DR MAY P. CHAN (Orcid ID : 0000-0002-0650-1266)

Article type : Review

Title: Cutaneous Manifestations of Lupus Erythematosus: A Practical Clinicopathologic Review for Pathologists

Running Title: Cutaneous Manifestations of Lupus Erythematosus

Authors: Carole Bitar, MD[1,2]; Tyler D. Menge, MD[1,2]; May P. Chan, MD[1,2]

[1]Department of Pathology, Michigan Medicine, University of Michigan, Ann Arbor, MI, USA
[2]Department of Dermatology, Michigan Medicine, University of Michigan, Ann Arbor, MI, USA

Corresponding author:
May P. Chan, MD
NCRC Building 35
2800 Plymouth Road
Ann Arbor, MI 48109, USA
Email: mpchan@med.umich.edu

Word count: 3952
Figures: 11
Table: 2

Disclosure statement: The authors have nothing to disclose.

Key words: Connective tissue disease, lupus erythematosus, antiphospholipid syndrome, plasmacytoid dendritic cells, vasculitis

Abstract

Accurate diagnosis of connective tissue diseases is often challenging and relies on careful correlation between clinical and histopathologic features, direct immunofluorescence studies, and laboratory workup. Lupus erythematosus (LE) is a prototype of connective tissue disease with a variety of cutaneous and systemic manifestations. Microscopically, cutaneous LE is classically characterized by an interface dermatitis, although other histopathologic patterns also exist depending on the clinical presentation, location, and chronicity of the skin lesions. In this article, we review the clinical, serologic, histopathologic, and direct immunofluorescence findings in LE-specific and LE-nonspecific skin lesions, with an emphasis on lesser known variants, newly described features, and helpful ancillary studies. This review will guide general pathologists and dermatopathologists in accurately diagnosing and subclassifying cutaneous LE.

Introduction

Connective tissue diseases are a heterogeneous group of autoimmune diseases affecting one or multiple organ systems. A complex interplay of immunologic, genetic, and environmental factors forms the pathogenetic basis of these diseases. Lupus erythematosus (LE) is one of the most common connective tissue diseases present worldwide and affecting all age groups, genders, and ethnicities.[1] Cutaneous manifestations are common in LE, and accurate diagnosis and subclassification of the disease is key to appropriate clinical management of these patients. This requires multidisciplinary clinicopathologic correlation between Dermatology, Rheumatology, and Pathology. While most pathologists are familiar with the classic histopathologic findings of cutaneous LE such as vacuolar interface dermatitis, follicular hyperkeratosis, and increased dermal mucin, other subtle features or less common variants may be easily overlooked. Failure to correlate with clinical findings further adds to the likelihood of delayed or under-diagnosis of this disease.

This article aims to provide a comprehensive review on the clinical and pathologic features of cutaneous LE, as well as updates on relatively new and useful ancillary tools in diagnosing this disease.

Classification of LE-associated skin lesions

Cutaneous LE may be confined to the skin or occur in the setting of systemic LE (SLE). It is estimated that 70-85% of SLE patients develop cutaneous lesions over the course of the disease, and that cutaneous LE may be the first presenting sign in about 25% of these patients.[2,3] Meanwhile, only a small subset (10-20%) of patients with cutaneous LE will eventually develop SLE, and the number varies between different subtypes of cutaneous LE.[4,5] For example, localized discoid LE (DLE) is associated with a much lower risk of developing SLE compared to acute cutaneous LE (ACLE). This underscores the importance of precise subclassification of cutaneous LE, which is based on clinical morphologies and duration of the lesions, as well as histopathologic changes observed in skin biopsies.

The first classification scheme of skin lesions associated with LE was proposed by Gilliam[6] and has undergone significant revisions since. These lesions are divided into LE-specific and LE-nonspecific groups. The LE-specific lesions, widely used synonymously with “cutaneous LE”, are specific to patients with LE with or without systemic involvement. These lesions are subclassified into acute, subacute, chronic, and intermittent forms. On the other hand, LE-

nonspecific lesions are commonly seen in SLE patients but may also be encountered in other diseases; a few examples are vasculitis, livedo reticularis, and urticaria. A simplified classification of the cutaneous signs in LE is shown in Table 1. All cutaneous LE subtypes and selected LE-nonspecific lesions are discussed in detail below.

Lupus erythematosus-specific skin lesions (Cutaneous lupus erythematosus)

The most common histopathologic pattern of this group is that of a vacuolar interface dermatitis involving the dermoepidermal junction, with a few exceptions. The composition and the depth of the inflammatory infiltrate are determined by the chronicity and the subtype of skin lesions. Early or acute lesions may contain neutrophils, whereas chronic lesions tend to show a predominance of lymphoplasmacytic infiltrate and extension into deeper dermis or subcutis. Different cutaneous LE subtypes are associated with different serologic profiles and risks of association with SLE, which are summarized in Table 2.

Acute cutaneous lupus erythematosus (ACLE)

Clinical features. ACLE is a transient photodistributed rash that can be localized to the head and neck or widespread. Its localized form is characterized by a symmetric malar or “butterfly” rash on the cheeks, nose, chin, and forehead sparing the nasolabial folds.[7,8] The lesions begin as small erythematous macules and papules which gradually become confluent. In its generalized form, widespread erythematous and edematous papules and plaques are found anywhere on the body, accentuated in sun-exposed areas.[7,8] When the hands and feet are affected, the knuckles are typically spared; this allows for distinction from Gottron papules in dermatomyositis. ACLE may heal with dyschromia but no scarring.[7,8] It is strongly associated with SLE and may be the presenting sign of this disease.

A rare and most severe variant is toxic epidermal necrolysis (TEN)-like ACLE, a life-threatening condition in which intense ACLE results in a vesiculobullous eruption that ultimately evolves into extensive sheet-like epidermal cleavage and necrosis over days to weeks.[9,10] A history of recent SLE exacerbation, photodistribution of lesions, minimal to mild mucosal involvement, and lack of inciting new medications favor this condition over Stevens-Johnson syndrome (SJS)/TEN clinically.[9]

Serology. Due to its strong association with SLE, patients with ACLE frequently test positive for antinuclear antibody (ANA), anti-dsDNA, anti-Sm, anti-Ro, and/or anti-U1-RNP.[11]

Histopathology. ACLE is a vacuolar interface dermatitis with relatively mild lymphocytic inflammation (Fig 1A). There may be dermal edema and microhemorrhage.[7,12] Neutrophils are present in very early lesions,[7] possibly reflective of the role of neutrophil extracellular trap (NET) in facilitating LE.[13] In TEN-like ACLE, there is robust basal vacuolar degeneration resulting in confluent dyskeratoses, subepidermal separation, and full-thickness epidermal necrosis (Fig 1B).[9,14,15] The additional findings of adnexal epithelial involvement, thickened basement membrane, and increased dermal mucin help support this diagnosis over SJS/TEN.[9]

Direct immunofluorescence. Results of direct immunofluorescence (DIF) are highly dependent on where the biopsy is taken from.[7] Lesional skin is almost always positive for a “lupus band”—a continuous band of granular immunoglobulin (IgG > IgM > IgA) and/or C3 deposits along the basement membrane zone (Fig 1C).[7] A positive lupus band test is seen in sun-exposed, non-lesional skin in 70-90% of SLE patients, but also in up to one-third of healthy individuals.[7,16] Conversely, a positive lupus band test in sun-protected, non-lesional skin or mucosa provides the highest specificity (up to 98%) but the lowest sensitivity (10-55%) for SLE.[7,16,17] As most patients test positive for ANA, epidermal nuclear binding for IgG may also be seen (Fig 1D).[18]

Subacute cutaneous lupus erythematosus (SCLE)

Clinical features. SCLE is a photodistributed rash with two main forms. The annular form is characterized by scaly annular or polycyclic erythematous papules and plaques, whereas the papulosquamous form is characterized by scaly and psoriasiform lesions.[19] It typically involves the upper trunk and upper extremities while sparing the face and scalp.[20] Lesions usually heal with dyschromia without scarring.[8] Although 40-50% of patients with SCLE meet the American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE, only 10-15% actually develop systemic disease.[21,22] Approximately 30% of cases are drug-induced.[23] Drug-induced SCLE occurs in older patients and is caused by a wide variety of drugs including diuretics, biologics, cardiologics, and chemotherapies.[23] Patients with SCLE commonly exhibit musculoskeletal symptoms with rare involvement of other organs.[8]

Serology. Incidence of ANA positivity was reported to be 50-80% in SCLE patients.[22,24-26] Many patients test positive for anti-Ro/SSA (40-100%).[24-27] Other autoantibodies are detected less frequently, including anti-La/SSB (15%), anti-dsDNA (5-24%), and anti-Sm (7-18%).[24-26,27]

Histopathology. The epidermis is usually atrophic with vacuolar interface dermatitis and hyperkeratosis.[12] Interface change tends to be intense with many cytoid bodies (Fig 2A).[27,28] The epidermal basement membrane may be thickened.[12] There is a superficial perivascular lymphocytic infiltrate, while deep periadnexal inflammation is typically absent.[12] Follicular plugging and pigment incontinence are less prominent compared to DLE.[12] Mucin deposition is more common in idiopathic SCLE, whereas leukocytoclastic vasculitis was associated with drug-induced SCLE.[23] Contrary to common belief, the presence of eosinophils does not necessarily support a drug-induced etiology.[23] Some annular SCLE lesions display robust basal degeneration and even epidermal necrosis (Fig 2B); these cases mimic erythema multiforme microscopically and have been referred to as “Rowell syndrome”, which is now a controversial term.[29]

Direct immunofluorescence. A “lupus band” is present in 65-80% of lesional skin, and in 20% of non-lesional skin.[23,30] A positive lupus band test is more common in idiopathic cases than drug-induced cases.[23] The most frequent immunoglobulin deposit is IgM or IgG, often coupled with C3.[23,30] Interestingly, some cases show a “dust-like” staining pattern in which fine particles of immunoglobulin deposits are scattered through the epidermis and in the superficial dermis (Fig 2C).[31] This dust-like pattern was previously considered to be specific for SCLE, but a more recent study has disputed its specificity by showing the same pattern in some cases of DLE, mixed connective tissue disease, and Sjögren syndrome.[32]

Discoid lupus erythematosus (DLE)

Clinical features. DLE is the most common form of chronic cutaneous LE.[8] Most lesions are localized on the face, ears, and scalp, however it can be generalized in up to 20% of patients.[7] The lesions are coin-shaped, erythematous, scaly papules or plaques with follicular plugging.[7] The periphery of the lesion is often hyperpigmented, whereas the center may be atrophic and hypopigmented.[8] Unlike SCLE, scarring is a prominent feature in DLE.[7,8] Involvement of the scalp results in scarring alopecia.[7] Only a small subset of patients present with systemic symptoms and ultimately develop SLE, particularly those with generalized DLE.[7] Up to 20% of SLE patients present with DLE.[7] A rare variant of DLE is hypertrophic/verrucous LE characterized by warty hyperkeratotic plaques resembling keratoacanthomas and hypertrophic lichen planus, present mainly on the face, trunk, and extensor surfaces.[11]

Serology. While ANA is commonly detected, most patients with skin-limited DLE demonstrated only low titers compared to those with associated systemic disease.[33] Anti-dsDNA antibody is detected in a minority of patients, and is more common in the setting of generalized DLE and/or systemic disease.[33] Similarly, autoantibodies against extractable nuclear antigens (ENAs) such as Sm, Ro, La, and RNP are relatively uncommon in patients with skin-limited or localized DLE.[33]

