Subacute Cutaneous Lupus Erythematosus
A two-decades' perspective

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ABSTRACT
The concept of SCLE as a distinctive subset in the disease spectrum of lupus erythematosus has been supported by the literature over the past 20 years. It is characterised by photo-distributed non-scarring papulosquamous and/or annular skin lesions with a LE-specific histopathology. Drug-induced aetiology and overlap with Sjögren's syndrome have been documented. The pathogenetic role of UV-light and the Ro antigen-antibody system have been actively investigated. Its management includes thorough evaluation, patient education, photoprotection, topical steroids, antimalarials and a variety of other agents. It is hoped that novel forms of immunotherapy can be established in the coming decade.

Keywords: cutaneous lupus erythematosus, subacute; anti-Ro antibody; ultraviolet light

INTRODUCTION
Subacute cutaneous lupus erythematosus (SCLE) as a distinct subset of lupus erythematosus (LE) was first suggested by Gilliam in 1977.1 In 1989, Sontheimer summarised the worldwide experience with SCLE ten years after their initial report on this disease2 and concluded that the clinical, serologic and genetic homogeneity of this LE subset was largely supported by the world literature.3 Over the past years, the concept of the disease continues to evolve as new knowledge has accumulated. It is therefore justified to outline the contemporary view of SCLE after two decades of intensive research.

SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS (SCLE) REVISITED

A. Epidemiology

The bulk of recent data suggest that SCLE lesions occur in 5 to 15% of reported LE patients in the United States, Europe and other countries.4 Most of the SCLE patients in the original cohort reported in 1979 were young to middle-aged white females and only 30% were male.5 Similar demographic features are noted in most other studies.

In a series of 30 Chinese SCLE patients, they were mainly young to middle aged and female predominant (female to male=2.8:1).5 From the statistics of Social Hygiene Service, lupus patients constitute only a small percentage of our workload (about 0.15%). However about one third of the lupus patients we saw in Social Hygiene Service of Hong Kong had SCLE. (table 1)

B. Cutaneous features

The hallmark of SCLE is a photo-distributed erythematous, non-scarring papulosquamous and/or annular eruption which has a LE-specific histopathology.2 Occasionally, the early lesion of annular SCLE may resemble erythema multiforme.
(Rowell's syndrome). The face is often spared in SCLE. When facial involvement does occur, it is usually in the form of malar erythema.6

Other types of LE-specific and LE-non-specific skin lesions can also be seen in SCLE. In the original cohort 19% of the 27 SCLE patients also had typical discoid LE skin lesions.2 In a subsequent study, 15% had discoid LE lesions and 15% had facial acute cutaneous LE lesions.6 Photosensitivity was found in 52% of patients in the original cohort.2 Subsequent studies have shown that 70-90% of patients with SCLE are photosensitive though the study by Shi et al (1987) reported that only 27% of their Chinese patients had photosensitivity.5

C. Systemic features

The initial impression on the generally good prognosis in SCLE patients was supported by the majority of published data.3 About half SCLE patients meet the American College of Rheumatology's revised criteria for the classification of SLE, but they often have a relatively mild disease course. Joint problem is the most common systemic feature present whereas significant renal or central nervous system disease is present in only about 10% of SCLE patients.3

However it must be emphasised that a few SCLE patients develop severe and sometimes fatal disease. A great challenge for the future will be to identify prognostic factors which can reliably predict the development of a severe systemic disease outcome in this LE subset.

D. Histopathology and immunopathology

In SCLE, histopathologic findings may include hyperkeratosis, epidermal atrophy, colloid bodies, basal cell liquefactive degeneration, thickening of the basement membrane, dermal oedema and a superficial perivascular and peri-adnexal infiltrate composed primarily of lymphocytes. Increased amounts of dermal mucin may also be present.

