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The Histologic Spectrum of Lupus Miliaris Disseminatus Faciei as Demonstrated By a Solitary Individual

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ABSTRACT

Lupus miliaris disseminatus faciei (LMDF) is an uncommonly encountered and incompletely understood acute granulomatous cutaneous eruption. Varying clinical and histopathologic manifestations have led to differing opinions regarding the pathogenesis and appropriate classification of this entity. Histopathologic examination is necessary for diagnosis, usually requiring the presence of epithelioid granulomas with caseation necrosis, as demonstrated by fully developed lesions. However LMDF is now generally understood to include a spectrum of histologic stages, which vary with clinical stage. We will discuss our encounter with a 60-year-old white female who demonstrated histopathologic features consistent with multiple stages of LMDF. Microscopically this patient additionally showed periapocrine granulomatous inflammation. As an atypical clinical presentation was also seen, we feel this one patient effectively demonstrates the clinical and histopathologic heterogeneity that may be seen in this condition. Lastly we will comment on our recognition of a questionable correlation linking androgen stimulation of the pilosebaceous apocrine unit to the development of LMDF.

Keywords: Lupus miliaris disseminatus faciei, Granulomatous rosacea, Axillary lupus miliaris disseminatus faciei, Acne agminata

INTRODUCTION

The pathogenesis of LMDF has been met with reasonable debate. A large number of ideas incompletely explain the pathogenesis of LMDF, leading many to suggest that multiple factors may actually be responsible [1]. Suggested by nomenclature, LMDF was historically regarded as a tuberculid but this concept was refuted in 1997 due to consistent lack of PCR or culture evidence of *Mycobacterium tuberculosis* [1-4]. Another proposal is that LMDF may be a reaction to an unknown infectious agent associated with cell-mediated immunity [1,5]. Recently, an association between *Propionibacterium acnes* and LMDF has been proposed due to PCR demonstration of *P. acnes* in 9 cases [6]. Other theories focus on the pilosebaceous unit as central to the pathogenesis of LMDF, since a perifollicular infiltrate is present in many, but not all, cases of LMDF [5,7]. A primary immune response to pilosebaceous units or follicular trauma leading to antigen exposure and subsequent granuloma formation may be involved in the pathogenesis. The presence of a lymphocytic perifollicular infiltrate with invasion into the follicular wall in early lesions of LMDF supports that the initial triggering event may be lymphocyte mediated [1,5].

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Damage of the follicular wall subsequently leads to release of follicular contents into the dermis and a granulomatous reaction then ensues [1,5,7]. While perifollicular granulomas could represent a non-immunologic foreign body reaction to follicular contents, evidence suggests a role for cell-mediated immunity as supported by the presence of intense staining of lysozyme in the epithelioid histiocytes and multinucleated giant cells [1]. Many regard LMDF to be a variant of granulomatous rosacea; however others emphasize a distinction between these two entities, which is supported by a clinical course of LMDF that is different than granulomatous rosacea [1,2,4,7]. It has been suggested that designation of LMDF may be most appropriate in cases that are clinically like sarcoidosis but histologically similar to granulomatous rosacea [8]. This places LMDF on a spectrum of granulomatous conditions, some of which are also incompletely understood.

Case Presentation

We encountered a 60-year-old female with a 6-month history of multiple mildly pruritic flesh colored periorbital papules (**Figure 1**). She endorsed occasional application of hydrocortisone 1% cream but denied use of additional products. She lacked significant past medical history, review of systems was noncontributory and she denied usage of antiperspirants containing aluminum-zirconium. Punch biopsy of a periorbital papule showed a discrete perifollicular epithelioid granuloma with a central zone of caseation necrosis (**Figure 2, 3**). AFB and fungal stains were negative and examination under polarized light identified no foreign material. Following a negative QuantiFERON-TB Gold test, a diagnosis of LMDF was applied. The patient was started on tacrolimus 0.1% ointment BID. At subsequent follow up 3 months later, significant improvement of the periorbital papules was demonstrated (many leaving oval violaceous macules) but multiple new pink papules of the bilateral axillary vaults had developed over the last month (**Figure 4**). Biopsy of an axillary papule demonstrated a mild superficial perivascular and superficial perifollicular infiltrate composed of lymphocytes, histiocytes and neutrophils (**Figure 5**). In the deep dermis, a caseating granuloma was present in addition to periapocrine granulomas (**Figure 6, 7**). The patient was started on Doxycycline 100mg PO BID. A 6-month follow-up appointment confirmed only mild improvement of the axillary lesions.