Histopathology. Chronicity of DLE lesions results in more prominent histopathologic changes compared to ACLE and SCLE.[7] The primary pattern is that of a vacuolar to lichenoid interface dermatitis involving the epidermis and the follicular epithelium, with prominent follicular hyperkeratosis and a superficial to deep perivascular lymphocytic infiltrate (Fig 3A).[7] Basement membrane thickening and dermal mucin deposition may be seen (Fig 3B).[7] Late, "burnt out" lesions reveal dermal scarring, melanin incontinence, and loss of adnexal structures.[12] The latter results in alopecic lesions on the scalp which may simulate lichen planopilaris, another inflammatory scarring alopecia with lichenoid inflammation.[34] Presence of a perivascular lymphocytic infiltrate, increased dermal mucin, and clusters of 10 or more CD123+ plasmacytoid dendritic cells (PDCs) would favor DLE over lichen planopilaris (Fig 3C).[33,35] In the hypertrophic variant, there is pseudoepitheliomatous hyperplasia in addition to the characteristic features of DLE (Fig 3D).[11] Despite some morphologic similarities, hypertrophic LE differs from squamous cell carcinoma by its lack of cytologic atypia and presence of PDC clusters.[11,36] Perforating elastic fibers were once described to be a distinctive feature of hypertrophic LE (Fig 3D, inset),[37] although a subsequent study found a higher frequency of this feature in keratoacanthoma and squamous cell carcinoma.[38]

Direct immunofluorescence. Lesional skin of DLE is positive for lupus band test with granular immunoreactants (C3 > IgG > IgM) along the dermoepidermal junction in 50-90% of cases.[7,39] Lesions from the trunk have a lower positivity for a lupus band test (approximately 20%).[7,40]

Chilblain lupus erythematosus

Clinical features. Chilblain LE is a rare form of chronic CLE that manifests as violaceous and edematous plaques on the acral surfaces, triggered mainly by cold and damp environment.[8,41] Patients typically have preceding and/or concomitant DLE on other sites.[41] Approximately 20% of patients will progress to SLE.[8,41] Clinical lesions of chilblain LE are indistinguishable from idiopathic perniosis/chilblains and are frequently associated with Raynaud phenomenon.[42,43] Su

et al developed a diagnostic scheme for chilblain LE which requires fulfillment of two major criteria: 1) acral skin lesions triggered by cold exposure and 2) evidence of cutaneous LE on histopathologic examination or DIF study; as well as one minor criterion: 1) coexistence of SLE or DLE, 2) response to lupus therapy, or 3) negative results of cryoglobulin and cold agglutinin studies.[44]

Serology. Antinuclear antibody is frequently detected. Anti-Ro and anti-dsDNA are also common, especially in patients with SLE.[43] Anti-Sm and anti-RNP are rarely detected.[43,45]

Histopathology. The major histopathologic pattern is that of a lymphocytic vasculitis, in which dermal vessels are infiltrated by lymphocytes, sometimes with associated fibrinoid necrosis of the vessel walls or thrombosis.[46,47] Other common features include papillary dermal edema, basal vacuolization, perieccrine lymphocytic infiltrate, increased dermal mucin, and erythrocyte extravasation (Fig 4A).[42,47,48] Interstitial fibrin exudate and dermal mucin favor chilblain LE over idiopathic perniosis (Fig 4B).[47,49] Clusters of CD123 positive PDCs are present in about a quarter of cases, but their presence fails to distinguish between chilblain LE and idiopathic perniosis.[47]

Direct immunofluorescence. Direct immunofluorescence findings in chilblain LE have not been well characterized. Granular deposition of IgM, IgA, and C3 at the dermoepidermal junction, and perivascular deposition of C3 and fibrinogen, have been reported.[42,44]

Lupus erythematosus panniculitis (LEP)

Clinical features. Lupus panniculitis is a form of chronic CLE that can present with or without DLE or SLE.[50-52] It manifests as subcutaneous painful nodules mainly affecting the upper extremities, face, scalp, and trunk.[53,54] It is more common in females and may occur in children.[55] The overlying skin may appear normal or display changes of DLE.[56,57] Lesions of LEP heal with lipoatrophy after regression.[56]

Serology. Antinuclear antibody is detected in the majority of patients, usually at low titers of 1:40-1:80.[56,58] Anti-dsDNA and anti-ENA antibodies may be additionally detected.[56]

Histopathology. Lupus panniculitis is predominantly a lobular panniculitis, but a mixed lobular-septal pattern may also be seen.[51,59] The key changes include a brisk lymphocytic infiltrate in the fat lobules (lymphocytic lobular panniculitis), paraseptal lymphoid nodules containing

germinal centers, and hyaline fat necrosis (Fig 5A, 5B).[57] Epidermal and dermal changes of DLE are present in 50-75% of cases.[51,60] Other features such as dermal sclerosis and calcification are less common.[56,58,59] The initial phase of LEP is believed to be a lymphocytic vasculitis, while hyaline and lipomembranous fat necrosis and calcification are end-stage changes resulting from ischemia.[51,61,62]

Distinction of LEP from subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is notoriously difficult.[60] Although rimming of individual adipocytes by atypical lymphocytes is characteristic of SPTCL, similar rimming can also be seen in LEP.[60,63] Presence of "Ki-67 hotspots" in rimming CD8+ atypical lymphocytes would strongly support a diagnosis SPTCL.[64,65] On the other hand, presence of CD123+ PDC clusters would favor LEP over SPTCL.[66] Presence of readily identifiable plasma cells also helps support LEP (Fig 5B), while hyaline fat necrosis and dermal mucin fail to distinguish between the two entities.[66]

Direct immunofluorescence. A positive lupus band test with deposits of IgG, IgM, IgA, and/or C3 at the dermoepidermal junction has been reported in 70-90% of patients with LEP.[57,58,67,68] In addition, deposition of IgM and C3 around blood vessels has been reported in >80% of cases.[58]

Tumid lupus erythematosus (TLE)

Clinical features. Tumid lupus is a photosensitive eruption characterized by erythematous urticarial plaques with minimal surface change.[69] The most common sites of involvement include the face, V area of the neck, and extensor surfaces of the upper extremities.[70] It runs an intermittent clinical course of relapse and spontaneous resolution without scarring or dyspigmentation. Association with SLE is rare.[71,72]

Serology. Test for ANA is usually negative, but can be detected at low titers in 25-44% of patients.[73-75]

Histopathology. Biopsies of TLE show a superficial to deep perivascular lymphocytic infiltrate and abundant dermal mucin (Fig 6A, 6B). Lymphocytic inflammation of adnexal structures may be seen, while epidermal involvement is absent or minimal.[69,76] The main histopathologic differential diagnosis of TLE includes polymorphous light eruption (PMLE), which cannot be reliably excluded by the presence of dermal mucin.[77] Clusters of CD123+ PDCs would favor a diagnosis of TLE,[78-80] especially when the skin lesions are present on the face (relatively

uncommon in PMLE). Jessner's lymphocytic infiltrate of the skin is now considered to be on the spectrum of TLE due to clinical and histopathologic similarities.[81,82]

Direct immunofluorescence. Results of DIF in TLE are variable, with some studies describing mainly negative results and others reporting IgG and IgM deposits at the basement membrane in 50-84% of cases.[69,73,76,83]

Neonatal lupus erythematosus (NLE)

Clinical features. Neonatal lupus erythematosus is an autoimmune disease resulting from placental transfer of maternal anti-Ro and anti-La antibodies.[84] It occurs in 1% of neonates whose mothers carry these autoantibodies. Cutaneous and cardiac manifestations are most common,[84,85] but hepatobiliary and hematologic diseases may occur as well.[86] Cutaneous NLE presents few days to weeks after birth.[86] Typical cutaneous lesions are annular erythematous plaques with central clearing, affecting the face and the scalp with an "owl-eye", "raccoon-eye", or "eye-mask" appearance in the periorbital areas.[86] The lesions may be desquamative or urticarial-like.[87] The neonates may suffer from a permanent heart block, while the rash is usually transient and heals with some pigmentary changes within weeks to months.[86,88]

Serology. Maternal anti-Ro antibody is the main antibody detected. Other antibodies include anti-La and anti-U1-RNP.[85,89] Only 10% of the patients will continue to have positive antibodies by 6-9 months.[90] The presence of anti-Ro is associated with cardiac presentation, while anti-La is associated with cutaneous disease.[91]

Histopathology. Most reported cases described histopathologic features similar to SCLE,[92] namely vacuolar interface dermatitis involving epidermis and adnexae, with epidermal atrophy and perivascular lymphocytic inflammation.[93] One study found that clinically urticarial-like lesions may be devoid of epidermal changes, and that rare cases may contain eosinophils.[87] More recently, non-bullous and histiocytoid neutrophilic dermatosis has gained increased recognition as another histopathologic manifestation of NLE.[94-96]

Direct immunofluorescence. Direct immunofluorescence may be negative or shows IgG, IgM, and/or C3 deposits at the basement membrane zone.[87]

Lupus erythematosus-nonspecific skin lesions

While LE-specific skin lesions only occur in LE, LE-nonspecific skin lesions are seen in SLE as well as other autoimmune or autoinflammatory conditions. This group encompasses a wide variety of skin diseases (Table 1). Of these, vascular damage is a common feature of SLE with both cutaneous and visceral manifestations, and may be subdivided into inflammatory vasculitis or thrombotic vasculopathy.[97] A few selected entities are discussed below.

Inflammatory vasculitis

Clinical features. Cutaneous vasculitis has been reported in almost one-third of patients with SLE.[98] It may affect small, medium-sized, and large vessels.[99] Clinical presentations vary depending on the size of the affected vessels, and may range from palpable purpura, urticarial vasculitis, erythematous papulonodular lesions, to ulcers.[99] Urticarial vasculitis appears as wheal-like, burning, and painful erythematous patches or plaques which last over 24 hours and often heal with hyperpigmentation.[100]

Histopathology. The most common finding in skin biopsies is leukocytoclastic vasculitis involving dermal small vessels, which may or may not be associated with thrombosis.[101] Precisely, there is an angiocentric neutrophilic infiltrate with nuclear debris (leukocytoclasis), fibrinoid necrosis of the vessel walls, and erythrocyte extravasation (Fig 7A). Fibrin deposition tends to be less conspicuous in urticarial vasculitis.[101] Another form of lupus vasculitis is lymphocytic vasculitis, in which lymphocytes infiltrate the vessel walls with or without associated fibrinoid necrosis or thrombosis (Fig 7B).[101]

Direct immunofluorescence. Lupus vasculitis frequently shows “full house” granular immune deposits in the vessels walls including C3, IgG, IgM, and IgA (Fig 7C). Other cases show some but not all immunoreactants. A lupus band may be observed at the basement membrane as well.[102]

Thrombotic vasculopathy

Clinical features. Many cutaneous diseases with thrombotic vasculopathy can be seen in the setting of SLE and are often associated with antiphospholipid syndrome (APS).[7] APS is a hypercoagulable state that can be primary or associated with SLE.[101] Venous and arterial thrombosis often results in pregnancy morbidity.[103] Cutaneous manifestations occurs in 50% of

patients with APS, among which livedo reticularis is the most common.[104] Other manifestations include atrophie blanche (livedoid vasculopathy), livedo racemosa, Degos-like papules, splinter hemorrhage, and thrombophlebitis.[7]

Serology. Patients with APS have at least one positive antiphospholipid antibody—lupus anticoagulant, anticardiolipin, or anti-β2 glycoprotein-I antibodies—on two separate occasions at least 12 weeks apart.[105] Lupus anticoagulant and triple positivity carry the highest risk of thrombosis.[106] Antinuclear antibody and ENA profiles may be positive or negative.[103]

