5.2 Subacute Cutaneous and Systemic Lupus Erythematosus

Donna M. Pellowski, Jane E. Kihslinger, and Richard D. Sontheimer

Definition and Classification

Lupus erythematosus (LE) is a polyclonal T and B lymphocyte autoimmune disease thought to result from a complex interplay of genetic and environmental factors. Clinical expression of LE ranges in continuum from minor cutaneous lesions to life-threatening vital organ dysfunction. Throughout this continuum skin manifestations are variable and common. In 1981 Gilliam and Sontheimer developed a classification system that divides lesions into LE specific and LE non-specific cutaneous disease. LE specific cutaneous disease includes three clinically, immunologically and genetically distinct disorders: acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE) and chronic cutaneous LE (CCLE). Histopathological differentiation between especially the first two disorders can be difficult.

This chapter focuses on the clinical features of SCLE and its management. SCLE is clinically characterized by nonscarring, nonindurated, erythematous, papulosquamous and/or annular skin lesions occurring in a symmetric, photodistributed pattern. Patients with SCLE tend to exhibit milder systemic symptoms than those with unselected systemic LE (SLE). Although not mandatory for diagnosis, the majority of SCLE patients produce anti-Ro/SSA autoantibodies.

Epidemiology

SCLE patients comprise approximately 3–32% of worldwide LE populations with the lowest reported rates in Korean and Chinese populations (Sontheimer

1989; Tebbe and Orfanos 1997; Lee 1998). SCLE is most frequent in young to middle-aged Caucasian females, but it can occur at any age and onset over age 60 years is possible (Chlebus et al. 1998). Seventy percent of the original SCLE cohort reported by Sontheimer et al. (1979) was female with a mean age of onset of 43.3 years and a range of 16–67 years. Eighty-five percent of the initial SCLE cohorts was Caucasian and 15% was African American or Hispanic, whereas the latter two groups comprised approximately 50% of the regional populations (Sontheimer et al. 1979). Other authors have reported similar demographic data (Callan and Klein 1988, Black et al. 2002). There have been five case reports of SCLE occurring in children 18 months to 9 years old (Buckley and Barnes 1995, Parodi et al. 2000, Siamopoulou-Mavridou et al 1989, Ciconte et al. 2002, Amato et al 2003).

Etiology and Pathomechanisms

Programmed epidermal keratinocyte death in association with a lymphohistiocytic infiltrate is a hallmark histopathological feature of of -LE specific skin disease. Abnormally high rates of epidermal keratinocyte apoptosis occurs in patient with cutaneous LE when exposed to a precipitating environmental stressor such as ultraviolet light (Orteu et al. 2001). Abnormal exposure of autoantigens associated with apoptosis occurring with in a pro-inflammatory environment is thought to result in loss of immunological tolerance to such autoantigens. Cytokines, cytotoxic drugs, cytotoxic T cells and UV light can induce keratinocyte apoptosis (Millard and McGregor 2001). Apoptotic keratinocytes undergo programmed intracellular proteolysis and present Ro autoantigen, DNA, ribonucleoproteins, and calreticulin on surface membrane blebs as they disintegrate. (Millard and McGregor 2001; Racila et al. 2003). It has been proposed that anti-Ro/SSA and anti-La/SSB may bind to exposed autoantigen resulting in complement-mediated lysis or antibody-dependent cell-mediated cytotoxicity (ADCC) and cytotoxic T lymphocytes can induce keratinocyte lysis causing further release of epidermal cytokines. Partial/relative C1q deficiency may inhibit clearance of apoptotic debris and may lead to increased autoantibody production (Racila et al. 2003). The TNF-α G-308A polymorphism can lead to increased apoptosis and leukocyte migration into the skin and may promote the inflammatory pathway of apoptotic debris clearance. Inducible nitric oxide synthases in endothelial cells and keratinocytes may also be associated with dysregulated keratinocyte apoptosis and inflammation, but its role in the pathogenesis of photosensitive LE remains unclear (Orteu et al. 2001). Expression of the adhesion molecules ICAM-1, VCAM-1, E-selectin, and P-selectin is increased in cutaneous endothelial cells of LE patients (Kuhn et al. 2002a). Local T-cell and endothelial activation are possibly involved in the persistence and extension of lesions (Norris 1993). *(Fig. 1).*

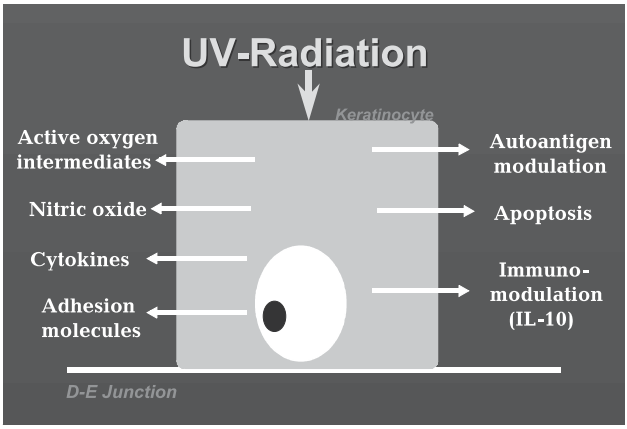

Fig. 1. Potential factors involved in the pathogenesis of UV-induced cutaneous LE

Immunogenetics

The earliest immunogenetic studies on SCLE patients suggested an association with several HLA class II phenotypes. HLA-DR3, a phenotype found in 25% of Caucasians in the US (Ahearn et al. 1982), was reported in some studies in at least half of SCLE patients (Sontheimer 1989; Vasquez-Doval et al. 1992), while others reported a lower frequency (Callen and Klein 1988; Drosos et al. 1990; Cohen and Crosby 1994). HLA-DR3 expression has been associated with annular more than papulosquamous SCLE lesions (Sontheimer et al. 1982; Herrero et al. 1988) and HLA class II phenotype expression has been even more closely associated with autoantibody production than with skin changes (Watson et al. 1991). HLA-DR3 and HLA-DR2 were first associated with the presence of anti-Ro/SSA antibody (Bell and Madisson 1980; Sontheimer et al. 1982; Watson et al. 1991), and subsequent work revealed that DQ alleles are the most frequent class II alleles associated with anti-Ro/SSA (Maddison 1999). Very high levels of anti-Ro/SSA production have been associated with the extended haplotype HLA-B8, DR3, DRw6, DQ2, DRw52 (Harley et al. 1986).

