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Cutaneous lupus erythematosus: a review

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This article reviews and updates information about the pathogenesis, clinical presentation, diagnosis, and treatment of cutaneous lupus erythematosus (LE). LE can present as a skin eruption, with or without systemic disease. Cutaneous LE (CLE) is subdivided into chronic CLE (CCLE), subacute CLE (SCLE), and acute CLE (ACLE). The prevalence of systemic LE (SLE) is 17 to 48 per 100,000 population worldwide [1]. Skin disease is one of the most frequent clinical complaints of patients suffering from SLE. It has been found to occur in up to 70% of patients during the course of the disease [1]. The most frequent mucocutaneous manifestations of SLE are malar rash (40%), alopecia (24%), and oral ulcers (19%) [2]. Tebbe et al [3] found that risk factors that are more likely to signal transition of CLE into SLE are high antinuclear antibody (ANA) titers (> 1:320) and the presence of arthralgias. CLE patients who exhibit these symptoms should be monitored closely, because they may be at increased risk to develop SLE.

Pathogenesis

Genetic associations

Genetic predisposition is probably the greatest risk factor of SLE [4]. The genes or loci for SLE susceptibility are mainly located on the long arm of chromosome 1 [5]. Linkage studies used in human SLE have identified high logarithm of odds scores for such regions as FcγRIIA at chromosome 1q23; the major histocompatability complex (MHC) at 6p21.3; and chromosome 1q31, which includes genes encoding interleukin (IL)-10 and Ro-60 [6–9]. Most autoimmune disorders are associated with certain HLA subtypes. ACLE usually occurs in the context of SLE and both are associated with HLA-DR2 and HLA-DR3 [10]. SCLE is associated with HLA-B8, HLA-DR3, HLA-DRw52, HLA-DQ1, and HLA-DQ2 [11].

The SLE murine models show that a single susceptibility gene may contribute to a particular phenotype [12]. The class III region of the MHC includes genes for complement components [7]. Genetic deficiencies in the complement components C2 and C4 have been strongly linked to SCLE [13–16]. C1q, C3, and C5 deficiencies have also been associated with discoid lupus erythematosus (DLE) and LE panniculitis [15,17–19]. Deficiencies in these complement components may cause failure to clear immune complexes and apoptotic cells [7,20]. Increased numbers of apoptotic cells, whether caused by increased formation or decreased clearance, are likely to cause increased immunologic stimulation including increased anti-Ro (SSA) antibody formation [15,16,21]. C1q, the first component of the classic complement pathway, binds directly and specifically to apoptotic keratinocytes [22]. There is evidence that C1q on apoptotic cells can bind to CD91 C1q receptor on macrophages, potentially playing a role in the clearance of apoptotic cells [23]. A C1q-deficient human is nearly guaranteed to develop SLE [22]. These patients tend to develop SLE at a younger age and there is no

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female predominance [22]. Mice with homozygous C1q deficiency have been found spontaneously to develop high titers of ANA and glomerulonephritis coupled with the accumulation of apoptotic bodies in the glomeruli [24]. Mice with homozygous deficiency in C2 and factor B are unable to activate C3 by either the classic or alternative complement pathway, and do not develop spontaneous autoimmunity unless coupled with homozygous C1q deficiency [25].

Tumor necrosis factor (TNF)-α and β are also encoded by MHC class III genes and the −308A form of the TNF-α promoter has been shown to have an increased incidence in patients with SCLE and SLE [26,168]. There is increased production of TNF-α in mitogen-activated peripheral blood lymphocytes or enriched monocyte cells with the −308A allele [27–30] and there is higher TNF-α in sera of whites and individuals homozygous for −308A have higher serum TNF-α levels than −308G homozygotes [31]. In addition, ultraviolet (UV) B activates the −308A TNF-α promoter significantly more than the wildtype −308G, suggesting a role for TNF-α in the UV-induced flares seen in photosensitive forms of LE [32]. The role of TNF-α in apoptosis of keratinocytes and exposure of translocated intracellular and intranuclear antigens to the immune system, a likely mechanism relevant to induction of SCLE, is discussed later. Heat shock protein (Hsp70) genes are located within the class III MHC region and increased expression has been shown to increase binding of anti-Ro antibodies to keratinocytes and exacerbate CLE [33,34].