Histopathology. The unifying histopathologic feature in various cutaneous manifestations of APS is occlusive nonvasculitic vasculopathy, in which fibrin thrombi are found in small or medium-sized vessels (Fig 8).[107] There might be evidence of hemorrhage and a mild inflammatory infiltrate due to damage of the vessel walls, however frank vasculitis is absent.[108] As these features are also seen in thrombotic vasculopathy from other causes, correlation with clinical history and serologic studies is key to the correct diagnosis of APS.[107]

Direct immunofluorescence. In APS, there is a characteristic granular deposition of C5b-C9 in the vessel walls.[109] Livedoid vasculopathy shows strong homogenous deposition of fibrinogen, C3, and IgM around the vessel walls.[110]

Bullous lupus erythematosus (BLE)

Clinical features. Bullous LE is a rare cutaneous manifestation of SLE that affects predominantly young African American women, and can be the presenting sign of SLE.[111-113] It presents as tense bullae mainly on the face, trunk, upper extremities, vermillion border, and oral mucosa.[114-118] The bullae occur on normal-appearing or erythematous skin.[114] Although the autoantibodies in BLE and epidermolysis bullosa aquisita (EBA) share the same target antigen (see below), clinically BLE differs from EBA in that the lesions heal without scarring or milia formation.[119] Bullous LE is associated with lupus nephritis, thus early diagnosis of this rare presentation can prevent further systemic complications.[120]

Histopathology. Bullous LE is characterized by a subepidermal split with a variable number of neutrophils in the blister cavity and the superficial dermis (Fig 9A). There may be neutrophilic microabscesses in the dermal papillae similar to those seen in dermatitis herpetiformis and linear IgA bullous dermatosis (Fig 9B).[115,117,121] Mucin deposition in the reticular dermis helps distinguish BLE from other subepidermal bullous diseases. Other features commonly seen in

cutaneous LE, such as interface dermatitis and thickened basement membrane, are typically absent in BLE.[119]

Direct immunofluorescence. Autoantibodies in BLE target type VII collagen located in the lamina densa.[114,116] All immunoglobulins can be seen along the basement membrane zone in a linear or granular fashion, with IgG being the most common (Fig 9C).[114] IgA is more frequently present in BLE than in other forms of lupus.[115,117] On salt-split skin, the immunoreactants localize to the floor of the split (Fig 9D),[122] and a “u-serrated” pattern may be observed in both BLE and EBA.[123]

Neutrophilic urticarial dermatosis (NUD)/Non-bullous neutrophilic lupus erythematosus

Clinical features. Neutrophilic urticarial dermatosis is an eruption of pink to red macules and plaques associated with fever, arthralgia, and leukocytosis.[124] It may occur in a variety of systemic autoinflammatory diseases such as SLE, adult-onset Still disease, Schnitzler syndrome, and cryopyrin-associated periodic syndrome.[124] Unlike urticarial vasculitis, the lesions are not painful and resolve in 24-48 hours without pigment alteration.[125] Non-bullous neutrophilic LE is a similar condition specifically described in the setting of SLE.

Histopathology. There is a dermal interstitial neutrophilic infiltrate with leukocytoclasis in the absence of fibrinoid vascular damage (Fig 10A).[124,126] The absence of true vasculitis is the main differentiating feature of NUD from urticarial vasculitis.[124,125] Neutrophilic epitheliotropism (neutrophils infiltrating epidermis and appendages) can be used as a diagnostic clue of NUD.[127] Non-bullous neutrophilic LE may display subtle vacuolar change where neutrophils “tag” along the basal epidermis (Fig 10B).[128,129]

Amicrobial pustulosis of the folds (APF)

Clinical features. Amicrobial pustulosis of the folds is a rare presentation of SLE that affects mainly young women.[130] It is characterized by sterile pustules distributed on skin folds, scalp, umbilicus, anogenital region, and external auditory canal.[130,131] Although APF is most frequently associated with SLE, it may rarely occur in association with other autoimmune diseases such as inflammatory bowel diseases, autoimmune hepatitis, and Hashimoto thyroiditis.[132,133]

Histopathology. APF is a neutrophilic dermatosis in which the key findings are spongiform pustulosis and a dermal neutrophilic infiltrate.[130,131] The pustules may be intracorneal,

subcorneal, intraepidermal, or overlying adnexal ostia (Fig 11).[132] Dermal neutrophils may be perivascular, interstitial, and/or perfollicular. Papillary dermal edema is common. An infectious etiology needs to be excluded by special stains and tissue cultures before a diagnosis is confirmed.[130,132]

Summary

The spectrum of cutaneous manifestations of LE is broad. Correct diagnosis and subclassification not only will guide treatment of the cutaneous lesions, but also provide information on the risk of associated systemic disease, and prompt appropriate clinical workup. As pathologic examination of skin biopsies alone is usually insufficient for precise subclassification, awareness of the clinical presentations and the laboratory findings in different LE subtypes is important in ensuring the best care and predicting prognosis for these patients.

Acknowledgements

CB and MPC performed the review of literature and wrote the paper.

TDM and MPC prepared the tables and figures.

CB, TDM, and MPC critically reviewed the manuscript.

References

1. Pons-Estel GJ, Ugarte-Gil MF, Alarcón GS. Epidemiology of systemic lupus erythematosus. Expert Rev Clin Immunol 2017;13:799-814.
2. Tebbe B, Orfanos CE. Epidemiology and socioeconomic impact of skin disease in lupus erythematosus. Lupus 1997;6:96-104.
3. Wysenbeek AJ, Guedj D, Amit M, Weinberger A. Rash in systemic lupus erythematosus: prevalence and relation to cutaneous and non-cutaneous disease manifestations. Ann Rheum Dis 1992;51:717-719.
4. Durosaro O, Davis MD, Reed KB, Rohlinger AL. Incidence of cutaneous lupus erythematosus, 1965-2005: a population-based study. Arch Dermatol 2009;145:249-253.

5. Grönhagen CM, Fored CM, Granath F, Nyberg F. Cutaneous lupus erythematosus and the association with systemic lupus erythematosus: a population-based cohort of 1088 patients in Sweden. Br J Dermatol 2011;164:1335-1341.
6. Gilliam JN, Sontheimer RD. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. J Am Acad Dermatol 1981;4:471-475.
7. Ribero S, Sciascia S, Borradori L, Lipsker D. The cutaneous spectrum of lupus erythematosus. Clin Rev Allergy Immunol 2017;53:291-305.
8. Walling HW, Sontheimer RD. Cutaneous lupus erythematosus: issues in diagnosis and treatment. Am J Clin Dermatol 2009;10:365-381.
9. Ziemer M, Kardaun SH, Liss Y, Mockenhaupt M. Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with lupus erythematosus: a descriptive study of 17 cases from a national registry and review of the literature. Br J Dermatol 2012;166:575-600.
10. Tankunakorn J, Sawatwarakul S, Vachiramon V, Chanprapaph K. Stevens-Johnson syndrome and toxic epidermal necrolysis-like lupus erythematosus. J Clin Rheumatol 2019;25:224-231.
11. Filotico R, Mastrandrea V. Cutaneous lupus erythematosus: clinico-pathologic correlation. G Ital Dermatol Venereol 2018;153:216-229.
12. Baltaci M, Fritsch P. Histologic features of cutaneous lupus erythematosus. Autoimmun Rev 2009;8:467-473.
13. Safi R, Al-Hage J, Abbas O, Kibbi AG, Nassar D. Investigating the presence of neutrophil extracellular traps in cutaneous lesions of different subtypes of lupus erythematosus. Exp Dermatol 2019;28:1348-1352.
14. Ting W, Stone MS, Racila D, Scofield RH, Sontheimer RD. Toxic epidermal necrolysis-like acute cutaneous lupus erythematosus and the spectrum of the acute syndrome of apoptotic pan-epidermolysis (ASAP): a case report, concept review and proposal for new classification of lupus erythematosus vesiculobullous skin lesions. Lupus 2004;13:941-950.
15. Romero LS, Bari O, Forbess Smith CJ, Schneider JA, Cohen PR. Toxic epidermal necrolysis-like acute cutaneous lupus erythematosus: report of a case and review of the literature. Dermatol Online J 2018;24.
16. Reich A, Marcinow K, Bialynicki-Birula R. The lupus band test in systemic lupus erythematosus patients. Ther Clin Risk Manag 2011;7:27-732.

17. Cardinali C, Caproni M, Fabbri P. The utility of the lupus band test on sun-protected non-lesional skin for the diagnosis of systemic lupus erythematosus. Clin Exp Rheumatol 1999;17:427-432.
18. Burrows NP, Bhogal BS, Russell Jones R, Black MM. Clinicopathological significance of cutaneous epidermal nuclear staining by direct immunofluorescence. J Cutan Pathol 1993;20:159-162.
19. Lipsker D. The need to revisit the nosology of cutaneous lupus erythematosus: the current terminology and morphologic classification of cutaneous LE: difficult, incomplete and not always applicable. Lupus 2010;19:1047-1049.
20. Wollina U, Hein G. Lupus erythematosus: uncommon presentations. Clin Dermatol 2005;23:470-479.
21. Sontheimer RD. Subacute cutaneous lupus erythematosus: 25-year evolution of a prototypic subset (subphenotype) of lupus erythematosus defined by characteristic cutaneous, pathological, immunological, and genetic findings. Autoimmun Rev 2005;4:253-263.
22. Tiao J, Feng R, Carr K, Okawa J, Werth VP. Using the American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics (SLICC) criteria to determine the diagnosis of systemic lupus erythematosus (SLE) in patients with subacute cutaneous lupus erythematosus (SCLE). J Am Acad Dermatol 2016;74:862-869.
23. Guicciardi F, Atzori L, Marzano AV, et al. Are there distinct clinical and pathological features distinguishing idiopathic from drug-induced subacute cutaneous lupus erythematosus? A European retrospective multicenter study. J Am Acad Dermatol 2019;81:403-411.
24. Vázquez-Doval J, Ruiz de Erenchun F, Sánchez-Ibarrola A, Contreras F, Soto de Delás J, Quintanilla E. Subacute cutaneous lupus erythematosus--clinical, histopathological and immunophenotypical study of five cases. J Investig Allergol Clin Immunol 1992;2:27-32.
25. Parodi A, Caproni M, Cardinali C, et al. Clinical, histological and immunopathological features of 58 patients with subacute cutaneous lupus erythematosus. A review by the Italian group of immunodermatology. Dermatology 2000;200:6-10.
26. Vera-Recabarren MA, García-Carrasco M, Ramos-Casals M, Herrero C. Comparative analysis of subacute cutaneous lupus erythematosus and chronic cutaneous lupus

erythematosus: clinical and immunological study of 270 patients. Br J Dermatol 2010;162:91-101.
27. Lee LA, Roberts CM, Frank MB, McCubbin VR, Reichlin M. The autoantibody response to Ro/SSA in cutaneous lupus erythematosus. Arch Dermatol 1994;130:1262-1268.
28. Herrero C, Bielsa I, Font J, et al. Subacute cutaneous lupus erythematosus: clinicopathologic findings in thirteen cases. J Am Acad Dermatol 1988;19:1057-1062.
29. Antiga E, Caproni M, Bonciani D, Bonciolini V, Fabbri P. The last word on the so-called 'Rowell's syndrome'? Lupus 2012;21:577-585.
30. George R, Mathai R, Kurian S. Cutaneous lupus erythematosus in India: immunofluorescence profile. Int J Dermatol 1992;31:265-269.
31. Nieboer C, Tak-Diamand Z, Van Leeuwen-Wallau HE. Dust-like particles: a specific direct immunofluorescence pattern in sub-acute cutaneous lupus erythematosus. Br J Dermatol 1988;118:725-729.
32. Lipsker D, Di Cesare MP, Cribier B, Grosshans E, Heid E. The significance of the 'dust-like particles' pattern of immunofluorescence. A study of 66 cases. Br J Dermatol 1998;138:1039-1042.
33. Oh EH, Kim EJ, Ro YS, Ko JY. Ten-year retrospective clinicohistological study of cutaneous lupus erythematosus in Korea. J Dermatol 2018;45:436-443.
34. Aslani FS, Sepaskhah M, Bagheri Z, Akbarzadeh-Jahromi M. Value of CD123 immunohistochemistry and elastic staining in differentiating discoid lupus erythematosus from lichen planopilaris. Int J Trichology 2020;12:62-67.
35. Rakhshan A, Toossi P, Amani M, Dadkhahfar S, Hamidi AB. Different distribution patterns of plasmacytoid dendritic cells in discoid lupus erythematosus and lichen planopilaris demonstrated by CD123 immunostaining. An Bras Dermatol 2020;95:307-313.
36. Walsh NM, Lai J, Hanly JG, et al. Plasmacytoid dendritic cells in hypertrophic discoid lupus erythematosus: an objective evaluation of their diagnostic value. J Cutan Pathol 2015;42:32-38.
37. Daldon PE, Macedo de Souza E, Cintra ML. Hypertrophic lupus erythematosus: a clinicopathological study of 14 cases. J Cutan Pathol 2003;30:443-448.
38. Shah K, Kazlouskaya V, Lal K, Molina D, Elston DM. Perforating elastic fibers ('elastic fiber trapping') in the differentiation of keratoacanthoma, conventional squamous cell carcinoma and pseudocarcinomatous epithelial hyperplasia. J Cutan Pathol 2014;41:108-112.