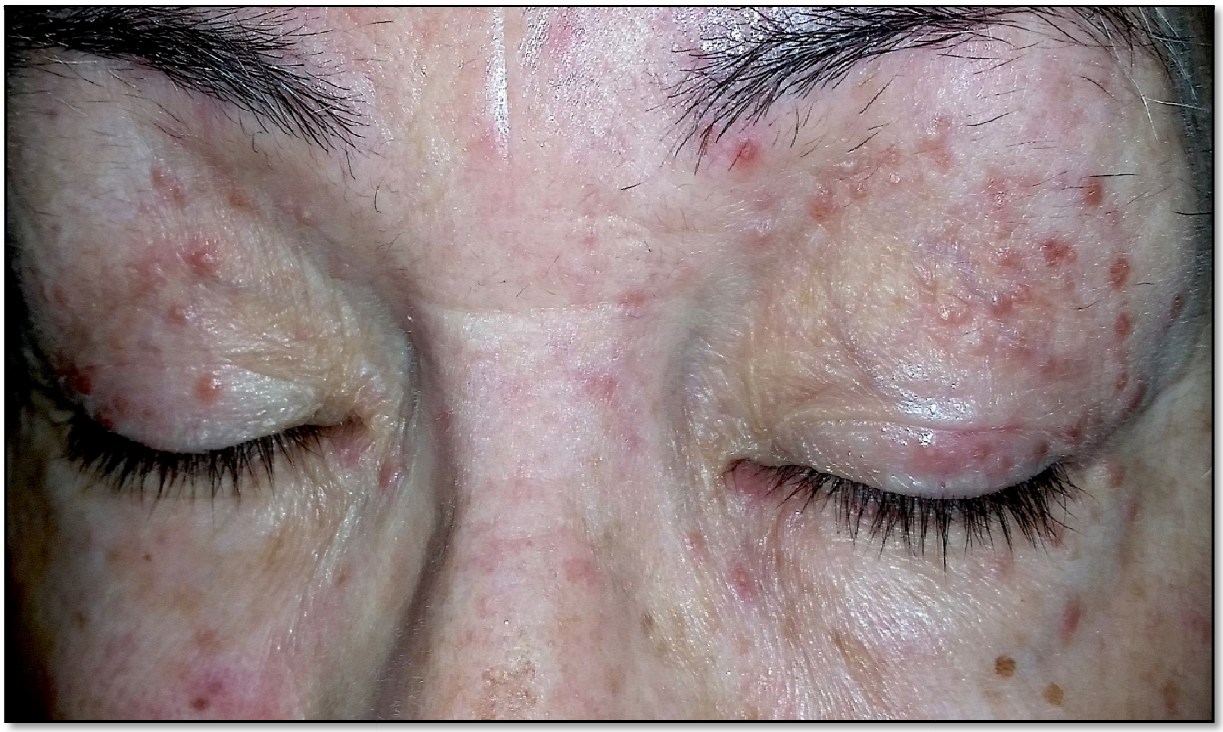

Figure 1. Periorbital papules

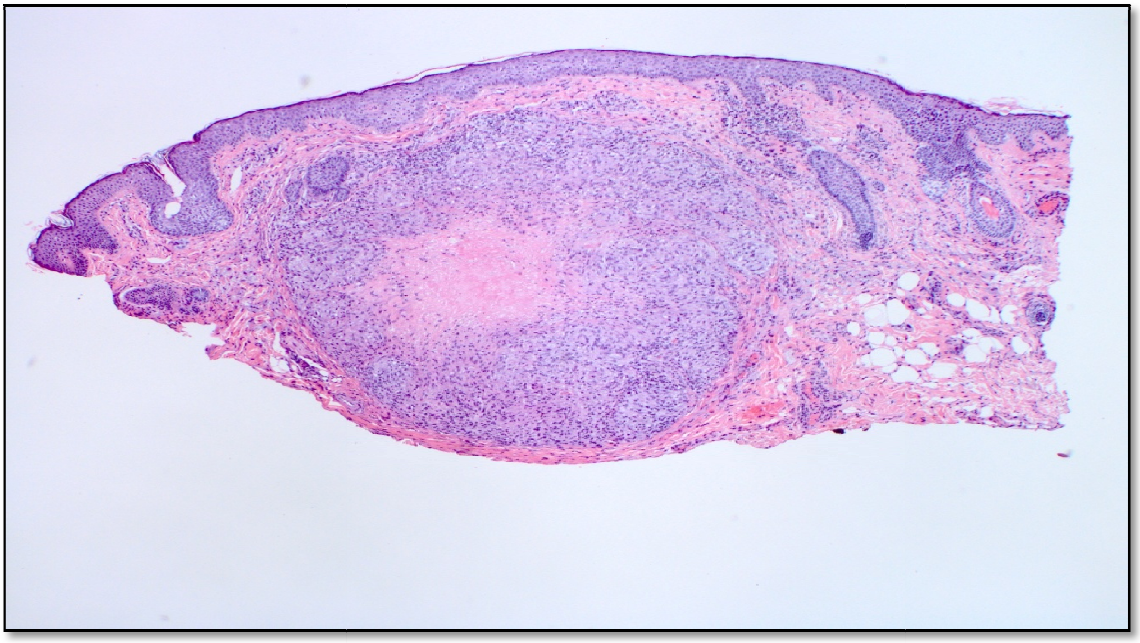

Figure 2. Low power magnification from punch biopsy of periorbital papule, perifollicular epithelioid cell granuloma surrounding caseation necrosis. This is the fully developed stage of LMDF

