

A Review of Lupus Miliaris Disseminatus Faciei-Like Histopathologic Changes in 10 Cases

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Abstract

Objective: To determine the clinical and histopathologic features of all lesions diagnosed as lupus miliaris disseminatus faciei via biopsy over the past 16 years at a single institution. Clinical features reviewed included age of patient, location and number of lesions, duration, description of primary lesion, size, and suspected clinical diagnosis or differential diagnosis. Histopathologic features reviewed included presence of caseation necrosis, depth of granuloma, presence of lymphocytic infiltrate, disruption of hair follicles, and presence of multinucleated giant cells.

Methods: The records of 10 patients (mean age, 50.4 years; range, 6 to 79 years) with characteristic histologic features of lupus miliaris disseminatus faciei were reviewed and the histopathologic findings and clinical features were analyzed. Formalin-fixed, paraffin-embedded specimens were examined by hematoxylin-eosin staining.

Results: The most common clinical appearance was a single papule located on the face. Two cases with solitary, extrafacial distributions were reported. All cases demonstrated epithelioid granulomas with a central area of caseation necrosis. The majority of granulomas were perifollicular in location and were comprised of histiocytes, lymphocytes, and multinucleated giant cells.

Conclusion: The 10 cases we report demonstrate the importance of recognizing the entity in solitary as well as extrafacial forms. Limiting the histologic diagnosis to fully developed lesions demonstrating epithelioid granulomas with caseation necrosis serves to clarify the diagnosis in the setting of diverse clinical presentations. Further information is needed to clarify the diagnosis, etiology, and pathogenesis of this disease, but an unusual host response to folliculitis or follicular injury likely plays a role in most cases.

Keywords: Lupus miliaris disseminatus faciei; Caseation necrosis, Caseous necrosis; Lupus miliaris; Acne agminata; Follicle centered granuloma; Epithelioid granuloma

Introduction

Lupus miliaris disseminatus faciei (LMDF) is an uncommon but distinct, chronic, inflammatory dermatosis characterized by abrupt development of generally asymptomatic, single to multiple, 1-3 mm brown-red, brown, to yellowish dome-shaped papules or nodules with occasional mild scaling [1-5]. Small pustules may rarely accompany the papules [3,6]. Distribution tends to be symmetrical, primarily involving the central and lateral face with the lower eyelids being most frequently affected [1-3,5]. However, multiple extrafacial sites of involvement and one case without any facial involvement have been reported [1,6,7]. Diascopy may reveal apple-jelly nodules [1-3]. LMDF most commonly affects young adults of both sexes although cases among children and the elderly have been reported [5,8]. Spontaneous resolution of the lesions is reported to occur over 1-4 years, often leaving small, pitted scars [1,5,6]. Microscopic findings are essential for diagnosis and characteristically reveal superficial granulomatous inflammation surrounding caseation necrosis that is often

perifollicular in distribution, although LMDF is now regarded as a spectrum classified into three histological stages: early, fully developed, and late [1]. Each stage has distinct histological findings. Fully developed lesions are further broken down into 4 groups based on the type of granulomatous reaction [1-4,9]. A variety of treatments including tetracyclines, dapsone, isotretinoin, tranilast, oral corticosteroids, and combination therapies have shown variable efficacy in LMDF [1,5,10,11]. Though efficacy is difficult to determine in this spontaneously resolving dermatosis, early diagnosis and treatment has demonstrated prevention of scar formation [1].

The etiology and pathogenesis of LMDF are unknown. It is considered by some to be part of a spectrum between granulomatous rosacea and sarcoidosis [6]. Others postulate an immune response to pilosebaceous units or a foreign body reaction to sebum, keratin, or Demodex folliculorum from ruptured follicles [1,3,4,9]. Studies revealing intense lysozyme reaction in LMDF suggest that an infectious agent may induce cell-mediated immunity, with subsequent formation of epithelioid cell granulomas [12]. The following report describes the clinical and histopathologic findings in 10 cases of LMDF seen in our institution over a 16-year period.

Materials and Methods

From January 1996 to September 2011, the records of 10 patients with a histopathologic diagnosis of lupus miliaris disseminatus faciei were collected from our dermatopathology archive. The records and archival slides were reviewed to determine the clinical appearance and distribution of skin lesions, their duration, and dermatologic history. Skin biopsy specimens stained with hematoxylin-eosin were reviewed, and additional sections obtained from the paraffin blocks were stained with Ziehl-Neelsen (AFB) and period acid-Schiff (PAS) stains.