39. George R, Kurian S, Jacob M, Thomas K. Diagnostic evaluation of the lupus band test in discoid and systemic lupus erythematosus. Int J Dermatol 1995;34:170-173.
40. Weigand DA. Lupus band test: anatomic regional variations in discoid lupus erythematosus. J Am Acad Dermatol 1986;14:426-428.
41. Millard LG, Rowell NR. Chilblain lupus erythematosus (Hutchinson). A clinical and laboratory study of 17 patients. Br J Dermatol 1978;98:497-506.
42. Hedrich CM, Fiebig B, Hauck FH, et al. Chilblain lupus erythematosus--a review of literature. Clin Rheumatol 2008;27:949-954.
43. Franceschini F, Calzavara-Pinton P, Valsecchi L, et al. Chilblain lupus erythematosus is associated with antibodies to SSA/Ro. Adv Exp Med Biol 1999;455:167-171.
44. Su WP, Perniciaro C, Rogers RS, 3rd, White JW, Jr. Chilblain lupus erythematosus (lupus pernio): clinical review of the Mayo Clinic experience and proposal of diagnostic criteria. Cutis 1994;54:395-399.
45. Doutre MS, Beylot C, Beylot J, Pompougnac E, Royer P. Chilblain lupus erythematosus: report of 15 cases. Dermatology 1992;184:26-28.
46. Crowson AN, Magro CM. Idiopathic perniosis and its mimics: a clinical and histological study of 38 cases. Hum Pathol 1997;28:478-484.
47. Wang ML, Chan MP. Comparative analysis of chilblain lupus erythematosus and idiopathic perniosis: histopathologic features and immunohistochemistry for CD123 and CD30. Am J Dermatopathol 2018;40:265-271.
48. Cribier B, Djeridi N, Peltre B, Grosshans E. A histologic and immunohistochemical study of chilblains. J Am Acad Dermatol 2001;45:924-929.
49. Boada A, Bielsa I, Fernández-Figueras MT, Ferrándiz C. Perniosis: clinical and histopathological analysis. Am J Dermatopathol 2010;32:19-23.
50. Requena L, Sánchez Yus E. Panniculitis. Part II. Mostly lobular panniculitis. J Am Acad Dermatol 2001;45:325-361; quiz 62-4.
51. Fraga J, García-Díez A. Lupus erythematosus panniculitis. Dermatol Clin 2008;26:453-463, vi.
52. Arnold HL, Jr. Lupus erythematosus profundus (Kaposi-Irgang) historical review and report of a case. Arch Derm Syphilol 1948;57:196-203.
53. Martens PB, Moder KG, Ahmed I. Lupus panniculitis: clinical perspectives from a case series. J Rheumatol 1999;26:68-72.

54. Rangel LK, Villa-Ruiz C, Lo K, et al. Clinical characteristics of lupus erythematosus panniculitis/profundus: a retrospective review of 61 patients. JAMA Dermatol 2020;156:1264-1266.
55. Verdier M, Anuardo P, Gormezano NWS, et al. Panniculitis in childhood-onset systemic lupus erythematosus: a multicentric cohort study. Adv Rheumatol 2019;59:3.
56. Peters MS, Su WP. Lupus erythematosus panniculitis. Med Clin North Am 1989;73:1113-1126.
57. Sánchez NP, Peters MS, Winkelmann RK. The histopathology of lupus erythematosus panniculitis. J Am Acad Dermatol 1981;5:673-680.
58. Arai S, Katsuoka K. Clinical entity of lupus erythematosus panniculitis/lupus erythematosus profundus. Autoimmun Rev 2009;8:449-452.
59. Fountain RB. Lupus erythematosus profundus. Br J Dermatol 1968;80:571-579.
60. Massone C, Kodama K, Salmhofer W, et al. Lupus erythematosus panniculitis (lupus profundus): clinical, histopathological, and molecular analysis of nine cases. J Cutan Pathol 2005;32:396-404.
61. Alegre VA, Winkelmann RK, Aliaga A. Lipomembranous changes in chronic panniculitis. J Am Acad Dermatol 1988;19:39-46.
62. Park HS, Choi JW, Kim BK, Cho KH. Lupus erythematosus panniculitis: clinicopathological, immunophenotypic, and molecular studies. Am J Dermatopathol 2010;32:24-30.61.
63. Massone C, Chott A, Metze D, et al. Subcutaneous, blastic natural killer (NK), NK/T-cell, and other cytotoxic lymphomas of the skin: a morphologic, immunophenotypic, and molecular study of 50 patients. Am J Surg Pathol 2004;28:719-735.
64. Sitthinamsuwan P, Pattanaprichakul P, Treetipsatit J, et al. Subcutaneous panniculitis-like T-cell lymphoma versus lupus erythematosus panniculitis: distinction by means of the periadipocytic cell proliferation index. Am J Dermatopathol 2018;40:567-574.
65. LeBlanc RE, Tavallaee M, Kim YH, Kim J. Useful parameters for distinguishing subcutaneous panniculitis-like T-cell lymphoma from lupus erythematosus panniculitis. Am J Surg Pathol 2016;40:745-754.
66. Chen SJT, Tse JY, Harms PW, Hristov AC, Chan MP. Utility of CD123 immunohistochemistry in differentiating lupus erythematosus from cutaneous T cell lymphoma. Histopathology 2019;74:908-916.
67. Tuffanelli DL. Lupus erythematosus panniculitis (profundus). Arch Dermatol 1971;103:231-242.

68. Marks R, Levene GM. Discoid lupus erythematosus and lupus erythematosus profundus in a child. Clin Exp Dermatol 1976;1:187-190.
69. Alexiades-Armenakas MR, Baldassano M, Bince B, et al. Tumid lupus erythematosus: criteria for classification with immunohistochemical analysis. Arthritis Rheum 2003;49:494-500.
70. Obermoser G, Sontheimer RD, Zelger B. Overview of common, rare and atypical manifestations of cutaneous lupus erythematosus and histopathological correlates. Lupus 2010;19:1050-1070.
71. Jatwani K, Chugh K, Osholowu OS, Jatwani S. Tumid lupus erythematosus and systemic lupus erythematosus: a report on their rare coexistence. Cureus 2020;12:e7545.
72. Patsinakidis N, Kautz O, Gibbs BF, Raap U. Lupus erythematosus tumidus: clinical perspectives. Clin Cosmet Investig Dermatol 2019;12:707-719.
73. Cozzani E, Christana K, Rongioletti F, Rebora A, Parodi A. Lupus erythematosus tumidus: clinical, histopathological and serological aspects and therapy response of 21 patients. Eur J Dermatol 2010;20:797-801.
74. Rodriguez-Caruncho C, Bielsa I, Fernández-Figueras MT, Roca J, Carrascosa JM, Ferrándiz C. Lupus erythematosus tumidus: a clinical and histological study of 25 cases. Lupus 2015;24:751-755.
75. Verdelli A, Coi A, Marzano AV, et al. Autoantibody profile and clinical patterns in 619 Italian patients with cutaneous lupus erythematosus. J Eur Acad Dermatol Venereol 2019;33:742-752.
76. Kuhn A, Sonntag M, Ruzicka T, Lehmann P, Megahed M. Histopathologic findings in lupus erythematosus tumidus: review of 80 patients. J Am Acad Dermatol 2003;48:901-908.
77. Vincent JG, Chan MP. Specificity of dermal mucin in the diagnosis of lupus erythematosus: comparison with other dermatitides and normal skin. J Cutan Pathol 2015;42:722-729.
78. Wackernagel A, Massone C, Hoefler G, Steinbauer E, Kerl H, Wolf P. Plasmacytoid dendritic cells are absent in skin lesions of polymorphic light eruption. Photodermatol Photoimmunol Photomed 2007;23:24-28.
79. Tomasini D, Mentzel T, Hantschke M, et al. Plasmacytoid dendritic cells: an overview of their presence and distribution in different inflammatory skin diseases, with special

emphasis on Jessner's lymphocytic infiltrate of the skin and cutaneous lupus erythematosus. J Cutan Pathol 2010;37:1132-1139.

80. Molina-Ruiz AM, Sanmartín O, Santonja C, Kutzner H, Requena L. Spring and summer eruption of the elbows: a peculiar localized variant of polymorphous light eruption. J Am Acad Dermatol 2013;68:306-312.
81. Weyers W, Bonczkowitz M, Weyers I. LE or not LE--that is the question: an unsuccessful attempt to separate lymphocytic infiltration from the spectrum of discoid lupus erythematosus. Am J Dermatopathol 1998;20:225-232.
82. Weber F, Schmuth M, Fritsch P, Sepp N. Lymphocytic infiltration of the skin is a photosensitive variant of lupus erythematosus: evidence by phototesting. Br J Dermatol 2001;144:292-296.
83. Ruiz H, Sánchez JL. Tumid lupus erythematosus. Am J Dermatopathol 1999;21:356-360.
84. Lee LA. Neonatal lupus erythematosus. J Invest Dermatol 1993;100:9s-13s.
85. Lee LA. Neonatal lupus: clinical features and management. Paediatr Drugs 2004;6:71-78.
86. Weston WL, Morelli JG, Lee LA. The clinical spectrum of anti-Ro-positive cutaneous neonatal lupus erythematosus. J Am Acad Dermatol 1999;40:675-681.
87. Peñate Y, Guillermo N, Rodríguez J, et al. Histopathologic characteristics of neonatal cutaneous lupus erythematosus: description of five cases and literature review. J Cutan Pathol 2009;36:660-667.
88. Buyon JP, Hiebert R, Copel J, et al. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. J Am Coll Cardiol 1998;31:1658-1666.
89. Provost TT, Watson R, Gammon WR, Radowsky M, Harley JB, Reichlin M. The neonatal lupus syndrome associated with U1RNP (nRNP) antibodies. N Engl J Med 1987;316:1135-1138.
90. Zuppa AA, Riccardi R, Frezza S, et al. Neonatal lupus: Follow-up in infants with anti-SSA/Ro antibodies and review of the literature. Autoimmun Rev 2017;16:427-432.
91. Yang X. Clinical features, autoantibodies, and outcome of neonatal lupus erythematosus. Fetal Pediatr Pathol 2020:1-7.
92. Lee LA. Maternal autoantibodies and pregnancy--II: The neonatal lupus syndrome. Baillieres Clin Rheumatol 1990;4:69-84.

