Granulomatous Rosacea Versus Lupus Miliaris Disseminatus Faciei—2 Faces of Facial Granulomatous Disorder: A Clinicohistological and Molecular Study

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Abstract: Granulomatous rosacea (GR) and lupus miliaris disseminatus faciei (LMDF) are 2 forms of facial granulomatous diseases. Although they show some morphological overlap, they have distinct clinical presentation. This study was performed to demonstrate the clinical and histological features of GR and LMDF and to establish their relationship to tuberculous etiology by molecular technique. All the cases of GR (n = 20) and LMDF (n = 10) diagnosed on skin biopsy over the past 6 years were reviewed along with their clinical detail. Polymerase chain reaction (PCR) was performed using primers specific for *Mycobacterium tuberculosis.* The mean age of patients with GR was 45 years 10 months (range 18–75 years) as compared to 33 years 5 months (range 18–57 years) in patients with LMDF. The GR cases comprised 13 men and 7 women patients, whereas all 10 LMDF cases were seen in men. GR cases had papular lesion over an erythematous base on face, whereas LMDF cases had papular/nodular/nodulocystic lesions on the face and neck. Histologically, GR cases showed small granulomas without necrosis in a background of variable lymphoid infiltrate and dilated capillaries, whereas LMDF showed large granulomas with caseous necrosis and minimal inflammation. Five cases (25%) of GR showed degenerating *Demodex folliculorum* mites. No case of GR or LMDF showed positivity for mycobacterial polymerase chain reaction. Despite some similarities, GR and LMDF show distinct clinical and histological features. Thus, LMDF is a distinct clinicopathological entity separate from the GR, with different etiopathogenesis. However, none of the conditions are related to a tuberculous etiology.

Key Words: granulomatous rosacea, lupus miliaris disseminatus faciei, polymerase chain reaction, *Mycobacterium tuberculosis*

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INTRODUCTION

Granulomatous inflammation in the skin biopsies is a common finding and can be seen in wide variety of diseases. It is often very difficult to achieve an accurate diagnosis of the disease condition based on histopathological findings alone because of the overlap in morphological features. It is quite difficult to give a completely satisfactory classification of conditions associated with granulomatous dermatitis with facial involvement specially.[1] Broadly, based on the etiology, it can be divided into infectious and noninfectious granulomas. In developing countries, up to 90% of granulomas may have an infectious etiology; therefore, before labeling as noninfectious granulomatous dermatitis, an infectious cause needs to be thoroughly ruled out with the help of special stains, culture, various ancillary tests, and molecular studies.[2]

Granulomatous rosacea (GR) is a variant of rosacea, apart from 4 recognized subtypes namely erythemotelangiectatic, papulopustular, phymatous, and ocular type. It is characterized by periorificial yellow, brown, or red monomorphic papules or nodules.[3] Although considered a variant, the patients may not have all the classical symptoms of rosacea such as flushing, erythema, and typical location, raising the doubt whether GR belongs to the spectrum of rosacea.[4] Differentiation between GR and other granulomatous lesions on face can be extremely challenging because of significant histological overlap.

Lupus miliaris disseminatus faciei (LMDF) is another granulomatous inflammatory condition characterized by multiple discrete yellow-brown to red, dome-shaped papules on the medial and lateral areas of the face, which often extends to the neck and chin.[5] LMDF often involves the eyelids, especially the lower eyelids. The exact etiology of LMDF is not known, but previously it was believed to be associated with tuberculosis (TB), sarcoidosis, and rosacea.[6] In some of the previous publications, LMDF was considered synonymous to GR because of similar histopathological features.[7,8] However, both the conditions have different clinical features and treatment modalities; hence, it is important to distinguish these entities.

The molecular studies using polymerase chain reaction (PCR) failed to identify the DNA of *Mycobacterium tuberculosis* in active lesions of LMDF.[6] However, there are only a few reports that showed absence of *M. tuberculosis* DNA in GR cases.[9] No previous study has addressed the presence of mycobacterial DNA in GR and LMDF from a country where TB is endemic.

