



# The Semantics of Lupus: What Is in a Name?

Brooke Walls, DO

First-year medical students are faced with the daunting challenge of learning medical terminology, a new language to them. As dermatology residents, we are engaged to further refine our language skills, as the mastery of eloquent description is of utmost importance in our specialty. One barrier to mastering this language is the barrage of confusing and often imprecise terminology. Much of the confusion stems from historical perspectives and imprecise terminology, which often encompasses diseases of various origins with similar clinical presentations. One classic example and source of much angst among dermatology residents is the term *lupus*. Herein I will briefly review the history of lupus and then distinguish the various diseases that bare this name (Table). My hope is to create greater understanding and appreciation of these diverse diseases with a historical perspective.

## Historical Perspective

Lupus is derived from the Latin word meaning wolf, often symbolizing a creature that borders on fantasy and garners up images of destruction.<sup>1</sup> Accordingly, in the past many disease processes that resembled a destructive ulcerative process were named lupus. Hippocrates is considered the first to have described cutaneous ulceration and lupus likely was included in this description.<sup>2</sup> Prior to the Middle Ages, Paracelsus and Giovanni Manardi used the term *lupus* to describe ulcerative lesions on the lower extremities.<sup>1,2</sup> Hans von Gersdorf was one of the first medical writers to use lupus to describe facial lesions.<sup>3</sup> In 1808, Robert Willan, the father of modern dermatology, used lupus to describe cutaneous tuberculosis of the

face, which is now referred to as lupus vulgaris.<sup>2</sup> The first documented description of lupus erythematosus (LE) was made by Laurent Biett in 1833 and was further described by Moriz Kaposi 4 decades later with the systemic association of systemic lupus erythematosus (SLE).<sup>2-4</sup> Over the next 2 decades, many scientists made considerable contributions to our understanding of SLE, which advanced with the discovery of the LE cell by Hargraves et al<sup>5</sup> in 1948. As the continued scientific discovery ensued, distinction between the diverse ulcerative diseases was made yet the terminology lupus remained.

## Distinguishing Between Diseases

Let us begin with LE, a heterogeneous group of inflammatory diseases that primarily affect the skin but may have systemic involvement. The pathogenesis encompasses a complex interplay of inflammatory and environmental components. Classification is based on the location and depth of the inflammatory infiltrate. The classic malar rash seen in acute SLE is a nonscarring process and primarily affects the epidermis. Chronic cutaneous LE includes discoid lupus erythematosus, LE tumidus, LE panniculitis, chilblain lupus erythematosus (CHLE), and a few rarer entities not discussed here. Discoid lupus erythematosus presents with firm indurated plaques on the head and neck and can result in scarring and permanent disfigurement. Discoid lupus erythematosus is likely the variant included in historical context and often historically diagnosed as cutaneous tuberculosis prior to readily available diagnostic tools.<sup>6,7</sup>

Lupus erythematosus tumidus often presents with erythematous and edematous plaques on the face or the trunk that tend to resolve without scarring. Histologic examination reveals a patchy lymphocytic infiltrate that is both superficial and deep, affecting the eccrine glands, as well as copious dermal mucin deposition.<sup>6</sup> Unlike other variants of LE, there is lack

From Nova Southeastern University College of Osteopathic Medicine, Largo, Florida.

The author reports no conflict of interest.