93. Bangert JL, Freeman RG, Sontheimer RD, Gilliam JN. Subacute cutaneous lupus erythematosus and discoid lupus erythematosus. Comparative histopathologic findings. Arch Dermatol 1984;120:332-337.
94. Satter EK, High WA. Non-bullous neutrophilic dermatosis within neonatal lupus erythematosus. J Cutan Pathol 2007;34:958-960.
95. Lee SH, Roh MR. Targetoid lesions and neutrophilic dermatosis: an initial clinical and histological presentation of neonatal lupus erythematosus. Int J Dermatol 2014;53:764-766.
96. Sitthinamsuwan P, Nitiyarom R, Chairatchaneeboon M, Wisuthsarewong W. Histiocytoid neutrophilic dermatitis, an unusual histopathology in neonatal lupus erythematosus. J Cutan Pathol 2015;42:996-999.
97. D'Cruz D. Vasculitis in systemic lupus erythematosus. Lupus 1998;7:270-274.
98. Vitali C, Bencivelli W, Isenberg DA, et al. Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. I. A descriptive analysis of 704 European lupus patients. European Consensus Study Group for Disease Activity in SLE. Clin Exp Rheumatol 1992;10:527-539.
99. Drenkard C, Villa AR, Reyes E, Abello M, Alarcón-Segovia D. Vasculitis in systemic lupus erythematosus. Lupus 1997;6:235-242.
100. Berti S, Moretti S, Lucin C, Amato L, Massi D, Fabbri P. Urticarial vasculitis and subacute cutaneous lupus erythematosus. Lupus 2005;14:489-492.
101. Crowson AN, Magro C. The cutaneous pathology of lupus erythematosus: a review. J Cutan Pathol 2001;28:1-23.
102. Lath K, Chatterjee D, Saikia UN, et al. Role of direct immunofluorescence in cutaneous small-vessel vasculitis: experience from a tertiary center. Am J Dermatopathol 2018;40:661-666.
103. Asherson RA, Khamashta MA, Ordi-Ros J, et al. The "primary" antiphospholipid syndrome: major clinical and serological features. Medicine (Baltimore) 1989;68:366-374.
104. Francès C, Niang S, Laffitte E, Pelletier F, Costedoat N, Piette JC. Dermatologic manifestations of the antiphospholipid syndrome: two hundred consecutive cases. Arthritis Rheum 2005;52:1785-1793.

105. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295-306.
106. Khamashta M, Taraborelli M, Sciascia S, Tincani A. Antiphospholipid syndrome. Best Pract Res Clin Rheumatol 2016;30:133-148.
107. Llamas-Velasco M, Alegría V, Santos-Briz Á, Cerroni L, Kutzner H, Requena L. Occlusive nonvasculitic vasculopathy. Am J Dermatopathol 2017;39:637-662.
108. Carlson JA, Chen KR. Cutaneous pseudovasculitis. Am J Dermatopathol 2007;29:44-55.
109. Magro CM, Roberts-Barnes J, Crowson AN. Direct immunofluorescence testing in the diagnosis of immunobullous disease, collagen vascular disease, and vascular injury syndromes. Dermatol Clin 2012;30:763-798, viii.
110. Hsiao PF, Wu YH. Distinct pattern of direct immunofluorescence in livedoid vasculopathy. Am J Dermatopathol 2010;32:240-243.
111. Contestable JJ, Edhegard KD, Meyerle JH. Bullous systemic lupus erythematosus: a review and update to diagnosis and treatment. Am J Clin Dermatol 2014;15:517-524.
112. Torres Saavedra FA, Campo LR, Mendez MV, et al. Bullous lupus as the first manifestation of systemic lupus erythematosus in the pediatric population: A diagnostic challenge in daily practice. Lupus 2020;29:1937-1942.
113. Fujimoto W, Hamada T, Yamada J, Matsuura H, Iwatsuki K. Bullous systemic lupus erythematosus as an initial manifestation of SLE. J Dermatol 2005;32:1021-1027.
114. Gammon WR, Briggaman RA. Bullous SLE: a phenotypically distinctive but immunologically heterogeneous bullous disorder. J Invest Dermatol 1993;100:28s-34s.
115. Camisa C, Sharma HM. Vesiculobullous systemic lupus erythematosus. Report of two cases and a review of the literature. J Am Acad Dermatol 1983;9:924-933.
116. Yell JA, Allen J, Wojnarowska F, Kirtschig G, Burge SM. Bullous systemic lupus erythematosus: revised criteria for diagnosis. Br J Dermatol 1995;132:921-928.
117. Camisa C. Vesiculobullous systemic lupus erythematosus. A report of four cases. J Am Acad Dermatol 1988;18:93-100.
118. Anyanwu CO, Ang CC, Werth VP. Oral mucosal involvement in bullous lupus. Arthritis Rheum 2013;65:2622.
119. Vassileva S. Bullous systemic lupus erythematosus. Clin Dermatol 2004;22:129-138.
120. Ng YY, Chang IT, Chen TW, Liou HN, Yang AH, Yang WC. Concomitant lupus nephritis and bullous eruption in systemic lupus erythematosus. Nephrol Dial Transplant 1999;14:1739-1743.

121. Burrows NP, Bhogal BS, Black MM, et al. Bullous eruption of systemic lupus erythematosus: a clinicopathological study of four cases. Br J Dermatol 1993;128:332-338.
122. Gammon WR, Woodley DT, Dole KC, Briggaman RA. Evidence that anti-basement membrane zone antibodies in bullous eruption of systemic lupus erythematosus recognize epidermolysis bullosa acquisita autoantigen. J Invest Dermatol 1985;84:472-476.
123. Vodegel RM, Jonkman MF, Pas HH, de Jong MC. U-serrated immunodeposition pattern differentiates type VII collagen targeting bullous diseases from other subepidermal bullous autoimmune diseases. Br J Dermatol 2004;151:112-118.
124. Kieffer C, Cribier B, Lipsker D. Neutrophilic urticarial dermatosis: a variant of neutrophilic urticaria strongly associated with systemic disease. Report of 9 new cases and review of the literature. Medicine (Baltimore) 2009;88:23-31.
125. Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. J Am Acad Dermatol 1992;26:441-448.
126. Gusdorf L, Bessis D, Lipsker D. Lupus erythematosus and neutrophilic urticarial dermatosis: a retrospective study of 7 patients. Medicine (Baltimore) 2014;93:e351.
127. Broekaert SM, Böer-Auer A, Kerl K, et al. Neutrophilic epitheliotropism is a histopathological clue to neutrophilic urticarial dermatosis. Am J Dermatopathol 2016;38:39-49.
128. Brinster NK, Nunley J, Pariser R, Horvath B. Nonbullous neutrophilic lupus erythematosus: a newly recognized variant of cutaneous lupus erythematosus. J Am Acad Dermatol 2012;66:92-97.
129. Gleason BC, Zembowicz A, Granter SR. Non-bullous neutrophilic dermatosis: an uncommon dermatologic manifestation in patients with lupus erythematosus. J Cutan Pathol 2006;33:721-725.
130. Schissler C, Velter C, Lipsker D. Amicrobial pustulosis of the folds: Where have we gone 25 years after its original description? Ann Dermatol Venereol 2017;144:169-175.
131. Boms S, Gambichler T. Review of literature on amicrobial pustulosis of the folds associated with autoimmune disorders. Am J Clin Dermatol 2006;7:369-374.
132. Wang MZ, Camilleri MJ, Guo R, Wieland CN. Amicrobial pustulosis of the folds: Report of 4 cases. J Cutan Pathol 2017;44:367-372.
133. Méndez-Flores S, Charli-Joseph Y, Saeb-Lima M, Orozco-Topete R, Fernández Sánchez M. Amicrobial pustulosis of the folds associated with autoimmune disorders:

systemic lupus erythematosus case series and first report on the association with autoimmune hepatitis. Dermatology 2013;226:1-4.

Figure Legends

Fig 1. Acute cutaneous lupus erythematosus. A, Vacuolar interface dermatitis involving sun-damaged skin. Sparse lymphocytes infiltrate the basal epidermis, causing vacuolar degeneration and necrosis of individual keratinocytes (cytoid bodies, arrows). B, Toxic epidermal necrolysis-like variant shows complete necrosis and detachment of epidermis and follicular epithelium as a result of robust interface dermatitis. C, A lupus band consisting of granular immunoglobulin deposits along the dermoepidermal junction. D, Nuclear binding for IgG in the epidermis. (C, D: Direct immunofluorescence, IgG)

Fig 2. Subacute cutaneous lupus erythematosus. A, Vacuolar interface dermatitis with many cytoid bodies (inset). A superficial perivascular lymphocytic infiltrate is present, whereas deep periadnexal inflammation is absent. B, Rowell syndrome is characterized by robust basal degeneration resulting in epidermal necrosis. Early re-epithelialization is observed under the partially detached, necrotic epidermis. C, In addition to a lupus band, dust-like immune deposits are observed in the papillary dermis. (C: Direct immunofluorescence, IgM)

Fig 3. Discoid lupus erythematosus. A, Vacuolar to lichenoid interface dermatitis with overlying hyperkeratosis and superficial to deep perivascular and periadnexal lymphocytic inflammation. B, Follicular hyperkeratosis giving rise to a "follicular plug". Epidermal basement membrane is thickened (arrows). Increased mucin is present in the dermis. C, Numerous CD123+ plasmacytoid dendritic cells are present, many of which are in aggregates. D, Hypertrophic variant demonstrates pseudoepitheliomatous hyperplasia with foci mimicking squamous cell carcinoma. Perforating elastic fibers may be seen (inset, arrows). (C: CD123 immunohistochemistry)

Fig 4. Chilblain lupus erythematosus. A, Acral skin with brisk superficial to deep perivascular and perieccrine lymphocytic inflammation, and prominent papillary dermal edema. B, Fibrin exudate in the dermal interstitium favors chilblain LE over idiopathic perniosis.

Fig 5. Lupus erythematosus panniculitis. A, Brisk lymphocytic infiltrate in the subcutaneous fat lobules, with paraseptal lymphoid nodules present at the periphery of these lobules. B, Hyaline fat necrosis is characterized by necrotic adipocytes which appear thickened and hyalinized. Plasma cells are readily identified, a feature that favors lupus panniculitis over subcutaneous panniculitis-like T-cell lymphoma.

Fig 6. Tumid lupus erythematosus. A, A superficial to deep dermal perivascular lymphocytic infiltrate with focal adnexal inflammation. The epidermis is uninvolved. B, Abundant dermal mucin appears as a bluish, stringy substance filling the spaces between dermal collagen bundles.

Fig 7. Inflammatory vasculitis. A, Leukocytoclastic vasculitis characterized by an angiocentric neutrophilic infiltrate with karyorrhectic nuclear debris, fibrinoid necrosis of the vessel walls, and extravasated erythrocytes indicative of vascular damage. B, Lymphocytic vasculitis shows infiltration of the vessel walls by lymphocytes. Fibrinoid necrosis of the vessel walls, as seen in this example, is not a prerequisite for lymphocytic vasculitis. C, Granular immune deposits in the vessel walls. (C: Direct immunofluorescence, IgG)

Fig 8. Thrombotic vasculopathy. Intraluminal fibrin thrombi are present in the superficial vessels in a patient with antiphospholipid syndrome. There is mild erythrocyte extravasation but inflammation remains minimal.

