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Cutaneous Lupus Erythematosus: Diagnosis and treatment

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Abstract

Cutaneous lupus erythematosus encompasses a wide range of dermatologic manifestations, which may or may not be associated with the development of systemic disease. Cutaneous lupus is divided into several subtypes, including acute cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, and chronic cutaneous lupus erythematosus. Chronic cutaneous lupus erythematosus includes discoid lupus erythematosus, lupus erythematosus profundus, chilblain cutaneous lupus, and lupus tumidus. Diagnosis of these diseases requires proper classification of the subtype, through a combination of physical exam, laboratory studies, histology, antibody serology, and occasionally direct immunofluorescence, while ensuring to exclude systemic disease. Treatment of cutaneous lupus consists of patient education on proper sun protection along with appropriate topical and systemic agents. Systemic agents are indicated in cases of widespread, scarring, or treatment-refractory disease. In this review, we discuss issues in classification and diagnosis of the various subtypes of CLE, as well as provide an update on therapeutic management.

Keywords

Cutaneous lupus erythematosus; Acute cutaneous lupus erythematosus; Subacute cutaneous lupus erythematosus; Chronic cutaneous lupus erythematosus; Discoid lupus erythematosus; lupus erythematosus profundus; Chilblain cutaneous lupus erythematosus; Lupus erythematosus tumidus; Systemic lupus erythematosus; Treatment; Diagnosis

A. Introduction

The autoimmune disease lupus erythematosus is associated with a broad range of cutaneous pathology. Cutaneous manifestations are frequently the presenting sign of lupus erythematosus (LE), and in the case of certain cutaneous lupus erythematosus (CLE) subtypes, they can occur in the absence of systemic disease. CLE is two to three times more frequent than SLE [1]. Similar to proposed etiologies for SLE, current theories discuss a multifactorial relationship leading to the development of cutaneous lupus including genetic susceptibility, autoimmune induction, and immune system damage.

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B. How is CLE currently classified?

At present, dermatologists use the only universally accepted criteria for the classification of SLE, which was set forth by the ACR. This scheme of eleven clinical and lab criteria was developed by rheumatologists for the purpose of distinguishing SLE from other autoimmune diseases. The ACR guidelines require four of eleven criteria to be met for a diagnosis of SLE, however, four of the criteria are cutaneous in nature (malar rash, discoid lesions, mucosal ulcers, and photosensitivity), which, some authors argue, skews diagnosis patterns in patients with exclusively cutaneous involvement. A 2012 multicenter database analysis from the European Society of CLE (EUSCLE) found that 48% of patients with four or more ACR criteria had CLE without systemic symptoms and concluded that the ACR criteria were inadequate in distinguishing CLE from SLE [2]. A dermatology position paper on the ACR criteria specifically questioned the usefulness of photosensitivity in SLE, as lesions can be delayed in onset and thus potentially not attributed to sun exposure, and is similarly seen in diseases such as dermatomyositis [3]. A Swedish population based study found that 25% of CLE patients previously held an SLE diagnosis, and that 20% of newly diagnosed CLE patients received a diagnosis of SLE within three years. Notably, the authors used ICD-9 codes without knowledge of how these diagnoses were made. Furthermore, many of these patients with an SLE diagnosis had very mild systemic symptoms or limited skin disease [4]. Wieczorek *et al* observed that patients with CLE who progress to SLE typically meet the mildest of SLE criteria [5]. In 2012, the Systemic Lupus International Collaborating Clinics Classification Criteria (SLICC) was proposed as an updated method for diagnosing SLE, including the revised dermatologic criteria of ACLE, CCLE, oral ulcers, and nonscarring alopecia. This validated SLICC criteria is undergoing further comparative testing with the ACR SLE criteria in various populations [6]. In addition, there is ongoing controversy over the classification of the cutaneous manifestations of LE from a dermatologic vantage point.