This study was aimed to differentiate GR from LMDF based on clinical and histopathological features. The role of *M. tuberculosis* was also evaluated in the disease pathogenesis of both entities using a sensitive DNA amplification technique.

MATERIALS AND METHODS

All the cases of GR and LMDF, diagnosed on skin biopsy over the past 6 years were retrieved from the archives

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The authors declare no conflicts of interest.

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of Department of Histopathology, PGIMER, Chandigarh. The clinical details were recorded from the biopsy request form and patient file. All the slides were reviewed by 3 pathologists (A.C., D.C., and U.N.S). In addition to the routine hematoxylin and eosin staining, special staining methods such as Ziehl–Neelsen (ZN), Giemsa, Fite–Faraco, and periodic acid–Schiff were performed to exclude the infective etiology for granulomatous inflammation in all cases. Primarily, the diagnosis was based on clinical presentation and characteristic histopathology features on biopsy. Small papular lesion with erythematous base on face was clinically diagnosed as GR (Fig. 1A), whereas yellow-brown to red papular lesions on face or neck with a centrofacial distribution and without an erythematous background were clinically diagnosed as LMDF (Fig. 1B). In cases with overlapping clinical features, histological features were used to distinguish between these 2 entities. Histologically, the presence of large epithelioid granuloma with central necrosis without significant vascular dilatation was taken in favor of LMDF, whereas small granuloma with variable vascular dilatation was suggestive of GR. In all cases, a consensus diagnosis was achieved taking into consideration both clinical and histological features.

DNA was extracted from the formalin-fixed, paraffin-embedded tissue by commercially available QAIGEN kit according to manufacturer's instruction. Mycobacterial DNA was amplified by PCR using in-house *M. tuberculosis* specific primers as described in previous publications.

The following primers were used:
mpt64 (forward)–5′CCTCGGCCACATACCAGTCC3′;
mpt64 (reverse)–5′TGTCCGGTCTGCTTGCTCAG3′.
Positive and negative controls were also put up.
A band at 240 bp was considered positive.

RESULTS

Within this study period, a total of 21 cases of GR and 10 cases of LMDF were diagnosed. One case of GR could not be retrieved, as block and slides were issued to the patient. Thus, a total of 20 cases of GR and 10 cases of LMDF were analyzed. The clinical and pathological features have been summarized in Table 1.

Clinical Presentation

The mean age of patients with GR was 45 years 10 months (range 18–75 years) as compared to 33 years 5 months (range 18–57 years) in patients with LMDF. The GR cases comprised 13 male patients and 7 female patients (M:F ratio 1.9:1), whereas all 10 LMDF cases were seen in men. All the LMDF cases except 1 showed lower eyelid involvement. Three cases of LMDF showed nodulocystic lesions. None of the GR or LMDF cases had any systemic clinical symptoms suggestive of TB or sarcoidosis. The clinical features of GR and LMDF have been described in Table 1.

Microscopic Examination

The GR and LMDF cases showed the presence of epithelioid cell granulomas with variable degree of inflammatory infiltrate. The epidermis was largely unremarkable in GR, except 1 case each showing mild acanthosis and focal basal cell vacuolization. The inflammation and granulomas in GR cases were seen in 4 patterns namely nodular (3/20), perifollicular (6/20), combined (6/20), and diffuse (5/20) (Figs. 2A–C). The granulomas in all the GR were tuberculoid type composed of epithelioid histiocytes, Langhans, and foreign body–type giant cells without central caseous necrosis. The granulomas were small, ill-formed to well-formed, with peripheral lymphoid infiltrate. In nodular pattern, the inflammatory infiltrate composed of lymphocytes, plasma cells, histiocytes, and scattered neutrophils was present in nodular configuration along with epithelioid cell granulomas randomly distributed in the dermis. In perifollicular pattern, the inflammation and granulomas were mainly located in perifollicular location mainly near the infundibulum of hair follicle. In 4 cases, the lymphocytes with or without neutrophils were entering into the follicle forming microabscesses. In 5 cases