A distinct extended haplotype called the "high human immune responder" 8.1 ancestral haplotype (A*01, B*08, DRB1*0301, DQB1*0201, TNFAB*a2b3, C2*C) has also been linked with anti-Ro/SSA production (Price et al. 1999, Lio et al. 2001). Located on human chromosome 6, the 8.1 ancestral haplotype is in linkage disequilibrium with the gene for tumor necrosis factor-alpha (TNF-α), an important proinflammatory mediator of the cutaneous innate immune response. A single nucleotide polymorphism in the promoter region of TNF-α G-308A, has been found to be associated with the SCLE phenotype (Werth et al. 2000, Millard et al. 2001a). Following exposure to UVB radiation in the presence of IL-1α, this promoter polymorphism produced

exaggerated levels of TNF-α in human keratinocytes, which may have a priming effect on the adaptive component of the LE autoimmune response (Werth et al. 2000).

Inherited deficiencies of C1q, C2, C3, and C4 complement have also been associated with SCLE (Callen et al. 1987; Johansson-Stephansson et al. 1989; M van Hees et al. 1992). It has been shown that homozygous complete congenital deficiency of C1q is the strongest single genetic risk factor yet identified for the development of SLE (Korb and Ahearn 1997, Walport et al. 1998, Barilla-LaBarca and Atkinson 2000, Topaloglu et al. 2000, Fishelson et al. 2001). Approximately 93% of individuals with a congenital C1q deficiency have developed early onset severe SLE with photosensitive cutaneous forms of LE among the most common disease presentation. Racila et al. (2003) recently reported a highly significant association between a C1q coding region single nucleotide polymorphism (SNP), C1QA-Gly70$_{GGA}$, and the SCLE phenotype. This SNP does not encode a different amino acid, but may alter C1q expression through an alternative splicing mechanism. Its presence correlates inversely with serum levels of C1q antigenic protein in SCLE patients. Since C1q binds calreticulin and is involved in clearance of cellular debris, C1q deficiency may result in decreased clearance of immunogenic material (Racila et al 2003).

Environmental Factors

Photosensitivity. Photosensitivity is seen in the majority of SCLE patients. UV light can induce the release of inflammatory mediators such as IL-1, TNF-α, IL-10 and oxygen free radicals at the level of the epidermis and dermis. In addition to natural light, cutaneous LE lesions have been provoked by exposure to psoralen with UVA (Dowdy et al. 1989; McGrath et al. 1990), UVB via unshielded fluorescent light (Rihner and McGrath 1992; Kuhn et al. 2001), radiation therapy (Balabanova et al. 1997), and even photocopier light (Klein et al. 1995). In addition, many drugs which have been reported to induce SCLE lesions often have photosensitization as a side effect of their use. Several researchers have used standardized phototesting protocols which involve exposing specific patches of skin to precise amounts of UVR or natural light in order to demonstrate photosensitivity in these patients (Sanders et al. 2003; as reviewed in Kuhn et al. 2001). One such study was able to diagnose photosensitivity in 100% of SCLE patients despite the use of steroids, antimalarials, or methotrexate in several patients tested (Sanders et al. 2003). Their testing also demonstrated that the majority of skin reactions appeared after more than a 1-week delay, which the authors postulated, could explain why many patients who reported a negative history of photosensitivity were found to have a positive phototest. This evidence reaffirmed the need to encourage all SCLE patients to use photoprotective measures despite history.

Table 1. Medications that May Induce SCLE Lesions

Diuretics	Thiazides Spironolactone	*Antimicrobials*	Griseofulvin Terbinafine
Calcium Channel Blockers	Diltiazem Verapamil Nifedipine Nitrendipine	*Antihistamines*	Cinnarizine/ Thiethylperazine
ACE inhibitors	Captopril Cilazapril	*Sulfonylureas*	Glyburide
Acid Blockers	Ranitidine Omeprazole	*Chemotherapy*	Taxotere
NSAIDS	Naproxen Piroxicam	*Others*	Interferon beta-1a Interferon alfa Etanercept Phenytoin
Beta Blockers	Oxprenolol		Procainamide d-penicillamine
Lipid-lowering	Pravastatin Simvastatin		Psoralen-UVA Insecticides

Drugs. Several drugs are associated with the induction of SCLE lesions (*Table 1*). Thiazide diuretics (Reed et al. 1985; Fine 1989; Parodi et al. 1989; Brown and Deng 1995), calcium channel blockers (Crowson and Magro 1997; Gubinelli et al. 2003; Marzano et al. 2003a) and angiotensin-converting enzyme (ACE) inhibitors (Patri et al. 1985; Fernandez-Diaz et al. 1995) have most commonly been reported. Others include spironolactone (Leroy et al. 1987), interferon beta-1a (Nousari et al. 1998), procainamide (Sheretz 1988), d-penicillamine (Sontheimer 1989), sulfonylureas (Sontheimer 1989), terbinafine (Brooke et al. 1998; Callen et al. 2001; Bonsmann et al. 2001), oxprenolol (Gange and Levene 1979), griseofulvin (Miyogawa et al. 1994), naproxen (Parodi et al. 1992), piroxicam (Roura et al. 1991), phenytoin (Ross et al. 2002), etanercept (Bleumink et al. 2001) and PUVA (McGrath et al. 1990). The combination of the antihistamines cinnarizine and thiethylperazine was cited as the cause of annular SCLE lesions in one patient (Toll et al. 1998). Personal anecdotal experience has suggested acid inhibitors such as omeprazole and ranitidine may also be a trigger for SCLE (RDS). Some hypothesize that hormones play a significant enough role in SCLE and that it may be reasonable to recommend that cutaneous LE patients avoid estrogen-containing contraceptives (Tebbe and Orfanos 1997). However, no cases of SCLE have been reported as a result of oral estrogen use. A recent retrospective study showed an association between certain medications and the onset of disease in 15 of 70 patients with Ro positive cutaneous lupus (Srivastava et al. 2003). Antihy-

pertensives were most commonly identified as possible triggers, in addition to statins, interferon alfa, and interferon beta. In that review, clinical disease began between 4 and 20 weeks, and improved 6–12 weeks after discontinuation of the offending drug.