Environment

It has been found that 69% of LE patients [35], 63% to 100% of SCLE patients, 70% of SLE patients, and 64% of DLE patients have a pathologic photoprovocation reaction when exposed to UVA and UVB light [36]. Because reactions to photoprovocation may be delayed, patients may not associate cutaneous flares with sun exposure. The presence of Ro/SSA or La/SSB antibodies is associated with photosensitivity [36,37]. Irradiation of human keratinocytes with UVB induces the apoptosis of keratinocytes, resulting in translocation of nuclear antigens (SSA/Ro, SSB/La, snRNP, and Sm) to the cell membrane [38]. TNF-α plays a role in induction of apoptosis [39], and patients with the −308A polymorphism are likely to have enhanced sensitivity to light. This apoptosis is associated with increased expression of p53 and proliferating cell nuclear antigen [40]. During the apoptotic process and through oxidative modification, autoantigens may become altered and this could result in immunocryptic epitopes and provide a challenge for immune tolerance [41]. It has been found that autoantigens are cleaved by intracellular proteases, which are activated during the apoptotic process [42–44]. Autoantigens also can be selectively phosphorylated during the apoptotic process by stress-activated protein kinases, and these kinases are recognized by autoantibodies from SLE patients [45]. The localized concentration of these antigens is speculated to challenge immune tolerance [11]. When stained, these autoantigens appear as apoptotic blebs on the surface of the keratinocytes [38]. In skin these blebs appear as a particulate staining over both the nuclei and cytoplasm of keratinocytes, with most intense staining in the lower levels of the epidermis [46].

It is hypothesized that keratinocyte-induced apoptosis of the nuclear proteins causes autoantibody production. The production of autoantibodies is time dependant after exposure to UV light, with antinucleosome antibodies produced in high titers before the appearance of anti-DNA and antihistone antibodies [47]. Anti-Ro/SSA, anti-La/SSB, and U1RNP antibodies have been found to appear 20 to 24 hours after keratinocyte UVB irradiation both in vivo and in vitro [48]. It is thought that following UV exposure and then cytokine release by cells, a transient increase in antibody binding to the surface may occur, making the keratinocyte more susceptible to killing by complement or antibody-dependant cellular cytotoxicity [49].

Drugs that induce CLE tend to be photosensitizers. They include angiotensin-converting enzyme inhibitors (cilazapril [50] and captopril [51]); calcium channel blockers (diltiazem, verapamil, and nifedipine) [52]; aldactone [53]; procainamide [54]; hydrochlorothiazide [55–57]; d-penicillamine [58]; beta-interferon 1a [59]; sulfonylureas [58]; oxyprenolol [60]; terbinafine [61]; griseofulvin [62]; cinnarizine and thiethylperazine [62]; naproxen [63]; COL-3 [64]; and piroxicam [65]. Uracil-tegafur [66] is reported to cause DLE. Long-term exposure to quartz (silica) is thought to induce CLE [67], and smoking has been found to be a risk factor for the development of DLE [68]. Laser-induced thermal injury has been reported to result in the onset of cutaneous lupus [69].

Cellular immune mechanisms

Different peripheral lymphocyte numbers are seen between the subtypes of CLE, and this suggests that there may be unique immune mechanisms causing the different manifestations of CLE [70]. Most of the infiltrating T cells seen in SLE lesions are CD28+, B7-1, and B7-2 [71].

Studies looking at chronic inflammation and dermal fibroblasts have found that on long-term TNF-α stimulation, membrane-bound IL-15 is involved in stimulating proliferation of accumulated, activated T cells [72]. Cytokine profiles performed on DLE lesions have shown that DLE is associated with type 1 cytokines characterized by the expression of IL-2 and interferon-γ [73]. The prevailing inflammatory cell population in DLE has been found to be CD45RA+ cells [74].

