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REVIEW

Cutaneous manifestations of lupus erythematosus: a practical clinicopathological review for pathologists

Carole Bitar,[1,2] Tyler D Menge[1,2] & May P Chan[1,2]

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

Bitar C, Menge T D & Chan M P

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Cutaneous manifestations of lupus erythematosus: a practical clinicopathological review for pathologists

Accurate diagnosis of connective tissue diseases is often challenging, and relies upon careful correlation between clinical and histopathological features, direct immunofluorescence studies and laboratory work-up. Lupus erythematosus (LE) is a prototype of connective tissue disease with a variety of cutaneous and systemic manifestations. Microscopically, cutaneous LE is classically characterised by an interface dermatitis although other histopathological patterns also exist, depending upon the clinical presentation, location and chronicity of the skin lesions. In this article, we review the clinical, serological, histopathological and direct immunofluorescence findings in LE-specific and LE non-specific skin lesions, with an emphasis upon 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.

Keywords: antiphospholipid syndrome, connective tissue disease, lupus erythematosus, plasmacytoid dendritic cells, vasculitis

Introduction

Connective tissue diseases are a heterogeneous group of autoimmune diseases affecting one or multiple organ systems. A complex interplay of immunological, 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 the appropriate clinical management of these patients. This requires multidisciplinary clinicopathological correlation between dermatology, rheumatology and pathology. While most pathologists are familiar with the classic histopathological 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 underdiagnosis of this disease.

This article aims to provide a comprehensive review on the clinical and pathological 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

Address for correspondence: May P Chan MD, NCRC Building 35, 2800 Plymouth Road, Ann Arbor, MI 48109, USA.
e-mail: mpchan@med.umich.edu

during the course of the disease, and that cutaneous LE may be the first presenting sign in approximately 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, localised 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 upon clinical morphologies and duration of the lesions, as well as histopathological 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-non-specific 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. Conversely, LE-non-specific lesions are commonly seen in SLE patients but may also be encountered in other diseases; for example, 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-non-specific lesions are discussed in detail below.

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

I. LE-specific skin lesions (cutaneous LE)
A. Acute cutaneous LE (ACLE)
a. Localised ACLE
b. Generalised ACLE
B. Subacute cutaneous LE (SCLE)
C. Chronic cutaneous LE
a. Discoid LE (DLE)
i.Localised DLE
ii.Generalised DLE
b. LE panniculitis
c. Chilblain LE
D. Intermittent cutaneous LE
a. Tumid LE
E. Neonatal LE (NLE)
II. LE-non-specific 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. Non-scarring alopecia
D. Papulonodular mucinosis

LE-specific skin lesions (cutaneous lupus erythematosus)

The most common histopathological 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 serological profiles and risks of association with SLE, as summarised in Table 2.

Acute cutaneous lupus erythematosus (ACLE)

Clinical features. Acute cutaneous lupus erythematosus is a transient photodistributed rash that can be localised to the head and neck or widespread. Its localised form is characterised 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 generalised form, widespread erythematous and oedematous 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. Acute cutaneous lupus erythematosus 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 favour 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]

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 oedematous papules and plaques in sun-exposed areas	Vacuolar interface dermatitis, mild lymphocytic infiltrate, dermal oedema, ± 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 generalised)	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 increased dermal mucin	Lupus band in 50–90% cases	ANA-negative or low titres in localised form; more common in generalised form
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 oedematous papules and plaques on acral surfaces, often triggered by cold/wet exposure	Lymphocytic vasculitis ± papillary dermal oedema, vacuolar change, peri-adnexal inflammation, increased dermal mucin and interstitial fibrin exudate	Variable	ANA, anti-dsDNA, anti-Ro
LE panniculitis	+/–	Subcutaneous 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-titre ANA
Tumid LE	+/–	Urticarial plaques involving photoexposed areas without scarring	Superficial to deep perivascular and peri-adnexal lymphocytic infiltrate, abundant dermal mucin, minimal epidermal changes	Variable	Often negative
Neonatal LE	+/–	Annular erythematous plaques with central clearing, usually on upper face and scalp, 'raccoon-eyes'	Similar to subacute cutaneous LE; some cases present as non-bullous and histiocytoid neutrophilic dermatosis	Variable	Anti-Ro (maternal) > anti-La, anti-U1-RNP

Table 2. (*Continued*)

Skin lesions	Association with SLE	Clinical features	Histopathology	DIF (lesional skin)	Serology
LE-non-specific skin lesions					
Vasculitis	+	Variable depending upon size of affected vessels; palpable purpura, urticarial vasculitis or ulcers	Angiocentric neutrophilic infiltrate with leucocytoclasis, 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 haemorrhages, 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 formation	Subepidermal bulla with neutrophils in blister cavity and dermal papillae	Linear or granular immune deposition along 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 leucocytoclasis but no fibrinoid vascular damage; ± subtle basal vacuolisation		
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.