Gilliam proposed a classification system that separated LE-specific lesions from LE-nonspecific lesions, based on histopathology. The various morphologies of CLE fall under the umbrella of LE-specific lesions, including acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE). CCLE encompasses discoid LE (DLE), LE profundus (LEP), chilblain LE (CHLE), and LE tumidus (LET) [7]. The Duesseldorf Classification in 2004 proposed a separate category for LET, entitled intermittent cutaneous LE (ICLE), although this division is not universally accepted [8]. LE-nonspecific lesions, on the other hand, include findings that are not characteristic of, but are frequently seen in SLE. Such lesions include Raynaud's phenomenon, periungual telangiectasias, livedo reticularis, and leukocytoclastic vasculitis.

C. How can we differentiate the CLE subtypes?

a. Acute Cutaneous Lupus Erythematosus

Acute cutaneous LE typically presents in the third decade of life and is frequently associated with active SLE [9] and [10]. There are localized and generalized forms of ACLE. The localized form is the frequently described malar, or "butterfly" rash, which refers to erythema that occurs over both cheeks, extends over the nasal bridge, and spares the nasolabial folds [11]. These lesions are classically transient, sun-induced, and non-scarring, although dyspigmentation can occur [12]. Patients may initially mistake this rash for a sunburn, and only seek medical attention when it persists for several days. A fine surface scale and/or edema may be associated with the erythema. Malar rashes have been reported to be present in up to 52% of SLE patients at the time of diagnosis, with clinical activity of the rash paralleling that of the systemic disease. This rash can be confused with acne rosacea

and seborrheic dermatitis, however the former is associated with the formation of papules and pustules, and the latter occurs within the nasolabial folds [13].

The more rare generalized form occurs above and below the neck, and has been referred to as a 'maculopapular rash of lupus' or 'photosensitive lupus dermatitis.' This presents as an often pruritic, widespread eruption of symmetric macules and papules that is photosensitive and may resemble a drug rash. Patients may have associated mucosal ulcerations/apthae, as well as diffuse hair thinning [14]. Generalized ACLE may resemble dermatomyositis as both diseases involve the dorsum of the hands, however, dermatomyositis affects the distal interphalangeal, proximal interphalangeal, and metacarpophalangeal joints, while they are spared in ACLE [13]. Cuticular overgrowth, as well as erythema or dilated vessels and drop-out of vessels in the periungual area are frequently seen. Lesions resembling erythema multiforme in ACLE or SCLE patients have been termed Rowell's syndrome [15]. Rarely, a severe acute form can resemble toxic epidermal necrolysis. Other differentials include drug-induced photosensitivity, pemphigus erythematosus, atopic dermatitis, contact dermatitis, and photocontact dermatitis.

Histologically, ACLE lesions show liquefactive degeneration of the basal layer, edema of the upper dermis, and a scattered interface, perivascular, and periadnexal lymphocytic infiltrate, all of which are generally less pronounced as compared to other CLE subtypes. Immunologically, a positive ANA is found in 95% of ACLE patients, as well as a high incidence of anti-dsDNA and anti-Sm antibodies [16]. Lesional direct immunofluorescence reveals granular immune deposits at the dermal-epidermal junction and perivascular deposits in the upper dermis, most commonly IgM [9].

b. Subacute Cutaneous Lupus Erythematosus

As with SLE, Subacute Cutaneous Lupus Erythematosus (SCLE) occurs primarily in young to middle aged women [11]. SCLE is highly photosensitive, with 70-90% of patients meeting the ACR definition of abnormal photosensitivity [17]. There are two morphologic variants of SCLE: annular and papulosquamous. A study of 58 SCLE patients found that 42% had annular SCLE and 39% exhibited papulosquamous SCLE, while 16% of patients showed features of both [18]. Other studies have found more papulosquamous SCLE [19] and [20]. The annular type is characterized by scaly annular erythematous plaques, which tend to coalesce and produce a polycyclic array [11]. The papulosquamous variant can resemble eczema or psoriasis, as well as pityriasis in some instances [12] and [21]. SCLE lesions occur in sun-exposed areas, including the upper thorax ('V' distribution), upper back, and the extensor surfaces of arms and forearms. The central face and scalp are usually spared, and lesions typically do not occur below the waist [11]. The cutaneous lesions are not indurated and heal without scarring, although vitiligo-like hypopigmentation may occur [22]. The differential diagnosis for SCLE also includes dermatomyositis, cutaneous T-cell lymphoma, tinea corporis, erythema annulare centrifugum, erythema gyratum repens, photolichenoid drug eruption, granuloma annulare, and pemphigus foliaceus. Many of these lesions have similar appearances, and histologic examination is often necessary for differentiation.

