into flattened squamous cells as they move superficially toward the corneal layer. The atypical keratinocytes are much larger than the spinous layer keratinocytes of the adjacent epidermis (far right).

B: A high-power view showing jumbled atypical keratinocytes in the lower portion of the epidermis. As a rule, there is overlying parakeratosis with a diminished/absent granular layer (although some cases break this rule).

C: Actinic keratosis usually spares the areas where adnexal structures connect to the epidermis. Note the sharp cutoff between the zone of small normal keratinocytes and orthokeratin at this acrosyringium (eccrine duct opening) and the large atypical keratinocytes and parakeratosis of the adjacent actinic keratosis on both sides of it.







opening. Again, I only use this approach when the morphology is strongly in favor of BCC but I need a bit of reassurance. If, on the other hand, if I favor a neuroendocrine carcinoma or other round blue cell tumor on H&E, I use the expanded workup described in the previous paragraph and handle the case very differently.

ACTINIC KERATOSIS

Actinic keratosis (AK) is an erythematous scaly lesion that arises in older adults due to keratinocytic dysplasia induced by chronic sun damage. A small subset of AK progress into SCC. Dermatologists often treat AK with liquid nitrogen, although if they are unsure whether the lesion is actually AK (versus SCC, BCC, or something else), they will biopsy it. Biopsy usually shows an atrophic epidermis with overlying parakeratosis and underlying solar elastosis; zones of parakeratosis in severely sun-damaged skin is a low-power clue for AK.

At higher power, there are large atypical basal layer keratinocyte nuclei with a disorganized jumbled arrangement (fig. 3-20). These still mature into flattened squamous cells as they move superficially toward the corneal layer. The granular layer is lost and there is overlying parakeratosis, both signs of an increased rate of epidermal keratinocyte proliferation. In some cases, the atypical cells bud down into elongated rete ("proliferative" AK) or extend down hair follicles or eccrine ducts (AK with adnexal

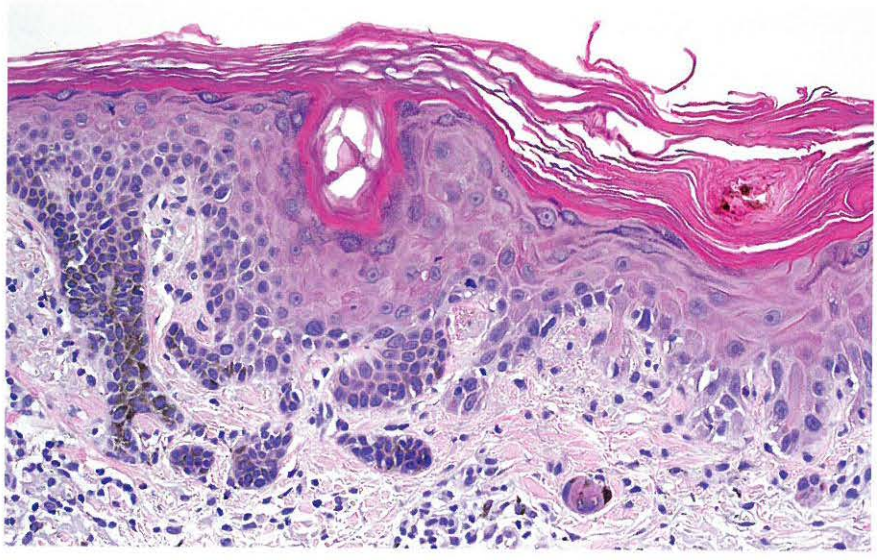


Figure 3-21

PIGMENTED ACTINIC KERATOSIS AND SOLAR LENTIGO

Multiple foci of actinic keratosis (right) and solar lentigo (left) often intermingle and blend into one another in the same biopsy.

extension). If there is a large downward bud from the epidermis with abundant pink glassy expansion of cytoplasm, I then often do deeper sections (usually "exhaust x5"; see above) to exclude invasive SCC. If there is a zone of full thickness atypia or pagetoid spread, I will make a diagnosis of SCC *in situ* instead of AK. SCC *in situ* is supposed to have full thickness atypia whereas AK is only partial thickness. While the distinction sounds simple, in real life it can be quite arbitrary and subjective to tell these two apart. If the lesion looks like AK but is broadly transected at the margin and I am concerned that it may be superficially sampled SCC, I will usually say "at least actinic keratosis" to indicate that although the lesion looks like AK in this biopsy, I may not be seeing the entire lesion.

Pigmented AK has the added finding of increased melanin pigment in the basal layer keratinocytes. They may clinically mimic melanoma (lentigo maligna type). Solar lentigo on severely sun damaged skin may have large atypical basal layer keratinocytes; some refer to these as "large cell acanthoma" (a term I personally do not use in reports) whereas others call them pigmented AK. I often utilize "pigmented actinic keratosis and solar lentigo" as the diagnostic terminology in my reports, as these two entities commonly coexist and intermingle on the same biopsy and have overlapping morphologic features (fig. 3-21). Regardless of terminology, the critical thing that the dermatologist needs to know in this scenario is that the lesion is not melanoma.

Hypertrophic AK (HAK) shows thick parakeratosis overlying an acanthotic epidermis that is expanded by atypical keratinocytes with abundant glassy cytoplasm (fig. 3-22). These lesions often arise on the dorsal hand/forearm, a site that gets abundant sun exposure. HAK tend to be biopsied more often by dermatologists because their thicker appearance clinically raises concern for invasive SCC. The overlying keratin may be so thick in some cases as to create a cutaneous horn, a firm scaly lesion that protrudes from the skin surface (fig. 3-23). The most common causes of cutaneous horn are AK, SCC, verruca, and occasionally SK. Cutaneous horns due to different underlying etiologies usually look the same clinically, and thus biopsy is the only way to reliably determine the underlying lesion.

SQUAMOUS CELL CARCINOMA, *IN SITU*

Squamous cell carcinoma in situ (*Bowen disease*) presents as an erythematous scaly plaque in chronically sun-damaged skin of elderly patients. The clinical differential diagnosis may include AK, superficial BCC, or even inflammatory dermatoses such as psoriasis or nummular eczematous dermatitis. SCC *in situ* can display a wide range of microscopic patterns (fig. 3-24). Some are acanthotic lesions composed of severely atypical keratinocytes that completely fill the epidermis with diffuse overlying parakeratosis; such cases are easy to diagnose. Others are subtler, either composed of glassy keratinocytes resembling HAK or of uniform small round

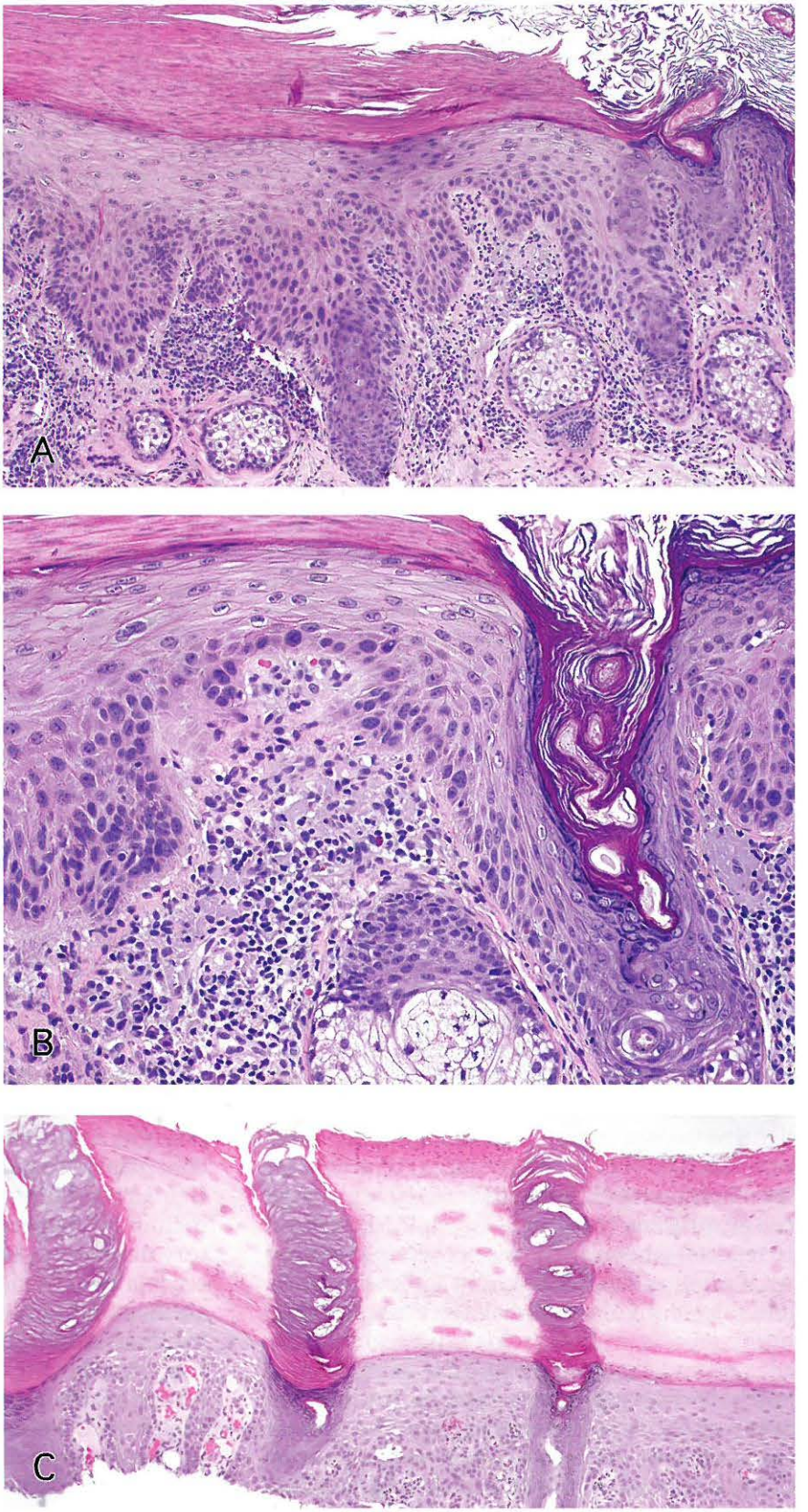


Figure 3-22

HYPERTROPHIC ACTINIC KERATOSIS (HAK)

A: This variant of AK has an acanthotic epidermis due to more abundant glassy cytoplasm in the keratinocytes. There is usually a thick broad zone of overlying parakeratosis. Contrast with the adjacent normal skin (far right).

B: Even though the epidermis is expanded and acanthotic, the atypical keratinocytes are still mostly in the lower epidermis, with maturation in the upper epidermis. The hair follicle (right) is mostly spared by the HAK, as evidenced by the overlying orthokeratin.

C: Multiple acrosyringia (eccrine sweat duct openings) are spared by this broad HAK, leaving alternating zones of dense pink parakeratosis (overlying the HAK) and columns of loose purplish orthokeratin (overlying the acrosyringia).

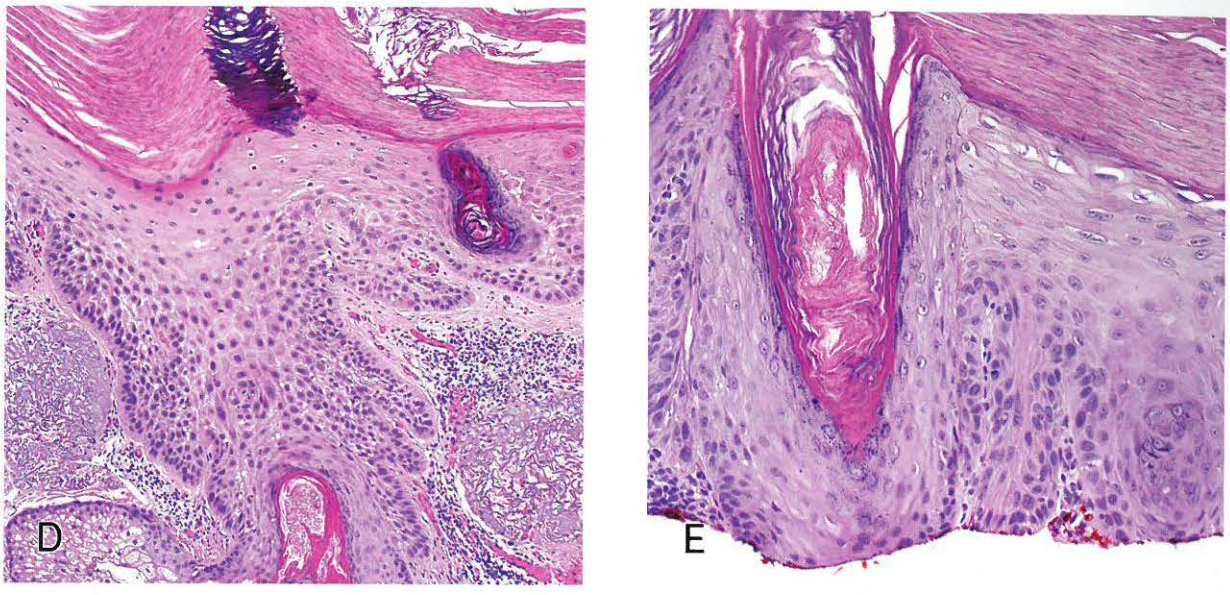


Figure 3-22, continued

D: The keratinocytes often have abundant pale "glassy" cytoplasm. This HAK extends down a hair follicle. However, full-thickness epidermal atypia is not present (as would be seen in squamous cell carcinoma *in situ*). The small column of purple orthokeratosis (center) in the corneal layer probably represents an adjacent spared acrosyringium that is outside the plane of this section.

E: This likely represents a HAK, but the long rete are broadly transected, which precludes evaluation of the deep aspect of the lesion. When much of the lesion is transected like this on a shave biopsy, and there is concern that an underlying invasive squamous cell carcinoma cannot be fully excluded, then I will use "at least hypertrophic actinic keratosis" for the diagnosis line.

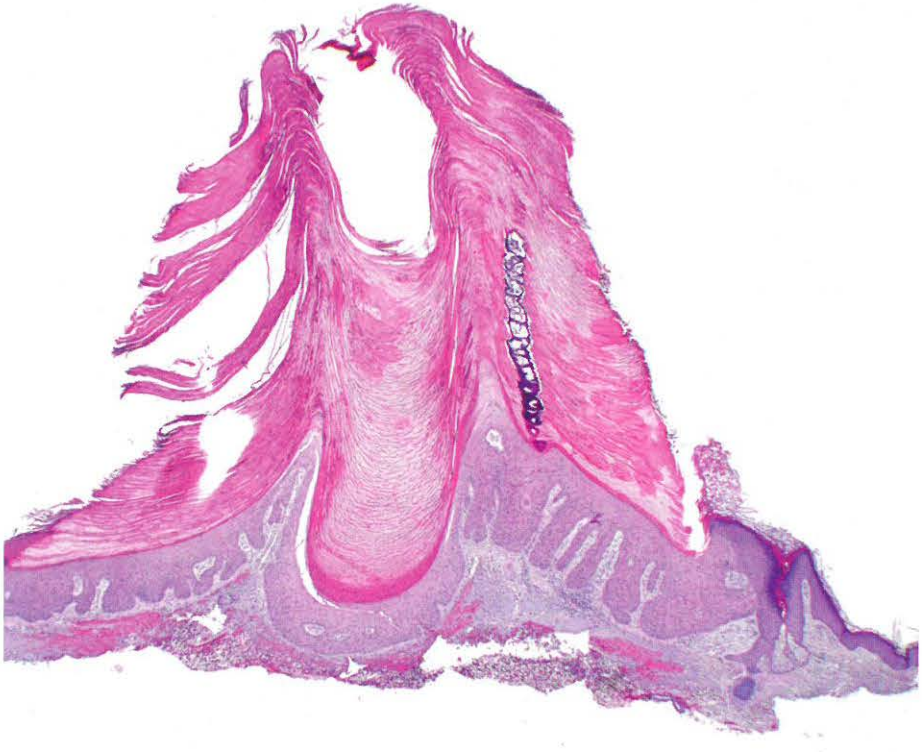


Figure 3-23

CUTANEOUS HORN

This HAK has a massive thick layer of overlying parakeratosis that extends far above the skin surface, which corresponds to the firm, scaly, cutaneous horn seen clinically. "Cutaneous horn" is a clinical term; it cannot be used as the pathologic diagnosis unless the underlying epidermal lesion that caused the horn (e.g., AK, HAK, SCC, verruca, or SK) is also identified and reported.

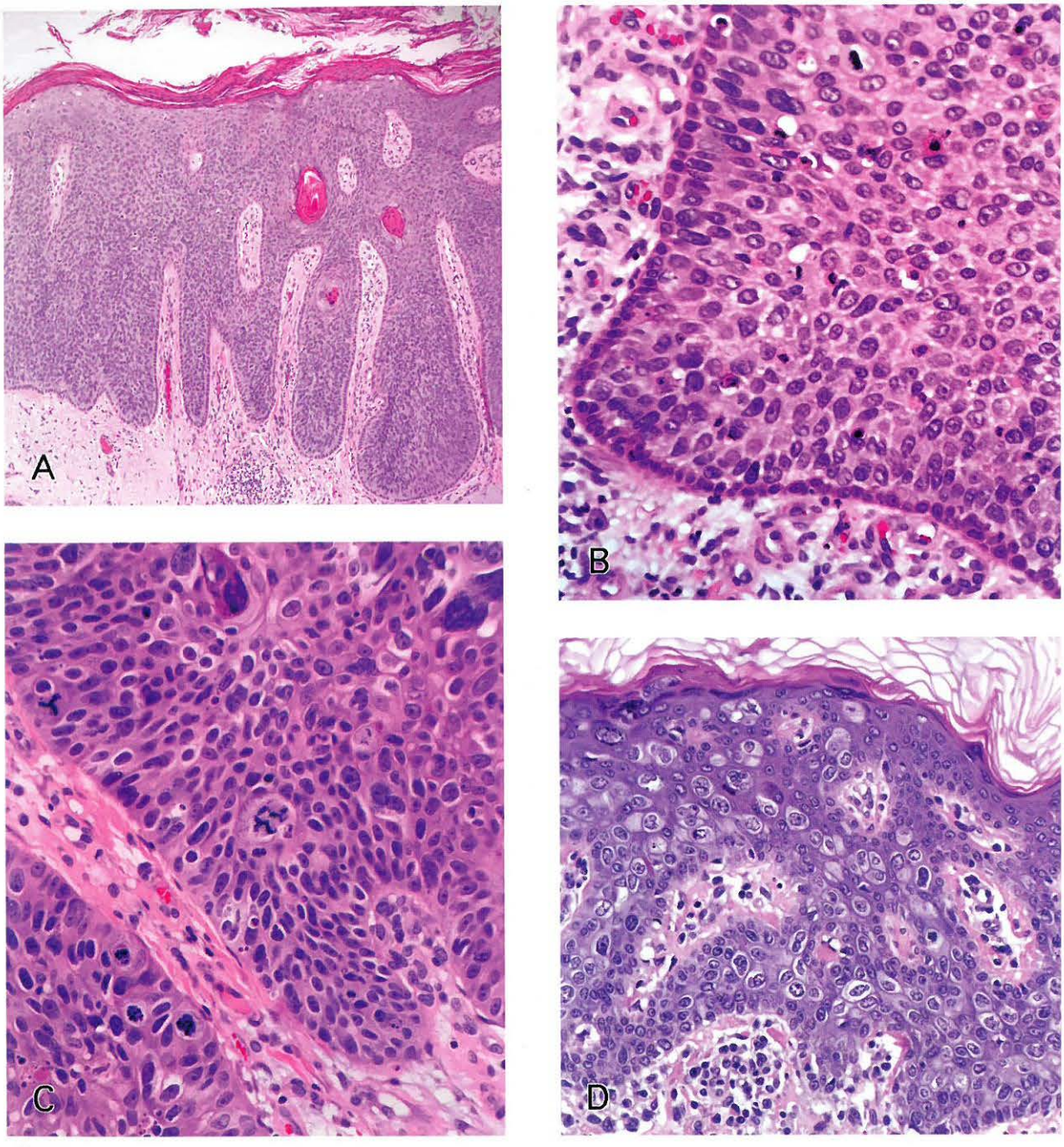


Figure 3-24

SQUAMOUS CELL CARCINOMA (SCC), IN SITU

A: The epidermis is expanded and filled by atypical hyperchromatic keratinocytes. The normal basal layer keratinocytes are mostly retained, creating a line of single cells along the base of the lesion ("eyeliner sign"). Parakeratosis is present over the lesion.

B: A closer look at the "eyeliner sign." Contrast the large atypical keratinocytes filling the epidermis with the single layer of small normal keratinocytes preserved along the basal layer.

C: Expanded rete are filled with SCC *in situ*. The "eyeliner sign" is absent in this case. There is a smooth border between epidermis and dermis, with no dermal invasion. Note the pleomorphism and atypical mitotic figures.

D: The tumor cells in this case have pale/clear cytoplasm and prominent pagetoid spread, which could cause confusion with melanoma *in situ* or Paget disease.

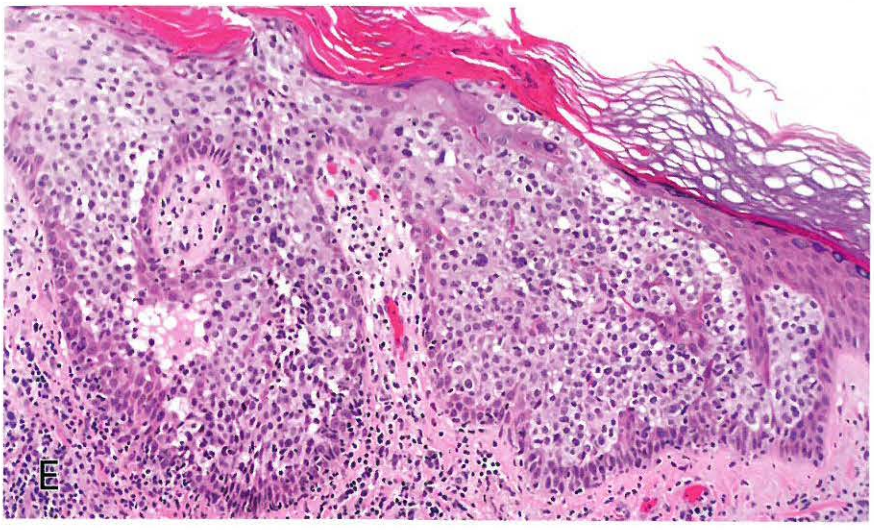


Figure 3-24, continued

E: This SCC *in situ* has pale/clear cells but the presence of solid zones of full-thickness intraepidermal atypia argues strongly against melanoma *in situ* or Paget disease. The "eyeliner sign" is additional evidence against melanoma *in situ*.

keratinocytes resembling clonal SK. In the latter scenario, finding increased mitotic figures high in the spinous layer may be a helpful clue. Some cases display prominent clear cell change or vacuolated cytoplasm, which can make them mimic porocarcinoma or sebaceous carcinoma.

SCC *in situ* is one of the three main entities that can show prominent pagetoid spread, the other two being melanoma and Paget disease (mammary or extra-mammary). Pagetoid SCC *in situ* extends into the adjacent epidermis as atypical single cells and nests that intermingle between normal background keratinocytes. In the pagetoid areas, SCC *in situ* is usually situated in the spinous layer, leaving the underlying preexisting normal basal layer keratinocytes intact. This band of normal basal keratinocytes beneath the pagetoid cells in SCC *in situ* is referred to as the "eyeliner sign." This sign may also be seen in Paget disease but is usually absent in melanoma, where the malignant melanocytes tend to replace the basal layer rather than preserve it.

Pagetoid SCC *in situ* usually has at least focal zones of full-thickness epidermal atypia; this is a very useful H&E clue to SCC *in situ*, since even florid examples of melanoma or Paget disease rarely show full thickness epidermal atypia. Melanoma can sometimes show "consumption" of the epidermis (fig. 4-2E), but this is often in rapidly growing invasive melanomas where the diagnosis of melanoma is otherwise obvious. In difficult cases, immunohistochemistry can usually distinguish between SCC *in situ*, Paget disease, and melanoma. I personally like to use p63 or p40 for SCC *in situ* (CK5/6 also works), SOX-10 or MART-1 for melanoma, and CK7 for Paget disease (CAM 5.2 and mucicarmine also work).

PAGET DISEASE

Paget disease refers to cutaneous involvement by adenocarcinoma (rare exceptions exist; see below) with a characteristic pattern of intraepidermal growth (fig. 3-25). *Mammary Paget disease* is usually due to underlying breast carcinoma that has spread via the lactiferous ducts to involve the skin of the nipple. Correctly diagnosing it is therefore very important since it is a cutaneous marker for more serious underlying disease. All patients with mammary Paget disease must be clinically worked up for underlying breast cancer.

Paget disease presents as painful, crusted, weeping, ulcerated, and/or erythematous skin changes on the nipple, usually unilaterally. It can clinically be confused with contact or eczematous dermatitis of the nipple; any nipple dermatitis that does not resolve with conservative therapy should be biopsied. If a nipple biopsy shows only spongiotic dermatitis, I diagnose it as such but usually add a comment recommending clinical follow-up and potentially a repeat biopsy if it does not resolve with topical steroids, since spongiotic dermatitis can be adjacent to unsampled Paget disease.

Extramammary Paget disease (EMPD) arises as a diffuse erythematous crusted plaque in the

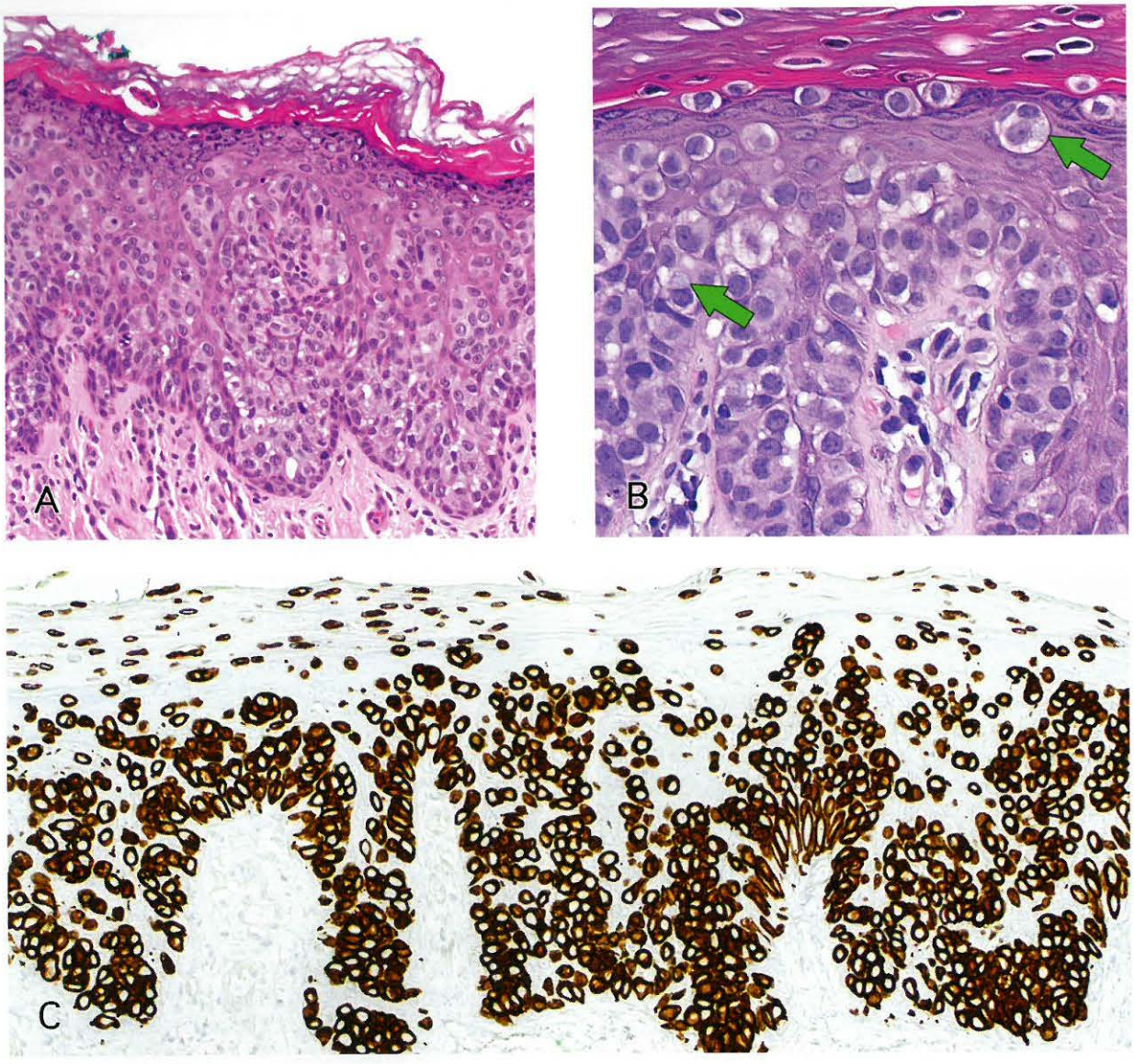


Figure 3-25

PAGET DISEASE

A: Numerous atypical epithelial cells with pale cytoplasm are scattered throughout all layers of the epidermis. Despite their abundance, they are intervened by normal keratinocytes and thus do not form zones of solid full-thickness atypia.

B: Large pale epithelial cells scatter into the upper reaches of the epidermis. Note the small intracytoplasmic droplets of blue mucin (arrows).

C: The tumor cells are strongly positive with a CK7 immunostain.

anogenital region. Most often, EMPD is primary, arising presumably from stem cells of sweat gland/duct origin and involving only the skin of the penis, scrotum, labia, perineum, and perianal area without internal visceral involvement. A smaller subset of EMPD is secondary, meaning that an internal visceral/mucosal carcinoma has spread out from an orifice secondarily involving the adjacent skin. This is usually anal or rectal adenocarcinoma spreading onto perianal skin, but less commonly, urothelial carcinoma spreading out of the urethral meatus onto the skin of the glans penis or even gynecologic carcinomas spreading out of the vagina onto the

skin/mucosa of the introitus or labia. Any time EMPD is directly contiguous with the anus, urethral meatus, or vaginal introitus, the possibility of secondary involvement from an internal carcinoma should be considered and ruled out by immunostains and additional clinical workup.

Mammary and extramammary Paget disease show similar microscopic features. There are atypical cells with abundant pale cytoplasm within the epidermis, arranged as scattered single cells and small nests intermingled among the background keratinocytes (this is the origin of the term "pagetoid"). Intracytoplasmic mucin droplets may be seen, and sometimes multiple tumor cells aggregate, forming small glandular structures within the epidermis. The basal layer keratinocytes are usually preserved, creating the "eyeliner sign" discussed above. In EMPD, foci of dermal invasion may sometimes be seen; this should be commented on in the pathology report, as there is potential for aggressive behavior in these cases (7).

Mammary Paget disease and primary EMPD usually strongly express CK7 but are negative for melanocytic markers and p63/p40. Mucicarmine may be used to highlight intracytoplasmic mucin within the tumor cells. Obviously, secondary EMPD will have cytologic features and an immunophenotype corresponding to the underlying internal visceral malignancy from which it arose. In particular, urothelial carcinoma is positive for p63/p40, which could potentially cause misdiagnosis as high-grade squamous intraepithelial lesion (HSIL)/SCC *in situ*.

SQUAMOUS CELL CARCINOMA, INVASIVE

Invasive SCC clinically presents as an erythematous scaly papule or nodule on chronically sun-damaged skin. The clinical differential often includes hypertrophic AK, verruca, inflamed SK, or BCC. Invasive SCC is classically characterized by islands or tongues of atypical keratinocytes with dense eosinophilic cytoplasm invading the dermis (fig. 3-26). There is usually adjacent dermal fibrosis and inflammation, representing a desmoplastic stromal reaction to the invasive tumor.

Invasive islands of SCC often show paradoxical maturation (i.e., they look less like the basal layer and more like the superficial spinous layer keratinocytes), with more abundant eosinophilic cytoplasm due to increased production of keratin. Some of this keratin takes the form of dense parakeratotic aggregates trapped within the middle of a nest of invasive tumor, the "keratin pearls" that are a classic feature of invasive SCC. Beginners often get the keratin pearls of SCC confused with the horn pseudocysts of SK because both are small cystic aggregates of keratin, but these are usually easy to tell apart. Keratin pearls are dense keratin, usually parakeratin, and they are present within dermal islands of atypical keratinocytes in invasive SCC. Horn pseudocysts are loose keratin, usually orthokeratin, and they are present within the acanthotic epidermis of SK.

SCC can show a variety of other histologic patterns. Some are verrucous/papillomatous on the surface with abundant overlying parakeratosis. Some are cystic and have bland nuclei with abundant dense eosinophilic "glassy" cytoplasm (see keratoacanthoma section below). Others have dramatic deeply infiltrative growth that can overlap with the features of infiltrative-type BCC (fig. 3-27). It is important to look carefully for perineural invasion in this form of SCC since these can be very aggressive. Some SCCs have moderately or even poorly differentiated areas where the cells become markedly atypical and have less abundant eosinophilic cytoplasm or more solid sheet-like growth. A subset of poorly differentiated SCC can have pleomorphic sarcomatoid morphology ("spindle cell SCC") (fig. 3-28). These can be histologically identical to spindle cell melanoma, atypical fibroxanthoma, pleomorphic dermal sarcoma, and other pleomorphic sarcomas; immunostains for p63/p40 (+), pancytokeratin (+/-), and S-100 protein/SOX-10 (-) are essential to sort out this differential diagnosis. *Spindle cell SCC* may sometimes lose expression of keratins, but strong nuclear p63/p40 expression is usually still present.

Acantholytic SCC has prominent dyscohesion of tumor cells, resulting in round glassy detached individual keratinocytes freely floating in empty spaces within tumor islands (fig. 3-29). In some cases of acantholytic SCC, only the outermost layer of tumor cells remains intact, which can create the appearance of gland or vascular lumen formation mimicking adenocarcinoma or angiosarcoma, respectively. Recognition of the free-floating acantholytic keratinocytes within the spaces is key to making the correct diagnosis.

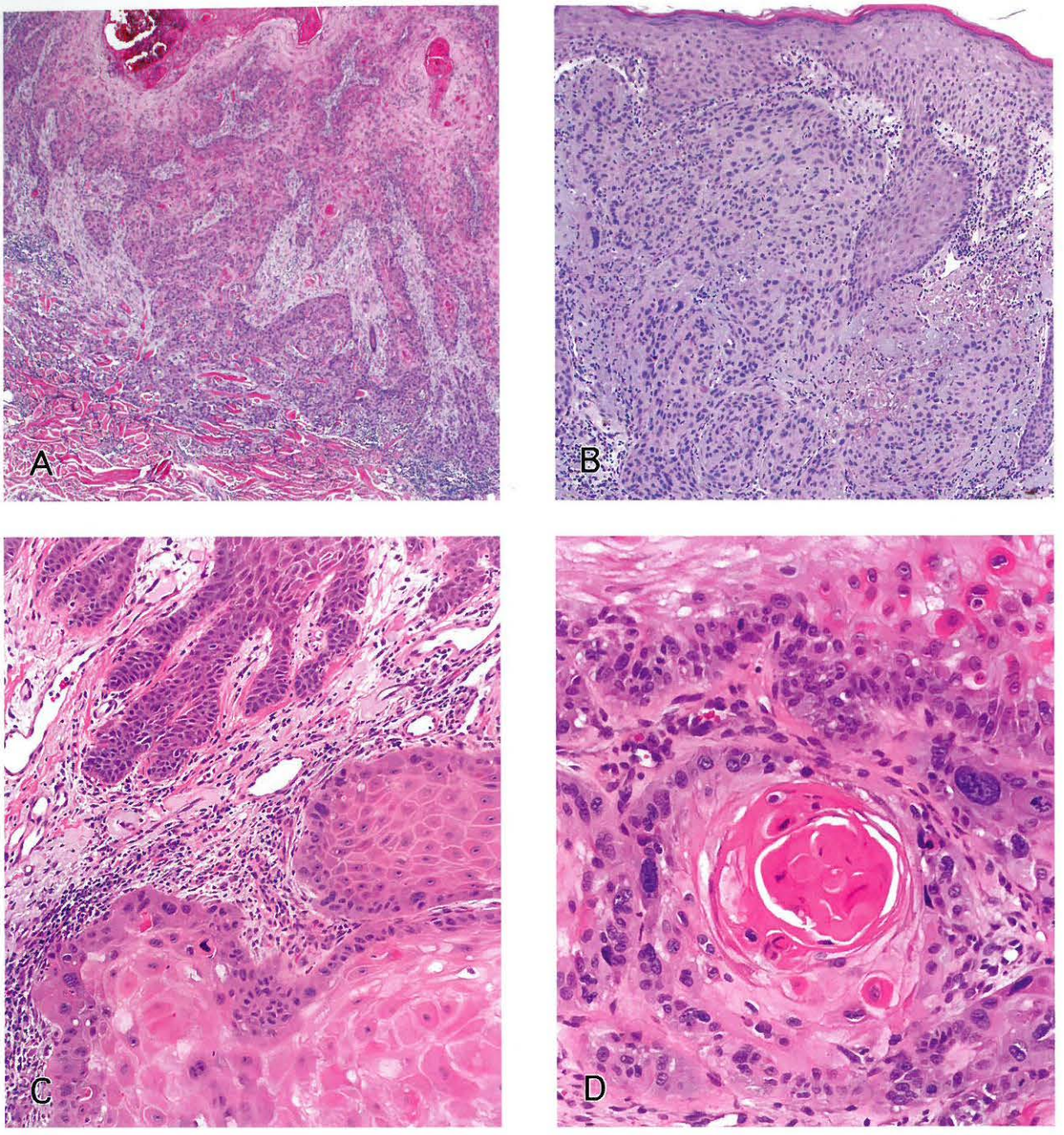


Figure 3-26

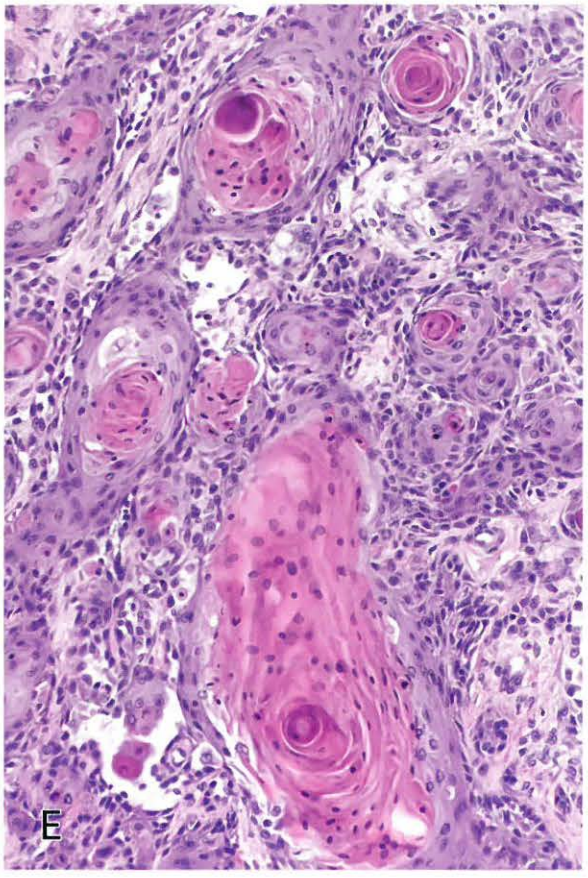
SQUAMOUS CELL CARCINOMA, INVASIVE

A: Islands of atypical keratinocytes invade the dermis. They range from pink (top) to blue (bottom) depending on the amount of cytoplasmic keratin they possess.

B: Some cases stain a more blue-grey color on H&E, causing the invasive component to blend in with the background solar elastosis. This case only shows focal connection to the overlying epidermis with little *in situ* component.

C: A large irregular tongue of tumor pushes down into the dermis (bottom). Note the abundant dense eosinophilic glassy cytoplasm in this case, as well as the nuclear atypia. Contrast with the small keratinocytes in the adjacent uninvolved epidermis (top).

D: Islands of atypical keratinocytes with glassy eosinophilic cytoplasm invade the dermis. The dense swirl of parakeratotic keratin within the center of the nest is a "keratin pearl."



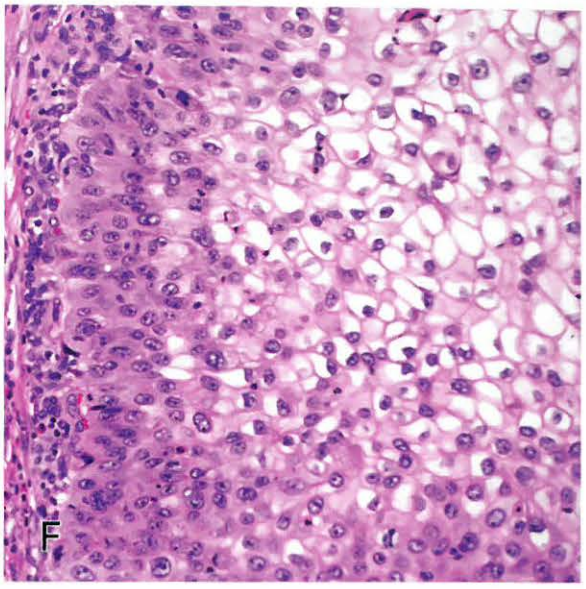


Figure 3-26, continued

E: Keratin pearls are dense keratin, usually with retained nuclei, and they are present within dermal islands of atypical keratinocytes. Do not confuse these with the horn pseudocysts of SK, which are made of loose keratin, usually without nuclei, and are present within the epidermis (see fig. 3-1).

F: Some cases of SCC may have true clear cell change.

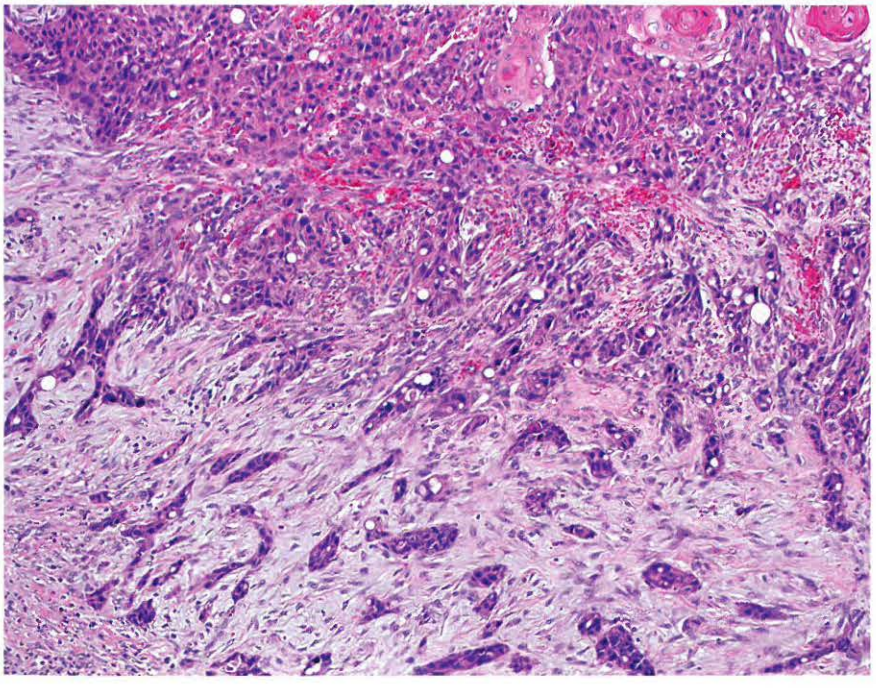


Figure 3-27

SQUAMOUS CELL CARCINOMA WITH INFILTRATIVE GROWTH

Cords and small islands of atypical basaloid cells infiltrate the dermis with a prominent background desmoplastic stromal response (bottom). These lesions would be difficult to distinguish from infiltrative BCC if not for the adjacent areas of obvious SCC with eosinophilic cytoplasm and keratin pearls (top). If there are doubts on a small biopsy, "infiltrating carcinoma" is used as the diagnosis line with a comment that it could be either BCC or SCC.

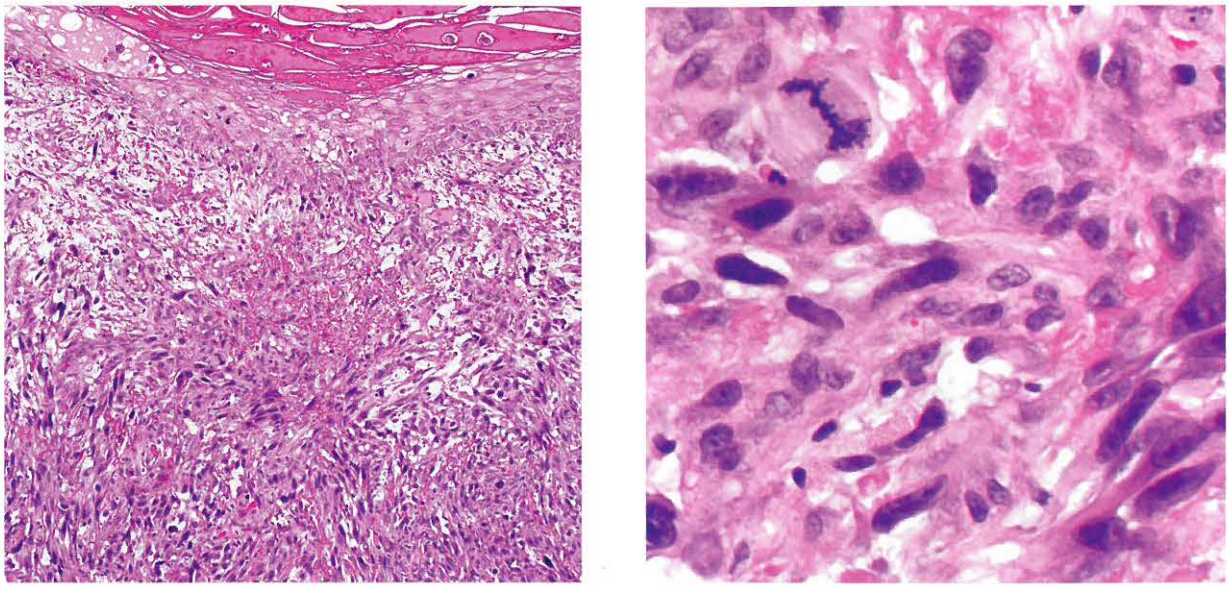


Figure 3-28

SPINDLE CELL SQUAMOUS CELL CARCINOMA (POORLY DIFFERENTIATED)

Left: The dermis is filled by a solid sheet of markedly atypical spindle cells. SCC *in situ* component is often lacking in the overlying epidermis.

Right: The spindle cells have hyperchromatic pleomorphic nuclei and atypical mitoses. Spindle cell melanoma, atypical fibroxanthoma, pleomorphic dermal sarcoma, and other pleomorphic sarcomas may show identical histologic features. If no adjacent areas of conventional SCC are seen, then immunostains are essential to confirm the diagnosis.

SCC with verrucous/papillomatous surface can have cytologically banal areas that closely mimic verruca or SK, especially superficially, with the more cytologically atypical areas with islands of invasive growth into the dermis only seen in the deep aspect of the lesion (fig. 3-30). Beware the broadly-transected superficial shave biopsy of a "verruca" on chronically sun-damaged skin! In that setting (which I see most often on the dorsal hand/forearm), I usually use "suggestive of superficially-sampled verruca vulgaris" with the "persist comment" discussed above. That said, verruca and SK actually can have some cytologic atypia, especially if inflamed, irritated, or growing in chronically sun-damaged skin, but as SCC can also closely mimic these benign lesions in its superficial aspect, caution must be used. If it looks most like verruca or SK but there is some atypia, especially if I cannot visualize the base of the lesion, then I will call it verruca or SK but add that there is some atypia that could be reactive and use the "persist comment."

If I am concerned about SCC because of obvious cytologic atypia or endophytic growth pattern, but the features fall short of what I can comfortably call SCC on the superficial biopsy, I tend to use more neutral terminology like "atypical endophytic (or verrucous) squamous proliferation" with a comment explicitly stating that I am concerned about SCC but cannot be sure on this biopsy. One could just make a diagnosis of SCC, but by being honest about my diagnostic uncertainty, I give the dermatologist the option to follow the patient closely, do curettage, do additional biopsy, or do complete excision, depending on the patient's clinical situation and the dermatologist's level of concern. When I am uncertain, I prefer this approach. Keep in mind that a large skin excision on the lower leg of an 85-year-old with severe vascular insufficiency is not a minor procedure. Even "simple" skin excisions can have serious morbidity and side effects in some settings, so aggressive treatment is not always the best option for the patient, especially if the diagnosis is not certain. Sometimes deeper sections or exhaust x5 can show more obvious areas of atypia that allow a definitive diagnosis to be made.

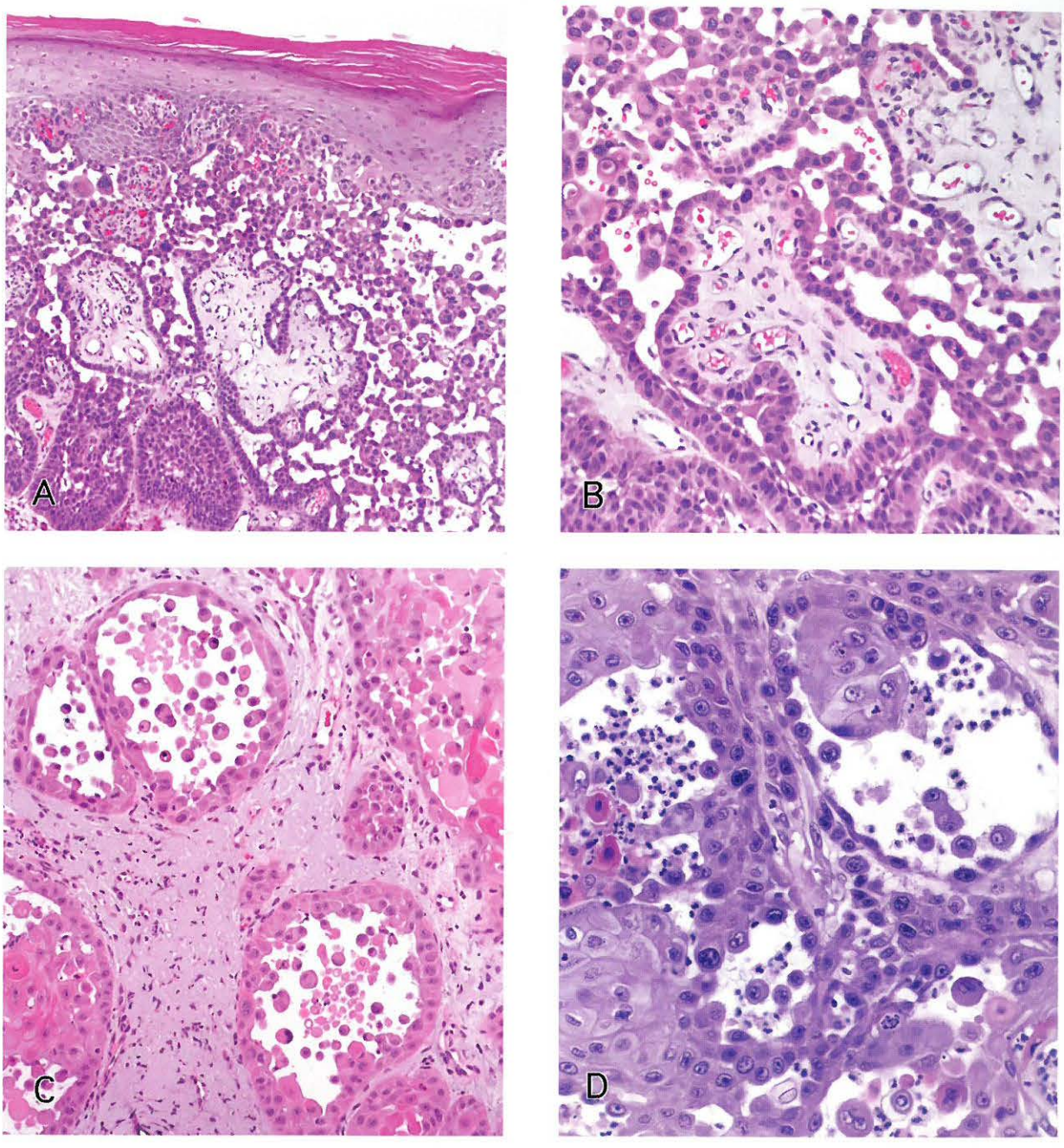


Figure 3-29

SQUAMOUS CELL CARCINOMA, ACANTHOLYTIC PATTERN

A: Prominent dyscohesion of tumor cells leads to detached individual keratinocytes floating freely in empty spaces within the tumor. Note the connection to the epidermis and the solid zones of intact nonacantholytic SCC (bottom left).

B: Areas resembling gland or vascular lumen formation mimic adenocarcinoma or angiosarcoma, respectively. Recognition of the acantholytic keratinocytes floating within the spaces (top left) is key to making the correct diagnosis. Solid zones of intact nonacantholytic SCC are present (bottom left).

C: The abundant glassy eosinophilic cytoplasm in this case makes the diagnosis easy. Free-floating rounded acantholytic keratinocytes are present in the pseudo-lumens of the nests. A solid zone of intact nonacantholytic SCC is also present (right).

D: As in other non-neoplastic acantholytic processes (see chapter 2), the detached acantholytic keratinocytes have dense cytoplasm and rounded cell borders.

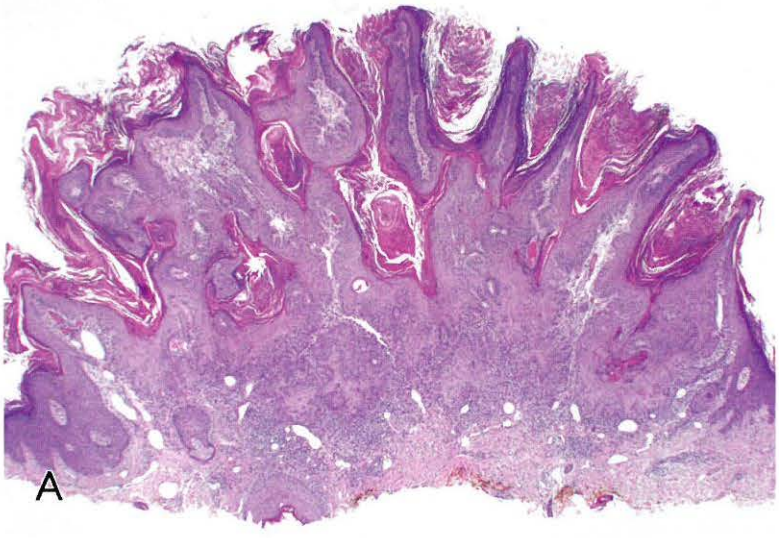
Figure 3-30

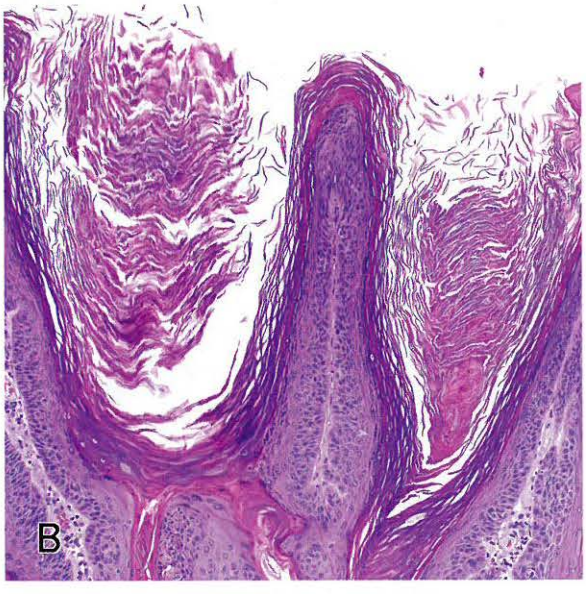
SQUAMOUS CELL CARCINOMA WITH VERRUCOUS/WARTY SURFACE

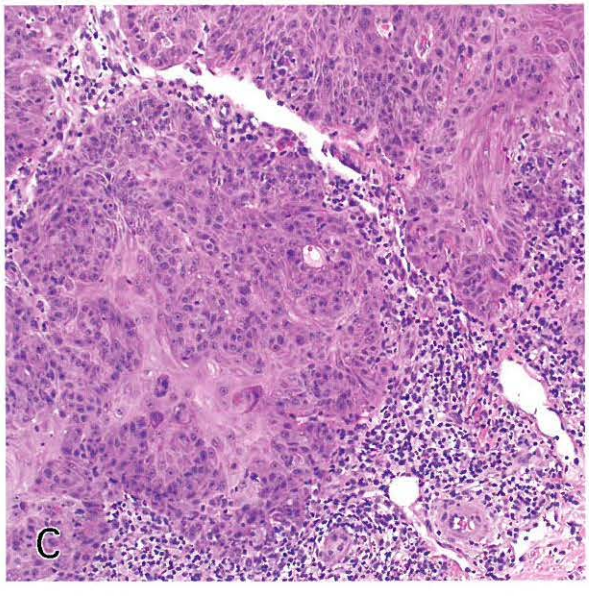
A: The superficial aspect of the lesion resembles a verruca, but the deep aspect shows invasive squamous cell carcinoma. A superficial shave biopsy from this lesion could easily be misdiagnosed as verruca.

B: A closer look at the superficial aspect. There is epidermal papillomatosis with parakeratosis over the tips of papillae and orthokeratosis elsewhere. There is minimal cytologic atypia. This area is essentially identical to a verruca (see fig. 3-33).

C: A closer look at the deep aspect. Multiple islands of atypical keratinocytes invade the dermis.







Keratoacanthoma is a rapidly growing, spontaneously regressing, dome-shaped papule or nodule with a central crater filled with a plug of keratin debris. This corresponds to the microscopic appearance, in which there is a cup-shaped or cystic proliferation of keratinocytes pushing down into the dermis (fig. 3-31). The cystic center of the lesion is filled with abundant keratin debris, which sometimes appears to erupt out of the opening to the skin surface like a keratin volcano. The proliferation is composed of keratinocytes with abundant glassy eosinophilic cytoplasm and mild nuclear atypia. If a lesion perfectly fits this description clinically and microscopically, I would feel comfortable definitively calling it a keratoacanthoma. The problem is that in real life, at least in my practice, this almost never happens. The shave biopsy is usually broadly transected, which prevents evaluation of the base of the lesion. I have seen lesions that resembled keratoacanthoma superficially but in their deep aspect had markedly atypical infiltrative areas of obvious SCC. Additionally, the classic clinical history is often lacking or unreliable. I believe that keratoacanthoma is a real entity, I am just unsure of how to practically and reliably make the diagnosis, to know which lesions truly behave in a benign fashion and regress/

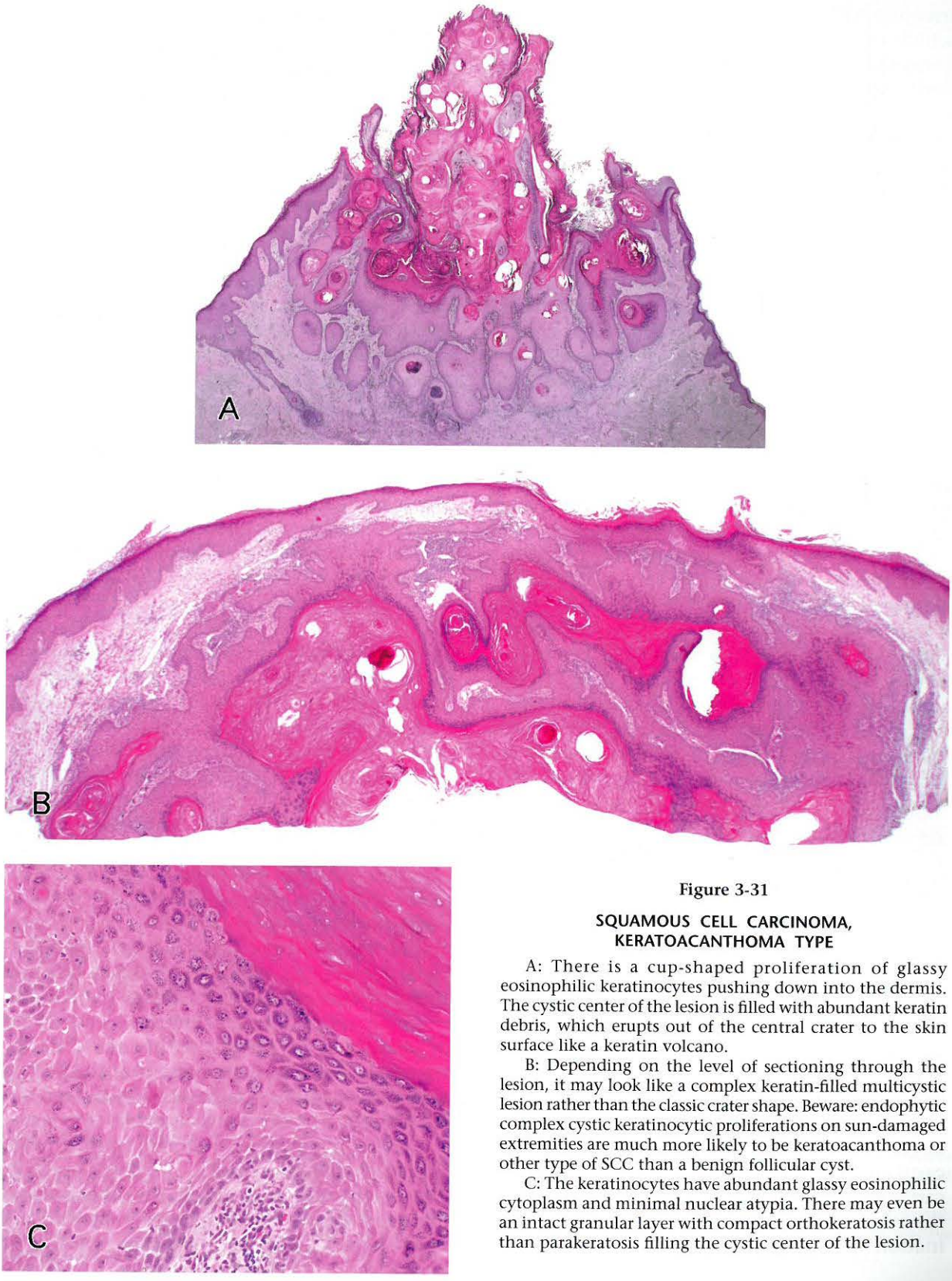


Figure 3-31

SQUAMOUS CELL CARCINOMA, KERATOACANTHOMA TYPE

A: There is a cup-shaped proliferation of glassy eosinophilic keratinocytes pushing down into the dermis. The cystic center of the lesion is filled with abundant keratin debris, which erupts out of the central crater to the skin surface like a keratin volcano.

B: Depending on the level of sectioning through the lesion, it may look like a complex keratin-filled multicystic lesion rather than the classic crater shape. Beware: endophytic complex cystic keratinocytic proliferations on sun-damaged extremities are much more likely to be keratoacanthoma or other type of SCC than a benign follicular cyst.

C: The keratinocytes have abundant glassy eosinophilic cytoplasm and minimal nuclear atypia. There may even be an intact granular layer with compact orthokeratosis rather than parakeratosis filling the cystic center of the lesion.

involute without need for further excision and which ones behave like SCC. In light of this, I was trained to call all of these lesions "SCC, keratoacanthoma type," and this is the terminology I still typically use. I have heard legitimate arguments against doing this (e.g., molecular differences, potential health insurance issues in the USA because of a cancer history, potential for surgical overtreatment in a lesion that could involute on its own). My views on this topic are still evolving. In my community, dermatologists almost always treat keratoacanthomas as SCC regardless of what terminology is used. You may need to adapt your terminology based on the way your local dermatologists handle these cases. The World Health Organization (WHO) Classification of Skin Tumours, 4th edition (2018) classifies keratoacanthoma as a subtype of SCC (2).

Endophytic complex cystic keratinocytic proliferations on sun-damaged extremities are much more likely to be SCC or keratoacanthoma than a benign follicular cyst. I am always cautious of making a diagnosis of follicular infundibular cyst on markedly sun-damaged skin on the extremities, especially if there is a broad opening to the epidermis. I either call these "suggestive of regressing keratoacanthoma-type SCC," or "atypical endophytic squamous proliferation" (as discussed above). Regressing keratoacanthomas are usually cystic, with an atrophic lining of keratinocytes with less abundant cytoplasm and minimal nuclear atypia. They usually have a zone of fibrosis and mixed inflammation under them that has resulted from the regression/involution.

CHONDRODERMATITIS NODULARIS HELICIS

Chondrodermatitis nodularis helicis (CNH) is a benign reactive condition that is mentioned here because it is a clinical mimic of SCC. It is a painful often ulcerated papule on the ear of elderly patients, usually on the helix or antihelix. It is caused by pressure-induced ischemia due to chronic compression of the ear against the pillow during sleep. This pushes the blood out of the affected area, causing ischemia and degeneration of the dermis and underlying cartilage. The body tries to eliminate this dying cartilage and dermis by extruding it out through the overlying epidermis ("transepidermal elimination" phenomenon).

The microscopic findings correspond to this process (fig. 3-32). The dermis shows a zone of eosinophilic ischemic changes often with frank fibrinoid necrosis. To the periphery of this zone of ischemia is a reactive proliferation of small vessels, the body's attempt to respond to the chronic ischemia with neovascularization. These small vessels have a distinct appearance and are almost always present in CNH; this feature alone in a biopsy from the ear is essentially diagnostic of CNH in my opinion. The epidermis is classically ulcerated overlying the zone of ischemia, with adjacent pseudoepitheliomatous hyperplasia; some cases only show epidermal acanthosis with no ulceration. When a biopsy is deep enough to show the elastic cartilage, it will display degenerative changes, including eosinophilia and disorganization of chondrocytes (in general, it just does not quite look like normal cartilage). It is important to note that cartilage need not be present in the biopsy to confidently make a diagnosis of CNH. The dermal and epidermal changes in the proper clinical context are diagnostic of CNH even if the cartilage is not sampled in the biopsy.

VERRUCA

Verruca vulgaris, the common wart, is a squamous proliferation caused by human papillomavirus (HPV). The features vary depending on the type of HPV and the anatomic site, but most verrucae have some combination of the following findings. The epidermis is acanthotic with papillomatosis (finger-like upward projections on the surface) and elongated rete (fig. 3-33). The rete at the periphery of the verruca often curve inward and point toward the center of the lesion ("in-toeing" of rete). There is hypergranulosis with large irregular keratohyaline granules and alternating ortho- and parakeratosis. Parakeratosis is often arranged into tall stacks situated on top of the tips of the papillae ("church spires" of parakeratosis), and serum or blood may be present within these stacks. Dilated blood vessels are present in the dermis within the papillae. Koilocytes may be seen but are not required to make a diagnosis of verruca.

Acral skin is a common site for warts to arise. *Palmar/plantar verrucae* are often endophytic. They have papillomatosis and the other features discussed above, but they usually sit within a bowl-shaped invagination so that the tips of

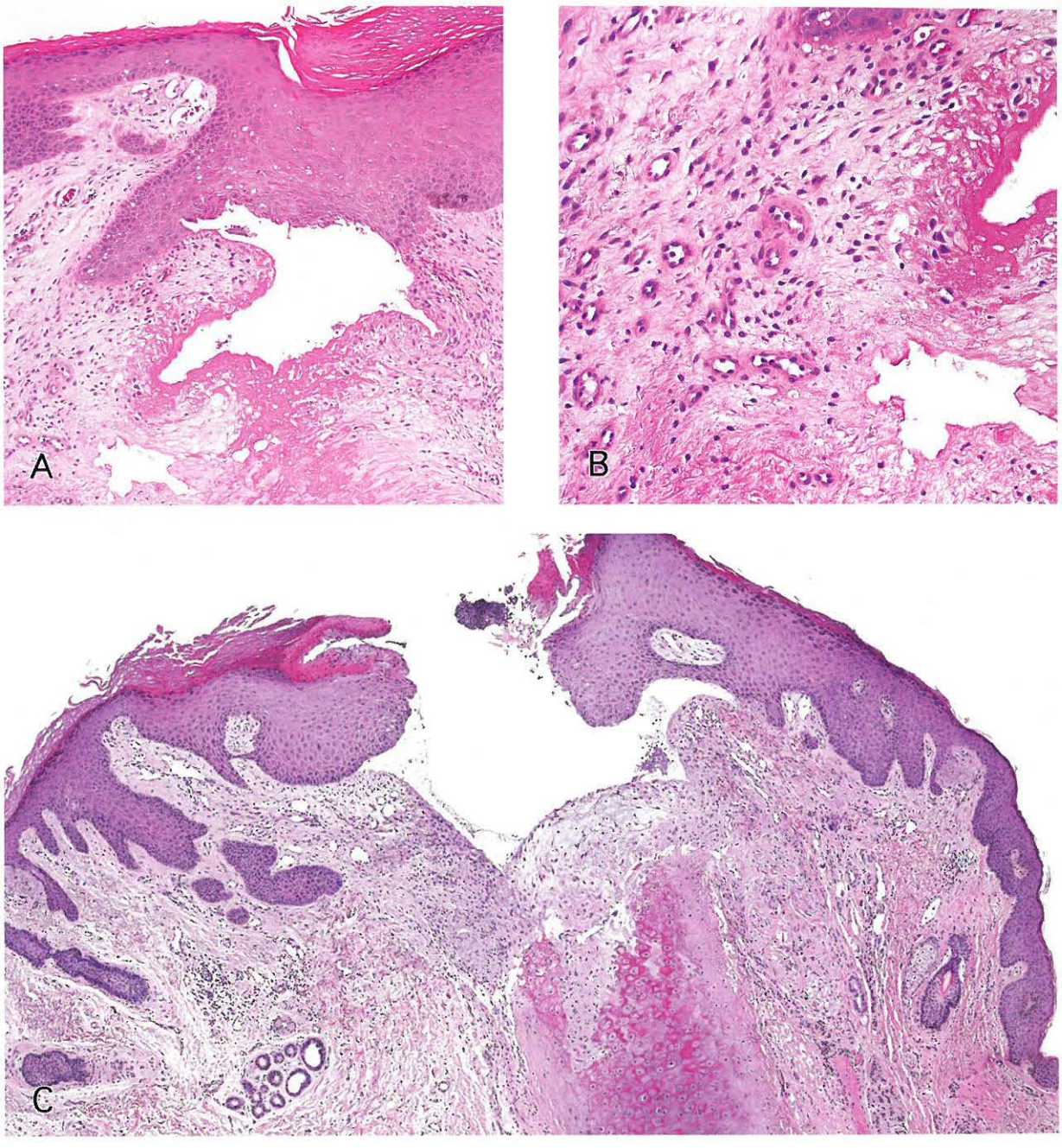


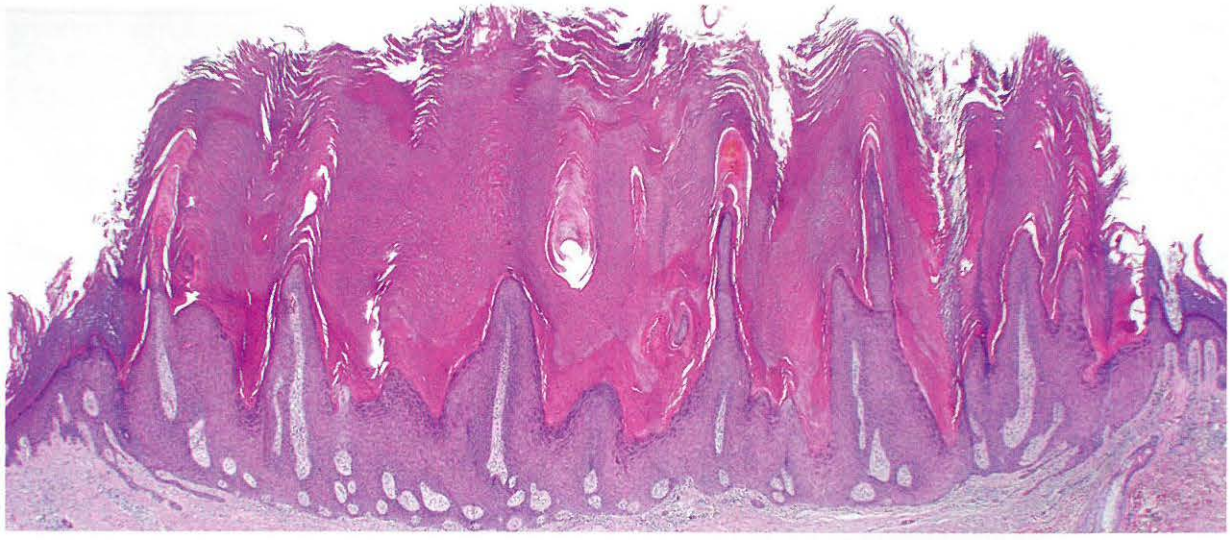
Figure 3-32

CHONDRODERMATITIS NODULARIS HELICIS (CNH)

A: The dermis shows a zone of eosinophilic ischemic changes with frank fibrinoid necrosis (bottom center). Fibrosis and a reactive proliferation of small vessels are present on both sides of the ischemic zone. The epidermis shows invagination and acanthosis overlying the ischemic zone.

B: Fibrinoid necrosis (right) is due to ischemia. The proliferation of small vessels (left) is the body's attempt to respond to that ischemia with neovascularization. These vessels are more numerous than normal dermal vessels. They have a distinct appearance and are almost always present in CNH.

C: If the biopsy is large/deep enough, degenerated cartilage may be seen beneath the dermal ischemic changes. However, the presence of cartilage is not required to make the diagnosis of CNH. This case also shows frank ulceration with reactive epidermal acanthosis on both sides of the ulcer.



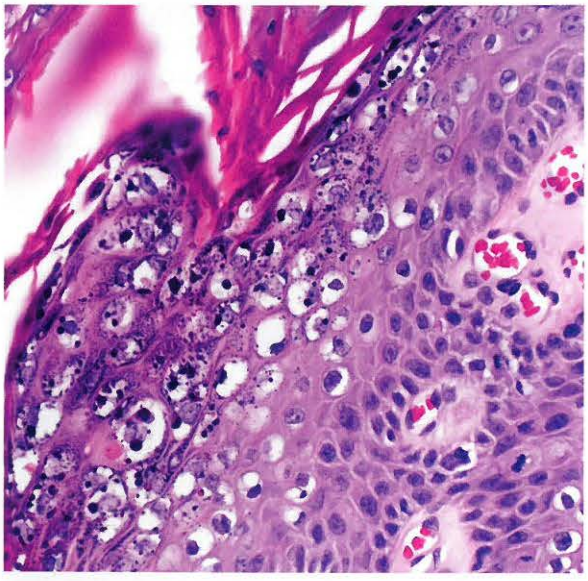


Figure 3-33

VERRUCA VULGARIS (VV)

Above: The epidermis is acanthotic with marked hyperkeratosis. There are multiple finger-like upward projections on the surface (papillomatosis). The elongated rete at the periphery of the verruca curve inward and point toward the center of the lesion ("in-toeing").

Right: A closer view of one of the papillae shows hypergranulosis with coalescing of smaller keratohyaline granules into large "chunky" dark purple ones. Dilated blood vessels are often present within the dermal cores of the papillae. This case has koilocytes (keratinocytes with enlarged nuclei and vacuolated cytoplasm due to HPV viral cytopathic effect), but many VV do not.

their papillary surface barely reach above the level of the adjacent epidermis.

Myrmecia-type verruca is a unique microscopic variant of palmar or plantar wart that has large irregular eosinophilic globules in addition to the chunky purple keratinohyaline granules found in other forms of verruca (fig. 3-34). These numerous globules give the wart a busy appearance that has been likened to ants swarming on the surface of an anthill, thus the name "myrmecia," which derives from the Greek word for ant. Beginners often confuse the myrmecia wart with molluscum contagiosum (see chapter 7), as both possess eosinophilic globules, but the distinction is easy. Myrmecia wart is almost always on acral skin, has papillomatosis and other microscopic features of verruca, and has irregular eosinophilic globules of varying size. Molluscum is rarely on acral skin, is an endophytic cup-shaped or cystic lesion without papillomatosis or other features of verruca, and has large regular eosinophilic globules that are all nearly the same size.

Verruca plana (flat wart) is different from verruca vulgaris clinically and microscopically. It presents as a small flat papule or plaque and may be multiple. Microscopically, it shows a zone of acanthosis with hypergranulosis. There is subtle undulating surface change rather than

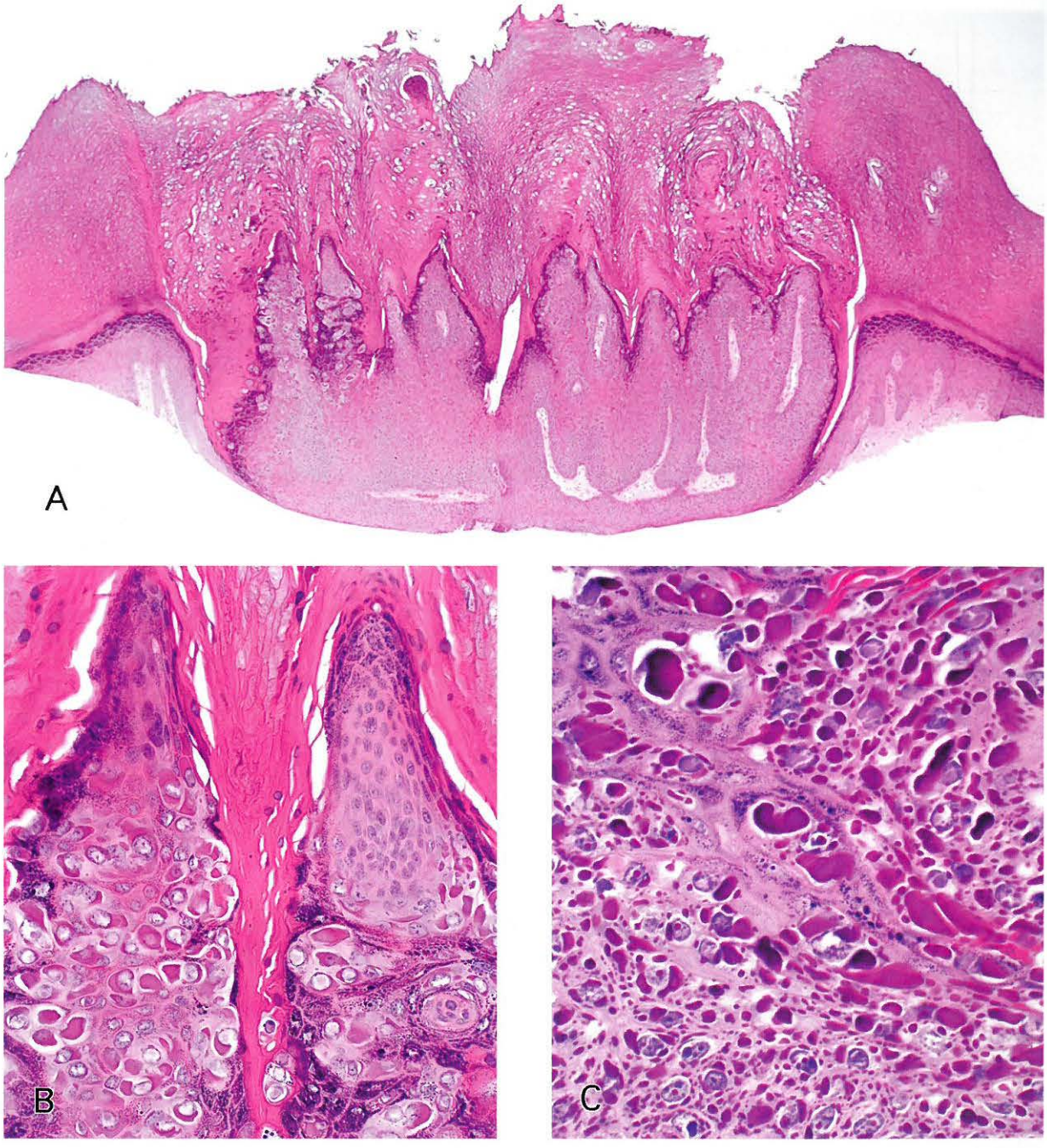


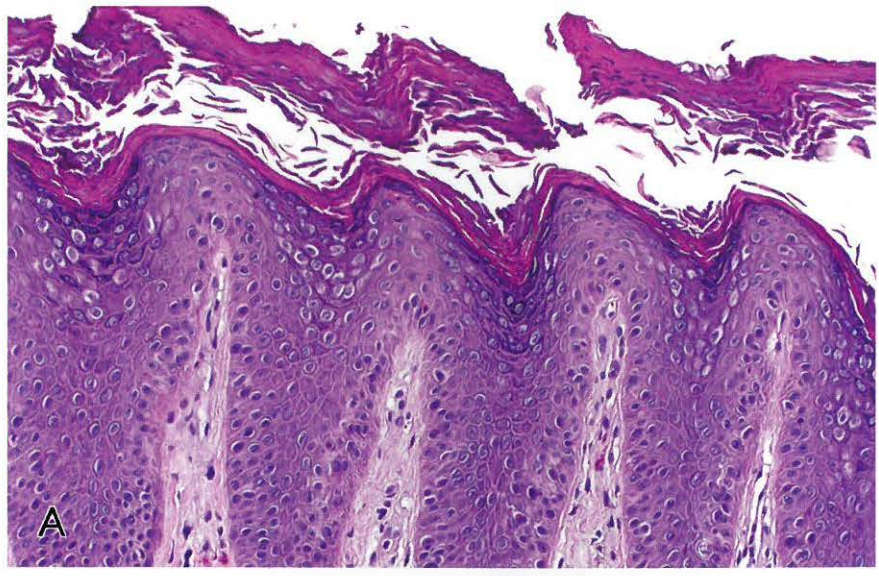
Figure 3-34

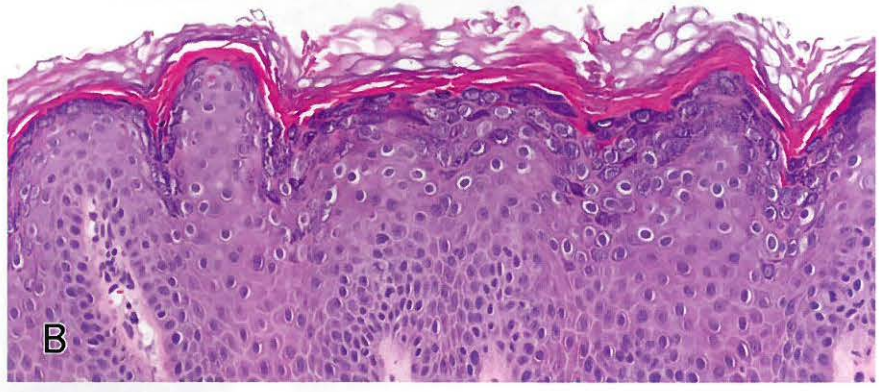
VERRUCA, MYRMECIA TYPE

A: Myrmecia warts, like other palmar/plantar verrucae, are often endophytic. There are multiple finger-like papillae on the surface, but they are sitting within a bowl-shaped invagination so that the tips just barely reach above the level of the adjacent epidermis.

B: Myrmecia-type verruca has large irregular eosinophilic globules. It also has other typical verruca features, such as papillomatosis, hypergranulosis, and alternating ortho- and parakeratosis.

C: The eosinophilic globules of myrmecia wart are of variable size and shape. Do not confuse them with the large uniform eosinophilic globules of molluscum contagiosum. Chunky purple keratohyaline granules are also present (center), similar to those seen in other types of verruca.





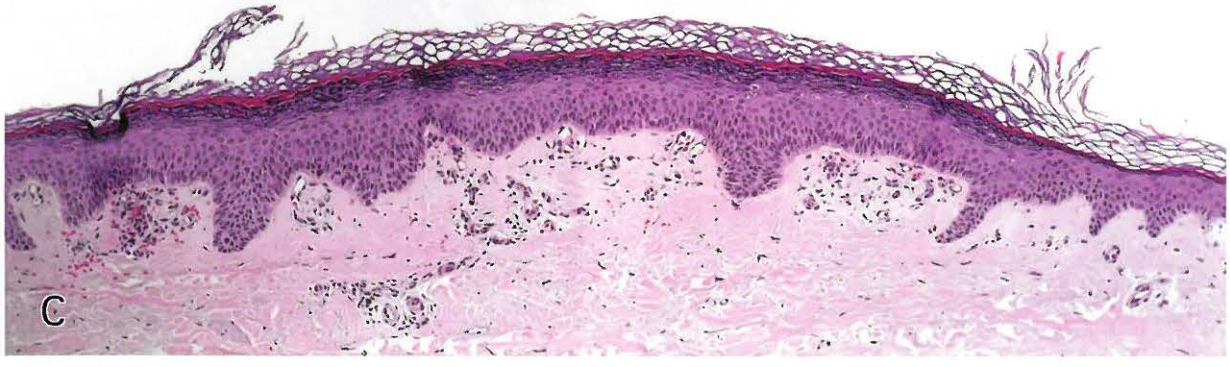


Figure 3-35

VERRUCA PLANA

A: There is subtle undulating surface change rather than the prominent finger-like papillomatosis of verruca vulgaris. There is alternating ortho- and parakeratosis.

B: Vacuolation artifact is present around superficial spinous layer keratinocytes.

C: Some lesions are very subtle. This case has mild acanthosis but little surface undulation. There is prominent hypergranulosis. At high-power, vacuolation was seen around superficial spinous layer keratinocytes.

the prominent finger-like papillomatosis of verruca vulgaris. Vacuolation artifact is often present around superficial spinous layer keratinocytes, giving a halo or "bird's eye" appearance (fig. 3-35). *Epidermodysplasia verruciformis* is a variant of verruca plana that has unique abundant blue-grey cytoplasm (see chapter 2).

CONDYLOMA ACUMINATUM

Condyloma acuminatum (anogenital wart) is caused by low-risk HPV, most often types 6 and 11. The warts range clinically from small smooth papules resembling seborrheic keratosis to large fungating or cauliflower-shaped pedunculated lesions.

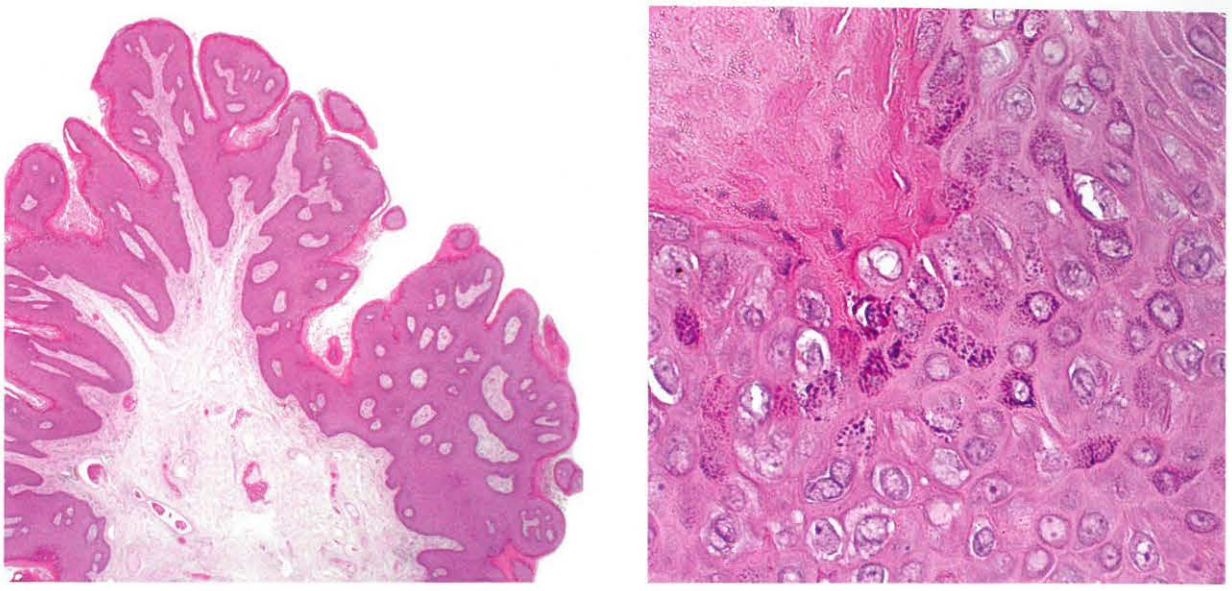


Figure 3-36

CONDYLOMA ACUMINATUM

Left: Condylomas have many features of verruca vulgaris, although they tend to have subtler rounded papillomatosis, resembling "knuckles," rather than the elongated finger-like papillomatosis of verruca vulgaris. Some, like this one, are pedunculated/polypoid while others are flat/sessile.

Right: Ideally, I like to find koilocytes to make a definitive diagnosis of condyloma. Koilocytes have clear/pale cytoplasm and enlarged nuclei. The wrinkled "raisinoid" appearance seen in cervical cytology specimens is often lacking in cutaneous koilocytes. Hypergranulosis and focal parakeratosis intermingle with dense orthokeratosis (top left).

Microscopically, condylomas show many features of verruca vulgaris, although they tend to have subtler rounded papillomatosis, resembling "knuckles," rather than the elongated finger-like papillomatosis of verruca vulgaris (fig. 3-36). Hypergranulosis, alternating parakeratosis and orthokeratosis, and dilated dermal blood vessels are useful clues. Koilocytes are often present.

Since HPV is usually a sexually transmitted infection, there may be serious social consequences of making this diagnosis, as well as other medical screening considerations. For this reason, when an anogenital lesion has some features of condyloma but lacks koilocytes, I utilize the diagnostic code word "verrucous keratosis" with a comment that "this could represent an HPV-induced lesion, but no definitive koilocytes are identified" and that the differential includes verruca vulgaris and seborrheic keratosis. Admittedly, this is not a satisfying way to handle these cases, but it allows the dermatologist to consider the possibility of condyloma and take other clinical features and the social and medical history into account.

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

High-grade squamous intraepithelial lesion (HSIL) is the current preferred terminology for full-thickness squamous dysplasia of the anogenital region, which is caused by high-risk HPV infection (8). This term encompasses lesions that would be called SCC *in situ* at other anatomic sites. I often add a comment in my report explaining this briefly, as some dermatologists are not yet familiar with this terminology.

HSIL usually has a distinct appearance that differs from most SCC *in situ* at other sites. The atypical keratinocytes filling the epidermis are usually hyperchromatic and basaloid rather than eosinophilic and glassy (fig. 3-37). Koilocytes, coalescing granules of hyperkeratosis, and other cytologic features suggestive of HPV may be present. When a biopsy shows SCC *in situ* but it is unclear whether the anatomic site is truly in or near the anogenital region (e.g., "inner thigh," "lower abdomen"), I often use SCC *in situ* as the line diagnosis with a comment that if this is in

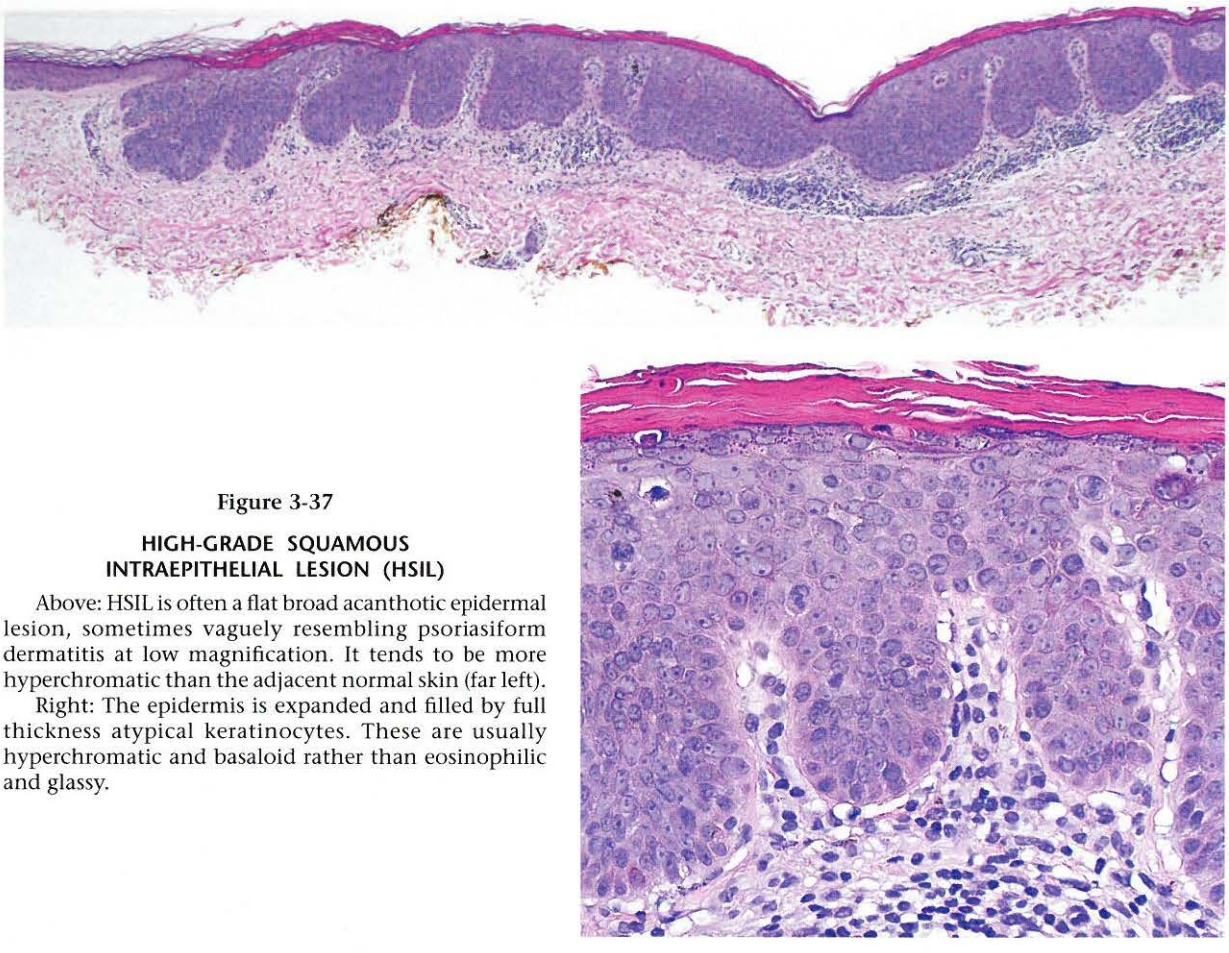


Figure 3-37

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL)

Above: HSIL is often a flat broad acanthotic epidermal lesion, sometimes vaguely resembling psoriasiform dermatitis at low magnification. It tends to be more hyperchromatic than the adjacent normal skin (far left).

Right: The epidermis is expanded and filled by full thickness atypical keratinocytes. These are usually hyperchromatic and basaloid rather than eosinophilic and glassy.

or near the anogenital region, HSIL may be more appropriate terminology. Areas of HSIL may be present within an otherwise typical condyloma, so be sure not to miss these.

VERRUCIFORM XANTHOMA

Verruciform xanthoma is a benign lesion that can mimic condyloma clinically and microscopically, but is not associated with HPV. It usually arises in the anogenital region or the oral cavity.

Verruciform xanthoma is a pedunculated papillomatous lesion with abundant overlying hyperkeratosis that is dense and dramatically eosinophilic. At low power, the abrupt pattern of keratinization is unique and is a clue to the diagnosis (fig. 3-38). At higher power, foamy histiocytes are present in the dermis within the papillae, confirming the diagnosis. Unlike some other forms of true xanthoma, verruciform xanthoma is not associated with serum lipid abnormalities.

VERRUCOUS CARCINOMA

Verrucous carcinoma is a locally aggressive carcinoma that lacks metastatic potential. It most commonly arises on the foot, in the oral cavity, or in the anogenital region. It has a verrucous appearance both clinically and microscopically, and because it lacks cytologic atypia, it can be challenging to diagnose. The surface can look nearly identical to a verruca, and diagnosis may be impossible on a small superficial biopsy. The key is finding large expansile rete that push down into the underlying dermis; an incisional/excisional biopsy is often required to identified this characteristic "pushing invasion" (fig. 3-39). If significant cytologic atypia or small infiltrative cords/islands/nests of tumor are seen, the lesion is probably SCC with warty features rather than verrucous carcinoma.

In older literature, verrucous carcinoma was sometimes used as a synonym for large "giant"

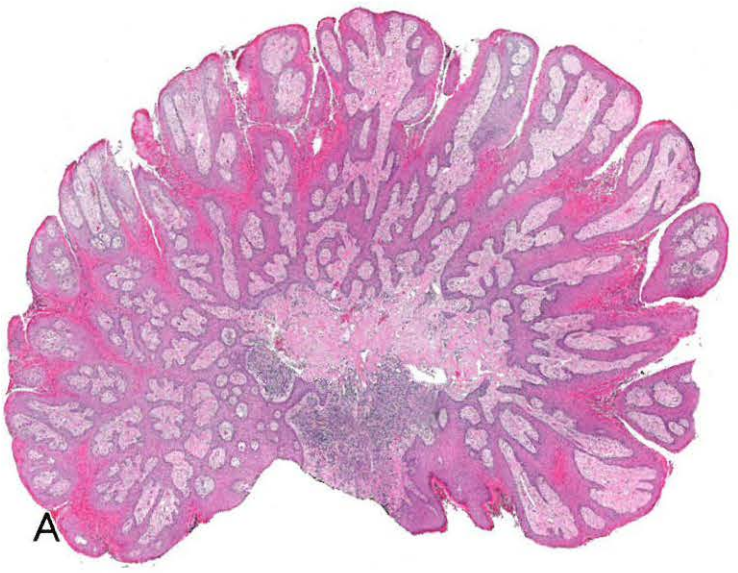


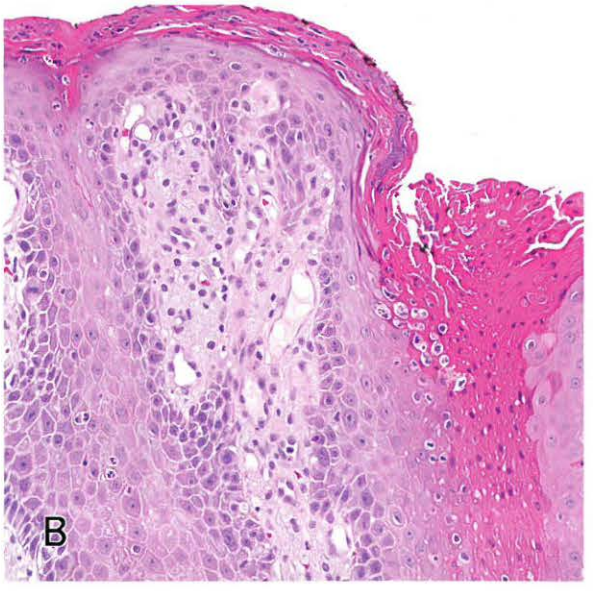
Figure 3-38

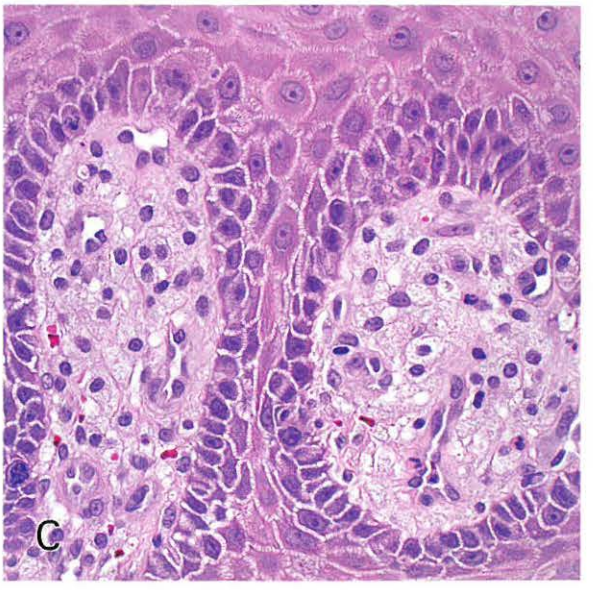
VERRUCIFORM XANTHOMA

A: The pedunculated papillomatous appearance can easily be confused with condyloma. The clue at low-power magnification is the abundant and brightly eosinophilic keratin on the surface of the lesion, giving the appearance of a wart/condyloma "set on fire."

B: The dermal cores of the papillae are packed with foamy histiocytes. On the epidermal surface (top) and within the crevices between papillae (right), there is an abrupt transition from keratinocytes into dense bright pink hyperkeratosis. This abrupt pattern of keratinization is characteristic.

C: A high magnification view shows foamy histiocytes filling the papillary dermis. They are not always as spectacular and abundant as in this case.





condylomas of the anogenital region. In modern times, these are usually regarded as separate entities, as strictly defined verrucous carcinoma is probably not caused by HPV (8).

Figure 3-39

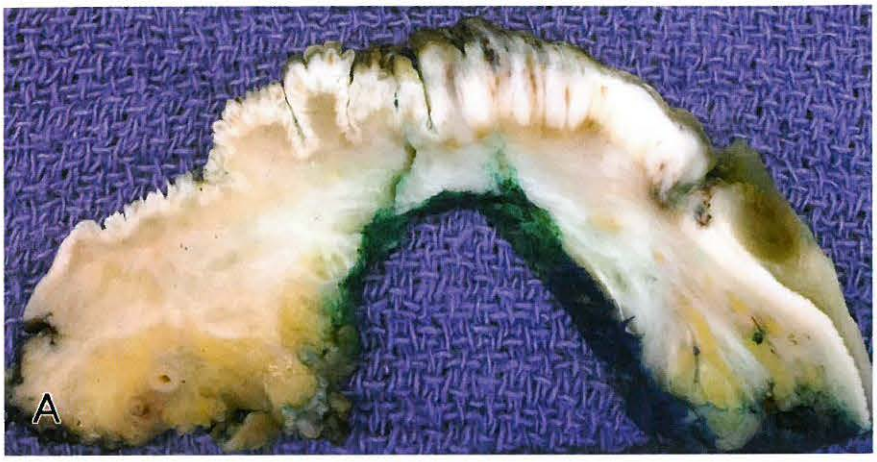
VERRUCOUS CARCINOMA

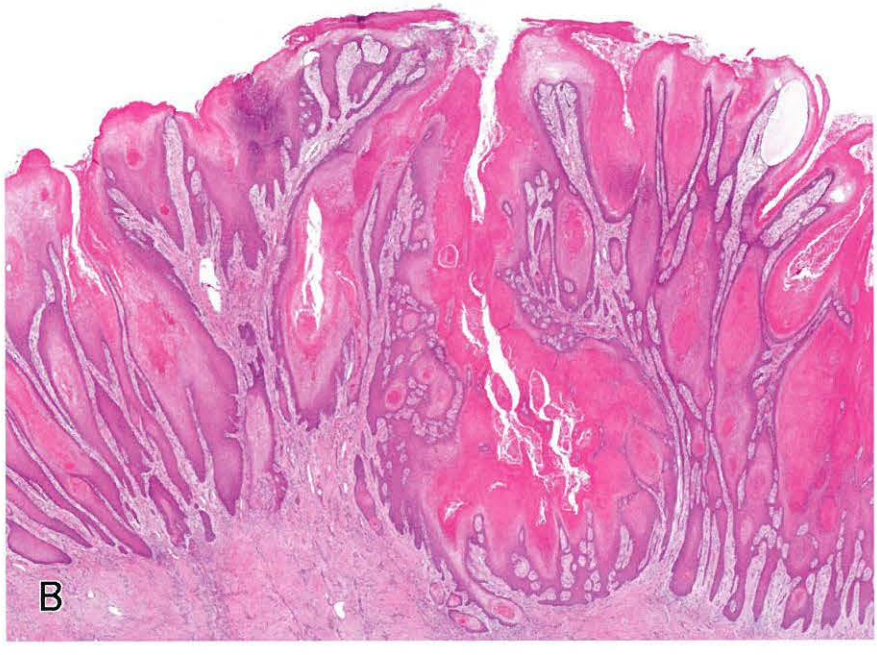
A: On this resection specimen from the foot, the epidermis is verrucous/papillomatous with massive expansion of rete pushing deeply into the dermis (center). Contrast with adjacent relatively normal skin (far left and far right).

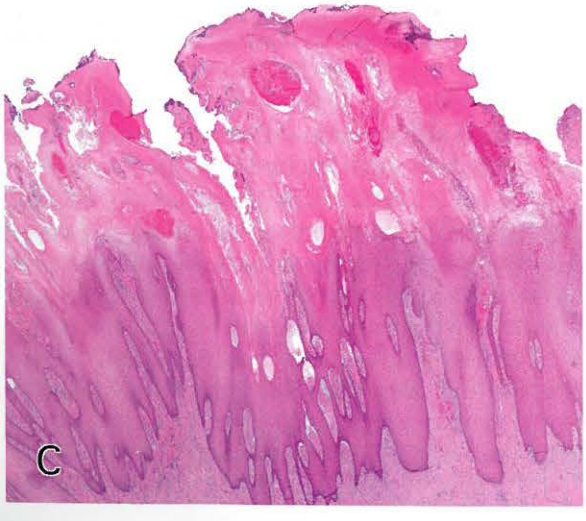
B: The microscopic low magnification appearance correlates with the gross cross section. The rete are massively expanded, pushing far down into the dermis. Some are narrow and greatly elongated (left) whereas others are bulbous and distended (center)

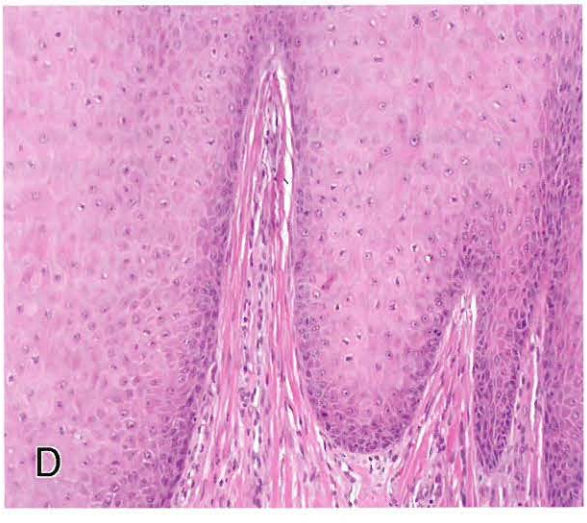
C: A superficial biopsy could easily be mistaken for a verruca, severe lichen simplex chronicus/prurigo nodularis, or verruciform xanthoma. The abundant dense hyperkeratosis in the clefts between papillae is a common finding. Clinical information plus a deep enough biopsy is needed to recognize the size and depth of the lesion and pushing "invasion" by expanded rete.

D: The tumor cells are bland keratinocytes with abundant glassy eosinophilic cytoplasm. Nuclear atypia is minimal to absent. If there is significant nuclear atypia, it is probably a true squamous cell carcinoma rather than a verrucous carcinoma.









REFERENCES

1. Fulton EH, Kaley JR, Gardner JM. Skin adnexal tumors in plain language: a practical approach for the general surgical pathologist. Arch Pathol Lab Med 2019. [Epub ahead of print]
2. Elder DE, Massi D, Scolyer RA, Willemze R. WHO classification of skin tumours, 4th ed. Lyon: IARC Press; 2018.
3. Bowen AR, LeBoit PE. Fibroepithelioma of Pinkus is a fenestrated trichoblastoma. Am J Dermatopathol 2005;27:149-54.
4. Czapiewski P, Majewska H, Kutzner H, Kazakov D, Renkielska A, Biernat W. TTF-1 and PAX5 are frequently expressed in combined Merkel cell carcinoma. Am J Dermatopathol 2016;38:513-6.
5. Agoff SN, Lamps LW, Philip AT, et al. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. Mod Pathol 2000;13:238-42.
6. Houcine Y, Chelly I, Zehani A, et al. Neuroendocrine differentiation in basal cell carcinoma. J Immunoassay Immunochem 2017;38:487-93.
7. Dai B, Kong YY, Chang K, et al. Primary invasive carcinoma associated with penoscrotal extramammary Paget's disease: a clinicopathological analysis of 56 cases. BJU Int 2015;115:153-60.
8. Chan MP. Verruciform and condyloma-like squamous proliferations in the anogenital region. Arch Pathol Lab Med 2018. [Epub ahead of print]

4 MELANOCYTIC LESIONS

One of the most common and important reasons to perform a skin biopsy is evaluation of a clinically suspicious pigmented lesion. Although many entities present as pigmented skin lesions (solar lentigo, seborrheic keratosis, postinflammatory pigmentary alteration), melanocytic lesions are among the most common. Evaluating melanocytic lesions and distinguishing benign melanocytic nevus from malignant melanoma is a crucial skill in dermatopathology. If epithelial lesions are the bread of our practice, then melanocytic lesions are the butter; the bulk of my cases every day fall into these two categories.

Missing a diagnosis of melanoma is one of the most serious mistakes in dermatopathology, both for the patient and the pathologist. Misdiagnosis of melanoma is a common cause for medical malpractice lawsuits in the field of pathology. The fear of missing a melanoma is prominent in the mind of every pathologist who looks at skin specimens (and rightly so!), but appropriate fear should not lead to excess anxiety or to overinterpretation of benign nevi as melanoma.

This chapter provides the basics of how I personally approach melanocytic lesions in my practice, along with practical recommendations for how to handle difficult cases. I still share challenging cases with my dermatopathology colleagues on a daily basis to obtain their input and opinions; many of these are difficult melanocytic lesions. If you have doubt about the possibility of melanoma, sending the case for expert consultation is usually a good idea.

Some areas of melanocytic pathology are controversial, with strong differences of opinion among experts and decades of heated debate about particular topics (dysplastic nevi and atypical spitzoid melanocytic lesions are prime examples). My approach may differ from what other dermatopathologists have taught you, and that is okay. Some of my views and opinions have changed since I entered practice, and I suspect (and hope) that my understanding will evolve over the coming years. This chapter, like the rest of this book, is an educational guide not a consensus statement or definitive rule book. Use it to help recognize these lesions and understand where the challenges and pitfalls are, but please do not treat this like dogma.

Before diving into the many subtypes of nevi and melanoma, it is important to establish some basics. You must learn to recognize melanocytes in normal skin and tell them apart from keratinocytes. You must learn the basic benign patterns and features commonly seen in nevi (Table 4-1, fig. 4-1). You must learn the atypical or worrisome features that are often signs of melanoma (Table 4-2, fig. 4-2). Finally, you must learn the pitfalls, the ugly things that are benign and the seemingly innocent things that are malignant (Tables 4-3, 4-4).

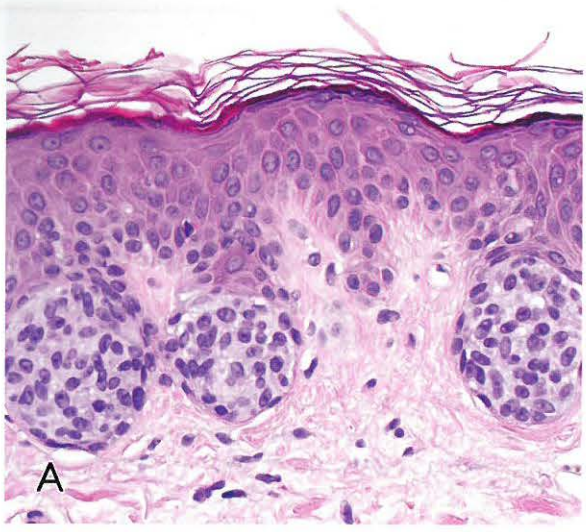
Melanocytic nevi are benign proliferations of melanocytes (also termed nevomelanocytes or nevus cells; I use all three of these words interchangeably when discussing melanocytes in nevi). These are either in the epidermis (*junctional nevus*), dermis (*intradermal nevus*), or both (*compound nevus*). The junctional (intraepidermal) melanocytes in nevi are usually arranged into

Table 4-1

FEATURES OF NEVUS

Symmetry (E[a] and D)
Maturation (D)
Basally oriented melanocytes (lack of upward pagetoid spread) (E)
Well-spaced junctional melanocytes (lack of confluent growth) (E)
Bland cytology (lack of cytologic atypia) (E and D)
Low or no mitotic activity (D)

[a]E = epidermal feature; D = dermal feature; E and D = both.



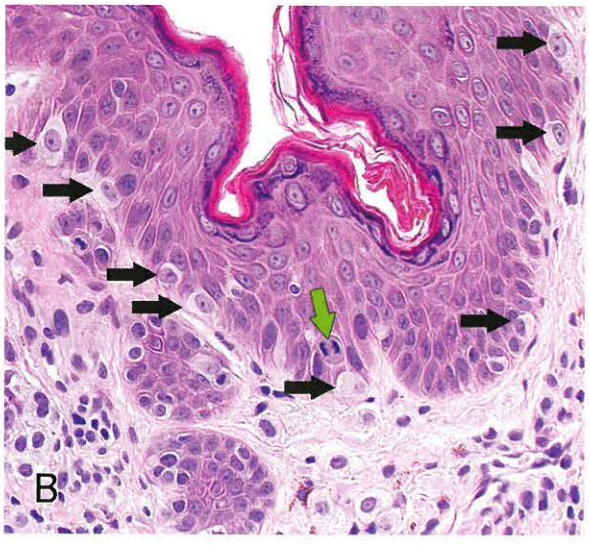


Figure 4-1

NEVUS BASICS

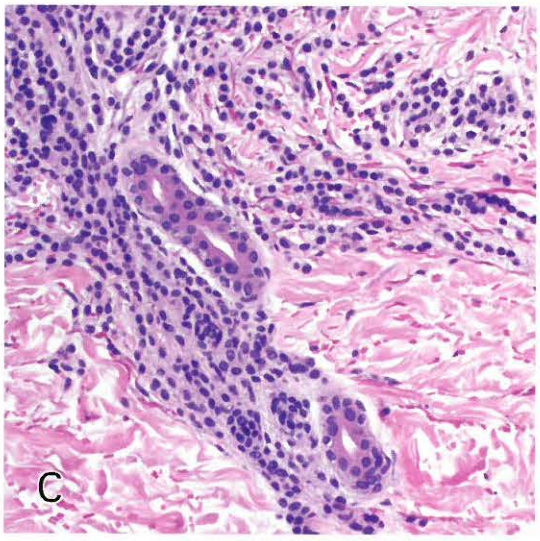
A: Nests of epithelioid melanocytes in a junctional nevus. Junctional nests are often located at the bottom tips of rete ridges.

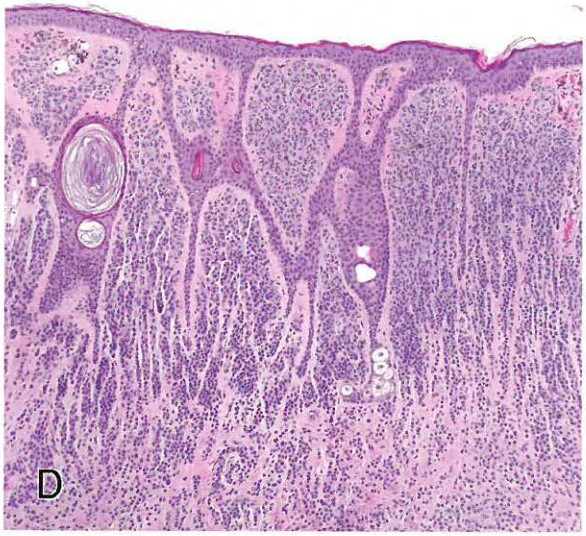
B: Single melanocytes (black arrows) may be present along the basal layer; they are spaced out and intervened by basal keratinocytes (i.e., no confluent growth). They may be large and epithelioid, particularly in congenital pattern nevi in young patients (shown here). The mitosis (green arrow) belongs to a basal keratinocyte not a melanocyte.

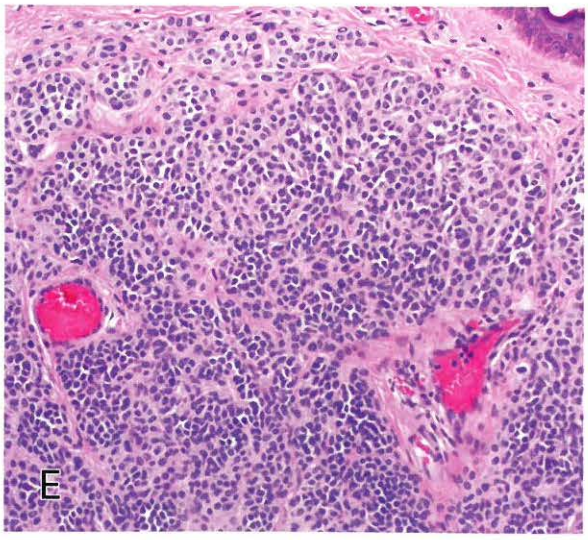
C: Dermal melanocytes trickle between reticular dermal collagen bundles as smaller clusters, cords, and single cells dispersing from one another as they descend deeper and deeper into the dermis.

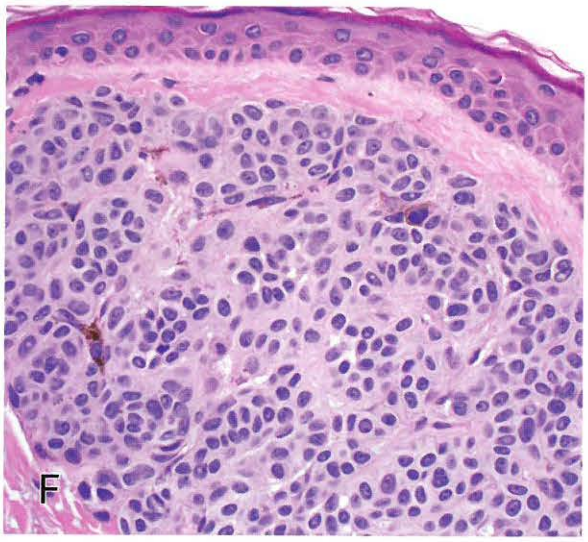
D: Normal maturation. With increasing dermal depth, melanocytes become smaller. They also transition from larger nests (superficial dermis) to smaller nests and single cells intervened by collagen (deep dermis).

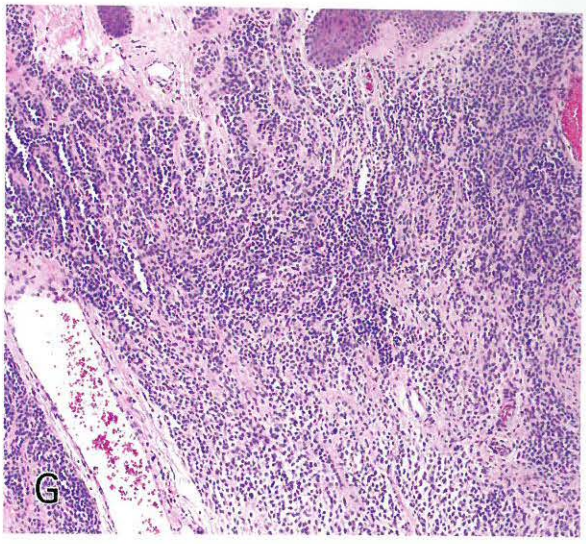
E: Larger epithelioid type A melanocytes (top) transition into small round blue type B melanocytes (bottom) as they move deeper into the dermis.











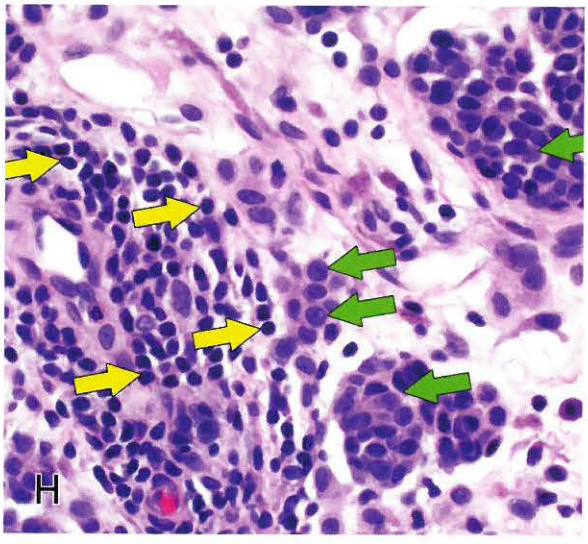


Figure 4-1, continued

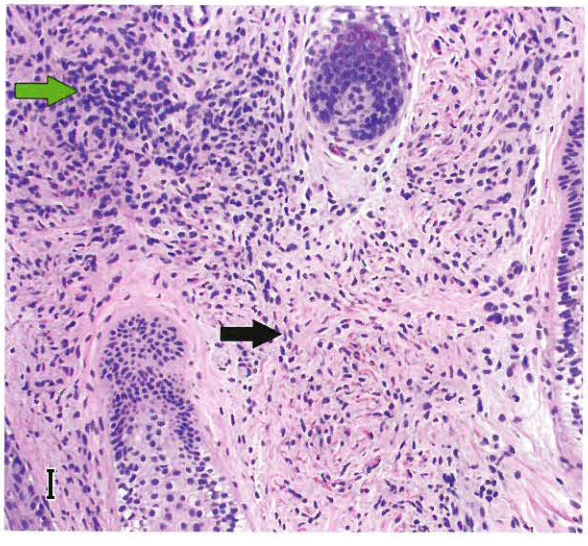
F: Type A melanocytes have oval to round nuclei and abundant pale pink or gray cytoplasm. Type A melanocytes often comprise nests in the junction and superficial dermis of nevi.

G: Type B melanocytes. At low power, these small round blue melanocytes resemble lymphocytes. When they are abundant, they can mimic an inflamed nevus.

H: Type B melanocytes (green arrows) are easily distinguished from lymphocytes (yellow arrows) at high power. Lymphocytes are smaller and have much darker chromatin.

I: Type C melanocytes. At the deep aspect of some nevi, the melanocytes take on a spindled shape with a neural appearance and have areas closely resembling neurofibroma (black arrow). Contrast with the type B melanocytes (green arrow).

J: Spindled type C melanocytes bear a striking resemblance to Schwann cells.



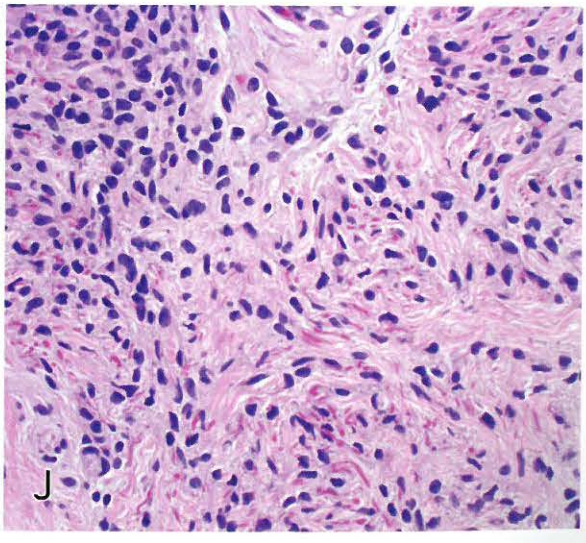


Table 4-2

FEATURES OF MELANOMA

Asymmetry (E and D)
Pagetoid spread (E)
Confluent growth and/or single cell predominance (E)
Lack of maturation (D)
Cytologic atypia (E and D)
Mitotic activity (D)

[a]E = epidermal feature; D = dermal feature; E and D = both.

aggregates or clusters, referred to as nests. Single melanocytes may also be present, but nests predominate over single cells in most nevi. When single junctional melanocytes are present in nevi, they are usually located along the basal layer (i.e., minimal or no pagetoid spread; see below), and they are spaced out and divided from one another by intervening keratinocytes (i.e., minimal or no confluent growth; see below).

In the intradermal component of a nevus, there may be single melanocytes, particularly

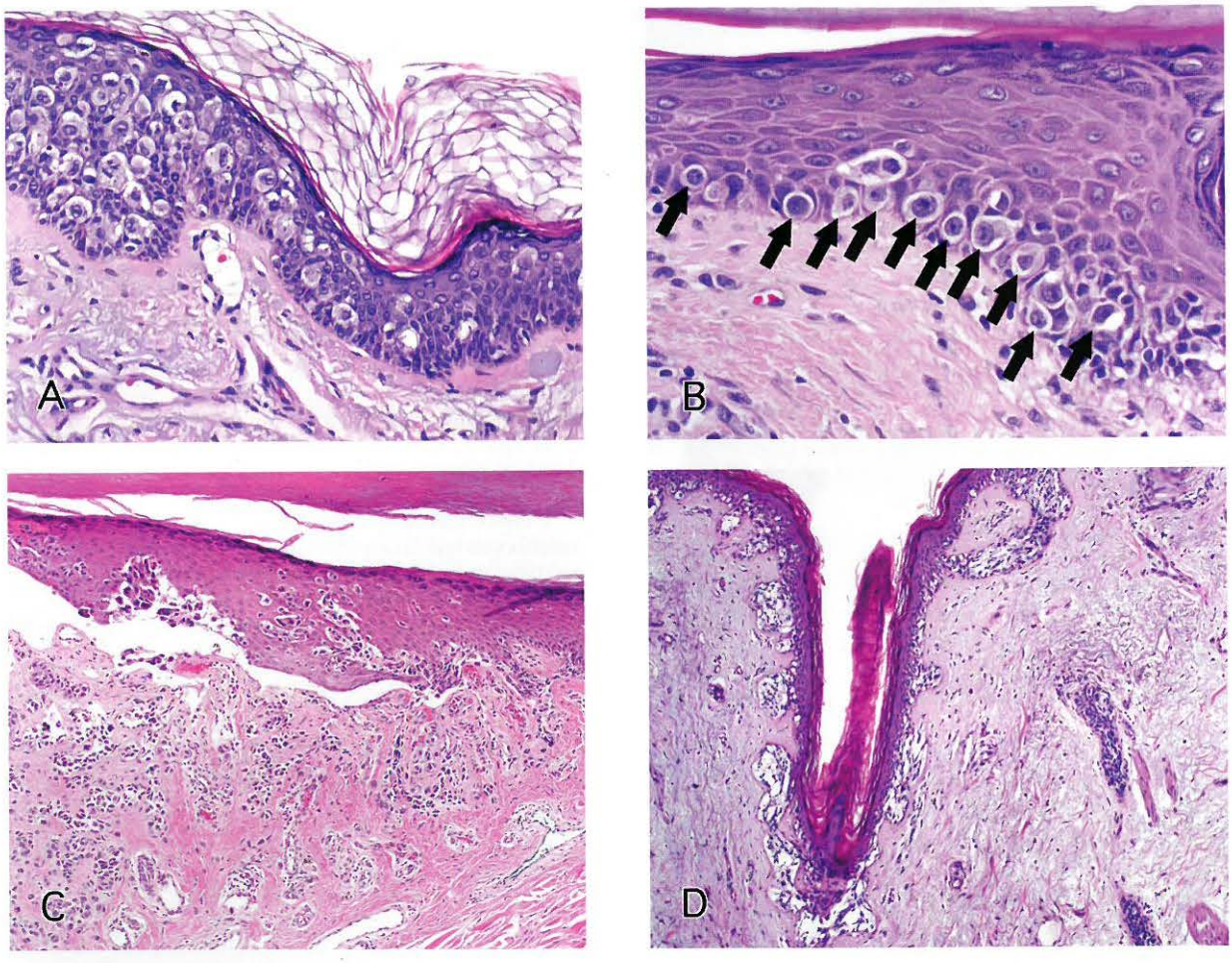


Figure 4-2

MELANOMA BASICS

A: Pagetoid spread refers to single melanocytes scattered upward into the epidermis above the basal layer, usually into the upper spinous layer or even the granular layer.

B: Confluent growth refers to increased numbers of single melanocytes (arrows) along the basal layer that crowd out (or even fully replace) the background basal keratinocytes.

C: The presence of a blister-like area within a melanocytic lesion, where the epidermis is detaching from the dermis, is a clue to melanoma. This "unzipping" artifact is usually evidence of confluent growth, as seen in this acral lentiginous melanoma.

D: In the lentigo maligna type of melanoma, melanocytes often involve hair follicles, trickling down into the follicle along the basal layer either as single cells or nests.

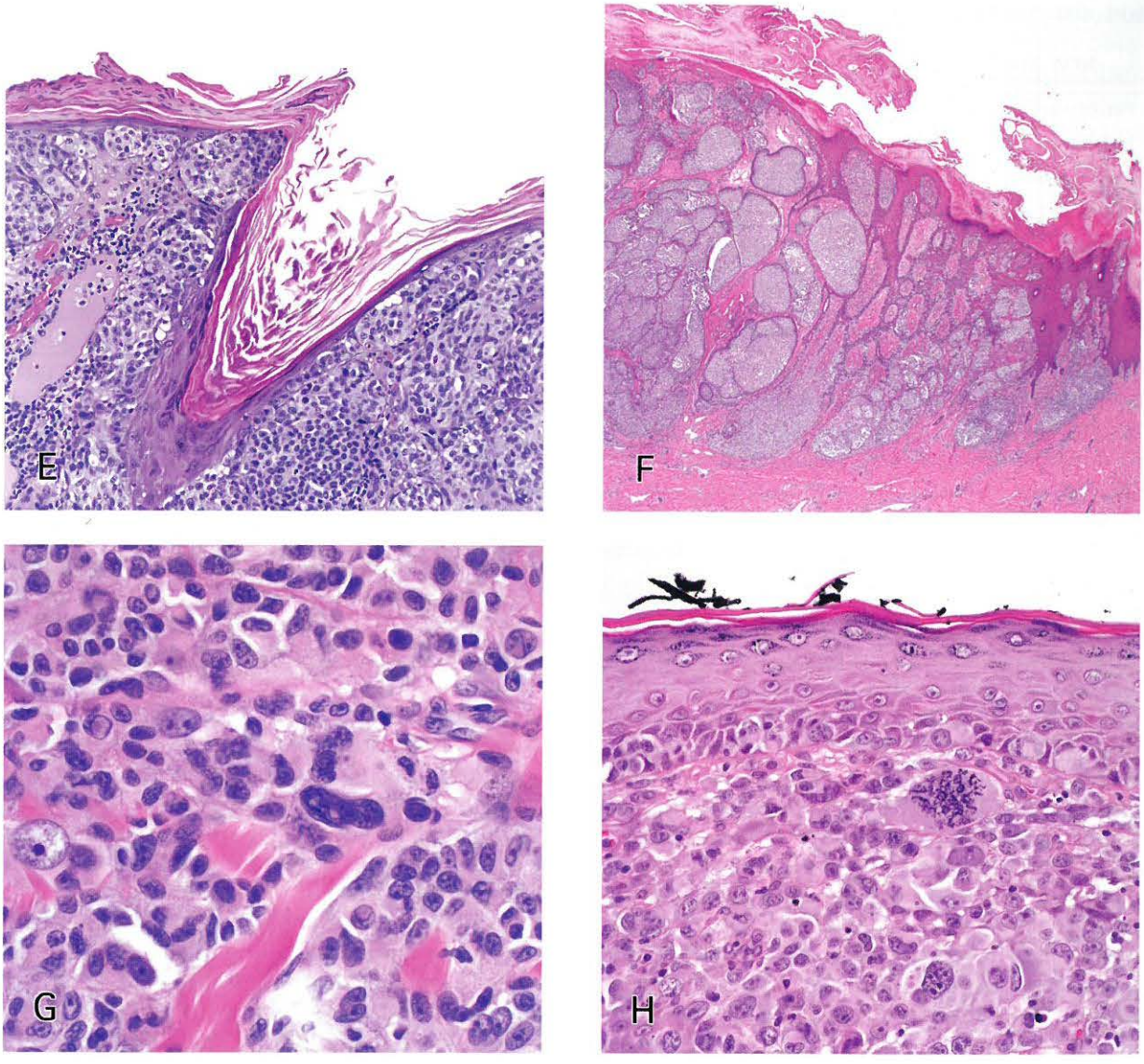


Figure 4-2, continued

E: Epidermal "consumption." Nests of melanoma are so numerous that they replace (consume) much of the epidermis (and the infundibular hair follicle epithelium too in this case) leaving only a thin strip of remaining keratinocytes above the melanocytes.

F: Abnormal maturation. Large nests are present from the superficial dermis all the way down to the deepest aspect of the lesion. There is no significant decrease in size of nests with depth.

G: Cytologic atypia. The malignant melanocytes show hyperchromasia, pleomorphism, and prominent nucleoli.

H: Sheets of invasive melanoma cells showing marked pleomorphism with coarse/clumping nuclear chromatin. A massive atypical mitotic figure is also present in the dermis.

in the deep aspect of nevi, where they trickle between collagen bundles and disperse from one another as they descend deeper and deeper into the dermis; this is part of the normal "maturation" pattern. Maturation (or zonation) is a feature of compound and intradermal nevi (junctional nevi do not have a dermal component, and thus the concept of maturation does not apply to them). Normal maturation indicates that the melanocytes individually get smaller as they go deeper into the dermis and that they transition from larger nests in the

Table 4-3

NEVI THAT LOOK DECEPTIVELY WORRISOME

Perineural "invasion" in congenital pattern nevi
Lymphatic "invasion" in congenital pattern nevi
Arrector pili "invasion" in congenital pattern nevi
Multinucleated dermal melanocytes mimicking pleomorphism at low power
Scattered large epithelioid single melanocytes along basal layer in congenital pattern nevi
Mitotic activity in nevi in pregnant women or infants
Traumatized/irritated/recurrent nevi
Spitz nevi
Nevi in special sites (acral, genital, nipple, scalp of kids, flexural sites, ear, lower leg/ankle)
Nevi with unusual maturation patterns (deep penetrating nevus, cellular blue nevus, combined nevus)

Table 4-4

MELANOMAS THAT LOOK DECEPTIVELY BENIGN

Nevoid melanoma
Desmoplastic melanoma
Subtle melanoma *in situ* (lentigo maligna type)
Nested melanoma mimicking dysplastic nevus on head/neck of sun-damaged elderly patient
Partial biopsy of large pigmented lesion (especially acral)
Melanoma arising in a benign nevus (look at every piece of tissue on the slide!)

superficial dermis into smaller nests and even single cells as they go deeper into the dermis.

Dermal melanocytes in a nevus often take one of three morphologic shapes: epithelioid cells (type A melanocytes), small round cells resembling lymphocytes at low power (type B melanocytes), and spindled cells with a neural appearance resembling a neurofibroma (type C melanocytes). Type A melanocytes are usually located toward the superficial aspect of the nevus. Deeper in the dermis they get more dispersed and transition into smaller type B and/or type C melanocytes; this is normal maturation. Some nevi only have type A melanocytes, others only have type C. Sometimes all three types are present in the same nevus. It is variable, and the letters/types themselves are not important, but they are a useful way to remember and conceptualize the morphologic variability of nevus cells and the way that nevus cells are supposed to mature with depth. Although dermatopathologists use the term "maturation" for this morphologic phenomenon, it is probably not an accurate description of what is really happening to the nevus cells biologically. Mitoses are usually absent or sparse in the dermal component of nevi.