Histopathology. Acute cutaneous lupus erythematosus is a vacuolar interface dermatitis with relatively mild lymphocytic inflammation (Figure 1A). There may be dermal oedema and microhaemorrhage.[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 (Figure 1B).[9,14,15] The additional findings of adnexal epithelial involvement, thickened basement membrane and increased dermal mucin help to support this diagnosis over SJS/TEN.[9]

Direct immunofluorescence. Results of direct immunofluorescence (DIF) are highly dependent upon where the biopsy is taken from.[7] Lesional skin is almost always positive for a 'lupus band' – a continuous band of granular immunoglobulin [immunoglobulin (Ig)G > IgM > IgA] and/or C3 deposits along the basement membrane zone (Figure 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

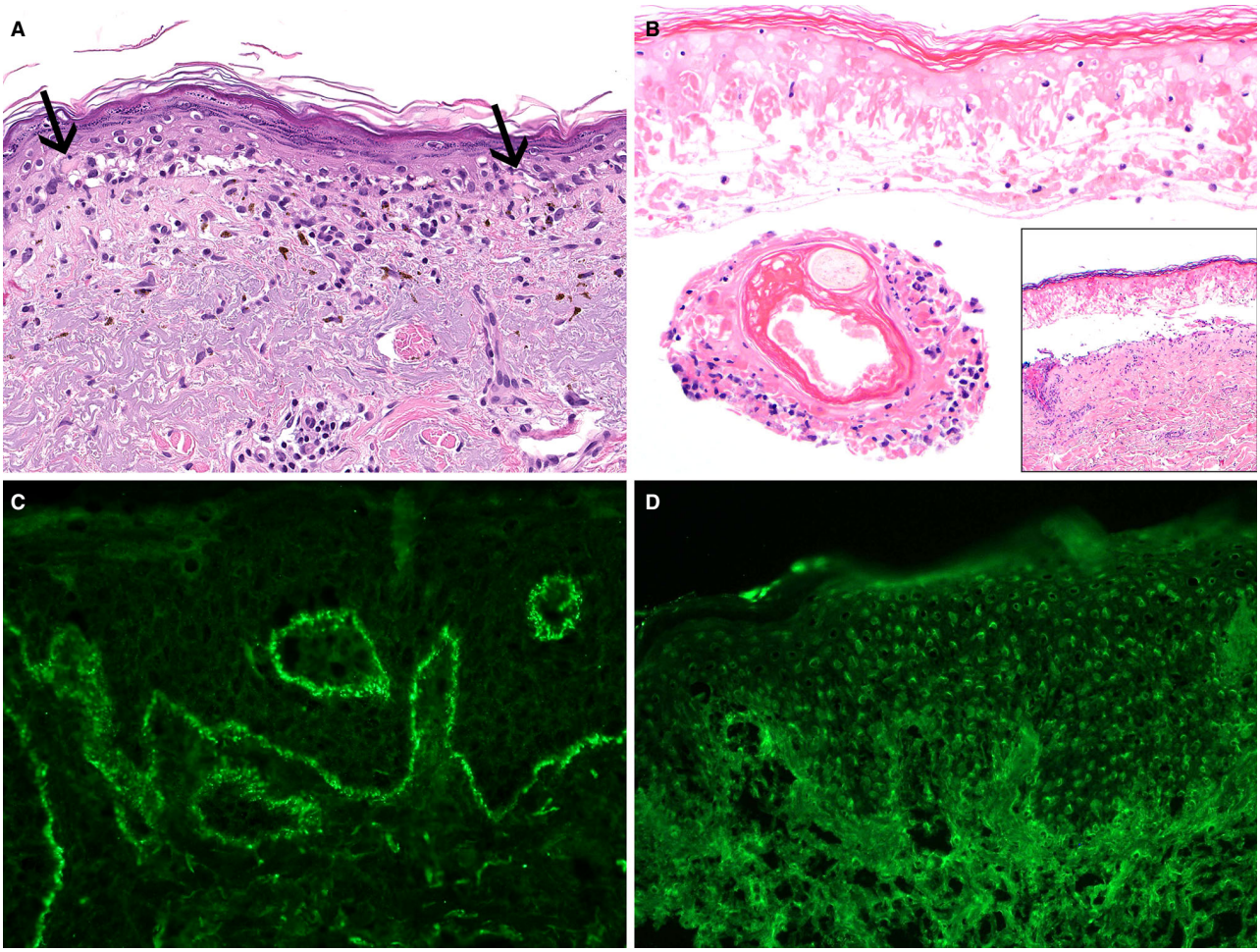

Figure 1. Acute cutaneous lupus erythematosus. **A,** Vacuolar interface dermatitis involving sun-damaged skin. Sparse lymphocytes infiltrate the basal epidermis, causing vacuolar degeneration and necrosis of individual keratinocytes (cytoid bodies, arrows). **B,** Toxic epidermal necrolysis-like variant 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 immunoglobulin (Ig)G in the epidermis. (**C,D,** direct immunofluorescence, IgG).

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 (Figure 1D).[18]

Subacute cutaneous lupus erythematosus (SCLE)

Clinical features. Subacute cutaneous lupus erythematosus is a photodistributed rash with two main forms. The annular form is characterised by scaly annular or polycyclic erythematous papules and plaques, whereas the papulosquamous form is characterised 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, biologicals, cardiologicals 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%).[24–27]

Histopathology. The epidermis is usually atrophic, with vacuolar interface dermatitis and hyperkeratosis.[12] Interface change tends to be intense, with many cytoid bodies (Figure 2A).[27,28] The epidermal basement membrane may be thickened.[12] There is a superficial perivascular lymphocytic infiltrate, while deep peri-adnexal 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 leucocytoclastic vasculitis was associated with drug-induced SCLE.[23] Contrary to common belief, the presence of eosinophils does not necessarily support a drug-induced aetiology.[23] Some annular SCLE lesions display robust basal degeneration and even epidermal necrosis (Figure 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 throughout the epidermis and in the superficial dermis (Figure 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. Discoid lupus erythematosus is the most common form of chronic cutaneous LE.[8] Most lesions are localised on the face, ears and scalp; however, it can be generalised 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 centre 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 generalised DLE.[7] Up to 20% of SLE patients present with DLE.[7] A rare variant of DLE is hypertrophic/verrucous LE characterised by warty

