The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Subacute cutaneous lupus erythematosus

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1 Introduction

Subacute cutaneous lupus erythematosus (SCLE) is a photosensitive dermatosis, categorized as a cutaneous lupus erythematosus (CLE) variant. It may occur in conjunction with various other disorders, e. g. systemic lupus erythematosus (SLE), Sjögren's syndrome, rheumatoid arthritis, and in patients with deficiencies in the second component of the complement system (C2d). Additionally, it may be induced by certain sun-sensitizing drugs.

SCLE is most common in Caucasian females, with a female-to-male ratio of 4 : 1 and is found in about 50 % of patients that suffer from SLE. The prevalence of SLE ranges from 17–48 : 100 000 with a peak around the ages of 40–60 years [1].

SCLE can coincide with discoid lupus erythematosus (DLE) and can lead to small vessel vasculitis. The skin lesions usually heal without scarring, no atrophy occurs, but a residual dyspigmentation may remain. The same criteria used to classify SLE tend to be positive in patients with SCLE, and serological analysis often helps to establish a diagnosis. A number of human leukocyte antigens (HLA) can be present in SCLE-patients: HLA-B8, HLA-DR3, HLA-DRw52, and HLA-DQ1; additionally, anti-Ro (SS-A) auto-antibodies are associated with SCLE. Together, these factors manifest clinically in an autoimmune response that culminates in keratinocyte apoptosis.

The prognosis of SCLE is generally better than for patients with SLE as the disease is less severe. However, in certain cases, a full systemic manifestation may occur, and end-organ failure is possible.

2 Diagnostic measurements for experts

The major elements leading to the diagnosis SCLE are the patient's history (e. g. photo-aggravating factors, hormones as possible trigger factors, family history), a careful clinical evaluation of the presentation of cutaneous symptoms, histological findings and serological markers such as ANA, Ro (SSA) and/or La (SSB) antibodies The histopathological and serological findings associated with SCLE

Table 1. Histological and serological parameters indicative of discoid lupus erythematosus.

Histology

– Atrophy of the epidermis
– Presence of inflammatory cell infiltrates:
  – around blood vessels,
  – around appendiceal structures and
  – in a subepidermal location.
– Vacuolar alterations of the basal cell layer

Serology

– Antinuclear antibodies
– Anti-native DNA (double-stranded or nDNA)
– Anti-Ro (SS-A) autoantibodies:
  – 90 % in patients with annular SCLE,
  – 80–85 % for papulosquamous SCLE,
  – > 95 % for patients with C2d deficiency, Sjögren's syndrome and vasculitis
  – > 90 % in mothers of children with neonatal lupus erythematosus and
– 70–80 % in cases of drug-induced SCLE.
– Anti-La (SS-B) autoantibodies in < 70 % of cases

are shown in Table 1. A detailed description of the laboratory tests follows in the sections 'Diagnostic tests' and 'Testing methods'.

Additionally, in order to establish a diagnosis pointing to SCLE, it may be useful to perform the lupus band test (LBT): biopsied tissue samples taken from both skin lesions and non-lesional skin are compared with each other. Affected samples usually reveal deposits of immunoglobulins and complement factors at the junctions of dermis and epidermis. In about 90 % of cases, lesional skin taken from SCLE patients shows a positive direct immunofluorescence. For SLE, the LBT is positive in affected and unaffected skin, whereas for SCLE unaffected skin samples do not fluoresce. But this test does not provide the means to distinguish between different forms of CLE. Hence, it is not specific for DLE, but it can indicate the necessity for further diagnostic tests [2].

SCLE may cause anaemia, leucopenia or thrombocytopenia, which can be detected by full blood cell counts. Additionally, inflammatory skin reactions possibly

result in an elevated erythrocyte sedimentation rate (ESR), whereas complement levels may be depressed and some patients may test positive for rheumatoid factor. Renal involvement of SCLE is tested for with urinalysis and is revealed by red and/or white blood cell casts.

Photoprovocation of uninvolved skin by dermatological experts may elucidate the diagnosis of SCLE in difficult situations.