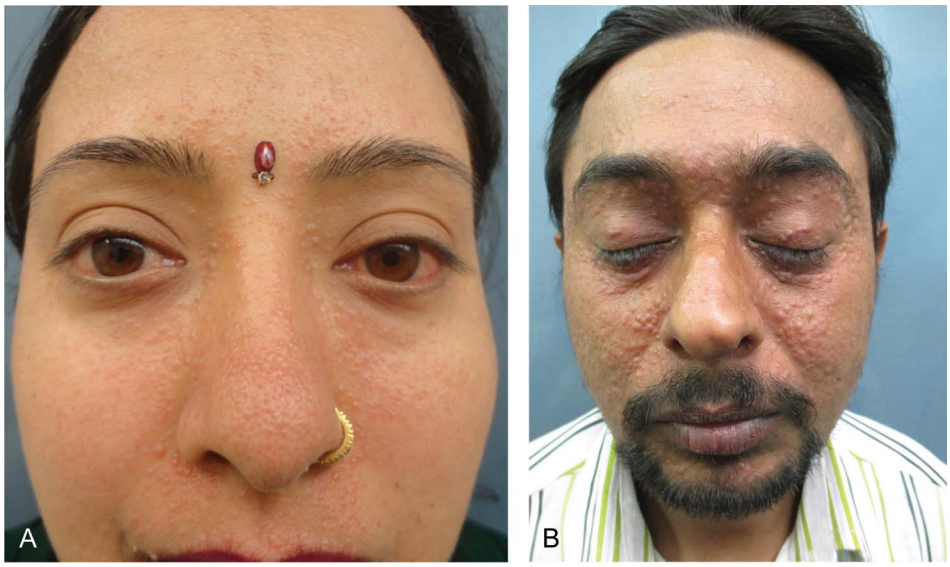

FIGURE 1. A, A case of GR showing popular lesions in an erythematous base in malar and periorbital region. B, A case of LMDF showing yellow-brown papules over the forehead, eyelids, cheeks, and chin.

TABLE 1. Clinical and Histological Comparison of GR and LMDF Cases

Characteristics	Granulomatous Rosacea (n = 20)	Lupus Miliaris Disseminatus Faciei (n = 10)
Mean age (range)	45 years 10 months (18–75 years)	33 years 5 months (18–57 years)
Sex distribution	13 males, 7 females	10 males
Site	Face	Face, neck
Types of lesion	Papules or papulonodular lesions	Red brown to pinkish papular to nodulocystic lesions
Erythematous base	85% (17/20)	0%
Caseating granulomas	0%	100% (10/10)
Inflammation pattern	Nodular (3/20), perifollicular (6/20), combined (6/20), and diffuse (5/20)	Perifollicular (9/10)
Solar elastosis	40% (8/20)	0% (0/10)
Capillary dilatation	50% (10/20)	0% (0/10)
Demodex folliculorum fragments	25% (5/20)	0% (0/10)
Mycobacterium PCR positivity	0% (0/12)	0% (0/4)

(25%), degenerating *Demodex folliculorum* mites were seen in the follicles with 1 case showing numerous eosinophils in the microabscess. In combined pattern, there was a combination of perifollicular and nodular patterns of inflammation, whereas diffuse form showed diffuse inflammation in the dermis with ill-formed to well-formed epithelioid cell granulomas and inflammatory infiltrate. The superficial dermis was showing elastotic degeneration (8/20) and dilated vascular channels (10/20).