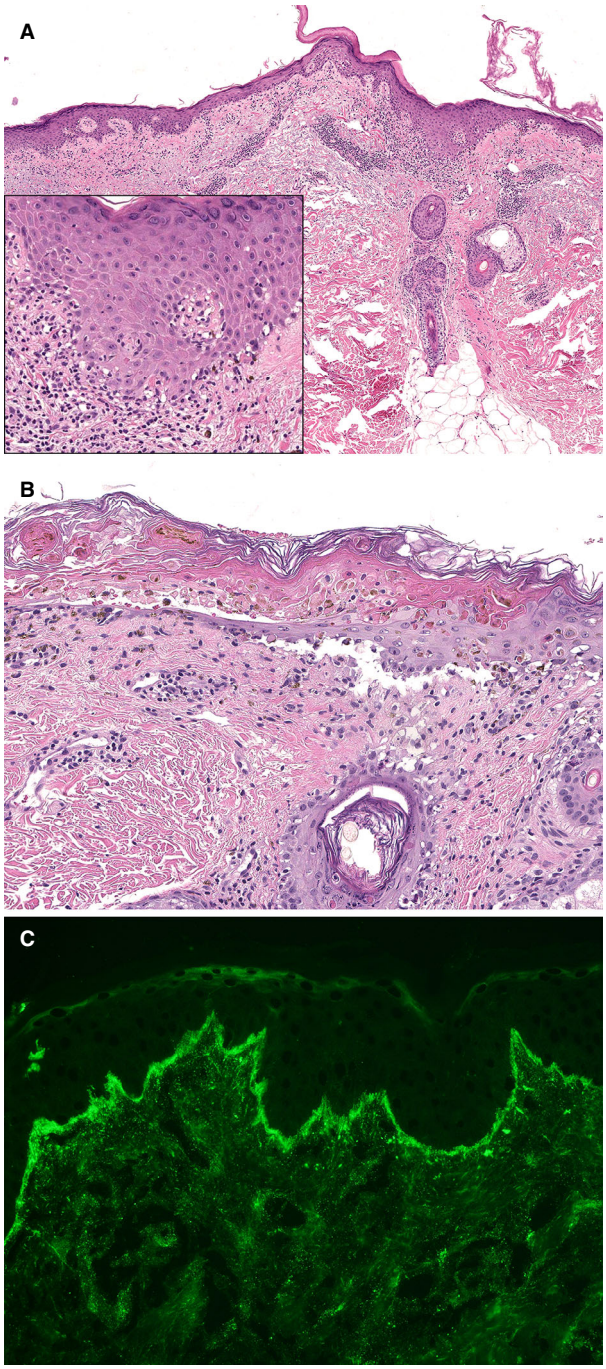

Figure 2. Subacute cutaneous lupus erythematosus. **A,** Vacuolar interface dermatitis with many cytoid bodies (inset). A superficial perivascular lymphocytic infiltrate is present, whereas deep peri-adnexal inflammation is absent. **B,** Rowell syndrome is characterised by robust basal degeneration resulting in epidermal necrosis. Early re-epithelialisation 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, immunoglobulin (Ig)M)].

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 titres 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 generalised 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 localised DLE.[33]

Histopathology. Chronicity of DLE lesions results in more prominent histopathological 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 (Figure 3A).[7] Basement membrane thickening and dermal mucin deposition may be seen (Figure 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] The presence of a perivascular lymphocytic infiltrate, increased dermal mucin and clusters of 10 or more $CD123^+$ plasmacytoid dendritic cells (PDCs) would favour DLE over lichen planopilaris (Figure 3C).[33,35] In the hypertrophic variant, there is pseudoepitheliomatous hyperplasia in addition to the characteristic features of DLE (Figure 3D).[11] Despite

