Cutaneous Lupus Erythematosus
Issues in Diagnosis and Treatment

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Contents

Abstract ................................................................. 366
1. Lupus Erythematosus (LE)-Specific Skin Disease .................................................. 367
   1.1 Acute Cutaneous LE (ACLE) ................................................................. 367
      1.1.1 LocalizedACLE .............................................................................. 367
      1.1.2 GeneralizedACLE ...................................................................... 367
   1.2 Subacute Cutaneous LE ............................................................................. 368
   1.3 Chronic Cutaneous LE .............................................................................. 368
      1.3.1 Classic Discoid LE (DLE) ................................................................. 368
      1.3.2 Hyperkeratotic/Verrucous DLE ......................................................... 369
      1.3.3 LE/Lichen Planus Overlap Syndrome ............................................. 369
      1.3.4 LE Panniculitis .............................................................................. 369
      1.3.5 LE Tumidus ..................................................................................... 369
      1.3.6 Chilblain LE ................................................................................... 370
      1.3.7 Mucosal LE .................................................................................... 370
   1.4 Neonatal LE ............................................................................................. 370
   1.5 Pregnancy in Patients with LE ..................................................................... 370
   1.6 Relationships between the Various Clinical Types of LE-Specific Skin Disease and Systemic LE (SLE) ................................................. 370
2. LE-Nonspecific Skin Disease ............................................................................... 371
   2.1 Cutaneous Vasculitis ................................................................................ 371
   2.2 Livedo Reticularis ................................................................................... 371
   2.3 Alopecia .................................................................................................. 372
   2.4 Digital Manifestations ............................................................................. 372
   2.5 Photosensitivity ...................................................................................... 372
   2.6 Bullous SLE ........................................................................................... 372
   2.7 Other Cutaneous Lesions ......................................................................... 372
3. Systemic Manifestations of SLE ......................................................................... 372
   3.1 Constitutional .......................................................................................... 372
   3.2 Musculoskeletal ........................................................................................ 372
   3.3 Cardiovascular ........................................................................................ 373
   3.4 Pulmonary ................................................................................................ 373
   3.5 Renal Disease .......................................................................................... 373
   3.6 CNS Disease ............................................................................................ 373
   3.7 Other Organ Systems .............................................................................. 373
   3.8 Neoplastic Disease ................................................................................ 373
4. Diagnosis of Cutaneous LE ................................................................................ 373
   4.1 Dermatopathology ................................................................................. 373
   4.2 Immunopathology .................................................................................. 373
   4.3 Serology ................................................................................................... 374
   4.4 Other Laboratory Findings ....................................................................... 374
Abstract

Cutaneous lupus erythematosus (LE) may present in a variety of clinical forms. Three recognized subtypes of cutaneous LE are acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE). ACLE may be localized (most often as a malar or ‘butterfly’ rash) or generalized. Multisystem involvement as a component of systemic LE (SLE) is common, with prominent musculoskeletal symptoms. SCLE is highly photosensitive, with predominant distribution on the upper back, shoulders, neck, and anterior chest. SCLE is frequently associated with positive anti-Ro antibodies and may be induced by a variety of medications. Classic discoid LE is the most common form of CCLE, with indurated scaly plaques on the scalp, face, and ears, with characteristic scarring and pigmented change. Less common forms of CCLE include hyperkeratotic LE, lupus tumidus, lupus profundus, and chilblain lupus. Common cutaneous disease associated with, but not specific for, LE includes vasculitis, livedo reticularis, alopecia, digital manifestations such as periungual telangiectasia and Raynaud phenomenon, photosensitivity, and bullous lesions. The clinical presentation of each of these forms, their diagnosis, and the inter-relationships between cutaneous LE and SLE are discussed. Common systemic findings in SLE are reviewed, as are diagnostic strategies, including histopathology, immunopathology, serology, and other laboratory findings.

Treatments for cutaneous LE initially include preventive (e.g. photoprotective) strategies and topical therapies (corticosteroids and topical calcineurin inhibitors). For skin disease not controlled with these interventions, oral antimalarial agents (most commonly hydroxychloroquine) are often beneficial. Additional systemic therapies may be subdivided into conventional treatments (including corticosteroids, methotrexate, thalidomide, retinoids, dapsone, and azathioprine) and newer immunomodulatory therapies (including efalizumab, anti-tumor necrosis factor agents, intravenous immunoglobulin, and rituximab). We review evidence for the use of these medications in the treatment of cutaneous LE.
it is well known that 20–25% of patients in unselected SLE patient cohorts will develop one or more classic DLE skin lesions at some time during their disease course.[1-3] The term ‘subacute cutaneous lupus erythematosus’ (SCLE) is often used in a similarly ambiguous fashion. This review will attempt to minimize such confusion. In addition, the review will employ the term ‘lupus erythematosus’ as the root designation for this disease category, rather than the term ‘systemic lupus erythematosus,’ to draw attention to confusing clinical concepts such as ‘bullous systemic lupus erythematosus.’ The use of ambiguous nomenclature in a complex heterogeneous clinical disorder such as LE can lead to confusion and management errors.

The classification of LE-related skin disease developed by James N. Gilliam in the 1970s includes two broad subheadings: LE-specific skin disease (synonym cutaneous LE) and LE-nonspecific skin disease.[1] LE-nonspecific skin disease includes those skin lesions, such as palpable purpura and urticaria-like lesions, which result from cutaneous small-vessel leukocytoclastic vasculitis. Although such skin lesions can be seen to occur as a result of the LE systemic autoimmune process, clinically and histopathologically identical skin lesions are seen in a number of other medical conditions unrelated to LE (e.g. essential mixed cryoglobulinemia secondary to hepatitis C virus infection, drug hypersensitivity reactions, and Henoch-Schönlein purpura). Thus, although such skin lesions can be associated with LE, they are not characteristic/diagnostic of LE. LE-nonspecific skin diseases are characteristically seen in association with clinically significant SLE. LE-specific skin disease (acute cutaneous LE [ACLE], SCLE, and CCLE) are not seen in other disorders and are thus highly characteristic of LE. The different types of LE skin disease share variable relationships with SLE. These relationships are illustrated in figure 1 and will be further discussed below.