An estimated 50% of SCLE patients meet criteria for SLE [23]. Patients with SCLE usually have only mild systemic symptoms, most commonly arthritis and myalgias, while severe systemic symptoms, such as lupus vasculitis, CNS lupus, and nephritis occur in less than 10% [24]. Immunologically, 70% of SCLE patients are anti-Ro (SS-A) positive, and overlap between Sjogren's syndrome and SCLE has been seen [12]. A multicenter study found 70-80% of SCLE patients were ANA positive, and only 5% had anti-dsDNA [16]. SCLE is frequently associated with the existence of human lymphocyte antigen (HLA)-DR3 [25]. Drug-induced SCLE is more common than in other subtypes, with terbinafine, tumour

necrosis factor- α inhibitors, antiepileptics, and proton pump inhibitors the most frequently reported culprits found in a 2012 population-based match case control study [26]. Pathologic examination of SCLE lesions demonstrates hydropic degeneration of the basal keratinocytes, dermal edema, hyperkeratosis, follicular plugging, and a sparse superficial inflammatory infiltrate [10]. The presence of “dust-like particles” representing IgG deposits on DIF is a highly specific but not sensitive finding in SCLE [27].

c. Chronic Cutaneous Lupus Erythematosus

Chronic cutaneous lupus includes discoid LE (DLE), LE profundus (LEP), chilblain LE (CHLE), and LE tumidus (LET).

i. Discoid Lupus Erythematosus—Discoid lesions are the most common lesions of CCLE. DLE occurs more frequently in women in their fourth and fifth decade of life [11]. Patients with DLE generally have a more benign disease course as compared to patients with other CLE subtypes, with only a reported 5-10% developing SLE throughout their disease course [28,29]. Studies have shown that patients with generalized DLE are more likely to progress to systemic disease, compared to patients with localized DLE [9,30]. Localized DLE commonly involves the head and neck, and particularly the scalp and ears. Generalized DLE, which occurs both above and below the neck, is less common and typically involves the extensor forearms and hands [11]. Occasionally, DLE can occur on mucosal surfaces, including lips, and oral, nasal, and genital mucosa. DLE lesions appear as a well-demarcated, scaly, erythematous macule or papule, which gradually develops into an indurated discoid (coin-shaped) plaque with an adherent scale that is painful to remove. Plaques tend to extend into the hair follicle, resulting in scarring alopecia. Through time, these lesions typically become atrophic, with hyperpigmentation peripherally and depigmentation centrally. Sun exposure or trauma (Koebner phenomenon) can exacerbate disease. Squamous cell carcinoma can occur within a DLE lesion [31]. Discoid lesions are very distinct in appearance from other entities, however the early indurated erythematous plaques of DLE can resemble those of psoriasis, lymphocytoma cutis, cutaneous T-cell lymphoma, granuloma faciale, polymorphous light eruption eruption, and sarcoidosis [32]. Buccal mucosal DLE may mimic lichen planus, however the former has a radial brush-like appearance originating from a central area of erythema [22]. An uncommon variant of DLE, hypertrophic or verrucous DLE, refers to extremely thickened lesions occurring on the arms, hands, and face. These lesions have features in common with keratoacanthomas and hypertrophic lichen planus.