Drug-induced *SCLE* should be differentiated from classical drug-induced *SLE*. The former is associated with Ro/SSA autoantibodies and a characteristic photodistributed rash, whereas the latter is dominated by histone autoantibodies and systemic symptoms such as fever, arthritis, myalgias, and serositis (Brogan and Olsen 2003). A lupus-specific skin rash is rarely present in the drug-induced form of SLE, and is much more commonly seen in idiopathic SLE (Rubin 2002). The medications which typically trigger SCLE (*Table 1*) are distinct from those that trigger classical SLE (e.g., hydralazine, procainamide, isoniazid, minocycline, sulfasalazine, etanercept), with exceptions, probably reflecting different underlying disease mechanisms.

Cutaneous Manifestations

Before Gilliam and Sontheimer classified it as a distinct entity, lesions of SCLE were referred to with varied nomenclature including symmetric erythema centrifugum, disseminated DLE, autoimmune annular erythema, subacute disseminated LE, superficial disseminated LE, psoriasiform LE, pityriasiform LE, and maculopapular photosensitive LE (Sontheimer et al. 1979).

Cutaneous lesions of SCLE typically begin with red macules or papules which evolve into psoriasiform and/or annular plaques on sun-exposed skin, characteristically the shoulders, upper back, extensor arms, V of the lower neck and upper chest, and back of the neck. The face is less commonly affected. Annular lesions tend to expand with central clearing and trailing scale. When active inflammation resolves, hypopigmentation is common, especially in the inactive centers of annular lesions. In Sontheimer's original cohort half presented with predominantly papulosquamous and half with predominantly annular lesions. Parodi reported similar findings (Parodi et al. 2000), whereas some cohorts have had a majority of annular lesions (Herrero et al. 1988; Chlebus et al. 1998; Black et al. 2002) and some have had a majority of papulosquamous lesions (Molad et al. 1987; Callen and Klein 1988; Cohen and Crosby 1994).

Atypical presentations of SCLE occur, including vesiculo-bullous forms. Well before the classification of SCLE as a subset of LE, Rowell et al. (1963), described EM-like (erythema multiforme) lesions in four so-called DLE patients who had a speckled ANA, rheumatoid factor and precipitating antibodies to the saline extract of human tissues (anti-Sj-T). Whereas EM and DLE can coexist, it has been suggested that Rowell's syndrome should now be reclassified as SCLE (Roustan et al. 2000). Lyon et al. (1998) reported two cases of delayed diagnosis of SCLE because of the clinical and histologic similarities

between SCLE and EM. Additional cases of EM-like SCLE lesions have been reported (Massone et al. 2000). In one patient the lesions developed changes similar to toxic epidermal necrolysis (Bielsa et al. 1987). Marginal vesicles were clinically evident in 38% of annular SCLE lesions that Herrero et al. observed (1988).

Rarer presentations of SCLE have also been reported including a morbilliform exanthem (Sontheimer 1985), exfoliative erythroderma (DeSpain and Clark 1988; Parodi et al. 2000), pityriasiform lesions (Sontheimer 1989; Parodi et al. 2000; Caproni et al. 2001), peculiar acral annular plaques (Scheinman 1994), progressive generalized poikiloderma (Pramatarov et al. 2000; Marzano et al. 2003b), sunlight induced papulonodular mucinosis (Sonntag et al. 2003), generalized erythroderma with acral bullae preceeding SCLE (Mutasim, 2003) and annular SCLE lesions that were eventually replaced by morphea (Rao et al. 1990).

SCLE patients may have other LE specific skin lesions. Localized ACLE not uncommonly occurs in the setting of SCLE and is characterized by an erythematous, edematous malar rash in a butterfly pattern that usually spares the nasolabial folds (Sontheimer 1989). Localized ACLE is usually more transient than SCLE and usually heals without scarring or pigmentary changes. Sontheimer has anecdotally suggested that the individuals who developed ACLE following SCLE might be predisposed to eventually developing findings of SLE such as nephritis (Sontheimer 1989).

Classical DLE is the most common form of CCLE and may be seen in some SCLE patients. DLE lesions are more common on the scalp and face and have more hypopigmentation, hyperpigmentation, scarring, follicular plugging, and adherent scale than SCLE lesions. Induration was the most important clinical feature differentiating DLE from SCLE lesions (David-Bajar et al. 1992). Lupus panniculitis, often reported in association with DLE, has recently been reported in association with SCLE (Morgan & Callen 2001).

SCLE patients may also have LE nonspecific skin findings. The most common are diffuse alopecia, mucositis, livedo reticularis, periungual telangiectasias, small vessel vasculitis, Raynaud's phenomenon, cutaneous sclerosis (Sontheimer 1989), and red lunulae (Wollina et al. 1999). Dystrophic calcinosis cutis (Marzano et al. 1999), multiple HPV-11 cutaneous squamous cell carcinomas (Cohen et al. 1992), and erythema gyratum repens, a rare paraneoplastic eruption (Hochedez et al. 2001), have been case reported.