Nevi usually have bland "nevoid" cytologic features, oval to round nuclei with fine chromatin, absent or small punctate nucleoli, and smooth nuclear membranes. Cytologic features are listed last because the architecture usually matters so much more than the cytologic features in deciding whether melanocytic lesions are benign or malignant.

Melanomas may share some of the benign features seen in nevi, but they usually deviate in one or more ways that help us to recognize their malignant potential (fig. 4-2). Melanomas may have nested melanocytes similar to nevi, but they usually also have areas where single melanocytes predominate within the epidermis, either as pagetoid spread or confluent growth. Pagetoid spread refers to single melanocytes scattered upward into the epidermis above the basal layer. Pagetoid spread tends to be very prominent in superficial spreading and acral lentiginous types of melanoma, but some melanomas have little or no pagetoid spread.

Confluent growth refers to increased numbers of single melanocytes along the basal layer that crowd or replace the background basal keratinocytes. The best examples of confluence are often found in acral lentiginous melanomas, where the basal layer may be completely replaced by malignant melanocytes. Unfortunately, many melanomas do not have such perfect confluent growth that fully replaces the basal layer, and some melanomas have no confluent growth. Although the concept of confluence sounds simple, evaluating it in practice can be subjective. It can be challenging to establish a practical threshold for how many single melanocytes along the basal layer are enough to be considered confluent growth. A few clues can help. When confluent melanocytes in a melanoma replace many of the normal basal keratinocytes (which have hemidesmosomes holding the epidermis down onto the basement membrane), this can lead to zones of artifactual detachment

of the epidermis from the underlying dermis during tissue processing. Confluent single melanocytes may be more easily appreciated when they spread down the skin adnexal structures, replacing the basal layer of hair follicle or sweat ductal epithelium. Some nevi display discrete nests of melanocytes within eccrine ducts or hair follicles, so the involvement of adnexa by itself does not always equate to melanoma.

Melanomas often show abnormal or absent maturation. They may have large melanocytes and large nests of melanocytes in the deep dermal aspect of the lesion. The invasive melanocytes may comprise diffuse sheets replacing the dermis. They may be arranged into multiple nests that are packed tightly together in the dermis. Evaluation of maturation can be difficult or even impossible in thin lesions where there are only a few nests of melanocytes in the dermis. It is a more useful feature to look for in thick melanocytic lesions that extend into the reticular dermis, where the presence or absence of maturation is easier to assess. Some melanomas have "pseudomaturation" where the invasive malignant melanocytes get smaller and trickle out into the dermis at the deep aspect of the lesion; this can yield a deceptively benign appearance at low-power magnification (see Nevoid Melanoma).

Dermal mitotic activity can be a helpful clue for diagnosis, although mitotic figures are not present in all melanomas. The presence of many mitoses or atypical mitoses, particularly in the deep dermis, is concerning for melanoma. Dermal mitotic activity also supports a diagnosis of melanoma when other atypical features are also present. Mitoses in the junctional/intraepidermal aspect of a melanocytic lesion are more challenging to evaluate because it can be difficult to determine whether the mitosis is in a melanocyte or a background basal keratinocyte (mitotic activity is totally normal in basal keratinocytes).

Cytologic (nuclear) atypia is seen in most melanomas. As with mitotic activity, cytologic atypia by itself does not necessarily indicate melanoma, but when severe, diffuse, and present in conjunction with other features of melanoma, it is strongly suggestive. Marked cytologic atypia is seen in some nevi, but use great caution before making such a diagnosis and ensure that no other features of melanoma are present. The evaluation of cytologic atypia in melanocytic lesions can be problematic, but helpful features include nuclear hyperchromasia, coarse/clumping chromatin, pleomorphism, irregular nuclear membranes, and large nucleoli.

All of these "rules" can be broken. No one feature alone makes a diagnosis of melanoma or nevus. No specific number of atypical features makes a diagnosis of melanoma. Unfortunately, there is no simple calculation for malignancy, like "if at least 3 out of the 6 atypical features are seen, then the diagnosis must be melanoma." It is not that easy. Dermatopathologists have to take all of the histologic features together with the clinical context in order to make the best possible final diagnosis. We must also consider some troublesome caveats and exceptions.

The threshold for defining and grading cytologic atypia is variable between different dermatopathologists, and even between individual dermatopathologists over time. Grading systems for cytologic atypia have been published (1). In practice, however, there still appears to be significant variability in the grading of cytologic atypia in melanocytic lesions (2,3). Much arguing has ensued over this topic in the dermatopathology world. If the giants of the field cannot resolve this issue to everyone's satisfaction, I surely will not be able to. If the reader finds this challenging, you are in good company.

Even if we accept objective criteria for how to define melanocytic nuclear atypia, the significance of that atypia varies depending on the scenario. For example, I often see obviously benign nevi with scattered large melanocytes that, taken out of their clinical and architectural context, would be considered "atypical" (fig. 4-3). I also occasionally see melanomas that have little cytologic atypia but are clearly malignant by nature of the architectural growth pattern. I tend to judge the significance of nuclear atypia differently depending on the patient age, anatomic site, amount of sun damage, and other unique aspects of each case. Some may not agree with that approach or may argue that it is not objective, but that is the honest answer of how I handle this in my own practice.

Not all that is pagetoid is melanoma. One pagetoid melanocyte does not make a melanoma, nor do two or three. There is no "magic number" of how many pagetoid melanocytes it takes to diagnose a lesion as melanoma. Nevi that

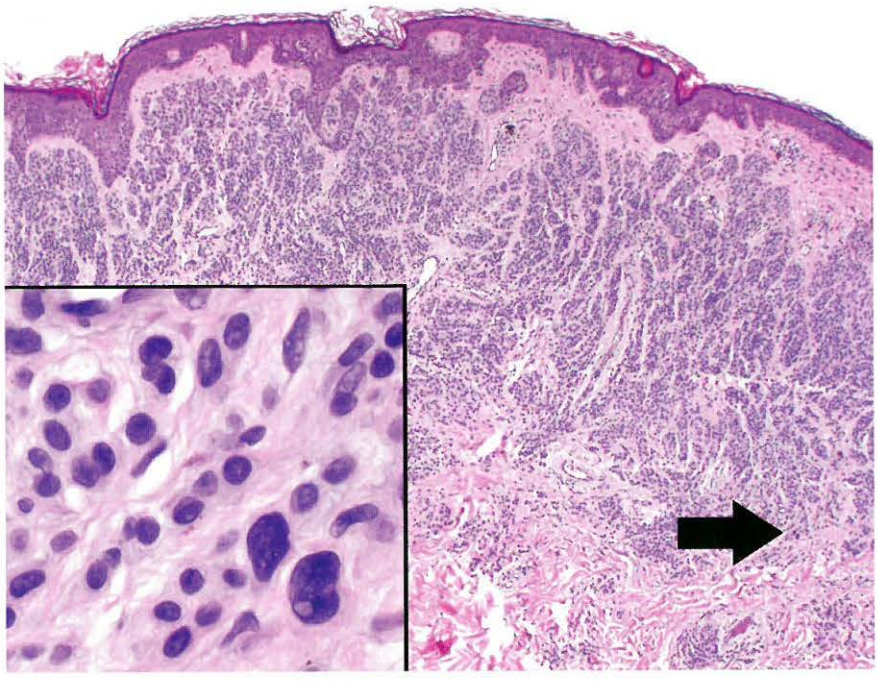


Figure 4-3

COMPOUND NEVUS WITH RANDOM "ATYPIA"

There is normal maturation and no pagetoid spread or confluent growth. Two intradermal melanocytes (arrow and inset) have hyperchromatic nuclei 3 to 4 times larger than neighboring melanocytes. This "atypia" is of no significance in this context; I do not mention it in the report.

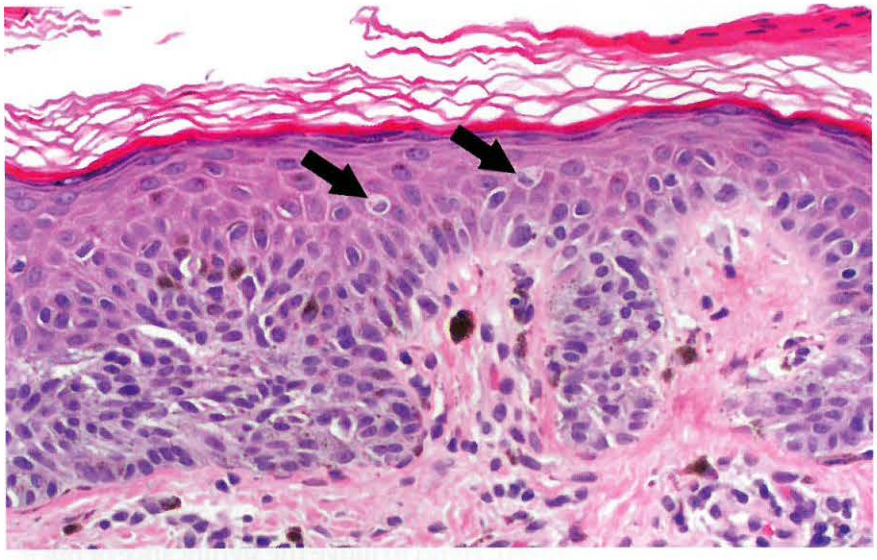


Figure 4-4

IRRITATED NEVUS WITH PAGETOID SPREAD

A nevus that has been rubbed, scratched, or otherwise irritated may show some pagetoid spread (arrows). Clues to irritation include parakeratosis (upper right), hypergranulosis, and papillary dermal fibrosis.

are irritated, scratched, or rubbed may have some pagetoid spread in the area of irritation (fig. 4-4). Spitz nevus and pigmented spindle cell nevus (of Reed) often have pagetoid spread in their central aspects. Other nonmelanocytic entities may also display pagetoid spread, including mammary or extramammary Paget disease, squamous cell carcinoma *in situ*, sebaceous carcinoma, Merkel cell carcinoma, and others.

Additionally, not all that appears to be pagetoid is truly pagetoid. Tangential sectioning can produce "pseudo-pagetoid" spread and a variety of other features that make melanocytic proliferations difficult to evaluate (fig. 4-5). Because rete ridges are three-dimensional structures, melanocytes located on the basal layer along the sides of rete ridges may sometimes artifactually appear to be pagetoid depending on how each rete is sectioned. Thus, I do not get too worried about occasional pagetoid melanocytes in the lower or mid-spinous layer of a lesion. Single melanocytes that are in the upper spinous layer or in

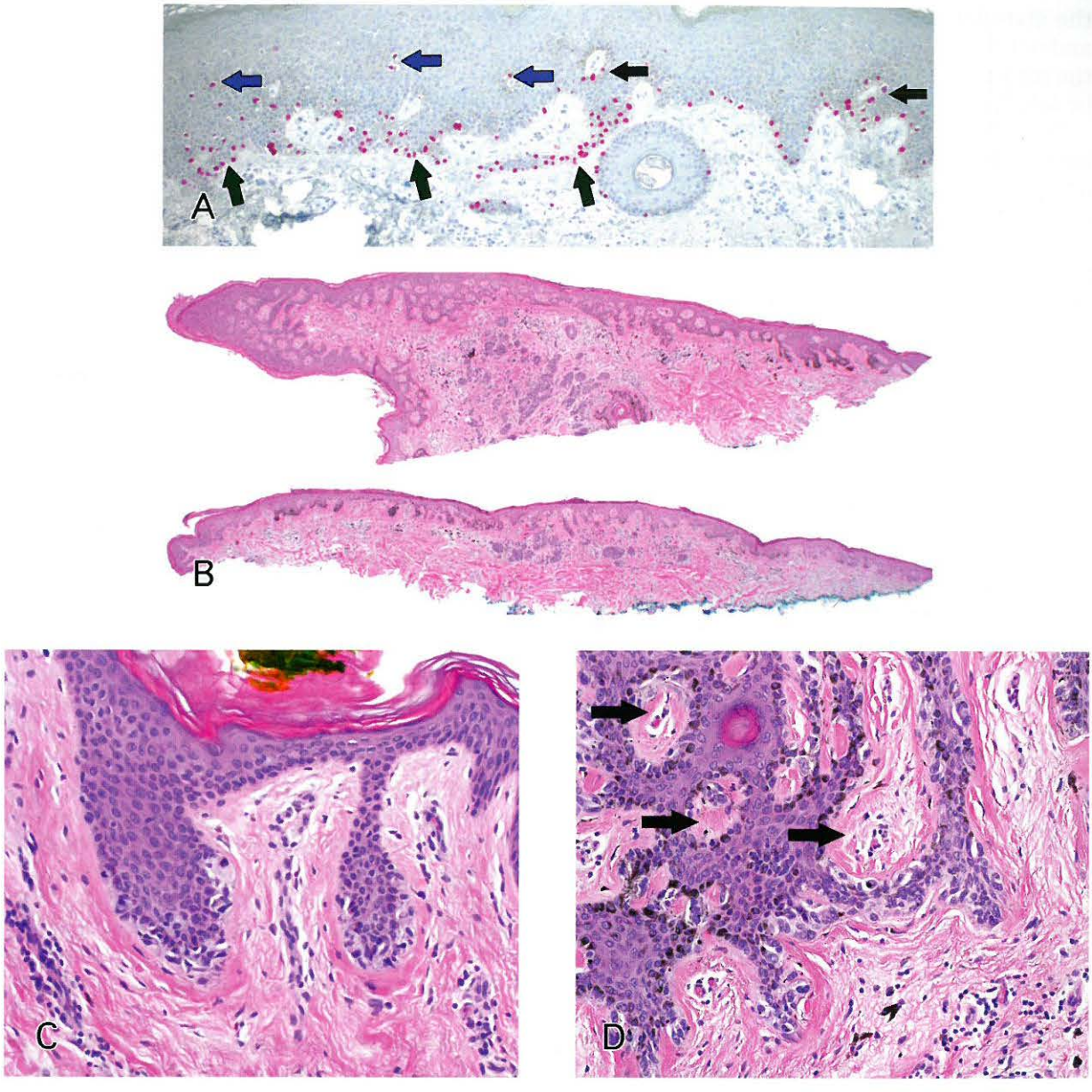


Figure 4-5

TANGENTIAL SECTIONING ARTIFACTS

A: Small islands of papillary dermis completely surrounded by epidermis are evidence of a tangential section. SOX-10 shows some melanocytes that appear to be pagetoid but are not; they are actually located in the basal layer around these islands of tangential dermal papillae (black arrows). The same is probably true of the melanocytes at the blue arrows, but we just cannot see the connection to dermal papillae in this plane of section. There is also a false appearance of increased melanocyte density at the basal layer (green arrows), another artifact of tangential sectioning.

B: Tangential sectioning of a nevus can produce a dramatically different appearance that looks architecturally atypical. This is a bisected shave biopsy of a nevus: one piece was embedded/sectioned tangentially (top) and the other was done correctly. The epidermis looks more complex and the dermal component much deeper and less mature in the tangential section.

C: Melanocytes are present down rete tips in this nevus (left).

D: When the same nevus is sectioned tangentially (right), the network of interconnected rete allows visualization of many more junctional nests than usual in a normal section. This produces a very "busy" appearance that can lead to unwarranted anxiety for the pathologist. If there are islands of papillary dermis fully encircled by epidermis (arrows), then the section is tangential.

the granular layer are probably truly pagetoid and not due to tangential sectioning. Even then, the presence of pagetoid melanocytes must still be taken in context.

Nevi in pregnant women and in babies can have brisk mitotic activity. If the lesion looks like an obvious nevus but has multiple mitoses, and if the patient is a woman in the reproductive age range, question whether the patient could be pregnant. Even outside of those unique clinical scenarios, occasional mitoses can be found in a subset of otherwise conventional nevi. One large study identified mitotic activity in 7.9 percent of nevi: these mitoses were usually in the papillary dermis (76.1 percent) and were usually single (80.4 percent), although some nevi showed 2 and 3 mitoses in a single specimen (15.9 and 3.4 percent, respectively) (4). If I find one mitosis in a nevus, I usually pause and look at the lesion again to be sure I think it is truly a nevus and that there are no other features concerning for melanoma. I usually look around a bit more with high power to be sure that mitoses are not abundant. But if everything else fits for nevus, I just sign the case out as a nevus and do not even mention the mitosis in the report. On the other hand, if I am already worried about other atypical features in the lesion and then I see one or more dermal mitoses, that will sometimes tip the balance and help me decide on a diagnosis of melanoma.

With some training and experience, the majority of melanocytic lesions can be diagnosed on hematoxylin and eosin (H&E) sections alone, without any ancillary studies. In a subset of cases, however, the clinical scenario or the histologic features raise some degree of uncertainty. Additional workup can be performed in these cases, depending on where the uncertainty lies.

Deeper sections can help ensure that the "worst" area of the lesion is visualized and that nothing more atypical is hidden unsampled deeper in the block. In obvious melanomas, deeper sections are sometimes helpful to detect invasion or to detect a deeper area of invasion than was seen on the initial sections.

Tangentially sectioned melanocytic lesions can be very challenging to diagnose because the usual architectural features that are used to decide between nevus and melanoma cannot be easily visualized (fig. 4-5). Unfortunately, re-embedding the tissue in the block is only helpful in a minority of these cases. Deeper levels sometimes help to resolve the issue by allowing a properly oriented area of the lesion to come into view.

Immunohistochemistry may be helpful in evaluating melanocytic lesions, but selection of the proper stain for the given question is essential. Pathologists most often use immunostains to determine the differentiation, histogenesis, or site of origin of a malignancy or other neoplasm. In melanocytic lesions, however, the melanocytic differentiation is usually obvious on H&E without using immunostains. Instead, the most common roles of immunostains in this situation are to help better visualize the melanocytes, help evaluate their pattern of growth, and assess for other features that help to distinguish nevus from melanoma. Different dermatopathologists have different styles or preferences regarding immunostains. I know some experienced dermatopathologists who rarely use immunostains for melanocytic lesions, but I personally find them to be useful when used appropriately in select cases (Table 4-5). Adequate training and practice are needed for their interpretation, and there are significant pitfalls that must be avoided.

Several of the most common melanocytic immunostains are discussed below along with their pros and cons.

SOX-10. This is a nuclear marker of melanocytes. It is highly sensitive for melanocytic differentiation (similar sensitivity as S-100 protein), but it is not specific, as it also stains Schwann cells, nerve sheath tumors, eccrine coil cells, and some sweat gland tumors, among others. SOX-10 is very useful for identifying subtle confluent growth and pagetoid spread of melanocytes within the epidermis (fig. 4-6). I use it most often in difficult biopsies of pigmented lesions on the face or scalp of sun-damaged elderly patients for which the clinical differential diagnosis is solar lentigo versus lentigo maligna type of melanoma (fig. 4-7). It can also be used to identify dermal invasion, desmoplastic melanoma, and metastatic melanoma (either distant or in lymph nodes).

MiTF. This is also a nuclear marker of melanocytes. It is an acceptable alternative to SOX-10 for evaluating the intraepidermal portion of a melanocytic lesion, although I find it to have less

Table 4-5

IMMUNOSTAINS FOR MELANOCYTIC LESIONS

Scenario	Best Options	Use with Caution	Do Not Use
Evaluate for pagetoid spread and/or confluence	SOX-10, MiTF	MART-1	S-100 protein
Evaluate for dermal invasion hiding in marked inflammation	SOX-10, MART-1	S-100 protein	MiTF
Metastatic melanoma in dermis/subcutis	SOX-10, S-100 protein	MART-1[a], HMB-45[a]	MiTF
Spindle cell melanoma (versus spindle cell SCC[b] versus AFX)	SOX-10, S-100 protein	MART-1[a], HMB-45[a]	MiTF
Desmoplastic melanoma	SOX-10, S-100 protein		MART-1, HMB-45, MiTF
Sentinel lymph nodes	SOX-10, MART-1	HMB-45, S100	MiTF

[a]Helpful if positive, but if negative, then must also do S-100 protein or SOX-10 to confirm lack of melanocytic differentiation.
[b]SCC = squamous cell carcinoma; AFX = atypical fibroxanthoma.

crisp staining quality than SOX-10. An important warning is needed here: MiTF often stains histiocyte nuclei, and I have seen it stain other nonmelanocytic tumors. Therefore, it is only useful for evaluating intraepidermal melanocytic lesions. I do not trust MiTF for evaluating dermal invasion, sentinel lymph nodes (5), or distant metastases of melanoma. I have seen pathologists diagnose a pleomorphic sarcoma or poorly differentiated carcinoma as metastatic melanoma merely because it had focal MiTF staining (despite negative S-100 protein, MART-1, and HMB-45). Do not make that mistake! I have also seen strong nuclear MiTF staining in sentinel lymph node histiocytes that could easily have been confused with metastatic melanoma cells. Because I have SOX-10 available in my laboratory, I no longer routinely use MiTF in my practice.

S-100 Protein. This is a nuclear and cytoplasmic marker of melanocytes. Like SOX-10, it is highly sensitive for melanocytic differentiation, but it is nonspecific and stains a wide variety of other cell types. If you attempt to use S-100 protein to evaluate the intraepidermal component of a melanocytic lesion, you will see numerous positive cells scattered throughout the spinous layer of the epidermis. These are S-100 protein-positive Langerhans cells, which normally reside in the epidermis; they can be easily confused with pagetoid melanocytes. Langerhans cells and other S-100 protein-positive dendritic cells are also present in the dermis, and thus S-100 protein tends to have a "dirty" staining pattern in the dermis that can make interpretation complicated. In fact, if an S-100 protein stain looks "clean" and has little or no scattered cells staining in the dermis, it makes me worry that the stain may have failed. Be sure to check your controls if this happens.

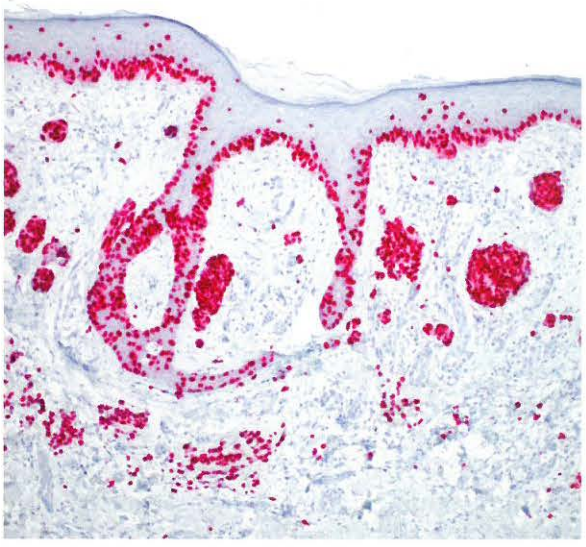


Figure 4-6

SOX-10 HIGHLIGHTING CONFLUENT GROWTH IN MELANOMA

The melanocytes replace basal keratinocytes and form a solid line along the basal layer that goes up and down the rete as well as across the inter-rete spaces. Scattered Pagetoid melanocytes are seen. Invasive nests of melanoma are also stained.

Because of the high background, S-100 protein cannot easily be used in the same manner as SOX-10 for evaluating the pattern of growth

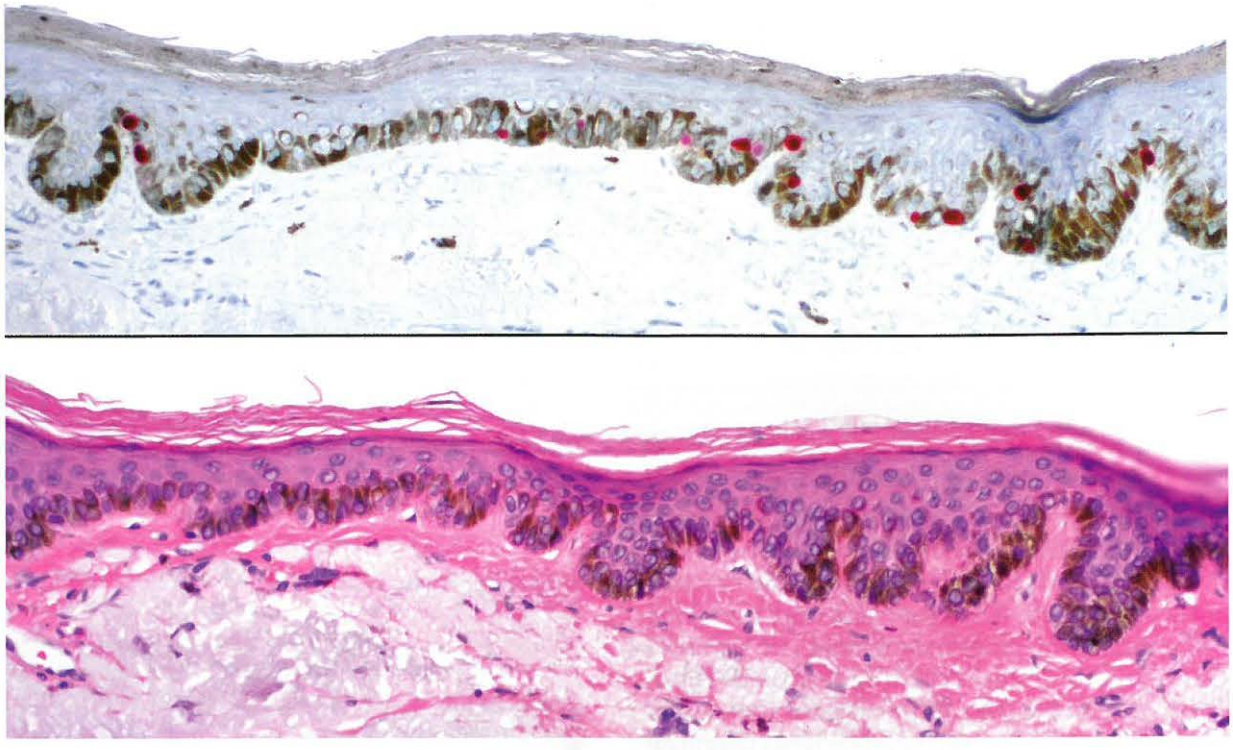


Figure 4-7

SOX-10 IN SOLAR LENTIGO

SOX-10 distinguishes melanocytes (red nuclei) from melanin-laden basal keratinocytes (dark brown cells) in heavily pigmented lentiginous lesions.

of intraepidermal melanocytes (fig. 4-8). If there is a pleomorphic high-grade malignant tumor in the dermis, however, S-100 protein is very useful for ruling out melanoma in that setting because of its high sensitivity (I have found SOX-10 to be equally useful). Although melanoma can lose expression of S-100 protein (SOX-10 can be lost also), this is rare and usually there are still some areas with retained expression.

Negative staining for S-100 protein (or SOX-10) in a tumor of unknown histologic origin is a strong argument against melanoma. S-100 protein and SOX-10 are also the best markers for identifying desmoplastic melanoma, which is negative for MART-1 and HMB-45.

MART-1 (Melan-A). This is a cytoplasmic marker of melanocytes. MART-1 and Melan-A are very similar: they both target the same melanocytic antigen (6). In my lab, we use MART-1, so I will refer to this antibody throughout the book. Although not quite as sensitive as S-100 protein or SOX-10, MART-1 is very specific for melanocytic differentiation. In the skin, the only other entities that express MART-1 are clear cell sarcoma and primary cutaneous PEComa (both are very rare).

If a patient has a history of melanoma, and there is now a nodule of tumor in the dermis that I favor to be recurrent or metastatic melanoma, MART-1 is a good stain to use to confirm it since it is both sensitive and specific. It is also useful in sentinel lymph nodes for melanoma. It detects subtle dermal invasion of melanoma when there is intense background inflammation or regression.

Although it could potentially be used to evaluate the intraepidermal component of a melanocytic lesion, it is more challenging to interpret than SOX-10 or MiTF because of its cytoplasmic (rather than nuclear) staining pattern (fig. 4-9). This can lead to overinterpretation as confluence, leading to overdiagnosis of melanoma (6). This is especially problematic in biopsies from sun-damaged

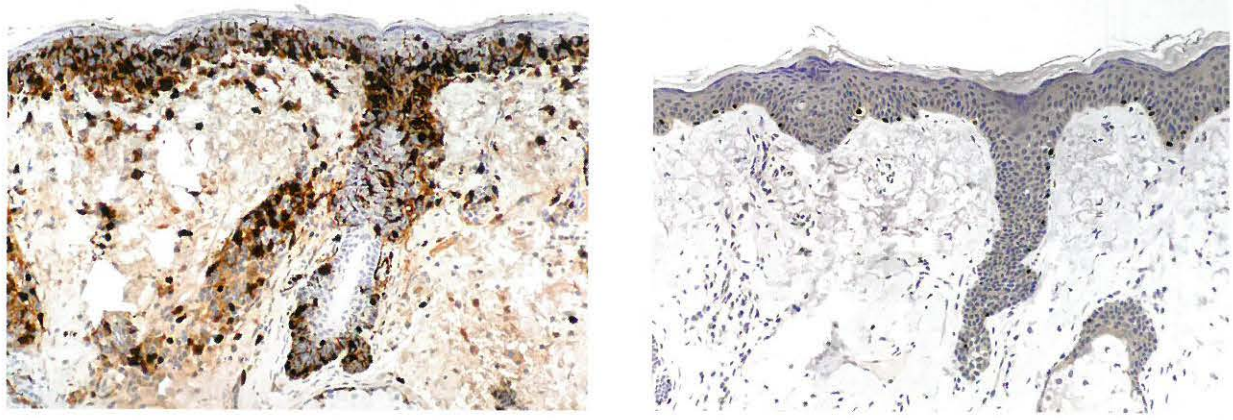


Figure 4-8

S-100 PROTEIN VERSUS SOX-10

Left: S-100 protein highlights not only melanocytes, but also intraepidermal and dermal Langerhans cells. S-100 protein should look "dirty" like this in the skin. If these scattered S-100-positive cells are totally absent, check the controls to be sure the immunostain worked correctly.

Right: SOX-10 immunostain on the same area of the same tissue block as left figure. The contrast is striking. Only evenly distributed normal junctional melanocytes are staining; the busy background of Langerhans cells seen on S-100 protein is gone. S-100 protein is a poor choice for evaluating confluent growth or pagetoid spread in melanocytic lesions.

skin where abundant solar-induced background melanocytic hyperplasia is a common finding.

Mast cells can show weak nonspecific cytoplasmic staining for a variety of immunostains. In particular, I notice this odd phenomenon most often with MART-1, desmin, pancytokeratin AE1/AE3, and myogenin. The key to identifying this is recognizing the evenly scattered distribution of single cells, the weak granular nature of the staining, and the fried egg shape of the cells at high power. Widely scattered single cells in the dermis or a lymph node that are weakly positive for MART-1 may actually be mast cells, not melanocytes. This phenomenon is easy to recognize once one is familiar with it, but in difficult cases, a CD117 or mast cell tryptase stain shows a similar evenly distributed pattern of single cells.

HMB-45. This is a cytoplasmic marker of melanocytes. Like MART-1, it is very specific for melanocytic differentiation, but is less sensitive (6). I also find it to have a more granular and less crisp staining pattern than MART-1. HMB-45 has been reported as a helpful tool in evaluating maturation: it stains junctional and superficial dermal nests but shows decreased or negative staining in the deeper dermal aspects of nevi (fig. 4-10). In contrast, melanomas are supposed to show stronger patchy staining for HMB-45 in the deep aspect of the lesion (7). I personally find this maturation staining pattern somewhat challenging to interpret with certainty in the atypical lesions where I would need it most. As a cytoplasmic marker, HMB-45 is not ideal for evaluating the intraepidermal component of a melanocytic lesion for the same reasons as for MART-1. It can, however, be used as a stain in sentinel lymph nodes, although I find it less helpful than SOX-10 or MART-1 in that setting. I do not use HMB-45 very often in my practice.

Despite my best efforts, I am sometimes still unable to decide with certainty whether a melanocytic lesion is benign or malignant. A full discussion of the complex topic of ambiguous melanocytic lesions is outside the scope of this book. This controversial area is debated among dermatopathology experts, and many terms have been suggested for this group of "gray zone" melanocytic lesions with uncertain malignant potential. For readers who are in training, this is a great topic to discuss with your dermatopathology

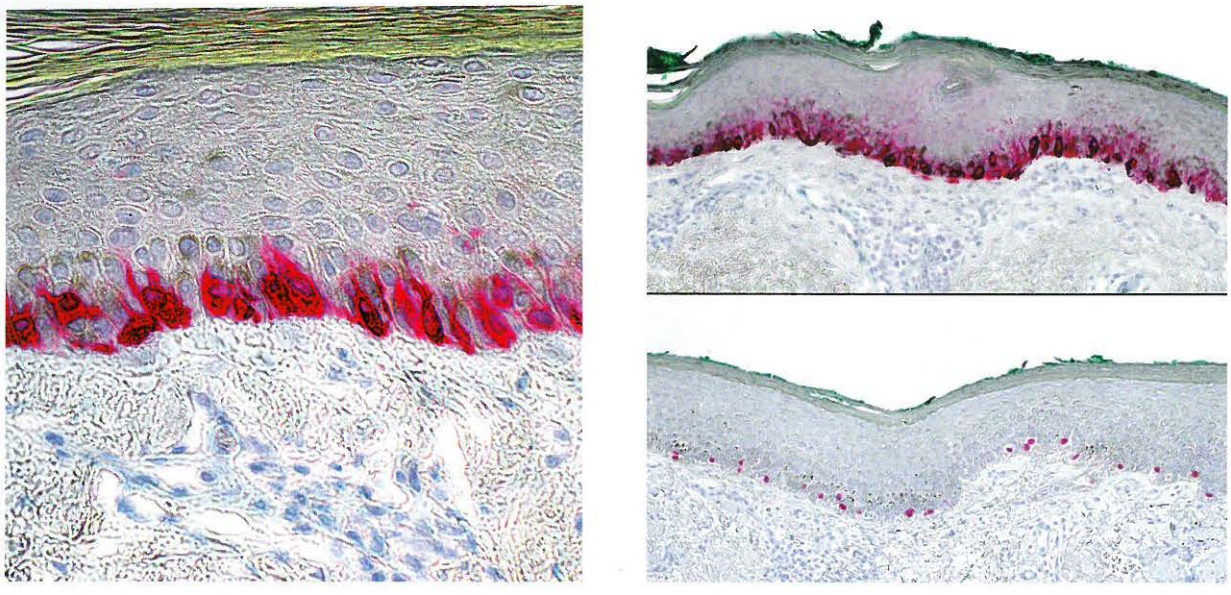


Figure 4-9

MART-1 VERSUS SOX-10

Left: Branching dendritic cytoplasmic processes on intraepidermal melanocytes strongly stain with MART-1. Dendrites from melanocytes outside the plane of section are visible in addition to those from within the plane of section, making the density of melanocytes look much greater than it actually is.

Right: This is sun-damaged skin with solar-induced melanocytic hyperplasia. The difference between MART-1 (top) and SOX-10 (bottom) staining on the same area of the same tissue block is striking. SOX-10 is superior to MART-1 when evaluating for confluent growth (see also fig. 4-36).

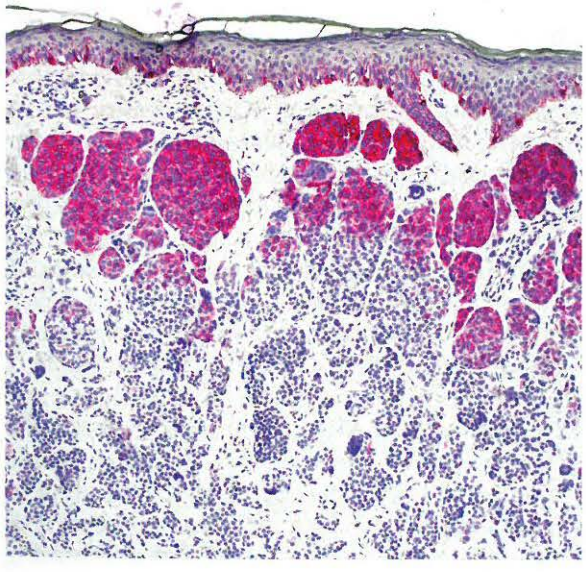


Figure 4-10

HMB-45 HIGHLIGHTING MATURATION IN A NEVUS

Junctional and superficial dermal melanocytes are positive, but expression becomes diminished or absent in the deeper intradermal aspect of the nevus.

mentors. Learning different approaches to handling complicated cases has been very valuable for me and allowed me to see the pros and cons of each so that I could better decide how I wanted to approach these cases in practice. I will briefly explain my approach below.

If I am not certain a lesion is benign, I am hesitant to use the word "nevus." I prefer to use a neutral term like "atypical melanocytic proliferation" with a comment stating that it is a difficult lesion and indicating whether I favor benign or malignant and explaining why I am uncertain. Although sometimes necessary, this type of diagnosis creates difficulty for the dermatologist and may lead to excess anxiety for the patient. Thus, before rendering an ambiguous diagnosis like this, I try to do everything I can to extract as much diagnostic information as possible from the lesion. I usually will have ordered deeper levels, immunostains, and molecular testing, and I will have obtained consultation from one of my dermatopathology colleagues. If the dermatologist requests that I send the case out for consultation to a

melanocytic pathology expert, I will gladly do so. Patient care should always come before ego. I also often learn a lot by seeing how experts deal with different challenging cases.

I tend to recommend conservative complete re-excision for ambiguous melanocytic lesions, and the dermatologist colleagues I have worked with usually seem to be comfortable with this and to appreciate the guidance. I have heard of some pathologists and some treating physicians who do not like recommendations on treatment to be included in the pathology report. Building rapport with your dermatologists and other treating physicians is a great step toward figuring out how to use language that best helps them help the patient. Ask them for suggestions and feedback and be willing to receive it.

NEVI AND OTHER BENIGN MELANOCYTIC PROLIFERATIONS

This section covers the major subtypes and patterns of nevi and related entities. These categories are useful for pathologists because they provide a basic framework for sorting out the various histologic features that can be seen in nevi. Some types of nevi, like dysplastic nevus or Spitz nevus, are treated differently by different dermatologists in light of the debate and controversy surrounding those entities. For most other nevi, the precise subclassification is not important for patient care. Distinguishing a junctional nevus from a compound nevus is not critical; distinguishing a melanoma from a nevus is.

Melanocytic Nevus: Junctional, Intradermal, Compound

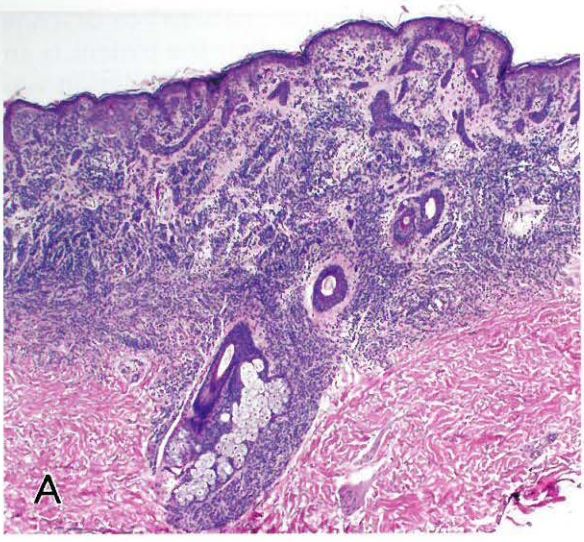
The main features of conventional melanocytic nevi were discussed in the introduction of this chapter. If a nevus does not fit for any of the subtypes described below, I just call it "junctional (or compound or intradermal) melanocytic nevus" on the diagnostic line of the report. These are like the "vanilla" forms of nevus, whereas the nevus subtypes below are the more interesting flavors.

Congenital Pattern Nevus

Congenital nevi have multiple unique histologic features (fig. 4-11). Many of these features are also present in noncongenital nevi acquired later in life, which is why I prefer to use the term "congenital pattern" to describe these findings, particularly if the patient is an adult and it is unclear whether the lesion was present at birth or not. Whether you include the "congenital pattern" modifier in the report or not is optional (I usually do). The important reasons to know about all of these features is: 1) they are unusual and confusing to beginners, and 2) they are reassuring findings that point toward the benign nature of a melanocytic lesion. Some dermatopathologists use eponyms such as Unna nevus and Miescher nevus (8); I usually lump both of these nevus subtypes into the "congenital pattern nevus" category, again acknowledging that they may not truly have been present since birth.

In congenital pattern nevi, melanocytes grow into the mid to deep dermis, with prominent single filing of melanocytes between reticular dermal collagen bundles. The melanocytes also have a tendency to be intimately associated with other dermal structures, often surrounding or tracking along hair follicles, eccrine sweat ducts, blood vessels, and nerves. The melanocytes can even infiltrate into the smooth muscle bundles of the arrector pili. I mentally envision that the nevus and the normal skin structures developed alongside one another during embryogenesis and thus they all got tangled up together (the biologic processes are obviously much more complex than this, but this is the story I like to use as a memory aid). Melanocytes bulging into vessel lumens can give the impression of lymphovascular "invasion." Do not be alarmed... these are all normal and reassuring findings. Do not report these as lymphovascular or perineural invasion.

Scattered enlarged melanocytic nuclei are often seen in congenital pattern nevi. In the context of an otherwise classic nevus, these "atypical" cells are of no concern (again, context is very important) (see fig. 4-3). Some cases show a pronounced exophytic papillomatous growth pattern with prominent horn pseudocyst formation, giving an appearance very similar to seborrheic keratosis. Some nevi have mature adipocytes scattered between the dermal melanocytes. Some nevi are composed almost entirely of type C melanocytes and have an appearance similar to neurofibroma. An unusual "pseudovascular" artifact occurs in some nevi (9). A superficial band of



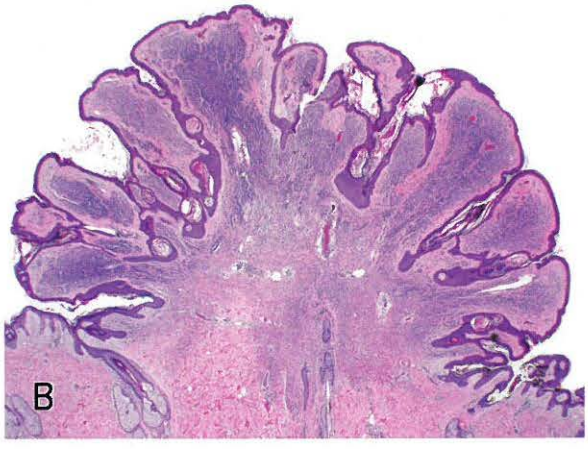


Figure 4-11

CONGENITAL PATTERN NEVUS

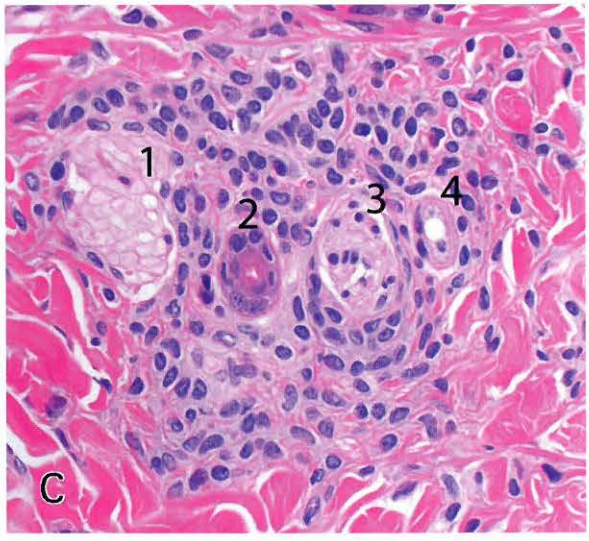
A: Melanocytes surround a hair follicle and track down into the reticular dermis.

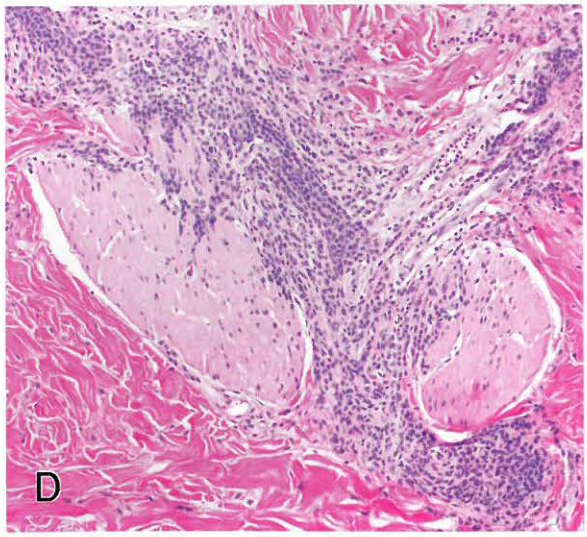
B: Some are pedunculated lesions with papillomatous surface architecture. Note the dark blue areas of the nevus; these are filled with type B melanocytes. Nevus cells are also seen tracking around hair follicles down into the deep dermis.

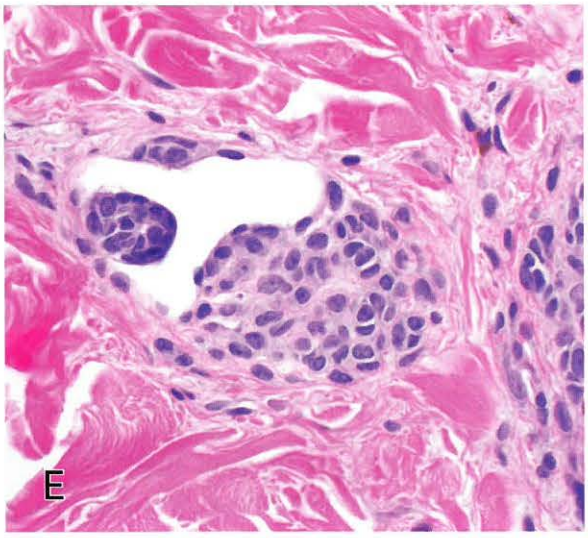
C: Congenital nevus. The intradermal nevus cells track along and surround many dermal structures, including arrector pili muscles (1), eccrine sweat ducts (2), nerves (3), and blood vessels (4), all of which are conveniently arranged alongside one another in this image.

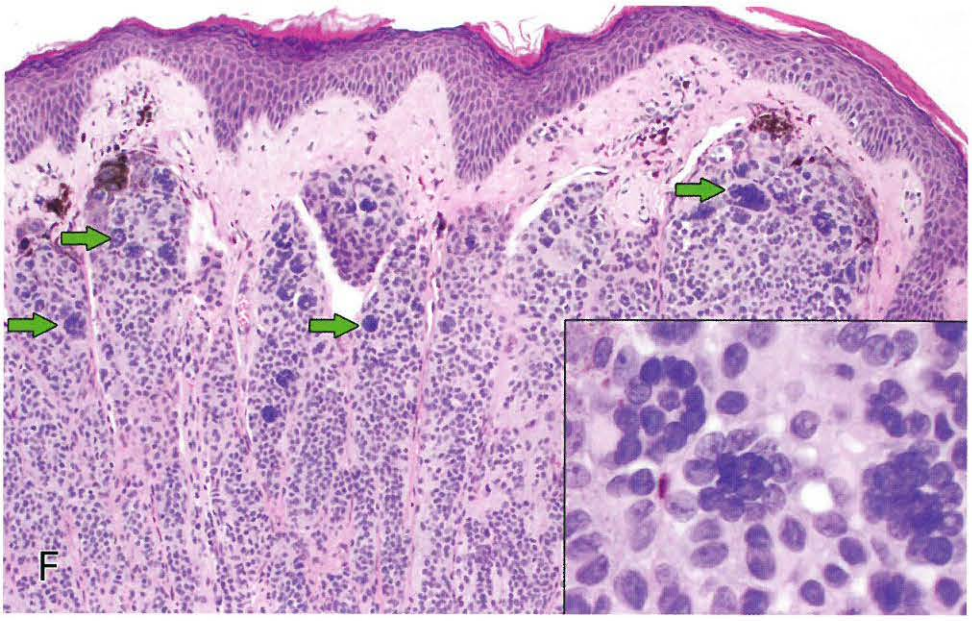
D: Nevus cells may surround and even infiltrate into arrector pili smooth muscle bundles.

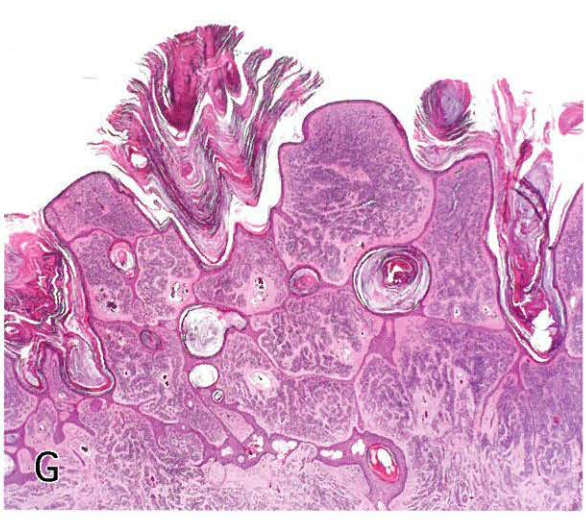
E: Congenital nevus with lymphatic involvement. Melanocytes surround and push into the lymphatic lumen. This is a normal benign finding; do not report it as lymphovascular invasion.











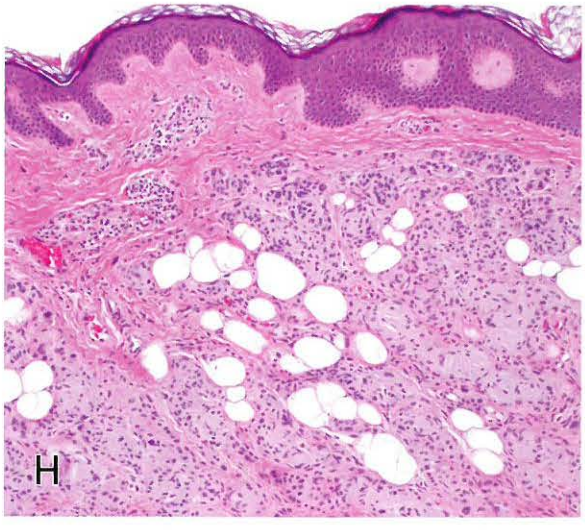


Figure 4-11, continued

F: Large hyperchromatic cells in the dermis (arrows) can mimic pleomorphism/atypia at low power, but they are actually multinucleated nevus cells with clustered overlapping nuclei (high-power inset).

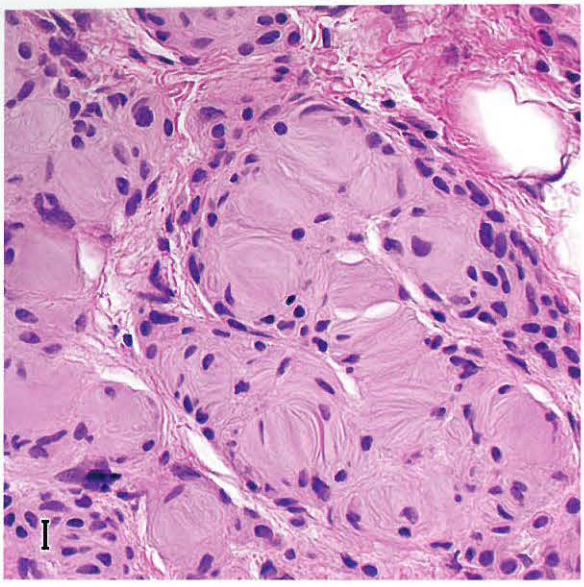
G: There may be pronounced exophytic papillomatous growth pattern with prominent horn pseudocyst formation giving an appearance very similar to seborrheic keratosis.

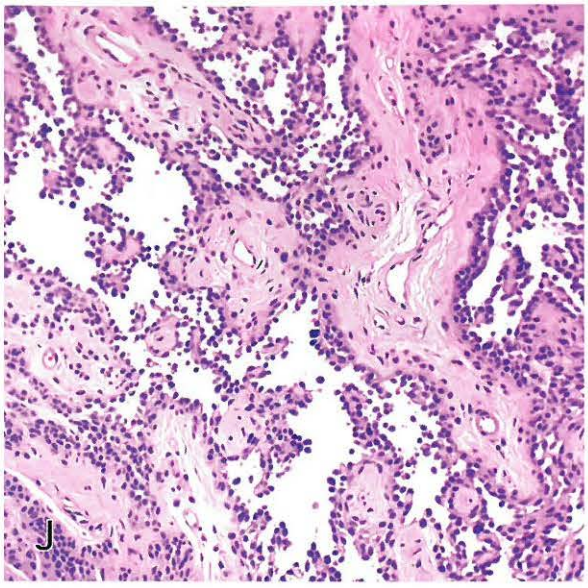
H: Mature adipocytes may be found in the intradermal portion of a nevus.

darkly pigmented melanocytes may sometimes be seen, particularly in patients with dark skin types (8). These are all histologic curiosities that are of no clinical significance. In young children with truly congenital nevi, particularly large or giant ones, the melanocytes often extend very deeply, filling the dermis and extending well into the subcutis, predominantly within subcutaneous septa. The deep aspect of these larger congenital nevi tends to be very spindled and "neurotized."

Balloon Cell Change

Nevi sometimes have melanocytes with abundant pale vacuolated cytoplasm, a phenomenon referred to as *balloon cell change* (figs. 4-12, 4-13).





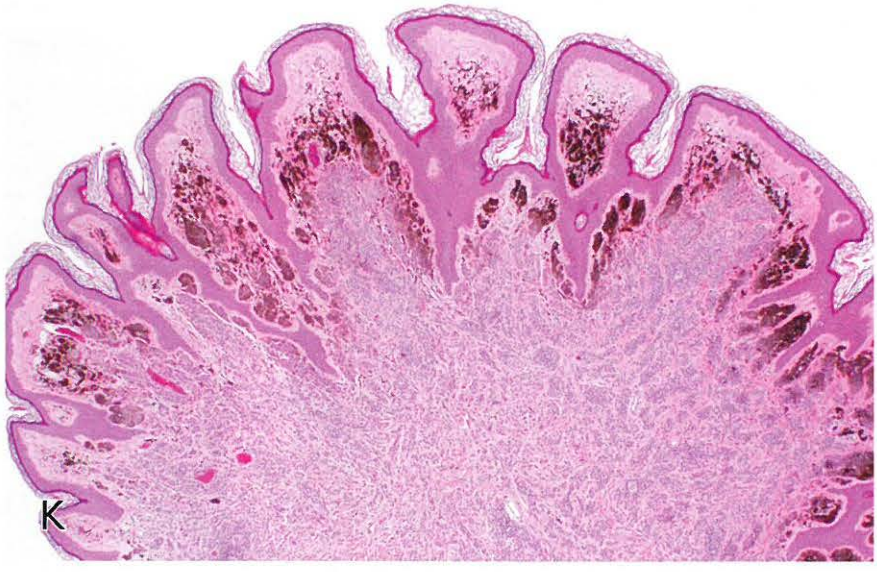


Figure 4-11, continued

I: "Neurotized" nevi may have Wagner-Meissner bodies identical to those of diffuse neurofibroma.

J: Pseudovascular artifact in an intradermal nevus. The dermal melanocytes lose cohesion and disperse from one another, creating a resemblance to vascular channels. Areas of conventional nevus are almost always present nearby.

K: A superficial band of darkly pigmented type A melanocyte may be present, particularly in patients with dark skin types.

This change is usually seen only focally, but occasionally it can be extensive and cause diagnostic confusion. Cytologic atypia may be more difficult to assess in nevi with extensive balloon cell change, since the abundant pale cytoplasm creates a different background in which to evaluate nuclear size and degree of hyperchromasia than what is seen in most nevi.

Balloon cell change may also be seen in melanoma. Again, the finding is often focal, and even when it is abundant, conventional melanoma is usually present adjacent to the balloon cell areas to aid in making the correct diagnosis. Rare cases of melanoma with extensive balloon cell change require immunohistochemistry to make the diagnosis.

"Halo" Phenomenon

Halo nevus is a clinical term referring to a pigmented nevus surrounded by a pale "halo" of depigmentation. They often occur in children or young adults. Histologically, these are nevi, often compound, with diffuse brisk lymphocytic inflammation in the dermis (fig. 4-14). The architectural pattern of the melanocytes can be difficult to appreciate because the melanocytes

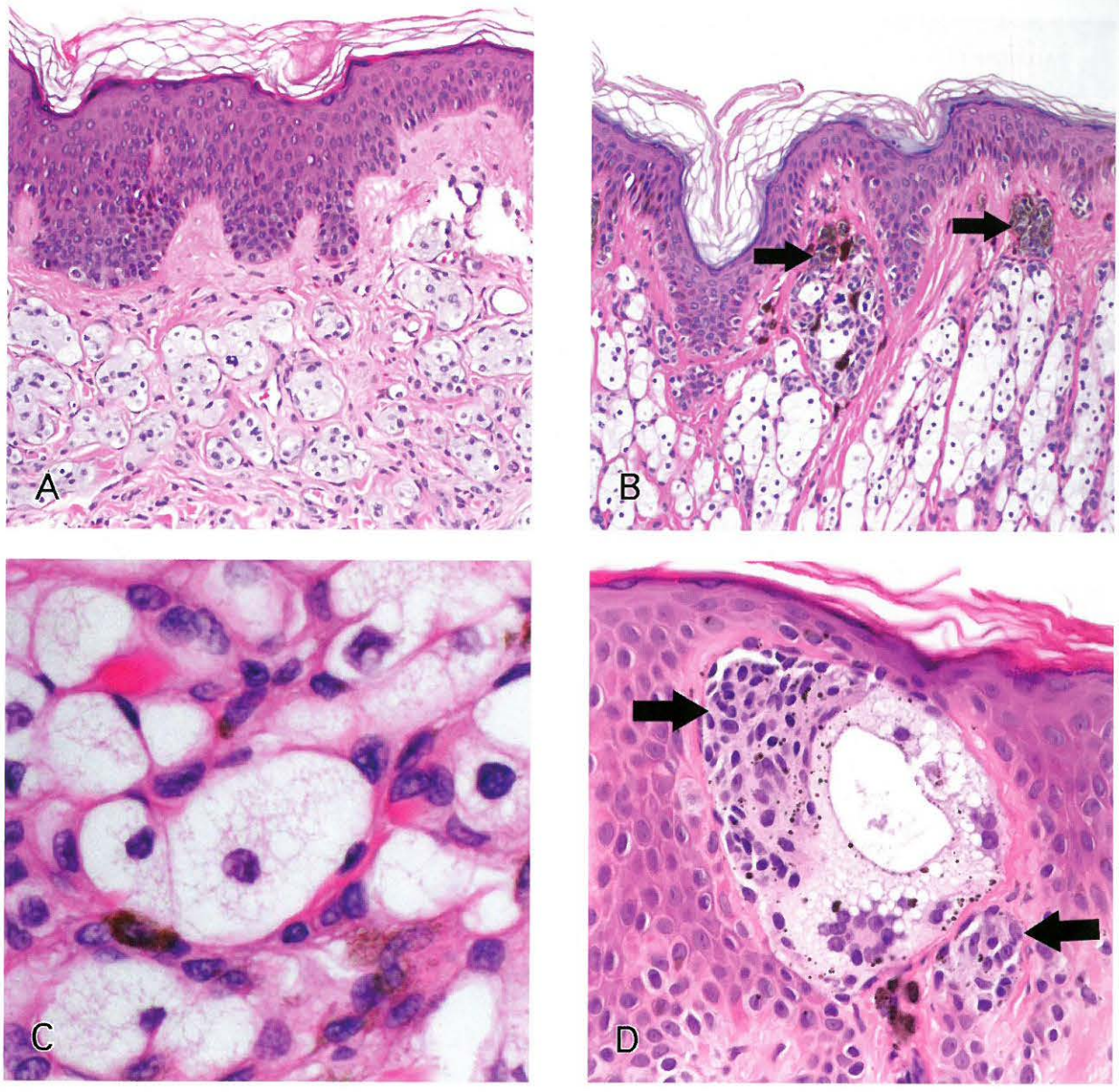


Figure 4-12

BALLOON CELL CHANGE IN NEVUS

A: There are nests of melanocytes with abundant pale cytoplasm.
B: Even when balloon cell change is abundant, background conventional nevus is usually present (arrows).
C: At high power, the pale foamy cytoplasm is filled with numerous fine vacuoles, similar to the appearance of xanthoma cells.
D: Sometimes the cytoplasmic vacuoles are larger, causing the melanocytes to resemble sebocytes. This sebocyte-like change is usually focal. Multinucleation sometimes coexists with this change. Note the presence of adjacent conventional nevus cells (arrows).

are hidden by the dense inflammatory infiltrate; SOX-10 or MART-1 immunostain helps visualize the architecture in these cases.

Nevi are sometimes markedly inflamed histologically but lack a halo of depigmentation clinically. In light of this, I use "compound melanocytic nevus, markedly inflamed" as my line diagnosis for these lesions. If the dermatologist indicated that a halo of depigmentation was present around the lesion clinically, then I will also add a comment stating: "the brisk inflammation in this nevus corresponds to the

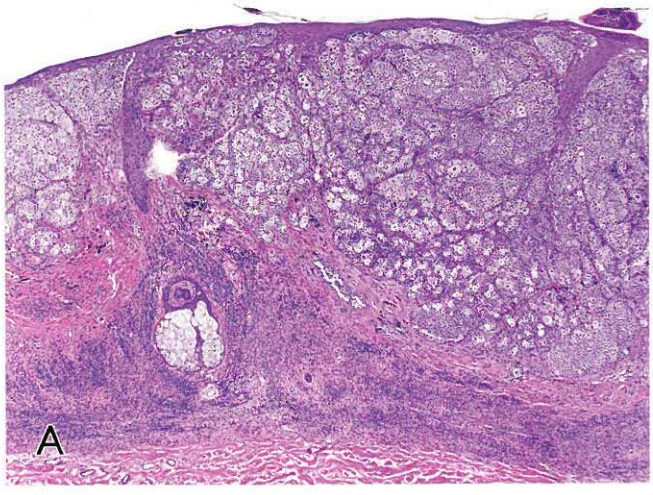
Figure 4-13

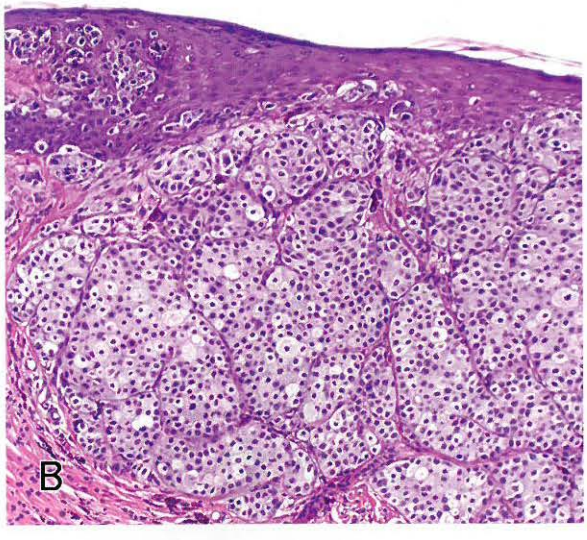
BALLOON CELL CHANGE IN MELANOMA

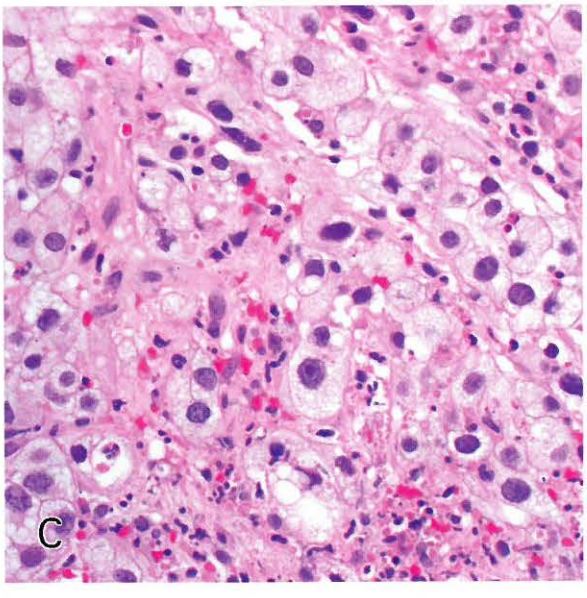
A: Many large nests of invasive melanoma are packed tightly together, filling the upper and mid dermis and showing no maturation. They have abundant pale cytoplasm. This melanoma (top) arose in a congenital nevus (bottom); the two components are separated by a zone of pink fibrosis.

B: Balloon cell change is seen mostly in the invasive portion of this melanoma. There is overlying melanoma *in situ*, with confluence and pagetoid spread, confirming the diagnosis without the need of immunostains.

C: This large ulcerated subungual melanoma had extensive balloon cell change. The entire tumor was composed of markedly atypical cells with abundant pale cytoplasm. Some had large vacuoles indenting the nuclei, mimicking sebocytes or even pleomorphic lipoblasts. Metastatic renal cell carcinoma or other clear cell neoplasm could also enter the differential diagnosis. Immunostains were needed in this case.







halo phenomenon observed clinically." Remember that brisk inflammation can also be present around melanomas or severely atypical nevi (and clinical depigmentation can be seen in those scenarios, too), so the presence of dense inflammation by itself does not automatically make a lesion a halo nevus. The underlying melanocytes must be evaluated to ensure that they are benign.

Recurrent Nevus (Regrowth Phenomenon)

A nevus that has been previously biopsied or incompletely excised may sometimes recur. Clinically, this usually presents as a new area of pigment arising within the biopsy/excision scar. Dermatologists often re-biopsy these pigment recurrences to ensure it is recurrent nevus rather than melanoma.

Histologically, *recurrent nevus* shows regrowth of melanocytes within the epidermis over the scar (fig. 4-15). The epidermis is usually atrophic, which means it is thin and has diminished or absent rete. There is often basal keratinocyte pigmentation and intermingled melanocytes that are predominantly arranged as single cells along the basal layer. The single melanocytes can be quite abundant in some cases and can mimic confluent growth. Additionally, there may be pagetoid spread and cytologic atypia. All

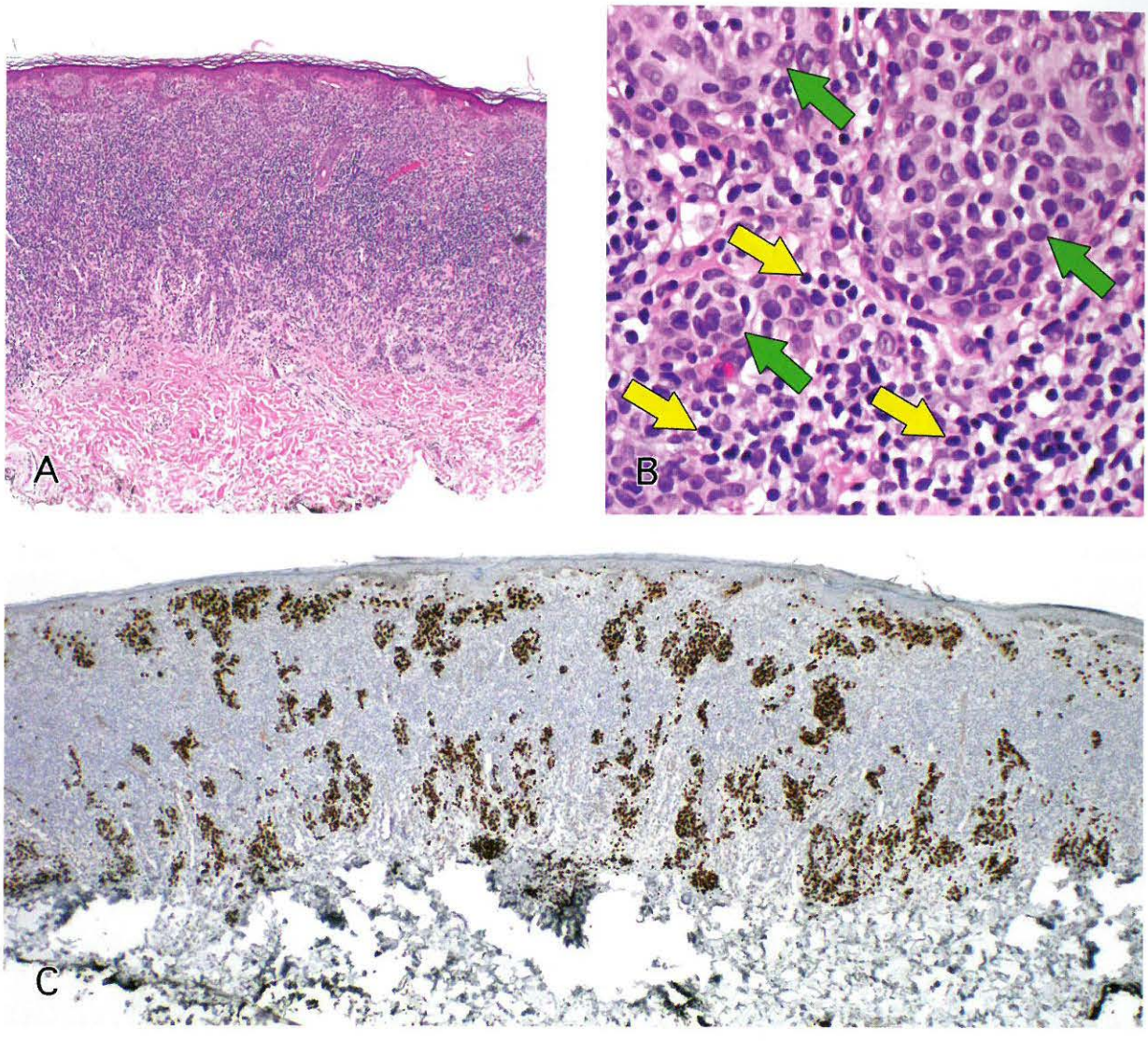


Figure 4-14

HALO NEVUS

A: There is a dense band of intradermal lymphocytes evenly distributed across the entire lesion. The architecture of the nevus cells can be difficult to appreciate on H&E due to the obscuring inflammation.

B: At high power, the melanocytes (green arrows) can be distinguished from the lymphocytes (yellow arrows) more easily. Lymphocyte nuclei are much smaller and darker than melanocyte nuclei. Junctional and superficial dermal melanocytes in halo nevus may have slightly enlarged nuclei, possibly representing a reactive change due to the inflammation or related to the young age of the patient.

C: Halo nevus. A SOX-10 immunostain highlights the melanocytes in the midst of the brisk inflammation, showing a compound nevus with symmetry, normal maturation, lack of confluence, and no pagetoid spread, all of which are reassuring features.

of these features together can easily be confused with melanoma *in situ* in particularly robust cases. Historically, recurrent nevus was sometimes referred to as "pseudomelanoma"; this term is useful for teaching, but I do not include it in the pathology report to avoid confusion. The key to avoiding this mistake is to recognize the epidermal atrophy and the presence of scar directly beneath the lesion. The atypical features should be in the epidermis above the scar but should not extend into the normal epidermis beyond the confines of the scar. Sometimes nests of

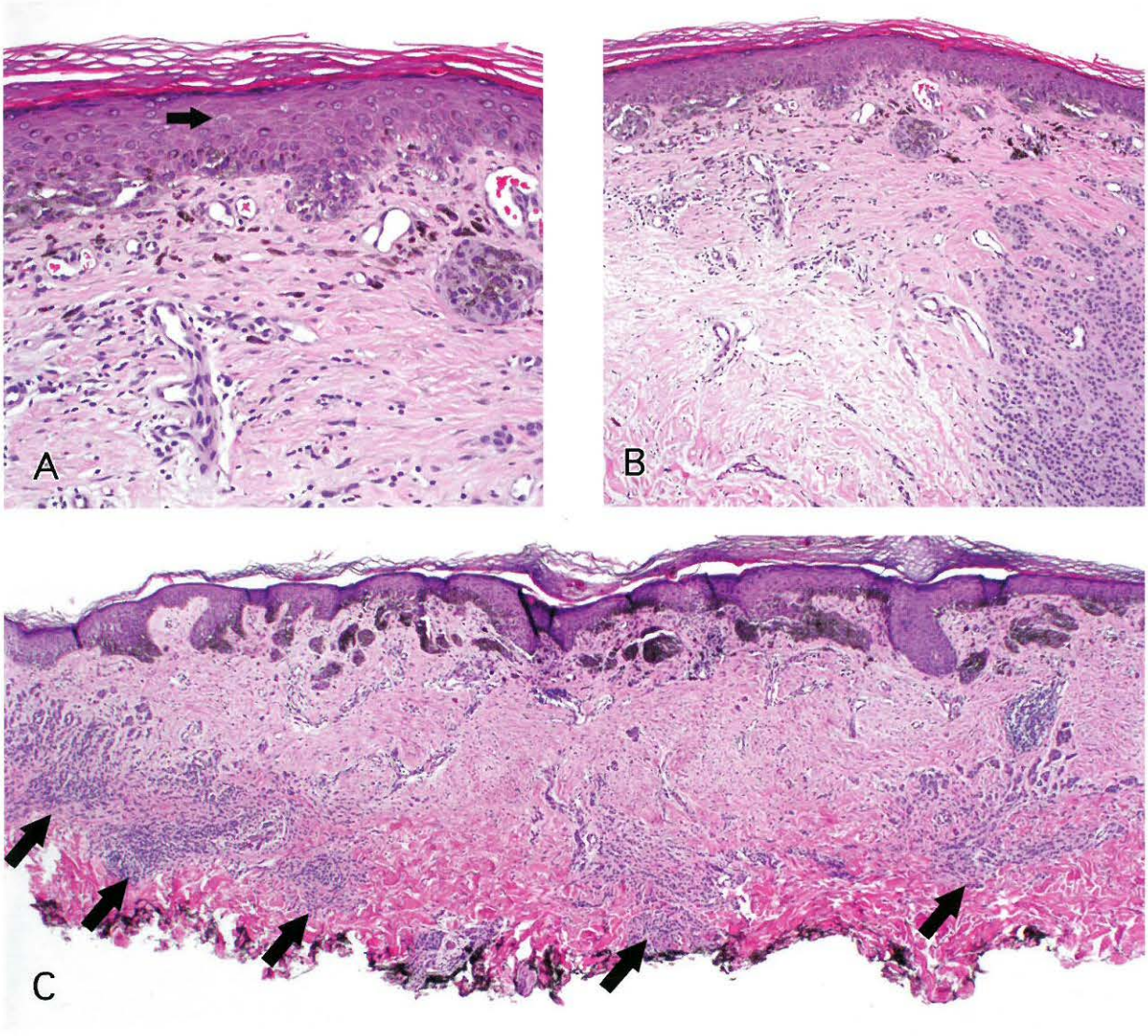


Figure 4-15

RECURRENT NEVUS

A: Atypical melanocytes are present as nests and single cells along the basal layer and in the superficial dermis. There is focal pagetoid spread (arrow). Note the dermal scar and the epidermal atrophy (i.e., rete are very small or absent; basal layer is flat rather than undulating with rete).

B: The atypical melanocytes are present over the scar only, representing regrowth of the residual nevus left behind after the previous biopsy (biopsy showed a compound congenital pattern nevus in this case). Residual nevus (bottom right) without any atypical features can be seen adjacent to the biopsy scar.

C: This case clearly demonstrates a zone of pale pink scar from the previous shave biopsy. Above the scar, the darkly pigmented recurrent nevus can be seen. Beneath the scar, there is residual nevus that was left behind by the previous biopsy (arrows).

atypical melanocytes are present within the superficial dermal aspect of the scar as well. The presence of an obviously benign residual nevus component left behind after the previous biopsy is helpful when it is present. This often takes the form of residual intradermal nevus present either deep or peripheral to the zone of scar.

Robust cases of recurrent nevus can present difficulty for the pathologist when the reassuring aspects listed above are not present. In small biopsies, the epidermis or dermis beyond

the scar may not be present for evaluation. The previous biopsy specimen (or even report) may be unavailable for review to confirm that the previous biopsy was truly a nevus rather than a melanoma misdiagnosed as a nevus. It is ideal to review the previous biopsy slide (or at least the report) if possible. When there is obvious nevus present adjacent to the scar or the previous pathology findings showed nevus, then I will state that the findings are consistent with recurrent nevus. If I favor a recurrent nevus but the previous biopsy results are not available and no residual nevus is present, I generally prefer to use terminology such as "recurrent melanocytic proliferation with underlying scar" in the diagnosis line. I then add a comment suggesting recurrent nevus but adding any caveats depending on the particular scenario (such as if the skin beyond the scar is not present for evaluation in the current biopsy). However, if there are markedly atypical features that raise concern about the possibility of melanoma, I explain this in the comment and recommend re-excision.

Irritation Changes

Nevi can develop focal scar and recurrent growth pattern due to other injury to the lesion, such as excoriation by fingernails or a nick by a shaving razor. In this situation, the majority of the lesion will be obvious nevus but there will be a small superficial zone of scar, with scattered single melanocytes in the atrophic epidermis over the scar. In this scenario, I diagnose the lesion definitively as a nevus, with an added comment that the zone of scar and regrowth is suggestive of previous excoriation or trauma to the lesion.

Nevi that are scratched, rubbed, or otherwise irritated (but to an extent short of complete epidermal ulceration) may show similar junctional features as are seen in recurrent nevus, with increased single melanocytes and some pagetoid spread in the zone of irritation (see fig. 4-4). Although it is difficult to be sure that a lesion has been irritated or scratched without a good clinical history, there are some histologic clues, including parakeratosis, adjacent lichen simplex chronicus changes in the epidermis, focal papillary dermal fibrosis, and pigment incontinence. Increased single melanocytes, including focal pagetoid spread, can be seen in irritated nevi, but this is usually a focal finding in the central aspect of an otherwise conventional nevus. Occasionally, it can be very challenging to distinguish a severely irritated nevus from melanoma with certainty, even for experts.

Acral Nevus

Nevi arising on or near acral skin have several unique histologic features in their junctional component. They often have a lentiginous growth pattern, with increased single melanocytes scattered along the basal layer (fig. 4-16). They may have pagetoid spread, and sometimes it is abundant. Cytologically, the melanocytes of *acral nevus* often have larger nuclei than most nevi from nonacral sites, and they have a tendency to display central punctate nucleoli. These features are acceptable in acral nevus and by themselves are not worrisome findings. I do not call these nevi "atypical" in the report unless there are markedly atypical features outside the normal spectrum of acral nevus. I never use the term "dysplastic nevus" for lesions arising on acral skin.

Acral lentiginous melanomas usually have marked cytologic atypia as well as true confluent growth, with a solid layer of atypical melanocytes replacing much of the basal layer keratinocytes (see Acral Lentiginous Melanoma). Unfortunately, acral lentiginous melanomas sometimes have subtle findings, particularly near their periphery, which may closely mimic acral nevus. One of the most useful clues for avoiding this pitfall is to obtain clinical information regarding the size of the lesion. If it is a small lesion and the biopsy was intended to sample all or most of the lesion, this is reassuring. If a biopsy looks like acral nevus but it is only a partial biopsy of a much larger pigmented acral lesion, then caution must be used. A comment may be added to the report to explain that the findings in the biopsy resemble acral nevus, but as it is a partial biopsy of a larger pigmented lesion, the findings may not be representative of the entire lesion. Additional biopsies may be needed if there is clinical concern for melanoma. Some acral melanomas may require more than one biopsy to identify definitive histologic features of melanoma.

Some nevi on the lower leg or ankle have features similar to acral nevus, particularly the lentiginous growth pattern of single melanocytes and the enlarged nuclei with punctate nucleoli (fig. 4-17). These lesions seem to occur

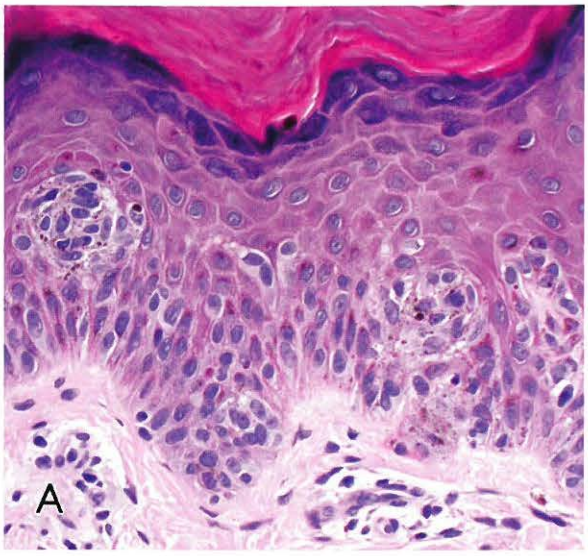
Figure 4-16

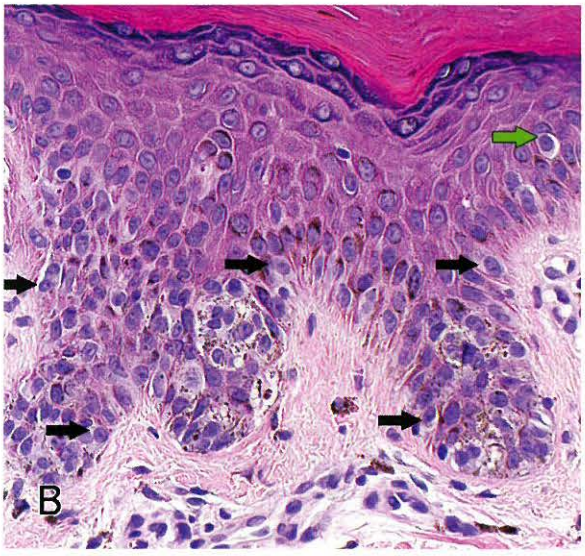
ACRAL NEVUS

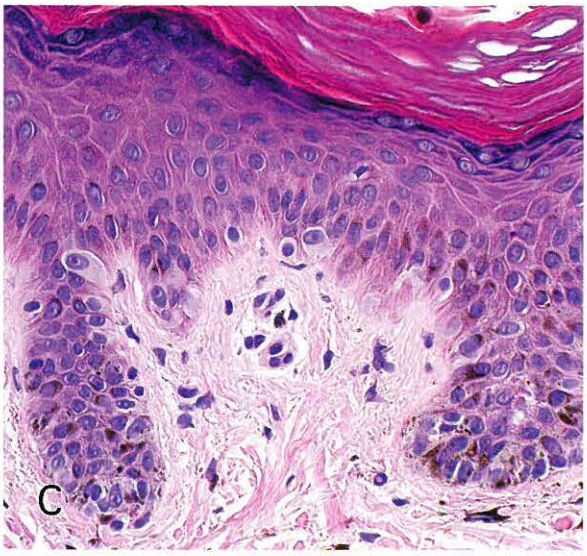
A: In addition to junctional nests, scattered single melanocytes are often present in increased numbers. Both nests and single melanocytes in this case show pagetoid spread up into the spinous layer of the epidermis.

B: Lentiginous single melanocytes grow along the basal layer (black arrows). They may have zones of increased density but are still intervened by keratinocytes; true confluence is not seen. Pagetoid spread, on the other hand, is often present and is not worrisome by itself (green arrow).

C: The melanocytes often have larger nuclei than most nevi from nonacral sites, and they have a tendency to display central punctate nucleoli. This is a normal finding for acral nevus.



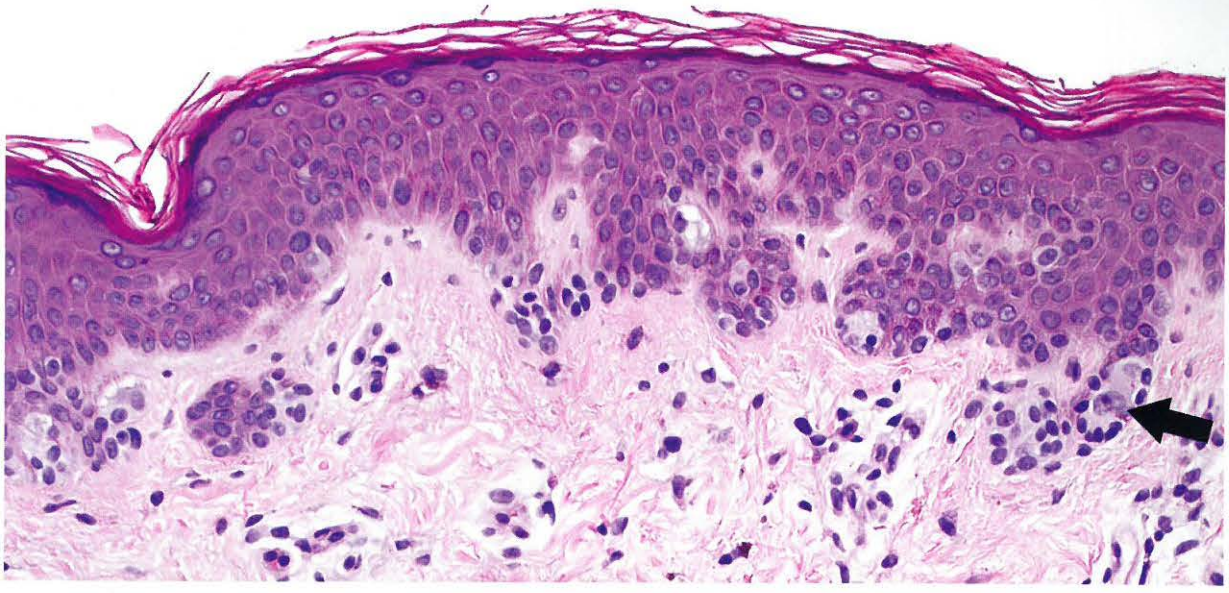




more often in women. They are small lesions, usually only several millimeters from side to side. Although they may have an abundance of single melanocytes rather than nests, they do not have confluent growth. Pagetoid spread is usually minimal. Most of these nevi lack severe cytologic atypia. Despite their "atypical" features, they display indolent behavior (10). Although these lentiginous nevi are most often described on the distal leg/ankle region, I often see nevi with similar features on the upper leg/thigh. My colleagues and I often refer to them colloquially as "leg type nevi" (this is not an official term, but it is an easy short hand way to convey the unique features). Be wary of making a diagnosis of melanoma *in situ* on the leg/ankle, particularly if the lesion is small and lacks severe cytologic atypia; it may actually be one of these unusual junctional nevi.

Unusual Features in Nevi Arising at "Special" Anatomic Sites

Nevi arising in certain anatomic sites may have unique histologic features that make them look different or even atypical. The list of these nevi of "special sites" published in the literature continues to grow. It is worthwhile to know about the more notable of these sites, since the features occasionally lead to diagnostic confusion and interpretation as either dysplastic nevus or melanoma.



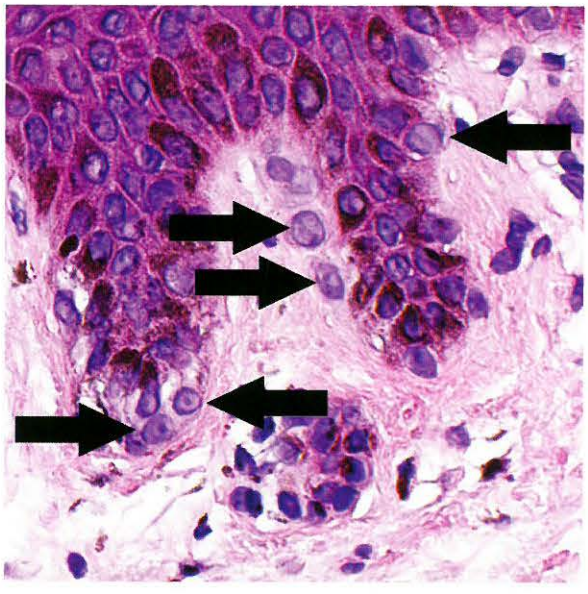


Figure 4-17

"LEG TYPE" LENTIGINOUS NEVUS

Above: Single melanocytes and small nests grow along the junction mostly down tips of elongated rete. Note the large melanocyte with prominent nucleolus (arrow).

Left: The cytologic features are often similar to those of acral nevus, with enlarged nuclei and central nucleoli (arrows).

Special sites include the genital region, the nipple/areola/breast, flexural areas, the ears, and the scalp of children (11). Nevi at these sites may show a variety of seemingly worrisome features including asymmetry, large junctional nests, some pagetoid spread, and cytologic atypia (fig. 4-18). The nuances of these lesions are outside the scope of this book. Caution is needed before making a diagnosis of melanoma or atypical nevus at one of these special sites where benign nevi are known to have unusual histologic features, particularly if the lesion has an otherwise nevoid appearance or if the patient is young.

Lentigo

A *lentigo* (plural: lentigines) is a small pigmented macule clinically. Histologically, lentigo shows elongation of the rete ridges with increased melanin pigment within basal keratinocytes (fig. 4-19). There may be increased single melanocytes scattered along the basal layer, but there is no confluence. No melanocytic nests are seen. Sometimes, the rete tips are enlarged or bent to one side. These elongated hyperpigmented rete have been compared to "hockey sticks" or "dirty puppy dog feet."

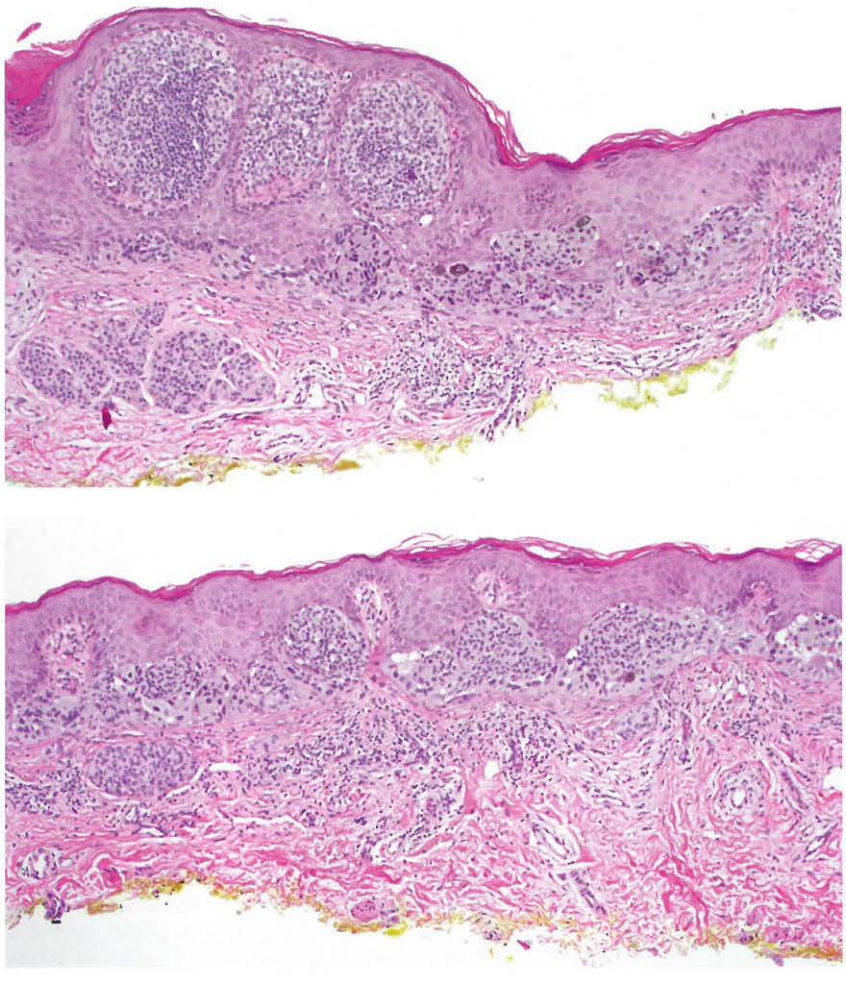


Figure 4-18

"SPECIAL SITE" NEVUS

Top: This nevus is from the vulva of a young girl. Some of the junctional nests are quite large. Some of the melanocytes have enlarged atypical nuclei and abundant grayish "dirty dishwater" cytoplasm.

Bottom: Nests of atypical melanocytes show prominent bridging between rete. The appearance can be very similar to dysplastic nevus.

Tangential sectioning of these elongated rete tips with pigmented keratinocytes can make them look like islands floating alone in the papillary dermis; do not mistake these for melanocytic nests (fig. 4-20). If there are true melanocytic nests, then do not use the term lentigo. Melanocytes arranged in nests indicate a true melanocytic proliferation (either nevus or melanoma, but not lentigo).

Lentigo simplex and solar lentigo can have a similar histologic appearance, but they are likely unrelated. Lentigo simplex may be a precursor of junctional nevus, and some true nevi ("lentiginous" nevi) have overlapping features with lentigo. Solar lentigo, on the other hand, is probably more closely related to seborrheic keratosis and is unrelated to nevus. If there is solar elastosis in the dermis, I use the term "solar lentigo". If the patient is young and lacks sun damage, I call it "lentigo simplex." If I cannot decide, I just call it "lentigo." It is benign regardless.

The term *melanotic macule* refers to a flat pigmented lesion arising on the skin/mucosa of the lips or the genital labia. It is composed of hyperpigmented basal keratinocytes without melanocytic nests, much like a lentigo (fig. 4-21). When the biopsy is from the labia and the treating physician is a gynecologist or other nondermatologist, I add a comment indicating that melanotic macule is a benign lesion, analogous to a lentigo, and that no further treatment is required.

Lentiginous Melanocytic Nevus

A nevus (either junctional or compound) displaying epidermal changes similar to those of lentigo simplex is referred to as *lentiginous melanocytic nevus*. The "lentiginous" adjective is optional and not essential for patient care, although I personally like to include this term in the pathology report. Lentiginous nevi are important because they tend to be darkly

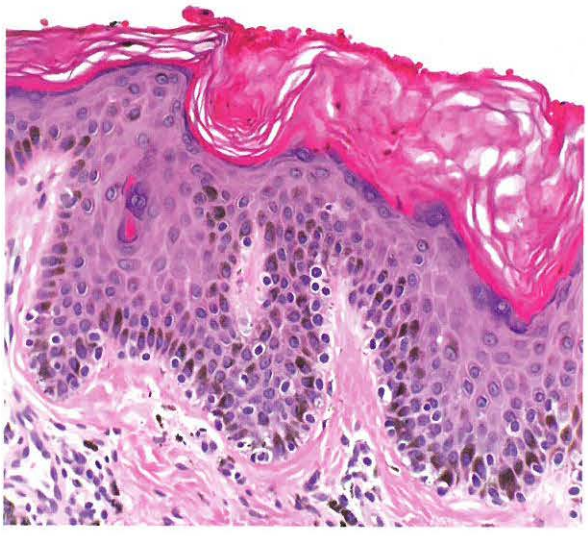


Figure 4-19

LENTIGO SIMPLEX

The rete are elongated and there is abundant cytoplasmic melanin pigment within basal keratinocytes. Scattered single melanocytes are present in increased number along the basal layer, but they are intervened by keratinocytes and show no confluence or pagetoid spread. There are no nests.

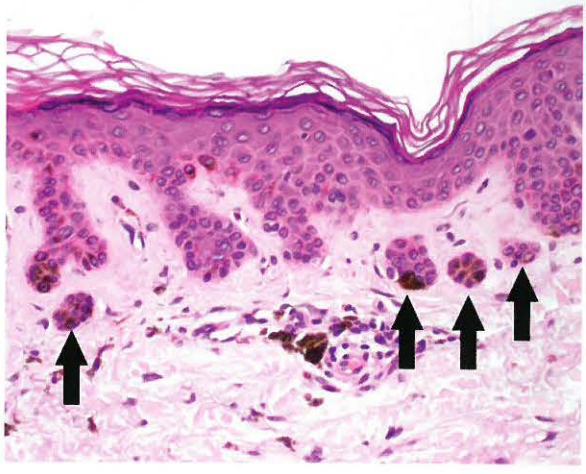


Figure 4-20

SOLAR LENTIGO

Tangential sectioning of pigmented rete tips can mimic the appearance of melanocytic nests (arrows). A closer look will show dense eosinophilic cytoplasm and intercellular spinous processes, proving that these are keratinocytes rather than melanocytes.

pigmented clinically and thus often get biopsied. Also, they have some histologic features that make them look more worrisome to the pathologist at first glance.

Histologically, they have elongated rete with hyperpigmented basal keratinocytes and scattered single melanocytes, similar to lentigo simplex, but with the additional presence of junctional melanocytic nests (fig. 4-22). The single melanocytes in lentiginous nevus are scattered along the basal layer, mostly down in the rete (i.e., they lack pagetoid spread), and the melanocytes are dispersed evenly between intervening hyperpigmented basal keratinocytes (i.e., they lack confluence). The nests in lentiginous nevus can be sparse and subtle, sometimes consisting of only a few melanocytes clustered together in a rete tip. If a lesion looks like lentigo but seems to have increased cellularity down some of the rete tips, it will often end up being a lentiginous nevus with nests showing up on deeper levels. Both lentigo simplex and lentiginous nevus are benign and may exist on a spectrum, so the distinction is not crucial for patient care.

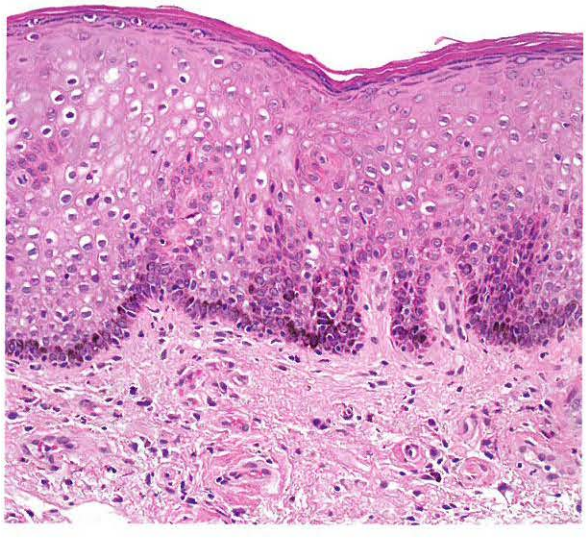


Figure 4-21

LABIAL MELANOTIC MACULE

Hyperpigmented basal keratinocytes are present along the tips and sides of elongated rete. Scattered single melanocytes (but not nests) may be seen along the basal layer intervened by pigmented keratinocytes. Melanophages are often present in the dermis/submucosa.

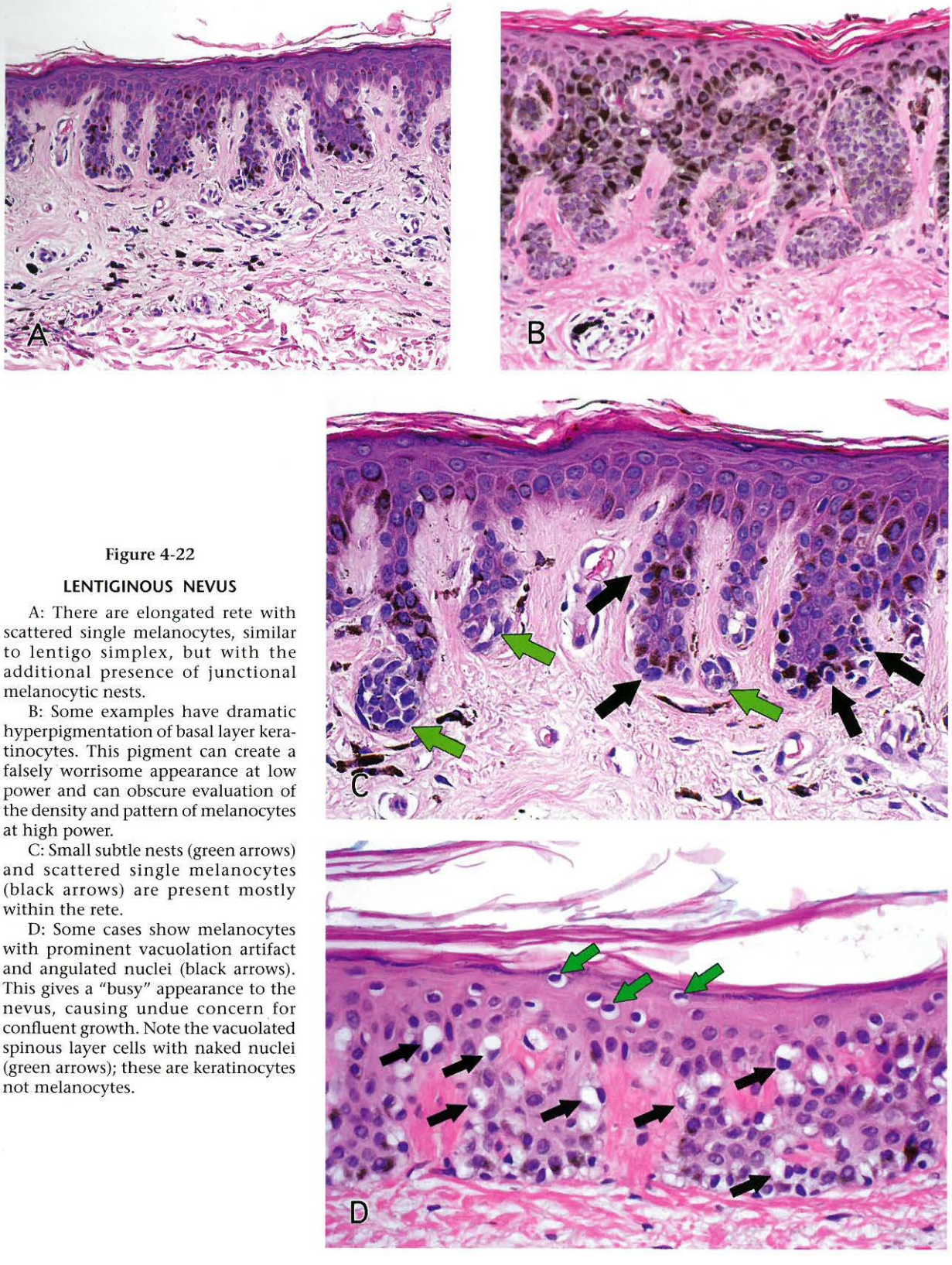


Figure 4-22

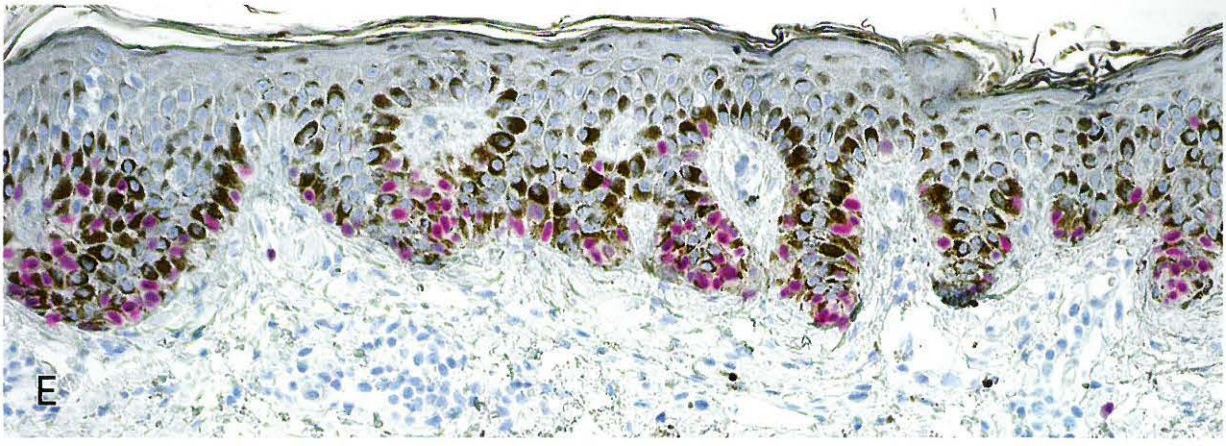
LENTIGINOUS NEVUS

A: There are elongated rete with scattered single melanocytes, similar to lentigo simplex, but with the additional presence of junctional melanocytic nests.

B: Some examples have dramatic hyperpigmentation of basal layer keratinocytes. This pigment can create a falsely worrisome appearance at low power and can obscure evaluation of the density and pattern of melanocytes at high power.

C: Small subtle nests (green arrows) and scattered single melanocytes (black arrows) are present mostly within the rete.

D: Some cases show melanocytes with prominent vacuolation artifact and angulated nuclei (black arrows). This gives a "busy" appearance to the nevus, causing undue concern for confluent growth. Note the vacuolated spinous layer cells with naked nuclei (green arrows); these are keratinocytes not melanocytes.



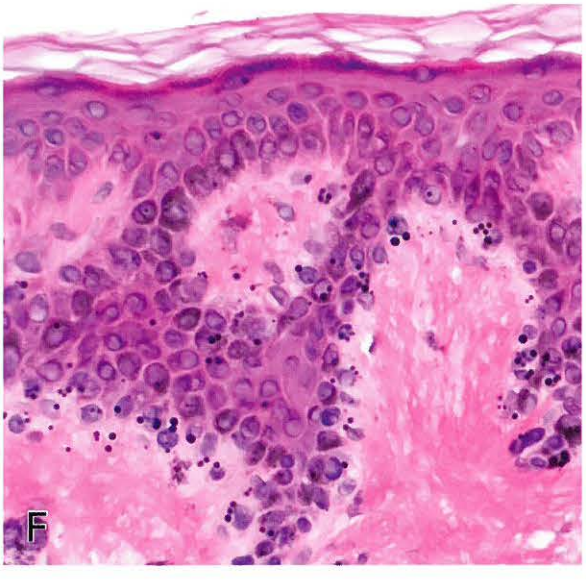


Figure 4-22, continued

E: SOX-10 (red chromogen) shows that melanocytes are located mostly down in the rete with sparing of the interrete spaces above the dermal papillae. There is no pagetoid spread. The darkly pigmented basal keratinocytes are clearly SOX-10 negative.

F: Some of the melanocytes have fine granular melanin pigment or dark punctate round globules of pigment ("macromelanosomes," demonstrated here in abundance), but in general they have far less pigment than the adjacent keratinocytes.

Lentiginous nevi are often challenging for dermatopathology beginners for a few reasons. One reason is the same reason that dermatologists often biopsy them: they may have abundant melanin pigment. At low magnification, the lesion often looks like a solid line of brown along the basal layer, giving the worrisome impression of confluent growth of pigmented melanocytes to those who are not familiar with this pattern. A closer examination shows that most of the pigment is actually in basal keratinocytes rather than melanocytes.

Like the melanocytes in normal skin and in the majority of nevi, the melanocytes in lentiginous nevus actually have pale gray or pink cytoplasm with little pigment. The abundant pigment in the basal keratinocytes can sometimes obscure the melanocytes and make it difficult to distinguish the two; SOX-10 immunostain with red chromogen can be very helpful in these cases. With practice, these lesions can often be diagnosed on H&E only since they have a distinct appearance once one is familiar with the optical illusions of lentiginous nevus.

There is one major potential pitfall here. The lentigo maligna type of melanoma, which occurs on the sun-damaged skin of the elderly (most often on the face or scalp), can be subtle in some cases and can have overlapping features with lentiginous nevus. Beware of making a diagnosis of lentiginous nevus (or any junctional nevus) when the biopsy is from the scalp of an 80-year-old man with a dermis completely filled with solar elastosis! See the Lentigo Maligna Melanoma section for more tips on how to recognize this sneaky type of melanoma.

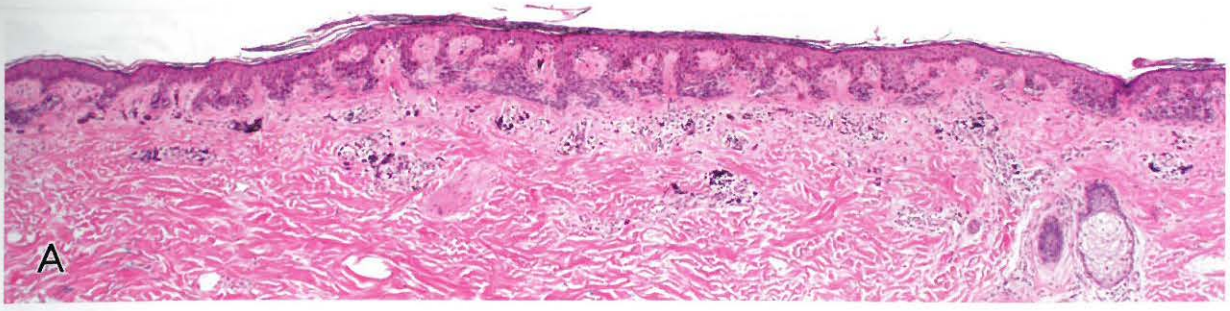


Figure 4-23

DYSPLASTIC NEVUS

A: They are usually thin broad lesions corresponding to their flat clinical appearance. The dermal component, when present, is usually in the papillary or superficial reticular dermis (not the deep dermis).

Dysplastic Nevus

This controversial and frustrating entity has been the focus of much argument and angst for many years in dermatopathology and clinical dermatology. Nomenclature (what do we call these nevi?), biologic potential (are they truly premalignant dysplasia?), significance of cytologic atypia, reproducibility of grading the degree of atypia (or if we should grade it at all), and the clinical implications of having a few versus many dysplastic nevi...these are just some of the points of vigorous debate. Some pathologists use different terms such as "Clark nevus" or "nevus with architectural disorder" to refer to these nevi. The term *dysplastic nevus* is used in this book, as it still appears to be the most widely used terminology.

The reader is encouraged to explore this controversial topic in greater depth by reading publications from various schools of thought (8,12–17).

Dysplastic nevus syndrome is a syndrome, either familial or sporadic, in which patients develop multiple clinically atypical nevi and show increased risk for developing melanoma. Solitary lesions in nonsyndromic patients may also have these histologic features (17). The term dysplastic nevus has been applied to all of these lesions, regardless of whether the patient has the syndrome or not.

Clinically, dysplastic nevi tend to be large pigmented macules with irregular borders, asymmetry, and color variation. These atypical clinical features may overlap with the features of melanoma, which prompts biopsy.

Histologically, dysplastic nevi are junctional or compound nevi that display a combination of cytologic atypia and certain architectural features, including shouldering (see below), lentiginous elongated rete, bridging of rete nests, and lamellar fibroplasia around rete (fig. 4-23). They are usually thin broad lesions corresponding to their flat clinical appearance. The dermal component, when present, is usually in the papillary or superficial reticular dermis; the deep dermis is not usually involved.

Compound dysplastic nevi often display "shouldering" in which the junctional component of the nevus extends to the periphery beyond the underlying dermal component of the nevus. Spread your arms out to both sides. If your chest represents the intradermal component of the nevus, then your shoulders and upper arms represent the junctional component (the "shoulders" of the lesion). Increased single melanocytes and nests reside mostly within elongated rete, either along the sides or at the tips, similar to the pattern seen in lentiginous nevi. Some are seen in the inter-rete space above the dermal papillae, but if there are many single melanocytes present between rete, this may represent confluent growth and be indicative of melanoma.

Nests of melanocytes within rete tips "bridge" across and connect to adjacent rete nests. Sometimes, bridging of melanocytic nests spans across multiple adjacent rete; do not confuse this with true confluent growth. The key is recognizing that the inter-rete spaces above the papillary dermal tips are mostly uninvolved.

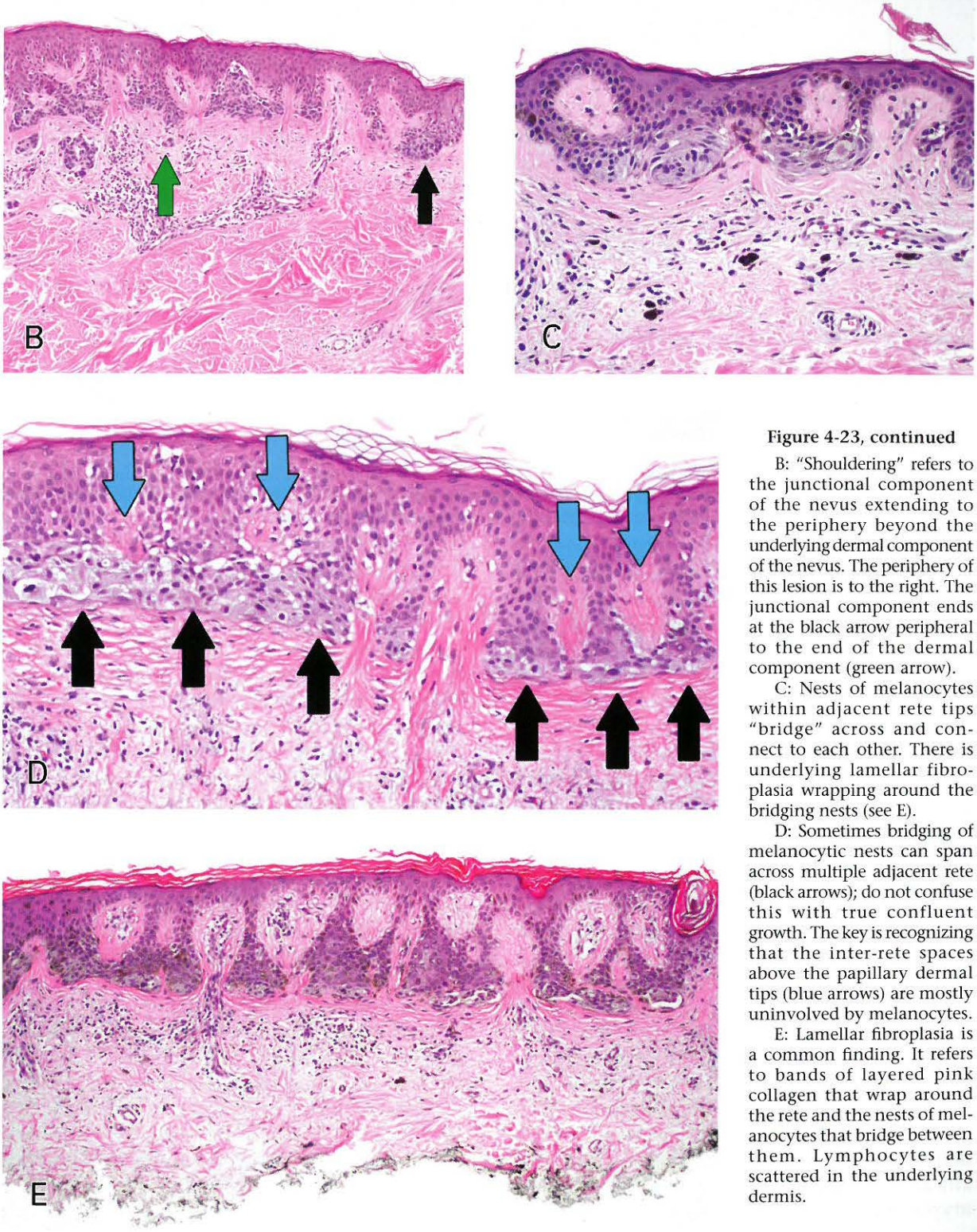


Figure 4-23, continued

B: "Shouldering" refers to the junctional component of the nevus extending to the periphery beyond the underlying dermal component of the nevus. The periphery of this lesion is to the right. The junctional component ends at the black arrow peripheral to the end of the dermal component (green arrow).

C: Nests of melanocytes within adjacent rete tips "bridge" across and connect to each other. There is underlying lamellar fibroplasia wrapping around the bridging nests (see E).

D: Sometimes bridging of melanocytic nests can span across multiple adjacent rete (black arrows); do not confuse this with true confluent growth. The key is recognizing that the inter-rete spaces above the papillary dermal tips (blue arrows) are mostly uninvolved by melanocytes.

E: Lamellar fibroplasia is a common finding. It refers to bands of layered pink collagen that wrap around the rete and the nests of melanocytes that bridge between them. Lymphocytes are scattered in the underlying dermis.

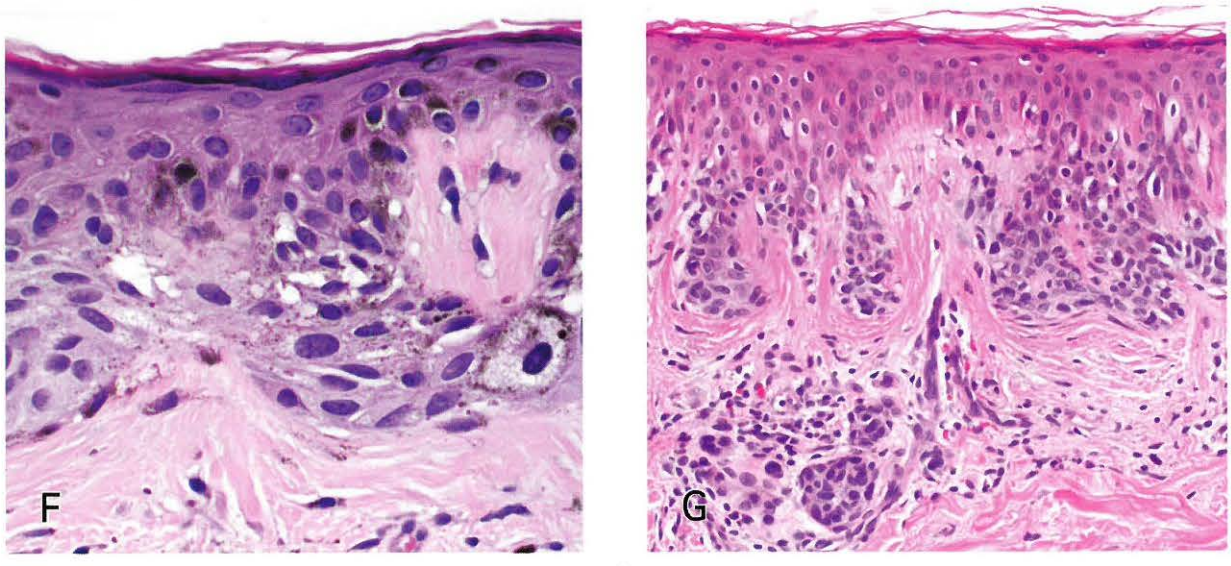


Figure 4-23, continued

F: The melanocytes display cytologic atypia. The nuclei in this case are 2-3 times larger than the nuclei of spinous layer keratinocytes. The melanocytes often have abundant grayish cytoplasm with fine dusty melanin pigment; the color has been likened to "dirty dishwater."

G: The intradermal component usually has normal maturation and bland nevoid melanocytes with minimal atypia. Superficial dermal nests may have some cytologic atypia similar to that in the overlying junctional component (as in this case). However, prominent or abundant dermal atypia should raise concern for melanoma.

The body often creates a "host response" to the dysplastic nevus, consisting of bands of layered pink collagen wrapping around the rete (lamellar fibroplasia) as well as variable amounts of dermal lymphocytic infiltrate and associated dermal melanophages. The individual architectural features by themselves do not make a dysplastic nevus, as none of the features alone is entirely specific. Congenital nevi can have shouldering and even bridging, but unlike most dysplastic nevi, they usually extend deeply into the reticular dermis. For this reason, I do not often apply the diagnosis of dysplastic nevus for a nevus that extends into the deep reticular dermis. Lamellar fibroplasia, pigment incontinence, and inflammation can be seen in irritated nevi. Elongated rete are present in lentiginous nevi. The diagnosis of dysplastic nevus is based on the presence of multiple dysplastic architectural features along with cytologic atypia taken together as a constellation of features.

The significance of cytologic atypia in dysplastic nevus is one of the key issues of the debate surrounding this entity. Most (but not all) authors agree that at least some cytologic atypia must be present to make a diagnosis of dysplastic nevus (17). Detailed criteria for grading cytologic atypia have been published (1). Grading is often performed in a three-tier fashion, classified into mild, moderate, severe (or some variation thereof). Some have argued that if we grade dysplastic nevi at all, it should be two-tier grading into high- versus low-grade categories (14). Some studies have found that a higher grade of atypia is associated with higher overall risk of developing melanoma (3,18). The applicability of these studies to individual patients is less clear, however, in light of the interobserver variability between dermatopathologists of grading cytologic atypia (2,13). Some dermatopathologists reject the use of the term "dysplastic nevus" altogether, arguing that they are not premalignant dysplasia and that this terminology only adds confusion (13,15).

I will briefly explain my still-evolving personal views on this topic and the way I approach these lesions. Most of my mentors used the term "dysplastic nevus" and most of them provided a grade for the degree of dysplasia/atypia. I have continued to use this system in my own practice (recognizing the many limitations) as the dermatologists I work with are familiar with this

terminology and know how to manage patients accordingly. In my opinion, distinguishing mild or even moderate dysplastic nevus from a conventional nevus is probably of little importance for the patient in most cases; studies have shown the rate of recurrence in these lesions is very low, even when incompletely excised (19).

Severe dysplastic nevus is more problematic, because the histologic features closely overlap those of melanoma. Distinguishing nevus from melanoma is far more important than deciding what grade to give a dysplastic nevus. I have not observed melanoma arising from dysplastic nevus any more often than I have seen it arising from conventional or congenital pattern nevus (much less often, in fact) (13). Even though I continue to use the term dysplastic nevus, I remain unconvinced that the majority of dysplastic nevi truly represent premalignant dysplasia (i.e., that they are more likely to evolve into melanoma eventually if left alone than any other nevus would be). Massi and LeBoit (8) eloquently summarize the issue: "Our belief is that if one were to posit a spectrum from 0 to 100, with zero being a wholly banal nevus and 100 an unequivocal melanoma, most lesions said to be dysplastic nevi would be closer to 0 than 100."

The treatment of dysplastic nevi varies among dermatologists (20). Most do not re-excise mild dysplastic nevi but often do re-excise or re-shave moderate dysplastic nevi. Severe dysplastic nevi are usually excised with a margin of normal skin around the biopsy site, similar to the treatment used for melanoma *in situ*. Re-excision of dysplastic nevus usually shows no residual lesion in the excision specimen (13). If there is residual dysplastic nevus, it is usually focal. If a re-excision shows a large/broad amount of residual melanocytic lesion, it may be worthwhile to review the original biopsy slides to ensure that the diagnosis was accurate.

Spitz Nevus

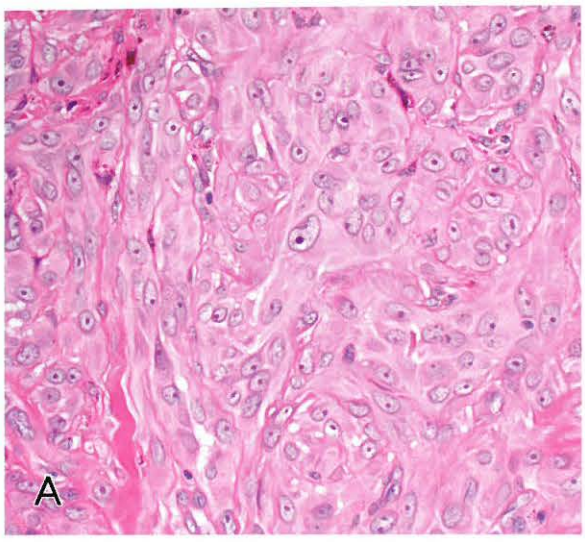
Spindle and epithelioid cell nevus (*Spitz nevus*) is yet another area of controversy in melanocytic dermatopathology. These pink, red, or skin colored papules or nodules arise most often in children or young adults. They are often mistaken clinically for hemangioma since they often lack melanin pigment. Sophie Spitz first described these lesions as "melanomas of childhood" in 1948 in light of their atypical histologic features compared to conventional nevi. Over time, it became clear that these were actually unusual benign nevi, not melanomas, in light of their indolent behavior (8,21). The same histologic features that made Dr. Spitz diagnose these lesions as melanoma are the same features that can lead to overdiagnosis of melanoma today to those who are not familiar with the unique histologic findings that are normal for Spitz nevus.

Spitz nevi may be junctional, compound, or intradermal. They are composed of large spindled and epithelioid melanocytes with distinct cytologic features that are different than the melanocytes of most other nevi (fig. 4-24). In the junction, they are arranged into nests that are often large and separated from the adjacent epidermis by clefting artifact. The epidermis around the junctional nests is often acanthotic.

At low power, Spitz nevi are symmetric and circumscribed. They "start and stop in a nest" abruptly at both peripheral edges of the lesion rather than trickling off as single cells into the adjacent epidermis. Pagetoid spread of single melanocytes or entire nests into the upper aspect of the epidermis, usually in the center of the lesion, is a common finding in Spitz nevus; by itself, pagetoid spread is not evidence of malignancy in this context. Kamino bodies (globules of pink basement membrane) are present in some Spitz nevi and are useful diagnostically when present.

Compound or intradermal Spitz nevi may extend deeply into the reticular dermis. The dermal component shows similar cytologic features to the junctional component. As with other nevi, there is usually maturation with depth. Occasional dermal mitoses may be seen.

Some melanomas have spitzoid features, albeit with the addition of marked cytologic atypia and other worrisome features (fig. 4-25). The distinction between benign Spitz nevus and spitzoid melanoma can be challenging, and some spitzoid lesions are difficult to categorize definitively as benign Spitz nevus or malignant spitzoid melanoma (22). These ambiguous gray zone spitzoid lesions have been referred to by a variety of terms. I use "atypical spitzoid neoplasm" with a comment stating whether I favor spitzoid melanoma or Spitz nevus, listing the difficulties of the case.



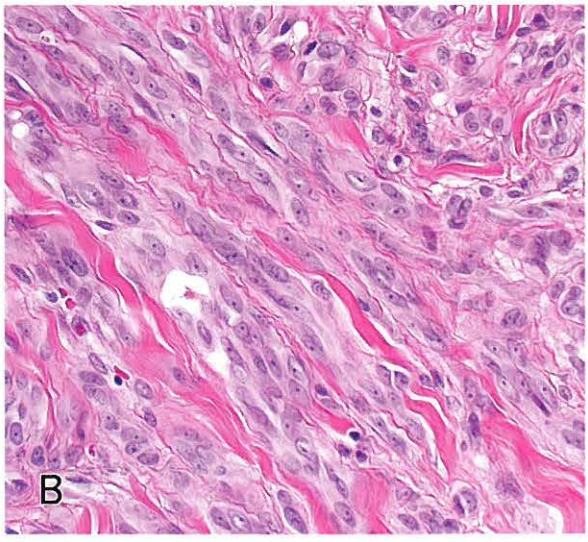


Figure 4-24

SPITZ NEVUS

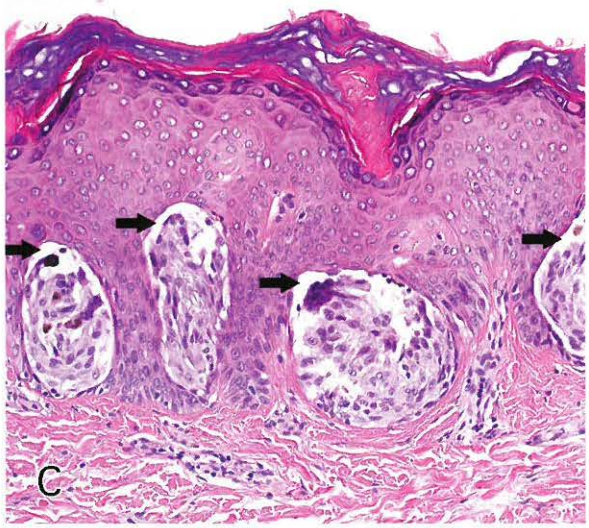
A: Melanocytes have abundant pale pink to gray cytoplasm and have large round to oval nuclei with fine chromatin and prominent central nucleoli. It is important to be able to recognize these "spitzoid" cytologic features.

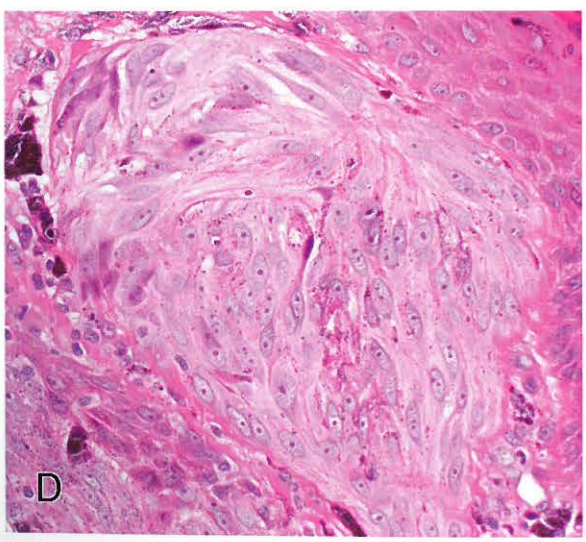
B: Spitzoid melanocytes may also be elongated with plump spindled nuclei.

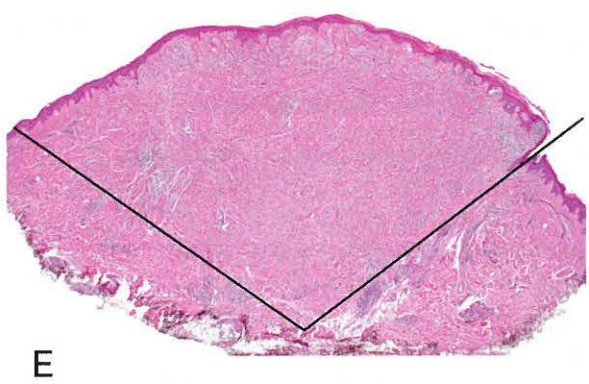
C: The junctional nests are usually large. There is often clefting artifact (arrows) between the periphery of the nest and the adjacent acanthotic epidermis.

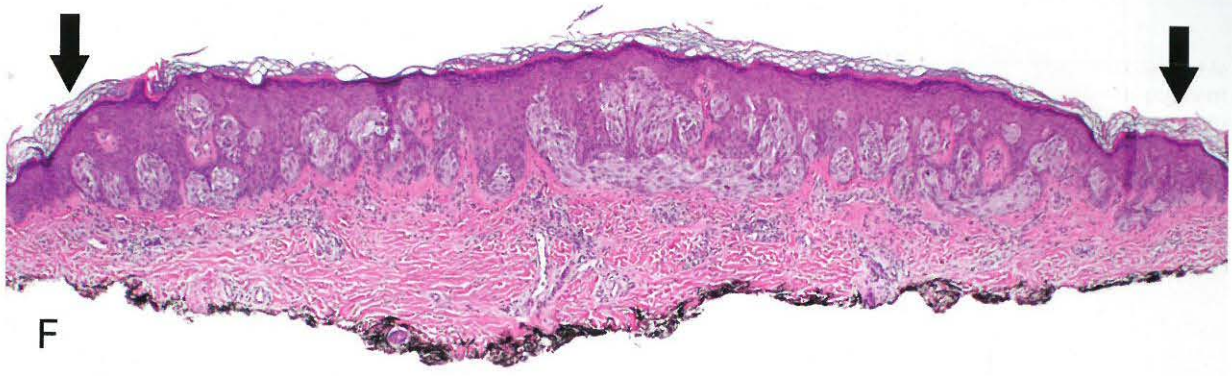
D: When the nests are composed of vertically oriented spindled spitzoid melanocytes, the appearance has been described as having a "raining down" pattern or as resembling "bunches of bananas" (or "bananas and chocolate" when the melanocytes are pigmented) (8).

E: Compound and intradermal Spitz nevi may extend deeply into the reticular dermis. They often have a wedge or upside-down pyramid shape (i.e., they are wider at the top and narrower at the bottom).









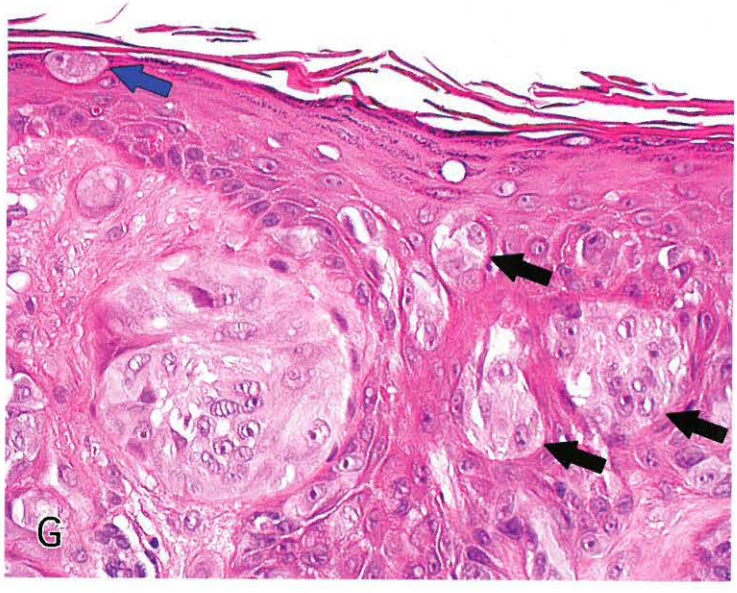


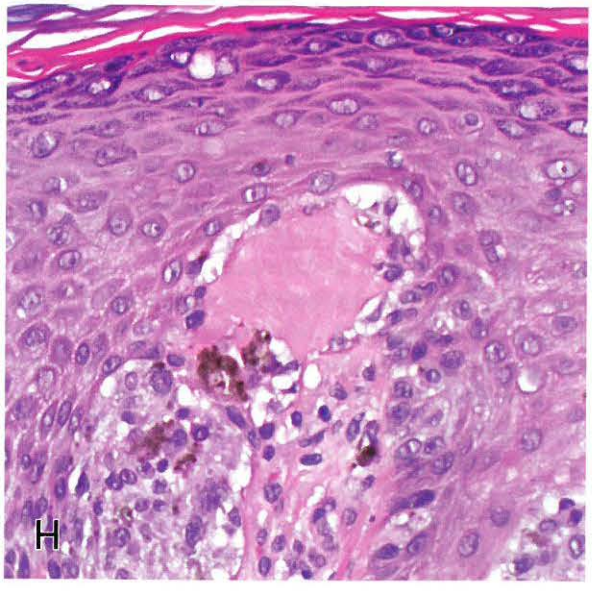
Figure 4-24, continued

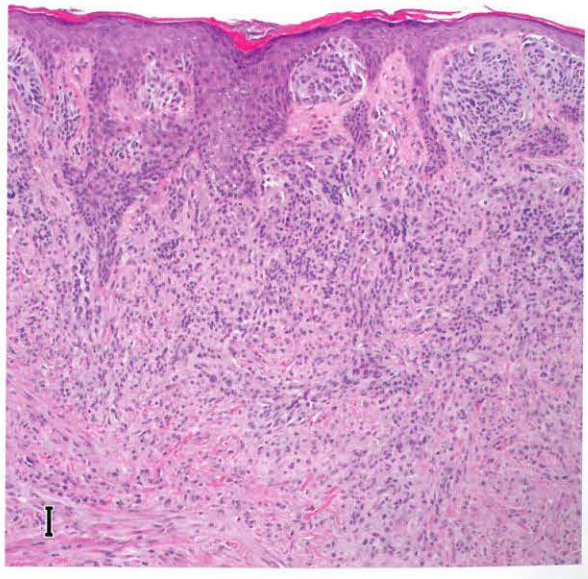
F: Like Reed nevus, Spitz nevus is circumscribed at low power, ending abruptly in nests at the periphery on both sides of the lesion (arrows).

G: Pagetoid spread may be seen, either as entire nests (black arrows) or as single melanocytes (blue arrow) scattering upward into the epidermis. This by itself is not a worrisome feature, particularly in the center of the lesion. However, use caution if significant pagetoid spread is seen at the peripheral edges of the lesion.

H: Kamino bodies are pink globules of basement membrane material (collagen type IV) found within the epidermis or at the dermal-epidermal junction in a subset of Spitz nevi.