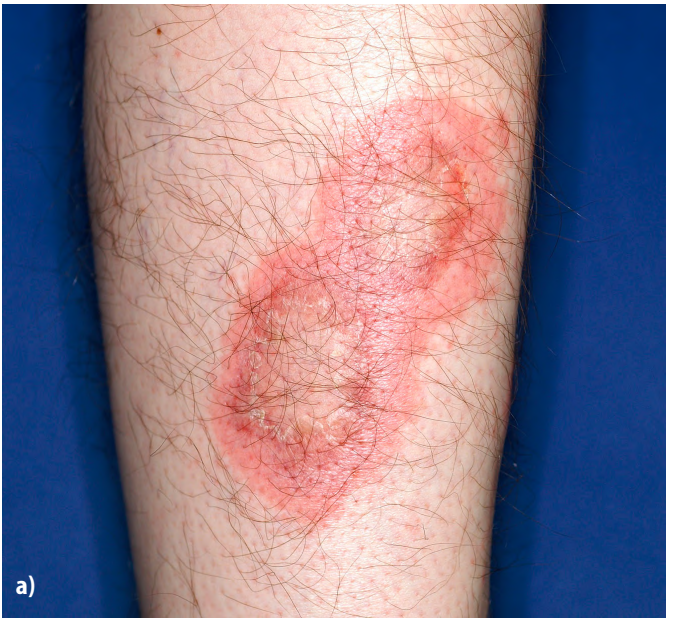
3 Requirements for family practitioners

SCLE primarily manifests in the skin, although the joints may also be affected in about half of the patients. In these cases, it is usually the small joints which are afflicted in a symmetrical pattern. In rare cases (< 2 %) arthritis may develop. Additionally, patients may feel fatigue, dryness of mouth and eyes and may manifest symptoms characteristic for SLE, such as neurologic or renal involvement, pericarditis and pleuritis. Hence, these factors should be included in the anamnesis if a practitioner finds SCLE-specific skin lesions.

The skin lesions start as popular eruptions with a photosensitive distribution that may wax and wane, depending on exposure and season. With time, the lesions may grow, conflate and turn into two different forms of skin defects: the papulosquamous or annular variants. The former can be confused with psoriasis (Fig. 1a), while the latter may look like erythema annulare centrifugum (Fig. 1b). Most patients tend towards one or the other variant, but additional DLE-type lesions may occur. Additionally, the unspecific cutaneous changes of lupus erythematosus (LE) may be present: ischaemic changes of the distal fingertips, livedo reticularis, mucosal leukoplakic or ulcerative lesions, palpable purpura or urticaria. An important clinical finding that distinguishes this type of lesion from others associated with cutaneous lupus erythematosus (CLE), such as DLE, is the fact that the lesions in SCLE-patients do not scar or atrophy.

Several unusual subtypes of SCLE have been described, such as tumid lupus erythematosus (TLE), Sjögren's syndrome-associated SCLE and erythema multiforme-like lesions in conjunction with DLE. It is unclear whether these variants are individual entities or consequences of SCLE itself.

Importantly, the entity of neonatal lupus erythematosus must be known by all practitioners who treat pregnant women positive for Ro (SSA) or La (SSB) antibodies. Neonatal lupus erythematosus is an uncommon, maternal auto-antibody-associated disease, characterised by cutaneous, cardiac, hepatic, haematological, neurological, and pulmonary involvement. Annular cutaneous signs manifest during the first month of life in most affected infants. Neonatal lupus erythematosus that affects the heart is usually discovered upon physical examination at birth but may be recognised with ultrasonography in utero.