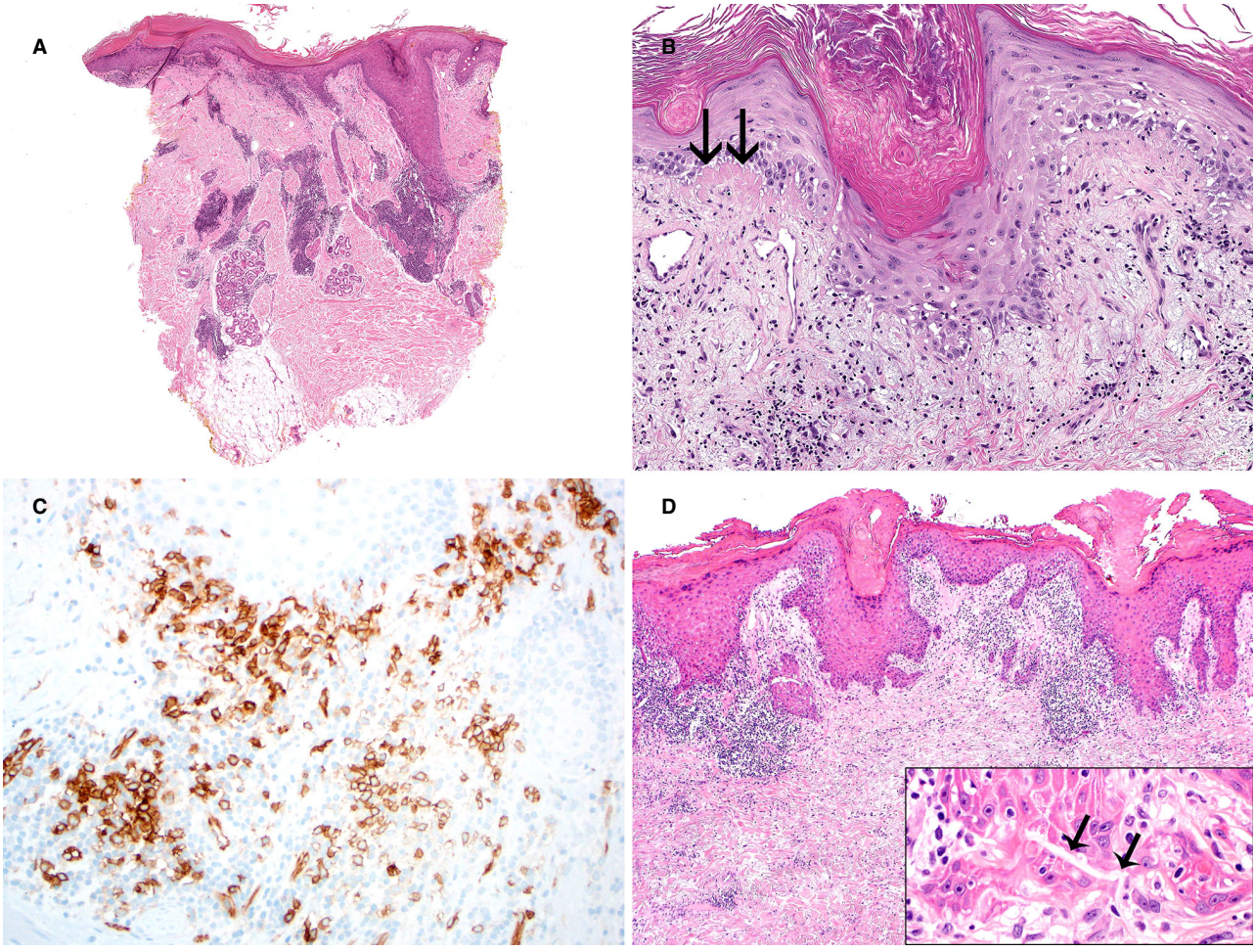

Figure 3. Discoid lupus erythematosus. **A,** Vacuolar to lichenoid interface dermatitis with overlying hyperkeratosis and superficial to deep perivascular and peri-adnexal lymphocytic inflammation. **B,** Follicular hyperkeratosis giving rise to a 'follicular plug'. Epidermal basement membrane is thickened (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 fibres may be seen (inset, arrows) (**C,** CD123 immunohistochemistry).

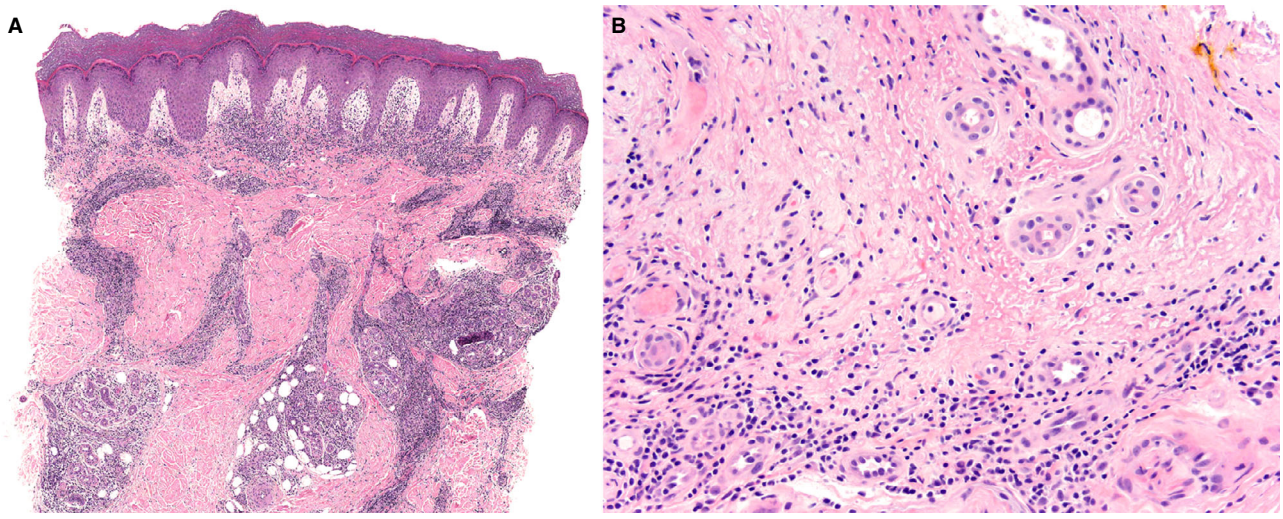

Figure 4. Chilblain lupus erythematosus. **A,** Acral skin with brisk superficial to deep perivascular and peri-eccrine lymphocytic inflammation and prominent papillary dermal edema. **B,** Fibrin exudate in the dermal interstitium favours chilblain LE over idiopathic perniosis.

some morphological similarities, hypertrophic LE differs from squamous cell carcinoma by its lack of cytological atypia and presence of PDC clusters.[11,36] Perforating elastic fibres were once described to be a distinctive feature of hypertrophic LE (Figure 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 oedematous 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 fulfilment of two major criteria: (1) acral skin lesions triggered by cold exposure and (2) evidence of cutaneous LE on histopathological examination or DIF study, as well as one minor criterion: (1) co-existence 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 histopathological 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 vacuolisation, peri-eccrine lymphocytic infiltrate, increased dermal mucin and erythrocyte extravasation (Figure 4A).[42,47,48] Interstitial fibrin exudate and dermal mucin favour chilblain LE over idiopathic perniosis (Figure 4B).[47,49] Clusters of CD123-positive PDCs are present in approximately 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 characterised. 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 titres 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 centres and hyaline fat necrosis (Figure 5A,B).[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 ischaemia.[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 of SPTCL.[64,65] Conversely, the presence of $CD123^+$ PDC clusters would favour LEP over SPTCL.[66] Presence of readily identifiable plasma cells also helps to support LEP (Figure 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 characterised by erythematous urticarial plaques with minimal surface change.[69] The most common sites of involvement include the face, the 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 titres in 25–44% of patients.[73–75]