I: When Spitz nevi involve the dermis, they usually show normal maturation. The melanocytes tend to intermingle between reticular dermal collagen bundles, get smaller in size, and transition from larger nests into smaller nests and single cells with increasing dermal depth.





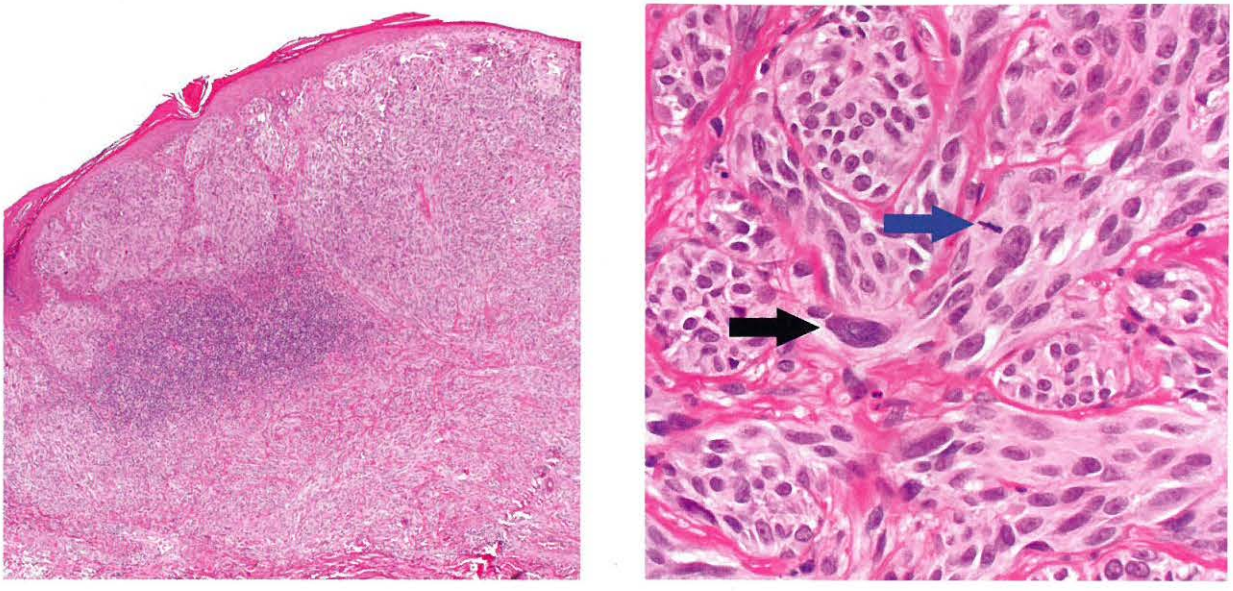


Figure 4-25

SPITZOID MELANOMA

Left: There is sheet-like growth superficially that pushes into the deep dermis. This is an abnormal maturation pattern. Right: The melanocytes have spitzoid cytologic features, but there is severe nuclear atypia (black arrow). Mitoses are increased in the dermal melanocytes (blue arrow).

Histologic features that are worrisome in a spitzoid lesion include many mitoses (approximately 5/mm2 on average in one study), mitoses close to the deep border of the lesion, severe nuclear atypia, ulceration, and asymmetry. These features have been correlated with aggressive behavior in one study (23).

As with other ambiguous melanocytic lesions, this is a controversial and challenging area of dermatopathology and is outside the scope of this book. Spitzoid lesions with the atypical features listed above, other nonclassic histologic findings, or a nonclassic clinical scenario (e.g., arising in an older adult) should be approached with great caution. These difficult spitzoid cases are probably best left to the experts given the difficulties and the high stakes for everyone involved.

Blue Nevus

Blue nevus is so named for the blue-gray appearance it displays clinically. The bluish color is due to the Tyndall effect, in which scattering of light causes the brown dermal melanin to have a bluish appearance (24). They are sometimes very darkly pigmented clinically, causing concern for melanoma.

Histologically, this same abundant pigment makes them easy to recognize: there is a dense accumulation of dark brown melanin in the dermis (fig. 4-26). The melanin is present within spindled dermal melanocytes as well as intervening melanophages. There is usually a background of sclerotic collagen, which may be quite prominent (*sclerotic blue nevus*).

Blue nevus is a purely intradermal lesion unless it is combined with some other type of nevus (see Combined Nevus). When pigment is sparse or absent, the term *hypopigmented blue nevus* may be used; these often have a similar appearance to dermatofibroma on H&E, with peripheral entrapment of reticular dermal collagen fibers (fig. 4-27). Most hypopigmented blue nevi still have focal melanin deposits in the spindle cells, whereas dermatofibromas usually have hemosiderin deposits, not melanin. Blue nevi do not usually induce epidermal hyperplasia whereas dermatofibromas do. Immunostains can distinguish between them, but since both lesions are benign and treated similarly, this is not usually needed. Cytologic atypia is minimal and mitoses are infrequent in blue nevus; if there is significant atypia or mitotic activity, consider the rare

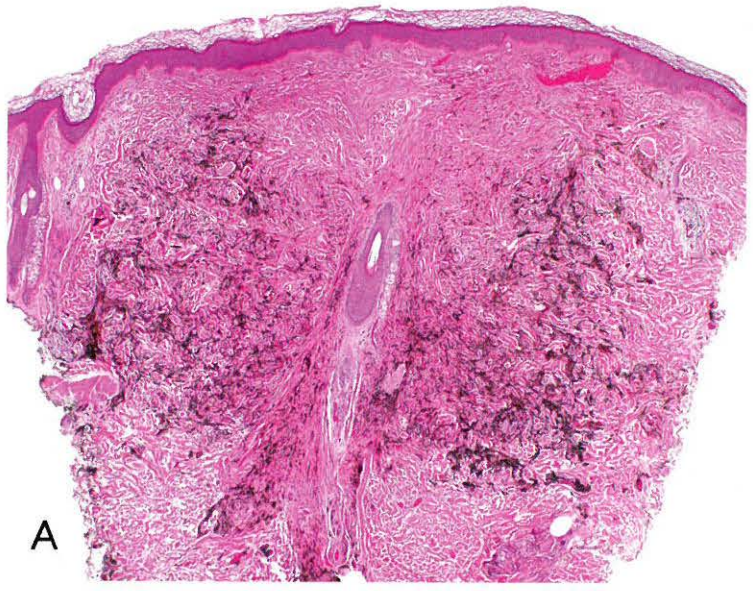


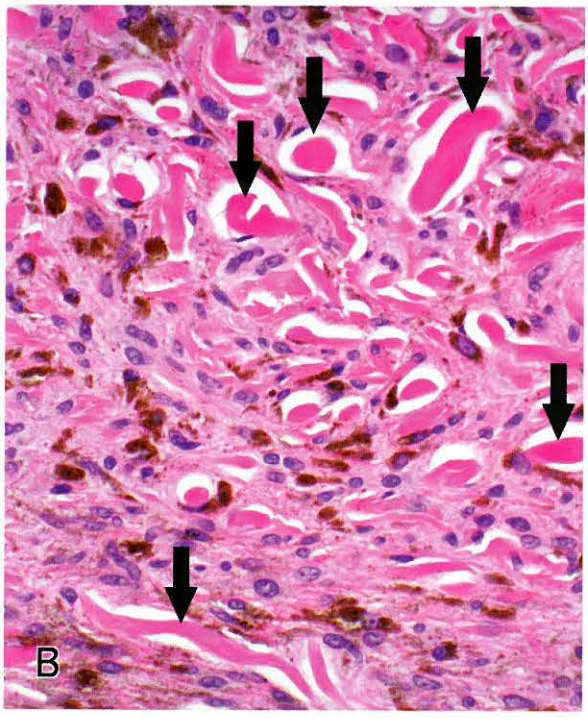
Figure 4-26

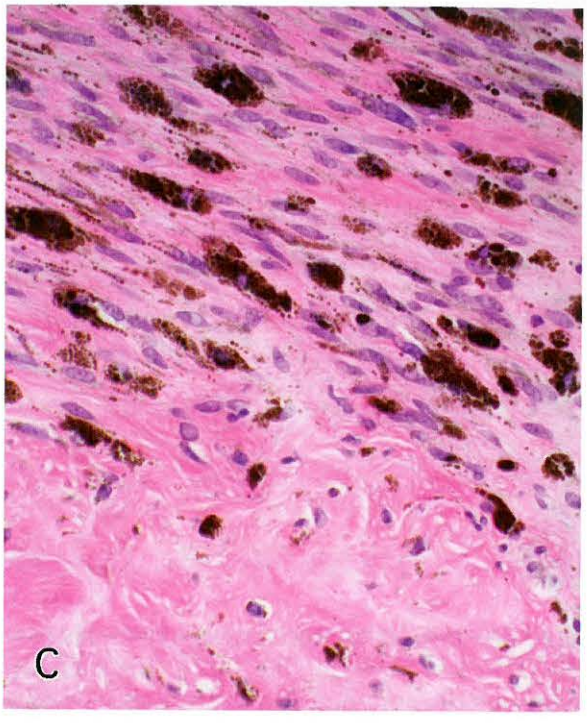
BLUE NEVUS

A: These nevi are immediately recognizable by their abundant brown melanin pigment in the dermis. They may track down into the reticular dermis around hair follicles producing a vague wedge shape. Some examples are much smaller than this one and only involve the superficial dermis.

B: Melanin is present within spindled dermal melanocytes as well as intervening melanophages. Entrapment of reticular dermal collagen bundles is a common feature (arrows).

C: Elongated spindled melanocytes with variable pigment intermingled with large heavily pigmented melanophages comprise blue nevus. Background sclerosis (bottom) is a common feature of blue nevi. When it is very prominent, the term "sclerotic blue nevus" may be used.





possibilities of melanoma arising from blue nevus or melanoma with blue nevus-like features (and then consider getting expert consultation, as these can be quite challenging to diagnose).

Spindled melanophages in the dermis due to pigment incontinence (from postinflammatory pigmentary alteration or any source) can sometimes resemble blue nevus but the clinical scenario is usually different, the pigmented cells are sparse, and there is minimal background sclerotic collagen. A melanocytic immunostain, like SOX-10 or MART-1, can easily distinguish pigment incontinence from blue nevus.

Cellular Blue Nevus

Cellular blue nevus is an uncommon variant usually seen in children or young adults, often on the buttock or sacral region. They are intradermal le-

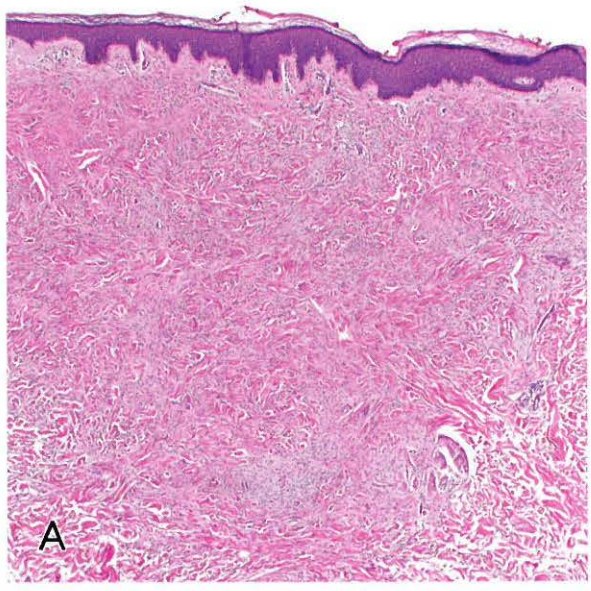
Figure 4-27

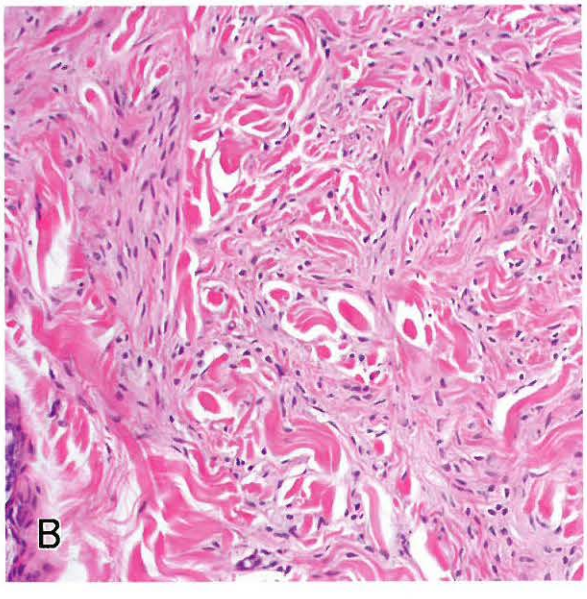
HYPOPIGMENTED BLUE NEVUS

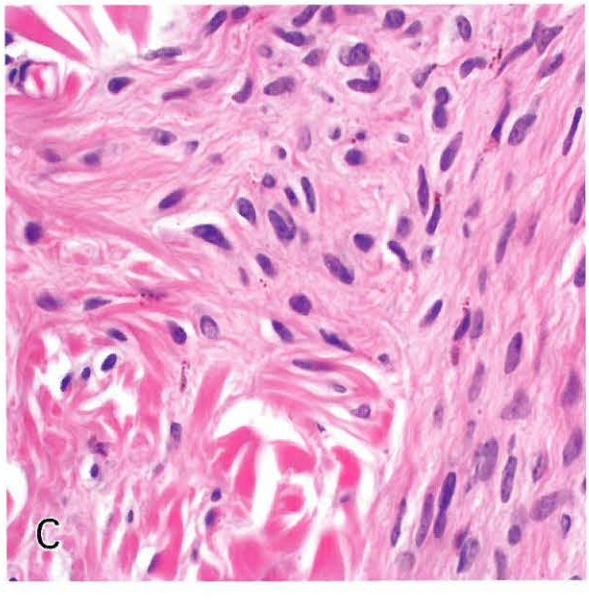
A: Bland spindled melanocytes fill the dermis. Note the background sclerosis and entrapment of collagen bundles. No pigment is appreciated at low power.

B: When melanin pigment is lacking, the bland spindled melanocytes entrapping collagen can closely simulate the appearance of dermatofibroma. The cells of blue nevus are usually smaller and more uniform in shape than those of dermatofibroma, but this distinction can be subtle.

C: Even though the lesion may look completely devoid of pigment at low power, most hypopigmented blue nevi have at least focal melanin present at high power. Dermatofibromas often have hemosiderin pigment whereas blue nevi have melanin; this is a useful clue for distinguishing between the two entities.







sions and are usually larger than conventional blue nevi. The low-power architecture is characteristic, with one or more nodular protrusions of tumor extending down into the deep dermis or subcutis (so called "dumbbell pattern") (fig. 4-28). These deep bulging protrusions of tumor tend to be more cellular than the more superficial aspect of the tumor; this nevus is one of the exceptions to the "rules" of normal maturation.

The cellular portion is usually composed of uniform spindle cells with larger nuclei than conventional blue nevus. Round cell areas may be present. The cells are arranged in sheets, packets/nests, or fascicles. There may be background sclerosis or zones of edema. Occasional mitoses are seen, even in the deep aspect of the tumor. Although the nuclei are large, they usually have small or absent nucleoli and lack pleomorphism. There may be abundant melanin pigment, although often the pigment is patchy or minimal to absent.

Large nucleoli, severe atypia, or many mitoses may suggest *clear cell sarcoma* (formerly called melanoma of soft parts) (figs 4-29). This rare sarcoma often arises in the tendons/aponeuroses on the distal extremities of young adults. It

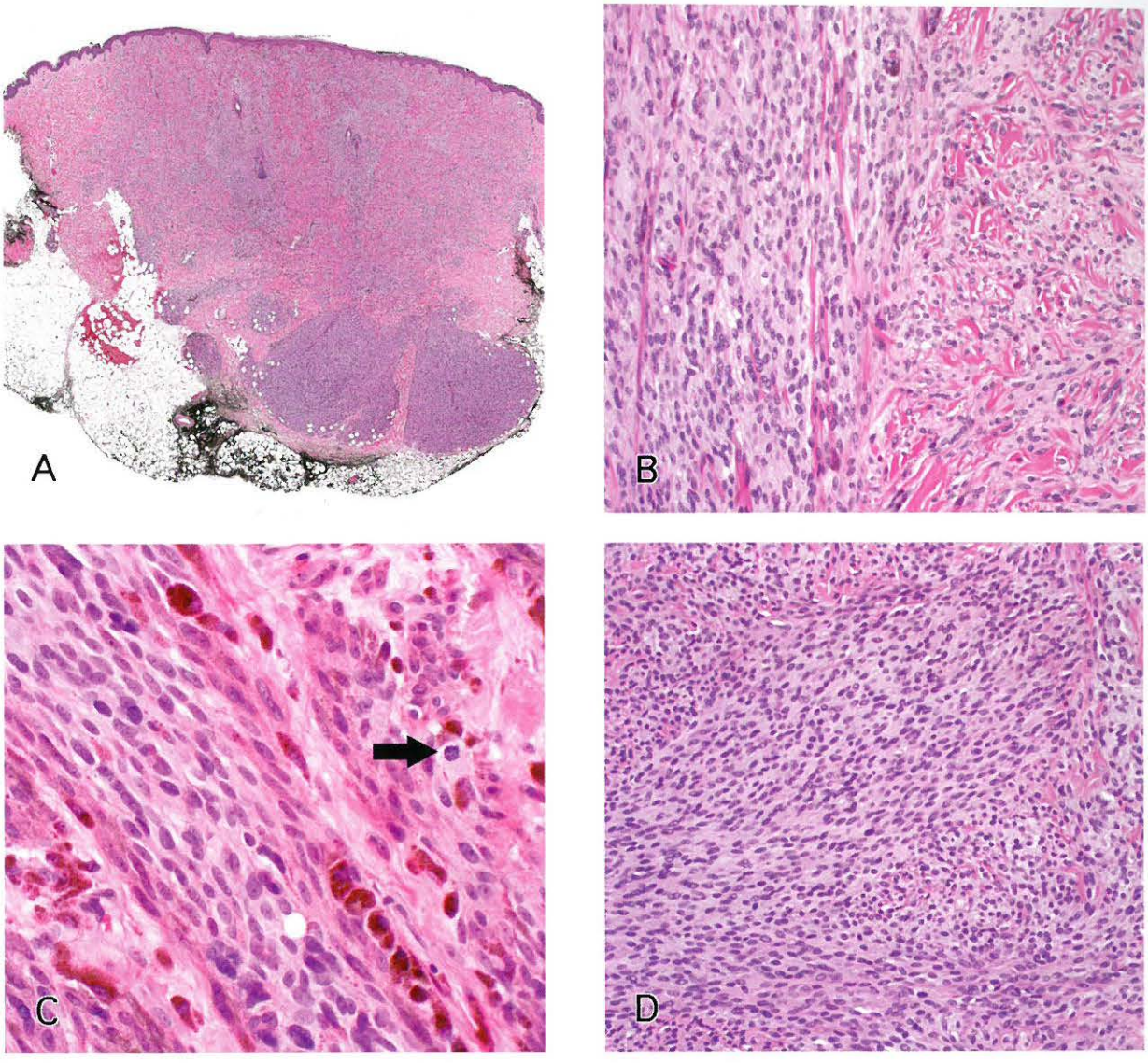


Figure 4-28

CELLULAR BLUE NEVUS

A: The low-power architecture is characteristic, with one or more nodular protrusions of tumor extending down from the dermis into the deep dermis or subcutis ("dumbbell pattern"). The deep bulging protrusions tend to be more cellular than the superficial aspect of the tumor; this is one of the exceptions to the "rules" of normal maturation.

B: Cellular blue nevus (left) often has adjacent zones of conventional blue nevus (right).

C: Pigmented spindled melanocytes in the cellular zones are often arranged in elongated nests or fascicles. Multinucleated melanocytes may be present. Occasional mitoses are often present (arrow).

D: Another example of fascicular growth. Cellular blue nevi are often hypopigmented.

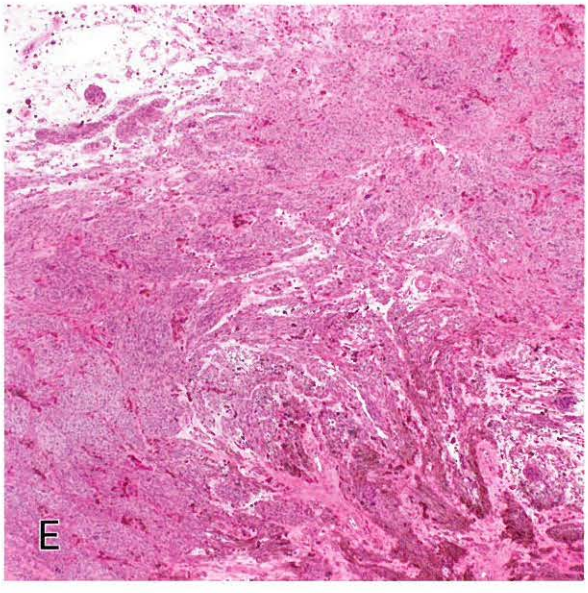
stains with melanocytic markers and has essentially identical immunophenotype to melanoma or cellular blue nevus (with the exception of CD117/CKIT, which is often expressed in nevi and melanoma but only rarely in clear cell sarcoma). The diagnosis can be made by a combination of histologic features and fluorescence *in situ* hybridization (FISH) analysis for *EWSR1* gene fusion, which is present in clear cell sarcoma but not in melanocytic neoplasms. Marked atypia or mitotic activity can also suggest blue nevus-like melanoma or melanoma arising from blue nevus.

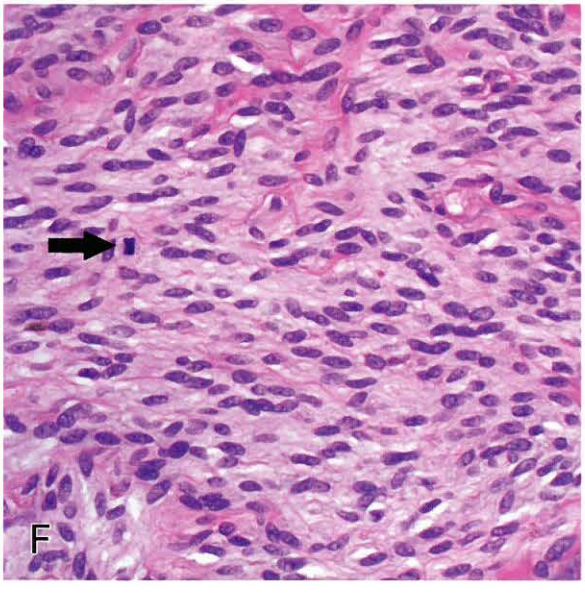
Figure 4-28, continued

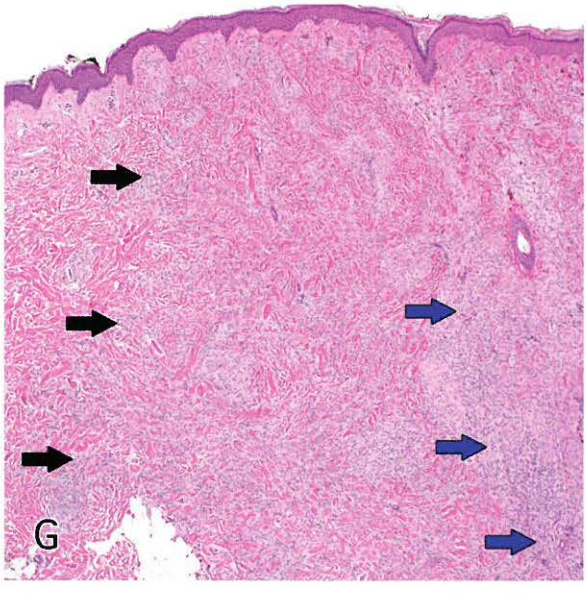
E: This example is highly pigmented. The fascicles and nests of melanocytes are intervened by abundant background edema.

F: Occasional mitoses may be seen, even in the deep aspect of the tumor (arrow). The nuclei are uniform, oval to spindled, and usually have small or absent nucleoli. Large nucleoli, marked nuclear atypia, or abundant mitoses should raise the possibilities of clear cell sarcoma or blue-nevus-like melanoma.

G: Areas of conventional blue nevus (black arrows) are often present in the superficial dermis toward the periphery; cellular zones tend to be in the central/deep aspect of the lesion (blue arrows). This is a very helpful clue to the diagnosis. Note the collagen entrapment. This is a closer view of the upper left portion of the lesion seen in A.







Deep Penetrating Nevus

Like cellular blue nevus, this uncommon nevus subtype is characterized by extension into the deep dermis (fig. 4-30). Unlike the bulging protruding nodularity seen at the base of cellular blue nevus, however, *deep penetrating nevi* typically have a wedge (upside down pyramid/triangle) shape. They often track along hair follicles into the deep dermis (blue nevi and cellular blue nevi may do this also). They tend to be smaller than cellular blue nevus in general, and they lack the zones of conventional blue nevus at the periphery that are a common finding in cellular blue nevus. They also have different cytologic features than cellular blue nevus: larger cells with abundant cytoplasm.

Data have suggested deep penetrating nevus may be related to Spitz nevus (25), which might explain the cytologic features. Like Spitz nevus, larger nuclei are acceptable, and occasional mitoses may be present in the dermis. Deep penetrating nevi are centered in the dermis, but junctional nests are sometimes present.

Some authors use the term "deep penetrating nevus" to refer to lesions that I would call

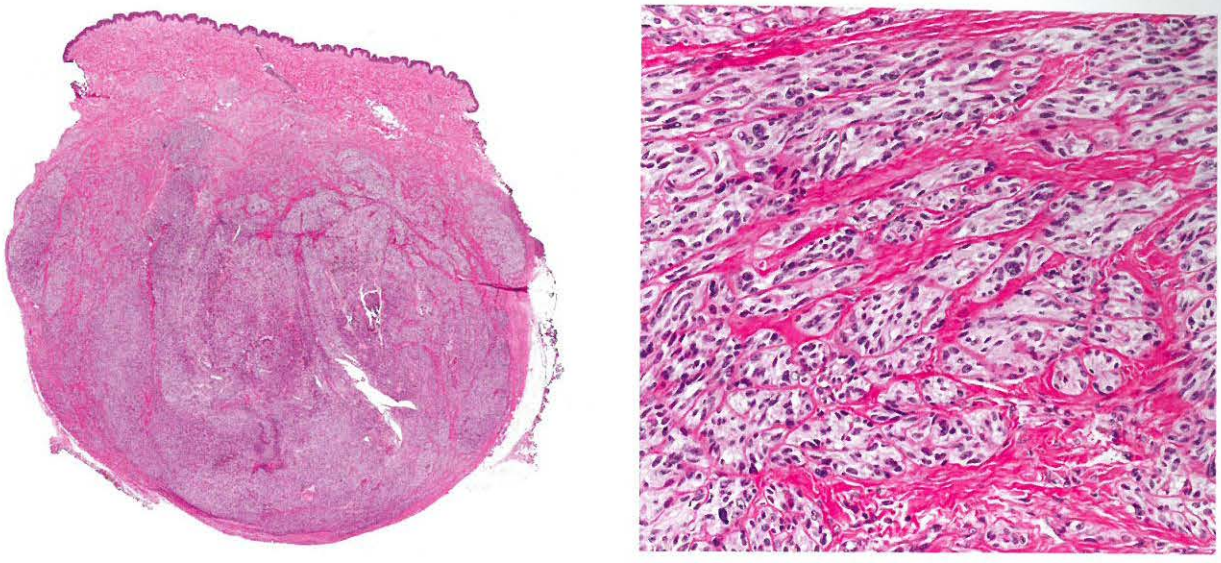


Figure 4-29

CLEAR CELL SARCOMA

Left: Most cases are deep nodules arising in the tendons/aponeuroses on the distal extremities of young adults. However, they can sometimes be centered in the dermis or subcutis, where they can mimic cellular blue nevus (or metastatic melanoma).

Right: Plump spindle cells with clear or pale cytoplasm are arranged in elongated nests/fascicles intervened by dense fibrous tissue, a classic pattern. Multinucleated tumor cells may be present. Prominent nucleoli are a characteristic finding in both spindled and multinucleated tumor cells. Melanin pigment may even be present in some cases.

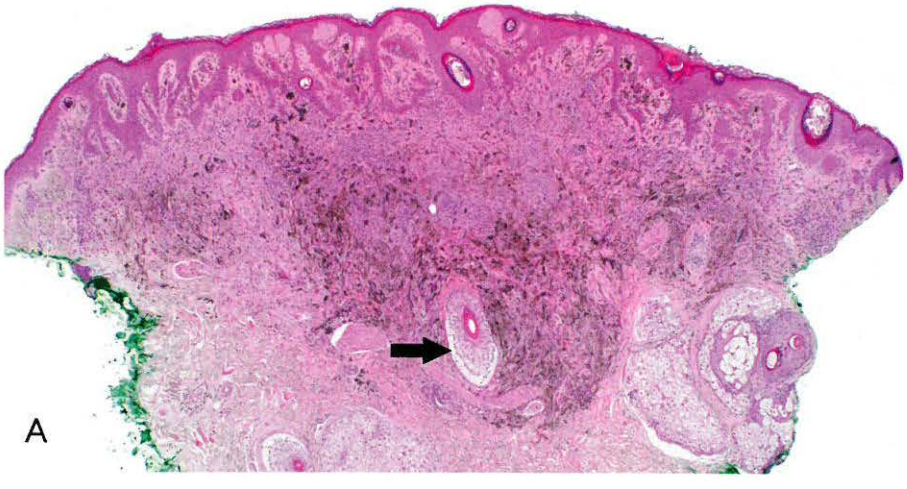


Figure 4-30

DEEP PENETRATING NEVUS

A: These are wider in the superficial dermis and get narrower with increasing depth into the dermis, creating a wedge/upside-down pyramid shape. They also have a tendency to track along hair follicles (arrow) as they proceed into the deep dermis.

"cellular blue nevus" (and vice versa). Furthermore, some cases have overlapping features. Deep penetrating nevus and cellular blue nevus are both benign nevi with unusual features that could cause them to be overdiagnosed as malignant to the unaware pathologist. Avoiding that pitfall is much more important than which nomenclature is used.

Pigmented Spindle Cell Nevus (of Reed)

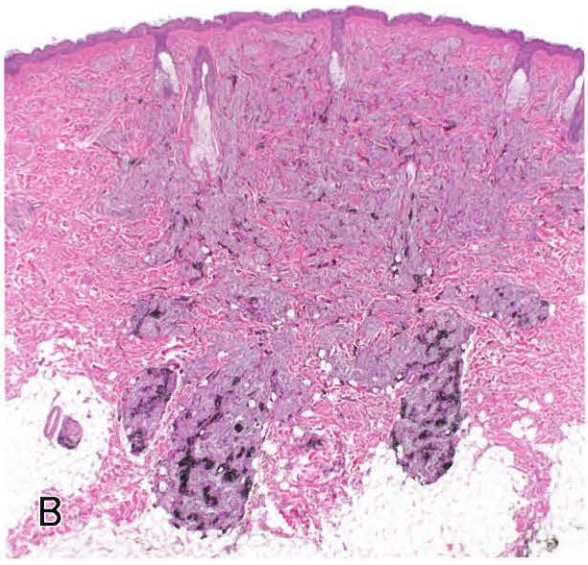
These small, circumscribed, darkly pigmented lesions often arise on the extremities of children or young adults. *Reed nevus* is regarded by some as a variant of Spitz nevus given the many overlapping histologic features between these entities (21). They are usually small thin lesions limited to the junction and papillary

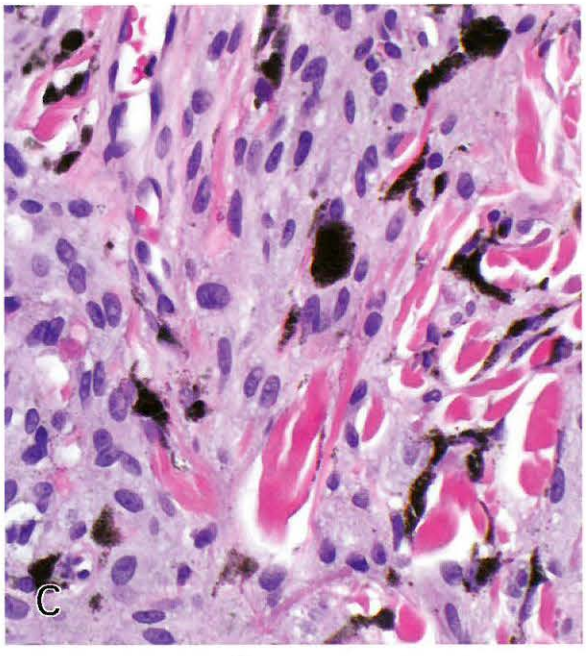
Figure 4-30, continued

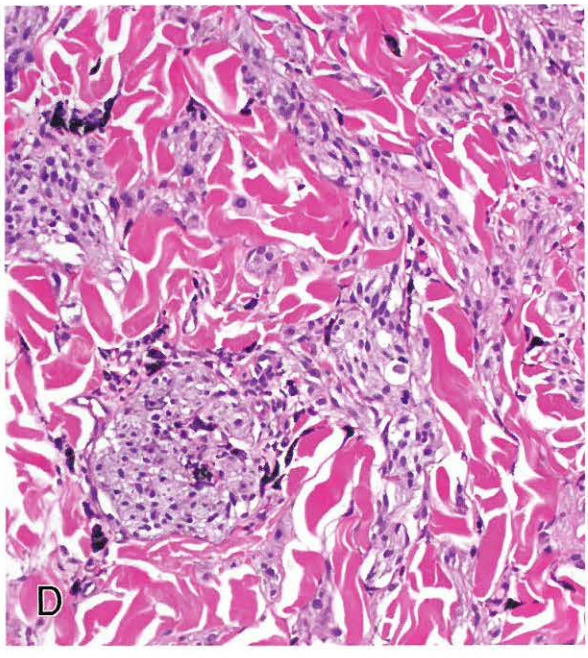
B: A bit of imagination may be required to see the wedge/upside-down pyramid shape. It is not as perfect here as in fig. A, but the lesion is still wider at the top and narrower at the bottom. In both figures, the density of pigment is most pronounced at the deep aspect.

C: The melanocytes of deep penetrating nevus often have plump spindled to oval nuclei. They possess abundant grayish cytoplasm with fine melanin pigment. Scattered darkly pigmented melanophages are present, a common feature. Deep penetrating nevus usually has larger nuclei and more abundant cytoplasm than cellular blue nevus.

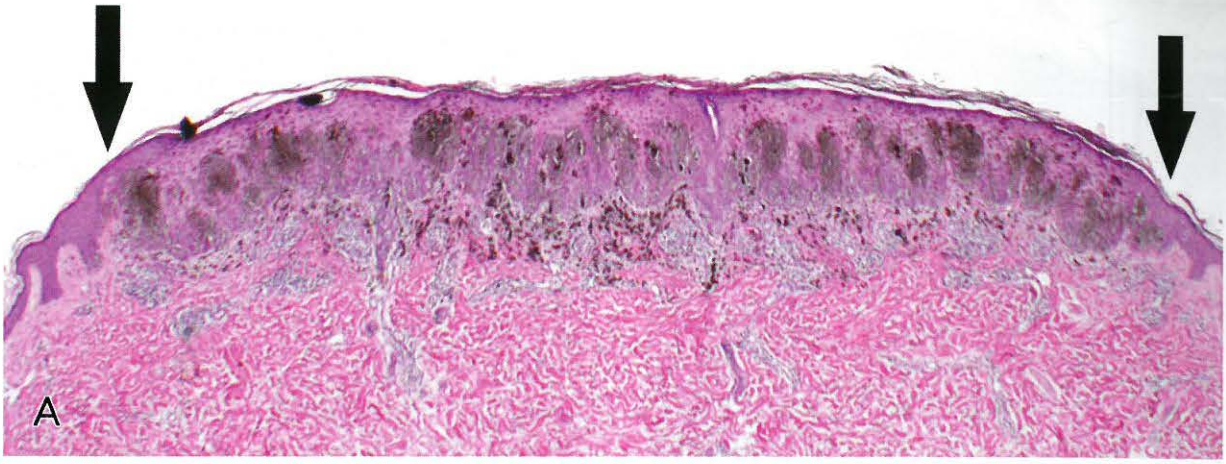
D: Deep penetrating nevus often shows an interstitial growth pattern. Grayish dermal melanocytes are arranged into elongated vague nests or cords that intercalate between pink reticular dermal collagen bundles. Scattered melanophages are present.

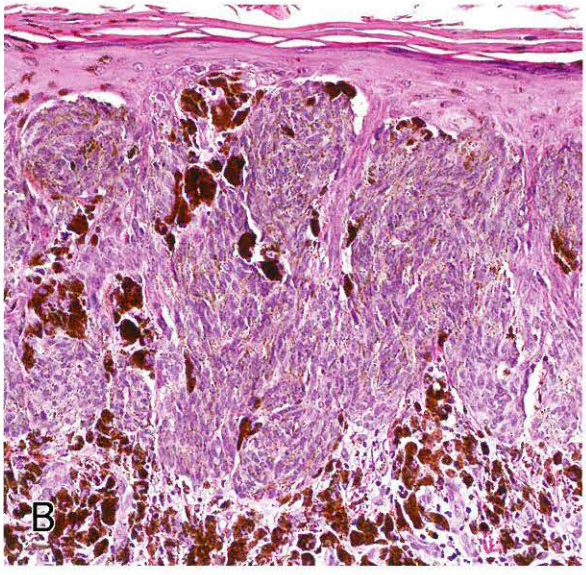


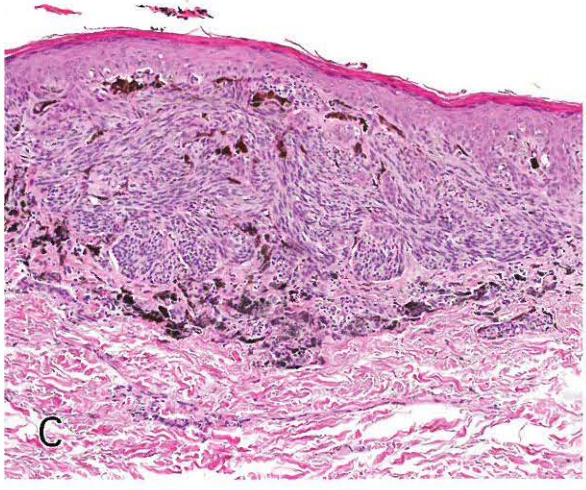




dermis; significant reticular dermal involvement is uncommon (fig. 4-31). They are usually well circumscribed histologically, with the lesion abruptly ending in a junctional nest of melanocytes at each peripheral edge of the lesion (similar to Spitz nevus). The nests are usually composed of enlarged plump, spindled melanocytes with abundant grayish cytoplasm, which often contains a variable amount of melanin pigment. The spindled melanocytes may run parallel to the epidermis forming bridges across rete (similar to the bridging seen in dysplastic nevus). Sometimes they are vertically oriented like "bunches of bananas," similar to Spitz nevus. There is often a band of abundant melanophages (+/- inflammation) in the superficial dermis directly under the lesion. Like Spitz nevus, Reed nevus may show pagetoid spread of nests or single cells in the central aspect of the lesion; by itself, this is not a worrisome feature. The small size, circumscription, and cytologic features taken together help confirm the diagnosis.







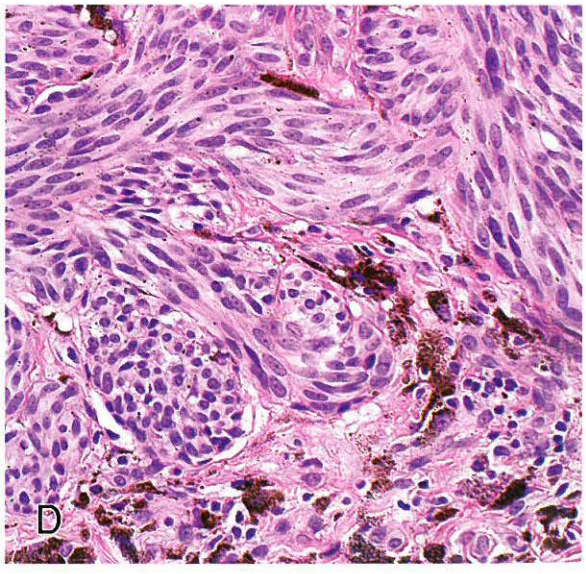


Figure 4-31

PIGMENTED SPINDLE CELL NEVUS (OF REED)

A: Reed nevi are small, thin, and circumscribed. They end in a nest abruptly at both peripheral borders of the lesion (arrows).

B: Junctional nests are composed of vertically oriented spindle cells with fine cytoplasmic melanin pigment. These hang down from the acanthotic epidermis like "bunches of bananas." A dense band of melanophages (and sometimes inflammation, too) may underlie the lesion, giving it the very dark pigmentation seen clinically.

C: In some cases, the nests of spindled melanocytes are oriented horizontally, running from rete to rete, parallel to the epidermis. This bridging appearance can resemble dysplastic nevus. If an apparent dysplastic nevus is small, darkly pigmented, ends abruptly in nests, and has spindled melanocytes, it might actually be a Reed nevus.

D: The melanocytes in Reed nevus have uniform plump spindled nuclei that may cytologically resemble the spindled melanocytes of Spitz nevus (Reed nevus may be merely a variant of Spitz nevus). Darkly pigmented melanophages are present in the underlying papillary dermis.

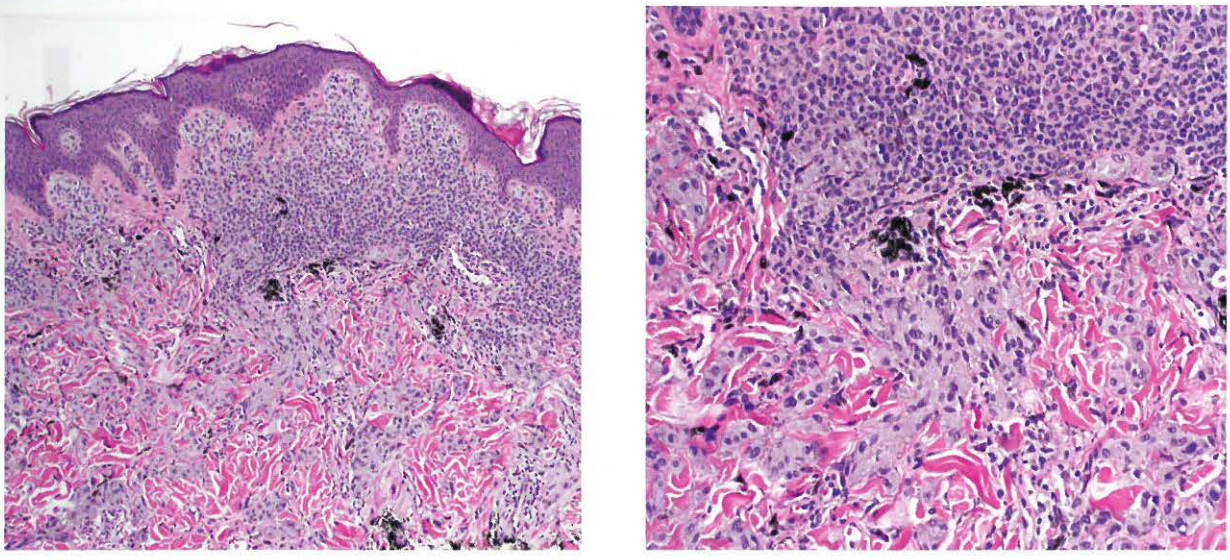


Figure 4-32

COMBINED NEVUS

Left: At low power, the lesion is clearly biphasic. This combined nevus has two components: common intradermal nevus (superficial dermis) and deep penetrating nevus (deeper dermis).

Right: The small round type B melanocytes (top of image) represent the common intradermal nevus component. The larger melanocytes with gray cytoplasm and scattered melanophages (bottom of image) represent the deep penetrating nevus component.

Reed nevi sometimes closely resemble dysplastic nevi at first glance, and the larger size of the cells makes it tempting to grade them as moderate or even severe dysplastic nevus. However, once one has considered the possibility of Reed nevus, the diagnosis quickly becomes apparent in most cases. Reed nevus, like Spitz nevus, can easily be overdiagnosed if one is not careful to consider them in the differential.

Combined Nevus

Combined nevus refers to the combination of two or more nevus subtypes within the same lesion (fig. 4-32). In many cases, common compound or intradermal nevus is present alongside a component of blue nevus, Spitz nevus, or deep penetrating nevus. Combined nevi are benign, but the presence of multiple components can make their features more difficult to evaluate to those who are not aware of this phenomenon. For example, a Spitz nevus component often displays much larger cells than the background compound nevus; the large size of the cells can impart an atypical appearance if the spitzoid cytologic features are not appreciated. A deep penetrating nevus component may have larger cells in the deep aspect of the lesion, raising concern for abnormal maturation. Once the different components are recognized and interpreted accordingly, the diagnosis is often much easier. If severe nuclear atypia or abundant mitotic activity is seen, however, be sure to exclude the possibility of an unusual melanoma.

MELANOMA

This section will cover the major subtypes and patterns of *melanoma* as well as individual pitfalls and clinical scenarios to be aware of for each. Four major histologic subtypes of melanoma have been historically recognized: superficial spreading, lentigo maligna, acral lentiginous, and nodular. Other histologic variants have been described that do not fit neatly into these four categories. The different subtypes of melanoma often have different clinical settings, different histologic features, and different underlying molecular abnormalities. Nonetheless, they are all unified by many common features. While some dermatopathologists still provide the histologic subtype on melanoma reports, some do not, since it is not usually needed for patient care (I usually provide it if the melanoma fits well into

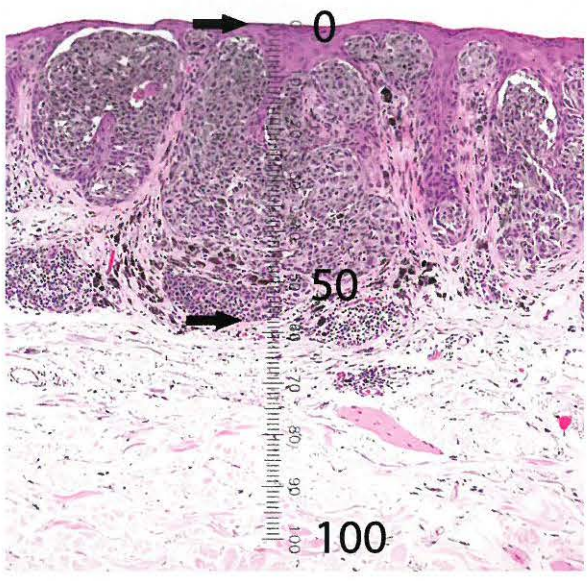


Figure 4-33

BRESLOW THICKNESS OF INVASIVE MELANOMA

Measure from the top of the granular layer (top arrow) to the deepest point of dermal invasion (bottom arrow). This is the view through a microscope ocular showing the micrometer insert that allows accurate measurement (for a microscope on 10X objective: 50 = 0.5 mm and 100 = 1 mm). The Breslow thickness/depth of invasion in this case is 0.57 mm, which I would round up to 0.6 mm in the report.

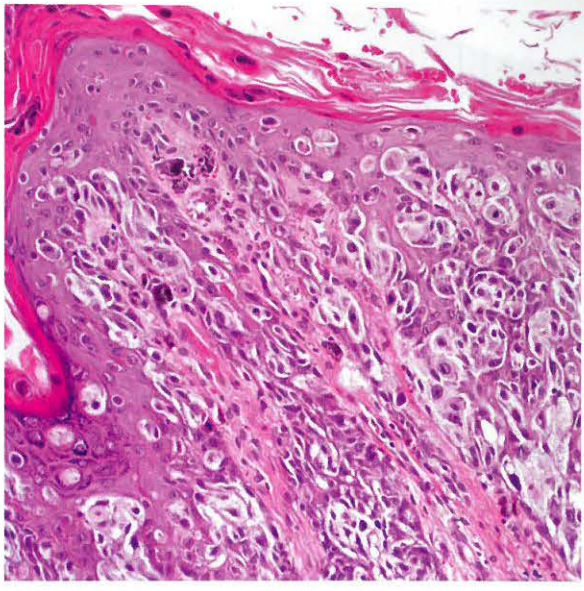


Figure 4-34

MELANOMA, SUPERFICIAL SPREADING TYPE

This subtype of melanoma often has large atypical epithelioid melanocytes arranged as a mixture of nests and single cells. Pagetoid spread is usually very prominent.

a subtype). The most important things for the pathologist to do are to recognize that a lesion is indeed melanoma, to identify if there is any invasion, to measure the depth of that invasion (Breslow thickness), to report the margin status, and to report any other prognostic factors that may be requested by the clinical team (or needed to satisfy laboratory accreditation requirements).

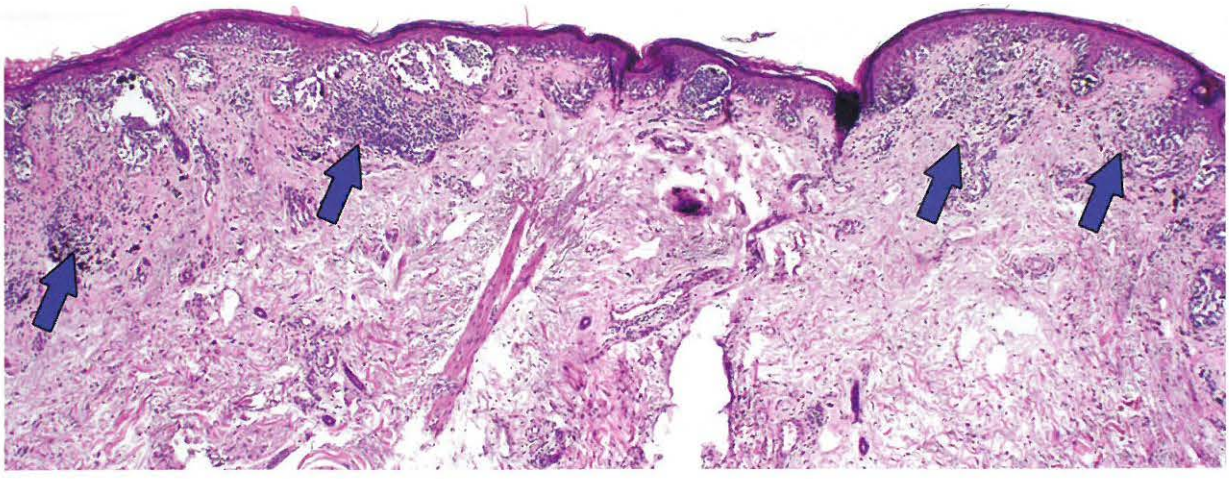
The most important feature that informs prognosis and treatment of a melanoma, regardless of histologic subtype, is Breslow thickness. Breslow thickness is the measurement (always given in mm; round it to the nearest 0.1 mm) from the granular layer of the epidermis down to the deepest point of dermal invasion (fig. 4-33). Regardless of histologic subtype, this is the single best predictor of melanoma behavior that can be obtained from the primary biopsy specimen.

The pT stage of the melanoma is based primarily on the Breslow thickness. The AJCC Cancer Staging Manual 8th edition, stages by Breslow thickness is as follows: T1: <1.0 mm (T1a: <0.8 mm; T1b: 0.8-1.0 mm or any T1 with ulceration); T2: >1.0-2.0 mm; T3: >2.0-4.0 mm; T4: >4.0 mm (T2/T3/T4a if ulceration is absent or T2/T3/T4b if ulceration is present). Other prognostic factors are often included in the report, but these are currently of less importance in determining prognosis or therapy for the patient. For additional nuances of staging, always refer to the most recent edition of the AJCC Cancer Staging Manual (26).

Wide local excision is the standard baseline treatment for melanoma. Sentinel lymph node biopsy may be offered to the patient depending on the Breslow thickness or other prognostic parameters. Sentinel lymph node biopsy (and nodal dissection) for melanoma provides prognostic information, but there is debate over whether these practices provide a survival benefit for most patients (27,28).

Superficial Spreading Melanoma

Superficial spreading melanoma is probably the "classic" example that comes to mind for most pathologists when they think of melanoma (fig. 4-34). Large atypical epithelioid melanocytes are arranged as a mixture of nests and single cells. Pagetoid spread is usually prominent.



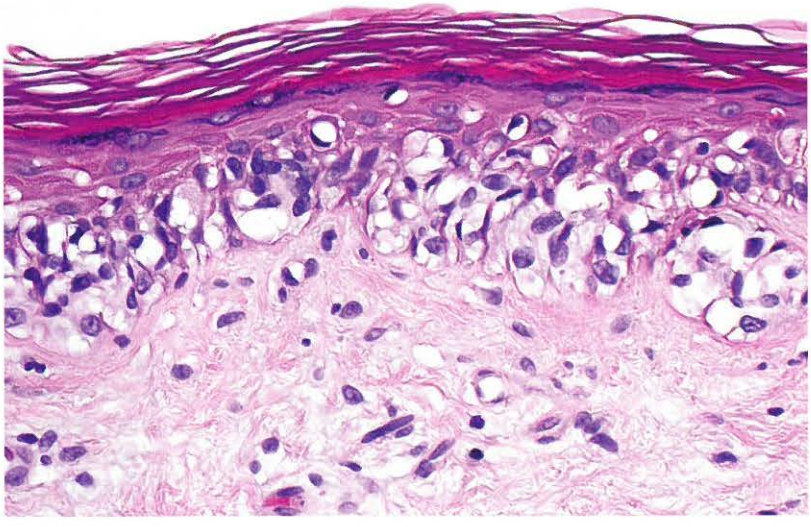


Figure 4-35

MELANOMA, LENTIGO MALIGNA TYPE

Above: Single melanocytes and nests are scattered along a broad expanse of elderly sun-damaged skin (note the atrophic epidermis and blue solar elastosis). Lymphocytic aggregates in the underlying dermis are a useful clue (arrows); the immune system recognizes the nefarious nature of this lesion.

Left: Large atypical single melanocytes replace the basal layer keratinocytes (confluent growth). This is a robust obvious example of lentigo maligna; some cases are much more subtle.

Lentigo Maligna Melanoma

Lentigo maligna melanomas occur almost exclusively in the chronically sun-damaged skin of older adults, with most arising on the face or scalp. They are characterized by atypical melanocytes trickling as single cells along the basal layer of an atrophic epidermis (fig. 4-35). The density and distribution of these single melanocytes varies from case to case and even in different areas of the same lesion. Zones of abundant single melanocytes with confluent growth may be intervened by zones with a paucity of melanocytes. Nests of melanocytes may be present, but single cells usually predominate. Many cases show minimal pagetoid spread. Cytologic atypia is often clearly visible, but in some cases, it may be subtle, making the architectural growth pattern the key to the diagnosis.

The variability and potential subtlety of findings can make the diagnosis of lentigo maligna challenging. The clinical scenario further complicates matters, since elderly sun-damaged patients often have many pigmented solar lentigines on their head and neck. Even though solar lentigo is unrelated to lentigo maligna melanoma, they can closely resemble one another clinically (thus the name for this subtype of melanoma). Biopsies for "solar lentigo versus lentigo maligna" are one of the more common types of specimens I see in my practice. Chronically sun-damaged skin tends to develop reactive melanocytic hyperplasia (fig. 4-36). Single atypical melanocytes along the basal layer due to melanocytic hyperplasia from chronic sun damage can closely mimic lentigo maligna melanoma *in situ*, especially when evaluating excision margins of a known lentigo

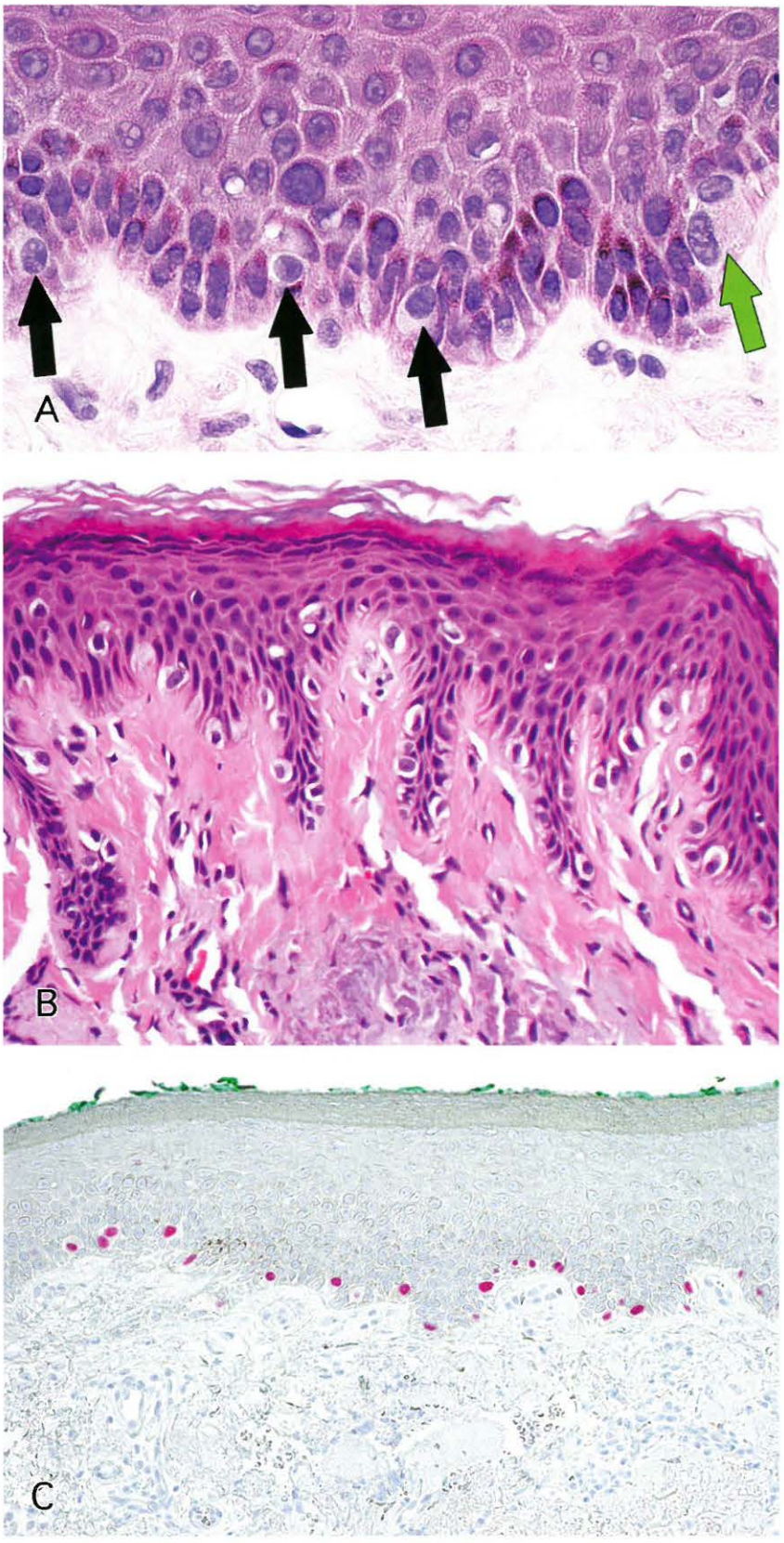


Figure 4-36

SOLAR-INDUCED MELANOCYTIC HYPERPLASIA

A: The melanocytes in this markedly sun-damaged skin have large hyperchromatic atypical nuclei with prominent nucleoli (black arrows). Multinucleated atypical melanocytes may even be seen (green arrow). The cytologic features of these reactive melanocytes can be identical to those of lentigo maligna.

B: The atypical melanocytes are increased in number but are still evenly spread out from one another by intervening keratinocytes (i.e., no confluent growth), which helps distinguish benign melanocytic hyperplasia from lentigo maligna. However, the distinction can be challenging if not impossible on small biopsies or on melanoma excision margins.

C: In difficult cases, SOX-10 immunostain helps confirm that the atypical melanocytes lack confluence. This is an excision specimen for squamous cell carcinoma with incidental background solar-induced melanocytic hyperplasia; the majority of the epidermis showed these large atypical but evenly spaced junctional melanocytes.

maligna or when dealing with a small biopsy of a larger pigmented lesion. Several clues can help with this scenario.

When single atypical melanocytes are increased in number but show a fairly even density across the entire epidermis with no nesting and no zones of confluence, melanocytic hyperplasia is favored. Assessing these findings is easier on a large biopsy or excision than on a small biopsy, of course. If additional biopsies from the patient are available from elsewhere in the same sun-exposed skin region, comparison with the density of melanocytes in those biopsies may be useful to establish a background "normal" melanocytic reference range for that patient's skin. The presence of nests (unless they are part of an incidental background nevus) is unacceptable for melanocytic hyperplasia. Melanocytic nests indicate either a nevus or a melanoma; in this setting where we are already concerned about the possibility of lentigo maligna, the finding of rare junctional nests is a feature that usually favors melanoma.

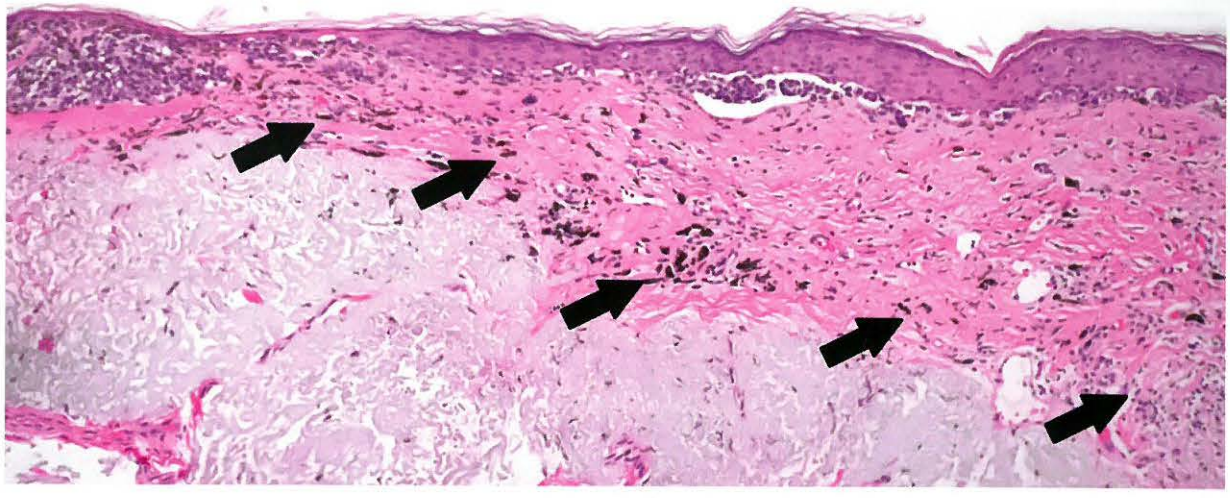
SOX-10 immunostain helps highlight confluent growth in subtle cases of potential lentigo maligna (this is the most common use of melanocytic immunostains in my practice). It takes experience and examination of SOX-10 on multiple cases of lentigo maligna versus melanocytic hyperplasia to be able to contrast the differences in density and establish a threshold for making a diagnosis of lentigo maligna melanoma *in situ*. If you use basal cell carcinoma or squamous cell carcinoma excision specimens as SOX-10 normal controls, you provide yourself with a nice opportunity to observe the striking increased density of melanocytes that can be seen in markedly sun-damaged background skin. Immunostains are useful adjuncts to H&E, but the diagnosis should not be based on immunostains alone. As for all of pathology, if the stain result does not make sense, stop and think things through before blindly accepting the result.

Confluence may be seen more easily in some cases by examining hair follicles or eccrine ducts. Some scattered single melanocytes may be seen in the basal layer of the follicular infundibulum but prominent spread of single melanocytes down adnexal structures is a concerning sign for lentigo maligna when the melanocytes are many or when they extend deep into the adnexa. Although pagetoid spread is infrequent in lentigo maligna, it may be present. The finding of more than a few upward scattered melanocytes on SOX-10 in this clinical scenario favors lentigo maligna.

In cases where the density or degree of cytologic atypia of junctional melanocytes is worrisome but falls short of melanoma, I use a diagnosis of "atypical junctional melanocytic proliferation" with a comment that this could represent robust solar-induced melanocytic hyperplasia, but an incompletely sampled lentigo maligna melanoma *in situ* cannot be excluded. A larger shave biopsy or an excision around the original biopsy site often resolves the dilemma.

There should be prominent solar elastosis in the dermis underlying lentigo maligna melanoma *in situ*. Solar elastosis is composed of blue-gray elastic fibers that build up in the dermis over many years of chronic sun exposure. Eventually, in severe cases, the reticular dermal collagen is replaced almost completely by elastosis. However, if there is a superficial zone of pink collagen over this diffuse layer of blue solar elastosis, this indicates new collagen deposition that occurred after the solar elastosis was formed (fig. 4-37). When such a zone of new collagen is seen underneath a lentigo maligna melanoma *in situ*, it must be investigated further. It could represent scar from previous excoriation or biopsy, regression changes in response to the melanoma (possibly obscuring focal invasive nests), or a subtle desmoplastic melanoma component arising from the melanoma *in situ*. Pink collagen replacing blue solar elastosis is a useful clue, but it only works in patients who have severe abundant solar elastosis.

If there is concern for lentigo maligna from the intraepidermal melanocytes, the finding of underlying regression is a further worrisome feature. Regression can look similar to scar tissue. Both have dense collagen fibers and fibroblasts, but in regression these are haphazardly arranged and in scar they are organized in parallel (figs 4-38). Scattered lymphocytes and melanophages in a disorganized fibrotic background are features suggestive of regression. When there is apparent dermal regression, examine the dermis closely to identify small nests or single cells of invasive melanoma hiding within the fibrosis and inflammation. SOX-10 or MART-1 immunostains (ideally red chromogen) can be helpful here, as can deeper levels.



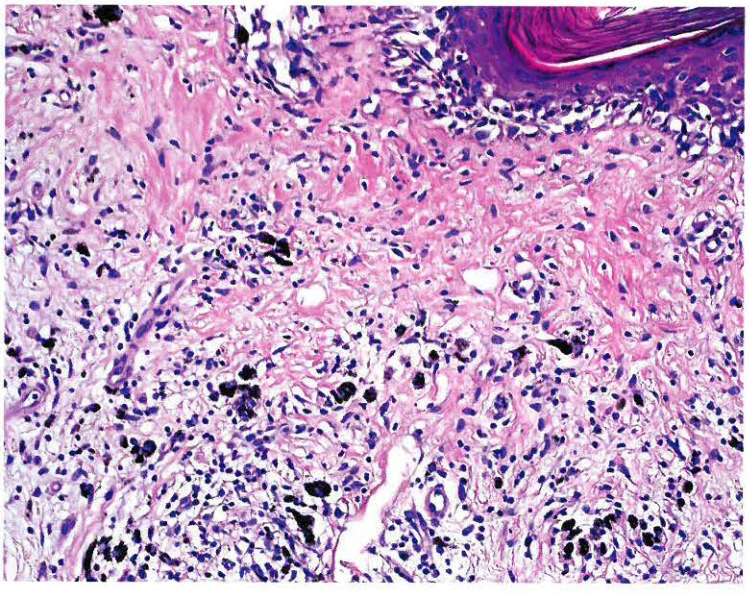


Figure 4-37

REGRESSION IN LENTIGO MALIGNA

Above: In severely sun-damaged skin, the presence of a superficial zone of pink collagen (right of arrows) pushing down and replacing the diffuse blue solar elastosis (left of arrows) indicates new collagen deposition (i.e., collagen has been deposited after the solar elastosis was formed). In this case, it is evidence of regression beneath a melanoma *in situ* (lentigo maligna type). Scar from biopsy or excoriation can produce a similar appearance, as can desmoplastic melanoma.

Left: The solar elastosis is replaced by fibrosis with disorganized collagen fibers. Lymphocytes and melanophages are present within the fibrosis. Note the confluent growth of atypical melanocytes along the overlying basal layer.

Some lentigo maligna melanomas have architectural features closely resembling dysplastic nevus, with multiple nests of melanocytes bridging across the tips of elongated rete ridges (fig. 4-39). Do not trust the apparent dysplastic nevus (or any nested junctional melanocytic proliferation) arising on the face of an elderly patient with abundant underlying solar elastosis...that lesion is melanoma until proven otherwise! A closer look or SOX-10 immunostain usually demonstrates confluent growth in the background to confirm the diagnosis.

Acral Lentiginous Melanoma

Acral lentiginous melanoma presents as a growing pigmented lesion of the palm or sole. It can also arise within the nail matrix and present as melanonychia (a linear streak of dark brown nail pigmentation); the great toenail and thumbnail are the most common sites. Some cases present in an advanced state and are amelanotic, mimicking an ulcer, abscess, paronychia, or pyogenic granuloma clinically. Although patients with dark skin types rarely get melanoma, when they do, it is usually the acral lentiginous type (Jamaican reggae legend Bob Marley died from acral lentiginous melanoma of the great toe). Caucasian patients also get acral lentiginous melanoma, although less commonly than superficial spreading or lentigo maligna types.

"Lentiginous" in the name refers to the abundance of single melanocytes seen along

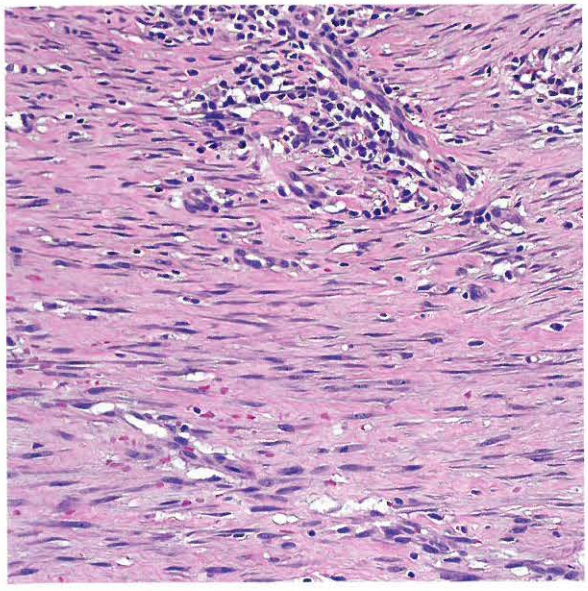


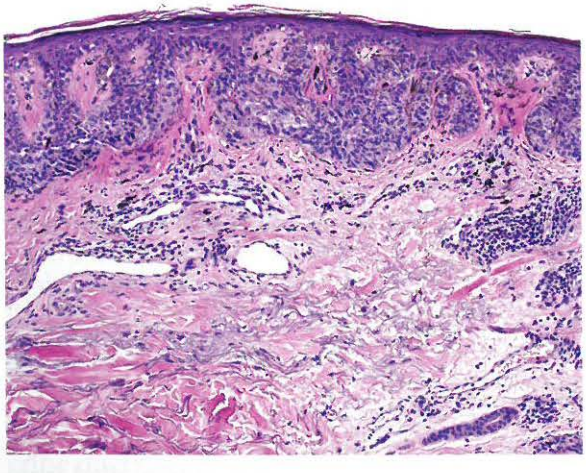
Figure 4-38

SCAR (VERSUS REGRESSION)

True scar is usually more organized than regression. There are myofibroblasts running parallel to the epidermis and to one another with intervening collagen fibers. Vertical vessels are often present (in larger scars) running perpendicular to the myofibroblasts and to the epidermis.

the basal layer in acral lentiginous melanoma. Usually these are numerous and display obvious confluent growth (fig. 4-40). Confluent growth down eccrine ducts is a characteristic feature that strongly supports a diagnosis of acral lentiginous melanoma when present. This finding can be so robust as to replace almost all of the eccrine ductal epithelial cells; this makes the cross section of a duct filled with *in situ* melanoma have an appearance similar to a nest of dermal invasion. Identifying the central duct lumen lined by pink cuticle helps recognize that this is *in situ* melanoma within a duct rather than invasive melanoma. Immunostains for p63/p40 or pancytokeratin highlight the background epithelial cells present between the melanoma *in situ* cells within the duct.

In situ spread down eccrine ducts helps confirm the diagnosis of melanoma but be sure to avoid these when measuring the Breslow thickness. Pagetoid spread is often abundant and cytologic atypia obvious in acral letiginous melanoma. Acral nevus may also have pagetoid spread, but it should not have marked cytologic atypia or confluent growth.



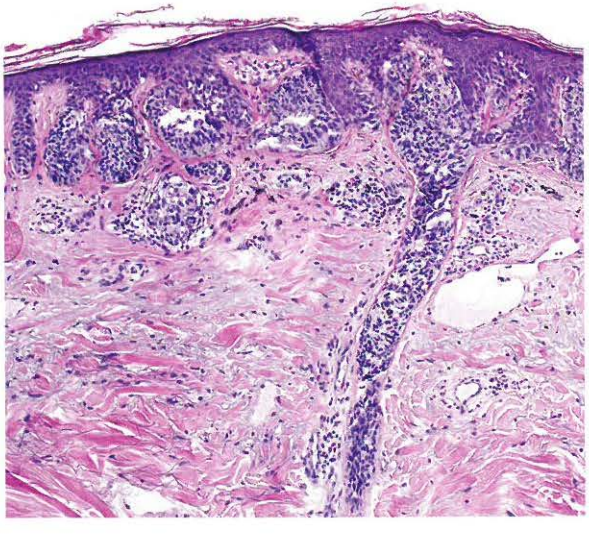


Figure 4-39

LENTIGO MALIGNA MIMICKING DYSPLASTIC NEVUS

Left: Nests of atypical melanocytes bridge between adjacent rete, much like a dysplastic nevus. But as this is a scalp lesion from a sun-damaged older adult, this is melanoma unless proven otherwise. SOX-10 stain showed pagetoid spread and areas of confluence (left and right are from the same case.)

Right: Despite the nested appearance at low power, confluent growth is evident in the underlying eccrine duct, which is almost completely replaced by atypical melanocytes.

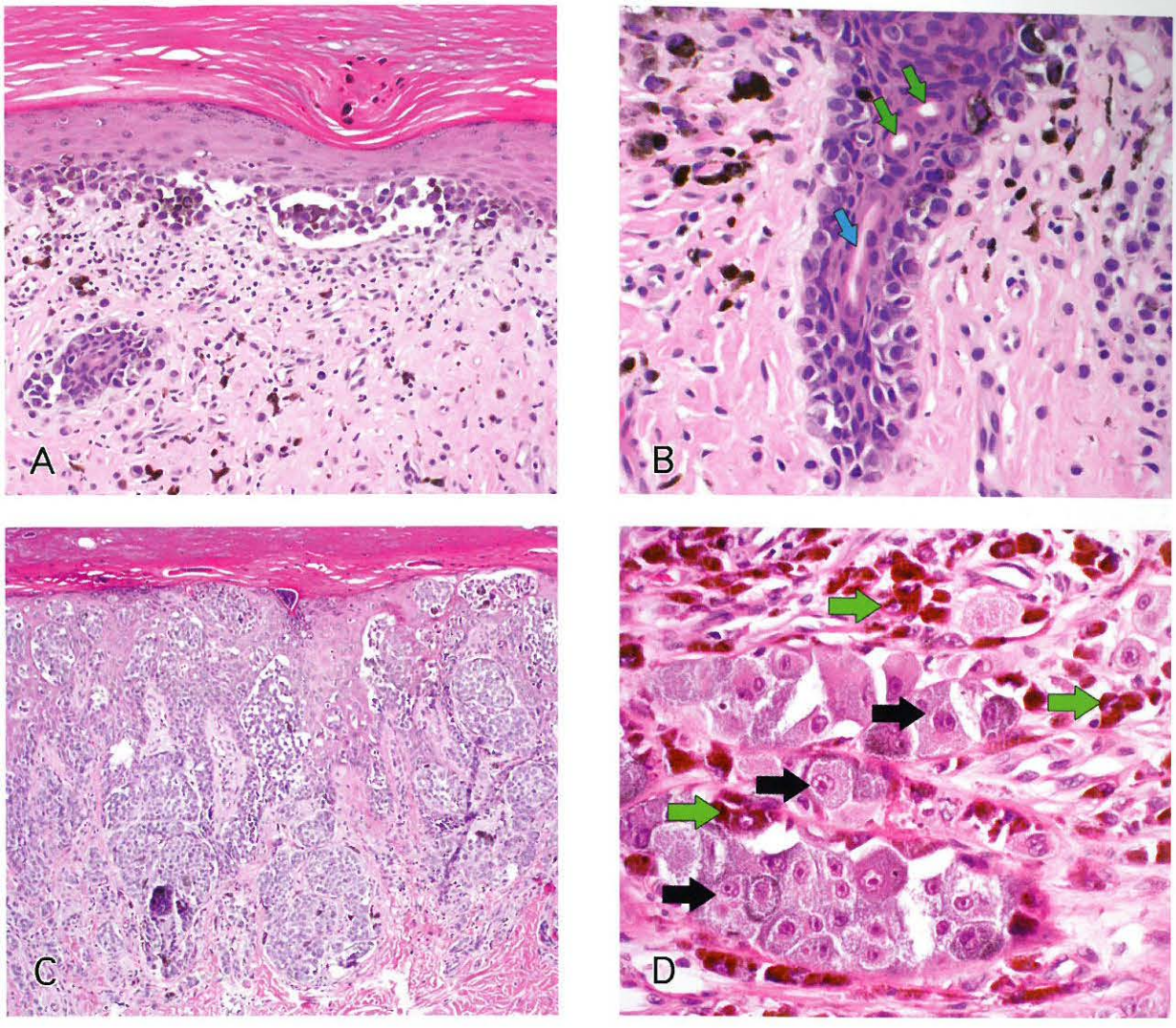


Figure 4-40

MELANOMA, ACRAL LENTIGINOUS TYPE

A: Numerous atypical melanocytes nearly replace the basal layer keratinocytes, producing the "unzipping" artifact that is characteristic of extensive confluent growth.

B: Confluent growth of atypical melanocytes (black arrows) down eccrine ducts is a classic feature. Note the central lumen of the duct with its thin layer of pink cuticle (cross sections = green arrows; longitudinal section = blue arrow).

C: Pagetoid spread is often abundant. Atypical melanocytes, both single and in nests, scatter upward throughout the entire epidermis and into the overlying stratum corneum.

D: Some cases have very darkly pigmented melanocytes (another broken "rule"). Melanoma cells tend to have fine melanin creating a "dirty" gray-brown cytoplasm (black arrows). Contrast these to the dense clumping of melanin seen in the much darker adjacent melanophages (green arrows).

Acral lentiginous melanomas sometimes develop abundant melanin pigment in their cytoplasm. Darkly pigmented cells in the epidermis or dermis are usually keratinocytes or melanophages (respectively) rather than melanocytes; acral lentiginous melanomas sometimes break this rule. The invasive component of acral lentiginous melanoma may be either epithelioid, spindled, desmoplastic, or a combination of those patterns. In my experience, there is often delay in clinical diagnosis of acral melanomas, likely due to a lack of awareness among both patients and

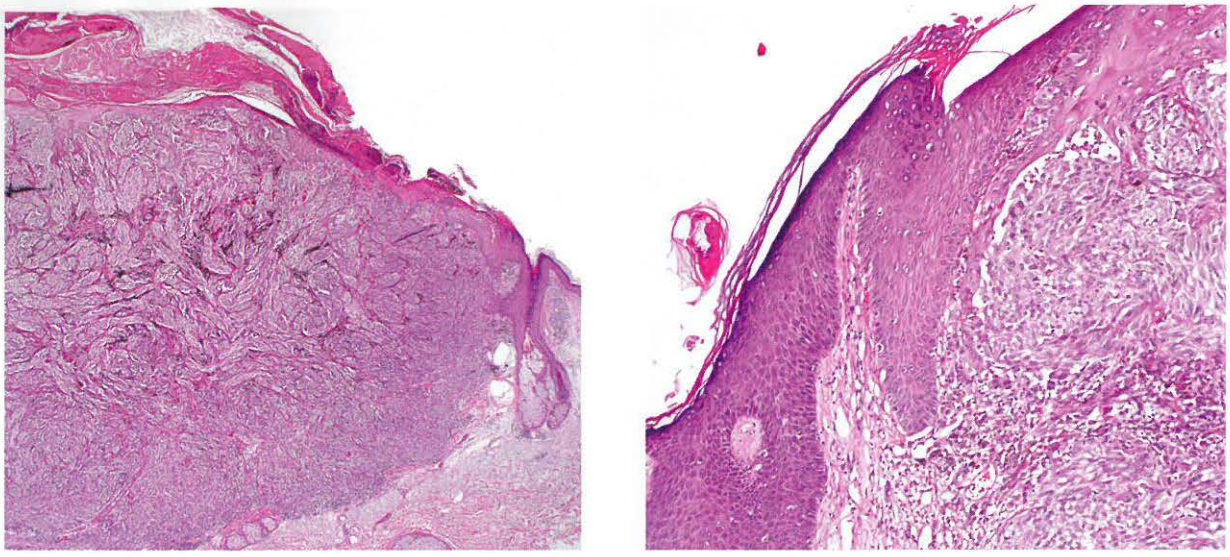


Figure 4-41

MELANOMA, NODULAR TYPE

Left: A large nodule of invasive melanoma extends deeply into the dermis. There is thick overlying crust due to epidermal ulceration; because of this, nodular melanoma can mimic pyogenic granuloma clinically.

Right: At the periphery of the lesion, both the invasive and *in situ* components abruptly stop. Melanoma *in situ* does not extend into the adjacent epidermis beyond the nodule of invasion.

physicians about this unusual presentation of melanoma. As such, invasive lesions often have a high Breslow thickness at the time of biopsy.

Nodular Melanoma

As the name implies, *nodular melanomas* present as large nodules clinically. Sometimes they are pedunculated or polypoid. They are often ulcerated. Some are amelanotic, having a red/pink rather than brown/black color to the naked eye; these are easily mistaken clinically for pyogenic granuloma or other types of non-melanocytic neoplasia.

Histologically, nodular melanomas are composed of a nodule of invasive melanoma that extends deeply into the dermis and/or subcutis (fig. 4-41). It is usually composed of sheets or densely packed nests of markedly atypical melanocytes, often with brisk mitotic activity. The melanoma *in situ* component is only present in the epidermis directly above the invasive dermal component. If melanoma *in situ* extends into the adjacent epidermis more than a few rete ridges beyond the periphery of the zone of dermal invasion, then the conventional rule is that the melanoma should not be classified as nodular melanoma but rather as one of the other subtypes (depending on the features of the *in situ* component and the clinical scenario). A nodule of deeply invasive melanoma can arise in any subtype of melanoma, but it is only referred to as a true "nodular type" when the *in situ* component is limited to the epidermis just above the invasive component. This indicates that the tumor is invading downward (so-called vertical growth phase) but not growing outward (so-called radial growth phase).

Regardless of nomenclature, any melanoma with a nodule of deep invasion has a significant risk for aggressive behavior. If the lesion has the appearance of nodular melanoma but lacks any obvious *in situ* component, the alternative possibility of metastatic melanoma must be considered.

Metastatic/Recurrent Melanoma

When there is a nodule of melanoma in the dermis and/or subcutis without any overlying *in situ* component, the possibility of local recurrence, satellite lesion, or cutaneous metastasis of melanoma must be considered. Invasive melanoma that was previously incompletely excised may recur as a dermal nodule within or

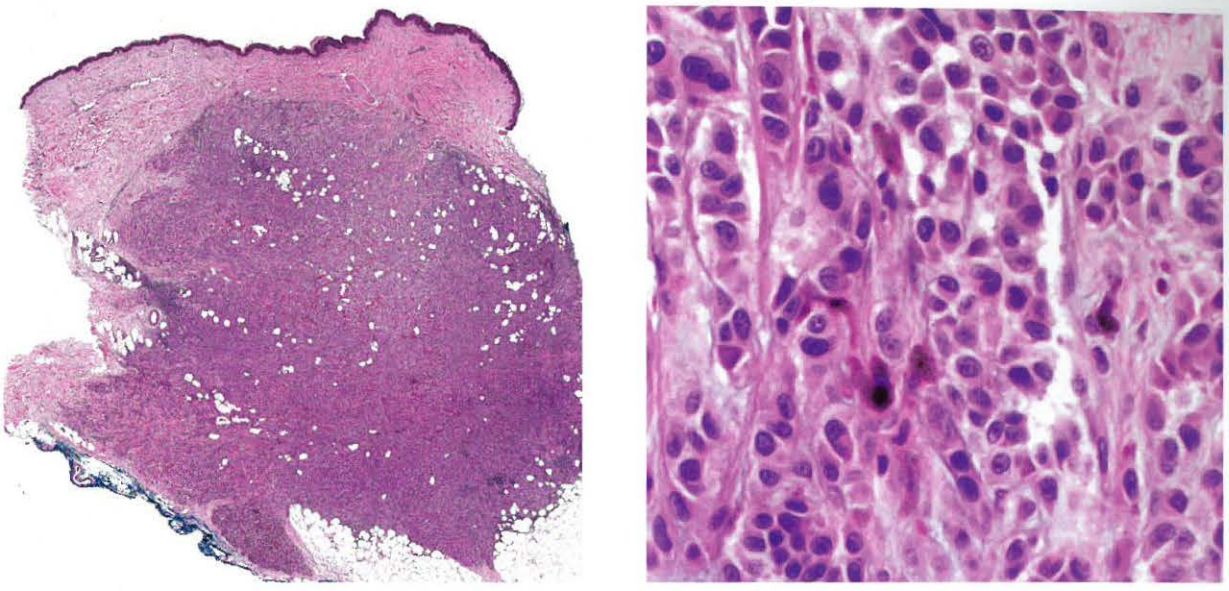


Figure 4-42

METASTATIC/RECURRENT MELANOMA

Left: There is a nodule in the dermis and subcutis but with no epidermal involvement.

Right: At high power, the tumor cells are often epithelioid with abundant cytoplasm, many mitoses, and large nucleoli. Nest formation and melanin pigment production, when present, are clues to melanoma (as opposed to poorly differentiated carcinoma or other malignancies).

directly adjacent to the surgical scar. Melanoma can also spread to adjacent but noncontiguous normal skin via lymphatic channels and form a clinically identifiable nodule referred to as a satellite lesion (<2 cm from primary) or in transit metastasis (>2 cm from primary) (26). Melanoma has a propensity to metastasize to skin at distant sites, in which case it represents stage IV disease.

Histologically, these cases are usually easy to recognize as melanoma. There is a large nodule of markedly atypical cells in the dermis/subcutis (fig. 4-42). Immunostains for S-100 protein, SOX-10, or MART-1 easily confirm this. The difficulty here is not in diagnosing the melanoma but rather in determining the scenario in which it is arising. The distinction is very important for prognosis and treatment. Clinical history is of the utmost importance here. If the patient has a history of melanoma, it is critical to know when, where, and, ideally, how thick it was. Discussion with the dermatologist or surgeon may be needed to determine exactly how close the current lesion is to the original biopsy/excision site. Sometimes, there is no known history of melanoma. Full body skin examination, inquiry into the possibility of any forgotten history of previous biopsy, and other forms of clinical work-up may be needed in these cases. Metastatic melanoma from an unknown primary is an uncommon but well-recognized phenomenon. If I am unable to obtain clinical information, I usually diagnose these cases as "melanoma involving dermis/subcutis" with a comment that no *in situ* component is seen and that the histologic pattern could fit with a recurrence, satellite, or metastasis.

There are two caveats. Some primary nodular melanomas can appear to lack a melanoma *in situ* component and thus mimic a cutaneous metastasis/satellite/recurrence. This may be due to extensive ulceration of the overlying epidermis, partial regression, or histologic sectioning variation (i.e., the examined sections did not cut through the areas with the *in situ* component). The distinction between these scenarios is of great therapeutic and prognostic importance. A primary nodular melanoma and a distant metastasis of melanoma from elsewhere are treated very differently. In these situations, it is often worth calling the treating physician to discuss the difficulty of the situation. The opposite

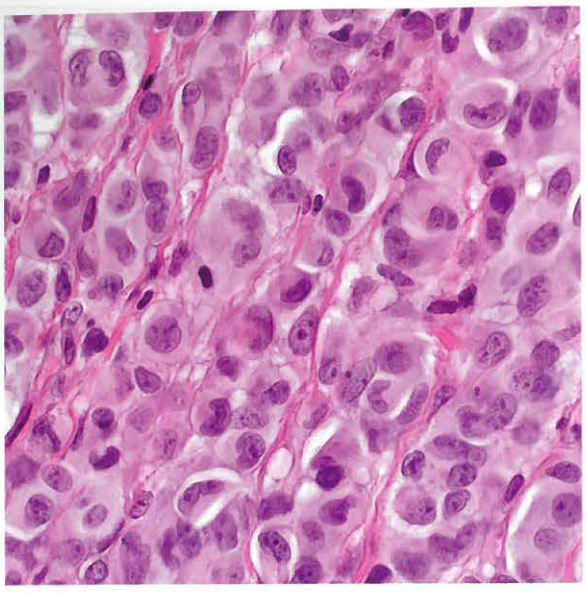


Figure 4-43

RHABDOID MELANOMA

Markedly atypical epithelioid tumor cells show abundant cytoplasm and eccentric displacement of nuclei, often with round eosinophilic perinuclear cytoplasmic globules.

situation is also problematic: some metastatic melanomas (or satellite lesions) have growth of tumor cells up into the overlying epidermis and give the false appearance of having a true melanoma *in situ* component. These are called *epidermotropic metastases*. They are nearly impossible to distinguish from primary melanoma unless the clinical history is known.

A nodule of apparent metastatic melanoma on the distal extremity of a young adult with no history of melanoma should suggest the possibility of clear cell sarcoma of soft parts. This rare soft tissue sarcoma can look similar to melanoma microscopically (although there are some histologic clues to tell them apart). It stains with all major melanocytic markers. However, unlike melanoma, it possesses a translocation of the *EWSR1* gene, which can be detected via breakapart FISH.

Rhabdoid Melanoma

Melanomas sometimes display prominent rhabdoid cytologic features (fig. 4-43). Rhabdoid cells are most often seen in large thick nodules of melanoma, either primary or metastatic. The finding is of no clinical significance by itself, but it is important for pathologists to keep melanoma in their differential diagnosis of tumors with rhabdoid features. Immunostains easily reveal melanocytic differentiation, however, S-100 protein or SOX-10 should not be used alone. These markers stain myoepithelial cells, which often possess rhabdoid cytologic features in the context of mixed tumor/myoepithelioma (I have seen a case of myoepithelioma misdiagnosed as melanoma because of strong diffuse S-100 protein staining in the rhabdoid myoepithelial cells; cytokeratin or other melanocytic markers had not been used). A variety of other neoplasms also show rhabdoid cytology, including soft tissue sarcomas like epithelioid sarcoma and some carcinomas. If the tumor is negative for melanoma markers, expanding the differential and the immunohistochemical panel may be necessary.

Spindle Cell Melanoma

Spindle cell melanoma refers to a melanoma in which the invasive component is composed of severely atypical spindle cells resembling high-grade sarcoma. These often arise on the head and neck of elderly sun-damaged patients. The diagnosis of malignancy is easy here because of the hypercellularity, pleomorphism, and mitotic activity that is usually present (fig. 4-44).

The challenge is in recognizing that the lesion is a melanoma rather than spindle cell squamous cell carcinoma, atypical fibroxanthoma/pleomorphic dermal sarcoma, leiomyosarcoma, solid spindled area of angiosarcoma, or some other high-grade sarcoma. There may be a melanoma *in situ* component in the overlying epidermis, but this is absent in many cases. The invasive component may have areas of conventional epithelioid melanoma cells arranged in nests in addition to the spindle cells. Even when purely spindled, the spindle cells tend to arrange themselves into vague nests or "packets."

When no obvious conventional melanoma areas are present, immunostains are required to confirm the diagnosis. S-100 protein, SOX-10, and MART-1 are good stains for this scenario, although spindle cell melanomas sometimes lose expression of MART-1 (and HMB-45). They may also have zones of S-100 protein or SOX-10 loss, although some areas with strong staining are usually still present; complete loss of S-100 protein and SOX-10 is rare in melanoma.

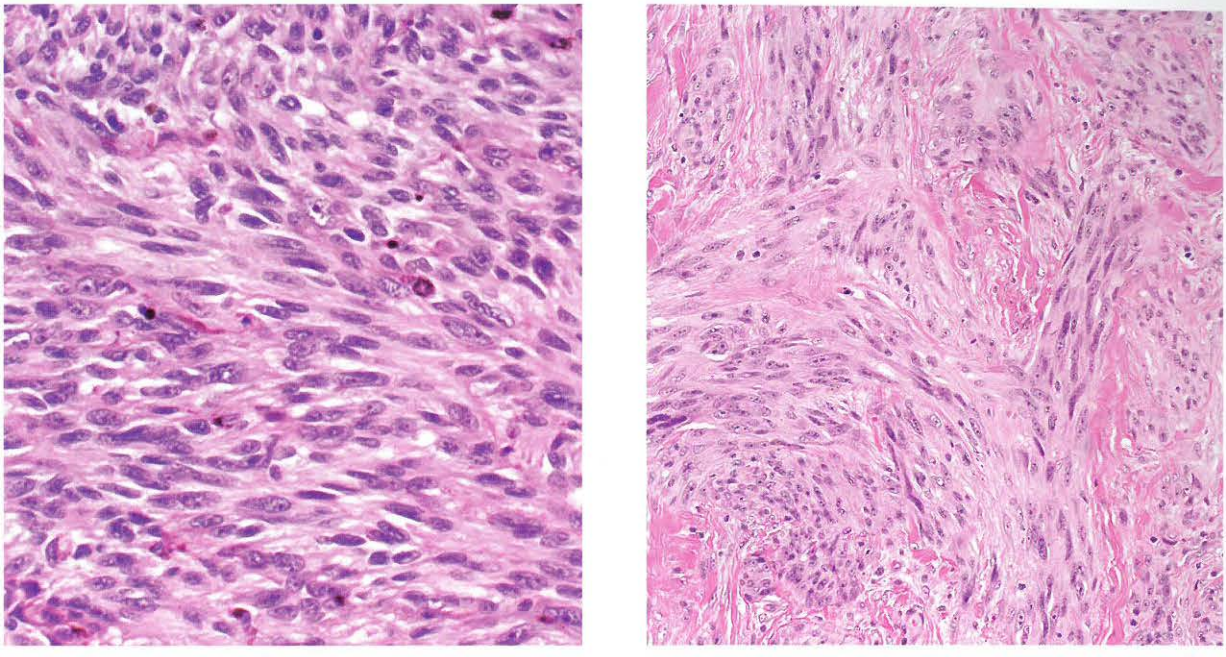


Figure 4-44

SPINDLE CELL MELANOMA

Left: Sheets or fascicles of markedly atypical spindle cells fill the dermis. The appearance is similar to high-grade sarcoma. Focal melanin production is present in this case, a useful clue.

Right: The invasive spindle cells are often arranged into "packets," elongated aggregates of spindle cells intervened by dermis/stroma. Packets are a hybrid between a fascicle and a nest. Even when spindled, melanocytes still try to make nests.

The immunostain panel that I currently prefer for pleomorphic spindle cell tumors of elderly sun-damaged skin is S-100 protein or SOX-10 for spindle cell melanoma, pancytokeratin AE1/AE3 (some prefer high molecular weight keratins instead) and p40 (or p63) for spindle cell squamous cell carcinoma, ERG or CD31 for angiosarcoma, and desmin for rhabdomyosarcoma and leiomyosarcoma. If all of these are negative, I make a diagnosis of atypical fibroxanthoma (or pleomorphic dermal sarcoma, if the tumor is large or invades the subcutis). The distinction between these different tumors is important for prognosis and therapy.

Desmoplastic Melanoma

Desmoplastic melanoma is a rare subtype of melanoma, but it is very important to know about because of its unique histologic features and clinical significance in contrast to most other melanomas (fig. 4-45). Most cases arise on the head and neck of elderly sun-damaged patients, where they sometimes are associated with overlying lentigo maligna melanoma *in situ* component. Many cases lack an *in situ* component, which often leads to diagnostic confusion.

The clinical appearance is often nonspecific, as pigment is usually lacking and the lesion may be a firm plaque resembling scar. Desmoplastic melanoma is composed of spindled melanocytes filling the dermis and often invading deeply into the subcutis. Unlike spindle cell melanoma, desmoplastic melanoma has much lower cellularity, has scattered rather than diffuse pleomorphism/atypia, and has an overall less malignant appearance at first glance. The low-power appearance often resembles scar, neurofibroma, or a benign fibroblastic neoplasm; misdiagnosis as one of these benign entities is an easy mistake to make, especially on a small superficial biopsy. At higher magnification, scattered pleomorphic hyperchromatic spindle cells are present, but these are usually scattered about rather than arranged in diffuse cellular sheets as in spindle cell melanoma. Many of the intervening spindle cells are bland

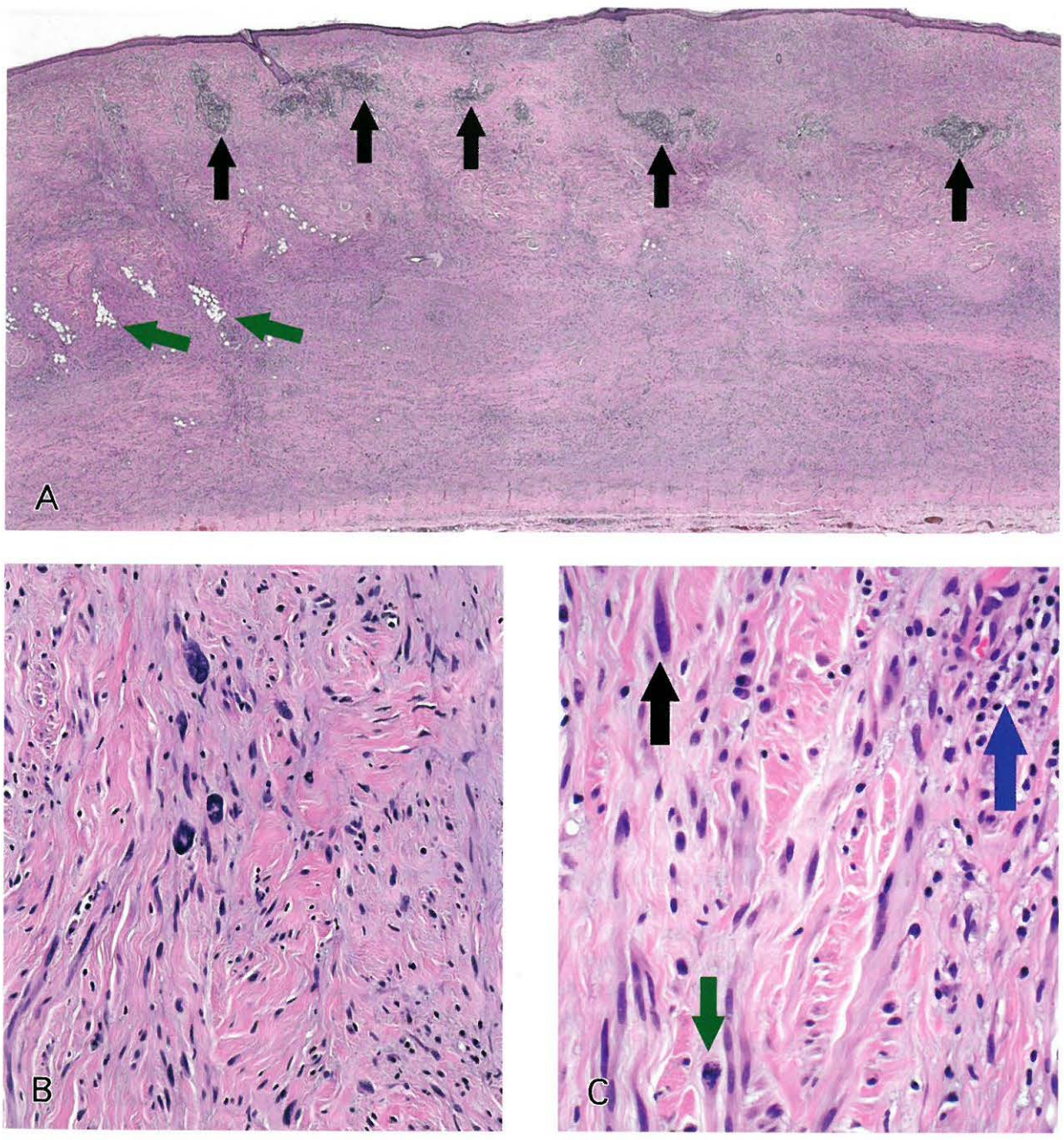


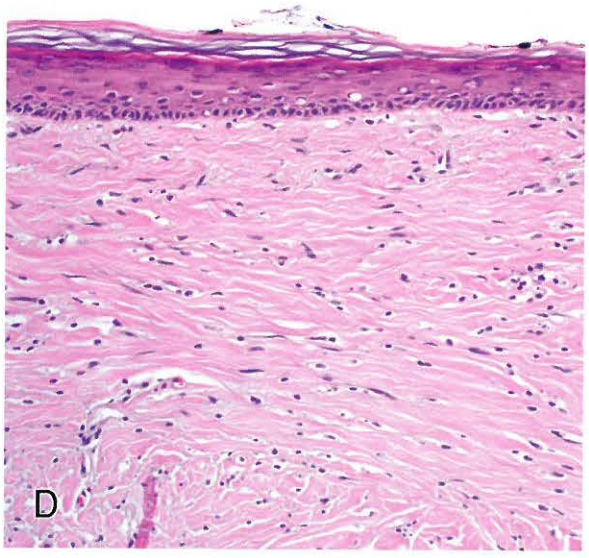
Figure 4-45

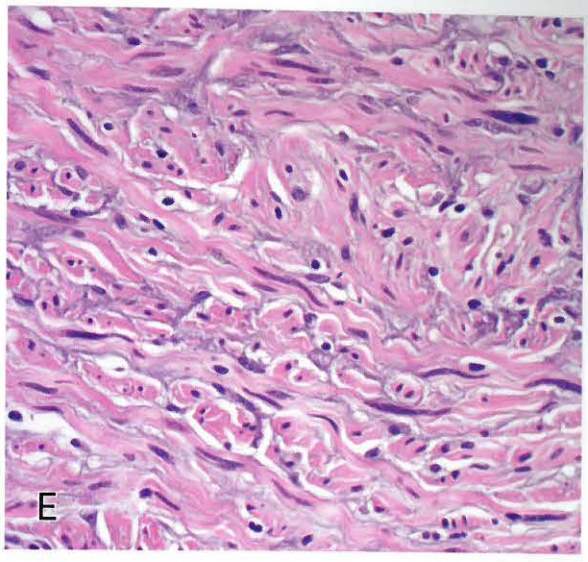
DESMOPLASTIC MELANOMA

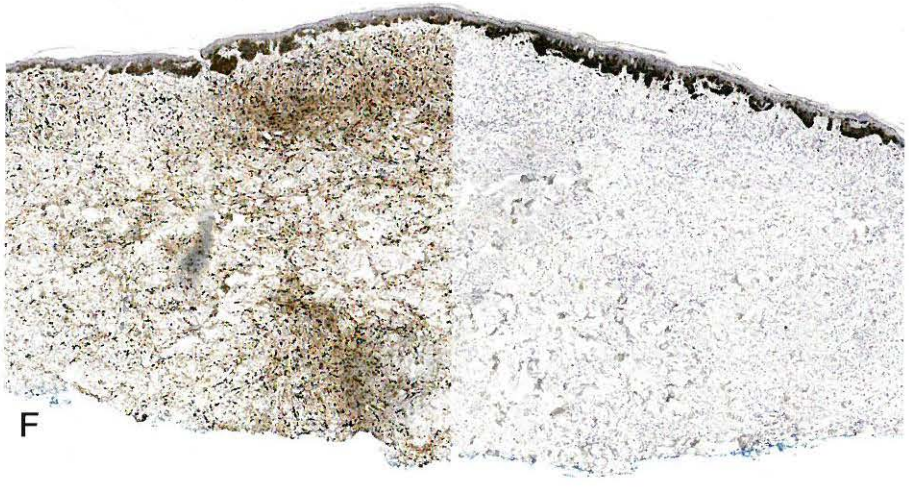
A: This scalp excision from an elderly patient shows a hypocellular fibrotic process invading and effacing the dermis and subcutis (note foci of residual subcutaneous fat at green arrows) and extending down to the galea (pink band along deep margin). Multiple lymphocytic aggregates are present (black arrows). This pattern represents desmoplastic melanoma until proven otherwise.

B: The spindle cells sit in a "desmoplastic" background: pink collagen fibers mixed with pale blue myxoid material separate tumor cells from one another. Scattered hyperchromatic pleomorphic cells are a useful clue. Contrast the low cellularity of this desmoplastic melanoma with the hypercellularity of spindle cell melanoma (figure 4-44).

C: Three useful clues to help confirm the diagnosis: scattered large hyperchromatic nuclei (black arrow), scattered mitoses (green arrow), and lymphocytic aggregates (blue arrow). Careful searching is sometimes required.







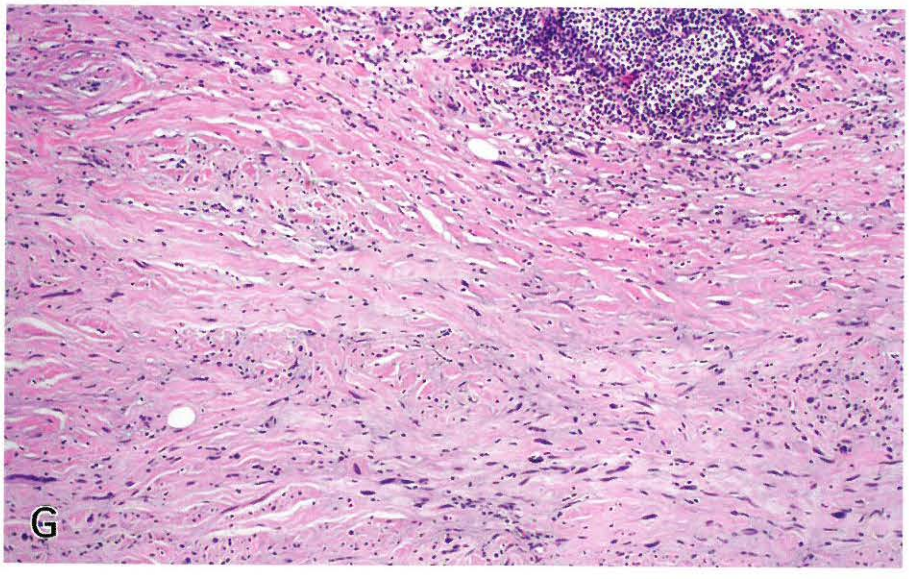


Figure 4-45, continued

D: The tumor cells can be quite bland and unremarkable. It is easy to see how a superficial biopsy from an area like this could easily be misdiagnosed as scar. Beware the apparent scar on sun damaged skin! S100 and/or SOX-10 are very useful in this scenario.

E: The tumor cells often have Schwannian cytologic features (serpiginous/buckled/"wavy" nuclei) and can closely mimic neurofibroma. This is a challenging differential; both entities have many overlapping features but very different treatment and prognosis.

F: Pure desmoplastic melanoma will be strongly and diffusely positive for S-100 protein (left) and SOX-10 (not shown) but negative for MART-1 (right) and other more specific melanocytic markers. Note the presence of melanoma *in situ* in the overlying epidermis, which is positive for both S-100 protein and MART-1.

G: Patchy aggregates of lymphocytes (top right) are present in most desmoplastic melanomas. Do not ignore them!

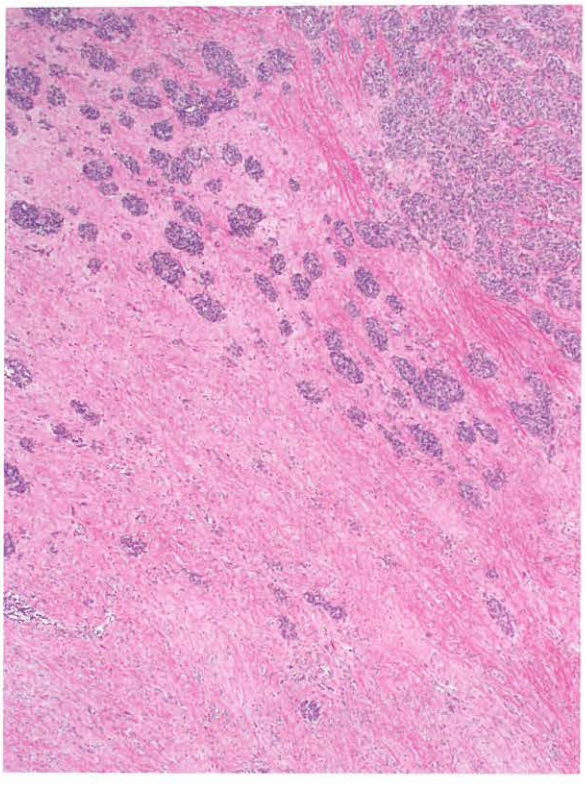


Figure 4-46

COMBINED DESMOPLASTIC AND CONVENTIONAL MELANOMA

Hypocellular pink desmoplastic melanoma (bottom) is intermingled with hypercellular nests and sheets of epithelioid melanoma (top).

or have only subtle atypia; they resemble fibroblasts or Schwann cells.

Some cases have areas that are very similar in appearance to neurofibroma. Unfortunately, neurofibromas can have scattered hyperchromatic spindle cells (degenerative "atypia"), and elderly patients can get neurofibromas even on the head and neck. All of these findings may be present in the same lesion (i.e., beware the apparent neurofibroma with atypia on sun-damaged elderly skin!). Distinguishing neurofibroma with degenerative atypia from desmoplastic melanoma is sometimes very difficult, as they both express S-100 protein and SOX-10 and lack other melanocytic markers like MART-1 and HMB-45. Mitoses are often present in desmoplastic melanoma but are rare in neurofibroma. The presence of mitoses in this setting strongly favors desmoplastic melanoma, but the absence of mitoses does not exclude it. Beware the apparent scar on sun-damaged skin, especially when there is no known reason for it to be there. Beware scattered enlarged hyperchromatic pleomorphic nuclei in an apparent neurofibroma on sun-damaged skin. Beware any bland spindle cell proliferation in the dermis on sun-damaged skin. Keep desmoplastic melanoma in your differential, even though it is rare. A high index of suspicion is crucial. If in doubt, do SOX-10 or S-100 protein stains or get an expert consultation.

Desmoplastic melanomas sometimes coexist with nondesmoplastic forms of melanoma, either conventional melanoma (epithelioid cells) or spindle cell melanoma (cellular sheets of markedly atypical spindle cells) (fig. 4-46). These "combined" desmoplastic melanomas must be distinguished from "pure" desmoplastic melanomas. For pure desmoplastic melanoma, the invasive component must be composed of 90 percent or greater desmoplastic melanoma with a less than 10 percent nondesmoplastic melanoma component. In the words of Busam et al. (29), the spindled melanocytes in desmoplastic melanoma are "dispersed and separated from each other by fibrous tissue, resulting in low cellular density." Densely cellular spindled zones should be regarded as spindle cell melanoma, not desmoplastic melanoma. Desmoplastic melanomas are often thick deep lesions at the time of diagnosis. However, pure desmoplastic melanoma appears to have a better prognosis than combined desmoplastic melanoma (or conventional melanoma) of comparable Breslow thickness. Pure desmoplastic melanomas are unlikely to metastasize to lymph nodes and have a lower risk for distant metastasis (29). Local recurrence remains a significant challenge, since these lesions often invade through the subcutis and all the way down to the galea or periosteum of the skull, making surgical clearance with free margins difficult to achieve.

Desmoplastic melanomas have a tendency to wrap and invade multiple nerves ("neurotropism") (fig. 4-47). This can be quite striking, with multiple large-diameter nerves completely overtaken by the melanoma. Other nondesmoplastic types of melanoma also show neurotropism, albeit less often than in desmoplastic melanoma. As with other cancers, perineural invasion in neurotropic melanoma imparts a significant risk of local recurrence (26).

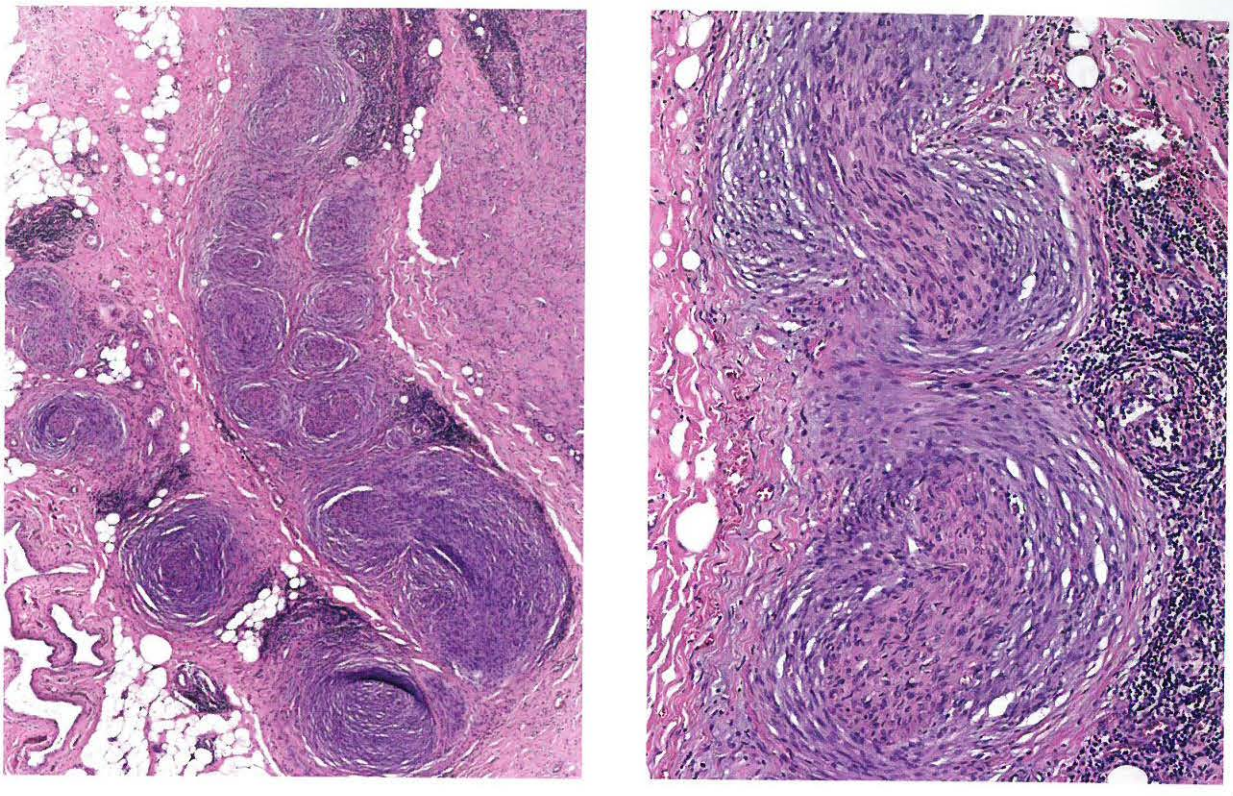


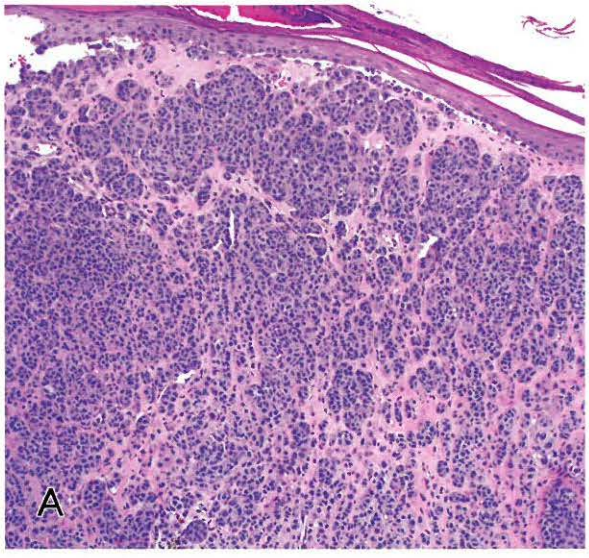
Figure 4-47

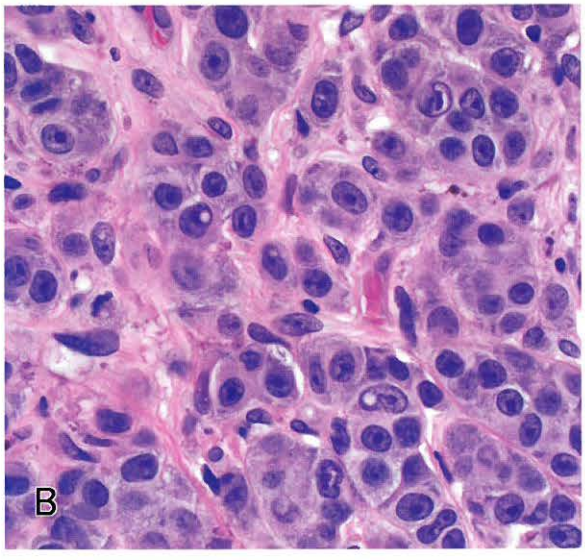
NEUROTROPIC MELANOMA

Left: These serpiginous nerves are tightly surrounded by layers of desmoplastic melanoma. Note the multiple lymphocytic aggregates adjacent to the involved nerves and within the background desmoplastic melanoma (top right).

Right: Not only is the nerve surrounded by desmoplastic melanoma, it is also filled with it. Tumor cells intermingle with the axons and Schwann cells until the tumor and the nerve become one.

Both spindle cell melanomas and desmoplastic melanomas may be misdiagnosed as malignant peripheral nerve sheath tumors (MPNST) by pathologists who are not familiar with these entities. A full discussion of MPNST is outside the scope of this book. In brief, MPNST is a high-grade sarcoma that usually arises as a large deep soft tissue mass, sometimes arising from a large neurofibroma, large nerve, or in a patient with neurofibromatosis 1. They paradoxically show loss of S-100 protein and SOX-10; these markers are completely negative in about 50 percent of MPNSTs, and in the remainder they are usually weak or patchy positive rather than diffuse strong positive (the exception being epithelioid MPNST, which is strongly S-100 protein positive). By immunohistochemistry, spindle cell and desmoplastic melanomas are usually easy to distinguish from MPNST. MPNST arising in the skin is rare (even in neurofibromatosis 1 patients); I strongly recommend against ever making that diagnosis without expert consultation. A small superficial nodule composed of strongly S-100 protein/SOX-10 positive malignant spindle cells is melanoma unless proven otherwise; it is almost certainly NOT MPNST. Spindle cell melanomas sometimes lose expression of MART-1 and HMB-45, and pure desmoplastic melanomas are almost always negative for those markers. Thus, the presence of only S-100 protein and SOX-10 expression in a spindle cell or desmoplastic melanoma is not surprising, and it should not suggest that the lesion might actually be MPNST (especially not if it is a superficial scalp nodule in an 80-year-old sun-damaged patient!). There are significant differences between MPNST and melanoma that could impact the clinical management of the patient.





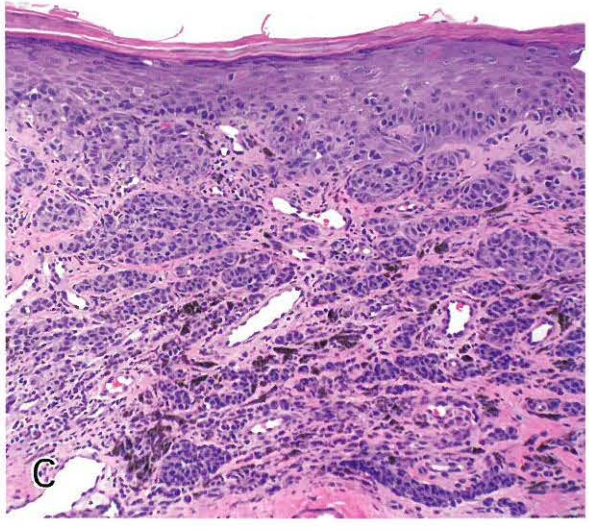


Figure 4-48

NEVOID MELANOMA

A: At low power, there is some resemblance to a nevus, with apparent maturation of dermal melanocytes. A clue to the malignant nature of this lesion is the hypercellularity of the dermal component: nests of dermal melanocytes are packed tightly together with little intervening dermal collagen.

B: A high-power view shows marked cytologic atypia, prominent nucleoli, and mitotic activity even in the deepest aspect of the lesion that appeared to be mature at low power. This is "pseudomaturation."

C: In some cases, elongated nests of dermal melanocytes are arranged parallel to the epidermis.

Nevoid Melanoma

Nevoid melanoma is not a specific subtype, but rather a descriptive term for a melanoma that histologically mimics a benign nevus. These melanomas usually resemble a thick compound nevus at low power with apparently normal maturation (fig. 4-48). The nests and individual melanocytes seem to get smaller with increasing depth into the dermis, but a closer look usually shows obvious cytologic atypia and mitotic activity. Pagetoid spread may be present in the overlying epidermis, which is an additional clue.

Occasionally cases have subtle features, both architecturally and cytologically; these are challenging even for experts. The main risk with nevoid melanoma is that it will be misdiagnosed as a nevus from low magnification without looking closer and recognizing the malignant features. I usually mention in my report that a melanoma has "nevoid features" mainly as a tip for future pathologists who might review the case or examine lymph nodes or distant metastases from the lesion, so that they can be aware that the melanoma might have deceptively benign-appearing features.

REFERENCES

1. Weinstock MA, Barnhill RL, Rhodes AR, Brodsky GL. Reliability of the histopathologic diagnosis of melanocytic dysplasia. The dysplastic nevus panel. Arch Dermatol 1997;133:953-8.
2. Duncan LM, Berwick M, Bruijn JA, et al. Histopathologic recognition and grading of dysplastic melanocytic nevi: an interobserver agreement study. J Invest Dermatol 1993;100:318S-21S.
3. Shors AR, Kim S, Argenyi Z, et al. Dysplastic naevi with moderate to severe histological dysplasia: a risk factor for melanoma. Br J Dermatol 2006;155:988–93.
4. O'Rourke EA, Balzer B, Barry CI, Frishberg DP. Nevic mitoses: a review of 1041 cases. Am J Dermatopathol 2013;35:30-3.
5. Hutchens KA, Heyna R 2nd, Mudaliar K, Wojcik E. The new AJCC guidelines in practice: utility of the MITF immunohistochemical stain in the evaluation of single-cell metastasis in melanoma sentinel lymph nodes. Am J Surg Pathol 2013;37:933-7.
6. Ferringer T. Immunohistochemistry in dermatopathology. Arch Pathol Lab Med 2015;139:83-105.
7. Prieto VG, Shea CR. Immunohistochemistry of melanocytic proliferations. Arch Pathol Lab Med 2011;135:853-9.
8. Massi G, LeBoit PE. Histological diagnosis of nevi and melanoma, 2nd ed. Heidelberg: Springer; 2013.
9. Kaley JR, Fullen DR, Gardner JM, et al. Vascular neoplasm or pseudovascular nevus? Potential pitfalls in diagnosis. J Biol Regul Homeost Agents 2015;29(Suppl 1):91-4.
10. Khalifeh I, Taraif S, Reed JA, Lazar AF, Diwan AH, Prieto VG. A subgroup of melanocytic nevi on the distal lower extremity (ankle) shares features of acral nevi, dysplastic nevi, and melanoma in situ. Am J Surg Pathol 2007;31:1130–6.
11. Hosler GA, Moresi JM, Barrett TL. Nevi with site-related atypia: review of melanocytic nevi with atypical histological features based on anatomic site. J Cutan Pathol 2008;35:889–98.
12. Shapiro M, Chren MM, Levy RM, et al. Variability in nomenclature used for nevi with architectural disorder and cytologic atypia (microscopically dysplastic nevi) by dermatologists and dermatopathologists. J Cutan Pathol 2004;31:523-30.
13. Rosendahl CO, Grant-Kels JM, Que SK. Dysplastic nevus: Fact and fiction. J Am Acad Dermatol 2015;73:507-12.
14. Cockerell CJ. Counterpoint: the "dysplastic" nevus. What I do and do not believe. J Am Acad Dermatol 2015;73:515-7.
15. Hurt MA. The melanocytic nevus described by Clark et al. What is its nature? What should it be named? An answer from history and from logic. J Cutan Pathol 2005;32:457-60.
16. Elder DE. Dysplastic naevi: an update. Histopathology 2010;56:112-20.
17. Calonje JE, Brenn T, Lazar A, McKee P. McKee's pathology of the skin, 4th ed. Edinburgh: Elsevier/Saunders; 2011.
18. Arumi-Uria M, McNutt NS, Finnerty B. Grading of atypia in nevi: correlation with melanoma risk. Mod Pathol 2003;16:764–71.
19. Goodson AG, Florell SR, Boucher KM, Grossman D. Low rates of clinical recurrence after biopsy of benign to moderately dysplastic melanocytic nevi. J Am Acad Dermatol 2010;62:591–6
20. Fung MA. Terminology and management of dysplastic nevi: responses from 145 dermatologists. Arch Dermatol 2003;139:1374–5.
21. Ferrara G, Argenziano G, Soyer HP, et al. The spectrum of Spitz nevi: a clinicopathologic study of 83 cases. Arch Dermatol 2005;141:1381-7.
22. Barnhill RL, Argenyi ZB, From L, et al. Atypical Spitz nevi/tumors: lack of consensus for diagnosis, discrimination from melanoma, and prediction of outcome. Hum Pathol 1999;30:513-20.
23. Gerami P, Busam K, Cochran A, et al. Histomorphologic assessment and interobserver diagnostic reproducibility of atypical spitzoid melanocytic neoplasms with long-term follow-up. Am J Surg Pathol 2014l;38:934-40.
24. Weismann K, Lorentzen HF. Dermoscopic color perspective. Arch Dermatol 2006;142:1250.
25. Bender RP, McGinniss MJ, Esmay P, Velazquez EF, Reimann JD. Identification of HRAS mutations and absence of GNAQ or GNA11 mutations in deep penetrating nevi. Mod Pathol 2013;26:1320-8.
26. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, eds. AJCC cancer staging manual, 8th ed. New York: Springer; 2017:563-581.
27. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med 2014;370:599-609.
28. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med 2017;376:2211-22.
29. Busam KJ, Mujumdar U, Hummer AJ, et al. Cutaneous desmoplastic melanoma: reappraisal of morphologic heterogeneity and prognostic factors. Am J Surg Pathol 2004;28:1518-25.

5 ADNEXAL TUMORS

A vast array of different tumors and proliferations can arise from the skin adnexal structures. These tumors are uncommon and show a wide range of histologic patterns. Differences of opinion about classification and terminology by dermatopathology experts over the years have resulted in an abundance of names for some of these entities. This makes adnexal tumors seem quite daunting to learn for the beginner in dermatopathology. This chapter will attempt to simplify classification, focusing on the more common or characteristic entities and on points of clinical importance. Wrangling over nuance is left for the experts to deal with.

There are three main categories of adnexal proliferations: sebaceous, sweat gland/duct, and hair follicle. Sebaceous proliferations usually possess bubbly vacuolated sebocytes, either few or many, depending on the entity and the individual lesion. Sweat gland/duct proliferations usually possess some form of ductal space or glandular lumen. Hair follicle proliferations usually possess one or more of the components of the normal hair follicle, including hair bulb/matrix, inner root sheath, outer root sheath, or infundibulum. If any of these features are seen in an epithelial tumor of the skin, an adnexal proliferation should be the main consideration. These features can be subtle or tricky in some cases. Keep adnexal tumors in the differential diagnosis any time an epithelial proliferation is encountered in the skin that does not easily fit into one of the more common epidermal proliferation categories discussed in chapter 3 (e.g., seborrheic keratosis, squamous cell carcinoma, basal cell carcinoma).

The first step for the beginner in dermpath is to recognize that one is dealing with a potential adnexal proliferation. The second step is to decide if it is in the sebaceous, sweat gland/duct, or hair follicle category. The third step is to try to name it. The fourth step is to make sure that it is benign and not malignant, as some forms of adnexal carcinoma can lack overt histologic and cytologic features of malignancy and must be recognized by distinct patterns and clinical scenarios (1).

SEBACEOUS PROLIFERATIONS

Sebaceous Hyperplasia

These usually present as yellow papules on the face of an adult. They typically have a central depression or "dell" in the middle of the lesion, so they are often recognizable to the dermatologist. Yet they are sometimes still biopsied because the clinical differential diagnosis includes basal cell carcinoma.

Microscopically, they look like very large but mature sebaceous glands bulging down into the dermis. They have a dilated opening directly to the skin surface, although it is not always visible in every histologic section of the lesion. Unlike normal sebaceous glands, *sebaceous hyperplasia* may lack an associated hair follicle. Mature sebocytes comprise the majority of the lesion; there is only a thin layer of blue basaloid cells around the periphery of each sebaceous lobule, similar to the appearance of normal adult sebaceous glands (fig. 5-1). Unlike many of the other sebaceous proliferations, sebaceous hyperplasia is not associated with Muir-Torre syndrome (a variation of hereditary nonpolyposis colorectal cancer syndrome/Lynch syndrome) that includes sebaceous neoplasms of the skin).

Sebaceous Adenoma

These also tend to present as yellow papules, most often on the face of an adult, and like other small skin papules, may clinically mimic basal cell carcinoma. Similar to sebaceous hyperplasia, they are composed of one or more enlarged lobules of mature sebocytes that usually connect to the epidermis and bulge down into the

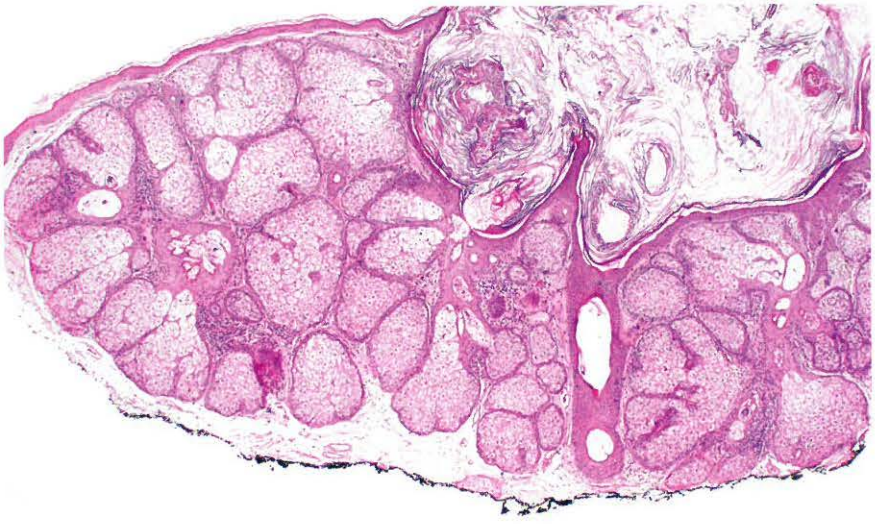


Figure 5-1

SEBACEOUS HYPERPLASIA

A cluster of very large but mature sebaceous glands bulge down into the dermis. There is a dilated opening from the glands directly to the skin surface.

dermis. However, unlike sebaceous hyperplasia, the peripheral layer of blue basaloid cells around each lobule is more prominent, usually several layers thick (fig. 5-2). Toward the periphery of each lobule, the sebocytes tend to be less mature than those of a normal sebaceous gland. The clear vacuoles, while still present, are fewer and are interspersed between pink or gray cytoplasm.

The combination of increased basaloid cells and decreased prominence of clear vacuoles gives *sebaceous adenoma* less of a white/pale appearance. The lobules are often more tightly grouped together than in sebaceous hyperplasia, yielding a more compact circumscription in many cases. Sebaceous adenomas are benign, although sometimes they are associated with Muir-Torre syndrome.

Sebaceoma

When a lesion resembles sebaceous adenoma but the blue basaloid cells comprise >50% of the lesion, the term *sebaceoma* is used (fig. 5-3). Like sebaceous adenoma, sebaceomas are benign but are sometimes associated with Muir-Torre syndrome. The basaloid cells of normal sebaceous glands represent a proliferative layer, similar to the basal layer of the epidermis. These are actively dividing epithelial cells, and thus they may display mitoses. The same is true of the blue basaloid cells in sebaceous adenoma. As the basaloid component is very prominent in sebaceoma, scattered mitoses are usually easily identified, and this may cause anxiety for the pathologist. Mitoses by themselves should cause no concern for malignancy. However, if the lesion is large and infiltrative, displays nuclear pleomorphism, or has atypical mitotic forms, this should prompt concern for the possibility of *sebaceous carcinoma*.

Sebaceomas are sometimes large; this alone is not a feature of malignancy. Yet if a large sebaceous lesion is only superficially sampled by a shave biopsy, the findings in the biopsy may not be representative of the entire lesion. Although sebaceous adenoma and sebaceoma are benign lesions that do not routinely require complete excision, if there is concern that the biopsy is not representative or if atypical features are present, complete excision is probably prudent to ensure that the lesion is not a sebaceous carcinoma in disguise.

Sebaceous Carcinoma

Sebaceous carcinomas are malignant neoplasms that may display aggressive behavior in a significant subset of cases (2). They are divided into two groups based on clinical scenario: periocular (more common) or extraocular. *Periocular sebaceous carcinomas* often arise on the upper eyelid. They can clinically mimic chalazion, other inflammatory processes, or other forms of skin cancer. They tend to spread into the conjunctiva in a pagetoid fashion, resulting in unique treatment challenges. *Extraocular sebaceous carcinomas* can occur elsewhere on the head and neck (away from the eye), on the trunk, or on the extremities. Extraocular sebaceous carcinomas, especially when arising outside the head and neck, are more likely to

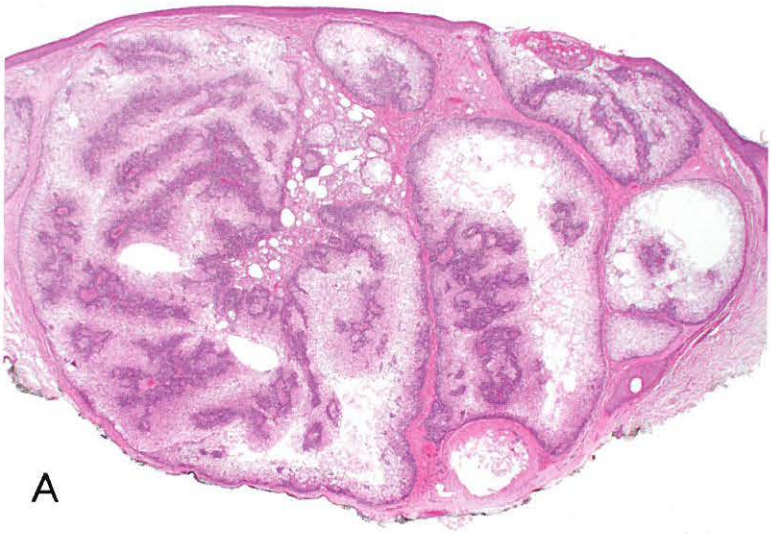


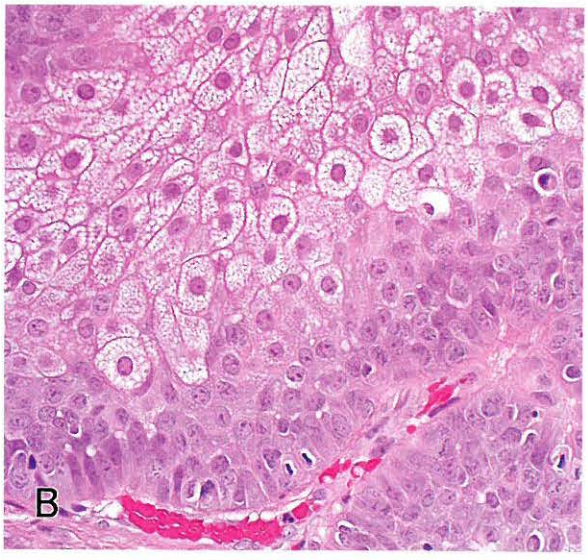
Figure 5-2

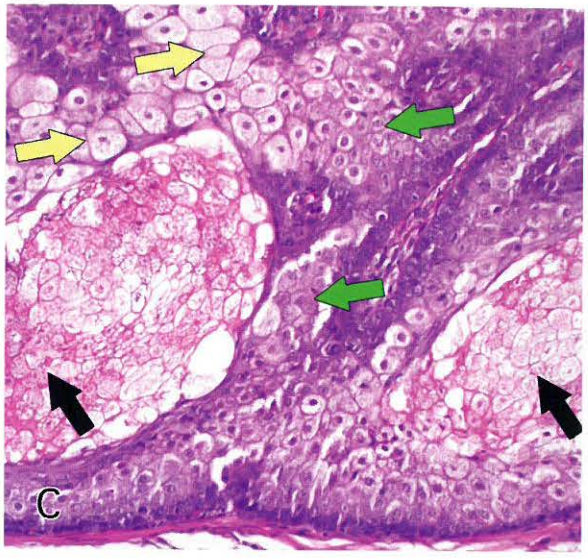
SEBACEOUS ADENOMA

A: Enlarged lobules of mature sebocytes bulge from the epidermis down into the dermis. The periphery of each lobule shows a more prominent rim of blue basaloid cells than is seen in sebaceous hyperplasia.