Results

The case series included 6 men and 4 women from 6 to 79 years of age (mean, 50.4 years). Seven patients presented with a single lesion,

the other three with multiple lesions. Locations included the cheek, cutaneous lip, medial canthus, eyelid, temple, antihelix, neck, and lower back (Table 1). One patient presented with a solitary lesion of the lower back with no facial involvement and another presented with a solitary lesion of the antihelix without facial involvement. The lesions had reportedly been present for “months” up to one year. Eight of 10 patients had a history of previous or coexisting dermatologic disease. One patient had a history of similar lesions previously diagnosed as rosacea, and two other patients had a history of facial lesions diagnosed as cystic acne.

Case No.	Age (y)	Sex	Site	Lesion No.	Clinical diagnosis Before Biopsy	Onset	Dermatologic History	Size (mm)
1	36	F	Cheek	1	EIC	Months	Cystic acne	8
2	67	M	Lower Back	1	Intradermal nevus vs. BCC	Months	SCC, BCC	4
3	79	F	Cutaneous Lip	1	Indurated AK	3 months	LPP	3
4	6	M	Face	Multiple	GA vs. sarcoidosis vs. deep molluscum vs. mucinosis	Months	None	0.5-2
5	57	M	Medial Canthus	1	Cyst vs. BCC	1 y	Rosacea	2
6	39	M	Antihelix	1	BCC	...	Plaque psoriasis	3
7	34	M	Eyelids, Medial Canthus, Neck	Multiple	GA vs. sarcoidosis vs. deep molluscum vs. mucinosis vs. BCC	...	GA	...
8	59	F	Lower Eyelid	1	BCC
9	58	F	Eyelids, Medial Canthus	Multiple	Granulomatous Rosacea	8-10 mo	Nodulocystic acne	03-May
10	69	M	Temple	1	BCC	...	BCC	...

Table 1: Clinical features of 10 cases of lupus miliaris disseminatus faciei. Abbreviations: EIC, epidermal inclusion cyst; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; AK, actinic keratosis; LPP, lichen planopilaris; GA, granuloma annulare; F, female; M, male.

Eight of the lesions were described as papules, the other two as nodules. One lesion had a centrally located pustule, and one had slight scaling. The average size of the lesions was 3.6 mm in diameter, ranging from 0.5 to 8 mm (Table 1). One patient was symptomatic with complaints of mild tenderness over the lesion. The clinical diagnosis or differential diagnosis at time of biopsy included basal cell carcinoma (BCC) in six cases and sarcoidosis, granuloma annulare (GA), and epidermal cyst in two cases each. Granulomatous rosacea, mucinosis, intradermal nevus, actinic keratosis, and deep molluscum were listed as clinical differential diagnoses in one case each (Table 1).

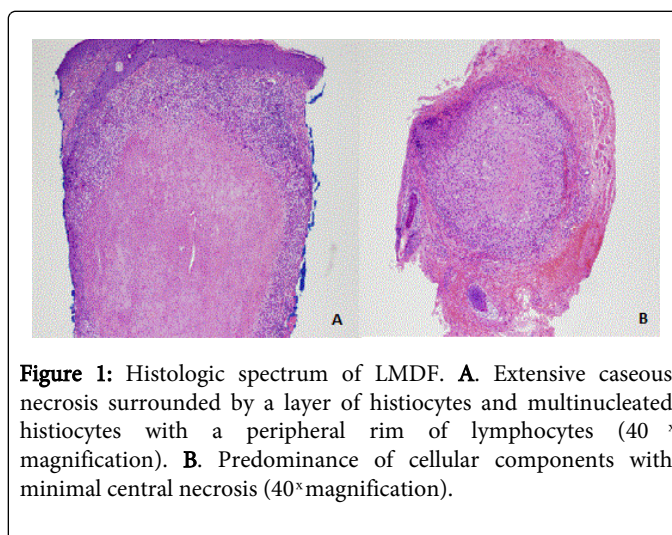


Figure 1: Histologic spectrum of LMDF. **A.** Extensive caseous necrosis surrounded by a layer of histiocytes and multinucleated histiocytes with a peripheral rim of lymphocytes (40^x magnification). **B.** Predominance of cellular components with minimal central necrosis (40^x magnification).

Histopathologically, there were epithelioid (sarcoidal) granulomas with central areas of necrobiosis or caseation necrosis in all specimens (Figure 1).

The granulomas were located in the upper dermis in six cases and in the mid dermis in two cases. In seven of the cases, a perifollicular distribution of the granulomas was noted (Figure 2).