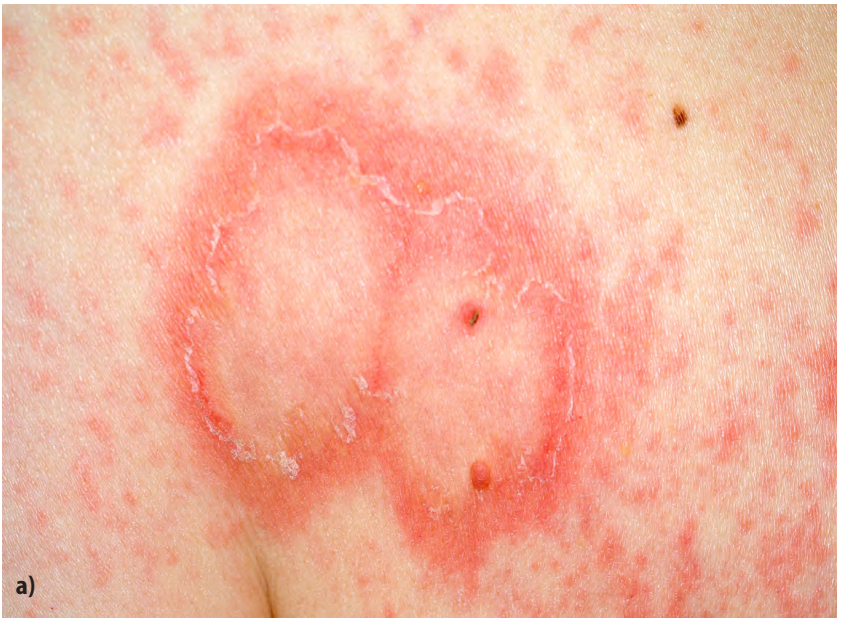
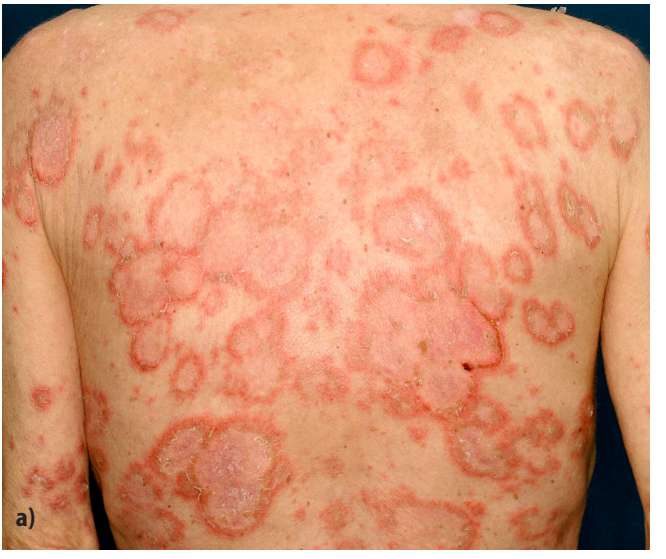
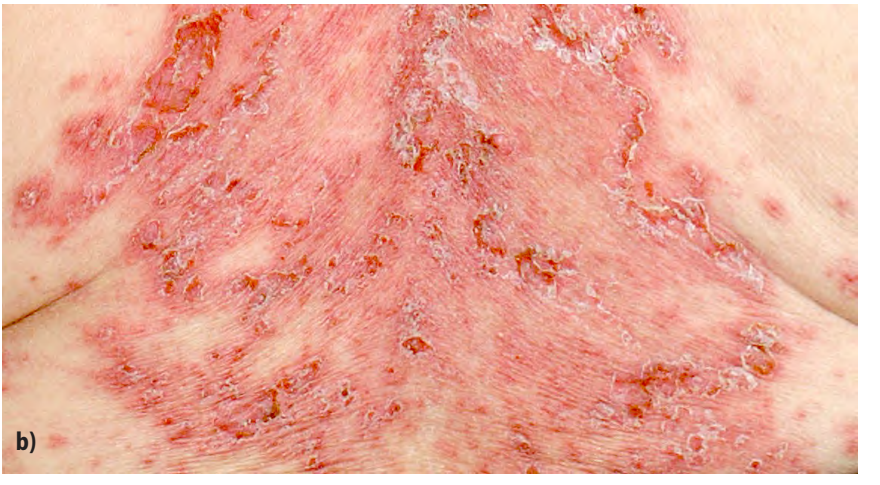


Figure 1. a) Annular lesions of SCLE.