Humoral immune mechanisms

The Ro/SSA system contains a 60-kd RNA-binding protein with a possible role in transcription regulation, and a 52-kd peptide that is a T-cell regulator [75]. La/SSB is a 48-kd peptide that serves as a transcription termination factor of RNA polymerase III [75]. In particular anti-SSA/Ro antibodies that recognize 60 kd (and to a lesser extent 52 kd [37]) in sera are the best indicator of photosensitive cutaneous lupus, such as SCLE, SLE, and neonatle (LE) [76]. NLE is the best example of how important anti-Ro/SSA antibodies are in pathogenesis of CLE. NLE is the neonatal equivalent of SCLE. Anti-Ro/SSA antibodies are produced in the mother and cross the placenta during pregnancy. The infant manifests cutaneous disease for the first few months of life only, while maternal anti-Ro/SSA antibodies are still present. This is a strong indicator that anti-Ro/SSA antibodies are causing or contributing to the disease.

Calreticulin is a calcium-binding autoantigen that can also be found on the surface blebs of epidermal keratinocytes following UVB-induced apoptosis [11]. It has been shown that calreticulin is able to bind to the 52-kd Ro/SSA protein and hYRNA, the RNA backbone of Ro/SSA ribonuclear particles [11,77]. This work also suggests that calreticulin plays a facilitating role in the binding of 60-kd Ro/SSA polypeptide to hYRNA [77]. Epitope spreading resulting in an antibody response to calreticulin has been found with peptide immunization using the antigens 60-kd Ro, 52-kd Ro, and La [78,79]. These data plus other work suggest that a subpopulation of calreticulin molecules could play a role in the formation of Ro/SSA ribonuclear particles through the ability to link the 52-kd Ro/SSA protein to hYRNA by calreticulin bridging and the ability to promote the binding of 60-kd Ro/SSA protein with hYRNA molecules [11]. It has been found that there is a far greater immunity to Epstein-Barr virus in the lupus population when compared with a control population, and the epitope of the virus is similar to that of the lupus autoantigen Sm [80]. One hypothesis for the development of these autoantibodies is through a primary exposure with an antigen with a similar epitope.

Other mechanisms in LE induction

Fas is a transmembrane glycoprotein receptor that has an intracellular death domain that initiates apoptosis when *Fas* ligand (*Fas*L belongs to the TNF family) binds to it. Bcl-2 and Bax are proteins associated with apoptosis whose genes are regulated by the tumor suppressor gene TP3 [81]. Increased *Fas* expression and decreased Bcl expression have been found in LE lesions when compared with healthy skin [82]. Increased expression of *Fas* and ICAM-1 (adhesion molecule 1) on keratinocytes has been found to be caused by interferon-γ [83].

Adhesion molecule expression in CLE lesions is significantly affected by the wavelength of light the lesions are exposed to [84]. UV radiation also induces delayed proinflammatory cytokine-mediated up-regulation of ICAM-1 in exposed human keratinocytes [85,86]. VCAM-1 staining intensity has been seen to be increased on endothelium from lesions in LE compared with lesions in systemic sclerosis and it is thought that endothelial events including VCAM-1 may also be important in sustaining chronic inflammation in CLE [87]. E-selectin is seen in significantly elevated levels in DLE patients with widespread lesions [88]. Lymphocytes interacting with the up-regulated adhesion molecules, ICAM-1, VCAM-1, and E-selectin, on keratinocytes could further enhance the cell-mediated death pathway.

Summary

There are many mechanisms involved in the induction of CLE. New advances in the understanding of genetic variations that contribute to the susceptibility and different disease manifestations will continue to enhance our understanding about this disease.

Diagnosis

The CLE is mainly diagnosed using clinical, serologic, and histologic criteria. Gilliam's classification scheme is used in the diagnosis of CLE. In this scheme cutaneous findings of LE are classified as ACLE, SCLE, CCLE, and LE nonspecific skin disease.

Serologic diagnosis of SLE is performed by testing patient sera for the presence of increased ANA and anti-dsDNA (native double-stranded DNA) titers. The frequency of finding positive ANA titers

in SLE patient is between 95% and 100% [89]. Anti-Smith antibody, although not present in a high frequency of SLE patients, is very specific for the disease [90]. The frequency of positive antinative DNA is 60% [89]. Serologic tests that are found in CLE are rheumatoid factor (positive frequency of 20% [89]); anti-Sm (positive frequency between 10% and 25% [89]); anti-Ro/SSA (positive frequency of 15% to 20% in SLE patients [89]); and anti-La/SSB (positive frequency between 5% and 20% [89]). Anti-ds DNA and anti-Sm antibodies are disease specific for SLE, anti-Ro/SSA antibodies are more prevalent in SCLE and NLE, and high titers of anti-U1RNP antibodies are more prevalent in mixed connective tissue disease [90]. Complement studies are also useful [10]. Approximately 40% of LE patients have antiphospholipid antibodies, which have the propensity to cause thrombosis and spontaneous abortion [90].