Fig 9. Bullous lupus erythematosus. A, Subepidermal bulla containing numerous neutrophils in the blister cavity. Neutrophils are also present in the superficial dermis. B, Early subepidermal split with neutrophils confined to the papillary dermis, morphologically mimicking dermatitis herpetiformis and linear IgA bullous dermatosis. C, Continuous linear deposition of C3 along the dermoepidermal junction. D, Salt-split skin reveals a "floor pattern" where immune deposition is found on the dermal side (floor) of the split. The epidermis (roof) is out of this field and is negative for immune deposition. (C, D: Direct immunofluorescence, C3)

Fig 10. Neutrophilic urticarial dermatosis/non-bullous neutrophilic lupus erythematosus. A, An interstitial neutrophilic infiltrate is present in the dermis without associated vasculitis. B, Tagging of neutrophils along the dermoepidermal junction and mild basal vacuolization are commonly seen in non-bullous neutrophilic lupus erythematosus.

Fig 11. Amicrobial pustulosis of the folds. Multiple pustules are present in the epidermis. Higher magnification of a subnormal pustule is shown in the inset. Sparse neutrophils are found in the superficial dermis.

Tables

Table 1. Classification of cutaneous manifestations of lupus erythematosus (LE).

I. LE-specific skin lesions (Cutaneous LE)
A. Acute cutaneous LE (ACLE)

- a. Localized ACLE
- b. Generalized ACLE

B. Subacute cutaneous LE (SCLE)

C. Chronic cutaneous LE
- a. Discoid LE (DLE)
  - i. Localized DLE
  - ii. Generalized DLE
- b. LE panniculitis
- c. Chilblain LE

D. Intermittent cutaneous LE
- a. Tumid LE

E. Neonatal LE (NLE)

II. LE-nonspecific skin lesions

A. Vascular diseases
- a. Inflammatory vasculitis
- b. Thrombotic vasculopathy (antiphospholipid syndrome)
- c. Livedo reticularis
- d. Raynaud phenomenon

B. Neutrophilic and urticarial dermatoses
- a. Bullous LE (BLE)
- b. Neutrophilic urticarial dermatosis (NUD)/Non-bullous neutrophilic LE
- c. Amicrobial pustulosis of skin folds (APF)

C. Nonscarring alopecia

D. Papulonodular mucinosis

Table 2. Summary of key findings in various skin lesions in lupus erythematosus.

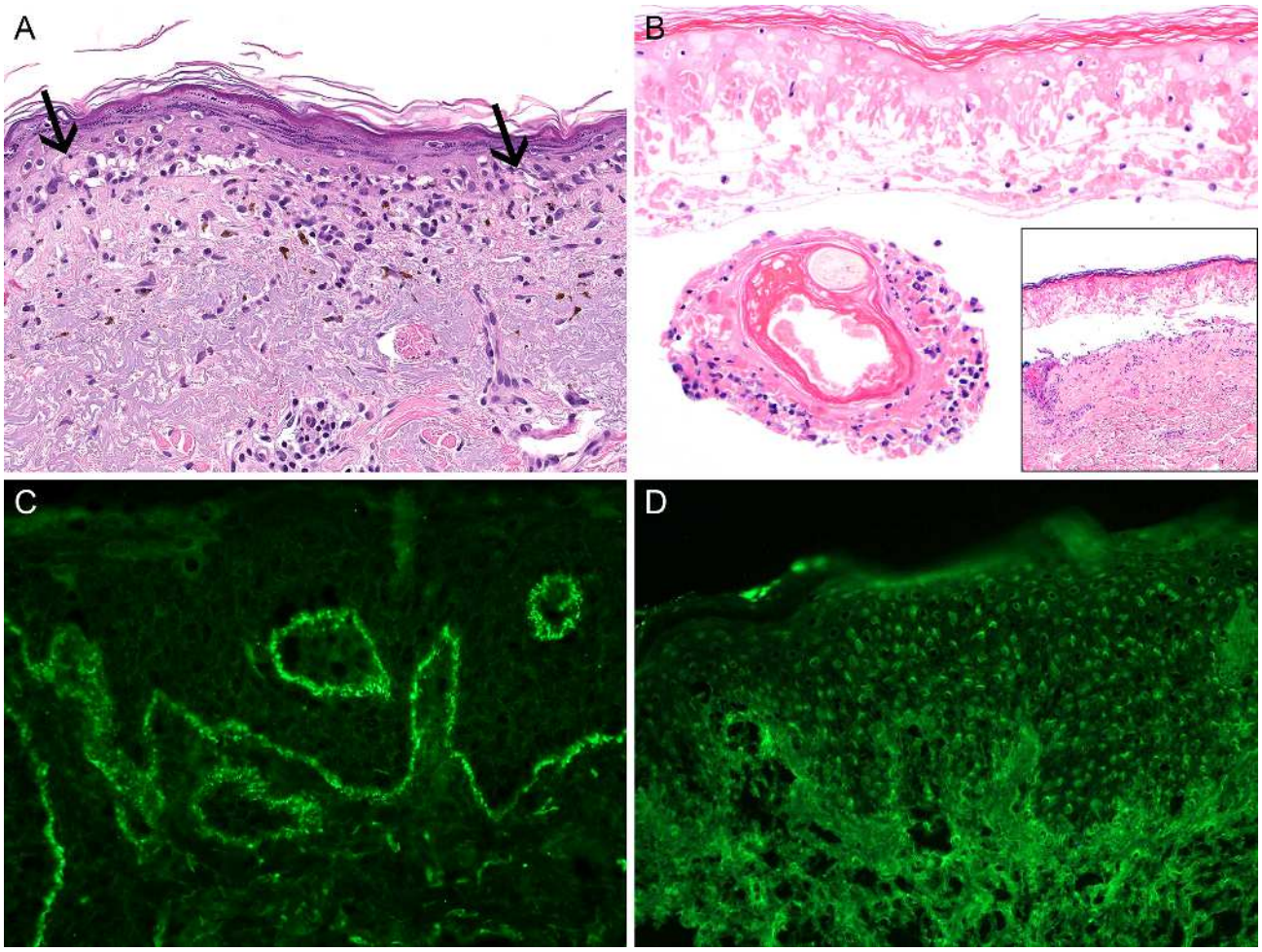
Skin lesions	Association with SLE	Clinical features	Histopathology	DIF (lesional skin)	Serology
LE-specific skin lesions					
Acute cutaneous LE	+++	Malar rash, erythematous and edematous papules and plaques in sun-exposed areas	Vacuolar interface dermatitis, mild lymphocytic infiltrate, dermal edema, +/- epidermal necrosis (TEN-like acute cutaneous LE)	Lupus band in ~100% cases, +/- epidermal nuclear binding of IgG	ANA, anti-dsDNA, anti-Sm, anti-Ro, and/or anti-U1-RNP
Subacute cutaneous LE	+	Annular or papulosquamous lesions, usually involving trunk and upper extremities, sparing face and scalp	Vacuolar interface dermatitis with many cytoid bodies, superficial perivascular lymphocytic infiltrate	Lupus band in 65-80% cases; +/- dust-like pattern	ANA (50-80%), anti-Ro > anti-La, anti-dsDNA, anti-Sm
Discoid LE	++ (higher risk if generalized)	Round, erythematous scaly papules and plaques, often on face, scalp, and ears, with scarring	Vacuolar to lichenoid interface dermatitis with adnexal involvement, follicular hyperkeratosis, and superficial to deep perivascular lymphocytic infiltrate, +/- basement membrane thickening and	Lupus band in 50-90% cases	ANA negative or low-titers in localized form; more common in generalized form

			increased dermal mucin		
Hypertrophic LE	++	Hypertrophic and hyperkeratotic lesions on face, trunk, and extensor surfaces, may mimic keratoacanthoma or hypertrophic lichen planus	Pseudoepitheliomatous hyperplasia with vacuolar to lichenoid interface dermatitis, increased dermal mucin	Same as discoid LE	Same as discoid LE
Chilblain LE	++	Violaceous and edematous papules and plaques on acral surfaces, often triggered by cold/wet exposure	Lymphocytic vasculitis +/- papillary dermal edema, vacuolar change, periadnexal inflammation, increased dermal mucin, and interstitial fibrin exudate	Variable	ANA, anti-dsDNA, anti-Ro
LE panniculitis	+/-	Subcutaenous painful nodules on upper extremities, face, scalp, and trunk, +/- overlying changes of discoid LE	Predominantly lobular lymphocytic panniculitis, paraseptal lymphoid nodules, +/- overlying changes of discoid LE	Lupus band in 70-90% cases	Low-titer ANA
Tumid LE	+/-	Urticarial plaques involving photoexposed areas without scarring	Superficial to deep perivascular and periadnexal lymphocytic infiltrate, abundant dermal	Variable	Often negative

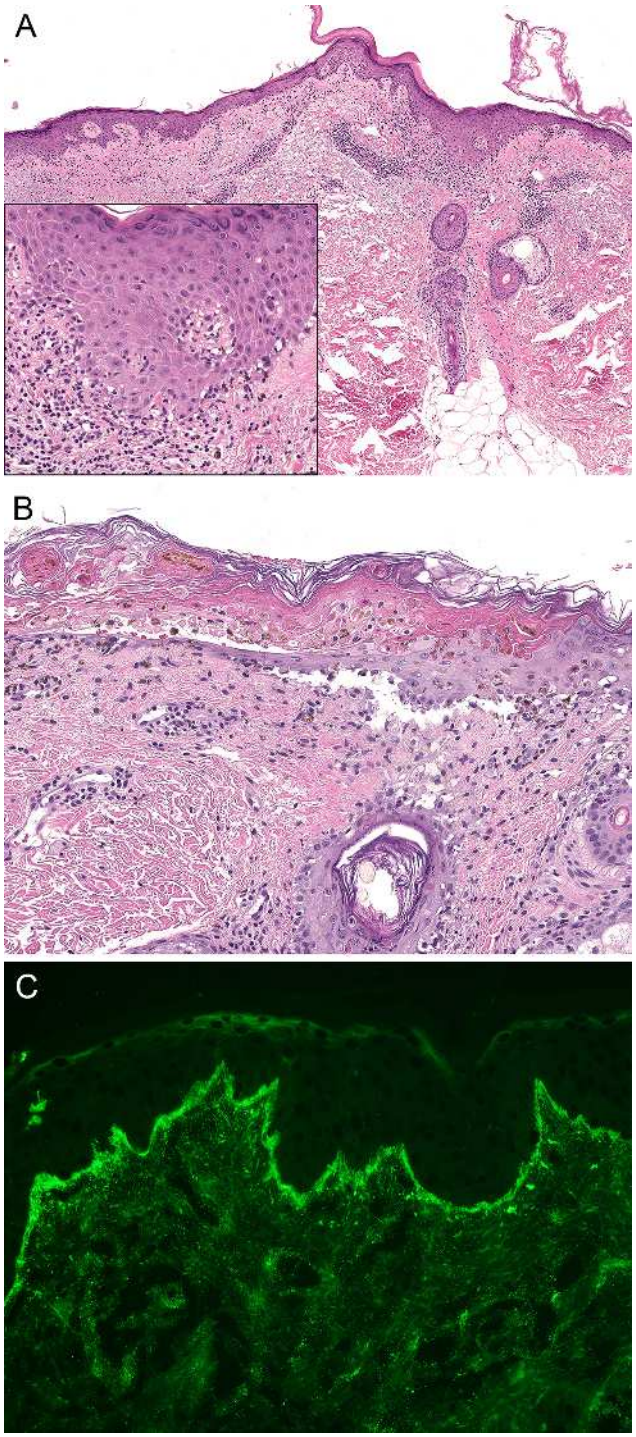
			mucin, minimal epidermal changes		
Neonatal LE	+/-	Annular erythematous plaques with central clearing, usually on upper face and scalp, “raccoon-eyes”	Similar to subcutaneous cutaneous LE; some cases present as non-bullous and histiocytoid neutrophilic dermatosis	Variable	Anti-Ro (maternal) > anti-La, anti-U1-RNP
LE-nonspecific skin lesions					
Vasculitis	+	Variable depending on size of affected vessels; palpable purpura, urticarial vasculitis, or ulcers	Angiocentric neutrophilic infiltrate with leukocytoclasis, fibrinoid necrosis of vessel walls, and erythrocyte extravasation	“Full house” granular immune deposits in vessel walls	----------
Vasculopathy (APS)	+++	Livedo reticularis, livedo racemosa, atrophie blanche, Degos-like papules, splinter hemorrhages, thrombophlebitis	Fibrin thrombi in small- or medium-sized vessels with minimal inflammation	Granular C5b-C9 in vessel walls (APS); fibrinogen, C3, and IgM around vessel walls (livedoid vasculopathy)	Lupus anticoagulant, anticardiolipin, or anti-β2 glycoprotein-I
Bullous LE	+++	Tense bullae on face, trunk, upper extremities, and oral mucosa, no scarring or milia	Subepidermal bulla with neutrophils in blister cavity and dermal papillae	Linear or granular immune deposition along	----------