B: The peripheral rim of basaloid germinative cells is several layers thick. Mitoses may be seen. Mature sebocytes with vacuolated cytoplasm still predominate over the basaloid cells.

C: Toward the periphery of each lobule, the sebocytes tend to be less mature, giving more of a pink or gray color (green arrows) than the white/pale color of more mature sebocytes (yellow arrows). Dead mature sebocytes here (black arrows) represent holocrine secretion phenomenon, not true tumor necrosis.





be associated with Muir-Torre syndrome; periocular sebaceous carcinomas usually lack this syndromic association (3–5).

Sebaceous carcinoma may show a range of histologic features (fig. 5-4). Well-differentiated sebaceous carcinomas may have a similar appearance to sebaceous adenoma or sebaceoma, with variable amounts mature sebocytes admixed with blue basaloid cells. With these, the tumor is obviously sebaceous, but it can be difficult to determine if it is malignant or benign. Marked cytologic atypia, abundant and atypical mitoses, and infiltrative and deep growth are features supporting sebaceous carcinoma rather than adenoma or sebaceoma.

Normal sebaceous glands display holocrine secretion (death of mature sebocytes to make sebum). Mature sebocytes may also die in sebaceous tumors; do not interpret this as true tumor necrosis or evidence of malignancy. Sheets of necrotic basaloid cells likely represent true tumor necrosis, but necrotic bubbly mature sebocytes likely do not. Further, true tumor necrosis in a malignant sebaceous lesion will usually be accompanied by other malignant findings. Be wary of making a diagnosis of malignancy in sebaceous tumors (or any adnexal tumor) based on necrosis alone.

Poorly differentiated sebaceous carcinomas can resemble poorly differentiated squamous cell carcinoma or basal cell carcinoma, or have

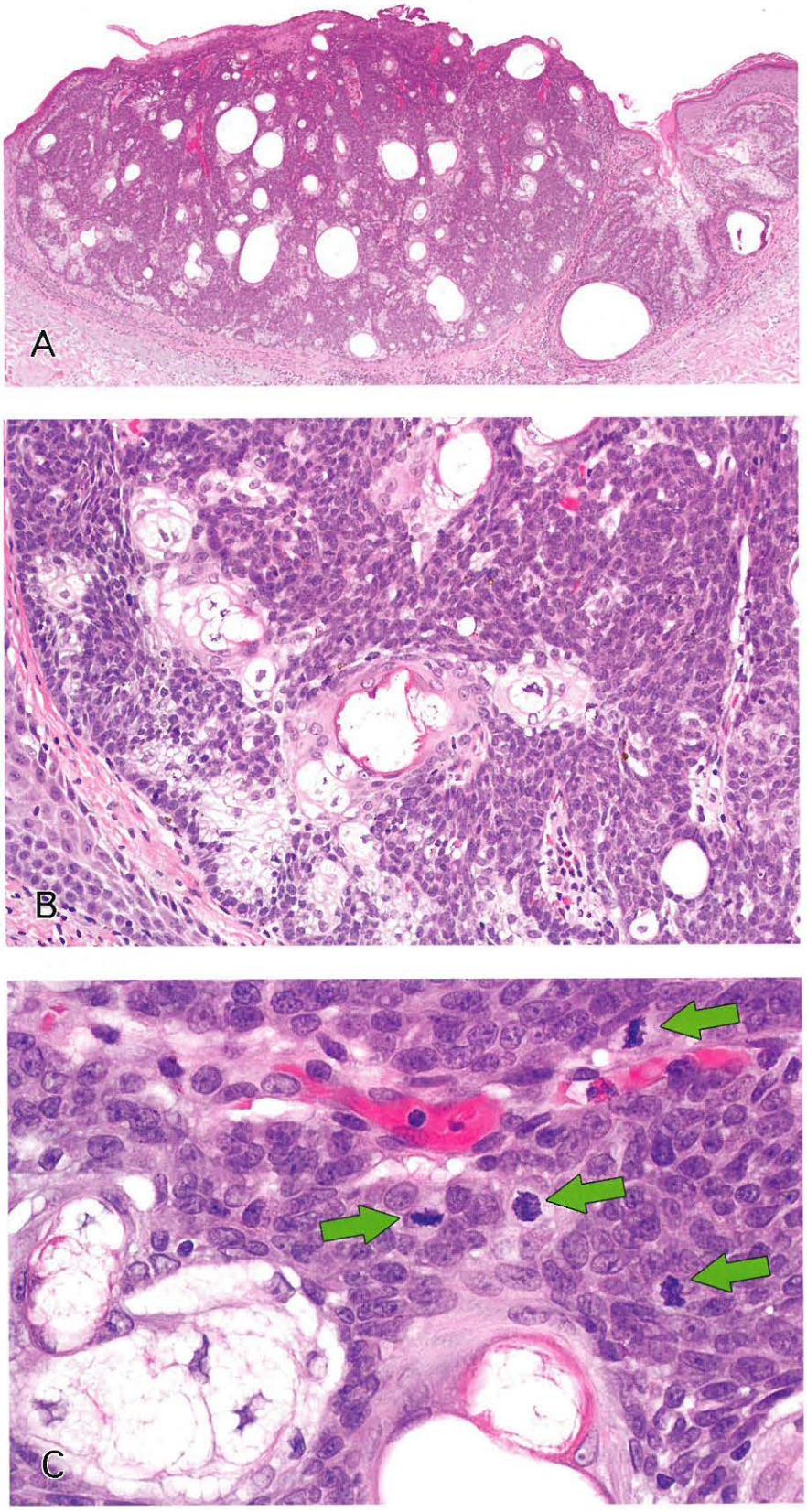


Figure 5-3

SEBACEOMA

A: The overall appearance is similar to sebaceous adenoma but the blue basaloid cells comprise greater than 50 percent of the lesion.

B: Mature sebocytes are still present, but the basaloid component predominates.

C: The basaloid cells are uniform and often display multiple mitoses (green arrows). Atypical mitotic forms and nuclear pleomorphism should not be seen.

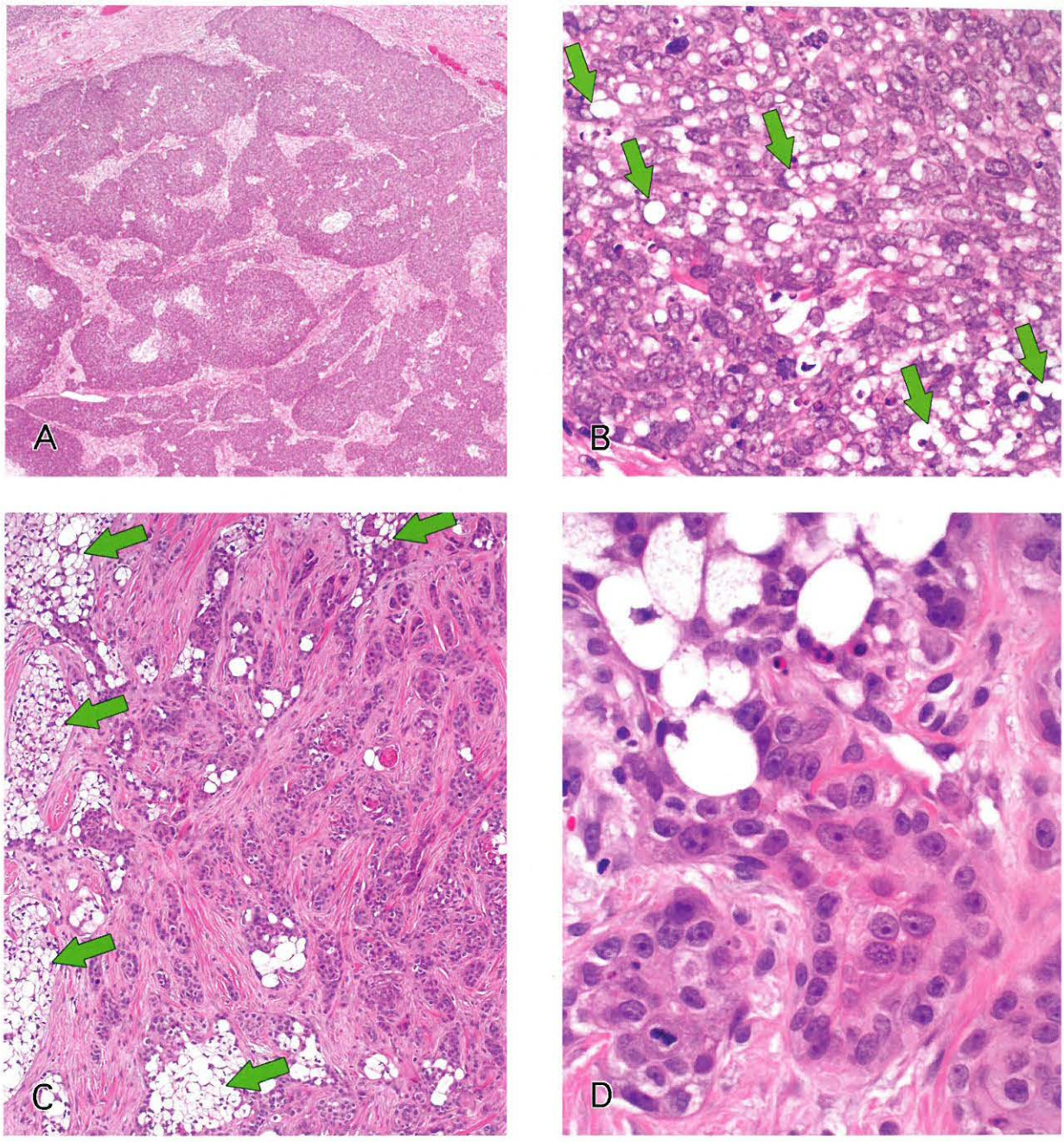


Figure 5-4

SEBACEOUS CARCINOMA

A: Poorly differentiated sebaceous carcinomas may be very basaloid, potentially mimicking basal cell carcinoma, Merkel cell carcinoma, or poorly differentiated squamous cell carcinoma.

B: At high power, the basaloid cells have pleomorphic atypical nuclei. Clear lipid vacuoles are present (green arrows). Distinguishing true sebaceous differentiation from artifactual vacuolation can be challenging in poorly differentiated sebaceous carcinomas, sometimes necessitating the use of immunohistochemistry.

C: This sebaceous carcinoma shows markedly infiltrative growth and areas that closely resemble squamous cell carcinoma (right). However, obvious sebaceous differentiation is also present (green arrows), confirming the diagnosis.

D: The tumor is composed of malignant keratinizing cells resembling those of squamous cell carcinoma (lower right) as well as multivacuolated sebocytes (upper left).

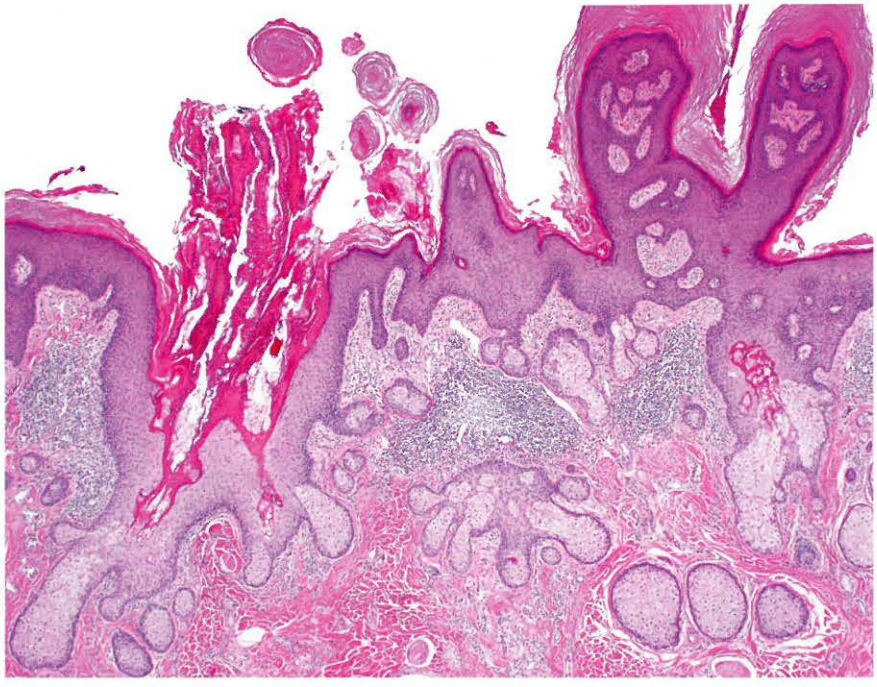


Figure 5-5

NEVUS SEBACEUS

There is epidermal acanthosis and papillomatosis, which can mimic verruca or seborrheic keratosis. Hair follicles are markedly diminished or absent. Large mature sebaceous glands with dilated openings empty directly onto the skin surface rather than into an associated follicle.

overlapping features of both. Sometimes they can even superficially resemble Merkel cell carcinoma. With these, the tumor is obviously malignant, but it can be difficult to determine whether it is sebaceous or some other carcinoma as vacuolated sebocytes can be scarce.

When I suspect a poorly differentiated sebaceous carcinoma (e.g., any carcinoma near the eye, especially if poorly differentiated), my approach is to look carefully at hematoxylin and eosin (H&E) stained slides to find vacuolated/clear/pale tumors cells then use immunostains to help determine if they are truly sebocytes or not. Epithelial membrane antigen (EMA) (highlights vacuoles) and Factor XIIIa (stains nuclei, but only works with clone AC-1A1) are the sebaceous markers I currently prefer, although neither is perfect. Adipophilin, androgen receptor, and other antibodies have also been reported to be helpful to confirm sebaceous differentiation in these difficult cases (6,7). If I still have doubt about sebaceous differentiation in a carcinoma after this, I make a diagnosis of invasive carcinoma with a comment that it may be a squamous cell carcinoma, but I cannot exclude sebaceous carcinoma. In extraocular sites, this is usually enough to ensure that the tumor will be treated adequately (excised with negative margins) and that the possibility of more aggressive behavior will be understood. Near the eye, however, there may be conjunctival involvement, which may necessitate significantly different treatment; expert consultation is probably a good idea in such cases.

Nevus Sebaceus

Nevus sebaceus is not a true sebaceous neoplasm, but rather a hamartomatous proliferation of epidermal, sebaceous, and other adnexal elements (fig. 5-5). Despite the name, it has nothing to do with melanocytes. These lesions usually present as a congenital hairless plaque on the scalp or face. During puberty, androgen hormones cause sebaceous glands to enlarge, making the plaque grow clinically and become more yellow and oily/greasy.

Histologically, nevus sebaceus usually shows epidermal acanthosis, which can mimic verruca or seborrheic keratosis. Hair follicles are markedly diminished or absent; this is a very useful clue. In adolescents or adults, there will also be increased numbers of large mature sebaceous glands, which typically empty directly onto the skin surface rather than emptying into an associated hair follicle like a normal sebaceous gland would. Before puberty, the sebaceous glands are small and immature and less obvious, so recognizing the other features of nevus sebaceus is important in order to make the diagnosis. Some

Table 5-1

PATTERN-BASED APPROACH TO SWEAT GLAND TUMORS[a]

Pattern	Tumors
Solid pink/clear/squamoid proliferation in epidermis and/or dermis +/- cysts	Acrospiroma family: Hidroacanthoma simplex Poroma Dermal duct tumor Hidradenoma
Blue basaloid nodules in dermis or subcutis	Spiradenoma Cylindroma
Tadpole/paisley tie	Syringoma Microcystic adnexal carcinoma Desmoplastic trichoepithelioma[b] Infiltrative/morpheaform BCC[b,c]
Cystic spaces with papillary projections	Syringocystadenoma papilliferum Hidradenoma papilliferum Digital papillary adenocarcinoma
Dermal or subcutaneous nodule with cords/chains/tubules and chondromyxoid stroma	Mixed tumor (chondroid syringoma) Myoepithelioma

[a]Adapted from Table 2 from Arch Pathol Lab Med 2019;143:832-851 with permission from Archives of Pathology and Laboratory Medicine. Copyright 2019 College of American Pathologists.
[b]These are not sweat gland tumors, but they enter the differential for this pattern and are thus included here.
[c]BCC = basal cell carcinoma.

nevus sebaceus have apocrine glands or eccrine glands with apocrine features in the underlying dermis; this is a very useful clue when present, as normal scalp does not possess apocrine glands.

A variety of adnexal tumors (mostly benign) may arise within nevus sebaceus, such as syringocystadenoma papilliferum, trichoblastoma/trichoepithelioma, or trichilemmoma. Most tumors resembling basal cell carcinoma within nevus sebaceus are probably trichoblastomas or trichoepitheliomas in actuality. True secondary malignancies arising in nevus sebaceus have been reported but are rare.

SWEAT GLAND/DUCT PROLIFERATIONS

Sweat gland tumors show a wide range of histologic patterns. The unifying feature is that they show gland or duct formation, usually in the form of tubules or cystic spaces of varying size within the tumor. These tumors can be difficult to learn because of confusing nomenclature that has changed over time and a tendency in the literature to debate whether a given tumor is of eccrine or apocrine origin. While splitting benign sweat gland tumors into different subcategories can be an enjoyable mental exercise for dermatopathologists like me who find adnexal tumors fascinating, it is probably of limited importance for patient care most of the time. Learning sweat gland tumors by whether they are eccrine or apocrine or otherwise histologically related is a difficult way to approach the topic. Instead, I prefer to use a pattern-based approach, grouping tumors based on the way they look microscopically rather than how they are related to one another biologically (Table 5-1) (1).

Pattern: Solid Pink/Clear/ Squamoid Proliferation in Epidermis or Dermis +/- Cysts

Acrospiroma is a synonym for *hidradenoma*. Several tumors share similar features with hidradenoma and are likely related: *hidroacanthoma simplex, poroma,* and *dermal duct tumor*. I like to think of these entities as the "acrospiroma family." All of these tumors are composed of uniform epithelial cells with varying amounts of pink, clear/pale, or squamoid cytoplasm. Although there are some differences (e.g., poromas tend to have less cytoplasm whereas hidradenomas have more), the cytologic features of these entities are similar.

My former fellow, Ed Fulton MD, proposed the "modeling clay" concept for the acrospiroma

family of tumors: if pink modeling clay represents the tumor cells, molding the clay into different shapes and placing it at different levels in the skin will yield different tumors. Hidroacanthoma simplex is purely intraepidermal. Poroma is intraepidermal but also has large fingers of tumor pushing down into the dermis. Dermal duct tumor has multiple nodules in the superficial dermis. Hidradenoma has one or multiple larger nodules in the deep dermis. The growth patterns are different, but they are all made of the same type of cells (the "pink modeling clay") (1). These tumors also display sweat ducts, ranging from small duct lumens all the way up to large cystically dilated ductal spaces.

Hidroacanthoma Simplex. I think of this as basically just a thin poroma. It is a small lesion with a slightly thickened epidermis that is filled with monotonous "poroid" cells. Unlike poroma, it lacks the elongated fingers of tumor pushing down into the dermis. The appearance is very similar to clonal seborrheic keratosis, except that hidroacanthoma simplex should have rare sweat duct lumens. I very rarely make this diagnosis in my practice.

Poroma. Poromas classically present as a sessile nodule on the sole or side of the foot, although they can arise at other sites. Uniform, small, round, "poroid" cells fill the epidermis and dramatically expand the rete, forming elongated fingers or tongues of tumor pushing from the epidermis down into the dermis (fig. 5-6). There is a sharp demarcation at the periphery of the lesion between the uniform poroma cells and the keratinocytes of the adjacent epidermis. Ductal differentiation is present, either as well-formed sweat ducts similar to normal eccrine ducts or as more immature ducts in the form small round empty spaces lined by a thin homogeneous layer of pink cuticle. Ulceration and inflammation are common findings. The stroma (papillary dermis) between the elongated fingers of tumor is usually markedly edematous. Dense pink collagen (basement membrane) may also be present in the dermis.

Some poromas are darkly pigmented and may clinically mimic melanoma. Microscopically, these show abundant melanin pigment and admixed dendritic melanocytes evenly scattered within the poroma. These are "passenger" melanocytes, similar to the phenomenon seen in some seborrheic keratoses and other epidermal neoplasms (see fig. 3-12). Do not mistake these for the pagetoid melanocytes of melanoma.

Porocarcinoma. Porocarcinoma is shaped like poroma, with expanded rete forming fingers/tongues of tumor that stretch down into the dermis, but it has malignant cytologic features instead of small bland poroid cells. Tongues or fingers of *in situ* porocarcinoma pushing deeply into the dermis can be difficult to distinguish from true invasion. On a shave biopsy where the lesion is transected, I like to use the terminology "porocarcinoma, at least *in situ*" in the report.

The other difficulty with porocarcinoma is that it can closely resemble squamous cell carcinoma (SCC) and vice versa. Obviously, porocarcinoma should have ductal structures, but SCC can mimic porocarcinoma by entrapping background normal eccrine ducts or by having prominent clear cell vacuolated cytoplasmic change that gives the impression of ducts. CD117 expression has been reported to favor porocarcinoma over SCC (8). CEA and EMA can also be used to highlight true ductal spaces. In cases where I am still uncertain between the two entities, I prefer to use a generic term like "carcinoma (*in situ* or invasive)" in the main diagnosis line with a comment that the differential includes SCC and porocarcinoma. This raises the possibility of more aggressive behavior and helps ensure appropriate treatment and follow-up.

Dermal Duct Tumor. These display multiple small nodules of poroid cells in the superficial dermis without connection to the epidermis. It is debatable whether this is a real entity or merely a poroma in which the connection to the epidermis is not visible in the plane of section or a smaller, superficial variant of hidradenoma. Again, all of the acrospiroma family of tumors have similar overlapping features, and the distinction between them does not have clinical significance. I rarely make this diagnosis in my practice. When I see lesions that could fit for this entity, I usually just call them poroma or hidradenoma instead.

Hidradenoma. Hidradenoma is a circumscribed deep dermal or subcutaneous nodule often with central cystic change and prominent clear cell change (fig. 5-7). Some cases extend upward and connect to the epidermis, showing

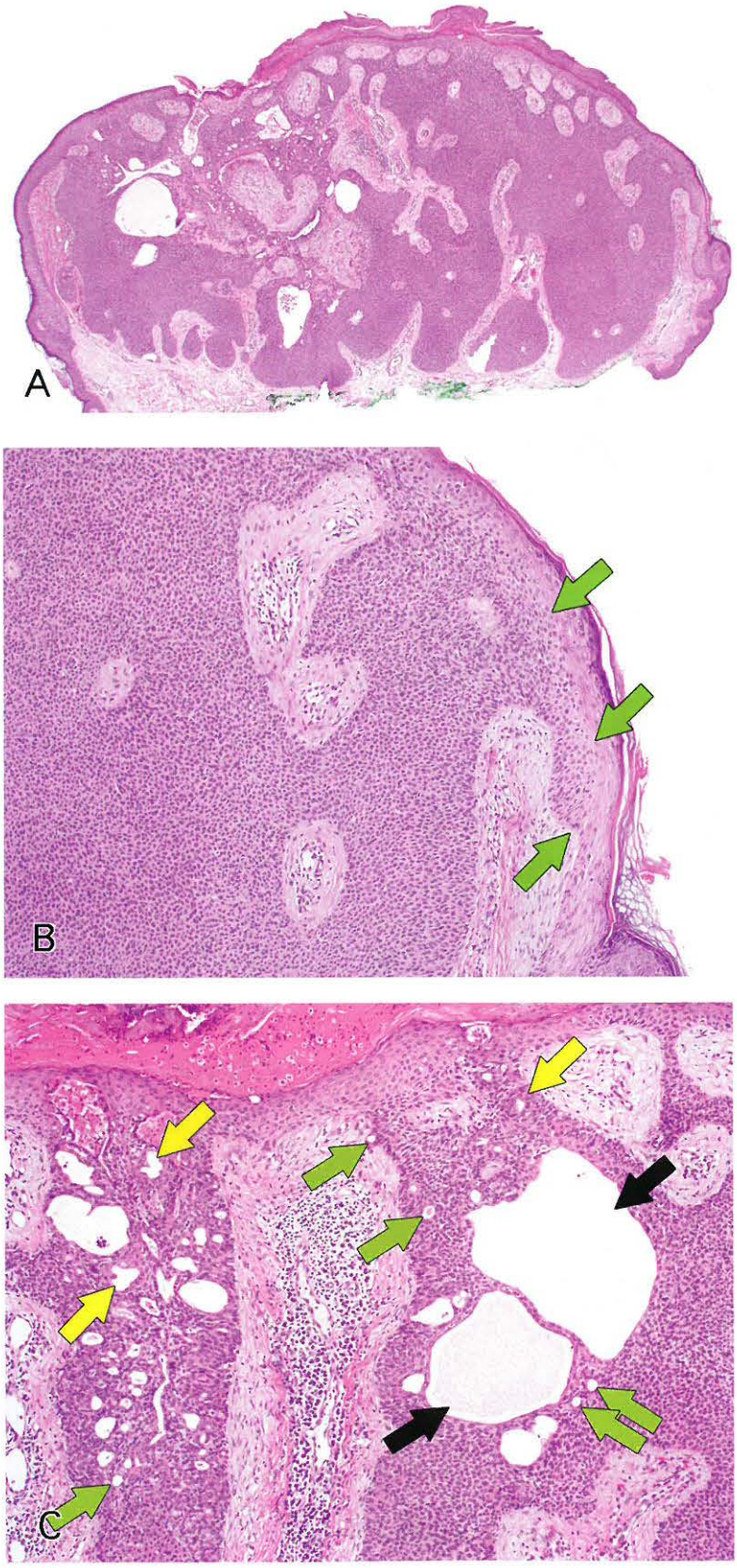


Figure 5-6

POROMA

A: The rete are dramatically expanded, forming elongated fingers or tongues of tumor pushing from the epidermis down into the dermis.

B: Uniform, small, round, "poroid" cells with eosinophilic cytoplasm comprise the tumor, filling the epidermis and forming the elongated fingers/tongues that push downward. There is a sharp demarcation at the periphery of the lesion between the uniform poroma cells and the keratinocytes of the adjacent epidermis (arrows).

C: Ductal differentiation is present, as well-formed sweat ducts similar to normal eccrine ducts (yellow arrows), as dilated cystic spaces (black arrows), or as more immature ducts in the form of small round empty spaces lined by a thin homogenous layer of pink cuticle (green arrows).

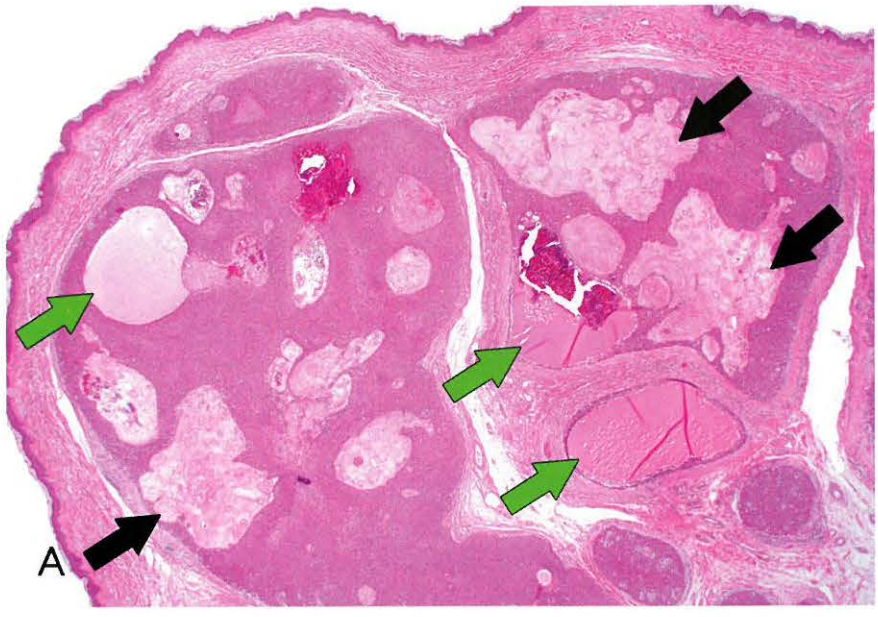
Figure 5-7

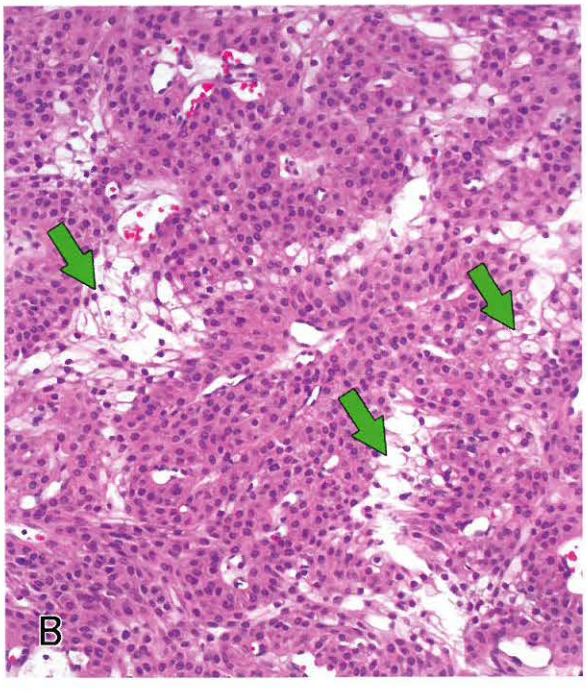
HIDRADENOMA

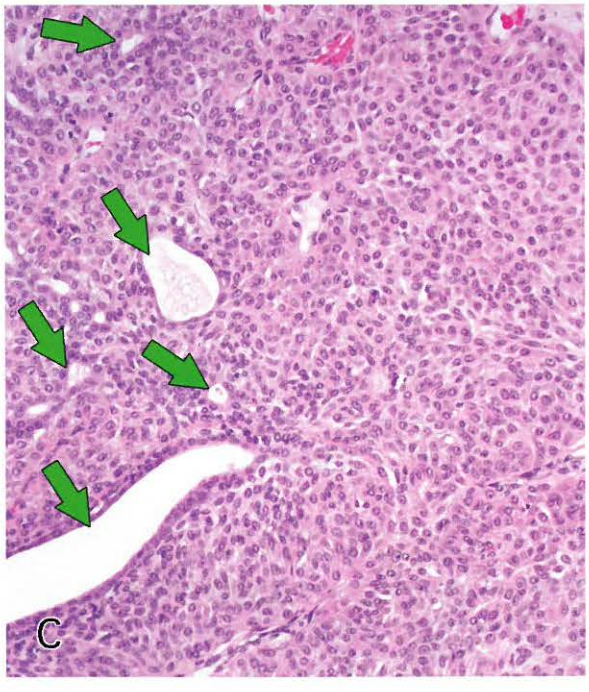
A: Multiple circumscribed pink nodules are present in the dermis. Multiple cystic spaces filled with secretions are present (green arrows), and there is hyalinization of stroma (black arrows).

B: The tumor cells have uniform round nuclei with abundant pale pink cytoplasm, imparting a squamoid cytologic appearance. Clear cell change is also a common feature (arrows).

C: Ductal structures are present and vary widely in size and shape (arrows).







overlap with poroma (I have started referring to these as hidradenoma/poroma hybrid tumors in reports). Ductal structures are present and vary widely in form: small ducts (white circles lined by pink cuticle), larger well-formed ducts, and/or large cystic spaces that are actually markedly dilated ducts. Cuboidal/columnar cells, sometimes with apocrine snouts, may line the ductal spaces.

As with poroma and many other adnexal tumors, dense pink basement membrane is often present in the intervening stroma. The cells of hidradenoma tend to have abundant pale pink cytoplasm. Squamous metaplasia is frequently seen. Clear cell change is also a common feature; when focal it is a useful clue to the diagnosis, but when extensive it can mimic metastatic renal cell carcinoma (RCC). Look for direct connection to

epidermis and/or adnexal structures, ducts/cystic spaces, and pink basement membrane as clues to favor hidradenoma rather than RCC. I find p63/p40 to be the most useful stain to differentiate between these entities: positive in hidradenoma (and most other adnexal tumors) but negative in RCC (1).

Hidradenoma arising in the skin of the breast can be confused with low-grade ductal carcinoma *in situ* or other breast parenchymal neoplasia. Clinical information about size, depth, and precise site of the lesion is crucial in this scenario. Immunostains for p63/p40 are helpful.

Hidradenocarcinoma. Malignant sweat gland tumors are rare overall, but this is one of the more common types that I encounter. *Hidradenocarcinoma (malignant acrospiroma)* can arise de novo or, less commonly, out of a preexisting benign hidradenoma. Similar to benign hidradenoma, these have nests of cells with pale pink or squamoid cytoplasm, ducts/cysts, and often clear cell change, but with the addition of malignant cytologic features and infiltrative growth pattern. Some hidradenocarcinomas display severe nuclear atypia, abundant mitoses (usually 4/10 high-power fields or more), atypical mitoses, and broad zonal necrosis. Others are more subtle cytologically and can only be recognized as malignant by their infiltrative growth, which takes the form of irregular angulated nests of tumor with stromal desmoplasia extending into adjacent tissue at the periphery of the main tumor mass. Hidradenocarcinomas have the potential for local recurrence and metastasis (9).

The term *atypical hidradenoma* can be used for hidradenomas with focal atypical features (increased mitotic activity, pleomorphism, large nucleoli) that fall short of definite malignancy. I use this term occasionally, particularly on partial biopsies where I cannot see the entire lesion, and I usually recommend complete excision. Atypical hidradenomas may recur locally (especially if incompletely excised) but are unlikely to metastasize (9). Occasional hidradenomas have small foci of necrosis but no other atypical features. There is not much data on this in the literature, but I believe these can probably be regarded as atypical hidradenomas and handled as above. Be sure to search carefully to ensure no other malignant features are present.

Pattern: Blue Basaloid Nodules in Dermis

Spiradenoma and *cylindroma* are both composed of blue basaloid nodules in the dermis. The two entities are closely related. They often coexist and merge with one another on the same slide; these are called *spiradenocylindroma* or *hybrid spiradenoma/cylindroma*. Just as all of the acrospiroma family of tumors are composed of the same type of pink cells ("pink modeling clay") but with different architectural arrangement, so spiradenoma and cylindroma are both composed of the same types of blue cells ("blue modeling clay") but arranged in different patterns. Acrospiroma (hidradenoma) and spiradenoma may sound similar in name, but they are usually easy to tell apart microscopically, even at low power: hidradenoma/acrospiroma is pink/pale/squamoid whereas spiradenoma (and cylindroma) is dark blue. Other non-sweat gland tumors to keep in the differential diagnosis for blue basaloid nodules in the dermis: BCC, Merkel cell carcinoma, and hair follicle tumors.

Spiradenoma. Spiradenoma consists of one or multiple circumscribed blue nodules in the dermis with no epidermal connection (fig. 5-8). These nodules are made up of closely aggregated nests and trabeculae of blue basaloid cells. The cells have uniform round nuclei, with smaller and darker nuclei at the periphery of nests/trabeculae and larger paler nuclei toward the center. These two populations are not always easy to see in every case. A third cell type is also usually present: small lymphocytes scattered throughout the tumor. Sweat ducts are present usually in the form of small lumens lined by bright pink eosinophilic cuticle on the inner surface of the duct. Larger cystic ducts are sometimes seen. The stroma often shows abundant basement membrane (type IV collagen) deposits. Significant stromal edema may be seen, yielding an unusual cystic or corded pattern in which strands of tumor cells appear to be suspended in empty space. Most spiradenomas are solitary and sporadic, but sometimes they are multiple or associated with Brooke-Spiegler syndrome (multiple spiradenomas, cylindromas, and trichoepitheliomas; due to *CYLD* gene mutation) or other heritable familial syndromes. Unlike most skin tumors, spiradenomas are often painful clinically.

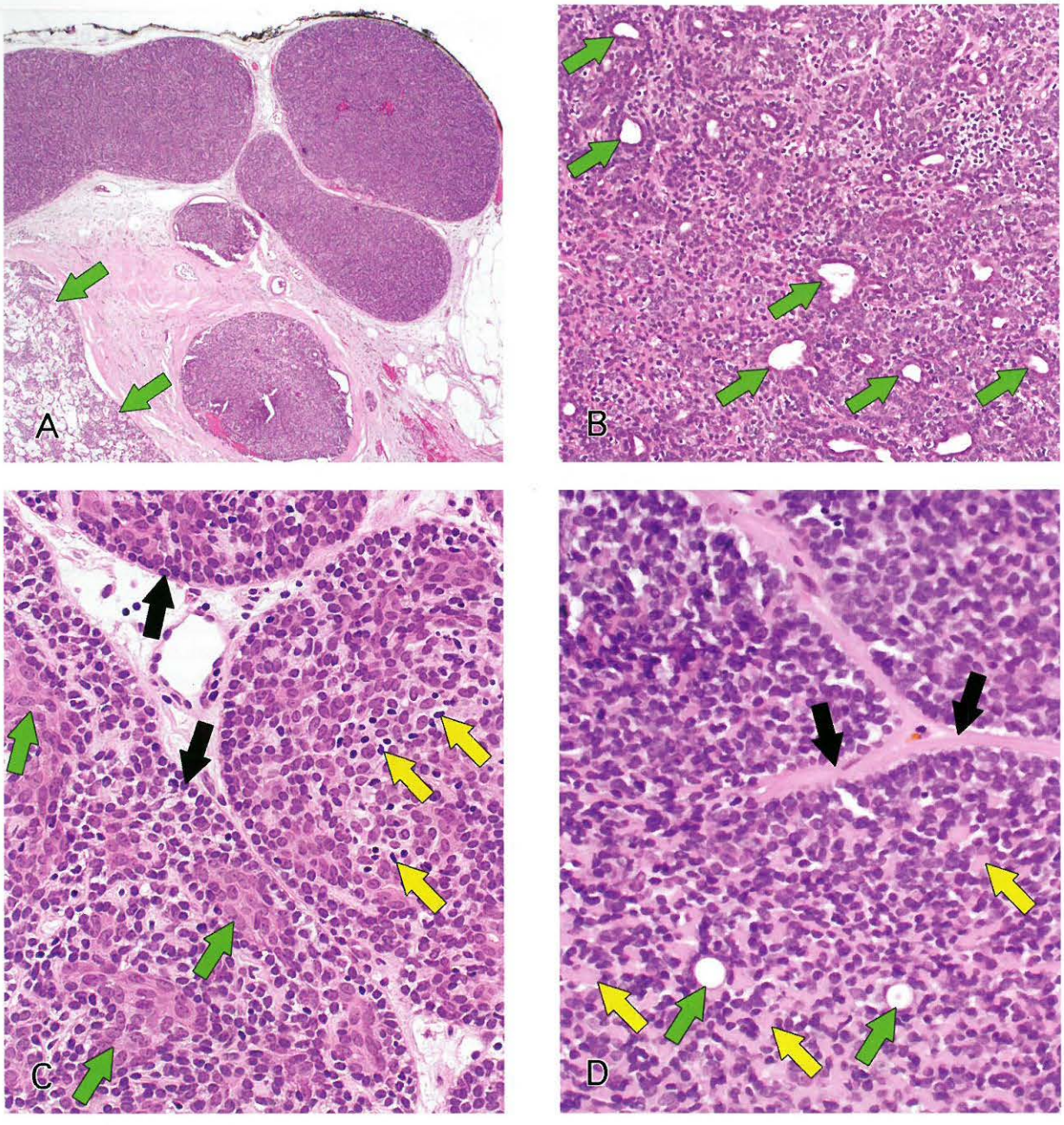


Figure 5-8

SPIRADENOMA

A: Multiple circumscribed blue nodules are present in the dermis and subcutis. One of the nodules demonstrates prominent stromal edema (arrows), which splays apart the cords and nests of tumor cells within the nodule.

B: The nodules are made up of closely aggregated nests and trabeculae of blue basaloid cells. They are packed so closely as to give a sheet-like appearance. Multiple sweat ducts are present (arrows).

C: The blue basaloid cells have uniform round nuclei, with smaller and darker nuclei (black arrows) at the periphery of nests/trabeculae and larger more pale nuclei (green arrows) toward the center. Lymphocytes are often scattered throughout the tumor (the smallest darkest cells in the tumor; yellow arrows).

D: The stroma often shows abundant basement membrane (type IV collagen) deposits, either around nests (black arrows) or as small globules within nests (yellow arrows). The ducts in this case are merely small round circles lined by a thin layer of pink cuticle (green arrows).

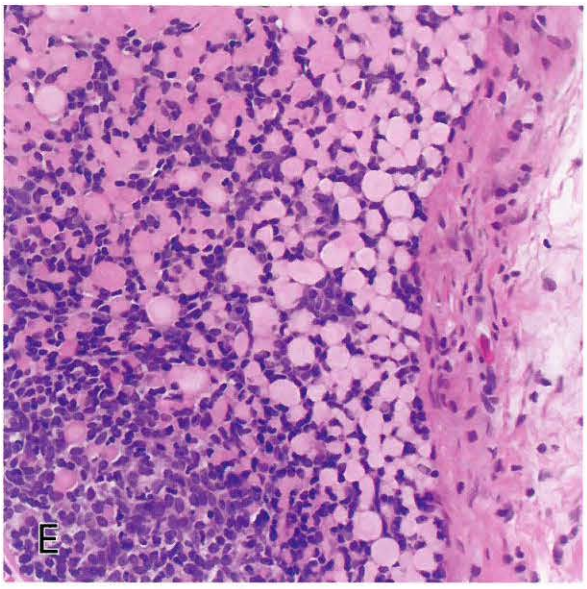


Figure 5-8, continued

E: The globules of pink basement membrane may be numerous in some cases.

Cylindroma. Cylindromas usually occur on the head and neck, especially the scalp, and they are much more common in women. This is a blue basaloid dermal proliferation without epidermal connection. Cylindroma has a different low power architecture than spiradenoma. The basaloid cells are arranged into geometric micronodules that mold together with neighboring micronodules to yield a "giraffe spot" or "jigsaw puzzle" pattern (fig. 5-9). The large sharply circumscribed nodules that characterize spiradenoma are lacking. However, the higher power appearance of cylindroma is nearly identical to spiradenoma. There is a dual population of bland basaloid cells with uniform round nuclei (darker and smaller nuclei at the periphery of micronodules and larger paler nuclei toward the center). There are small sweat ducts lined by an inner pink cuticle, but they may be infrequent. Cylindromas usually display striking basement membrane deposition, both as numerous round pink "droplets" scattered among the tumor cells within the micronodules and as thick pink layers surrounding entire micronodules.

Most cylindromas are solitary and sporadic, but sometimes they present as numerous lesions covering the scalp (historically referred to as "turban tumor" syndrome, but now recognized as a variant of Brooke-Spiegler syndrome) (1).

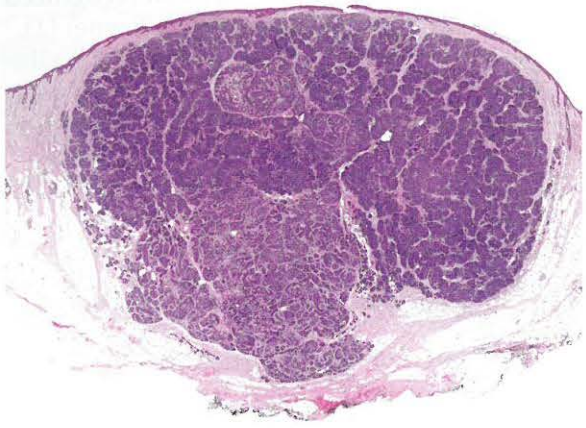
Spiradenocarcinoma and Malignant Cylindroma. While malignant variants exist, they are exceedingly rare and outside the scope of this book. They usually show areas of frankly malignant carcinoma arising out of a benign background component of spiradenoma or cylindroma. If you see atypical features in a spiradenoma or cylindroma, it is probably wise to get an expert consultation.

Pattern: Tadpoles/Paisley Tie

The tadpole/paisley tie pattern differential diagnosis includes *syringoma, microcystic adnexal carcinoma (MAC), desmoplastic trichoepithelioma (DTE),* and *infiltrative/morpheaform BCC.* Only the first two entities on this list are sweat gland tumors, but all are discussed in this section since sorting out this differential can be challenging, especially on small biopsies.

Syringoma. These often present clinically as multiple small papules on the face. They consist of multiple small sweat ducts aggregated together to form a small nodule in the dermis (fig. 5-10). Some of the round ductal structures have "tails," providing a tadpole or paisley tie appearance. Duct lumens are obvious and easy to identify even at low power; they resemble normal eccrine ducts. The background dermis is usually sclerotic. Some syringomas have pale/clear cytoplasmic change, which may be associated with diabetes.

Microcystic Adnexal Carcinoma (MAC). MAC classically presents as a firm skin-colored plaque on the nasolabial/periorbital face of adults (10,11). It often infiltrates well beyond the clinically visible edge of the tumor and may invade deeply into underlying tissues. Metastasis and mortality are rare, but local recurrence is common because of the aggressive infiltrative growth pattern, which may result in significant morbidity (12,13). Microscopically, MAC displays thin cords of bland epithelial cells that infiltrate the deep dermis, subcutis, and sometimes even the deep skeletal muscle (fig. 5-11). Perineural invasion is often seen. Duct formation is usually present, but it may be focal and subtle. The tubules/cords of cells are tightly compressed, making the lumens very narrow and difficult to appreciate. Obvious sweat ducts like those of syringoma may be seen, but they



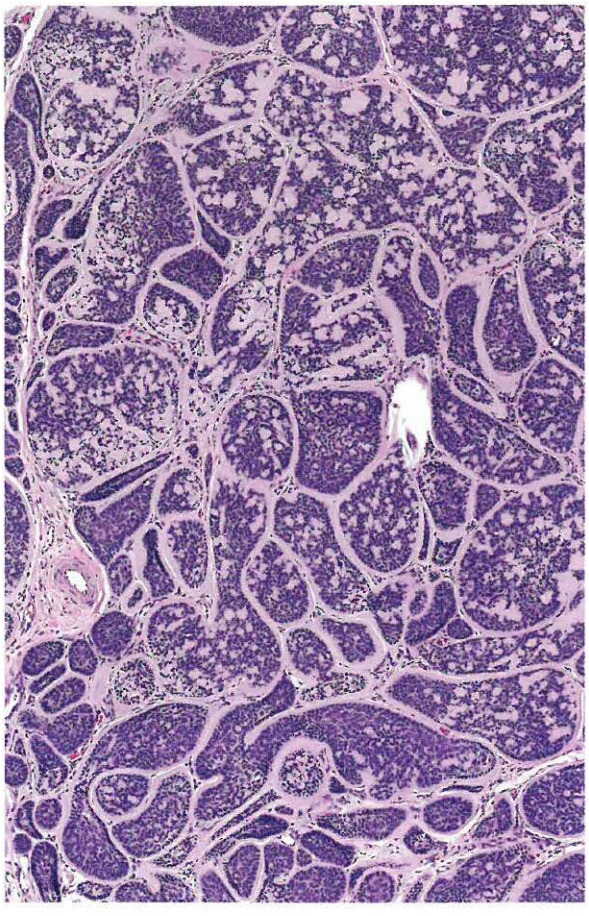
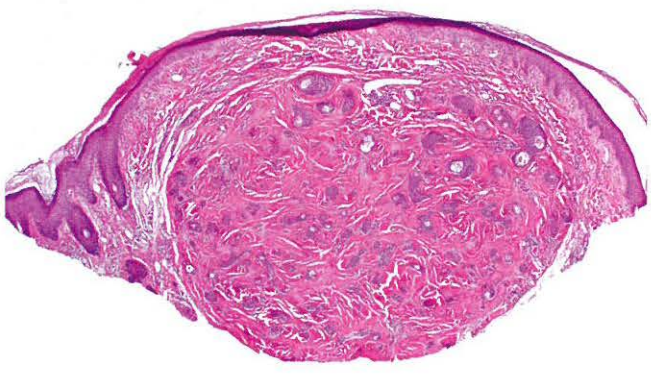


Figure 5-9

CYLINDROMA

Above: There is a blue basaloid dermal proliferation without epidermal connection. It is composed of numerous small nests; the large sharply circumscribed nodules that characterize spiradenoma are lacking.

Right: The basaloid cells are cytologically identical to those of spiradenoma, but they are arranged into geometric micronodules that mold together to yield a "giraffe spot" or "jigsaw puzzle" pattern. Prominent pink basement membrane is a common finding, either forming a thick rim around each nest or as small globules within nests (similar to fig. 5-8E); this case shows both patterns.



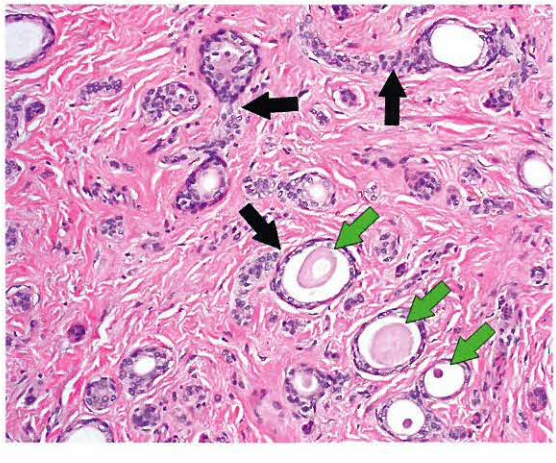


Figure 5-10

SYRINGOMA

Above: Multiple small sweat ducts are aggregated together to form a small nodule in the dermis. Note the dense sclerosis in the background compared to adjacent dermis; this is a common feature.

Right: Some of the round ductal structures have "tails," providing a tadpole or paisley tie appearance (black arrows). Open duct lumens are easily identified, and many contain pink sweat secretions (green arrows).

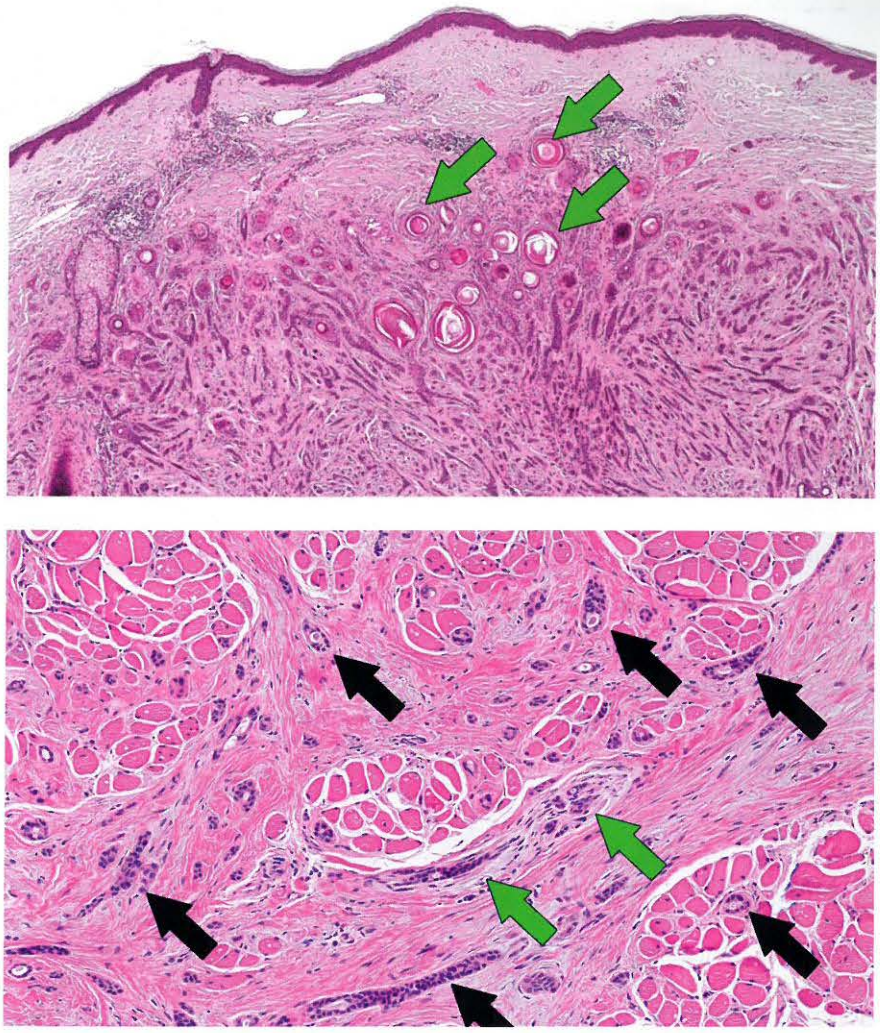


Figure 5-11

MICROCYSTIC ADNEXAL CARCINOMA

Top: Small keratin-filled cysts are present superficially (arrows). Beneath this are many infiltrative cords of basaloid cells. Unlike syringoma, duct lumens are usually difficult to identify in the superficial aspect of the lesion. (Courtesy of Rajendra Singh, M.D., and PathPresenter.net.)

Bottom: In the deep aspect of this microcystic adnexal carcinoma (different case than top), ducts are easier to identify. They lack cytologic atypia and closely resemble normal eccrine ducts, except that they are invading deep skeletal muscle (black arrows) and nerve (green arrows).

are usually sparse and deeply located. The superficial dermis often contains small cysts filled with keratin, a useful but not totally specific clue; desmoplastic trichoepithelioma and other entities can also have small keratin cysts.

MAC is a carcinoma by nature of its infiltrative growth, not its cytologic features. It has bland uniform cells that cytologically resemble benign normal eccrine ducts. Pleomorphism, necrosis, and high mitotic rate should not be present; if they are, the tumor is probably infiltrative SCC or BCC or some other carcinoma rather than MAC.

Distinguishing MAC from the other entities in the tadpole/paisley tie differential can be challenging on small biopsies and is usually clinically important. While infiltrative/morpheaform BCC has similar behavior and treatment as MAC, syringoma and DTE are totally benign entities.

MAC versus DTE is the most difficult aspect of the tadpole/paisley tie differential. DTE has small keratin cysts in the superficial dermis and cords of bland cells, features it shares with MAC, but it lacks ducts (fig. 5-12). However, the ductal lumens in MAC are often compressed and subtle, which can make them hard to identify. When the ducts are not visible, MAC and DTE look strikingly similar, especially on a superficial shave biopsy. The most helpful thing to tell them apart is a large enough biopsy where the base of the lesion can be visualized. DTE should be small and limited to the dermis whereas MAC is usually larger and deeply infiltrative.

MAC versus syringoma is usually much easier. The duct lumens in syringoma are abundant and

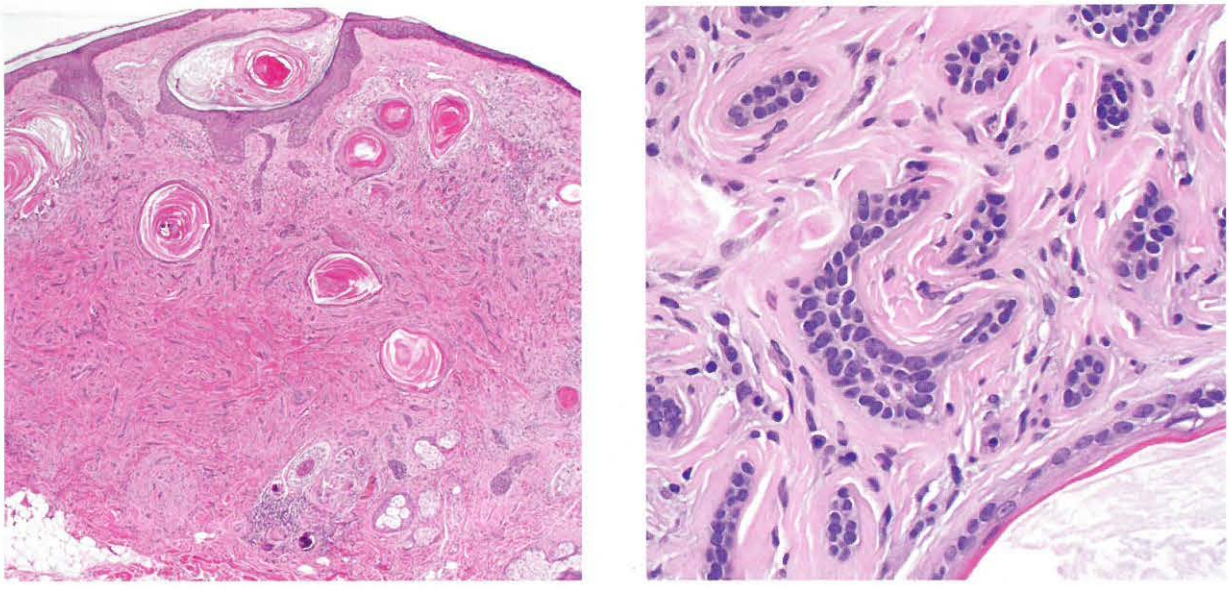


Figure 5-12

DESMOPLASTIC TRICHOEPITHELIOMA

Left: There are small keratin-filled cysts and cords of bland basaloid cells in a dense collagenous stroma. The appearance can closely mimic the superficial aspect of a microcystic adnexal carcinoma.

Right: Bland basaloid cells form cords and small nests embedded in a densely sclerotic stroma. Keratinous cysts are present (bottom right).

easy to see on H&E. DTE lacks ducts. The ducts in MAC are often subtle, especially at the superficial aspect of the lesion. If a superficial shave biopsy shows multiple sweat ducts with obvious lumens, it is probably syringoma not MAC.

Infiltrative BCC is included in the tadpole/paisley tie differential, but it is usually the easiest to distinguish from MAC, DTE, and syringoma. Although the infiltrative cords of basaloid tumor cells in BCC can have a tadpole shape, they lack ducts. Larger nests of more obvious BCC are often present in the biopsy. Infiltrative BCC also has a characteristic desmoplastic myxoid stroma that serves as a helpful clue. Both infiltrative BCC and MAC have similar clinical behavior, with high risk of local recurrence but low risk of metastasis or mortality, and both need complete excision with negative margins.

When I am uncertain and the biopsy is small, I use a diagnosis of "infiltrative basaloid neoplasm" with a comment explaining the differential and recommending conservative complete excision to allow the entire lesion to be microscopically examined. Various immunostains have been reported as useful in sorting out the tadpole/paisley tie differential. I occasionally use some of these, but as I often still end up giving a descriptive diagnosis and requesting re-excision, I tend to skip these immunostains in most cases. I believe a larger sample is usually much more helpful than immunohistochemistry here (1).

Pattern: Cystic Spaces with Papillary Projections

Syringocystadenoma Papilliferum (SCAP). SCAP is a benign sweat gland tumor that occurs most often on the scalp of children, where it presents as a warty or ulcerated plaque. It often arises in a preexisting nevus sebaceus. The microscopic appearance is very characteristic (fig. 5-13). The epidermal surface is exophytic and verrucous. Multiple dilated glandular channels open from the skin surface and branch down into the underlying dermis. Papillary islands with central fibrovascular cores float within these dilated channels. The channels and the floating islands/papillae are lined by a double layer of bland cuboidal to columnar sweat duct-type epithelium, sometimes showing apocrine snouts. Numerous plasma cells are a common

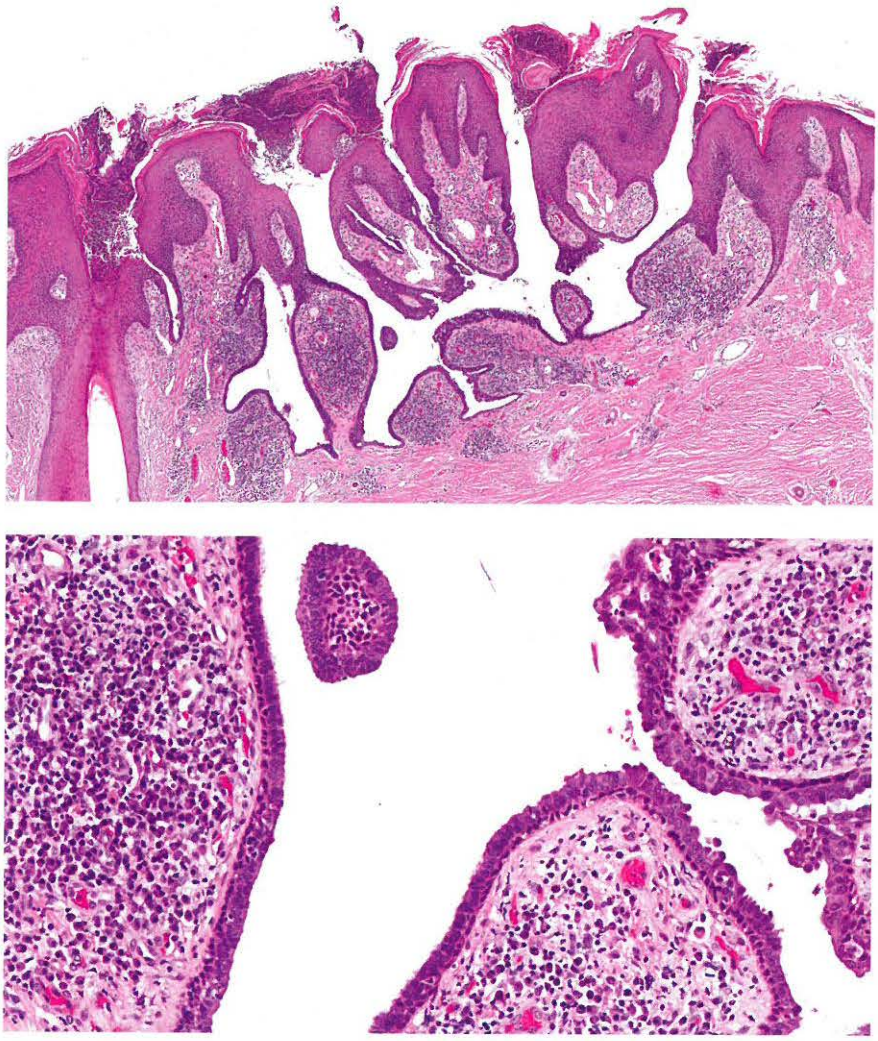


Figure 5-13

SYRINGOCYSTADENOMA PAPILLIFERUM

Top: The epidermal surface is exophytic and verrucous with overlying scale-crust. Multiple dilated glandular channels open from the skin surface and branch down into the underlying dermis. Papillary islands with central fibrovascular cores float within these dilated channels.

Bottom: The channels and the floating islands/papillae are lined by a double layer of bland cuboidal to columnar sweat duct-type epithelium, sometimes showing apocrine snouts. Numerous plasma cells are present in the fibrovascular cores, a classic feature.

finding in the fibrovascular cores of the islands/papillae and in the adjacent dermis.

Hidradenoma Papilliferum. Hidradenoma papilliferum is a benign sweat gland tumor that almost always arises in the anogenital region of women. It is a circumscribed cystic dermal lesion containing many papillae packed closely together creating a "maze-like" pattern (fig. 5-14). The cystic spaces and the papillae are lined by a double layer of bland cuboidal to columnar cells, often with apocrine snouts, similar to that of SCAP.

Digital Papillary Adenocarcinoma. This rare sweat gland tumor presents as a nodule on the distal finger (or sometimes toe), usually of middle-aged adult men. Local recurrence is common, and some cases metastasize to regional lymph nodes or lung, sometimes long after initial diagnosis. Treatment involves wide local excision or even digit amputation in some cases.

The tumor displays single or multiple nodules in the deep dermis or subcutis with no epidermal connection (fig. 5-15). The nodules are usually circumscribed and surrounded by dense fibrosis, although some may be infiltrative at the periphery. The nodules characteristically display prominent cystic spaces with variable numbers of papillae and/or micropapillae projecting into the spaces. Solid areas are usually composed of cellular sheets of oval, round, or even plump spindle cells. Ducts/tubules punctuate the solid zones; these are lined by columnar to cuboidal epithelium. The solid zones with tubules have a biphasic appearance that in some cases resembles a biphasic synovial sarcoma. Squamoid whorls may be seen.

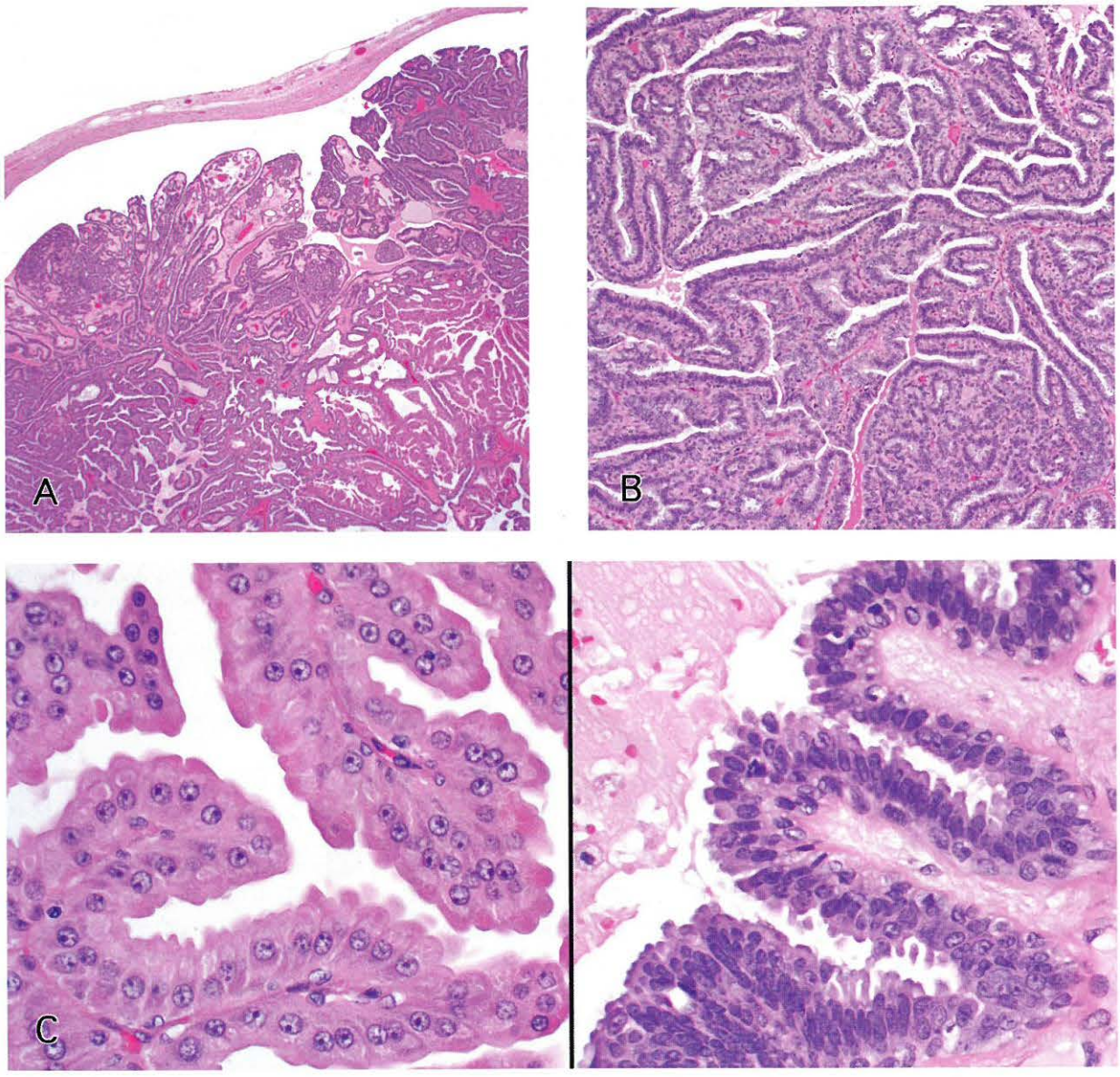


Figure 5-14

HIDRADENOMA PAPILLIFERUM

A: Many papillae are packed closely together within a cystic space.
B: The branching papillae and intervening glandular channels create a "maze-like" pattern.
C: The cystic spaces and papillae are lined by a double layer of bland cuboidal to columnar cells, often with apocrine snouts (right) and frank apocrine metaplasia (left).

Most cases of digital papillary adenocarcinoma have a deceptively benign appearance by conventional cytologic and histologic criteria; they usually have banal nuclei and low mitotic activity. The digital location and presence of papillae are the crucial keys to recognizing this tumor and not misdiagnosing it as a benign tumor. Digital papillary adenocarcinoma should be in the initial differential diagnosis for any adnexal tumor on the digits until it can be confidently excluded. If there is any doubt, I strongly recommend expert consultation. A lot is at stake for both the pathologist and the patient here.

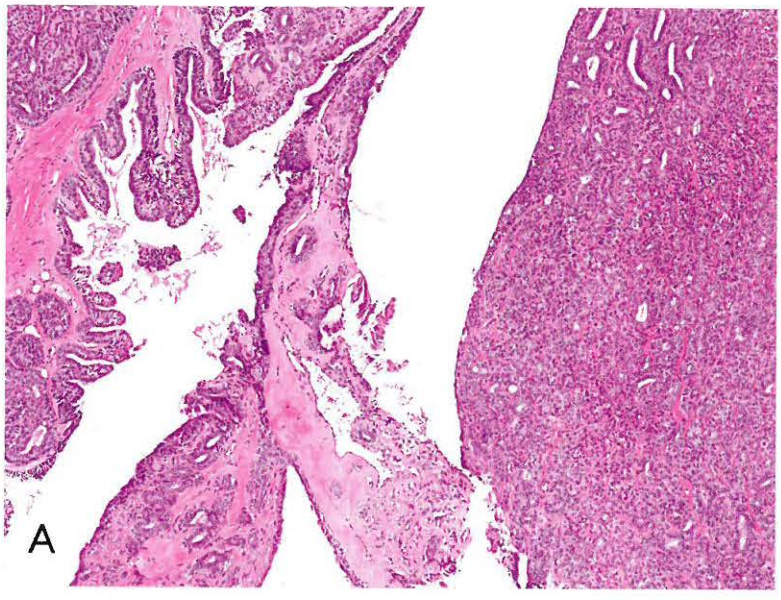


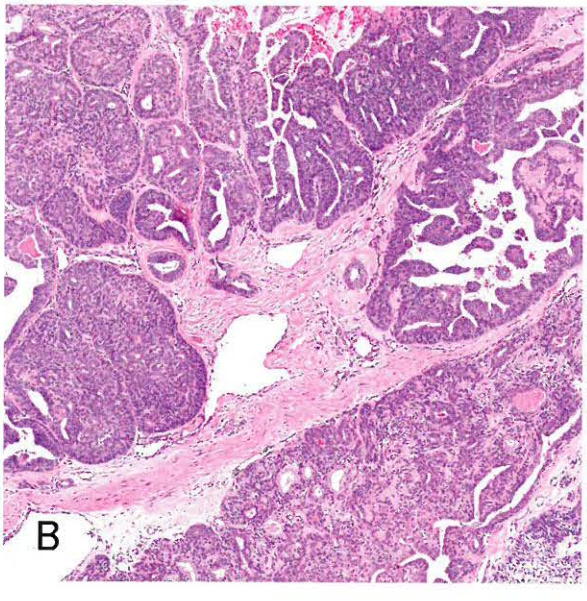
Figure 5-15

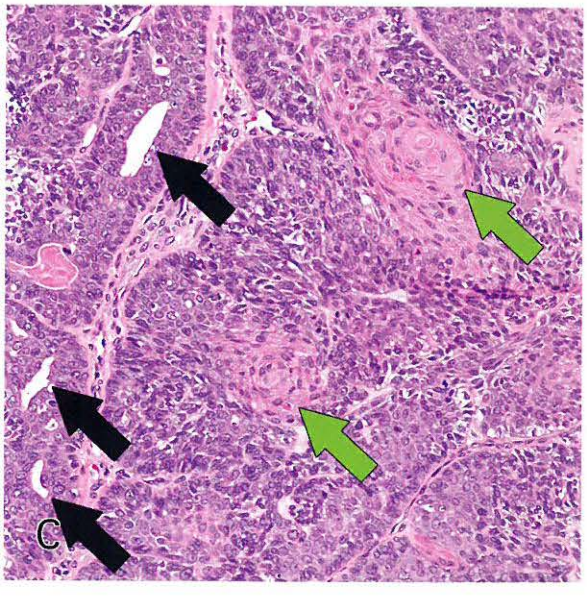
DIGITAL PAPILLARY ADENOCARCINOMA

A: There are both solid and cystic zones. Papillae protrude into the cystic spaces. Tubules/ducts punctuate the solid zones.

B: Papillae and micropapillae project into the cystic spaces. Multiple predominantly solid cellular nodules are also present.

C: The solid areas show multiple tubules/ducts/glands lined by bland cuboidal cells (black arrows). Cytologic atypia is often absent or minimal. The squamoid whorls are a characteristic finding but not always seen (green arrows).





Pattern: Dermal Nodule with Cords/Chains/ Tubules and Chondromyxoid Stroma

Mixed Tumor (Chondroid Syringoma). Similar to salivary gland mixed tumor (pleomorphic adenoma), cutaneous mixed tumor consists of two intermingled cell types: epithelial and myoepithelial (fig. 5-16). Tumors composed mostly of myoepithelial cells with minimal or no epithelial component are referred to as myoepithelioma; cutaneous mixed tumor and myoepithelioma probably exist on a spectrum.

Mixed tumors have a wide range of histologic patterns. The most common form is a circumscribed dermal nodule with glands/ducts/tubules arranged haphazardly in a chondromyxoid stroma. The ducts are lined by bland cuboidal to columnar cells similar to those of normal sweat ducts and of many of the other sweat gland tumors discussed previously. The epithelial component may display other adnexal differentiation including apocrine, sebaceous, or even follicular. The stroma can vary greatly from sclerotic to myxoid to chondroid, and

may contain mature fat, cartilage, and bone in variable amounts. Myoepithelial cells are present in the basal layer of glands/ducts and also scattered about in the stroma. Myoepithelial cells range from epithelioid to plasmacytoid to spindled to clear cell in their cytomorphology.

Mixed tumor is also called *chondroid syringoma* although that name is misleading as they do not really look like a syringoma and they do not always have cartilage. Myoepithelial cells are a dominant component of mixed tumor/myoepithelioma, but other sweat gland tumors may also possess variable populations of myoepithelial cells. Myoepithelial cells typically coexpress S-100 protein along with cytokeratin and EMA. Calponin is also usually positive. However, smooth muscle actin (SMA), p63, and other markers of normal myoepithelial cells are often surprisingly negative in myoepithelial neoplasms (14,15).

Malignant variants of mixed tumor and myoepithelioma are very rare and are challenging to diagnose. Marked cytologic atypia is probably the most reliable feature of malignancy in these tumors (14,16). Expert consultation is recommended before making a diagnosis of myoepithelial carcinoma or malignant mixed tumor.

Primary Cutaneous Mucinous Carcinoma. Primary cutaneous mucinous carcinoma usually arises on the head and neck (especially near the eye) of elderly adults. It usually has indolent behavior. The classic microscopic appearance is nests of round cells floating in a sea of pale blue mucin in the dermis and/or subcutis (fig. 5-17). Fibrous septa divide the sea of mucin into individual pools. The nuclei are often bland cytologically although some possess more nuclear atypia. Apocrine snouts are commonly present.

A large study by Kazakov et al. (17) found a spectrum of morphologic features similar to those seen in mucinous carcinoma of the breast, suggesting that this tumor may be a cutaneous analog. They also found that many cases of primary cutaneous mucinous carcinoma arose from *in situ* precursor lesions similar to ductal hyperplasia, atypical ductal hyperplasia, and ductal carcinoma *in situ* of the breast. Some precursor lesions to primary cutaneous mucinous carcinoma have neuroendocrine differentiation; these are known as "endocrine mucin-producing sweat gland carcinoma" (18). Identifying a coexisting precursor lesion, either by H&E or by immunohistochemical detection of a peripheral myoepithelial layer in some parts of the lesion, proves that the mucinous carcinoma is of cutaneous origin rather than a metastasis (17,19).

When an *in situ* precursor lesion is not identified, it can be challenging to determine whether the mucinous carcinoma is a cutaneous primary versus a metastasis. Statistics and clinical information are most helpful in this situation. Metastatic mucinous carcinoma to the skin is rare. When mucinous carcinoma of the breast involves the skin, it usually involves the skin on or near the breast (via direct extension or local recurrent growth) rather than metastasis to the skin of the head and neck (17). Immunostains will not help much in this scenario, as both skin and breast mucinous carcinomas have a similar immunophenotype (often positive for CK7, ER, and PR, but negative for CK20) (19).

Intestinal mucinous carcinomas can rarely metastasize to the skin, but they usually display dirty necrosis, a useful clue (17). Intestinal mucinous carcinomas usually express CK20 and CDX-2; these stains may be useful if there is concern for metastasis from an intestinal primary. I find the clinical scenario to be the most helpful: if the lesion is near the eye and there is no known history of mucinous carcinoma elsewhere, then it is most likely primary cutaneous mucinous carcinoma.

Sweat Gland Tumor Immunohistochemistry

Although most sweat gland tumors can be diagnosed on H&E, immunohistochemistry is sometimes helpful in challenging cases. A full discussion of the nuances of immunostaining patterns in sweat gland tumors is outside the scope of this book. However, the beginner should be aware of some of these markers so as to avoid confusion by unexpected stain results.

Sweat gland tumors express various cytokeratins. EMA and carcinoembryonic antigen (CEA) highlight the luminal surface of sweat ducts (normal and neoplastic). Most benign and malignant skin adnexal tumors (sebaceous, sweat gland, and follicular) express nuclear p63 and p40 (with the notable exception of mucinous carcinoma), making these useful markers for distinguishing primary cutaneous adnexal carcinomas from metastatic adenocarcinoma from a visceral pri-

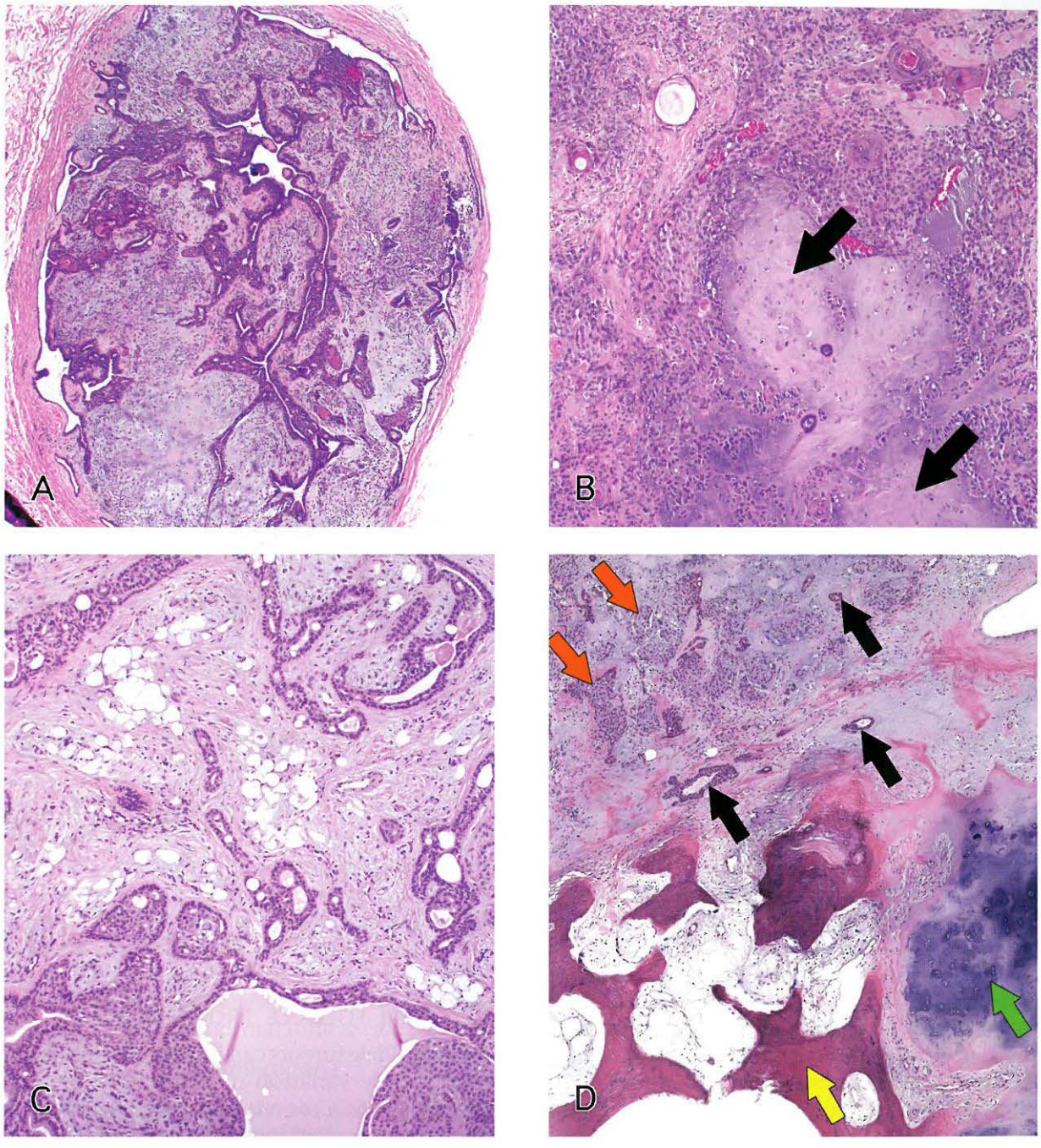


Figure 5-16

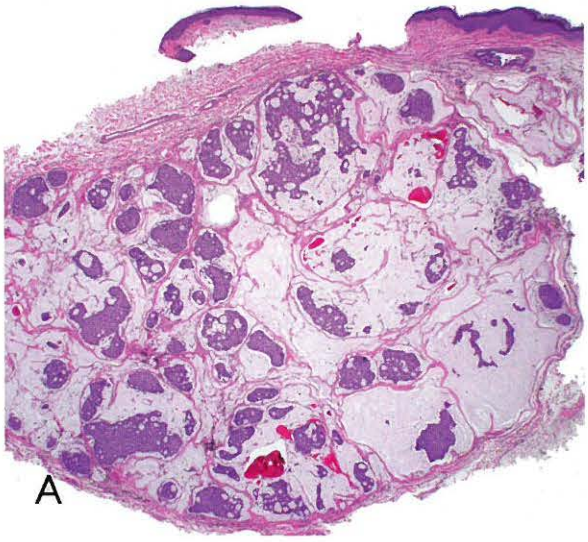
MIXED TUMOR (CHONDROID SYRINGOMA)

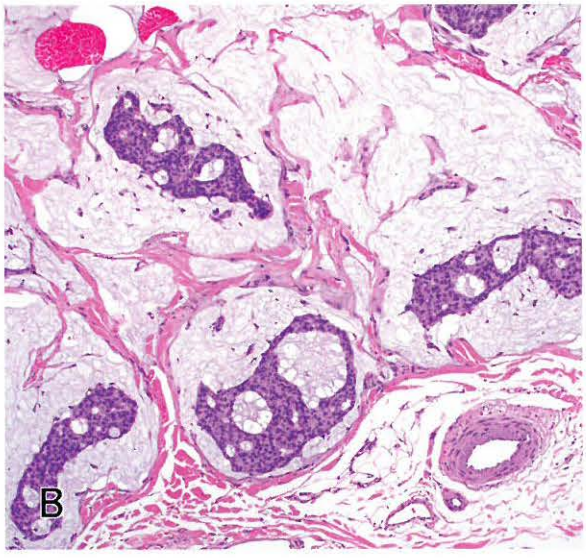
A: This is a circumscribed dermal nodule with glands/ducts/tubules arranged haphazardly in a chondromyxoid stroma. This is the "classic" appearance, but mixed tumors can show a wide range of patterns.

B: Disorganized epithelial and myoepithelial components are intermingled with chondromyxoid stroma (arrows).

C: This example shows well-formed ducts/glands and cystic spaces lined by double layer cuboidal to columnar epithelium. The stroma is myxoid and contains mature adipocytes.

D: This mixed tumor shows obvious cartilage (green arrow) and bone (yellow arrow). The ducts (black arrows) and myoepithelial cell aggregates (orange arrows) in the background are the key to recognizing this as a mixed tumor rather than a bone/cartilage tumor.





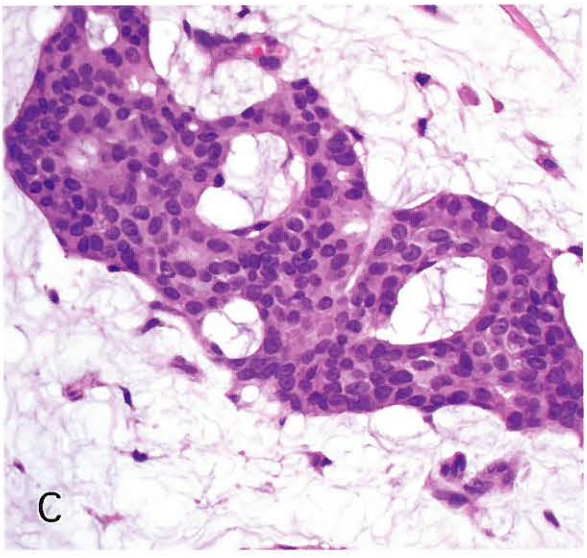


Figure 5-17

PRIMARY CUTANEOUS MUCINOUS CARCINOMA

A: Fibrous septa divide this dermal sea of mucin into individual pools.

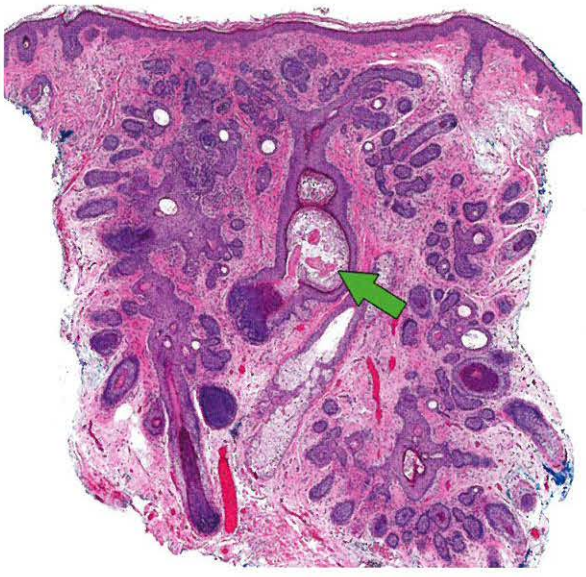
B: Nests of round cells are floating in a sea of pale blue mucin.

C: The nuclei are often bland cytologically although some cases show more atypia.

mary site (20–22). SCC (primary or metastatic), BCC, urothelial carcinoma, and many salivary carcinomas also express p63 and p40 (21). GATA3 is positive in many skin adnexal tumors, SCC, and numerous other tumors throughout the body (23). Breast markers including GCDFP-15, ER, PR, and occasionally even Her2 can be expressed by sweat gland tumors. Distinguishing sweat gland carcinoma from metastatic breast carcinoma can be very challenging without clinical information and imaging studies. SOX-10 is expressed in most cylindromas and spiradenomas; DOG1 is also expressed in cylindroma (24). CD117 (CKIT) may be positive in porocarcinoma (8).

HAIR FOLLICLE PROLIFERATIONS

Hair follicle tumors can be complicated. They show a wide variation of patterns. They may mimic BCC, SCC, or other tumors. The different entities often overlap with one another morphologically and do not always fit neatly into a single diagnostic box. Varying classification schemes and terminologies published in the literature have added complexity to the situation. One of my earliest dermpath mentors, Ronald Rapini MD, sums up the situation perfectly: "Classifying snowflakes is easier" (25). But don't lose hope yet! I like to use a simplified approach to follicular tumors that focuses on the basic



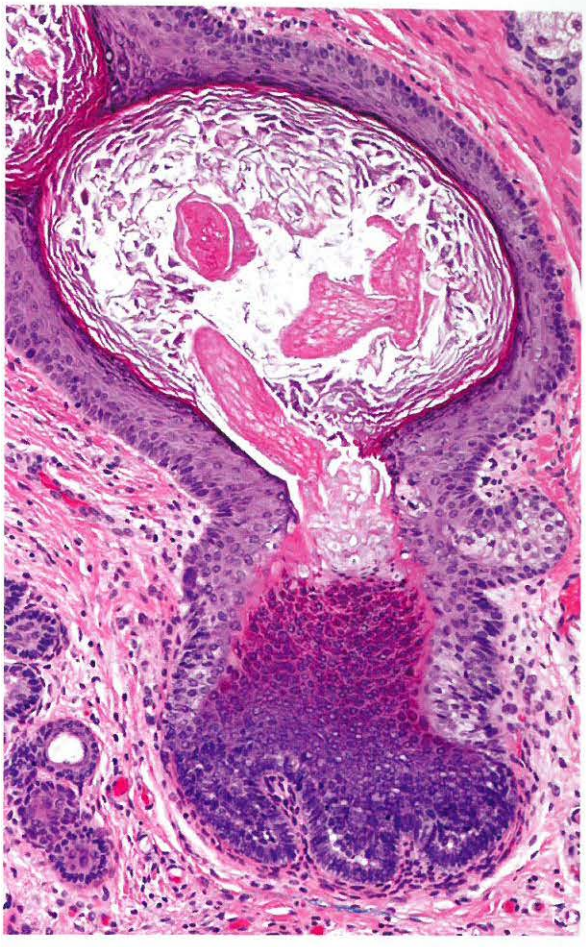


Figure 5-18

TRICHOFOLLICULOMA

Above: Multiple immature hair follicle roots are budding outward from a central dilated hair follicle (arrow). The dilated follicle opens to the skin surface, although the epidermal connection is not always visible in the given section as this case demonstrates.

Right: The dilated central follicle has a lining resembling normal epidermis and contains keratin debris. The immature follicles budding out of it resemble normal follicle roots but are smaller and less organized. The surrounding pink fibrous stroma is classic for follicular tumors.

patterns and the clinically relevant aspects rather than splitting hairs (yes, I just did that) over nomenclature and embryology. Hopefully, it will be easier than classifying snowflakes. It is useful to know the basic histology of normal hair follicles before trying to learn about follicular tumors, as many of these tumors recapitulate various parts of the normal follicle (see fig. 6-1).

Trichofolliculoma

Trichofolliculoma consists of multiple immature hair follicle roots budding outward from a central dilated hair follicle (fig. 5-18). The lesion has a "hen and chicks" appearance, with "baby" follicles (the "chicks") budding out from the central "mother" follicle (the "hen") (25). The dilated follicle opens to the skin surface, although the epidermal connection is not always evident depending on the plane of sectioning, which can make the central follicle look like a cyst. The dilated central follicle has a lining that resembles normal epidermis, recapitulating the infundibulum of a normal hair follicle. Keratin debris and fragments of hair shaft may be present in the central dilated follicle. The immature follicles budding out of the main cystic follicle resemble normal hair follicle roots, but they are smaller and less organized. As with many other benign follicular proliferations, the entire lesion is usually surrounded by dense fibrous stroma.

Several other benign lesions also have a dilated central follicle opening to the skin surface: folliculosebaceous cystic hamartoma (aka sebaceous trichofolliculoma), dilated pore (of Winer), and pilar sheath acanthoma. Folliculosebaceous cystic hamartoma is very similar to trichofolliculoma, except that there are mature sebaceous glands (rather than small immature hair follicle roots) budding off of the central cystic follicle (fig. 5-19). Dilated pore has a large central cystic follicle opening to the skin surface but with nothing budding out from it (i.e., no

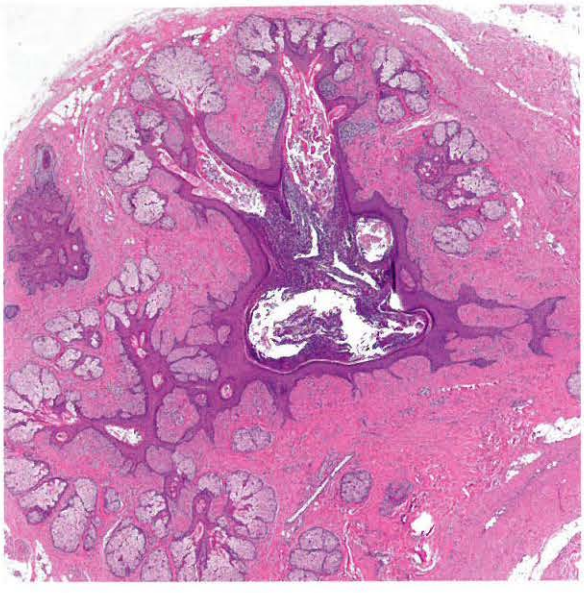


Figure 5-19

FOLLICULOSEBACEOUS CYSTIC HAMARTOMA (SEBACEOUS TRICHOFOLLICULOMA)

Basically, it looks like a trichofolliculoma but with sebaceous glands instead of immature hair follicles budding out of the central dilated follicle. The pink fibrous follicular stroma is abundant in this case.

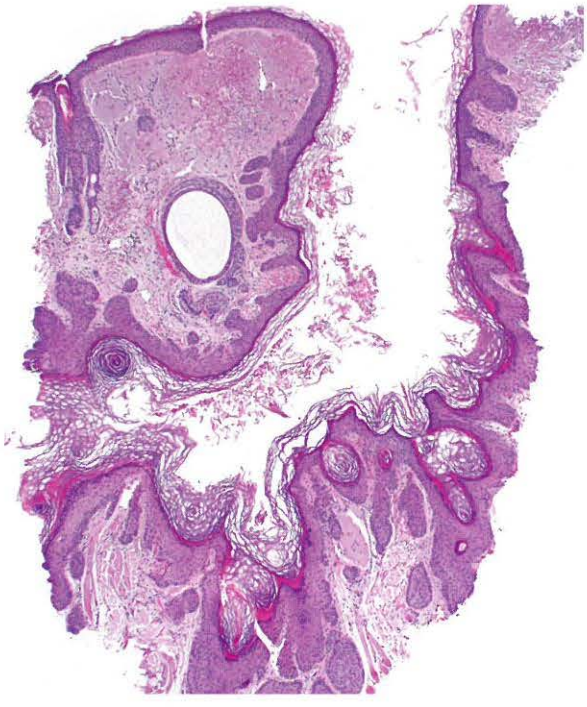


Figure 5-20

DILATED PORE OF WINER

There is a large central cystic follicle opening to the skin surface but with nothing budding out from it (i.e., no sebaceous glands or immature hair roots; contrast this with figs. 5-18 and 5-19). The epithelial lining is thin and looks like epidermis.

sebaceous glands or immature hair roots) (fig. 5-20). The epithelial lining of a dilated pore is thin and looks like epidermis. Dilated pore looks identical to the punctum (opening to the skin surface) overlying a follicular cyst of the infundibular type, which is what some dilated pores may actually represent. Pilar sheath acanthoma is a rare lesion that looks similar to dilated pore, but with much thicker acanthotic epithelial lining. It has large expanded rete budding out from the central cystic follicle, but there are no hair roots or sebaceous glands budding out.

Trichoepithelioma

Trichoepitheliomas are benign hair follicle tumors composed of dermal nests or cords of basaloid cells with peripheral palisading, yielding a pattern similar to that of BCC (fig. 5-21). They are usually small and superficial, and they often connect to normal hair follicle or the overlying epidermis. The nests are surrounded by a fibrous often cellular stroma. The oval to spindle stromal cells tend to aggregate and coalesce around the basaloid nests, forming small nodules (papillary mesenchymal bodies) that push into the basaloid nests, recapitulating how the hair papilla invaginates into the hair bulb in a normal follicle. The appearance reminds me of holding a balloon (the basaloid nest) in one hand and pressing your fist (the papillary mesenchymal body) into it with the other hand. Papillary mesenchymal bodies are a classic feature but not always present. Calcifications, keratin cysts, and keratin granulomas are commonly present.

Distinguishing trichoepithelioma from BCC is easy in cases with classic features, but it can be quite challenging when those features are absent or when viewing a small partial biopsy. I find the stromal features to be most helpful in making the distinction, since the nests of basaloid cells can look nearly identical cytologically in the two entities. Rather than the loose myxoid/mucinous stroma of BCC, trichoepithelioma has the dense fibrous stroma that is characteristic of many hair follicle tumors. Mucin-filled cleft

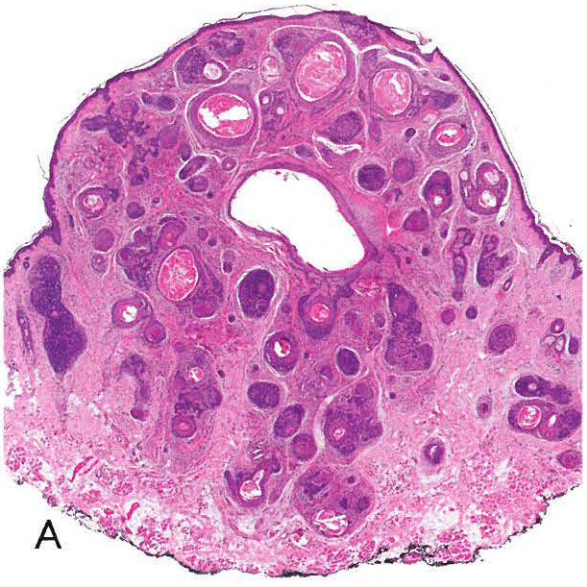


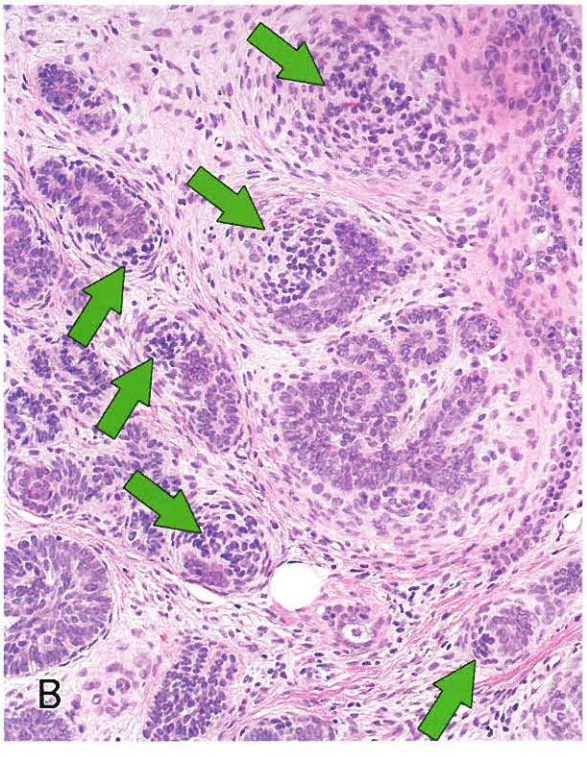
Figure 5-21

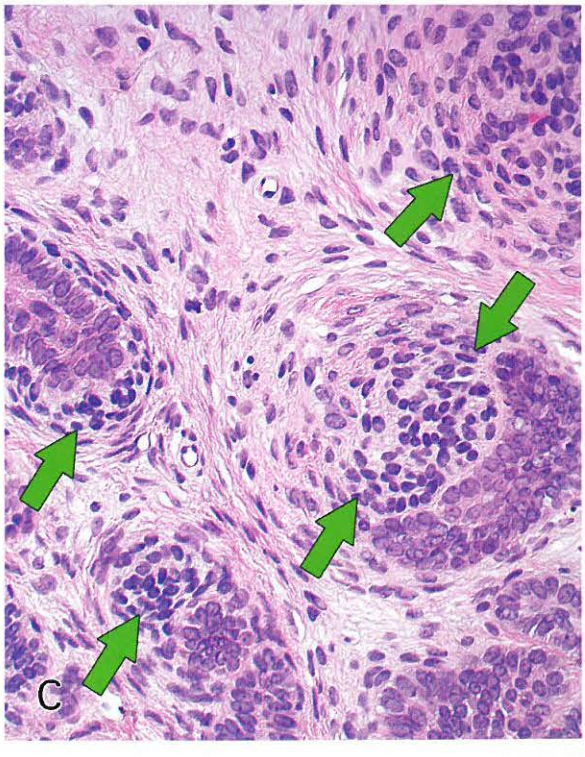
TRICHOEPITHELIOMA

A: Dermal nests of basaloid cells are surrounded by pink fibrous stroma. Multiple keratin cysts are present.

B: Nests of basaloid cells have peripheral palisading but lack clefting artifact with mucin like basal cell carcinoma usually has. The nests are surrounded by pink cellular fibrous stroma and multiple papillary mesenchymal bodies are present (arrows).

C: Papillary mesenchymal bodies (arrow): oval to spindle stromal cells aggregate and coalesce around the basaloid nests, forming small nodules that push into the nests. This is a classic feature but not always present.





artifact between the basal layer of the nests and the surrounding stroma is a feature of BCC and is not usually seen in trichoepithelioma (although pools of mucin are sometimes present within the nests themselves in trichoepithelioma). Papillary mesenchymal bodies are rarely seen in BCC and strongly favor trichoepithelioma (or other benign follicular proliferations). Ulceration, deep infiltrative growth, and perineural invasion favor BCC over trichoepithelioma.

Various immunostains have been studied in attempt to distinguish trichoepithelioma and other follicular tumors from BCC. I do not routinely use immunostains for these cases in my practice, with the exception of CK20, which I have found to be helpful on occasion. CK20 highlights normal

Merkel cells that are usually scattered throughout trichoepithelioma and other follicular tumors but are typically absent from BCC (26). Ber-EP4 is not helpful in this differential diagnosis, as it stains BCC, trichoepithelioma, and trichoblastoma (27). When I am uncertain, especially if it is a partial shave biopsy of a lesion from sun-damaged facial skin, I make a diagnosis of "basaloid neoplasm" with a comment that the differential includes trichoepithelioma and BCC (I try to at least favor one over the other if I can). This allows the dermatologist to decide whether to do additional treatment or to watch and wait, depending on the clinical scenario and their level of concern.

Trichoblastoma

Trichoblastoma probably exists on a spectrum with trichoepithelioma. Both are benign follicular tumors with a basaloid appearance that can mimic BCC, so it is a good idea to keep all three entities in the differential diagnosis for basaloid neoplasms. I think of trichoblastoma like trichoepithelioma's big brother. Trichoblastomas are often larger and deeper and lack connection to the epidermis whereas trichoepitheliomas are usually smaller superficial tumors that show epidermal connection. The distinction is not of clinical importance since both are benign.

Trichoblastoma commonly presents as a slow-growing nodule, sometimes several centimeters, on the scalp or other head and neck sites of middle aged or older adults. It is a blue cellular nodule/s in the dermis or subcutis composed of basaloid nests arranged in a variety of patterns (fig. 5-22). The nests are composed of uniform basaloid cells with peripheral palisading, and may be large or small. Sometimes they are interconnected by thin cords or strands of tumor cells. There is usually no connection to the epidermis or normal hair follicles. The lesion is usually surrounded by the characteristic cellular and/or fibrous stroma that is seen in trichoepithelioma and other follicular neoplasms. Papillary mesenchymal bodies are sometimes present.

Features that distinguish trichoblastoma from BCC are discussed in the trichoepithelioma section above. The presence of characteristic fibrous stroma and absence of clefting artifact around nests support trichoblastoma/trichoepithelioma instead of BCC. As with trichoepithelioma, if there is uncertainty in making the distinction from BCC, I use a term like "basaloid neoplasm" with a comment that the differential includes trichoblastoma/trichoepithelioma and BCC.

Rare examples of trichoblastoma can undergo malignant transformation, either in the epithelial cells or the spindled stromal cells. Marked cytologic atypia, zonal necrosis, and atypical mitotic forms are clues for this. However, normal mitoses and individual apoptotic cells are often present in benign trichoblastomas and are not by themselves indicative of malignancy. Expert consultation is recommended before making this challenging diagnosis.

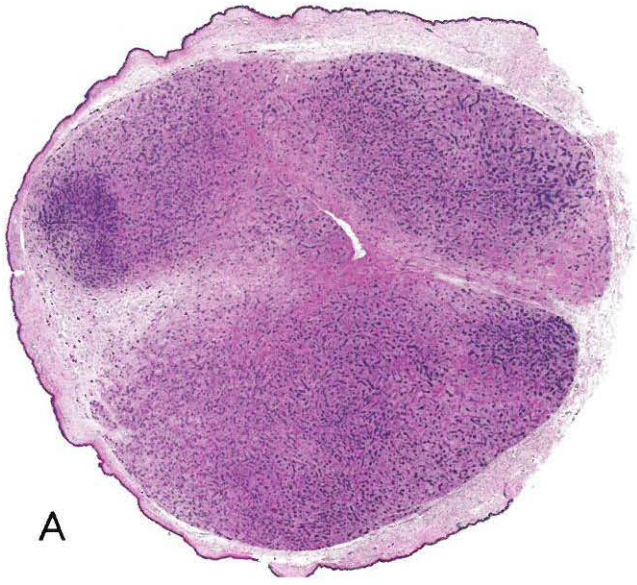
Desmoplastic Trichoepithelioma (DTE)

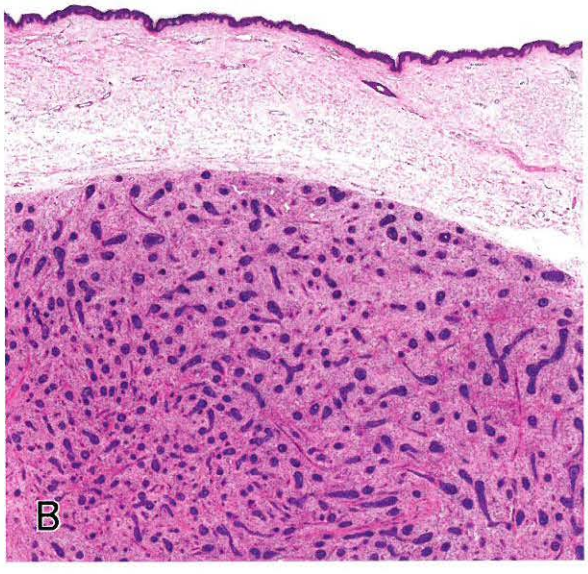
DTE presents as a small papule on the face of adults (women > men). Although it is considered a variant of trichoepithelioma, it has a totally different microscopic appearance (see fig. 5-12). It does not have the blue basaloid nodules seen in conventional trichoepithelioma, trichoblastoma, or nodular BCC. Instead, DTE has the tadpole/paisley tie pattern previously discussed in the sweat gland tumor section. Bland basaloid or squamoid cells form thin cords/chains arranged haphazardly within a dense fibrous stroma in the dermis. Small keratin cysts, keratin granulomas, and calcifications are often present. Like conventional trichoepithelioma, DTE also usually has scattered passenger Merkel cells that can be detected with CK20 immunostain.

The differential diagnosis for DTE includes MAC, syringoma, and infiltrative/morpheaform BCC, with the distinction from MAC being the most challenging (see section on MAC for further discussion). When I favor DTE but only have a small shave biopsy (i.e., the deep border of the lesion is not visible), I usually add a comment requesting conservative complete excision to be sure I am not missing a superficially sampled MAC.

Trichilemmoma

This benign follicular proliferation is quite common. It presents in adults as a small papule on the nose/face, often clinically resembling a verruca (some believe it may actually be a variant of verruca rather than a follicular neoplasm). It also has a verrucous appearance microscopically, with papillomatosis, hypergranulosis, tiers of parakeratosis, and dilated papillary dermal





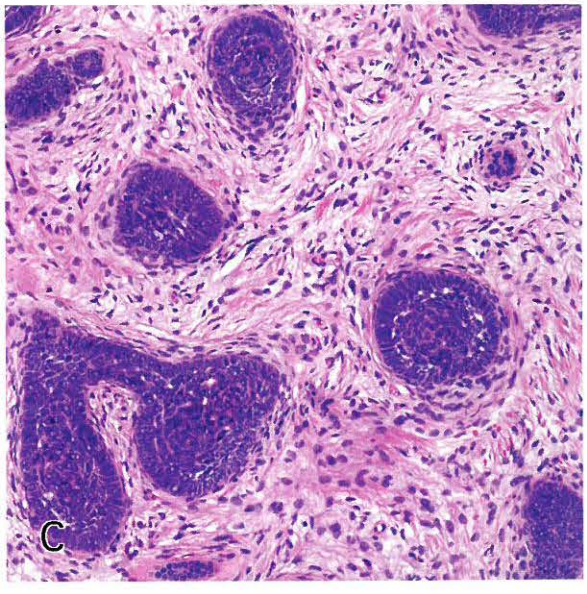


Figure 5-22

TRICHOBLASTOMA

A: There is a blue deep dermal cellular nodule with no epidermal connection.

B: Multiple basaloid nests are embedded in a cellular fibrous stroma. There is no clefting artifact. Note the sharp circumscription of the lesion and how the follicular stroma is distinctly different from adjacent dermis.

C: Nests of basaloid cells with peripheral palisading are surrounded by pink cellular fibrous stroma, just like trichoepithelioma. This case shows small nests but some cases have large nests or even solid nodules.

vessels (fig. 5-23). Below this verrucous surface, the epidermis expands and bulges/pushes down into the upper to mid dermis forming a bowl shape. The keratinocytes in this bulging/pushing area usually show pale/clear cytoplasm, and the basal layer shows prominent nuclear palisading, at least focally; these features are recapitulating the outer root sheath of a normal hair follicle. Dense pink basement membrane deposits may be present in the dermis.

Desmoplastic trichilemmoma is a benign morphologic variant of trichilemmoma that has a central zone with cords of basaloid/squamoid cells arranged haphazardly in a desmoplastic and/or myxoid/mucinous stroma. These areas of desmoplastic change can closely resemble infiltrative BCC or SCC, especially on a small biopsy. Identifying adjacent conventional trichilemmoma (clear/pale cells and peripheral palisading), which is usually present at the periphery of the lesion, is the key to making the correct diagnosis and avoiding unnecessary additional surgery for the patient. However, on a small superficial biopsy, these areas may be absent, making the distinction nearly impossible. The desmoplastic pattern in trichilemmoma is a

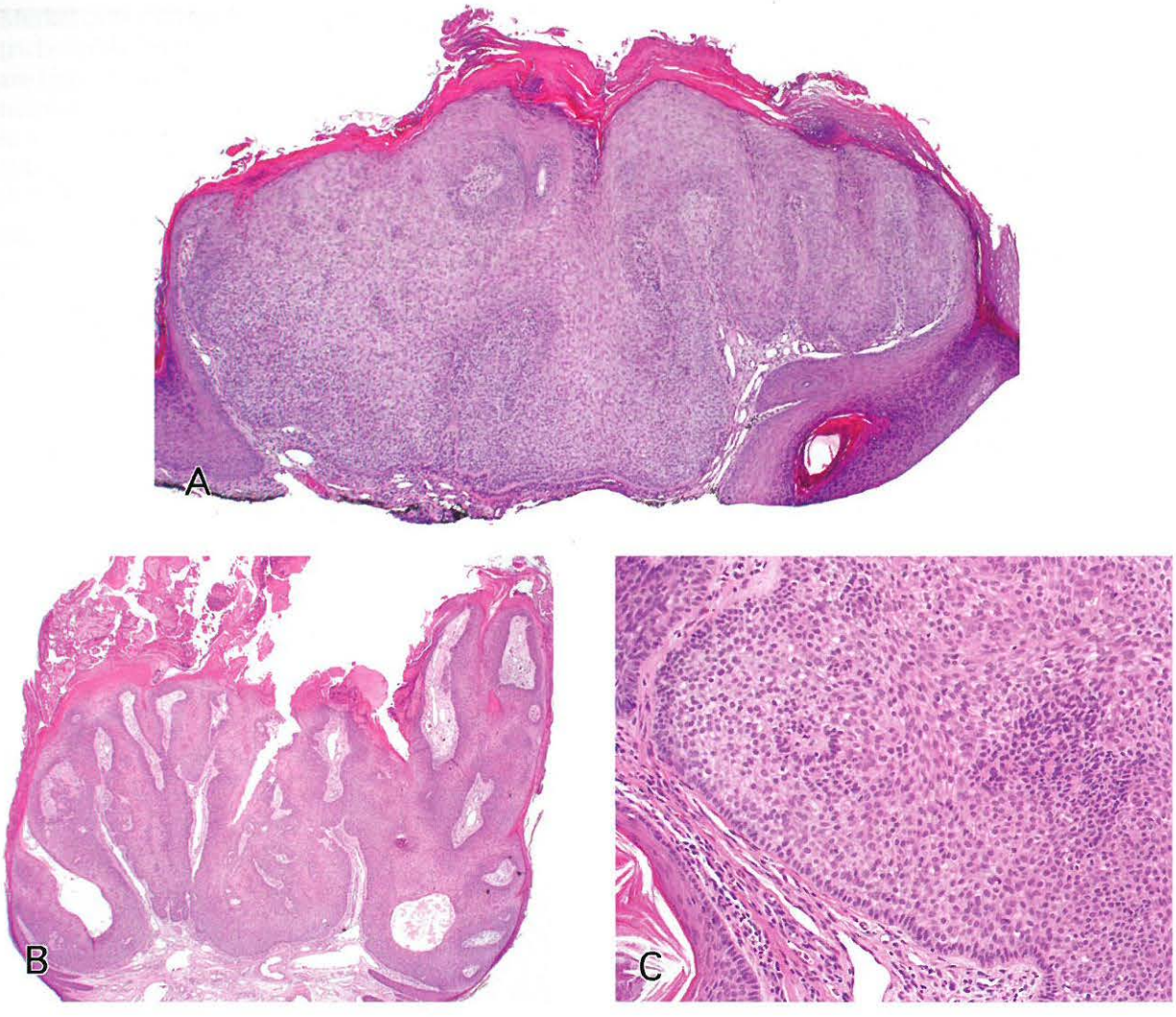


Figure 5-23

TRICHILEMMOMA

A: The epidermis expands and bulges/pushes down into the dermis forming a bowl shape. The keratinocytes are pale to clear. There is surface verrucous change.

B: The verrucous surface change is prominent in this example. The pale keratinocytes bulging down into the dermis are the key to recognizing this as a trichilemmoma rather than a verruca vulgaris.

C: The keratinocytes show pale/clear cytoplasm with prominent nuclear palisading along the basal layer. There is no clefting artifact.

potential pitfall for pathologists but is of no clinical significance; these are totally benign. When there is uncertainty on a small biopsy between desmoplastic trichilemmoma and infiltrative BCC/SCC, I use a term like "basaloid neoplasm" and a comment to explain the uncertainty and give a differential diagnosis.

Patients with Cowden syndrome (an autosomal dominant disease due to germline *PTEN* mutation) develop multiple trichilemmomas and have increased risk for visceral carcinomas (including thyroid, breast, and endometrial). My former dermatology residents taught me a fun way to remember this: Cowden syndrome is associated with "trichilem-mooo-mas" (a cow says "mooo"). Most trichilemmomas seen in my practice are solitary and sporadic rather than syndromic. I do not routinely mention

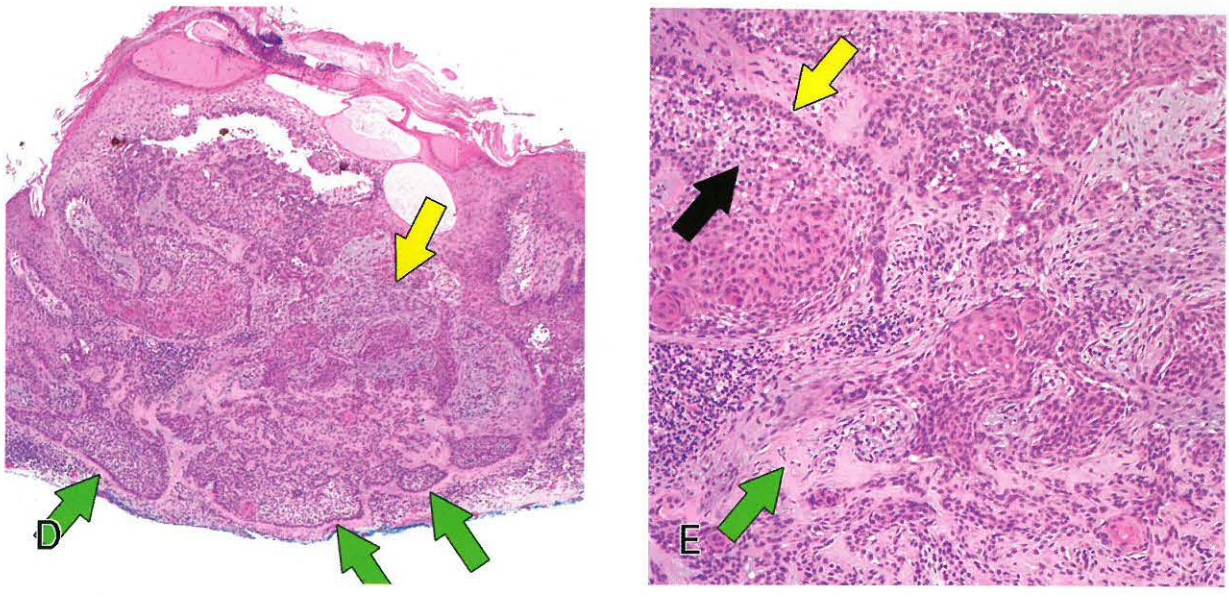


Figure 5-23, continued

D: There is a central zone with cords of basaloid/squamoid cells arranged haphazardly in a desmoplastic and myxoid/mucinous stroma (yellow arrow). Identifying adjacent conventional trichilemmoma at the periphery of the lesion (green arrows) is the key to making the correct diagnosis

E: The central areas of desmoplastic change can closely resemble infiltrative BCC or SCC, especially on a small biopsy. Focal clear cell change (black arrow), peripheral palisading (yellow arrow), and dense pink basement membrane (green arrow) are clues for trichilemmoma here.

Cowden syndrome in my report unless there are multiple trichilemmomas or some other history suggestive of Cowden syndrome.

Pilomatricoma

This is a benign follicular tumor that recapitulates the hair matrix (bulb/root). It presents as a firm nodule, often on the face of children, although it can arise at others sites and occur in adults. It is an irregular dermal nodule composed of two main components: 1) pink sheets of dead keratinocytes ("ghost" or "shadow" cells), and 2) sheets of small round blue basaloid cells (resembling the matrical cells seen in the root/bulb of normal hair follicles) (fig. 5-24). These components are mixed together haphazardly and are present in variable amounts, ranging from extensive sheets of round blue matrical cells in some cases to only pink ghost/shadow cells with no identifiable matrical cells in others.

The surrounding dermis is usually fibrotic and briskly inflamed with abundant granulomatous infiltrate and foreign body giant cells. Calcifications are common, and some cases even have metaplastic bone. The round blue matrical cells often have brisk mitotic activity; this alone is not a feature of malignancy in pilomatricoma. Malignant pilomatricoma (matrical carcinoma) would also have severe nuclear atypia/pleomorphism, atypical mitotic figures, and/or infiltrative growth.

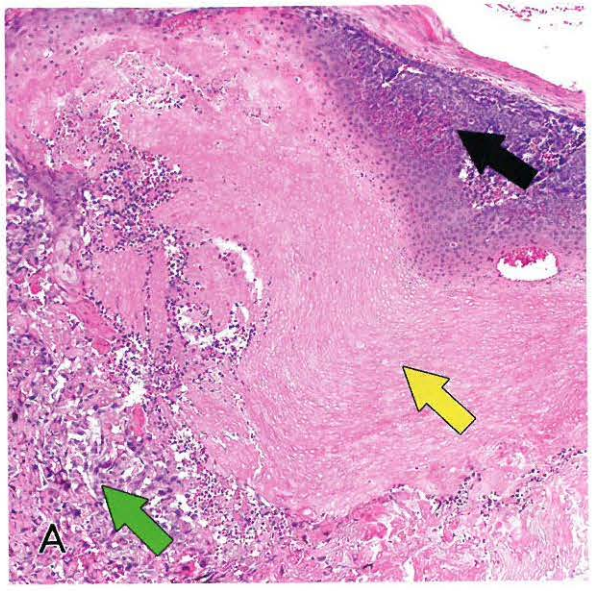
Figure 5-24

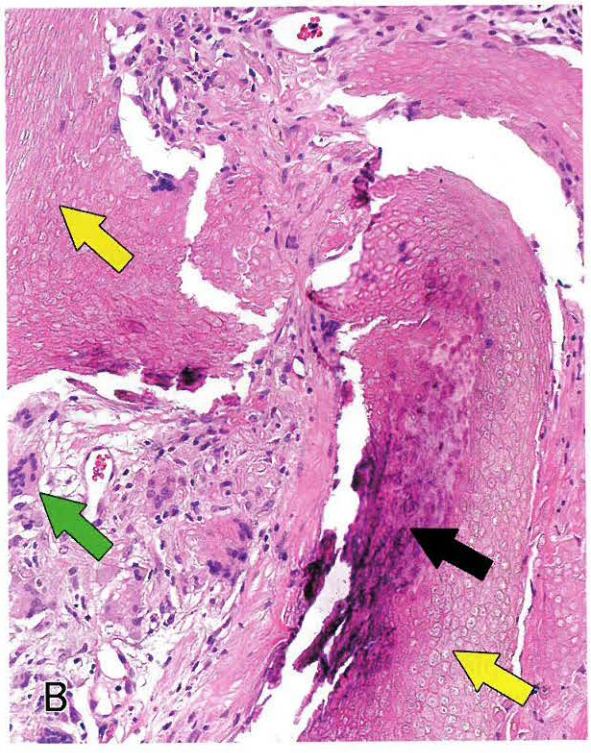
PILOMATRICOMA

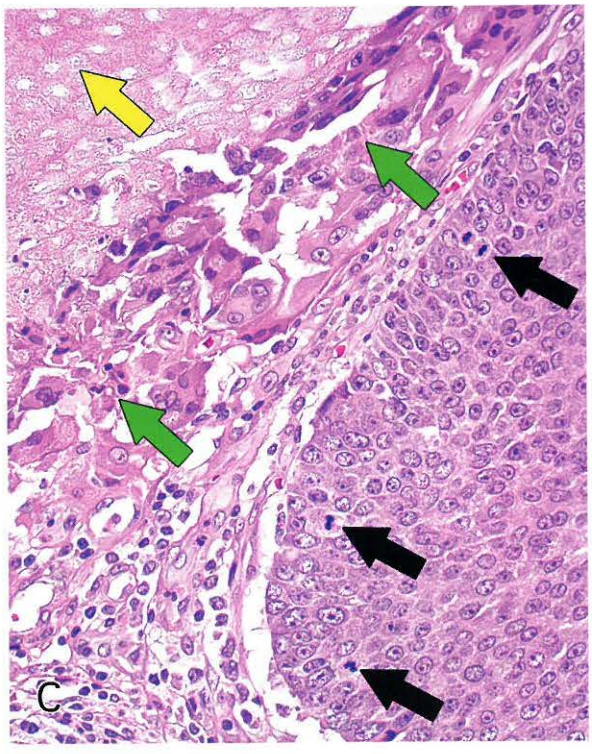
A: Pilomatricoma is composed of two components in varying amounts: 1) pink sheets of dead keratinocytes ("ghost" or "shadow" cells) (yellow arrow) and 2) sheets of small round blue basaloid matrical cells (black arrow). Brisk background inflammation is common (green arrow).

B: Some cases show only pink ghost/shadow cells (yellow arrows) with no identifiable blue matrical cells. Calcifications are common (black arrow), as are multinucleated foreign body giant cells (green arrow).

C: The round blue matrical cells have uniform nuclei and often show brisk mitotic activity (black arrows). Pleomorphism or atypical mitotic figures are not present. Note the adjacent ghost cells (yellow arrow) and giant cell reaction (green arrows).







REFERENCES

1. Fulton EH, Kaley JR, Gardner JM. Skin adnexal tumors in plain language: a practical approach for the general surgical pathologist. Arch Pathol Lab Med 2019 [Epub ahead of print]
2. Dasgupta T, Wilson LD, Yu JB. A retrospective review of 1349 cases of sebaceous carcinoma. Cancer 2009;115:158-65.
3. Lazar AJ, Lyle S, Calonje E. Sebaceous neoplasia and Torre-Muir syndrome. Curr Diagn Pathol 2007;13:301-19.
4. Shalin SC, Lyle S, Calonje E, Lazar AJ. Sebaceous neoplasia and the Muir-Torre syndrome: important connections with clinical implications. Histopathology 2010;56:133-47.
5. Tetzlaff MT, Singh RR, Seviour EG, et al. Next-generation sequencing identifies high frequency of mutations in potentially clinically actionable genes in sebaceous carcinoma. J Pathol 2016;240:84-95.
6. Clark LN, Elwood HR, Uhlenhake EE, Smoller BR, Shalin SC, Gardner JM. Nuclear factor XIIIa staining (clone AC-1A1 mouse monoclonal) is a highly sensitive marker of sebaceous differentiation in normal and neoplastic sebocytes. J Cutan Pathol 2016;43:657-62.
7. Uhlenhake EE, Clark LN, Smoller BR, Shalin SC, Gardner JM. Nuclear factor XIIIa staining (clone AC-1A1 mouse monoclonal) is a sensitive and specific marker to discriminate sebaceous proliferations from other cutaneous clear cell neoplasms. J Cutan Pathol 2016;43:649-56.
8. Goto K, Takai T, Fukumoto T, et al. CD117(KIT) is a useful immunohistochemical marker for differentiating porocarcinoma from squamous cell carcinoma. J Cutan Pathol 2016;43:219-26.
9. Nazarian RM, Kapur P, Rakheja D, et al. Atypical and malignant hidradenomas: a histological and immunohistochemical study. Mod Pathol 2009;22:600-10.
10. Ohtsuka H, Nagamatsu S. Microcystic adnexal carcinoma: review of 51 Japanese patients. Dermatology 2002;204:190-3.
11. LeBoit PE, Sexton M. Microcystic adnexal carcinoma of the skin. A reappraisal of the differentiation and differential diagnosis of an underrecognized neoplasm. J Am Acad Dermatol 1993;29:609-18.
12. Gabillot-Carre M, Weill F, Mamelle G, et al. Microcytic adnexal carcinoma: report of seven cases including one with lung metastasis. Dermatology 2006;212:221-8.
13. Burns MK, Chen SP, Goldberg LH. Microcystic adnexal carcinoma: ten cases treated by Mohs micrographic surgery. J Dermatol Surg Oncol 1994;20:429-34.
14. Hornick JL, Fletcher CD. Myoepithelial tumors of soft tissue: a clinicopathologic and immunohistochemical study of 101 cases with evaluation of prognostic parameters. Am J Surg Pathol 2003;27:1183-96.
15. Jo VY, Fletcher CD. p63 immunohistochemical staining is limited in soft tissue tumors. Am J Clin Pathol 2011;136:762-6.
16. Jo VY, Fletcher CD. Myoepithelial neoplasms of soft tissue: an updated review of the clinicopathologic, immunophenotypic, and genetic features. Head Neck Pathol 2015;9:32-8.
17. Kazakov DV, Suster S, LeBoit PE, et al. Mucinous carcinoma of the skin, primary, and secondary: a clinicopathologic study of 63 cases with emphasis on the morphologic spectrum of primary cutaneous forms: homologies with mucinous lesions in the breast. Am J Surg Pathol 2005;29:764-82.
18. Zembowicz A, Garcia CF, Tannous ZS, Mihm MC, Koerner F, Pilch BZ. Endocrine mucin-producing sweat gland carcinoma: twelve new cases suggest that it is a precursor of some invasive mucinous carcinomas. Am J Surg Pathol 2005;29:1330-9.
19. Qureshi HS, Salama ME, Chitale D, et al. Primary cutaneous mucinous carcinoma: presence of myoepithelial cells as a clue to the cutaneous origin. Am J Dermatopathol 2004;26:353-8.
20. Ivan D, Nash JW, Prieto VG, et al. Use of p63 expression in distinguishing primary and metastatic cutaneous adnexal neoplasms from metastatic adenocarcinoma to skin. J Cutan Pathol 2007;34:474-80.
21. Lee JJ, Mochel MC, Piris A, Boussahmain C, Mahalingam M, Hoang MP. p40 exhibits better specificity than p63 in distinguishing primary skin adnexal carcinomas from cutaneous metastases. Hum Pathol 2014;45:1078-83.
22. Ko JS, Habermehl G. Cutaneous metastases: a review and diagnostic approach to tumors of unknown origin. Arch Pathol Lab Med 2018 [Epub ahead of print]
23. Mertens RB, De Peralta-Venturina MN, Balzer BL, Frishberg DP. GATA3 expression in normal skin and in benign and malignant epidermal and cutaneous adnexal neoplasms. Am J Dermatopathol 2015;37:885-91.
24. Lezcano C, Ho J, Seethala RR. Sox10 and DOG1 expression in primary adnexal tumors of the skin. Am J Dermatopathol 2017;39:896-902.
25. Rapini RP. Practical dermatopathology, 2nd ed. Philadelphia: Elsevier Saunders; 2012.
26. Katona TM, Perkins SM, Billings SD. Does the panel of cytokeratin 20 and androgen receptor antibodies differentiate desmoplastic trichoepithelioma from morpheaform/infiltrative basal cell carcinoma? J Cutan Pathol 2008;35:174-9.
27. Ansai S, Takayama R, Kimura T, Kawana S. Ber-EP4 is a useful marker for follicular germinative cell differentiation of cutaneous epithelial neoplasms. J Dermatol 2012;39:688-92.

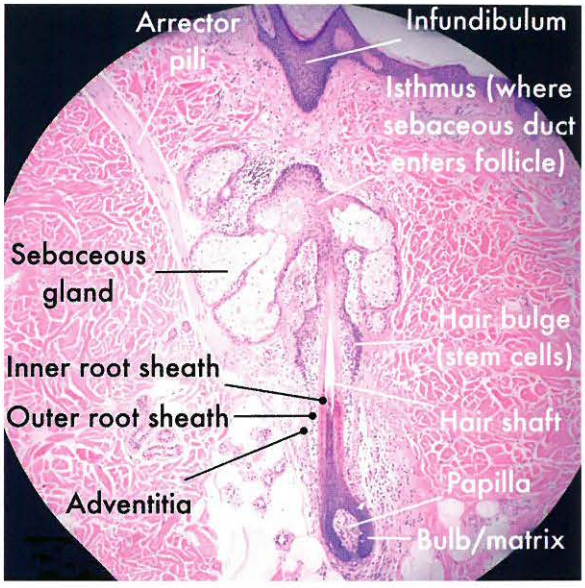
6 CYSTS

Cysts are common benign skin lesions consisting of an epithelial lining with a central open space that is often filled with keratin debris. The classification of cysts is based on the type of epithelial lining. Most cutaneous cysts are probably of hair follicle origin, and the various types of lining epithelia are analogous to different parts of the normal hair follicle (fig. 6-1). Some cysts are of sweat gland origin (e.g., hidrocystoma) and some tumors develop secondary cystic change (e.g., hidradenoma). There are a few other rare cysts that this chapter won't cover, so if you encounter something not discussed here, dig deeper in a full size dermatopathology textbook or the literature.

Cysts present clinically as skin-colored or erythematous nodules. Many, many different tumors (e.g., dermatofibrosarcoma protuberans, adnexal tumors, cutaneous metastases) have an identical clinical appearance. Some pseudocysts have a cystic appearance, although they lack a true epithelial lining (e.g., digital mucous cyst, ganglion cyst). A clinical differential diagnosis of "cyst" usually just means that there is a dermal or subcutaneous nodule but what is actually making that nodule could be many different things.

EPIDERMOID CYST (FOLLICULAR CYST, INFUNDIBULAR TYPE)

Epidermoid cysts are often called "epidermal inclusion cyst" by pathologists and "sebaceous cyst" by surgeons, although both terms are technically incorrect. True epidermal inclusion cysts do look similar but they are due to penetrating



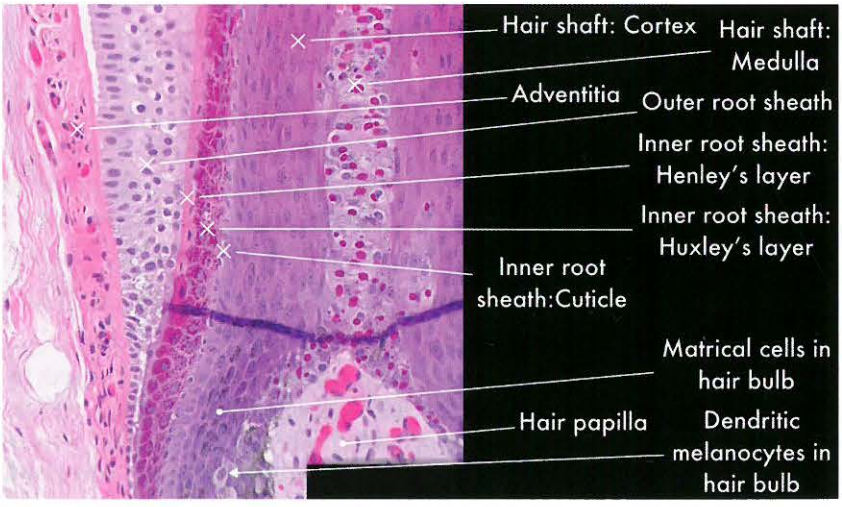


Figure 6-1

HAIR FOLLICLE HISTOLOGY

Above: Many cysts arise from (or recapitulate) various parts of the normal hair follicle.