CCLE

The CCLE is thought to be two to three times more frequent than SLE, with the common age of onset being 20 to 40 years of age [1]. CLE is considered to have a less severe course and a better prognosis than SLE. Both disease entities, however, can result in limited patient quality of life and disability from work. CLE is considered to be the third most common cause of industrial disability from dermatologic disease, after atopic dermatitis and contact dermatitis [91]. It has been found that 45% of patients with CLE experience some form of vocational handicap [1,91]. Early diagnosis, treatment, and patient education are imperative in improving patient standard of living and socioeconomic outcome.

Although CLE is considered to carry a better prognosis than SLE, 67% to 70% of SCLE patients and 14% to 27% of DLE patients have extracutaneous signs of disease [1]. Patients who have more generalized skin involvement tend to have more systemic symptoms than those with lesions localized to the head and neck [1].

The CCLE most commonly occurs in patients who have long-term low-grade illness. It can, however, also occur in patients who are suffering from acute episodes of life-threatening SLE [93]. CCLE includes multiple manifestations, such as discoid LE (localized and generalized); hypertrophic DLE; lupus panniculitis; mucosal DLE; lupus tumidus; and chilblains LE.

The DLE usually occurs in the third to fourth decade of life [1,46,94]. Fifteen percent of patients with DLE have been found to have a history of Raynaud's phenomenon [1]. Up to 25% to 40% of these patients remit spontaneously with only 5% to 10% going on to develop SLE [95]. Twenty percent of patients with generalized DLE and 5% with localized DLE go on to develop SLE. DLE clinically appears as one or more sharply demarcated scaly erythematous papules or plaques with an adherent scale extending into the follicular orifices [46]. Involvement is usually on the head and neck region (up to 80% [1]) with a predilection for the scalp and the ears [46]. Scalp lesions tend to result in a scarring alopecia. There is an increased incidence if alopecia areata with LE [96]. There can also be mucosal involvement. Lesions tend to heal with atrophy and scar formation [1]. Generalized DLE, especially when involving the trunk, is associated with progression to systemic LE. Squamous cell carcinoma (SCC) can develop in DLE lesions [97]. Serologically, patients with DLE have a lower tendency to be positive for ANA, double-stranded DNA, Sm, U1RNP, and Ro/SSA antibodies [10].

The lupus band test can be a useful criterion to distinguish patients with LE from those without LE [98]. A positive lupus band test is found in 80% to 90% of erythematous lesions in SLE and in 50% of nonlesional skin of SLE [4]. Immune deposits are more commonly composed of IgM [98,99] and IgG [4,98]. A positive lupus band test on nonlesional, non–sun-exposed skin has been found to correlate with a worse prognosis [98,100] and disease activity [101,102], elevated anti-DNA titers [100,103], leukopenia [104], hypocomplementemia [103], and a rim pattern ANA [101,103]. False-positive lupus band tests may occur with lichen planus [105], polymorphous light eruption [106], rosacea [107], drug-induced lupus [102,108], and facial telangiectasia [107]. The lupus band test is rarely used in clinical practice today if the histopathology already establishes the diagnosis. When there is a positive lupus band test with DLE (greater than 90% of the time [98]), the most common immune deposits are reported to be C3 and IgM [94]. C1q deposits have been found in 88% of DLE patients who have concurrent SLE [94]. Serologically, patients with DLE have been found to have less ANA positivity than SCLE and ACLE [94].

