Best Practice & Research Clinical Rheumatology 27 (2013) 391–404

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

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Cutaneous lupus erythematosus: Diagnosis and treatment

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Keywords:
Cutaneous lupus erythematosus
Acute cutaneous lupus erythematosus
Sub-acute cutaneous lupus erythematosus
Chronic cutaneous lupus erythematosus
Discoid lupus erythematosus
Lupus erythematosus profundus
Lupus erythematosus tumidus
Systemic lupus erythematosus
Treatment
Diagnosis

A B S T R A C T

Cutaneous lupus erythematosus (CLE) 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 sub-types, including acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE). CCLE includes discoid lupus erythematosus (DLE), LE profundus (LEP), chilblain cutaneous lupus and lupus tumidus. The diagnosis of these diseases requires proper classification of the sub-type, through a combination of physical examination, laboratory studies, histology, antibody serology and occasionally direct immunofluorescence, while ensuring to exclude systemic disease. The 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 chapter, we discuss issues in classification and diagnosis of the various sub-types of CLE, as well as provide an update on therapeutic management.

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Introduction

The auto-immune disease lupus erythematosus (LE) is associated with a broad range of cutaneous pathology. Cutaneous manifestations are frequently the presenting sign of LE, and in the case of certain cutaneous LE (CLE) sub-types, they can occur in the absence of systemic disease. CLE is two to three

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1521-6942/$ – see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.berh.2013.07.008

times more frequent than systemic lupus erythematosus (SLE) [1]. Similar to proposed aetiologies for SLE, current theories discuss a multifactorial relationship leading to the development of cutaneous lupus, including genetic susceptibility, auto-immune induction and immune-system damage.

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 American College of Rheumatology (ACR). This scheme of 11 clinical and lab criteria was developed by rheumatologists for the purpose of distinguishing SLE from other auto-immune diseases. The ACR guidelines require four of 11 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, skew diagnosis patterns in patients with exclusively cutaneous involvement. A 2012 multicentre 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 at the 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 3 years. Notably, the authors used ICD-9 (International Classification of Diseases, Ninth Revision) 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 acute CLE (ACLE), chronic CLE (CCLE), oral ulcers and non-scarring alopecia. This validated SLICC is undergoing further comparative testing with the ACR SLE criteria in various populations [6]. In addition, there is an 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 ACLE, sub-acute CLE (SCLE) and CCLE. The 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 leucocytoclastic vasculitis.

How can we differentiate the CLE sub-types?

Acute cutaneous lupus erythematosus

ACLE typically presents in the third decade of life and is frequently associated with active SLE [9,10]. There are localised and generalised forms of ACLE. The localised 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 oedema 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 generalised 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]. Generalised ACLE may resemble dermatomyositis as both the 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, oedema 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 sub-types. Immunologically, a positive ANA is found in 95% of ACLE patients, as well as a high incidence of anti-double-stranded DNA (anti-dsDNA) and anti-Sm antibodies [16]. Lesional direct immunofluorescence (DIF) reveals granular immune deposits at the dermal–epidermal junction and perivascular deposits in the upper dermis, most commonly immunoglobulin M (IgM) [9].

Subacute cutaneous lupus erythematosus

As with SLE, 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 [19,20]. The annular type is characterised by scaly annular erythematous plaques, which tend to coalesce and produce a polycyclic array [11] (Fig. 1). The papulosquamous variant can resemble eczema or psoriasis, as well as pityriasis in some instances (Fig. 2) [12,21]. 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 $<$10% [24]. Immunologically, 70% of SCLE patients are anti-Ro (SS-A) positive, and an overlap between Sjogren's syndrome and SCLE has been seen [12]. A multicentre study found that 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 sub-types, with terbinafine, tumour necrosis factor-α inhibitors, antiepileptics and proton pump inhibitors being the most frequently reported culprits found in a 2012 population-based matched case–control study [26]. The pathologic examination of SCLE lesions demonstrates hydropic degeneration of the basal keratinocytes, dermal oedema, 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].