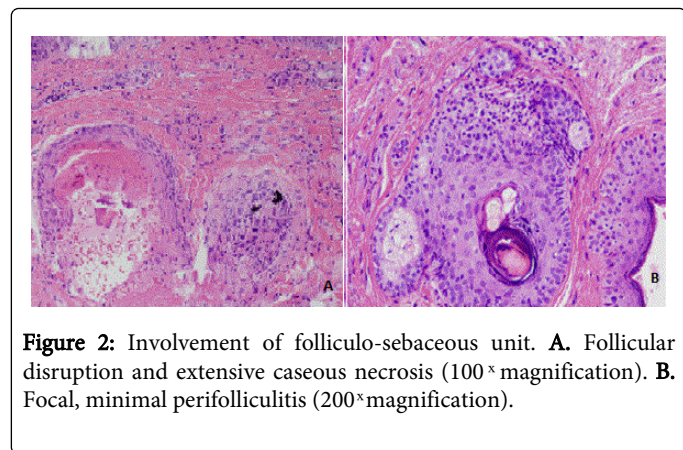


Figure 2: Involvement of folliculo-sebaceous unit. **A.** Follicular disruption and extensive caseous necrosis (100 × magnification). **B.** Focal, minimal perifolliculitis (200 × magnification).

Lymphocytes were seen in eight cases (Figure 1-3); the lymphocytes formed an outer layer surrounding the granuloma in four cases (Figure 3).

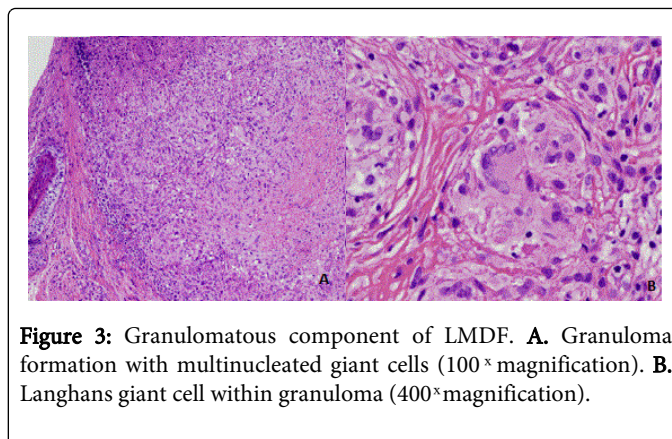


Figure 3: Granulomatous component of LMDF. **A.** Granuloma formation with multinucleated giant cells (100 × magnification). **B.** Langhans giant cell within granuloma (400 × magnification).

Disruption of hair follicles in approximation to the granulomas was noted in two cases (Figure 1B and Figure 2B). One case demonstrated a perifollicular lymphocytic infiltrate with minimal follicular invasion. Multinucleated giant cells were seen in eight cases (Figure 3). AFB and PAS stains were performed on five of the cases and were all negative (Table 2).

Case No.	Granuloma Type	Caseation Necrosis	Granuloma location	Granuloma contents	Disruption of hair follicle	MN cells	giant	AFB PAS &
1	Epithelioid (sarcoidal)	Yes	Unable TBD*	Histiocytes, sparse lymphocytes	No	Yes		Neg
2	Epithelioid	Yes	Upper dermis	Histiocytes, outer layer of lymphocytes	Yes	No		Neg
3	Epithelioid	Yes	Upper dermis (perifollicular)	Histiocytes, outer layer of lymphocytes	No	Yes		NA
4	Epithelioid	Yes	Upper dermis (perifollicular)	Histiocytes, lymphocytes	Yes	Yes		NA
5	Epithelioid	Yes	Mid dermis (perifollicular)	Histiocytes, outer layer of lymphocytes	No	Yes		NA
6	Epithelioid	Yes	Upper dermis (perifollicular)	Histiocytes, lymphocytes	No	Yes		Neg
7	Epithelioid	Yes	Upper dermis (perifollicular)	Histiocytes, outer layer lymphocytes	No	Yes		Neg
8	Epithelioid	Yes	Upper dermis (perifollicular)	...*	...*	...*		NA
9	Epithelioid	Yes	Mid dermis (perifollicular)	Histiocytes, lymphocytes	No	Yes		Neg
10	Epithelioid	Yes	Unable TBD*	Histiocytes	...*	Yes		NA

Table 2: Histologic features of 10 cases of lupus miliaris disseminatus faciei. Fields marked with * indicate the data was not able to be determined because the original slides and paraffin block were no longer available for review and the data was not included in the original dermatopathology report. Abbreviations: TBD, to be determined; MN, multinucleated; AFB, acid fast bacteria; PAS, periodic acid-schiff; NA, Not applicable (stain not done); Neg, negative.