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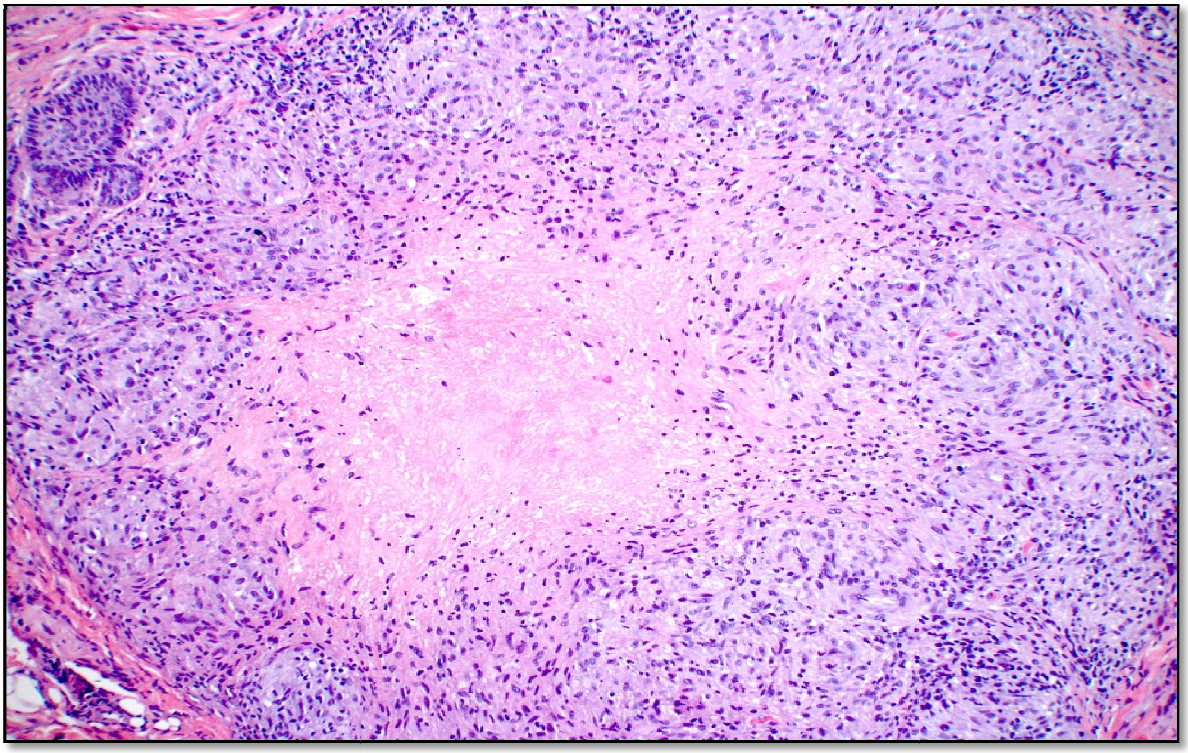
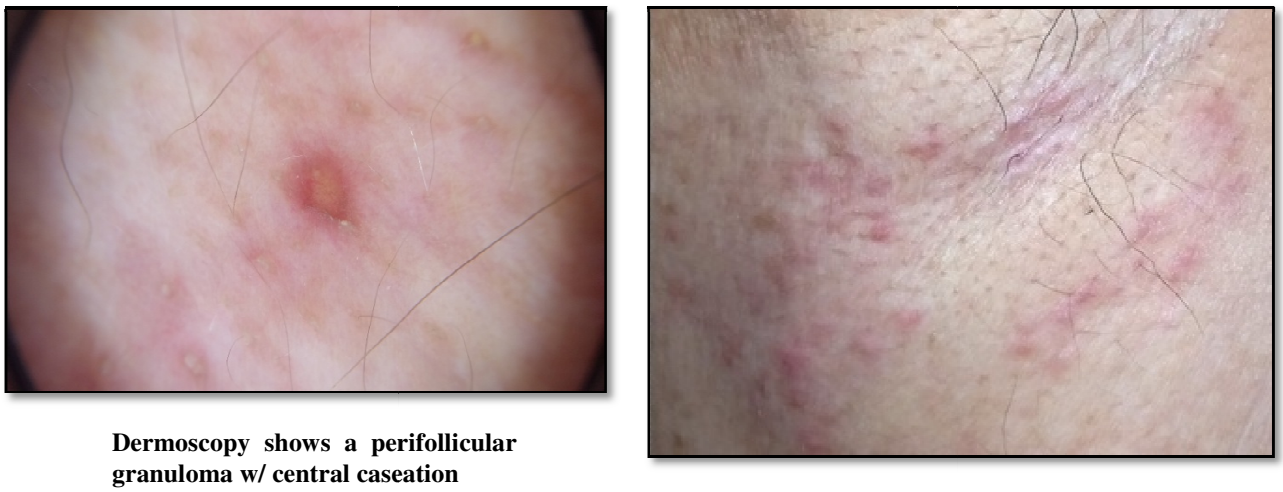


Figure 3. High power magnification from punch biopsy of periorbital papule, perifollicular epithelioid cell granuloma surrounding caseation necrosis. This is the fully developed stage of LMDF.