Histopathology. Biopsies of TLE show a superficial to deep perivascular lymphocytic infiltrate and abundant dermal mucin (Figure 6A,B). Lymphocytic inflammation of adnexal structures may be seen, while epidermal involvement is absent or minimal.[69,76] The main histopathological 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 favour 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 histopathological similarities.[81,82]

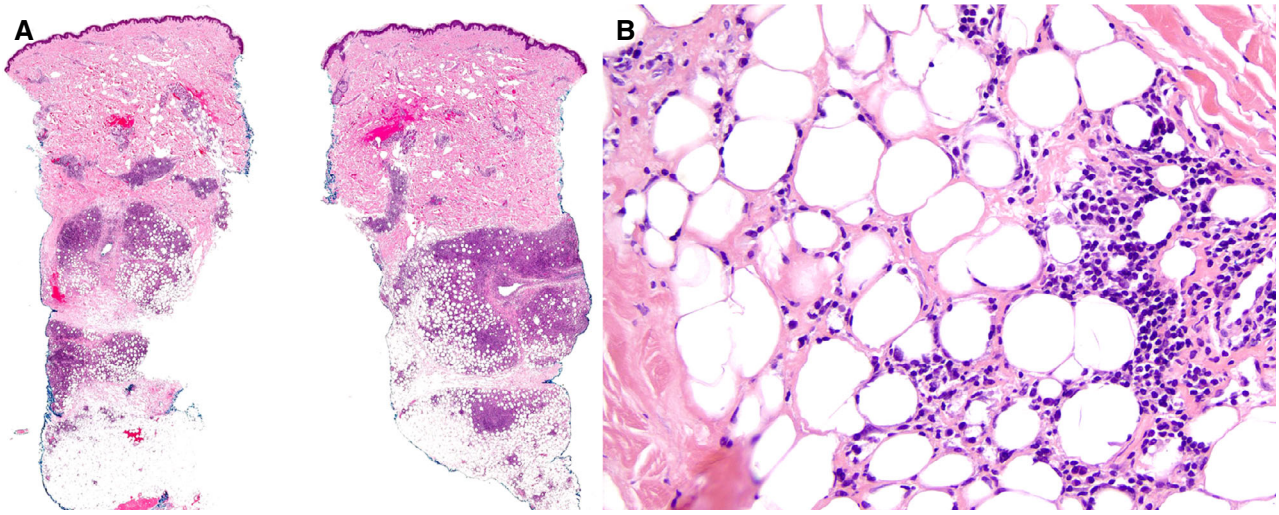

Figure 5. Lupus erythematosus panniculitis. **A,** Brisk lymphocytic infiltrate in the subcutaneous fat lobules, with paraseptal lymphoid nodules present at the periphery of these lobules. **B,** Hyaline fat necrosis is characterised by necrotic adipocytes which appear thickened and hyalinised. Plasma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

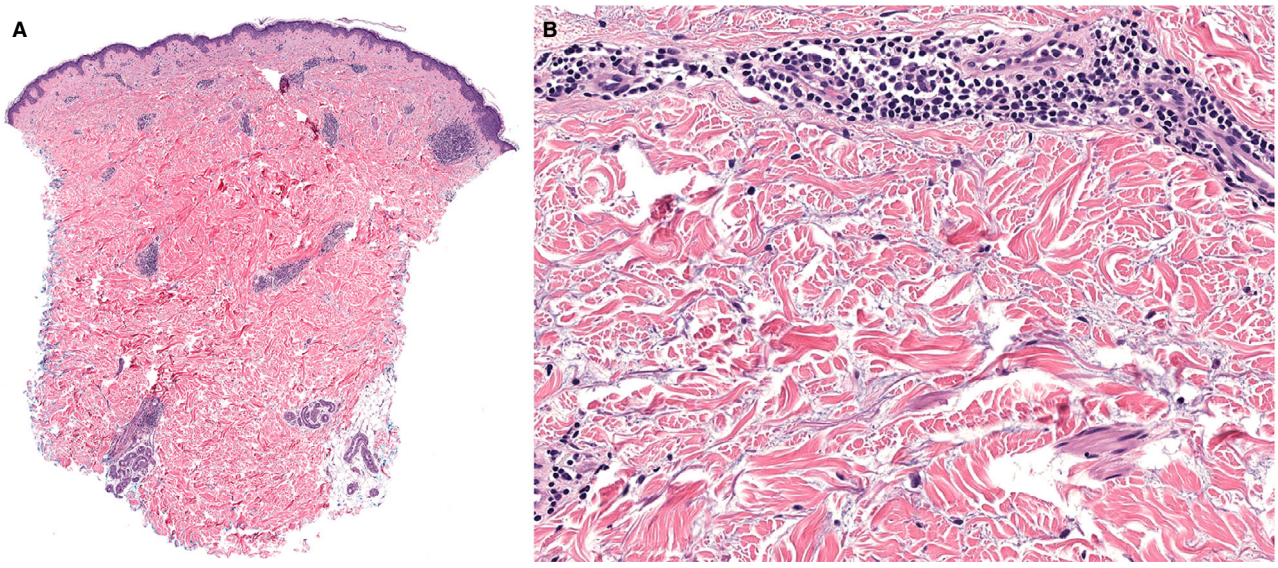

Figure 6. Tumid lupus erythematosus. **A,** A superficial to deep dermal perivascular lymphocytic infiltrate with focal adnexal inflammation. The epidermis is uninvolved. **B,** Abundant dermal mucin appears as a bluish, stringy substance filling the spaces between dermal collagen bundles.