Hypertrophic CCLE represents 2% of the lesions seen in CLE [109]. Lesions mainly occur on the face, extensor extremities, palms, and soles [109]. Lesions are papulonodular and hyperkeratotic in nature. They can present as scaly plaques covered by adherent horny white material or regionally diffuse hyperkeratosis that looks like a chalky dust applied over the skin [109]. This variant of CCLE

may show pseudocarcinomatous hyperplasia on biopsy and can be confused with SCC [109]. Fortunately, patients with hypertrophic CCLE usually have classic DLE lesions elsewhere on their bodies, aiding in diagnosis [110].

Lupus panniculitis (lupus profundus) can occur alone or in the setting of SLE (10% [111]), DLE (33% [111]), and other autoimmune diseases. It is a lobular panniculitis that tends to occur most commonly in middle-aged women [111]. Plaque or nodular lesions are seen 97% of the time, often accompanied with scarring, pain, erythema, and sometimes ulceration [111]. Most lesions are found in areas of increased fat deposition, such as the trunk, breasts, buttocks, and proximal arms and legs [111]. Serologically, ANAs may be found to be low in titer or nonexistent. Hypergammaglobulinemia has been found to be present (42% [111]) along with low total complement (7% [111]) and C4 levels (22% [111]). The major morbidity in this disease is usually disfigurement and disability related to pain [111]. There is seldom death from lupus panniculitis, and the course of disease is characterized by periods of remission and exacerbation [111]. It is important to obtain ample biopsy material to confirm the diagnosis, because a number of cases of subcutaneous lymphoma have given a clinical appearance of lupus panniculitis [112].

Tumid CCLE is characterized by smooth, nonscarring, erythematous to violaceous, single or multiple plaques with no surface changes, such as follicular plugging [113]. Lesions are photodistributed [114] and are easily photoinduced [113]. Lesions can coalesce to produce gyrate configurations and tend to resolve spontaneously with no scarring or dyspigmentation [113]. Tumid CCLE lesions can coexist with DLE lesions [114] and have been reported to mimic alopecia areata when present in the scalp [96]. Histologically, there is perivascular and periadnexal superficial and deep lymphocytic infiltration with distinct subepidermal edema and mucin deposition between collagen bundles [113]. Direct immunoflourescene findings (DIF) are commonly negative [113].

Chilblain CCLE is a rare manifestation of CLE. It acquired its name because it looks like frostbite. Lesions are located on fingers, toes, calves, heels, knees, elbows, nose, or ears and are aggravated with cold exposure [109]. They can be violaceous, infiltrated, pruritic, or painful when exposed to cold. Ulceration is common in digital pulp lesions and lesions on the soles easily become necrotic [109]. As chilblain lesions evolve, they may take on the clinical appearance of DLE lesions [10]. Serologic findings have included increased serum immunoglobulin levels and positive rheumatoid factor [115]. DIF may show speckled staining of ANA [115]. There are usually no detectable cold agglutinins, cryoglobulins, or circulating anticoagulants [115].

SCLE

The SCLE is the more photosensitive subset of CLE. It usually presents in the third or fourth decade of life (mean age of onset in one study was found to be 30.6 [94]), although children and elderly individuals are also affected. Women are three to four times more affected than men [116]. It presents as a photodistributed, nonscarring papulosquamous or annular, polycyclic eruption that can be isolated or can involve mild extracutaneous manifestations [46]. Lesions are easily photoprovoked and can persist for long periods of time. One study found 42% of the patients studied exhibit annular SCLE, 39% have psoriasiform-type SCLE, and 16% to have both manifestations [116]. Twenty-seven percent of the patients had nonspecific LE lesions, such as malar eruption, livedo reticularis, and periungual telangiectasia [116]. SCLE has been reported to present as pityriasis-like [117], and to be associated with generalized poikiloderma [118]. Approximately 20% of patients with SCLE have DLE lesions that appeared before the onset of the SCLE lesions [58,119].

The neck was affected in 83% of patients with 66% of patients exhibiting lesions on the face, 39% on the extensor arms, 21% on dorsal hands, 16% on the lower limbs, and 12% on the scalp [116]. Lesions tend to heal without scar formation. Histologically, patients with SCLE have an interface lichenoid dermatitis with suprabasilar exocytosis of lymphocytes showing satellitosis to necrotic spinous layer keratinocytes [58]. The use of antibody to C5b-9, although not specific, has been found to help subclassify SCLE [120].