Discussion

The clinical presentation of LMDF has classically been described as multiple, smooth, 1-3 mm brown-red, brown, to yellowish dome-shaped papules to nodules distributed symmetrically on the central and lateral face and around the eyelids, more often involving the lower eyelids [1-5]. Other locations have been described including the ears, neck, axillae, arms, hands, legs, groin, genitals, scalp, and trunk [1,3,6,7,13,14]. One case report described LMDF without any facial involvement; the papules were located on the neck and chest only [7]. This entity has been described with a variety of names including acne agminata, acnitis, papular tuberculid, lupoid rosacea, and the more recent facial idiopathic granulomas with regressive evolution (F.I.G.U.R.E.) [1,2,3,15]. The clinical differential diagnosis in the classical presentation is broad and includes granulomatous rosacea, perioral dermatitis, small-nodular sarcoidosis, corticosteroid dermatitis resembling rosacea, acne vulgaris, polymorphic light eruption, eruptive syringomas, and multiple trichoepitheliomas [1,2]. In our study of 10 patients, we have found clinical presentations that vary from the classic description of LMDF. Seven of the patients presented with solitary lesions only, which resulted in a differential diagnosis including epidermal cyst, basal cell carcinoma, and indurated actinic keratosis. Two of the patients presenting with solitary lesions had no facial involvement; the papules were located on the lower back and antihelix only. In the 3 cases with multiple lesions, a typical distribution was found on the central to lateral face with a predilection for the periorbital areas. This highly variable clinical presentation demonstrates the diagnostic challenge concerning LMDF.

The characteristic histopathologic finding of LMDF is a lesion of the superficial to mid-dermis with epithelioid cell granulomas surrounding areas of caseation necrosis [4]. However, some authors have proposed that there is a histopathologic spectrum of lesions that can be divided into three stages: early (less than one month duration and size less than 2 mm), fully developed (3-6 month duration and size 3-4 mm), and late stage (greater than 8 months duration) [2,10]. The early lesions are characterized by superficial perivascular and periappendageal infiltrates composed primarily of lymphocytes with a few histiocytes and neutrophils. Some of the early lesions have demonstrated lymphocytes within follicular walls [2,9]. Fully developed lesions typically demonstrate perifollicular epithelioid granulomas, sometimes with follicular rupture. The granulomas are comprised of histiocytes (macrophages), a variable number of multinucleated giant cells of the Langhans or foreign body type, occasional neutrophils, and a peripheral rim of lymphocytes [1,2,9]. The fully developed lesions are subclassified into four groups: sarcoidal or epithelioid granulomas, sarcoidal granulomas with neutrophilic abscess formation, sarcoidal granulomas with caseation necrosis, and a mixture of sarcoidal and tuberculoid granulomas [2,4,9]. Late stage granulomas contain scattered lymphocytes, histiocytes, and neutrophils amidst extensive perifollicular fibrosis with mild thinning of the epidermis [2,9]. Hyperkeratosis, dilatation of pilosebaceous units, follicular plugging, and pigment incontinence have been variably present [2].

In our report of 10 patients, the presence of an epithelioid granuloma with central caseation necrosis or necrobiosis was the requirement for histologic diagnosis. Therefore, only the fully developed lesions subclassified as sarcoidal (epithelioid) granuloma with central caseation necrosis are represented in our sample. If the diagnostic criteria were expanded to include the histologic presentation of early and late lesions as well as the other sub-

classifications of fully developed lesions, the sample size would almost certainly have increased. However, an increase in false positive results would be expected if the histologic inclusion criteria were expanded in the context of diverse clinical presentations. With such an approach, a wide variety of granulomatous disorders might qualify for inclusion, including granulomatous rosacea, granulomatous perioral dermatitis, acneiform folliculitis, and a number of cutaneous infections. Therefore, we advocate focusing the histologic diagnostic criteria on fully developed lesions demonstrating classic epithelioid granulomas with central caseation necrosis. Finding these changes in a biopsy obtained in the context of multiple lesions can be of considerable importance, since early lesions of LMDF (which may show only nonspecific perivascular and perifollicular infiltrates comprised of lymphocytes, macrophages, and neutrophils) may be amenable to treatment and the prevention of scar formation [1]. In the setting of solitary lesions, especially on the trunk and extremities, the finding of epithelioid granulomas with central caseation necrosis may be thought to represent a reaction to a ruptured follicle or folliculitis. We suggest that the presence of epithelioid granulomas with central caseation in these cases warrants consideration that these entities may actually represent part of the spectrum of disease of LMDF.