		formation		basement membrane; u-serrated pattern; floor pattern on salt-split skin	
Neutrophilic urticarial dermatosis/ Non-bullous neutrophilic LE	+	Pink to red macules and plaques, associated with fever and arthralgia	Dermal interstitial neutrophilic infiltrate with leukocytoclasis but no fibrinoid vascular damage; +/- subtle basal vacuolization	----------	----------
Amicrobial pustulosis of the folds	+	Sterile pustules in skin folds, scalp, umbilicus, anogenital region, and external auditory canal	Spongiform pustulosis and dermal neutrophilic infiltrate	----------	----------

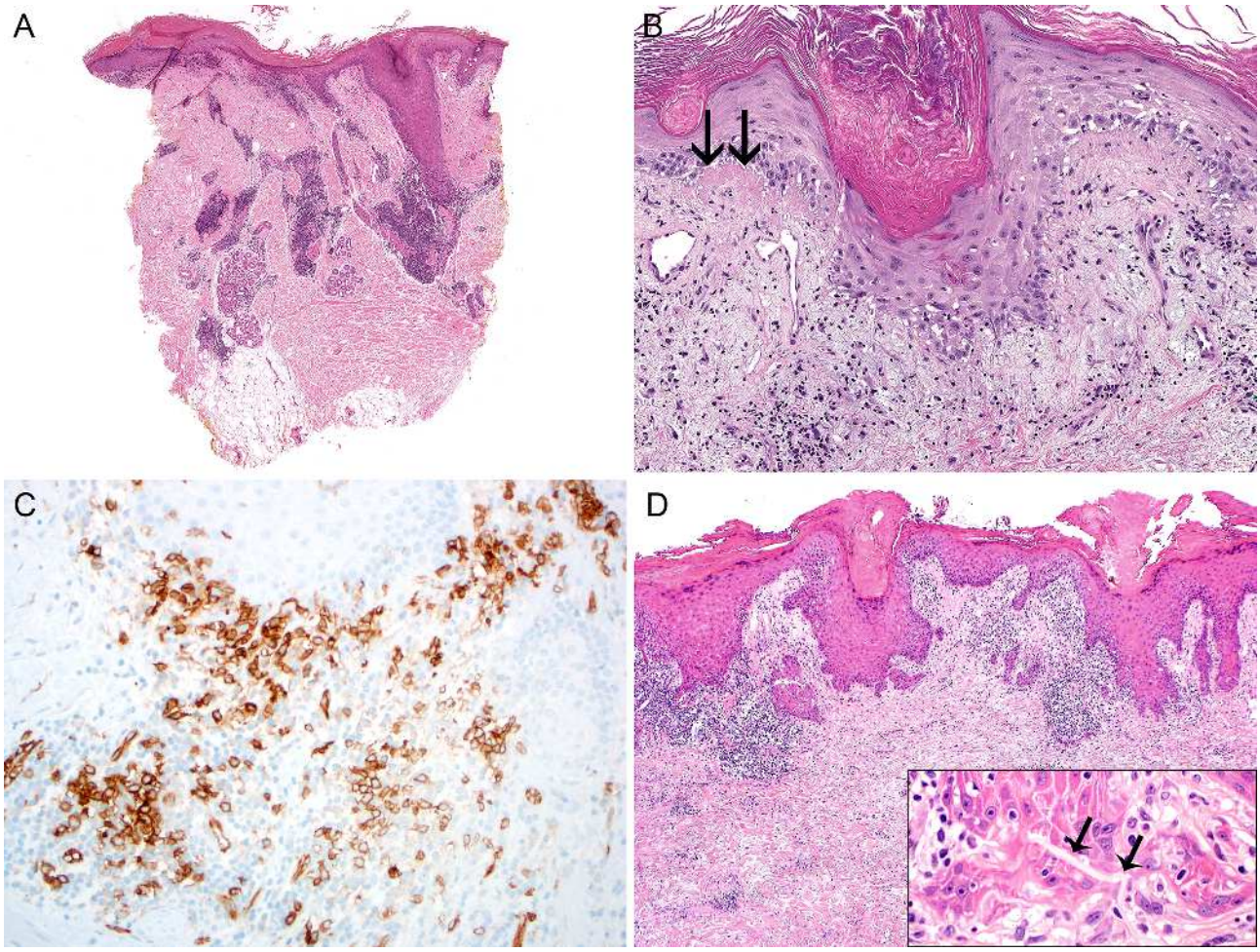
ANA, antinuclear antibody; APS, antiphospholipid syndrome; DIF, direct immunofluorescence; LE, lupus erythematosus; SLE, systemic lupus erythematosus; TEN, toxic epidermal necrolysis; +++, strongly associated; ++, moderately associated; + rarely associated; -, not associated.