Dermoscopy shows a perifollicular granuloma w/ central caseation

Figure 4. Perifollicular papules of axillary skin

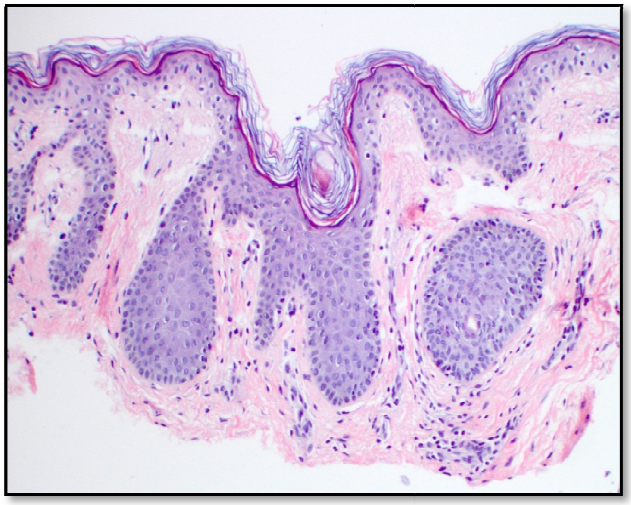


Figure 5. Shave biopsy of axillae with sparse superficial perifollicular and perivascular infiltrate. This is the early stage of LMDF.

