The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Discoid lupus erythematosus

Thomas Werfel

1 Introduction

Cutaneous lupus is a family of diseases that are classified by the cause of the clinical signs and symptoms into three major groups:

- Acute cutaneous lupus erythematosus
- Cutaneous lupus erythematosus
- Chronic cutaneous lupus erythematosus

Discoid lupus erythematosus (DLE) is the major form of chronic cutaneous lupus erythematous. It is a chronic, photosensitive dermatosis that usually occurs as an independent disorder. However, it may also develop in patients with systemic lupus erythematosus (SLE).

DLE manifests in the shape of reddish discs with adjacent desquamating areas. These flakes do not detach from the skin, and manual removal reveals a keratotic plaque beneath. Tissue atrophies develop in the central region of the disc, which causes scarring and alopecia in hirsute skin. Ultraviolet (UV) light and certain drugs induce and exacerbate these skin defects, and they can arise together with the lesions of subacute cutaneous lupus erythematosus (SCLE) and malar rash.

There are two subclasses of DLE: *localized DLE* is defined as limited to the head and neck, whereas *widespread DLE* targets other areas as well and has the higher potential to progress into full-fledged SLE.

The prevalence of DLE is about 50–85 % in all patients with cutaneous lupus erythematosus (CLE), which occurs as often as SLE, i. e. with an incidence of 17–48 : 100 000. DLE manifests mainly in women (gender ratio 2 : 1) between the ages of 20–40 years with a mean age of 38 years [1]. DLE is slightly more common in African Americans than in Caucasians or Asians.

Currently, the causes of DLE are not understood in detail, but a genetic predisposition is likely. The development of the skin lesions may be due to the autoimmune induction of a heat-shock protein in keratinocytes as a reaction to ultraviolet light (UV) light exposure or stress. This protein may target T-cells, causing epidermal cell cytotoxicity [2].

2 Diagnostic measurements for experts

DLE is a disease that primarily manifests in the skin, limiting the clinical diagnostic approaches to physical, histological and serological parameters. While there are clinically asymptomatic patients, some may report mild pruritus or transient pain together with the appearance of lesions. A systemic involvement is rare and occurs in approximately 5 % of DLE patients, leading to arthralgia or arthritis. Hematological and serologic abnormalities most often coincide with the *widespread* variant of DLE.

In order to establish a diagnosis pointing to DLE, it may be useful to perform the lupus band test (LBT): biopsied tissue samples, taken both from 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 DLE patients shows a positive direct immunofluorescence. For SLE, the LBT is positive in affected and unaffected skin, whereas for CLE, unaffected skin samples do not fluoresce. Using this test, however, it is not possible to distinguish between different forms of CLE. Hence, it is not specific for DLE, but can lead the expert in the right direction [3].

The most common histological findings characteristic for and indicative of DLE are listed in Table 1, together with the serological parameters. However, these are positive only in the minority of approx. 35 % of patients with DLE. A detailed description of the laboratory tests follows in the sections 'Diagnostic tests' and 'Testing methods'.

3 Requirements for family practitioners

Patients usually consult their general practitioner because of changes in the skin. The clinical attributes of the skin lesions are quite characteristic and their pattern is usually photodistributed, although even skin unexposed to sunlight may be affected.

The primary lesion manifests as an erythematous papule or plaque. Initially, scaling is slight, progressing together with lesion size, resulting in a thick, adherent scale with possible changes in pigmentation: hypopigmentation may occur in the center of the lesion, whereas hyperpigmentation tends to be apparent at the active border.

As lesions age, they grow and cause the formation of keratinous plugs which obstruct follicular openings. The final stage of the lesion is inactivation with atrophy and scarring (see Fig. 1), which may lead to permanent alopecia (see Fig. 2). Uncommon manifestations of DLE are hypertrophic or verrucous lesions appearing on the arms and fingers. These features do not necessarily manifest in all lesions.