Patients with SCLE often have circulating antibodies to Ro/SSA directed to two antigenically distinct ribonuclearprotein antibodies of 60 kd and 52 kd [121]. ELISA has been found to be the most sensitive and specific method to detect these antibodies for serologic diagnosis [121]. ANA is positive in 70% to 80% of SCLE patients [10]. Approximately 50% [122] to 71% [116] of SCLE patients are Ro/SSA positive (especially the annular variant [123]). Parodi et al [116] found that 86% of SCLE patients studied exhibited reactants at the dermal-epidermal junction. In this study they also found 71% of SCLE patients had anti-Ro/SSA antibodies and only 5% of the patients had anti-dsDNA [116]. The presence of

"dust-like particles" of IgG deposition on DIF is a specific but not sensitive pattern in SCLE [124] that is associated with the presence of Ro/SSA autoantibodies [125].

ACLE

Patients with ACLE have a 100% chance of developing SLE during the course of their disease [122]. ACLE usually presents rather abruptly in the context of a systemic illness [126]. This type of CLE is seldom examined with routine histology. These patients are on average in their third decade of life [94], and have signs and symptoms of SLE, along with the confirmatory serologic findings [127]. In one study women were found to be six times more affected than men [94]. There are localized and generalized forms. Localized ACLE is commonly manifested as the classic malar or butterfly rash seen in LE. The generalized form is commonly seen as photosensitive lupus dermatitis or a maculopapular lupus rash. Patients may have diffuse thinning or a receding frontal hairline with broken hairs (lupus hair); telangiectasias and erythema of the proximal nail fold; cuticular abnormalities; and nail-fold changes [119].

An ACLE presenting as bullous [126] and toxic epidural necrolysis (TEN)-like lesions has also been described. Bullae are most common on sun-exposed skin and neutrophils, not lymphocytes, are seen histologically [126]. Lesions have been found to occur more on the face (87%) and upper limbs (73%) than on the trunk (36%) [94]. Serologically, 95% of ACLE patients are ANA positive and often have anti-dsDNA and anti-Sm antibodies [10].

Typical lesions exhibit vacuolar alteration at the dermal-epidermal junction with an interface, perivascular, and periadnexal infiltrate that is composed of lymphocytes [127]. Examination of ACLE skin using DIF shows granular deposition of multiple immunoreactants at the dermal-epidermal junction and around the superficial dermal vasculature [127] with the most common immune deposit being C1q [94].

Treatment

The goals of managing CLE are to prevent lesion progression and to improve patient appearance. Standard therapy consists of patient education on heat, sun, and drug avoidance, along with the use of sunscreens. Giving patients agents, such as Dermablend (Johnson Products, Chicago, IL) or Cover Mark (Cosmetic Essence Inc, Monarchy, NJ), to camouflage dyspigmentation [10,11,128] can be helpful. Lesions should not be manipulated because new lesions may appear at the site of surgical manipulation [128]. Patients should be educated about sun-protective clothing with Food and Drug Administration sun-protective factors [11,129], and use a broad-spectrum sunscreen with a sun-protection factor above 15. Sunscreens found to be most effective contain parsol 1789, mexoryl SX, and mexoryl XL as UVA protectants (not available in the United States) and octocrylene as UVB protectant [130]. Patients who notice lesion induction through glass windows should use a sunscreen that also contains a UVA screen, such as Durascreen, Ombrelle, PresunUltra, and Shade UVA [128], or apply UV blocking films to home and automobile windows (Solis films, Southwall Technologies Dallas, TX). Opaque physical blockers, such as zinc oxide or those containing microparticles of titanium dioxide, provide excellent broad-spectrum coverage [11].

Localized CCLE is sometimes effectively treated with topical corticosteroids. Low-potency agents (hydrocortisone, aclomethasone, desonide, or hydrocortisone valerate) should be used on the face with mid-potency agents (fluorinated corticosteroids, such as betamethasone valerate or triamcinolone acetonide) on the trunk and arms, and high-potency agents (halobetasol, clobetasol, or betamethasone disproportionate) on the soles and palms [128]. For lesions on the scalp a steroid lotion or foam should be prescribed [128]. Patients can also be taught to self-taper after a short period of time so stronger steroids can be used on new areas. For localized lesions, intralesional corticosteroids can be effective.