Histologic examination of a longstanding active DLE lesion reveals hyperkeratosis, dilated compact keratin-filled follicles, vacuolar degeneration of the basal keratinocytes, and an intensely inflammatory dermal infiltrate. Serologically, DLE patients have a lower incidence of ANA, dsDNA, Sm, U1RNP, and Ro/SSA antibodies, as compared to other CLE subtypes [32]. Ninety percent of DLE lesions have a positive lupus band test, with C3 and IgM as the most common immune deposits [14].

ii. Lupus Erythematosus Profundus—LE profundus (LEP), or panniculitis, features painful firm subcutaneous nodules with occasionally overlying DLE occurring in areas of increased fat deposition, such as the upper arms and legs, face, and breasts. LEP tends to have a chronic course, characterized by remission and flares, and ultimately leaving atrophic scars [10]. Histology shows lobular panniculitis with a dense lymphocytic infiltrate. Biopsy is critical in these cases, as lesions have frequently been shown to closely resemble subcutaneous lymphoma [33]. Biopsy specimens should be reviewed by a dermatopathologist, as diagnosis can be difficult, occasionally requiring the use of cell markers and gene rearrangements.

iii. Chilblain Lupus—Chilblain Lupus (CHLE) is a rare form of CLE resembling frostbite. Lesions appear as painful, violaceous plaques and nodules in cold-exposed areas. Central erosions or ulcerations may occur on acral surfaces, such as fingers, toes, heels, nose, and ears. Chilblain lupus occurs when there is a temperature drop, and can be difficult to distinguish from frostbite. Pathology shows epidermal atrophy, interface vacuolization, and a perivascular mononuclear infiltrate. Twenty percent of patients with CHLE develop features of SLE at some point in their disease course [34].

iv. Lupus Erythematosus Tumidus—Lupus tumidus is a subtype of CLE characterized by extreme photosensitivity and a benign course occurring preferentially in men. Clinically, these lesions appear on the face as erythematous, edematous, urticaria-like polycyclic plaques with sharp raised borders and smooth surfaces. Unlike classic DLE lesions, follicular plugging does not occur. Histologically, these lesions exhibit a dense perivascular and periadnexal infiltrate without involvement of the interface. DIF testing is typically negative, and 10% of patients are ANA positive [35]. Some authors have suggested a separate category for LET, entitled Intermittent Cutaneous Lupus Erythematosus (ICLE), but there is not agreement and there are some who feel this could also be a lupus-associated skin disease [22].

D. How can we properly diagnose CLE?

In order to properly diagnose cutaneous manifestations of LE, the physician must first correctly classify the subtype and exclude systemic involvement of the disease. As discussed earlier, diagnosis based solely on ACR criteria should be avoided, as the ACR criteria was designed to distinguish between the various autoimmune diseases. Rather, CLE diagnosis should be based on the findings of patient history, clinical exam, laboratory studies, serology, as well as histology and direct immunofluorescence (DIF) exam of skin biopsies if the histology is not diagnostic.

Detailed skin examination is crucial for classifying the CLE subtype. Over 60 schemes for measuring disease activity have been devised, all of which were deemed to be of limited utility for dermatologists in a review by Liang *et al* [36,37]. In 2005, Albrecht *et al* developed the Cutaneous Lupus Area and Severity Index (CLASI), a system for quantitatively measuring disease activity and damage [38]. This index, which accounts for lesional morphology as well as anatomic location, has since been validated by reliability testing for both dermatologists and rheumatologists [39]. A large study by Jolly *et al* further validated the CLASI tool, which has proven to be a valuable resource for research into CLE pathogenesis and treatment [40]. This tool is being used in many international studies and has been shown to be responsive to improvement in disease activity, as well as correlate with quality of life and a number of biomarkers [41-45]. Further physical exam should investigate for signs that may be seen in systemic disease, such as vasculitic lesions. Blood tests can be individually tailored based on the level of suspicion for systemic involvement. Complete blood count (CBC) should be performed to evaluate for anemia, thrombocytopenia, or leukopenia, which could be related to systemic LE. It is important to screen for renal disease with serum creatinine, serum urea, and urinalysis. Antibody testing is critical and should begin with an ANA screen. A negative ANA is useful in that it is rare for patients with SLE to test negative, while a positive ANA can be seen in patients with CLE, with or without systemic disease. Furthermore, a positive ANA is seen in up to 35% of apparently normal individuals at a dilution of 1:40, particularly in the elderly [46]. Further autoantibody profile yielding positive dsDNA, Sm, and ribosomal P is highly specific for SLE, and these autoantibodies serve as markers for the development of systemic disease. Autoantibodies to Ro, La, U1RNP, histones, and ssDNA can be seen in SLE, but they are not disease-specific.