Left: A closer look at the many different components of a normal hair follicle. This image shows the complex transition from the matrical cells of the hair bulb/root into the inner and outer root sheaths and developing hair shaft.

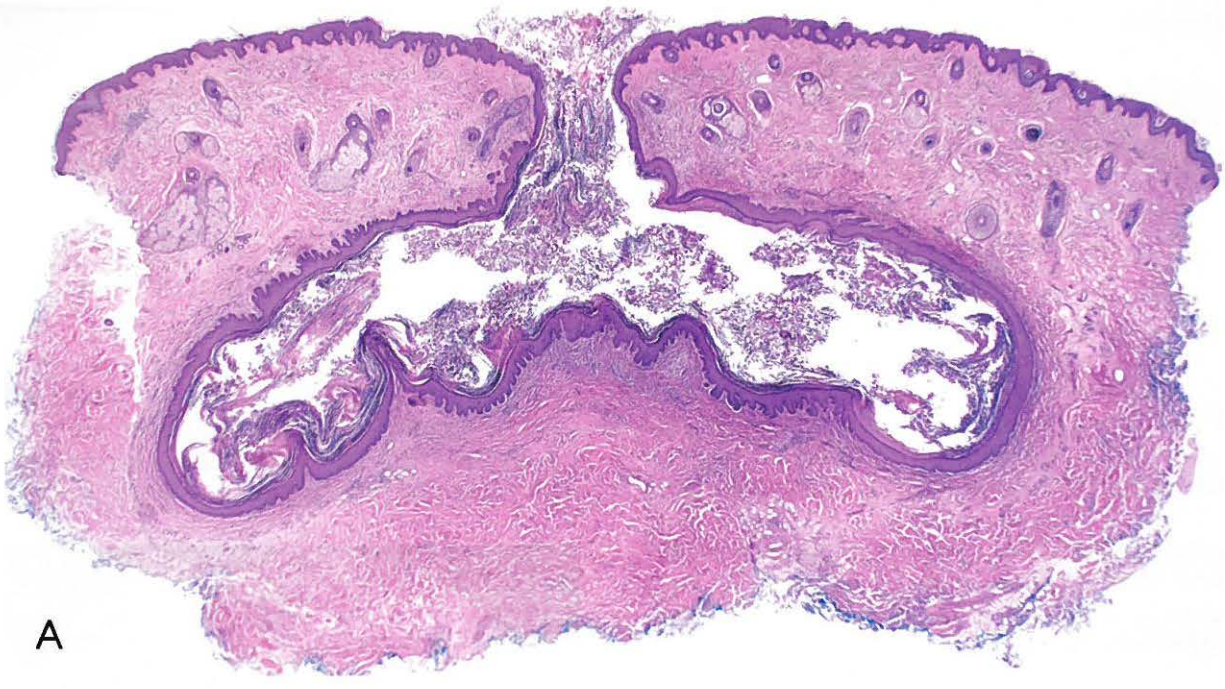


Figure 6-2

FOLLICULAR CYST, INFUNDIBULAR TYPE

A: A rare example excised intact (most often, these specimens consist of only fragments of cyst wall and flaky keratin cyst contents). This perfect section shows the cyst connecting to the skin surface via a narrow opening (essentially a "dilated pore"), which corresponds to the "punctum" seen clinically.

injury in which epidermis is displaced into the dermis and grows into a cyst in the midst of a scar. The closest thing to a true "sebaceous cyst" would be a steatocystoma (see below).

Follicular infundibular cysts are lined by stratified squamous epithelium that closely resembles the normal epidermis (and the infundibular portion of the hair follicle, the portion of the follicle that opens to the epidermis) (fig. 6-2). The granular layer is present. They are filled with loose flaky keratin debris. When they rupture, they produce mixed inflammation and a granulomatous reaction, often with giant cells. Sometimes a neutrophilic abscess forms around a ruptured cyst; if this is particularly robust, I will usually mention in a comment that abscess is also present, and if it persists, correlation with microbial cultures would be recommended. I do not routinely use periodic acid–Schiff (PAS), GMS, or Gram stains for granuloma or abscess that is obviously due to a ruptured cyst. Scar will eventually develop after the cyst ruptures. Sometimes an old ruptured cyst will only have scar and naked hair shafts or focal granulomas with keratin debris ("keratin granuloma") but no obvious cyst epithelial lining (fig. 6-3).

Small superficial follicular infundibular cysts are called "milia" (singular: "milium") (fig. 6-4); these are sometimes biopsied from the face since they can clinically mimic basal cell carcinoma (BCC). If a biopsy of a small facial papule that clinically was concerning for BCC shows only a small area of granulomatous infiltrate, I usually diagnose this as "suggestive of ruptured cyst or follicle" (fig. 6-5). Special stains for infection are usually not needed in this situation. If there are many neutrophils or plasma cells in a nonfacial location, or an unusual clinical scenario, then I may do special stains for infection.

PILAR/TRICHILEMMAL CYST (FOLLICULAR CYST, ISTHMUS-CATAGEN TYPE)

These cysts are usually easily diagnosed by looking at the glass slide with the naked eye; no microscope required! They are perfectly circumscribed pink nodules, often from the scalp, that

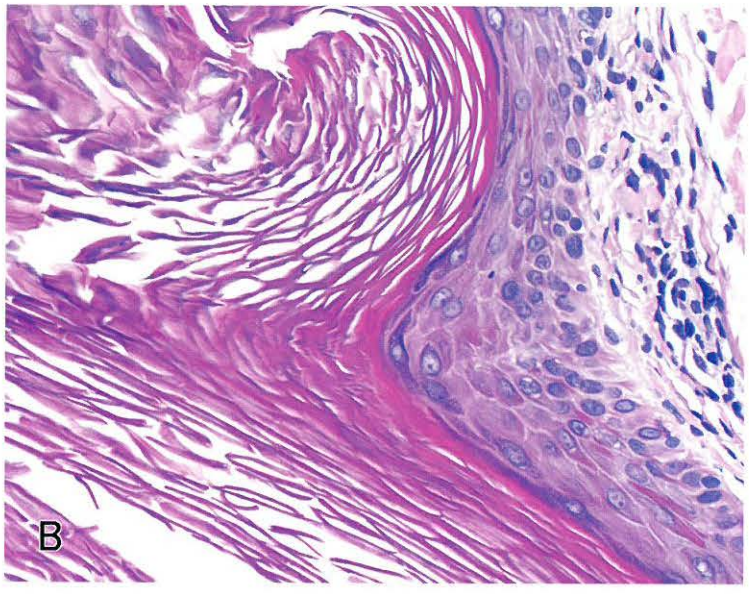
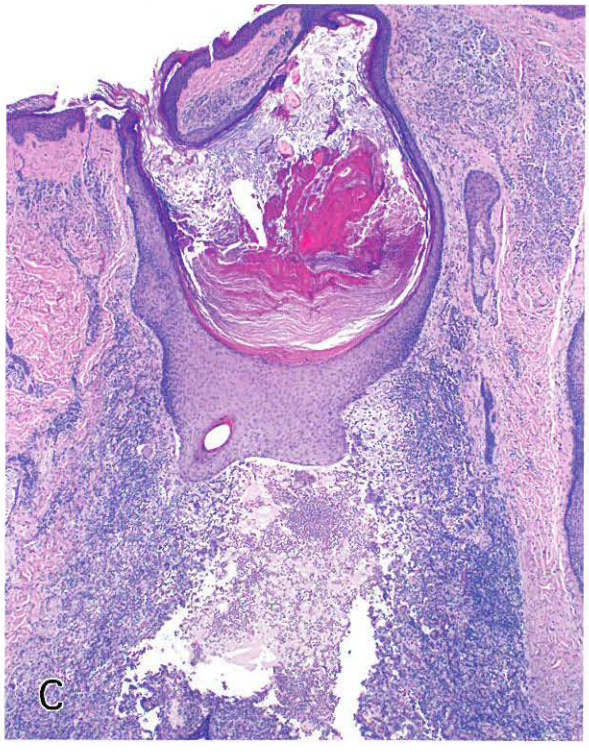


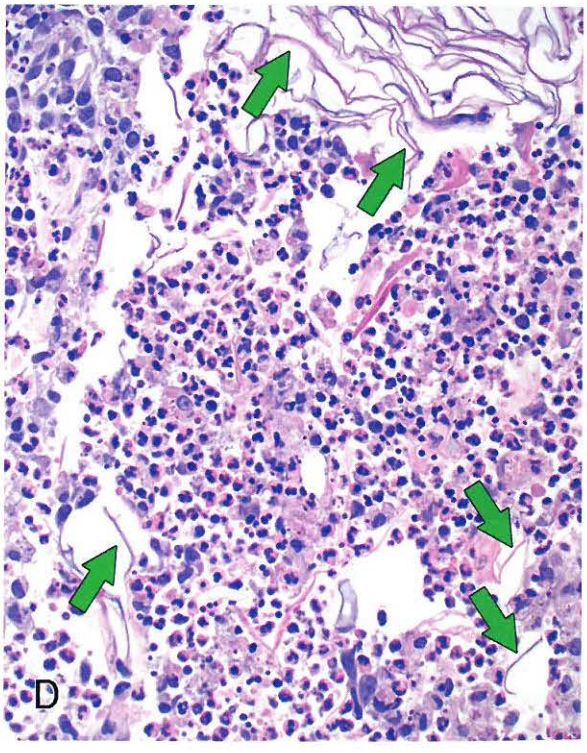
Figure 6-2, continued

B: The cyst is lined by stratified squamous epithelium that closely resembles the infundibular portion of the hair follicle (which looks like normal epidermis). Note the presence of a granular layer. It is filled with loose flaky keratin debris.

C: A ruptured follicular infundibular cyst. The displacement of keratin debris into the dermis produces a robust inflammatory response.

D: A neutrophilic abscess can form adjacent to a ruptured cyst. The presence of loose keratin flakes (arrows) within the inflammation is evidence of a ruptured cyst even if the cyst lining is not present.





have foci of purple calcification (fig. 6-6). They usually "pop out/shell out" surgically and can be easily removed intact by the dermatologist, like a marble in the skin.

Microscopically, the solid pink appearance is due to dense compact keratin that fills the entire cystic space. Calcifications in the keratin debris are commonly seen. The cyst lining is bland stratified squamous epithelium and the granular layer is usually absent or markedly diminished. This lining recapitulates the isthmus of the hair follicle, the zone where the sebaceous gland drains into the follicle via the sebaceous duct. The glassy keratinocytes from the lining transition directly into a dense sheet of compact keratin that fills the cyst (trichilemmal keratinization pattern).

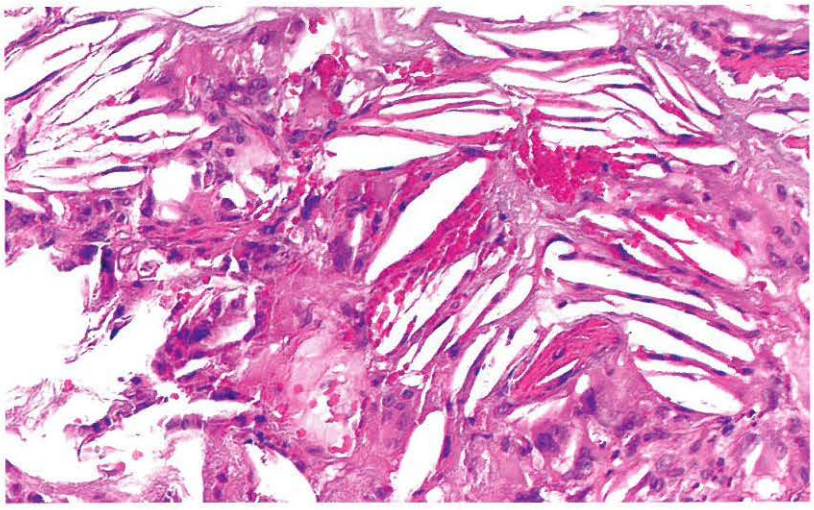


Figure 6-3

KERATIN GRANULOMA

Flakes of keratin debris (left) from an old ruptured cyst are surrounded by a dense aggregate of histiocytes and foreign body giant cells (right). Clefting artifact around the keratin flakes produces a pattern similar to cholesterol clefts.

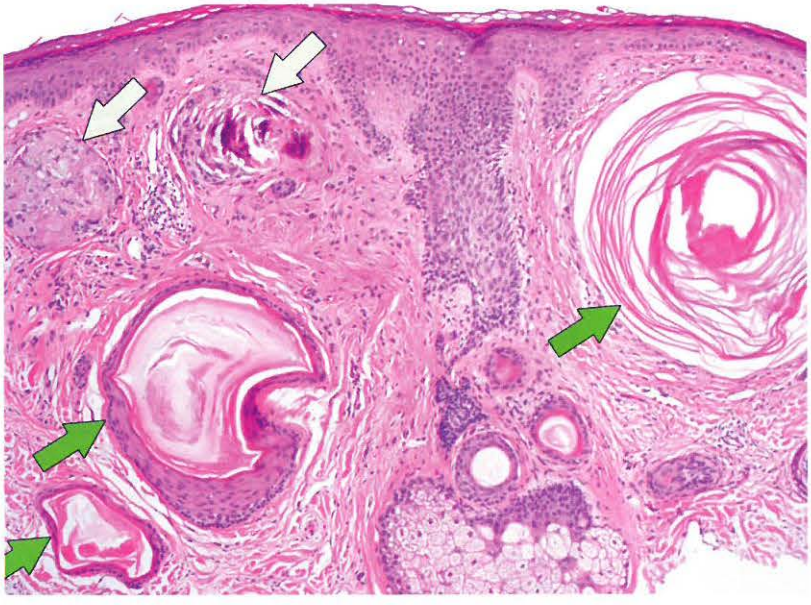


Figure 6-4

MILIA

These are small superficial follicular infundibular cysts (green arrows). Some of the milia have previously ruptured, leaving behind only small keratin granulomas (yellow arrows).

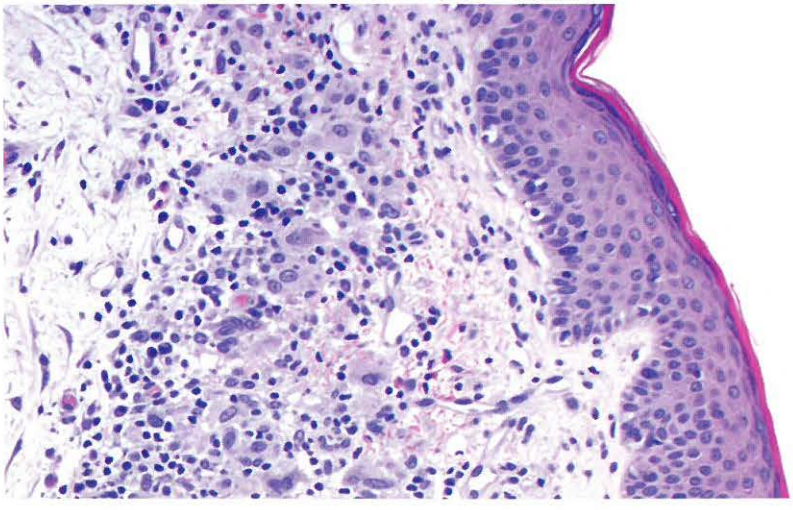
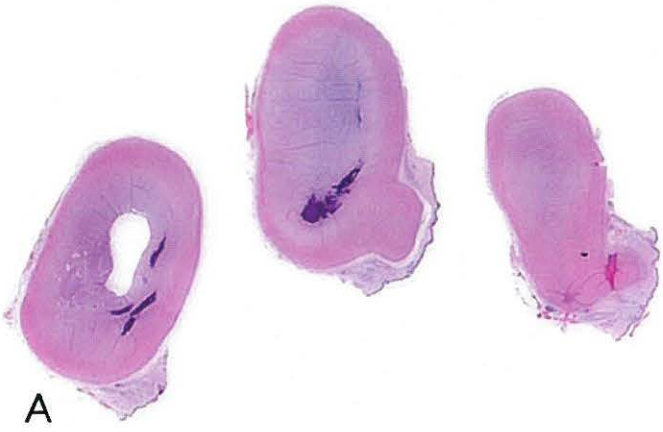
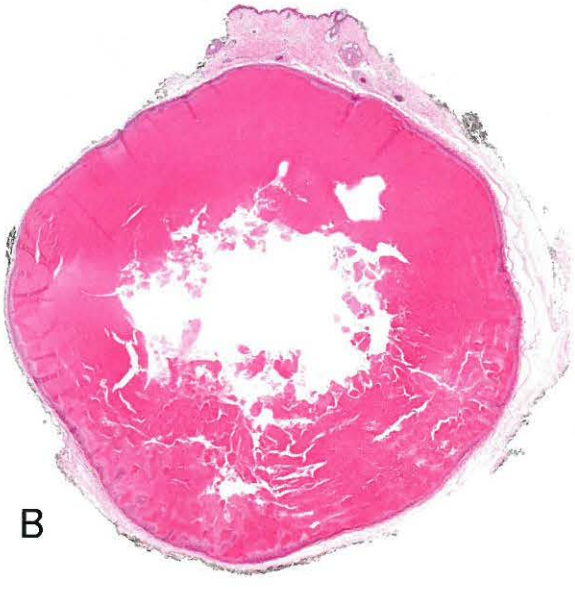


Figure 6-5

"SUGGESTIVE OF RUPTURED CYST OR FOLLICLE"

If a biopsy of a small facial papule that clinically was concerning for basal cell carcinoma (BCC) shows only a small area of granulomatous infiltrate, mixed inflammation, and/or scar, I usually diagnose this as "suggestive of ruptured cyst or follicle."





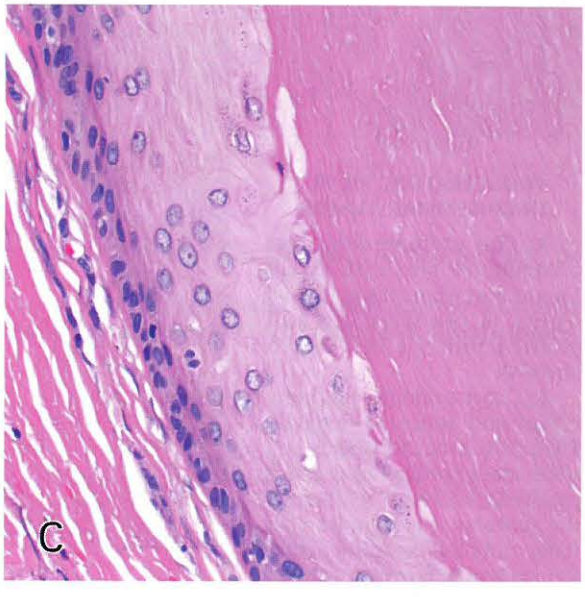


Figure 6-6

PILAR/TRICHILEMMAL CYST

A: These cysts can usually be diagnosed easily just by looking at the glass slide with the naked eye; no microscope required. They are sharply circumscribed dermal nodules that usually "pop out/shell out" surgically and are thus received intact by the laboratory. They are filled with dense pink keratin, often with purple foci of calcification.

B: Dense compact orthokeratin fills the cyst completely or nearly so (sometimes the center is artifactually absent). Contrast this dense keratin to the loose flaky keratin contents of a follicular infundibular cyst (fig. 6-2A,B).

C: The cyst is lined by stratified squamous epithelium with glassy pink cytoplasm. The granular layer is usually absent or markedly diminished. These glassy keratinocytes transition directly into the dense pink keratin filling the cyst.

PROLIFERATING PILAR/ TRICHILEMMAL TUMOR

These are nodules with zones resembling pilar/trichilemmal cyst but also with more solid zones composed of proliferating squamous epithelium that fills the center of the cyst, partially or completely filling it (fig. 6-7). The appearance is similar to that of well-differentiated squamous cell carcinoma (SCC), but the lesion is usually a circumscribed deep nodule without connection to the epidermis, may be in a younger patient, and also usually has areas of obvious pilar/trichilemmal cyst lining. The dense compact pink keratin is intermingled with the proliferating squamous areas giving a "rolls and scrolls" appearance, which is a helpful clue on small partial biopsies.

Without seeing the periphery of the lesion, the diagnosis can be difficult to make with certainty. Complete excision to allow for examination of the entire tumor is useful in difficult cases. Rare malignant variants exist, which are usually large and infiltrative. I recommend expert consultation before making a diagnosis of malignant proliferating pilar/trichilemmal tumor, since it is much more likely to be a benign case that just looks scary due to lack of familiarity with the proliferative pattern of this lesion.

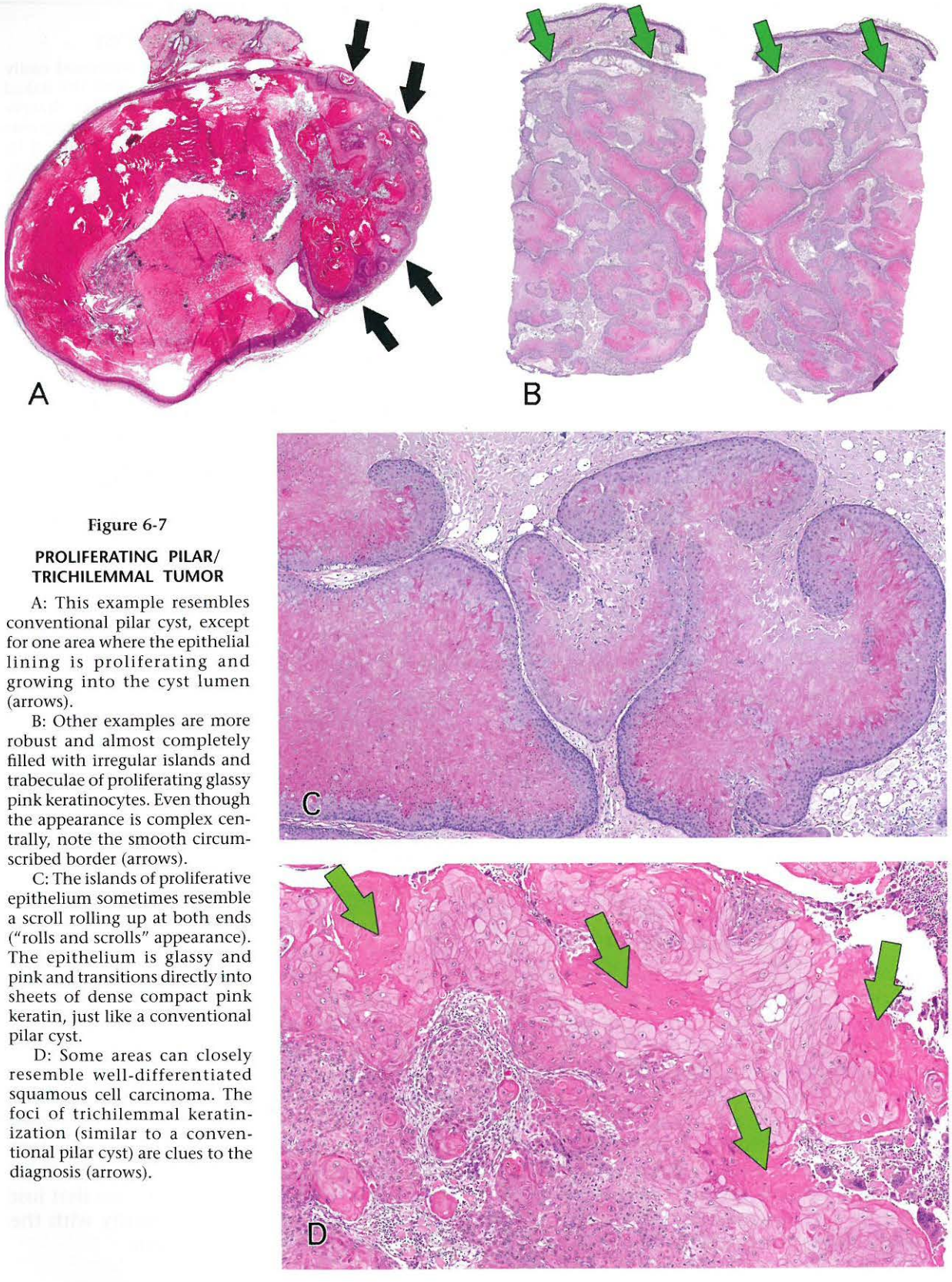


Figure 6-7

PROLIFERATING PILAR/ TRICHILEMMAL TUMOR

A: This example resembles conventional pilar cyst, except for one area where the epithelial lining is proliferating and growing into the cyst lumen (arrows).

B: Other examples are more robust and almost completely filled with irregular islands and trabeculae of proliferating glassy pink keratinocytes. Even though the appearance is complex centrally, note the smooth circumscribed border (arrows).

C: The islands of proliferative epithelium sometimes resemble a scroll rolling up at both ends ("rolls and scrolls" appearance). The epithelium is glassy and pink and transitions directly into sheets of dense compact pink keratin, just like a conventional pilar cyst.

D: Some areas can closely resemble well-differentiated squamous cell carcinoma. The foci of trichilemmal keratinization (similar to a conventional pilar cyst) are clues to the diagnosis (arrows).

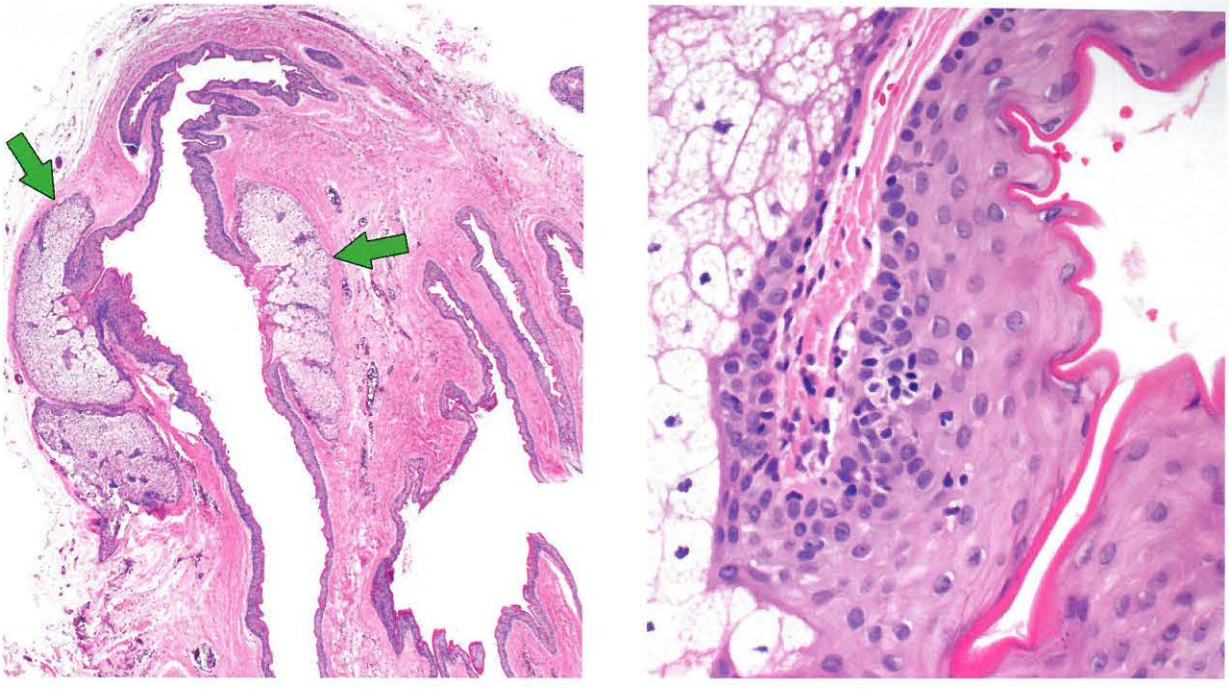


Figure 6-8

STEATOCYSTOMA

Left: Mature sebaceous glands are often seen emptying directly into the cyst lumen (arrows). The cyst wall may be convoluted.

Right: The cyst lining is stratified squamous epithelium with a characteristic wavy "shark-tooth" surface covered by a thick pink cuticle layer of keratin on the luminal surface (right). Note the mature sebaceous gland (left) connected to the cyst lumen.

STEATOCYSTOMA

This may be the closest thing to true "sebaceous cysts" that exist in humans. It is a cyst with a lining of stratified squamous epithelium with a wavy "shark-tooth" surface that has a thick pink cuticle layer on the surface (fig. 6-8). This thick pink layer is similar to the lining of the sebaceous duct, which is part of the hair follicle unit. Mature sebaceous glands are often seen emptying directly into the cyst lumen. When multiple tiny hair shafts are present in the cyst lumen, it is referred to as a *vellus hair cyst* (fig. 6-9).

HIDROCYSTOMA AND CYSTADENOMA

Hidrocystomas are benign simple sweat duct cysts. They are translucent papules on the upper cheek, more often in women. They are composed of one or several dilated cysts in the dermis with a double layer of benign cuboidal epithelium (resembling that of normal sweat ducts) (fig. 6-10). Apocrine snouts are sometimes seen in the lining. A small superficial shave

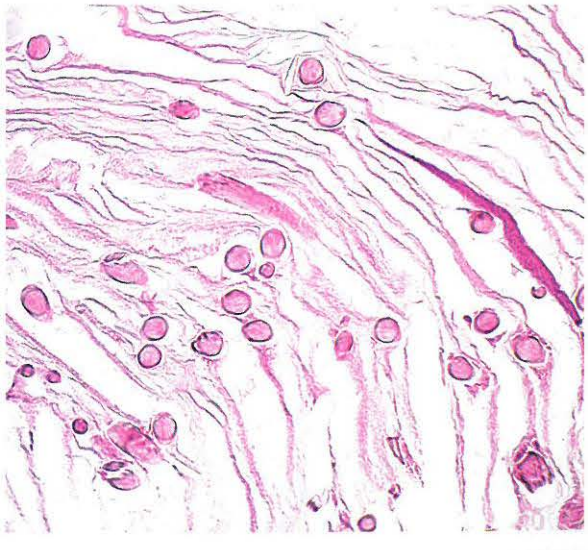


Figure 6-9

VELLUS HAIR CYST

Multiple tiny hair shafts are present in the cyst lumen intermingled with flakes of loose keratin debris. The cyst lining (not shown) is often similar to that of steatocystoma.

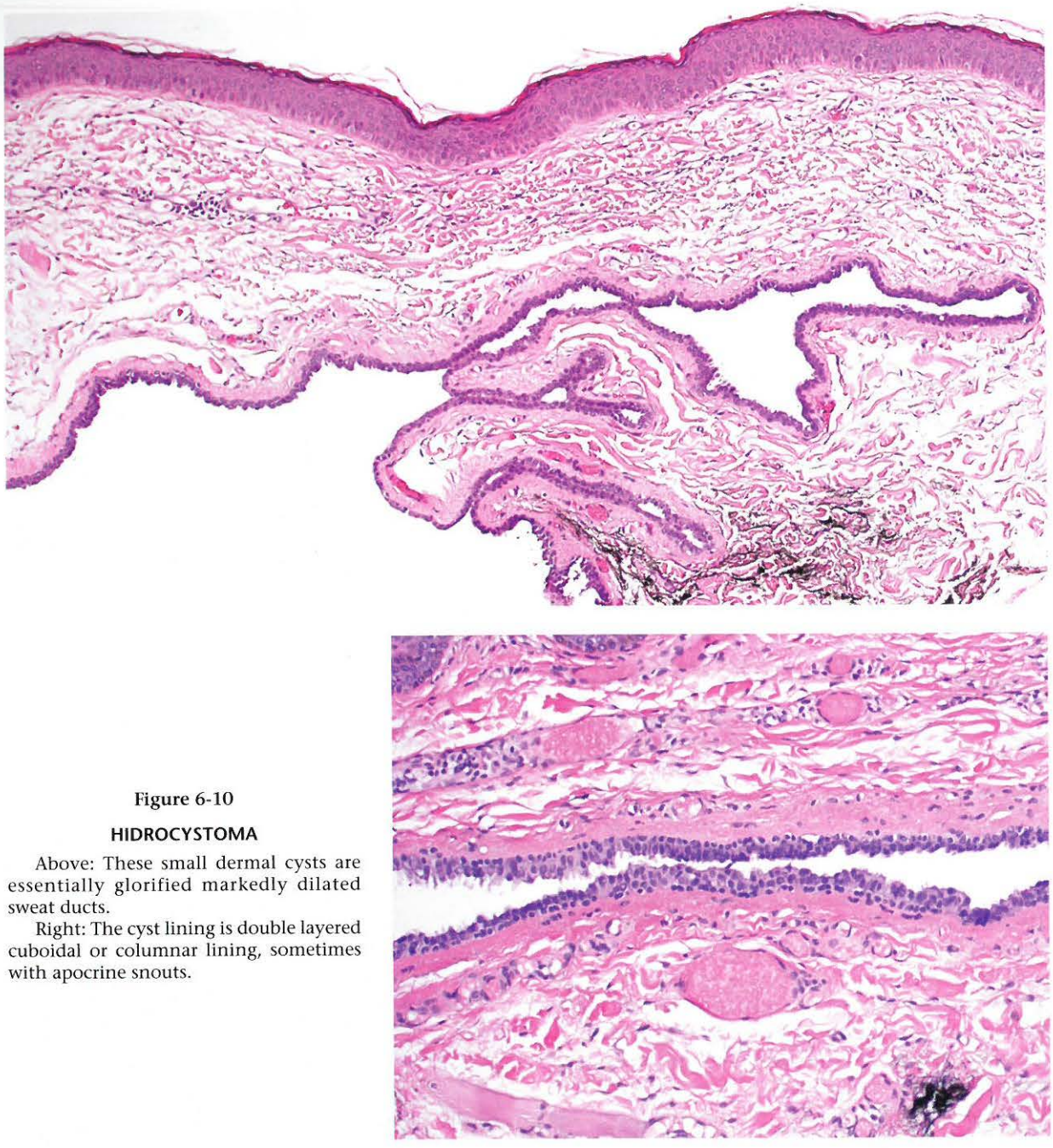


Figure 6-10

HIDROCYSTOMA

Above: These small dermal cysts are essentially glorified markedly dilated sweat ducts.

Right: The cyst lining is double layered cuboidal or columnar lining, sometimes with apocrine snouts.

biopsy (as is common when dermatologists biopsy a small papule on the face) may only barely sample the surface of the lesion; there may be only a tiny strip of cuboidal epithelium along the base of the shave.

A hidrocystoma that has areas of more complex or thicker epithelium is referred to as *cystadenoma*. These remind me a bit of usual ductal hyperplasia of the breast.

7 INFECTIOUS DISEASES

Infectious diseases involving the skin are numerous. I have attempted to select only the most relevant ones, which was a challenging task. I have focused on infections that essentially only occur in skin, as well as ones that occur elsewhere in the body, but have a unique appearance or special clinical significance when they occur in the skin. I have also focused more on infections likely to be encountered in the United States, as that is where I practice and these are entities with which I have the most personal experience. There are many more infections in dermatopathology that are not mentioned here due to limited space: lobomycosis, paracoccidiomycosis, protothecosis (an algae that infects humans), larva migrans, sparganosis (a worm you can get from eating raw snake or frog meat), amoebiasis, and others. The reader is encouraged to consult other textbooks to learn more about these additional infections. In particular, pay special attention to infections that are endemic to the area where you practice. General histologic clues for cutaneous infection are listed in Table 7-1.

IMPETIGO AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Impetigo is bacterial infection in the stratum corneum, usually due to *Staphylococcus aureus* or *Streptococcus pyogenes*. It is common in childhood but also seen in adults. Impetigo sometimes occurs as a secondary process ("impetiginization") on top of an underlying primary inflammatory dermatosis, such as atopic/eczematous dermatitis. The stratum corneum shows parakeratosis, serum crust, neutrophils, and cocci bacteria (fig. 7-1). The bacteria are often visible with the hematoxylin and eosin (H&E) stain, but sometimes Gram stain can be helpful in identifying them (note that bacteria may also be positive

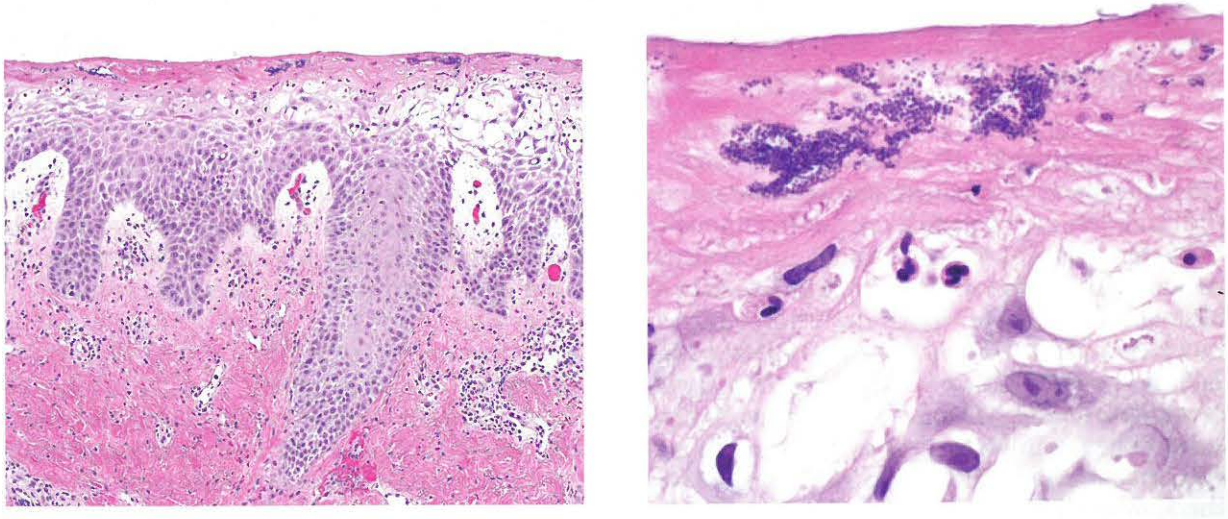


Figure 7-1

IMPETIGO

Left: The spongiotic epidermis has a layer of overlying scale crust (pink fibrin with parakeratosis).
Right: Colonies of cocci bacteria and scattered neutrophils are embedded in the scale crust.

Table 7-1

GENERAL HISTOLOGIC CLUES FOR CUTANEOUS INFECTION

Pattern	Type of Infection
Neutrophils in stratum corneum or subcorneal blister	Tinea (dermatophytosis) Impetigo
Neutrophilic abscess in dermis or subcutis	Bacterial abscess Deep fungal infection[a] Atypical mycobacteria Many others
Granulomatous (or histiocyte-rich) dermatitis with plasma cells and/or neutrophils	Deep fungal infection[a] Atypical mycobacteria Leprosy Tuberculosis
Ischemic changes in epidermis, dermis, or eccrine coils Dermal hemorrhage without inflammation in immunosuppressed patient Thrombi in vessels	Angioinvasive fungal infection
Pseudoepitheliomatous epidermal hyperplasia	Deep fungal infections (especially coccidioidomycosis, blastomycosis, chromoblastomycosis, phaeohyphomyosis) Leishmaniasis Some atypical mycobacteria Tuberculosis verrucosa cutis Various noninfectious mimics (squamous cell carcinoma, halogenoderma, granular cell tumor, others)
Linear/serpiginous granulomas or histiocytic infiltrate Granulomas or histiocytic infiltrate tracking along nerves	Leprosy
"Burrow" in stratum corneum Dense mixed inflammation with many eosinophils Scattered atypical CD30+ lymphocytes	Scabies
Psoriasiform acanthosis with lichenoid lymphoplasmacytic infiltrate Superficial and deep perivascular dermatitis with plasma cells	Syphilis

[a]"Deep fungal infection" refers to fungal infection involving the dermis, subcutis, or deeper soft tissues (e.g., phaeohyphomycosis, coccidioidomycosis, blastomycosis).

on periodic acid–Schiff diastase [PASD] stain). The abundant parakeratosis and serum result in the classic "honey-colored" crust seen clinically.

Bacterial toxins can lead to acantholysis in the underlying epidermis, creating a subcorneal blister filled with neutrophils, acantholytic keratinocytes, and bacteria: this is *bullous impetigo* (fig. 7-2). This should not be confused with *staphylococcal scalded skin syndrome* (SSSS), which is also a subcorneal acantholytic blistering process but without bacteria or neutrophils (fig. 7-3). In SSSS, the *S. aureus* bacteria are growing elsewhere in the body and their circulating toxins cause sterile blistering of the skin at remote sites. Clinically, SSSS is very different from impetigo. It results in widespread skin sloughing and can clinically mimic *Stevens-Johnson syndrome/toxic epidermal necrolysis* (SJS/TEN), although they are different histologically. In SJS/TEN the blistering is due to interface dermatitis whereas in SSSS it is due to subcorneal acantholysis (see chapter 8).

HERPES

Herpetic dermatitis results from either *herpes simplex virus* (HSV type 1 or 2) or *varicella zoster virus* (VZV). HSV and VZV both produce painful erythematous vesicles that eventually ulcerate and crust. HSV usually causes oral or genital blisters whereas VZV causes either widespread acute crops of vesicles in unvaccinated children or adults (varicella, also known as "chicken pox") or dermatomal vesicles in older adults

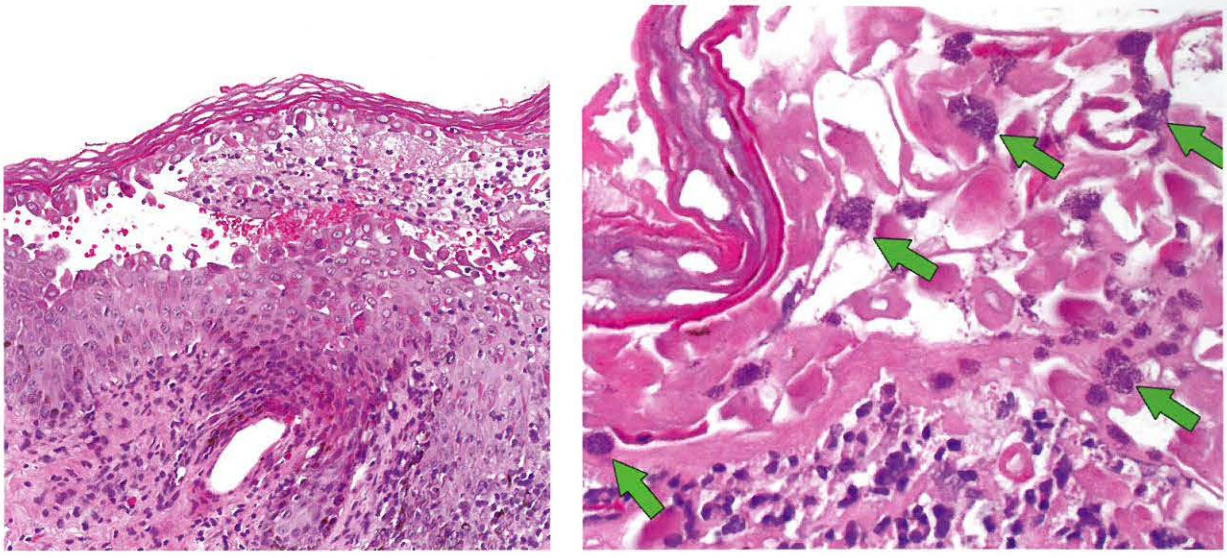


Figure 7-2

BULLOUS IMPETIGO

Left: There is a subcorneal blister due to acantholysis.
Right: At higher power, purple aggregates of cocci bacteria (arrows) and neutrophils are intermingled with bright pink necrotic acantholytic keratinocytes.

(zoster). Immunocompromised patients can get disseminated herpetic dermatitis, which is a medical emergency.

HSV and VZV produce essentially identical histologic features: acantholytic blisters with brisk inflammation (fig. 7-4). The blisters are often ulcerated and necrotic with nuclear debris and many neutrophils ("dirty necrosis"). A brisk superficial and deep perivascular lymphocytic infiltrate is often present, and lichenoid interface alteration may also be seen. When hair follicles are infected, it results in destruction and necrosis of the follicle and sebaceous gland. These features are clues for herpes. The diagnosis is confirmed by identifying herpetic viral cytopathic effect in acantholytic keratinocytes within the blister, characterized by large nuclei with multinucleation, nuclear molding, and margination of chromatin (the "3 Ms" of herpes). Nuclei will also have homogenized "ground (frosted) glass" chromatin and may have large eosinophilic (Cowdry type A) viral nuclear inclusions.

I use a diagnosis of "herpetic dermatitis" as the top line of my report. If the dermatologist needs to know which type of herpes it is, then I can perform HSV and VZV immunostains upon request. In ulcers with extensive necrosis and inflammation, viral cytopathic effect may be obscured. Immunostains for HSV or VZV are helpful in these cases if there is suspicion for herpes clinically or histologically. These immunostains can show an unusual cross-reactivity with cocci bacteria on the skin surface, so when cocci aggregates are visible on H&E-stained slides, use caution interpreting the HSV and VZV immunostains.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum virus (a member of *Poxviridae*) produces an indolent skin infection common in children and also sometimes in adults. It produces pearly papules with central umbilication, which correspond microscopically to a polypoid lesion with a cup-shaped crateriform invagination down from the epidermis (fig. 7-5). When the section is not from the center of the lesion, the epidermal connection is not visible, which gives the appearance of a polyp with a cyst in the middle of it. The invagination/cyst is lined by benign keratinocytes with large round uniform eosinophilic cytoplasmic inclusions (molluscum bodies or Henderson-Patterson bodies). These bodies extrude out into the keratin debris in the middle of the invagination/cyst. Once these are identified, the diagnosis is easily made.

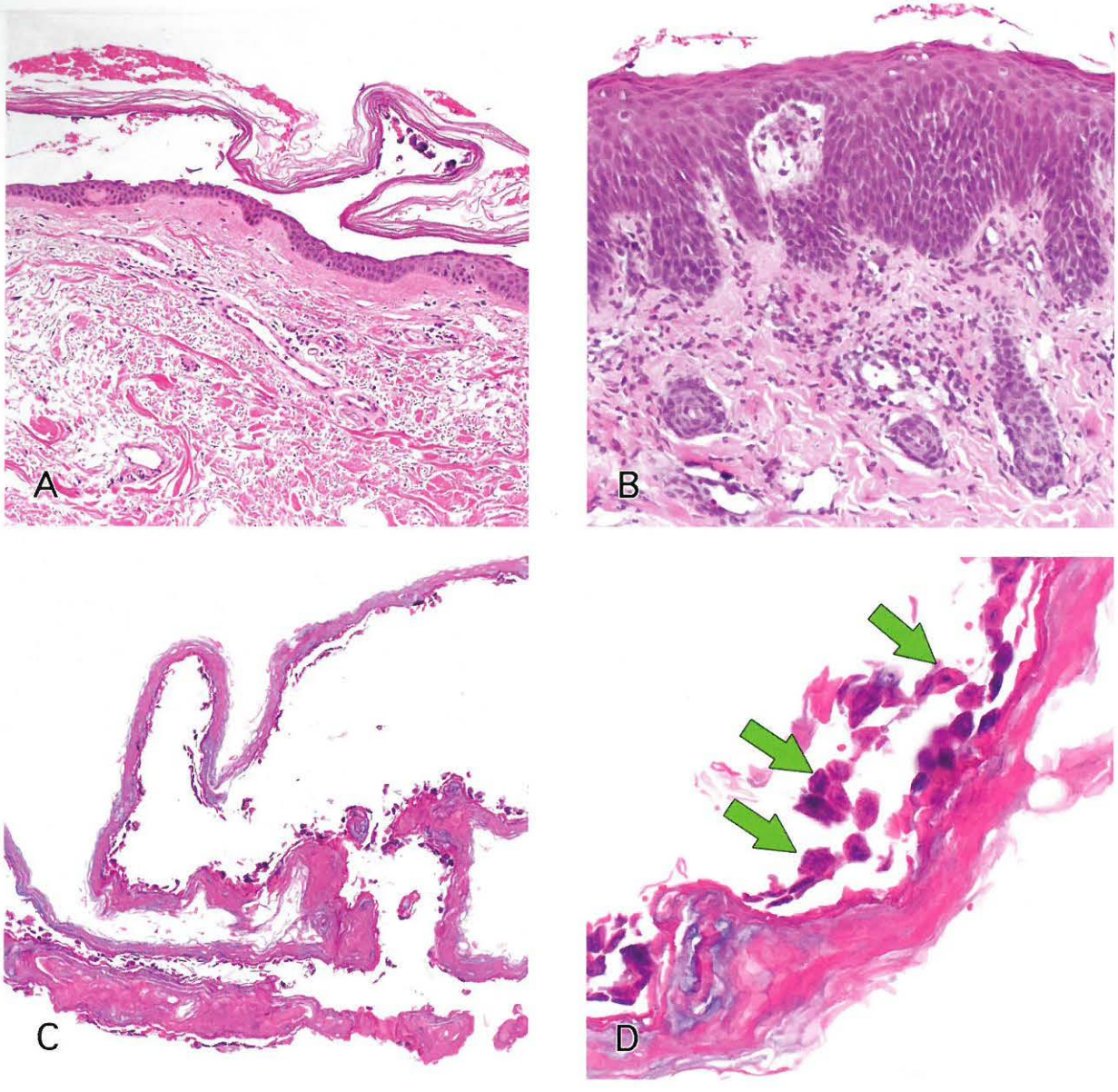


Figure 7-3

STAPHYLOCOCCAL SCALDED SKIN SYNDROME (SSSS)

A: SSSS is also a subcorneal acantholytic blistering process, but unlike bullous impetigo, it does not have bacteria or neutrophils in the blister cavity.

B: The epidermis may appear relatively normal at first; until one notices that the corneal layer is missing. It has completely detached due to extensive acantholysis.

C: The detached corneal layer may sometimes be found elsewhere on the slide, away from the main biopsy.

D: At higher power, free-floating keratinocytes (arrows) from the granular and superficial spinous layers are evidence that extensive acantholysis has caused detachment of the stratum corneum.

In some cases, the lesion ruptures, with very brisk inflammation that can obscure identification of the molluscum bodies. This can be so robust as to mimic lymphoma occasionally. Tangentially-sectioned molluscum that just shows the very edge of the invagination/cyst may display intradermal nests of enlarged keratinocytes but no obvious molluscum bodies.

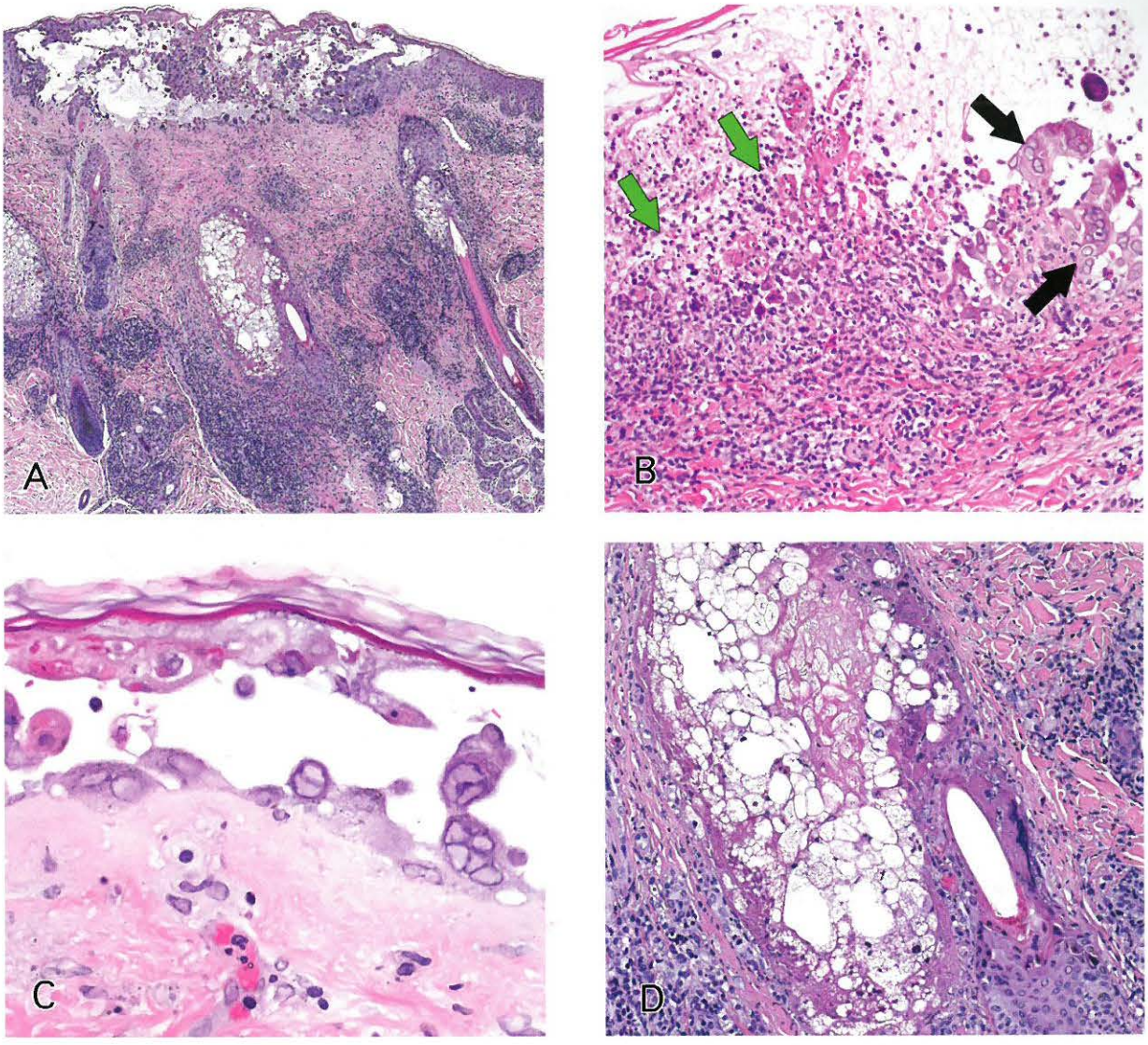


Figure 7-4

HERPES

A: There is an intraepidermal blister with brisk inflammation within the blister cavity. Superficial and deep perivascular inflammation is also present in the dermis. There is necrosis of a hair follicle and sebaceous gland (center).

B: Acantholytic keratinocytes with herpetic viral cytopathic effect are often present at the periphery of the blister (black arrows). There are also necrotic acantholytic keratinocytes mixed with neutrophils and debris ("dirty necrosis") (green arrows).

C: Acantholytic keratinocytes within the blister have large nuclei with multinucleation, nuclear molding, and margination of chromatin (the "3 Ms" of herpetic viral cytopathic effect). The nuclei have pale hazy homogenized "ground/frosted glass" chromatin.

D: Necrosis and destruction of a sebaceous gland and hair follicle; these are important clues for herpetic folliculitis (same case as fig. "A").

Cases like this can mimic an epidermal or adnexal neoplasm. Deeper sections usually reveal the molluscum bodies making the diagnosis obvious.

Myrmecia-type verruca is sometimes confused with molluscum because it has eosinophilic globules. These globules are much smaller and more irregular in size than molluscum bodies. Additionally, myrmecia warts have papillomatosis and other histologic features of verruca, and they occur on acral skin, all features that argue against molluscum (see chapter 3).

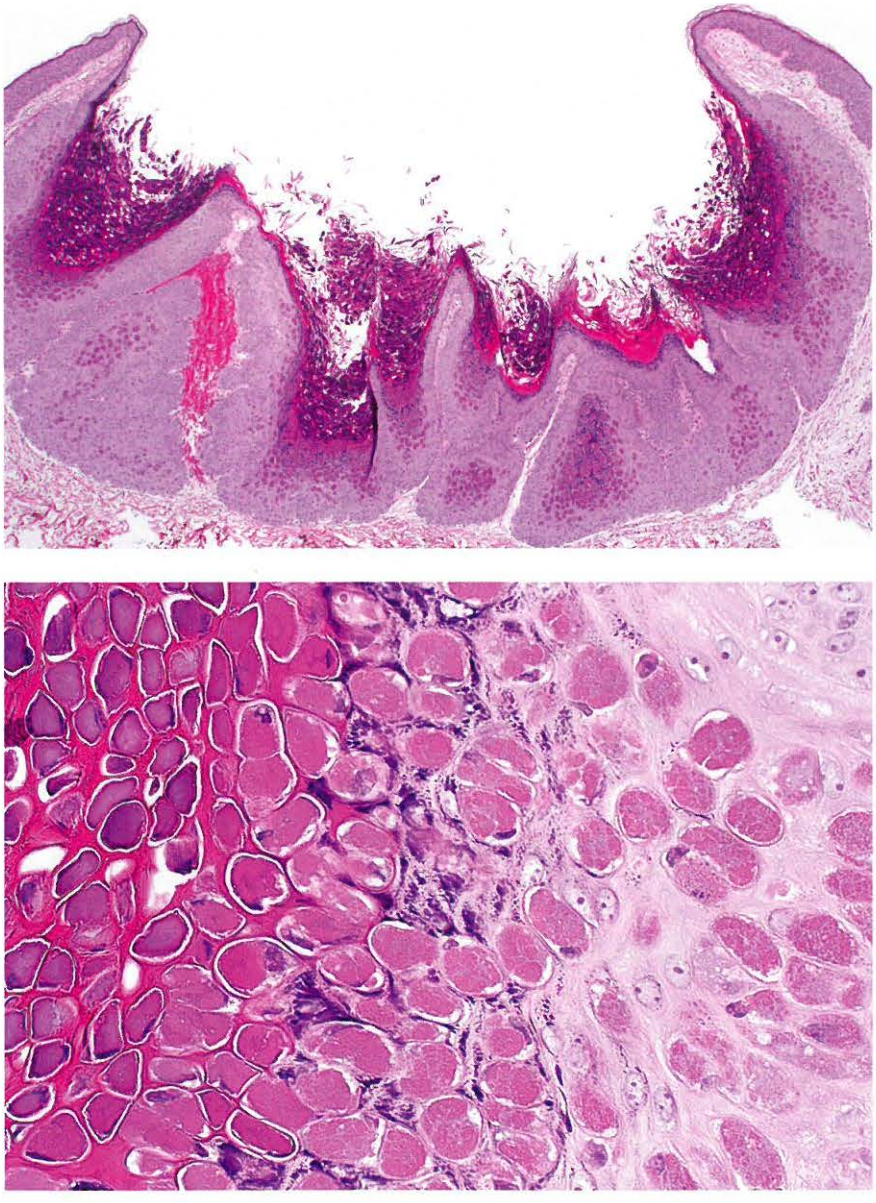


Figure 7-5

MOLLUSCUM CONTAGIOSUM

Top: The classic appearance is a polypoid lesion with a cup-shaped crateriform invagination. It is lined by enlarged benign keratinocytes and filled with loose keratin debris and numerous molluscum bodies.

Bottom: Large round uniform eosinophilic cytoplasmic viral inclusions (molluscum bodies or Henderson-Patterson bodies) form within the keratinocytes (right) and then extrude out into the keratin debris in the middle of the invagination/cyst (left).

TINEA (DERMATOPHYTOSIS)

Dermatophyte fungi (Genus: *Epidermophyton, Trichophyton,* and *Microsporum*) can cause a variety of skin infections, which are clinically classified by the body site involved (*tinea capitis*, scalp; *tinea cruris*, groin; *tinea pedis/manuum*, feet/hands; *tinea corporis*, elsewhere on the body). The species vary by body site and geographic location.

Tinea often presents as erythematous scaly patches or plaques with a raised border imparting an annular (ring-like) appearance (thus the misnomer "ringworm"). Microscopically, the main changes are in the epidermis: spongiosis, compact orthokeratosis and/or parakeratosis, and neutrophils in the stratum corneum (fig. 7-6). There may be perivascular lymphocytes and eosinophils in the dermis.

Most cases resemble spongiotic dermatitis, but some cases show minimal changes and resemble normal skin. Spongiotic vesicles filled with neutrophils are seen in some cases (*bullous tinea*) (fig. 7-7). Fungal hyphae are present in the stratum corneum and arranged parallel to the underlying epidermis; they are usually invisible

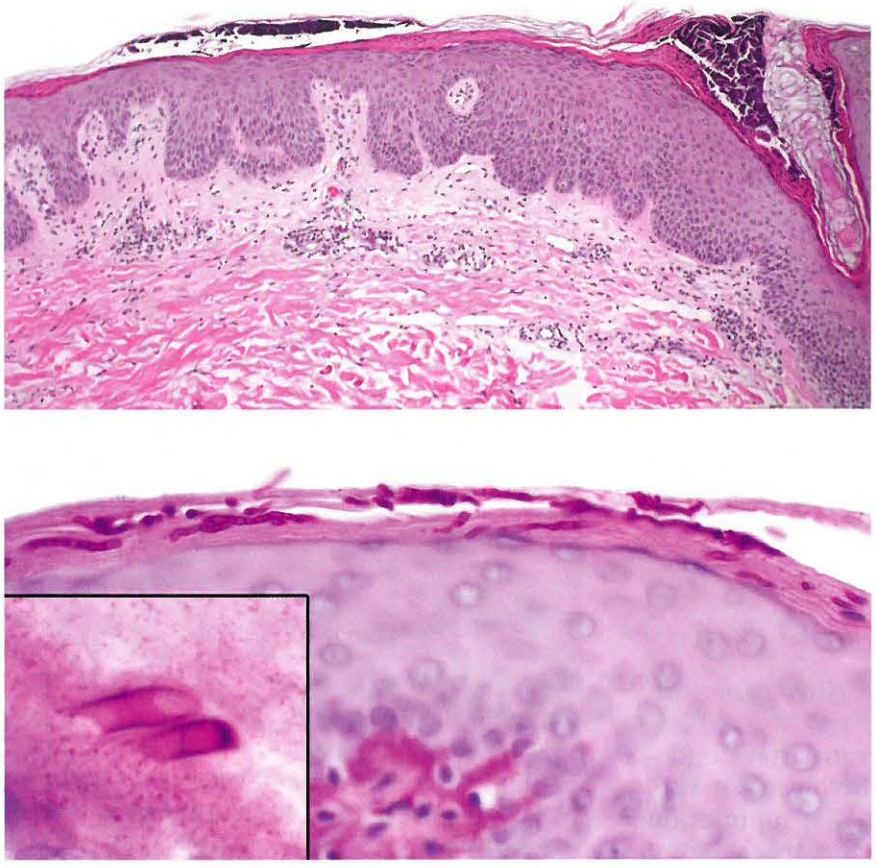


Figure 7-6

TINEA (DERMATOPHYTOSIS)

Top: The acanthotic epidermis shows mild spongiosis, compact parakeratosis, and neutrophil aggregates within the stratum corneum.

Bottom: Periodic acid–Schiff with diastase (PASD) stain highlights the fungal hyphae as thin hollow tubes (inset) within the compact keratin of the stratum corneum. The hyphae are usually arranged parallel to the epidermis.

or nearly so with H&E, and thus require either PASD (my preference) or Gomori methenamine silver (GMS) to highlight them. Some dermatopathologists use fungal stains on nearly all spongiotic dermatoses, but I tend to be more selective. Table 7-2 lists the scenarios for which I usually use PASD to rule out tinea.

Distinguishing tinea from inflammatory dermatoses is clinically important; many inflammatory diseases are treated with topical corticosteroids, whereas tinea usually gets worse with corticosteroids and may develop unusual clinical features (*tinea incognito*). This is not life threatening, but it may cause significant morbidity for the patient.

Tinea capitis causes scaling of the scalp with patchy alopecia and sometimes boggy induration (*kerion*); it is more common in children. The histologic features vary depending on the species. Fungal hyphae and small round spores form a layer coating the outer surface of hair shafts (*ectothrix* pattern), or spores entirely fill and replace the center of hair shafts (*endothrix*

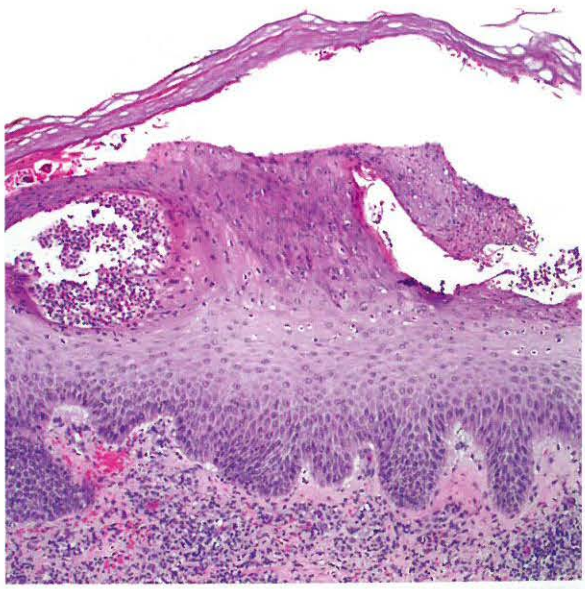


Figure 7-7

BULLOUS TINEA (DERMATOPHYTOSIS)

Some cases of dermatophytosis develop spongiotic intraepidermal vesicles filled with neutrophils.

Table 7-2

WHEN TO ORDER PASD TO RULE OUT TINEA

Spongiotic dermatitis or nonspecific features in biopsy from groin, hands, feet
Spongiotic dermatitis with neutrophils in stratum corneum
Spongiotic blister with neutrophils
Rash getting worse or not responding with topical corticosteroid use
Clinical differential includes tinea or other annular entities (e.g., granuloma annulare [GA], subacute cutaneous lupus erythematosus [SCLE], erythema annulare centrifugum [EAC]), but shows spongiotic dermatitis or only nonspecific changes microscopically)[a]
Biopsy performed for rash but shows essentially normal skin microscopically

[a]Unless there are obvious features of GA or SCLE present, in which case I do not usually perform PASD.

pattern) (fig. 7-8). The organisms stain with PASD and GMS.

Tinea corporis may sometimes have endothrix or ectothrix hair shaft involvement also. Hair follicles infected by tinea may rupture and produce neutrophil abscesses in the adjacent dermis. Deeper levels may be needed to find the hair shaft with the fungal organisms.

Some cases of tinea capitis produce brisk mixed inflammation and fibrosis mimicking inflammatory scarring alopecia, and these cases sometimes show no obvious fungal organisms even with PASD/GMS. For inflammatory alopecia in young adults, occult tinea capitis should be in the differential diagnosis so the dermatologist can consider a trial of antifungal therapy.

Onychomycosis is nail plate infection usually caused by dermatophytes and rarely by other types of fungi. Fungal hyphae are present in the nail plate or the subungual keratin debris on PAS or GMS stain (fig. 7-9). If only yeast are present, I mention them in my report but add a comment that they may merely be *Candida* or *Malassezia* (formerly *Pityrosporum*) skin flora that are incidental bystanders rather than the causative agents. If I see large segmented hyphae, a mixture of different types of hyphae or yeast, or other unusual morphologic features, I add a comment suggesting a non-dermatophyte fungus and recommending cultures if clinically

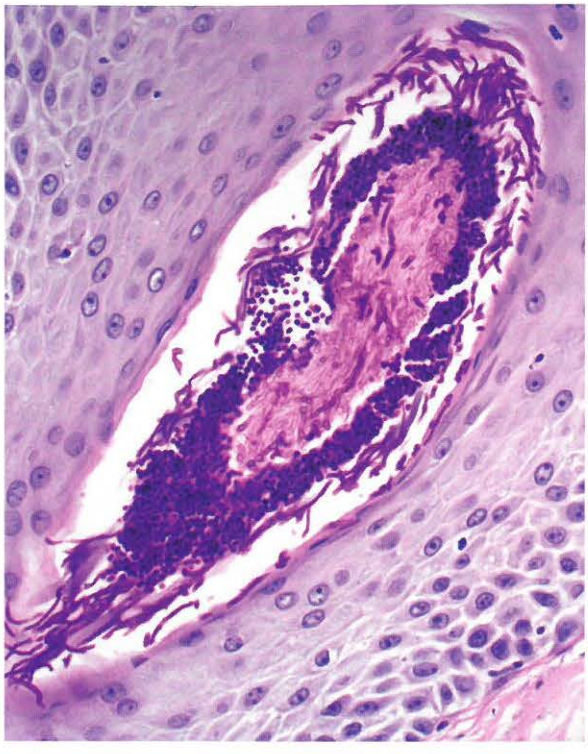


Figure 7-8

TINEA CAPITIS (DERMATOPHYTOSIS)

PASD stains shows fungal hyphae and small round spores forming a thick layer coating the outer surface of a hair shaft within a follicle (ectothrix pattern).

indicated. Non-dermatophyte onychomycosis may require different therapeutic agents. Cocci bacteria are often adherent to the underside of the nail plate and may stain with PAS; do not confuse these with fungi. Bacteria are much smaller than fungal yeast or spores and can be easily distinguished with a bit of practice.

ERYTHRASMA

Erythrasma can clinically mimic tinea, since it causes erythematous plaques in the groin or axilla. One clinical trick to recognize erythrasma is using a Wood's lamp (blacklight), which makes the plaques fluoresce a coral pink color.

Erythrasma is caused by tiny Gram-positive rod bacteria, *Corynebacterium minutissimum*, that are present in the stratum corneum (fig. 7-10). These are much smaller than dermatophyte fungi and appear as thin, bluish, short thread-like organisms visible on H&E. They are embedded in dense orthokeratin of the stratum corneum.

Inflammation is often minimal. The bacteria are also highlighted by Gram stain or PASD.

TINEA (PITYRIASIS) VERSICOLOR

Malassezia furfur (formerly *Pityrosporum ovale*) is a dimorphic fungus that is part of the normal skin flora as budding yeast in the stratum corneum. When it overgrows and causes infection, it is called *tinea versicolor* (no relationship to the dermatophytosis forms of tinea discussed above).

Clinically, tinea versicolor shows brown patches with fine scale on the trunk, neck, or face. In dark skin, the patches are often hypopigmented. Microscopically, both yeast and hyphae are seen in the stratum corneum (resulting in the classic "spaghetti and meatballs" appearance on skin scrapings treated with potassium hydroxide (KOH); this pattern is not always obvious on H&E sections) (fig. 7-11). Unlike dermatophyte fungi, *Malassezia* fungi have a light blue to purple color on H&E and are thus easily visualized without PASD or GMS. Sometimes there is spongiosis and mild inflammation, but in many cases the skin has an essentially normal microscopic appearance aside from slightly thickened compact orthokeratosis.

Malassezia requires lipid to grow, and sebaceous secretions are an ideal source of this.

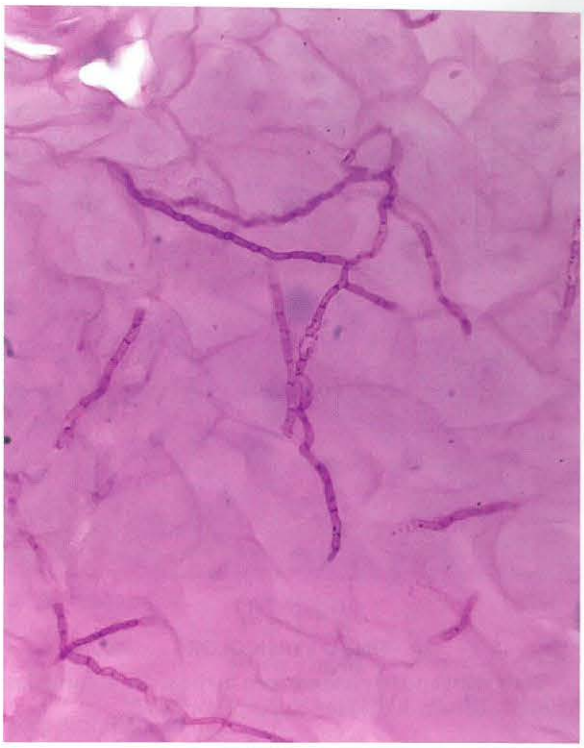
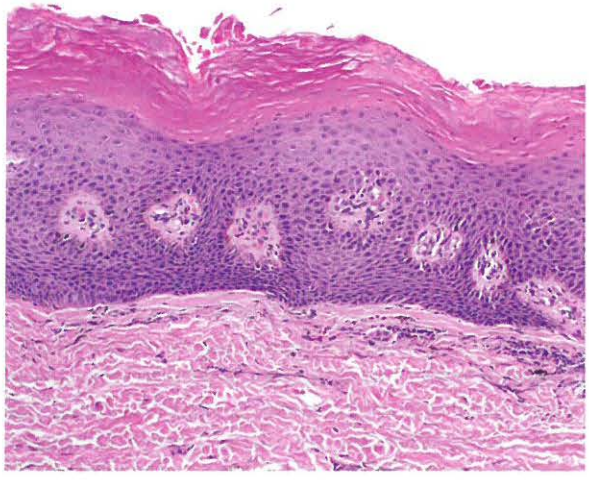


Figure 7-9

ONYCHOMYCOSIS

Thin, branching, septate, fungal hyphae are present in the nail plate on PAS stain.



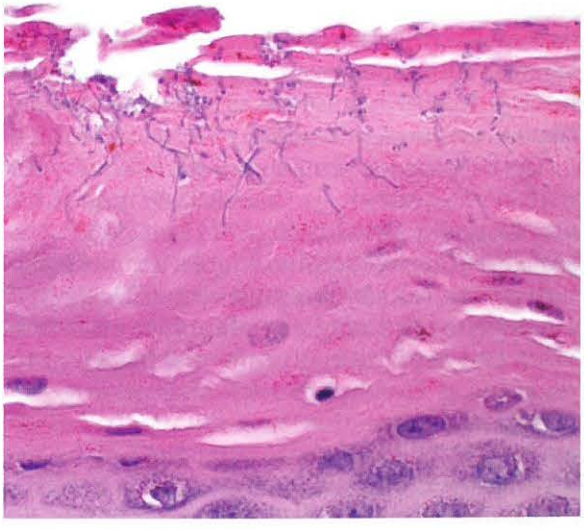


Figure 7-10

ERYTHRASMA

Left: There is epidermal acanthosis with thick compact orthokeratin in the corneal layer. Inflammation is often minimal.
Right: Multiple thin, bluish, thread-like bacteria are embedded in the dense orthokeratin of the stratum corneum as seen on this H&E stain. They are much smaller than dermatophyte fungi.

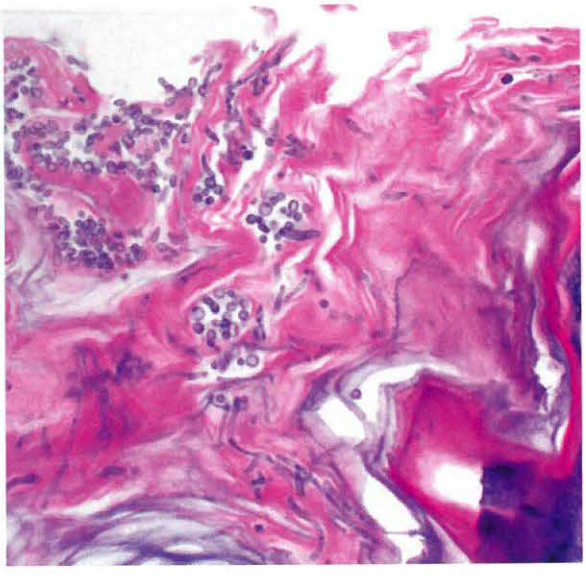


Figure 7-11

TINEA VERSICOLOR

Both yeast and hyphae are seen in the stratum corneum. They are usually light blue to purple on H&E.

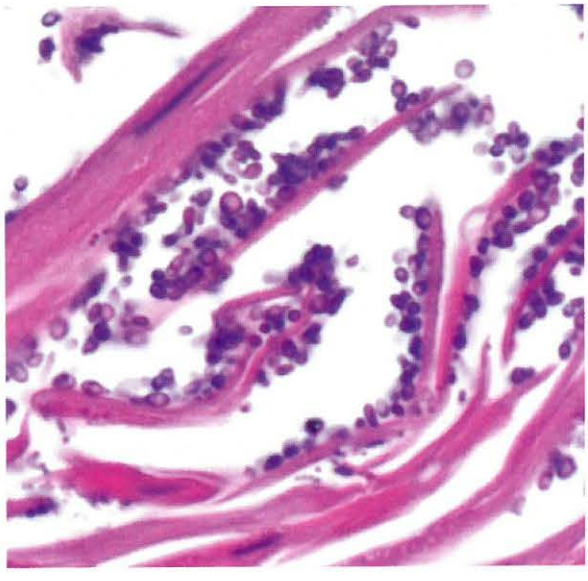


Figure 7-12

INCIDENTAL *MALASSEZIA (PITYROSPORUM)* YEAST

Small blue-purple budding yeast (but no hyphae) are present in the thick stratum corneum overlying an actinic keratosis. They are easily visible on this H&E stain. This is a common incidental finding that does not need to be reported.

Accordingly, *Malassezia* are found incidentally on routine skin biopsies as budding yeast (without hyphae), in places where sebum gets entrapped, such as the follicular infundibula, or the thick stratum corneum overlying hyperkeratotic lesions such as seborrheic keratosis or hypertrophic actinic keratosis; there is no need to report this incidental finding (fig. 7-12). It is not tinea versicolor unless hyphae are present in addition to yeast.

Do not confuse incidental *Malassezia* yeast with dermatophytosis (which has hyphae but no yeast) when evaluating PASD or GMS stains. *Malassezia* can sometimes cause a form of folliculitis that clinically resembles acne (*Malassezia/Pityrosporum folliculitis*), so when I see *Malassezia* yeast present within an inflamed follicle, I report this as "folliculitis with *Malassezia* yeast" with a comment that it is uncertain if these are incidental flora or causative organisms; the distinction is best made clinically.

Candida resemble *Malassezia* microscopically, as they are also budding yeast that stain light blue to purple on H&E, and their pseudohyphae can look similar to the *Malassezia* hyphae seen in tinea versicolor (fig. 7-13). One microscopic clue is that pseudohyphae of *Candida* tend to grow perpendicular to the epidermis, "diving down" through the corneal layer, whereas the hyphae of *Malassezia* (and also of dermatophytes) tend to grow parallel to the epidermis, "surfing the waves" of the stratum corneum. The anatomic site is also helpful, since *Candida* usually grows in moist areas such as the groin, inframammary folds, or lips, whereas *Malassezia* usually grows on dry skin. If I am uncertain, I mention in a comment that the differential includes both organisms so that the dermatologist can either treat with an agent that covers both or perform cultures depending on the clinical scenario.

TINEA NIGRA

Tinea nigra is an uncommon but very distinct fungal disease that only occurs in skin. It is called "tinea" but is not due to dermatophyte fungi but rather to various species of pigmented dematiaceous fungi (particularly *Hortaea werneckii*). The fungi infect the surface of acral skin causing an enlarging pigmented patch that can clinically mimic acral melanoma. Skin biopsy shows pigmented fungal hyphae in the stratum corneum that are visible with H&E stain (fig. 7-14).

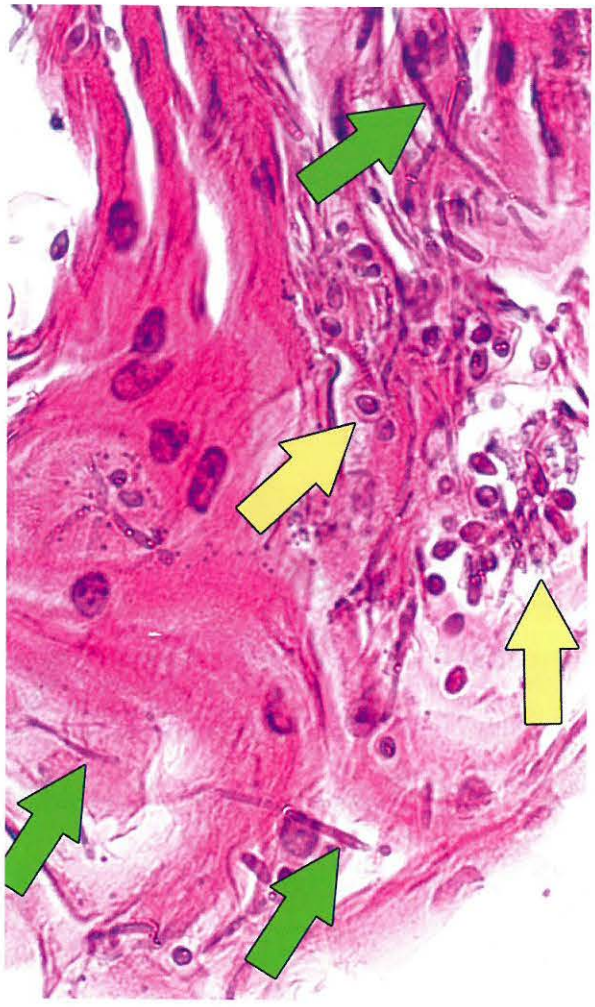


Figure 7-13

CANDIDA

Both yeast (yellow arrows) and (pseudo)hyphae (green arrows) are seen in the stratum corneum. They are usually light blue to purple on H&E. The microscopic appearance can be very similar to tinea versicolor.

ANGIOINVASIVE FUNGAL INFECTION

Fusarium and *Aspergillus* species and some other fungi can invade blood vessels and disseminate systemically, where they may secondarily involve the skin. Although *Aspergillus* may involve skin as a primary infection due to traumatic inoculation, in general, invasive hyphae in the dermis/subcutis (especially within vessels), should be regarded as systemic disease until proven otherwise. This represents a serious medical emergency and a phone call to the treating physician is warranted when this diagnosis is made.

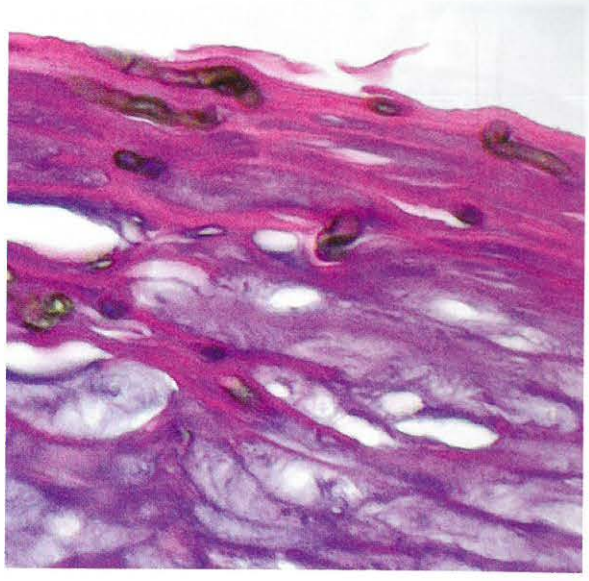


Figure 7-14

TINEA NIGRA

Brown fungal hyphae are present in the stratum corneum (H&E stain).

Cutaneous angioinvasive fungal infection is most often seen in immunocompromised patients. It manifests as erythematous or violaceous plaques which may undergo ischemic necrosis and ulcerate, progressing to black eschars. Biopsy shows variable amounts of ischemic necrosis of the epidermis and dermis, characterized first by eccrine coil necrosis, followed by degeneration and loss of nuclei in the epidermis as well as the dermis (fig. 7-15). Complete ischemia eventually causes an infarct with a zone of entirely necrotic epidermis and dermis.

Recognizing skin ischemia is a crucial clue not only for angioinvasive fungal infection but also for other serious occlusive vascular processes including calciphylaxis and various coagulopathies. Once ischemia is identified microscopically, the slide should be searched to identify the source. If it cannot be identified, then a deeper biopsy may be needed. These cases can end in disaster if the ischemic changes are overlooked by the pathologist (1).

In angioinvasive fungal infection, the ischemia is due to blockage of dermal/subcutaneous vessels, which are filled with fibrin thrombi mixed with fungal hyphae. The hyphae traverse the vessel walls and invade the dermis,

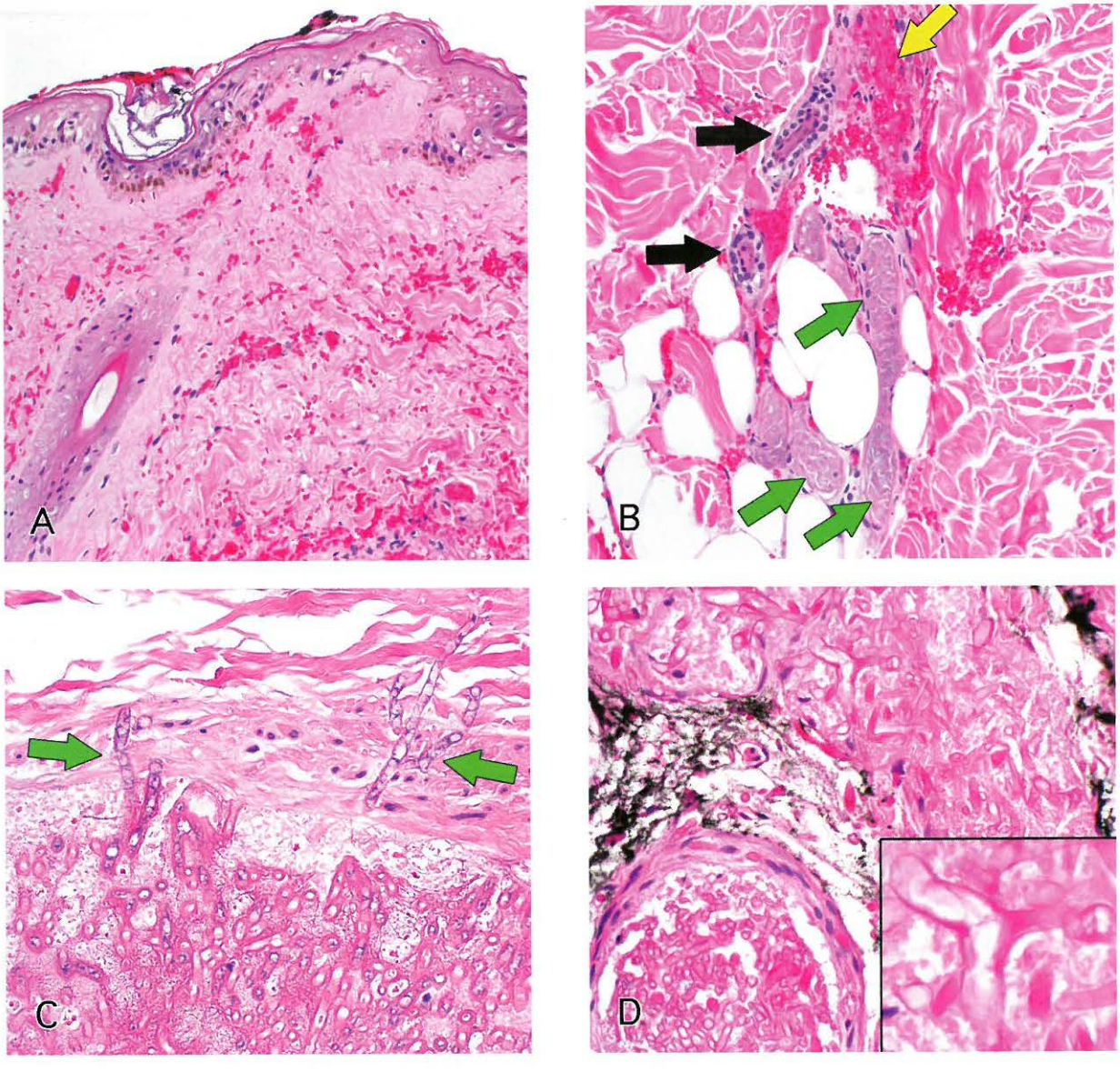


Figure 7-15

ANGIOINVASIVE FUNGUS

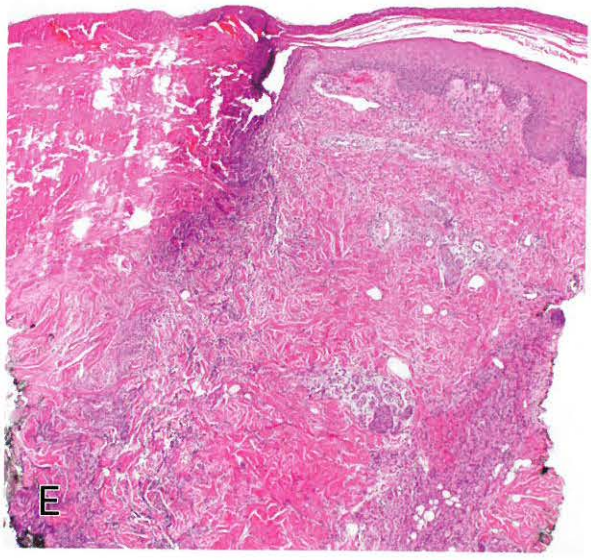
A: The epidermis and hair follicle epithelium are undergoing ischemic necrosis; they are pale pink due to loss of nuclei. In this profoundly neutropenic patient, the dermis looks strikingly red/pink and "wiped out" due to the combination of blood and ischemia in the dermis with no corresponding inflammatory response.

B: This eccrine coil is completely pink due to ischemic necrosis (green arrows). The eccrine duct, however, is still viable (black arrows). The adjacent dilated vessel is filled with blood and fibrin thrombus (and fungi, although they are not visible from this magnification) (yellow arrow).

C: Branching septate fungal hyphae completely fill the lumen of a vessel (bottom) and invade through the muscular vessel wall (arrows) into the adjacent dermis.

D: Fungal hyphae fill the lumen of a vessel (bottom left). They also form a tangled mass in the adjacent dermis (top right). These are broad, ribbon-like, aseptate, wide-angle branching fungal hyphae (inset), which culture proved to be *Rhizopus*.

with corresponding hemorrhage. In profoundly neutropenic patients, the dermis often looks strikingly red/pink and "wiped out" due to the combination of blood and ischemia in the dermis, with no corresponding inflammatory response due to the patient's immunosuppression.



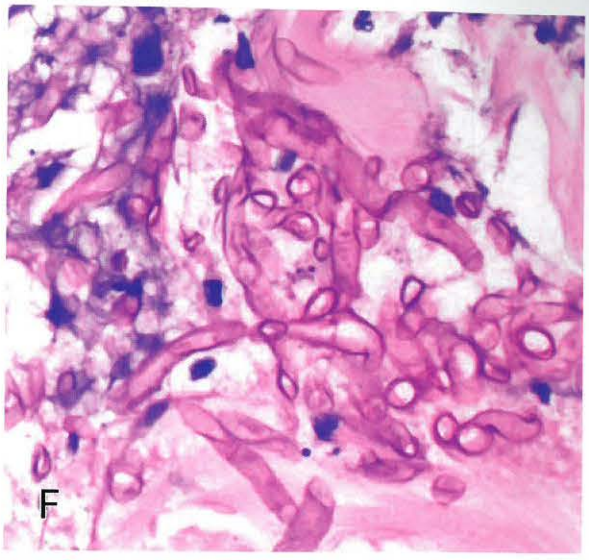


Figure 7-15, continued

E: This biopsy is from the edge of a black eschar in a stem cell transplant patient. There is a sharply demarcated zone of complete epidermal and dermal necrosis, representing the edge of a wedge-shaped infarct (left).

F: These broad, ribbon-like, apparently aseptate, wide-angle branching fungal hyphae were seen at the edge of the infarct on PASD stain (same case as E). Although they resemble *Zygomycete* fungi, culture surprisingly grew *Aspergillus niger*. The only reliable way to determine the species of invasive hyphal fungi is by culture or molecular techniques.

The hyphae of *Fusarium* and *Aspergillus* are essentially identical to one another: thin, septate hyphae with acute angle branching. *Fusarium* may also have yeast-like spores in addition to the hyphae (2). The hyphae are often visible on H&E but if they are not, and if there is any suspicion for angioinvasive fungus, PASD or GMS should be performed (I sometimes use both stains if I have strong suspicion).

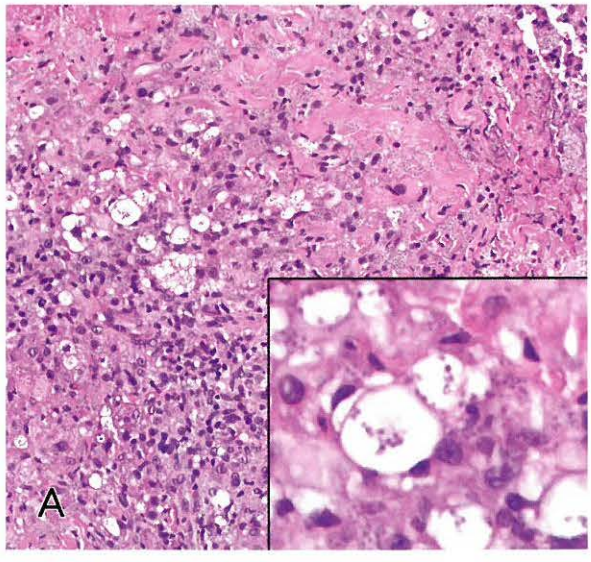
Zygomycete fungal infections (including *Rhizopus, Mucor, Absidia*, and a few others) usually cause deadly infections of the nasal sinuses and brain, but they can occasionally involve the skin, either as secondary disseminated disease or as primary cutaneous infection from a contaminated wound. The overall features are similar to the other angioinvasive fungi discussed above, except that *Zygomycete* fungal hyphae are classically broad and ribbon-like, with 90 degree branching and no significant septation.

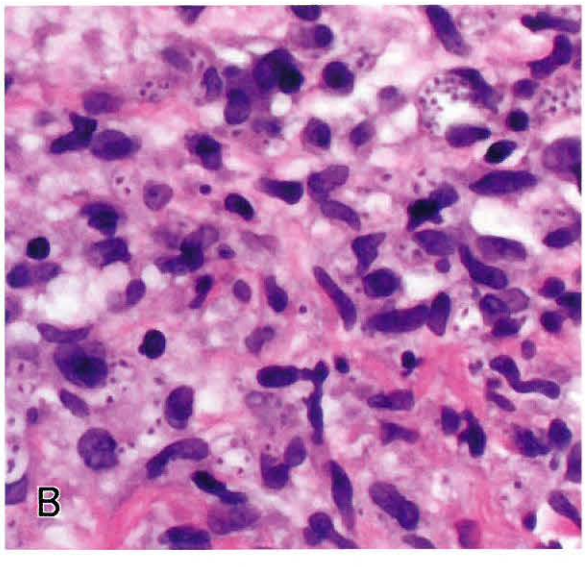
Sometimes invasive fungi break the rules and mimic one another (I have seen *Aspergillus* that mimicked *Mucor* on tissue sections). The only reliable way to determine the species of invasive hyphal fungi is by culture or molecular techniques; an excellent article by Sangoi et al. (3) is a great reference to use if your clinical colleagues give you trouble for not speciating the fungus on tissue biopsy. A final caveat: ischemic ulcers from nonfungal etiologies sometimes develop a layer of fungi within the serum crust on the surface of the ulcer (but not within the dermis/subcutis), which usually represents secondary colonization of the surface by *Candida* or *Malassezia*; do not confuse this with angioinvasive fungus.

HISTOPLASMOSIS

Histoplasma capsulatum is a dimorphic fungus endemic to the United States (Ohio and Mississippi river valleys) and other areas worldwide. The fungus is present in soil and bat/bird guano, and when dislodged into the air it is inhaled into the lungs. Infection can disseminate from the lungs and secondarily involve the skin in immunocompromised patients, producing multiple papules and nodules in the skin. Mucosal involvement is also common.

On biopsy, the epidermis is usually normal while the dermis is effaced by a dense lymphoplasmacytic and histiocytic infiltrate with granulomas. Numerous tiny (2 to 4 μm) uniform round intracytoplasmic yeast are present within the histiocytes (fig. 7-16). The yeast are surrounded by small artifactual halos (giving the





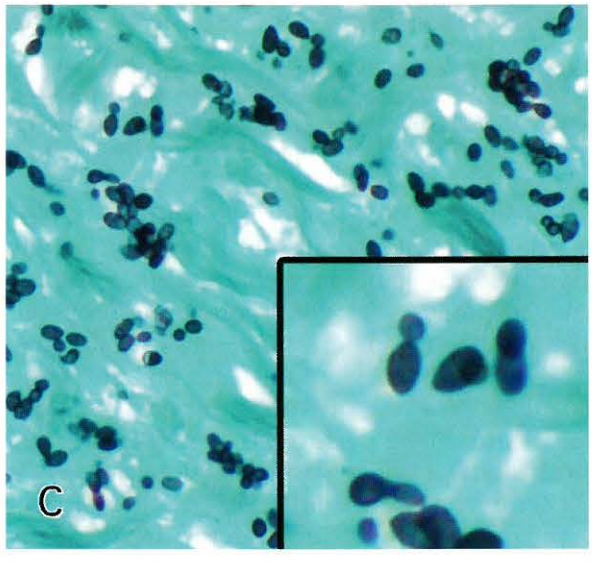


Figure 7-16

HISTOPLASMOSIS

A: The dermis is effaced by a dense histiocytic infiltrate with multiple intracytoplasmic vacuoles. Clusters of tiny yeast are seen in these vacuoles at high magnification (inset).

B: Uniform round tiny intracytoplasmic yeast are present within the histiocytes. The yeast are surrounded by small artifactual halos (giving the false appearance of "capsules").

C: The narrow budding of the yeast is more easily visualized on GMS stain.

false appearance of "capsules") and arranged in small clusters within intracytoplasmic vacuoles. They stain with GMS and PASD, although they can usually be identified on H&E.

Leishmaniasis can look very similar to histoplasmosis microscopically (see below). GMS staining is particularly helpful in revealing the narrow budding of the yeast in histoplasmosis, a finding not seen in leishmaniasis.

LEISHMANIASIS

Various species from the protozoal genus *Leishmania* can cause skin infections. These organisms live in many animal reservoirs and are transmitted to humans via the phlebotomine sandfly vector. *L. tropica* and *L. brasiliensis* cause cutaneous and mucocutaneous involvement, respectively, whereas *L. donovanii* causes visceral disease. The cutaneous form is predominantly seen in the Middle East whereas the mucocutaneous form occurs mainly in South America (Brazil, Bolivia, Peru).

Skin lesions present as multiple papules, nodules, plaques, and ulcers. The histologic features vary depending on the immune status of the patient, species of organism, and chronicity of infection. Chronic infections show perineural granulomas similar to leprosy, with few organisms. Acute infections have mixed inflammation with histiocytes and numerous organisms (4–5).

The Leishmania amastigotes are tiny (2 to 4 µm), uniform, round intracytoplasmic organisms (fig. 7-17). Their size and appearance are quite similar to *Histoplasma* yeast, except that *Leishmania* amastigotes possess a small rod-shaped structure called a kinetoplast in their nucleus. Kinetoplasts are very difficult to see reliably without an oil immersion 100x objective, and I have also seen definitive cases of histoplasmosis that looked like they had kinetoplasts. Another classic feature of leishmaniasis is that the organisms are distributed around the outer rim of vacuoles (the "Marquee sign"). Yet I have seen cases of histoplasmosis that had this pattern. Thus, I do not rely on these features alone. Stains can help here, as *Leishmania* are negative for GMS. For histoplasmosis, microbial cultures of tissue and blood, urine antigen testing, and other laboratory tests help further support the diagnosis if the biopsy results are uncertain. Travel history and geographic area where the patient lives can also be helpful. The geographic distribution of *Leishmania* may be changing; there are a growing number of reported cases of endemic *Leishmania* (*L. mexicana*) acquired within the United Staste (6). A few other organisms not discussed in this book can rarely enter the differential diagnosis, including *Toxoplasma gondii* and *Penicillium marneffei*.

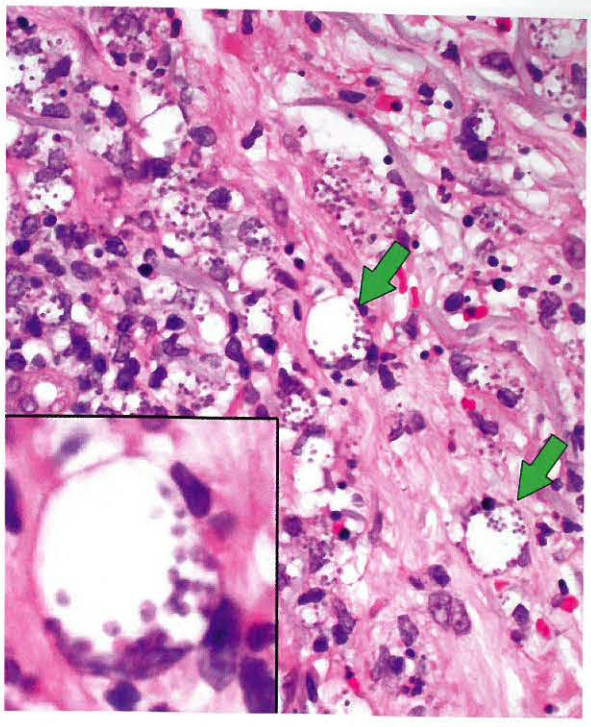


Figure 7-17

LEISHMANIASIS

The tiny uniform organisms are present in intracytoplasmic vacuoles (arrows) within dermal histiocytes. They are often distributed around the outer rim of these vacuoles (the "Marquee sign") (inset).

COCCIDIOIDOMYCOSIS

Coccidioides immitis (and *C. posadasii*) are highly virulent dimorphic fungi found in the southwestern United States, northern Mexico, and parts of Central and South America. Inhalation of soil/dust contaminated with fungal arthrospores results in pulmonary infection, which may progress to disseminated secondary infection of skin and other sites in immunocompromised patients.

In the skin, coccidioidomycosis presents as verrucous plaques and nodules, most often on the face. Biopsy shows granulomatous dermatitis with neutrophil microabscesses. Scattered large (80 µm) thick-walled spherules are present in the dermis (fig. 7-18). The spherules contain multiple small round endospores, although some spherules are ruptured and empty. The organisms are usually easy to identify on H&E, although they also stain with GMS and PASD (note that the empty degenerated spherules are sometimes PASD negative).

Coccidioides skin infections often induce prominent pseudoepitheliomatous epidermal hyperplasia. When fungal elements are sparse or the biopsy is superficial, these robust reactive epidermal changes can mimic squamous cell carcinoma or other diseases that also show prominent pseudoepitheliomatous epidermal hyperplasia (including other invasive fungal infections, leishmaniasis, tuberculosis verrucosa cutis, halogenoderma, granular cell tumor, and others) (4,7–8).

CRYPTOCOCCOSIS

Cryptococcus neoformans is a dimorphic environmental fungus (lives in soil, bird droppings) found worldwide. It causes pulmonary infection after inhalation, which may disseminate to skin or other organs, particularly in the immunocompromised (an unexpected diagnosis of cutaneous *Cryptococcus* warrants clinical work-up for human immunodeficiency virus (HIV) or other source of immunocompromise).

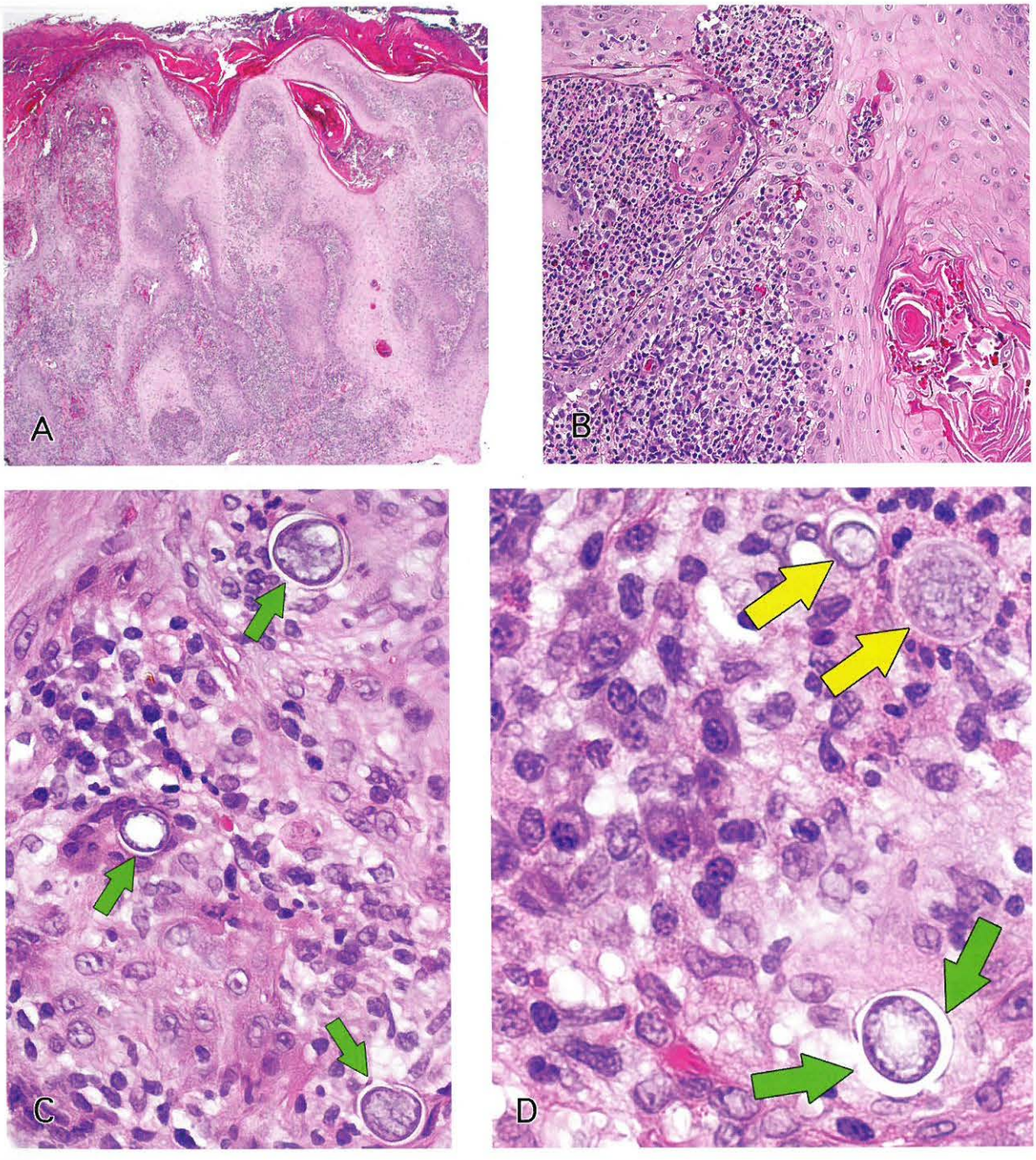


Figure 7-18

COCCIDIOIDOMYCOSIS

A: There is often reactive pseudoepitheliomatous hyperplasia of the overlying epidermis. This can be so robust as to mimic squamous cell carcinoma. The brisk inflammation is a clue to look for fungus.

B: Neutrophil microabscesses and multinucleated giant cells are entrapped within the pseudoepitheliomatous hyperplasia. These are good clues for intradermal fungal infection.

C: Scattered large (80 µm) thick-walled spherules are present in the dermis (arrows). They are usually easy to identify on H&E.

D: The spherules are filled with multiple small round endospores, imparting a central granular bluish appearance (yellow arrows). Note the thick clear wall seen around some spherules (green arrows).

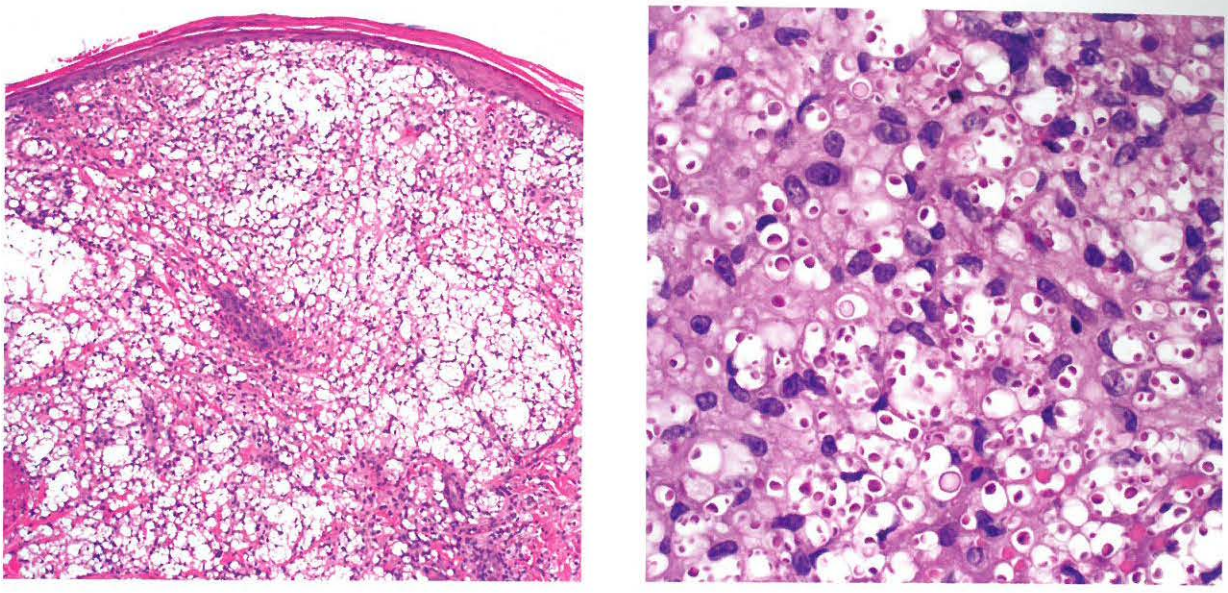


Figure 7-19

CRYPTOCOCCOSIS

Left: The dermis is filled with numerous yeast, which possess thick mucopolysaccharide capsules. The capsule material may be so abundant as to cause pale "gelatinous edema" of the dermis or to mimic sebaceous neoplasms or lipogenic processes, as shown here.

Right: Numerous round yeast of varying size ("pleomorphic," ranging from 4 to 20 μm) are present in the dermis. The characteristic pale halo around each yeast is due to the organism's thick mucopolysaccharide capsule.

Numerous round yeast of varying size ("pleomorphic," ranging from 4 to 20 μm) are present in the dermis; each yeast is surrounded by a characteristic pale halo due to the organism's thick mucopolysaccharide capsule (fig. 7-19). The capsule may be so abundant as to cause "gelatinous edema" of the dermis or to mimic sebaceous neoplasms or lipogenic processes. Some yeast show narrow-based budding. The degree of histiocytic/granulomatous infiltrate varies depending on the patient's immune status. Multiple intracytoplasmic yeasts may be seen around the periphery of multinucleated giant cells, resembling Touton giant cells (*Crouton cells*, a portmanteau of *Cryptococcus* and "Touton" created by Sanjay Mukhopadhyay and Marcela Saeb Lima via Twitter) (9).

The yeast cell walls are GMS and PASD positive. The mucopolysaccharide capsule is mucicarmine and Alcian blue positive (the "capsule-deficient" variant is negative for these stains). In most cases, the organisms are easily recognized on H&E. Culture or molecular testing are the gold standards for species identification, but it can usually be distinguished from other species by the variable size of the yeast and the characteristic capsules (4–5).

BLASTOMYCOSIS

Blastomyces dermatitidis is also a dimorphic environmental fungus found in soil and decaying organic debris, mostly in North America (southeastern United States, Mississippi, and Ohio river valleys). Skin involvement may be secondary from systemic disseminated infection or primary from direct traumatic inoculation.

Blastomycosis causes verrucous plaques or ulcers due to the abundant reactive pseudoepitheliomatous hyperplasia typically seen in the epidermis at sites of infection; this can mimic squamous cell carcinoma clinically and histologically. The dermis displays a granulomatous infiltrate with giant cells and neutrophil microabscesses. The yeast are large (8 to 15 μm) and round, with broad-based budding (small yeast variants also exist) (fig. 7-20). They are positive for GMS and PASD. Their appearance is characteristic, but culture or molecular analysis is recommended to definitively confirm the species (10).

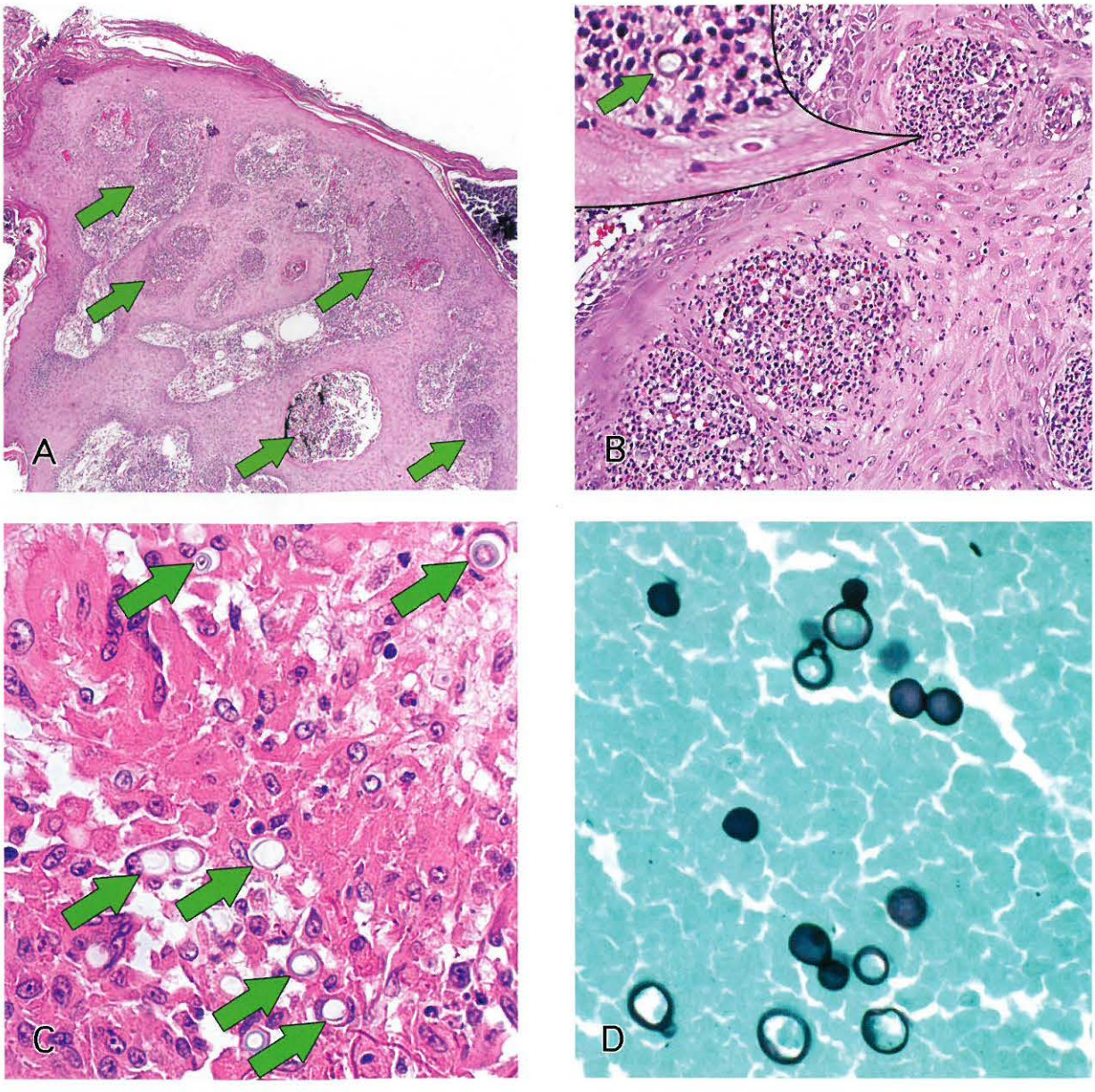


Figure 7-20

BLASTOMYCOSIS

A: There is robust reactive pseudoepitheliomatous hyperplasia of the overlying epidermis with entrapped neutrophil microabscesses (arrows).

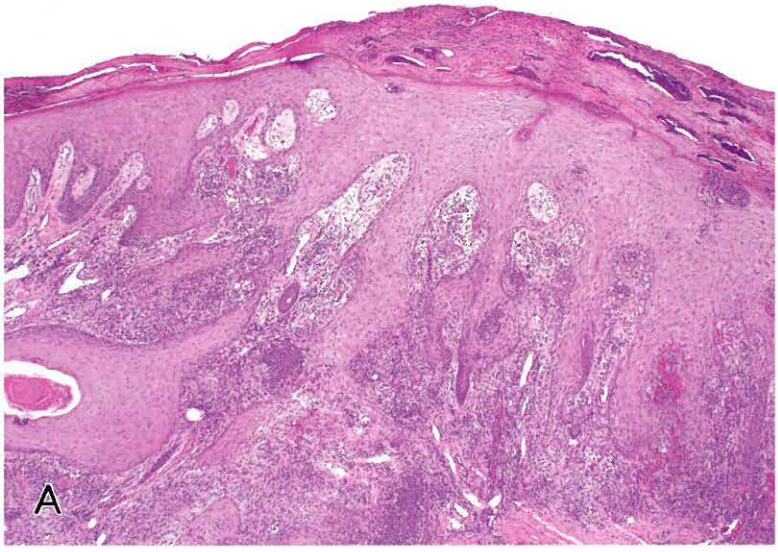
B: Scattered yeast may be found within the neutrophil microabscesses (inset arrow).

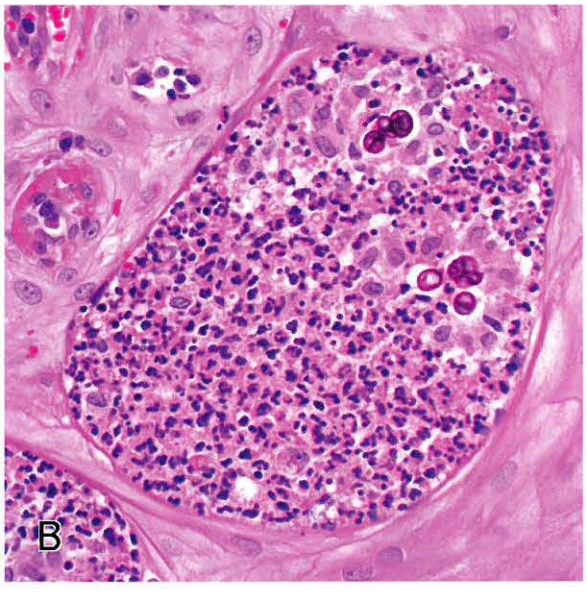
C: Multiple large (8 to 15 μm) round thick-walled yeast are present in the dermis, surrounded by granulomatous infiltrate (arrows).

D: On this GMS stain, broad-based budding of the large yeast is more easily seen.

CHROMOBLASTOMYCOSIS AND PHAEOHYPHOMYCOSIS

Various species of pigmented *dematiaceous fungi* may cause invasive fungal infections in the skin. These fungi are found in the environment on soil or plant material. The fungi enter the skin via traumatic implantation or wound contamination (11). An erythematous crusted nodule or plaque arises at the site of trauma.





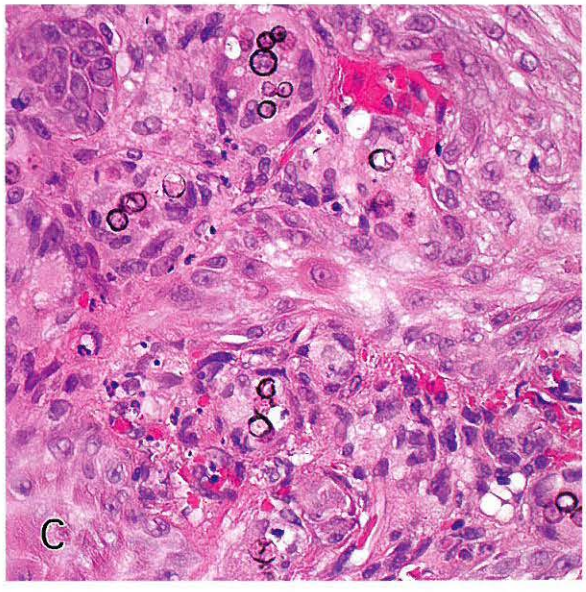


Figure 7-21

CHROMOBLASTOMYCOSIS

A: This is another deep fungal infection that tends to produce pseudoepitheliomatous hyperplasia and neutrophil microabscesses, similar to coccidioidomycosis and blastomycosis (compare to figs. 7-18A and 7-20A).

B: Round brown pigmented yeast-like structures (sclerotic/Medlar bodies) are present within the neutrophil microabscesses.

C: Pigmented round sclerotic/Medlar bodies may be surrounded by granulomatous infiltrate or present within giant cells.

On biopsy, the epidermis often has prominent pseudoepitheliomatous hyperplasia. The dermis is granulomatous, often with neutrophil microabscesses. Pigmented fungi in the dermis are usually visible on H&E in one of two forms. When the fungi are round pigmented yeast-like structures (sclerotic/Medlar bodies), the term *chromoblastomycosis* is used (fig. 7-21). When they are pigmented septate hyphae, the term *phaeohyphomycosis* is used (fig. 7-22). These are descriptive morphologic terms rather than actual fungal genus/species names.

Culture or molecular analysis is essential if the treating physician needs to know the species of the causative organism. PASD, GMS, and Fontana-Masson are positive in the organisms but are usually not needed.

SCABIES

The *scabies mite* (*Sarcoptes scabei variant hominis*) is a common arthropod skin infestation found worldwide. It is common in children but can occur in all ages. The mite creates a "burrow" beneath the stratum corneum, where it tunnels along the surface of the skin but does not invade the underlying dermis. This produces intensely pruritic linear erythematous lesions on the hands or erythematous nodules on the trunk or genital region.

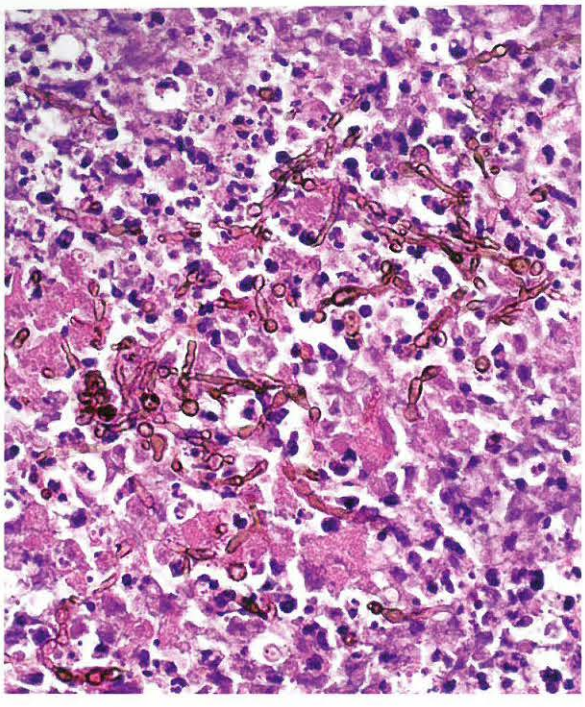


Figure 7-22

PHAEOHYPHOMYCOSIS

When pigmented hyphae are present, the term phaeohyphomycosis is used.

Mites are usually rare and may be hard to find on biopsy; deeper sections are a good idea if there are any clinical or microscopic features to suspect scabies. Finding the intact mite itself, eggs, feces (scybala), or egg/mite fragments within a burrow between the corneal and granular layer of the epidermis is diagnostic of scabies infestation (fig. 7-23). Other clues include brisk mixed dermal inflammation usually with numerous eosinophils, although the density can be less abundant in some cases. Fibrin thrombi within small dermal vessels are often seen, a curious finding described by my colleague, Dr. Sara Shalin (12).

When no definitive mites/eggs/scybala are found, the histologic differential could include arthropod bite reaction, the urticarial phase of bullous pemphigoid, drug eruption, or even lymphomatoid papulosis or other hematopoietic diseases when the infiltrate is very brisk. Large atypical CD30-positive cells (probably activated T cells) can be seen in longstanding scabies or in arthropod bite reactions (13,14).

If the histologic features are compatible with scabies but I see no definitive evidence of the organism, I often include this line in the com-

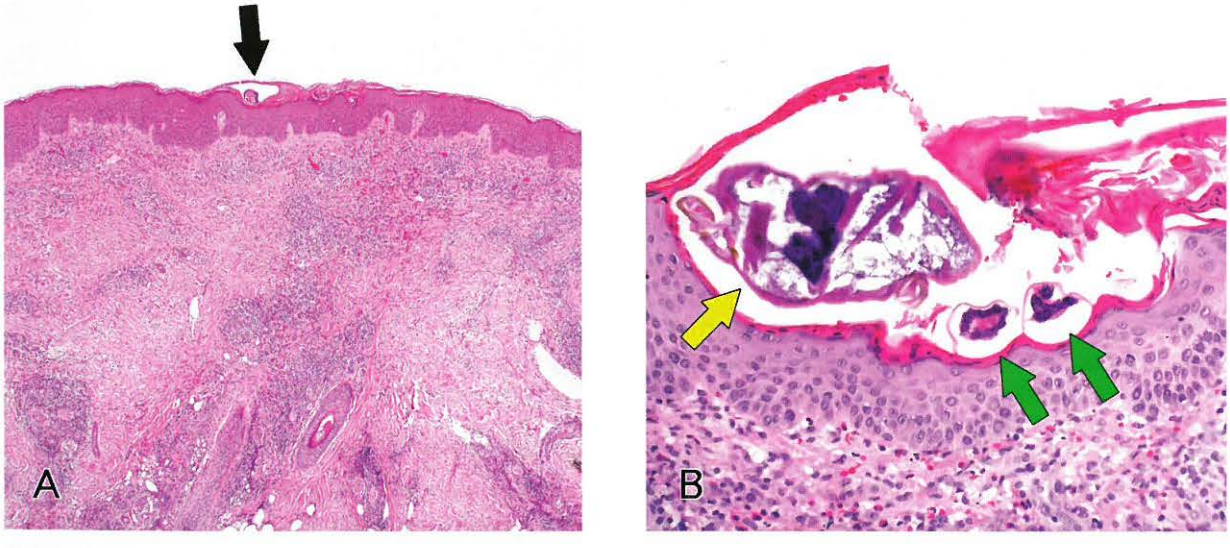
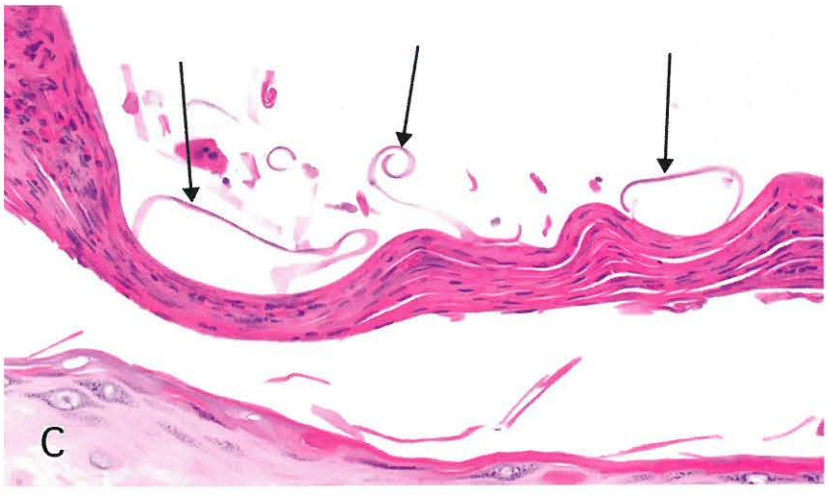


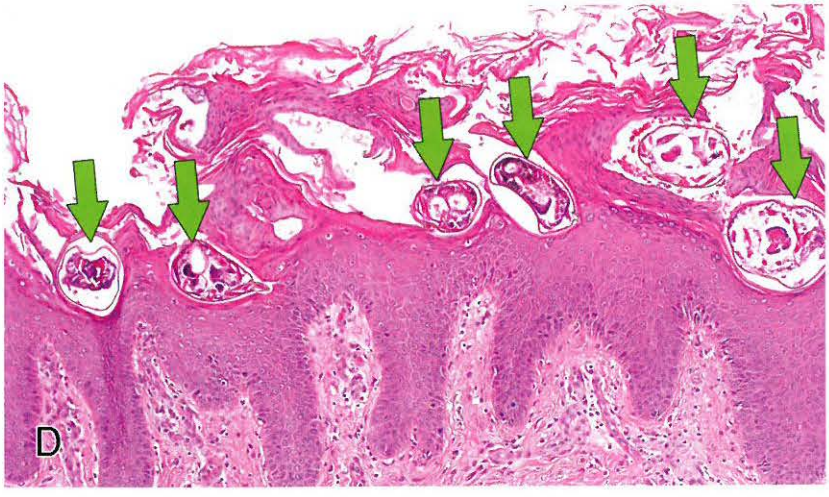
Figure 7-23

SCABIES

A: A scabies mite is present within its subcorneal burrow (arrow). There is abundant superficial and deep dermal inflammation, similar to an arthropod bite reaction. The mite is present in only one small focus of the entire biopsy; multiple deeper sections are sometimes needed to find the mite.

B: An adult mite (yellow arrow) and two eggs (green arrows) are present within a subcorneal burrow. There are many eosinophils in the underlying dermis.





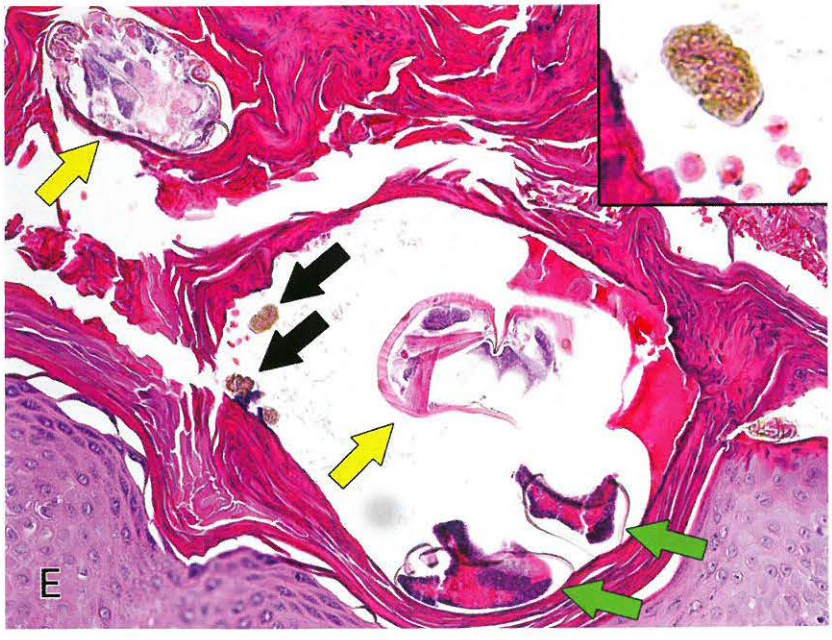


Figure 7-23, continued

C: Coiled fragments of empty scabies eggshells in the stratum corneum ("pink pigtails") (arrows) are diagnostic of scabies even when the mite itself is not seen on the biopsy.

D: In crusted (formerly "Norwegian") scabies, numerous scabies mites (arrows) are present within the thick hyperkeratotic stratum corneum.

E: Adult mites (yellow arrows), eggs (green arrows), and scybala (black arrows and inset) are all present in this case of crusted scabies.

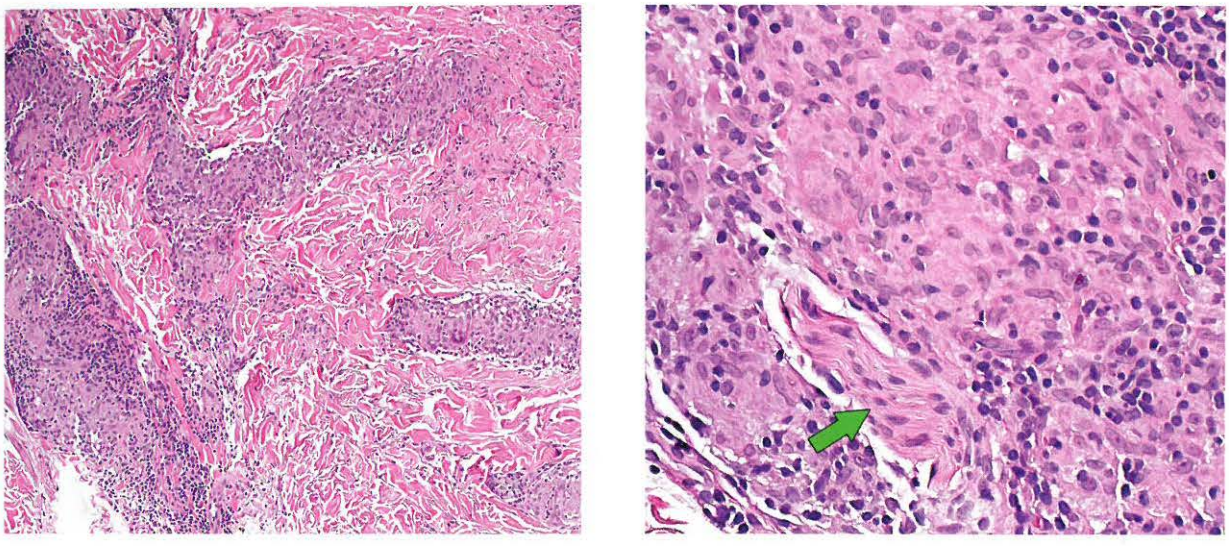


Figure 7-24

LEPROSY, TUBERCULOID TYPE (PAUCIBACILLARY)

Left: Well-formed non-necrotizing dermal granulomas show a linear or serpiginous pattern due to their tracking along small dermal nerves. This pattern is classic for leprosy.

Right: The granulomas are sarcoidal, composed of closely aggregated epithelioid histiocytes with dense pink cytoplasm. Note the small nerve (arrow) that the granuloma is formed around.

ment: "Scabies could produce a similar histologic pattern. However, no scabetic mites are identified on multiple deeper sections." This alerts the dermatologist to the possibility of scabies. They can then choose to pursue mineral oil examination of skin scrapings or treat the patient empirically if they have clinical concern for scabies.

There is also a diffuse hyperkeratotic variant called *crusted* (formerly "Norwegian") *scabies* that can mimic psoriasis or ichthyosis clinically. Fortunately, it is an easy diagnosis to make microscopically, as unlike conventional scabies, crusted scabies has thick hyperkeratosis with numerous mites. The mite species is the same; it is just a different clinical presentation.

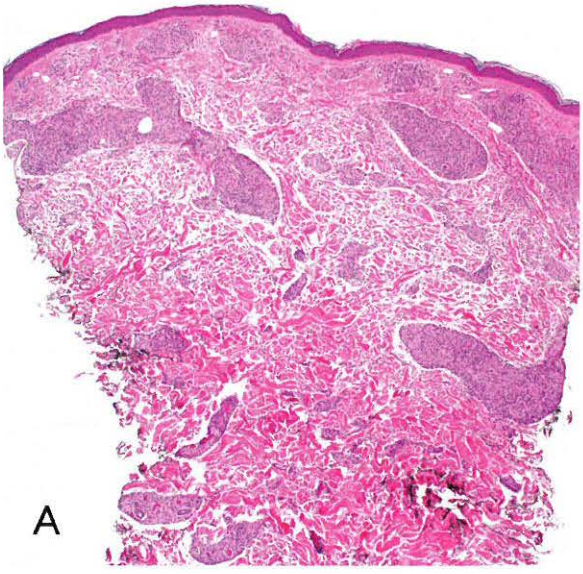
LEPROSY

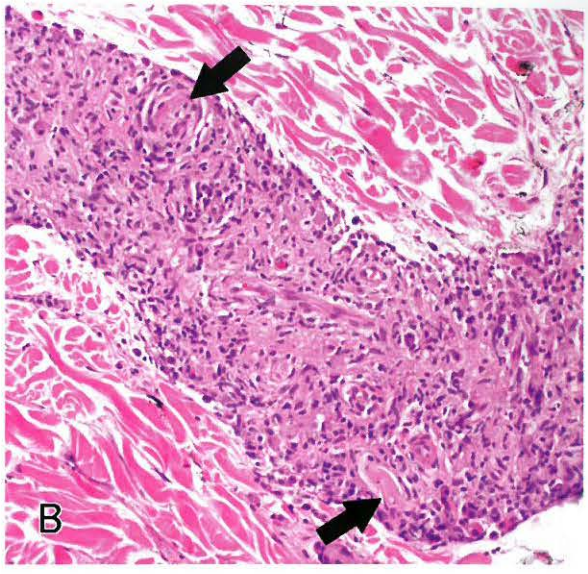
Leprosy (*Hansen disease*) has been hugely important throughout history. Although it is now rare in the United States, some cases are still seen either in immigrants/travelers or as endemic leprosy contracted from exposure or close proximity to nine-banded armadillos in Texas, Arkansas, and the Southeast United States. Leprosy is still a significant public health issue in many other countries.