Lasers are being used in increasing frequency to treat superficial localized lesions of CLE. The pulse dye laser has been found to be efficacious in the treatment of vascular lesions of CLE [131] and has been used in treatment of SCLE [132]. There is a clearance rate of 70% reported, with few side effects and no scarring [131]. The argon laser has also been found to be effective in treatment of vascular lesions seen in DLE [133]. There has, however, been a case reported of CLE induced by thermal injury from laser treatment [69]. Scarring secondary to CCLE can be treated using the carbon-dioxide laser [134]. Risks associated with laser treatment are pigmentary changes with the 532-nm laser and temporary hyperpigmentation in 25% to 30% of patients. This usually resolves in 2 to 3 months [135]. The risk of scarring associated with laser treatment is low, with a higher incidence seen on the chest or neck [135]. Textural changes are more common following treatment with one of the continuous-wave

lasers [136]. Possible contraindications to laser treatment include isotretinoin intake in the past 2 years and a history of keloid or hypertrophic scars [135]. Localized DLE lesions have been treated with cryosurgery [137].

Disseminated CLE with no systemic symptoms and lesions refractory to intralesional and topical corticosteroids are treated with antimalarials. Hydroxychloroquine sulfate is usually the first-line antimalarial drug of choice [2]. In oral doses of 400 mg/d or less than 6.5 mg/kg/d it is safer to use than its sometimes more effective counterpart, chloroquine phosphate. Patients should be informed that onset of response may take 6 to 8 weeks, so they continue to comply with treatment. If this regimen is ineffective it is often useful to add quinacrine (100 mg/d) to the hydroxychloroquine regimen. Quinacrine can be bought at compounding pharmacies [92]. If patients fail the combination hydroxychloroquine and quinacrine, then switching from hydroxychloroquine to chloroquine phosphate can be beneficial at times. The use of chloroquine phosphate results in a slightly greater incidence of eye toxicity and should be dosed at less than 3.5 mg/kg/d [138]. Therapy adding quinacrine (100 mg/d) to chloroquine ($<$305 mg/kg/d) has also been found to be effective in treatment of refractory CLE [128]. Hydroxychloroquine and chloroquine should not be used in combination because there is an additive risk of retinopathy [92]. Patients should be monitored by an ophthalmologist every 6 months for hydroxychloroquine and every 4 months after a baseline examination for chloroquine [92]. The eye examination should include a funduscopic examination; visual field testing (including central fields with a red object); and visual acuity testing [10].

Other adverse side effects of antimalarials are blue-gray hyperpigmentation; urticarial eruption; bleaching of lightly pigmented hair; gastrointestinal upset (distention, nausea, diarrhea, and heartburn); myopathy; cardiomyopathy; and rare central nervous system effects (headache, insomnia, nervousness, seizures, and psychosis) [10,92,130]. Hydroxychloroquine may lower the seizure threshold [92]. Desirable effects of hydroxychloroquine are lowering of cholesterol levels and antithrombotic effects [92]. Antimalarials also improve fatigue, fever, headache, arthralgias, arthritis, pleuritis, and pericardial inflammation [92]. Quinacrine can cause headache, dizziness, gastrointestinal distress, yellow discoloration of skin, sclera and bodily secretions [10], blue-black skin discoloration [92], and hematologic toxicity [130]. Eczematous, lichenoid, and exfoliative skin eruptions are also associated with quinacrine [92].

It has been shown that patients who smoke are less responsive to antimalarial treatment [139], so patients should be encouraged to discontinue smoking to avoid potentially more toxic drug regimens. Low-dose systemic corticosteroids have been found to be ineffective in treating CCLE, but may be useful when treating severe DLE or SCLE patients short-term while the antimalarials are being started. Because patients with LE are more prone to develop avascular necrosis, use of systemic steroids should be minimized [92].