Systemic Disease

Thirty to 63% of SCLE patients have four or more American College of Rheumatology (ACR) diagnostic criteria for SLE (Sontheimer 1989; Chlebus et al. 1998; Parodi et al. 2000; Black et al. 2002). Musculoskeletal symptoms such as arthritis and arthralgias are the most common systemic manifestations

observed. Overall, most patients with SCLE tend to have mild systemic disease and it appears that isolated joint symptoms are a marker for milder disease. Some authors have reported musculoskeletal symptoms in 100 percent of their SCLE cohorts (Molad et al. 1987; Johansson-Stephansson et al. 1989). Renal and central nervous system (CNS) disease has been seen in 20% or less of SCLE cohorts (Cohen and Crosby 1994; Sontheimer 1989; Johansson-Stephansson et al. 1989; Chlebus et al. 1998; Parodi et al. 2000, Black et al. 2002). SCLE cohorts who have nephritis, papulosquamous lesions, high ANAs (>1:640), or who require high dose immunosuppressive therapy may have a worse prognosis (Sontheimer 1985, Cohen and Crosby 1994, Tebbe et al. 1997, Chlebus et al. 1998). Fatalities have rarely been reported in patients with severe systemic manifestations (Sontheimer 1989; Gunmundsen et al. 1992).

Sjogren's syndrome is the most common autoimmune disease associated with SCLE. The HLA-B8, DR3, DRw6, DQ2, and DRw52 extended haplotype is common to both Sjogren's syndrome and SCLE cohorts (Provost et al. 1988). The association with HLA-DR is probably more related to high circulating Ro/SS-A autoantibodies rather than to SCLE skin lesions. High Ro/SS-A antibody titers have also been associated in Sjogren's and LE patients with HLA-DQw1/DQw2 (Harley et al. 1986; Hamilton et al. 1988). *(Fig. 2).* In early studies twelve percent of SCLE cohorts developed Sjogren's syndrome. (Sontheimer et al. 1981). Subsequent studies with longer observation periods have reported the coincidence of Sjogren's syndrome to be as high as 43% (Black et al. 2002). In SCLE patients, the presentation of Sjogren's syndrome may be atypical. Rapidly progressive hypokalemic flaccid tetraparesis caused by a distal renal tubular acidosis was attributed to unrecognized Sjogren's syndrome in an SCLE patient (De Silva et al. 2001). Furthermore, annular erythema of Sjogren's syndrome is considered to be the Asian counterpart of SCLE in white persons. These patients have annular lesions similar to SCLE; however, they lack histopathologic findings at the dermal-epidermal junction of LE. It has been suggested that this is a subset of SCLE and that the relative absence of HLA DR3 in Japanese patients may account for the differences in disease expression (Haimowitz et al. 2000).

Other autoimmune disorders associated with SCLE include rheumatoid arthritis (Cohen et al. 1986; Sontheimer 1989, Pantoja et al. 2002), autoimmune thyroiditis (Sontheimer 1989; Ilan and Ben Yahuda 1991), hereditary angioedema (Gudat and Bork 1989), and autoimmune polyglandular syndrome type II (Schmidt's syndrome) (Wollina and Schreiber, 2003).

SCLE has been associated with various malignancies and some authors have suggested that SCLE is a paraneoplastic dermatosis (Brenner et al. 1997). Reported malignancies include lung, gastric, breast, uterine and hepatocellular carcinoma (Brenner et al. 1997, Ho et al. 2001), Hodgkin's disease (Castenet et al. 1995), malignant melanoma (Modley et al. 1989), and meningioma (Richardson and Cohen 2000). The significance of these anecdotal observations remains to be determined and the authors do not routinely screen new SCLE patients for occult malignancy.

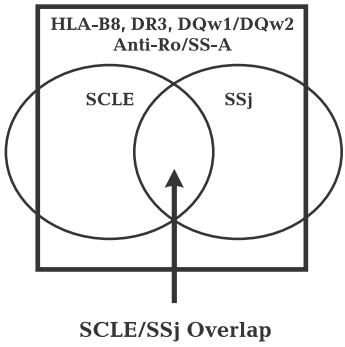

Fig. 2. Immunogenetic associations of SCLE and Sjogren's syndrome

SCLE has been associated with a myriad of other diseases. Polymorphic light eruption (PLE), an inherited photosensitivity disorder, has frequently been associated with SCLE and they may have a common genetic predisposition (Millard et al. 2001b). Two-thirds of SCLE cohorts develop PLE and PLE cohorts have an increased relative risk of SCLE (Millard et al. 2001b). Case reports of porphyria cutanea tarda (Camp and Davis 1997), Sweet's syndrome (Goette 1985), Crohn's disease (Ashworth 1992), gluten sensitive enteropathy (Messenger and Church 1986), and X-linked Chronic Granulomatous Disease Carrier Status (Cordoba-Guijarro et al. 2000) have been associated with SCLE. Because of the infrequency of the latter reports, they may be incidental.

Differential Diagnosis

The clinical diagnosis of SCLE is not always obvious. Annular lesions can be confused with erythema annulare centrifugum, granuloma annulare, erythema gyratum repens, autoinvolutive photoexacerbated tinea corporis (Dauden et al. 2001), or EM. Papulosquamous lesions may be confused with photosensitive psoriasis, lichen planus, eczema, pitiryiasis rubra pilaris, disseminated superficial actinic porokeratosis, contact dermatitis, tinea faciei (Meymandi et al. 2003) and dermatomyositis. Lesional photodistribution, characteristic histopathology and Ro/SS-A autoantibodies are useful in distinguishing SCLE from its differential diagnosis.