Initial studies showed that a granular, band-like pattern of immunoglobulins and complement components deposits at the dermo-epidermal junction of lesional skin (the so-called 'lupus band') could be detected by direct immunofluorescence in 60% of SCLE patients, compared to higher percentages for acute cutaneous LE and discoid LE lesions. Other studies have given similar or higher frequencies.3 Thus the presence of immunoreactants at the dermo-epidermal junctions help to support a diagnosis of SCLE but their absence does not exclude it. Furthermore such immune deposits are not specific for LE, as 20% of biopsy specimens from sun-exposed skin of normal young adults have shown positive immunofluorescence consistent with LE.7

In addition, Nieboer et al (1988) reported a 'dust-like particle' pattern of inter- and intracellular IgG deposition scattered throughout the basal layer of the...
epidermis and the subepidermal region in about 30% of SCLE lesional skin biopsies. In a comparative study of 27 LE patients, such a particulate pattern was observed in all SCLE lesional specimens as well as in non-lesional sun-exposed and non-lesional unexposed skin. Similar particulate epidermal staining was found in human skin grafted onto immunosuppressed mice after intravenous infusion of anti-Ro-antibody-containing human serum. Such staining was not seen after infusion of normal serum, and could be blocked by removal of the anti-Ro antibodies. These suggest that the particulate epidermal deposition of IgG may indicate the binding of anti-Ro antibodies.

**E. Laboratory and serologic findings**

Antinuclear antibodies (ANAs) were found in the majority of SCLE series in which a human ANA substrate was used. Mouse or rat liver tissue sections were used as ANA substrate in those studies which had the lowest frequency of ANA positivity. These rodent tissue substrates are known to be relatively deficient in the Ro antigen.

The majority of SCLE patients are reported to have anti-Ro antibodies in most published works. Double immunodiffusion is the method most often used. ELISA (enzyme-linked immunosorbent assay) technique is more sensitive and has been shown to give higher percentages of positivity for the same series of patients in several studies. Anti-La antibodies are also found in patients with SCLE though in a lower percentage.

Antibodies to double-stranded DNA are noted in about 10-25% and rheumatoid factor in approximately one-third of the patients.

**F. Genetic associations**

Sontheimer and co-workers reported an increase in the human histocompatibility antigen (HLA) DR3 in their initial SCLE cohort. Subsequent studies by other groups have found that 50% or more of SCLE patients have the HLA-DR3 phenotype whereas this phenotype is normally found in only 25% of the United States white population. HLA-DR2 is also associated with SCLE. Watson et al (1991) suggests that the HLA-DR associations of SCLE relates more to the anti-Ro antibody response in these patients rather than to the SCLE skin lesion, because they found that no HLA associations were noted upon removal of Ro-positive patients from previous studies.

**G. Disease associations**

SCLE has been reported in association with rheumatoid arthritis and Sjögren's syndrome. The relationship between SCLE and Sjögren's syndrome is of more prognostic significance. An entity of Sjögren's/lupus erythematosus (SS/LE) overlap syndrome is recognised and these patients frequently have cutaneous findings similar to those seen in SCLE, though cutaneous vasculitis lesions are more common (in about one-thirds of cases in a series of 33 anti-Ro antibody positive SS/LE overlap patients). In addition, they have concomitant features of sicca complex and frequently demonstrate neuropsychiatric and pulmonary disease.

**H. Drug-induced subacute cutaneous LE**

Reed and co-workers (1985) reported 5 patients who developed cutaneous lesions with the clinical and histologic characteristics of SCLE plus the presence of anti-Ro antibodies while taking hydrochlorothiazide. Recently, 9 patients on calcium channel blockers for hypertension were reported to develop a skin eruption consistent with SCLE. Discontinuation of the drug led to clearance in most patients. These reports emphasise the need for a thorough drug history in the evaluation of patients with SCLE.

**PATHOGENESIS OF SCLE - THE ROLE OF RO/ANTI-RO SYSTEM**

The pathogenesis of subacute cutaneous LE has been under intensive research for the last two decades. Two areas have received most attention: the role of anti-Ro antibodies and ultraviolet (UV) radiation. Both SCLE and neonatal LE (NLE) are associated with anti-Ro antibodies. They constitute the closest link between specific antibodies and cutaneous disease in LE. NLE presents with isolated congenital heart block and/or papulosquamous eruption which is very similar to SCLE. In the following paragraphs the evidences for and against the pathogenetic role of anti-Ro are outlined.
Evidences supporting the pathogenetic role of anti-Ro in SCLE or NLE:
1. Anti-Ro antibodies are found in most patients with SCLE and nearly all patients with NLE (for the latter, also in their mothers).
2. NLE skin lesions generally resolves within the first six months of life, corresponding to the disappearance of maternally derived antibodies like anti-Ro.
3. Ro antigen is normally expressed in the human epidermis and cardiac tissue, which are the major target organs.  
4. IgG antibodies are deposited in the skin in SCLE and in the skin and heart in NLE. There is evidence that these deposits are anti-Ro.
5. Ultraviolet (UV) light exposure can modulate Ro antigen expression in vivo and in vitro in a manner that enhances binding of anti-Ro to keratinocytes. Recently, Casciola-Rosen et al (1994) showed that the keratinocytes which demonstrated cell surface binding of anti-Ro following UV irradiation had the morphologic characteristics of cell undergoing apoptosis. They were able to identify the clustering of Ro antigen in blebs at the surface of apoptotic cells.
6. Antibodies to Ro can induce cellular cytotoxicity of targets with cell surface expression of the antigen.