The complexity of the clinical illness experienced by LE patients leads many primary care physicians to ascribe any change that occurs in the skin of an LE patient to the underlying LE autoimmune process. As with healthy individuals and individuals with unrelated clinical disorders, LE patients can develop common skin disorders such as acne vulgaris, herpes zoster, atopic eczema, cutaneous fungal infections, and drug eruptions, etc. Ascribing such skin lesions to LE autoimmunity can lead to confusion and management errors.

1. Lupus Erythematosus (LE)-Specific Skin Disease

1.1 Acute Cutaneous LE (ACLE)

ACLE may present in either a localized (more common) or generalized (less common) distribution. Both forms of ACLE are photosensitive and transient, generally lasting days to weeks. Bullous lesions may be present as a reflection of intense skin inflammation. Post-inflammatory dyschromia (often hyperpigmentation) typically ensues after the active phase of the eruption. In a study of 600 patients with SLE, LE-specific skin disease was seen in 354 (59%).[6]

1.1.1 Localized ACLE

Localized ACLE usually presents as a characteristic ‘butterfly’ facial rash (figure 2). It is characterized by symmetric confluent erythema and edema overlying the malar cheeks (wings of the butterfly) and extending over the bridge of the nose (body of the butterfly).[1,2] The eruption may involve the forehead and the anterior neck, although typically spares the nasolabial folds. This butterfly rash is present at diagnosis in 40–52% of SLE patients.[3,6]

1.1.2 Generalized ACLE

Generalized ACLE is present both above and below the neck and may present as a widespread morbilliform eruption. It has been referred to as a ‘photosensitive lupus dermatitis’ or ‘maculopapular rash of lupus.’ There is often erythema and edema of the hands, particularly over the dorsal and interphalangeal areas, sparing the skin overlying the interphalangeal and metacarpophalangeal joints.[1,2] This generalized eruption may be present in about one-third of patients with SLE.[7]

In both subtypes of ACLE, flare-ups of cutaneous disease tend to parallel systemic disease activity. However, exceptions to this rule do occur. One of the authors (Richard Sontheimer) has observed several adult, White women experience recurrent generalized ACLE over several decades without accompanying clinical or laboratory evidence of SLE disease activity or injury.
ACLE lesions typically resolve without atrophic dermal scarring. However, post-inflammatory hyperpigmentation/hypopigmentation can persist long after active inflammation has subsided. Such post-inflammatory dyschromia tends to be most marked in darkly complexioned individuals.

1.2 Subacute Cutaneous LE

As with SLE, this cutaneous LE subphenotype appears most commonly in young and middle-aged adult women, though drug-induced forms may be seen in either sex and at older ages of onset. SCLE presents a symmetric erythematous eruption of nonindurated macules and papules that soon become surmounted by fine scale. In time, one of two morphologic forms typically develops in patients: scaly annular lesions (annular SCLE) or scaly papulosquamous plaques (papulosquamous SCLE; figure 3). As annular SCLE lesions become confluent they produce a polycyclic array, whereas merging papulosquamous SCLE lesions produce a retiform array. Both forms are highly photosensitive, with the predominant distribution on the upper back, shoulders, neck and anterior chest (‘V’ distribution), and extensor arms and forearms. SCLE tends to spare the central face and scalp, and very seldom occurs below the waist. Uncommon clinical variants of SCLE include exanthematous, pityriasiform, exfoliative erythroderma, follicular erythematous, and acral annular.

Compared with SLE, patients presenting with SCLE skin lesions tend to have milder systemic disease and are less likely to have systemic disease activity parallel cutaneous flare-ups. Musculoskeletal symptoms are relatively common in SCLE patients, though severe systemic manifestations such as systemic vasculitis, renal disease, and CNS disease occur in less than 10% of patients. Up to 70% of SCLE patients will exhibit positive anti-Ro (Sjögren syndrome antigen A [SS-A]) autoantibodies. Anti-Ro antibodies are frequently associated with SCLE-related photosensitivity.

SCLE lesions typically resolve without atrophic dermal scarring. However, as with other forms of LE-specific skin disease, post-inflammatory hyper- and hypopigmentation can follow in the wake of SCLE disease activity.

Drugs are increasingly being implicated as environmental triggering factors in SCLE. Examples of medications reported to induce SCLE are included in table 1. These medications are generally considered to unmask SCLE in an immunogenetically susceptible individual, perhaps via photosensitizing mechanisms.

1.3 Chronic Cutaneous LE

1.3.1 Classic Discoid LE (DLE)

The most common clinical subtype of CCLE is classic DLE. Classic DLE lesions occur in 20% of patients with SLE at some point in their disease course. Classic DLE is categorized as either localized (above the neck) or generalized (above and below the neck, with typical involvement of the extensor forearms and hands). The localized form is far more common. Although most patients presenting with DLE lesions never develop features of clinically significant SLE, this is somewhat more likely to occur in patients presenting with generalized DLE.

DLE lesions are characteristically indurated and most commonly affect the scalp, face, ears (particularly the conchal bowls), anterior neck, and extensor arms. The scalp is affected in >60% of patients. The malar (‘butterfly’) eruption with sparing of relatively sun-protected areas such as the eyelids, nasolabial folds, and mental crease.

Fig. 2. Acute cutaneous lupus erythematosus demonstrating the malar (‘butterfly’) eruption with sparing of relatively sun-protected areas such as the eyelids, nasolabial folds, and mental crease.

Fig. 3. Papulosquamous subacute cutaneous lupus erythematosus. Scaly papulosquamous plaques on the upper back.
patients with DLE. Clinically, a lesion of DLE starts as a well demarcated scaly purplish macule or papule, which gradually expands into a discoid (coin-shaped) plaque (figure 4). Peripheral scale and hyperpigmentation are typically present, and the center of the lesion is often hypopigmented and atrophic, leading to a depressed scar. In some cases, adjacent lesions may coalesce into irregular plaques. Adherent scale often extends into dilated hair follicles, leading to plugging of the follicle. Over half of patients will develop significant and destructive scarring, with scarring alopecia developing in over one-third of patients. Arthralgia may occur in patients with CCLE and may indicate an increased risk of development of SLE. Common triggers for DLE lesions include trauma (Koebner effect), exposure to UV radiation, exposure to the cold, infection, dermatitis, and burns.

Aside from classic DLE, several other variants of CCLE are recognized. These are discussed below.

### 1.3.2 Hyperkeratotic/Verrucous DLE

This form of CCLE features thickened lesions on the extensor arms, hands, and face. Lesions may clinically resemble keratoacanthoma or hypertrophic lichen planus. Increased dermal elastin fibers are noted histologically, occasionally with transpidermal elimination.