The LMDF cases showed well-formed epithelioid cell granulomas predominantly (9/10) centered on the pilosebaceous units with follicular destruction and central caseous and fibrinoid necrosis (Fig. 2D). These central necrotic areas were surrounded by palisaded histiocytes (Fig. 2E). In 2 cases, the granulomas were becoming confluent. The adjacent areas showed nondescript mild inflammatory infiltrate composed of lymphocytes and histiocytes. Two cases showed acanthosis, and no case showed *D. folliculorum* infestation, capillary dilatation, or solar elastotic degeneration. Special stains to rule out infectious etiology were negative in all GR and LMDF cases (Fig. 2F).

Molecular Analysis

DNA was successfully isolated only in 16 cases (12 GR and 4 LMDF). The PCR study using specific primers did not detected DNA of *M. tuberculosis* in any of the GR (n = 12) or LMDF (n = 4) cases (Fig. 3).

DISCUSSION

Cutaneous TB is a relatively rare manifestation of TB accounting for only 1%–2% of extrapulmonary TB cases in different series.[10] In developing countries such as India, TB remains a major public health problem. In western world, there is resurgence of TB because of HIV/AIDS infection. As India has one of the high incidences for both TB and HIV/AIDS, granulomatous reaction at any organs leads to reflex testing to rule out tubercular infection. The diagnostic modalities include Monteux test, culture methods, direct demonstration of organisms at involved site, and PCR studies using organism-specific primers.[11,12] Culture studies if available has good sensitivity and high specificity, however, takes a long time (6–8 weeks in conventional Lowenstein Jensen medium or 3 weeks in BACTEC culture). Direct demonstration of organisms in skin biopsy requires a very high load of organisms and thus has low sensitivity. In recent times, there has been enthusiasm about application of PCR studies for diagnosis of TB, using both fresh and formalin-fixed paraffin-embedded tissue.[13,14] Its utility is limited in diagnosing cutaneous TB especially from formalin-fixed paraffin-embedded tissues and resource-restricted settings.[15,16] Most of the granulomatous dermatitis with variable necrosis will be attributed to tubercular in etiology in high prevalence countries such as India. But, there are other noninfectious dermatitis, which also can show significant caseous necrosis such as LMDF and rarely GR. Distinguishing cutaneous TB from these noninfectious granulomatous skin lesions is of paramount importance because of different treatment modalities.

In this study, ZN stain failed to highlight any acid fast bacilli in GR and LMDF cases, and *M. tuberculosis* DNA was also not detected by molecular methods. In addition, the other special stains did not reveal any microorganisms ruling out infectious etiology for the granulomatous inflammation in the skin biopsies. Therefore, these cases can be categorized into noninfectious granulomatous dermatitis entities, although other rare infectious causes such as nontubercular mycobacteria can be associated with granuloma formation. Although useful to rule out tuberculous etiology in granulomatous dermatitis cases, the role of mycobacterial PCR is limited in resource restricted settings.

In this study, the GR cases showed predominantly papular lesions, but other presentations such as papulopustular (2/20) and papulonodular (1/20) was also seen. Although considered as distinct variant of rosacea, some of the studies have not found unifying clinical picture of GR in subset of patients of rosacea.[7,17,18] Therefore, it is considered as histological variant rather than clinical subtype, and considerable experience is needed to predict in the rosacea cases, which