## Various Diseases Called Lupus

Disease	Classification/Etiology	Clinical Findings	Histologic Findings
Acute SLE	CTD; inflammatory and environmental (same for all LE variants)	Varies (malar rash, discoid lesions)	Superficial lymphocytic infiltrate with interface changes
DLE	CACLE	Indurated plaques often on the head and neck	Superficial and deep lymphocytic infiltrate with follicular plugging
LE tumidus	CACLE	Erythematous plaques on the face and trunk	Spare the epidermis; periadnexal lymphocytic infiltrate; mucin deposition
LE panniculitis (lupus profundus)	CACLE	Indurate plaques that eventuate into depressed areas; can be disfiguring; one-third have overlying discoid lesions	Lobular panniculitis; intense lymphoplasmocytic inflammation within deep dermis; widened septa of subcutaneous fat; occasional lymphoid follicles; +/- epidermal changes consistent with LE
Chilblain LE (SLE pernio)	CACLE	Erythematous purple plaques located on acral sites precipitated by cold	Interface dermatitis; epidermal atrophy; dyskeratotic keratinocytes; lymphocytic infiltrate, especially around eccrine coils
Perniosis (chilblain)	Inflammatory/vasculopathic	Cold-induced inflammatory vasculopathic disorder of acral areas	Perivascular lymphocytic infiltrate (cuffing) with perieccrine involvement
Lupus pernio	Granulomatous sarcoidosis	Violaceous papules/plaques on nose and cheeks	Naked noncaseating granulomas
Lupus vulgaris	Infectious <i>Mycobacterium tuberculosis</i>	Verrucous plaques of the central face that can be destructive	Tuberculoid granulomas with caseation necrosis; paucibacillary
Lupus miliaris disseminatus faciei	Granulomatous; likely a spectrum: granulomatous rosacea to sarcoid	Discrete red-brown papules on central face, including eyelids	Caseation and noncaseation epithelioid granulomas

Abbreviations: SLE, systemic lupus erythematosus; CTD, connective-tissue disease; LE, lupus erythematosus; DLE, discoid lupus erythematosus; CACLE, chronic cutaneous lupus erythematosus.

of epidermal involvement.<sup>8</sup> Controversy exists as to whether LE tumidus is a distinct entity, a variant of Jessner lymphocytic infiltrate, or a variant of LE.<sup>9</sup>

Lupus erythematosus panniculitis, also known as lupus profundus, is a lobular panniculitis that presents with tender indurated plaques on the proximal

extremities of the face, breasts, and buttocks.<sup>6</sup> The lesions eventuate into depressed areas that can be quite disfiguring. One-third of patients have overlying discoid lesions in conjunction with the panniculitis. Histology may reveal vacuolar interface dermatitis. Most characteristic is a deep dermal lymphocytic infiltrate with widened septa and a lobular panniculitis. Abundant dermal mucin, occasional plasma cells, and lymphoid follicles also may be identified.<sup>6</sup>

Chilblain lupus erythematosus (SLE pernio) is characterized by dusky red- to purple-colored plaques on the distal fingers and toes and less commonly on the nose and ears. They are first brought on by cold moist environments, do not remit completely, and tend to be pruritic, followed by pain and possible necrosis.<sup>6,10</sup> Familial cases have been described with an association with mutations in the three prime repair exonuclease 1 gene, *TREX1*, which plays a role in apoptotic single-stranded DNA damage induced by killer lymphocytic protease granzyme A. Lymphoblasts that are heterozygous for this mutation were notably less sensitive to granzyme A-mediated cell death.<sup>10</sup> Differentiation from idiopathic chilblains and lupus pernio is based on the Mayo Clinic diagnostic criteria for diagnosis of CHLE.<sup>11</sup> There are 2 major criteria: skin lesions in acral locations induced by exposure to cold or a drop in temperature, and evidence of LE in the skin lesions by histopathologic examination or indirect immunofluorescence. There are 4 minor criteria: coexistence of SLE or other skin lesion of discoid lupus erythematosus, response to anti-LE therapy, and negative results of both cryoglobulins and cold agglutinin studies.<sup>11</sup> Both major criteria and 1 minor criterion need to be present to diagnose CHLE. Histopathologic examination reveals characteristic LE changes including interface dermatitis, epidermal atrophy, dyskeratotic keratinocytes, and lymphocytic infiltrate, especially around the eccrine coils.<sup>12</sup>

Idiopathic chilblain, also known as perniosis, presents with a similar clinical appearance to CHLE with symmetric distribution but fails to meet the Mayo Clinic diagnostic criteria for CHLE.<sup>13</sup> A workup to rule out SLE is necessary, as it has been reported that a higher percentage of patients with chilblains eventuate into SLE.<sup>14</sup> Histologic examination is characteristic for cuffed perivascular lymphocytic infiltrate, often with papillary dermal edema.<sup>6</sup>