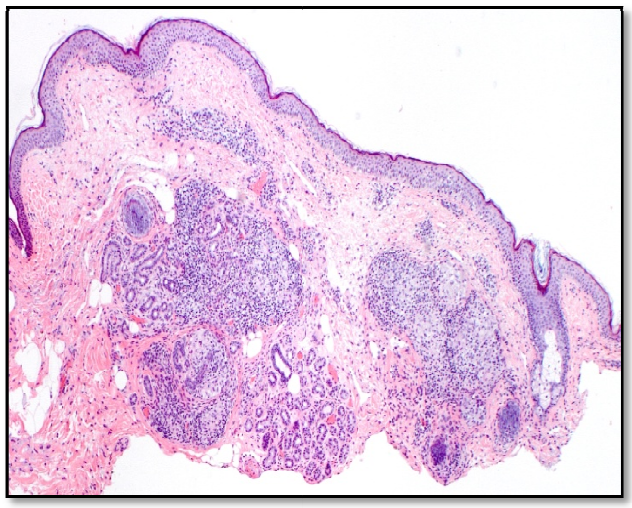


Figure 6. Shave biopsy of axillary papule with superficial perifollicular and peri-glandular granulomatous inflammation.

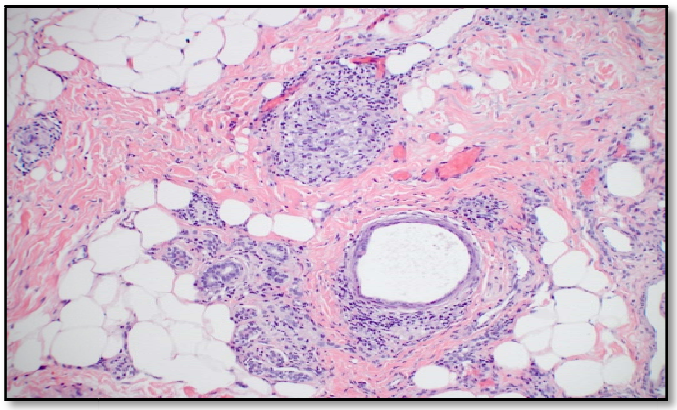


Figure 7. Punch biopsy of axillae showing deep peri-glandular granulomatous inflammation