On the other hand, there are observations against the pathogenetic role of anti-Ro:
1. Most patients with systemic LE and Sjögren’s syndrome (SS) having high levels of anti-Ro antibody do not develop photosensitive cutaneous LE skin lesions, although a small group of patients with SS/SCLE overlap have been described.
2. Not all patients with SCLE have anti-Ro antibodies. A few NLE patients also do not have anti-Ro.
3. Only 1% of all babies born to anti-Ro positive mothers have clinical evidence of NLE. The risk is higher (about 6 - 13%) if the mothers have anti-Ro and systemic LE.
4. There was no significant relationship between the circulating anti-Ro antibody levels and skin disease activity in a study of 80 serum specimens from 12 patients with SCLE.
5. Pathology simulating LE-specific skin disease has not developed in animal models where passive transfer of human anti-Ro antibodies resulted in IgG binding to the epidermal cells in human skin explants.
6. Anti-Ro antibodies are found in unaffected skin of SCLE patients.

From the discussion above, one can appreciate the following points:
1. the strongest evidence for the pathogenetic role of anti-Ro comes from NLE and has been extended to SCLE as well;
2. it has not been conclusively shown that anti-Ro when deposited in the skin causes disease, although there is circumstantial evidence that it can;
3. since antibody deposition alone does not result in skin lesions, something further must occur for triggering tissue injury and clinical disease.

To prove that anti-Ro does cause disease, a better animal model is needed. An immunocompetent experimental model which incorporates autologous antibody triggers and immune effector mechanisms, such as might be constructed in a human Ro transgenic mouse model, may provide better answers.

PRINCIPLES OF MANAGEMENT OF SCLE

A. Patient evaluation

The objectives of the evaluation of a patient with suspected SCLE are (i) to confirm the diagnosis, (ii) to determine the pattern and extent of systemic involvement and (iii) to develop a long term management plan.

The diagnosis of SCLE rests on the presence of a photo-distributed erythematous, non-scarring papulosquamous and/or annular eruption with a LE-specific histopathology. The clues to diagnosis often come from the photo-distribution plus the histopathology and immunofluorescence findings. The presence of anti-Ro antibodies can support (but is not essential for) the diagnosis.

A thorough drug history should be taken. A family history should also be taken and, if positive, would raise the possibility of a genetic complement component deficiency.

A review of the major organ systems should be made to look for any systemic involvement. The
symptoms of Sjögren’s syndrome should be specifically asked for as their presence in an anti-Ro antibody-positive patient with SCLE is associated with neuropsychiatric and pulmonary disease.\textsuperscript{15}

Initial laboratory evaluation should include, at the minimum, a complete blood count, erythrocyte sedimentation rate, urinalysis and blood chemistry profile. Serological tests like antinuclear antibodies, anti-double-stranded DNA (anti-dsDNA) antibody and C3, C4 level are often performed. It is suggested that follow-up laboratory assessment should be considered at 6- to 12-month interval, unless patient develops symptoms that necessitate an earlier assessment.

With all the above information in mind, one can formulate a management plan which involves patient education, local therapy and systemic therapy. One should also consider the need to enlist the help of other specialists depending on the overall pattern of disease uncovered.

B. Patient education

Education on the current understanding of LE in general and SCLE in particular is helpful in patient management. The reassurance that most SCLE patients generally do run a benign course is an important concept to communicate. They should be warned specifically the importance of photo-protection. In addition, medications that can induce and aggravate SCLE should be avoided.

C. Local therapy

Treatment of SCLE lesions with moderate to potent topical corticosteroids is often helpful in localised disease. Care must be taken when lesions are widespread of when the disease involves the face. In these cases topical steroids are best used adjunctively to other therapies.\textsuperscript{25} Intralesional corticosteroids are also useful in localised disease.