Chronic cutaneous lupus erythematosus

Chronic cutaneous lupus includes DLE, LEP, CHLE and LET.

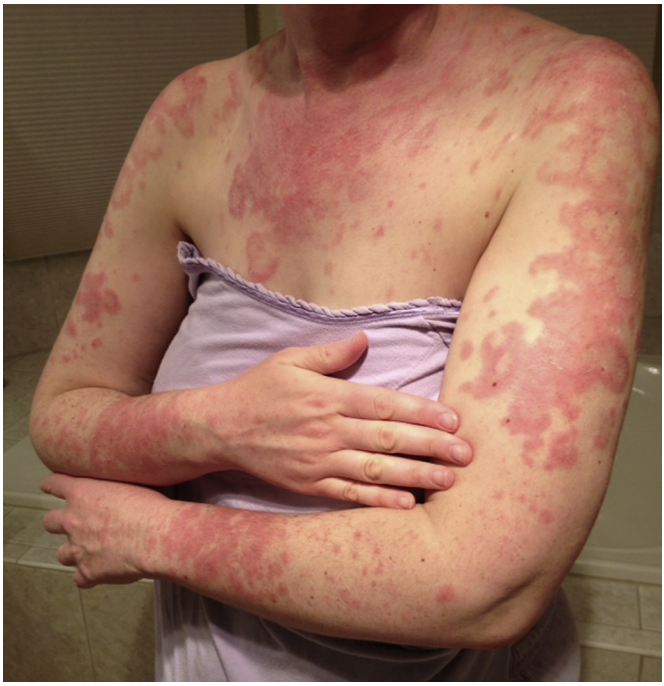

Fig. 1. SCLE, annular polycyclic. Scaly annular erythematous plaques coalesce into polycyclic arrays.

Discoid lupus erythematosus

Discoid lesions are the most common lesions of CCLE. DLE occurs more frequently in women in their fourth and fifth decades of life. [11] Patients with DLE generally have a more benign disease course as compared to patients with other CLE sub-types, with only a reported 5–10% developing SLE throughout their disease course [28,29]. Studies have shown that patients with generalised DLE are more likely to progress to systemic disease compared to patients with localised DLE [9,30]. Localised DLE commonly involves the head and neck and particularly the scalp and ears. Generalised 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 (Fig. 3). Sun exposure or trauma (Koebner phenomenon) can exacerbate a 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 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.

A 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 sub-types [32]. Ninety percent of DLE lesions have a positive lupus band test, with C3 and IgM being the most common immune deposits [14].

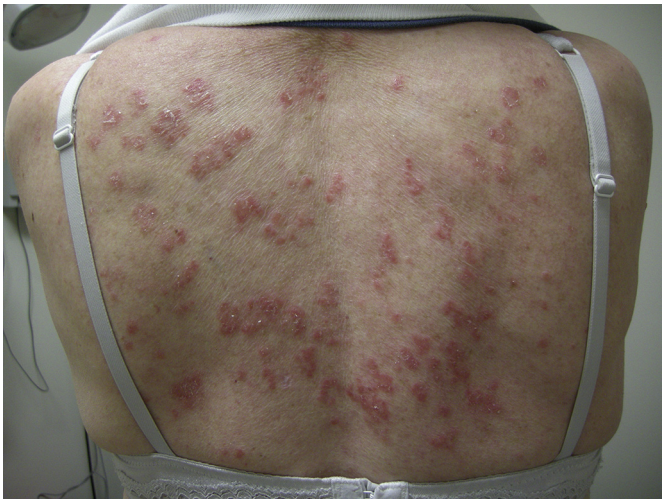

Fig. 2. SCLE, papulosquamous. Psoriaform lesions which coalesce to form retiform arrays.