### 1.3.3 LE Lichen Planus Overlap Syndrome

This form of CCLE, also referred to as ‘lupus planus,’ has overlapping features of hyperkeratotic DLE and lichen planus.

### 1.3.4 LE Panniculitis

LE panniculitis is characterized by the involvement of the deep dermis and underlying adipose tissue, presenting as firm, depressed nodules. One to three percent of patients with cutaneous LE will demonstrate this clinical variant. Half of patients will have classic DLE findings overlying the deep nodules or elsewhere. Although many authors use the terms LE panniculitis and LE profundus interchangeably, some authors reserve the term LE profundus to indicate cases with DLE changes superimposed over LE panniculitis lesions. Lesions may be located on the trunk, proximal extremities, face, and breasts. LE profundus located on the breasts, also termed ‘lupus mastitis,’ may clinically mimic breast carcinoma. Differentiation from subcutaneous panniculitis-like T-cell lymphoma may be challenging. Considerable morbidity can result from dystrophic calcification that typically develops deep within chronic LE profundus lesions.

### 1.3.5 LE Tumidus

LE tumidus presents as deeply erythematos, urticarial plaques with minimal surface change, no follicular plugging, and rich mucin deposition histologically. Differentiation from Jessner lymphocytic infiltrate may be difficult, although LE tumidus is more likely to involve the face and has a strong

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**Table 1. Medication classes associated with triggering of cutaneous lupus erythematosus**

<table>
<thead>
<tr>
<th>Subacute cutaneous lupus erythematosus pattern</th>
<th>Systemic lupus erythematosus pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors (e.g. captopril)</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Antiepileptics (e.g. phenytoin)</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Antimalarials (e.g. hydroxychloroquine)</td>
<td>Lipid-lowering medications (e.g. pravastatin, simvastatin)</td>
</tr>
<tr>
<td>Antimicrobial agents (e.g. griseofulvin, terbinafine, and tetracycline)</td>
<td>Minocycline</td>
</tr>
<tr>
<td>β-Adrenoceptor antagonists (e.g. acebutolol)</td>
<td>Procainamide</td>
</tr>
<tr>
<td>Calcium channel blockers (e.g. diltiazem and nifedipine)</td>
<td>Tumor necrosis factor-α inhibitors (e.g. etanercept and infliximab)</td>
</tr>
<tr>
<td>Chemotherapeutic agents (e.g. tamoxifen and docetaxel [taxotere])</td>
<td>NSAIDs (e.g. naproxen and piroxicam)</td>
</tr>
<tr>
<td>NSAIDs (e.g. naproxen and piroxicam)</td>
<td>Proton pump inhibitors (e.g. omeprazole)</td>
</tr>
<tr>
<td>Proton pump inhibitors (e.g. omeprazole)</td>
<td>Thiazide diuretics (e.g. hydrochlorothiazide)</td>
</tr>
<tr>
<td>Sulfonylureas (e.g. glyburide)</td>
<td>Others (e.g. bupropion, leflunomide and interferon-α)</td>
</tr>
</tbody>
</table>

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**Fig. 4.** Chronic cutaneous lupus erythematosus. Discoid lupus erythematosus, demonstrating coin-shaped plaques with dense peripheral inflammation and central scale.
female predominance.\(^{28}\) This form of LE is reported to be the most photosensitive of all LE subtypes, with positive photoprovocative testing in 43 of 60 patients in one study.\(^{29}\) Patients presenting with LE tumidus are typically ANA negative and rarely display clinical features of SLE.

### 1.3.6 Chilblain LE

Chilblain LE appears as violaceous papules and plaques that characteristically appear on the fingers and/or toes but can also be seen on the ears and face. The eruption is triggered or exacerbated by cold, damp, environmental exposure. The development of this subtype of LE may be dependent on climate. A British survey found that 15 of 73 (20.5\%) SLE patients had chronic chilblain LE.\(^{30}\) Conversely, an estimated 20\% of patients with chilblain LE will go on to develop features of SLE.\(^{31}\) A familial form is characterized by mutations in the TREX1 (endonuclease repair) gene.\(^{32}\)

### 1.3.7 Mucosal LE

Mucosal LE most commonly occurs in the context of DLE. In a study of 90 patients with cutaneous LE or SLE, oral disease was present in ten (11\%).\(^{33}\) The oral mucosa is most commonly affected, though the nasal, conjunctival, and genital mucosa may be involved. In a study of 46 patients (34 women and 12 men) with oral lesions in the context of LE, the lips and buccal mucosa were most commonly affected. Of these patients, 36 of 46 (78\%) had a diagnosis of CCLE, and 10 of 46 (22\%) had SLE.\(^{34}\) Clinically, the eroded plaques are well demarcated by irregular white borders with radiating striae. The appearance may resemble that of oral lichen planus.\(^{3}\) Lesions on the palate often have a honeycomb appearance. Histologically, a lymphocyte-rich interface mucositis is seen, and direct immunofluorescence is similar to that in cutaneous LE.\(^{35}\) Nonspecific oral ulceration may also be observed in 18–30\% of SLE patients, often at the onset of the disease.\(^{6,30}\)

### 1.4 Neonatal LE

Neonatal LE occurs most commonly in the setting of maternal anti-Ro autoantibodies. Nearly all infants with neonatal LE will have passively transferred IgG anti-Ro antibodies.\(^{36}\) However, only about 1\% of anti-Ro-positive mothers will have infants with neonatal LE.\(^{36}\) The cutaneous eruption is symmetric, annular, and photo-exacerbated, bearing strong resemblance to SCLE both in clinical appearance and histologically. The distribution of neonatal LE favors the face (particularly periorbital) and scalp.\(^{37}\) The eruption may be present at birth, or otherwise develops during the first several weeks of life.

The primary concern of infants with neonatal LE is congenital heart block, thought to be caused by anti-Ro/La antibodies attacking cardiac conduction tissue. Progression to complete heart block is generally irreversible and may require a pacemaker.\(^{38}\) About half of infants with neonatal LE will have cutaneous findings, half will have congenital heart block, and 10\% will have both.\(^{39}\) It is estimated that 80\% of all cases of congenital heart block are attributable to neonatal LE.\(^{38}\) Cardiomyopathy is also possible. As such, all infants with neonatal LE should have an ECG. About 10\% of cases will have either liver disease (including transaminitis, hyperbilirubinemia, and potentially liver failure) or hematologic disease (most commonly thrombocytopenia).\(^{36}\) A complete blood count and assessment of liver function should thus be performed.