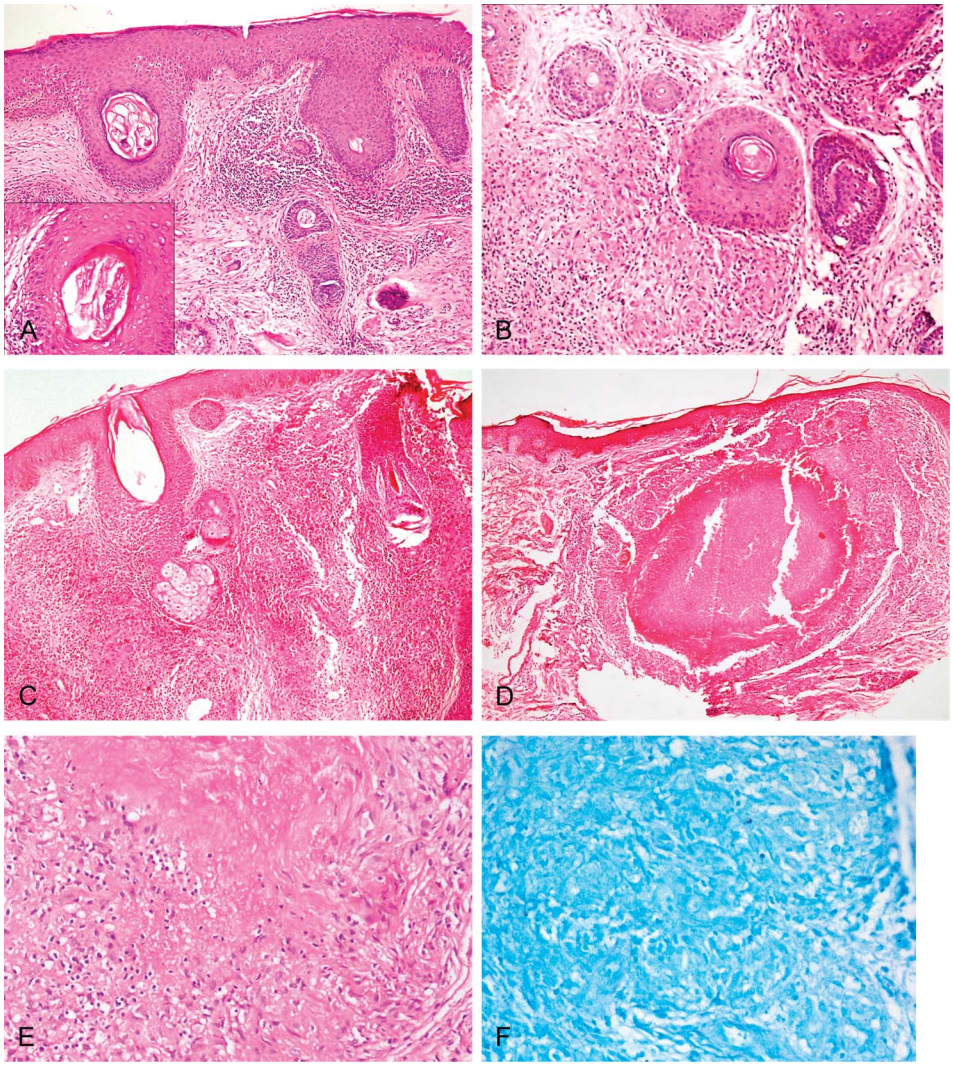

FIGURE 2. A–C, Photomicrograph of GR. A, Nodular pattern of inflammation, with the presence of tiny epithelioid cell granulomas with occasional giant cells (HE, ×100). Inset showing degenerated fragments of *Demodex folliculorum* (HE, ×200). B, Perifollicular pattern of granulomatous inflammation (HE, ×200). C, GR showing mixed perifollicular and nodular pattern of inflammation (HE, ×100). D–F, Photomicrograph of LMDF. D, LMDF showing perifollicular granuloma with central caseous necrosis (HE, ×100). E, Same case, showing caseous necrosis, surrounded by palisading histiocytes (HE, ×400). F, Stain for acid fast bacilli is negative (ZN stain, ×1000).

might show granulomas on histopathology. On microscopic examination, it shows variable patterns of inflammation, but constant feature is tuberculoid granulomas in the dermis. Upper dermal inflammation is more common, and the upper dermis looks busy under lower magnification. The demonstration of granulomas in GR cases also depends on the age of the lesion at the time of biopsy. Histologically, the GR was classified by Sanchez et al[18] based on the location of the inflammatory infiltrate into perifollicular, nodular, diffuse, and combined patterns. Although the exact cause is not known, various factors such as *D. folliculorum* infestation, delayed hypersensitivity reaction to keratinized cells, and antigens released from the pilosebaceous units have been hypothesized to be associated with GR.[19,20] We found degenerating *D. folliculorum* in 5 of our cases (25%) of GR, further strengthening the association. Most of the GR cases showed papular lesions on an erythematous base clinically and solar elastotic degeneration along with dilated capillary channels in the upper dermis, suggesting a close pathogenetic association with rosacea, thus justifying inclusion into the rosacea spectrum.