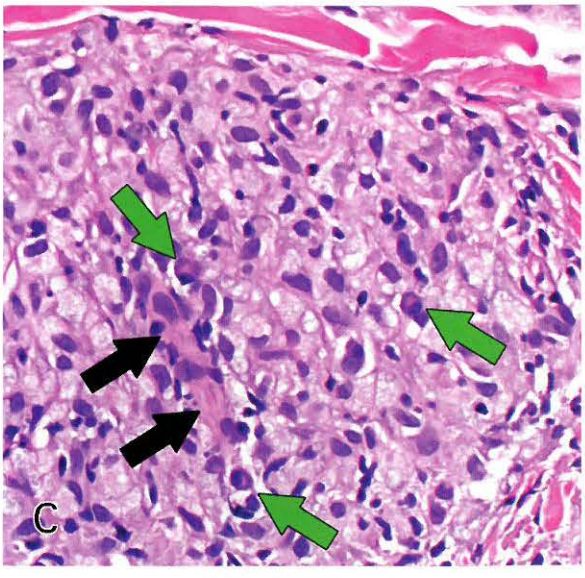
Cutaneous infection by the acid-fast bacillus (AFB), *Mycobacterium leprae*, produces a wide range of clinical manifestations. The precise subclassification of these is complex, but the simplified concept is that the intensity of the host immune response leads to varying presentations including: tuberculoid leprosy (paucibacillary; mild disease), lepromatous leprosy (multibacillary; severe disease), and borderline forms between those two extremes.

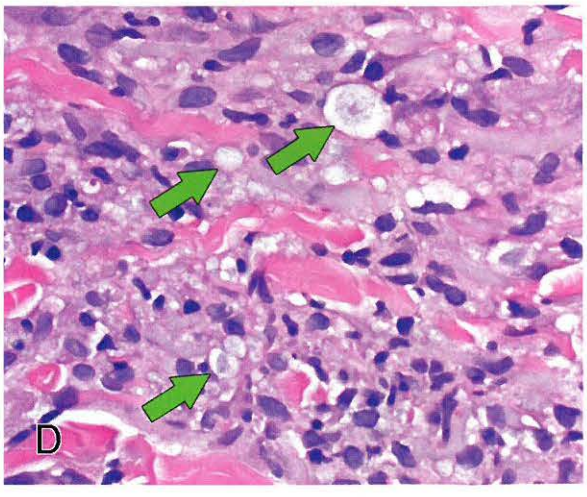
The *M. leprae* organism is a small bacillus rod that stains red on the Fite AFB stain (Fite is the primary AFB stain I use in my practice). Tuberculoid leprosy shows well-formed non-necrotizing dermal granulomas with few organisms (fig. 7-24). Lepromatous leprosy has more diffuse sheets of foamy histiocytes with numerous organisms clustered into small vacuoles ("globi") (fig. 7-25). In both forms, the granulomas/histiocytes tend to track along nerves, forming a serpiginous or linear pattern, a classic clue to leprosy. Plasma cells are often present.

The histologic differential includes other infectious diseases including cutaneous tuberculosis (extremely rare in the United States), atypical mycobacteria, and (for tuberculoid cases) sarcoidosis. Sarcoidosis can also show perineural granulomas and some clinical features mimicking leprosy (15). Molecular testing confirms the









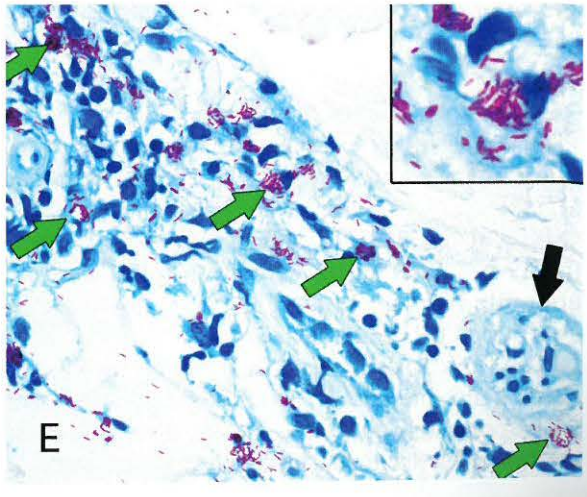


Figure 7-25

LEPROSY, LEPROMATOUS TYPE (MULTIBACILLARY)

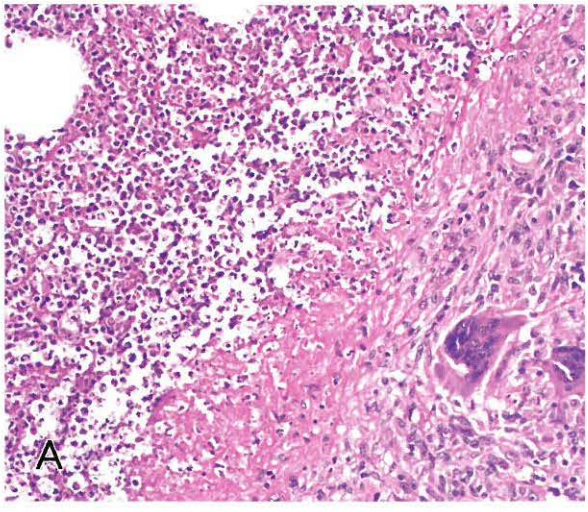
A: The granulomatous infiltrate is arranged in a linear or serpiginous pattern. The appearance is similar to tuberculoid leprosy at low magnification.

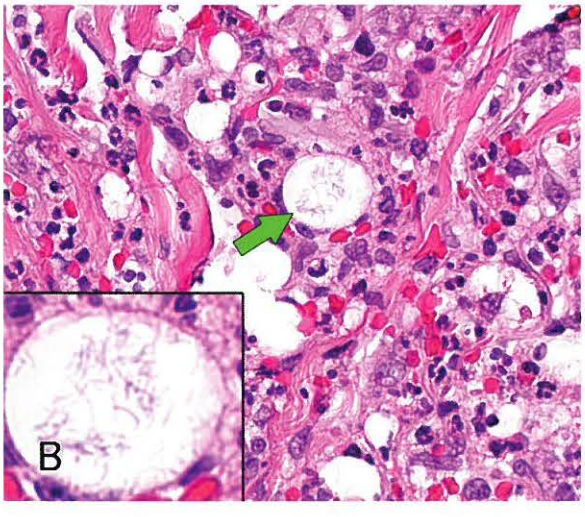
B: Serpiginous granulomatous infiltrate tracks along small nerves (arrows) in the dermis.

C: At higher magnification, the histiocytes have pale frothy/foamy cytoplasm due to the numerous intracellular *M. leprae* bacilli within them. Scattered plasma cells are present (green arrows). Note the small nerve in the infiltrate (black arrows).

D: Small vacuoles ("globi") are present in a sheet of histiocytes (arrows). The granular blue material within these vacuoles is composed of numerous *M. leprae* bacilli.

E: Numerous *M. leprae* bacilli are seen within histiocytes on Fite acid-fast stain. The clusters of organisms correspond to the globi vacuoles seen on H&E (green arrows and inset). An adjacent nerve is present (black arrow).





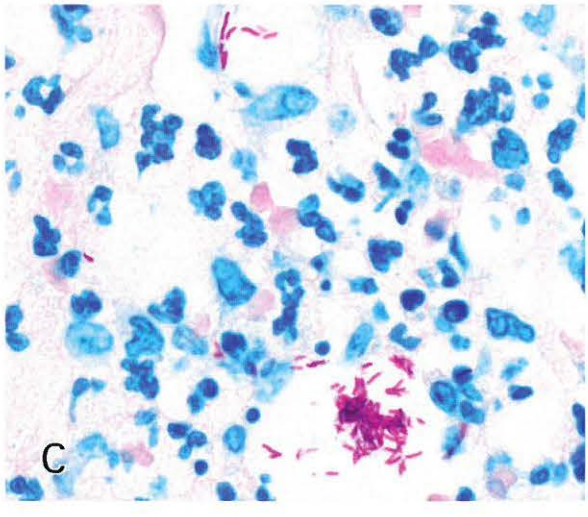


Figure 7-26

ATYPICAL MYCOBACTERIA

A: Some cases display suppurative granulomas. There is central necrosis with numerous neutrophils (left) surrounded by a rim of epithelioid and spindled histiocytes and multinucleated giant cells (right). This case was *M. marinum* by culture.

B: Other cases show dermal sheets of loosely aggregated foamy histiocytes intermingled with neutrophils. Note the vacuole containing blue thin bacilli (arrow and inset), analogous to the globi seen in lepromatous leprosy. This was *M. chelonae* by PCR.

C: Fite stain shows numerous acid-fast bacilli clustered within a vacuole (same case as B).

diagnosis when there is uncertainty, although in tuberculoid cases, where organisms are very sparse, it may be falsely negative, which creates a complicated diagnostic challenge (16).

ATYPICAL MYCOBACTERIA

Many species of non-*Tuberculosis*, non-*Leprae* mycobacteria also cause cutaneous infection, including *M. chelonae*, *M. kansasii*, *M. fortuitum*, *M. ulcerans*, *M. marinum*, and others (4–5). These "atypical" AFB are the kind I see most often in my practice, along with occasional cases of endemic leprosy; I have not yet seen a case of cutaneous tuberculosis.

The clinical scenario varies based on species, including ulcerated or verrucous nodules, sometimes with sporotrichoid spread. Often, the infection is contracted by a contaminated wound, often on the extremities. Infection may persist for years prior to diagnosis.

The histologic features vary widely and include well-formed granulomas (similar to tuberculoid leprosy), poorly formed granulomatous infiltrate with sheets of histiocytes (similar to lepromatous leprosy), neutrophil abscesses, and ulceration or pseudoepitheliomatous hyperplasia of the epidermis (fig. 7-26). Other infections also produce these histologic features, as discussed throughout this chapter. If careful search of the Fite-stained section shows no organisms but there is still clinical concern for infection, I usually recommend cultures and/or molecular testing of the paraffin block.

Rarely, a robust reactive spindle cell proliferation can cause pseudotumoral forms of leprosy (*histoid leprosy*) and atypical mycobacteria

(*mycobacterial pseudotumor*). In a spindle cell proliferation with granulomas, plasma cells, or other features suspicious for infection, consider doing a Fite stain.

SYPHILIS

This sexually transmitted infection caused by the spirochete bacterium, *Treponema pallidum*, has caused immense human suffering throughout history. The discovery of penicillin allowed it to be easily treated and its incidence declined dramatically over time, although recently there has been a resurgence in the incidence of syphilis (particularly in association with HIV co-infection) (17).

As everyone learns in medical school, there are several stages of syphilis. Primary syphilis is an ulcer (chancre) in the genitals that arises within weeks of sexual contact with an infected partner. Secondary syphilis presents a month or two later as a widespread generalized eruption of skin macules or papules with particular predilection for the palms and soles. Tertiary syphilis involves the soft tissue, aorta, and/or brain, arising after years if the patient is left untreated; thankfully this is rare in modern times.

Secondary syphilis is what we see most often in dermatopathology. It classically shows elongated thin rete ridges, a band-like lymphoplasmacytic infiltrate underneath the epidermis, and a superficial and deep perivascular lymphoplasmacytic infiltrate (figs. 7-27, 7-28). However, the range of features is broad. Some cases show little epidermal change and only perivascular lymphocytes and plasma cells, while others have such a robust dermal infiltrate as to suggest lymphoma. Granulomas can be present raising consideration for other infections. Syphilis can also present as warty lesions in the anogenital area called *condyloma lata*.

Clinically, syphilis shows a diverse range of presentations. It's not called "The Great Mimicker" for nothing. Treponemal immunostain is very helpful for confirming the diagnosis as it highlights the spirochete organisms that populate the basal portion of the epidermis and sometimes also the area around the papillary dermal blood vessels. Warthin-Starry silver stain was classically used for this, but in my experience, it has such abundant background debris as to make it almost impossible to interpret. I only use the immunostain in my practice (never

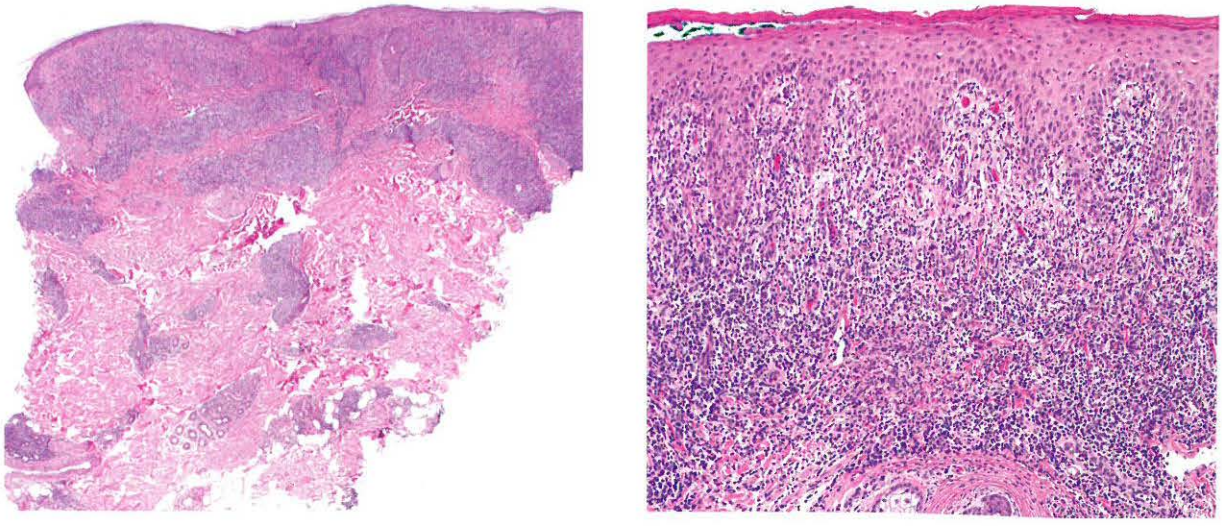


Figure 7-27

SYPHILIS

Left: There is dense band-like inflammation underneath the epidermis, and brisk superficial and deep perivascular inflammation. The infiltrate in this case was particularly robust.

Right: The combination of psoriasiform and (pseudo) lichenoid patterns is very characteristic of syphilis. The rete are long and thin. The brisk band-like lymphoplasmacytic infiltrate directly abuts the epidermis and intermingles with the rete.

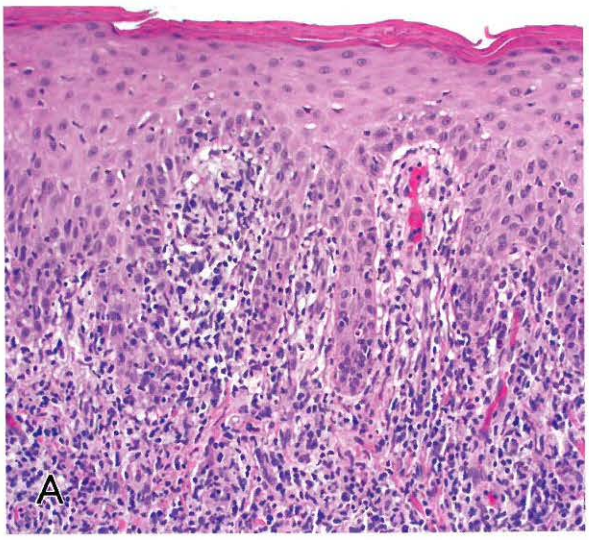


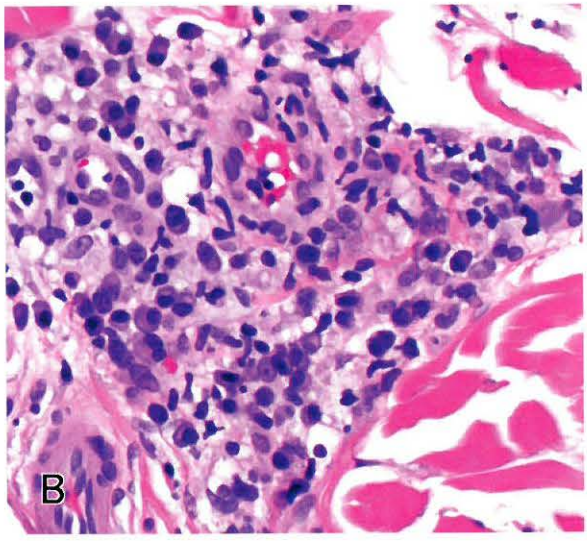
Figure 7-28

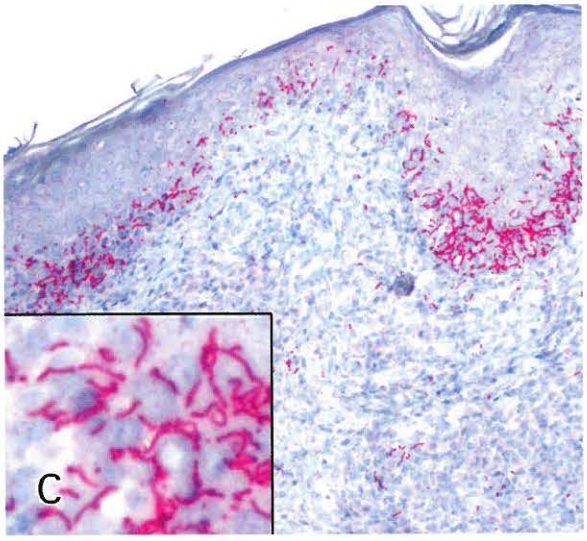
SYPHILIS

A: A band-like infiltrate of lymphocytes and plasma cells fills the papillary dermis. Lymphocyte exocytosis into the epidermis may be robust. However, unlike a true lichenoid dermatitis, apoptotic keratinocytes are usually absent or far fewer than would be expected for the density of the infiltrate.

B: Numerous plasma cells are clustered around a small dermal blood vessel.

C: A Treponemal immunostain with red chromogen shows numerous spirochete bacteria present along the basal aspect of the epidermis. Scattered spirochetes are present in the superficial dermis as well. The spirochetes are thin, elongated, thread-like organisms with a subtle spiral/corkscrew shape (inset).





Warthin-Starry). I order the Treponemal immunostain much more often than I actually find it positive for syphilis, yet I have found it positive several times when I least suspected syphilis. It is important to maintain a high index of suspicion, since syphilis is easy to miss clinically and microscopically, easy to treat, and potentially morbid to the patient (and their sexual partners) if left untreated. If the immunostain is not available, then serologic testing may be helpful to further confirm a diagnosis of syphilis.

REFERENCES

1. Abate MS, Battle LR, Emerson AN, Gardner JM, Shalin SC. Dermatologic urgencies and emergencies: what every pathologist should know. Arch Pathol Lab Med 2019. [Epub ahead of print]
2. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. Clin Microbiol Rev 2011;24:247-80.
3. Sangoi AR, Rogers WM, Longacre TA, Montoya JG, Baron EJ, Banaei N. Challenges and pitfalls of morphologic identification of fungal infections in histologic and cytologic specimens: a ten-year retrospective review at a single institution. Am J Clin Pathol 2009;131:364-75.
4. Grayson W. Infectious diseases of the skin. In: Calonje EI, Brenn T, Lazar, A, McKee PH, eds. McKee's pathology of the skin: with clinical correlations, 4th ed. Philadelphia: Elsevier Saunders; 2012.
5. Patterson JW. Weedon's skin pathology, 4th ed. London: Churchill Livingstone Elsevier; 2016.
6. McIlwee BE, Weis SE, Hosler GA. Incidence of endemic human cutaneous leishmaniasis in the United States. JAMA Dermatol 2018;154:1032-9.
7. Welsh O, Vera-Cabrera L, Rendon A, Gonzalez G, Bonifaz A. Coccidioidomycosis. Clin Dermatol 2012;30:573-91.
8. Carpenter JB, Feldman JS, Leyva WH, DiCaudo DJ. Clinical and pathologic characteristics of disseminated cutaneous coccidioidomycosis. J Am Acad Dermatol 2010;62:831-7.
9. Gardner JM. 2016. "Crouton" giant cell of Marcela & Sanjay. CRypto + tOUTON = Crouton. Clue to cryptococcus. coined by @MarcelaSaebL @smlungpathguy #pathology. (Twitter). 20 Nov. Available from: https://twitter.com/jmgardnermd/status/800388439094894593. Accessed 10/10/2018.
10. Saccente M, Woods GL. Clinical and laboratory update on blastomycosis. Clin Microbiol Rev 2010;23:367-81.
11. Malakzai MO, Sahak JG, Campbell R, et al. Multifocal but non-disseminated phaeohyphomycosis in a healthy man via a unique mechanism: ejection from MVA into a vegetable field in Afghanistan resulting in multiple contaminated skin wounds. J Cutan Pathol 2017;44:620-4.
12. Elwood H, Berry RS, Gardner JM, Shalin SC. Superficial fibrin thrombi ... and other findings: a review of the histopathology of human scabietic infections. J Cutan Pathol 2015;42:346-52.
13. Gallardo F, Barranco C, Toll A, Pujol RM. CD30 antigen expression in cutaneous inflammatory infiltrates of scabies: a dynamic immunophenotypic pattern that should be distinguished from lymphomatoid papulosis. J Cutan Pathol 2002;29:368-73.
14. Cepeda LT, Pieretti M, Chapman SF, Horenstein MG. CD30-positive atypical lymphoid cells in common non-neoplastic cutaneous infiltrates rich in neutrophils and eosinophils. Am J Surg Pathol 2003;27:912-8.
15. Munday WR, McNiff J, Watsky K, DiCapua D, Galan A. Perineural granulomas in cutaneous sarcoidosis may be associated with sarcoidosis small-fiber neuropathy. J Cutan Pathol 2015;42:465-70.
16. Arthur C, Gardner JM, Han JY. A 9-year-old boy with a chronic rash. J Pediatric Infect Dis Soc 2015;4:381-4.
17. Lang R, Read R, Krentz HB, et al. Increasing incidence of syphilis among patients engaged in HIV care in Alberta, Canada: a retrospective clinic-based cohort study. BMC Infect Dis 2018;18:125.

8 INFLAMMATORY DERMATOSES

Inflammatory dermatopathology is challenging, and not only to beginners. Rashes may seem insignificant compared to other human diseases, but once you see a patient with severe psoriasis or atopic dermatitis, with scarring and depigmentation from discoid lupus erythematosus, or in the burn unit in critical condition due to toxic epidermal necrolysis, then you will realize that inflammatory dermatoses can be immensely morbid and sometimes even fatal.

Inflammatory skin diseases are often difficult for pathologists because they require a very different approach to examining the slide, different language from that used for inflammatory conditions elsewhere in the body, and a general clinical knowledge about a wide variety of different skin diseases, some of which most doctors (aside from dermatologists) have never heard of. Dermatologists often recognize and treat rashes based on clinical appearance only. For complicated or difficult to manage cases, they may resort to skin biopsy. Therefore, it is often the non-classic cases that are biopsied, which increases the difficulty even more.

Admittedly, all of this is a daunting task, which is why pathology-trained dermatopathologists must spend a significant portion of their fellowship seeing patients in dermatology clinic (currently, in the United States, at least 1,000 clinical dermatology patients must be seen during fellowship in order to sit for the board examination). Yet even without this intense clinical training, pathologists can still add value when diagnosing inflammatory skin biopsies by learning a few basic rules and tips.

Look at the provided clinical differential. Look up the clinical and histologic features of the diseases listed if you are not familiar with them. If a nondermatologist did the biopsy, you may have little or no clinical information, which is a frustration all dermatopathologists face on a regular basis; clinical photographs can be a huge help in this situation. Next, look at the slide to determine the primary inflammatory pattern (Table 8-1). Sometimes multiple inflammatory patterns are present together, which can make it challenging to decide which is the primary one.

One thing that is always the wrong diagnosis in dermatopathology: "acute/chronic inflammation." These terms are often inaccurate, and they are not helpful to the dermatologist. In pathology, neutrophils are usually regarded as acute inflammation and lymphocytes as chronic inflammation. Yet in the skin, there are acute dermatoses that are lymphocyte mediated (e.g., toxic epidermal necrolysis) and chronic dermatoses that have neutrophils (e.g., psoriasis). Completely remove "acute inflammation" and "chronic inflammation" from your vocabulary when looking at skin biopsies! Just describe where the inflammation is and what kind of cells it is made up of. That will suffice.

Punch biopsy is usually the preferred biopsy type for evaluating inflammatory dermatoses as it allows for examination of the deep dermis and (hopefully) the subcutis. Attempt to correlate the pattern seen microscopically with the clinical features or differential diagnosis provided by the dermatologist. In inflammatory dermatopathology especially, if the microscopic diagnosis does not fit clinically, it is probably not the correct diagnosis. This is a major difference from many other parts of pathology. Tumors often look like nondescript masses. The surgeon may think it is benign, but if we see pleomorphism, necrosis, and numerous mitoses, then it is malignant regardless of what the clinical impression may be. This is not how things work for inflammatory dermatopathology, and pathologists must adjust their minds to this. We also must remember that while making a definitive diagnosis is always the goal, it is often not possible with inflammatory skin biopsies. Sometimes the best

Table 8-1

INFLAMMATORY PATTERNS AND CORRESPONDING DISEASES

Inflammatory Pattern	Key Features	Example Diseases
Spongiotic	Intraepidermal edema/spongiosis Lymphocyte exocytosis in epidermis +/- parakeratosis and serum in corneal layer	Atopic/eczematous dermatitis Nummular dermatitis Dyshidrotic dermatitis Contact dermatitis Seborrheic dermatitis Eczematous drug eruption Acute generalized exanthematous pustulosis (AGEP)
Psoriasiform	Epidermal acanthosis with elongated rete	Psoriasis Pityriasis rubra pilaris (PRP) Zinc and other nutritional deficiencies Glucagonoma syndrome Secondary syphilis
Vacuolar Interface	Vacuoles along basal layer (at "interface" of dermis and epidermis) Apoptotic/dying keratinocytes in epidermis Sparse lymphocytes along basal layer	Erythema multiforme Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum (SJS/TEN) Acute graft versus host disease (GVHD) Fixed drug eruption Lupus erythematosus Dermatomyositis
Lichenoid Interface	Vacuoles along basal layer (at "interface" of dermis and epidermis) Apoptotic/dying keratinocytes in epidermis Dense band of lymphocytes along basal layer and papillary dermis	Lichen planus Lichenoid drug/hypersensitivity reaction Lichen striatus Lichen nitidus
Superficial Perivascular	Lymphocytes around superficial dermal vessels	Viral exanthems Drug eruptions Urticaria
Superficial and Deep Perivascular	Lymphocytes around superficial and deep dermal vessels	Drug eruptions Arthropod bite reaction Polymorphous light eruption (PMLE) Perniosis Erythema annulare centrifugum (EAC) Lupus erythematosus Secondary syphilis

we can do is to state what inflammatory pattern is present and to give a differential diagnosis.

Of nearly equal importance is the ability to rule out possible diagnoses that are listed in the clinical differential. Say the dermatologist is deciding between psoriasis and lichen planus clinically. On the biopsy, we may see overlapping features of psoriasis and chronic spongiotic dermatitis (a common scenario), but we do not see lichenoid interface alteration. Thus, we may not be certain if there are enough features to make a diagnosis of psoriasis, but we can at least say with certainty that there are no features of lichen planus in this biopsy. That negative information by itself can sometimes be a great help to the dermatologist.

Unlike neoplasms, in which the tumor is usually removed and examined, a diagnosis is made, and definitive treatment is then performed, rashes are dynamic and may evolve over time. A biopsy today may not show diagnostic features but if the patient gets worse and comes back to clinic in two weeks, a repeat biopsy may then be diagnostic. When we cannot make a definitive diagnosis on a rash, our goal is to help the dermatologist narrow down their clinical differential by excluding whatever diseases we can, thus guiding their decision on the best management for the

Table 8-1, continued

Inflammatory Pattern	Key Features	Example Diseases
Granulomatous	Histiocyte-rich dermal infiltrate +/- well-formed granulomas +/- other inflammatory cells	Infections (especially fungal and mycobacterial) Sarcoidosis Granulomatous foreign body reaction Keratin granuloma (ruptured cyst or folliculitis) Granulomatous drug eruption Granulomatous rosacea
Palisaded Necrobiotic Granulomatous	Palisading granulomas Central zone of degenerated collagen/ mucin/fibrin	Granuloma annulare Deep granuloma annulare Actinic granuloma Annular elastolytic granuloma Necrobiosis lipoidica diabeticorum (NLD) Necrobiotic xanthogranuloma (NXG) Rheumatoid nodule
Leukocytoclastic Vasculitis (LCV)	Neutrophils & nuclear dust/debris around dermal vessels (leukocytoclasis) Fibrinoid necrosis of vessel walls Extravasated erythrocytes in dermis	Cutaneous LCV Henoch-Schönlein purpura (HSP) Levamisole-induced vasculitis (cocaine use) Cryoglobulinemia, mixed-type (II or III) Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) Granulomatosis with polyangiitis (Wegener) Polyarteritis nodosa (PAN)
Thrombotic Vasculopathy	Intravascular thrombi in dermis No LCV	Disseminated intravascular coagulation (DIC) Hemolytic uremic syndrome (HUS) Other systemic coagulopathies Cryoglobulinemia, type I
Panniculitis	Inflammation of subcutaneous fat +/- fat necrosis +/- septal fibrosis	Erythema nodosum Lupus panniculitis Lipodermatosclerosis Pancreatic fat necrosis Calciphylaxis Alpha-1 antitrypsin deficiency Post-traumatic fat necrosis

patient. Talk to your dermatologist, especially when you have a difficult biopsy. I routinely discuss cases with my dermatologists, and by brainstorming with them about difficult cases, we often either arrive at a reasonable diagnosis or at least a plan for further workup.

This chapter will not attempt to cover every inflammatory skin disease. There are excellent textbooks that already do that. Instead, each major inflammatory pattern is discussed and illustrated, along with some common examples of diseases that are typified by that given pattern. More esoteric or rare diseases are also covered when they are of particular clinical importance. The major inflammatory patterns are listed in Table 8-1. Once you learn these patterns, you can open up a major dermatopathology reference textbook to learn more nuanced details about the various diseases in the differential diagnosis.

SPONGIOTIC PATTERN

Spongiosis refers to intraepidermal edema. In *spongiotic dermatitis*, edema fluid is present between the keratinocytes, pushing them apart from one another (fig. 8-1). This leaves visible white space between the keratinocytes microscopically, which also allows the desmosomes ("spines") between the keratinocytes to be more obvious. Lymphocytes are often present in the epidermis ("exocytosis") along with the edema fluid. When the spongiosis is abundant, spongiotic vesicles may form; this can be particularly dramatic in acral skin. Langerhans cells may aggregate within these spongiotic vesicles (Langerhans cell "microabscesses"). Spongiotic dermatitis usually has

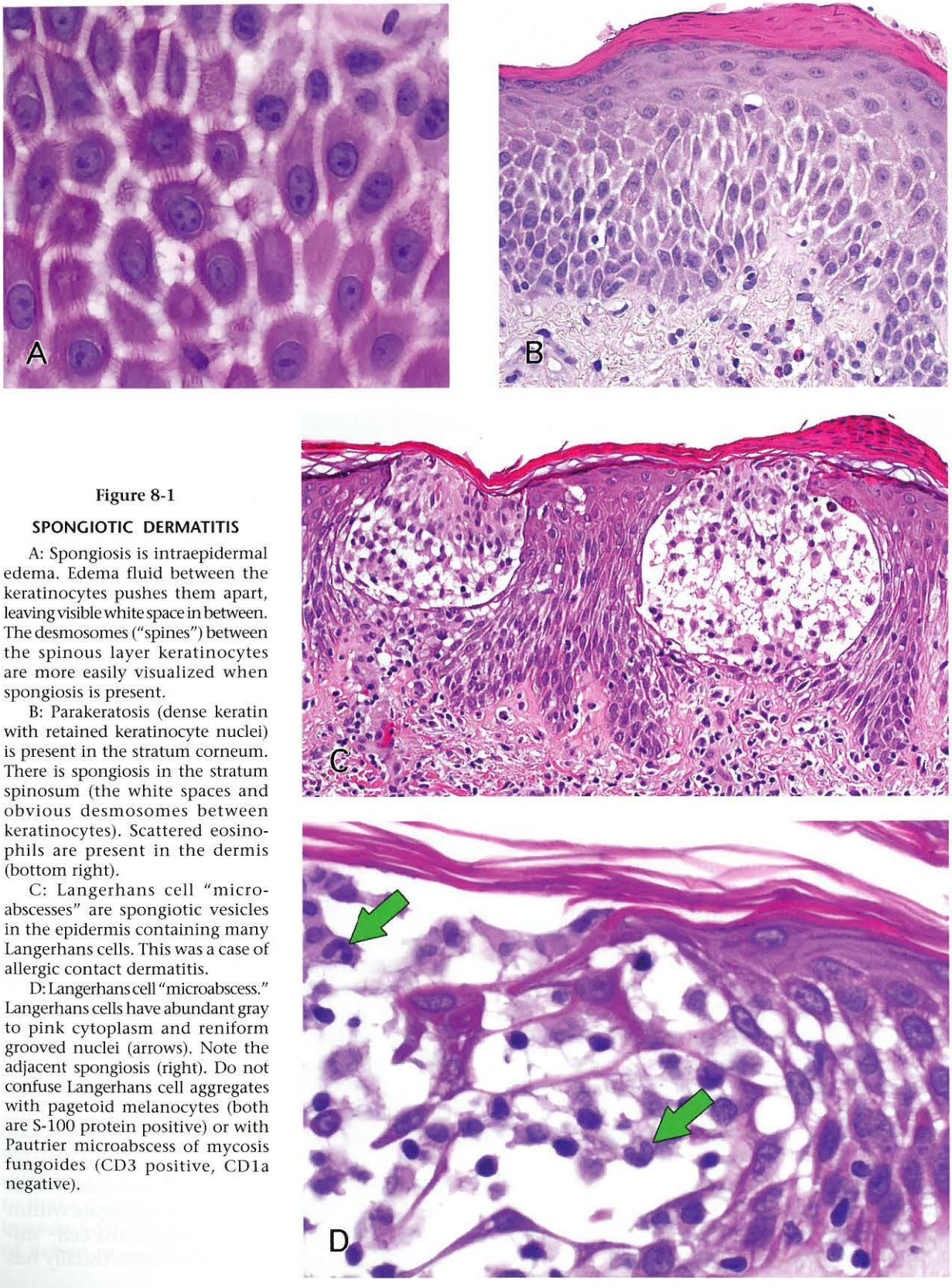


Figure 8-1

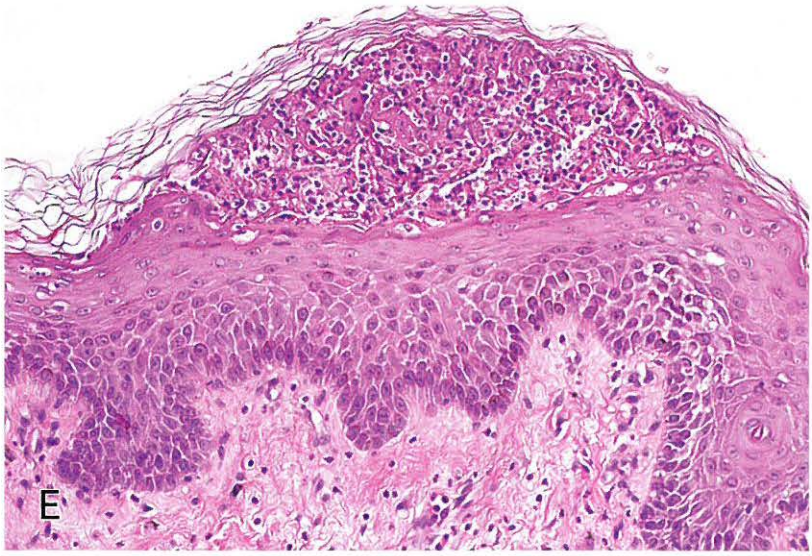
SPONGIOTIC DERMATITIS

A: Spongiosis is intraepidermal edema. Edema fluid between the keratinocytes pushes them apart, leaving visible white space in between. The desmosomes ("spines") between the spinous layer keratinocytes are more easily visualized when spongiosis is present.

B: Parakeratosis (dense keratin with retained keratinocyte nuclei) is present in the stratum corneum. There is spongiosis in the stratum spinosum (the white spaces and obvious desmosomes between keratinocytes). Scattered eosinophils are present in the dermis (bottom right).

C: Langerhans cell "microabscesses" are spongiotic vesicles in the epidermis containing many Langerhans cells. This was a case of allergic contact dermatitis.

D: Langerhans cell "microabscess." Langerhans cells have abundant gray to pink cytoplasm and reniform grooved nuclei (arrows). Note the adjacent spongiosis (right). Do not confuse Langerhans cell aggregates with pagetoid melanocytes (both are S-100 protein positive) or with Pautrier microabscess of mycosis fungoides (CD3 positive, CD1a negative).



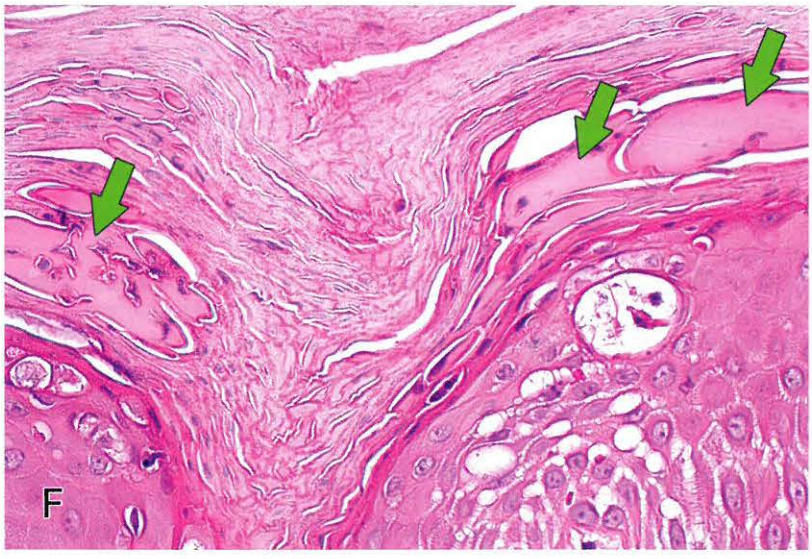


Figure 8-1, continued

E: Subcorneal pustule: a collection of neutrophils is present beneath the stratum corneum. There is epidermal spongiosis. This was a case of acute generalized exanthematous pustulosis (AGEP).

F: Serum (arrows) is often present in the stratum corneum in addition to parakeratosis. It has a homogenous glassy pink appearance and may contain neutrophils and debris. This was a case of dyshidrotic dermatitis.

some degree of parakeratosis, and serum is often present in the stratum corneum. This correlates to the oozing and crusting appearance that these dermatoses often have clinically.

The dermis often shows a superficial perivascular lymphocytic infiltrate, often with eosinophils. While most dermatologists (and dermatopathologists) like to know if eosinophils are present or not, essentially any spongiotic dermatitis can have them; eosinophils are not a reliable way to distinguish between different forms of spongiotic dermatitis. It is true that contact dermatitis often (but not always) has abundant eosinophils, but eosinophils can be present in any of the other forms of spongiotic dermatitis, too. Thus, the different forms of spongiotic dermatitis can all look essentially identical microscopically.

We can tell the dermatologist that a biopsy shows spongiotic dermatitis, but the clinical features are essential in deciding which type of spongiotic dermatitis it represents. Common examples of spongiotic dermatitis include atopic/eczematous dermatitis, nummular dermatitis, dyshidrotic dermatitis (on acral skin), contact dermatitis, seborrheic dermatitis, and eczematous drug eruption. Less common dermatoses may also have spongiosis. Remember that dermatophytosis (tinea) may also mimic spongiotic dermatitis microscopically (see chapter 7).

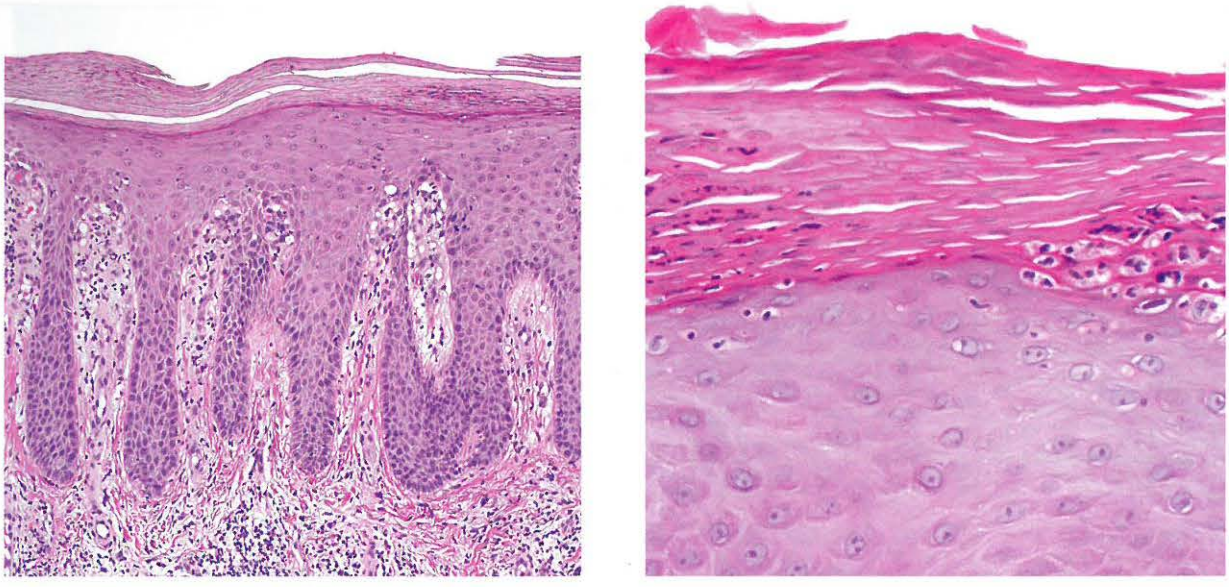


Figure 8-2

PSORIASIS

Left: There is epidermal acanthosis with uniform regular elongation of rete ridges. The corneal layer is replaced by broad confluent zones of parakeratosis, and the granular layer is absent.

Right: Neutrophils aggregates ("Munro microabscesses") in the corneal layer are a very characteristic finding in psoriasis. Note the abundant parakeratosis and absent granular layer.

Acute generalized exanthematous pustulosis (AGEP) is a form of drug reaction that clinically presents with the sudden onset of numerous small pustules usually in patients who recently received antibiotics. Thus, it is rarely in the same clinical differential diagnosis with the other spongiotic dermatoses discussed above, although it has spongiosis microscopically. The classic triad of findings includes: 1) epidermal spongiosis, 2) subcorneal neutrophil pustules, and 3) eosinophils (fig. 8-1E).

PSORIASIFORM PATTERN

Psoriasiform dermatitis is characterized by epidermal acanthosis and regular elongation of rete ridges. *Psoriasis* is the prototypical example (fig. 8-2). In addition to psoriasiform acanthosis, it also shows broad confluent zones of parakeratosis with a decreased or absent granular layer. Neutrophil aggregates are usually present in the corneal layer ("Munro microabscesses"). Unlike in spongiotic dermatitis, serum is usually absent from the corneal layer, correlating to the dry scale seen clinically in psoriasis versus the wet oozing scale in spongiotic dermatitis. Dilated tortuous capillaries are present in the papillary dermis. There is usually little inflammation in the dermis aside from mild superficial perivascular lymphocytes.

Eosinophils are classically absent or very rare in psoriasis, although exceptions do exist. Easily identified eosinophils should make one at least reconsider the diagnosis of psoriasis. Chronic lichenified contact dermatitis can develop psoriasiform hyperplasia and have eosinophils. Psoriasiform drug eruptions can also have eosinophils.

Other diseases that may show the psoriasiform pattern include pityriasis rubra pilaris (PRP), zinc and other nutritional deficiencies, glucagonoma syndrome, and secondary syphilis (see chapter 7). If the biopsy resembles psoriasis but the clinical impression does not favor that, I use a diagnosis of "psoriasiform dermatitis" with a comment that in the proper clinical setting this could represent psoriasis but that other diseases can also show a psoriasiform pattern. Even though psoriasis is "just a rash," it is a chronic sometimes debilitating disease with potential systemic implications. I try not to make the diagnosis lightly so as not to inappropriately

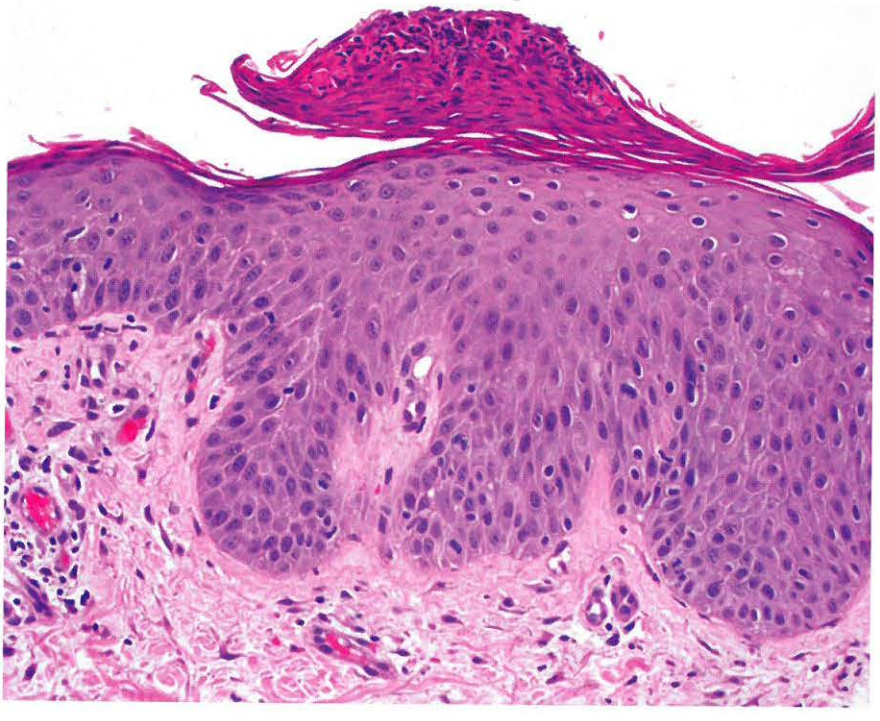


Figure 8-3

GUTTATE PSORIASIS

Parakeratosis is present as focal tufts/mounds rather than the broad diffuse zones seen in classic plaque psoriasis. The elongation of rete is also much subtler. Tufts of parakeratosis can be seen in various other dermatoses, particularly ones with "pityriasis" in the name. The neutrophils within the parakeratosis here (top of the tuft) are a helpful clue for guttate psoriasis.

label the patient with such a diagnosis. I once saw a young woman break down in tears after being told she had psoriasis; I never forgot it. The guttate form of psoriasis often has a unique appearance clinically and shows subtler microscopic features with less obvious psoriasiform epidermal changes than seen in classic plaque psoriasis (fig. 8-3).

INTERFACE PATTERN (VACUOLAR AND LICHENOID)

Interface dermatitis is characterized by dying keratinocytes along the basal layer of the epidermis (i.e., at the interface between the epidermis and dermis). Scattered lymphocytes are seen "attacking" the basal layer, leaving behind varying numbers of bright pink apoptotic keratinocytes with pyknotic or absent nuclei interspersed with empty vacuoles/bubbles along the basal layer ("liquefactive" degeneration). These dead/dying keratinocytes are referred to by a wide variety of names including necrotic keratinocytes, dyskeratotic keratinocytes, cytoid bodies, and Civatte bodies. As the basal layer is damaged, the normally sharp interface line between the epidermis and dermis becomes blurred and less clear, which is a useful clue to interface alteration/dermatitis.

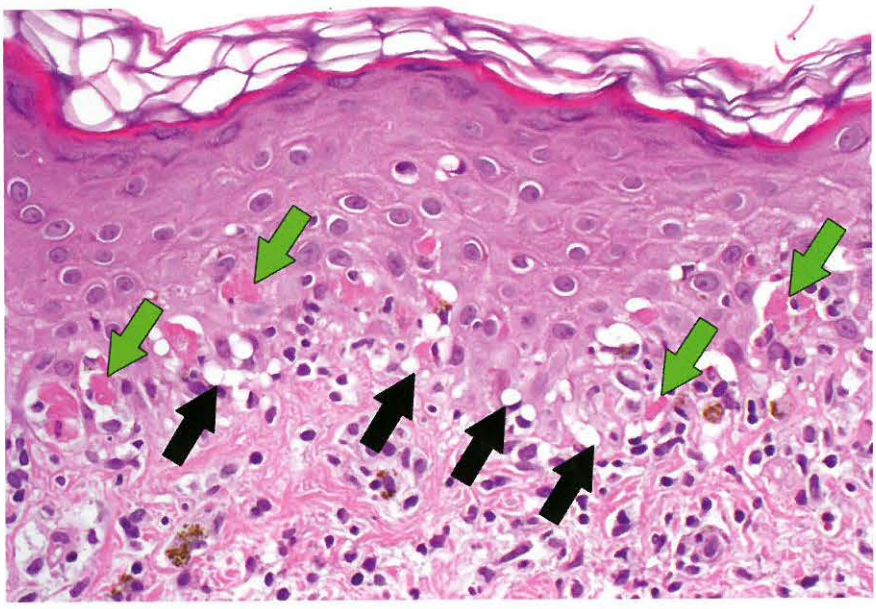
Interface dermatitis takes one of two forms: vacuolar or lichenoid. Both forms show apoptotic keratinocytes and damage of the basal layer as described above, but in the lichenoid form, the interface change is accompanied by a dense band of lymphocytes beneath the epidermis, whereas in the vacuolar form, the lymphocytes are sparse (figs. 8-4, 8-5). Important diseases with *lichenoid interface dermatitis* include lichen planus, lichenoid drug/hypersensitivity reaction, lichen striatus, and lichen nitidus. Important examples of *vacuolar interface dermatitis* include erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum, acute graft versus host disease (GVHD), fixed drug eruption, lupus erythematosus, and dermatomyositis. These entities are discussed in more detail below.

The list of lichenoid dermatoses is different from the list of vacuolar interface dermatoses, but in real life, the distinction between vacuolar and lichenoid interface is not always clear microscopically. Sometimes vacuolar interface dermatitis can have more abundant lymphocytes than usual and sometimes lichenoid dermatitis can be less cellular than usual. Keep this in mind when looking at the microscopic pattern and the clinical differential diagnosis.

Figure 8-4

VACUOLAR INTERFACE DERMATITIS

Empty vacuoles/bubbles along the basal layer (black arrows) represent vacuolar change (liquefactive degeneration) due to destruction of basal keratinocytes by lymphocytes. Multiple bright pink dying/apoptotic keratinocytes (green arrows) are evidence of this. The interface between epidermis and dermis is blurred and unclear; it is hard to tell where one ends and the other begins. This case was erythema multiforme clinically.



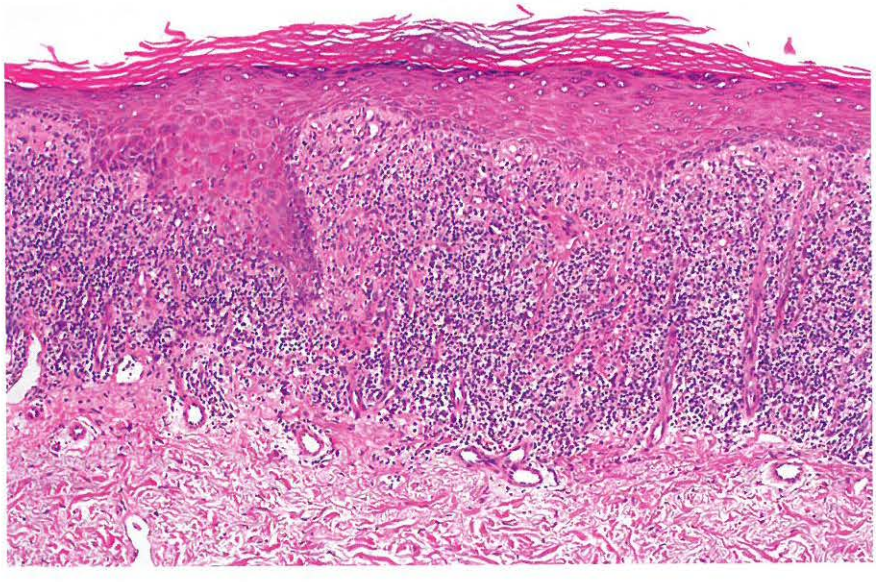


Figure 8-5

LICHENOID INTERFACE DERMATITIS

There is a dense band of lymphocytes directly beneath the epidermis. High magnification would show vacuolar interface change similar to fig. 8-4. This case was lichen planus, the prototypical example of lichenoid interface dermatitis.

Lichen Planus

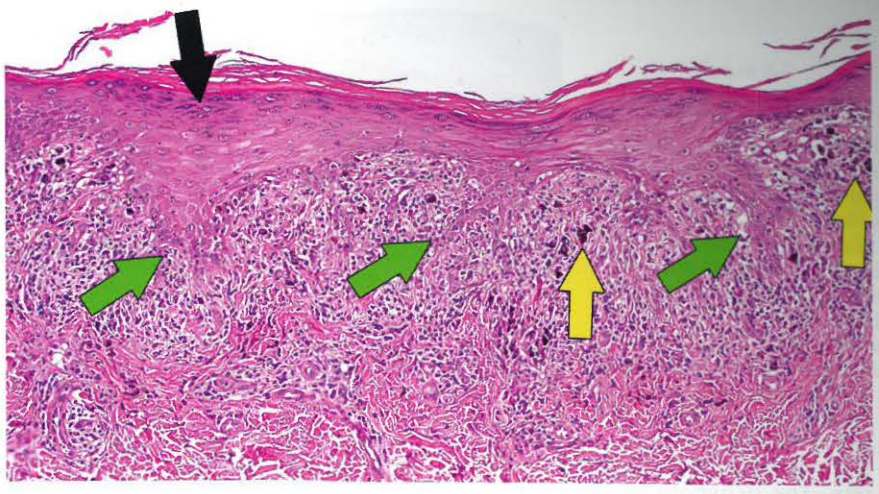
Lichen planus (LP) is the prototypical example of lichenoid interface dermatitis. It presents as multiple purple, pruritic (itchy), polygonal papules and plaques (the "5 P's"). It classically has thick orthokeratosis (usually no parakeratosis) and thick wedge-shaped hypergranulosis. The brisk lichenoid interface change often causes the rete to become jagged and "saw-toothed" (figs. 8-5, 8-6). The inflammation in lichen planus is usually limited to the superficial dermis. Eosinophils and plasma cells are usually absent or infrequent. If many eosinophils are seen, consider a lichenoid drug/hypersensitivity eruption. If many plasma cells are seen, consider secondary syphilis. If it looks like LP microscopically but the clinical differential diagnosis is "r/o BCC" and it is a solitary lesion on the chest, then it is a lichenoid keratosis (see chapter 3). If it looks like LP microscopically but also has lymphocytes around an eccrine coil in the deep dermis, then it might be lichen striatus (fig. 8-7) if the clinical appearance fits (linear dermatosis, usually in children).

Hypertrophic LP is a unique variant that usually occurs on the anterior lower legs. It presents as

Figure 8-6

LICHEN PLANUS

There is thick compact orthokeratosis with no/minimal parakeratosis. The granular layer shows "wedge-shaped" zones of hypergranulosis (black arrow). The rete are "saw-toothed" with jagged/pointed tips (green arrows). The classic lichenoid band of lymphocytes is present just beneath the epidermis. In dark skinned patients, melanin pigment incontinence is often present (yellow arrows).



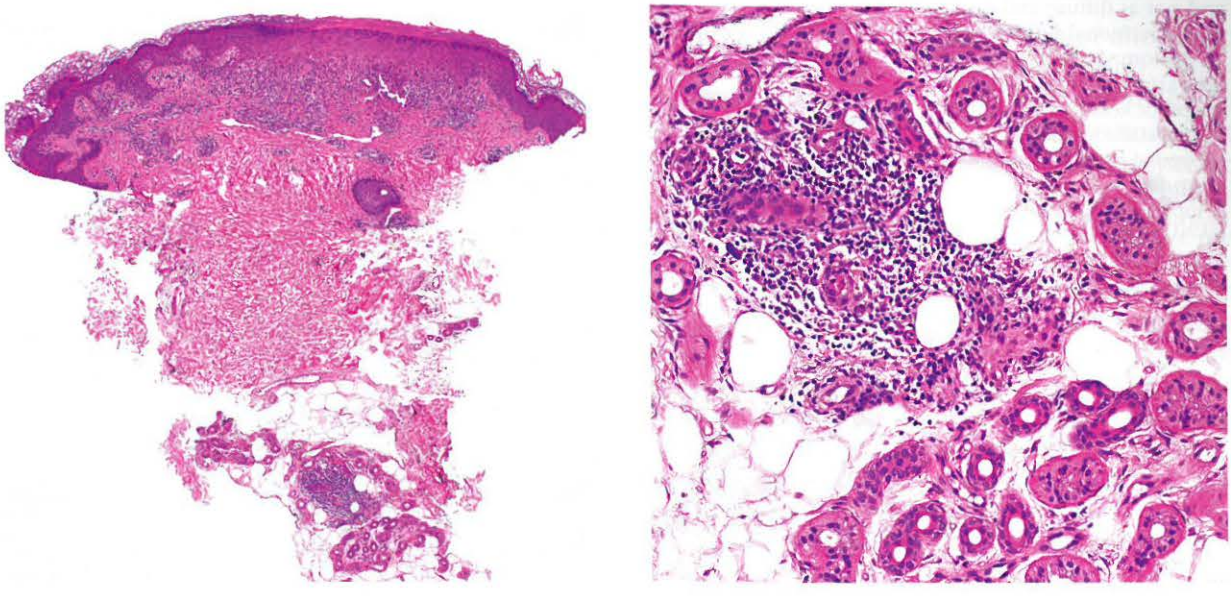


Figure 8-7

LICHEN STRIATUS

Left: Superficially, there is lichenoid dermatitis that looks identical to lichen planus. Deeper, there is lymphocytic infiltrate surrounding an eccrine coil.

Right: Lymphocytes surround an eccrine coil. This finding distinguishes lichen striatus from lichen planus.

multiple hyperkeratotic itchy papules or nodules. Microscopically, it shows marked epidermal acanthosis, often with expanded broad rete with glassy keratinocytes; a superficial biopsy of these areas can be confused with squamous cell carcinoma (SCC). The lichenoid band of lymphocytes is often patchy and the lichenoid interface change is focused mostly at the tips of the expanded rete (fig. 8-8). Unlike conventional LP, eosinophils are usually present in the dermis in hypertrophic LP.

Lichen Nitidus

Lichen nitidus presents as numerous tiny flat-topped papules clinically. Microscopically, each of these very small papules corresponds to a nodular aggregate of lymphocytes and histiocytes centered in the papillary dermis, with some

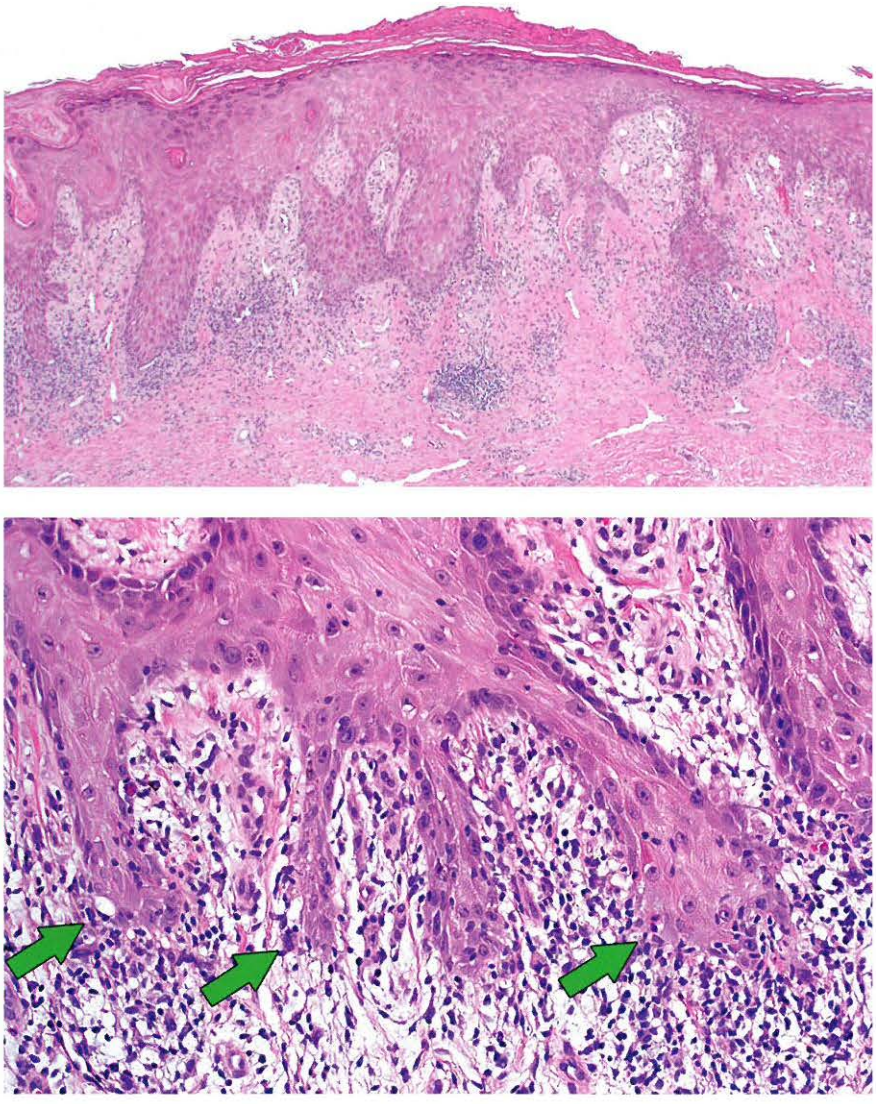


Figure 8-8

HYPERTROPHIC LICHEN PLANUS

Top: There is hyperkeratosis and hypergranulosis. The epidermis is hypertrophic and has a glassy pink appearance with elongated and expanded rete. The lichenoid band of lymphocytes may be patchy and not as diffuse and dense as in conventional lichen planus.

Bottom: Lichenoid interface alteration with vacuoles and apoptotic keratinocytes is focused mostly at the tips of the elongated expanded rete (arrows). Note the abundant eosinophilic glassy cytoplasm of the keratinocytes; on superficial biopsy, these can be easily confused with squamous cell carcinoma.

overlying interface alteration (fig. 8-9). The adjacent rete ridges usually reach down and "clutch" the nodule of inflammatory cells, yielding the classic "ball and claw" microscopic appearance.

Erythema Multiforme

Erythema multiforme (EM) is a reactive immune response that often occurs secondary to herpetic infection elsewhere in the body (i.e., no herpes is present in the skin lesions of EM). It usually presents as multiple erythematous edematous targetoid skin lesions. EM is a classic example of vacuolar interface dermatitis. Dying keratinocytes are seen at the basal layer and also are often scattered higher in the spinous layer. The lesions arise quickly, and thus the stratum corneum usually has its normal "basket-weave" appearance with no parakeratosis, as the latter requires some time to develop (nicely demonstrated in fig. 8-4).

Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis Spectrum

Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum (SJS/TEN) is also a reactive immune response involving skin similar to EM but much more severe. It usually arises secondary to a drug (often an antibiotic). SJS/TEN may have targetoid lesions similar to those of EM but has much greater body surface area involvement, with sloughing of skin and mucosa. The oral mucosa is almost always involved in SJS/TEN, so this clinical information is crucial.

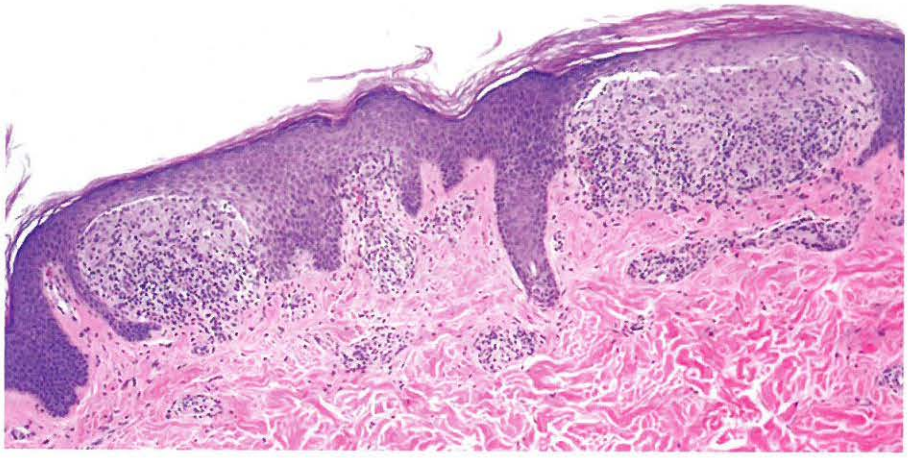


Figure 8-9

LICHEN NITIDUS

Discrete nodules of lymphocytes and histiocytes are present within dermal papillae. Each nodule fills and expands one dermal papilla. The adjacent rete ridges at each side of the nodule tend to extend downward and inward to "clutch" the nodule of inflammatory cells ("ball and claw" pattern).

Microscopically, these diseases show robust vacuolar interface change, which leads to epidermal detachment and eventually to full-thickness epidermal necrosis (fig. 8-10). EM and SJS/TEN can look identical microscopically. In some cases of EM, the vacuolar interface change can be so robust as to cause the epidermis to detach, creating a blister (bullous EM) (see fig. 9-1); when this happens, full-thickness epidermal necrosis can develop. Conversely, in early lesions of SJS/TEN where the epidermis has not yet detached there will be vacuolar interface change without full-thickness necrosis. Only the clinical presentation and extent of body surface area involvement can distinguish EM from SJS/TEN; the presence or absence of full-thickness epidermal necrosis does not distinguish between these diseases. Similarly, the distinction between SJS and TEN must be made clinically rather than microscopically. SJS has less than 10 percent body surface area involvement, TEN has greater than 30 percent, and SJS/TEN "overlap" syndrome has 10 to 30 percent (1). I leave this distinction up to the dermatologists and usually just report the biopsy as "vacuolar interface dermatitis, consistent with SJS/TEN spectrum." TEN has significant morbidity and mortality. The patients are usually sent to the burn unit. This is not a diagnosis to make lightly or to even mention in the differential diagnosis unless there is clinical information to suggest it. When I make a diagnosis of SJS/TEN spectrum, I call the dermatologist to report it to them verbally because of the seriousness and rapid course of this disease. Usually these are in patients who are so sick that the dermatologist is already calling me to check on the status of the biopsy.

Acute Graft Versus Host Disease (GVHD)

Acute GVHD is a complication of allogeneic hematopoietic stem cell transplantation. Transplanted lymphocytes from the donor (graft) attack the skin, liver, and gastrointestinal tract of the patient (host). The rash has a nonspecific morbilliform appearance and often arises before obvious liver or gastrointestinal involvement, which prompts a dermatology consult. Unfortunately, early acute GVHD has a nonspecific histologic appearance: sparse vacuolar interface alteration. The clinical differential diagnosis for acute GVHD usually includes drug eruption and viral exanthem, both of which can also have sparse vacuolar interface alteration. The dermatopathologist can rarely do any better than the dermatologist at distinguishing between these entities. In my report, I make a diagnosis of "vacuolar interface dermatitis" with this comment: "Although these findings could represent acute GVHD, drug eruption or viral exanthem could have similar histologic features and should be excluded clinically."

Early cases of acute GVHD may have very mild vacuolation of the basal layer with rare dying keratinocytes, so even if the biopsy is nearly normal histologically, acute GVHD usually cannot be fully excluded. Thus, a biopsy performed for early acute GVHD is often an exercise in futility. Although studies have suggested that skin biopsy is of limited use in diagnosing acute GVHD, the hematology/oncology team is often persistent in requesting a dermatology consultation and biopsy (1). Gentle ongoing education of our clinical colleagues is needed, but, admittedly, progress is often slow.

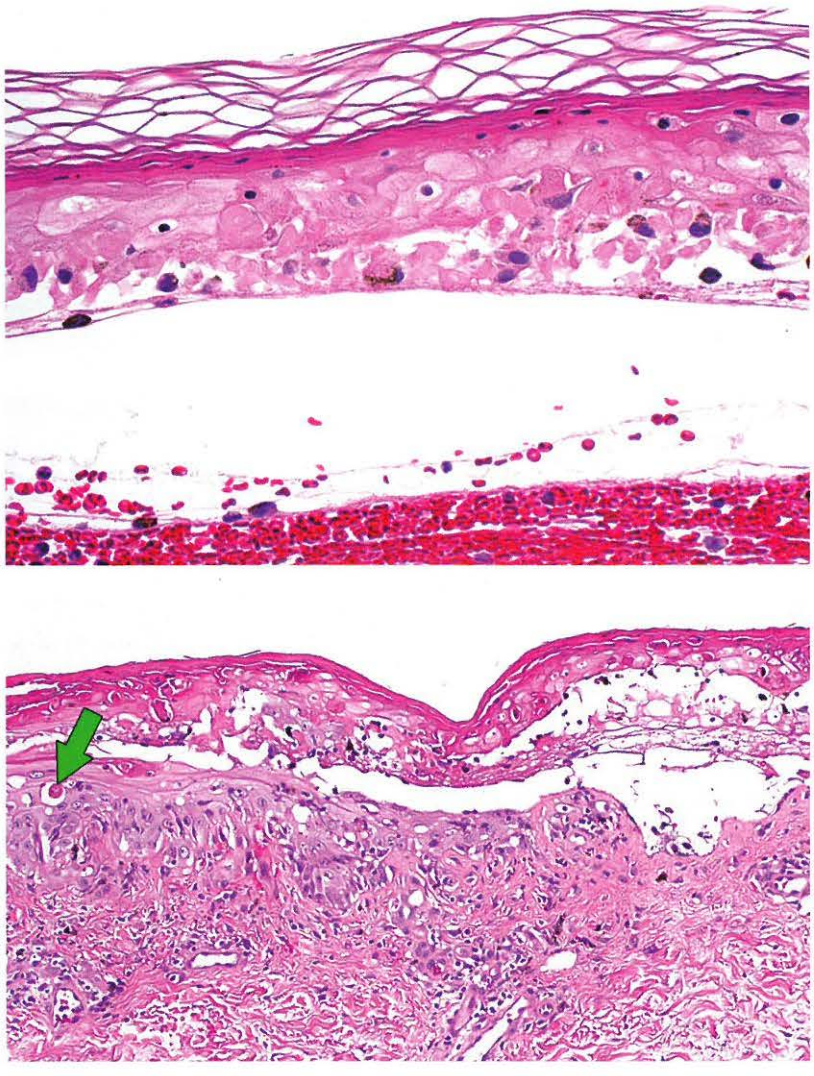


Figure 8-10

STEVENS-JOHNSON SYNDROME/ TOXIC EPIDERMAL NECROLYSIS SPECTRUM (SJS/TEN)

Top: The detached epidermis shows full-thickness necrosis (most of the keratinocytes lack nuclei). The normal "basket weave" stratum corneum is evidence that the epidermis died and detached very quickly. The diagnosis of SJS/TEN here was made by identifying vacuolar interface alteration in adjacent skin (right) in conjunction with the clinical scenario.

Bottom: Detached necrotic epidermis forms a subepidermal blister (right). At the periphery of the blister, there is partially intact/viable epidermis (left), which shows vacuolar interface alteration with scattered individual apoptotic keratinocytes (arrow).

Chronic GVHD is much less common than acute GVHD. It is usually easier to recognize clinically and microscopically. It shows either lichenoid interface change, sclerosis of the dermis resembling morphea/scleroderma, or a combination of these patterns.

Fixed Drug Eruption

Fixed drug eruption (FDE) is an unusual entity. It presents as erythematous or violaceous skin plaques, often on the extremities or genitalia, that arise after the patient takes an oral drug (often a nonsteroidal anti-inflammatory drug). It resolves when the patient stops taking the drug. If the patient takes the same drug again in future, the plaques will return at the same site/s as before.

Microscopically, the classic triad of features for FDE are: 1) interface alteration (this often shows overlap between vacuolar and lichenoid patterns), 2) papillary dermal fibrosis with pigment incontinence (melanophages in the dermis), and 3) dermal eosinophils. The plaques often develop a brown appearance due to the melanophages in the dermis (essentially a form of postinflammatory hyperpigmentation) (2).

Lupus Erythematosus

Lupus erythematosus is an immune-mediated connective tissue disease. It has several clinical forms, including systemic lupus erythematosus (SLE), subacute cutaneous lupus erythematosus (SCLE), and discoid lupus erythematosus (DLE). SLE presents as fixed erythematous, slightly

scaly plaques on the cheeks and nasal bridge (the classic "butterfly rash"), usually in women (ratio, 9:1). These patients have systemic involvement affecting a wide range of organ systems. SCLE presents as nonindurated, nonscarring, often annular (ring-shaped) erythematous lesions, usually arising in sun-exposed skin. About half of patients with SCLE have systemic involvement. DLE presents as scaly erythematous plaques, often on the head and neck, which heal with scarring that may be severe and disfiguring. DLE often causes significant hyper- or hypopigmentation in patients with dark skin. Although patients with SLE can develop discoid skin lesions, most patients with discoid lupus do not have systemic involvement (2).

Lupus erythematosus is characterized by vacuolar interface alteration (fig. 8-11). Occasional cases have more lymphocytes and show an overlap between vacuolar and lichenoid patterns. As with other interface dermatoses, melanophages may be seen in the superficial dermis (pigment incontinence), especially in patients with dark skin. There is often superficial and deep perivascular and periadnexal (around hair follicles and eccrine coils) lymphocytic infiltrate. Vacuolar interface alteration may also be seen in the hair follicle epithelium. Plasma cells are often present but eosinophils are classically rare or absent. Increased mucin may be present between reticular dermal collagen bundles.

Not all cases of lupus erythematosus show all of the features mentioned above. In early SLE, the changes may be subtle, with only mild vacuolar interface alteration. In DLE, there is often atrophy of the epidermis, thick compact orthokeratosis (sometimes focal parakeratosis), effaced rete ridges, thickened dense pink basement membrane, and enlarged reactive basal keratinocytes with glassy cytoplasm. When DLE arises on the head and neck of older sun-damaged adults, it can be mistaken for actinic keratosis or even SCC both clinically (because it is a discrete scaly lesion) and microscopically (because of the enlarged glassy keratinocytes). Dilated hair follicles plugged with keratin, predominance of orthokeratosis more than parakeratosis, abundant dermal mucin, and robust perivascular and periadnexal lymphocytic infiltrate are all clues for a diagnosis of DLE.

Lupus erythematosus classically shows a "lupus band" on direct immunofluorescence of involved lesional skin (and also sometimes in nonlesional clinically normal skin). This is granular or "shaggy" linear deposition of IgM (most common), IgG, IgA, and/or C3 along the basement membrane zone. However, many cases of lupus erythematosus are negative for a lupus band, and conversely, some normal patients who do not have lupus erythematosus will be lupus band positive (particularly if the biopsy is from sun-exposed skin).

Aside from classic cases of DLE (and a few other situations), I usually find it difficult to reliably distinguish the different subtypes of lupus erythematosus based on microscopic features alone. The clinical appearance is crucial, so I usually leave subclassification up to the dermatologists. If the clinical differential includes lupus erythematosus, and the biopsy shows classic features as discussed above, then I will usually use a line diagnosis of "lupus erythematosus" with a comment that other connective tissue diseases could show similar features. If the clinical differential does not include lupus erythematosus or the microscopic findings are not classic, then I will use a line diagnosis of "vacuolar interface dermatitis" with a comment that these changes could potentially represent lupus erythematosus in the proper clinical context.

Dermatomyositis

Dermatomyositis is an immune-mediated disease that causes symmetrical proximal muscle weakness and distinct skin findings, including violaceous periorbital edema (heliotrope rash), erythema on the face and around the neck/shoulders/upper chest (the "shawl area"), violaceous papules on the knuckles (Gottron papules), and periungual erythema and telangiectasia. The skin findings may arise long before the muscle weakness (2). Dermatomyositis may show overlapping histologic features with lupus erythematosus, although dermatomyositis usually has sparser vacuolar interface alteration, less dermal lymphocytic infiltrate, no periadnexal inflammation, and more abundant dermal mucin.

SUPERFICIAL AND/OR DEEP PERIVASCULAR LYMPHOCYTIC PATTERN

Perivascular lymphocytic infiltrate is a component of most inflammatory dermatoses. Even clinically normal skin often has a small number of lymphocytes present around superficial

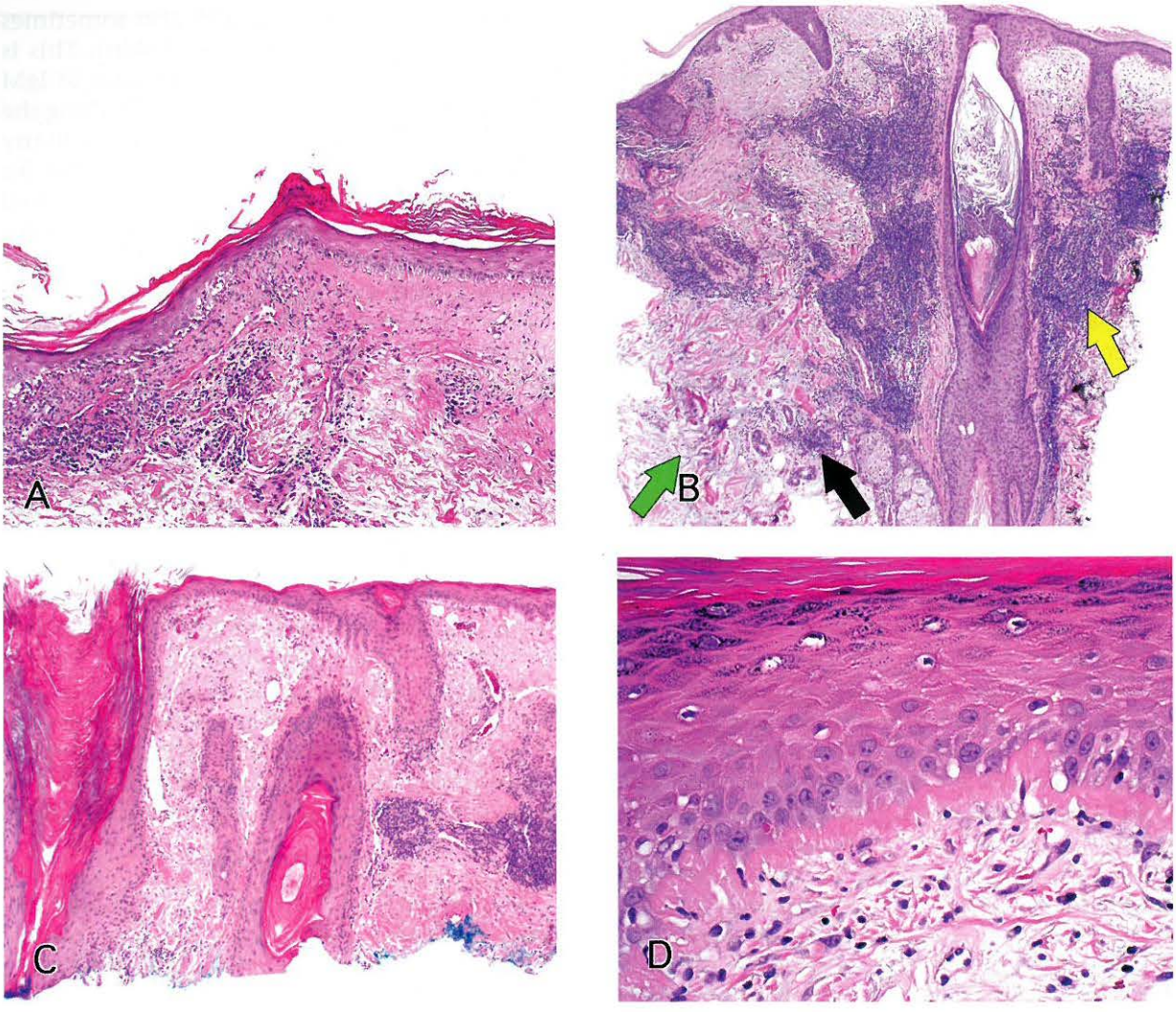


Figure 8-11

LUPUS ERYTHEMATOSUS.

A: There is interface alteration that may have variable density of inflammation. This case shows an overlap between lichenoid (left) and vacuolar (middle) patterns. Sometimes it is "burnt out," leaving dense papillary dermal sclerosis behind with little inflammation (right). The compact orthokeratosis in the overlying stratum corneum is a common feature.

B: There is a superficial and deep perivascular lymphocytic infiltrate. The infiltrate is also periadnexal, surrounding hair follicles (yellow arrow) and eccrine coils (black arrow). The hair follicle is dilated and filled with keratin. Blue mucin is often present in the reticular dermis (green arrow).

C: In discoid lupus erythematosus, dilated follicles "plugged" with dense keratin may be pronounced (left). A dense perivascular lymphocytic infiltrate is present in the adjacent dermis (right).

D: The basement membrane may be very thick and hyalinized in some cases.

dermal vessels. When this is the only finding on a biopsy of a rash, a diagnosis of "superficial perivascular dermatitis" can be used. This is a nonspecific finding that can be seen in viral exanthems, drug eruptions, urticaria, and a wide range of other entities. It can also be present as a component of spongiotic dermatitis and many other inflammatory dermatoses. Some diseases have both a superficial and deep dermal perivascular lymphocytic infiltrate, including drug eruption, arthropod bite reaction, polymorphous light eruption, perniosis, erythema annulare centrifugum, lupus erythematosus, secondary syphilis (see chapter 7), and many others.

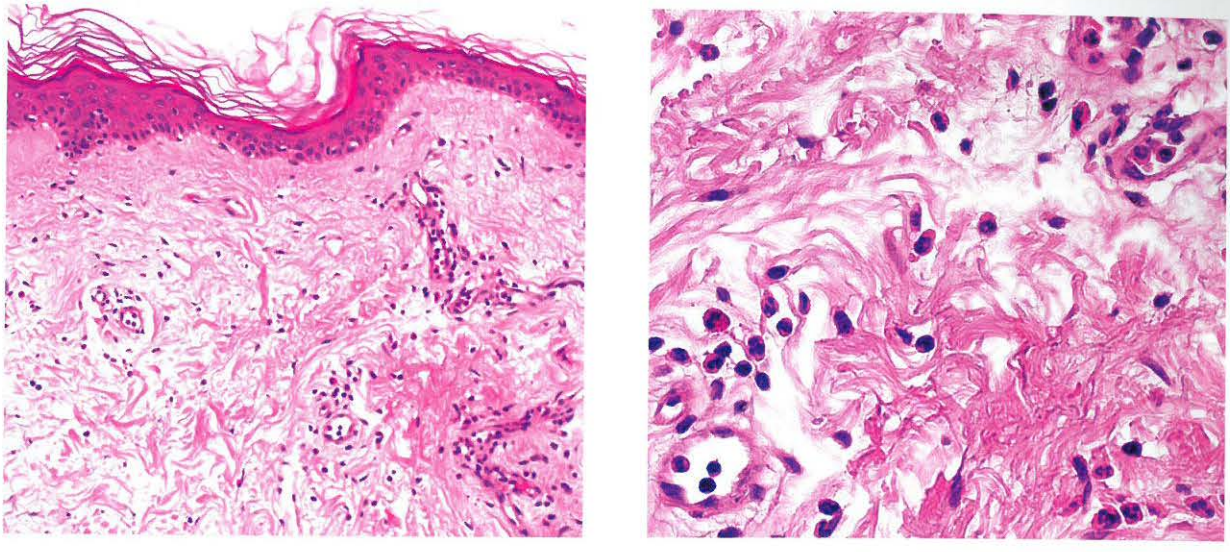


Figure 8-12

URTICARIA

Left: The dermis is pale due to extra white space between dermal collagen bundles; this is evidence of dermal edema. The inflammatory infiltrate is usually sparse. At low magnification, urticaria often looks like normal skin.

Right: In addition to perivascular lymphocytes, the infiltrate is composed of sparse scattered mast cells, eosinophils, and neutrophils. Neutrophils may also be clustered within the lumens of small blood vessels (upper right), a useful clue to the diagnosis.

Drug Eruption

Drug eruption can look like almost any inflammatory pattern microscopically, including spongiotic, vacuolar, lichenoid, granulomatous, or superficial and/or deep perivascular lymphocytic infiltrate. As Ronald Rapini says: "A skin biopsy usually cannot prove that a rash is a drug eruption, and often cannot prove that it is not" (3). This is a frustrating situation for all involved.

"Dermal hypersensitivity reaction" is the term I use to refer to nonspecific superficial and/or deep perivascular lymphocytic infiltrate with eosinophils but with minimal epidermal changes. It is a pattern that may be seen in drug eruptions, arthropod bite reactions, and urticaria, among others. Many of my dermatology colleagues do not love this term, which is understandable because it is a nonspecific pattern and these patients are often difficult to treat. It is not an easy thing to take an elderly patient off all of their drugs, one at a time, to see if their rash improves. I suppose I could just say "perivascular lymphocytic infiltrate with eosinophils" with the same differential to avoid the term "dermal hypersensitivity reaction" but the frustrating situation is still the same. I wish I had better advice to give on this topic, but it is still a common problem I struggle with in my own practice. Communication with the dermatologist is still the best way to handle complex cases.

Urticaria

Urticaria is a very common hypersensitivity reaction that may have many underlying causes but is often idiopathic. It presents with raised erythematous "wheals" ("hives" in nonmedical terminology) that are usually pruritic. Some patients have dermatographism, where stroking the skin produces a wheal in that same area. The individual wheals are evanescent, usually resolving within hours (2).

A biopsy of urticaria often looks like essentially normal skin at low power. Edema may be present, visualized microscopically as extra white space between reticular dermal collagen bundles; this finding is often subtle and thus can be both easily overlooked (when it is actually present) and easily hallucinated/imagined (when it is not actually present) by the pathologist. At higher magnification, a sparse perivascular infiltrate of lymphocytes will usually be seen, along with sparse scattered mast cells, eosinophils, and neutrophils (fig. 8-12). Scattered neutrophils in the dermis or neutrophils

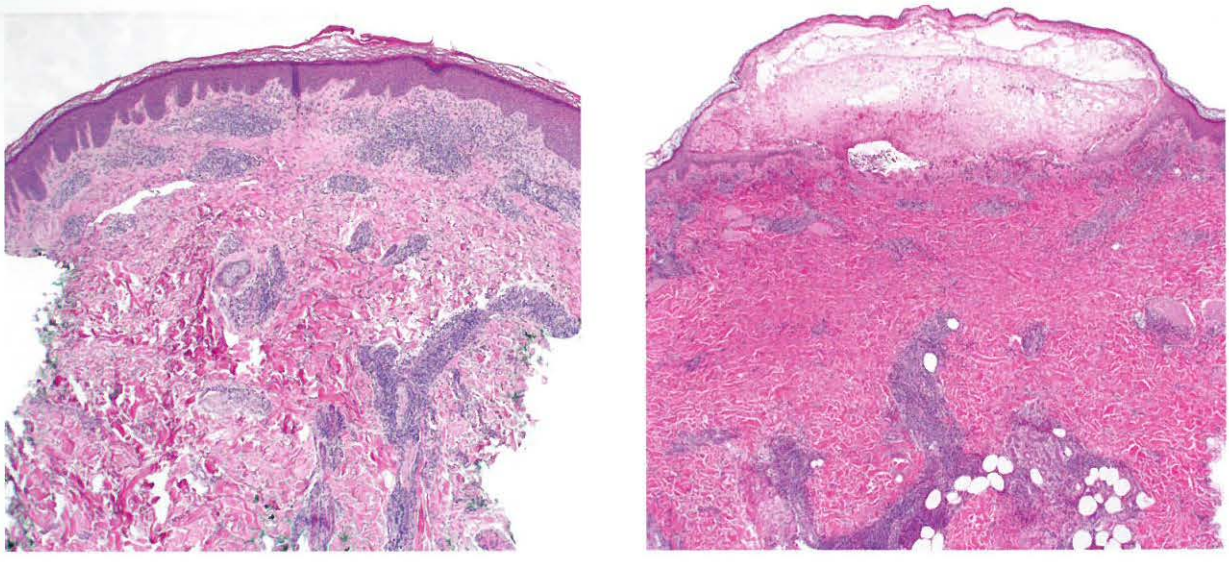


Figure 8-13

ARTHROPOD BITE REACTION

Left: There is a superficial and deep perivascular lymphocytic infiltrate that is "wedge-shape" or "top-heavy" (i.e., inflammation is denser in the superficial dermis).

Right: Massive dermal edema may lead to blister formation (bullous arthropod bite reaction). The presence of a deep perivascular infiltrate with many eosinophils favors a bullous arthropod bite reaction over bullous pemphigoid or other immunobullous disease.

clustered within the lumens of small blood vessels are both useful clues for a diagnosis of urticaria. This clue must be taken in context with the clinical features, as scattered neutrophils in the dermis may also be seen adjacent to unsampled folliculitis (cut deeper sections) or when neutrophils are on their way up to the epidermis (e.g., inflamed ulcers, pustules, etc).

If the lesions are urticarial in appearance clinically and there are features of vascular damage present microscopically (e.g., hemorrhage, nuclear dust, fibrin around vessels) or individual urticarial lesions are clinically "fixed" (present for more than 24 hours), then a diagnosis of *urticarial vasculitis* can be considered. This uncommon diagnosis is usually difficult to recognize by histologic features alone and requires correlation with the clinical information.

Arthropod Bite Reaction

Arthropod bite reaction usually displays a superficial and deep perivascular lymphocytic infiltrate, often with a vaguely "wedge-shape" or "top-heavy" distribution, meaning the inflammation is denser in the superficial dermis (fig. 8-13). The epidermis may have a focal central area of spongiosis and erosion/ulceration, either from the site where the arthropod actually bit or from excoriation by the patient (or both). The dermis is often edematous. Eosinophils are often present and may be numerous, and they often extend deep into the dermis or even the subcutis. The eosinophils tend to not only be around vessels but also out in the interstitial area (between reticular dermal collagen bundles). Eosinophils are sometimes so numerous that they cluster around dermal collagen bundles, degranulate, and coat the collagen bundle in eosinophil granules. These "flame figures" are classically seen in a rare disease called *Wells syndrome* (*eosinophilic cellulitis*), which is a diagnosis of exclusion, but I see them most often in exuberant bug bites (fig. 8-14). Young children (toddlers around the age of 2) and elderly patients with chronic lymphocytic leukemia/small lymphocytic lymphoma have a particular tendency to get very robust arthropod bite reactions. Scabies can show an overlapping pattern with arthropod bite reactions (see chapter 7). At the site of tick bites, the tick mouthpart is sometimes still seen embedded in the dermis among the inflammatory changes (fig. 8-15).

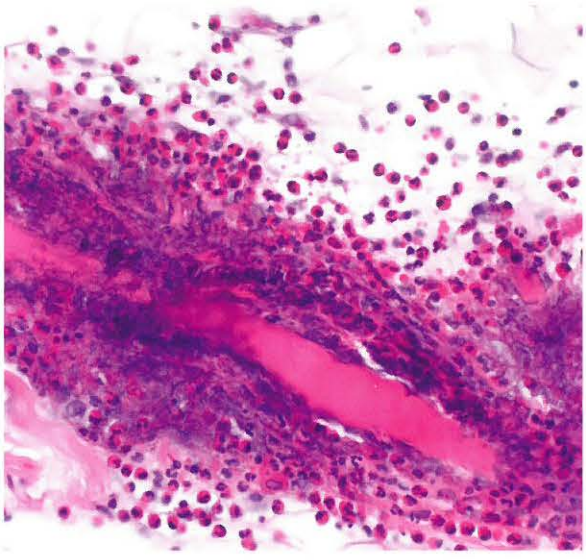


Figure 8-14

"FLAME FIGURE"

Numerous degranulating eosinophils surround a degenerated dermal collagen bundle. These "flame figures" may be seen in Wells syndrome (eosinophilic cellulitis) or in exuberant arthropod bite reactions.

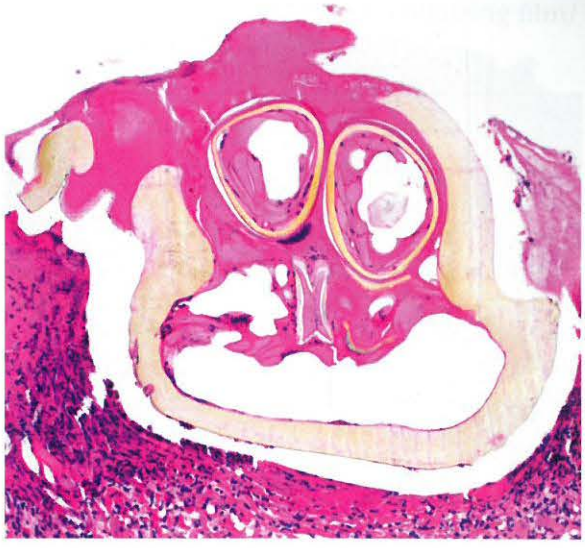


Figure 8-15

TICK MOUTHPARTS

At the site of tick bites, the tick mouthpart is sometimes still seen embedded in the dermis surrounded by fibrin, necrosis, and mixed inflammation. It is made of chitin, which has a unique yellowish refractile appearance.

Polymorphous Light Eruption

Polymorphous light eruption (PMLE) is a photodermatitis that usually presents in young women. Erythematous papules, plaques, and vesicles arise after exposure to sun or other ultraviolet light. Biopsy classically shows a superficial and deep perivascular lymphocytic infiltrate with prominent papillary dermal edema. However, the disease is called "polymorphous" for a reason: a wide range of clinical and pathologic findings have been reported (2).

Perniosis

Perniosis (chilblains) is an unusual reactive process due to cold temperatures; it is more common in cold damp climates or during winter months. It presents clinically as painful erythematous to violaceous papules or nodules on the distal extremities (especially fingers and toes) (2). The microscopic features are very similar to those of PMLE, albeit on acral skin (fig. 8-16).

While we are on this topic, here are some confusing dermatology names you should know about. Some patients with lupus erythematosus also develop perniosis (chilblains); this is called *chilblain lupus erythematosus*. This is not to be confused with *lupus pernio*, which is an old school name for sarcoidosis of the nose or cheeks and is unrelated to either lupus erythematosus or perniosis. The term "lupus" was applied to many diseases in the olden days that we now understand to be unrelated to lupus erythematosus. For example, "lupus vulgaris" is actually a form of cutaneous tuberculosis. The dermatology forefathers accomplished some amazing things considering the limited diagnostic tools available in their days, but their terminologies created major headaches for future generations of medical students, residents, and fellows!

Erythema Annulare Centrifugum

Erythema annulare centrifugum (EAC) is an inflammatory dermatosis of uncertain origin that presents with annular erythematous lesions on the extremities or trunk. The periphery of these rings may expand outward and leave behind a trailing ring of slight scale and a central zone of clearing (nonerythematous normal skin).

Microscopically, EAC shows superficial and deep perivascular lymphocytic infiltrate that is tightly cuffed/aggregated around vessels ("coat sleeve" pattern). The epidermis is usually

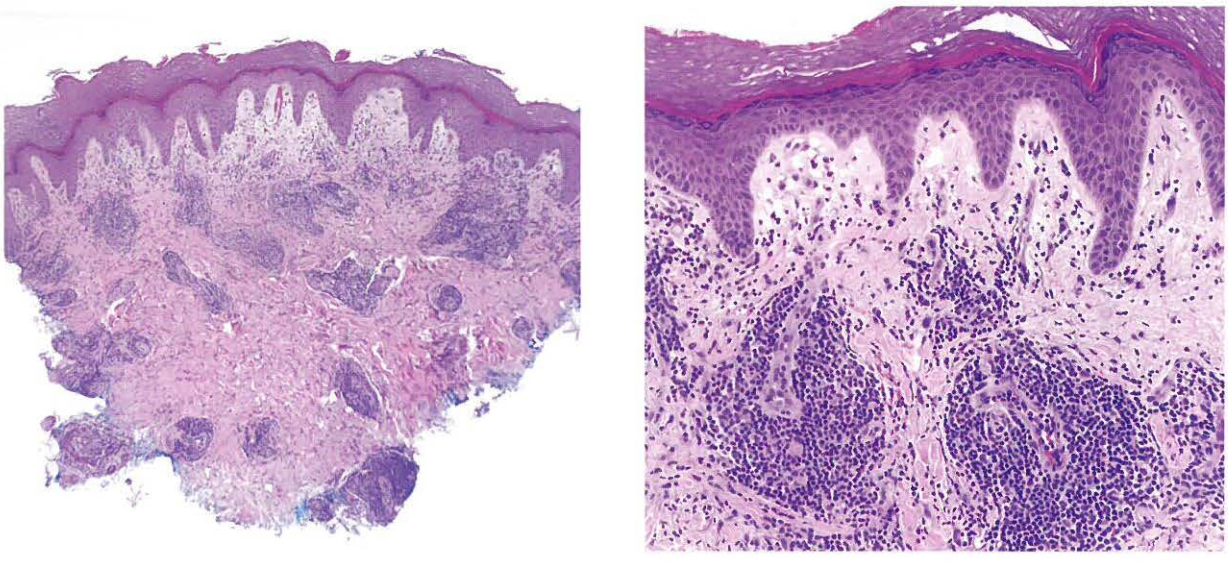


Figure 8-16

PERNIOSIS

Left: A classic example of superficial and deep perivascular lymphocytic infiltrate. The acral location and prominent papillary dermal edema are clues to the diagnosis.

Right: The papillary dermis has a pale loose appearance because it is filled and expanded by edema fluid. There is a robust perivascular lymphocytic infiltrate. Perniosis and polymorphous light eruption (PMLE) both share these features; the acral site and clinical scenario are keys to distinguishing perniosis from PMLE.

normal. However, there is a superficial variant of EAC that has mostly superficial dermal perivascular lymphocytic infiltrate; it may have mild spongiosis and focal parakeratosis (2).

Tumid Lupus Erythematosus

Tumid lupus erythematosus is characterized by indurated erythematous plaques often on the chest. Microscopically, it varies from other forms of lupus erythematosus in that it lacks vacuolar interface alteration. Instead, it shows only superficial and deep perivascular lymphocytic infiltrate, usually with abundant dermal mucin. Most patients with tumid lupus erythematosus lack systemic involvement, elevated ANA, or other diagnostic criteria of lupus erythematosus, raising the question of whether tumid lupus is truly a variant of lupus erythematosus (2). *Reticular erythematous mucinosis* (REM) shows essentially identical histologic features and a very similar clinical presentation; it may be closely related to (or even the same thing as) tumid lupus erythematosus.

GRANULOMATOUS PATTERN

Granulomas may be seen in sarcoidosis, foreign body reaction, granulomatous rosacea, and infectious processes (particularly mycobacterial or fungal; see chapter 7). *Granulomatous dermatitis* is sometimes used to refer to any histiocyte-rich dermal infiltrate, even if well-formed granulomas are not present. Examples of granulomatous dermatitis include sarcoidosis, granulomatous foreign body reaction, keratin granuloma from ruptured cyst/folliculitis (see chapter 6), granulomatous drug eruption, and granulomatous rosacea.

Sarcoidosis

Sarcoidosis in the skin shows tightly organized non-necrotizing granulomas in the dermis, usually with little associated inflammation (fig. 8-17). It is a diagnosis of exclusion, as tuberculoid leprosy, other infections, and other granulomatous processes can produce a similar histologic pattern.

Foreign Body Granuloma

Granulomatous foreign body reaction usually shows large giant cells with multiple eccentrically arranged nuclei. Asteroid bodies, which are a classic (but nonspecific) feature of sarcoidosis, are also commonly present in foreign body granulomas

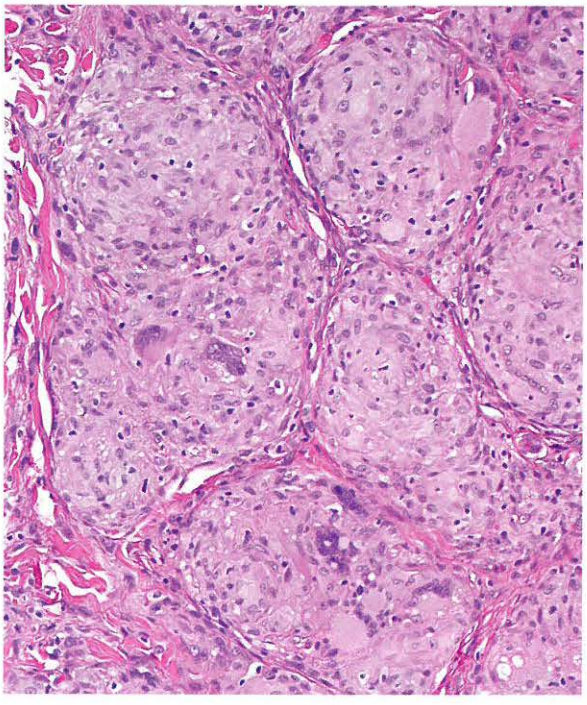


Figure 8-17

SARCOIDOSIS

Histiocytes and multinucleated giant cells are packed tightly into well-circumscribed non-necrotizing granulomas in the dermis. There is usually very little associated lymphocytic or neutrophilic inflammation in sarcoidosis. Infection and other granulomatous processes must be excluded since they can produce a similar pattern.

(see fig. 2-39). Streak/tear artifacts in the tissue (as seen in sections with calcifications or non-decalcified bone) are a useful clue to exogenous/foreign material in the setting of granulomatous dermatitis (see fig. 2-41). Exogenous material is usually refractile and often polarizable.

A polarizing lens is a critical microscope accessory in dermatopathology. If you cannot obtain these lenses, a cheap substitute can be made using two sheets of polarized plastic film or two lenses detached from a pair of cheap polarized sunglasses. Just put one piece of film or lens above the slide and one below the stage over the light source, turn up the light intensity, and slowly rotate one of the lenses. Foreign bodies that are polarizable will stand out as bright white or rainbow colored depending on what they are composed of. You may need to go to high magnification to see very small specks of polarizable foreign material. Remember to turn the light source back to normal before removing the polarizing film/lenses (or your retinas will regret it)!

PALISADED NECROBIOTIC GRANULOMA PATTERN

Palisaded necrobiotic granuloma is a unique type of granuloma in which histiocytes palisade around a central area of degenerated collagen, mucin, or fibrin. This pattern of granuloma is seen in granuloma annulare, deep granuloma annulare, actinic granuloma of O'Brien, annular elastolytic granuloma, necrobiosis lipoidica diabeticorum (NLD), necrobiotic xanthogranuloma (NXG), and rheumatoid nodule.

Granuloma Annulare

Granuloma annulare (GA) is a common idiopathic granulomatous dermatitis. It usually presents as papules arranged in a ring or arc shape, often on the dorsal hands or feet. It is often a solitary lesion, but some patients have multiple or even generalized lesions. Nonannular forms exist, including linear and papular variants, so the ring-shaped clinical description is not always required for the diagnosis of GA (2).

Microscopically, histiocytes form palisades around a central zone of degenerated collagen (necrobiosis) and mucin (fig. 8-18). Nuclear dust may be seen. The mucin often imparts a bluish appearance to the center of the granulomas. Sometimes the palisading and necrobiosis are subtle; a useful clue is that histiocytes often trickle between adjacent reticular dermal collagen bundles ("interstitial" GA). This pattern can vaguely resemble the collagen entrapment seen at the periphery of dermatofibroma. Perivascular lymphocytes and scattered eosinophils are often present (2,4).

Some cases show distortion or loss of elastic fibers within the granulomas and elastophagocytosis (tangled elastic fibers being engulfed by giant cells) (fig. 8-19). Other granulomatous diseases may show elastophagocytosis, including actinic granuloma of O'Brien (in sun-damaged skin with solar elastosis) and annular elastolytic granuloma; I believe these are likely just variants of GA. I also regularly encounter foci of dermal elastophagocytosis as an incidental finding.

Deep GA is a more robust form of GA that forms nodules in the subcutis. Changes of conventional GA may be present in the overlying dermis. It often arises on the lower extremities

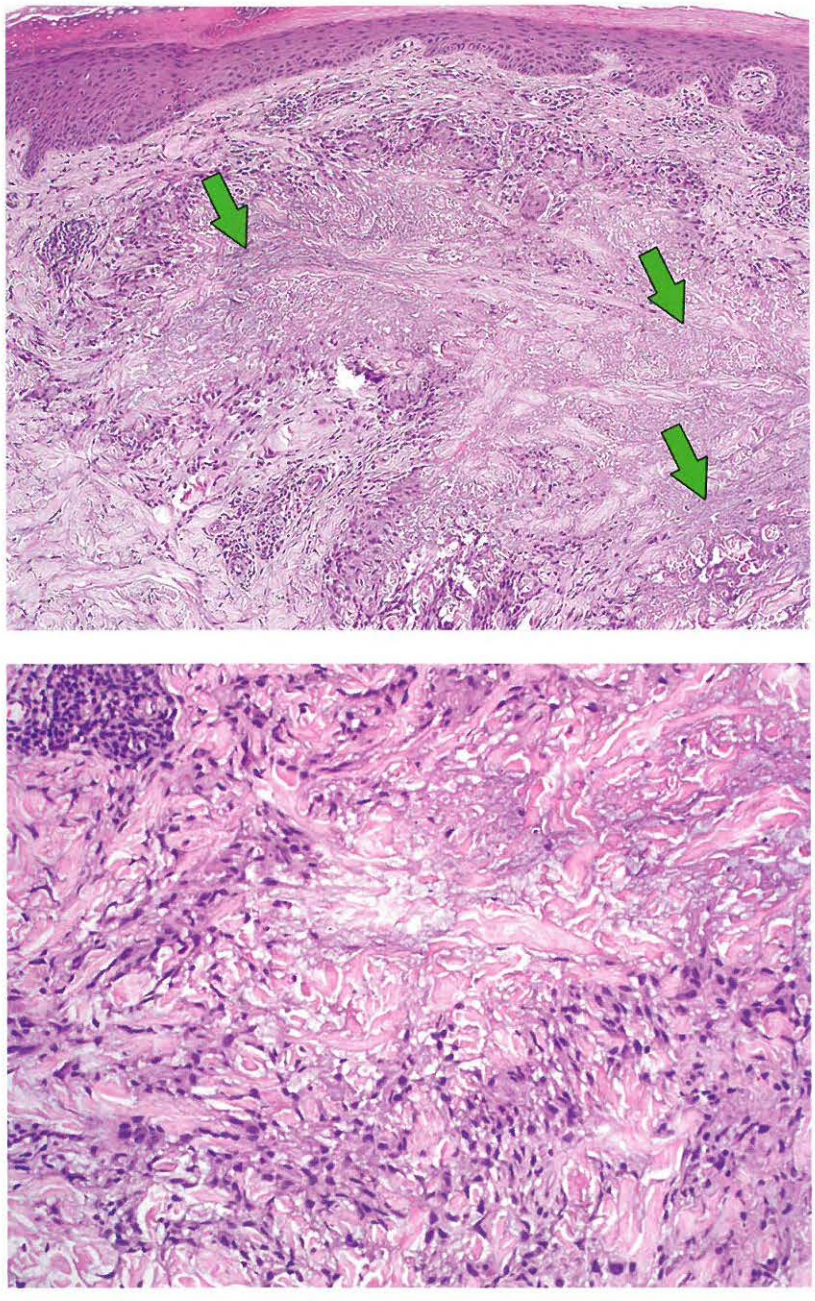


Figure 8-18

GRANULOMA ANNULARE (GA)

Top: A zone of degenerated collagen (necrobiosis) and mucin (arrows) is surrounded by a rim of palisading histiocytes. The abundant mucin in this case imparts a bluish appearance to the central necrobiotic zone; in some cases the mucin and necrobiosis are more subtle.

Bottom: The central zone of necrobiosis and mucin has a smudgy washed-out appearance (top right). Pink collagen bundles are present, but the normal dermal fibroblasts are few or absent (I think of this as essentially a form of dermal collagen necrosis). Spindled histiocytes palisade around the necrobiosis and often trickle outward, intermingling between the adjacent reticular dermal collagen bundles (bottom and left). This "interstitial" pattern of GA can vaguely resemble the collagen entrapment seen at the periphery of dermatofibroma.

(especially tibial area) of children or young adults, but can also occur in other sites such as the upper extremities, trunk, or head and neck. The granulomas are usually large and well-formed, with prominent palisading. The necrobiotic centers of the granulomas are usually bluish in appearance due to mucin ("blue granulomas") (fig. 8-20), but they sometimes may also show a reddish hue due to fibrin deposition, which causes them to mimic rheumatoid nodule. (5)

Rheumatoid Nodule

Rheumatoid nodules are large necrobiotic palisaded granulomas that arise in the deep dermis/subcutis of patients with rheumatoid arthritis, usually adults. They often arise near joints: common sites include the elbow, forearm, hands and feet. Although they are usually deep, the superficial dermis is often involved also. A lymphoplasmacytic infiltrate may be present

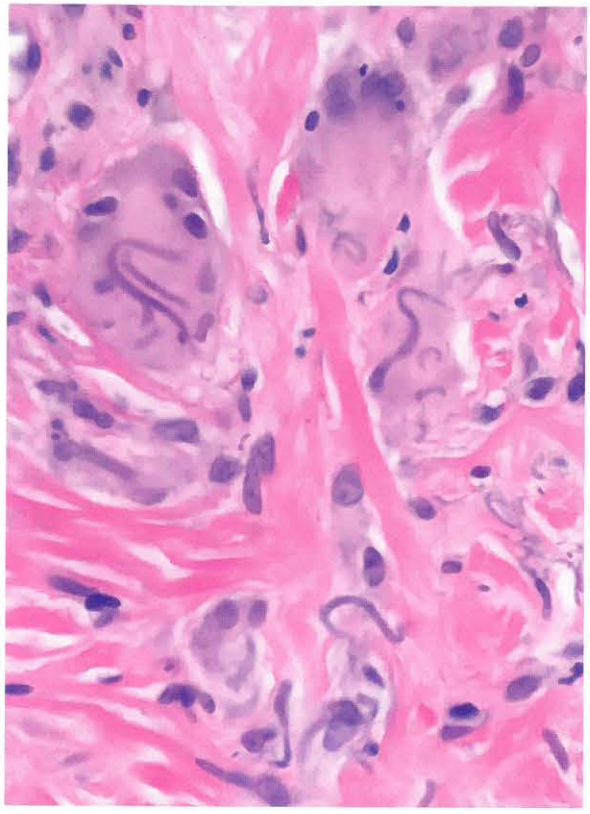


Figure 8-19

ELASTOPHAGOCYTOSIS

Tangled blue-gray elastic fibers are present in the cytoplasm of multinucleated giant cells.

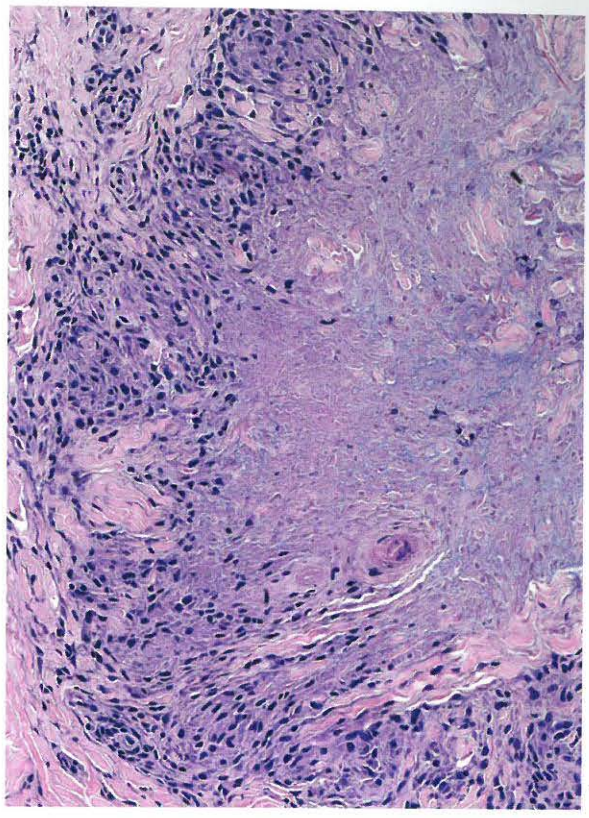


Figure 8-20

DEEP GRANULOMA ANNULARE

The appearance is very similar to conventional GA, although it is deeper in the skin and the palisading histiocytes may be more prominent. Deep GA usually has a "blue granuloma" appearance due to abundant mucin in the central zone of necrobiosis.

around the granulomas, a helpful clue. Nuclear debris and scattered neutrophils are commonly present in the center of the granulomas; this is not necessarily an indication of infection. That said, I have seen rare cases that I thought would surely be rheumatoid nodule that turned out to be positive for AFB on Fite stain. My mentor Mark Edgar once told me, "Don't argue with granulomas...just do the infectious stains." Sage advice.

The necrobiotic zones in rheumatoid nodule are usually deep red due to fibrin deposition ("red granulomas") (fig. 8-21). Deep GA can also have fibrin and be a "red granuloma," but the converse is not true, as blue mucin is reportedly seen only in deep GA not in rheumatoid nodule (5). In some cases, microscopic distinction is impossible; I use the term "palisaded necrobiotic granuloma" in the diagnosis line of these cases with a comment that it could be either rheumatoid nodule or deep GA and that clinical correlation to exclude rheumatoid arthritis is recommended. Obviously, in children, these usually end up being deep GA, as rheumatoid arthritis is rare in children.

Epithelioid sarcoma is a rare sarcoma that arises as a nodule in the dermis, subcutis, or deep soft tissue of the distal extremities in young adults. It often has central zones of necrosis that can cause it to mimic deep GA or rheumatoid nodule at low power. At high power, the distinction is usually easy, as the cells of epithelioid sarcoma have very dense abundant eosinophilic cytoplasm and large atypical nuclei, and the central areas are true tumor cell necrosis rather than fibrin or degenerated collagen (fig. 8-22). Mitoses are often present in deep GA and rheumatoid nodule as well as in

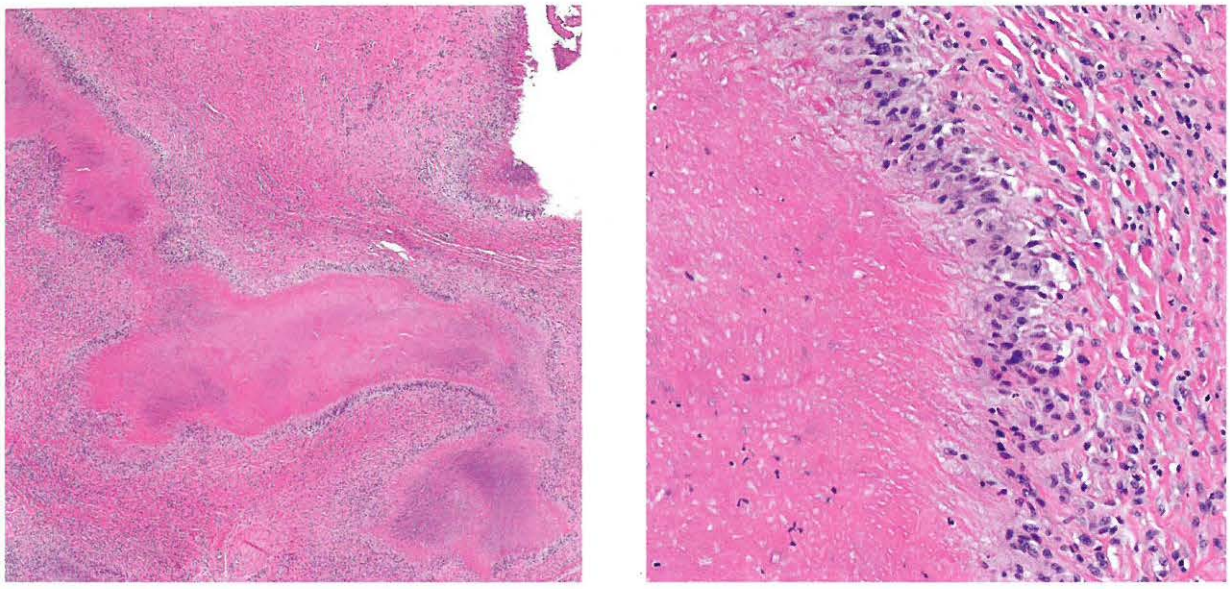


Figure 8-21

RHEUMATOID NODULE

Left: Large palisaded granulomas with zones of central necrobiosis are present in the soft tissue, often near a joint.

Right: The central necrobiotic zones in rheumatoid nodule are usually a dark pink/red color due to abundant fibrin deposition (left); they are "red granulomas". This fibrin-rich central zone is surrounded by a peripheral rim of palisading histiocytes (center), adjacent fibrosis, and mixed inflammation (right).

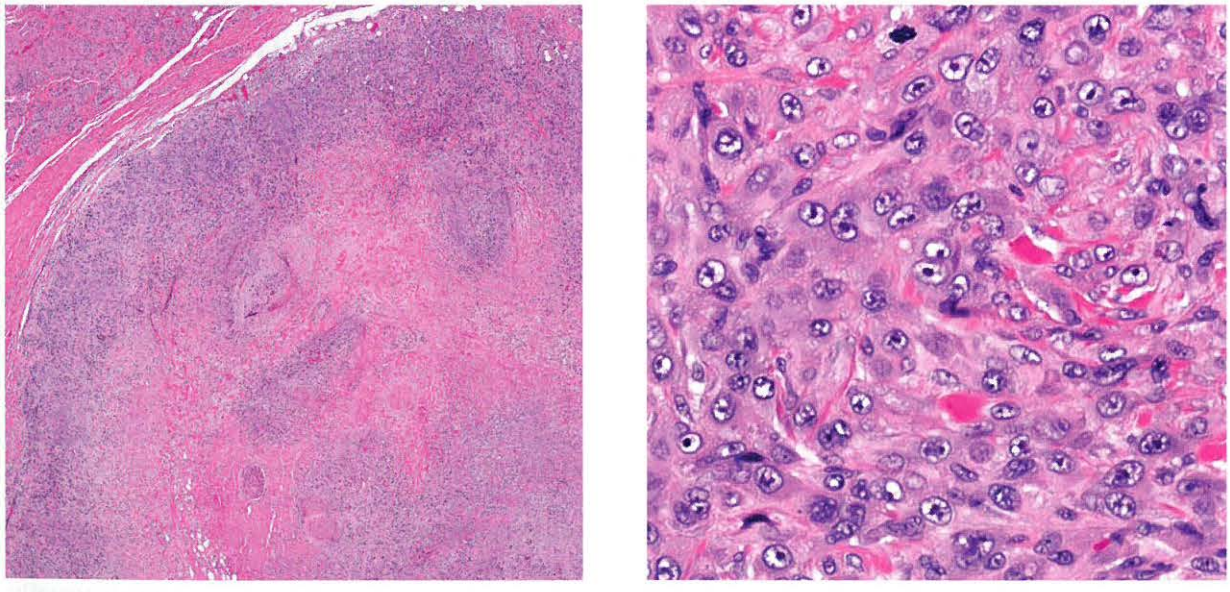


Figure 8-22

EPITHELIOID SARCOMA (MIMICKING RHEUMATOID NODULE)

Left: The presence of central zones of necrosis in this rare sarcoma can resemble a palisaded necrobiotic granuloma at low magnification, making it a treacherous mimic of deep GA or rheumatoid nodule.

Right: The tumor cells have abundant dense pale or eosinophilic cytoplasm, which can give them a histiocytoid (or even squamoid) appearance. Unlike the histiocytes of deep GA or rheumatoid nodule, these tumor cells have large atypical nuclei, often with pale/cleared chromatin.

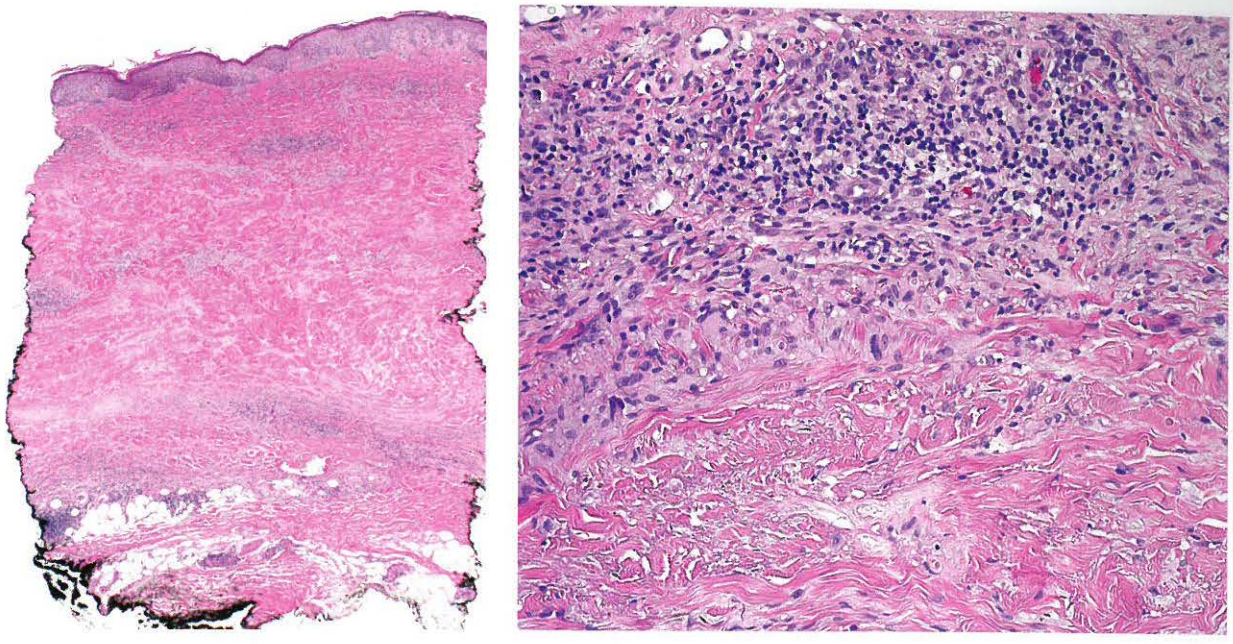


Figure 8-23

NECROBIOSIS LIPOIDICA (NLD)

Left: The dermis is replaced by alternating layers of fibrosis, necrobiosis, fibrin, and mixed inflammation with prominent plasma cells. The appearance has been likened to a parfait or layered cake, although some cases (like this one) do not have very many layers. The process is mostly centered in the dermis although it often extends down into the subcutis as well.

Right: Zones of necrobiosis (bottom) are layered between zones of lymphoplasmacytic and histiocytic infiltrate (top).

epithelioid sarcoma, so mitotic activity by itself is not necessarily a worrisome finding. If there is any doubt, immunostains can easily resolve it: epithelioid sarcoma expresses cytokeratin and EMA and shows loss of nuclear INI-1/SMARCB1 expression (6). It is important to keep this very rare but very bad sarcoma in your differential anytime you see a case of deep GA or rheumatoid nodule. Pitfalls are called pitfalls because we don't see them coming. We must anticipate them so that we are vigilant and not caught unaware.

Necrobiosis Lipoidica

Necrobiosis lipoidica (diabeticorum) (NLD) presents as a yellowish atrophic plaque usually on the anterior lower leg of adults, often in the setting of diabetes. Since some patients actually do not have diabetes, the recent trend has been to drop the "diabeticorum" from the name. The dermis is replaced by alternating layers of fibrosis, necrobiosis, fibrin, and mixed inflammation with prominent plasma cells (fig. 8-23). The appearance has been likened to a parfait or layered cake. The process is mostly centered in the dermis and does not usually have multinodular subcutaneous granulomas, which in addition to the classic clinical appearance, helps distinguish it from deep GA or rheumatoid nodule.

Necrobiotic Xanthogranuloma

Necrobiotic xanthogranuloma (NXG) is a very rare disease that presents in older adults as yellowish papules, nodules, or plaques, classically in the periorbital area but also at other sites. It is usually associated with paraproteinemia (usually monoclonal IgG kappa), and some patients have underlying myeloma or B-cell lymphoma.

Granulomatous infiltrates alternating with zones of eosinophilic necrobiosis fill the dermis and extend into the subcutis. Foamy histiocytes, Touton giant cells, and foreign body giant cells are present in the infiltrate. Characteristically, the giant cells have bizarre angulated shapes and numerous hyperchromatic nuclei. Asteroid bodies are common. Cholesterol clefts are often seen (fig. 8-24).

If a biopsy looks like a very robust florid case of NLD, think about NXG in your differential

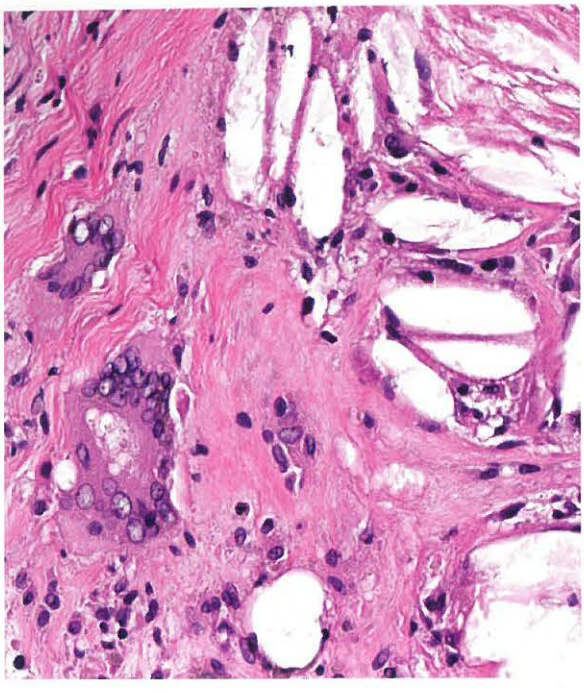


Figure 8-24

NECROBIOTIC XANTHOGRANULOMA (NXG)

Cholesterol clefts (top right) and large, often bizarre, multinucleated giant cells (bottom left) are characteristic features of NXG. Otherwise, it resembles NLD.

diagnosis. The unique giant cells, abundance of lipid material (both foamy histiocytes and cholesterol clefts), and clinical scenario together are usually enough to distinguish NXG from NLD (2). In difficult cases, more clinical information, a larger repeat biopsy, and serum/urine protein electrophoresis may help make the distinction.

VASCULITIS PATTERN

Leukocytoclastic vasculitis (LCV) is neutrophil-mediated destruction of small dermal blood vessels. There are three major microscopic features: 1) neutrophilic infiltrate around vessels with nuclear dust/debris (leukocytoclasis), 2) fibrinoid necrosis of vessel walls often with endothelial swelling, and 3) hemorrhage of erythrocytes into the dermis (fig. 8-25). Fibrin thrombi may be present within some of the damaged vessels. Vasculitis may occur as a superficial process limited to the skin (*cutaneous LCV*) or it may be seen in the skin as a secondary manifestation of systemic vasculitides, including *Henoch-Schönlein purpura* (HSP), *levamisole-induced vasculitis* (from cocaine use), *mixed-type (type II or III) cryoglobulinemia, eosinophilic granulomatosis with polyangiitis* (aka *allergic granulomatosis* or

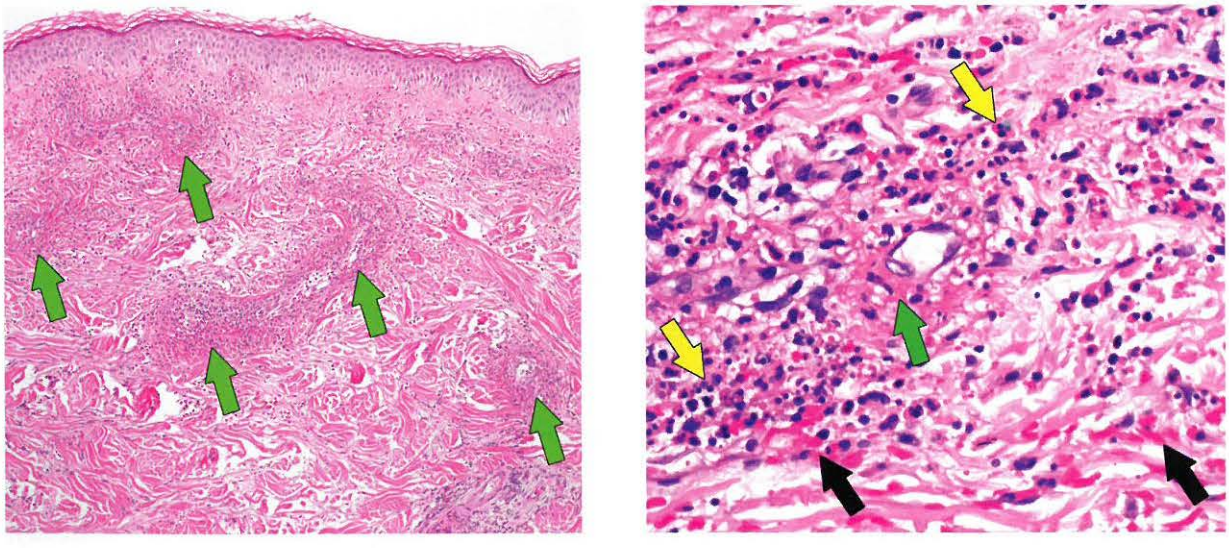
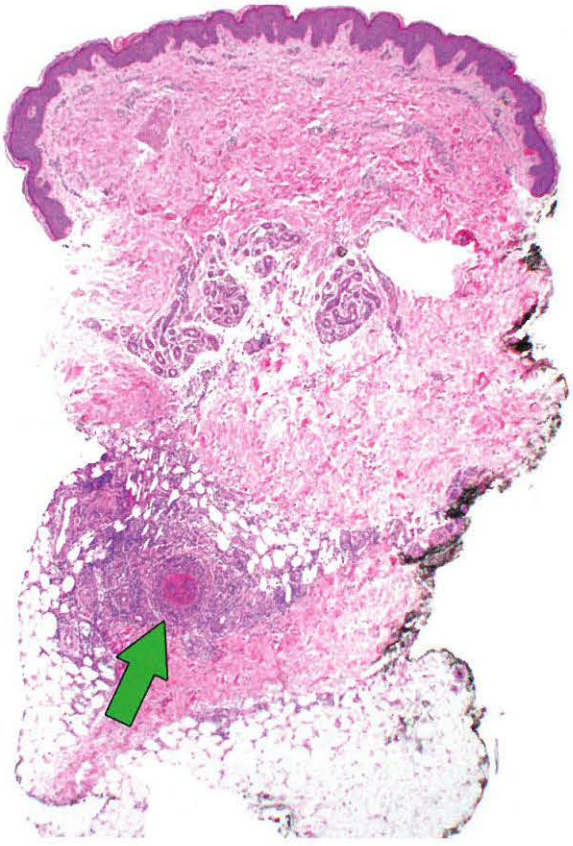


Figure 8-25

LEUKOCYTOCLASTIC VASCULITIS (LCV)

Left: Fibrin and neutrophils around damaged blood vessels (arrows) usually can be appreciated even at low magnification.

Right: A small blood vessel (center) is surrounded by homogenous pink fibrin (green arrow) and extravasated erythrocytes (black arrows), evidence of vascular damage. The neutrophils and fragments of nuclear debris (yellow arrows) are evidence that the vascular damage is due to leukocytoclasis.



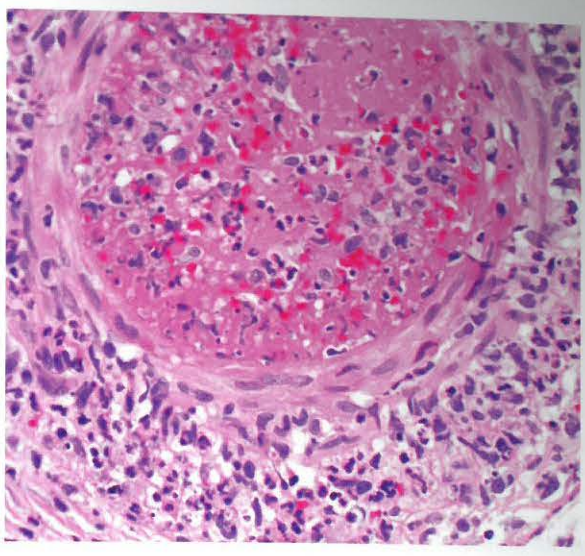


Figure 8-26

POLYARTERITIS NODOSA (PAN)

Left: Inflammation surrounds a medium-sized muscular artery at the dermal-subcutaneous junction (arrow). Unlike LCV, there is usually only a solitary vessel involved on a punch biopsy specimen.

Above: Neutrophils infiltrate the muscular wall of the artery. In this case, the vessel lumen is filled with fibrin thrombus.

Churg-Strauss syndrome), and *granulomatosis with polyangiitis (Wegener granulomatosis)*.

Microscopic clues that raise suspicion for systemic vasculitis are LCV that is so brisk as to cause bullae or epidermal necrosis or LCV that involves the deep dermal or subcutaneous vessels. If LCV has many eosinophils, Churg-Strauss syndrome or a drug-induced LCV may be considered. If LCV is seen in conjunction with granulomatous dermatitis, Churg-Strauss or Wegener syndrome may be considered and clinical workup including ANCA studies should be undertaken. Polyarteritis nodosa (PAN) is a unique form of vasculitis that involves a medium-sized muscular artery at the dermal-subcutis junction rather than the small superficial dermal vessels (fig. 8-26).

Pigmented purpuric dermatosis (PPD), also known as *capillaritis*, sometimes enters the clinical differential of LCV. It presents as multiple tiny erythematous to orange-brown "cayenne pepper" macules, usually on the anterior lower legs. Biopsy shows superficial perivascular lymphocytic infiltrate with extravasated erythrocytes and hemosiderin deposition, but neutrophils or LCV are not seen (fig. 8-27). Hemosiderin deposits may be focal and subtle; an iron stain may help in identifying them. I sometimes see cases that I believe fit with PPD clinically and histologically but lack hemosiderin. Vascular stasis and ecchymosis can show hemorrhage and hemosiderin and thus resemble PPD microscopically, but PPD will usually have more prominent perivascular lymphocytic infiltrate than stasis or ecchymosis.