The eruption is transient and generally clears by the age of 6 months as the maternal anti-Ro antibodies disappear. Scarring is unusual, although pigmentary changes and telangiectasia may be slow to improve.\(^{37}\) Infants with neonatal LE do not appear to be at particularly high risk of developing SLE later in life, but are at risk of developing other autoimmune diseases.\(^{39}\)

### 1.5 Pregnancy in Patients with LE

Aside from the fetal risks associated with anti-Ro autoimmunity, pregnant patients with SLE present special concerns. Pregnancy may proceed without complication in patients with inactive SLE, though pregnancy may also induce a disease flare-up. In addition, the management of active SLE is hampered by adverse fetal effects of immunosuppressive medications. SLE is associated with increased hypertensive complications, preterm birth, low birth weight, and stillbirth, with the degree of risk correlated with the severity of maternal disease.\(^{40}\) Recurrent pregnancy loss is particularly associated with antiphospholipid antibody syndrome. The main clinical risk factors for a complicated pregnancy course and outcome are active disease, hypertension, and nephritis.\(^{41}\) It is recommended that pregnant women with SLE undergo frequent ultrasonography and fetal heart rate monitoring during the second and third trimesters.\(^{40}\)

### 1.6 Relationships between the Various Clinical Types of LE-Specific Skin Disease and Systemic LE (SLE)

The large shaded circle in figure 1 represents the population of patients who can be classified as having SLE by virtue of displaying four or more of the American College of Rheumatology (ACR) classification criteria.\(^{42,43}\) The smaller circles represent populations of patients displaying the various clinical types of LE-specific skin disease.
Although the large majority of patients experiencing ACLE skin lesions have accompanying clinically significant SLE disease activity/damage, a small percentage of such patients can experience recurrent ACLE skin disease activity in an isolated fashion over many years.

Approximately 50% of SCLE patients can be classified as having SLE based upon ACR criteria. However, SCLE patients tend to predominantly display only the cutaneous, musculoskeletal, and serologic criteria for SLE. In reality, only 10–15% of patients presenting with SCLE skin lesions develop functional impairment of vital internal organs as a result of SLE disease activity over their disease course.[1-3,8]

This illustration emphasizes the concept that patients whose presenting illness is dominated by CCLE skin disease (predominantly classic DLE) rarely go on to experience systemic complications of SLE. However, it must be remembered that unselected patients with SLE have a 20–25% risk over their lifetime of developing one or more classic DLE skin lesions. As with classic DLE, patients presenting with other forms of CCLE (e.g. LE profundus, LE tumidus, and hypertrophic/verrucous DLE) have a very low risk of developing clinically significant SLE during their disease course. The figure also illustrates the observation that patients presenting with SCLE skin lesions have a 20% risk of also displaying classic DLE or ACLE skin lesions at some timepoint in their disease course.

The sizes of the circles in this illustration are drawn to approximate scale. Recent population-based epidemiologic studies from Mayo Clinic (Rochester, MN, USA) suggest that patients with isolated forms of LE-specific skin disease (predominantly classic DLE and SCLE patients) are equally prevalent as those with SLE (Davis M, personal communication).

2. LE-Nonspecific Skin Disease

Many skin changes are associated with LE, particularly SLE, but are not specific to the disease process itself. That is to say, identical lesions can be seen in disease settings other than LE. LE-nonspecific skin lesions tend to be strongly associated with SLE, and some can reflect SLE disease activity (e.g. vasculitis). The most common types of LE-nonspecific skin lesions are reviewed below.

2.1 Cutaneous Vasculitis

Cutaneous vasculitis is reported to occur in 11–70% of SLE patients.[3,30,44,45] In a large series of patients with SLE, vasculitis was diagnosed in 76 of 670 (11%), with a female-to-male ratio of 8.5 : 1.[45] Vasculitis in the context of LE typically presents as small-vessel cutaneous leukocytoclastic vasculitis. This pattern was observed in 86% of patients in the above study.[45] A generalized or acral distribution may be observed. Palpable purpura on the lower extremities is the most common clinical presentation (figure 5). Urticarial vasculitis may also be observed in less dependent areas of skin. Less commonly, vasculitis of the medium-sized vessels in the dermis and subcutis may produce tender nodules resembling periarteritis nodosa. Medium-vessel vasculitis is much more likely to present with mononeuritis multiplex, ulcerated cutaneous lesions, and visceral vasculitis.[45] Isolated visceral vasculitis is uncommon.[45] The presence of cutaneous vasculitis may predict the development of LE nephritis.[46]

Fig. 5. Lupus vasculitis. Palpable purpuric papules and plaques on the lower extremities in a patient with flaring systemic lupus erythematosus. Cutaneous biopsy showed leukocytoclastic vasculitis in addition to specific features of cutaneous lupus erythematosus.

2.2 Livedo Reticularis

Livedo reticularis is seen in 22–35% of SLE patients.[44] The presence of livedo reticularis is associated with the presence of cutaneous vasculitis.[45] Livedo reticularis is also seen in 11–37% of patients with antiphospholipid antibody syndrome[47,48] and has been proposed as a minor criterion for this syndrome.[49] In a study of 128 patients with primary antiphospholipid antibody syndrome, only 11 (8%) developed SLE during a mean follow-up duration of 9 years.[48] Patients with both SLE and antiphospholipid antibody syndrome may be particularly likely to demonstrate livedo reticularis.[50] However, it must be remembered that livedo reticularis is a cutaneous finding that can be seen in other medical disorders, some of which SLE patients can experience (e.g. cholesterol embolization).
2.3 Alopecia

Scarring alopecia is common in DLE, occurring in one-third or more of patients.[19] Nonscarring alopecia is also common in other forms of LE.[6] In one study of 73 SLE patients, 40% demonstrated nonscarring alopecia.[30] Telogen effluvium may develop concurrently with a flare-up of LE disease activity.[1] Nonscarring alopecia may occur in association with systemic therapies for SLE.[3] A recent review reported that some form of alopecia occurs in 38–78% of patients with cutaneous LE.[51]

2.4 Digital Manifestations

Periungual telangiectasia occurs in 10–15% of SLE patients[52] but is a more frequent and characteristic finding in other connective tissue diseases such as dermatomyositis and systemic sclerosis. Raynaud phenomenon is reported in up to 60% of SLE patients.[30] Splinter hemorrhages (resulting from thrombotic microangiopathy) and sclerodactyly may also be seen.[3]