Lupus erythematosus 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, characterised by remission and flares, and ultimately leaves atrophic scars [10]. The 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.

Chilblain lupus

CHLE is a rare form of CCLE 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. CHLE occurs when there is a temperature drop and can be difficult to distinguish from frostbite. The pathology shows epidermal atrophy, interface vacuolisation and a perivascular mononuclear infiltrate. Twenty percent of patients with CHLE develop features of SLE at some point in their disease course [34].

Lupus erythematosus tumidus

Lupus tumidus is a sub-type of CCLE characterised by extreme photosensitivity and a benign course occurring preferentially in men. Clinically, these lesions appear on the face as erythematous, oedematous, 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 the 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 CLE (ICLE), but there is no agreement and there are some who feel this could also be a lupus-associated skin disease [22].

How can we properly diagnose CLE?

In order to properly diagnose cutaneous manifestations of LE, the physician must first correctly classify the sub-type and exclude systemic involvement of the disease. As discussed earlier, diagnosis based solely on ACR criteria should be avoided, as the ACR criteria were designed to distinguish

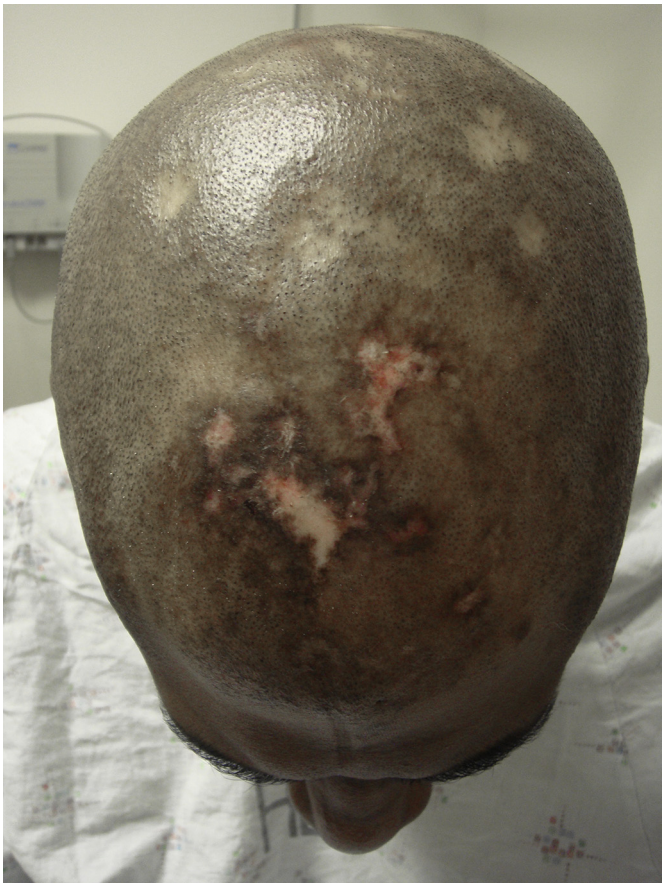

Fig. 3. DLE of the scalp. Longstanding discoid lesions show atrophy, with hyperpigmentation peripherally and depigmentation centrally.

between the various auto-immune diseases. Rather, CLE diagnosis should be based on the findings of patient history, clinical examination, laboratory studies, serology as well as histology and DIF examination of skin biopsies if the histology is not diagnostic.

A detailed skin examination is crucial for classifying the CLE sub-type. 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 examination 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 anaemia, thrombocytopenia or leucopenia, 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 single-stranded DNA (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 sub-type, but in general CLE lesions share the features of vacuolar or hydropic change and lymphocytic infiltrates. 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 also 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 auto-immune 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 the CLE sub-type. Standardised photoprovocation testing in a multicentre trial demonstrated that lesions were inducible in half of the CLE patients; however, it may not be reproducible, and the authors suggested that UVA and UVB exposure may be a clinically and academically useful means of evaluating photosensitivity and disease activity [48,49].