Laboratory Findings

Serology. Whereas various autoantibodies have been found in SCLE cohorts, the Ro/SS-A autoantibody is the characteristic laboratory marker. Anti-Ro/

SSA is present in approximately 70% of SCLE cohorts by the classical Ouchterlony double immunodiffusion technique (Sontheimer 1989; Lee et al. 1994; Chlebus et al. 1998; Parodi et al. 2000) with its frequency ranging from 40–82% depending on the method of assay. ELISA (enzyme-linked immunosorbent assay) has been shown to be the most sensitive test for determining Ro/SS-A autoantibodies (Lee et al. 1994) and is the assay technique currently used in most clinical laboratories in the USA. Unfortunately, up to 10% of the normal population demonstrate Ro antibodies by such commercial ELISA techniques. Anti-La/SS-B usually occurs with less frequency and is seldom seen in the absence of anti-Ro/SS-A. Anti-nuclear antibody (ANA) tested with human substrate was found in 60–88% of SCLE cohorts and less frequent when animal substrate was used (Callen and Klein 1988; Herrero et al. 1988; Ng et al. 2000; Reichlin 2000). Other autoantibodies are present with varying frequencies in SCLE (*Table 2)*.

Miscellaneous laboratory. Particularly if they have concomitant SLE, many SCLE patients have laboratory abnormalities including leukopenia, lymphocytopenia (Wenzel et al. 2002), thrombocytopenia, anemia, elevated erythrocyte sedimentation rate, elevated BUN and creatinine, hypergammaglobulinemia, proteinuria, hematuria, and urine casts. Complement levels may be depressed as a result of either genetic deficiency or consumption secondary to immune complex formation.

Histopathology

The histopathologic features of LE specific skin disease include hyperkeratosis, epidermal atrophy, liquifactive vacuolar basal cell degeneration, and nodular perivascular and perifollicular mononuclear cell infiltrates. Some authors have reported degrees of LE specific features among LE subsets. SCLE has more epidermal atrophy, but less hyperkeratosis, basement membrane thickening, follicular plugging and inflammatory cell infiltrates when compared to DLE (Bangert et al. 1984; David-Bajar and Davis 1997). Since the histologic findings typically mirror the clinical findings, this is expected, and corresponds to the fine less adherent scale, lack of induration and less frequent alopecia of SCLE. Herrero et al biopsied the border of annular vesicular lesions in a SCLE cohort group with a high frequency of anti-Ro/SSA and the HLA DR3 phenotype (Herrero et al. 1988). Epidermal necrolysis was prominent and the authors suggested this immunophenotype may correlate with the histologic findings. However, other authors have reported variable success in differentiating LE subsets. Bangert et al. (1984) were unable to distinguish the histology between papulosquamous and annular SCLE lesions.

Table 2. Serological Findings in Patients with SCLE

Serology	Frequency range (percent)
ANA	60–88
Anti-Ro/SS-A	40–82
Anti-La/SS-B	12–71
Anti-dsDNA	1–33
Anti-U1RNP	0–53
Anti-Sm	0–12
Anticardiolipin	10–16
Rheumatoid factor	36–48
VDRL (false positive)	7–33
Antithyroid	18–44
Antilymphocyte	33

Data obtained from Sontheimer et al. (1982); Sontheimer (1989); Johansson- Stephensson et al. (1989); Marschalko et al. (1989); Konstadoulakis et al. (1993); Cohen and Crosby (1994); Chlebus et al. (1998); Parodi et al. (2000); Ng et al. (2000); Wenzel et al.(2000) and Black et al. (2002)

Immunopathology

Lesional skin. Direct immunofluorescence (DIF) is an adjunctive diagnostic test for all subsets of LE. DIF of lesional skin shows immunoglobulins (IgG, IgA, IgM) and complement components in a granular band-like pattern at the epidermal basement membrane (DEJ). In the original cohort (Sontheimer et al. 1979), 40 percent of SCLE patients had a negative DIF. Therefore a positive DIF can help to confirm the diagnosis of LE, but a negative test cannot rule it out.

Nieboer et al. (1988) observed a distinctive "dust-like particle" pattern of IgG deposition near the DEJ of lesional skin in 30% of SCLE patients. Valeski et al. (1992) correlated this pattern with the presence of Ro/SSA autoantibodies. However, Lipsker et al (1998) retrospectively reviewed 4374 cutaneous DIF specimens and found a dust-like particle pattern in only 66 specimens from 60 individuals. Of those 60 persons 85% had some form of connective tissue disease, 53% had SCLE and 36% had Ro/SSA antibodies. Lipsker et al. concluded that whereas these particles are highly suggestive of connective tissue disease in general, the dust-like pattern is not specific for SCLE. Furthermore, since some investigators have not been able to appreciate this DIF pattern due probably to differences in immunofluorescence microscopy techniques, its meaning remain controversial (David-Bajar and Davis 1997).

Nonlesional Lupus Band Test (LBT). A 'positive' LBT shows a 'band' of immunoglobulin and complement reactants at the DEJ of nonlesional skin. The diagnostic and prognostic significance of the LBT is the subject of ongoing debate (Sontheimer and Provost 1996; David-Bajar and Davis 1997). Twenty-six percent of a SCLE cohort had a positive LBT when sun-protected flexor forearm skin was biopsied (Sontheimer and Gilliam 1979). When three or more immunoreactants are present in the LBT of sun-protected skin, the diagnostic specificity for SLE is very high (Velthuis et al. 1992) and a positive LBT correlates with a higher risk of lupus nephritis (Davis and Gilliam 1984). It is unclear if the LBT provides added value to more available, less invasive testing such as serologic assays for double-stranded DNA autoantibodies. The greatest utility of the LBT may be in patients with atypical clinical and laboratory presentations of SLE.

Evaluation and Management

Effective management of SCLE patients relies upon adequate baseline evaluation and ongoing surveillance during treatment. The initial history and physical should include a comprehensive review of systems in order to uncover evidence of systemic disease. Additionally, laboratory workup should include a complete blood count with differential, platelet count, erythrocyte sedimentation rate, urinalysis, and blood chemistry profile. In addition to histopathology and ANA, Ro/SS-A autoantibodies, determination of C3, C4 and CH50 may also be helpful depending on clinical symptoms. Follow-up intervals for re-examination and laboratory monitoring should be customized to the individual patient as well as selected treatment modality.