2.5 Photosensitivity

Photosensitivity is included as a diagnostic criterion for SLE and is very common in all forms of cutaneous LE. Photosensitivity was observed in 46 of 73 (63%) SLE patients.[30] Photoexacerbated urticaria was reported in 32 of 73 (44%) patients.[30]

2.6 Bullous SLE

Bullous SLE is an example of LE-nonspecific inflammation that results in subepidermal vesiculobullous skin changes.[1-3,53] Bullous SLE typically occurs in the context of active SLE, often accompanied by LE nephritis. Bullous SLE skin lesions typically display neutrophilic infiltration, with papillary microabscess formation on skin biopsy similar to that of dermatitis herpetiformis and the inflammatory variant of epidermolysis bullosa acquista. However, the immunofluorescence microscopy findings are more typical of those of LE.[53] Circulating antibodies to type VII collagen autoantibodies have been described in such patients, indicating shared immunopathologic features with epidermolysis bullosa acquista.[54,55] The term bullous SLE can be viewed as an example of ambiguous nomenclature, as other clinical pathologic patterns of blistering skin disease can occur in patients with cutaneous and systemic LE.[1]

2.7 Other Cutaneous Lesions

Other lesions noted that are associated with LE include bullae, rheumatoid nodules, calcinosis cutis, anetoderma, thrombophlebitis, erythromelalgia, erythema multiforme, acanthosis nigricans, lichen planus, and leg ulcers.[3] Cheilitis, episcleritis, and facial edema are reported in less than 5% of patients.[30]

3. Systemic Manifestations of SLE

As discussed above, extracutaneous symptoms are not uncommon in cases of cutaneous LE. Musculoskeletal symptoms, including myalgia and arthralgia, have been seen during long-term follow-up in over half of patients with SCLE.[17,51] Symptoms of the nervous system, including headaches and sensory changes, are also observed.[51] These symptoms tend to be much milder than in patients with SLE. The development of new or worsening symptoms of arthralgia in patients with cutaneous LE should raise suspicion of the development of systemic disease. We review below the common systemic manifestations of SLE.

3.1 Constitutional

Fatigue is present in a high proportion of SLE patients, may correlate with periods of disease activity, and is associated with pain, sleeplessness, and depression.[56] Fever and weight loss are also common, present in more than 80% of patients at the time of diagnosis.[3] SLE patients have increased mortality compared with the general population. A multinational study of over 9000 SLE patients demonstrated a standardized mortality ratio of 2.4 in SLE.[5]

3.2 Musculoskeletal

Musculoskeletal symptoms, primarily arthritis or arthralgia, may be present in 90–100% of SLE patients.[57] Joint pain is the most common presenting symptom of SLE, affecting 83% of patients at some stage in the disease course.[4] The proximal interphalangeal joints are most commonly involved, followed by the knees, wrists, and metacarpophalangeal joints. Joint deformity may occur late in the course of the disease secondary to ligament laxity (Jaccoud arthropathy). Involvement is typically symmetric. Morning stiffness is present in up to one-half of patients, and 30% will experience muscle pain. Tendonitis and tenosynovitis may occur in 10% of patients. Fibromyalgia is relatively common, occurring in 10 of 60 (17%) patients in one series, with activity of fibromyalgia independent of SLE disease activity.[58] The risk of avascular bone necrosis is elevated in patients with SLE. The use of systemic corticosteroids in this setting increases this risk.
3.3 Cardiovascular

Up to one-quarter of patients exhibit pericarditis, usually presenting as acute chest pain. Atherosclerosis and arteritis increase the risk of myocardial infarction. The risk of cardiovascular death is significantly elevated in SLE, particularly in patients aged 20–39 years, who had a 16-fold increased risk of death in a large population-based study.[59]

3.4 Pulmonary

SLE can affect the lungs at the level of the pleura, parenchyma, airway, vasculature, and musculature.[60] Pleural effusion is seen in up to 40% of patients. Patients are also at increased risk of pneumonitis, pulmonary embolism, pulmonary hemorrhage, pulmonary hypertension, and pneumonia.

3.5 Renal Disease

Renal disease occurs in 34–67% of SLE patients, with proteinuria being the most common finding.[4,61] LE nephritis is associated with a poor prognosis. End-stage renal failure may occur in up to 20% of LE nephritis patients.[61]

3.6 CNS Disease

Neuropsychiatric manifestations are seen in up to two-thirds of patients with SLE.[1-3,61] Seizures occur in about 15% of patients, typically early in the disease course, and are most commonly generalized.[61] Peripheral neuropathy (most commonly sensory) and cranial nerve signs both occur in about 15% of patients. Debilitating headache, optic neuritis, Guillain-Barré syndrome, and multiple sclerosis may occur. Cerebrovascular accidents are more common when antiphospholipid antibodies are present. Psychiatric disorders include psychosis, depression, and anxiety.[61]

3.7 Other Organ Systems

Abdominal pain is a relatively common complaint and can relate to mesenteric vasculitis or pancreatitis.[1-3] Hepatosplenomegaly may occur in 20–30% of patients. Elevated transaminases may occur with active disease and/or consequent to medications. Up to one-half of patients may have lymphadenopathy. Conjunctivitis or episcleritis occurs in about 15% of patients.[50]

3.8 Neoplastic Disease

A recent retrospective study of >30,000 SLE patients found a significant overall increased risk of cancer (standardized incidence ratio of 1.14), with a particularly high risk of vulvar and liver cancers.[62]

4. Diagnosis of Cutaneous LE

Diagnosis of cutaneous LE depends upon the clinical setting and the nature of the eruption as described in section 1. Cutaneous histopathology is qualitatively similar in each form of LE-specific skin disease, and is useful in contributing to the diagnosis of LE but not in determining the clinical subtype. Assessment of the autoantibody profile is useful in determining the presence of SLE but has a more limited role in the diagnosis of skin-limited LE. Because many cases of SLE will initially present with cutaneous findings, all patients presenting with features of cutaneous LE should be evaluated with a comprehensive history, with a systems review focused upon those systems most frequently involved, as well as a complete physical examination for cutaneous and extracutaneous manifestations. A complete blood count, and assessment of liver and, in particular, renal function, and an autoantibody profile will be appropriate for the majority of patients presenting with cutaneous LE. Communication with the patient’s primary care physician is important, and referral to other specialists, including rheumatology, nephrology, and neurology, may be indicated if concerns for systemic disease are disclosed.