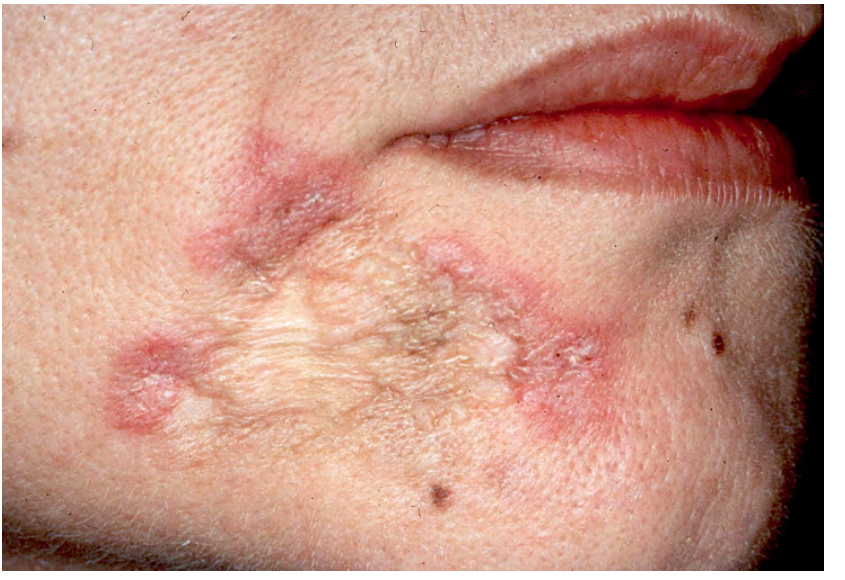

Figure 1. Chronic DLE lesion with scarring.

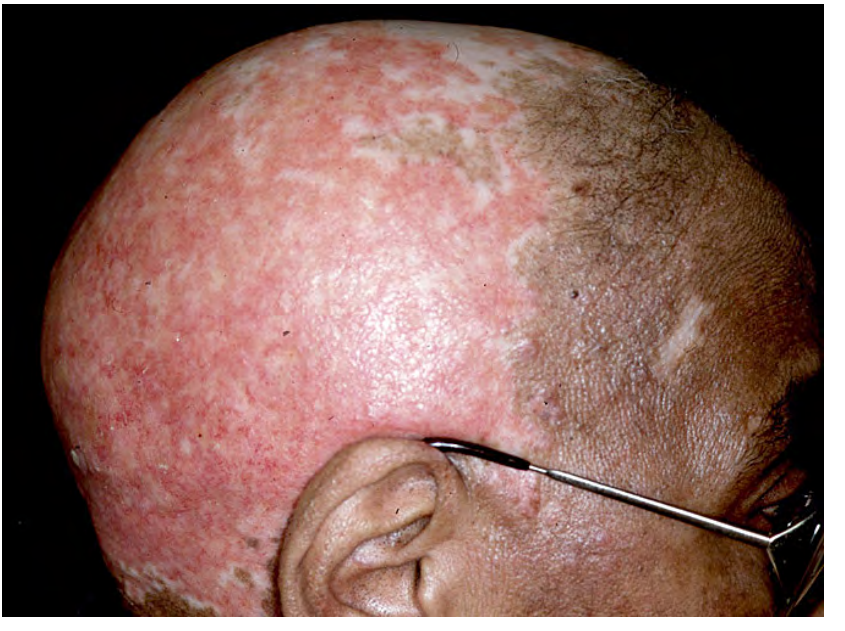

Figure 2. Alopecia induced by scarring DLE.

After diagnosis it is advisable to refer the patients to an institution specialized in dermatology.

4 Follow up

Generally, patients should be instructed in the importance of sun-protective measures and their effect on the prognosis. Also, patients should be advised to quit smoking as it negatively affects the efficacy of some drugs.

Patients with DLE should be followed at regular intervals since treatments generally take several weeks to months to show any effect. During follow up visits, the practitioner should document any newly developed symptoms in order to recognize a potential systemic dissemination of the disease. The 'Score of Activity and Damage in DLE' (SADDLE) allows the measurement of disease progression

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

Histology
– Atrophy of the epidermis
– Discontinuous distribution of pigments
– Follicular plugging
– Hyperkeratosis
– Presence of inflammatory cell infiltrates
– Thickening of the basal membrane
– Vacuolar alterations of the basal cell layer
Serology
– Antinuclear antibodies*
– Anti-native DNA (double-stranded or nDNA)*
– Anti-Ro (SS-A) autoantibodies (in rare cases)*
– Anti-Sm*
– Anti-annexin 1 antibodies**
– Ro52 protein upregulation**

* In "classical" cutaneous DLE the serology of autoantibodies is negative in most cases, see text.