Adequate patient education is essential. Disease-provoking factors such as sunlight, artificial ultraviolet (UV) exposure, photosensitizing drugs and even tobacco use are all modifiable factors, and alteration of these may be of value in the course of the disease. If possible, potentially offending drugs should be eliminated. Initial medical therapy should focus on maximizing local measures before systemic agents are introduced.

Local Therapy

Protection from UV exposure. The importance of avoiding direct sunlight especially during midday hours and summer months should be stressed. A relatively lower danger from UV radiation while outdoors can be realized if one's shadow is longer than one is tall. SCLE patients should also be advised to avoid use of artificial tanning devices. Tightly woven clothing and broad-brimmed hats should be worn when outdoors. Specialty clothing lines which offer maximal UV protection are currently being marketed over the internet

for those anticipating prolonged sun exposure. Examples of internet sites include www.sunprecautions.com, www.sunproof.com and www.sunprotectiveclothing.com.

In order to achieve maximal shielding from sunlight, broad spectrum sunscreens should be used in conjunction with photo-protective clothing. Water resistant or waterproof agents that block both UVA and UVB with a sun protection factor (SPF) of 30 or greater should be selected and generously applied. Since it has been shown that the amount of sunscreen that consumers put on is less than that applied under laboratory conditions when determining SPF ratings (Azurdia et al. 1999) it is important to use high SPF products to insure adequate protection under real-life conditions. Additionally, products with Parsol 1789 (avobenzone), zinc oxide or titanium dioxide provide broad UVA protection, offering a possible added value for SCLE patients (Callen et al. 1991a). Standardized testing to determine the best sunscreen for maximal protection in SCLE patients is needed. Stege et al. (2000) tested 3 commercially available sunscreens via photoprovocative testing with UVA and UVB and showed that while all three sunscreens tested were at least somewhat beneficial, they differed significantly in their abilities to protect against development of skin lesions and against the corresponding upregulation of ICAM-1 in exposed skin. These differences were found in spite of the fact that all 3 contained both Parsol 1789 and Titanium Dioxide. Sunscreens should be applied 30 min. before sun exposure and reapplied after bathing or significant perspiration. Stick-type sunscreens formulated for the lips may be better tolerated around the eyes than other sun blocking products. UV blocking films such as Llumar® UV Shield™ (www.uv-shield.com) should be placed over home and automobile windows. Plastic films or shields may be applied over fluorescent lighting, which can be a small source of UV irradiation. Corrective camouflage cosmetics such as Dermablend® (www.dermablend.com) and Covermark® (www.covermark.com) offer the dual benefit of being highly effective physical sunscreens as well as aesthetically pleasing cosmetic masking agents which can provide great psychological benefit for these patients.

Topical agents. Superpotent topical class I agents are appropriate initial agents in the management of SCLE. Twice daily application to lesional skin for two weeks followed by a two week rest period is recommended in order to minimize the risk of steroid atrophy and telangiectasia. Intralesional steroids are not as effective in the treatment of SCLE as they are in DLE. Additionally, most SCLE patients have lesions that are too numerous to be managed in this manner. Topical tacrolimus may be of some benefit especially on the face and on skin lesions with less hyperkeratosis (Bohm et al. 2003), without the skin atrophy side effect seen with topical steroids. A speculative review concerning the utility in SCLE of new technology for defecting the stratum corneum barrier has recently been presented (Ting and Sontheimer 2001). Unfortunately, the majority of patients do not respond adequately to local therapy, and systemic therapy is usually required.

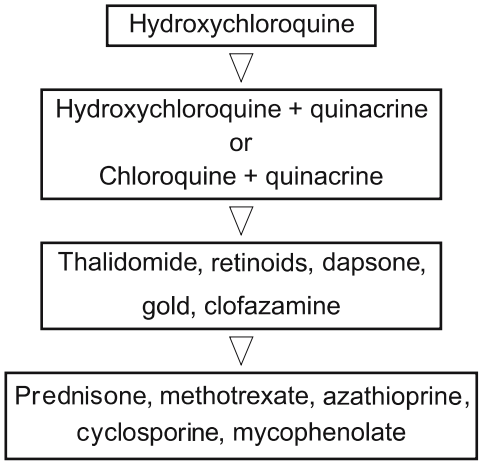

Fig. 3. Suggested algorithm for prescribing systemic medications in SCLE

Systemic Therapy

Antimalarials. The aminoquinolone antimalarial agents have been the most efficacious of systemic agents used in the treatment of SCLE and represent first-line systemic therapy (see *Fig. 3*). Up to 75 percent of patients have responded to one or a combination of drugs within this class (Furner 1990a). Initial treatment should begin with hydroxychloroquine sulfate not to exceed a dose of 6 mg/kg lean body mass/day. It requires 6–8 weeks to achieve equilibrium blood levels. If an adequate clinical response is achieved, the dose can be decreased to 3 mg/kg lean body mass/day for maintenance for at least one year in order to minimize recurrence. If there is no significant improvement by 2 months, quinacrine hydrochloride 100 mg/day can be added (Feldman et al. 1994). If there is an inadequate response to this combination regimen after 4–6 weeks, chloroquine diphosphate 3 mg/kg lean body mass/day can be substituted for hydroxychloroquine while continuing quinacrine.

A rare, but well-known side effect of the antimalarial agents is retinal toxicity. When using either hydroxychloroquine or chloroquine, ophthalmologic evaluation is required. The current surveillance guidelines recommend follow-up ophthalmologic examination 5 years after an initial baseline exam in uncomplicated individuals on hydroxychloroquine. Complicated individuals (i.e. those who have taken antimalarials for greater than 5 years, those taking larger than recommended daily doses, those with high body fat levels, those greater than 60 years of age, and those with liver or kidney disease) should have yearly screening examinations. (Marmor et al 2002; Marmor 2003) Examination should include fundoscopic assessment, visual field testing (including central fields with a red object) and visual acuity testing. The use of an Amsler grid at home may allow early self-detection of visual field defects.