4.1 Dermatopathology

Histologic features of LE include interface dermatitis consisting of a mononuclear cell infiltrate at the dermoepidermal junction, basal layer degeneration, perivascular and periadnexal inflammation, mucin deposition, and hyperkeratosis.[1-3] SCLE characteristically shows dermal edema and some degree of epidermal atrophy. Classic DLE may demonstrate more pronounced follicular plugging and inflammation extending deeper into the dermis. Features of ACLE are often less striking than other forms of LE.

4.2 Immunopathology

In all clinical forms of LE-specific skin disease, immunopathology of lesional skin via direct immunofluorescence often shows deposition of immunoglobulin (often IgG) and complement components (often C3) at the dermal-epidermal
junction (the so-called lesional lupus band test). However, these findings may be present in other connective tissue diseases. Immune deposits are also found at the dermal-epidermal junction in nonlesional skin of SLE patients. The diagnostic specificity of this finding (nonlesional lupus band test) is highest when three or more immunoreactants are present and when the specimen is obtained from sun-protected skin. In a study of sun-protected nonlesional specimens from 65 LE patients, the lupus band test had a low sensitivity (10.5%) but high specificity (97.8%) when two different immunoreactants were present. However, the lesional lupus band test is not useful in distinguishing patients with different clinical forms of LE-specific skin disease from those with SLE. As such, routine histopathology is generally preferred to direct immunofluorescence in establishing the diagnosis of LE. A positive lesional lupus band test is not required for the diagnosis of LE but may be helpful when other studies are equivocal.

4.3 Serology

Serologic assessment of autoantibodies is especially important in SLE. Laboratory studies directed at the common internal target organs of SLE (including the assessment of renal, hepatic, and hematopoietic function) are critical for assessing the degree of systemic involvement. Virtually all patients with SLE have a positive ANA, with modern immunoassays employing human tumor cell lines as substrates. A titer of $\geq 1:160$ is typically seen in SLE, and higher titers ($\geq 1:320$) are predictive of SLE rather than cutaneous LE. However, even high levels of ANA are by no means specific for SLE. Conversely, low positive ANA titers do not help distinguish cutaneous from systemic LE. Anti-double-stranded DNA is highly specific for SLE and is present in about 70% of patients. Anti-Smith (Anti-Sm) antibodies are also highly specific for SLE but are present in only 25% of patients. Anti-Sm antibodies persist throughout the disease, whereas anti-DNA antibodies tend to increase in titer when systemic disease is active, and decrease or disappear during remission. Anti-histone and anti-C1q antibodies also correlate with systemic disease activity. Anti-La (SS-B) and anti-Ro (SS-A) antibodies are also seen in SLE with less specificity. Maternal anti-Ro antibodies confer a risk for neonatal LE and congenital heart block. Anti-Ro antibodies are particularly common in SCLE, occurring in approximately 60% of patients; anti-La, anti-single-stranded DNA, and anti-U1 ribonucleoprotein protein are present in 10% or less of SCLE patients. Anti-Ro antibodies may be found in about 25% of DLE patients; anti-La and anti-U1 ribonucleoprotein protein are present in 10% or less of DLE patients. Anti-single-stranded DNA antibodies in a patient with DLE may indicate an increased risk of development of SLE. Anti-histone antibodies are commonly associated with drug-induced SLE.

Antiphospholipid antibodies, including lupus anticoagulant antibodies, anticardiolipin antibodies, and $\beta_2$-glycoprotein-I antibodies, are present in the context of antiphospholipid antibody syndrome (i.e., venous and/or arterial thrombosis, thrombocytopenia, and recurrent spontaneous abortions). SLE is the most common underlying disorder in secondary antiphospholipid antibody syndrome. In addition, many patients with SLE will demonstrate autoantibodies to these and other phospholipid antigens without meeting diagnostic criteria for antiphospholipid antibody syndrome.

4.4 Other Laboratory Findings

Many SLE patients will exhibit a mild to moderate degree of anemia, usually normocytic or normochromic. Leukopenia is present in about 17% of patients. Lymphopenia may be seen during disease flare-ups. Inflammatory markers such as the erythrocyte sedimentation rate are markedly elevated during SLE disease activity. C-reactive protein has a complicated relationship with SLE disease activity and is thought to be used best as a biomarker of bacterial infection in the setting of SLE. Elevated serum $\gamma$-globulin is found in 80% of patients with active disease. Rheumatoid factor is present in 14% of patients, and mixed IgG-IgM cryoglobulins are found in 10%. Serum complement levels are usually depressed during active disease.

5. Treatment of Cutaneous LE

As many drug classes have now been implicated as inducers of cutaneous LE, particularly SCLE (table I), consideration should be given to discontinuing any such suspected medications. Smoking cessation should also be encouraged, as evidence indicates that smoking can directly exacerbate LE disease activity and interfere with the efficacy of therapy with antimalarial agents.

5.1 Photoprotection

As cutaneous LE is highly photosensitive, and as both cutaneous and systemic disease flare-ups may be triggered by UV radiation, sun-protective counseling will benefit all LE patients. Patients should be advised to avoid prolonged direct sun exposure, particularly during the middle of the day and in...
summer. Use of protective clothing, including tightly woven clothing and a broad-brimmed hat, should be encouraged. Generous application of sunscreens offering physical and chemical blocking components protecting against both UVA and UVB are essential, with reaplication every 2 hours if outdoors. Sunscreens containing titanium dioxide or zinc oxide (physical blocking agents) and avobenzone or ecamsule (chemical blocking agents) of sun protection factor ≥30 are encouraged. Sun exposure while operating a vehicle can be significant for LE patients, so these protective strategies should be observed while driving.

5.2 Corticosteroids

Topical corticosteroids may be helpful in the treatment of cutaneous LE but are usually inadequate as monotherapy. Medium potency (e.g. triamcinolone acetonide 0.1%) to high potency (e.g. clobetasol propionate 0.05% and betamethasone dipropionate 0.05%) may be used twice daily. Vehicles include ointments, creams, foams, lotions, solutions, and gels. The choice of a specific vehicle may relate to occlusiveness and physician/patient preference. One controlled trial has shown increased efficacy of a high-potency topical corticosteroid (fluocinonide 0.05% cream) compared with a low-potency topical corticosteroid (hydrocortisone 1% cream). Use for 2 weeks followed by a 1- to 2-week rest period may limit cutaneous adverse effects such as atrophy and telangiectasia. Systemic absorption is possible with widespread application of high-potency formulations. In cutaneous LE, the potential benefit of higher-potency corticosteroids on atrophy-prone areas such as the face may outweigh the risk of disfiguring skin disease.