THROMBOTIC VASCULOPATHY PATTERN

Thrombotic vasculopathy refers intravascular thrombi (without LCV) in the dermis (fig. 8-28), which is usually caused by a hypercoagulable state. Type I cryoglobulinemia produces a similar microscopic appearance, although the vessel lumens are actually filled with bright pink cryoglobulin deposits (sometimes alongside fibrin thrombi). When I find luminal thrombi in the dermis, I routinely include a comment that laboratory workup is needed to rule out systemic coagulopathy or cryoglobulinemia.

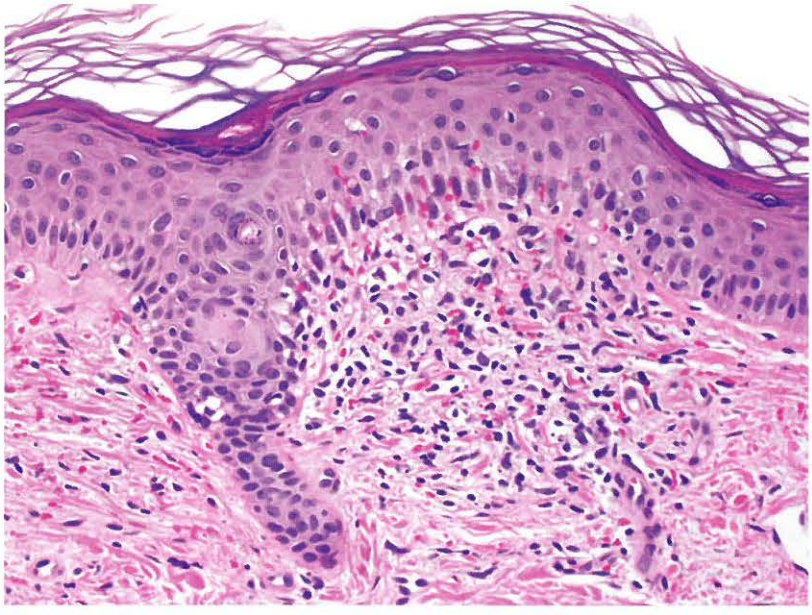


Figure 8-27

PIGMENTED PURPURIC DERMATOSIS (PPD)

Lymphocytes surround small vessels in the papillary dermis as well as scattered extravasated erythrocytes. Hemosiderin deposition is usually present (not shown here).

PANNICULITIS PATTERN

Panniculitis refers to inflammation of the subcutaneous fat. The clinical presentation varies depending upon the type of panniculitis. Classically, panniculitis is subdivided into lobular and septal patterns based on where the inflammation is predominantly located (mostly within the fat lobules versus mostly in the intervening septa between the lobules). I do not find this concept to be very helpful, since aside from erythema nodosum (which usually is indeed a strikingly septal pattern), most other cases of panniculitis show a mixture of these patterns. There are other microscopic clues that I find more useful, and of course, the clinical impression is often crucial. Some important examples of panniculitis and related diseases include erythema nodosum, lupus panniculitis, lipodermatosclerosis, pancreatic fat necrosis, calciphylaxis, alpha-1 antitrypsin deficiency panniculitis, and post-traumatic fat necrosis.

One problem that I often encounter is a clinical suspicion for panniculitis but a punch biopsy that has minimal or no subcutis present for evaluation. In such a case, I describe whatever findings are present, but I also explicitly state that there is no/minimal subcutis present and thus evaluation for panniculitis is not possible on this biopsy and that if further evaluation for panniculitis is needed, a wedge/incisional biopsy or a "double punch" ("telescoping") biopsy may be helpful (7). Wedge/incisional biopsy is the most ideal for evaluating panniculitis, but as this type of biopsy is more time consuming and difficult to perform clinically, I rarely receive this type of specimen in my practice. With a double punch biopsy, the dermatologist takes a punch biopsy like usual, but then performs a second punch in the same biopsy hole allowing a plug of subcutaneous fat to be removed. Ask your dermatologists to notify you on the requisition sheet when they perform this procedure so that the second piece of fat is not inadvertently overlooked in the specimen container during gross examination.

Erythema Nodosum

Erythema nodosum is a common panniculitis that typically arises as multiple erythematous indurated tender nodules on the lower extremities, often in young women. Oral contraceptives, various infections, and many other associations and potential etiologies have been reported (2).

Histologically, erythema nodosum is the classic example of septal panniculitis. The subcutaneous septa are expanded by a mixed inflammatory infiltrate composed of lymphocytes, histiocytes, and sometimes eosinophils (fig. 8-29). Although the infiltrate is predominately in the septa, it often also spills over into the fat lobules (again, this is why I do not love the septal versus lobular pattern approach to panniculitis). Small granulomas and giant cells are often seen in the septa.

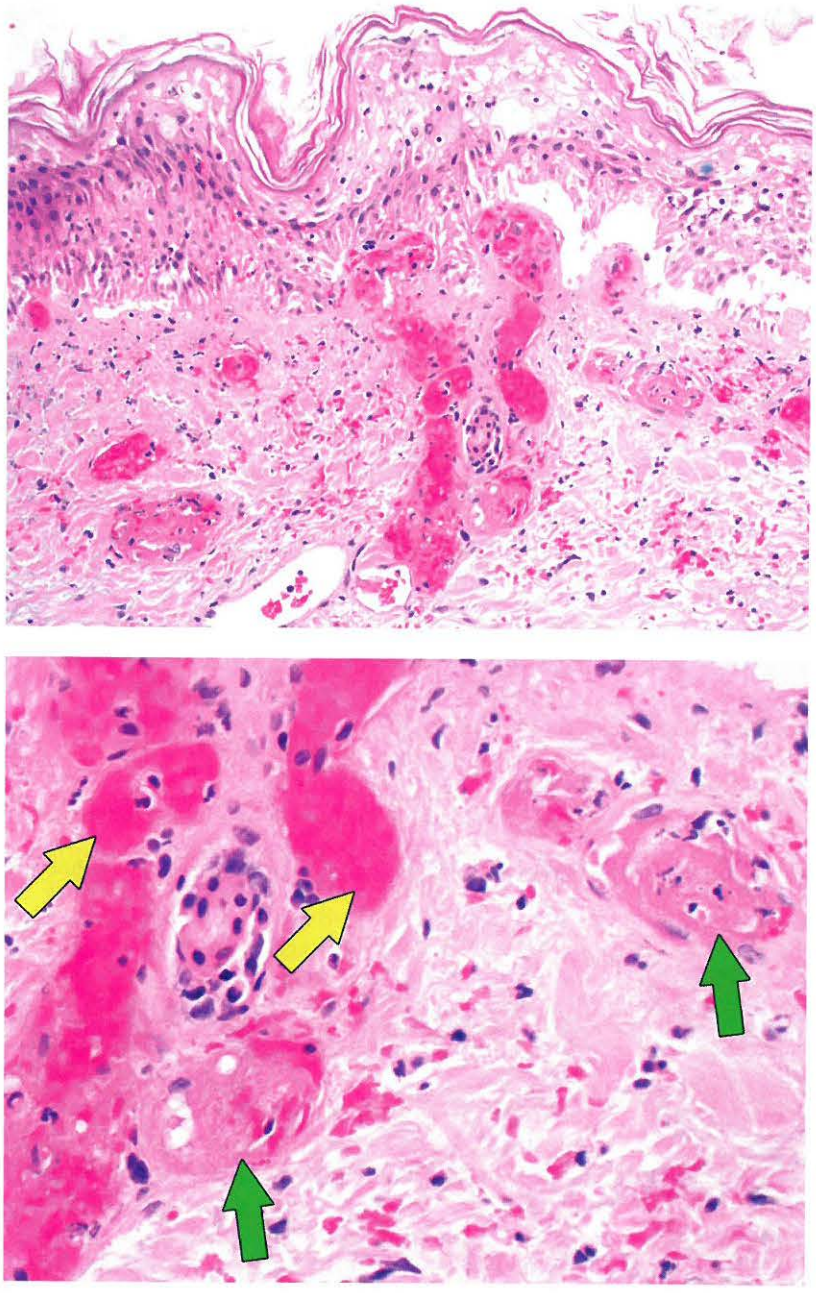


Figure 8-28

THROMBOTIC VASCULOPATHY

Top: Epidermal necrosis (pale pink "washed-out" appearance due to degeneration and loss of keratinocyte nuclei) is a crucial clue for acute ischemia in the skin. The multiple fibrin thrombi filling dermal vessels are evidence that the ischemia in this case is due to thrombotic vasculopathy. Urgent clinical workup for coagulopathy is essential.

Bottom: Contrast the homogenous smudgy pale pink luminal fibrin thrombi (green arrows) with the brighter deeper pink/red of erythrocytes in the adjacent congested blood vessels (yellow arrows). Flipping the microscope condenser will often allow the individual erythrocyte outlines to be visualized in congested vessels, avoiding confusion with true fibrin thrombi.

Hemorrhage is typically present, and zones of fibrinoid necrosis may also be seen. Neutrophils may be present in early lesions. Septal fibrosis is common in older lesions (2).

Lupus Panniculitis

Lupus panniculitis (lupus erythematosus profundus) is seen in a subset of patients with DLE or SLE. In many patients, no other features of lupus erythematosus are present. It presents as firm painful nodules, often on the breast, outer upper arms, face, back, or buttocks. The overlying skin may be normal or have features of DLE. Lupus panniculitis is often chronic and recurrent; lesions may resolve forming depressed scars with fat atrophy (2).

The histologic appearance is very characteristic. There is a brisk infiltrate of lymphocytes and plasma cells in the deep dermis and subcutis, sometimes with germinal center formation. In well-developed lesions, there is diffuse dense

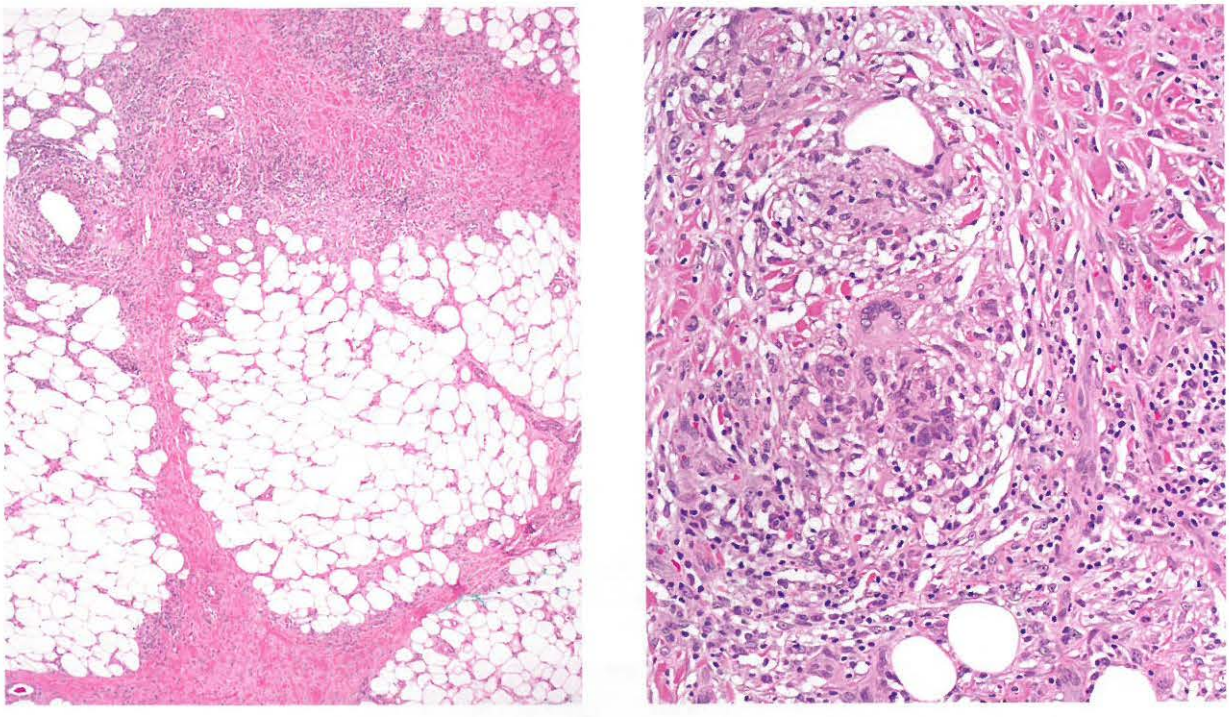


Figure 8-29

ERYTHEMA NODOSUM (EN)

Left: This is the classic example of septal panniculitis. The subcutaneous septa are expanded by a mixed inflammatory infiltrate and fibrosis.

Right: Small granulomas and giant cells are often seen in the septa accompanied by an infiltrate composed of lymphocytes, histiocytes, and sometimes eosinophils.

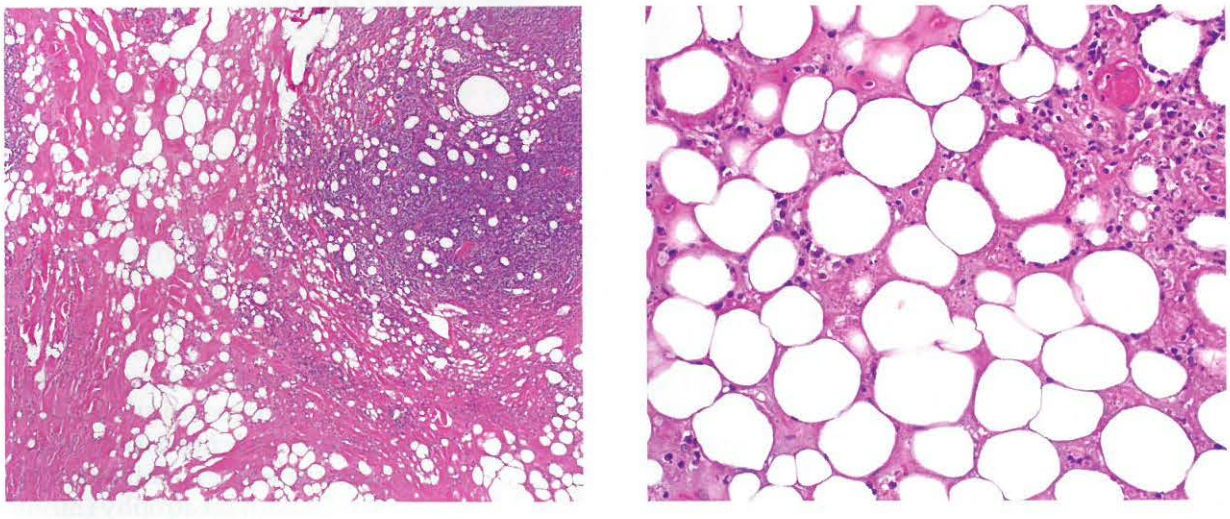
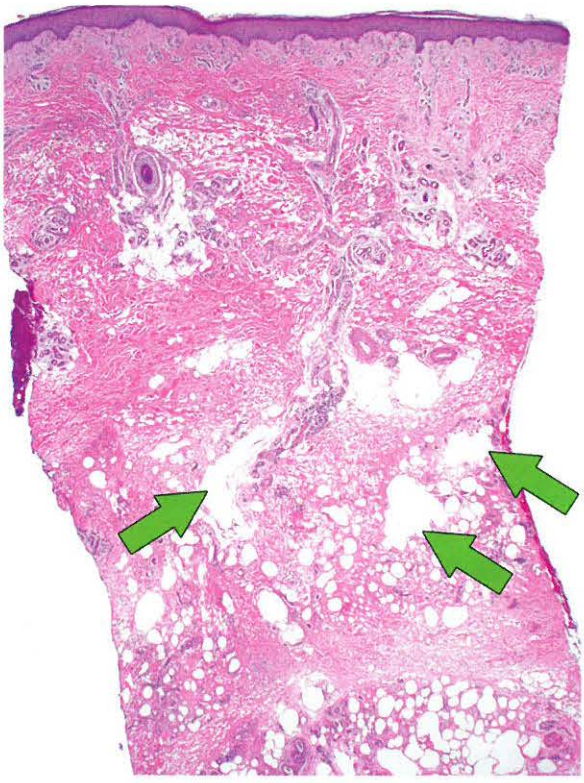


Figure 8-30

LUPUS PANNICULITIS

Left: The subcutaneous fat is diffusely hyalinized and eosinophilic due to a mixture of sclerotic collagen and fibrinoid necrosis. There is a brisk infiltrate of lymphocytes and plasma cells.

Right: Fibrin and nuclear debris are present between the adipocytes.



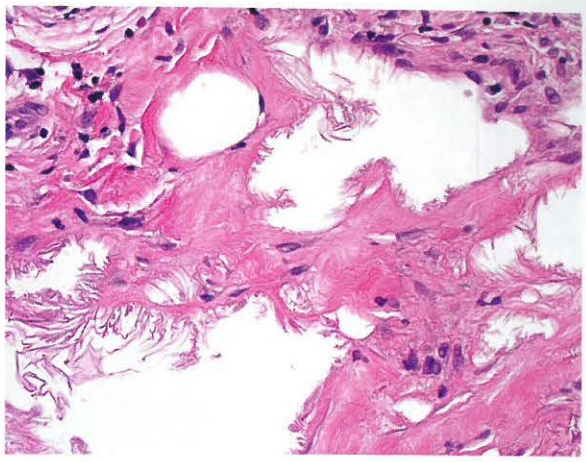


Figure 8-31

LIPODERMATOSCLEROSIS

Left: The papillary dermis shows stasis vascular changes. There is diffuse fibrosis of the dermis and subcutis. Microcystic spaces of fat necrosis (arrows) are present in the subcutis.

Above: The fat necrosis has a unique "arabesque" pattern: small pseudocystic areas are lined by tiny frilly infolded fronds of eosinophilic material representing broken down adipocyte membrane remnants (lipomembranous change).

eosinophilic hyalinization intermingled with the adipocytes, representing sclerotic collagen and fibrinoid necrosis (fig. 8-30). Nuclear debris is often present. Vascular damage and hyalinized vessels may be seen (2). The overlying dermis and epidermis may be normal or may show features of conventional lupus erythematosus, as discussed previously.

The most important entities in the differential diagnosis are panniculitis-like T-cell lymphoma (alpha-beta) and gamma-delta T-cell lymphoma, both of which show a panniculitis-like pattern of subcutaneous involvement that can mimic lupus panniculitis (see chapter 11). Additionally, other connective tissue diseases can show panniculitis with similar features to lupus panniculitis (2).

Lipodermatosclerosis

Lipodermatosclerosis (sclerosing panniculitis, membranous lipodystrophy) is a chronic form of fat necrosis with scarring and atrophy that arises in adults with venous stasis. It presents as very firm ("woody") atrophic plaques of the bilateral lower legs. The atrophy of the distal lower leg with relative sparing of the proximal portion gives the lower leg an "inverted champagne bottle" appearance (2). The dermis is often fibrotic with obvious stasis vascular changes (see fig. 2-19). The subcutis shows ischemic changes, foamy histiocytes, microcystic fat necrosis, septal fibrosis, and eventually in chronic lesions, fat atrophy with sclerosis of the subcutis.

The fat necrosis in this disease has a unique pattern, with small pseudocystic areas lined by minute infolded fronds of eosinophilic material representing broken down adipocyte membrane remnants (fig. 8-31). This frilly "arabesque" pattern, referred to as membranous fat necrosis or lipomembranous change, is a characteristic finding in lipodermatosclerosis, but it may also be seen in fat necrosis from other causes (such as trauma).

Pancreatic Fat Necrosis

Pancreatic fat necrosis (pancreatic panniculitis) presents as very painful erythematous nodules on the trunk or lower extremities of patients with pancreatitis, pancreatic carcinoma, or other pancreatic diseases. Increased levels of circulating lipase and other pancreatic enzymes lead to destruction of the subcutaneous fat with

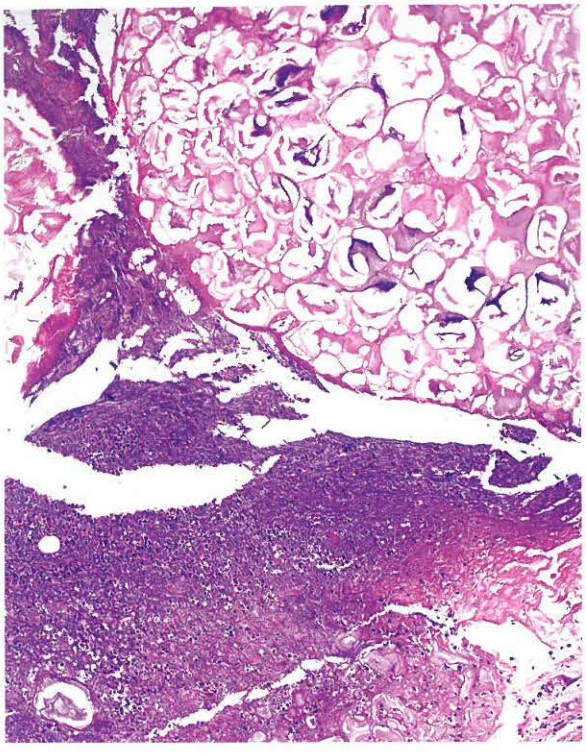


Figure 8-32

PANCREATIC FAT NECROSIS (PANCREATIC PANNICULITIS)

The subcutis shows zones of fat necrosis with retained outlines of individual necrotic adipocytes ("ghost cells") (top). Calcification is deposited directly onto the necrotic fat, giving it a unique bluish-purple color (saponification). Neutrophils, nuclear dust, and necrotic debris with fine calcification are also present (bottom).

zonal fat necrosis and associated saponification (essentially, soap formation due to calcium combining with the free lipid from the necrotic adipose tissue) (fig. 8-32). These lesions often ulcerate and drain yellowish necrotic fat material.

Histologically, there is zonal necrosis of fat in the subcutis with retained outlines of individual necrotic adipocytes ("ghost cells"). Stippled bluish-purple calcification is deposited onto the necrotic fat (saponification). There is surrounding hemorrhage and inflammation, including neutrophils and foamy histiocytes. The microscopic features are identical to those seen in the peripancreatic fat in acute pancreatitis. Clinical and laboratory workup are essential to identify the cause if the patient has no known previous diagnosis of pancreatitis or other pancreatic disease. Due to the serious nature of the underlying pancreatic diseases, there is significant mortality in these patients (2).

Calciphylaxis

Calciphylaxis usually occurs in end stage renal disease patients who are on dialysis, although it can rarely present in patients without renal disease. It is a very serious disease with high morbidity and mortality: 50 to 80 percent of patients die within a year of diagnosis. Calcium deposits within the walls of blood vessels in the subcutis lead to ischemia and skin infarction. These infarcts present clinically as extremely painful, violaceous plaques or ulcerated eschars, often on adipose-rich areas of the body (breast, buttock, abdomen, thighs) as well as the lower legs (1).

Histologically, the key to the diagnosis is the presence of calcification in the walls of small and medium-sized vessels in the subcutis (fig. 8-33). In some cases, these are obvious and abundant, but more often they are very focal and subtle, requiring careful searching, deeper levels, or von Kossa stain to identify them. These subtle cases may show only tiny stippled basophilic calcium deposits in the subcutaneous vessel walls, in subcutaneous adipose tissue between adipocytes, and around eccrine coils. Aside from the calcification, there are other histologic clues to the diagnosis. Acute ischemic changes such as necrosis of the epidermis, eccrine coils, and dermis may be seen, including full-thickness zonal skin infarction if the center of an eschar is biopsied. Lobular reactive vascular proliferations (dermal angioplasia or diffuse dermal angiomatosis) due to chronic ischemia are a common finding in the reticular dermis. In the clinical scenario described above, finding these vessels alone, even without calcifications seen on the biopsy, is strongly suggestive of calciphylaxis. Fibrin thrombi are often present in dermal or subcutaneous vessels (1).

It is important to note that calcification can be seen in vessel walls in scenarios other than calciphylaxis, most notably *Mönckeberg arteriosclerosis (medial calcific sclerosis)*, in which calcifications are present in the muscular media layer of arteries (fig. 8-34). Mönckeberg arteriosclerosis may occasionally be seen in the subcutis as an incidental finding of little or no clinical significance. In calciphylaxis, the calcification usually involves small capillary vessels in addi-

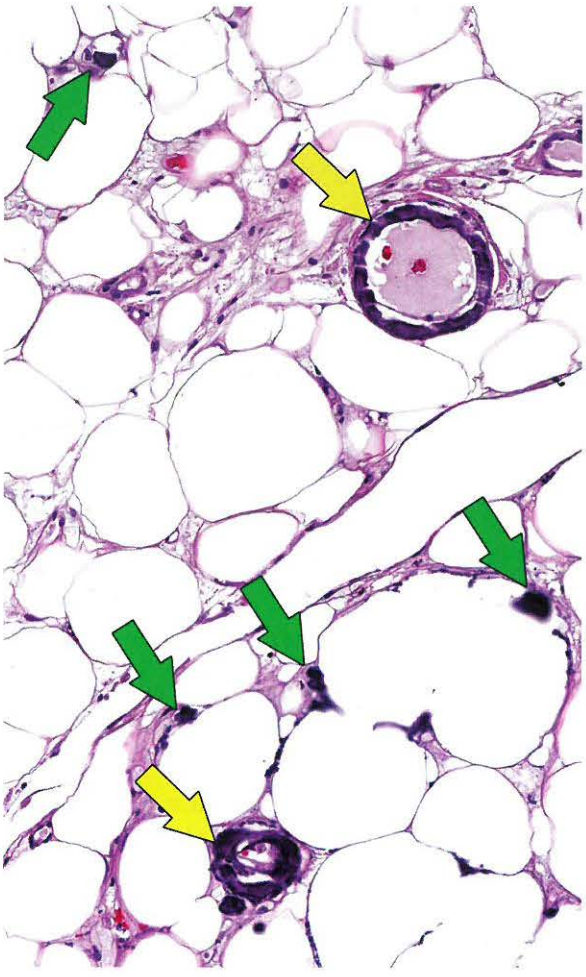


Figure 8-33

CALCIPHYLAXIS

The classic feature is calcification in the walls of small subcutaneous vessels (yellow arrows). Not all cases are this dramatic and obvious. The calcifications may also take the form of tiny granules between the necrotic adipocytes (green arrows).

tion to medium-sized vessels, ischemic changes will be present, and most importantly, the clinical scenario will fit. I have never seen calciphylaxis show up as merely an incidental finding.

Traumatic Fat Necrosis

Traumatic fat necrosis can be seen after blunt trauma or other injury. Pockets of foamy histiocytes are present in the subcutis (see fig. 2-12E), sometimes with hemorrhage, hemosiderin, and in early lesions, neutrophils. Sometimes a nodule of completely necrotic fat can become walled-off by fibrosis and develop cystic change. Fat necrosis may also be seen at drug injection sites or in patients with factitial disease. Examination under polarized light may identify any polarizable foreign material and is strong support for injection or other penetrating injury as the etiology (2).

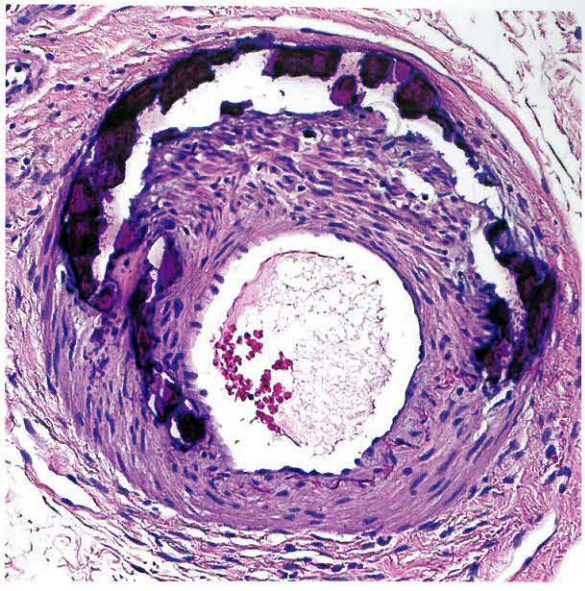


Figure 8-34

MÖNCKEBERG ARTERIOSCLEROSIS (MEDIAL CALCIFIC SCLEROSIS)

Large calcifications are present in the muscular wall of a subcutaneous artery. This case was an incidental finding in a melanoma excision specimen. Do not confuse this with calciphylaxis!

MISCELLANEOUS DISEASES

Granuloma Faciale

Granuloma faciale is an unusual inflammatory process that arises as one or several red to brown nodules or plaques on the face of adults. Histologically, these are composed of a diffuse dense dermal infiltrate of lymphocytes, histiocytes, eosinophils, and neutrophils (fig. 8-35). The name is a misnomer; there are no actual granulomas in granuloma faciale. The infiltrate is classically separated from the overlying epidermis by a thin band of uninvolved dermis (i.e., a Grenz zone; this is one of the few diseases where I actually find the Grenz zone to be a useful feature). The key to the diagnosis is the presence of multiple different inflammatory cell types all intermingled together, particularly the neutrophils.

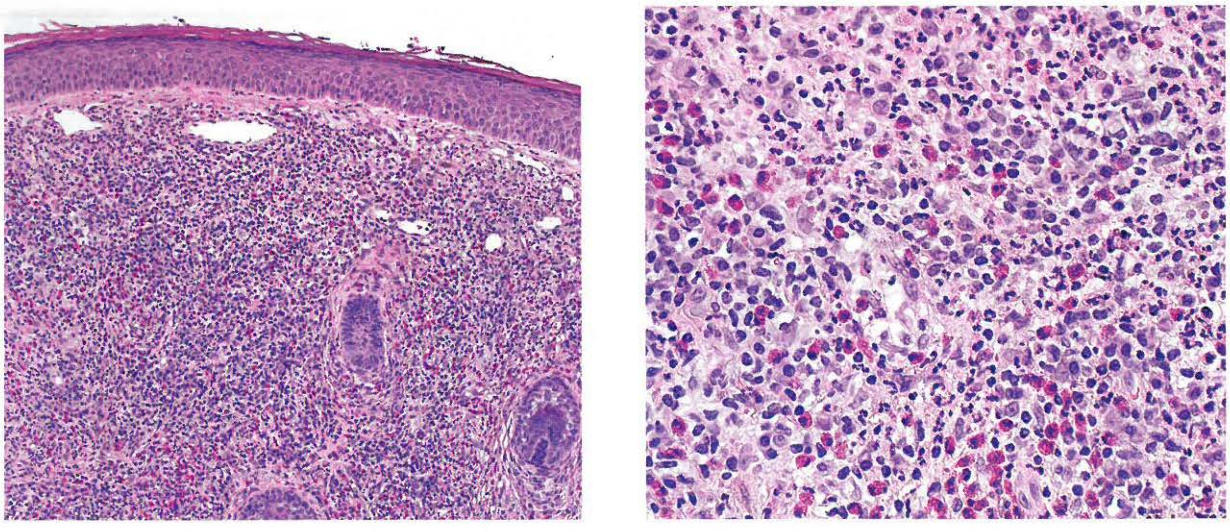


Figure 8-35

GRANULOMA FACIALE

Left: The dermis is replaced by a diffuse dense mixed inflammatory infiltrate. A thin "Grenz zone" of uninvolved dermis separates the infiltrate from the overlying epidermis.

Right: The infiltrate is usually composed of lymphocytes, histiocytes, eosinophils, and neutrophils. This unusual mixture of inflammatory cell types, particularly the intermingled neutrophils, is the key to recognizing this entity. Despite the name, there are no granulomas.

Granuloma faciale is actually thought to represent a localized form of leukocytoclastic vasculitis. Fibrin, hemorrhage, vascular damage, and neutrophil nuclear dust are often present, although they may be subtle (2).

Sweet Syndrome

Sweet syndrome (*acute febrile neutrophilic dermatosis*) is an acute-onset inflammatory disease that presents with tender, erythematous "juicy" papules on the head and neck and upper extremities (especially dorsal hands), usually in adults. Patients appear ill with systemic symptoms including fever, joint pain, and leukocytosis. Sweet syndrome is sometimes associated with underlying malignancy, particularly acute myeloid leukemia (AML). Histologically, there is prominent papillary dermal edema and a diffuse dermal infiltrate of neutrophils (fig. 8-36).

The main differential diagnosis clinically and pathologically is infection; this should be excluded by microbial cultures and special stains. The distinction is very important clinically, as Sweet syndrome is treated with high-dose corticosteroids, which is exactly the opposite of how an infection would be treated. Other neutrophilic dermatoses, including pyoderma gangrenosum, can show similar histologic findings to Sweet syndrome; clinical information is crucial to making the diagnosis.

Histiocytoid Sweet syndrome is a variant of Sweet syndrome in which the infiltrate is composed of histiocytoid cells instead of mature neutrophils. These histiocytoid cells stain with myeloperoxidase, making them a very close mimic for the immature myeloid cells of AML. Histiocytoid Sweet is complicated and outside the scope of this book, but readers should be aware of this pitfall, as it is a close mimic of leukemia cutis both clinically and histologically (1).

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is a noninfectious neutrophilic dermatosis that presents with rapidly growing ulcers that are often difficult to treat, chronically recurrent, and very morbid to the patient. An underlying systemic disorder is present in at least 50 percent of PG patients, including inflammatory bowel disease (most common), arthritis, or hematologic malignancies (most often AML).

PG begins as tender violaceous pustules/nodules that quickly evolve into cribriform ulcerations with "undermined" borders (1). Unfortunately, the

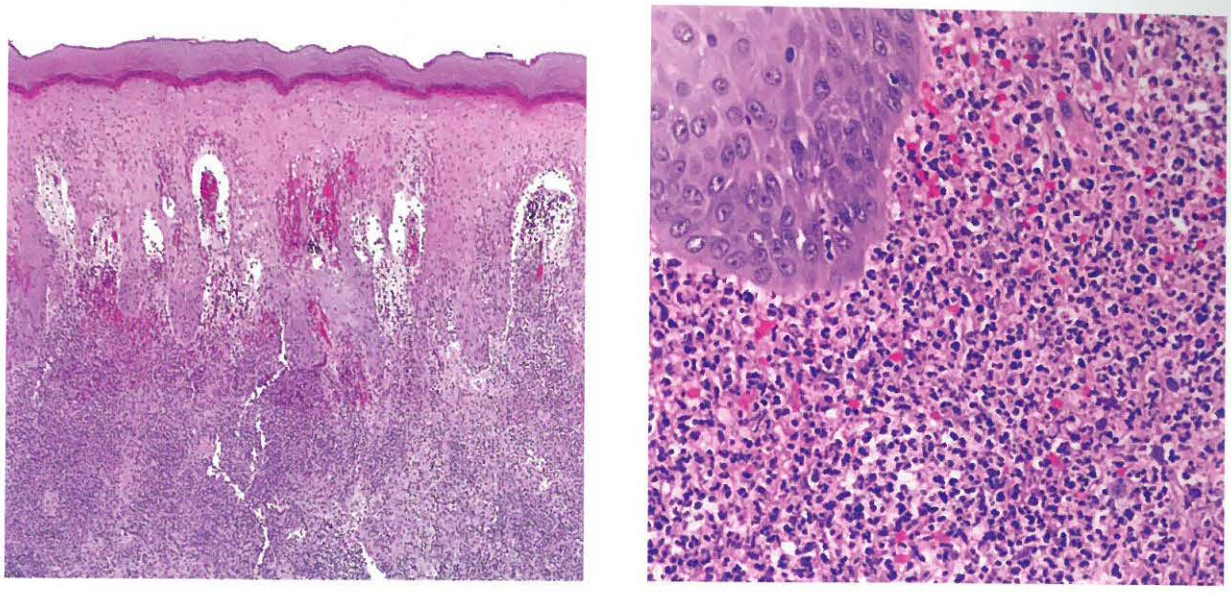


Figure 8-36

SWEET SYNDROME

Left: There is a diffuse dermal infiltrate of neutrophils. Hemorrhage is also present in this case. The dermal papillae are pale and expanded due to prominent papillary dermal edema, which corresponds with the edematous "juicy" clinical appearance of the papules.

Right: The infiltrate is composed of sheets of neutrophils. Infection must be excluded by special stains or culture, as an infectious abscess could have an identical appearance.

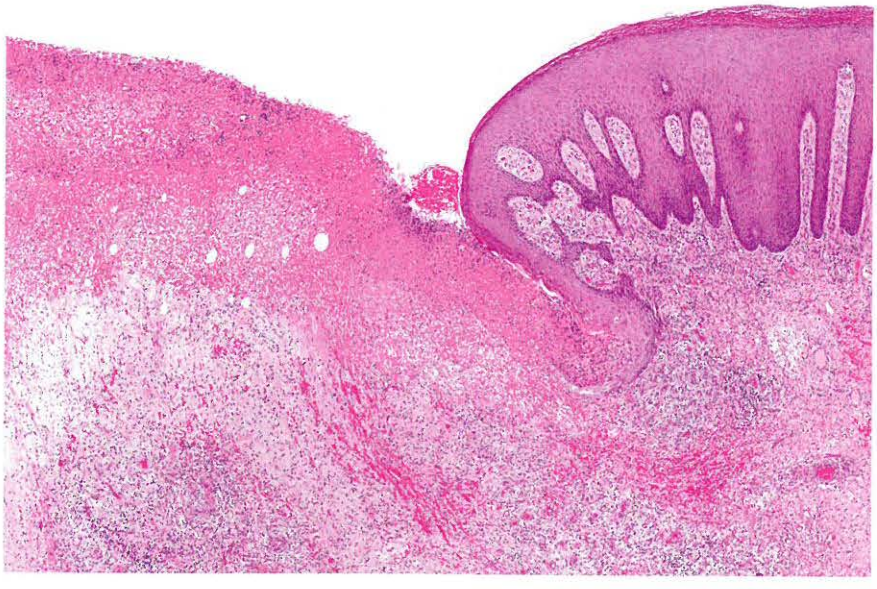


Figure 8-37

PYODERMA GANGRENOSUM

The infiltrate characteristically extends into the dermis underlying the intact skin beyond the edge of the ulcer, which correlates with the undermined ulcer edges and rolled border seen clinically. Usually, there will be sheets of neutrophils in the dermis (identical to fig. 8-36, right), although many cases (like this one) show few neutrophils. This patient had a known history of PG with classic clinical features.

histologic features of PG are nonspecific, making PG a diagnosis of exclusion that requires clinical input by the dermatologist. Early active lesions often show a diffuse dermal infiltrate of neutrophils, sometimes with leukocytoclastic vasculitis (fig. 8-37). These biopsies have features essentially identical to those of infectious abscess. Infectious special stains are needed, and even when these are negative, I add a comment to the report that correlation with microbial cultures is recommended.

In ulcerated lesions with active advancing borders, the infiltrate characteristically extends into the dermis underlying the intact skin beyond the edge of the ulcer, which correlates with the undermined ulcer edges that are seen clinically. Biopsy from the central ulcer bed of chronic longstanding lesions of PG, however, may show only granulation tissue, necrosis, or lymphocytic infiltrate with few or absent neutrophils. These features can be essentially identical to those of nonhealing chronic ulcers from a variety of different etiologies (1). One large study of PG found that the classic neutrophilic infiltrate was only identified in 7 percent of PG cases on biopsy (8). Thus, the diagnosis of PG is essentially impossible to make by histologic features alone.

I rely heavily on the clinical impression of the dermatologist. If they think it is PG, it usually is, unless I can prove it to be something else histologically. The main purpose of biopsy is therefore to exclude other causes of ulcer, such as infection or coagulopathy (1). If a biopsy for "rule out PG" only shows ulcer, mixed inflammation, and granulation tissue but no significant neutrophilic infiltrate, I give a descriptive diagnosis and add this comment: "No classic features of pyoderma gangrenosum are identified; however, some cases of pyoderma gangrenosum can show nonspecific changes on biopsy. If there is continuing clinical concern for pyoderma gangrenosum, a repeat biopsy including the border of the ulcer may be helpful."

Non-dermatologists are often completely unfamiliar with PG and may misdiagnose it clinically as necrotizing fasciitis or infectious abscess. This leads to disastrous consequences as necrotizing fasciitis is treated with antibiotics and surgical debridement, while PG is treated with systemic immunosuppressive therapies such as cyclosporine or high-dose corticosteroids. Furthermore, PG patients often exhibit pathergy phenomenon, meaning that trauma (including surgery) can induce or worsen ulcers. If I suspect PG and the biopsy is from a non-dermatologist, I will raise that possibility in the report and recommend a dermatology consult. Note that "PG" is a common dermatology abbreviation for both pyoderma gangrenosum and pyogenic granuloma (lobular capillary hemangioma); do not confuse these two very different and totally unrelated diseases.

Perforating Disorders

There are a variety of *perforating disorders* in the skin, all of which have the common feature of *transepidermal elimination phenomenon*. In this process, something in the dermis is expelled out of the skin via an invaginated channel through the overlying epidermis. Clinically, these diseases usually demonstrate a nodule with a central plug of debris. Microscopically, there is an invagination of the epidermis, which is sometimes ulcerated at the bottom. Degenerated collagen or elastic fibers (or suture [see fig. 2-44C,D], other foreign material, necrotic dermis or cartilage, depending on which disease it is) are seen "perforating" through the epidermis and accumulating along with keratin debris within the center of the invagination; this correlates with the central plug of debris seen clinically (fig. 8-38).

Examples of perforating disorders include reactive perforating collagenosis, elastosis perforans serpiginosa, and many others. A full discussion of these is outside the scope of the book, but recognizing the perforating pattern and understanding the transepidermal elimination process is important in dermatopathology. Sutures, foreign body granulomas, and some cases of granuloma annulare show secondary perforating/transepidermal elimination. Transepidermal elimination is also a characteristic feature of chondrodermatitis nodularis helicis (see chapter 3).

Lichen Sclerosus

Lichen sclerosus (*et atrophicus*) (LSA) usually presents in the anogenital region of women, particularly involving the labia minora or adjacent regions. Less commonly, it presents in the glans penis or foreskin (*balanitis xerotica obliterans*) where it often results in phimosis in uncircumcised men. Occasionally, it can arise on the trunk or other nonanogenital sites (*extragenital LSA*). In both sexes, the lesions are white papules or plaques with a wrinkled/crinkled surface.

Early inflammatory lesions of LSA show lichenoid dermatitis that can closely resemble lichen planus. As the lesions evolve, a band of homogenized eosinophilic collagen is deposited directly beneath the basal layer (fig. 8-39). As the infiltrate of lymphocytes moves down deeper into the dermis, it leaves behind an ever-widening band of homogenized eosinophilic collagen

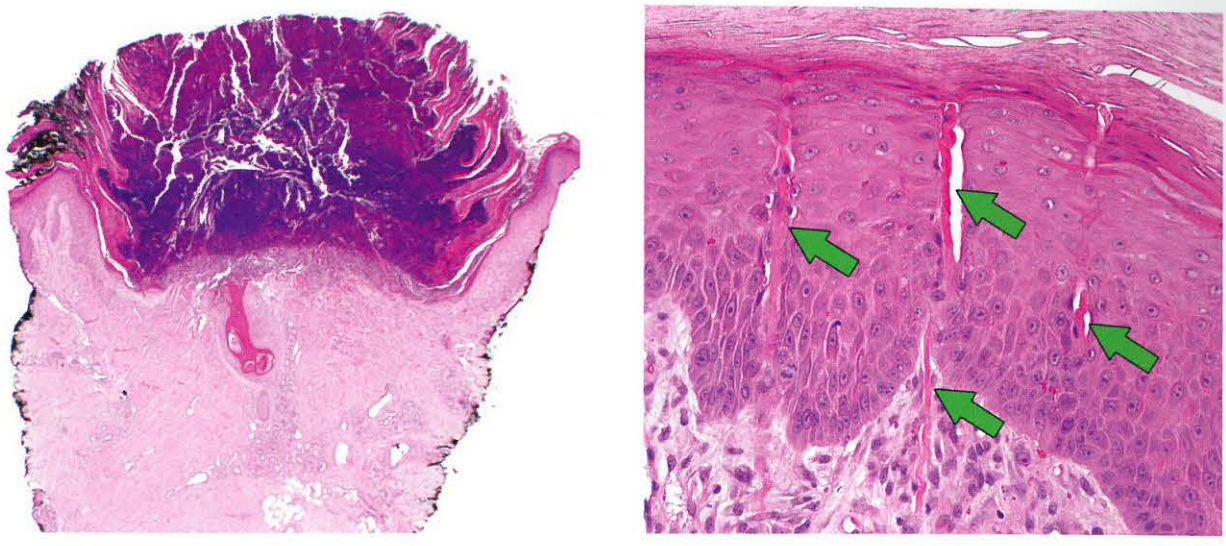


Figure 8-38

PERFORATING DISORDER

Left: There is a cup-shaped epidermal invagination, which is filled with keratin and degenerated debris that often has a dark purple color. This correlates with the central keratotic plug seen clinically.

Right: In this case of reactive perforating collagenosis, pink collagen bundles are seen "perforating" through the epidermis (transepidermal elimination phenomenon) (arrows).

separating the leading edge of inflammation from the overlying epidermis. In well-developed lesions of LSA, there is a thick band of homogenized eosinophilic collagen, but there may only be focal vacuolar change, pigment dropout, and rare dying keratinocytes to hint at the interface dermatitis that gave rise to the whole process. SCC and differentiated vulvar intraepithelial neoplasia (dVIN; a subtle non-human papillomavirus (HPV) form of dysplasia that has a higher risk of transforming into invasive SCC) may arise in a background of LSA (9).

Morphea and Scleroderma

Morphea is essentially a localized form of scleroderma that only involves the skin. It presents as a violaceous plaque, sometimes linear, that eventually becomes white, sclerotic, and atrophic as the disease progresses. It often presents in young adults or children (2).

Early lesions show a lymphoplasmacytic infiltrate in the dermis and increased density of reticular dermal collagen. More advanced lesions show diffuse dense sclerosis of the entire reticular dermis, sometimes with extension into the subcutis (fig. 8-40). The adipocytes that usually surround eccrine coils and hair follicles begin to disappear as the sclerosis "squeezes them out" of the dermis. Eventually, in established lesions, all of the adnexa disappear. A punch biopsy often has a square appearance due to the firm density of the dermis.

It can sometimes be difficult to distinguish the thick dense reticular dermis of normal trunk skin from a subtle case of morphea. The clinical impression helps a lot, as does the presence of plasma cells, the loss of adipocytes around the adnexa, and the loss of the adnexa themselves, all of which support a diagnosis of morphea. The papillary dermis is characteristically spared in morphea, except in cases of "morphea-lichen sclerosus overlap," an entity which shows lichen sclerosus features in the papillary dermis as well as morphea features in the reticular dermis.

Systemic sclerosis (scleroderma) is a severe autoimmune disease that causes tightening of the skin, visceral involvement, and a variety of other manifestations, including CREST syndrome. It has a high morbidity and mortality. The microscopic features can look nearly identical to morphea, except that the lymphoplasmacytic infiltrate tends to be more prominent in morphea (2). Clinical information is crucial to making a diagnosis of systemic sclerosis.

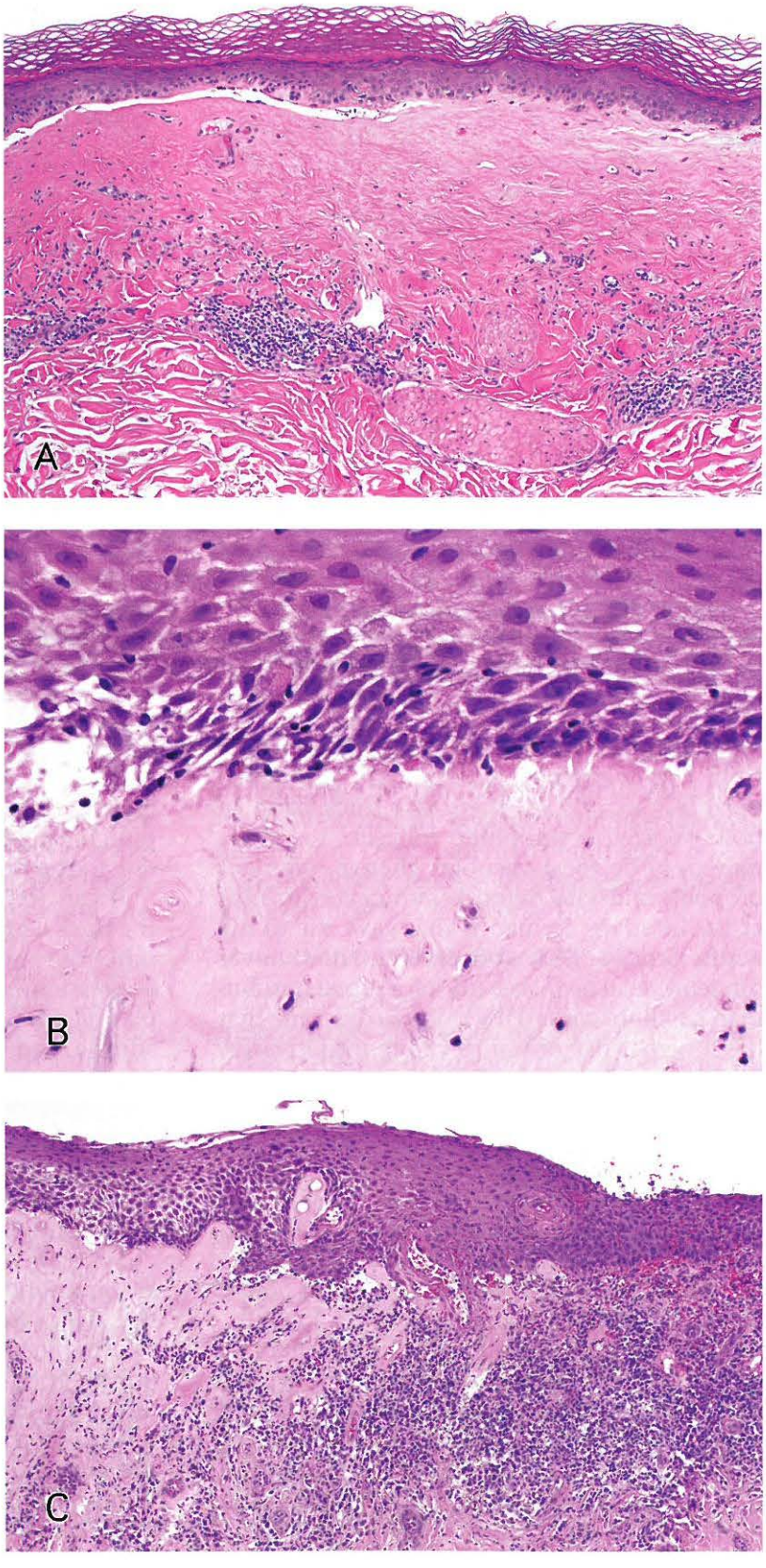


Figure 8-39

LICHEN SCLEROSUS (ET ATROPHICUS) (LSA)

A: There is epidermal atrophy (note the loss of rete) with a broad band of a dense homogenized eosinophilic collagen in the superficial dermis. Directly below this zone of sclerosis is a band of lymphocytes (and histocytes, too, particularly in extragenital LSA). Contrast the sclerotic collagen in the superficial dermis with the normal reticular dermal collagen in the deep dermis (bottom).

B: The papillary dermis is replaced by dense sclerotic collagen, creating a homogenized pink appearance. Subtle vacuolar interface change and scattered apoptotic basal keratinocytes may be seen in some cases, all that is left of the interface dermatitis that gave rise to the whole process.

C: Early inflammatory lesions of LSA show lichenoid dermatitis that can closely resemble lichen planus (right). As the lesions evolve, a band of homogenized eosinophilic collagen is deposited directly beneath the basal layer (left).

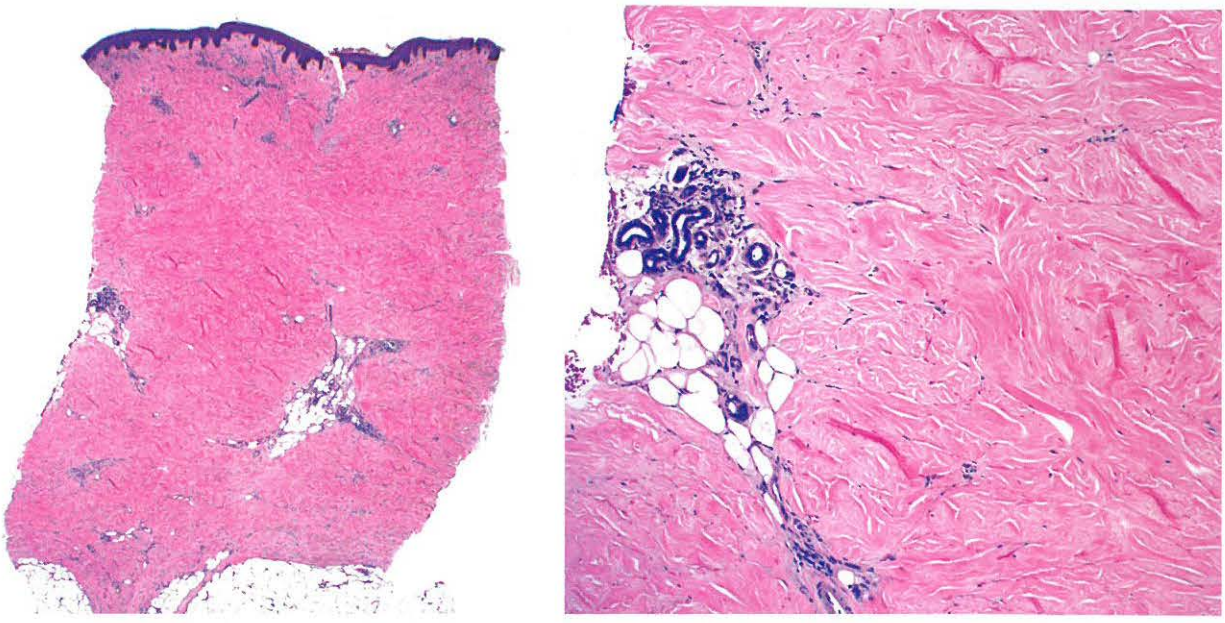


Figure 8-40

MORPHEA

Left: There is diffuse dense sclerosis of the entire reticular dermis, in this case with extension into the subcutis. The papillary dermis is typically spared. At low magnification, a biopsy of morphea can have a similar appearance to normal trunk skin. The paucity of adnexal structures is a clue to the diagnosis.

Right: The reticular dermal collagen bundles are closely packed together (right), creating a somewhat homogenized appearance. A lonely remaining eccrine coil (left) is atrophic; the coil and its surrounding adipocytes are essentially being crushed and squeezed out by the increasingly dense dermal collagen.

REFERENCES

1. Abate MS, Battle LR, Emerson AN, Gardner JM, Shalin SC. Dermatologic urgencies and emergencies: What every pathologist should know. Arch Pathol Lab Med. 2019. [Epub ahead of print]
2. Calonje JE, Brenn T, Lazar A, McKee P. McKee's Pathology of the skin: with clinical correlations, 4th ed. Edinburgh: Elsevier/Saunders; 2012.
3. Rapini RP. Practical dermatopathology, 2nd ed. Philadelphia: Elsevier Saunders; 2012.
4. Romero LS, Kantor GR. Eosinophils are not a clue to the pathogenesis of granuloma annulare. Am J Dermatopathol 1998;20:29-34.
5. Lindberg MR. Diagnostic pathology. Soft tissue tumors, 2nd ed. Philadelphia: Elsevier; 2016.
6. Ha CT, Nousari HC. Surgical pearl: double-trephine punch biopsy technique for sampling subcutaneous tissue. J Am Acad Dermatol 2003;48:609-10.
7. Binus AM, Qureshi AA, Li VW, Winterfield LS. Pyoderma gangrenosum: a retrospective review of patient characteristics, comorbidities and therapy in 103 patients. Br J Dermatol 2011;165:1244-50.
8. van de Nieuwenhof HP, Bulten J, Hollema H, et al. Differentiated vulvar intraepithelial neoplasia is often found in lesions, previously diagnosed as lichen sclerosus, which have progressed to vulvar squamous cell carcinoma. Mod Pathol 2011;24:297-305.

9 BLISTERS

BLISTERS: GENERAL FEATURES

A basic knowledge of the major forms of blistering skin disease (*bullous dermatoses*) and their clinical and histologic features is an essential survival skill in dermatopathology. Small blisters (<0.5 cm) are called vesicles and large blisters (>0.5 cm) are called bullae (1). Skin blisters can be caused by trauma (friction or suction), thermal injury (burning or freezing), excessive edema, congenital defects in epidermal or basement membrane structural proteins, or autoimmune (immunobullous) processes. This chapter will focus mostly on immunobullous diseases since they are the most important to know about for daily practice.

When evaluating a blister microscopically, three major questions must be answered: 1) what is the level of split? 2) what type of inflammatory cells are present and how abundant are they? and 3) is there interface alteration (vacuolar or lichenoid, see chapter 8) in the intact adjacent epidermis? Answering these three questions will greatly narrow down the differential diagnosis, especially when combined with the clinical information.

Blisters occur because of failure of one of the structural elements of the epidermis or basement membrane. It is critical to have a basic understanding of these structural components and how they hold the epidermis together and keep it attached to the underlying dermis. Keratinocytes are attached to one another by desmosomes (the "spines" seen between keratinocytes in the spinous layer). Numerous keratin intermediate filaments (keratins 1 and 10 in the spinous layer and keratins 5 and 14 in the basal layer) span the cytoplasm of keratinocytes, crisscrossing back and forth, attaching the inner aspects of desmosomes to one another. The combination of numerous desmosomes connecting keratinocytes to one another and keratin filaments connecting desmosomes to one another creates a very strong network that allows the epidermal keratinocytes to hold together against the minor frictions and impacts of everyday life.

The basal layer keratinocytes have desmosomes on their tops and sides (which keeps them attached to adjacent basal keratinocytes and to the overlying network of spinous layer keratinocytes) but also have specialized hemidesmosomes on their bottoms. The hemidesmosomes keep the basal layer of the epidermis firmly attached to the underlying basement membrane, which is composed of collagen type IV and other molecules. Collagen type VII anchoring fibrils form hooks or loops that attach the basement membrane to the underlying dermis. Failure of any of these components can lead to a blister.

Which component may have failed can usually be determined by microscopically identifying the layer/level in which the roof of the blister separated from the floor of the blister (i.e., the "level of split"). Most blisters are due to a split occurring: 1) just beneath the basal layer (subepidermal split), 2) just above the basal layer (suprabasilar intraepidermal split), or 3) between the spinous layer and the overlying granular/corneal layers (subcorneal intraepidermal split). A subepidermal blister usually indicates a problem with hemidesmosomes, basement membrane, or anchoring fibrils. An intraepidermal split usually indicates a problem with desmosomes or, less often, with keratin filaments.

A subepidermal blister that has been present for some time can begin to re-epithelialize, making it mimic an intraepidermal blister. True intraepidermal blisters usually show some degree of acantholysis or a single layer of basal keratinocytes that have a hobnail or rounded surface (like the "tombstone" pattern seen in pemphigus vulgaris). Re-epithelialized subepidermal blisters, on the other hand, have multilayered keratinocytes with a smooth surface

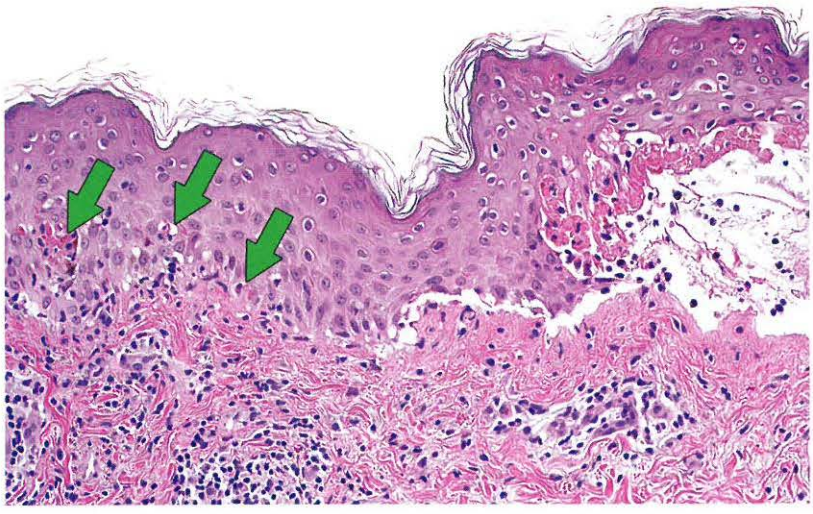


Figure 9-1

BLISTER DUE TO INTERFACE DERMATITIS

Although this blister appears to be subepidermal (right), it is actually due to interface dermatitis. The adjacent intact epidermis at the periphery of the blister (left) shows vacuolar interface change and dying keratinocytes (arrows). This case was bullous erythema multiforme based on the clinical scenario.

lining the floor of the blister and no acantholysis is present (see fig. 2-17).

Interface dermatitis can sometimes be so severe that it produces blistering or sloughing of the epidermis (e.g., Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS/TEN], bullous erythema multiforme, bullous fixed drug eruption, bullous acute graft versus host disease [GVHD]; see chapter 8). Blisters due to interface dermatitis appear subepidermal, but the roof of the blister often has a ragged appearance with variable numbers of dying keratinocytes. However, any blister roof that has been detached for long enough from the underlying dermis (where the epidermis gets its blood supply) may become ischemic and begin to die. Thus, the presence of dying keratinocytes in the blister roof is not enough by itself to prove that the blister is due to interface dermatitis.

The best way to determine if the blister is due to interface dermatitis is to evaluate the intact skin adjacent to the blister cavity to see if vacuolar change and dying keratinocytes are present (fig. 9-1). When the entire biopsy shows only blister, this can be impossible. This is why biopsies should ideally be taken from the edge of a blister or should encompass an entire blister (when the blisters are very small). When intact epidermis is not present in the biopsy, check for any hair follicles or eccrine ducts that may be present. Dying keratinocytes or vacuolar change in the adnexa is a useful clue for interface dermatitis. Also, if a second biopsy of perilesional skin was sent to the lab for direct immunofluorescence (DIF), checking the frozen hematoxylin and eosin (H&E) stain of the DIF specimen can sometimes allow interface dermatitis to be identified. In very difficult cases, the remaining frozen tissue can be thawed, fixed in formalin, processed, and paraffin embedded to produce a higher quality H&E section (only after DIF has been successfully performed and interpreted).

Other inflammatory diseases also produce blisters, usually due to abundant edema. Massive spongiosis (intraepidermal edema) can produce small spongiotic vesicles which appear as irregular intraepidermal blisters microscopically (see fig. 8-1); examples include severe contact dermatitis, dyshidrotic dermatitis (hand eczema), and bullous dermatophytosis (see fig. 7-7). Bullous arthropod bite reactions occur when the inflammatory response produces such massive dermal edema that the epidermis is lifted away from the dermis by the edema fluid, essentially creating a subepidermal blister by force (see fig. 8-13). Any disease that has prominent acantholysis can produce intraepidermal blisters microscopically (although these may not have a bullous appearance clinically), including Grover disease (see fig. 2-32), Darier disease, Hailey-Hailey disease (see fig. 2-34), and herpes infection (see fig. 7-4).

BULLOUS PEMPHIGOID

Bullous pemphigoid (BP) is a relatively common immunobullous disease. It usually arises in elderly patients as tense intact fluid-filled bullae surrounded by background erythema (2). The early urticarial phase of BP may show only

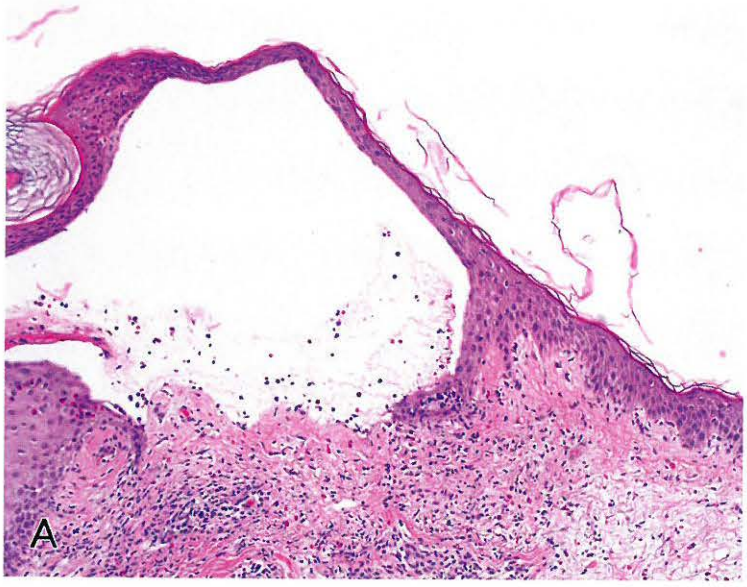


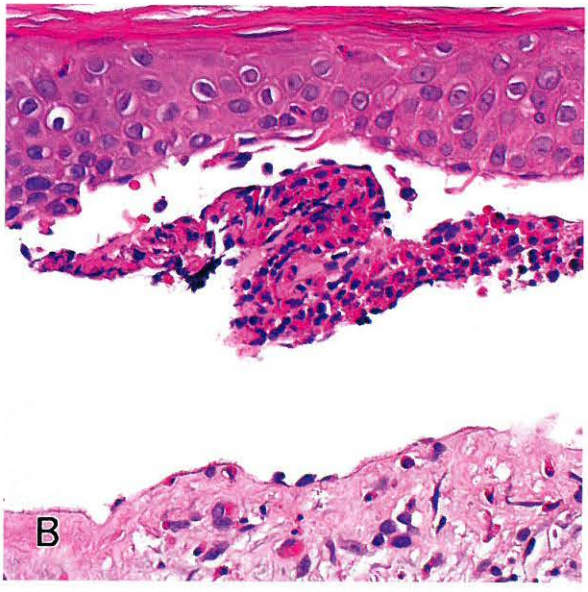
Figure 9-2

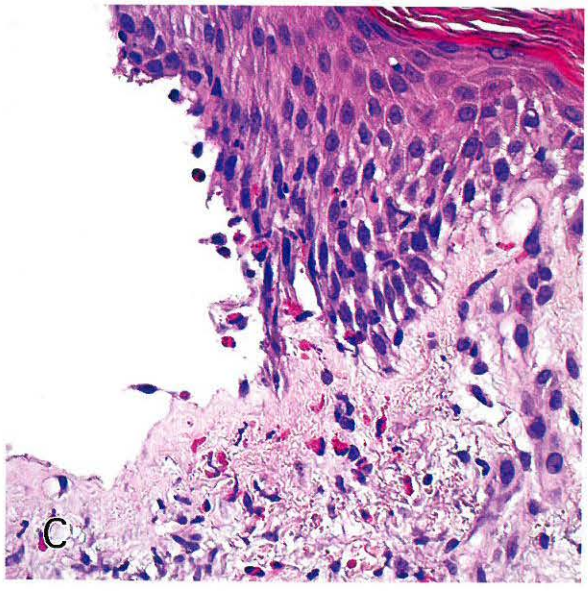
BULLOUS PEMPHIGOID (BP)

A: There is a subepidermal blister with fibrin and scattered inflammatory cells present in the blister cavity. There is also inflammation in the superficial dermis.

B: The epidermis (blister roof) has cleanly detached from the underlying dermis (blister floor); no residual basal keratinocytes are present on the floor of the blister. There are numerous eosinophils within the blister cavity.

C: Eosinophils are present within the subepidermal blister (left). The intact epidermis at the periphery of the blister (right) shows spongiosis and intraepidermal eosinophils ("eosinophilic spongiosis").





erythematous edematous plaques clinically with no blister formation. Rarely, BP arises during pregnancy (*pemphigoid gestationis*, also referred to by the misnomer *"herpes" gestationis*). Some patients have oral involvement.

BP is due to autoantibodies targeting either BPAG1 or BPAG2 (BPAG = Bullous Pemphigoid AntiGen) proteins, both of which are components of the hemidesmosome. This can be demonstrated by DIF, which shows linear deposition of IgG and C3 along the basement membrane zone. When a blister cavity can be seen on DIF (or when salt split skin technique is performed), the immunodeposits localize to the roof of the blister because the antibodies are targeting the hemidesmosomes, which are within the detached basal keratinocytes.

On H&E, BP is characterized by a subepidermal split, usually with abundant inflammation (particularly eosinophils) within the blister cavity and the superficial dermis (fig. 9-2). The appearance is very characteristic, although bullous arthropod bite reaction can be a close mimic. Confirmation via DIF (or serum enzyme-linked immunosobent assay [ELISA] testing) is ideal to make the diagnosis definitively.

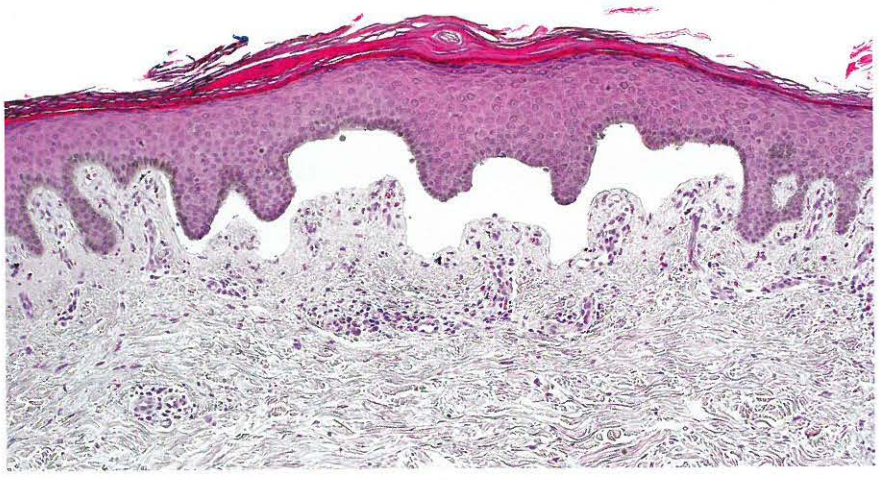


Figure 9-3

EPIDERMOLYSIS BULLOSA ACQUISITA (EBA)

There is a subepidermal blister with minimal inflammation. Dermal scarring and milia are often present (as in porphyria cutanea tarda; see fig. 9-4, left) but are not seen in this biopsy.

In the urticarial phase of BP, there is edema and mixed inflammation with eosinophils in the superficial dermis but no blister is seen. This is easy to miss as it resembles the nonspecific "dermal hypersensitivity reaction" pattern that can be seen in drug eruptions and arthropod bite reactions (see chapter 8). Overlying "eosinophilic spongiosis" with eosinophils infiltrating the epidermis is another useful clue for early evolving BP (3).

I always try to keep urticarial BP in mind when I see prominent eosinophils in the dermis or epidermis of elderly patients that I cannot otherwise account for. If there is any doubt, I raise the possibility in a comment and recommend repeat biopsy for DIF should the dermatologist have concern for an immunobullous process.

EPIDERMOLYSIS BULLOSA ACQUISITA

Epidermolysis bullosa acquisita (EBA) is a rare immunobullous disease that presents in adults (as opposed to congenital forms of epidermolysis bullosa which usually present in childhood). Patients develop blisters on the hands, feet, knees, or elbows, often after mild trauma. The blisters heal with scarring, and small milial cysts are typically seen within the scars (1). EBA is due to autoantibodies targeting the collagen type VII anchoring fibrils that hold the basement membrane down to the dermis (the recessive dystrophic form of congenital epidermolysis bullosa is also caused by defective collagen type VII, but via a gene mutation not an auto-antibody).

Histologically, EBA shows a subepidermal blister on H&E and linear IgG and C3 deposition along the basement membrane zone on DIF, features that can mimic BP. However, unlike BP, EBA classically has minimal inflammation and often shows dermal fibrosis/scar (fig. 9-3). When a blister cavity can be seen on DIF (or when salt split skin technique is performed), the immunodeposits localize to the floor of the blister (as opposed to the roof as in BP), because the antibodies are targeting the anchoring fibrils which are firmly attached to the dermis.

There is an inflammatory variant of EBA that can closely mimic BP histologically. DIF of a blister (or with salt split skin technique) is needed to distinguish these from one another (1).

PORPHYRIA CUTANEA TARDA

Porphyria cutanea tarda (PCT) is the most common form of porphyria. PCT presents in adulthood as blisters arising on sun-exposed skin, especially the dorsal hands. These heal with scarring and milia formation. PCT is due to a sporadic (most common) or familial defect in the uroporphyrinogen decarboxylase enzyme, which results in increased uroporphyrin levels in blood and serum (1).

Histologically, PCT shows subepidermal blister formation, usually with minimal inflammation, and often with dermal fibrosis/scar (fig. 9-4). Aggregates of homogenized eosinophilic material may be seen adhering to the underside of the blister roof ("caterpillar bodies"). The papillary dermal capillaries have thickened hyalinized vessel walls, which stain for periodic acid–Schiff with diastase (PASD). C3 and other immunodeposits may be seen around these vessels on DIF.

When the histologic features are suggestive of PCT, I recommend testing of urine and/or

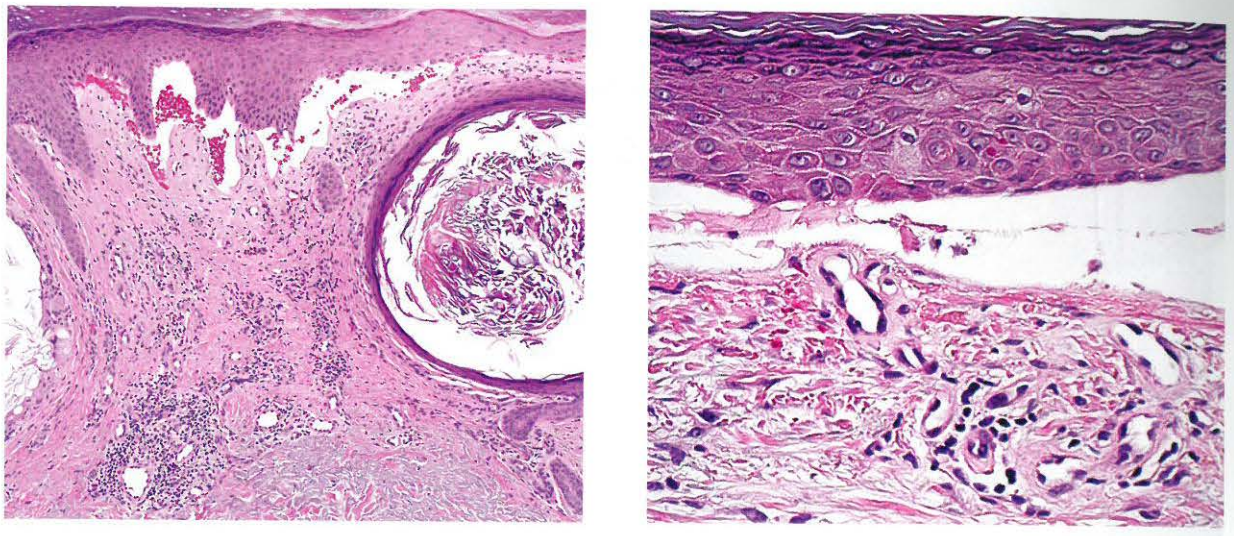


Figure 9-4

PORPHYRIA CUTANEA TARDA (PCT)

Left: There is a pauci-inflammatory subepidermal blister. The superficial dermis shows a thick layer of fibrosis/scar, which has pushed down the solar elastosis (a small portion is seen at bottom right). Milia (small cysts) are present within the scar.

Right: The subepidermal blister of PCT usually has little or no inflammation. Classically, the dilated papillary dermal capillaries have thickened hyalinized vessel walls, but this finding is often subtle and difficult to appreciate.

serum porphyrin levels to confirm the diagnosis. Also, the urine of PCT patients shows pink-red fluorescence when examined with a Wood's lamp (black light).

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis (DH) is an autoimmune blistering disease that presents with clusters of multiple, small, itchy papules and vesicles, often on the extensor surfaces such as the elbows and knees. (4) They are often excoriated because they are so pruritic; intact blisters may not be evident clinically or microscopically. Most DH patients also have gluten-sensitive enteropathy (Celiac disease), although it is often asymptomatic (5). Thus, only a subset of patients carry an established diagnosis of celiac disease at the time of skin biopsy (6).

DH is the result of IgA autoantibodies against tissue transglutaminase. DIF will show granular deposition of IgA in the papillary dermal tips. On H&E, small collections of neutrophils (microabscesses) are seen in the papillary dermal tips (fig. 9-5). As adjacent microabscesses merge together, a small subepidermal vesicle is formed. Fibrin and eosinophils may also be present in the blister cavity (4).

If you are considering DH on a biopsy but are uncertain, mention it as a possibility in the comment. Then recommend either repeat biopsy for DIF, serum testing for tissue transglutaminase autoantibodies, or both.

LINEAR IGA DISEASE

Linear IgA disease is a rare autoimmune blistering disease that can occur in adults or children. It is often precipitated by exposure to antibiotics or other medications, although a wide variety of other associations have been reported (4). It can display a variety of clinical appearances that may resemble DH, BP, or erythema multiforme. Annular or polycyclic erythematous lesions surrounded by multiple small blisters ("string of beads" or "cluster of jewels" appearance) is a classic clinical description (1,4).

DIF shows linear deposition of IgA along the basement membrane zone. These IgA autoantibodies target a variety of components of the basement membrane region. On H&E, the classic finding is a subepidermal blister with abundant neutrophils (fig. 9-6). Small neutrophil microabscesses can be seen in dermal papillae in adjacent skin, which can make DH and linear IgA disease difficult to distinguish

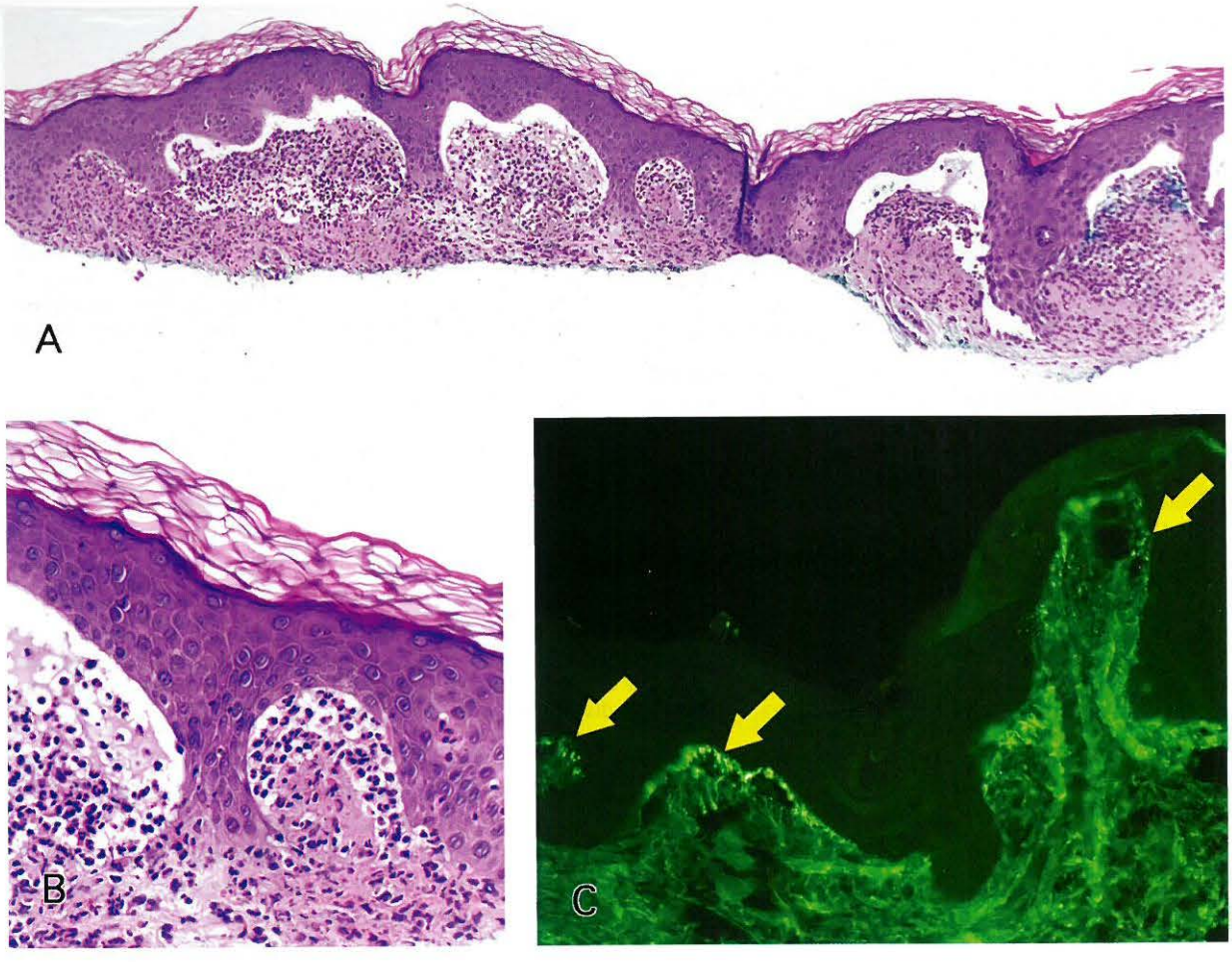


Figure 9-5

DERMATITIS HERPETIFORMIS (DH)

A: Multiple small subepidermal blisters are present between rete; each is centered on the tip of a dermal papilla.
B: Numerous neutrophils aggregate at the papillary dermal tips, forming microabscesses that create these tiny blisters.
C: Direct immunofluorescence shows granular deposition of IgA at the basement membrane zone within the papillary dermal tips (arrows), corresponding to the same location where the neutrophil aggregates and tiny blisters are forming.

from one another on a small biopsy unless it is accompanied by a second biopsy for DIF.

PEMPHIGUS

Pemphigus is a group of several different blistering diseases caused by autoantibodies against desmosome proteins. These autoantibodies cause keratinocytes to detach from one another, resulting in acantholysis and intraepidermal blister formation. The level of split within the epidermis depends on which desmosomal protein is targeted by the autoantibody. The blister is directly above the basal layer (suprabasilar) in *pemphigus vulgaris* and *pemphigus vegetans* but is higher up in the spinous layer (subcorneal) in *pemphigus foliaceus* and *pemphigus erythematosus* (1).

Pemphigus vulgaris is the most common form of pemphigus. It usually presents in adults as flaccid fragile bullae that easily rupture and leave behind open crusted erosions and ulcers. Oral involvement (mucosal erosions and ulcers) is present in the majority of patients, making this a crucial piece of clinical information when considering a diagnosis of pemphigus vulgaris. Other mucosal sites are often involved, including the esophagus and the anogenital area (1).

Histologically, the epidermis shows an acantholytic intraepidermal blister (fig. 9-7). The

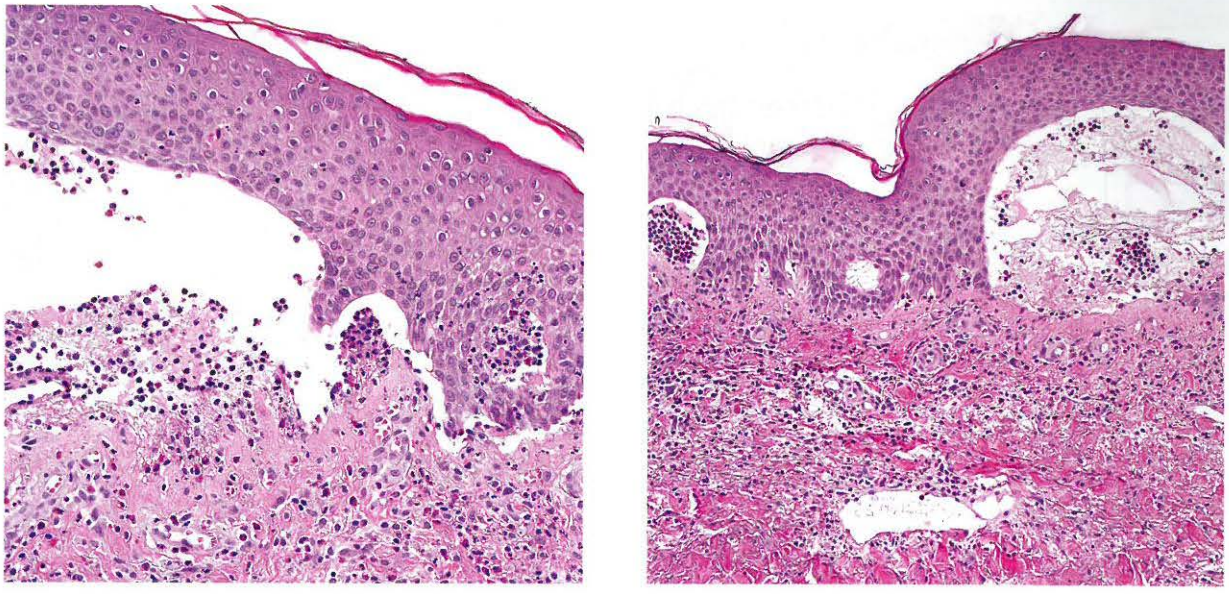


Figure 9-6

LINEAR IgA DISEASE

Left: The classic finding is a subepidermal blister with abundant neutrophils. Many eosinophils were also present in this example.

Right: Small neutrophil microabscesses identical to those of DH can be seen in dermal papillae in the skin adjacent to the larger blisters. Because of this, DH and linear IgA disease can sometimes be impossible to distinguish from one another on a small biopsy without clinical information or direct immunofluorescence.

floor of the blister is lined by a single layer of basal keratinocytes. The basal keratinocytes have detached from adjacent and overlying keratinocytes because their desmosomes have been disabled by the autoantibodies, but they are still firmly attached to the basement membrane by their hemidesmosomes. This pattern of acantholysis, with a retained basal layer, can be seen extending down adnexa as well. There may be mixed inflammation in the dermis.

Pemphigus foliaceus is a less common variant of pemphigus that usually presents with crusted erosions or scaly erythematous plaques rather than obvious blisters. Unlike pemphigus vulgaris, it rarely has oral involvement. Histologically, it shows a subcorneal blister, often with a completely detached blister roof (i.e., missing stratum corneum) and only rare detached acantholytic keratinocytes (fig. 9-8). The H&E appearance of pemphigus foliaceus can be nearly identical to staphylococcal scalded skin syndrome, or, if neutrophils are present, to bullous impetigo (see chapter 7) (1).

Pemphigus is characterized by "net-like" intercellular deposition of IgG and C3 on DIF, corresponding to the patient's autoantibodies against desmosomal proteins (desmogleins) (fig. 9-9). In pemphigus vulgaris, the deposits usually involve the entire epidermis, whereas in pemphigus foliaceus, they are usually restricted to the granular layer and superficial aspect of the spinous layer. The distinction between these patterns can be subtle and thus clinical and H&E correlation is needed. Pemphigus foliaceus auto-antibodies target desmoglein 1, which is present mostly in skin. Pemphigus vulgaris auto-antibodies target desmoglein 3, which is present mostly in oral mucosa; auto-antibodies against desmoglein 1 are often present as well. This explains why pemphigus vulgaris usually shows mucosal involvement while pemphigus foliaceus is usually limited to the skin (1).

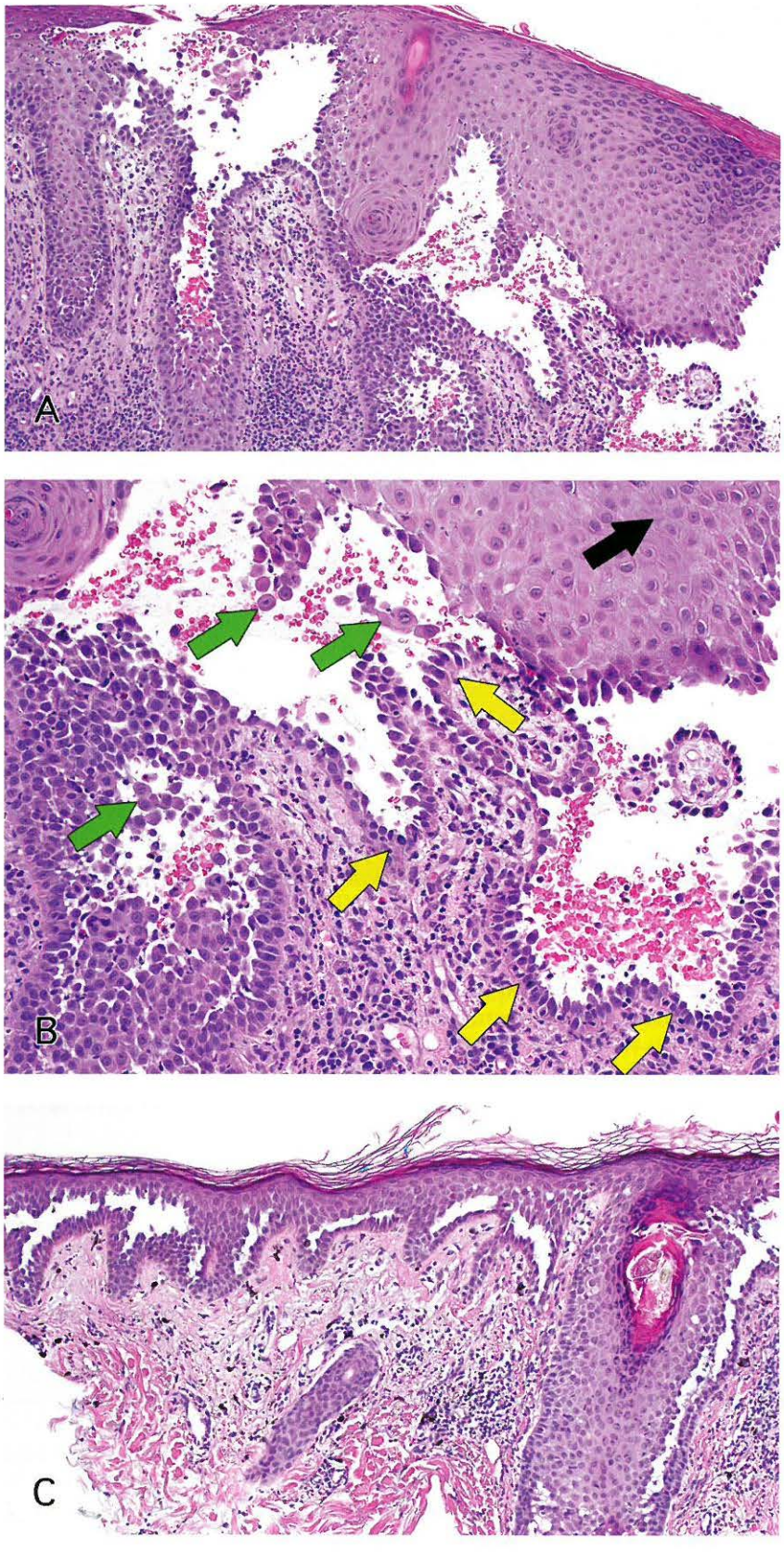


Figure 9-7

PEMPHIGUS VULGARIS

A: There is an acantholytic intraepidermal blister. Abundant inflammation is present in the dermis.

B: Acantholysis is clearly seen, as evidenced by free-floating rounded keratinocytes within the blister cavity (green arrows). As the blister develops further, the epidermis detaches (black arrow), leaving the "tombstone row" of basal keratinocytes clinging to the floor of the blister cavity (yellow arrows).

C: Adnexal involvement is common in pemphigus vulgaris. Intraepidermal acantholysis with suprabasilar blister formation is seen both within the epidermis (left) and extending down a hair follicle (right).

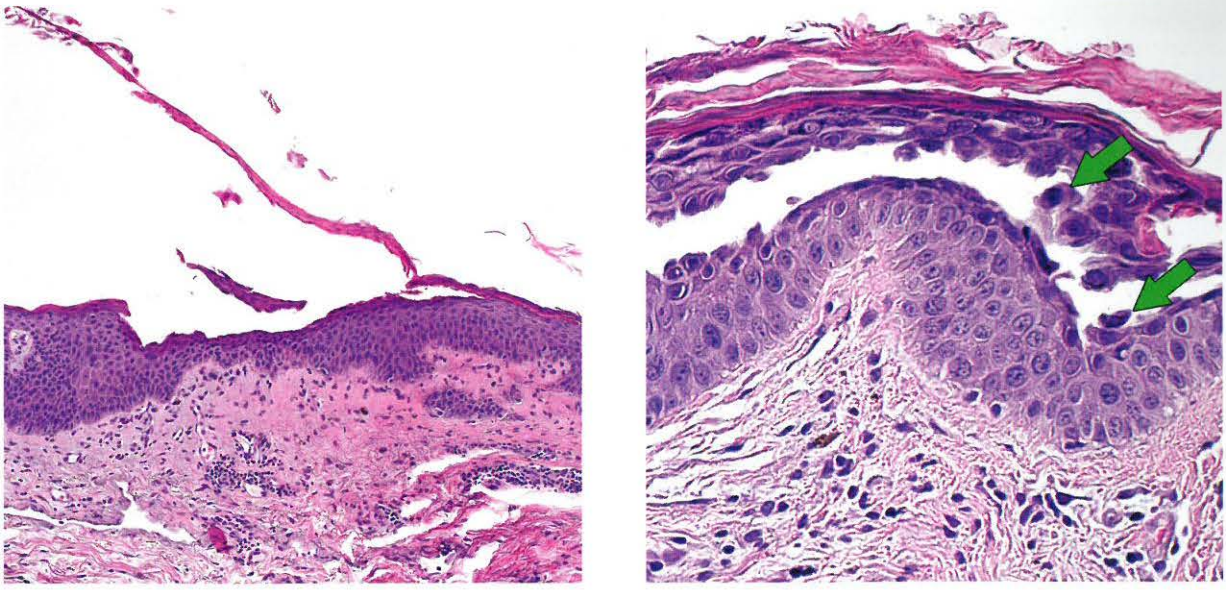


Figure 9-8

PEMPHIGUS FOLIACEUS

Left: Subcorneal acantholysis can lead to complete detachment of a thin layer of superficial epidermis (left), resulting in a "missing stratum corneum." This can closely mimic staphylococcal scalded skin syndrome microscopically.

Right: Acantholysis is seen in the superficial stratum corneum and stratum granulosum, resulting in a subcorneal split. The lower portion of the epidermis is intact. Scattered detached acantholytic keratinocytes are present in the blister cavity (arrows).

REFERENCES

1. Calonje JE, Brenn T, Lazar A, McKee P. McKee's Pathology of the Skin, 4th ed. Edinburgh: Elsevier/Saunders; 2011.
2. Abate MS, Battle LR, Emerson AN, Gardner JM, Shalin SC. Dermatologic urgencies and emergencies: what every pathologist should know. Arch Pathol Lab Med 2019. [Epub ahead of print]
3. Nishioka K, Hashimoto K, Katayama I, Sarashi C, Kubo T, Sano S. Eosinophilic spongiosis in bullous pemphigoid. Arch Dermatol 1984;120:1166-8.
4. Weedon D. Weedon's Skin Pathology, 3rd ed. Edinburgh: Churchill Livingstone/Elsevier; 2009.
5. Oxentenko AS, Murray JA. Celiac disease and dermatitis herpetiformis: the spectrum of gluten-sensitive enteropathy. Int J Dermatol 2003;42:585-7.
6. Alonso-Llamazares J, Gibson LE, Rogers RS 3rd. Clinical, pathologic, and immunopathologic features of dermatitis herpetiformis: review of the Mayo Clinic experience. Int J Dermatol 2007;46:910-9.

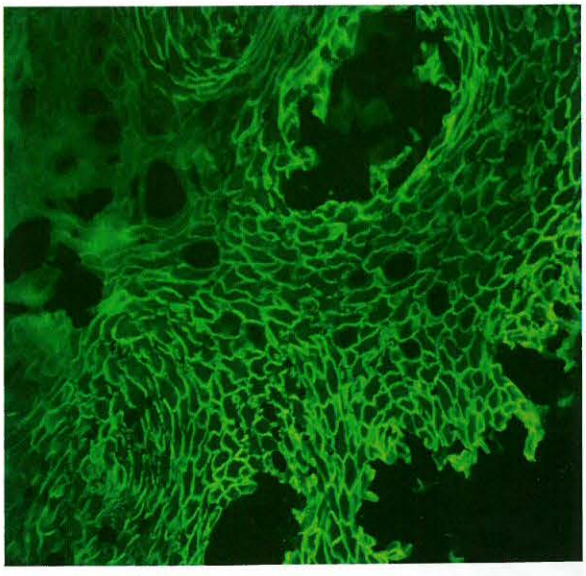


Figure 9-9

PEMPHIGUS: DIRECT IMMUNOFLUORESCENCE

Individual epidermal keratinocytes are surrounded by intercellular deposits of IgG and C3, creating the "net-like" pattern that is classic for pemphigus. In pemphigus vulgaris, the deposits usually involve the entire epidermis, whereas in pemphigus foliaceus, they are usually restricted to the superficial epidermis. This biopsy was from pemphigus vulgaris.

10 DEPOSITION DISEASES

Various lipid, protein, mineral, or mucopolysaccharide substances can accumulate in the skin leading to deposits that can be visualized by light microscopy. Some of these are merely incidental findings whereas others may be clues to serious systemic illnesses.

LIPID DEPOSITION

Xanthomas are caused by lipid deposition within the skin or soft tissue. All forms are characterized by aggregates or sheets of lipid-laden foamy histiocytes (xanthoma cells), but the clinical presentation and additional histologic features vary depending on the subtype. Xanthomas may be associated with hyperlipidemia; in some cases, the specific subtype of xanthoma can provide a clue to the particular form of lipoprotein abnormality the patient may have (1).

Planar xanthomas, also referred to as *xanthelasma* when located near the eye (the most common site), present as yellowish macules or plaques. They possess aggregates or sheets of foamy histiocytes in the superficial dermis (fig. 10-1). About half of patients with xanthelasma have hyperlipidemia (2).

Tuberous xanthomas are usually larger red-yellow papules or nodules on the buttocks, elbows, or knees. They show nodules of foamy histiocytes in the reticular dermis and sometimes subcutis; they may also display fibrosis and cholesterol clefts with giant cell reaction (2).

Tendinous xanthomas present as nodules deep to the skin, usually arising in the Achilles tendon or other tendons, fascia, or ligaments in the extremities. Foamy histiocytes are aggregated within tendon or other dense regular connective

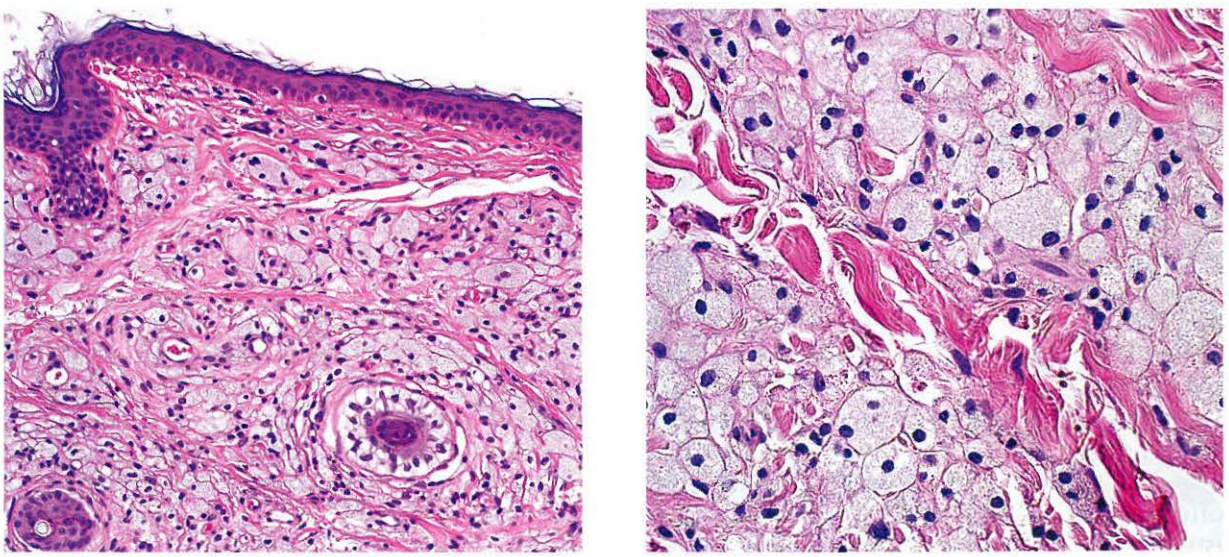


Figure 10-1

XANTHELASMA

Left: Aggregates of foamy histiocytes fill the dermis. There is almost no inflammation.

Right: Foamy lipid-laden histiocytes (xanthoma cells) have abundant pale cytoplasm with numerous very small clear vacuoles. The vacuoles often scallop/indent the borders of the nuclei, although that is difficult to appreciate in this image.

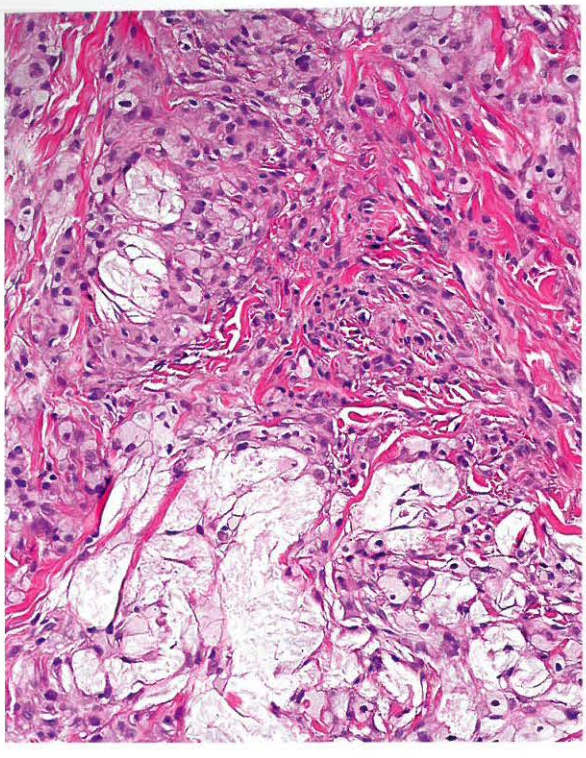


Figure 10-2

ERUPTIVE XANTHOMA

Sheets of foamy histiocytes fill the dermis (top). Additionally, frothy extracellular lipid deposits are often present (bottom), a unique finding that is characteristic for the eruptive subtype of xanthoma.

tissues. I rarely ever see this form of xanthoma biopsied or excised in my practice. Most patients with tuberous or tendinous xanthoma have underlying hyperlipidemia (2).

Eruptive xanthomas present as crops of multiple, small, yellow to red papules that may wax and wane over time. They have a predilection for the buttocks and extensor aspect of the limbs. These patients usually have underlying hypertriglyceridemia. Histologically, there are varying numbers of foamy histiocytes in the dermis depending on the age of the lesion. Additionally, frothy extracellular lipid deposits are often present, a unique finding that is characteristic of eruptive xanthoma and not usually seen in the other xanthoma subtypes (fig. 10-2) (2).

Foamy xanthomatous histiocytes can be seen in many other lesions aside from xanthomas. *Lipidized dermatofibromas* (aka "ankle-type," as they usually arise on the lower leg) often have abundant foamy histiocytes intermingled with arcs and rings of hyalinized pink collagen (fig. 10-3). These can be recognized by the presence of other conventional features of dermatofibroma, such as overlying epidermal hyperplasia, blunting of rete, peripheral plump spindle cells entrapping reticular dermal collagen bundles, and hemorrhage and hemosiderin deposition.

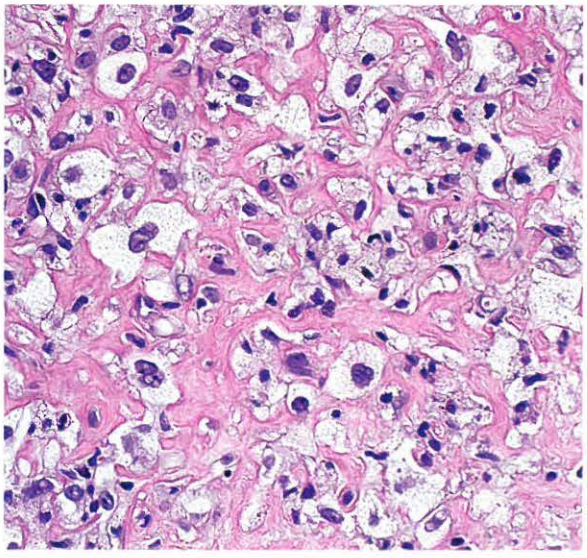
Xanthomatous cells are often present in other entities, as well, including verruciform xanthoma (see chapter 3), juvenile xanthogranuloma (see chapter 11), and tenosynovial giant cell tumors (giant cell tumor of tendon sheath and pigmented villonodular synovitis) (3). Necrobiosis lipoidica and necrobiotic xanthogranuloma (NXG) often have foamy histiocytes, and NXG may also show cholesterol clefts (see chapter 8). Frothy histiocytes laden with numerous acid-fast bacilli in lepromatous leprosy and some atypical mycobacterial infections can vaguely resemble lipid-laden xanthomatous foamy histiocytes (see chapter 7).

AMYLOID DEPOSITION

As in other organ systems, amyloid in skin is amorphous, dense, eosinophilic material that often displays cracking artifact. Cutaneous amyloid is most often derived either from immunoglobulin light chains (*AL amyloid*) or from keratin and other byproducts of keratinocyte breakdown (2).

Cutaneous deposition of light chain AL amyloid may be a manifestation of serious systemic disease (*primary amyloidosis* or *myeloma-associated amyloidosis*) or it may be indolent and limited to the skin only (*nodular amyloidosis*). The amyloid itself is essentially identical in both of these scenarios with a hematoxylin and eosin (H&E) stain and by special techniques (figs. 10-4, 10-5). Amyloid deposits may be seen throughout the dermis and subcutis, but there is a propensity to deposit around blood vessels and adnexa.

AL amyloid from both systemic and nodular amyloidosis stains a dark reddish salmon color with the Congo red stain with classic "apple green" birefringence when examined with polarized light. A strong light source is needed to observe the apple green birefringence. One trick I discovered is to turn on the microscope camera and then polarize the slide. The camera will adjust to the diminished light from the



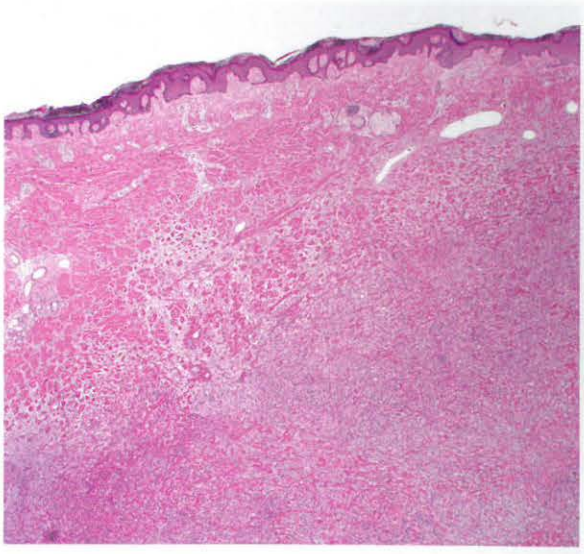
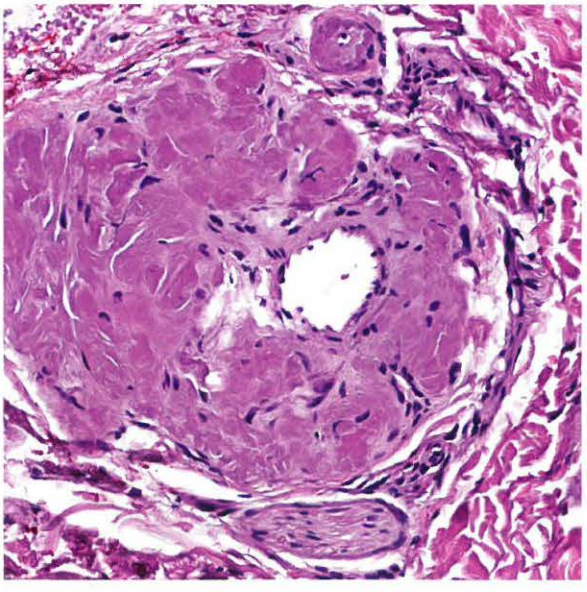


Figure 10-3

DERMATOFIBROMA, LIPIDIZED TYPE

Left: At high magnification, there are numerous foamy histiocytes in the dermis. There are rings and arcs of bright pink sclerotic collagen wrapping around these foamy histiocytes; this unique finding helps distinguish lipidized dermatofibroma from xanthoma.

Right: At low magnification, the lesion shows characteristic features of conventional dermatofibroma, including entrapment of reticular dermal collagen bundles at the periphery of the tumor and overlying epidermal hyperplasia with flattened "tabled" rete ridges.



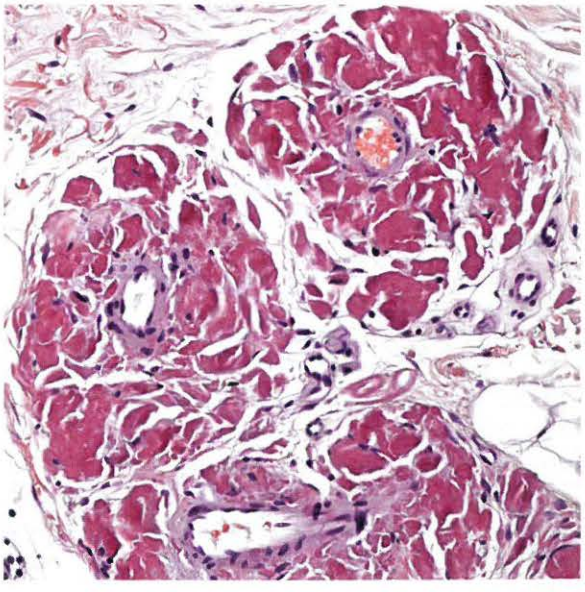


Figure 10-4

SYSTEMIC AMYLOIDOSIS

Left: A thick layer of AL amyloid is deposited around a dermal blood vessel. Contrast the amorphous dense eosinophilic amyloid (center) with the reticular dermal collagen (bottom right). The color and consistency are different. The fine white artifactual cracks in the amyloid are common.

Right: AL amyloid surrounding multiple blood vessels stains a dark reddish salmon color on Congo red stain. Contrast this with the pale background dermal collagen (upper left). Note the prominent cracking artifact in the amyloid.

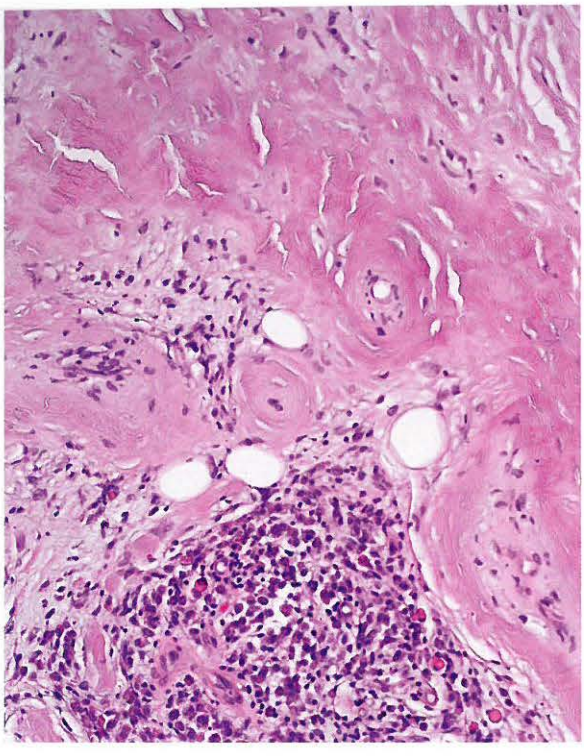


Figure 10-5

NODULAR AMYLOIDOSIS

The amorphous eosinophilic AL amyloid of nodular amyloidosis is identical to that of systemic amyloidosis. The presence of numerous plasma cells (bottom) adjacent to the amyloid is a clue for nodular rather than systemic amyloidosis, but clinical workup is still essential to exclude systemic involvement.

polarizer by increasing its sensitivity, which will often help the birefringence to stand out better. Normal reticular dermal collagen also shows some birefringence under polarized light, with a yellow-greenish color. The color is slightly different, but it is easy to be fooled if you are not familiar with this pitfall. I always examine the Congo red control both by regular and polarized light to readjust and refresh my visual memory of exactly what true amyloid should look like. On cases with which I struggle, a visit to my friendly nephropathology colleague down the hall usually helps a lot, as those who see a lot of medical kidney are pros at recognizing amyloid. As both systemic and nodular amyloidosis are composed of AL light chain amyloid, they show identical mass spectrometry findings. Thus, mass spectrometry cannot determine whether there is systemic involvement; full clinical workup is required.

Systemic amyloidosis presents clinically as purpuric/hemorrhagic, sometimes waxy lesions, usually around the eyes or on the hands. Further clinical workup will usually show evidence of a clonal plasma cell proliferation including an M-protein on serum or urine protein electrophoresis. Amyloid deposition may also be found in the heart, kidneys, or liver. It is this internal organ involvement that gives this disease a poor prognosis (2).

Nodular amyloidosis presents clinically with waxy papules or plaques on the trunk, extremities, or face (2). Plasma cells within the skin (rather than elsewhere in the body) locally produce the light chains that lead to the cutaneous AL amyloid deposits in nodular amyloidosis (4). These plasma cells are often seen with an H&E stain intermingled with the cutaneous deposits in nodular amyloidosis, providing a useful clue to the possibility of skin-limited nodular amyloidosis (2). I add a comment that clinical workup must be performed to evaluate for systemic involvement any time I diagnose probable AL amyloid on a skin biopsy.

Macular amyloidosis and *lichen amyloidosis* are related entities (under the umbrella term *primary localized cutaneous amyloidosis*) characterized by deposits of keratinocyte-derived amyloid (figs. 10-6, 10-7) (5). This amyloid has the same amorphous eosinophilic appearance as AL amyloid, but it is limited to the papillary dermis and does not surround vessels or adnexa. It has cracking artifact, much like AL amyloid, but scattered melanin pigment is often seen in these cracks, another useful clue for keratinocyte-derived amyloid. In macular and lichen amyloidosis, basal layer keratinocytes die and break down (probably due to chronic irritation or some other trauma) (2). Their keratin filaments and other proteins fall into the underlying papillary dermis, making amorphous amyloid aggregates. The cytoplasmic melanin pigment normally found in the basal keratinocytes also falls down and gets caught up in the amyloid. The phenomenon is similar to the papillary dermal cytoid bodies seen in some cases of lichen planus and other lichenoid interface dermatoses.

Macular amyloidosis presents as hyperpigmented pruritic patches on the upper back (2). It is most common in Asian, Middle Eastern,

or Central/South American patients (5). The papillary dermal amyloid deposits in macular amyloidosis are often very small and subtle, so look closely if there is clinical suspicion. Pigment incontinence is a helpful clue. At low power, the biopsy may look like completely normal skin.

Lichen amyloidosis presents as multiple papules most often on the shins. These are extremely pruritic, and secondary lichenification and excoriation is a common finding. The deposits of amyloid are identical to those of macular amyloidosis, but they are usually more abundant. The overlying epidermis usually shows lichenification from the chronic itching and scratching, with irregular epidermal acanthosis and hypergranulosis. The appearance can be very similar to lichen simplex chronicus and prurigo nodularis; identifying the papillary dermal amyloid deposits with cracking artifact that contains focal melanin pigment is the key to making the diagnosis.

As macular and lichen amyloidosis are not derived from light chains, they are totally unrelated to the systemic forms of AL amyloidosis. When the treating physician is not a

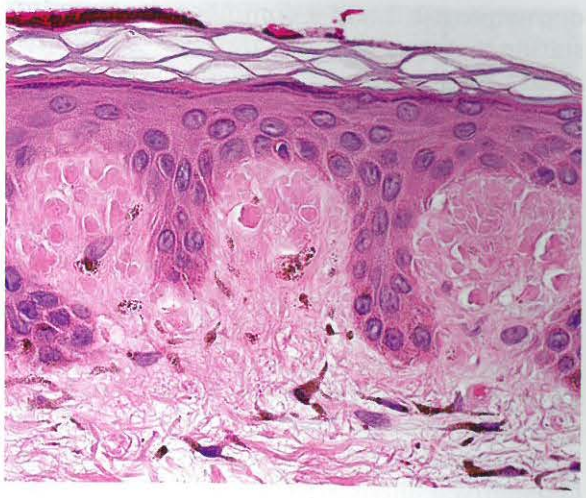


Figure 10-6

MACULAR AMYLOIDOSIS

Keratinocyte-derived amyloid is amorphous dense eosinophilic material with cracking artifact, much like AL amyloid. However, it is limited to the papillary dermis and does not surround vessels or adnexa. Another useful clue is the presence of scattered melanin pigment in and around the amyloid deposits. High magnification is often needed to detect these focal amyloid deposits; at low magnification, macular amyloidosis usually resembles normal trunk skin.

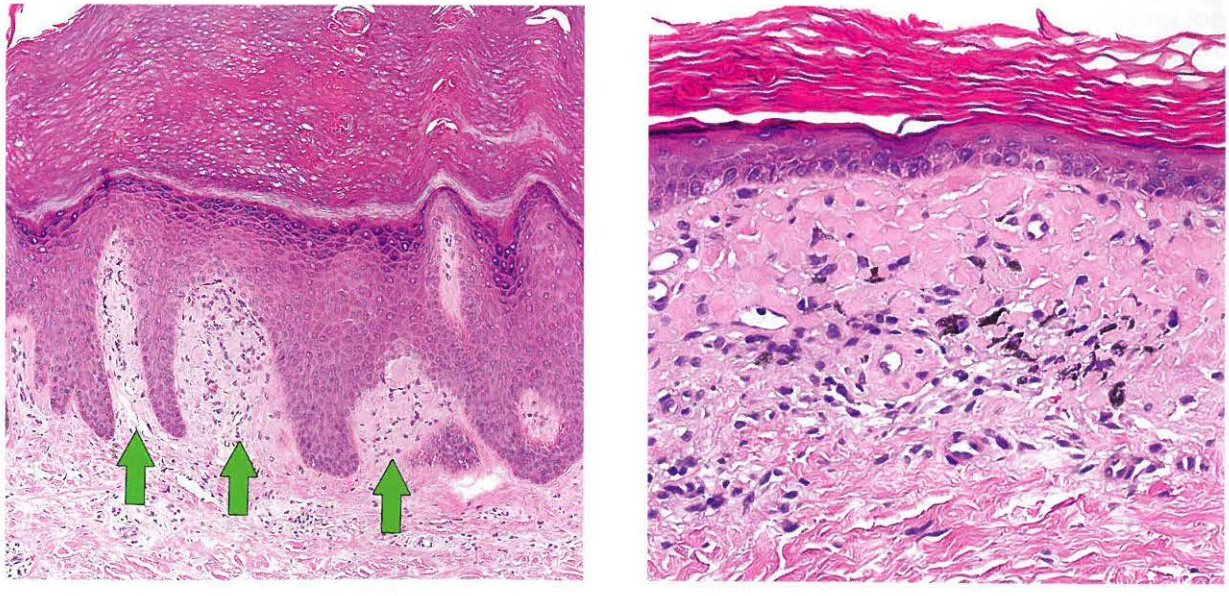


Figure 10-7

LICHEN AMYLOIDOSIS

Left: Aggregates of keratinocyte-derived amyloid fill several dermal papillae (arrows). The overlying epidermis often exhibits lichen simplex chronicus changes.

Right: Homogenous pale pink amyloid fills the papillary dermis. Note the intermingled melanin pigment present within many of the artifactual cracks; this is a useful clue that the amyloid is keratinocyte-derived. Contrast the color and texture of the papillary dermal amyloid (top) against the brighter pink collagen fibers in the underlying reticular dermis (bottom).

dermatologist, I add a comment to the report stating that these diseases are due to keratin-derived amyloid and are unrelated to systemic amyloidosis. I have seen patients receive expensive invasive workups that generated unnecessary anxiety because of miscommunication or misunderstanding about this point. Distinction of keratinocyte-derived amyloid from light chain-derived amyloid is usually easily accomplished on H&E, although mass spectrometry can confirm this when needed.

I have read and been taught a variety of different things regarding the use of Congo red, other special stains, or even specific cytokeratin immunostains for distinguishing keratinocyte-derived amyloid from light chain-derived amyloid. My reading of the literature on this topic has only led me to further confusion. In my own attempts at using some of these stains in keratinocyte-derived amyloid cases, the results were disappointing and not helpful. Fortunately, H&E is still king.

Keratin-derived amyloid may also be seen in the stroma around basal cell carcinomas and various adnexal tumors. As this phenomenon is not associated with systemic amyloidosis, I do not usually even mention it in the report so as to avoid causing undue anxiety. A variety of other unusual forms of amyloidosis also exist. Several other esoteric diseases can produce deposits of homogenized pink material that can resemble amyloid: *colloid milium, lipoid proteinosis, cutaneous collagenous vasculopathy*, and some forms of *porphyria*.

MUCOPOLYSACCHARIDE (MYXOID/MUCIN) DEPOSITION

Mucopolysaccharides such as hyaluronic acid are an important component of the ground substance that fills the interstitial space between cells and collagen bundles in the dermis. Increased amounts of dermal mucopolysaccharides can be seen as bluish granular/wispy material between reticular dermal collagen bundles in a wide range of diseases. This bluish material is often referred to as "mucin" by dermatologists or "myxoid" by pathologists; those terms are used interchangeably throughout this book. Mucin special stains, such as Alcian blue or colloidal iron, can help highlight the presence of mucin, but these stains are easy to overinterpret without experience. If mucin is obvious on H&E, special stains are not needed. If mucin is not obvious on H&E, then a special stain may suggest that mucin is there when it is actually not. Mucin stains may be helpful in select scenarios, but in most cases they are not needed.

Pretibial myxedema (*thyroid dermopathy*) occurs in a small subset of patients with Graves' disease (autoimmune hyperthyroidism). It presents as indurated nodules or plaques most often on the anterior lower legs but occasionally in other sites, as well. It is usually a late finding in Graves' disease, but I have seen rare cases where it was the first sign of underlying thyroid disease. Biopsy shows abundant mucin deposition replacing the reticular dermal collagen with no associated increase in dermal fibroblasts or fibrosis (fig. 10-8). There may be overlying epidermal hyperplasia (2).

Scleredema presents as a firm, indurated, nonpitting edematous plaque most often on the posterior neck and upper back. It may present in childhood acutely after an upper respiratory infection or in obese adults with diabetes (2). On biopsy, the changes are usually subtle. The dermis is thickened with enlarged reticular dermal collagen bundles, but as scleredema usually presents on the trunk, it can be difficult to decide if the dermis is truly thickened or is just normal trunk skin. Mucin is present between these thick reticular dermal collagen bundles (fig. 10-9). There is no significant increase in dermal fibroblasts. Unlike pretibial myxedema, which shows a diffuse sea of mucin replacing the dermal collagen, the mucin in scleredema is usually scant and present only in the interstitial spaces between the thick collagen bundles. A mucin stain can help to confirm the diagnosis of scleredema. I do not see biopsies of scleredema very often in my practice, but perhaps this is due to referral bias, as my dermatology colleagues tell me that they see it on a regular basis in clinic but usually are able to diagnose it without biopsy.

Scleromyxedema (*lichen myxedematosus*) is a rare disease that is mentioned here because of its similar sounding name to scleredema and pretibial myxedema. It presents as waxy papules that become generalized and coalesce into plaques. This eventually results in induration and tightening of the skin that can resemble

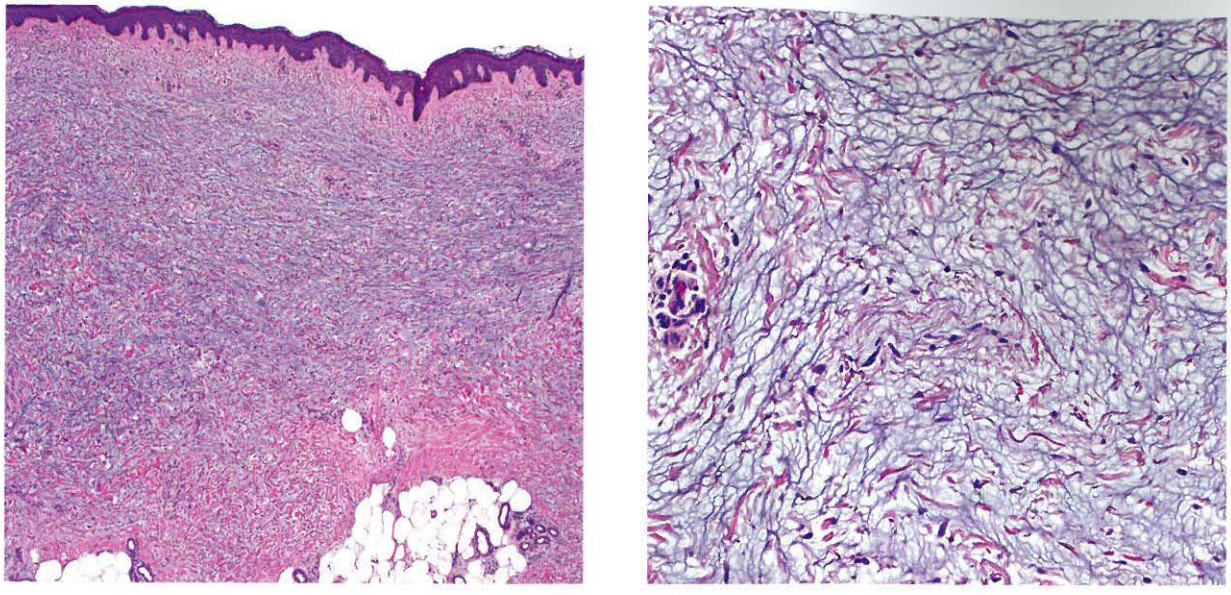


Figure 10-8

PRETIBIAL MYXEDEMA

Left: The reticular dermis is filled with a sea of blue mucin. There is slight overlying epidermal hyperplasia.
Right: At high magnification, the reticular dermal collagen is mostly replaced by abundant blue mucin. There are very few fibroblasts and no associated fibrosis.

scleroderma/systemic sclerosis. It is usually associated with paraproteinemia, most commonly IgG lambda. Histologically, there is increased dermal mucin, but with prominent associated fibrosis and increased dermal fibroblast density (fig. 10-10); the latter two findings easily distinguish it from pretibial myxedema and scleredema (2). In some cases, the increased fibroblasts are so prominent so as to vaguely resemble a dermatofibroma or other spindle cell neoplasm. Dermatofibromas may show many morphologic variations, but rarely have mucin or myxoid change. *Nephrogenic systemic fibrosis* (NSF), a now rare disease caused by giving gadolinium contrast to patients with insufficient renal function, has a nearly identical histologic appearance to scleromyxedema.

Focal cutaneous mucinosis is just a small localized collection of mucin and scattered stellate fibroblasts in the superficial to mid dermis (fig. 10-11). It usually presents as a solitary skin papule. A superficial biopsy of *cutaneous myxoma (superficial angiomyxoma)* can look very similar. If the lesion extends into the deep dermis or subcutis, has prominent branching vessels, has scattered neutrophils within it, or shows adnexal

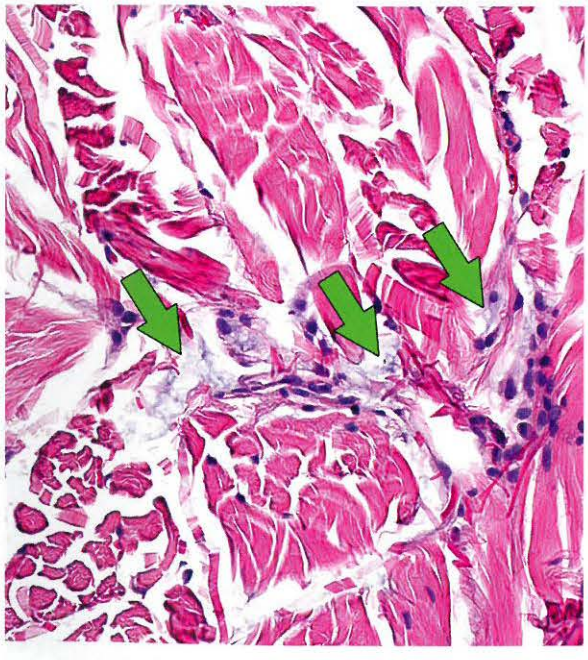


Figure 10-9

SCLEREDEMA

The reticular dermal collagen bundles are slightly thicker than usual. There is focal deposition of blue mucin between these bundles (arrows). The findings are usually subtle, as this image demonstrates.

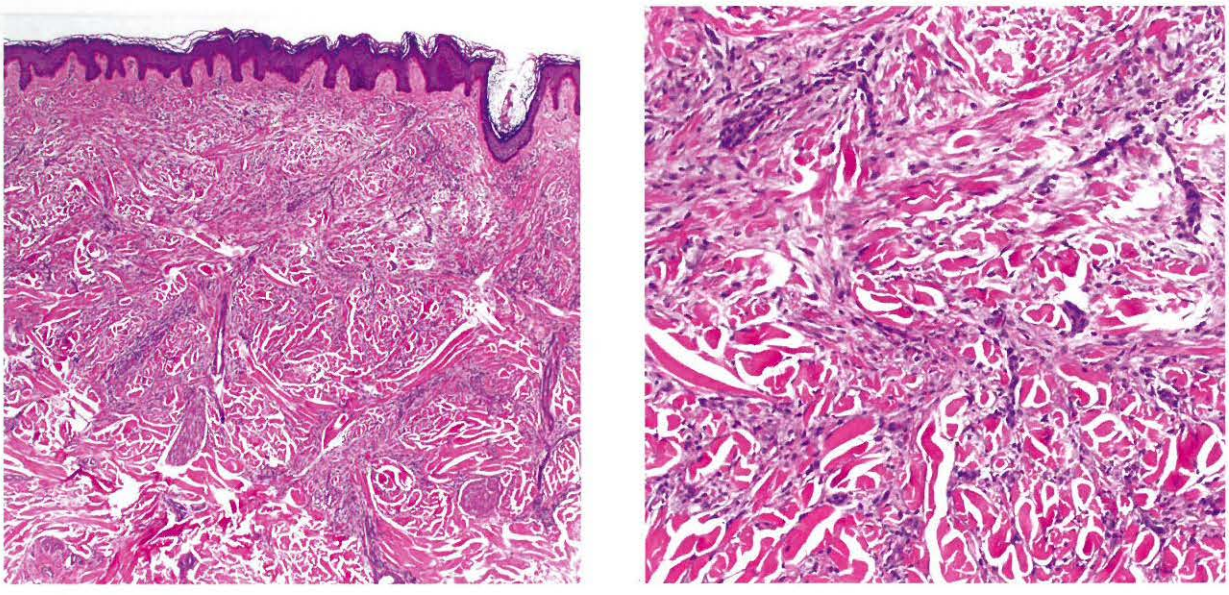


Figure 10-10

SCLEROMYXEDEMA

Left: There is subtle blue mucin deposition in the reticular dermis along with abundant fibrosis and increased cellularity (contrast with relatively uninvolved dermis at bottom of image).

Right: The fibrosis and increased fibroblast density easily distinguish scleromyxedema from pretibial myxedema and scleredema. Entrapment of collagen fibers, as seen here, can cause scleromyxedema to vaguely resemble dermatofibroma. However, myxoid change is almost never seen in dermatofibromas.

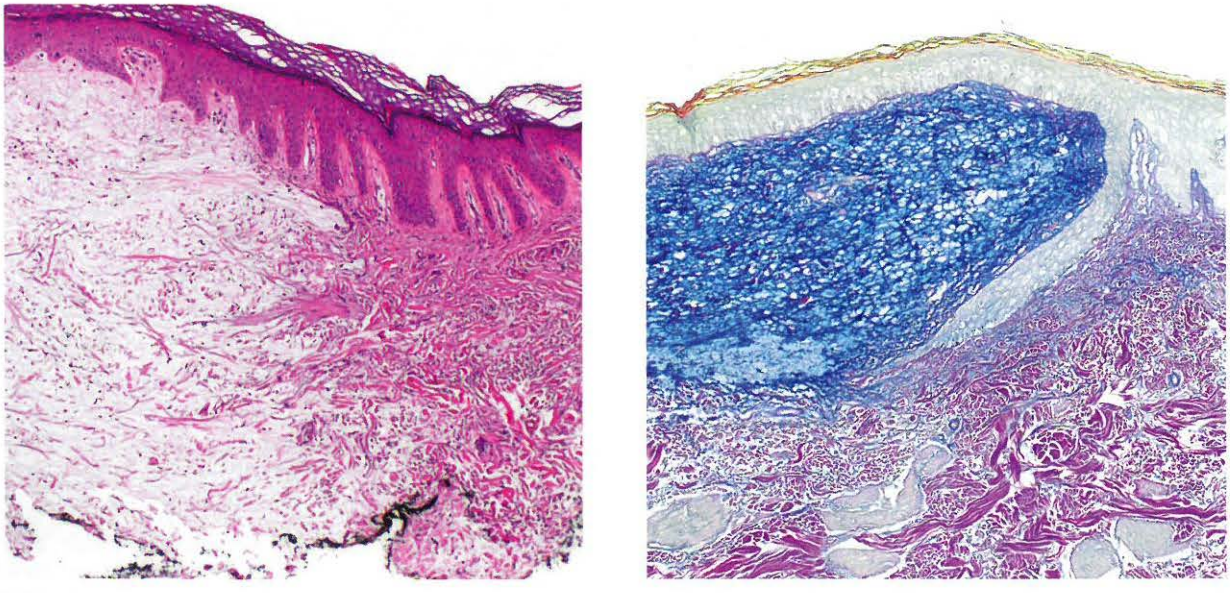


Figure 10-11

FOCAL CUTANEOUS MUCINOSIS

Left. A small nodular zone of mucin is present in the dermis (left). Adjacent dermis (right) is uninvolved.

Right: Colloidal iron stain turns mucin a more vibrant shade of blue (the stain was performed for educational rather than diagnostic purposes here). Note how localized the mucin collection is (upper left). (Different case than left figure.)