** Attractive in vitro parameter due to recent findings.

nDNA, nuclear DNA.

via a reliable scoring system [4]. Annually, routine laboratory studies should be performed, including complete blood cell counts, renal function and urinalysis. Further antibody testing is only indicated after a change in symptoms.

Early treatment of DLE lesions can prevent scarring and atrophy, otherwise permanent follicular and skin defects may occur. Systemic progression of the disease is rare, but may lead to life-threatening sequelae. Development of malignant neoplasms can occur in rare cases — hence, new growths within inactive lesions should be removed.

While disfigurement — which is the most important long-term problem in this disease — is possible and pain may persist in some lesions, prognosis in terms of mortality for DLE is good.

5 Management

The treatment of discoid lupus erythematosus focuses on the improvement of the patient's appearance, the care of existing lesions, the limitation of scarring and on the prophylaxis against the development of additional lesions. Standard therapies include sun protective measures, medication with corticosteroids for the treatment of lesions and antimalarials if a systemic treatment is required.

5.1 Sun protection

Generally, the first step in DLE therapy is to protect exposed skin from UV light, both UVA and UVB. Decreased activity during daylight hours with high UV loads between 10 am and 4 pm may help some individuals, while others exhibit an extremely high photosensitivity and require sunscreens and protective clothing. Obviously, sources of intense artificial light (such as solaria) should be avoided as well. Some patients may benefit from additional cosmetic measures to cover especially prominent scar tissue with wigs or makeup.

5.2 Corticosteroids

Corticosteroids suppress inflammation and downregulate several components of the patient's immune system. The generation and recruitment of inflammatory cells, such as eosinophils, mast cells and T-lymphocytes is reduced. Corticosteroids are most commonly applied topically and more rarely injected into the lesion, depending on individual conditions. The daily dosage of corticosteroids should be limited to avoid systemic toxicity and to reduce the potential for local atrophy. Topical application of tacrolimus has also been reported to be beneficial in some cases.

5.3 Antimalarials

If a systemic agent is required for DLE, the immunomodulatory drug of choice among antimalarials is (hydroxy-)chloroquine, whereas chloroquine should be considered as a second-line therapeutic drug. Both agents limit complement-dependent antigen-antibody reactions and they inhibit chemotaxis of eosinophils as well as locomotion of neutrophils. The efficacy of these drugs is reduced by first- and second-hand smoking.

5.4 Surgery

For some patients, it may be necessary to excise scarred lesions in order to counteract especially disfiguring scarring. This may be achieved surgically or via laser therapy. However, both methods can lead to a reactivation of inactive lesions. Hence, it is advisable to treat a test area and to check if the DLE flares before therapy is commenced.

6 Diagnostic tests

In general, no single diagnostic tool exists that can detect the presence of DLE in all patients. Instead, a combination of serological tests, immunopathological and histological approaches can be applied for a positive diagnosis.

The commonly employed serological tests include the detection of antinuclear antibodies (ANA), which are positive in approximately 35 % of all patients with DLE. Well defined autoantibodies such as anti-Ro (SS-A) autoantibodies, anti-native DNA (double-stranded or nuclear DNA) and anti-Sm antibodies are more likely positive in DLE variants associated with systemic disease.

Recently, anti-annexin 1 antibodies have been discovered as a viable means to diagnose DLE [5]. On the other hand, anti-native DNA antibodies and ANA have been proven to be characteristic for lupus erythematosus and only occur in low concentrations in patients with the cutaneous forms of lupus erythematosus (CLE).