Intralesional corticosteroid therapy (e.g. triamcinolone solution 5–10 mg/mL) may be used for localized areas of cutaneous LE. Localized hypertrophic discoid lesions, or particularly recalcitrant or symptomatic lesions of other forms of LE, may be particularly amenable to this modality. Persistent subcutaneous atrophy is a notable risk. Most patients with SCLE or extensive CCLE will have too many lesions for this approach to be practical.

Oral corticosteroids (e.g. prednisone as a 1 mg/kg burst, with tapering over 2–4 weeks) may be helpful in gaining control of a problematic flare-up, but are not recommended for routine use because of the temporary effects and likely dose-related adverse effects, including osteoporosis and adrenal suppression. Osteonecrosis, which is associated with SLE, can be a rare complication of even brief courses of systemic corticosteroids. Oral corticosteroids may be particularly appropriate as temporary therapy while beginning slower-acting corticosteroid-sparing medications. However, every effort should be made to identify a corticosteroid-sparing treatment regimen for long-term management.

5.3 Topical Calcineurin Inhibitors

Topical tacrolimus ointment and pimecrolimus cream have shown efficacy in treating cutaneous LE. Case reports and case series have shown efficacy in the treatment of DLE, SCLE, and the malar eruption of ACLE. The thicker cutaneous lesions of DLE may be less likely to respond as a result of poor penetration. These medications tend to be well tolerated and moderately effective. One randomized trial demonstrated similar efficacy of tacrolimus ointment to clobetasol in treating facial LE. These agents have an excellent profile of cutaneous safety and are particularly useful in treating atrophy-prone areas on the face, eyelid, and intertriginous skin, where long-term topical corticosteroid use should be limited. The use of these medications in treating cutaneous LE has recently been reviewed.

5.4 Topical Retinoids

Hyperkeratotic lesions of DLE may respond to topical retinoid therapy. Topical tretinoin and tazarotene have both been reported effective in individual case reports. Cutaneous irritation is the primary adverse effect.

5.5 Antimalarials

Oral aminoquinolone antimalarial agents have shown efficacy and a favorable safety profile in treating cutaneous LE. A randomized trial showed improvement of cutaneous LE in 15 of 30 (50%) patients treated with hydroxychloroquine after 8 weeks of therapy, and better tolerability compared with acitretin. Up to 75% of patients will demonstrate a response to single-agent or combination therapy. Hydroxychloroquine sulfate is the preferred agent because of its efficacy and tolerability. Initial therapy with hydroxychloroquine at 6.5 mg/kg/day in divided doses (typically 200 mg twice a day) generally shows a clinical response in 2–3 months. If an inadequate response is seen at that time, mepacrine (quinacrine) 100 mg/day can be added (mepacrine must be obtained from compounding pharmacies in the US). If the response to dual therapy remains inadequate after an additional 4–6 weeks, chloroquine 4 mg/kg/day (typically 250 mg/day) can be substituted for hydroxychloroquine.
Hydroxychloroquine and chloroquine should not be used together because of the increased risk of retinopathy.\textsuperscript{[3]} One study demonstrated clinical remission with the addition of mepacrine in five of six SLE patients who had been previously refractory to hydroxychloroquine, prednisone, azathioprine, and methotrexate.\textsuperscript{[86]} The milder systemic manifestations of SLE, including malaise, fatigue, and musculoskeletal symptoms, will often improve with antimalarials, as well. Antimalarials have also been shown to decrease the frequency of systemic disease flare-ups.\textsuperscript{[3]}

Once a clinical response is attained, the dosage of hydroxychloroquine can be reduced to 200 mg/day. Treatment for 1–2 years is recommended to fully suppress cutaneous LE activity.\textsuperscript{[3]} Cigarette smoking can reduce the efficacy of antimalarials through mechanisms that are not completely understood. Because of the possible retinopathic effects of hydroxychloroquine and chloroquine, ophthalmologic examination, including funduscopic examination and visual field testing, should be obtained at baseline and repeated at routine intervals (yearly for at-risk patients and every 5 years for uncomplicated patients).\textsuperscript{[87]} Routine laboratory monitoring of hematologic and hepatic function is commonly performed although seldom discloses medication-related abnormalities.

5.6 Other Systemic Medications

5.6.1 Conventional Medications

An evidence-based review of immunomodulating systemic medications for recalcitrant cutaneous LE was published in 2004.\textsuperscript{[88]} Options include thalidomide,\textsuperscript{[89,90]} methotrexate,\textsuperscript{[91–93]} azathioprine,\textsuperscript{[94]} dapsone,\textsuperscript{[95–104]} clofazimine,\textsuperscript{[105]} cyclosporine (ciclosporin),\textsuperscript{[106,107]} cyclophosphamide,\textsuperscript{[108]} sulfasalazine,\textsuperscript{[109]} and retinoids.\textsuperscript{[110–117]} Gold and interferon-\(\alpha\) are seldom used currently because of a low benefit-to-risk ratio.\textsuperscript{[118]} Much of the data to support the use of these medications derive from anecdotal case reports and relatively small case series, with few randomized, controlled trials available. These medications are often used in combination with oral corticosteroids and/or antimalarials. Some of the reports regarding these medications have been conducted for noncutaneous therapy of patients with refractory SLE, with observation of the cutaneous effects in addition to other organ systems.\textsuperscript{[93,96,98,102,105]} Clinical experience is probably greatest with methotrexate and thalidomide.

Methotrexate

Methotrexate is a dihydrofolate reductase inhibitor that is administered most commonly as a single weekly oral dose. If a single dose is not tolerated, most often because of gastrointestinal adverse effects, patients can often accommodate two or three divided oral doses 12 hours apart. Methotrexate can also be administered subcutaneously, intramuscularly, or intravenously. In a retrospective study of 139 patients with refractory cutaneous LE, 42 of 43 (98\%) patients treated with low-dose methotrexate showed a positive clinical response. Treatment-associated adverse effects necessitating discontinue of therapy occurred in seven patients (16\%).\textsuperscript{[91]}

Prior to this study, a 2001 review of 14 clinical trials involving 207 patients with cutaneous LE or SLE found methotrexate (usually in weekly doses of 10–20 mg) to be generally effective and well tolerated.\textsuperscript{[93]} Bone marrow suppression and hepatotoxicity are the most serious adverse effects. Methotrexate is also associated with pulmonary fibrosis, gastrointestinal disturbance, impaired fertility, and teratogenicity.