Discussion

Our patient demonstrates the varying histologic presentations of LMDF, which have been previously well described to vary with the stage of disease evolution at the time of biopsy [3]. Recent attention has been devoted to this broad spectrum of histologic findings that may be demonstrated in LMDF. This spectrum is divided into three histologic stages: early, fully developed and late [1]. Fully developed lesions may be additionally divided into four groups, defined by the type of granulomatous reaction that is present [1]. Demonstrated by microscopic examination of axillary skin of our patient, the early stage of LMDF exhibits a superficial perivascular and perifollicular infiltrate composed predominantly of lymphocytes and with a lesser degree of histiocytes and neutrophils (**Figure 5**) [1,2]. Present in fully developed lesions and demonstrated by punch biopsy of the periorbital papule of our patient, the characteristic histopathologic finding in LMDF is a lesion in the superficial to mid-dermis with epithelioid cell granulomas surrounding areas of caseation necrosis (**Figure 4a,4b**) [1,2]. Fully developed lesions may be associated with a ruptured hair follicle and demonstrate superficial perifollicular granulomatous inflammation composed of lymphocytes, histiocytes and multinucleated giant cells surrounding caseation necrosis [1-3]. These granulomas are composed of histiocytes, multinucleated giant cells (Langerhans or foreign body type), scarce neutrophils and a peripheral rim of lymphocytes [1,2]. Finally, late stage lesions show perifollicular fibrosis with few scattered histiocytes, lymphocytes and neutrophils. While recognition of the histopathologic variability may be important in this condition, confusion is best avoided by restricting the diagnosis of LMDF to lesions demonstrating epithelioid granulomas with caseation necrosis [1]. As opposed to the histopathologic variability seen in this condition, the clinical characteristics of LMDF are generally reproducible. The typical course is one of acute onset with spontaneous resolution over 2-4 years, usually leaving residual pitted scars [2,4,5,9]. LMDF is predominantly a condition of young to middle-aged individuals [5]. The appearance in individuals in the 7th decade of life, as in our patient, is unusual. To our knowledge, the oldest patient reported to have LMDF was 71 and few patients over the age of 50 have been published [10,11]. Interestingly, the literature reflects a striking gender disparity in LMDF. A recent review of 35 patients with LMDF showed that all patients with LMDF over the age of 30 were female, whereas patients under the age of 30 were predominantly male [11]. To our knowledge, there have been no attempts to explain the impressive gender predilection that varies with age in LMDF. LMDF almost always involves the face, with striking predilection for the periorbital skin, especially the lower eyelids [2,4,12,13]. Extrafacial involvement is uncommon, with only three prior reports of axillary LMDF [4,2,14]. Of the three reported cases of axillary LMDF, two also occurred in females over the age of 50 (ages 53, 55) [14,15]. The third case of axillary LMDF occurred in a 36-year-old male [14]. If including our patient, three of the four cases of axillary LMDF developed in females over 50 years of age; a situation which is only of mention due to a well recognized predilection of LMDF for an (even) younger population. As explained, the pilosebaceous apparatus is thought to be central to the development of LMDF. Anatomic sites of predilection of LMDF include those that are rich in pilosebaceous units, but lesions of LMDF also occur in regions of skin that contain apocrine glands such as the periocular skin, the axillae and genitalia [9]. The distribution of skin lesions in our patient strictly and symmetrically involved the periocular and axillary skin. Biopsies demonstrated both perifollicular and periapocrine granulomatous inflammation. While the latter could simply have developed due to adjacent inflammation, it could also represent apocrine involvement in this patient's disease. And because apocrine and pilosebaceous glands are intimately associated with hair follicles, it seems possible that all could be involved in some cases of LMDF [16,17].

Stages	Clinical	Histopathology
Early	Size <2mm Duration <1 month	Superficial perivascular and periappendageal infiltrates composed of lymphocytes, few histiocytes and neutrophils
Fully Developed	Size 3-4mm Duration 3-6 months	Perifollicular epithelioid granulomas composed of histiocytes, multinucleated giant cells, neutrophils, peripheral rim of lymphocytes. Occasional follicular rupture.
Late	Duration >8 months	Extensive perifollicular fibrosis, scattered lymphocytes, histiocytes and neutrophils

Table 1: Histologic stages of LMDF

As both apocrine and sebaceous glands are under the control of androgens, we wonder if such hormonal interactions could explain some of the disparities we have mentioned above: the general predilection of LMDF for a young age group, the male predominance under 30 years of age, the striking female predominance in females over 30, and the four cases of axillary LMDF appearing in ideal candidates for either androgen excess or hyperreactivity [17,18]. A similar conclusion was posed by Walchner et al following their experience with a 30-year-old female who initially developed LMDF during the third trimester of pregnancy [19]. LMDF initially improved in the postpartum period but subsequently flared 6 months postpartum [19]. Interestingly, the patient later developed cutaneous lupus erythematosus. The authors concluded that a possible common pathogenic pathway between LMDF and LE might exist, initially involving a localized autoimmune-like process restricted to sebaceous glands with subsequent antigen expression provoked by hormonal factors [19]. Our patient presented

with LMDF at a late age and in an atypical cutaneous location, whilst simultaneously demonstrating multiple stages of LMDF histopathologically. An extensive review of the literature led to recognition of notable trends in LMDF. This information was applied to our patient's case, facilitating conclusions that support the relevance of pilosebaceous units in the pathogenesis of LMDF.

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