How is CLE treatment approached?

Prevention

In treating CLE, dermatologists aim at preventing the formation and progression of lesions and improving skin appearance through a combination of patient education and topical and systemic therapies (Fig. 4). 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 mg cm^{-2}) with a sun protection factor (SPF) of at least 50 should be applied 20–30 min prior to expected exposure. This recommendation is based on the findings of a vehicle-controlled, randomised, double-blind trial of 25 photosensitive CLE patients, which reported 100% protection from UVA and UVB irradiation with a broad-spectrum sunscreen [51]. Physical sunscreens such as titanium dioxide or zinc oxide provide particularly a 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. analysed the UV exposure risk of indoor fluorescent light bulbs exacerbating photosensitive disease and concluded that the lowest UV irradiance should be used to minimise 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 D_3, or cholecalciferol, is advised [54].

Topical therapies

The treatment of CLE lesions should begin with topical therapies, including steroids and/or calcineurin inhibitors. Despite the longstanding use of topical corticosteroids, only one randomised

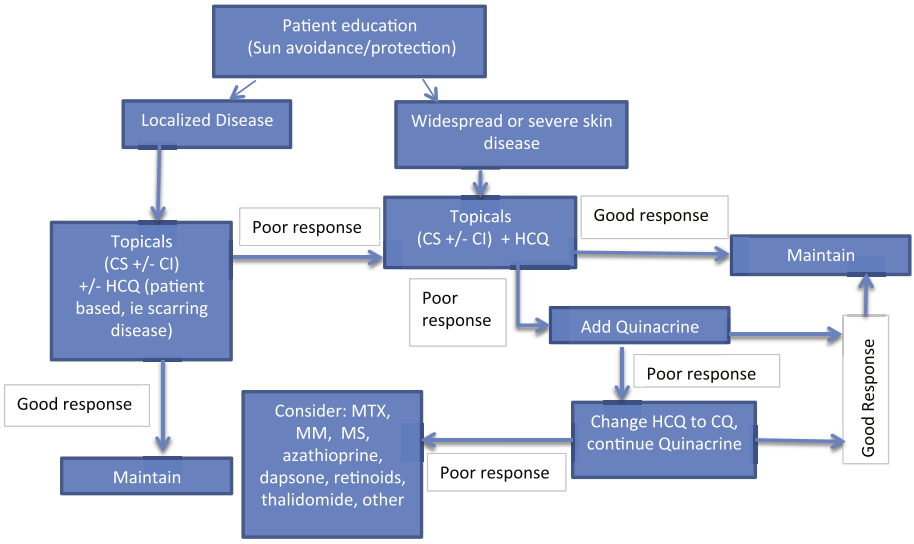

Fig. 4. Algorithm for cutaneous lupus erythematosus treatment. Localized disease is initially treated with topical agents (either corticosteroids (CS) or calcineurin inhibitors (CI)). Hydroxychloroquine (HCQ) is also oSen used, depending on the site or if there is scarring disease. Widespread or scarring 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.

controlled trial examining the 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 fluocinonide 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. Intra-lesional injections of triamcinolone may be beneficial in patients with refractory localised DLE [57].

Calcineurin inhibitors have emerged in recent years as an alternative topical option for various CLE sub-types. A double-blind, randomised 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 randomised, vehicle-controlled multicentre trial, 20 patients with CLE lesions treated with tacrolimus 0.1% ointment showed a 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 multicentre randomised 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 end point, the modified Localised CLASI (LCLASI) score, an unvalidated outcome measure [61].

Physical treatments for CLE include laser therapy, cryotherapy and dermabrasion. The efficacy of pulsed-dye and argon lasers 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 the reported side effects of the treatment.