This is important since retinal changes may become irreversible if not found early. The risk of retinal toxicity may be minimized if certain daily doses of hydroxychloroquine (6 mg/kg/day) and chloroquine (3 mg/kg/day) are not exceeded (Lanham and Hughes 1982). Hydroxychloroquine and chloroquine should not be used together because of an enhanced risk of retinal toxicity. Quinacrine has not been shown to cause retinal toxicity. However, it is associated with a higher incidence of side effects than the others, including headaches, gastrointestinal intolerances, hematologic and dermatologic manifestations. Quinacrine is more likely to induce hemolysis in patients who are glucose-6-phosphate dehydrogenase (G6PD) deficient (Trenholme and Carson 1978).

All of the antimalarials have dermatologic side effects. Blue-black pigmentation of sun-exposed skin, the palatal mucosa and nails has been seen with these agents. They can rarely cause a bleaching of lightly pigmented hair. The antimalarials can also induce a lichenoid hypersensitivity drug reaction in the skin which can be confused with the appearance of true cutaneous LE lesions including SCLE. Thus, if new skin lesions appear in an SCLE patient on antimalarial therapy, one should consider the possibility of a superimposed lichenoid drug reaction. Quinacrine can cause diffuse reversible yellowing of the skin, especially in fair-skinned individuals. Other potential side effects of the antimalarials include hematologic (e.g. bone marrow suppression, aplastic anemia), neuropsychiatric (e.g. toxic psychosis, grand mal seizures), cardiac (e.g. arrhythmias, cardiomyopathy) and muscular. These are less common than in the past, when higher daily dosage regimens of antimalarials were used. Periodic laboratory monitoring of hematological and hepatic function is helpful in identifying any patient who might suffer an idiosyncratic reaction. Johansen and Gran (1998) reported two cases of ototoxicity associated with hydroxychloroquine. Hearing loss has been associated with chloroquine and quinine in the past, but this was the first report of such with hydroxychloroquine.

There is evidence that patients with cutaneous LE who smoke are less likely to respond to antimalarial therapy than nonsmokers (Rahman et al. 1998; Jewell and McCauliffe 2000). In addition to the well-known dangers of smoking, this represents another reason to strongly encourage tobacco cessation in the SCLE patient. Appropriate referrals should be made if counseling or drug therapy is needed to accomplish this goal.

Thalidomide. Thalidomide is a potent anti-inflammatory agent which acts in part via downregulation of TNF-α, a proinflammatory cytokine which may be involved in the pathogenesis of SCLE as discussed above. Treatment with 50–300 mg/day can be very effective in otherwise-refractory cutaneous LE (Stevens et al. 1997; Georgala et al. 1998; Warren et al. 1998; Duong et al. 1999; Ordi-Ros et al. 2000). In general, about 75 percent of cutaneous LE patients will respond to antimalarial monotherapy or combination therapy. It appears that thalidomide can be effective in 75 percent of antimalarial-refractory cutaneous LE. Because of the high rate (approximately 75 percent)

of relapse after withdrawal of the medication, it has been suggested that low maintenance doses for long periods of time may be necessary (Ordi-Ros et al. 2000). Alternatively, other forms of therapy such as antimalarials can be used to maintain thalidomide-induced remissions. Since thalidomide is a potent teratogen, special precautions must be taken when prescribing the drug. Other second-line drugs should be considered in females of child-bearing potential. Thalidomide is available in the United States under the name Thalomid. Physicians and pharmacies are required to register with the manufacturer, the Celgene Corporation. Once registered, Celgene will send the physician specially developed materials (System for Thalidomide Education and Prescribing Safety (STEPS) to educate patients in the prevention of birth defects.

Another important adverse effect of thalidomide is sensory neuropathy, which is sometimes irreversible. Routine clinical assessment for neuropathy is the single most effective means to detect the early development of neuropathy (Duong et al. 1999). Nerve conduction tests are recommended at baseline and periodically during treatment, but the role of these is not well defined. Evidence of neuropathy, by either high clinical suspicion or by electrophysiologic data is an indication to withdraw the drug (Stevens et al. 1997). Other side effects of thalidomide include amenorrhea, drowsiness, weight gain, vomiting, constipation, migraine headaches, and skin eruptions. Some of these side effects are improved on lower daily doses and when the drug is given at bedtime. A case of toxic pustuloderma secondary to thalidomide was reported in a patient with refractory cutaneous LE (Rua-Figueroa et al. 1999). While clear evidence of thrombosis in SCLE patients on thalidomide is lacking, Piette et al. (2002) also warned about the potential thrombotic risk associated with thalidomide therapy. There are known cases of thrombosis in cancer, Bechet's syndrome, and SLE patients including one SCLE patient with antiphospholipid antibodies (Flageul et al. 2000) on thalidomide therapy. The authors emphasized the need for increased surveillence in SCLE patients treated with thalidomide. These concerns are especially valid since SCLE patients often have additional prothrombotic risk factors such as smoking, estrogen-containing contraceptive use, antiphospholipid antibodies, or stopping antimalarial therapy like hydroxychloroquine which has antithrombotic properties.

Dapsone. Dapsone (Diaminodiphenylsulfone) has been used successfully in some antimalarial-refractory SCLE cases (McCormack et al. 1984; Holtman et al. 1990; Neri et al. 1999) but overall experience with this agent for cutaneous LE has been disappointing (Sontheimer and Provost 1996; Callen 1997). An initial dose of 25 mg twice daily can be increased to 200–300 mg/day as needed. Frequent monitoring is required to evaluate for potential renal, hepatic, and hematologic toxicity, including hemolysis and/or methemoglobinemia that occur especially in patients deficient in G6PD enzyme activity.