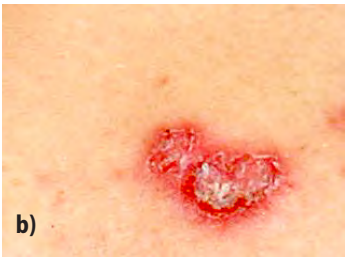


Figure 1. a) Annular lesions of SCLE.
b) Papulosquamous lesions of SCLE.

4 Follow up

Generally, patients should be instructed on the importance of sun-protective measures and their effect on the prognosis. Also, they should be schooled to recognize the symptoms of SLE as this requires a reassessment of treatment.

Patients with SCLE should be followed at regular intervals since the degree of treatment success varies among individuals and between the administered drugs. Changes in therapeutic strategy should only be made after a sufficiently long period of observation and follow up.

Assessments should be performed once or twice a year with the following laboratory tests: complete blood cell counts, renal function and urinalysis. Also, some SCLE-patients are vitamin D deficient and may require regular supplementation. In patients with SLE as co-morbidity, the sequential assessment of antinuclear antibody (ANA)-and anti-dsDNA antibody levels may be useful as a predictor of the disease's progression.

Without SLE, patients usually have a good prognosis with no persistent skin changes other than occasional dyspigmentation. Spontaneous remission is possible, but a chronic, periodical fluctuation is more common with exacerbation in the spring or summer. In rare cases, the disorder progresses into a severe systemic form with the danger of life-threatening sequelae.

5 Management

The lesions caused by SCLE are mostly located on exposed skin, may be viewed as disfiguring and have a detrimental effect on a patient's quality of life. Hence, the primary goal is to improve appearance and to prevent the formation of additional lesions. Topical corticosteroids and calcineurin antagonists are administered to treat local manifestations of the disease. Antimalarials are also given for most affected patients with SCLE. In more severe cases, systemic immunosuppressants are applied.

5.1 Sun protection

Generally, the first step in SCLE therapy is to protect exposed skin from ultraviolet (UV) light. Decreased activity during daylight hours with high UV loads between 10 am and 4 pm may help some individuals, while others exhibit extremely high photosensitivity and require sunscreens or protective clothing. Obviously, sources of intense artificial light (such as solaria) should be avoided as well. Usually, no further cosmetic measurements are required.

5.2 Corticosteroids

Corticosteroids and topical calcineurin antagonists suppress inflammation and down-regulate several components of the patient's immune system. The proliferation and recruitment of inflammatory cells, such as eosinophils, mast cells and T-lymphocytes, is reduced by corticosteroid therapy. Corticosteroids and calcineurin antagonists (e. g. tacrolimus) can be applied topically to treat single lesions.

5.3 Antimalarials

In most cases the immunomodulatory drug of choice is (hydro-)cychloroquine. Antimalarials limit complement-dependent antigen-antibody reactions, and they inhibit chemotaxis of eosinophils as well as locomotion of neutrophils. (Hydro-) cychloroquine can be combined with quinacrine in refractory CLE.

5.4 Immunosuppressive drugs

Systemic steroids can be used additionally in exacerbations of the disease. For long-term treatment of severe forms of SCLE, azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, and methotrexate are the established drugs of choice.

6 Diagnostic tests

To make a positive diagnosis of SCLE, the most useful serological tests include the detection of ANA, anti-Ro (SS-A) and anti-La (SS-B) autoantibodies and anti-native DNA (double-stranded or nuclear DNA). Most patients with SCLE test positive for anti-Ro autoantibodies with slight differences in the expression rates, depending on the specific variant and patient characteristics (Table 1). Also, anti-Ro antibodies are less frequently found in other types of CLE, such as DLE, and may be employed to distinguish between SCLE and DLE. Other than that, human leukocyte antigens have been associated with SCLE, specifically HLA-B8, HLA-DR3, HLA-DRw52, and HLA-DQ1 [3, 4]. However, HLA typing is not established in the clinical routine diagnosis of SCLE.