The etiology and pathogenesis of LMDF are unknown. As the name implies, LMDF was once thought to be caused by *Mycobacterium tuberculosis*, but no organisms have been demonstrated and no culture or polymerase chain reaction (PCR) evidence of mycobacterial disease has been confirmed [16]. The caseation observed in LMDF is thought to be a form of coagulation necrosis caused by abscesses rather than the caseation associated with *Mycobacterium tuberculosis* [4]. The presence of nuclear dust and neutrophils within the zones of caseation necrosis suggests that neutrophils may indeed play a role in inducing this change [9]. Shitara found granulomas next to hair follicles in only 43 percent of 81 patients with LMDF, despite having performed multiple levels through the paraffin blocks [17]. Nevertheless, an immune response to the pilosebaceous unit seems highly likely to be involved in the granuloma formation in many cases of LMDF [9]. The presence of a predominately lymphocytic perifollicular infiltrate with invasion of the follicular wall in early lesions suggests the possibility of an attack on hair follicles by lymphocytes as the initial triggering event that leads to damage of the follicular wall and eventual release of potential antigens into the dermis. The presence of granulomas in the vicinity of ruptured follicles in fully developed lesions lends further support to this theory [9]. The granuloma formation could be regarded as a reaction to breakdown products of the pilosebaceous unit such as keratin and sebum or to antigens exposed during follicular rupture [4,10,18]. Epithelioid granulomas have been experimentally produced by intradermal injection of sebum and comedones [19]. While this finding could represent a non-immunological foreign body granuloma reaction, the presence of moderate to intense staining of lysozyme in the epithelioid histiocytes and multinucleate giant cells of LMDF suggests a role for cell-mediated immunity.

LMDF has been considered to be a form of granulomatous rosacea, supported by the frequent close association with pilosebaceous units [1,17]. However, LMDF is often clinically distinct from rosacea, since LMDF is self-limited with spontaneous resolution over 1-4 years (usually between 12-24 months), often leaves disfiguring scars, does not present with erythema, flushing, or telangiectasia, is not exacerbated by heat or spicy foods, and is often improved with oral corticosteroid treatment [1,3,5]. LMDF has also been considered as a form of periorificial dermatitis (POD), however, POD usually presents

with a background of erythema and scaling, may be accompanied by burning or stinging sensations, does not heal with scarring, and does not show caseation necrosis on histopathology [20]. These characteristics help to distinguish POD from LMDF. Periorificial dermatitis is considered by some to be a form of granulomatous rosacea [21]. Some authors argue that childhood granulomatous periorificial dermatitis (CGPD) is a variant of LMDF found in children [22]. If the broader histopathologic definitions of LMDF were to be considered, distinguishing between these two entities would prove to be challenging. Sarcoidosis is also considered in the differential diagnosis of LMDF. Sarcoidosis is considered to be a cell mediated granulomatous disease. Its pathogenesis may be related to that of LMDF, and it has a similar clinical presentation and disease progression - a wide distribution of papules to nodules that frequently undergo spontaneous resolution and may improve with the use of systemic corticosteroids [6]. Some consider LMDF to fall on a spectrum between granulomatous rosacea and sarcoidosis [6]. Another proposal is that LMDF may be a reaction to an as-yet unknown infectious agent associated with cell-mediated immunity [12]. In fact, the variations in clinical and histologic presentation and the dissimilarities in response to therapy suggest the possibility that more than one mechanism may play a role in producing the lesions of LMDF [1,3]. These findings further support the need to consider the diagnosis of LMDF for both solitary and extrafacial lesions demonstrating epithelioid granulomas with caseation necrosis, especially when follicular destruction is present.

In summary, our study of these 10 cases expands upon what is known both clinically and histologically about lupus miliaris disseminatus faciei. It appears to be a granulomatous reaction most often related to destruction of the pilosebaceous unit and the resultant antigen exposure, but it remains clinically distinct from granulomatous rosacea and periorificial dermatitis, and in fact the etiology may be multifactorial. To prevent diagnostic confusion, we advocate limiting the histologic criteria to include only fully developed lesions demonstrating epithelioid granulomas with caseous necrosis [17]. The presence of solitary lesions in the majority of our patients and exclusively extrafacial involvement in 2 patients demonstrates the importance of histopathology in aiding diagnosis of LMDF. Furthermore, it suggests that there is likely a spectrum of disease with a variety of clinical manifestations linked by a similar histopathologic finding of epithelioid granuloma with caseous necrosis. The reporting of more clinical cases and histologic findings will eventually enable us to better understand and diagnose this perplexing entity and will provide further clues to elucidate its pathogenesis.

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