The cornerstone of CLE diagnosis is a lesional biopsy for histology. Histologic findings vary by subtype, but in general CLE lesions share the features of vacuolar or hydropic change and lymphocytic infiltrates. Direct immunofluorescence (DIF) of lesional biopsies can supplement non-definitive histologic findings. The lesional lupus band test refers to the finding of immunoglobulins and complement at the dermal-epidermal junction of a lesional biopsy, a classic finding in CLE. Deposits are typically granular in appearance, and most commonly contain IgG and IgM, although IgA can be found [47]. Although CLE lesions generally have a positive lesional lupus band test, a negative test does not exclude the diagnosis. Likewise, a positive lesional lupus band test does not secure the diagnosis, as false positive tests can occur in sun-damaged skin. In most cases, clinical and histologic findings provide sufficient information to make a diagnosis of CLE, and therefore a DIF is usually unnecessary. Non-lesional lupus band tests are seen in SLE, and have been reported in multiple other autoimmune diseases, including rheumatoid arthritis, Sjogren's syndrome, dermatomyositis, scleroderma, and leprosy [13]. With improved serum lupus serologies, a lupus band test is no longer considered a helpful test in determining whether a patient has SLE.

Photoprovocation is a potential adjunct to histopathological diagnosis of CLE subtype. Standardized photoprovocation testing in a multicenter trial demonstrated that lesions were inducible in half of CLE patients, however may not be reproducible, and the authors suggested that UVA and UVB exposure may be a clinically and academically useful means for evaluating photosensitivity and disease activity [48,49].

E. How is CLE treatment approached?

a. Prevention

In treating CLE, dermatologists aim to prevent the formation and progression of lesions, and to improve skin appearance through a combination of patient education, and topical and systemic therapies (Fig 1). Patient education on heat, sun, and drug avoidance is standard. Patients should be advised to avoid manipulation of lesions, as this can induce new lesions [12]. Makeup products such as Dermablend or Covermark should be offered to camouflage lesions. Strict sunscreen adherence is a critical component of therapy, as UVA and UVB irradiation has been shown to induce CLE lesions [50]. Sufficient amounts of sunscreen ($2\text{mg}/\text{cm}^2$) with a sun protection factor (SPF) of at least 50 should be applied 20-30 minutes prior to expected exposure. This recommendation is based on the findings of a vehicle-controlled, randomized, double-blind trial of 25 photosensitive CLE patients, which reported 100% protection from UVA and UVB irradiation with broad spectrum sunscreen [51]. Physical sunscreens such as titanium dioxide or zinc oxide provide particularly good broad-spectrum protection. Some patients experience photosensitivity behind glass windows, through which UVA rays are penetrable, and in these cases, UV-blocking films can be applied and sunscreens that contain Mexoryl XL will be particularly critical for blocking UVA wavelengths [12]. Patients should be advised to avoid tanning, sunbathing, outdoor employment, and travel to regions near the equator. Klein et al analyzed the UV exposure risk of indoor fluorescent light bulbs exacerbating photosensitive disease, and concluded that the lowest UV irradiance should be used to minimize cumulative dose [52]. Some compact fluorescent bulbs emit more UVB than incandescent bulbs, and thus shielding of bulbs is important [53]. It is important to consider the risk of vitamin D deficiency in sun-avoiding patients, as sunlight is required for vitamin D synthesis. 25-hydroxyvitamin D levels should be monitored and supplementation with at least 400 IU of Vitamin D₃, or cholecalciferol, is advised [54].