Severe CLE can be treated with immunosuppressives. Azathioprine has been found to work particularly well with nonscarring lesions of SCLE [128] and acral DLE [140]. Very low doses of azathioprine (25 to 50 mg/d) can also be effective in patients with acral DLE [92]. Methotrexate (10 to 20 mg/wk) [141–144], cyclophosphamide, cytarabine [145], cyclosporine [146], and mycophenolate mofetil [147] have all been reported to be effective treatments. High-dose intravenous immunoglobulin (1 g/kg/d for 2 consecutive days) has also been reported to be effective with minimal side effects [148,149], and the use of extracorporeal photochemotherapy [150].

Thalidomide when started at 100 mg/d and decreased to 50 to 25 mg/d for maintenance therapy after remission, has been shown to produce excellent results in patients refractory to antimalarial therapy [151,152]. Patients have been found to note improvement within 2 weeks after starting treatment and maximum benefit is achieved within 3 months [152]. It is thought to work by reducing the activity of TNF-α and inhibiting angiogenesis [153]. Administration may result in an increase in the lymphocyte count and a decrease in the C-reactive protein [154]. The most common adverse effects reported are sedation, constipation, and weight gain [153,155]. Amenorrhea has also been found to be a side effect of therapy [152,156]. Lesions tend to recur on cessation of treatment [152], but may be easier to control with other therapies after thalidomide. Peripheral neuropathy is a serious side effect that should be monitored in patients on long-term therapy [153,155]. There has been a case of pustuloderma reported associated with thalidomide treatment of CLE [157]. Because thalidomide is a potent teratogen, pregnancy must be avoided in women [128].

Dapsone (25 to 150 mg/d) is found to be effective in patients with vasculitic LE lesions, nonscarring CLE, bullous LE, and oral ulcerations [128]. Combined with hydroxychloroquine, dapsone has been found to be effective in the treatment of DLE [158]. Clofazimine is also good for treating CLE. It has been found that two thirds of patients with DLE who

received 100 mg/d oral clofazimine for 3 to 6 months benefited from treatment [159]. The most notable side effect reported was a pink-to-reddish discoloration of the skin [159] that is slowly reversible with discontinuation of the drug [10].

Retinoids used both topically and orally can be effective in the treatment of hypertrophic DLE and acral CLE [92,119,130,160]. Good results using retinoid etretinate are seen in men with DLE [160]. One study compared the efficacy of oral acetretin (50 mg/d) with hydroxychloroquine (400 mg/d) in the treatment of CLE and found overall improvement in 46% of the patients on acetretin and 50% of the patients taking hydroxychloroquine [161]. Both drugs where found to provide effective treatment in 50% of cases of CLE [161]. There was a higher incidence of side effects in the acetretin group [161]. Retinoids are teratogenic and frequent laboratory evaluation should be carried out to avoid drug-induced hepatitis and hypertriglyceridemia [10]. Bony changes consistent with diffuse idiopathic skeletal hyperostosis syndrome, headaches, pseudotumor cerebri, xerosis, visual disturbances, sun sensitivity, and alopecia have been associated with long-term retinoid therapy [10]. Laboratory parameters, including β-human chorionic gonadotropin in women, lipid profile, liver function tests, and complete blood count, should be measured every month of therapy [162].

Auranofin when used in the same manner as in patients with rheumatoid arthritis is reported to work best in nonscarring forms of CLE [128]. Chimeric CD4 monoclonal antibody infusions [163] have been found to be more effective than the use of interferon-α, which can exacerbate lupus and rarely causes long-term remission [164]. The use of cefuroxime, a second-generation cephalosporin, at 500 mg/d, was reported to resolve SCLE lesions in three patients [165]. Vitamin E, dosed at 1000 IU/d and increased as tolerated, has been given to treat SCLE and DLE, with marked improvement in superficial disease of recent onset [166]. Low-dose aspirin therapy is recommended in patients with antiphospholipid antibodies [92]. Patients with a history of thrombotic events should be treated with long-term warfarin [92]. The newer TNF inhibitors may play a role in future treatment of CLE, but have not been studied well enough at this time to make recommendations as to their use. There is concern that these inhibitors have induced autoimmune disease and are associated with production of anti-dsDNA antibodies [167].

The diagnosis of CLE requires a good history and physical examination, serologic analysis, and histologic evaluation. Thorough characterization of the type of CLE can aid prognostically and therapeutically. Patients should be educated that CLE may persist for decades and should be aware of symptoms that may mark progression to more serious disease.

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