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 haematological diseases may also occur.[86] Cutaneous NLE presents a 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 peri-orbital 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 histopathological 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 histopathological manifestation of NLE.[94–96]

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

LE-NON-SPECIFIC SKIN LESIONS

While LE-specific skin lesions only occur in LE, LE-non-specific 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]

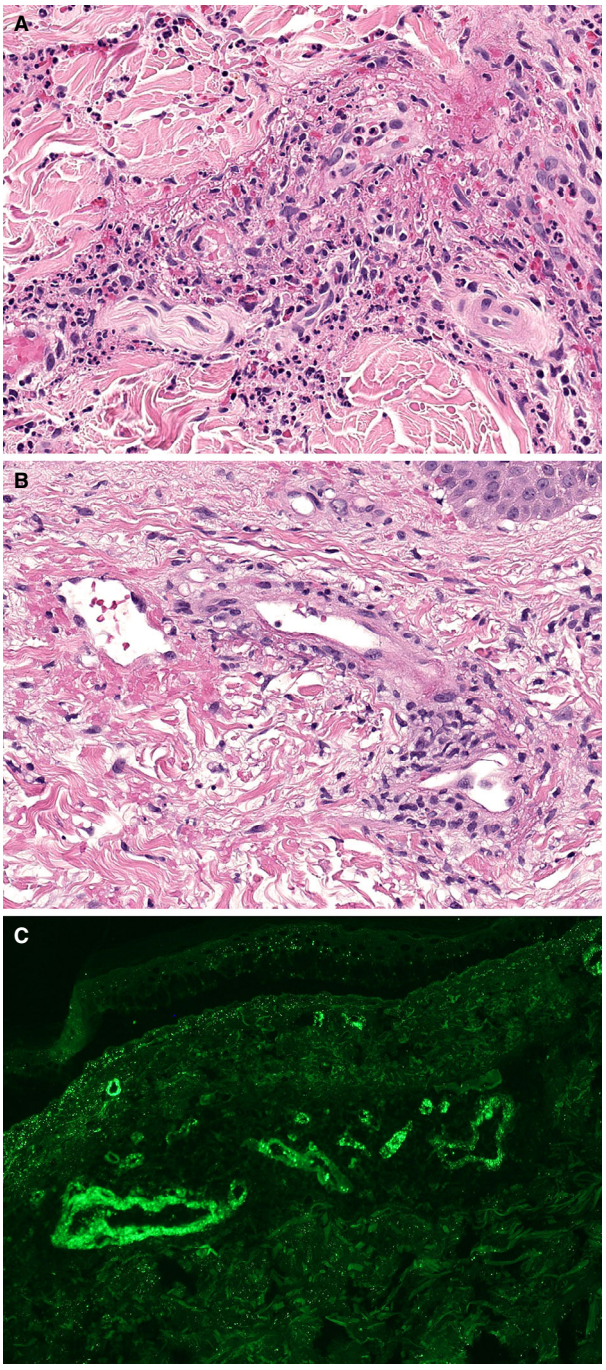

Figure 7. Inflammatory vasculitis. **A,** Leucocytoclastic vasculitis characterised by an angiocentric neutrophilic infiltrate with karyorrhectic nuclear debris, fibrinoid necrosis of the vessel walls and extravasated erythrocytes indicative of vascular damage. **B,** Lymphocytic vasculitis shows infiltration 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, immunoglobulin (Ig)G].

Clinical presentations vary depending upon 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 more than 24 h and often heal with hyperpigmentation.[100]

Histopathology. The most common finding in skin biopsies is leucocytoclastic 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 (leucocytoclasis), fibrinoid necrosis of the vessel walls and erythrocyte extravasation (Figure 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 (Figure 7B).[101]

Direct immunofluorescence. Lupus vasculitis frequently shows 'full house' granular immune deposits in the vessel walls, including C3, IgG, IgM and IgA (Figure 7C). Other cases show some, but not all, immunoreactants. A lupus band may also be observed at the basement membrane.[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

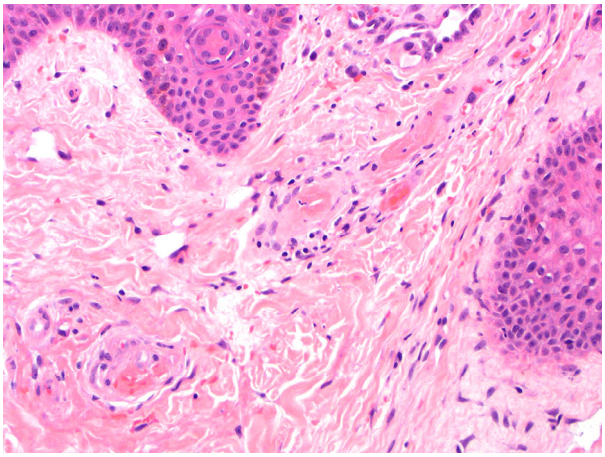

Figure 8. Thrombotic vasculopathy. Intraluminal fibrin thrombi are present in the superficial vessels in a patient with antiphospholipid syndrome. There is mild erythrocyte extravasation but inflammation remains minimal.