Thalidomide

Thalidomide is arguably the most uniformly beneficial and rapid-acting agent in the treatment of cutaneous LE. In a prospective trial of 48 patients with DLE (18), SCLE (six), or SLE with cutaneous disease (24), the overall response rate to thalidomide was 81\%, with remission achieved in 60\%.\textsuperscript{[89]} In a retrospective study of 65 patients with refractory cutaneous LE treated with thalidomide, 63 (97\%) showed a complete or partial response to therapy.\textsuperscript{[90]} Between these two studies, peripheral neuropathy occurred in over one-third of patients (41 of 113; 36\%).\textsuperscript{[90]} Peripheral neuropathy, primarily affecting sensory nerves, is a major concern. This typically presents as loss of sensation of the distal limbs, with painful paresthesia of the hands and feet, and may be irreversible. In addition to the well known risk of teratogenicity, thalidomide has also been implicated in producing secondary amenorrhea and a hypercoagulable state. Sedation and constipation are common adverse effects.

Azathioprine

In a series of six patients with recalcitrant cutaneous LE (four with SCLE and two with DLE), four (67\%) responded to treatment, though one developed medication-related pancreatitis.\textsuperscript{[94]}

Dapsone

In a 1986 study, 16 of 33 (48\%) patients with DLE showed a clinical response to dapsone, with half of those patients showing an excellent response.\textsuperscript{[101]} Dapsone may be particularly useful in the treatment of highly inflammatory forms of LE, such as bullous SLE and lupus profundus,\textsuperscript{[55,102,103]} and some cases of inflammatory DLE.\textsuperscript{[104]} Hematologic, renal, and hepatic toxicity may occur, and laboratory monitoring is required.\textsuperscript{[95–104]}

Oral Retinoids

Oral retinoids, including isotretinoin and acitretin, both given at a dosage of approximately 0.5–1 mg/kg/day, have
shown efficacy in treating cutaneous LE,[110-117] particularly hyperkeratotic or verrucous LE.[113-116] In a 1986 US study, eight of ten patients with CCLE or SCLE improved during a 16-week course of isotretinoin (80 mg/day).[110] In a 1988 German study, 15 of 20 patients with cutaneous LE (including five with SCLE) showed good clinical response to acitretin.[117] In a 1989 Italian study of 23 patients with cutaneous LE (19 with CCLE and four with SCLE), 20 (87%) improved with a 16-week course of isotretinoin at a maximal dosage of 0.5 mg/kg/day.[112] In a 1991 study, six of six patients who had responded poorly to prednisone and antimalarials improved with isotretinoin at a dosage of 1 mg/kg/day.[113] However, it has been our experience that systemic retinoids are not a practical long-term strategy for treating cutaneous LE, considering the high frequency of adverse effects resulting from mucocutaneous dryness and the rapid relapses of cutaneous LE activity following withdrawal of these agents. Isotretinoin and acitretin are both highly teratogenic, necessitating careful attention to contraception.

Clofazimine

In a comparative study, clofazimine was associated with significant improvement in the cutaneous manifestations of SLE in 12 of 16 (75%) patients and was comparable to the response of patients treated with chloroquine (14 of 17; 82%).[105]

Mycophenolate Mofetil

Reports on the efficacy of mycophenolate mofetil are mixed. Two patients with SCLE resistant to corticosteroids, antimalarials, and azathioprine showed a good response to this medication.[119] However, a recent case series and systematic review found that mycophenolate mofetil had minimal evidence to support a beneficial effect of the medication for cutaneous LE.[120,121]

5.6.2 Newer Immunomodulatory Agents

A recent study of DLE patients showed clinical improvement in 12 of 13 patients treated with subcutaneously injected efalizumab,[122] a monoclonal antibody to CD11a approved for the treatment of psoriasis. Efalizumab also improved the malar eruption of SLE and the eruption of SCLE in single case reports.[123,124] Efalizumab has also been reported to induce SCLE.[125] Efalizumab was voluntarily withdrawn from the market in 2009 due to three cases of progressive multifocal leukoencephalopathy in patients who had taken this medication over 3 years.

Although cutaneous LE has been reported to respond to treatment with injectable anti-tumor necrosis factor (TNF) agents,[126] it should be noted that anti-TNF agents have been frequently associated with triggering drug-induced cutaneous LE,[127,128] with 92 anti-TNF-induced cases in one series.[129] Intravenous immunoglobulin therapy has shown promising results. In a case series of 12 patients with cutaneous LE, a complete or near-complete response was seen in five patients (42%) and a partial response was seen in two (17%).[130] In addition, four cases of refractory SCLE responded to intravenous immunoglobulin.[131,132]

A single case of refractory cutaneous SLE showed a positive response to rituximab, a chimeric antibody directed against CD20 on the surface of B cells.[133] A recent controlled trial showed no benefit of testosterone patches in treating SLE.[134]

Recent work by several groups has demonstrated that class I interferon signaling is upregulated locally in cutaneous disorders, including LE-specific skin disease, that display a lichenoid tissue reaction/interface dermatitis histopathologic pattern.[135,136] This may explain the observed cases of SLE induced or unmasked during interferon therapy.[137-139] This raises the possibility that therapeutic modulation of class I interferon signaling might have a beneficial impact on LE-specific skin disease. Early clinical trials of an interferon-α-neutralizing recombinant monoclonal antibody MEDI-545 (MedImmune, Gaithersburg, MD, USA) are currently underway for SLE and other autoimmune disorders.

6. Conclusions

Cutaneous LE may occur in association with systemic LE, may portend systemic LE, or may stand alone as a skin-limited disease. These manifestations may interrelate in an intricate manner. Regardless of the particular context, cutaneous LE is often associated with significant morbidity for patients. The variations in clinical presentation may pose a diagnostic challenge for physicians. The multiple treatment options available, common associated adverse medication effects, and the clinical variability in treatment response among patients also present significant therapeutic complexities. The authors hope this review will be of assistance to other clinicians in navigating these challenges.

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