b. Topical Therapies

Treatment of CLE lesions should begin with topical therapies, including steroids and/or calcineurin inhibitors. Despite the longstanding use of topical corticosteroids, only one randomized controlled trial examining efficacy in CLE exists. In a 12-week cross-over study of 78 DLE patients, excellent improvement or resolution of lesions was seen in 27% of patients treated with fluocononide 0.05% cream, as compared to 10% of patients treated with hydrocortisone 1% cream at 6 weeks. These findings support the improved efficacy of high-dose over low-dose steroids [55,56]. However, in light of the common side effects of topical steroids, such as atrophy, telangiectasia, and steroid-induced dermatitis, the lowest potency allowing for resolution should be used for the shortest duration possible. Potency and vehicle are important considerations in selecting an appropriate topical steroid. Low potency steroids, such as hydrocortisone 1% or fluocinolone acetonide 0.01% can be used for thin-skin areas, including the face and groin. Mid potency steroids, such as triamcinolone acetonide are appropriate for the trunk and extremities. For thick skin areas, including the scalp, palms, and soles, high-potency steroids, such as clobetasol propionate, should be chosen. Topical steroids are often prescribed as creams, as they are a more tolerable form of application. Patients with more severe disease may require ointments. Foams and solutions are appropriate for lesions on the scalp. Intralesional injections of triamcinolone may be beneficial in patients with refractory localized DLE [57].

Calcineurin inhibitors have emerged in recent years as an alternative topical option for various CLE subtypes. A double-blind, randomized controlled trial treated half the face of 20 patients with tacrolimus 0.1% ointment and the other half with clobetasol propionate 0.05% ointment. The two ointments showed equal efficacy, however 61% of patients developed telangiectasias on the clobetasol side as early as week 3, indicating that tacrolimus may be a better option as it lacks the inherent side effects of steroids [58]. In another randomized, vehicle-controlled multicenter trial, 20 patients with CLE lesions treated with tacrolimus 0.1% ointment showed significant improvement after 28 and 56 days, but not after 84 days [59]. Topical calcineurin inhibitors have a 'black box' warning for a heightened risk of malignancy, although there is no evidence to suggest a causal relationship [60].

R-salbutamol is a beta2-adrenergic receptor agonist used for the treatment of asthma. A 2009 multicenter randomized-controlled trial investigated the use of R-salbutamol in the treatment of DLE and found statistically significant improvements in pain, itch, scaling, ulceration, and global assessment as compared to placebo. There was, however, no significant change in the primary endpoint, the modified Localized Cutaneous Lupus Area and Severity Index (LCLASI) score, an unvalidated outcome measure [61].

Physical treatments for CLE include laser therapy, cryotherapy, and dermabrasion. The efficacy of pulsed-dye and argon laser has been shown in several case reports and series. An open prospective study of 12 DLE patients treated with pulsed-dye laser demonstrated efficacy after 6 weeks of treatment [62]. Purpura, pain, and post-inflammatory pigmentary changes are reported side effects of treatment.

c. Systemic Therapies

Systemic therapies are indicated in cases where there is widespread or scarring disease, or in cases refractory to topical treatments. When systemic treatments are prescribed, topical agents are typically continued as adjunctive therapy. Presently, there are no medications specifically approved for the treatment of CLE. The drugs used for the treatment of the various subtypes of CLE are generally also used for the treatment of SLE, with the exception of thalidomide.

i. Antimalarial Drugs—Oral antimalarials are considered first-line systemic therapy for all CLE subtypes. Hydroxychloroquine, chloroquine, and quinacrine are the three currently used antimalarials. A 1992 randomized, double-blind, multicenter study compared hydroxychloroquine (400mg/day) with acitretin (50mg/day) in various CLE subtypes in an 8-week trial. The authors found that the 30 patients on hydroxychloroquine had a 50% improvement rate, as opposed to a 46% improvement rate in the 28 patients on acitretin, with hydroxychloroquine being much better tolerated [63]. The efficacy of chloroquine was shown in a 2005 double-blind, randomized controlled trial, demonstrating a response rate of 82.4% as compared to 75% in patients treated with clofazamine [64]. Antimalarials can take 2 to 3 months for maximum efficacy, and therefore patients are often bridged with topicals and intralesional injections.