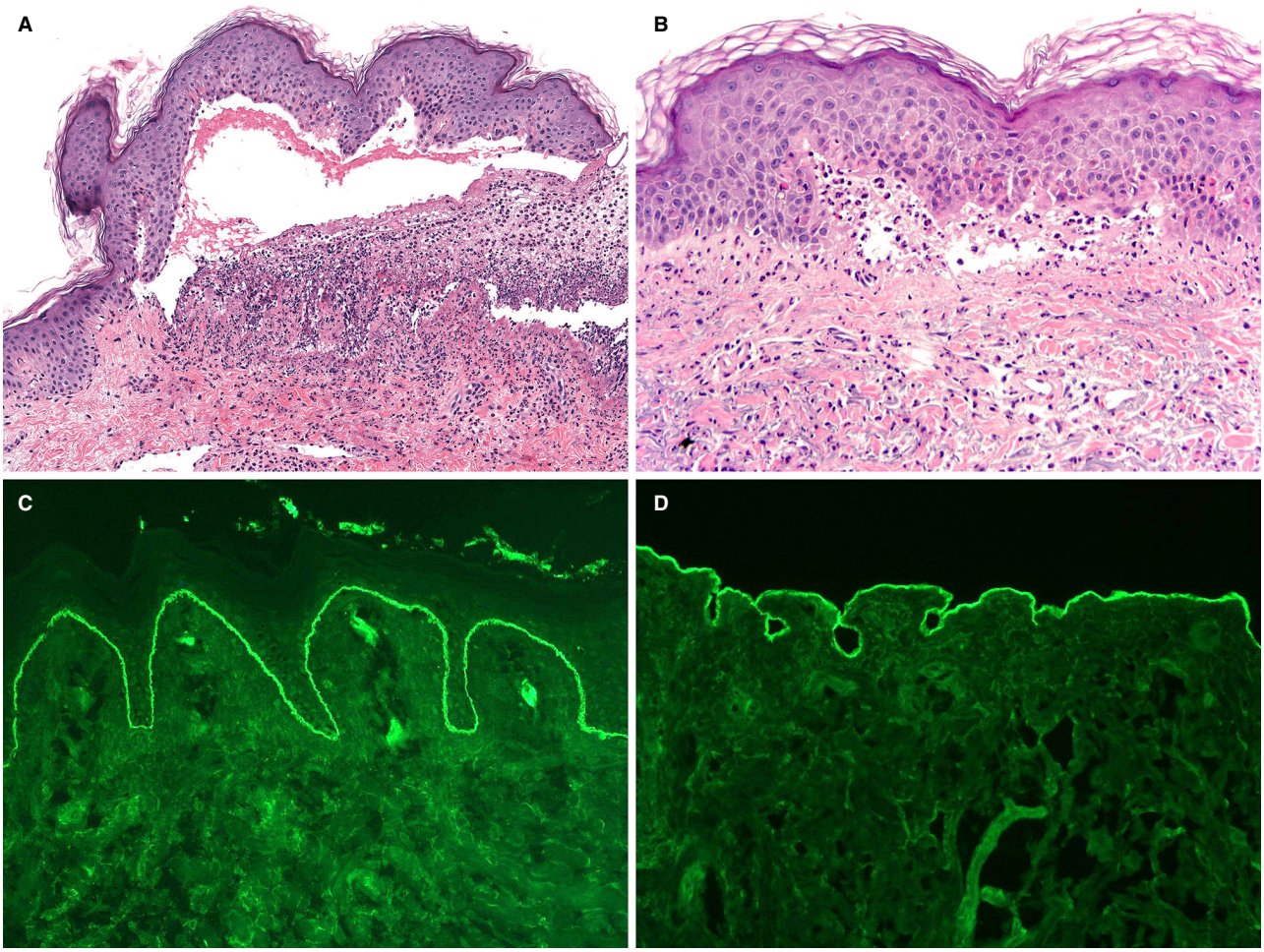

Figure 9. Bullous lupus erythematosus. **A,** Subepidermal bulla containing numerous neutrophils in the blister cavity. Neutrophils are also present in the superficial dermis. **B,** Early subepidermal split with neutrophils confined to the papillary dermis, morphologically mimicking dermatitis herpetiformis and linear immunoglobulin (Ig)A 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).

and arterial thrombosis often results in pregnancy morbidity.[103] Cutaneous manifestations occur 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 haemorrhage 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 histopathological feature in various cutaneous manifestations of APS is occlusive non-vasculitic vasculopathy, in which fibrin thrombi are found in small or medium-sized vessels (Figure 8).[107] There might be evidence of haemorrhage 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 serological 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