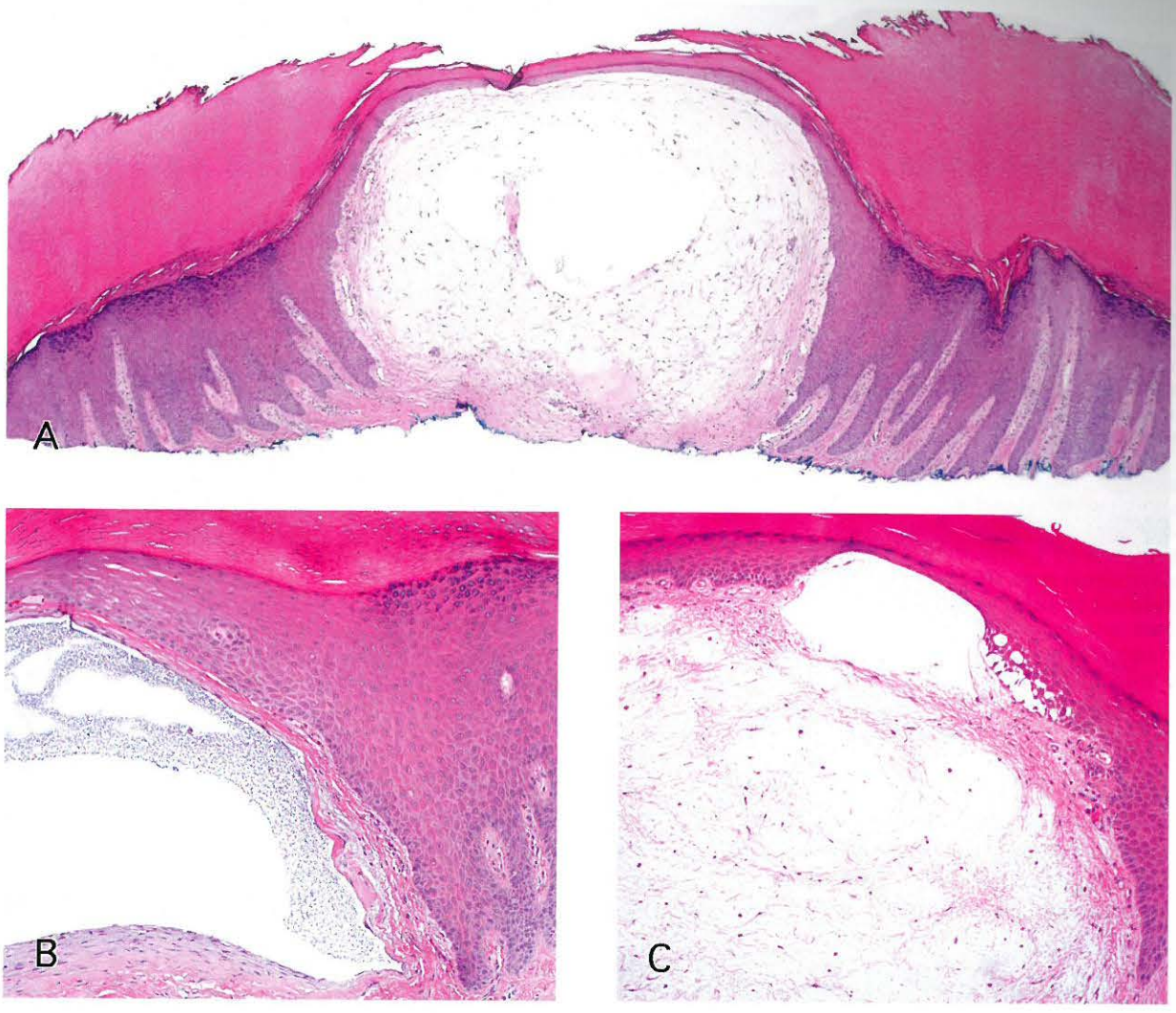


Figure 10-12

DIGITAL MUCOUS CYST

A: A small nodule of mucin is present in the superficial dermis, pushing up into the overlying epidermis. The thick stratum corneum of the adjacent epidermis is evidence of the acral location.

B: Sometimes the mucin washes out during processing, leaving a partially or completely empty pseudocystic space surrounded by a layer of fibrosis but with no epithelial lining. Note the focal residual blue mucin within the pseudocystic space.

C: Other times, mucin intermingles with the background fibroblasts and collagen to form a loose zone of myxoid change resembling the consistency of a myxoma.

entrapment, then myxoma is favored. Both lesions are benign, but cutaneous myxomas have a tendency for local recurrence (6).

Digital mucous/myxoid cyst is a translucent papule that presents on the digit, usually on the proximal nail fold directly adjacent to the nail. Biopsy shows a nodule of mucin in the superficial dermis, pushing up into the overlying epidermis (fig. 10-12). Sometimes the mucin washes out during processing, forming a pseudocystic space. Other times, mucin intermingles with the background fibroblasts and collagen to form a loose edema-like zone of myxoid change.

Many other diseases show increased mucin or myxoid change. Dermal mucin is a common finding in lupus erythematosus and reticular erythematous mucinosis (see chapter 8). Mucin is also sometimes seen as a nonspecific finding in

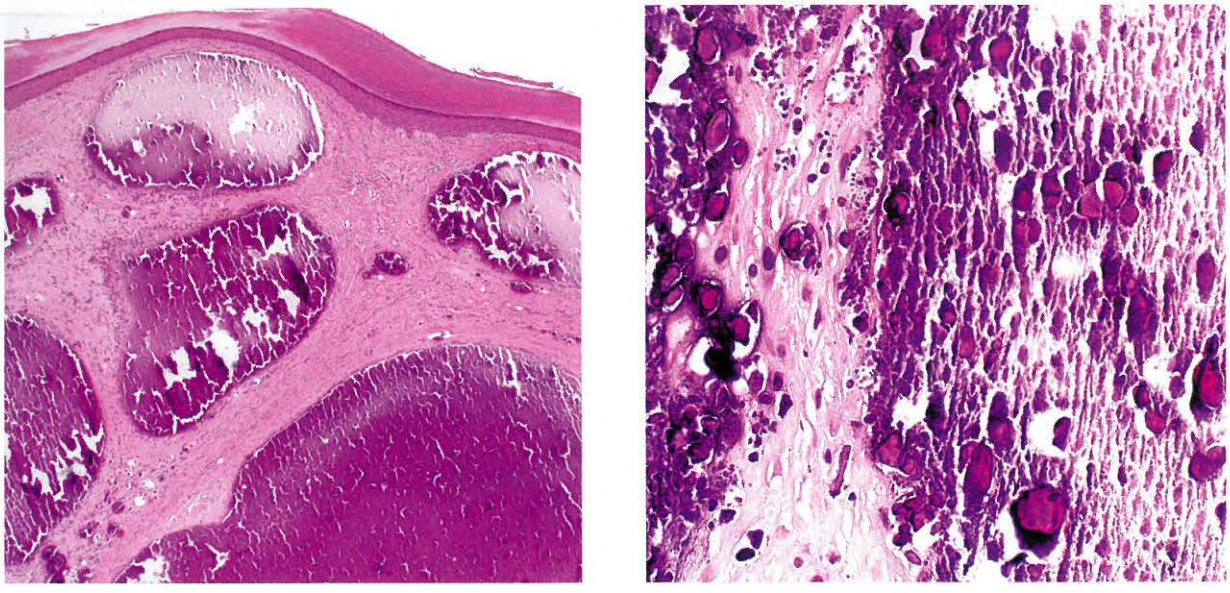


Figure 10-13

CALCINOSIS CUTIS

Left: There are multiple dermal aggregates or "pools" of deep blue/purple calcium phosphate with associated dermal fibrosis. Right: The calcium ranges in texture from large irregular "chunky" fragments (left) to fine granular "grungy" calcium particles (right).

otherwise normal individuals, particularly around the eccrine coils at acral sites. Many different tumors have myxoid change, including myxoid variants of *neurofibroma* and *dermatofibrosarcoma protuberans, nerve sheath myxoma, cellular neurothekeoma,* and *myxofibrosarcoma* (6).

MINERAL/CRYSTAL DEPOSITION

Calcinosis cutis is somewhat of an umbrella term that refers to calcification of the dermis that may be due to various causes. It may be dystrophic calcification occurring within damaged or degenerated tissue, it may be related to serum calcium or phosphate abnormalities, it may be due to underlying systemic diseases (e.g., dermatomyositis), or it may be idiopathic (2).

Calcinosis cutis presents clinically as white-yellow nodules that sometimes break open and drain to the skin surface. The microscopic appearance varies from case to case, but most show dermal aggregates of deep blue/purple calcium phosphate deposits, often with associated fibrosis and giant cell reaction (fig. 10-13). The calcium may range from large irregular "chunky" fragments all the way down to fine granular "powdery" calcium particles that form pools in the dermis. When similar calcium deposits form larger masses in the deep soft tissue or synovium, the term *tumoral calcinosis* may be used. Other forms of calcinosis cutis include *scrotal calcinosis* (multiple nodules of calcinosis cutis on the scrotum) and *subepidermal calcified nodule* (a solitary nodule of calcinosis cutis on the eyelid/face of a child).

Osteoma cutis is a small focus of bone found within the dermis, usually on the face. It is most often an incidental finding seen in the background skin on cancer excision specimens (in that setting, I do not even mention it in the report). It likely represents metaplastic bone formation in response to an old ruptured follicle or other previous injury. Recognition of lamellar bone lines or osteocytes in lacunae distinguishes the bone of osteoma cutis from the non-bone calcifications of calcinosis cutis (fig. 10-14).

Gout is the result of monosodium urate crystal deposition in the skin or soft tissue, resulting in an erythematous extremely painful nodule/s on the toes, ears, or other sites (gouty tophus). On H&E sections, the needle-shaped gout crystals are usually not visible (see below), but instead there are large pale pink nodules

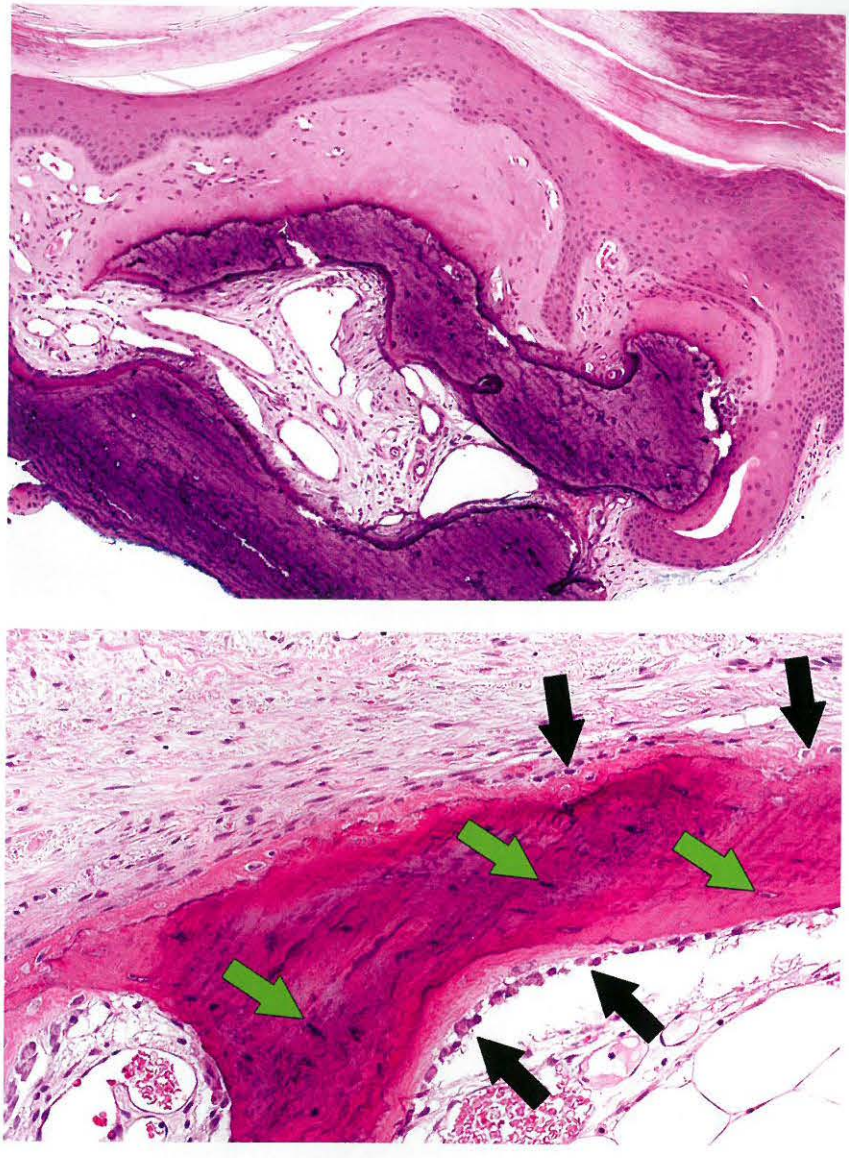


Figure 10-14

OSTEOMA CUTIS

Top: Metaplastic bone is present within the dermis, surrounded by fibrosis and reactive blood vessels. The bone is deep purple due to abundant calcium mineralization in this nondecalcified specimen. There is also reactive change in the overlying epidermis.

Bottom: The amount of calcium mineralization may vary from case to case (or be altered by decalcification), resulting in bone that ranges from the deep purple color seen in the top figure to the more eosinophilic appearance seen here. Regardless of the color, bone can be identified by osteocytes in lacunar spaces (green arrows), a rim of osteoblasts (black arrows), and concentric lamellar lines if the bone is mature (not seen here in the immature woven bone in this case). These features are not seen in the disorganized calcium of calcinosis cutis.

where the crystal aggregates used to be. These have a light fluffy appearance (think pink clouds or cotton candy). Histiocytes and foreign body giant cells often form a rim around the outside of these pink nodules (fig. 10-15).

Since urate crystals are water soluble, I had always heard that formalin fixation of the biopsy specimen was responsible for the lack of polarizable crystals on H&E sections and that only a fresh smear or an alcohol-fixed biopsy specimen from a tophus would allow the polarizable needle-shaped urate crystals to be visualized. While these two methods work, the H&E staining process itself is probably the more significant culprit for dissolving the crystals than the formalin fixation. Using a special nonaqueous alcoholic eosin staining method will prevent the crystals from dissolving (7). Alternatively, you can try this cool trick: cut an unstained paraffin section from the tissue block and examine it under polarized light (with no stain or coverslip or anything; just an unstained slide) (8). This often allows the urate crystals to be seen under polarization. Additionally, you will be stunned by the sea of beautiful Maltese crosses that fill the entire area around the tissue; this is undissolved paraffin wax (as demonstrated in this video: http://bit.ly/2u2ytmR). Even

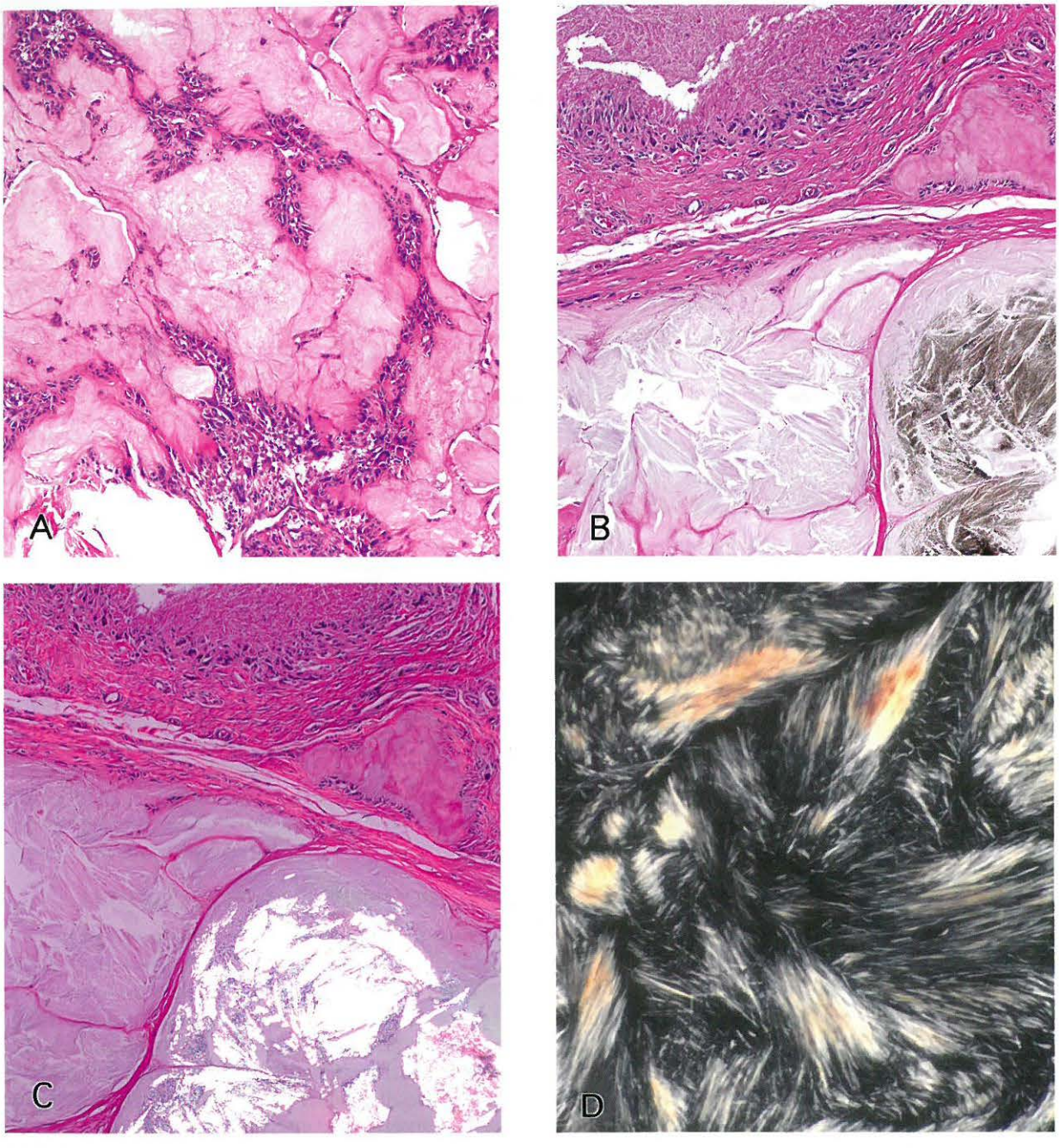


Figure 10-15

GOUT

A: Large pale pink nodules are all that is left of the dissolved urate crystals. These have a light fluffy appearance that resembles pink clouds or cotton candy. The dark cellular zones here represent histiocytes and foreign body giant cells forming a rim around each nodule.

B: The gout nodules on the top have a rim of foreign body giant cells while those on the bottom left do not. The dark brown refractile area in the bottom right nodule represents residual intact urate crystals that have not been dissolved.

C: The dark brown area from B is brightly birefringent on polarized light examination due to residual intact urate crystals. The other nodules (left and top) lack any residual urate crystals and thus do not polarize.

D: At high magnification, needle-shaped urate crystals are birefringent on polarized light examination. They range from white to yellow to rainbow appearance.

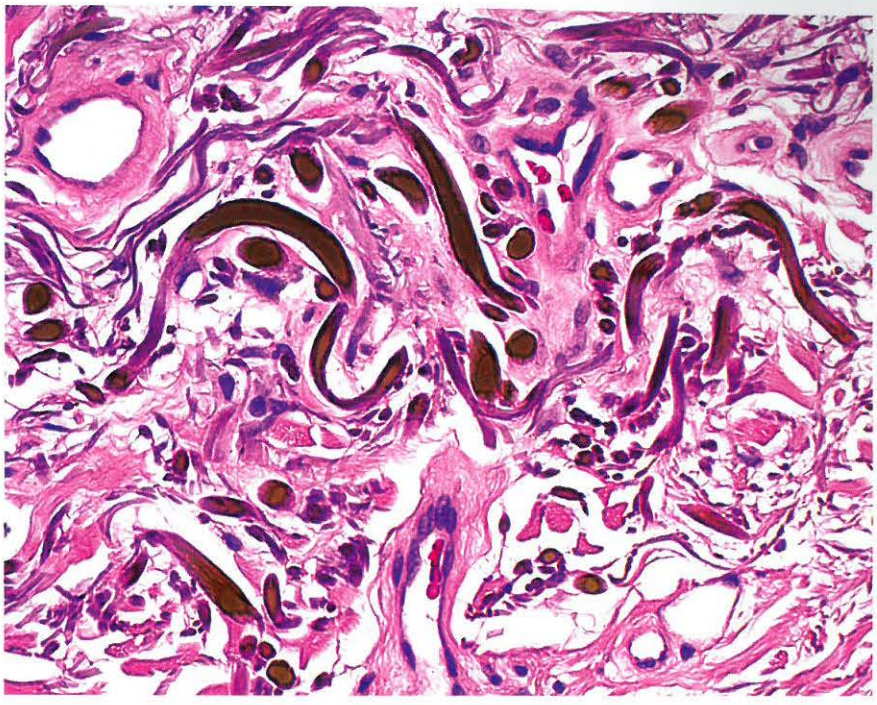


Figure 10-16

OCHRONOSIS

Curved yellowish brown fibers are seen in the dermis an H&E-stained section.

without using these alternative methods to find polarizable urate crystals, the distinct H&E appearance alone is usually enough to easily make a diagnosis of gout.

Ochronosis

Ochronosis is uncommon but merits brief mention because of its unique appearance. It is due to the deposition of melanin-like pigment upon dermal collagen fibers, which turns them yellowish-brown on H&E (fig. 10-16). It may occur as an inherited enzyme disorder (*alkaptonuria*, where the patient also has black urine) or it may be acquired from topical application of certain skin lightening creams, such as hydroquinone (2,9).

REFERENCES

1. Cruz PD Jr, East C, Bergstresser PR. Dermal, subcutaneous, and tendon xanthomas: diagnostic markers for specific lipoprotein disorders. J Am Acad Dermatol 1988;19(Pt 1):95-111.
2. Calonje JE, Brenn T, Lazar A, McKee P. McKee's Pathology of the skin: with clinical correlations, 4th ed. Edinburgh: Elsevier/Saunders; 2012.
3. Gardner JM. Pigmented villonodular synovitis (PVNS) & giant cell tumor of tendon sheath. [Video]. YouTube. https://youtu.be/E35364G8kFY. Published November 29, 2018. Accessed March 9, 2019.
4. Breathnach SM. Amyloid and amyloidosis. J Am Acad Dermatol 1988;18(Pt 1):1-16.
5. Kibbi AG, Rubeiz NG, Zaynoun ST, Kurban AK.. Primary localized cutaneous amyloidosis. Int J Dermatol 1992;31:95-8.
6. Riddle ND, Gardner JM. The pale blue slide: Avoiding myx-ups and mishaps in cutaneous myxoid tumors. Diagn Histopathol 2016;22:152–66.
7. Shidham V, Chivukula M, Basir Z, Shidham G. Evaluation of crystals in formalin-fixed, paraffin-embedded tissue sections for the differential diagnosis of pseudogout, gout, and tumoral calcinosis. Mod Pathol 2001;14:806-10.
8. Johnson G, Gardner JM, Shalin SC. Polarizable crystals in apocrine sweat gland tumors: A series of three cases. J Cutan Pathol 2017;44:698-702.
9. Levin CY, Maibach H. Exogenous ochronosis. An update on clinical features, causative agents and treatment options. Am J Clin Dermatol 2001;2:213-7.

11 HEMATOPOIETIC INFILTRATES

I still find hematopathology to be quite challenging, even in the skin. Many entities have a very similar appearance on hematoxylin and eosin (H&E)-stained slides and require a significant amount of ancillary workup. Reactive infiltrates can mimic neoplastic ones and vice versa. Classification schemes change often and new entities are constantly described. Entire books have been devoted to the topic of cutaneous hematopathology, so there is no way this chapter could possibly do justice to this vast and convoluted topic. I focus only on select cutaneous hematopathology diseases here; many entities are only briefly mentioned or skipped altogether because they are too complicated to deal with appropriately in the limited space available.

JUVENILE XANTHOGRANULOMA

Juvenile (solitary) xanthogranuloma (JXG) is a benign non-Langerhans histiocytic proliferation that presents as a yellow, orange, red, or brown papule or nodule, usually solitary and located on the head and neck. As the name implies, it most often arises in young children, but a significant subset occurs in adults (1,2).

JXG is composed a mixture of histiocytes (often foamy), multinucleated Touton giant cells, eosinophils, and other inflammatory cells; these components are present in varying proportions from case to case, imparting a wide range of different appearances (fig. 11-1). Classic examples of JXG have numerous eosinophils and Touton giant cells, but either or both of these cell types may be sparse or even absent in some cases, which makes the diagnosis more challenging. Early lesions may be small and composed mostly of uniform mononuclear histiocytes with pale cytoplasm that fill the papillary dermis; these cases may closely resemble a mastocytoma. Older lesions may become fibrotic and resemble

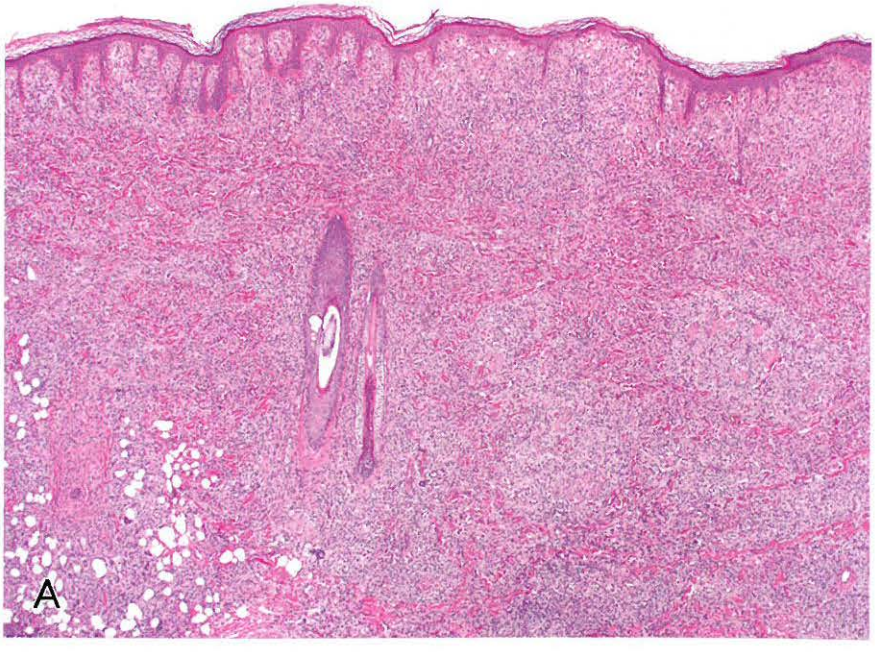


Figure 11-1

JUVENILE (SOLITARY) XANTHOGRANULOMA (JXG)

A: The dermis is filled with a histiocyte-rich infiltrate (the pale pink appearance of the infiltrate at low magnification is a clue to abundant histiocytes). Lesions may be sessile papules/nodules or polypoid.

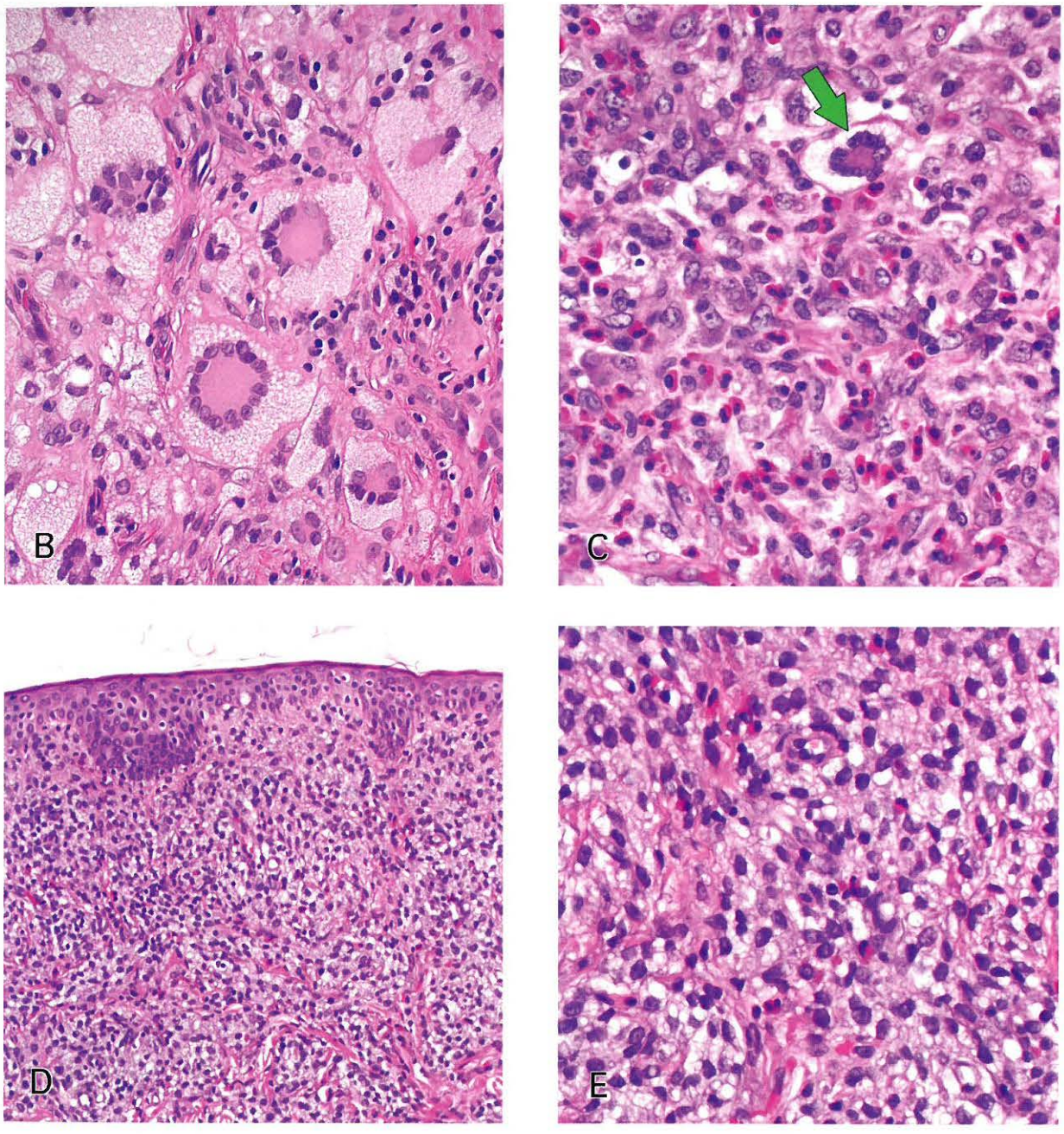


Figure 11-1, continued

B: Multinucleated Touton giant cells are a classic feature of JXG, although their number may vary widely from case to case. Touton giant cells have a ring of nuclei. Inside the ring is pink homogenized cytoplasm. Outside the ring is foamy bubbly cytoplasm. It is like a piece of candy with a smooth creamy center and crispy outer shell.

C: The infiltrate is mainly composed of mononuclear histiocytes, but other inflammatory cells are usually admixed, particularly eosinophils. Some JXGs, like this one, have numerous eosinophils, but other cases have few or even none. Note the Touton giant cell (arrow). When small, Touton giant cells may be hard to see; the ring of foam on the outside is a helpful clue.

D: Early lesions may be small and composed mostly of uniform mononuclear histiocytes with pale cytoplasm that fill the papillary dermis; these cases may closely resemble mastocytosis/mastocytoma (compare with fig. 11-5).

E: The pale slightly foamy cytoplasm of the uniform histiocytes in early JXG gives them a very similar appearance to mast cells. Scattered eosinophils are a useful clue for JXG, but eosinophils may also be seen in mastocytosis/mastocytoma. The cells in this case were CD117 negative, arguing against a mast cell proliferation.

dermatofibroma; the presence of eosinophils in an apparent dermatofibroma always makes me consider the alternative possibility of JXG. Some cases have many large histiocytes with dense eosinophilic cytoplasm that closely resemble the cells of reticulohistiocytoma (see below).

RETICULOHISTIOCYTOMA

Reticulohistiocytoma is a benign non-Langerhans histiocytic proliferation that presents as a solitary red to brown to yellow papule or nodule in adults. When multiple lesions are present (*multicentric reticulohistiocytosis*), the lesions have a predilection to arise on the fingers and may also involve the mucosa or even viscera. Multicentric reticulohistiocytosis is often associated with serious underlying systemic problems, including severe destructive arthropathy (particularly of the interphalangeal joints of the fingers), autoimmune diseases, internal malignancy, and hyperlipidemia (1). The individual lesions of multicentric reticulohistiocytosis can have an identical histologic appearance to solitary reticulohistiocytoma, so the distinction must be made clinically.

Biopsy shows a dermal sheet of large epithelioid histiocytes with abundant dense eosinophilic cytoplasm, often with a two-toned appearance: a more amphophilic purplish hue toward the center of the histiocyte with a paler eosinophilic color toward the periphery (fig. 11-2). Some of these large histiocytes may be multinucleated. Lymphocytes and neutrophils are often present in the background (3). Foamy histiocytes, Touton giant cells, and eosinophils may be present, although if they are abundant, consider the alternative possibility of JXG.

Even though reticulohistiocytoma and JXG appear to be distinct unrelated diseases biologically, they have an overlapping spectrum of histologic features. The presence of large histiocytes with dense eosinophilic cytoplasm favors reticulohistiocytoma over JXG. If the lesion is solitary, then the distinction between the two entities is usually not clinically important.

The large size of the histiocytes could potentially cause confusion with malignancy, such as melanoma or epithelioid sarcoma (3). Immunostains could easily exclude these entities in difficult cases, although usually a H&E stain is all that is needed to make the diagnosis of reticulohistiocytoma.

LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis (LCH) is a neoplastic proliferation of Langerhans cells that can involve the skin, bones, soft tissue, lungs, and other sites. LCH has a variety of clinical presentations ranging from solitary localized lesions to multisystem disseminated disease. The disseminated form is the one most often encountered in the skin. It usually presents in infants (or very rarely in adults) as numerous red-brown tiny papules on the scalp, groin, axillae, chest, or back (1). Sheets of Langerhans cells fill the papillary dermis and sometimes extend into the deeper reticular dermis (fig. 11-3). Unlike most other histiocytoses, LCH often infiltrates the overlying epidermis. Langerhans cells are normally found in the mid-spinous layer of the epidermis, so Langerhans cells (both normal and neoplastic ones) possess the ability to cross the basement membrane and enter the epidermis whereas other histiocytes do not. Eosinophils are often present in the background.

The uniform histiocytes of LCH are usually smaller than the histiocytes of reticulohistiocytoma or Rosai-Dorfman disease. In LCH, the histiocytes have nuclear grooves that give them either a coffee bean or kidney/reniform shape, depending on the angle of section through the cell. LCH expresses S-100 protein, CD1a, and Langerin (CD207) by immunohistochemistry.

Increased Langerhans cell density in the dermis can be seen in many reactive processes and inflammatory dermatoses, and adjacent to various neoplasms. Clusters of Langerhans cells within intraepidermal spongiotic vesicles can be seen in contact dermatitis and other spongiotic dermatoses or in the epidermis overlying arthropod bite reactions. I have seen aggregates of Langerhans cells within dermatofibromas (particularly when there is aneurysmal change) and occasionally within JXG. It is important not to confuse these entities with LCH, which is a neoplastic process that may have significant clinical implications. The histologic features in combination with the clinical information is usually enough to distinguish these from true LCH. When there is any uncertainty, I discuss the case with the dermatologist and request clinical follow up and/or a repeat biopsy.

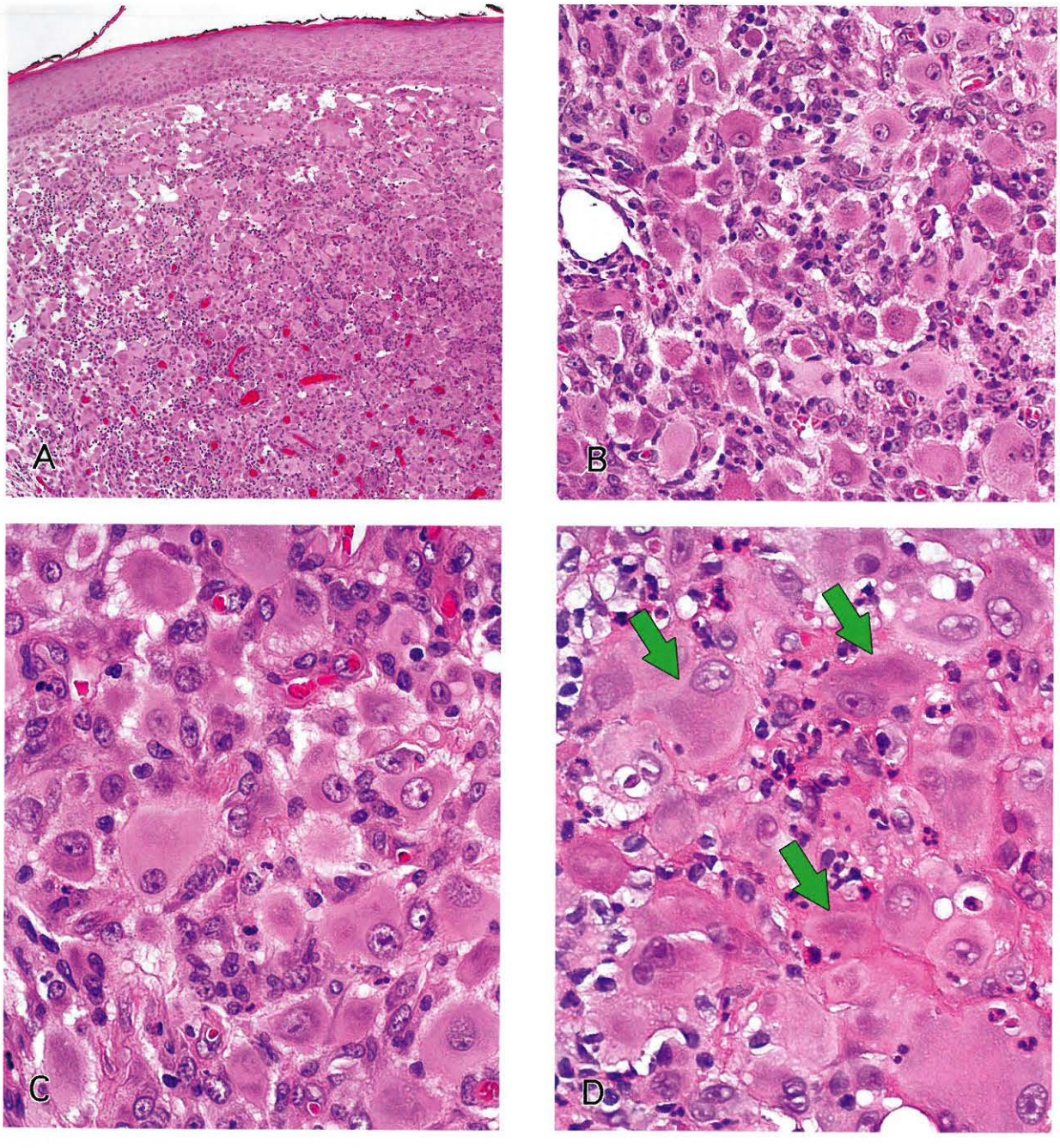


Figure 11-2

RETICULOHISTIOCYTOMA

A: Like JXG, the dermis is filled with a mixed infiltrate that is rich in histiocytes.

B: There are numerous large epithelioid histiocytes with abundant dense eosinophilic cytoplasm. Smaller histiocytes and other inflammatory cells are intermingled between them.

C: A closer look at the epithelioid histiocytes. They can be so large as to potentially cause confusion with melanoma or epithelioid sarcoma. Immunostains can easily exclude those entities in difficult cases, but usually only H&E stain is needed.

D: The histiocytes often have a characteristic "two-toned" appearance, showing a more amphophilic purplish hue toward the center of the histiocyte with a paler eosinophilic color toward the periphery (arrows). Lymphocytes and neutrophils are often present in the background.

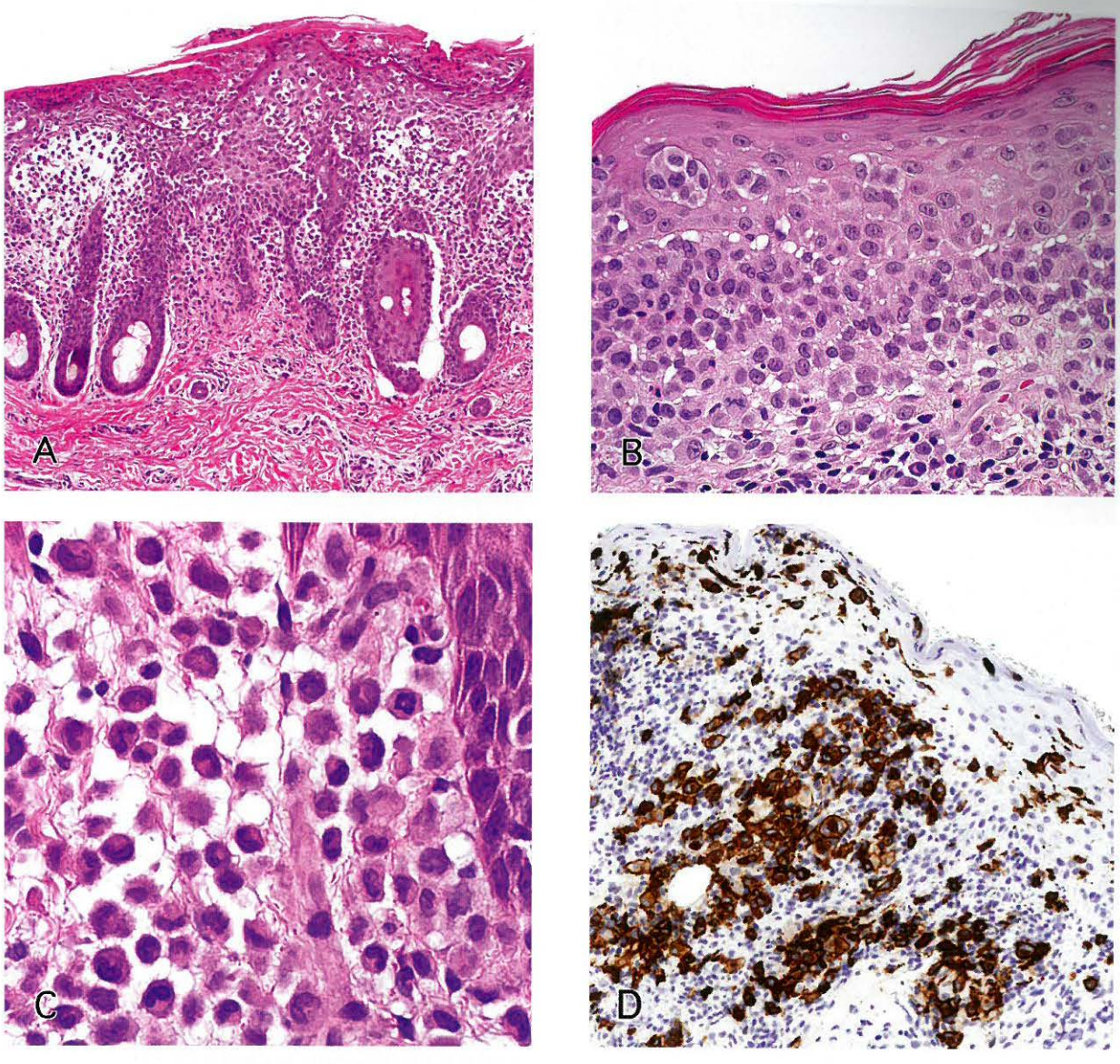


Figure 11-3

LANGERHANS CELL HISTIOCYTOSIS (LCH)

A: Numerous histiocytes fill the papillary dermis and extensively infiltrate into the overlying epidermis.

B: A closer view shows how the dermal-epidermal junction is partially obscured by the numerous Langerhans histiocytes infiltrating the epidermis. Do not confuse these with pagetoid melanocytes! Both are S-100 protein positive; CD1a (positive in Langerhans cells) and SOX-10 (positive in melanocytes) could sort this differential out if needed.

C: Langerhans histiocytes have nuclear grooves that give them either a coffee bean or kidney/reniform shape, depending on the angle of section through the cell.

D: CD1a immunostain highlights numerous Langerhans cells clustered in the dermis with scattered cells infiltrating the epidermis.

Indeterminate dendritic cell tumor (*indeterminate cell histiocytosis*) is a very rare disorder but worth mentioning here because it is a close mimic of LCH. It is usually characterized by one or multiple skin papules that histologically show cells filling the dermis that have many similarities to Langerhans cells, save for the absence of Birbeck granules. These cells express S-100 protein and CD1a but are negative for Langerin (4). Langerin serves as a more readily

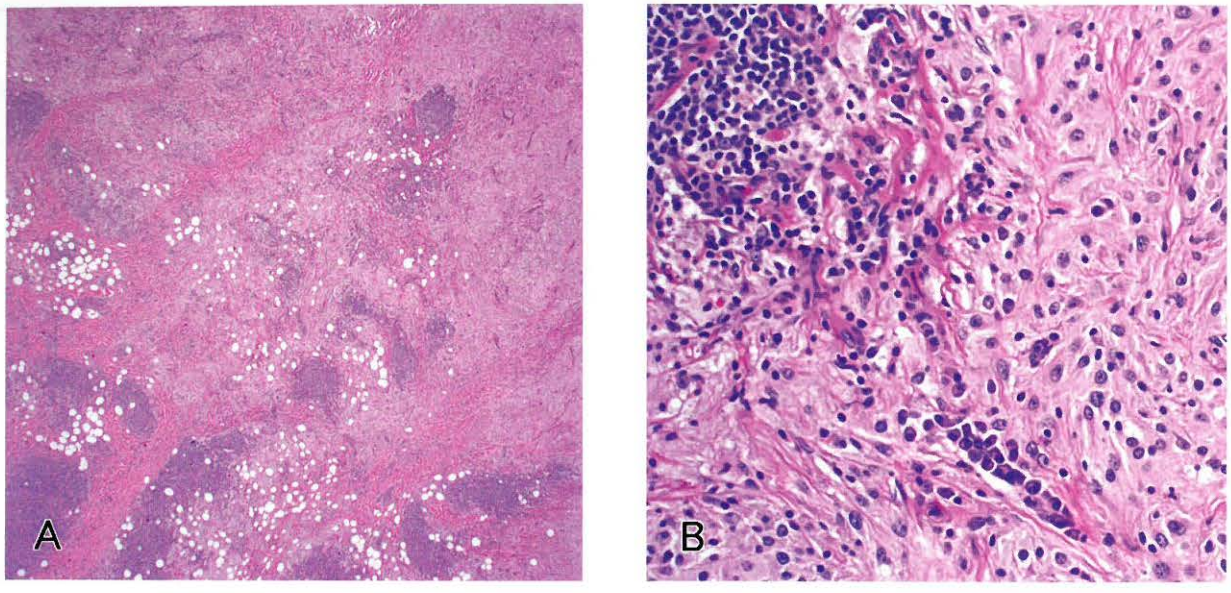


Figure 11-4

ROSAI-DORFMAN DISEASE (RDD)

A: At low magnification, RDD usually has a "pink and blue" appearance. The pink zones represent sheets of large histiocytes with abundant pale eosinophilic cytoplasm. The blue zones represent lymphocytic aggregates (bottom left). Note the white fat cells entrapped within the tumor; extranodal RDD is often centered in the subcutis.

B: A closer look at RDD. The large histiocytes have abundant pale pink or gray cytoplasm. Lymphocytes (top left) and plasma cells (bottom center) are usually present.

available surrogate marker for Birbeck granules in lieu of electron microscopy in these cases. I keep this entity in the differential for cases where the biopsy shows features suggestive of LCH but the clinical scenario does not fit well for LCH (e.g., one or few skin papules in an adult).

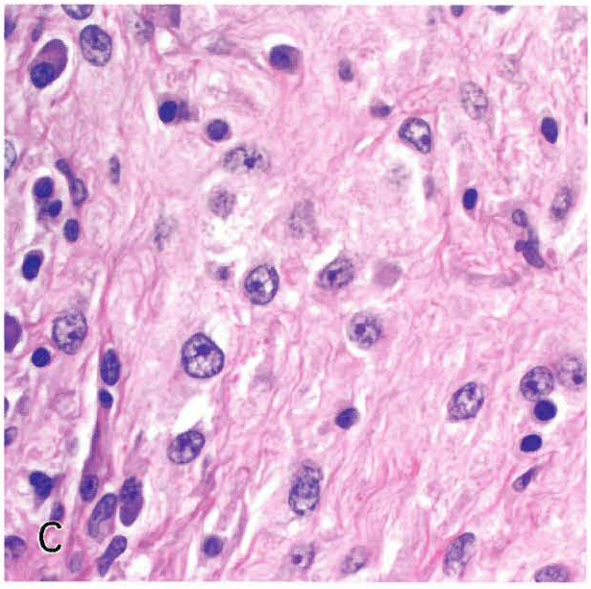
ROSAI-DORFMAN DISEASE

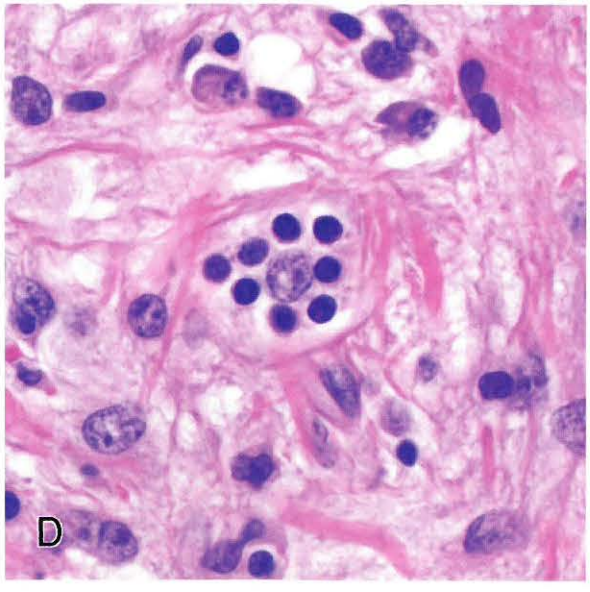
Rosai-Dorfman disease (RDD) is a histiocytic proliferation that was originally described within lymph nodes (*sinus histiocytosis with massive lymphadenopathy*). It can also present as a soft tissue mass (*extranodal RDD*); some of these patients also have nodal involvement. "RDD" throughout the rest of this chapter will refer to extranodal RDD. Cutaneous RDD is usually centered in the subcutis; it may also extend into the overlying dermis but cases of dermal-only RDD are rare in my experience.

At low magnification, RDD usually has a "pink and blue" appearance (fig. 11-4). The pink zones represent sheets of large histiocytes with abundant pale eosinophilic cytoplasm. The blue zones represent lymphocytic aggregates, sometimes with germinal center formation. At higher magnification, the large histiocytes of RDD have very distinct cytologic features: large round nuclei with pale vesicular chromatin and prominent central nucleoli. With a bit of practice, they are usually easy to distinguish from reactive histiocytes or other histiocytic proliferations. The nuclear features are the most useful diagnostic feature to help confirm (or exclude) the diagnosis of RDD. Plasma cells are usually present in the background, often aggregated around elongated blood vessels, which is another helpful clue.

The histiocytes of RDD usually express S-100 protein, which can be used to support the diagnosis in difficult cases. Some cases of RDD become very sclerotic and inflamed, which can obscure the small residual pockets of RDD histiocytes; S-100 protein immunostain highlights the characteristic histiocytes in those cases.

"Emperipolesis," the classic buzzword for RDD, refers to lymphocytes or other inflammatory cells floating within the abundant cytoplasm of the large histiocytes. Emperipolesis is usually present in RDD, but it often looks





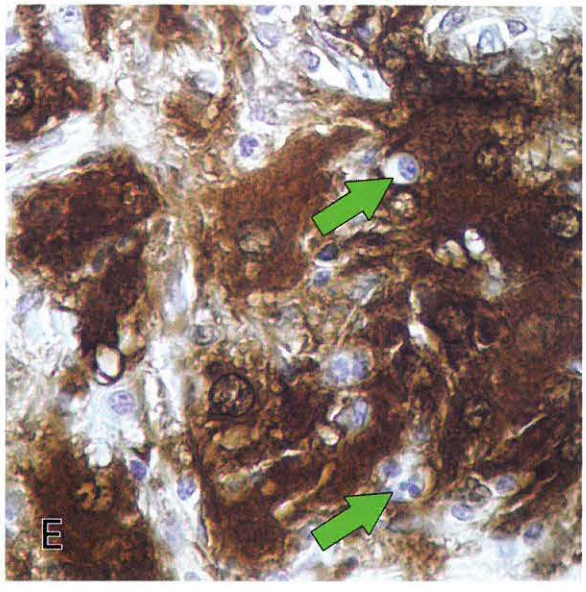


Figure 11-4, continued

C: The histiocytes of RDD have very distinct cytologic features: large round nuclei with pale vesicular chromatin and prominent central nucleoli. Plasma cells are usually present (top left). The scattered small dark nuclei are lymphocytes within histiocyte cytoplasm; this is technically emperipolesis although it does not look like the classic "textbook" picture of it.

D: This is the classic "textbook" picture of emperipolesis: multiple lymphocytes (or other inflammatory cells) are present within the cytoplasm of a large RDD histiocyte. In many cases, however, it is less dramatic than seen here.

E: The large histiocytes express S-100 protein. Emperipolesis is sometimes visualized more easily on an S-100 protein immunostain than on H&E since the cytoplasmic vacuoles containing the inflammatory cells (arrows) stand out more clearly against the darkly stained histiocyte cytoplasm.

less dramatic than the classic images shown in lectures and textbooks. When I am trying to take a picture of emperipolesis for a lecture, I often have to hunt around over numerous fields to find a classic "picture perfect" example of it. Emperipolesis is sometimes visualized more easily on an S-100 protein immunostain than on H&E since the cytoplasmic vacuoles containing the inflammatory cells stand out more clearly against the darkly stained histiocyte cytoplasm.

Nevertheless, the diagnosis of RDD can usually be made easily on H&E using the histologic and cytologic features discussed above regardless of whether or not emperipolesis is identified. Emperipolesis is not totally specific for RDD and can be seen in other diseases. Emperipolesis is a pretty microscopic curiosity that when present is the "icing on the cake" for a diagnosis of RDD, but I do not use it as a primary or gold standard diagnostic feature.

RDD and LCH are often discussed together in dermatopathology education courses since both are composed of histiocytes that express S-100 protein. Despite that similarity, these two diseases are otherwise quite different both histologically and clinically; I almost never seriously

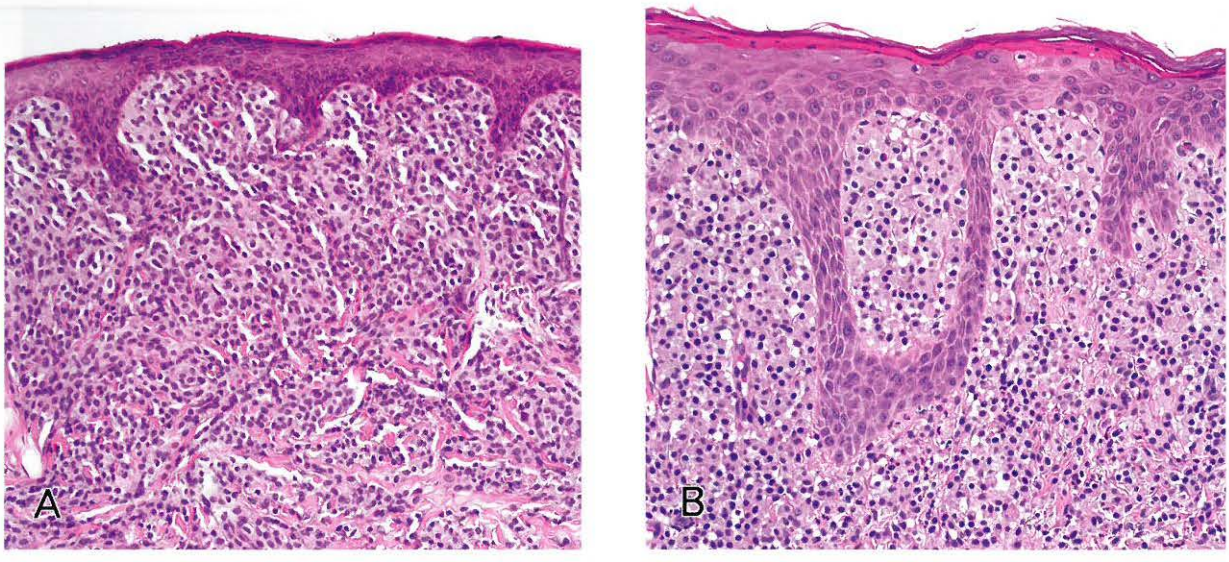


Figure 11-5

MASTOCYTOSIS

A: Numerous mast cells fill the papillary dermis and also extend down into the reticular dermis. The infiltrate is often pale purple to slightly blue.

B: The dermal papillae are completely packed with mast cells. In this case, the cytoplasm is pale pink-gray. Unlike LCH, the infiltrate is confined to the papillary dermis and does not infiltrate the epidermis. It respects the boundary of the basement membrane.

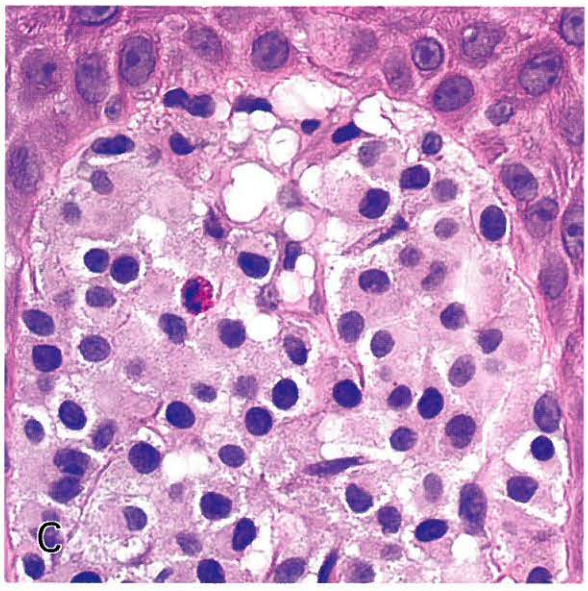
consider RDD in my differential diagnosis for LCH or vice versa.

MASTOCYTOSIS

Mast cell proliferations in the skin can take several forms clinically. *Mastocytoma* is usually a solitary nodule in young children that "urticates" (produces wheals/hives) when stroked (Darier sign). *Urticaria pigmentosa* (UP) is another form of mastocytosis in childhood that presents as a generalized eruption of multiple red-brown urticarial papules. *Telangiectasia macularis eruptiva perstans* (TMEP) is the adult form of cutaneous mastocytosis, presenting with flat red-brown macules that often have telangiectasias. Some patients with mastocytosis also have systemic involvement. These different forms can show an overlapping spectrum of features microscopically. On my pathology report, I usually simply make a line diagnosis of "mastocytosis" and allow the dermatologist to decide which form it fits best with clinically.

A general rule that I find useful is that cutaneous lesions of mastocytosis tend to have lower cellularity with increased age of the patient. In children, mastocytosis lesions (mastocytoma and UP) usually have numerous mast cells, which correspond to a raised papule or nodule clinically (fig. 11-5). These mast cells fill the papillary dermis and may also extend into the reticular dermis. LCH could enter the differential diagnosis, as it also presents with a cellular mononuclear infiltrate that fills the papillary dermis. An easy clue to tell them apart is that LCH usually infiltrates the epidermis whereas mastocytosis does not: mast cells respect the boundary of the basement membrane. In adults, mastocytosis lesions (TMEP) usually have a sparse dermal infiltrate of mast cells, which corresponds to a flat macule clinically. TMEP is one of the "invisible dermatoses," as biopsies often resemble normal skin on H&E at low magnification. A closer look may reveal a subtle increase in dermal cellularity, although it is not always obvious that the cells are mast cells.

Cytologically, mastocytosis may have the classic "fried egg" appearance of normal mast cells (oval nuclei with a moderate amount of granular bluish cytoplasm), but they may also have spindled or histiocytoid morphology,



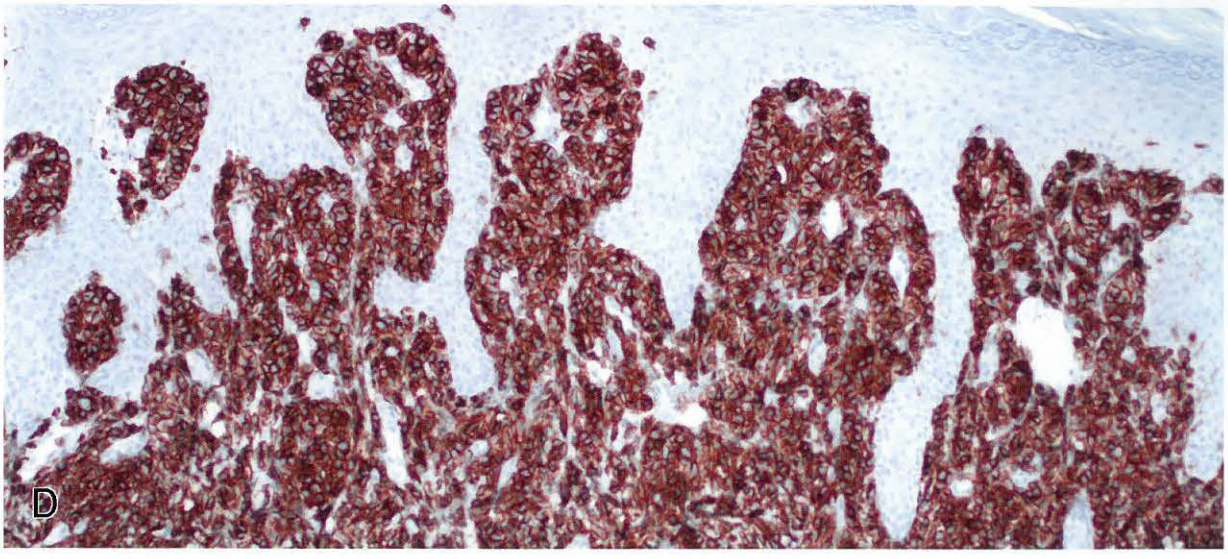


Figure 11-5, continued

C: A closer look at the mast cells shows uniform oval to round nuclei and abundant pale granular cytoplasm. Scattered eosinophils may be present.

D: The mast cells are strikingly positive on a CD117 (CKIT) immunostain.

which can make them difficult to recognize on H&E. Immunostains (CD117 [CKIT] or mast cell tryptase) or special stains (Giemsa or toluidine blue, both of which are metachromatic, turning the mast cell cytoplasmic granules a magenta or purple color) are often needed to confirm the diagnosis in these subtle cases.

Even with these stains, it can still be difficult in some cases to know how many mast cells is enough to make a diagnosis of mastocytosis. Clustering of mast cells around vessels is the most useful clue. As usual, a discussion with the dermatologist is often helpful. Increased dermal mast cells can also be seen in inflammatory and reactive conditions. If an immunostain shows increased mast cells but without clustering, I usually state in the microscopic description that mast cells are increased but are within a range that I would expect for the degree of inflammation present and that no clustering around vessels is appreciated. If I have any concern for mastocytosis, I add a comment that the increased mast cells are suspicious for possible mastocytosis but fall short of a definitive diagnosis on this biopsy; clinical follow up with repeat biopsy may be helpful in confirming the diagnosis.

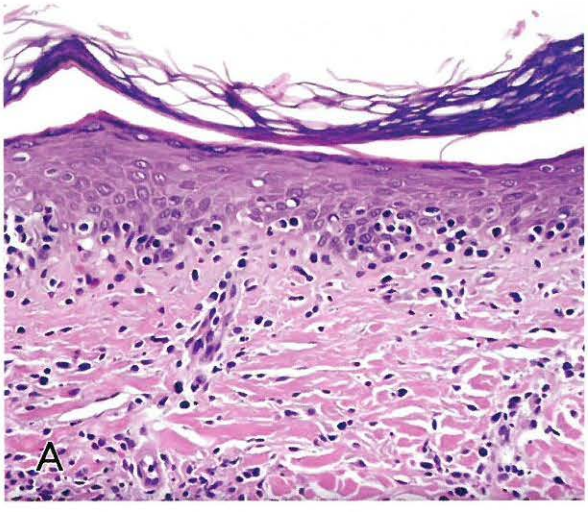
Figure 11-6

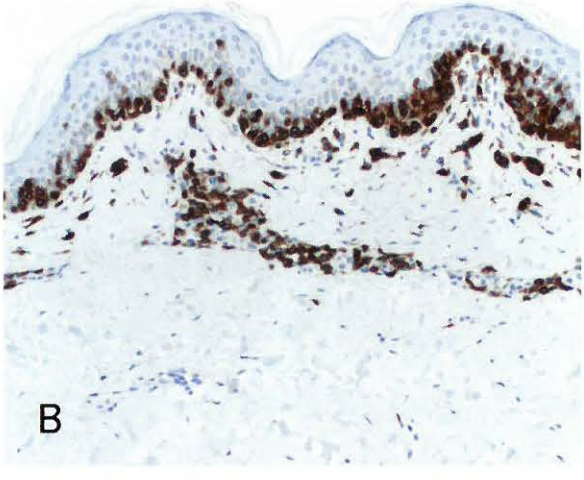
MYCOSIS FUNGOIDES (MF)

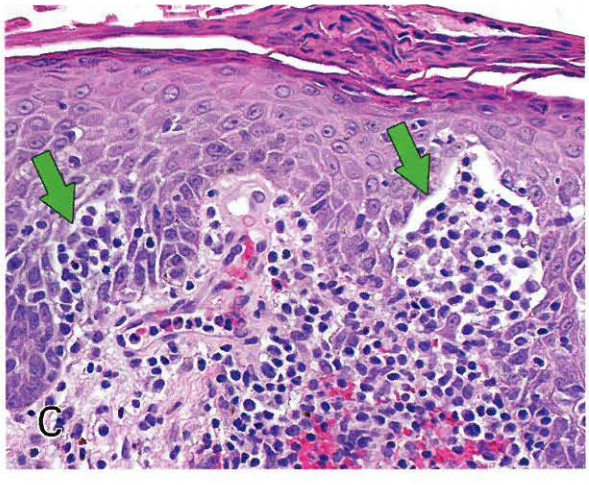
A: "Tagging" of individual lymphocytes along the basal layer is one form of epidermotropism. The lymphocytes are often surrounded by white vacuoles or "halos." This pattern can mimic vacuolar interface dermatitis, but unlike true interface dermatitis, dying/apoptotic keratinocytes are usually rare or absent in MF (exceptions exist). The thick wiry collagen in the papillary dermis is a common finding.

B: A CD3 immunostain highlights numerous lymphocytes tagging along the basal layer. Note the absence of spongiosis.

C: Small intraepidermal clusters of lymphocytes (Pautrier microabscesses; arrows) are another form of epidermotropism. These could mimic the Langerhans cell aggregates seen in spongiotic dermatitis. However, there is a relative lack of spongiosis for how many lymphocytes are in the epidermis here ("too much for too little"); this is a very useful clue for MF.







MYCOSIS FUNGOIDES

Mycosis fungoides (MF) is the most common form of *cutaneous T-cell lymphoma* (CTCL). The terms MF and CTCL are often used interchangeably in practice, although this is not technically correct as there are multiple other forms of CTCL aside from MF. MF has patch, plaque, and tumor stages. A classic clinical history is a patient with longstanding erythematous or hyperpigmented scaly patches on sun-protected sites like the buttocks or trunk. The patch stage of MF is often misdiagnosed as chronic eczematous/atopic dermatitis or other spongiotic dermatitis, both clinically and microscopically, sometimes for many years before diagnosis. MF is incurable but usually indolent, although some cases progress to tumor stage and show aggressive behavior (5).

The most characteristic classic microscopic feature of MF is epidermotropism (fig. 11-6). T cells infiltrate the epidermis, both as solitary lymphocytes and also as small clusters (Pautrier microabscesses), and show "tagging" of individual lymphocytes along the basal layer. Lymphocytes may also be present in the epidermis in inflammatory dermatoses, of course, but they are accompanied by other features of inflammatory response. Spongiotic dermatitis has exocytosis of lymphocytes into the epidermis, but there is also prominent spongiosis. Vacuolar and lichenoid interface dermatitis show lymphocytes along the basal layer, but there are also dying keratinocytes present. In MF, spongiosis, dying keratinocytes, and other inflammatory features are usually absent or much less than would be expected for the number of lymphocytes present in the epidermis ("too much for too little" is a catchphrase I like

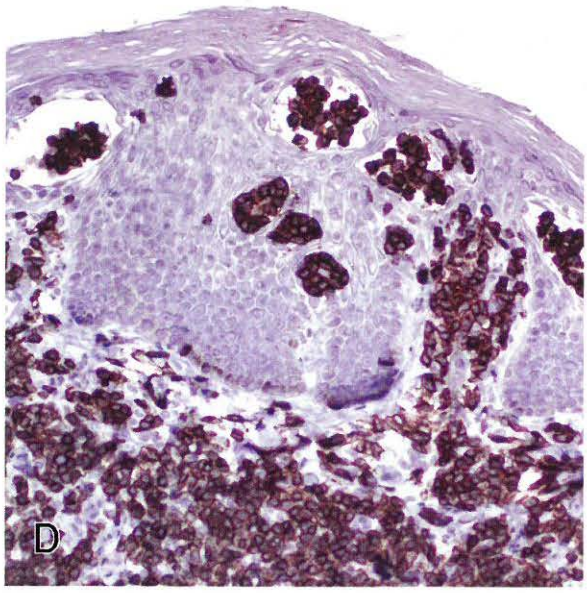


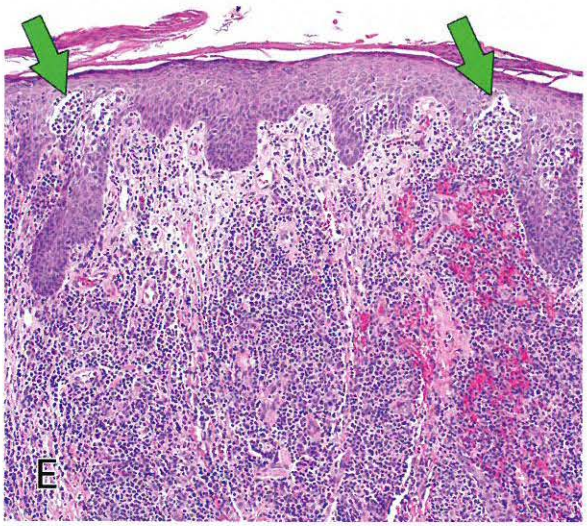
Figure 11-6, continued

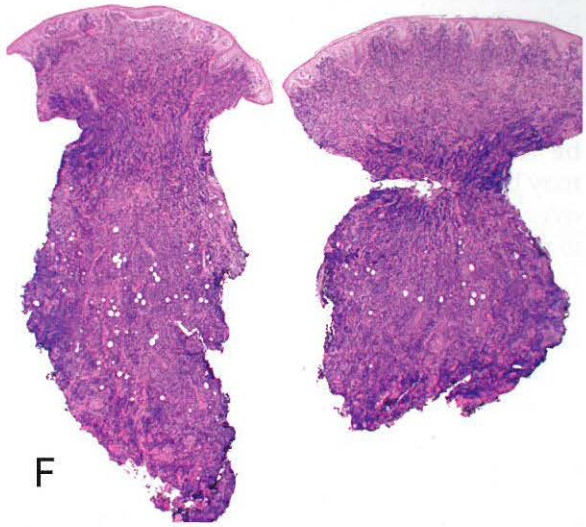
D: Multiple intraepidermal Pautrier microabscesses are highlighted on this CD3 immunostain, proving that they are T cells rather than Langerhans cells. Langerhans cells are positive for CD4, as are the T cells in most cases of MF; CD3 and/or CD1a can help distinguish them.

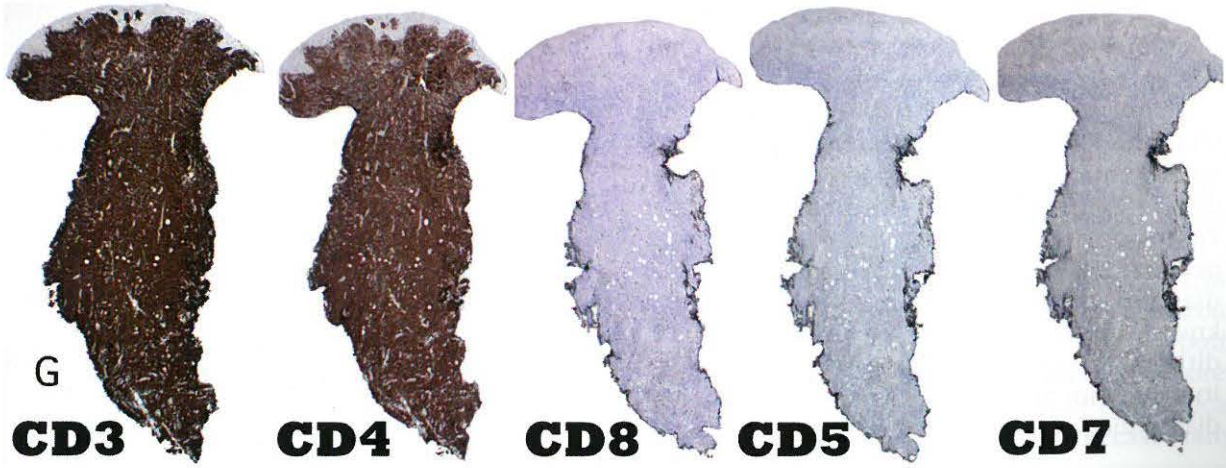
E: Plaque stage MF usually has a denser dermal infiltrate of lymphocytes and more obvious epidermotropism. Note the Pautrier microabscesses (arrows).

F: Tumor stage MF presents as nodules or masses clinically. Microscopically, it shows sheets of lymphocytes filling the dermis (and also the subcutis in this case). Epidermotropism is sometimes absent in these cases. A known history of MF or areas of conventional patch or plaque stage MF in the background skin away from the tumoral areas is needed to distinguish tumor stage MF from other forms of T-cell lymphoma.

G: MF is classically CD3+, CD4+, and CD8 negative (exceptions exist). There may be "loss" of normal T-cell markers like CD5 or CD7, particularly in tumor stage MF. Unfortunately, the immunostains rarely work as perfectly as shown here, and when they do, it is usually in cases that are already obvious on H&E. This is the same case as figure F.







to use for this, meaning there is too much of a lymphocytic infiltrate but too little spongiosis or other corresponding inflammatory features). The presence of wiry collagen fibers in the papillary dermis is another useful clue for MF, although chronic spongiotic dermatitis can show this too. Some cases have a dense band-like lymphocytic infiltrate in the superficial dermis in addition to the above features.

Unfortunately, cytologic atypia is often not a helpful feature in making a diagnosis of MF, as many early patch stage cases of MF have small lymphocytes that closely resemble normal or reactive lymphocytes histologically. On electron microscopy, the lymphocytes of MF classically have a wrinkled cerebriform appearance. However, this is very difficult to use as a diagnostic feature on light microscopy. It is true that wrinkled lymphocyte nuclei are seen in many cases of MF if one looks closely, but on the other hand, I can hallucinate wrinkled lymphocytes in almost any inflammatory infiltrate.

The microscopic features of MF vary depending on the stage. In patch stage MF, there may be few lymphocytes, and epidermotropism may be subtle or even absent. Multiple biopsies over time are often required to arrive at a firm diagnosis of MF in these cases, because the microscopic features may be essentially impossible to distinguish from inflammatory dermatoses at first. When there is suspicion for MF clinically or pathologically but the histologic features fall short of a definitive diagnosis, I usually add a comment that I do not favor MF on this biopsy, but that clinical follow-up and repeat biopsies over time are recommended. The criteria and scoring system described by Guitart et al. (6) is useful in standardizing the diagnostic terminology, especially for cases that are suspicious but not entirely diagnostic for MF.

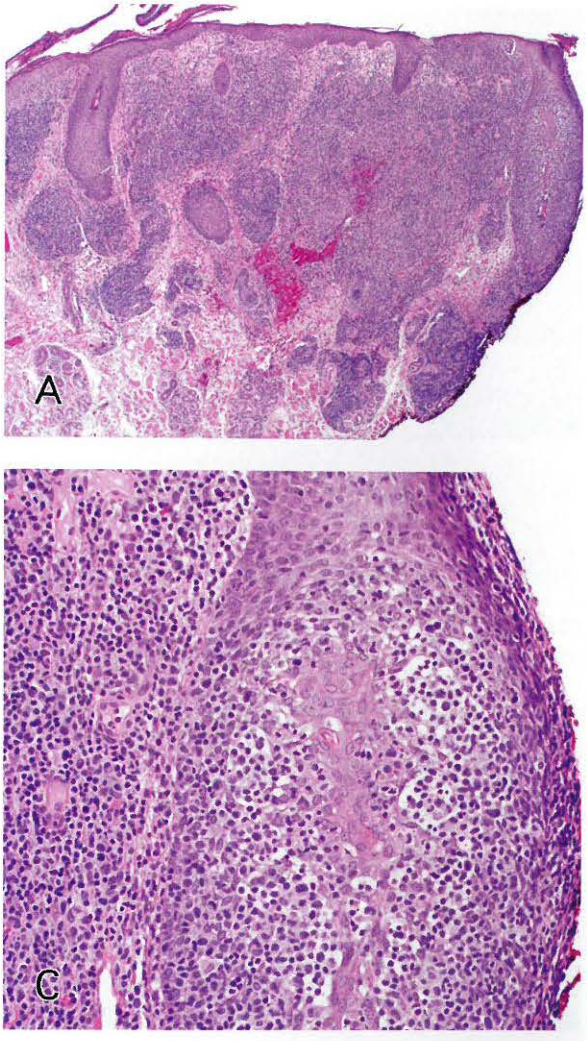
Plaque stage MF tends to have more obvious characteristic microscopic features, such as epidermotropism. Tumor stage MF may show diffuse sheets of lymphocytes filling the dermis. Tumor stage cases may lack epidermotropism or other typical features of MF. To arrive at the diagnosis, the patient should ideally have a known history of biopsy-proven MF or an additional biopsy of patch or plaque stage lesions in nontumor areas of background skin showing diagnostic features of MF. Some cases of tumor stage MF have large cell transformation, in which over 25 percent of the tumor cells are large (>4x the size of a small lymphocyte); these patients often have a poor prognosis (7).

Immunohistochemistry and T-cell receptor (*TCR*) gene rearrangement analysis can be helpful in confirming a diagnosis of MF in some cases. Classically, MF is composed of T cells that express CD3 and CD4 and that often show loss or diminished expression of CD7 (4,8). More advanced cases may show loss of CD5 or other normal T-cell markers (4). The Pautrier microabscesses in MF can mimic the Langerhans cell microabscesses seen in contact dermatitis and other forms of spongiotic dermatitis. Langerhans cells express CD4 (just like most cases of MF) but they are negative for CD3; beware of using CD4 without a corresponding CD3 when working up a case of potential MF, as the CD4-positive Langerhans cells can mimic epidermotropism.

Like other T-cell lymphomas, MF has a clonal *TCR* gene rearrangement. Unfortunately, in real life, the cases where these ancillary tests work best are often the cases where the diagnosis is already obvious on H&E. In subtle cases of patch stage MF, where the diagnosis is very difficult due to sparse cellularity of lymphocytes, immunostains are often difficult to interpret and TCR analysis may show false negative results. Where the ancillary studies are most needed, they tend to perform most poorly in my experience, which is frustrating. Reactive processes may have positive TCR clonality studies and may have overlapping immunohistochemical findings with MF, which further complicates the situation.

Ancillary testing can be useful to help support a diagnosis of MF, but over-reliance on these tests in lieu of clinical information and H&E features can easily lead to misdiagnosis. A 2018 publication of appropriate use criteria in dermatopathology discusses the appropriateness of ancillary testing in MF in much greater depth (9).

Some cases of MF lack CD4 and instead express CD8 and other cytotoxic T-cell markers (10,11). These cases of CD8+ MF must be distinguished from *primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma*, which is a more aggressive form of lymphoma that can very closely mimic CD8+ MF, although it often has a more severe presentation and rapid onset clinically (12).



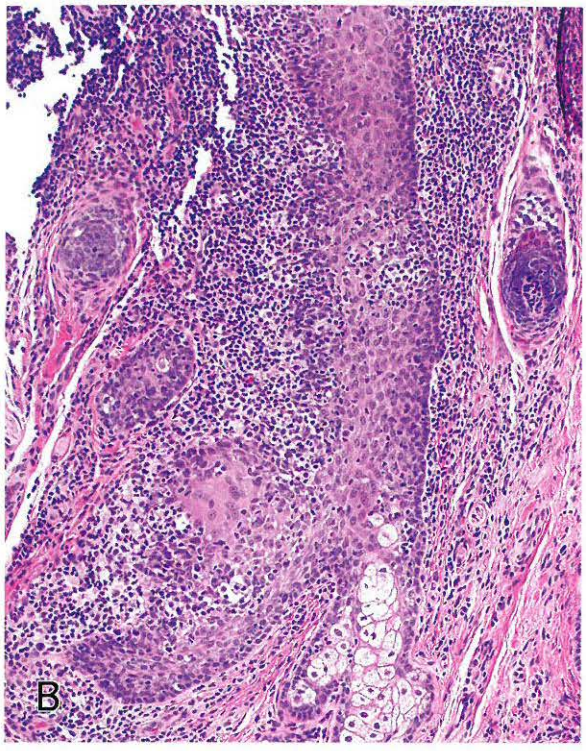


Figure 11-7

FOLLICULOTROPIC MYCOSIS FUNGOIDES

A: A dense dermal infiltrate of T cells invests hair follicles (folliculotropism; far right). In this case, eccrine coils are also surrounded by T cells (syringotropism; bottom).

B: A hair follicle is surrounded and infiltrated by T cells.

C: Hair follicles may become markedly expanded due to the extensive intrafollicular T-cell infiltrate. This is a closer view of the same follicle shown at the far right of A.

Epidermotropism can be seen in a variety of other lymphomas and lymphoproliferative diseases aside from MF (8). A definitive diagnosis of MF must only be made when the histologic findings fit well with the clinical scenario.

Some cases of MF are adnexotropic instead of epidermotropic; neoplastic T cells surround and infiltrate eccrine coils (*syringotropic MF*) and/or hair follicles (*folliculotropic MF*) (fig. 11-7). Folliculotropic MF often presents as papules on the head and neck, sometimes with alopecia, a clinical appearance that is quite different from the classic type of MF discussed above (4,8). In folliculotropic MF, the hair follicles are often expanded by abundant intrafollicular mucin (*follicular mucinosis*) in addition to being infiltrated by lymphocytes (fig. 11-8). Follicular mucinosis may also be seen as an idiopathic incidental finding outside the setting of MF (13,14).

CD30-POSITIVE T-CELL LYMPHOPROLIFERATIVE DISORDERS

CD30-positive T-cell lymphoproliferative disorder is a descriptive diagnosis that encompasses several entities, all of which are characterized by large atypical CD30+ lymphocytes in the dermis. I use this descriptive diagnosis in my biopsy report, along with the following comment:

"The histologic differential includes *lymphomatoid papulosis* (LYP) and *primary cutaneous anaplastic large cell lymphoma* (PC-ALCL), both of which can have identical histologic features and must be distinguished based on clinical features. *Systemic/nodal ALCL* can occasionally

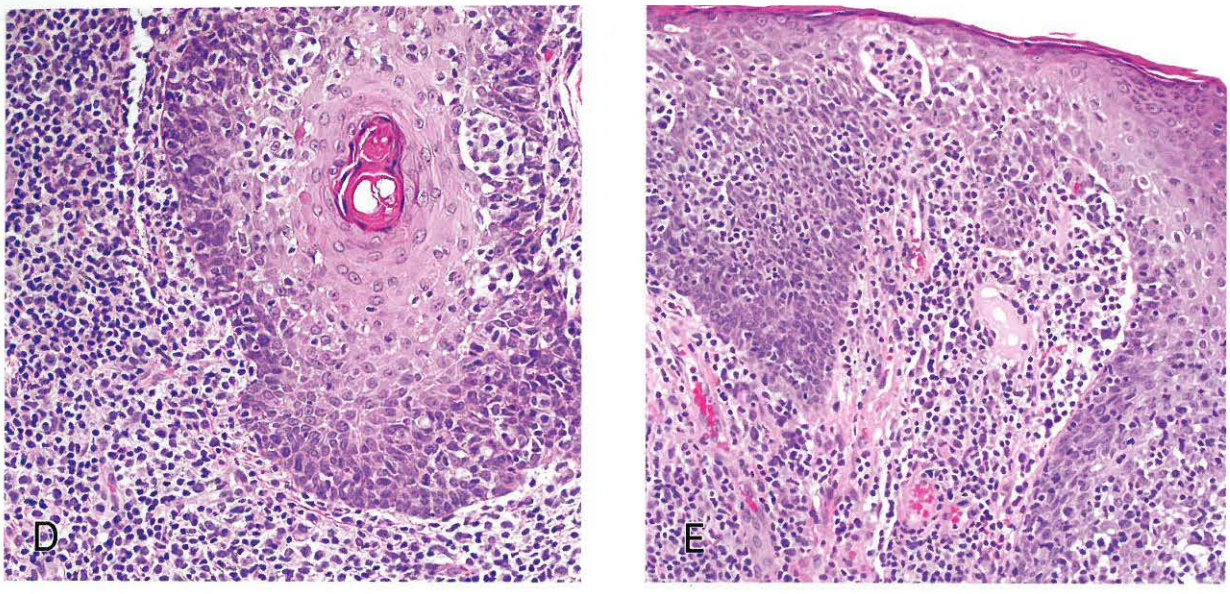


Figure 11-7, continued

D: The hair follicle epithelium is infiltrated by T cells. Some Pautrier microabscesses are present (top right). There is a dense infiltrate of small T cells closely surrounding the follicle.

E: Numerous lymphocytes infiltrate the infundibula of these two hair follicles. Epidermotropism is also present in this case; note the Pautrier microabscess (top center) and numerous scattered single lymphocytes within the epidermis. In many cases of folliculotropic/adnexotropic MF, only adnexal structures are involved and the epidermis is relatively spared.

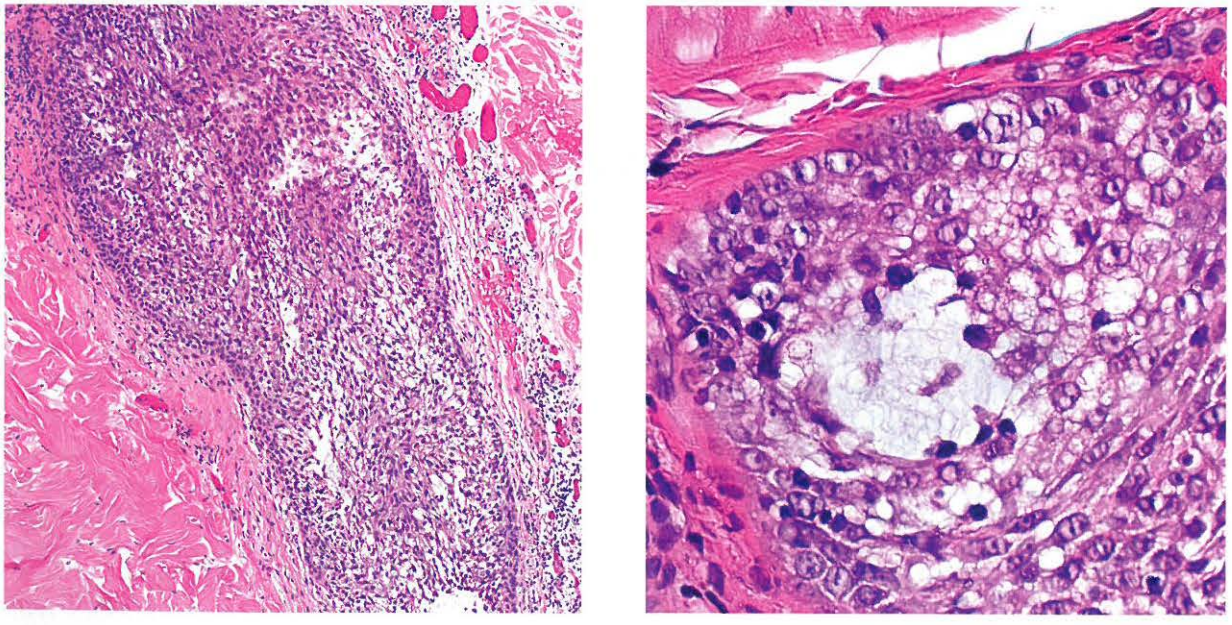
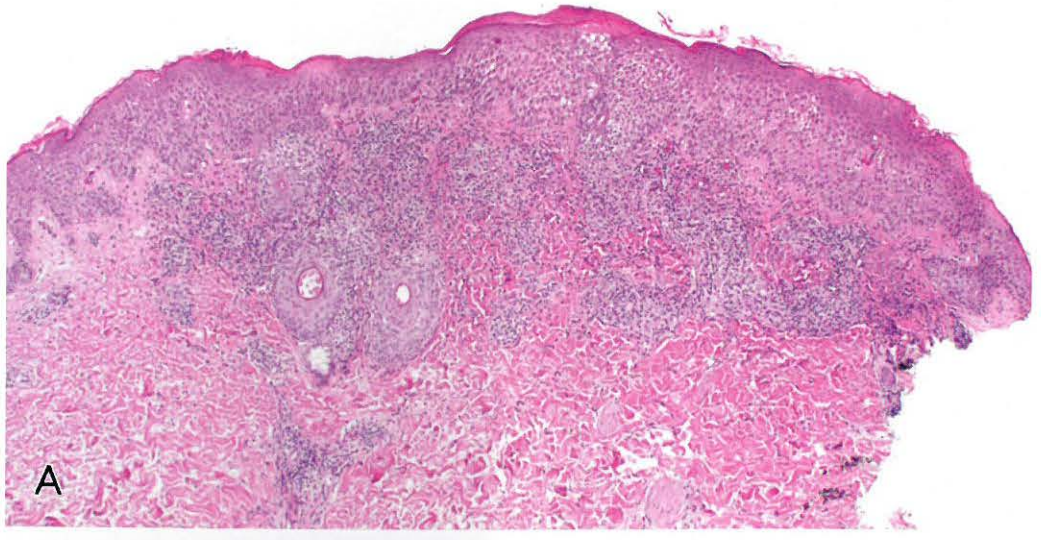


Figure 11-8

FOLLICULAR MUCINOSIS

Left: A hair follicle is markedly distended and expanded. The low-power appearance often resembles follicular spongiosis, but a closer look will reveal mucin between the spaced-out follicular keratinocytes.

Right: Bluish mucin is present between the keratinocytes within a hair follicle.



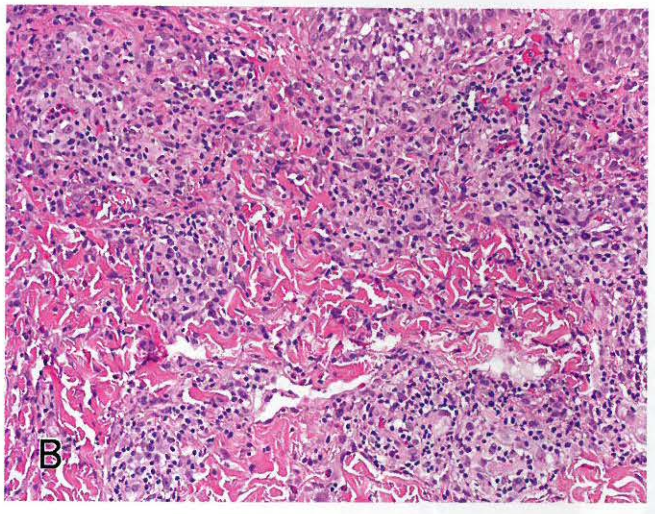


Figure 11-9

LYMPHOMATOID PAPULOSIS (LYP)

A: There is a moderately dense mixed infiltrate in the superficial dermis, giving a vaguely wedge-shaped silhouette. Note how discrete the zone of involved dermis is (i.e., it is flanked by relatively normal skin on both sides); this corresponds to the small papules seen clinically in this case. Spongiosis may sometimes be present in the overlying epidermis, but the dermal infiltrate is usually much denser than would be seen in most forms of spongiotic dermatitis.

B: A closer look shows the patchy distribution of the infiltrate. It is composed of a mixture of small lymphocytes, larger histiocytoid cells (many of which are actually atypical CD30+ T cells), and scattered eosinophils.

involve the skin and have a very similar histologic appearance. *CD30+ large cell transformation of MF* would also be a diagnostic possibility if the patient has a known history or skin exam findings suggestive of MF; correlation with results of a complete dermatologic examination and/or any previous biopsy is essential." Some additional nuances of this differential diagnosis are discussed below.

LYP presents as multiple recurrent erythematous edematous "juicy" papules/nodules that "wax and wane" over time (i.e., each individual lesion arises and then regresses spontaneously within 12 weeks) (8). Microscopically, LYP is characterized by large atypical CD30+ T cells, which may be arranged in a variety of patterns (fig. 11-9). These histologic patterns were originally subdivided into types A, B, and C, although more recently types D and E have been added the growing LYP alphabet soup. (8,15) Types A and C are the most common forms I see in my practice.

In type A LYP, the large atypical CD30+ T cells are scattered individually or as small clusters within the dermis, with a brisk background infiltrate of smaller lymphocytes (mostly T cells) and often many eosinophils. The histologic differential diagnosis for type A LYP includes arthropod bite reaction and scabies, both of which can have scattered large CD30+ reactive T cells (immunoblasts) present in the inflammatory infiltrate (see chapter 7) (16,17). Clinical presentation and the disease course over time are sometimes the only way to distinguish a brisk arthropod bite reaction from LYP. Finding a scabies mite (either on deeper sections or on a

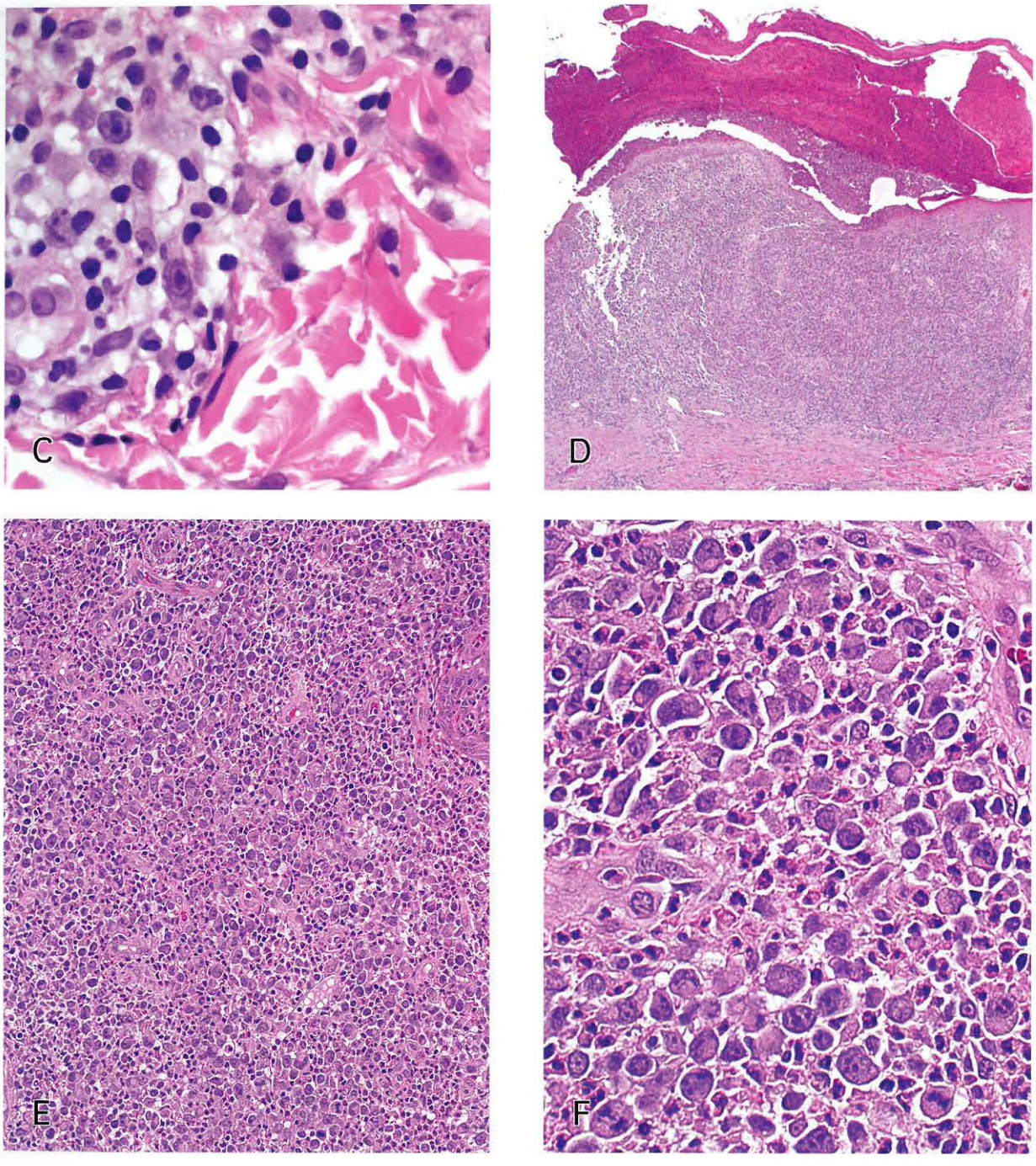


Figure 11-9, continued

C: There are scattered large atypical T cells (left); these were positive on a CD30 immunostain. Eosinophils are often present (not shown). This was a case of type A LYP (figs. A through C are from the same case).

D: The superficial dermis is filled with a relatively discrete zone of infiltrate, but it is much denser than that seen in figure A. There is also epidermal ulceration with overlying scale crust in this case.

E: A closer look shows a dense sheet of large markedly atypical cells with intervening smaller mixed inflammatory cells.

F: These large markedly atypical cells were CD30+ T cells by immunohistochemistry. The clinical history in this case was of multiple waxing and waning papules and nodules that resolved spontaneously. This was a case of type C LYP (figs. D through F are from the same case). Despite the very worrisome histologic appearance, LYP has an excellent prognosis.

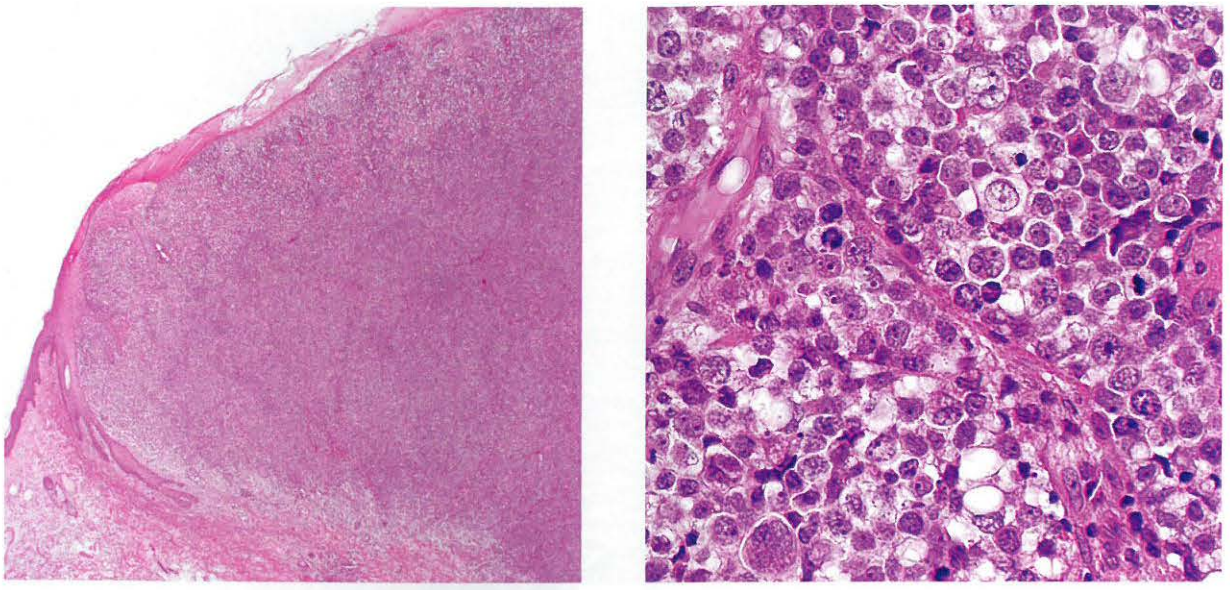


Figure 11-10

PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA (PC-ALCL)

Left: This presented as a large solitary nodule clinically. Biopsy showed a hypercellular dermal sheet of large atypical T cells. Right: A closer look shows numerous markedly atypical large T cells that were CD30+ but ALK-1 negative by immunohistochemistry. Based on the clinical scenario, this was PC-ALCL. Type C LYP, nodal/systemic ALCL secondarily involving the skin, or tumor stage MF with large cell transformation could all have an identical appearance to that shown here. Despite the very worrisome histologic appearance, the prognosis of PC-ALCL is excellent.

skin scraping mineral oil prep performed by the dermatologist) or patient improvement with anti-scabies therapy would, of course, support scabies over LYP.

Angiolymphoid hyperplasia with eosinophilia (ALHE), also known as *epithelioid hemangioma*, can sometimes enter the differential for type A LYP, as well, since it can show scattered large CD30+ cells (18). ALHE usually presents as solitary or closely clustered papules/nodules rather than multiple generalized waxing and waning lesions, and microscopically, it has prominent vessels with large epithelioid endothelial cells.

In difficult cases, I mention that there are increased CD30+ cells and that LYP would be a possibility in the right clinical setting and that clinical follow up is recommended with repeat biopsies over time if the process persists.

In type C LYP, the large atypical CD30+ T cells are numerous, forming a diffuse sheet that fills the dermis. The histologic appearance is essentially identical to that of PC-ALCL, nodal/systemic ALCL secondarily involving the skin, or a tumor stage nodule of MF with CD30+ large cell transformation (see below).

PC-ALCL most often presents as a solitary nodule, although some cases may be multifocal. (1) Histologically, PC-ALCL is identical to type C LYP, with hypercellular dermal sheets of large atypical T cells that strongly and diffusely (>75 percent of cells) express CD30 (fig. 11-10). These usually co-express CD4, although some cases may show loss of T-cell markers. ALK-1 is usually negative. By definition, to make a diagnosis of PC-ALCL, the patient must not have a known history or clinical evidence of MF (8). Despite their very worrisome histologic appearance, both LYP and PC-ALCL have an excellent prognosis.

Nodal/systemic ALCL can sometimes secondarily involve the skin. Although it is unrelated to PC-ALCL, it has a nearly identical histologic appearance. ALK-1 is positive in the majority of nodal ALCLs but is almost always negative in PC-ALCL. However, an aggressive subset of nodal ALCL is ALK-1 negative, and these cases can be impossible to distinguish from PC-ALCL (or type C LYP) without clinical workup. Thus, while a positive ALK-1 stain on a skin biopsy showing ALCL very strongly suggests nodal ALCL, a negative ALK-1 stain cannot exclude

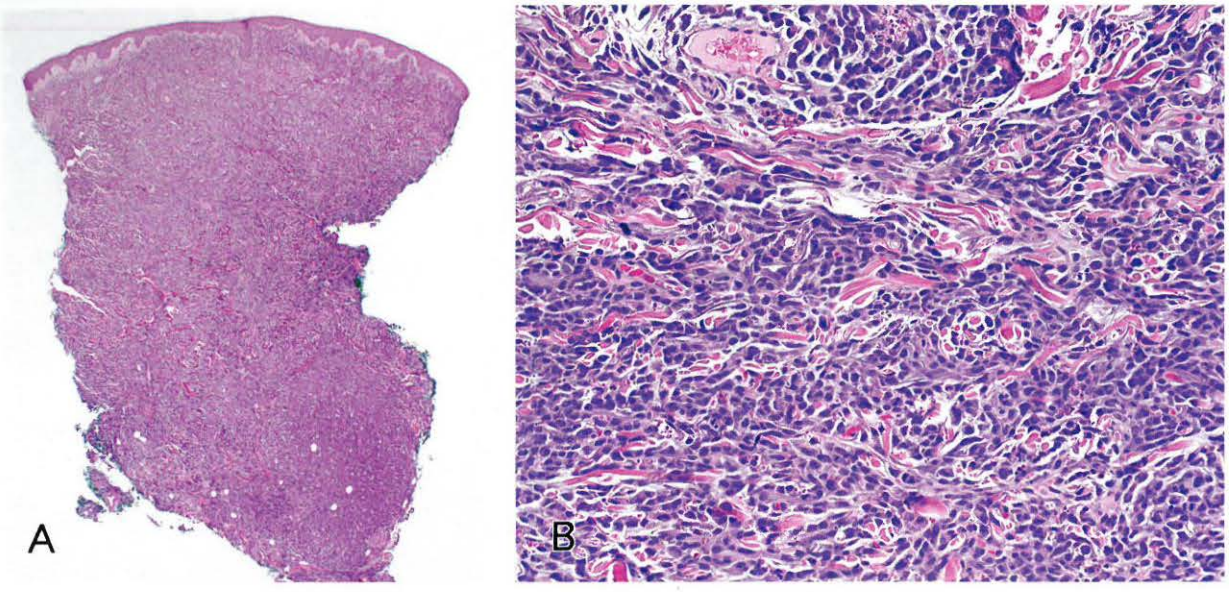


Figure 11-11

LEUKEMIA CUTIS (ACUTE MYELOID LEUKEMIA [AML] INVOLVING SKIN)

A: The dermis and subcutis are filled by a hypercellular infiltrate of round blue cells.

B: The round blue myeloid blasts fill the dermis, often intercalating between the preserved reticular dermal collagen bundles as shown here. I find this pattern is a useful clue for AML leukemia cutis.

that possibility. I usually perform ALK-1 alongside CD30 when working up these cases, but even if ALK-1 is negative, I still mention the possibility of nodal ALCL in the comment.

Tumor stage MF with large cell transformation may express CD30, mimicking LYP and PC-ALCL. The clinical presentation is the key to distinguishing these entities. Large cell transformation of MF often presents as one or multiple nodules, but there is usually conventional patch or plaque stage MF in the background skin away from the nodules. Complete dermatologic examination and correlation with any previous biopsy results to identify conventional MF in the background skin is crucial to making a diagnosis of large cell transformation of MF.

LEUKEMIA CUTIS

Leukemia cutis is skin involvement by leukemia, with *acute myeloid leukemia* (AML) being one of the most common types to do so. The monocytic and myelomonocytic subtypes of AML have a particular tendency to involve the skin (19). Underlying blood/bone marrow involvement is usually present, although rare "aleukemic" exceptions exist, where only skin is involved. In some cases, the skin lesions are the presenting symptom of the patient's leukemia (19).

In AML leukemia cutis, round blue myeloid blasts fill the dermis, often intercalating between the preserved reticular dermal collagen bundles, a useful clue (fig. 11-11). Leukemia cutis is a serious and urgent diagnosis that requires a phone call or other direct communication to report it to the dermatologist so that clinical workup and treatment can be expedited.

If the patient has a known history of leukemia, comparison with the immunophenotype on previous biopsy or flow cytometry reports can be very helpful in guiding the immunohistochemical workup on the skin biopsy. When the history is not known, workup is more difficult, as the myeloid blasts in AML leukemia cutis are often negative for the markers expressed by normal myeloid blasts in the bone marrow, such as CD117 and CD34 (20). CD43, CD68, and lysozyme are very sensitive markers for myeloid leukemia cutis, but they are not specific (20,21). Other nonspecific markers that may be expressed include myeloperoxidase, CD163, CD4, and CD56 (20,21,22).

The differential diagnosis for leukemia cutis includes other hematopoietic malignancies,

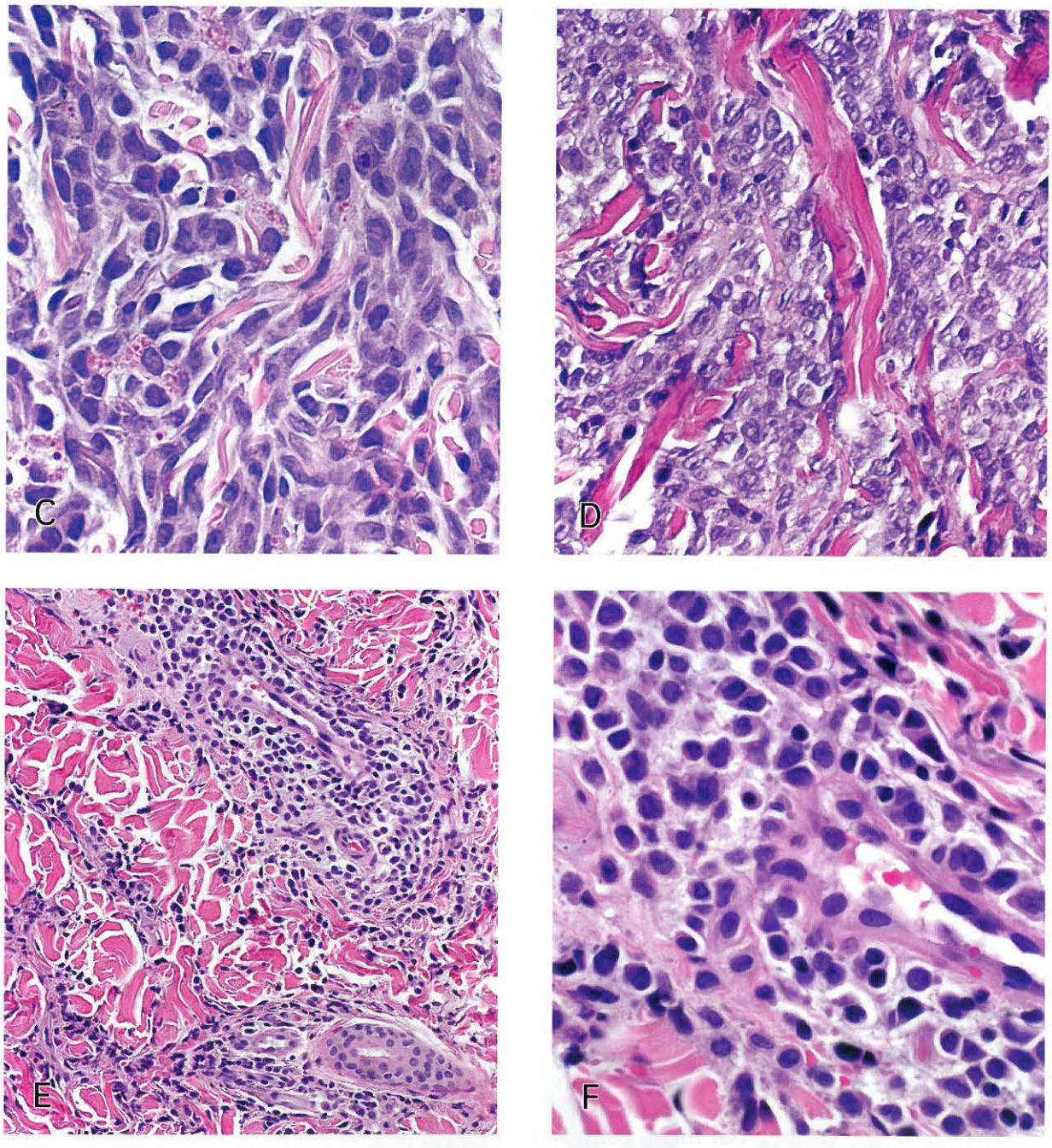


Figure 11-11, continued

C: Many cases of AML leukemia cutis have monocytic or myelomonocytic differentiation. The monocytoid/histiocytoid cytologic features are clearly visible here. This case was positive for lysozyme, CD4, and patchy myeloperoxidase.

D: Other cases may have a more atypical round blue cell appearance. The blasts fill the spaces in between the background reticular dermal collagen bundles.

E: In some treacherous cases, the blasts are sparse. These perivascular blasts could easily be confused with a histiocyte-rich inflammatory process.

F: A closer look at the infiltrate from E. These blasts have a monocytoid/histiocytoid appearance. They are larger than the cells of most inflammatory dermatoses, but they are not overtly malignant cytologically. This case of acute myelomonocytic leukemia proved to be fatal. When I see large histiocytoid cells in the dermis, I try to always keep subtle leukemia cutis in my differential diagnosis.

particularly *blastic plasmacytoid dendritic cell neoplasm, diffuse large B-cell lymphoma*, and *multiple myeloma* involving skin. It also includes *Merkel cell carcinoma, metastatic carcinoma or melanoma*, and other nonhematopoietic malignant round blue cell tumors. Immunohistochemistry can usually sort out this differential diagnosis.

In some treacherous cases, the blasts resemble histiocytes and can be sparse. These subtle cases can mimic inflammatory dermatoses. When I see large histiocytoid cells in the dermis, I try to always keep subtle leukemia cutis in my differential diagnosis. If I have any doubts, I do an immunostain panel, consult my hematopathology colleagues, and recommend correlation with a complete blood count and clinical follow-up.

SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA

Subcutaneous panniculitis-like (alpha-beta) T-cell lymphoma (SPTCL) presents as multiple violaceous to erythematous deep plaques or nodules, a clinical appearance that resembles that of panniculitis. Microscopically, the subcutaneous fat is infiltrated diffusely by small to medium-sized hyperchromatic lymphocytes (fig. 11-12). Individual adipocytes are often surrounded by these lymphocytes ("rimming" of adipocytes). Fat necrosis and nuclear debris are present, as are histiocytes with phagocytosis of nuclear debris. The infiltrate is located within the subcutis without epidermal involvement and with no or very minimal involvement of the dermis. The neoplastic T cells are usually positive for CD3, CD8, TIA-1, granzyme B, perforin, and beta F1 but negative for CD4 and CD56 (1,4,8,23).

Lupus panniculitis can have overlapping microscopic features with SPTCL; subcutaneous sclerosis, numerous plasma cells, and germinal center formation are features favoring lupus panniculitis. Some have suggested a relationship between these two entities, but this is controversial. Many patients with SPTCL also have lupus erythematosus (or other autoimmune diseases) (1,23).

Other forms of lymphoma also infiltrate the subcutis and mimic SPTCL, most notably primary cutaneous gamma-delta T-cell lymphoma. In the past, *primary cutaneous gamma-delta T-cell lymphoma* was lumped together under the SPTCL terminology, since it has a very similar

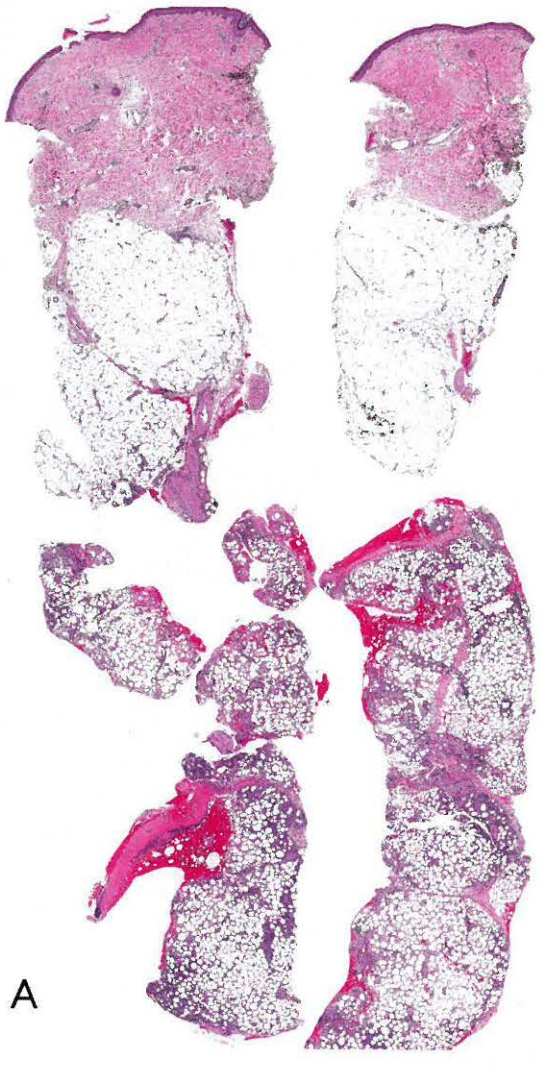


Figure 11-12

SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA (SPTCL)

A: This is a "double punch" biopsy. The first superficial punch (bisected; top two pieces) shows an essentially normal dermis and only focal subcutaneous involvement. The second deeper punch into the deep subcutis (bisected; bottom two pieces) shows a diffuse infiltrate involving most of the subcutaneous adipose tissue.

pattern of subcutaneous infiltration. However, more recent data have shown that it should be regarded as a separate entity because of its very different clinical behavior (23).

Currently, the term subcutaneous panniculitis-like T-cell lymphoma refers exclusively to the alpha-beta form of subcutaneous T-cell lymphoma; it is an indolent disease with a relatively good

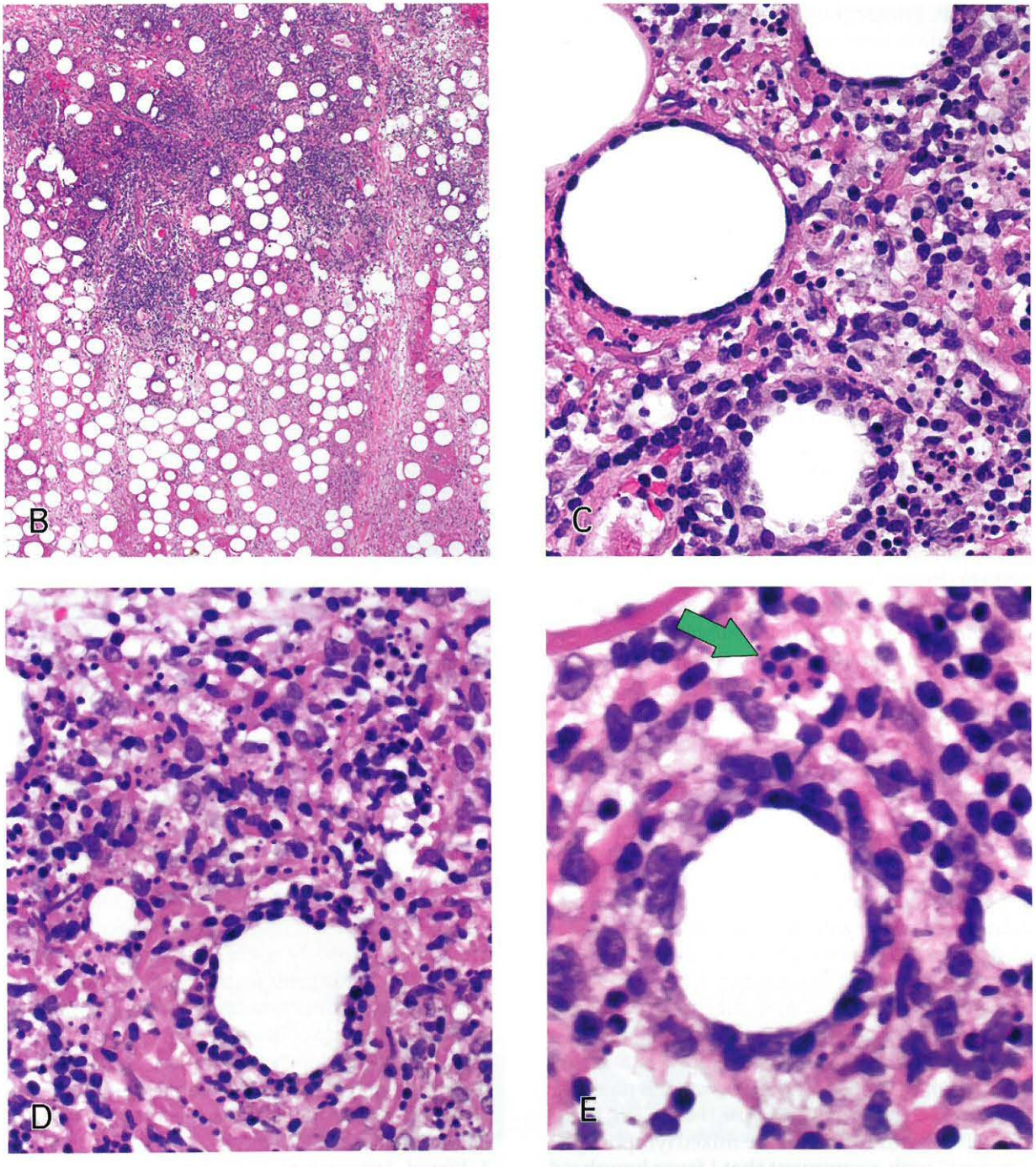


Figure 11-12, continued

B: An infiltrate of lymphocytes percolates between the subcutaneous adipocytes. Note the fibrinoid necrosis (bottom right). The appearance can resemble lupus panniculitis/profundus.

C: Individual adipocytes are often surrounded by hyperchromatic atypical lymphocytes ("rimming" of adipocytes).

D: Another example of rimming of atypical hyperchromatic lymphocytes around an individual adipocyte. Numerous tiny fragments of nuclear debris are scattered in the background.

E: A large histiocyte has multiple fragments of nuclear debris that it has consumed via phagocytosis (arrow); these "bean bag" cells are a classic finding but are not always seen. A solitary adipocyte is rimmed by hyperchromatic atypical lymphocytes (center).

prognosis. Primary cutaneous gamma-delta T-cell lymphoma is now regarded as a separate entity; it is an aggressive disease with poor prognosis (1,4,8). Primary cutaneous gamma-delta T-cell lymphoma usually involves all levels of the skin (subcutis, dermis, and epidermis), often with ulceration, whereas SPTCL is mostly limited to the subcutis and rarely ulcerates. Gamma-delta T-cell lymphomas are usually CD56 positive, beta F1 negative, and double negative for both CD4 and CD8, an immunophenotype that is very different from SPTCL (1,4,8).

DENSE DERMAL LYMPHOCYTIC INFILTRATES

A dense dermal infiltrate of small lymphocytes is a frustrating scenario that I often encounter in my practice (fig. 11-13). A variety of low-grade lymphomas have this general microscopic appearance as do a variety of benign reactive "pseudolymphomas." Some of the main entities in the differential diagnosis include *reactive lymphocytic hyperplasia,* robust arthropod bite reactions, *primary cutaneous marginal zone lymphoma,* and *primary cutaneous follicle center lymphoma.* Additionally, low-grade systemic B-cell lymphomas can secondarily involve the skin, as can *chronic lymphocytic leukemia* (fig. 11-14).

Since entering practice, I have struggled over how far to go in working up these dense infiltrates. Many times, I would work up a case with multiple immunostains and even B-cell or T-cell receptor gene rearrangement only to end up with a nonspecific descriptive diagnosis anyway. Additionally, as many of these low-grade cutaneous lymphomas have a very good prognosis, I began to wonder if such extensive workup was always necessary.

I still do not know what the "right" answer is, but my basic approach is to perform a limited panel of B-cell or T-cell markers. If it is a mixed population of B cells and T cells, or if it is mostly T cells but with a normal ratio of CD4 to CD8, I usually will diagnose it as a "dense mixed lymphocytic infiltrate" with a comment that I favor lymphoid hyperplasia or other robust reactive process rather than a lymphoproliferative process, but that clinical follow-up is recommended, and that if there is persistence, recurrence, or clinical concern for malignancy, a repeat biopsy would be recommended or additional workup could be performed on the current biopsy upon the dermatologist's request. If my initial panel shows either mostly B cells or mostly T cells with abnormal CD4 to CD8 ratio (or loss of normal T-cell markers), then I will expand my immunohistochemical panel, consider B-cell or T-cell receptor gene rearrangement, and most importantly, obtain consultation from my friendly hematopathology colleagues!

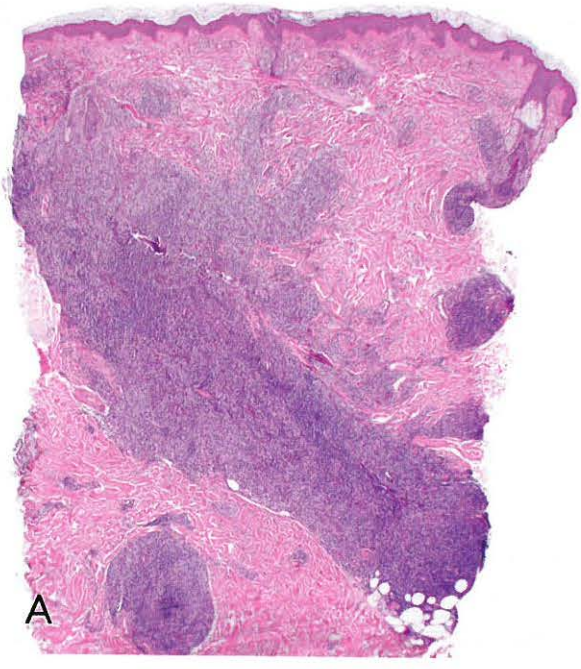
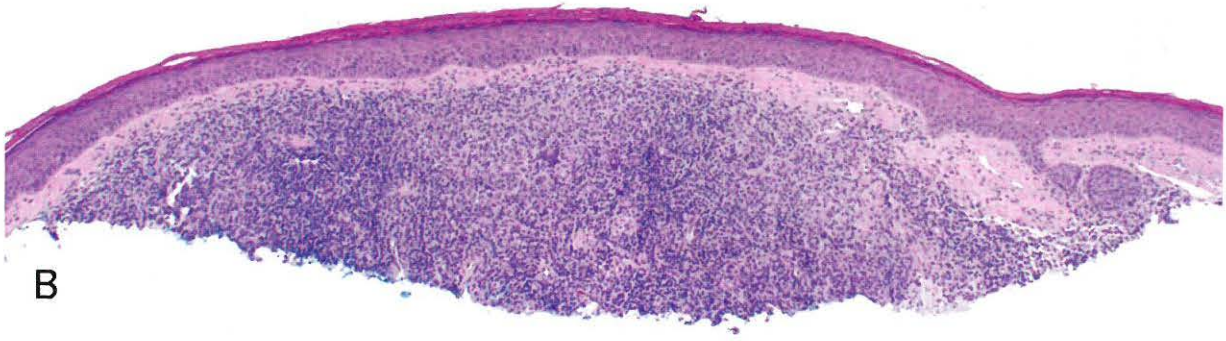


Figure 11-13

DENSE DERMAL LYMPHOCYTIC INFILTRATE

A: This dense dermal infiltrate of small lymphocytes is "bottom heavy" (i.e., it is denser and more abundant in the deep dermis than in the superficial dermis). This is one clue for a cutaneous lymphoma. This case turned out to be primary cutaneous marginal zone lymphoma after further workup.

For more in depth reading and a simplified approach to this and other challenging aspects of cutaneous hematopathology, I highly recommend *Diagnosis of Cutaneous Lymphoid Infiltrates: A Visual Approach to Differential Diagnosis and Knowledge Gaps* by Antonio Subtil (8). His book has given me fresh hope that I may yet come to a better understanding of this complex part of dermatopathology.



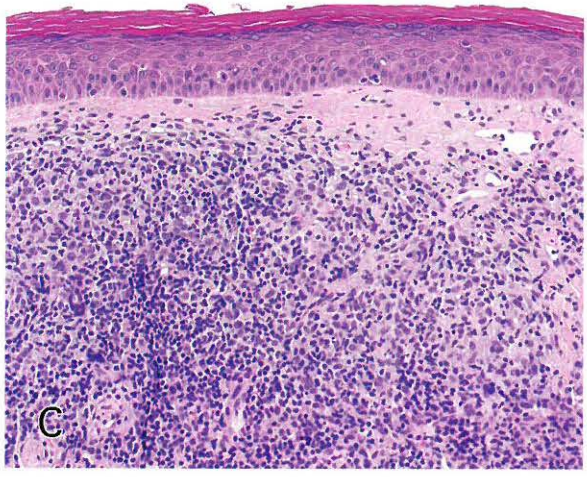
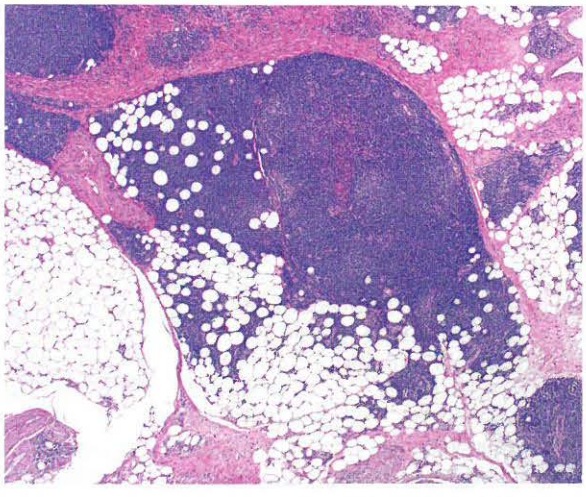


Figure 11-13, continued

B: This is a frustrating scenario that I often encounter in my practice. It is a dense infiltrate but is only a superficial shave biopsy. Clinically it was a small papule on the upper lip of an older adult. The clinical impression was "rule out basal cell carcinoma." How far should one go in working up such cases?

C: A closer look at the dense dermal infiltrate from B. Most of the cells are small lymphocytes but some scattered larger cells are also present. This case was worked up and turned out to be a reactive mixed B-cell and T-cell infiltrate.



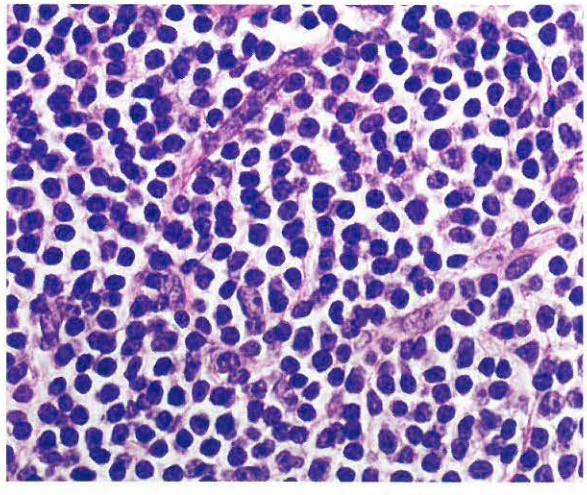


Figure 11-14

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) SECONDARILY INVOLVING SKIN

Left: These dense sheets of uniform small lymphocytes (CD20+, CD5+ B cells) were present in the dermis and subcutis in a wide local excision specimen performed for a large deeply infiltrative SCC. This incidental finding led to discovery of the patient's previously undiagnosed CLL. Further workup showed extensive nodal and marrow involvement by CLL.

Right: The lymphocytes of CLL are small round and very monotonous/uniform. A lymphocytic infiltrate (perivascular or sheet-like) that seems more dense, abundant, or uniform than a usual reactive infiltrate is a clue for CLL. I use CD20, CD3, and CD5 as a screening immunostain panel (in addition to checking the patient's chart for a history of CLL and a complete blood count for lymphocytosis).

REFERENCES

1. Calonje E, McKee PH. McKee's pathology of the skin: with clinical correlatinos, 4th ed. Edinburgh: Elsevier/Saunders; 2012.
2. Ederle A, Kim KH, Gardner JM. Eruptive xanthogranuloma in a healthy adult male. J Cutan Pathol 2017;44:385-7.
3. Miettinen M, Fetsch JF. Reticulohistiocytoma (solitary epithelioid histiocytoma): a clinicopathologic and immunohistochemical study of 44 cases. Am J Surg Pathol 2006;30:521-8.
4. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Arber DA, Hasserjian RP, Le Beau MM, Orazi A, Siebert R, eds. WHO Classification of tumours of haematopoietic and lymphoid tissues, 4th ed. Lyon: International Agency for Research on Cancer; 2017.
5. Gru A, McHargue C, Salavaggione A. A systematic approach to the cutaneous lymphoid infiltrates: a clinical, morphologic and immunophenotypic evaluation. Arch Pathol Lab Med [in press]
6. Guitart J, Kennedy J, Ronan S, Chmiel JS, Hsiegh YC, Variakojis D. Histologic criteria for the diagnosis of mycosis fungoides: proposal for a grading system to standardize pathology reporting. J Cutan Pathol 2001;28:174-83.
7. Pulitzer M, Myskowski PL, Horwitz SM, et al. Mycosis fungoides with large cell transformation: clinicopathological features and prognostic factors. Pathology 2014;46:610-6.
8. Subtil A. Diagnosis of cutaneous lymphoid infiltrates: a visual approach to differential diagnosis and knowledge gaps. Cham: Springer Nature Switzerland AG; 2019.
9. Vidal CI, Armbrect EA, Andea AA, et al. Appropriate use criteria in dermatopathology: Initial recommendations from the American Society of Dermatopathology. J Cutan Pathol 2018;45:563-80.
10. Lu D, Patel KA, Duvic M, Jones D. Clinical and pathological spectrum of CD8-positive cutaneous T-cell lymphomas. J Cutan Pathol 2002;29:465-72.
11. Martinez-Escala ME, Kantor RW, Cices A, et al. CD8+ mycosis fungoides: A low-grade lymphoproliferative disorder. J Am Acad Dermatol 2017;77:489-96.
12. Guitart J, Martinez-Escala ME, Subtil A, et al. Primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphomas: reappraisal of a provisional entity in the 2016 WHO classification of cutaneous lymphomas. Mod Pathol 2017;30:761-72.
13. Behrens EL, Jabcuga C, Gardner JM, Parker SR, Parker DC. A case of syringolymphoid hyperplasia with follicular mucinosis. Dermatopathology 2016;3:28-35.
14. Rongioletti F, De Lucchi S, Meyes D, et al. Follicular mucinosis: a clinicopathologic, histochemical, immunohistochemical and molecular study comparing the primary benign form and the mycosis fungoides-associated follicular mucinosis. J Cutan Pathol 2010;37:15-9.
15. Kempf W, Mitteldorf C, Karai LJ, Robson A. Lymphomatoid papulosis—making sense of the alphabet soup: a proposal to simplify terminology. J Dtsch Dermatol Ges 2017;15:390-4.
16. Gallardo F, Barranco C, Toll A, Pujol RM. CD30 antigen expression in cutaneous inflammatory infiltrates of scabies: a dynamic immunophenotypic pattern that should be distinguished from lymphomatoid papulosis. J Cutan Pathol 2002;29:368-73.
17. Cepeda LT, Pieretti M, Chapman SF, Horenstein MG. CD30-positive atypical lymphoid cells in common non-neoplastic cutaneous infiltrates rich in neutrophils and eosinophils. Am J Surg Pathol 2003;27:912-8.
18. Cham E, Smoller BR, Lorber DA, Victor TA, Cibull TL. Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia) arising on the extremities. J Cutan Pathol 2010;37:1045-52.
19. Moyer AB, Rembold J, Lee NE, Johnson G, Gardner JM. Leukemia cutis as the presenting symptom of acute myeloid leukemia: report of three cases. Dermatol Online J 2018;24(5).
20. Cronin DM, George TI, Sundram UN. An updated approach to the diagnosis of myeloid leukemia cutis. Am J Clin Pathol 2009;132:101-10.
21. Cibull TL, Thomas AB, O'Malley DP, Billings SD. Myeloid leukemia cutis: a histologic and immunohistochemical review. J Cutan Pathol 2008;35:180-5.
22. Cho-Vega JH, Medeiros LJ, Prieto VG, Vega F. Leukemia cutis. Am J Clin Pathol 2008;129:130-42.
23. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood 2008;111:838-45.

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