Retinoids. The synthetic retinoids, isotretinoin and acitretin, have been shown to significantly improve SCLE lesions in doses of 1/2–1 mg/kg/day (Furner 1990b; Richardson and Cohen 2000). Their long-term use may be

limited by the potential for teratogenicity, mucocutaneous dryness, photosensitivity, hepatitis, hypertriglyceridemia, mood alteration, psuedotumor cerebri, and bony changes consistent with diffuse idiopathic skeletal hyperostosis (DISH) syndrome.

Clofazimine and Gold. Although these agents have been successfully used in the treatment of refractory cutaneous LE (Costner et al. 2004; Crovato 1981), they are both limited by their potential for toxic side effects.

Systemic corticosteroids and other immunosuppressive agents. These agents are usually reserved for those patients who have not responded to less toxic therapies. However, they may be needed before an adequate trial of less toxic drugs is completed in those patients with severe disease. Pulsed intravenous methylprednisolone at a dose of 1 g for three consecutive days provided improvement of SCLE patients in the presence of systemic LE (Goldberg and Lidsky 1984). The side effects of steroids, especially when used over long periods of time are worrisome. They are more appropriately used as adjunctive treatment and tapered off if possible. Steroid-sparing agents that may be of benefit in refractory SCLE include methotrexate (Boehm et al. 1998, Kuhn et al. 2002b), azathioprine (Callen et al. 1991b), cyclosporine, and mycophenolate. Mycophenolate is increasingly being reported as an effective option for refractory SCLE. Hanjani and Nousari (2002) reported one SCLE patient treated with 3 g/day of mycophenolate with complete resolution at 3 months and no flare by 10 months after failing multiple prednisone tapers and antimalarials. Schanz et al. (2002) presented two additional cases of antimalarial, azathioprine, and high dose steroid refractory SCLE which completely resolved within a few weeks on 2g/day of mycophenolate. In one patient this response was successfully maintained for over 24 months on a lower dose of at least 1 g/day. Mycophenolate offers a lower toxicity profile than some of the other immunosuppressants. A thorough understanding of potentially harmful side effects is imperative with all of these medications, and close monitoring is essential.

Immune regulation. Five patients, including one SCLE patient with refractory cutaneous LE, who received infusions of chimeric CD4 monoclonal antibody showed improvement and became more responsive to conventional treatments (Prinz et al. 1996). Intravenous immunoglobulin may lead to improvement of cutaneous LE lesions (Genereau et al. 1999; Goodfield et al. 2004), but its study and use is limited mostly by cost-prohibitiveness. Recombinant IFN-α 2a, allowed a complete response in two of four SCLE patients (Thivolet et al. 1990). However, the use of IFN-α has also been associated with the induction and/or exacerbation of SCLE (Srivistava et al. 2003) and SLE. Caution should therefore be used in this setting.

Fautrel et al. (2002) reported the resolution of SCLE in a rheumatoid arthritis patient using etanercept, an anti-TNFα recombinant biologic agent. Etanercept and infliximab have both been associated with the development of anti-double-stranded DNA antibodies and a lupus-like syndrome in some RA and Crohn's patients. A small number of case reports suggests the possi-

bility of etanercept-induced SCLE (Bleumink et al. 2001). Thus, there is some concern regarding the induction or unmasking of cutaneous or systemic LE with the use of either of these agents in cutaneous LE. Rituximab (Rituxan), a recombinant monoclonal antibody which inhibits CD20 expressing B cells, has shown efficacy in small numbers of systemic and cutaneous LE patients (Kneitz et al 2002; Perotta et al 2002). Finally, other biologic drugs which inhibit antigen presenting cell-T cell interaction are speculated to be of benefit in SCLE, although more study is needed. Some examples include alefacept (Amevive), an inhibitor of the LFA3:CD2 interaction, and efalizumab (Raptiva), an inhibitor of the LFA-1:ICAM-1 interaction.

Other. Two antineoplastic drugs, cyclophosphamide and cytarabine, were beneficial in refractory SCLE (Schulz and Menter 1971; Yung and Richardson 1995). Although sulfasalazine, phenytoin, danazol, dehydroepiandrosterone sulfate (DHEAS) and cefuroxime axetil have all been suggested in the treatment of cutaneous lupus, they have not been effectively used by the authors.

Ultraviolet A-1 phototherapy (UVA-1). Finally, it has been suggested that cutaneous lupus patients may benefit from low doses of longer wavelength (340–400 nm) UV irradiation (Sonnichsen et al. 1993; McGrath 1997). According to McGrath (1997), this modality reduced the need for medication and attenuated autoimmune antibody levels. These results should be interpreted with caution. Conflicting data indicate that UVA, including long wave UVA, may play a role in cutaneous LE (Lehmann et al. 1990; Nived et al. 1993). Additionally, in an SLE murine model, UVA-1 irradiation was associated with increased renal disease and death (Cai et al. 2000).

Prognosis

Because SCLE has been recognized for little over two decades, long-term outcomes of patients are not yet known. Most patients tend to have intermittent recurrent skin lesions without significant disease progression, while some may experience permanent remissions. Approximately 15 percent of patients developed active SLE in the original cohort. More recent studies addressing prognosis have revealed similar findings (Chlebus 1998). In addition, an informal long-term prospective follow-up study of SCLE patients who presented from 1971–1995 in the Department of Dermatology at UT Southwestern Medical Center in Dallas was initiated by one of the authors (RDS, unpublished observation). To date, 18 of 130 patients have been evaluated. Mean duration of follow-up was 12.6 years. Thirty-nine percent had inactive skin and systemic disease at follow-up. The most common complaints other than skin lesions and photosensitivity were fatigue, arthralgias and Raynaud's phenomenon. In addition, many patients had a subjective history of depression. Lesions were predominantly papulosquamous in this particular population. Facial involvement, hypopigmentation and telangiectasias were common, while true scarring rarely occurred. At least one, and possibly three, out of

130 died of causes related to SLE (pancreatic vasculitis). A larger number of SCLE patients needs to be examined in a prospective study to more firmly establish its course, ANA and Ro/SS-A prevalence, overlap with other connective tissue diseases, as well as prognosis.

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