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 an adjunctive therapy. Presently, there are no medications specifically approved for the treatment of CLE. The drugs used for the treatment of the various sub-types of CLE are generally also used for the treatment of SLE, with the exception of thalidomide.

Antimalarial drugs

Oral antimalarials are considered first-line systemic therapy for all CLE sub-types. Hydroxychloroquine, chloroquine and quinacrine are the three currently used antimalarials. A 1992 randomised, double-blind, multicentre study compared hydroxychloroquine (400 mg day^{-1}) with acitretin (50 mg day^{-1}) in various CLE sub-types 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, randomised controlled trial, demonstrating a response rate of 82.4% as compared to 75% in patients treated with clofazamine. [64] Antimalarials can take 2–3 months for maximum efficacy; therefore, patients are often bridged with topicals and intra-lesional injections.

Hydroxychloroquine sulphate is considered the drug of choice. At a dose of up to 6.5 mg kg^{-1} day^{-1}, 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^{-1}, limited to no more than 3.5–4.0 mg kg^{-1} day^{-1} to minimise 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 100 mg day^{-1}, as aplastic anaemia 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 the 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 counselled on smoking cessation [67,68]. The 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 and psychosis). Hydroxychloroquine may reduce the seizure threshold. Quinacrine can cause yellow discolouration of skin, sclera and bodily fluids. The American Academy of Ophthalmology recommends regular retinopathy screening for patients on antimalarials at intervals based on the risk status [69]. Antimalarial therapy is contraindicated in patients with pre-existing retinopathy, blood disorders and myasthenia gravis [70].

Systemic corticosteroids

Patients who 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 an 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 0.5–1.0 mg kg^{-1} day^{-1} can be tapered over 2–4 weeks [71].

Immunosuppressants

Approximately half of the patients refractory to antimalarials respond to immunosuppressants [41]. Methotrexate is a therapy for CLE if antimalarials do not work, with recommended doses of 7.5–25 mg 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 the treatment [72]. 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 sub-types in multiple case reports and small studies, including a prospective nonrandomised study of 10 treatment-refractory SCLE patients treated with mycophenolate sodium [73]. Another suggested treatment option is azathioprine, which was shown to successfully treat DLE in several small case series [74–76].

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 an improved SLE disease activity on musculoskeletal and mucocutaneous parameters in data pooled from two phase-III trials [77]. Further investigation is needed to determine the role of these and other immune response modifiers in the treatment of CLE.

Immunomodulators

Dapsone (25–150 mg day^{-1}) has shown to be effective in some case 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, haemolysis, methaemoglobinaemia or a hypersensitivity reaction; therefore, monitoring for haematologic and hepatic toxicities is critical. Patients with glucose-6-phosphate dehydrogenase deficiency should not take dapsone.

Multiple case series support the use of thalidomide (50–100 mg day^{-1}) 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 [78,79]. 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 [80–82].

Oral retinoids

Oral retinoid is an alternative therapy if antimalarials do not work. Acitretin has been shown to be effective in half of the CLE patients in a randomised 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 sub-types with alitretinoin, which may prove to be an effective alternative therapy pending further investigation [83]. 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 (1 month for isotretinoin and 2 months for acitretin) [70]. Retinoids can also cause hyperlipidaemia and hepatotoxicity; therefore, careful monitoring of lipids and liver function tests is necessary during treatment [14].

Summary

CLE comprises a range of dermatologic manifestations, including ACLE, SCLE and CCLE. The ACR criteria, which include four cutaneous signs, may lead to overdiagnosis of SLE in patients with predominantly cutaneous disease. The diagnosis of CLE requires proper classification of the sub-type, which is best accomplished by a focus on the clinical and histologic findings. Serology and DIF 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.

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 the criteria for SLE, while nearly all patients with ACLE will meet the criteria for 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 the 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. Randomised controlled trials are needed to assess the efficacy and safety of potential alternative therapies, including lenalidomide, anti-interferon alfa and anti-CD4 antibody.

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