Today, anti-Ro antibodies are detected via indirect immunofluorescence (IIF), employing human mitotic epidermoid (HEp-2) cancer cell lines, transfected with multiple copies of the specific DNA sequence that carries the information of the Ro autoantigen. About 15–20 % of these cells over-express the antigen, allowing anti-Ro autoantibodies to bind to cell nuclei, forming stable antigen-antibody complexes. After washing, the cells are incubated with an anti-human antibody conjugated to fluorescein. This three-part complex can be visualized using fluorescent microscopy. Positive samples will emit apple-green fluorescence with a staining pattern characteristic of the particular nuclear antigen distribution within

the cells. If the sample is negative for anti-Ro antibodies, the nucleus will not show a clearly discernible fluorescence pattern, while those positive for anti-Ro antibodies stain as follows: in interphasic cells, a strong nuclear and speckled staining is apparent for Ro positive cells (Fig. 2), while metaphasic cells show no staining in the chromosome region and a variable staining outside the chromosome region [5].

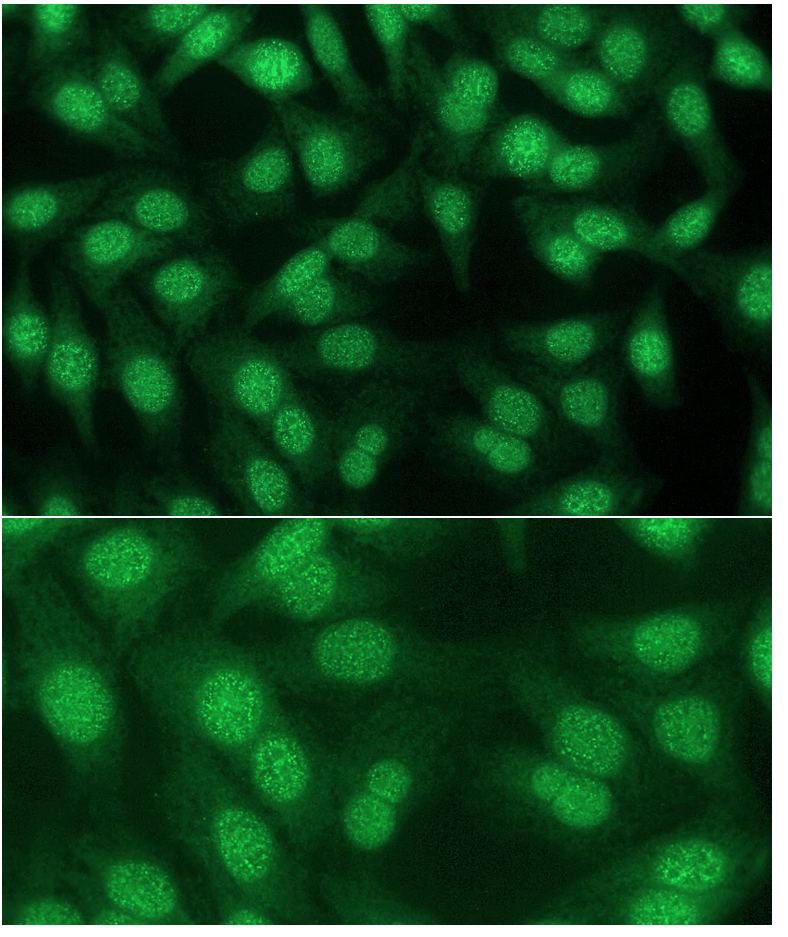


Figure 2. Indirect immunofluorescence of cells positive for anti-Ro autoantibodies. Cells show a characteristic speckled staining pattern.

7 Testing methods

The most effective serologic tests to diagnose SCLE are immunoassays targeting anti-Ro autoantibodies via IIF.

The established method for the diagnosis of DLE remains the physical examination of the patient's skin for the clinical manifestations of the disease. The skin lesions are very characteristic and distinct from those found in DLE and other diseases. Together with the histological assessment of biopsied tissue samples, the attending physician can make a positive diagnosis and may use serology to monitor the progression of the disease.

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