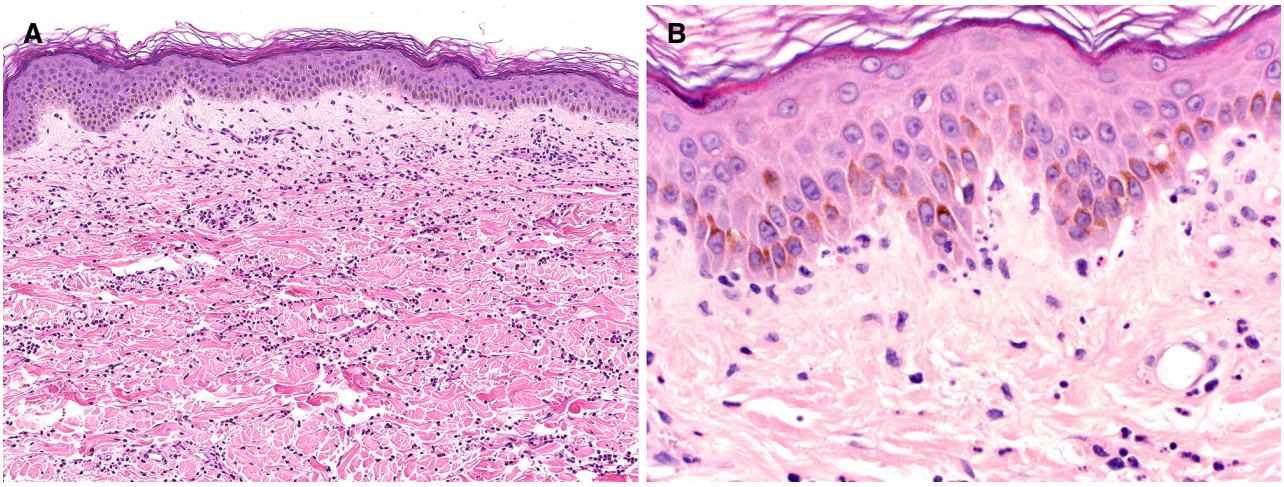

Figure 10. Neutrophilic urticarial dermatosis/non-bullous neutrophilic lupus erythematosus. **A,** An interstitial neutrophilic infiltrate is present in the dermis without associated vasculitis. **B,** Tagging of neutrophils along the dermoepidermal junction and mild basal vacuolisation are commonly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

homogeneous 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 characterised by a subepidermal split with a variable number of neutrophils in the blister cavity and the superficial dermis (Figure 9A). There may be neutrophilic microabscesses in the dermal papillae similar to those seen in dermatitis herpetiformis and linear IgA bullous dermatosis (Figure 9B).[115,117,121] Mucin deposition in the reticular dermis helps to 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 (Figure 9C).[114] IgA is more frequently present in BLE than in other forms of lupus.[115,117] On salt-split skin, the immunoreactants localise to the floor of the split (Figure 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 leucocytosis.[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 h 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 leucocytoclasis in the absence of fibrinoid vascular damage (Figure 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 for NUD.[127] Non-bullous neutrophilic LE may display a subtle vacuolar change, where neutrophils 'tag' along the basal epidermis (Figure 10B).[128,129]

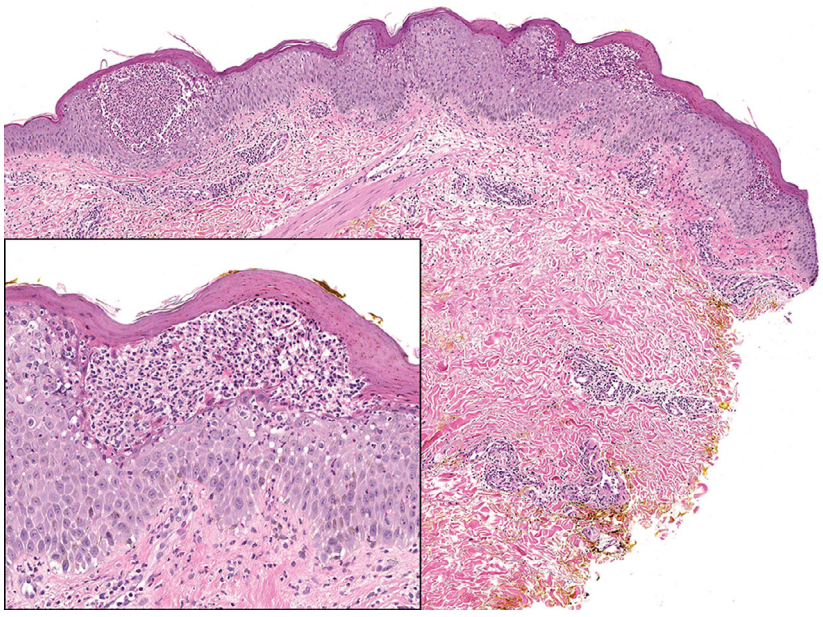

Figure 11. Amicrobial pustulosis of the folds. Multiple pustules are present in the epidermis. Higher magnification of a subnormal pustule is shown in the inset. Sparse neutrophils are found in the superficial dermis.

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 characterised by sterile pustules distributed on skin folds, scalp, umbilicus, anogenital region and the 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 (Figure 11).[132] Dermal neutrophils may be perivascular, interstitial and/or perfollicular. Papillary dermal oedema is common. An infectious aetiology 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 will also provide information regarding the risk of associated systemic disease and prompt appropriate clinical work-up. As pathological 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.

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Conflict of interest

The authors have nothing to disclose.

References

1. Pons-Estel GJ, Ugarte-Gil MF, Alarcón GS. Epidemiology of systemic lupus erythematosus. *Exp. 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**; 13030/qt5r79d67k.
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. Invest. 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. Trichol.* 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 III, 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 YE. Panniculitis. Part II. Mostly lobular panniculitis.. *J. Am. Acad. Dermatol.* 2001; **45**; 325–364; quiz 62–64.
51. Fraga J, García-Díez A. Lupus erythematosus panniculitis. *Dermatol. Clin.* 2008; **26**(4); 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.
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 peri-adipocytic 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. Invest. 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; **39**; 1–7.
92. Lee LA. Maternal autoantibodies and pregnancy – II. The neonatal lupus syndrome. *Baillières. 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* 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* 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.* 2014; **93**; e351.
127. Broekaert SMC, 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 SM. 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.