Proteins of the Ro-family have recently been reported to be specific for intracellular reactions involved in CLE and Sjögren's syndrome [6]. Epidermal keratinocytes taken from lesional skin reveal nuclear and cytoplasmic upregulation of Ro52, especially in layers adjacent to the basement membrane. This protein is also present in endothelial and lymphocytic infiltrates within the dermis. Today, monoclonal antibodies (mAbs) against Ro52 have been created that can be employed in immunohistochemical testing for CLE. Usually, second-level methods, such as indirect immunofluorescence (IIF), counterimmunoelectrophoresis (CIE) or enzyme-linked immunosorbent assays (Elisa) are performed for the detection of antigens in patient sera. In the case of Ro52, though, the overexpression of the protein itself is measured via immunosorbent assays.

A schematic representation of the sandwich Elisa method is shown in Fig. 3: a buffered solution of anti-Ro52 mAbs is added to the microtitre plate, where they adhere via charge interactions (Fig. 3a), and the remaining free plastic surface is blocked with non-reacting proteins. Next, serum is added (Fig. 3b), which may contain the pathologic levels of the Ro52 protein, which binds to the mAbs and forms antigen-antibody complexes (Fig. 3c). After washing (Fig. 3d), a secondary antibody that is enzyme-linked to a detection molecule is added (Fig. 3e). The latter is activated via a specific substrate, causing a color reaction that can be measured photometrically (Fig. 3f).

Annexin 1 suppresses the generation of inflammatory mediators like prostaglandins, thromboxanes and leukotrienes, resulting in an anti-inflammatory reaction. The levels of anti-annexin 1 antibodies are significantly elevated in patients with CLE as compared to healthy subjects, especially for patients with DLE. These are detected by Elisa tailored to annexin 1. The specificity of this test for CLE can be as high as 95 % [5]. However, no correlation between disease progression and antibody levels has been elucidated as yet.

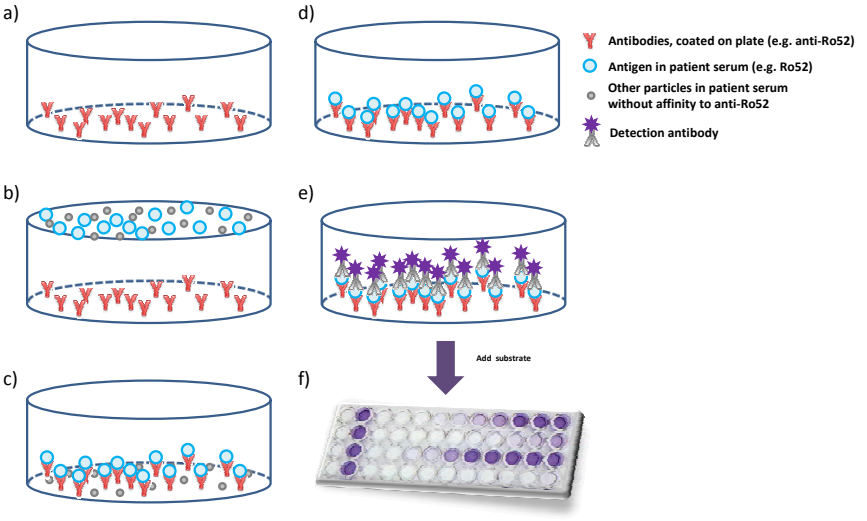

Figure 3. Schematic representation of the sandwich Elisa method: a) antibody on microtitre plate, b) add serum with target antigen, c) formation of antibody-antigen complexes, d) washed plate, only antibody-antigen complexes remain, e) add secondary enzyme-linked detection antibody, f) microtitre plate with colored, positive samples after addition of activating substrate.

7 Testing methods

Due to the low specificity of the presented serologic testing methods for DLE, their diagnostic value remains unclear. Only very recent methods, targeting specific molecules, such as anti-Ro52- and anti-annexin 1 antibodies, show high sensitivity and specificity for the discoid variant of CLE. However, these methods are relatively new and still need to prove their applicability in daily laboratory routine.

The most efficient method for the diagnosis of DLE remains the physical examination for the clinical manifestations of the disease. The skin lesions are very characteristic and distinct from those found in SCLE 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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