Lupus pernio is cutaneous sarcoidosis that is characterized by violaceous, brown, or yellowish papules and nodules that often affect the face, especially the nose and cheeks. It is important to recognize this entity, as it can lead to destruction and scarring. Lupus pernio can present with granulomatous lesions in the upper aerodigestive tract; therefore, ear, nose,

and throat evaluation is recommended.<sup>15</sup> Clinically, lupus pernio may mimic CHLE; however, distinction can be made by histopathology.<sup>16</sup> Lupus pernio is characterized by a dense dermal infiltrate of noncaseating granulomas composed of epithelioid histiocytes.<sup>15,16</sup>

Lupus vulgaris is a rare form of cutaneous tuberculosis that is disseminated by hematogenous, lymphatic, or direct extension.<sup>17</sup> Lupus vulgaris is seen in patients with strong immunity, a positive purified protein derivative (tuberculin) reaction, absent or scant lesional tubercle bacilli, and often negative cultures. Characteristically it presents with verrucous plaques of the central face that can be destructive. Histologic examination reveals tuberculoid granulomas with a lymphohistiocytic infiltrate. Identification of mycobacteria is difficult and Ziehl-Neelsen and Fite stains often are negative.<sup>18</sup> Polymerase chain reaction analysis recently has been employed as a sensitive diagnostic tool; however, it is expensive and false-positives may occur in patients with latent or recently treated infection.<sup>18</sup> At the turn of the century, lupus was intimately associated with cutaneous tuberculosis.<sup>19</sup> Currently, lupus is more commonly associated with LE. It should be cautioned that the shorthand terminology of lupus alone is erroneous and may lead to confusion. Cutaneous tuberculosis is still prevalent, thus underlying the importance of precise diagnostic terms that should be employed by dermatologists.

Lupus miliaris disseminatus faciei (LMDF) is a rare granulomatous process of unknown etiology that presents with the abrupt onset of a distinctive facial eruption and spontaneous resolution, often with scarring.<sup>20,21</sup> The characteristic lesions are reddish to yellow-brown papules on the central face, particularly around the eyelids and central face. The abrupt onset of the eruption and characteristic distribution along with spontaneous resolution with scarring is classic and distinguishes it from granulomatous rosacea. Histologic examination reveals superficial granulomatous inflammation with perifollicular caseating granulomas, though different histologic patterns recently have been reported and may represent a spectrum of disease.<sup>22</sup> Classification is still controversial and recent publications advocate that LMDF should be viewed as a distinct entity. Skowron et al<sup>23</sup> promoted the less confusing term *facial idiopathic granulomas with regressive evolution* to replace LMDF, but to date, it has not been widely accepted.

## Conclusion

Although this review is brief, I hope it provides a framework that will help organize the various diseases that bare the name lupus into a useful and understandable system on which to build knowledge and

understanding. Additionally, may this review be a nidus for further exploration and spark the curiosity of academic endeavors.