Hydroxychloroquine sulfate is considered the drug of choice. At a dose of up to 6.5 mg/kg/day, it is considered safer than its more effective counterpart, chloroquine, due to a lower incidence of retinopathy. Chloroquine can be given at a dose of 125-250 mg/day, limited to no more than 3.5-4.0 mg/kg/day to minimize retinal toxicity. Hydroxychloroquine and chloroquine should not be used together, due to the unacceptable risk of retinopathy [14]. Typically, if a patient fails hydroxychloroquine, quinacrine is added for a synergistic effect, without an increased risk of retinopathy. This combination heightens efficacy, with a reported 67% improvement rate in patients who had previously failed hydroxychloroquine monotherapy [65]. If a patient fails this combination, a switch to chloroquine is considered. Quinacrine can be continued with chloroquine. Quinacrine is commonly prescribed at a dose of 100mg/day, as aplastic anemia has been reported at higher doses. Frances *et al* recently linked complete remission to higher blood concentrations of hydroxychloroquine, and suggested the implementation of monitoring to improve management of refractory CLE [66]. Patients who smoke have worse CLE and are more refractory to treatment with antimalarials and other systemic therapies. Patients should therefore be counseled on smoking cessation [67,68]. Side effects of antimalarials include xerosis, exanthematous or lichenoid drug eruptions, urticaria, blue-gray skin hyperpigmentation, ocular toxicity, gastrointestinal upset, myopathy, cardiomyopathy, and rare central nervous system side effects (dizziness, headache, insomnia, psychosis). Hydroxychloroquine may reduce the seizure threshold. Quinacrine can cause yellow discoloration of skin, sclera, and bodily fluids. The American Academy of Ophthalmology recommends regular retinopathy screening for patients on antimalarials at intervals based on risk status [69]. Antimalarial therapy is contraindicated in patients with pre-existing retinopathy, blood disorders, and myasthenia gravis [70].

ii. Systemic Corticosteroids—Patients that fail antimalarial combinations are often also refractory to other systemic treatments. Systemic corticosteroids are generally avoided in CLE patients due to the well-known side effects. LE patients are particularly susceptible to the side effects of steroids, as they are at increased risk of developing avascular necrosis at baseline. They may, however, be beneficial for short courses in patients with severe CLE, since other therapies may require time for onset of action. In such instances, doses of prednisone of 0.5 to 1.0mg/kg/day can be tapered over two to four weeks [71].

iii. Immunosuppressants—Approximately half of patients refractory to antimalarials respond to immunosuppressants [72]. Methotrexate is a therapy for CLE if antimalarials don't work, with recommended doses of 7.5 to 25mg orally or subcutaneously once a week [71]. A retrospective analysis of 43 treatment-refractory CLE patients treated with oral or subcutaneous methotrexate found improvement in 98% of cases. Seven patients developed severe side-effects necessitating withdrawal from treatment [73]. Potential side effects include gastrointestinal toxicity, bone marrow suppression, nephrotoxicity, hepatotoxicity,

and interstitial pneumonitis [71]. It is important to supplement patients taking methotrexate with folic acid.

Mycophenolate mofetil and mycophenolate sodium have been shown to be effective in treating all CLE subtypes in multiple case reports and small studies, including a prospective nonrandomized study of ten treatment-refractory SCLE patients treated with mycophenolate sodium [74]. Another suggested treatment option is azathioprine, which was shown to successfully treat DLE in several small case series [75-77].

iii. Biologics—Rituximab, a chimeric monoclonal antibody that targets CD20, has shown efficacy in case reports of refractory SCLE patients and SLE patients with cutaneous lesions [71]. Belimumab, a B lymphocyte stimulator specific inhibitor, demonstrated improved SLE disease activity on musculoskeletal and mucocutaneous parameters in data pooled from two phase III trials [78]. Further investigation is needed to determine the role of these and other immune response modifiers in the treatment of CLE.

iv. Immunomodulators—Dapsone (25 to 150mg/day) has shown to be effective in some cases series in the treatment of bullous LE, lupus panniculitis, SCLE, and DLE. The combined results of three case series of 55 CLE patients treated with dapsone demonstrated a 55% improvement rate [57]. Dapsone can cause agranulocytosis, hemolysis, methemoglobinemia, or a hypersensitivity reaction, and therefore monitoring for hematologic and hepatic toxicity is critical. Patients with glucose-6-phosphate dehydrogenase deficiency should not take dapsone.