D. Systemic therapy

\textbf{Antimalarial therapy}

Antimalarial therapy is the treatment of choice when local therapy fails or is unlikely to be successful. It is successful in about 80% of patients with SCLE.\textsuperscript{3} The most commonly used agents are hydroxychloroquine, chloroquine and mepacrine, all being useful in the management of cutaneous lesions, arthritis and mild serositis in lupus erythematosus. In general, hydroxychloroquine is the best tolerated and therefore often used first.\textsuperscript{26} Therapeutic effect is not observed till at least 6 weeks have elapsed. If there is no significant improvement, mepacrine can be added. Combination antimalarial therapy has been reported to be effective in two small series of treatment-resistant cutaneous LE.\textsuperscript{27, 28} Owing to the delayed effect of antimalarial, it is sometimes necessary to give a short burst of oral corticosteroids to gain faster control of widespread SCLE lesions.

\textbf{Antimalarial-refractory SCLE}

Patients who have been managed with photoprotection, topical steroids, and an adequate trial of anti-malarial therapy but continue to develop new lesions or fail to respond adequately can be considered to be antimalarial refractory.\textsuperscript{29} Before moving to more toxic and less well studied therapies, the following points should be considered in these patients:

i) check compliance with the previous therapy

ii) assess possibility of lichenoid drug reaction due to antimalarial therapy

iii) assess possibility of drug-induced SCLE

iv) re-assess the diagnosis of SCLE.

If the disease is indeed antimalarial refractory, various classes of other therapeutic agents can be tried. However, the evidence in literature for their use is mainly derived from case reports, case series, or open trials of small number of patients.

Various retinoids have been tried in the treatment of SCLE. Cases refractory to antimalarial and/or oral corticosteroids may respond. However, skin lesions often relapse with discontinuation of drug use and long term treatment may be necessary to maintain control.\textsuperscript{26} A randomised double-blind study comparing acitretin and hydroxychloroquine had shown that both drugs were effective in about 50% of patients (discoid LE and SCLE) but side effects were more common in patients on acitretin, necessitating discontinuation in 14% of patients (4 out of 28).\textsuperscript{30} Dapsone has also been tried in a small number of SCLE patients.\textsuperscript{26}
Systemic corticosteroids and immunosuppressive therapy are used to treat patients with SCLE recalcitrant to other forms of therapy or with systemic involvement. Occasionally they may be used as an initial mode of therapy to gain control of disease activity in patients with very severe skin manifestations. However the application of such agents to the treatment of cutaneous LE generally carries an unfavourable risk-benefit ratio. Azathioprine and cyclophosphamide were reported to be useful in small case series.

Thalidomide has been used in the treatment of severe and refractory discoid LE and SCLE as a last resort. Improvement is prompt though relapses are common after discontinuation. Maintenance therapy is often needed. In Hong Kong, the drug is only released on a compassionate basis to those SCLE patients who have found the condition severely debilitating or associated with severe psychological stress and are found resistant to all other treatment modalities. A consent form has to be signed by the patient for restricting the use of the medication to the subject only and for agreeing to conform to strict contraception during treatment. It is administered under close supervision in Sai Ying Pun Social Hygiene Service.

Immunomodulatory therapies like interferon-alpha and immunotherapy using anti-CD4 monoclonal antibody infusion have been experimented.

To sum up, a treatment algorithm of SCLE is suggested in figure 1. However it cannot be over-emphasised that the choice of therapy for antimalarial-refractory disease is largely personal, and should depend on the evaluation of risk to benefit ratio for each individual patient.

CONCLUSION

The discovery of SCLE has generated a lot of research, especially on the pathogenetic role of ultraviolet radiation and Ro antigen/antibody system. However, two major problems remain unresolved. First is the identification of parameters to predict the risk of systemic involvement in patients presenting with predominant cutaneous manifestations. Second is the establishment of more logical preferably evidence-based guidelines for the management of antimalarial-refractory disease. It is hoped that with the continuing advances in the understanding of immunopathogenesis of SCLE, novel forms of immunotherapy may be

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Figure 1: A suggested treatment algorithm of SCLE
established to open a new era of therapeutics in the coming decade.

Learning points:
Anti-Ro antibodies are found in most but not all patients with SCLE, and in nearly all patients with NLE.
The presence of Sjögren’s syndrome in an anti-Ro antibody-positive SCLE is associated with neuropsychiatric and pulmonary disease.

References