## REFERENCES

1. Boltzer JW. Systemic lupus erythematosus, I: historical aspects. *MD State Med J*. 1983;32:439-441.
2. Mallavarapu RK, Grimsley EW. The history of lupus erythematosus. *South Med J*. 2007;100:896-898.
3. Holubar K. Terminology and iconography of lupus erythematosus: a historical vignette. *Am J Dermatopathol*. 1980;2:239-242.
4. Sierra X. *Historia de la Dermatologia*. Barcelona, Spain: MRA; 1994. <http://sfhd.chez.com/ecrits/hist1.htm>. Accessed January 16, 2013.
5. Hargraves MM, Richmond H, Morton R. Presentation of two bone marrow elements: the tart cell and the LE cell. *Proc Staff Meet Mayo Clin*. 1948;23:25-28.
6. Lee LA. Lupus erythematosus. In: Bologna JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*. 2nd ed. London, England: Elsevier Ltd; 2008:561-574.
7. James WD, Berger TG, Elston DM. Connective tissue disease. In: James WD, Berger TG, Elston DM. *Andrews' Diseases of the Skin: Clinical Dermatology*. 10th ed. United Kingdom: Saunders Elsevier; 2006:155-165.
8. Calonje E, Brenn T, Lazar A, et al. Superficial and deep perivascular inflammatory dermatoses. In: Calonje E, Brenn T, Lazar A, et al, eds. *McKee's Pathology of the Skin With Clinical Correlations*. 4th ed. China: Elsevier Saunders; 2012:259-280.
9. Rémy-Leroux V, Léonard F, Lambert D, et al. Comparison of histopathologic-clinical characteristics of Jessner's lymphocytic infiltration of the skin and lupus erythematosus tumidus: Multicenter study of 46 cases. *J Am Acad Dermatol*. 2008;58:217-223.
10. Hedrich CM, Fiebig B, Hauck FH, et al. Chilblain lupus erythematosus—a review of literature. *Clin Rheumatol*. 2008;27:949-954.
11. Su WPD, Perniciario C, Rogers RS, et al. Chilblain lupus erythematosus (lupus pernio): clinical review of the Mayo Clinic experience and proposal of diagnostic criteria. *Cutis*. 1994;54:395-399.
12. Helm TN, Jones CM. Chilblain lupus erythematosus lesions precipitated by the cold. *Cutis*. 2002;69:183-184.
13. Takci Z, Vahaboglu G, Eksioğlu H. Epidemiological patterns of pemphigus, and its association with systemic disorder [published online ahead of print October 22, 2012]. *Clin Exp Dermatol*. 2012;37:844-849.
14. Doutre MS, Beylot C, Beylot J, et al. Chilblain lupus erythematosus: report of 15 cases. *Dermatology*. 1992;184:26-28.
15. Calonje E, Brenn T, Lazar A, et al. Granulomatous, necrobiotic and perforating dermatoses. In: Calonje E, Brenn T, Lazar A, et al, eds. *McKee's Pathology of the Skin*. 4th ed. China: Elsevier Saunders; 2012:281-288.
16. Arias-Santiago SA, Giron-Prieto MS, Callejas-Rubio JL, et al. Lupus pernio or chilblain lupus?: two different entities. *Chest*. 2009;136:946-947.
17. Umapathy KC, Begum R, Ravichandran G, et al. Comprehensive findings on clinical, bacteriological, histopathological and therapeutic aspects of cutaneous tuberculosis. *Trop Med Int Health*. 2006;11:1521-1528.
18. Rhodes J, Caccetta TP, Tait C. Lupus vulgaris: difficulties in diagnosis [published online ahead of print February 23, 2012]. *Aust J Dermatol*. doi:10.1111/j.1440-0960.2011.00874.x.
19. Mascaro JM. 'Angela's ashes' (lupus vulgaris: from yesterday to the third millennium. *J Eur Acad Dermatol Venereol*. 2002;16:311-312.
20. van de Scheur MR, van der Waal RI, Starink TM. Lupus miliaris disseminatus faciei: a distinctive rosacea-like syndrome and not a granulomatous form of rosacea. *Dermatology*. 2003;206:120-123.
21. Lipoff J, Friedman A. Sound-alike and look-alike terms in dermatology: the Unified Division of Dermatology of the Albert Einstein College of Medicine. *J Drugs Dermatol*. 2011;10:1196-1198.
22. Al-Mutairi N. Nosology and therapeutic options for lupus miliaris disseminatus faciei. *J Dermatol*. 2001;38:864-873.
23. Skowron F, Causeret AS, Pabion C, et al. F.I.G.U.R.E.: facial idiopathic granulomas with regressive evolution. Is 'lupus miliaris disseminatus faciei' still an acceptable diagnosis in the third millennium? *Dermatology*. 2000;201:287-289.