Multiple case series support the use of thalidomide (50 to 100mg/day) in CCLE, SCLE, and tumid lupus erythematosus. Thalidomide is notoriously teratogenic and its use is limited by peripheral neuropathy, the incidence of which is maximal during the first year of treatment [79,80]. Lenalidomide, a thalidomide analogue, has recently been investigated as a potential alternative, showing clinical potential in a case series and two small open-label trials [81-83].

v. Oral Retinoids—Oral retinoid is an alternative therapy if antimalarials do not work. Acitretin has been shown to be effective in half of CLE patients in a randomized controlled trial, while isotretinoin's efficacy has been seen in multiple case reports [57]. Kuhn *et al* recently reported on the successful off-label treatment of three cases of various CLE subtypes with alitretinoin, which may prove to be an effective alternative therapy pending further investigation [84]. As these agents are highly teratogenic, it is critical to ensure the use of effective contraception in women of childbearing potential, both during and after treatment (one month for isotretinoin, two months for acitretin) [70]. Retinoids can also cause hyperlipidemia and hepatotoxicity, and therefore careful monitoring of lipids and liver function tests is necessary during treatment [14].

Summary

Cutaneous lupus erythematosus comprises a range of dermatologic manifestations, including acute cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, and chronic cutaneous lupus erythematosus. The ACR criteria, which include four cutaneous signs, may lead to overdiagnosis of SLE in patients with predominantly cutaneous disease. Diagnosis of CLE requires proper classification of the subtype, which is best accomplished by a focus on the clinical and histologic findings. Serology and direct immunofluorescence are less helpful in making the diagnosis. CLE treatment combines sun protection, topical therapies, and systemic agents. Antimalarials are considered first line treatment. Multiple agents are under investigation as alternative therapies.

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Practice Points

- The 11 ACR criteria, which include four cutaneous signs, may overestimate the incidence of SLE in patients with exclusively cutaneous disease.
- Approximately 50% of SCLE patients and 10% of DLE patients will meet criteria for SLE, while nearly all patients with ACLE will meet criteria SLE.
- Lesional biopsy is the cornerstone of CLE diagnosis. Direct immunofluorescence and serology are less helpful.
- Patient education regarding proper sun protection is a critical component of therapy.
- Treatment begins with topical agents, including steroids and/or calcineurin inhibitors.
- Systemic therapies are indicated in widespread, scarring, or treatment-refractory cases. Antimalarials are considered first line.

Research Agenda

- Future studies are needed to better define CLE within the continuum of LE, with recognition that CLE predominant patients may meet criteria for SLE but not be systemically ill.
- Discussion of revision of the CLE classification scheme is ongoing, with the suggestion that CLE may be better regarded as LE targeting the skin.
- Better insight into the pathogenesis of CLE might help direct future therapies.
- A significant minority of patients remain refractory or intolerant to traditional first line therapies. Randomized controlled trials are needed to assess the efficacy and safety of potential alternative therapies, including lenalidomide, anti-interferon alfa, and anti-CD4 antibody.

Fig. 1.

Algorithm for cutaneous lupus erythematosus treatment. Localized disease is initially treated with topical agents (either corticosteroids (CS) or calcineurin inhibitors (CI)).

Hydroxychloroquine (HCQ) is also often used, depending on the site or if there is scarring disease. Widespread or scarring disease treatment starts with topicals and HCQ. If this fails, quinacrine is added to HCQ. If this regimen fails, a switch to chloroquine (CQ) can be made, while continuing quinacrine. If this fails, other options include mycophenolate mofetil (MM) or mycophenolate sodium (MS), azathioprine, dapsone, retinoids and thalidomide can be considered. In the case of failure of these agents, experimental therapy can be considered.