Previously, LMDF was considered to be a variant of lupus vulgaris or a tuberculid because of close resemblance of histopathological features showing epithelioid cell granuloma with central caseous necrosis. However, a negative Monteux

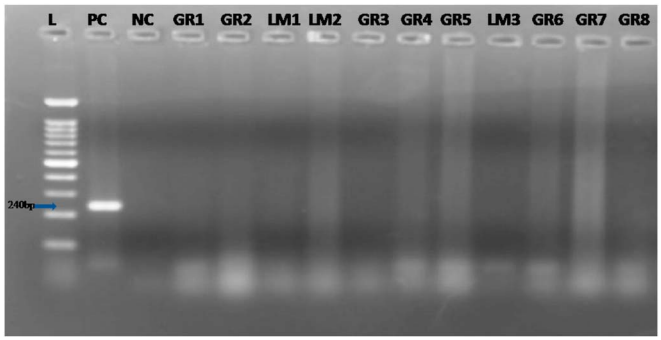

FIGURE 3. Gel electrophoresis of nucleic acid amplification product. First lane from left is DNA ladder. Second lane is positive control, showing a band at 240 bp. Third lane is negative control. All cases of GR and LMDF show negative results.

test and special stains as well as cultures from active lesions of LMDF failed to demonstrate the *M. tuberculosis* organism. Similarly, the molecular studies using sensitive PCR failed to detect *M. tuberculosis* DNA in these samples, and the patients did not respond to antitubercular therapy.[6,21] Therefore, the theory of tuberculous origin of LMDF is no more accepted. Other theory of pathogenesis is based on close localization of granulomas to pilosebaceous units indicating some form of immune reaction to released antigens that gain access into the dermis through injured hair follicles.[22] Also, the reaction to products released by *D. folliculorum* residing in hair follicles was hypothesized as one of the cause for LMDF similar to GF, but has not been substantiated in other reports.[8] We also failed to demonstrate *D. folliculorum* in any case of LMDF.

LMDF was considered by some authors to be a form of GR because of perifollicular localization of granulomas, but it has distinct features, which can be used to differentiate it from GR.[5] The GR lesions have periorifacial localization limited to face with diffuse erythematosus base and occur predominantly in older individuals. The lesions show exacerbation with different stimuli such as hot drinks, alcohol, steroids, and extremes of temperature, respond to tetracycline and resolve without scarring. Although LMDF has exactly opposite features with occurrence in younger individuals, involvement of extrafacial sites, absence of erythema, telangiectasia, or ocular symptoms responds to corticosteroids and shows self-limited course with scarring. All patients with LMDF in our study were men, whereas women constituted 35% of the GR cases. We did not observe capillary dilatation, significant lymphoid infiltrate, or presence of *D. folliculorum* in LMDF on histological examination, which were the characteristic features of GR. Although both GR and LMDF showed epithelioid cell granulomas centered around pilosebaceous units, granulomas of GR were small and devoid of necrosis, whereas LMDF was characterized by large granulomas with central necrosis simulating TB morphologically. Although necrosis has been rarely described in GR, we did not observe necrosis in any of the GR cases. Two cases of LMDF showed acanthosis, whereas the epidermis was largely unremarkable in GR. Hence, these findings indicate that, despite overlapping features, LMDF is a distinct clinicopathological entity with different etiopathogenesis and treatment and hence needs to be classified separately from GR. In addition, the PCR data did not show the presence of tuberculous DNA in any of these entities, thereby ruling out any association with tuberculous etiology.

A larger prospective study to compare clinicohistological features may be further useful in appropriate classification of these 2 granulomatous dermatosis with predominant facial involvement.

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