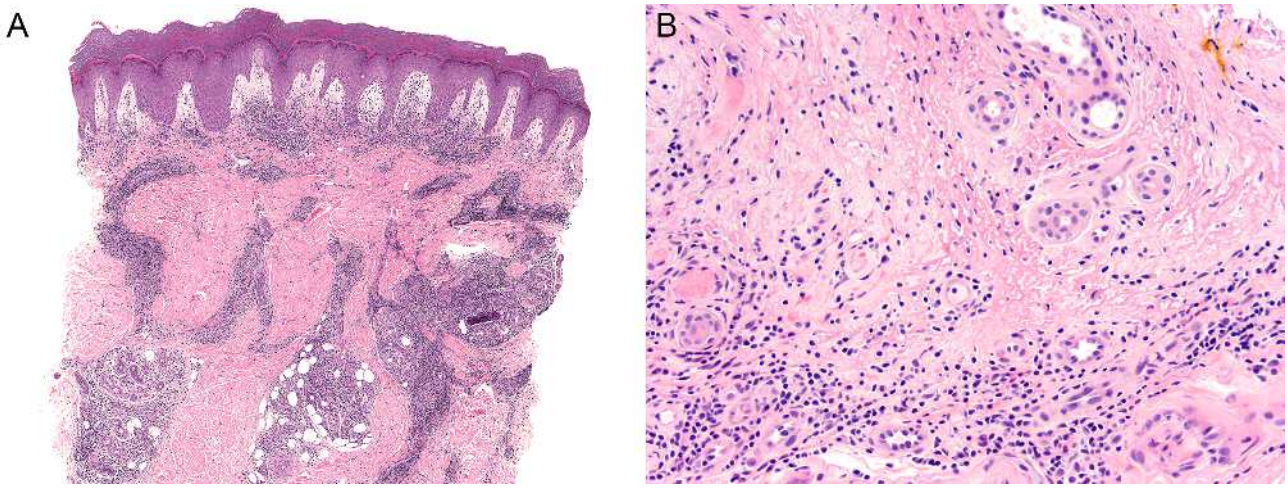
his_14440_f1.tif



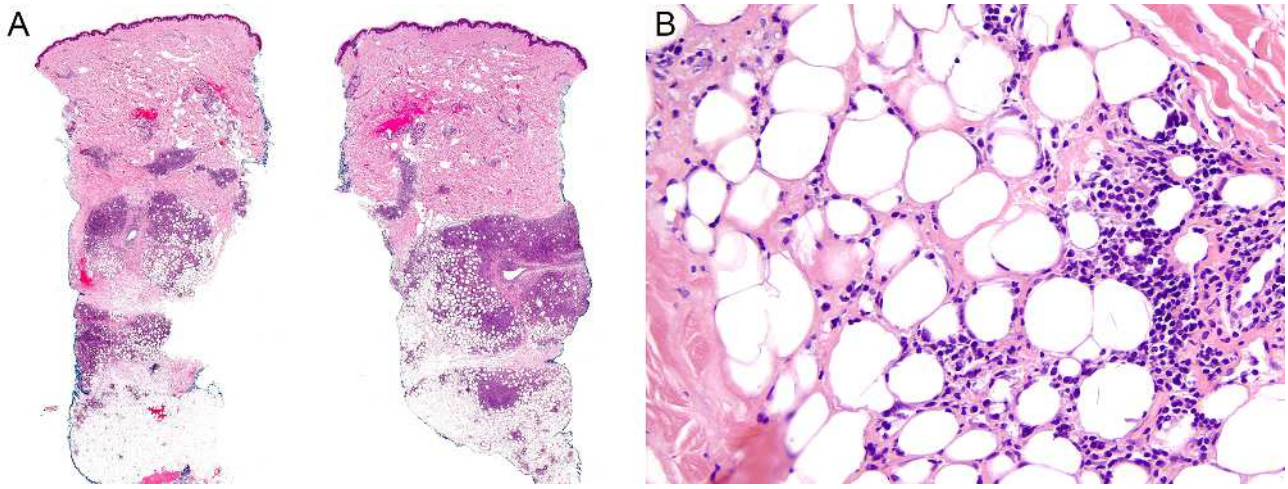
his_14440_f2.tif



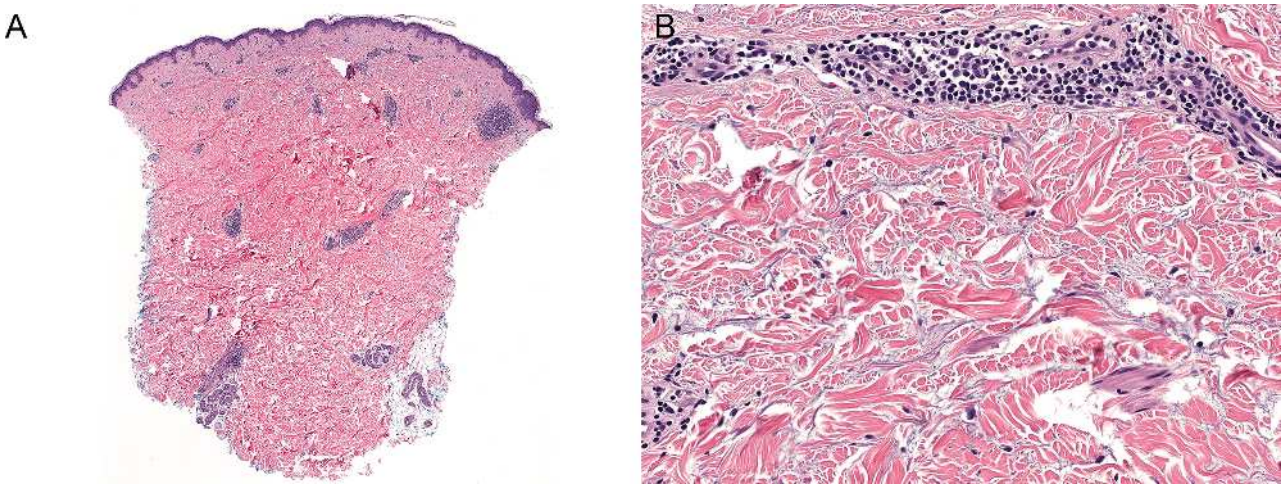
his_14440_f3.tif



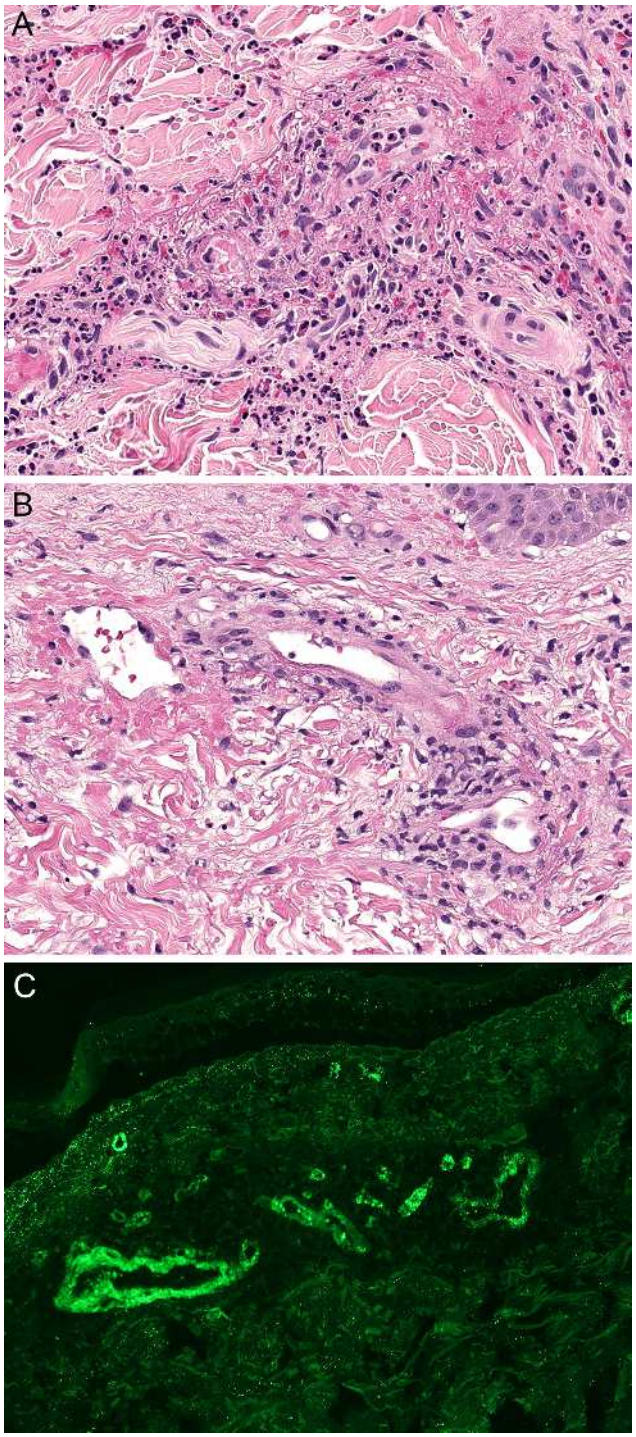
his_14440_f4.tif



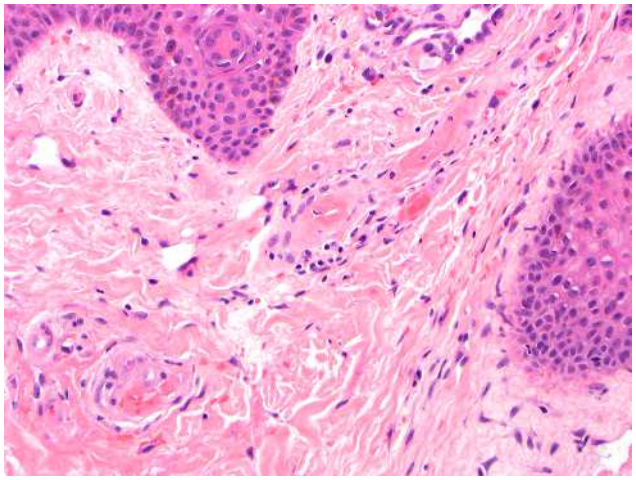
his_14440_f5.tif



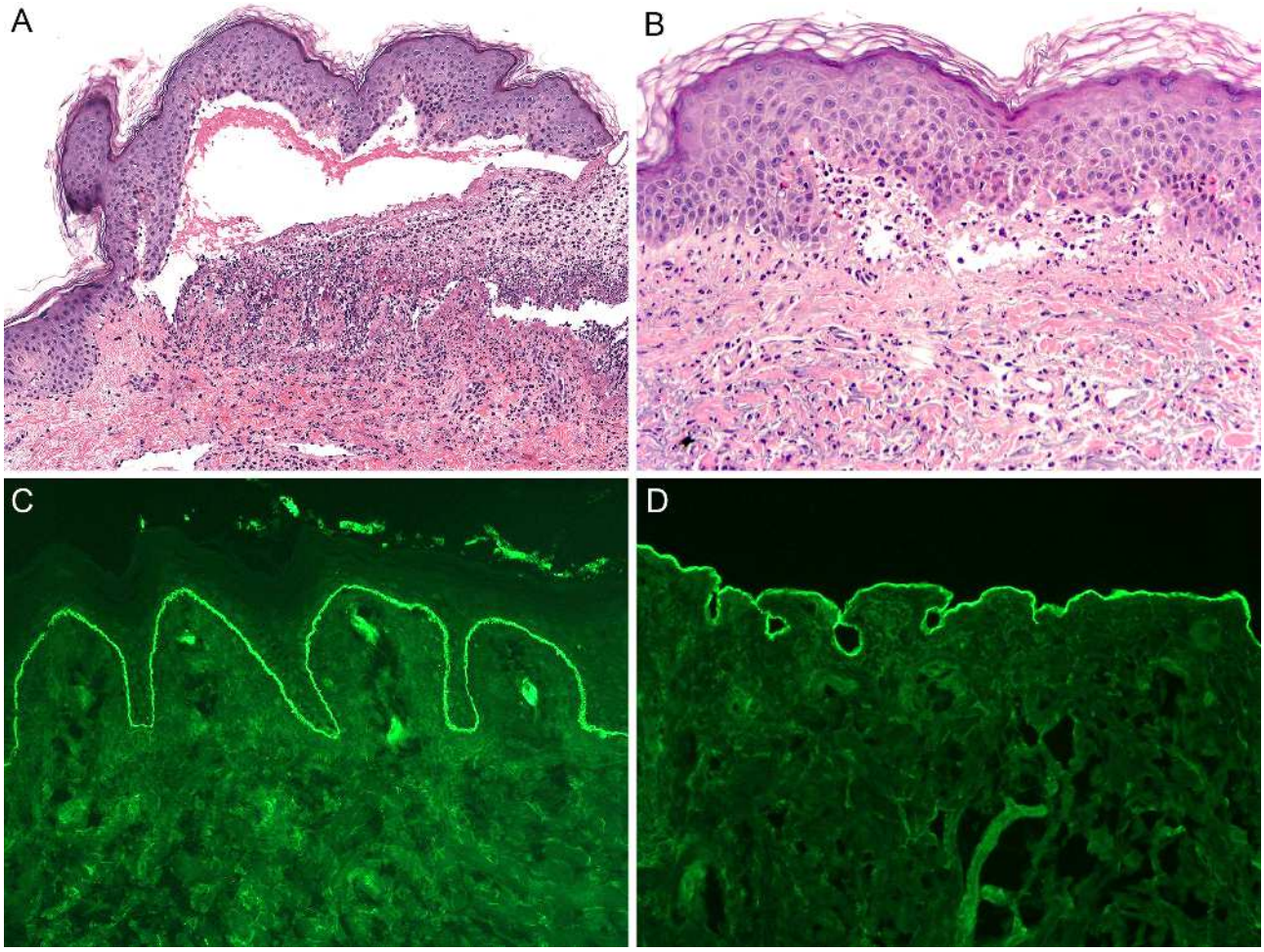
his_14440_f6.tif



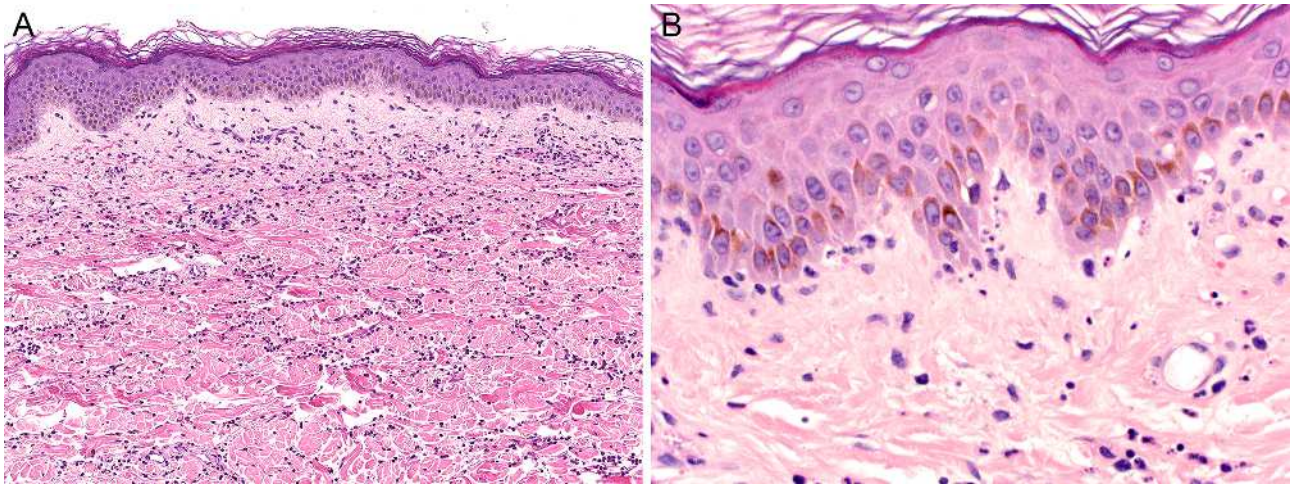
his_14440_f7.tif



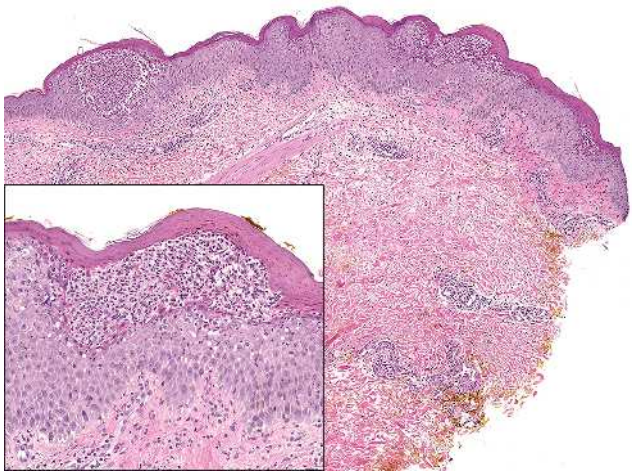
his_14440_f8.tif



his_14440_f9.tif



his_14440_f10.tif



his_14440_f11.tif